5 Minute JournalClub

POST-SABCS Issue 1, 2013

For more visit ResearchToPractice.com/5MJCSABCS2013

Research To Practice®

CME Information

LEARNING OBJECTIVES

- Apply the results of emerging research evaluating the optimal dose of fulvestrant to the clinical care of postmenopausal patients with locally advanced or metastatic breast cancer.
- Evaluate the contributory effects of bevacizumab when added to standard endocrine therapy for postmenopausal patients with unresectable, locally advanced or metastatic breast cancer.
- Integrate new clinical trial data supporting the extended use of adjuvant tamoxifen beyond 5 years to the treatment of patients with localized estrogen receptor-positive breast cancer.
- Describe the rationale for and emerging efficacy and tolerability data with the novel combination of endocrine therapy and a cyclin-dependent kinase 4/6 inhibitor for postmenopausal women with hormone receptor-positive advanced breast cancer.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME Information (Continued)

HOW TO USE THIS CME ACTIVITY
This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCSABCS2013/1/CME.

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:

Lisa A Carey, MD
Richardson and Marilyn Jacobs Preyer Distinguished
Professor for Breast Cancer Research
Chief, Division of Hematology and Oncology
Physician-in-Chief
North Carolina Cancer Hospital
Associate Director for Clinical Research
Lineberger Comprehensive Cancer Center
Chapel Hill, North Carolina

CME Information (Continued)

Advisory Committee, Consulting Agreements and Speakers Bureau: Amgen Inc, Bristol-Myers Squibb Company, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; *Research Support:* Genentech BioOncology, GlaxoSmithKline, Sanofi.

Rowan T Chlebowski, MD, PhD
Professor of Medicine
David Geffen School of Medicine at UCLA
Chief, Division of Medical Oncology and Hematology
Harbor-UCLA Medical Center
Torrance, California

Advisory Committee: AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals Corporation; *Consulting Agreement:* Pfizer Inc; *Speakers Bureau:* Novartis Pharmaceuticals Corporation.

Clifford Hudis, MD
Chief, Breast Cancer Medicine Service
Solid Tumor Division
Department of Medicine
Memorial Sloan-Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, New York

CME Information (Continued)

No real or apparent conflicts of interest to disclose.

Edith A Perez, MD
Deputy Director at Large, Mayo Clinic Cancer Center
Group Vice Chair, Alliance of Clinical Trials in Oncology
Serene M and Frances C Durling Professor of Medicine
Mayo Clinic
Jacksonville, Florida

Contracted Research: Genentech BioOncology, Genomic Health Inc, GlaxoSmithKline.

Sir Richard Peto
Professor of Medical Statistics
Co-director, Clinical Trial Service Unit
University of Oxford
Oxford, United Kingdom

No real or apparent conflicts of interest to disclose. Prof Peto was not paid for his interview.

5 MinuteJournalClub

POST-SABCS Issue 1, 2013

SABCS highlights: Should adjuvant tamoxifen now be administered for 10 years?

In 1995 the National Cancer Institute (NCI) mailed a “Clinical Alert” to oncologists strongly cautioning them to limit the duration of adjuvant tamoxifen (TAM) to 5 years based on data from NSABP and Scottish trials demonstrating no advantage and perhaps a detriment with prolonged endocrine treatment. While investigators worldwide endorsed this recommendation, legendary Oxford statistician Sir Richard Peto and his cadre were not convinced and regularly noted (most memorably in a fiery exchange during the 2000 NIH/NCI Breast Cancer Consensus Conference) that the available data on TAM duration were inadequately powered to answer the question. Further, they believed there was a substantial likelihood that longer treatment would yield greater benefit and to that end championed the launch of 2 massive international trials — ATLAS and aTTom — comparing 5 years to 10 years of TAM.

More than a decade later, this past December during the San Antonio Breast Cancer Symposium, Peto (as usual) had the last word when his colleague Richard Gray presented the dramatic findings from the ATLAS trial demonstrating

a clear-cut and meaningful advantage in favor of continuing TAM for 10 years. As ATLAS was quite likely the biggest story coming out of the meeting by the river, we decided to kick off this year's post-SABCS series by profiling that and other endocrine-related papers:

1. ATLAS (10 versus 5 years of adjuvant TAM)

Perhaps the most fascinating aspect of this historic study is how ER-positive disease evolves over time and the impressive carryover effect of endocrine treatment that persists for up to a decade after discontinuation. Several weeks after San Antonio, in another in a series of audio interviews I've done with Dr Peto stretching back more than 20 years, he emphasized the profound delayed impact of adjuvant hormonal therapy and pointed out that the full measure of benefit of 10 years of TAM won't be determined until about 2018.

Although more follow-up is welcome, it also seems that there is now a rapidly developing consensus based on the ATLAS findings that treatment should be continued out to 10 years in patients who remain premenopausal after 5 years of TAM. Treatment for patients who become menopausal during the first 5 years of TAM is far less clear cut, but switching to an aromatase inhibitor and continuing therapy is another logical option. For postmenopausal women with an intact uterus, the risk-benefit profile of 10 years of TAM is controversial.

2. Encouraging data with letrozole in combination with a cyclin-dependent kinase (CDK) inhibitor

CDKs play a critical role in regulating cell-cycle progression, and laboratory evidence suggests possible synergy between CDK inhibition and endocrine treatment. Those observations led to a randomized Phase II trial in postmenopausal women comparing the CDK inhibitor PD 0332991 combined with letrozole to letrozole alone, which at San Antonio demonstrated an improvement in progression-free survival (PFS) from 7.5 to 26.1 months in favor of the combination, with minimal additional toxicity, mainly myelosuppression. Although there was considerable excitement surrounding these impressive results, all agree that a Phase III trial will determine if this is for real or just iniparib-esque hype that will lead to disappointment.

3. Survival benefit of 500 mg vs 250 mg fulvestrant

With an overall survival (OS) hazard rate of 0.81, this is one of the few Phase III breast cancer trials of any type that shows that dose really can matter. The study supports the current widely used practice of administering 500-mg fulvestrant, and one wonders if this fascinating agent will ever be studied in an adjuvant trial.

4. Bevacizumab (bev) and endocrine treatment for metastatic disease (LEA trial)

Same old story here as this Phase III study demonstrated a modest trend for PFS benefit in favor of bev without any effect on survival. This leads to a logical question: Is this the end of the line for anti-angiogenic agents in breast cancer

until the ECOG adjuvant bev trial results mature? The answer is not as simple as you might think given the surprising positive trial results recently reported in metastatic gastric cancer showing a PFS and OS advantage for monotherapy with a monoclonal antibody to the VEGF receptor 2 (ramucirumab) suggesting that we may not have seen the end of positive research findings with this strategy.

5. SWOG-S1207: Adjuvant everolimus with endocrine treatment

This important study, highlighted during the conference's ongoing clinical trials session, supports the notion that "the best clinical option is often trial participation." Many patients with ER-positive, HER2-negative tumors have less than optimal long-term outcomes with endocrine treatment and chemotherapy, and this study allows patients the opportunity to maybe fare better by adding an agent with encouraging supportive data in the metastatic setting.

Next in this series: Metastatic HER2-positive disease — where the world awaits the much-needed approval of the antibody-drug conjugate trastuzumab emtansine (T-DM1), and we review more data from San Antonio on the other major recent addition to the field, the HER2 dimerization inhibitor pertuzumab.

Neil Love, MD
Research To Practice
Miami, Florida

Long-Term Effects of Continuing Adjuvant Tamoxifen to 10 Years versus Stopping at 5 Years After Diagnosis of Oestrogen Receptor-Positive Breast Cancer: ATLAS, a Randomised Trial

Davies C et al.

Proc SABCS 2012;Abstract S1-2.

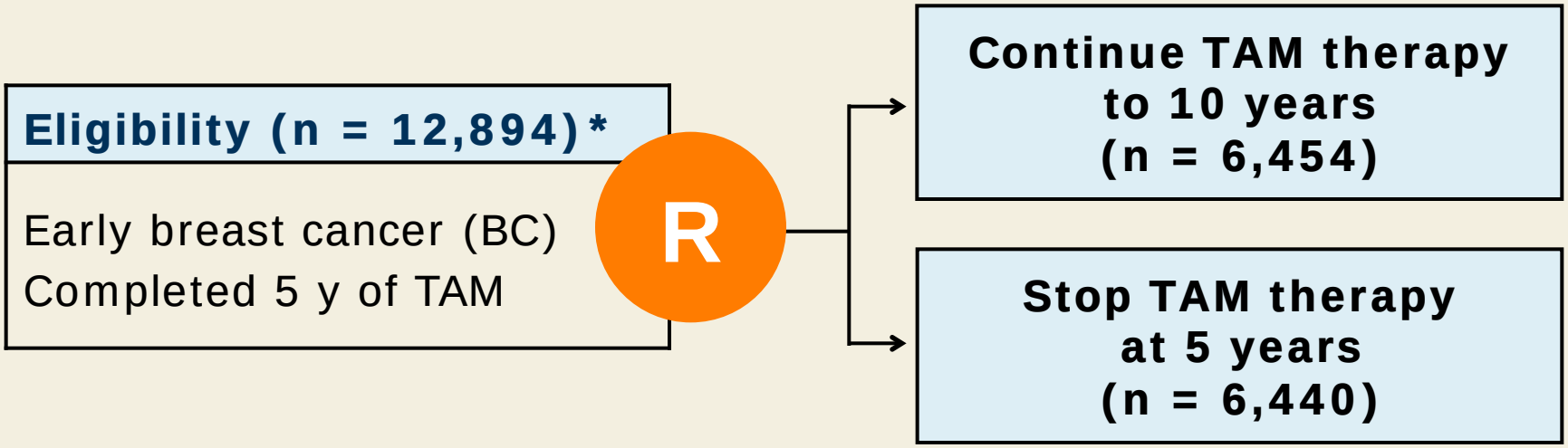
Lancet 2012;[Epub ahead of print].

Background

- For women with estrogen receptor (ER)-positive early breast cancer, previous studies have shown that treatment with tamoxifen (TAM) for 5 years:
  - Significantly decreases breast cancer recurrence throughout the first 10 years.
  - Substantially reduces the breast cancer mortality rate throughout the first 15 years after diagnosis (*Lancet* 2011;378:771-84).
- However, little is known about how 10 years of TAM compares to the current standard of treatment for 5 years.
- The randomized Phase III ATLAS trial assessed the effects of continuing TAM therapy for 10 years rather than stopping at 5 years.

Davies C et al. *Lancet* 2012;[Epub ahead of print].

ATLAS Trial Design



* Of the study's entire population, ER-positive BC: 6,846 (53%); ER-negative BC: 1,248 (10%); unknown ER status: 4,800 (37%)

- Yearly follow-up forms sent by central organizers recorded recurrence, incidence of second cancer, hospital admission or death.
- Besides duration of TAM therapy, disease management was at physician's discretion.
- Recurrence was defined as first recurrence of any form of BC after ATLAS entry.

Davies C et al. *Lancet* 2012;[Epub ahead of print].

Recurrence Rate for Patients with ER-Positive BC

No. of years since diagnosis	Continue TAM to 10 y (n = 3,428)	Stop TAM at 5 y (n = 3,418)
5 y (study entry)	—	—
10 y (treatment end)	13.1%	14.5%
15 y (10 y since study entry)	21.4%	25.1%

- BC recurrences (continuing TAM to 10 y vs stopping at 5 y): 617 vs 711 ($2p = 0.002$)

Davies C et al. *Lancet* 2012;[Epub ahead of print].

BC Mortality (Overall Rate per Rate in Women without Recurrence) for Patients with ER-Positive BC

No. of years since diagnosis	Continue TAM to 10 y (n = 3,428)	Stop TAM at 5 y (n = 3,418)
5 y (study entry)	—	—
10 y (treatment end)	5.8%	6.0%
15 y (10 y since study entry)	12.2%	15.0%

- BC mortality (continuing TAM to 10 y vs stopping at 5 y): 331 vs 397 ($2p = 0.01$)

Davies C et al. *Lancet* 2012;[Epub ahead of print].

Select Adverse Events (Any ER Status)

Event	Continue TAM to 10 y (no.)	Stop TAM at 5 y (no.)	Event RR (2*p*-value)
Second cancer incidence			
Contralateral BC	419	467	0.88 (0.05)
Endometrial cancer*	116	63	1.74 (0.0002)
Nonneoplastic disease†			
Stroke	130	119	1.06 (0.63)
Pulmonary embolus	41	21	1.87 (0.01)
Ischemic heart disease	127	63	0.76 (0.02)

* Mainly endometrial adenocarcinoma but includes all other uterine tumors except cervical cancer; uterine tumors exclude those with recorded hysterectomy at study entry

† Ever hospitalized or died

Davies C et al. *Lancet* 2012;[Epub ahead of print].

Event Rate Ratios in ER-Positive Disease from Time of Diagnosis in Meta-Analysis and ATLAS Trial

	5 y TAM vs none: Meta-analysis	10 y TAM vs 5 y: ATLAS	10 y TAM vs none*
Breast cancer recurrence ≥10 y	0.94	0.75	0.70
Breast cancer mortality ≥10 y	0.73	0.71	0.52

* Product of rate ratios, estimated effect

"Taken together with the results from trials of 5 years of tamoxifen versus none, the results from ATLAS show that 10 years of effective endocrine therapy can approximately halve breast cancer mortality during years 10-14 after diagnosis."

Davies C et al. *Lancet* 2012;[Epub ahead of print].

Side Effects and Main Effects of 10 Years of TAM on 15-Year Mortality in Meta-analysis and ATLAS Trial

	5 y TAM vs none: Meta-analysis	10 y TAM vs 5 y: ATLAS	10 y TAM vs none (by addition)
Endometrial cancer and PE mortality	0.2% loss	0.25 loss	0.4% loss
Breast cancer mortality	9% gain	3% gain	12% gain

Estimated effects of 10 y TAM vs 0 on 15-y mortality:
Absolute gain ~30 x absolute loss

Davies C et al. *Proc SABCS* 2012;Abstract S1-2.

Author Conclusions

- For women with ER-positive breast cancer, the continuation of TAM treatment for 10 years instead of stopping at 5 years results in a further reduction in recurrence and mortality, especially after year 10.
- The ATLAS study, taken together with results from previous trials of 5 years of TAM treatment versus none, suggests that 10 years of TAM treatment can approximately halve breast cancer mortality during the second decade after diagnosis.

Davies C et al. *Lancet* 2012;[Epub ahead of print].

Editorial: Extended Adjuvant Tamoxifen for Breast Cancer — A New Era

"Overall the benefits of extended tamoxifen seemed to outweigh the risks substantially. This finding raises questions about the possible benefit of extension of adjuvant endocrine therapy… No data are available regarding use of aromatase inhibitors for more than 5 years or long-term toxic effects from extended treatment."

"Confirmation of the ATLAS trial by meta-analysis of all extended tamoxifen treatment trials should herald a change of practice, with the standard of care revised to 10 years rather than 5 years of tamoxifen in patients for whom tamoxifen is indicated. This change should open up a whole new era of clinical trials to assess the benefit of extended adjuvant endocrine therapy of breast cancer."

Powles TJ et al. *Lancet* 2012;[Epub ahead of print].

Investigator Commentary: ATLAS — Long-Term Effects of Continuing Adjuvant TAM for 10 y versus 5 y After Diagnosis

For the ATLAS trial, we wanted results that would apply, globally, to all women with ER-positive BC. Many physicians were uncertain as to whether to continue with TAM beyond 5 y, especially with the alert that going beyond 5 y could be dangerous. We encouraged TAM continuation beyond 5 y when both the patient and physician were substantially uncertain about how to proceed. Although many did not know whether it would be harmful or beneficial, they thought the difference would be minimal either way. ATLAS showed that 10 y is somewhat more effective than 5 y. Even though TAM can cause pulmonary embolus and endometrial cancer, the gain albeit small, is 10 times more than the hazards in terms of life or death. ATLAS should be seen as a trial of longer versus shorter hormonal endocrine therapy (ET). The conclusion that 10 y is a little better than 5 y of ET points to the prevention of cancer recurrence and improved long-term survival. I believe that this conclusion will continue to hold even if treatment moves on from TAM to other such agents.

Interview with Sir Richard Peto, January 11, 2013

Investigator Commentary: ATLAS — Long-Term Effects of Continuing Adjuvant TAM for 10 y versus 5 y After Diagnosis

Sir Richard Peto will certainly tell you he believed the existing data were not definitive, so he wanted to do a study. ATLAS was a controversial trial, but Professor Peto felt that the biology was in favor of longer TAM duration. It is remarkable that they were able to get the study under way. It is a practice-changing trial that gets us thinking about the nature of BC and ET.

The results are fascinating, demonstrating that after 5 y of TAM, continuing versus stopping TAM produces little effect in year-5 to year-10 while administering treatment (hazard ratio of 0.9). Thereafter, in year 10 to year 15 the authors reported statistically significant reductions in BC incidence, BC mortality and overall mortality for women with ER-positive disease. These results are spectacular.

Interview with Rowan T Chlebowski, MD, PhD, January 9, 2013

Results of a Randomized Phase 2 Study of PD 0332991, a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor, in Combination with Letrozole vs Letrozole Alone for First-Line Treatment of ER+/HER2- Advanced Breast Cancer (BC)

Finn RS et al.

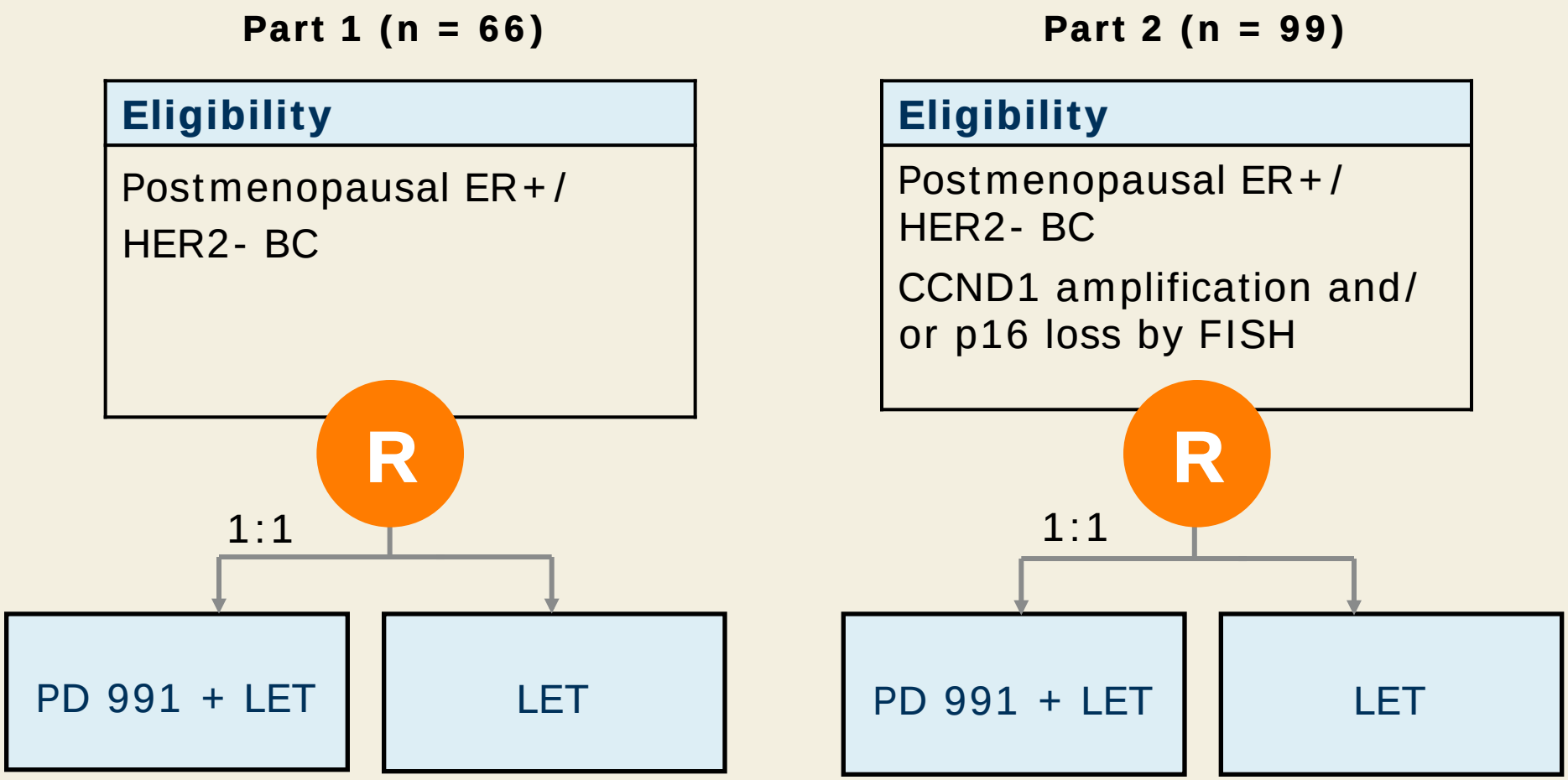
Proc SABCS 2012;Abstract S1-6.

Background

- Preclinical studies identified an association between sensitivity to PD 0332991 and the luminal ER subtype, elevated expression of cyclin D1 and Rb and reduced p16 expression[1], and also synergistic activity between tamoxifen and PD 0332991[2] ([1]*Breast Cancer Res* 2009;11(5):R77; [2]*Nat Rev Can* 2011;11:558).
- The current 2-part, Phase II trial was designed to evaluate PD 0332991 and letrozole (PD 991 + LET) versus letrozole alone in postmenopausal patients with ER+/HER2- breast cancer (BC).
- Interim analysis of Part 1 of this Phase II study showed a significant improvement in PFS with PD 991 + LET versus LET alone (IMPAKT Breast Cancer Conference 2012;Abstract 292).
- **Study objective:** Interim analysis of combined results of patients in both Part 1 and Part 2 of the Phase II study.

Finn RS et al. *Proc SABCS* 2012;Abstract S1-6.

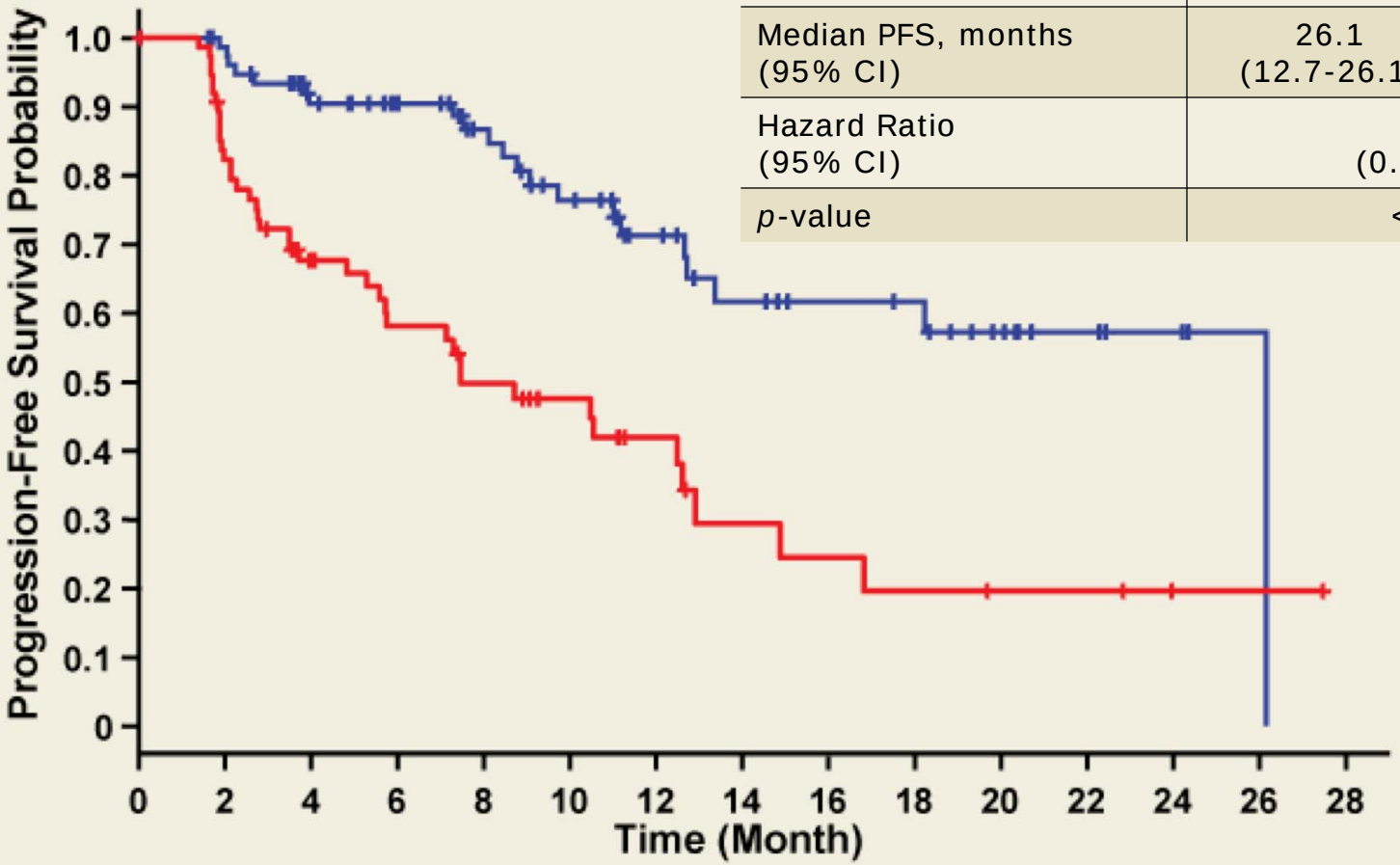
Phase II Study Design



Finn RS et al. *Proc SABCS* 2012;Abstract S1-6.

Primary Endpoint: Progression-Free Survival

	PD 991 + LET (n = 84)	LET (n = 81)
Number of Events (%)	21 (25)	40 (49)
Median PFS, months (95% CI)	26.1 (12.7-26.1)	7.5 (5.6-12.6)
Hazard Ratio (95% CI)	0.37 (0.21-0.63)	
p-value	<0.001	



With permission from Finn RS et al. *Proc SABCS* 2012;Abstract S1-6.

Best Overall Response: Patients with Measurable Disease

Response rate	PD 991 + LET	LET
Objective response (n = 64, 65)	45%	31%
Complete response	0%	0%
Partial response	45%	31%
Clinical benefit rate (n = 84, 81)	70%	44%

Finn RS et al. *Proc SABCS* 2012;Abstract S1-6.

Select Treatment-Related Adverse Events (AEs)

Grade 3/4 AEs (≥10%)	PD 991 + LET (n = 83)	LET (n = 77)
Neutropenia	61.4%	1.3%
Leukopenia	16.9%	0%
Anemia	6%	1.3%
Fatigue	4.8%	1.3%
Thrombocytopenia	1.2%	0%

Finn RS et al. *Proc SABCS* 2012;Abstract S1-6.

Author Conclusions

- In patients with ER+/HER2– breast cancer, the combination of PD 0332991 with letrozole shows statistically significant improvement in median PFS compared to letrozole alone.
- These results confirm the preclinical observations made with PD 0332991 in breast cancer models.
- The combination is generally well tolerated, with uncomplicated neutropenia as the most frequent adverse event.
- A randomized Phase III study is planned to start in 2013.

Finn RS et al. *Proc SABCS* 2012;Abstract S1-6.

Investigator Commentary: Phase II Study of PD 0332991 with Letrozole versus Letrozole Alone for First-Line Treatment of ER-Positive, HER2-Negative Advanced Breast Cancer

The results of this randomized Phase II study comparing PD 0332991 with letrozole to letrozole alone demonstrated remarkable results in terms of progression-free survival (26.1 mo versus 7.5 mo). Because cyclin D is important for mitosis, inhibiting CDK 4/6 may be universally effective. Few patient-perceived side effects were reported, including Grade 3 myelosuppression but no febrile neutropenia. We will have to see whether these results are borne out in the Phase III study.

Interview with Rowan T Chlebowski, MD, PhD, January 9, 2013

This study showed a striking improvement in progression-free survival with PD 0332991 in combination with letrozole versus letrozole alone, and these results are exciting. We should be enthusiastic about the planned Phase III study. Currently PD 0332991 is being studied in trials as a single agent and in combination with chemotherapy.

CDK inhibitors have been studied for years, and this study was a breakout result in breast cancer. CDKs are important in cell cycle progression throughout the “malignancy spectrum,” and CDK inhibitors may also be effective in other cancers.

Interview with Clifford Hudis, MD, January 11, 2013

Final Analysis of Overall Survival for the Phase III CONFIRM Trial: Fulvestrant 500 mg versus 250 mg

Di Leo A et al.

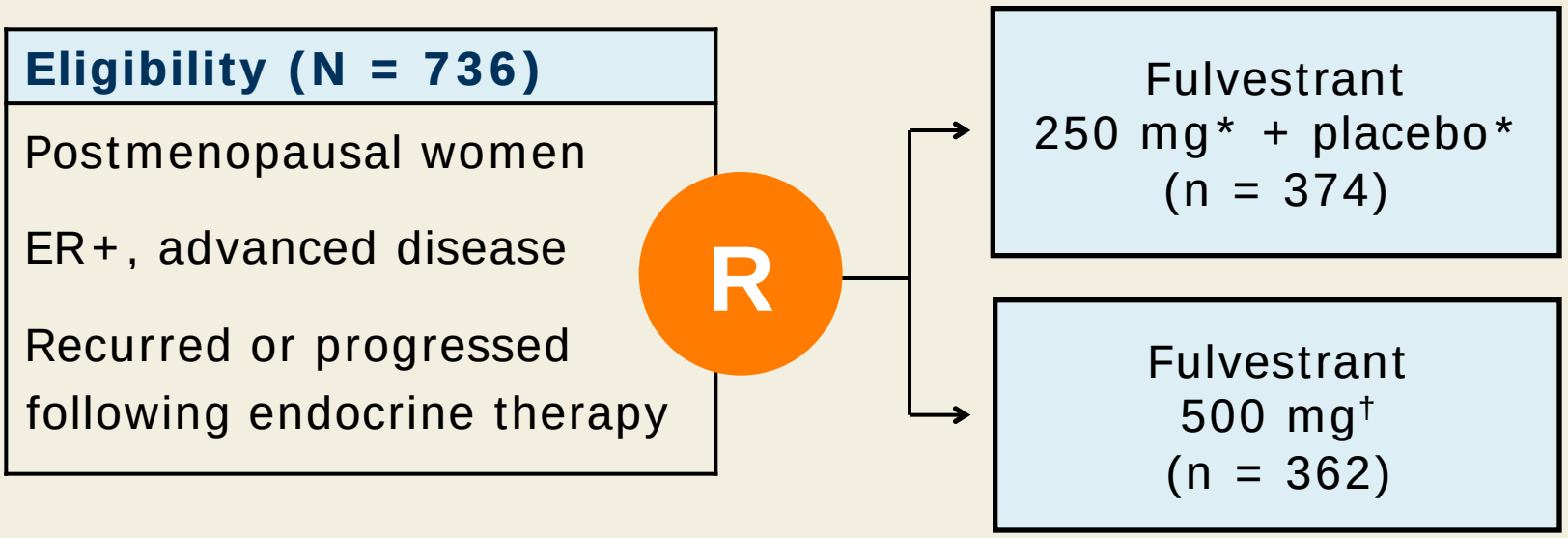
Proc SABCS 2012;Abstract S1-4.

Background

- Primary analysis of the CONFIRM trial for postmenopausal women with locally advanced or metastatic breast cancer demonstrated that with fulvestrant 500 mg versus 250 mg.
  - A statistically significant increase in progression-free survival was recorded (median PFS: 6.5 vs 5.5 months, $p = 0.006$).
  - The median overall survival was 25.1 months and 22.8 months, respectively, after the death of 50% of patients ($p = 0.091$).
    (*J Clin Oncol* 2010;28:4594-600)
- **Study Objective:** To present follow-up analysis of overall survival after the death of 75% of patients on the trial.

Di Leo A et al. *Proc SABCS* 2012;Abstract S1-4.

CONFIRM Study Design



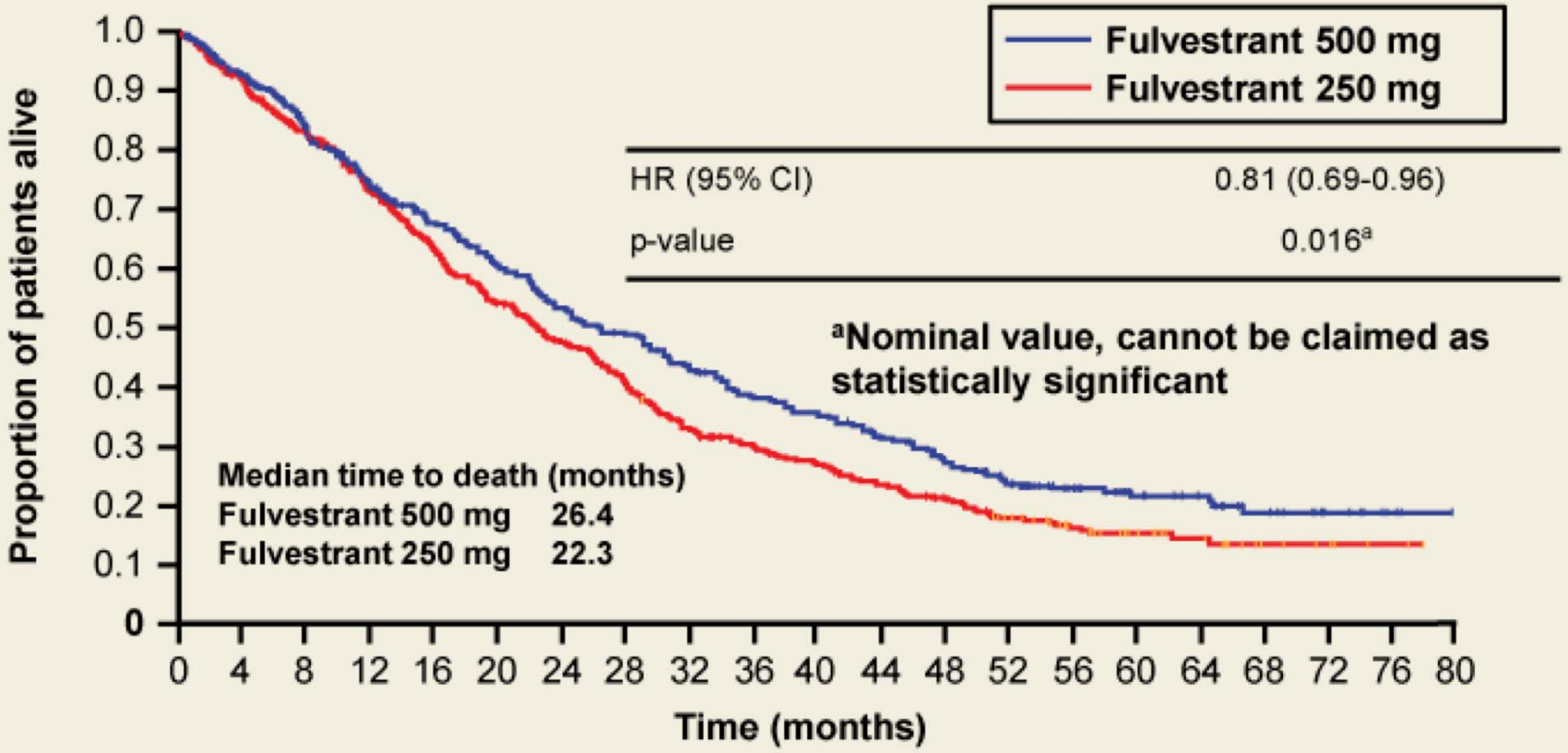
*1 injection IM; †2 injections (250 mg each) IM

After the primary analysis:

- 50% of patients had died
- Patients on fulvestrant 250 mg were permitted to cross over to 500 mg

Di Leo A et al. *Proc SABCS* 2012;Abstract S1-4.

Secondary Endpoint: Overall Survival



With permission from Di Leo A et al. *Proc SABCS* 2012;Abstract S1-4.

First Subsequent Therapies

Type of first subsequent therapy	Fulvestrant 500 mg (n = 230)*	Fulvestrant 250 mg (n = 239)*
Chemotherapy/anti-HER2	59%/0%	59%/0.4%
Endocrine therapy other than fulvestrant†	35%	31%
Objective response/clinical benefit	8%/33%	8%/41%

* Patients with available information

† 2.1% (8/374) of patients crossed over from 250 mg to 500 mg of fulvestrant.

Di Leo A et al. *Proc SABCS* 2012;Abstract S1-4.

Select Serious Adverse Events (SAEs) with Outcome of Death

SAEs	Fulvestrant 500 mg (n = 361)	Fulvestrant 250 mg (n = 374)
Acute myocardial infarction	0%	0.5%
Acute renal failure	0%	0.3%
Cardiopulmonary failure	0.3%	0%
Dyspnea	0.6%	0%
Hypertension	0%	0.3%
Meningitis	0%	0.3%

Patients with at least 1 SAE: Fulvestrant 500 mg = 9.7%; fulvestrant 250 mg = 7.2%
Total SAEs: Fulvestrant 500 mg = 1.4%; fulvestrant 250 mg = 1.9%

Di Leo A et al. *Proc SABCS* 2012;Abstract S1-4.

Author Conclusions

- Final OS analysis at 75% maturity shows that fulvestrant 500 mg is associated with a 4.1-month increase in median OS and a 19% reduction in the risk of death compared to 250 mg of fulvestrant.
- These results are consistent with previously reported PFS and OS data (*J Clin Oncol* 2010;28:4594).
- Analysis of first subsequent therapies does not support any imbalance between the study arms.
- Only 2% of patients crossed over from 250 to 500 mg. However, activity for fulvestrant 500 mg after pretreatment with 250 mg of fulvestrant is unknown.
- The safety results are consistent with those previously reported for 500 mg of fulvestrant.

Di Leo A et al. *Proc SABCS* 2012;Abstract S1-4.

Investigator Commentary: Final Analysis of the Phase III CONFIRM Trial: Fulvestrant 500 mg versus 250 mg

The CONFIRM trial compared fulvestrant at what used to be the conventional dose of 250 mg versus 500 mg in postmenopausal women with advanced breast cancer. The first analysis demonstrated an improvement in progression-free survival and a nonsignificant increase in overall survival.

This study was the final analysis of overall survival after 75% of the events had occurred. One cannot argue with the improvement in overall survival. The results showed a 4-month improvement in overall survival and a 19% reduction in the risk of death.

Only 2% of the patients crossed over from the 250-mg to the 500-mg dose. An analysis of the first subsequent therapy showed that both the arms were similar and most of the patients went on to receive chemotherapy. It is unlikely that imbalance between the 2 arms altered the survival results. Based on the results of this study, I would administer fulvestrant at 500 mg in my practice.

Interview with Lisa A Carey, MD, January 17, 2013

Phase III Trial Evaluating the Addition of Bevacizumab to Endocrine Therapy as First-Line Treatment for Advanced Breast Cancer — First Efficacy Results from the LEA Study

Martin M et al.

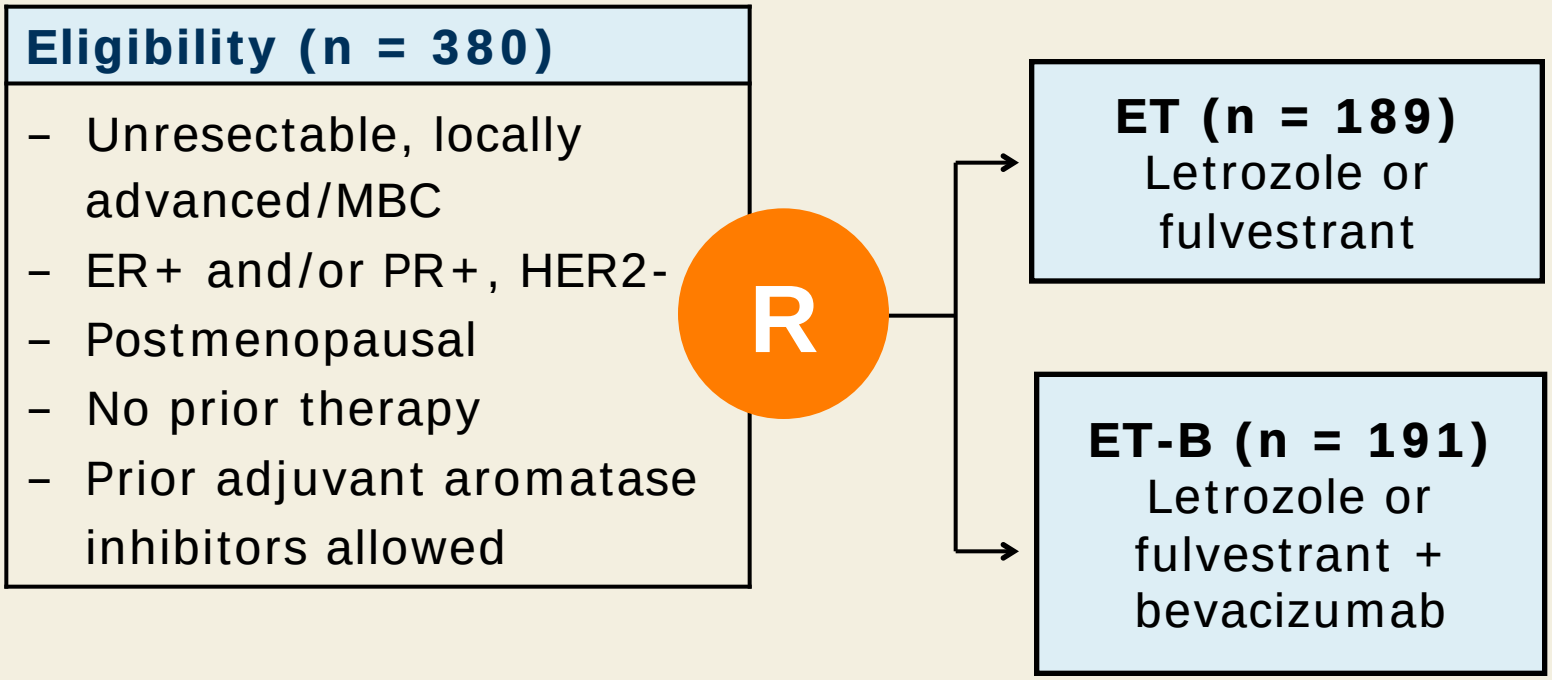
Proc SABCS 2012;Abstract S1-7.

Background

- High vascular endothelial growth factor (VEGF) levels in tumor tissue from breast cancer are associated with a decreased response to endocrine therapy.
- Downregulation of VEGF may overcome resistance and improve efficacy of hormonal therapy (*JCO* 2005;23:4695-704).
- The combination of endocrine therapy with bevacizumab has been shown to be safe and active in Phase II trials (*JCO* 2010;28:628-33).
- **Objective:**
  - Determine if anti-VEGF treatment can delay resistance to endocrine therapy in patients with hormone receptor-positive advanced breast cancer.

Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

LEA Phase III Study Design



A median progression-free survival (PFS) improvement from 9 months in the ET arm to 13 months in the ET-B arm was assumed (HR = 0.69), requiring a total of 232 PFS events and 354 patients (80% power, 2-sided alpha level of 5%).

Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

Survival Outcomes

	ET (n = 189)	ET-B (n = 191)	HR	*p*-value
Median PFS	13.8 mo	18.4 mo	0.83	0.14
PFS events	131	117*	—	—
Median OS	42 mo	41 mo	1.18	0.469
OS events	42	42	—	—

* Seven while on treatment

OS = overall survival

Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

Select Treatment-Related Adverse Events

Grade 3/4 AEs	ET	ET-B	*p*-value
Anemia	0.6%	1.1%	NS
Leukopenia	0%	2.1%	NS
Fatigue	0.6%	2.1%	0.373
Hypertension	0%	3.2%	0.03
Liver enzyme elevation	0%	1.6%	0.249
Proteinuria	0%	1.1%	0.499
Thromboembolic events	0%	2.1%	0.124

NS = not significant

Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

Author Conclusions

- No statistically significant increase was seen in PFS for ET with bevacizumab versus ET alone.
- An increase of smaller magnitude (ie, <31% reduction in PFS with bevacizumab) cannot be ruled out.
- Adding bevacizumab to ET as first-line therapy had no impact on overall survival.
- Biomarker studies can help to select the population that might benefit from bevacizumab in addition to hormonal treatment.

Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

Investigator Commentary: Phase III LEA Study on the Addition of Bevacizumab to Endocrine Therapy for Advanced BC

The LEA study demonstrated that the addition of bevacizumab to endocrine therapy resulted in an improvement in PFS that was not statistically significant, and there was no change in overall survival. More toxicity occurred on the arm with bevacizumab, but it was reasonably well tolerated. Our conventional selection criteria are not designed for anti-angiogenic agents, which have nothing to do with the tumor but everything to do with the microenvironment. Unless we come up with a selection strategy for these agents, it is going to be difficult to incorporate them into our armamentarium.

Interview with Lisa A Carey, MD, January 17, 2013

All of the studies to date have consistently shown that adding bevacizumab to therapy improves PFS without having an effect on overall survival. The results of the LEA study are consistent with previous studies. Bevacizumab remains an interesting agent in breast cancer, but it does not change the outcome of the disease enough to warrant its routine use.

Interview with Edith A Perez, MD, January 17, 2013

S1207: Phase III Randomized, Placebo-Controlled Clinical Trial Evaluating the Use of Adjuvant Endocrine Therapy +/- One Year of Everolimus in Patients with High-Risk, Hormone Receptor-Positive and HER2-neu Negative Breast Cancer (NCT01674140)

Chavez-MacGregor M et al.

Proc SABCS 2012;Abstract OT2-2-04.

Background

- The PI3K/AKT/mTOR signaling pathway has been associated with resistance to endocrine therapies (ETs) in hormone receptor (HR)-positive breast cancer (BC) (*Int J Cancer* 2006;118(2):284).
- Everolimus is an mTOR inhibitor that has been shown to increase progression-free survival when combined with aromatase inhibitors (*N Engl J Med* 2012;366(6):520).
- Everolimus in combination with tamoxifen increased the time to disease progression among patients with metastatic BC previously treated with aromatase inhibitors (*J Clin Oncol* 2012;30(22):2718).

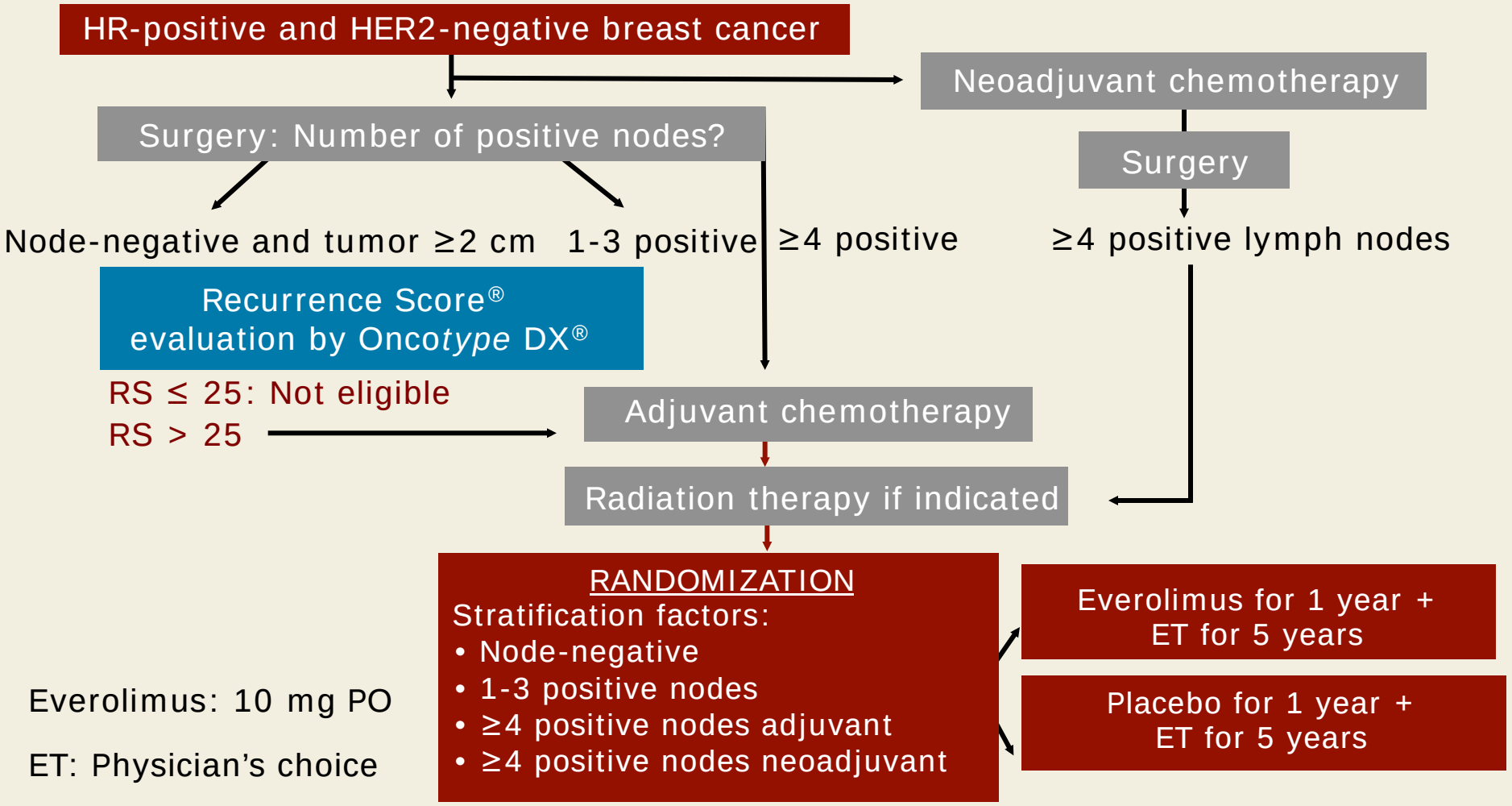
Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

SWOG-S1207 Study Objectives

- **Primary objective:** To determine whether 1 year of everolimus in combination with standard adjuvant ET improves invasive disease-free survival (IDFS) for patients with high-risk, HR-positive, HER2-negative BC.
- **Secondary objectives include:**
  - Overall survival (OS)
  - Distant recurrence-free survival
  - Safety and toxicity
  - Quality of life
  - Collection of specimens for translational studies
  - Evaluation of adherence

Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

Phase III SWOG-S1207 Trial Design



Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

SWOG-S1207: Statistical Considerations

- Target accrual for randomization: n = 3,500
- Expected accrual start date: January 2013
- The study is designed to have a 90% power (with a 2-sided α = 0.05) in order to detect an effective hazard ratio of 0.75 for everolimus versus placebo
  - This will correspond to a gain in IDFS of approximately 4.3% at 5 years
- All patients will be followed for 10 years to assess OS and long-term adverse events
- Expected duration from trial activation to reporting of IDFS is approximately 7 years

Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

Planned Studies: Behavioral and Health Outcomes

- All patients at community clinical oncology program institutions will be able to participate
- Patients who have already started ET are ineligible
- **Objectives:**
  - To determine the severity of symptoms, evaluate quality of life and assess whether fatigue and development of anemia are associated with biomarkers of inflammation
- **Statistical Design:**
  - N = 492 in order to have 90% power to detect a difference of 1/3 standard deviation between treatment groups (α-level = 0.05)

Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

Planned Translational Studies

- Mandatory samples to be collected:
  - Blood
  - Tissue if available (1 paraffin block of the primary tumor, positive lymph node and negative lymph node)
- Tissues from biopsies at the time of recurrence will be collected.

Chavez-MacGregor M et al. *Proc SABCS* 2012;Abstract OT2-2-04.

Investigator Commentary: S1207 — Adjuvant ET with or without Everolimus for High-Risk, HR-Positive and HER2-Negative BC

The trial has interesting inclusion criteria. For patients (pts) who are node-negative or have 1 to 3 positive nodes, the Recurrence Score (RS) must be high. All pts with ≥4 positive nodes are included. The investigators are trying to avoid administering everolimus to a population at low risk. My only concern is that its efficacy was documented in pts with acquired resistance to AIs, but this is de novo therapy. As it has toxic effects, careful selection of pts for whom ET alone may be insufficient, with the RS criterion, is a good idea.

Interview with Lisa A Carey, MD, January 17, 2013

This study is reasonable because the BOLERO-2 trial demonstrated PFS improvements by adding everolimus to exemestane for ER-positive advanced BC. Although BOLERO-2 was conducted in a refractory population, it makes sense to move this agent to the adjuvant setting. There are questions about whether everolimus will have a lower possibility of efficacy in the first-line setting because it is active in the refractory setting. Also, this study will include the collection of biospecimens that will contribute to the understanding of the biology of the disease. I would enroll patients on this study.

Interview with Edith A Perez, MD, January 17, 2013