5 Minute JournalClub

POST-SABCS Issue 4, 2013

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CME Information

LEARNING OBJECTIVES

- Evaluate the impact of adjuvant chemotherapy on survival for patients with isolated local and regional recurrence of breast cancer, and apply this information to patient care.
- Assess the benefits and side effects of adding bevacizumab to taxane- or anthracycline-based chemotherapy in the adjuvant setting for triple-negative breast cancer.
- Consider the clinical utility of eribulin mesylate as a treatment option in comparison to capecitabine for patients with previously treated locally advanced or metastatic breast cancer based on recent Phase III trial results.
- Describe the early efficacy and toxicity data from the ongoing trial investigating eribulin mesylate as first-line therapy for locally recurrent or metastatic HER2-negative breast cancer.

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:

CME Information (Continued)

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CME Information (Continued)

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5 MinuteJournalClub

POST-SABCS Issue 4, 2013

A Practice-Changing Paper on Adjuvant Chemotherapy After Surgical Excision of Local Recurrence and Other San Antonio Highlights

Last June at ASCO, Dr Sandra Swain presented results from one of the most anticipated trials ever introduced by a generation of clinical scientists focused on adjuvant chemotherapy for breast cancer. NSABP-B-38 was launched in 2004 after the groundbreaking CALGB-9741 study documenting the benefit of dose-dense AC → paclitaxel, and it accrued 4,894 patients in an attempt to determine if that regimen with or without gemcitabine yielded better outcomes than TAC. Perhaps even more striking than the results of this trial (all 3 arms had similar efficacy) was that by the time it matured, much of the research community was indifferent about the outcome, having already diverted its full attention to the new world of targeted and novel agents.

As an enlightened thinker and President of ASCO, Dr Swain may have as much to say about biologically driven cancer therapy as anyone, but when I recently interviewed her for an upcoming audio program, among the fascinating topics we explored was a somewhat unexpected paper from San Antonio that may turn out to be one of the most clinically meaningful data sets on adjuvant chemotherapy

in quite some time. **The CALOR trial** was a collaboration between Dr Swain's NSABP and the BIG and IBCSG groups and asked the logical but pretty much unaddressed question of whether patients with a local recurrence in the breast or chest wall who have been rendered clinically disease free by surgical excision would benefit from the addition of "pseudoadjuvant" chemotherapy.

The study demonstrated that physician's choice chemotherapy yielded similar benefits to traditional adjuvant treatment (DFS HR 0.59, $p = 0.0455$; OS HR 0.41, $p = 0.02$), but unfortunately the study was underpowered with a final accrual of 162 patients compared to the original goal of 977. Importantly, most of the benefit was observed in individuals with ER-negative tumors, and one wonders if these data will lead to studies of genomic assays like Onco*type* on local recurrence, a practice that NSABP chair Dr Norman Wolmark already utilizes clinically.

Although few breast cancer mavens have adopted Dr Wolmark's next-generation strategy, most — including Dr Swain — have suddenly changed their algorithms and now carefully consider postop chemotherapy for patients with local recurrence. Of course, CALOR wasn't the only interesting and potentially applicable chemo-related data set we saw in San Antonio, and the following help further define what we know and don't know:

301 trial of eribulin versus capecitabine

Eribulin — a sea sponge-derived microtubule inhibitor — entered US practice in 2010 as late-line treatment for metastatic disease and, as is common across all cancer medicine, significant interest developed in potentially moving the agent up in the treatment sequence. At San Antonio we were treated to the results of

those efforts in the form of a major Phase III report comparing the drug to perhaps the most commonly used cytotoxic after a taxane, capecitabine. Although the hope was that eribulin would show greater efficacy, in fact the findings were generally quite similar except perhaps in patients with ER-negative tumors, for whom a trend was evident favoring eribulin.

To get a sense of what these findings — and those from **a related Phase II SABCS data set with eribulin up front** — mean, we queried the 8 investigators participating in our recent breast cancer think tank. Dr Lisa Carey did a good job capsulizing the perspectives of many in the room by stating, “This was not a disappointment. The study was moving a drug that we all have become comfortable with in the very late-line setting to an earlier setting, and if it is as good as a drug like capecitabine, then it is another option with a totally different toxicity profile. I found this to be a useful study and one that helps with practice.”

On the flip side, there was unanimity among the think tank faculty that the exact sequence of these agents is probably not consequential in the long run and often decisions are made based on toxicity, method of administration, patient preferences and convenience. Importantly, however, several investigators stated they sometimes lean more toward capecitabine for older patients with ER-positive, HER2-negative tumors and agents like eribulin for triple-negative disease.

Related to the issue of sequencing multiple agents in the metastatic setting, at our CME satellite symposium in San Antonio, Dr George Sledge stated his belief that chemotherapy is often overused at the end of life and is a key component of “futile care.” Although arguments can be made for either side of the issue, this Saturday in Washington DC at the annual Oncology Nursing Society Congress we are going

to discuss the case of a 54-year-old woman treated at Dana-Farber who in June 2012 made the difficult decision between going to hospice and taking one more shot at chemo. She ultimately elected to go for fifth-line therapy and experienced a partial remission with minimal toxicity that continues to this time, and the patient was able to spend the summer in Cape Cod watching her grandchildren continue to grow. Which agent the patient received is not as important as the fact that this case both exemplifies the complexity of Dr Sledge's comment and supports the notion that chemotherapy can and still does play an important role in providing patients with best-quality care.

BEATRICE: Adjuvant chemotherapy/bevacizumab (bev)

At SABCS we saw the first presentation of the **BEATRICE trial** evaluating adjuvant bev with a physician's choice taxane- and/or anthracycline-based regimen in patients with triple-negative disease. Given the diminished recent role of bev in the metastatic setting and the well-publicized failure of the adjuvant trial in colorectal cancer, these negative results were not too surprising. Interestingly, Dr Wolmark is still frustrated that the signal of an impressive reduction in recurrence observed when bev was on board in the NSABP-C-08 colon cancer trial has not been further pursued. BEATRICE, like C-08, used one year of bev, and Norm continues to believe that more benefit would be seen with a greater duration of treatment, although this is not likely to be studied.

Next...The final issue of this SABCS-focused series: Late reports from the first generation of adjuvant trastuzumab trials and other related presentations.

Neil Love, MD
Research To Practice
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Chemotherapy Prolongs Survival for Isolated Local or Regional Recurrence of Breast Cancer: The CALOR Trial (Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer; IBCSG 27-02, NSABP B-37, BIG 1-02)

Aebi S et al.

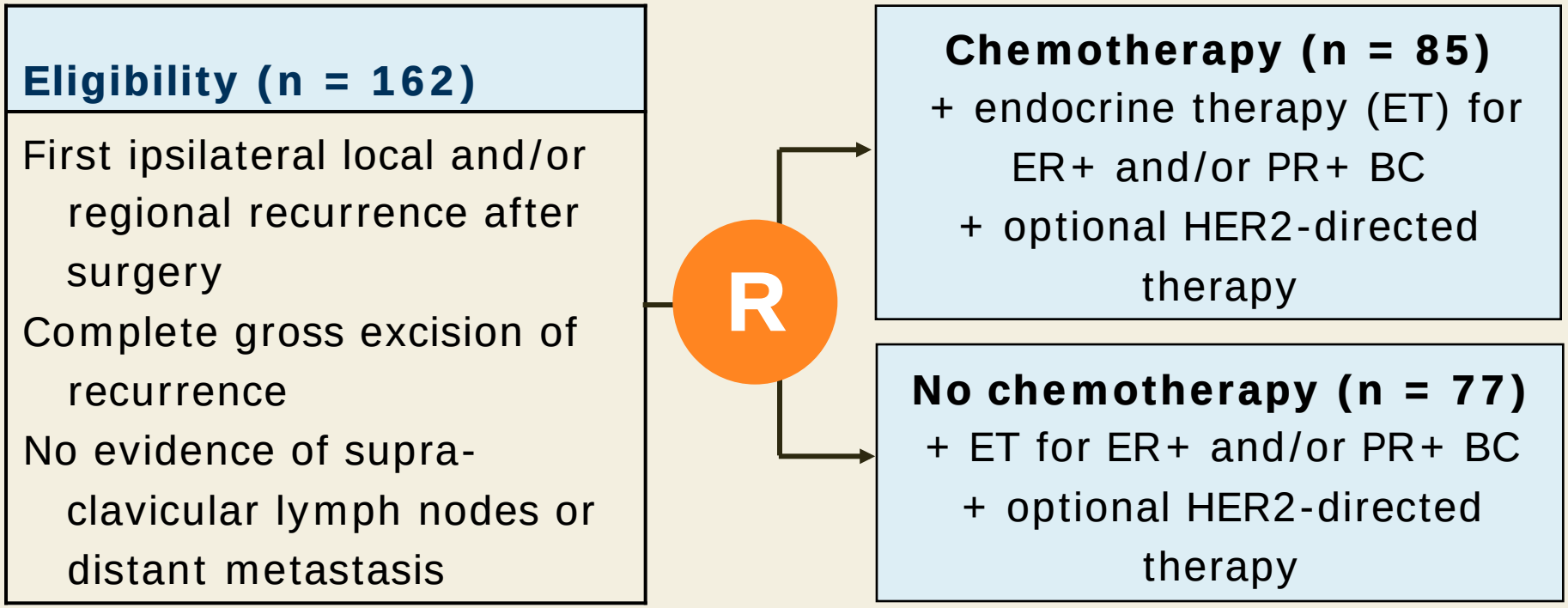
Proc SABCS 2012;Abstract S3-2.

Background

- Patients with isolated local or regional recurrences (ILRR) of breast cancer (BC) have a high risk of developing distant metastases and death from BC.
- The results of the randomized Phase III SAKK 23/82 trial comparing tamoxifen to observation demonstrated that tamoxifen significantly improved the postrecurrence disease-free survival (DFS) for patients with ER-positive BC after local treatment of ILRR (*Ann Oncol* 2003;14:1215).
- However, no prospective randomized trial of adjuvant chemotherapy for ILRR has been published in the past 30 years.
- **Study objective:** To investigate the impact of chemotherapy on DFS and overall survival (OS) after ILRR.

Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

Phase III CALOR Trial Design



- Patients with resected ILRR were stratified according to prior chemotherapy, ER and/or PR status of the recurrent tumor and location of recurrence prior to randomization.
- Chemotherapy chosen by investigators: ≥2 drugs, 3-6 mo of therapy
- Radiation therapy mandatory for patients with microscopically involved margins

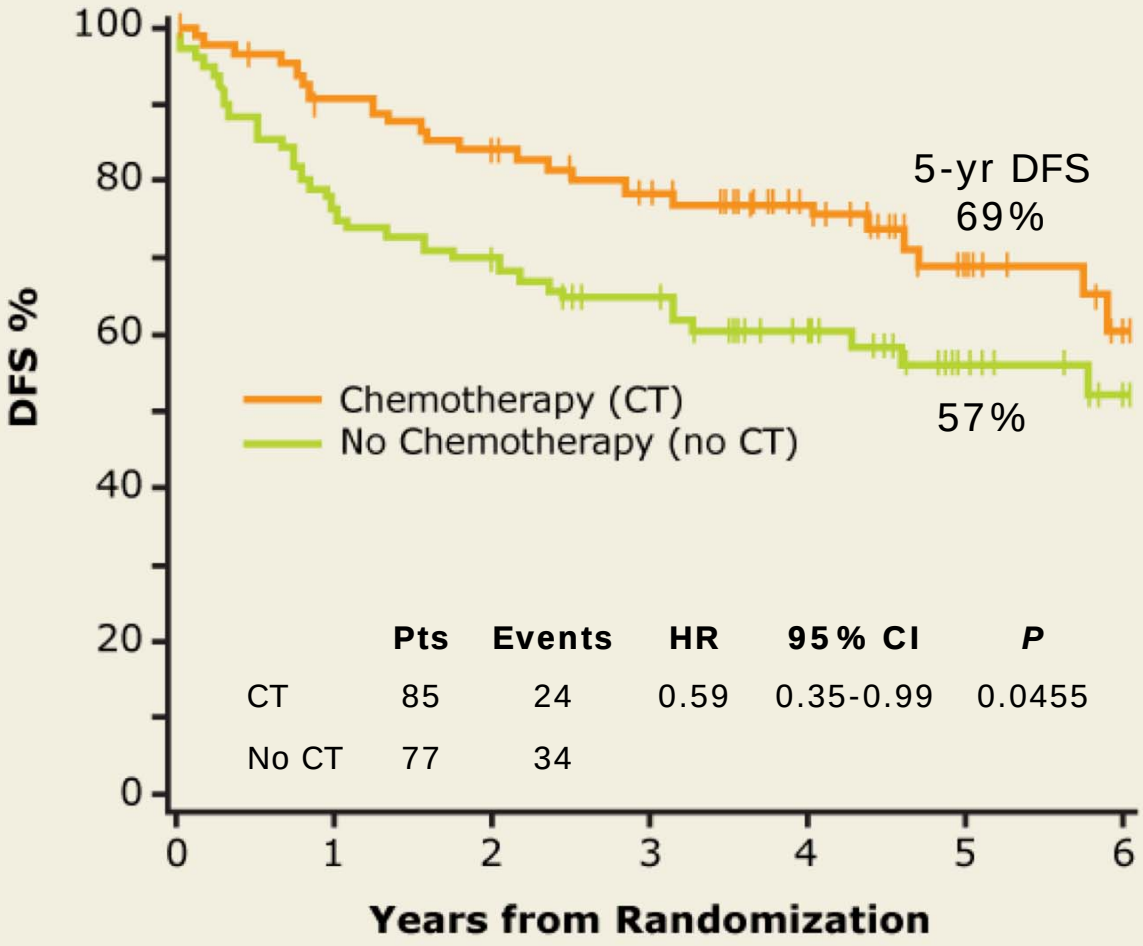
Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

Statistical Considerations

- Original sample size for hazard ratio (HR) of 0.74:
  - 977 patients, 347 DFS events
- Due to low accrual rate and newer, more effective chemotherapies, amendment 3 in 2008 resulted in a revised sample size for HR of 0.6:
  - 265 patients, 124 events
  - 5-year DFS for the observation group = 50%
  - $1-\beta = 0.8$, log-rank $\alpha = 0.05$, 1 interim analysis
- On January 31, 2010, the trial was closed with 162 patients (no interim analysis).
- Analysis was conducted when the median follow-up reached 4 years, with a minimum follow-up of 2.5 years.

Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

DFS: Overall Population



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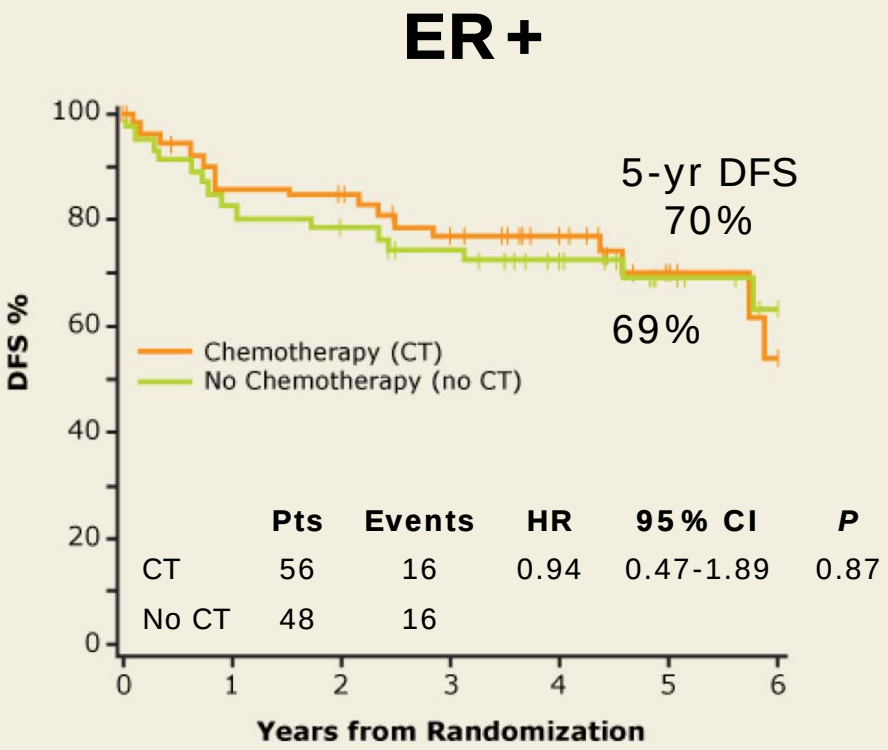
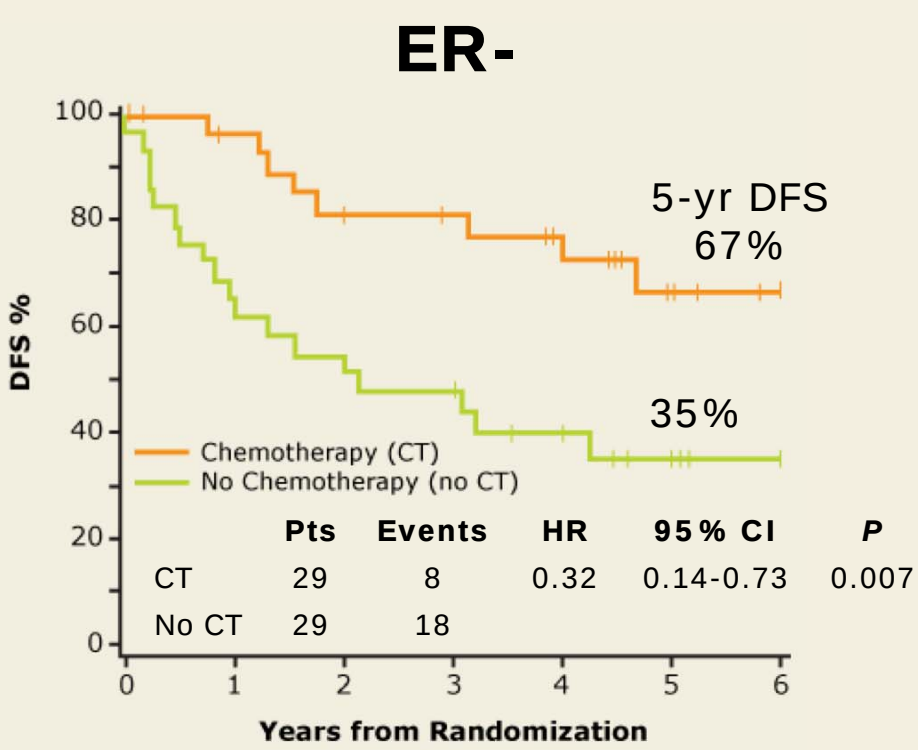
DFS by ER Status





Univariate interaction term: Treatment x ER: $p = 0.044$

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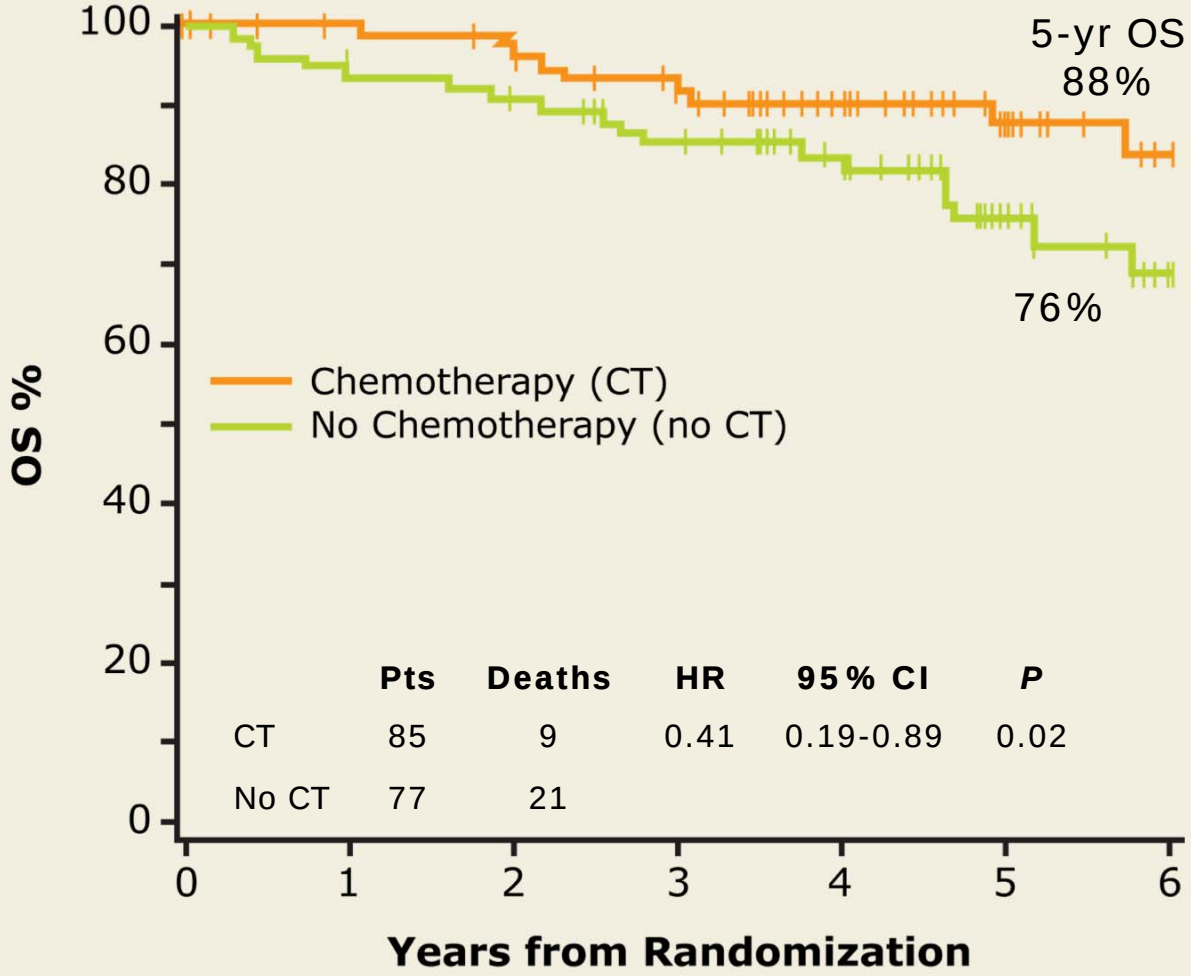
Multivariate Analysis of DFS

	Hazard ratio	*p*-value
ER status (positive/negative)	0.76	0.32
Location of ILRR		
Breast	Reference	Reference
Mastectomy scar or chest wall	0.90	0.79
Lymph nodes	0.99	0.99
Prior chemotherapy (yes/no)	1.002	0.99
Interval from primary surgery (per y)	0.91	0.002
Treatment (chemotherapy/none)	0.50	0.01

- Interaction term:
  - Treatment x ER in ILRR: $p = 0.05$

Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

OS: Overall Population



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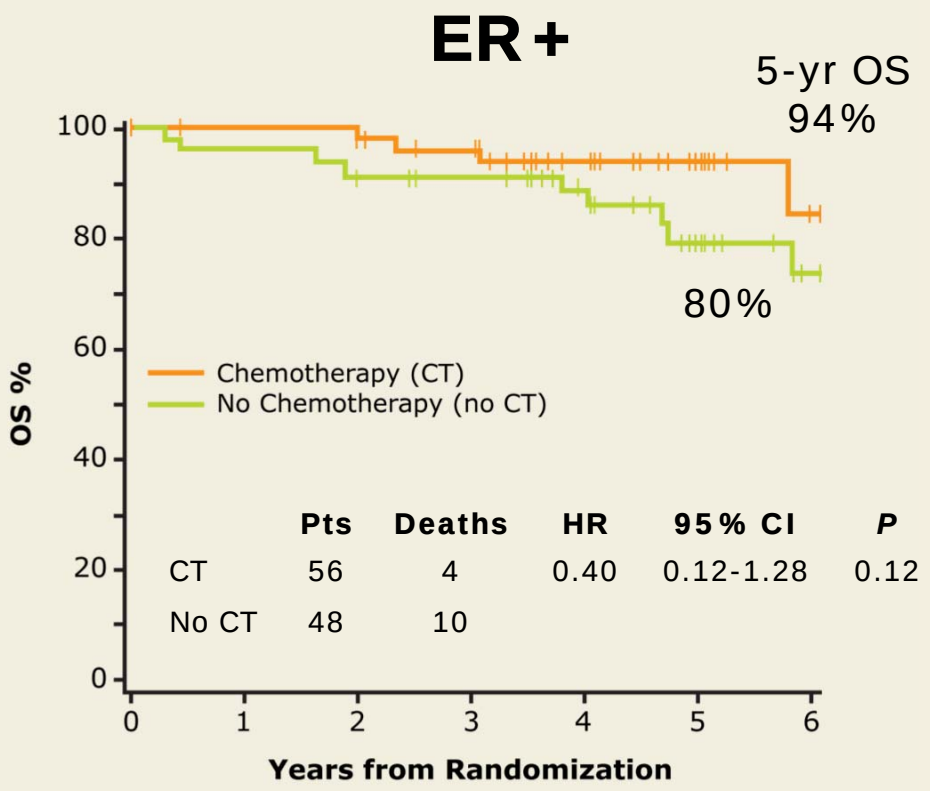
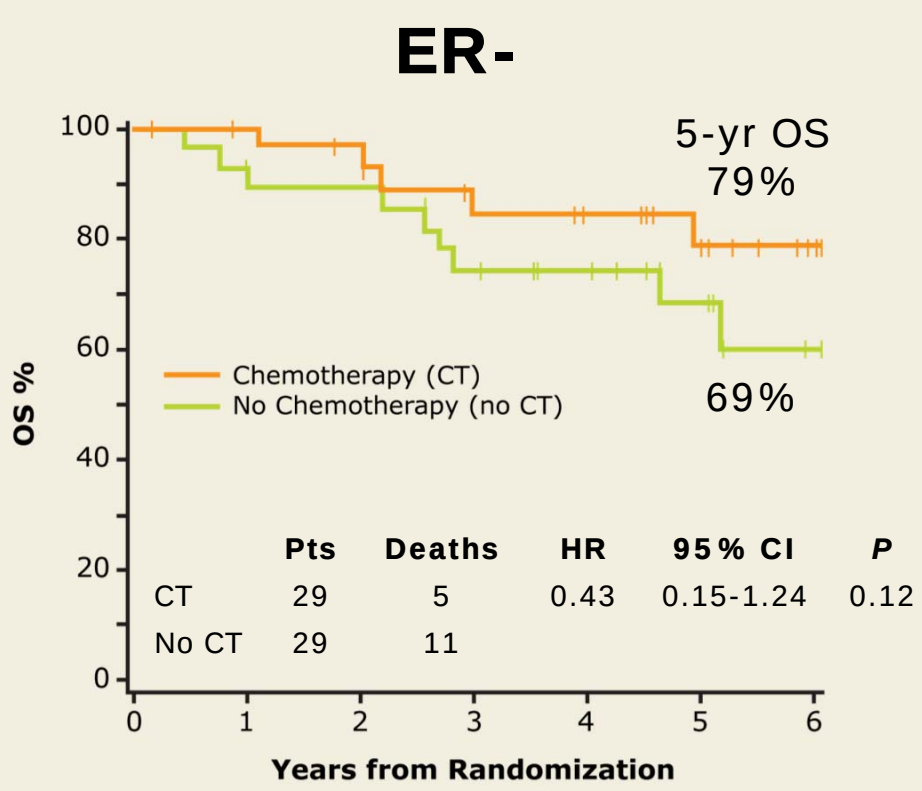
OS by ER Status





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Multivariate Analysis of OS

	Hazard ratio	*p*-value
ER status (positive/negative)	0.76	0.49
Location of ILRR		
Breast	Reference	Reference
Mastectomy scar or chest wall	0.73	0.55
Lymph nodes	0.75	0.65
Prior chemotherapy (yes/no)	1.97	0.12
Interval from primary surgery (per y)	0.80	0.0008
Treatment (chemotherapy/none)	0.37	0.02

Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

Author Conclusions

- Adjuvant chemotherapy reduced the risk of:
  - DFS events by 41% (ER-positive, 6%; ER-negative, 68%)
  - Death by 59% (ER-positive, 60%; ER-negative, 57%)
- Adjuvant chemotherapy should be recommended for patients with completely resected isolated local or regional recurrence of breast cancer:
  - The data are strongest for patients with ER-negative recurrences.
  - Longer follow-up is needed for patients with ER-positive recurrences.
- The pattern of locoregional recurrences and the impact of chemotherapy on second ILRR was presented as a poster at SABCS 2012 (Abstract P6-07-06).

Aebi S et al. *Proc SABCS* 2012;Abstract S3-2.

Investigator Commentary: CALOR — A Phase III Trial Evaluating Chemotherapy for ILRR of Breast Cancer

It's easy to assume that local or regional recurrence of BC occurs because the primary tumor was not properly resected or that the patient should have received radiation therapy. The answer to the question of how much systemic therapy a patient should receive for local or regional recurrence is unknown. It is impressive that a study that didn't complete its full accrual demonstrated a survival benefit. I believe that local or regional management and systemic treatment of BC are complementary to each other. Before the results of this study were published, I would have stated that local BC recurrence was a local/regional problem.

Interview with Kimberly L Blackwell, MD, January 8, 2013

This is a practice-changing study that had a difficult time with accrual of patients. This trial ran the risk of being underpowered to find a statistical difference. CALOR demonstrated impressive and statistically significant improvements in DFS and OS with adjuvant chemotherapy versus no chemotherapy. However, I would view the subset analyses showing that patients with ER-negative BC seemed to benefit more than those with ER-positive BC with caution because these tumors took 5 years to recur. Because patients with ER-positive BC are likely receiving ET, these results may be premature in this subpopulation.

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

A Phase III, Open-Label, Randomized, Multicenter Study of Eribulin Mesylate versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes

Kaufman PA et al.

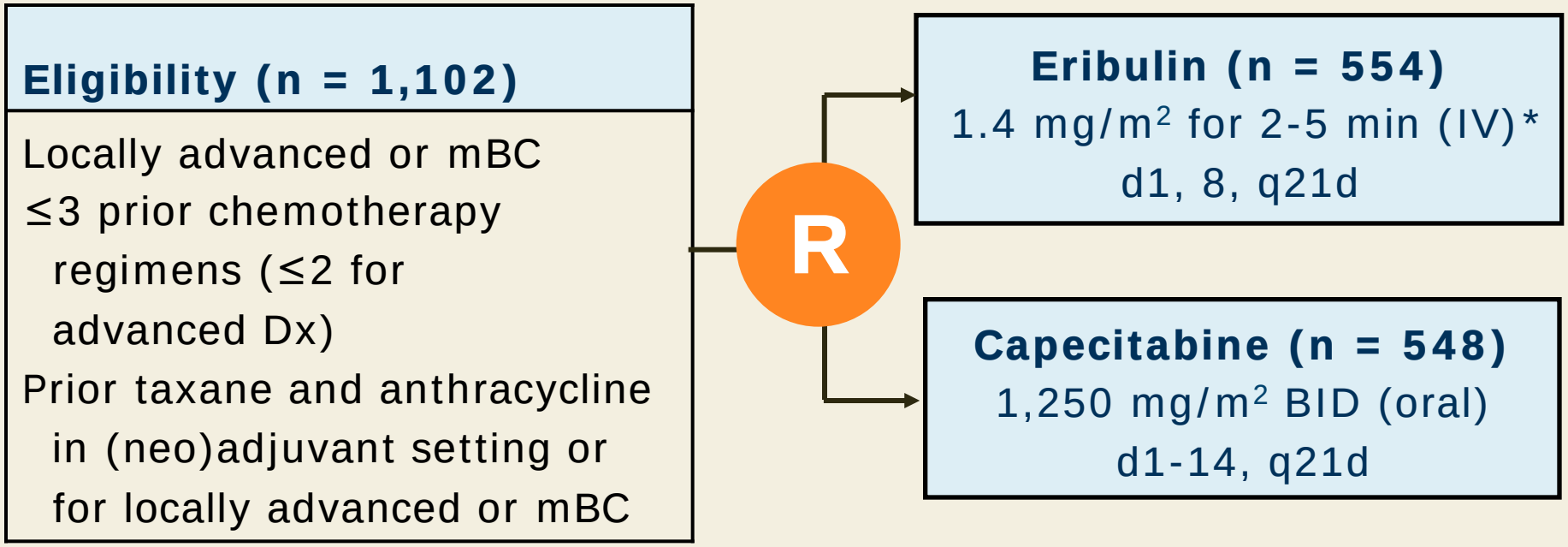
Proc SABCS 2012;Abstract S6-6.

Background

- The Phase III EMBRACE trial demonstrated a significant 2.5-month survival advantage with eribulin versus treatment of physician's choice for patients with locally recurrent or metastatic breast cancer (mBC) who previously received ≥2 chemotherapeutic regimens for advanced BC (*Lancet* 2011;377:914).
- Capecitabine is a widely used agent for the treatment of first-, second- and third-line mBC and is approved for mBC that is resistant to paclitaxel and an anthracycline-based regimen.
- **Study objective:** To compare the efficacy and safety of eribulin to capecitabine for patients with locally advanced or mBC previously treated with anthracyclines and taxanes.

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

Phase III Study 301 Design



* Equivalent to 1.23 mg/m^2 of eribulin

- **Coprimary endpoints:** Overall survival (OS) and progression-free survival (PFS)
- **Secondary endpoints include:** Quality of life, overall response rate (ORR), duration of response and safety
- Patients were stratified according to geographical region and HER2 status.

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

Statistical Considerations for Coprimary Endpoints

- Primary predefined analyses for ITT population
  - 2-sided log-rank test, stratified for HER2 and geographic region
  - Hazard ratio (HR) based on Cox regression model
- Planned for enrollment (n = 1,100)
  - OS determination: 905 events
  - Final analysis: 82% of events
  - Sufficient for 90% probability if HR ≤0.8 (Type I error: 0.04)
- 2 planned interim analyses of OS by O'Brien-Fleming spending function: 453 and 603 deaths
- Final analysis would be positive vs capecitabine if either:
  - OS is significantly improved with eribulin ($p \leq 0.0372$)
  - PFS by independent review is significantly prolonged with eribulin ($p \leq 0.01$); HR for OS (eribulin/capecitabine) is <1

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

Coprimary Endpoints: OS and PFS

Outcome	Eribulin (n = 554)	Cape (n = 548)	Hazard ratio	*p*-value
Median OS	15.9 mo	14.5 mo	0.879	0.056
1-year OS	64.4%	58.0%	NR	0.035
2-year OS	32.8%	29.8%	NR	0.324
3-year OS	17.8%	14.5%	NR	0.175
Median PFS				
Independent review	4.1 mo	4.2 mo	1.079	0.305
Investigator review	4.2 mo	4.1 mo	0.977	0.736

Cape = capecitabine; NR = not reported

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

OS: Prespecified Subgroup Analysis

Median OS	Eribulin	Cape	Hazard ratio
HER2 status			
Positive	14.3 mo	17.1 mo	0.965
Negative	15.9 mo	13.5 mo	0.838
ER status			
Positive	18.2 mo	16.8 mo	0.897
Negative	14.4 mo	10.5 mo	0.779
Triple-negative BC (TNBC)			
Yes	14.4 mo	9.4 mo	0.702
No	17.5 mo	16.6 mo	0.927
Overall	**15.9 mo**	**14.5 mo**	**0.879**

Hazard ratio <1.0 favors eribulin

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

Response Rates

Response	Independent review		Investigator review	
	Eribulin (n = 554)	Cape (n = 548)	Eribulin (n = 554)	Cape (n = 548)
ORR	11%	12%	16%	20%
	p-value = 0.849		*p*-value = 0.100	
SD	57%	55%	60%	51%
PD	23%	24%	18%	23%
NE	2%	1%	6%	6%
Unknown	8%	8%	0%	0%
Unconfirmed CR/PR	—	—	4%	3%
CBR	26%	27%	33%	34%

ORR = objective response rate; SD = stable disease; PD = progressive disease;
NE = not evaluated; CR = complete response; PR = partial response; CBR = clinical benefit rate

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

Select Adverse Events (Incidence >10%, All Grades; 1%, Grade 3/4)

Grade	Eribulin (n = 544)		Cape (n = 546)	
	All	3/4	All	3/4
Neutropenia	54%	46%	16%	<5%
Leukopenia	31%	15%	10%	<3%
Febrile neutropenia	2%	<3%	<1%	<2%
Hand-foot syndrome	<1%	0%	45%	14%
Alopecia	35%	—	4%	—
Diarrhea	14%	1%	29%	<6%
Vomiting	12%	<2%	17%	2%
Peripheral sensory neuropathy	13%	4%	7%	<1%
Dyspnea*	10%	<3%	11%	<4%

* Grade 5 events occurred in 0.7% (eribulin) and 0.5% (cape)

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

Author Conclusions

- This trial did not demonstrate a statistically significant superiority of eribulin to capecitabine in either OS or PFS.
  - Median OS: 15.9 mo (eribulin), 14.5 mo (cape); HR: 0.879
- Prespecified exploratory analyses suggested that particular patient subgroups may have greater therapeutic benefit with eribulin and this may warrant further study.
  - TNBC (HR: 0.702)
  - ER-negative (HR: 0.779)
  - HER2-negative (HR: 0.838)
- Eribulin and capecitabine demonstrated similar overall activity in this study, which included patients in the first-, second- or third-line treatment setting.
- The toxicity profiles of eribulin and capecitabine were consistent with previously known side effects.

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

Investigator Commentary: A Phase III Trial Comparing Eribulin to Capecitabine for Previously Treated Locally Advanced or mBC

In my practice, I'm impressed with eribulin activity. After its approval, I have administered it to patients with heavily pretreated BC. For instance, a patient with PD on every other agent was started on eribulin 9 weeks ago, and her liver lesions have already reduced in size by 50%. Unfortunately, there are no biomarkers to predict response. It was disappointing to discover that eribulin was not superior to capecitabine because it's always good to have a drug that's better than one that's been available for a decade.

Interview with Kimberly L Blackwell, MD, January 8, 2013

This is an important trial for clinical practice. Both eribulin and capecitabine are FDA approved for refractory mBC. This trial showed that eribulin was fairly equivalent to capecitabine in terms of efficacy. Some may view it as a negative study because it failed to demonstrate that eribulin was better than capecitabine. However, I view it as a positive trial showing that there are available options for patients with mBC. The toxic effects for both agents were manageable. Interestingly, in the prespecified subset analysis of patients with TNBC, ER-negative or HER2-negative BC, it appeared that eribulin may offer an advantage over capecitabine. These data support the ongoing evaluation of eribulin in a subset of patients with TNBC.

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

Results of a Phase 2, Multicenter, Single-Arm Study of Eribulin Mesylate as First-Line Therapy for Locally Recurrent or Metastatic HER2-Negative Breast Cancer

Vahdat L et al.

Proc SABCS 2012;Abstract P1-12-02.

Background

- The Phase III EMBRACE study demonstrated a significant survival benefit with eribulin for patients with metastatic breast cancer (mBC) (*Lancet* 2011;377:914).
  - The majority of the women in EMBRACE had HER2-negative disease and had received at least 2 chemotherapeutic regimens.
- The tolerability and positive Phase III findings suggest that eribulin may be beneficial when given earlier in the course of treatment for HER2-negative, advanced breast cancer.
- **Objective:** Evaluate the efficacy and safety of single-agent eribulin mesylate as first-line therapy for locally recurrent or metastatic HER2-negative breast cancer.

Vahdat L et al. *Proc SABCS* 2012;Abstract P1-12-02.

Phase II Study Design

Eligibility (N = 48)

- Locally recurrent or metastatic HER2-negative BC
- >12 mo neoadjuvant or adjuvant chemotherapy
- >2 wk radiation therapy or endocrine therapy

→ Eribulin mesylate 1.4 mg/m^2, IV days 1, 8 q3wk

Primary endpoint: Objective response rate

Secondary endpoints: Safety, time to first response, duration of response, progression-free survival, quality of life

Vahdat L et al. *Proc SABCS* 2012;Abstract P1-12-02.

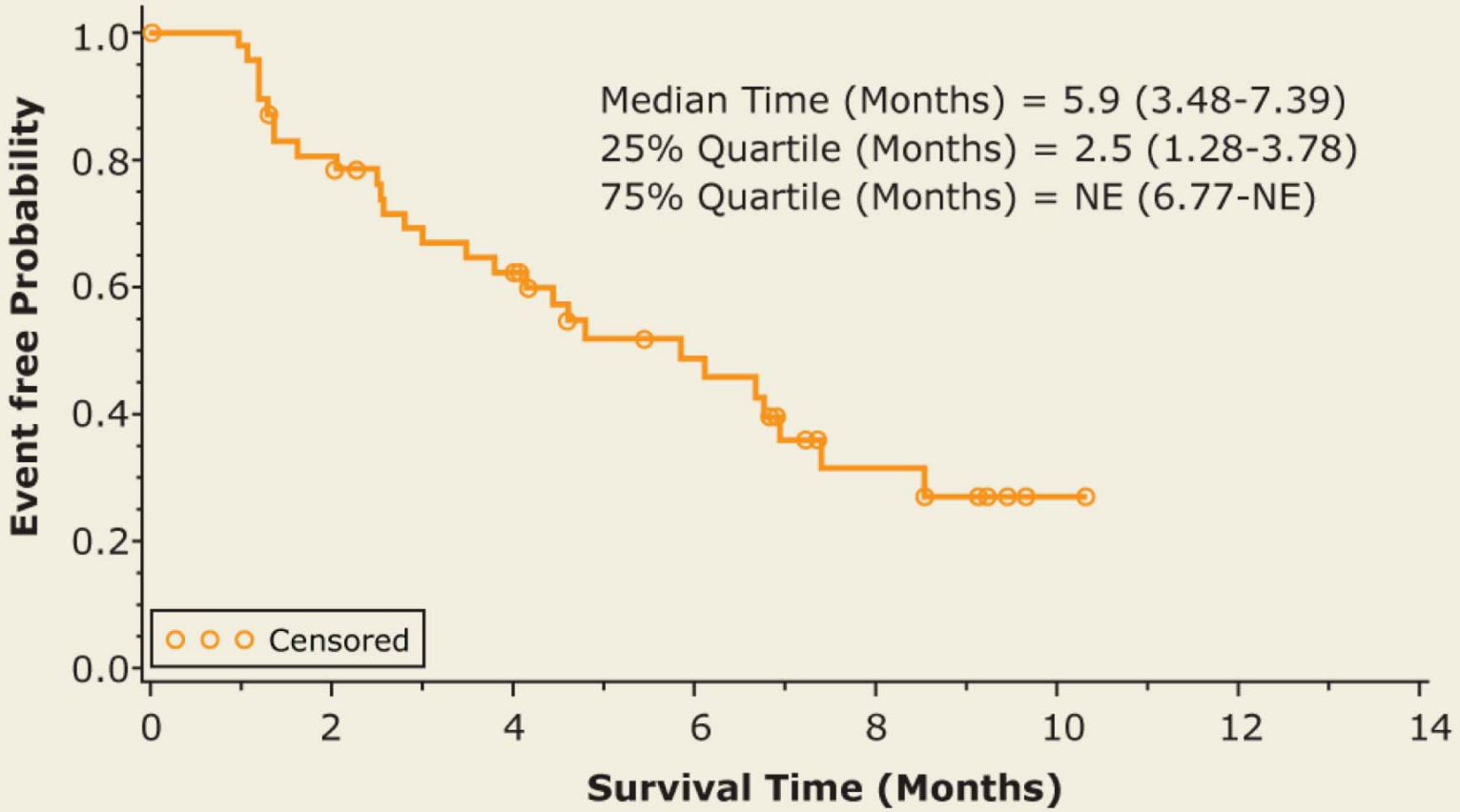
Best Tumor Responses

Resonse	All (n = 48)	ER+ (n = 35)	Triple-negative (n = 10)
Objective response rate Complete response (CR) Partial response (PR)	27.1% 0 27.1%	28.6% 0 28.6%	30% 0 30%
Stable disease (SD)	47.9%	54.3%	30%
Progressive disease (PD)	22.9%	17.1%	30%
Clinical benefit rate (CR + PR + durable SD)	45.8%	54.3%	30%

- 3 patients with ER-/PR+ disease had no objective response (1 SD, 2 PD)
- Median duration of objective response: 7.4 mo
- Median time to first response: 1.4 mo

Vahdat L et al. *Proc SABCS* 2012;Abstract P1-12-02.

Progression-Free Survival



At Risk	48	37	27	16	7	1	0
Event (cum.)	0	9	17	22	27	28	28

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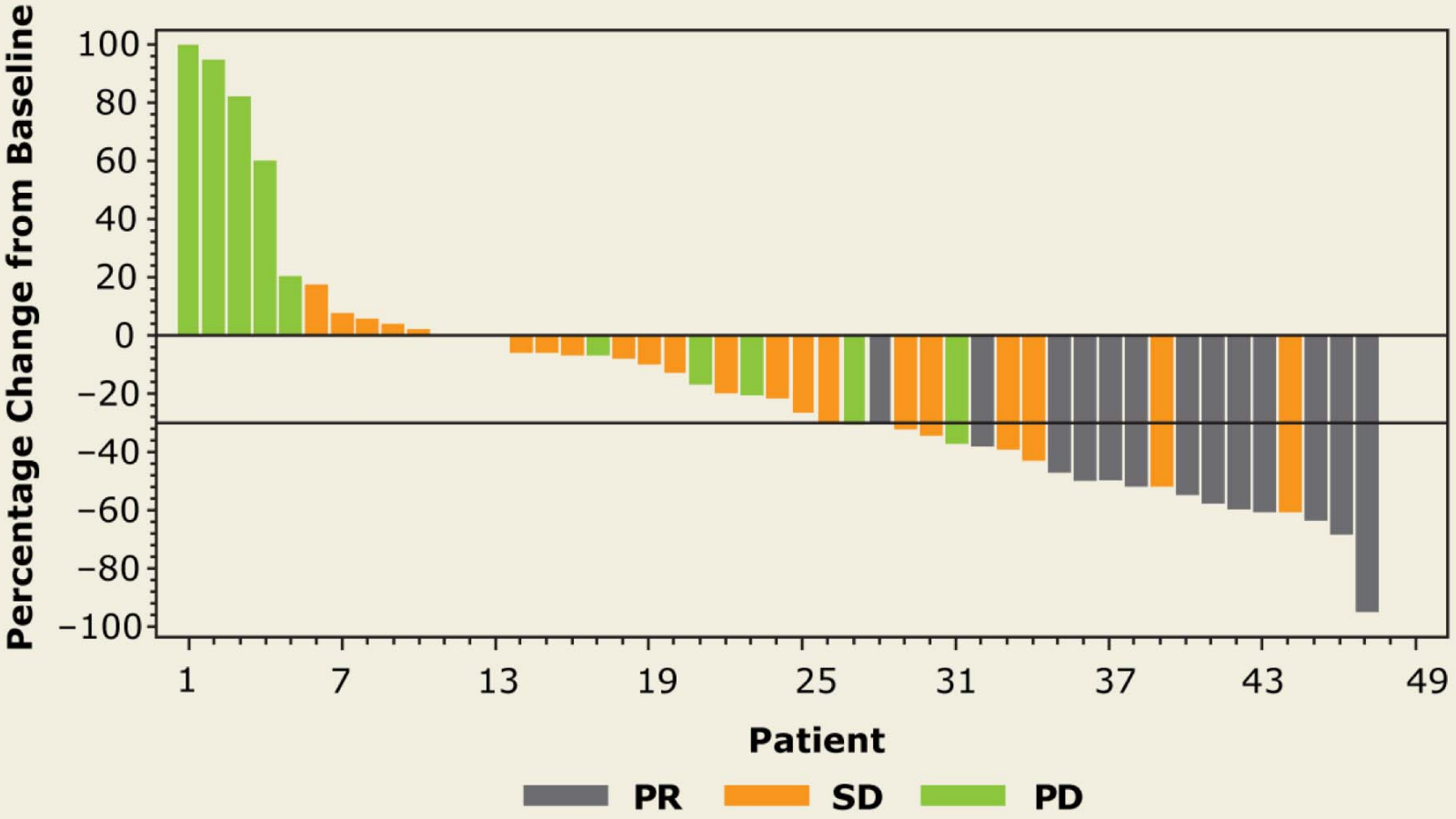
Percentage Change in Total Sum of Target Lesion Diameters from Baseline to Postbaseline Nadir



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Most Common Treatment-Related and Treatment-Emergent (TRTE) Adverse Events (AEs)

AEs (>25% of patients)	All grades (n = 48)	Grade 3/4 (n = 48)
Alopecia	75%	N/A
Neutropenia	72.9%	50%
Fatigue	54.2%	2.1%
Nausea	47.9%	0%
Peripheral neuropathy (PN)	47.9%	12.5%

- Growth factors were administered to 18 (37.5%) patients
- TRTE AEs led to dose adjustment in 26 (54.2%) patients
  - 17 (35.4%) and 20 (41.7%) patients had their dose reduced and delayed, respectively
  - 4 (8.3%) patients discontinued treatment due to an AE (3 due to PN)

Vahdat L et al. *Proc SABCS* 2012;Abstract P1-12-02.

Author Conclusions

- The preliminary results of this first-line study suggest that eribulin has antitumor activity in ER+/HER2- and triple-negative metastatic or recurrent breast cancer with an acceptable safety profile. These findings warrant larger studies.
- Alopecia, neutropenia and fatigue were the most common treatment-related adverse events (occurring in >50% of patients).
- The most common Grade 3/4 adverse event was neutropenia, occurring in 50% of patients.
- This study has completed enrollment and final results are expected by the end of 2013.

Vahdat L et al. *Proc SABCS* 2012;Abstract P1-12-02.

Investigator Commentary: Phase II Study of Eribulin Mesylate as First-Line Therapy for Locally Recurrent or Metastatic HER2-Negative Breast Cancer

This is a preliminary analysis of a single-arm Phase II study of eribulin mesylate as first-line therapy for advanced breast cancer. The data should be interpreted with caution until the final analysis is completed.

About 50 patients with HER2-negative advanced breast cancer received eribulin in the first-line setting. The drug appears to have some activity, with a response rate of about 30% and progression-free survival of approximately 3 to 7 months depending on whether the patients had ER-positive or triple-negative breast cancer.

The usual side effects, such as neutropenia and neuropathy, were seen, but only a few were serious. A differential signal of activity in ER-positive and triple-negative breast cancer was not evident from these data. Without a randomized study, it is not known how eribulin will compare to more conventional agents. However, the PFS with first-line weekly paclitaxel in the CALGB-40502 study was more than 10 months.

Interview with Lisa A Carey, MD, February 25, 2013

Primary Results of BEATRICE, a Randomized Phase III Trial Evaluating Adjuvant Bevacizumab-Containing Therapy in Triple-Negative Breast Cancer

Cameron D et al.

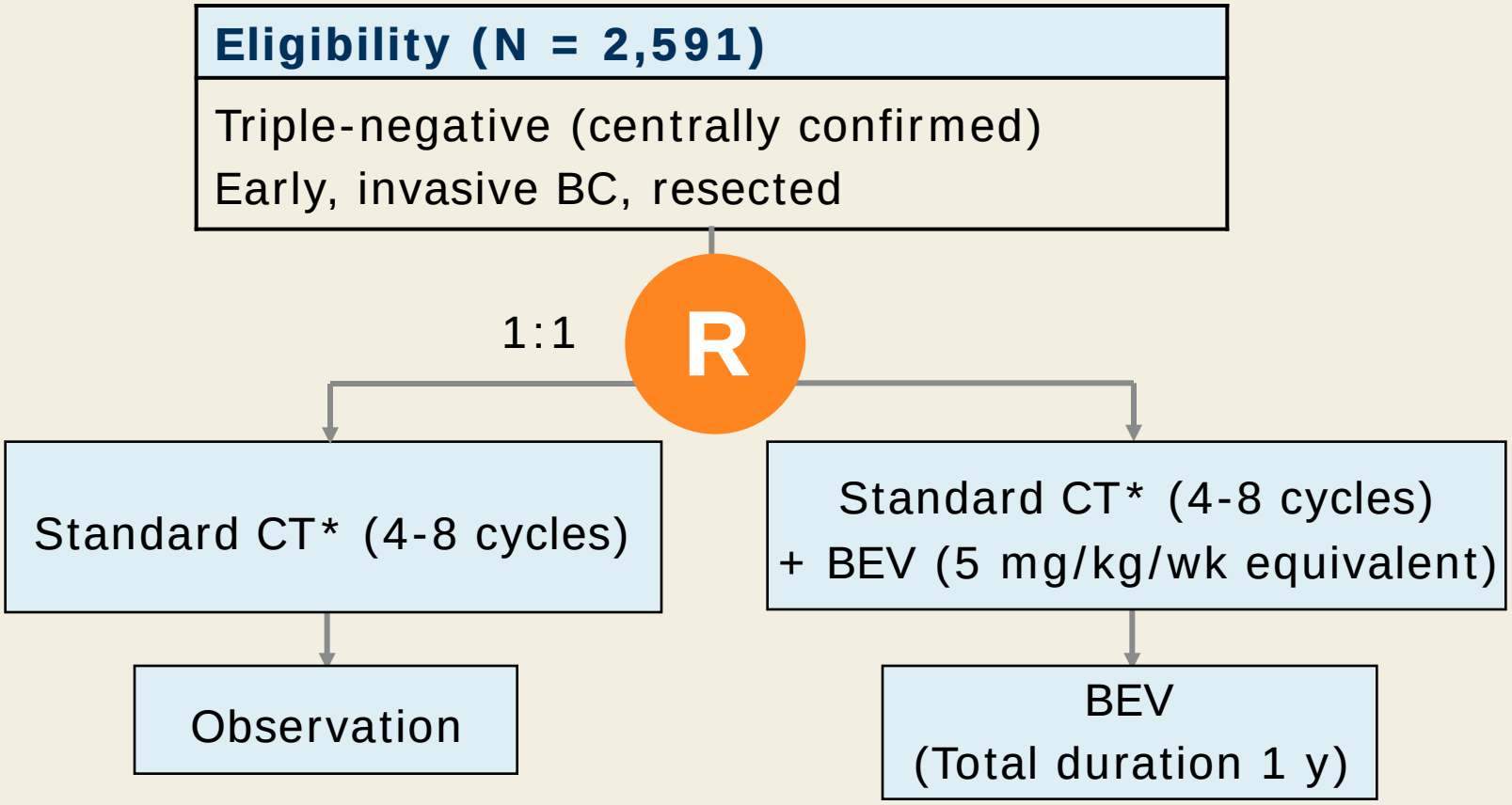
Proc SABCS 2012;Abstract S6-5.

Background

- There are no targeted treatment options for triple-negative breast cancer (TNBC), a clinically important breast cancer subgroup.
- In metastatic breast cancer, bevacizumab (BEV), an anti-VEGF antibody, significantly improved progression-free survival when combined with chemotherapy (*J Clin Oncol* 2011;29:4286).
- High VEGF concentrations have been observed in estrogen receptor-/progesterone receptor-negative tumors.
- BEV may be beneficial in TNBC based on its ability to target the angiogenic switch before tumor vascularization and the dependency of micrometastases on angiogenesis (*Nat Med* 1995;1:149).
- **Objective:** Evaluate the addition of BEV to chemotherapy (CT) in the adjuvant setting for patients with TNBC.

Cameron D et al. *Proc SABCS* 2012;Abstract S6-5.

Phase III BEATRICE Study Design



* Investigator's choice: Taxane based (≥4 cycles), anthracycline based (≥4 cycles) or anthracycline + taxane (3-4 cycles each)

Cameron D et al. *Proc SABCS* 2012;Abstract S6-5.

Primary Endpoint : Invasive Disease-Free Survival (IDFS)

IDFS*	CT (n = 1,290)	CT + BEV (n = 1,301)
3-y IDFS	82.7%	83.7%
HR (*p*-value)	0.87 (0.181)	
Events, n (%)	205 (15.9%)	188 (14.5%)
Median duration of follow-up	31.5 mo	32 mo

* ITT population, 388 events required for 80% power to detect an HR = 0.75

Cameron D et al. *Proc SABCS* 2012;Abstract S6-5.

Interim Overall Survival*

	CT (n = 1,290)	CT + BEV (n = 1,301)
Events, n (%)	107 (8.3%)	93 (7.1%)
HR (*p*-value)	0.84 (0.2318)	

* 59% of required events

Cameron D et al. *Proc SABCS* 2012;Abstract S6-5.

Select Adverse Events by Treatment Phase

Grade ≥3 AEs	Chemotherapy phase		Observation/BEV alone phase	
	CT (n = 1,271)	CT + BEV (n = 1,288)	CT (n = 1,271)	CT + BEV (n = 1,288)
All Grade ≥3 AEs	3%	11%	<1%	9%
ATE	<1%	<1%	<1%	<1%
VTE	1%	2%	<1%	<1%
Bleeding	<1%	<1%	<1%	0%
CHF/LVD	<1%	<1%	<1%	2%
Hypertension	<1%	7%	<1%	5%
Proteinuria	<1%	<1%	0%	2%

ATE = arterial thromboembolic event; VTE = venous thromboembolic event; CHF = congestive heart failure; LVD = left ventricular dysfunction

Cameron D et al. *Proc SABCS* 2012;Abstract S6-5.

Author Conclusions

- The results of BEATRICE, the first randomized Phase III trial of BEV in early TNBC, demonstrated a better than anticipated 3-year IDFS.
- There was no statistically significant improvement in IDFS with the addition of 1 year of BEV to adjuvant CT for TNBC.
- Overall, adverse events were consistent with the established safety profile of BEV in metastatic BC.

Cameron D et al. *Proc SABCS* 2012;Abstract S6-5.

Future Directions

- Further follow-up is required to assess any potential impact of BEV on overall survival.
  - Prespecified overall survival analysis will be performed after 340 deaths or 5 years median follow-up, whichever is earlier (results estimated late 2013).
- First biomarker results for plasma VEGF-A and VEGFR-2 were reported by Carmeliet et al (*Proc SABCS* 2012; Abstract P3-06-34).
  - Additional protocol-specified biomarker analyses are ongoing.

Cameron D et al. *Proc SABCS* 2012;Abstract S6-5.

Investigator Commentary: Primary Results of the Phase III BEATRICE Trial Evaluating Adjuvant Bevacizumab in TNBC

BEATRICE evaluated the addition of adjuvant bevacizumab (BEV) to chemotherapy followed by single-agent BEV versus observation for patients with TNBC. The study was designed for patients with TNBC because BEV showed the most benefit in this subset of patients with metastatic disease. Data from preclinical studies also support the use of BEV in patients with TNBC.

In this study, the investigators were looking for a 25% improvement in IDFS with BEV, but no difference between the two arms was observed after a follow-up of approximately 32 months. Overall survival was good but was similar in the two groups. The expected toxicities were observed. Congestive heart failure and hypertension were higher in the BEV arm. The results of this study are disappointing with no signal for activity of BEV in the adjuvant setting for TNBC.

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