5 Minute JournalClub

Key ASCO Presentations

Issue 5, 2010

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CME Information

LEARNING OBJECTIVES

- Compare and contrast morbidity and long-term outcomes with SNR versus ALND in patients with clinically and histologically node-negative early breast cancer.
- Apply the results of new research to the appropriate use of IHC testing for patients with negative sentinel nodes by H&E.
- Counsel patients with T1N0M0 breast cancer and H&E-detected sentinel node metastases about the benefits and risks of completion ALND.
- Demonstrate knowledge of the efficacy and safety of targeted intraoperative radiation therapy (TARGIT) in the treatment of early breast cancer.
- Recall the safety and early clinical activity of pertuzumab with T-DM1 in patients with HER2-positive mBC.
- Describe potential prognostic and/or predictive biomarkers for patients with HER2-positive mBC treated with pertuzumab and trastuzumab.
- Counsel patients with mBC about the incremental benefit of bevacizumab when it is combined with diverse chemotherapeutic regimens in the first- and second-line settings.
- Recall the Phase III efficacy and safety of eribulin in the clinical management of heavily pretreated advanced breast cancer.
- Identify patients with advanced breast cancer who may benefit from the introduction of eribulin into the treatment algorithm.

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CME Information (Continued)

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No real or apparent conflicts of interest to disclose.

Clinical Trials Evaluating the Role of Sentinel Node Resection in Patients with Early-Stage Breast Cancer

Krag DN et al.
Proc ASCO 2010;Abstract LBA505.

Cote R et al.
Proc ASCO 2010;Abstract CRA504.

Giuliano AE et al.
Proc ASCO 2010;Abstract CRA506.

Overview

- Data from three clinical trials evaluating the role of sentinel node biopsy were presented at ASCO 2010.
  - NSABP-B-32: A Phase III trial comparing sentinel node (SN) resection to conventional axillary lymph node dissection (ALND) in clinically node-negative breast cancer.[1]
  - ACOSOG Z0010: A multicenter prognostic study of SN and bone marrow (BM) micrometastases in clinical T1-2 N0 M0 breast cancer.[2]
  - ACOSOG Z0011: A randomized trial of ALND in clinical T1-2 N0 M0 breast cancer with a positive sentinel node.[3]

[1] Krag DN et al. *Proc ASCO* 2010;Abstract LBA505; [2] Cote R et al. *Proc ASCO* 2010;Abstract CRA504; [3] Giuliano AE et al. *Proc ASCO* 2010;Abstract CRA506.

NSABP-B-32: Introduction

- Trial design: Patients were randomly assigned to SN resection plus ALND (Group 1) versus SN resection alone (Group 2) with ALND performed only if sentinel nodes were positive.
- Eligibility: Operable, clinically node negative, invasive breast cancer.
- Primary endpoints: Overall survival, disease-free survival and regional control.
- 5,611 patients enrolled, of which 3,989 (71.1%) were SN negative and followed for events.
  - Follow-up information is available for 99% of these patients (1,975 in Group 1 and 2,011 in Group 2).
- Median time on study was 95.3 months.

Krag DN et al. *Proc ASCO* 2010;Abstract LBA505.

NSABP-B-32: Efficacy Data

	Group 1	Group 2	Group 1 vs Group 2
5-year overall survival (OS)[1]	96.4%	95.0%	—
OS unadjusted HR	—	—	1.20 (p = 0.12)
OS adjusted HR[2]	—	—	1.19 (p = 0.13)
5-year disease-free survival (DFS)[1]	89.0%	88.6%	—
DFS unadjusted HR	—	—	1.05 (p = 0.54)
DFS adjusted HR[2]	—	—	1.07 (p = 0.57)
Recurrences	**Group 1**	**Group 2**	***p*-value**
Local recurrences	54	49	0.55
Regional node recurrences as first event	8	14	0.22

[1] Kaplan-Meier estimates, [2] HR adjusted for lumpectomy vs mastectomy, tumor size and patient age

Krag DN et al. *Proc ASCO* 2010;Abstract LBA505.

NSAPB-B-32: Conclusions

- No significant differences were observed in OS, DFS or regional control between the patients who underwent SN resection plus ALND (Group 1) versus those who underwent SN resection alone (Group 2).
- Morbidity was decreased in patients who underwent SN resection alone (data not shown).
- When the SN is negative, SN surgery alone with no further ALND is an appropriate, safe and effective therapy for patients with clinically node-negative breast cancer.

Krag DN et al. *Proc ASCO* 2010;Abstract LBA505.

Investigator comment on the results of NSABP-B-32: Sentinel node resection versus axillary dissection in clinically node-negative breast cancer

NSABP-B-32 didn't provide any surprises. Women who had negative sentinel node biopsies were randomly assigned to axillary node dissection or not. There were no differences in disease-free or overall survival between the groups, although those who underwent axillary lymph node dissection were more likely to experience complications. Essentially, this study indicates that in patients with a negative sentinel node biopsy there is absolutely no reason to consider further surgery.

Interview with Eric P Winer, MD, July 6, 2010

ACOSOG Z0010: Introduction

- Trial design: Patients underwent lumpectomy and SN biopsy with bilateral iliac crest bone marrow (BM) aspiration.
  - BM and histologically negative SN were centrally assessed by immunohistochemistry (IHC) for cytokeratin.
- Eligibility: Clinical T1/T2, N0, M0 breast cancer
- 5,210 patients were found to be eligible and evaluable.
  - Histologic SN metastases were found in 1,215 patients (24.0%).
  - IHC detected an additional 349 patients (10.0%) with SN metastases.
  - BM metastases were identified by IHC in 104 of 3,413 (3.0%) patients examined.

Cote R et al. *Proc ASCO* 2010;Abstract CRA504.

ACOSOG Z0010: Overall Survival (OS) Data

	H&E negative & IHC positive	H&E negative & IHC negative	H&E positive
5-year OS by SN status	96%	96%	93%

OS Data for SN H&E Negative Patients

	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
SN IHC negative SN IHC positive	1.00 (ref) 0.92 (0.63, 1.33)	0.65	1.00 (ref) 0.86 (0.44, 1.68)	0.66
BM IHC negative BM IHC positive	1.00 (ref) 1.90 (1.13, 3.20)	0.016	1.00 (ref) 1.82 (0.78, 4.23)	0.16

*Adjusted for multiple other prognostic factors (eg, sentinel node IHC status, ER, age, tumor size, treatment effect, etc)

Cote R et al. *Proc ASCO* 2010;Abstract CRA504.

ACOSOG Z0010: Conclusions

- 5-year OS was 93% in patients with H&E-positive SNs.
- Detection of BM occult metastases by IHC identifies patients with clinical T1/2, N0, M0 at significantly increased risk for death; however, it is not an independent prognostic factor (HR = 1.90, $p = 0.016$ on univariable analysis; HR = 1.82, $p = 0.16$ on multivariable analysis adjusted for other important prognostic factors).
- IHC detected SN metastases do not appear to impact overall survival (HR = 1.92, $p = 0.65$ on univariable analysis; HR = 0.86, $p = 0.66$ on multivariable analysis).
- Routine examination of SN by IHC is not supported in this patient population by this study.

Cote R et al. *Proc ASCO* 2010;Abstract CRA504.

Investigator comment on the results of ACOSOG Z0010: Prognostic significance of sentinel node and bone marrow micrometastases

ACOSOG Z0010 provided practice-changing data. Despite the recommendations of ASCO and the College of American Pathologists, immunohistochemistry (IHC) is still being performed on H&E-negative sentinel nodes — it's routinely performed. We now have Phase III data that clearly indicate it is not important to perform IHC on sentinel nodes negative on H&E because it does not inform us about prognosis and it can lead us to harm patients, because it clearly influences treatment decisions in ways that we can now conclude are inappropriate.

Interview with Kathy D Miller, MD, June 11, 2010

Investigator comment on the results of ACOSOG Z0010: Prognostic significance of sentinel node and bone marrow micrometastases

ACOSOG Z0010 is an important trial that involved over 5,000 women and evaluated two separate issues. They investigated the prognostic implication of finding isolated tumor cells via IHC in a sentinel node and the implications of finding IHC-detected cells within the bone marrow.

They demonstrated that women who had micrometastatic involvement on H&E staining had a worse outcome than those who did not, but there was no prognostic implication associated with finding isolated tumor cells by IHC on a sentinel node biopsy. Importantly, the investigators in this trial were blinded to the results, so their treatments were not adjusted based on finding isolated tumor cells. The practice of performing IHC routinely on a sentinel node biopsy should go by the wayside as a result of this study. I believe there may be one exception, which is, if for whatever reason a pathologist believes he or she is seeing something that they want to define further or if a patient has invasive lobular cancer, in which it's often difficult with routine H&E to identify tumor cells, then the use of IHC may be worth considering. Otherwise, for the patient who has a negative sentinel node biopsy by H&E, there is no role at this time for further staining.

Interview with Eric P Winer, MD, July 6, 2010

ACOSOG Z0011: Introduction

- Trial design: Patients with clinically node-negative breast cancer who underwent SN biopsy and had 1 or 2 SN with H&E-detected metastases were randomly assigned to ALND or no further axillary specific treatment.
- Eligibility: Clinical T1-2, N0 breast cancer, H&E detected metastases in SN, lumpectomy with whole breast irradiation, and adjuvant systemic therapy by choice.
- Primary endpoints: OS, DFS and locoregional control.

Giuliano AE et al. *Proc ASCO* 2010;Abstract CRA506.

ACOSOG Z0011: Efficacy Data

	SN biopsy only (n = 436)	ALND (n = 420)	*p*-value
Locoregional recurrence[1] Local (breast) Regional (axilla, supraclavicular) Total	 1.8% 0.9% 2.8%	 3.6% 0.5% 4.1%	0.11
5-year OS[2]	92.5%	91.8%	0.25
5-year DFS[2]	83.9%	82.2%	0.14

[1] Median follow-up is 6.3 years
[2] Median follow-up is 6.2 years

"It is highly improbable that the 0.9% or 2.8% locoregional recurrence with SN only would significantly impact survival."

Giuliano AE et al. *Proc ASCO* 2010;Abstract CRA506.

ACOSOG Z0011: Conclusions

- No significant difference in DFS or OS between patients treated with SN biopsy alone or with SN biopsy followed by ALND.
- Only older age, estrogen receptor-negative status and lack of adjuvant systemic therapy were associated with worse OS by multivariable analysis (data not shown).
- This study does not support the routine use of ALND in limited nodal metastatic breast cancer. The role of this operation should be reconsidered.

Giuliano AE et al. *Proc ASCO* 2010;Abstract CRA506.

Investigator comment on the results of ACOSOG Z0011: Axillary dissection in patients with a positive sentinel node

ACOSOG Z0011 was a bold study, which unfortunately did not reach its accrual goal. An important eligibility criterion was that women had to undergo conservative surgery and radiation therapy, in which the lower portion of the axilla is included. As a result, we cannot necessarily apply these findings to women who have a mastectomy.

They found that women who had a sentinel node biopsy only had no higher rate of in-breast recurrence and no higher rate of axillary recurrence than women who had a full axillary lymph node dissection (ALND). It's worth pointing out that among the women who had the full ALND, 27 percent had additional positive lymph nodes found at the time of surgery. So, in general, these women were at relatively low risk of having additional axillary disease.

This study does not indicate that we should abandon ALND in all women who have a positive sentinel lymph node. If a woman has a positive sentinel node biopsy, is planning to have a lumpectomy and radiation therapy and is at relatively low risk of having additional disease in the axilla, then ALND may be safely omitted.

Interview with Eric P Winer, MD, July 6, 2010

Implications for Clinical Practice

- IHC of H&E-negative sentinel nodes is not useful clinically.
- Since only one in 33 bone marrow is IHC-positive and since it is not an independent prognostic factor, IHC of bone marrow provides no clinically important benefit in women with negative sentinel nodes.
- ALND does not add benefit to sentinel lymph node biopsy alone in patients with clinically node-negative disease
- ALND is of no clinical benefit in women with positive sentinel nodes, with the following caveats:
  - <3 positive nodes, nodes not matted, breast-conserving therapy with whole breast irradiation, adjuvant systemic therapy as needed.

Wood W. ASCO 2010;Discussant.

Targeted Intraoperative Radiotherapy versus Whole Breast Radiotherapy for Breast Cancer (TARGIT-A Trial): An International, Prospective, Randomised, Non-Inferiority Phase 3 Trial

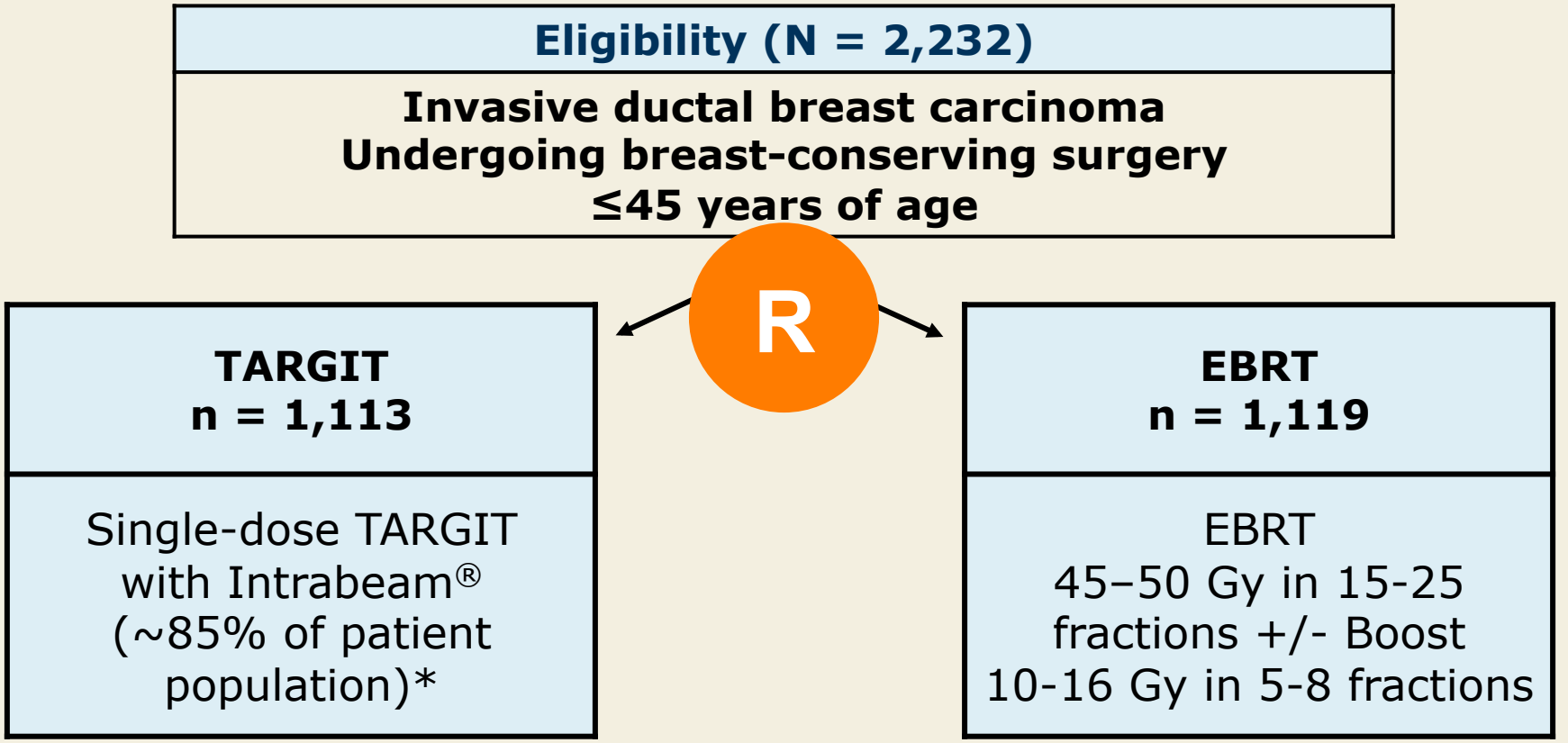
Baum M et al.
Proc ASCO 2010;Abstract LBA517.
Vaidya JS et al.
Lancet 2010;[Epub ahead of print].

Introduction

- Local recurrence after breast-conserving surgery is located in the index quadrant 90% of the time.
- Restriction of radiation therapy to immediate area surrounding the tumor bed following removal of primary tumor may be adequate (*Br J Cancer* 1996;74:820).
- External beam radiation therapy (EBRT) is a safe and effective treatment.
  - Side effect risk is low but schedule can be inconvenient and is often untenable for elderly women.
- **Current study objective:**
  - Evaluate the approach of substituting targeted intraoperative radiotherapy (TARGIT) for the conventional policy of whole breast EBRT in selected patients with early breast cancer.

Baum M et al. *Proc ASCO* 2010;Abstract LBA517; Vaidya JS et al. *Lancet* 2010;[Epub ahead of print].

Targeted Intraoperative Radiotherapy (TARGIT-A) Study Design



* Plus EBRT (45-50 Gy, no boost) in patients at high risk (~15%); Pre-specified criteria (unsuspected lobular carcinoma, lymphovascular invasion, etc)

Baum M et al. *Proc ASCO* 2010;Abstract LBA517; Vaidya JS et al. *Lancet* 2010;[Epub ahead of print].

Local Recurrence Rates in the Conserved Breast

	TARGIT n = 1,113	EBRT n = 1,119	*p*-value
Local recurrence rate	1.2%	0.95%	0.41
95% confidence interval	0.53–2.71	0.39–2.31	—

* Restricted to 4 years as less than 420 patients (<20%) have follow-up beyond this point. All patients (with maximum follow-up of 10 years) are included in the analysis.

Baum M et al. *Proc ASCO* 2010;Abstract LBA517; Vaidya JS et al. *Lancet* 2010;[Epub ahead of print].

Complications

	TARGIT n = 1,113	EBRT n = 1,119	*p*-value
Any	196 (17.6%)	174 (15.4%)	0.19

Clinically important wound complications	TARGIT	EBRT	*p*-value
Hematoma requiring surgical evacuation	11 (1.0%)	7 (0.6%)	0.338
Seroma requiring more than 3 aspirations	23 (2.1%)	9 (0.8%)	0.012
Infection requiring intravenous antibiotics or surgery	20 (1.8%)	14 (1.3%)	0.292

Baum M et al. *Proc ASCO* 2010;Abstract LBA517; Vaidya JS et al. *Lancet* 2010;[Epub ahead of print].

Complications

Major toxicity	TARGIT n = 1,113	EBRT n = 1,119	*p*-value
Skin breakdown or delayed wound healing	31 (2.8%)	21 (1.9%)	0.155
RTOG toxicity Grade 3-4	6 (0.5%)	23 (2.1%)	0.002
Major toxicity	37 (3.3%)	44 (3.9%)	0.443

Baum M et al. *Proc ASCO* 2010;Abstract LBA517; Vaidya JS et al. *Lancet* 2010;[Epub ahead of print].

Conclusions

- For selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of TARGIT should be considered as an alternative to EBRT delivered over several weeks.
- Rate of local recurrence is not statistically different among TARGIT and EBRT groups at 4 years (1.2% vs 0.95%, p = 0.41)
  - Non-inferiority established for TARGIT
- Frequency of any complications and major toxicity overall were similar in TARGIT group versus EBRT group.
  - Major toxicity (3.3% vs 3.9%, p = 0.44)
  - RTOG toxicity Grade 3 to 4 (0.5% vs 2.1%, p = 0.002)

Baum M et al. *Proc ASCO* 2010;Abstract LBA517; Vaidya JS et al. *Lancet* 2010;[Epub ahead of print].

Investigator comment on the results of the TARGIT trial of intraoperative radiation therapy

The real challenge of this study was that 90 percent of local recurrences after surgery with or without radiation therapy are in the index quadrant, even though 70 percent of cases have other foci outside the index quadrant. So we now believe that the out-of-the-index-quadrant foci are latent disease. We challenged conventional thinking in two ways: Using partial breast irradiation and completing treatment within 25 to 45 minutes during surgery.

Local recurrence rates were low and equivalent to external beam radiation therapy (EBRT). At a median of four years, the Kaplan-Meier curves are superimposable, with a difference of 0.25 percent in a good-prognosis group of patients.

There were no overall differences in toxicity, but in terms of RTOG radiation toxicity, there was significantly more Grade 3/4 toxicity, particularly skin complications, with EBRT. There was a specific wound complication of seroma with the intraoperative approach. Interestingly, the cosmesis is better with intraoperative radiation therapy due to the seroma, which acts as a "biological implant." We also believe there are other long-term cosmesis advantages, particularly following oncoplastic surgery, because the intraoperative approach provides perfect conformal treatment at the time of surgery.

Interview with Michael Baum, MD, ChM, June 6, 2010

Investigator comment on the results of the TARGIT trial of intraoperative radiation therapy

The TARGIT study randomly assigned patients to intraoperative or external beam radiation therapy. They did not observe any significant difference in outcome between the two groups, which, at least on the surface, would suggest that a targeted, more limited, less time-consuming therapy might be as effective as administering external beam radiation therapy. The problem is that the two-year follow-up is short.

This is not a treatment that we should all be embracing at the moment, but it is a treatment that we should pay attention to and it's a study result that we should follow. It's quite likely that in the years ahead these more targeted, localized therapies will be the way to go for some patients with breast cancer.

Interview with Eric P Winer, MD, July 6, 2010

A Phase IB/II Trial of Trastuzumab-DM1 (T-DM1) with Pertuzumab for Women with HER2-Positive, Locally Advanced or Metastatic Breast Cancer Who Were Previously Treated with Trastuzumab

Miller K et al.

Proc ASCO 2010;Abstract 1012.

Introduction

- Phase II trials have shown that T-DM1, a HER2-targeted antibody-drug conjugate, has encouraging single-agent activity in heavily pretreated patients with HER2-positive metastatic breast cancer.
- Pertuzumab is a HER2-targeted monoclonal antibody that inhibits HER2 dimerization with other members of the HER2 receptor family.
- **Current study objective:**
  - Assess the safety and efficacy of T-DM1 and pertuzumab combination therapy in patients with HER2-positive locally advanced or metastatic breast cancer.
  - Preliminary efficacy and safety results are presented only for relapsed patients evaluable as of December 14, 2009.

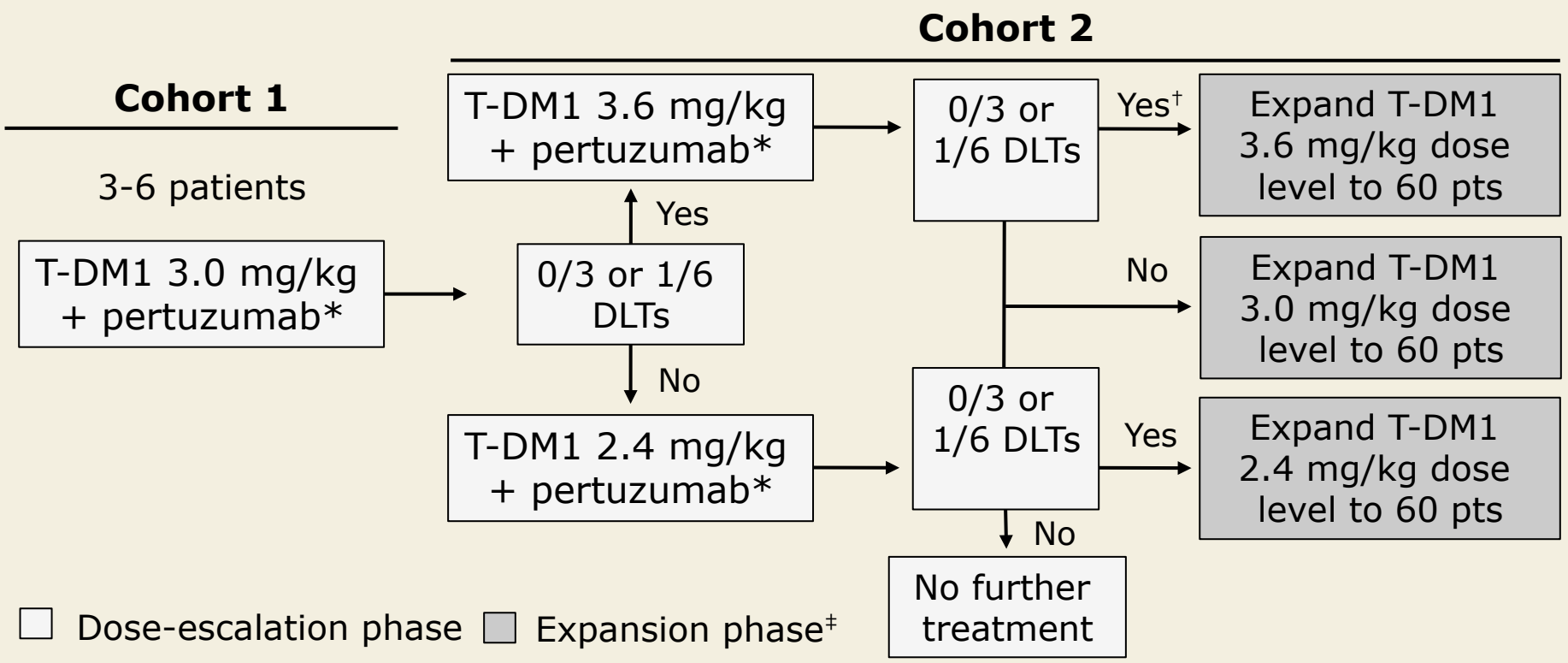
Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Study Design

- Key inclusion criteria:
  - Measurable disease with histologically confirmed locally advanced or metastatic HER2-positive breast cancer
    - FISH+ or CISH+ or IHC3+
  - No prior T-DM1 or pertuzumab therapy
  - Prior HER2 therapy in the second-line or beyond setting
  - Cardiac ejection fraction >55%
- In this 3 + 3 design, patients (N = 9) received pertuzumab (840 mg, cycle 1; 420 mg, cycle 2 and beyond) with T-DM1 (3.0 mg/kg in Cohort 1 and, in the absence of dose-limiting toxicity (DLT), 3.6 mg/kg in Cohort 2).
- Additional patients were added to the expansion phase (N = 58) after the dose escalation phase was completed.

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Trial Schema



* Full-dose pertuzumab, cycle 1 loading dose (840 mg, 420 mg all subsequent cycles)
† Patients enrolled in initial cohort may now receive 3.6 mg/kg T-DM1 in subsequent cycles along with full-dose pertuzumab
‡ 20 first-line and 40 relapsed patients were to be included in this phase

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Response in Relapsed Patients

	Cohort 1 (n = 3)	Cohort 2 (n = 25)	Total (n = 28)
Complete response	0	0	0
Partial response	66.7%	32.0%	35.7%
Stable disease	33.3%	48.0%	46.4%
Progressive disease	0	16.0%	14.3%
Missing	0	4.0%	3.6%

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Safety

- Dose reductions due to AEs in 6 patients:
  - Hematologic events (n = 3), nausea/vomiting (n = 1) and increased liver enzymes (n = 2)
- Serious AEs were observed in 7 patients:
  - Grades 3 and 5 pneumonia (n = 2), Grade 3 nausea/diarrhea/fatigue/vomiting (n = 1), Grade 3 cellulitis (n = 1), dyspnea (n = 1), hematuria (n = 1) and URI (n = 1)
- One discontinuation of both drugs (Grade 3 LV dysfunction)
- One death occurred unrelated to treatment (Grade 5 pneumonia in patient who died concomitantly of disease progression)

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Grade 3/4 Adverse Events

Event	Patients, %
Fatigue	13.6%
Thrombocytopenia	11.3%
AST increase	6.8%
Nausea	4.5%
Vomiting	4.5%
Diarrhea	2.3%
Dyspnea	2.3%

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Conclusions

- The dose of T-DM1 was determined to be 3.6 mg/kg in combination with full-dose pertuzumab (840 mg loading dose followed by 420 mg).
- T-DM1 plus full-dose pertuzumab has an encouraging safety and tolerability profile.
- The preliminary efficacy data of T-DM1 plus pertuzumab for relapsed patients are encouraging.
  - Overall response rate was 35.7%.
  - All responses were confirmed partial responses.

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Investigator comment on the results of a Phase Ib/II trial of T-DM1 with pertuzumab for patients with advanced HER2-positive BC treated with trastuzumab

In the Phase I dose-escalation cohort of this study, we observed no obvious increase in toxicity, and we were able to escalate doses of both T-DM1 and pertuzumab to what we considered standard Phase II doses. The trial then expanded into two Phase II cohorts — patients refractory to trastuzumab and a smaller first-line therapy cohort of patients who received neoadjuvant or adjuvant trastuzumab but had not received trastuzumab for mBC. We did not present data for this first-line therapy cohort but reported on the first 28 out of 44 patients in the refractory cohort.

The toxicities with the combination appear similar to what would be expected from T-DM1 alone, including mild fatigue and some thrombocytopenia, which was not clinically significant. No obvious cardiotoxicity was observed, although all of these patients had previously received trastuzumab and most had received lapatinib as well. Response rates were between 25 to 30 percent in this refractory population. We were certainly encouraged by these results and by the apparent lack of increased toxicity.

Interview with Kathy D Miller, MD, June 11, 2010

Investigator comment on the results of a Phase Ib/II trial of T-DM1 with pertuzumab for patients with advanced HER2-positive BC treated with trastuzumab

T-DM1 is an antibody-drug conjugate, or trastuzumab linked to a small amount of the chemotherapeutic agent maytansinoid. With T-DM1, the trastuzumab moiety binds to the HER2-positive cancer cell, the molecule is internalized and the chemotherapy is released in a targeted fashion.

Two prior Phase II studies with T-DM1 demonstrated that it was quite effective, based on response rates of approximately 35 percent in patients with highly refractory, HER2-positive mBC. Pertuzumab is another monoclonal antibody that binds to a different site on HER2 and prevents heterodimerization of HER2 with either HER1 or HER3.

In Kathy's study, they demonstrated that T-DM1 and pertuzumab could safely be administered together. It's difficult to comment on efficacy in this small study, although response rates with the combination were similar to what has been observed with T-DM1 alone. This does not mean that this combination will not be more effective than T-DM1, particularly in a different setting.

Interview with Eric P Winer, MD, July 6, 2010

Pertuzumab and Trastuzumab: Exploratory Biomarker Correlations with Clinical Benefit in Patients with Metastatic HER2-Positive Breast Cancer

Cortes J et al.

Proc ASCO 2010;Abstract 1066.

Introduction

- Pertuzumab (P) is a monoclonal antibody targeted against HER2 that prevents HER2 dimerization and induces antibody-dependent cell-mediated cytotoxicity.
- P monotherapy demonstrated activity against HER2-positive breast cancer (BC), although combination with trastuzumab (H) enhanced the antitumor effect of P (*Cancer Res* 2009;69:9330).
- Phase II trial of P and H combination therapy in patients with HER2-positive BC that had progressed on prior H therapy demonstrated a clinical benefit rate (CBR) of 50% and an objective response rate (ORR) of 24.2% (*J Clin Oncol* 2010;28:1138).
- **Current study objective:**
  - Evaluate a set of biomarkers for their prognostic or predictive utility for patients with HER2-positive metastatic BC (mBC) treated with P and H.

Cortes J et al. *Proc ASCO* 2010;Abstract 1066.

Trial Schema

Eligibility (N = 66)

HER2-positive metastatic breast cancer

Progression on trastuzumab-based therapy as last treatment for metastatic disease

Measurable disease at baseline

Tumor samples collected at the time of primary surgery

→

P + H

P 840 mg loading dose → 420 mg q3w

H 4 mg/kg loading dose → 2 mg/kg weekly or 8 mg/kg loading dose → 6 mg/kg q3w

Protein and mRNA levels of potential prognostic or predictive significance were measured using immunohistochemistry and/or quantitative RT-PCR, immunoassay or FISH.
mRNA levels were used to divide patients into low HER2 expression (<median) and high HER2 expression (≥median) groups.

Cortes J et al. *Proc ASCO* 2010;Abstract 1066.

Summary and Conclusions

- Exploratory biomarker analyses demonstrated:
  - Low HER2 mRNA expression was significantly correlated with higher ORR (p = 0.0046) and CBR (p = 0.0014) and improved progression-free survival (PFS) (p = 0.0082) compared to higher mRNA expression levels.
  - ORR for patients with HER2-positive BC was not correlated to levels of HER2 protein.
  - HER2 and HER3 mRNA levels were correlated to one another.
  - Low HER3 mRNA levels were associated with a less pronounced correlation with improved ORR, CBR and PFS.
- Further investigation of these biomarkers is warranted to advance the prediction of efficacy endpoints.

Cortes J et al. *Proc ASCO* 2010;Abstract 1066.

A Meta-Analysis of Overall Survival Data from Three Randomized Trials of Bevacizumab (BV) and First-Line Chemotherapy as Treatment for Patients with Metastatic Breast Cancer (MBC)[1]

Progression-Free Survival in Patient Subgroups in RIBBON-2, a Phase III Trial of Chemotherapy Plus or Minus Bevacizumab for Second-Line Treatment of HER2-Negative, Locally Recurrent or Metastatic Breast Cancer[2]

[1] **O'Shaughnessy J et al.**
Proc ASCO 2010;Abstract 1005.
[2] **Brufsky A et al.**
Proc ASCO 2010;Abstract 1021.

Background for Meta-Analysis

- Three randomized Phase III trials have demonstrated that BV improves progression-free survival (PFS) when added to chemotherapy in front-line MBC.
  - E2100 (*J Clin Oncol* 2009;27:4966)
  - AVADO (*Proc ASCO* 2008;Abstract LBA1011)
  - RIBBON-1 (*Proc ASCO* 2009;Abstract 1005)
- BV combined with chemotherapy improved PFS in the above studies irrespective of HR status, sites of metastases, disease-free interval and prior adjuvant taxane use.
- **Current study objective:**
  - To quantify the treatment benefit of BV combined with chemotherapy by performing a meta-analysis of patient data from the E2100, AVADO and RIBBON-1 trials.

O'Shaughnessy J et al. *Proc ASCO* 2010;Abstract 1005.

Comparison of the 1st-Line MBC Studies

	E2100	AVADO[1]	RIBBON-1[1]
Number of Patients	722	488[2]	1,237
Chemotherapy	Paclitaxel	Docetaxel	Capecitabine, Taxanes, Anthracyclines
Primary Endpoint	PFS[3]	PFS[4]	PFS[4]
Key Secondary Endpoints	OS, ORR	OS, ORR, 1-Year Survival	OS, ORR, 1-Year Survival

PFS = progression-free survival; OS = overall survival; ORR = objective response rate

[1] Permitted continuing on bevacizumab or crossing over to bevacizumab; [2] Includes patients from the chemotherapy alone and chemotherapy with BV 15 mg/kg cohorts; [3] Primary endpoint analysis based on independent radiologist's assessment; [4] Primary endpoint analysis based on investigator's assessment

O'Shaughnessy J et al. *Proc ASCO* 2010;Abstract 1005.

Overview of Efficacy Results from Individual Studies

	E2100		AVADO		RIBBON-1 (Capecitabine)		RIBBON-1 (Taxane, Anthra)	
	Non-BV	BV	Non-BV	BV[1]	Non-BV	BV	Non-BV	BV
Median PFS (months)	5.8	11.3	8.0	8.8	5.7	8.6	8.0	9.2
Hazard Ratio	0.48		0.62		0.69		0.64	
p-value	<0.0001		0.0003		0.0002		<0.0001	

Anthra = Anthracycline
[1] Bevacizumab 15 mg/kg data

O'Shaughnessy J et al. *Proc ASCO* 2010;Abstract 1005.

Results of Meta-Analysis of Phase III Studies

	Non-BV (n = 1,008)	BV (n = 1,439)	Hazard Ratio	*p*-value
PFS (in months)	6.7	9.2	0.64	<0.0001
OS (in months)	26.4	26.7	0.97	0.56
1-Year Survival	77%	82%	—	0.003

PFS = progression-free survival; OS = overall survival

O'Shaughnessy J et al. *Proc ASCO* 2010;Abstract 1005.

Conclusions

- Bevacizumab, when combined with first-line chemotherapy, results in clinically and statistically meaningful improvement in PFS.
- No statistically or clinically significant difference in overall survival (OS) is seen in this meta-analysis.
  - In MBC, the duration of survival post-progression (SPP) affects the ability of Phase III trials to report an effect on OS (*J Natl Cancer Inst* 2009;101:1642).
  - The probability of affecting OS is lower in patient populations with longer SPP (SPP was 20 mo in the three trials used in the meta-analysis).
- Pooled analysis suggests an early survival benefit at one year.

O'Shaughnessy J et al. *Proc ASCO* 2010;Abstract 1005.

Investigator comment on the results of a meta-analysis of overall survival data from three randomized trials of bevacizumab with first-line chemotherapy

The take-home message of this meta-analysis of ECOG-2100, AVADO and RIBBON-1 is there was an improvement in progression-free survival (PFS) of about 26 percent, a 17 percent improvement in response rate and no overall survival benefit from the addition of bevacizumab to first-line chemotherapy.

Interestingly, when they examined the number of subsequent agents these patients received after progression, approximately one quarter of the patients had four or more regimens in the metastatic setting. At least 90 percent of patients had three regimens of therapy. So this raises the issue of post-progression survival.

A nice article was published in the *JNCI* last year, in which statisticians modeled a trial that had a significant PFS benefit of three months. Patients had a post-progression survival of approximately 24 months. They demonstrated that in order to show a statistically significant survival benefit, 2,400 to 2,500 patients would be required. So this tells us that if patients have a long survival post progression, a huge trial will be needed to demonstrate that the up-front intervention was effective in impacting overall survival.

Interview with Adam M Brufsky, MD, PhD, June 18, 2010

Investigator comment on the results of a meta-analysis of overall survival data from three randomized trials of bevacizumab with first-line chemotherapy

Unfortunately, in this meta-analysis there was no improvement in overall survival. Sometimes it's argued that the reason we don't see survival benefits in the first-line setting in patients with mBC is due to the length of survival and the fact that subsequent therapies may dampen the effect of an earlier treatment. However, this was a more-than-adequately powered analysis that should have been able to demonstrate a small improvement in overall survival, and yet it did not.

When faced with a new patient who has metastatic breast cancer and who will be receiving chemotherapy, the decision to add bevacizumab should not be based on hoping that she will live longer. It's a decision that needs to focus on the improvement in progression-free survival only. In my mind, the time when we want to focus on using bevacizumab is in that first-line setting for a patient who has either a high disease burden or a great deal of symptoms, for whom controlling the cancer longer or getting a response will lead to an improvement in quality of life. At the moment, we don't have reason to believe we will extend a woman's life.

Interview with Eric P Winer, MD, July 6, 2010

Investigator comment on the results of a meta-analysis of overall survival data from three randomized trials of bevacizumab with first-line chemotherapy

One of the big questions has been whether bevacizumab impacts survival in patients with mBC. No survival advantage has been observed in any of the individual first-line studies, but each was woefully underpowered to address survival. With three randomized trials now, the meta-analysis was conducted and none of the messages regarding efficacy and safety have changed from the individual studies. The improvements in progression-free survival and response rate absolutely held up, and no rare toxicity issues emerged. Importantly, no overall survival advantage was evident with the addition of bevacizumab to first-line chemotherapy.

Overall survival is clearly an important endpoint, but it is a composite that is driven by the patient's age and comorbidities and the inherent biology of her disease, some of which may not be changed by the therapy that we administer. It's partly driven by toxicity and the ability to receive therapy. To a small extent, it may be altered by initial therapy. It may also be altered by second-, third-, fourth- or fifth-line therapy. So, in essence, first-line therapy must have a large impact in order to demonstrate an overall survival benefit. That's not true for progression-free survival.

Interview with Kathy D Miller, MD, June 11, 2010

Progression-Free Survival in Patient Subgroups in RIBBON-2, a Phase III Trial of Chemotherapy Plus or Minus Bevacizumab for Second-Line Treatment of HER2-Negative, Locally Recurrent or Metastatic Breast Cancer

Brufsky A et al.

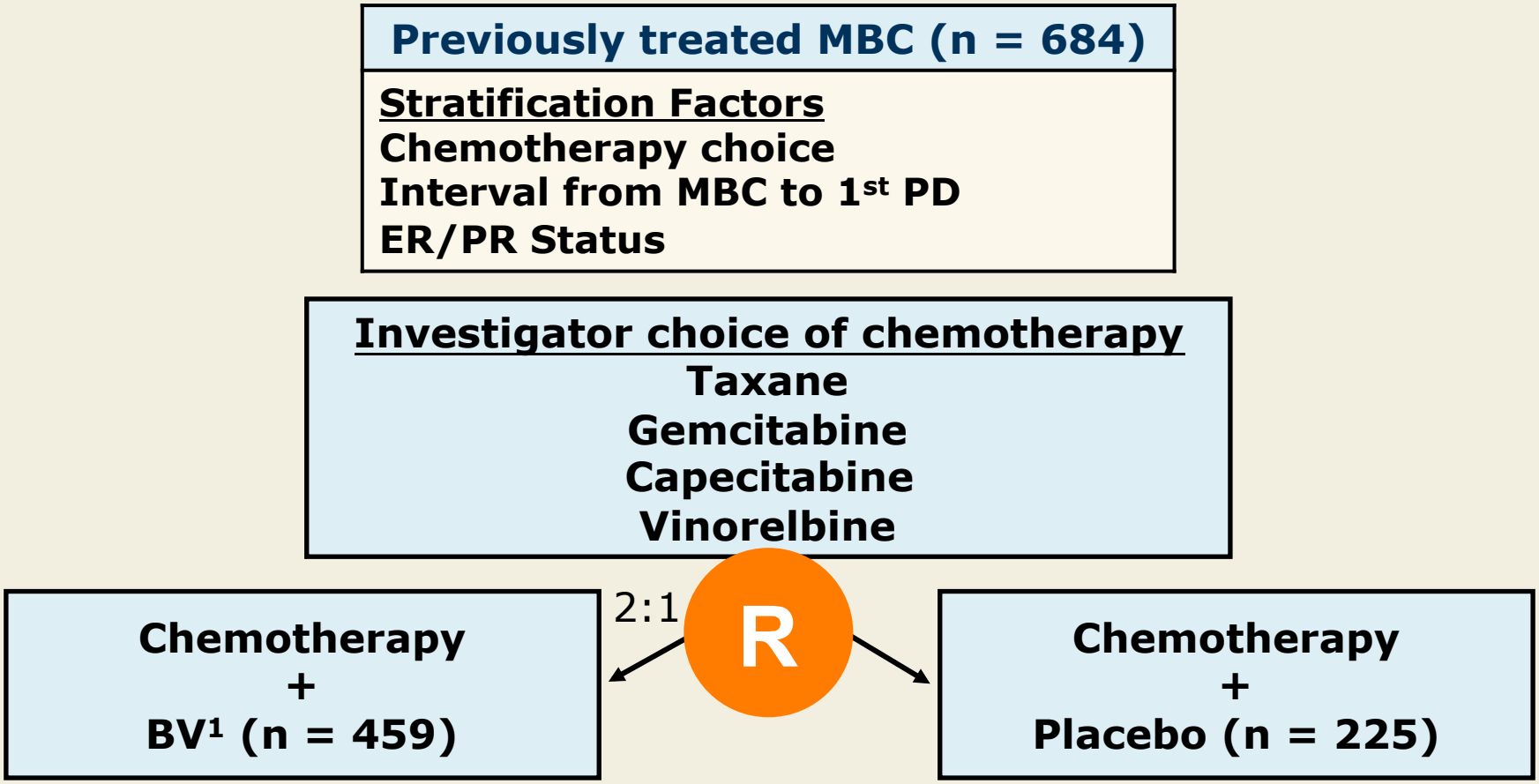
Proc ASCO 2010;Abstract 1021.

Background

- Three Phase III trials (E2100[1], AVADO[2] and RIBBON-1[3]) have established that bevacizumab (BV) improves progression-free survival (PFS) when added to first-line chemotherapy ([1] *J Clin Oncol* 2009;27:4966, [2] *Proc ASCO* 2008;Abstract LBA1011, [3] *Proc ASCO* 2009;Abstract 1005).
- RIBBON-2 has shown improved PFS when BV is combined with various chemotherapies as second-line therapy for metastatic breast cancer (*Proc SABCS* 2009;Abstract 42).
- **Current study objective:**
  - To analyze PFS in prespecified and exploratory subgroups of RIBBON-2 patients.

Brufsky A et al. *Proc ASCO* 2010;Abstract 1021.

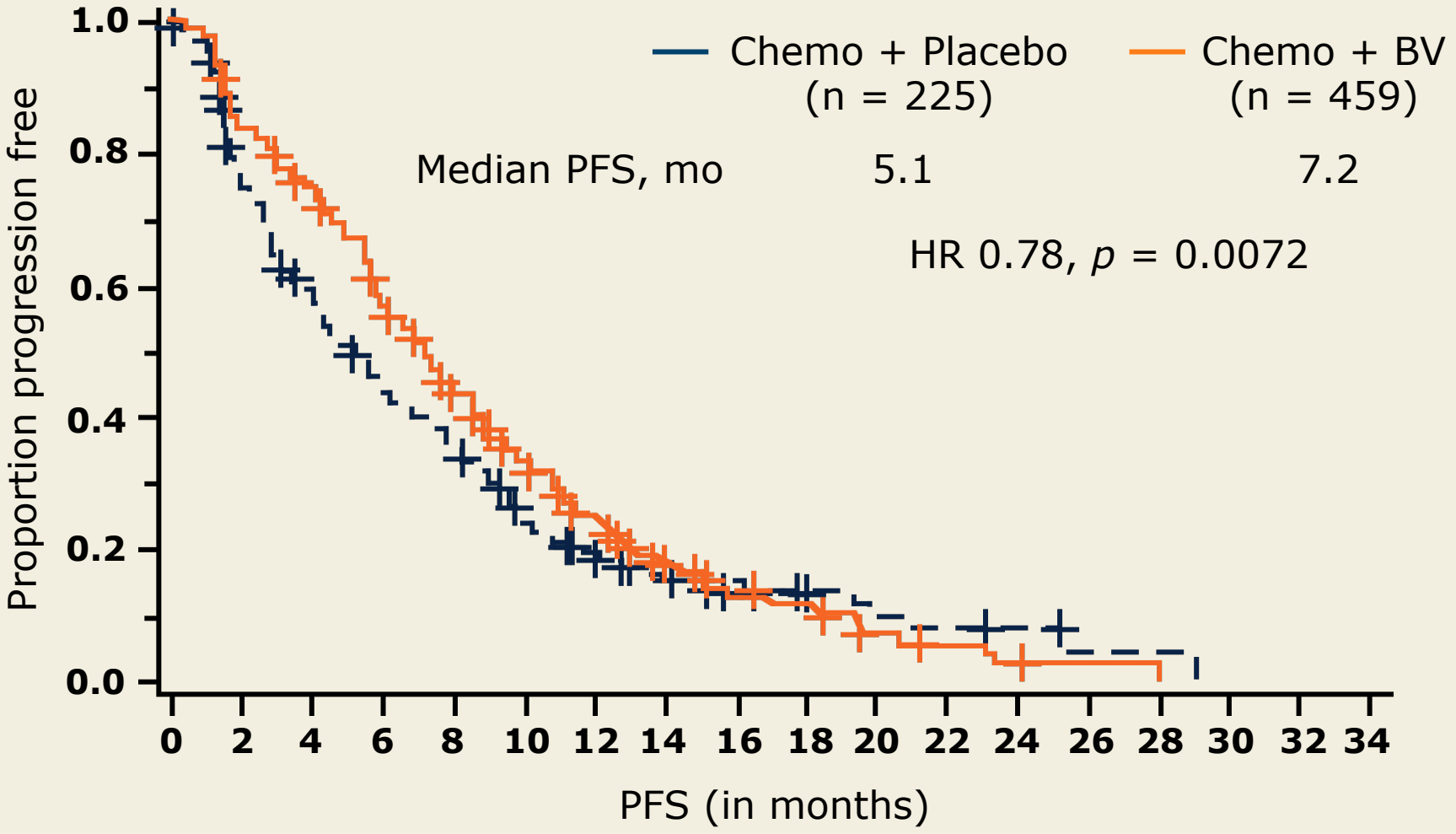
RIBBON-2 Study Design



[1] BV 10 mg/kg q2 weeks or 15 mg/kg q3 weeks

Brufsky A et al. *Proc ASCO* 2010;Abstract 1021.

Primary Endpoint (PFS)



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Median PFS by Chemotherapy Cohorts

Group	PFS in months (Chemo + BV)	PFS in months (Chemo + Placebo)	Hazard Ratio
All Patients (n = 684)	7.2	5.1	0.78
Taxanes (n = 304)	8.0	5.8	0.64
Gemcitabine (n = 160)	6.0	5.5	0.90
Capecitabine (n = 144)	6.9	4.1	0.73
Vinorelbine (n = 76)	5.7	7.0	1.42

Brufsky A et al. *Proc ASCO* 2010;Abstract 1021.

Median PFS by Other Cohorts

Group	PFS in months (Chemo + BV)	PFS in months (Chemo + Placebo)	Hazard Ratio
All Patients (n = 684)	7.2	5.1	0.78
Age <65 (n = 539) Age ≥65 (n = 145)	7.0 7.4	5.2 4.5	0.82 0.58
HR Positive (n = 494) HR Negative (n = 190)	7.4 6.5	6.0 2.8	0.89 0.53
Time from metastatic dx to PD <6 mo (n = 192)	7.2	4.2	0.67
Time from metastatic dx to PD ≥6 mo (n = 492)	7.2	5.6	0.81
Triple Negative (n = 159) Non-Triple Negative (n = 498)	6.0 7.4	2.7 6.0	0.49 0.89

dx = diagnosis; PD = progressive disease

Brufsky A et al. *Proc ASCO* 2010;Abstract 1021.

Conclusion

- RIBBON-2 subgroup analysis is consistent with the primary results of RIBBON-2.
- RIBBON-2 subgroup analysis suggests that BV provides a PFS benefit when combined with various chemotherapies.
- RIBBON-2 subgroup analysis suggests that the PFS benefit is observed in patients with differing clinical characteristics and disease histories.

Brufsky A et al. *Proc ASCO* 2010;Abstract 1021.

Investigator comment on the results of RIBBON-2: Second-line chemotherapy ± bevacizumab

In RIBBON-2 we treated 684 patients with second-line chemotherapy of the investigator's choice, which typically included taxanes, gemcitabine, capecitabine or vinorelbine. Patients were randomly assigned two-to-one to chemotherapy with or without bevacizumab and treated until disease progression. In the initial overall study results, progression-free survival improved from 5.1 to 7.2 months with the addition of bevacizumab.

In the analysis presented at ASCO, we evaluated progression-free survival by the individual chemotherapy cohorts. The bottom line is that the taxanes work quite well, regardless of whether it's paclitaxel, docetaxel or *nab* paclitaxel. Capecitabine was effective when combined with bevacizumab. Gemcitabine did not work well, and for reasons that are puzzling, there may have been a detriment in combining vinorelbine with bevacizumab. However, there were few patients on the vinorelbine control arm, which could account for these findings.

Intriguingly, in a subgroup analysis of patients with triple-negative mBC, the progression-free survival improved from 2.7 months to 6 months, which is similar to what would happen with PARP inhibitors.

Interview with Adam M Brufsky, MD, PhD, June 18, 2010

A Phase III Study (EMBRACE) of Eribulin Mesylate versus Treatment of Physician's Choice in Patients with Locally Recurrent or Metastatic Breast Cancer Previously Treated with an Anthracycline and a Taxane

Twelves C et al.

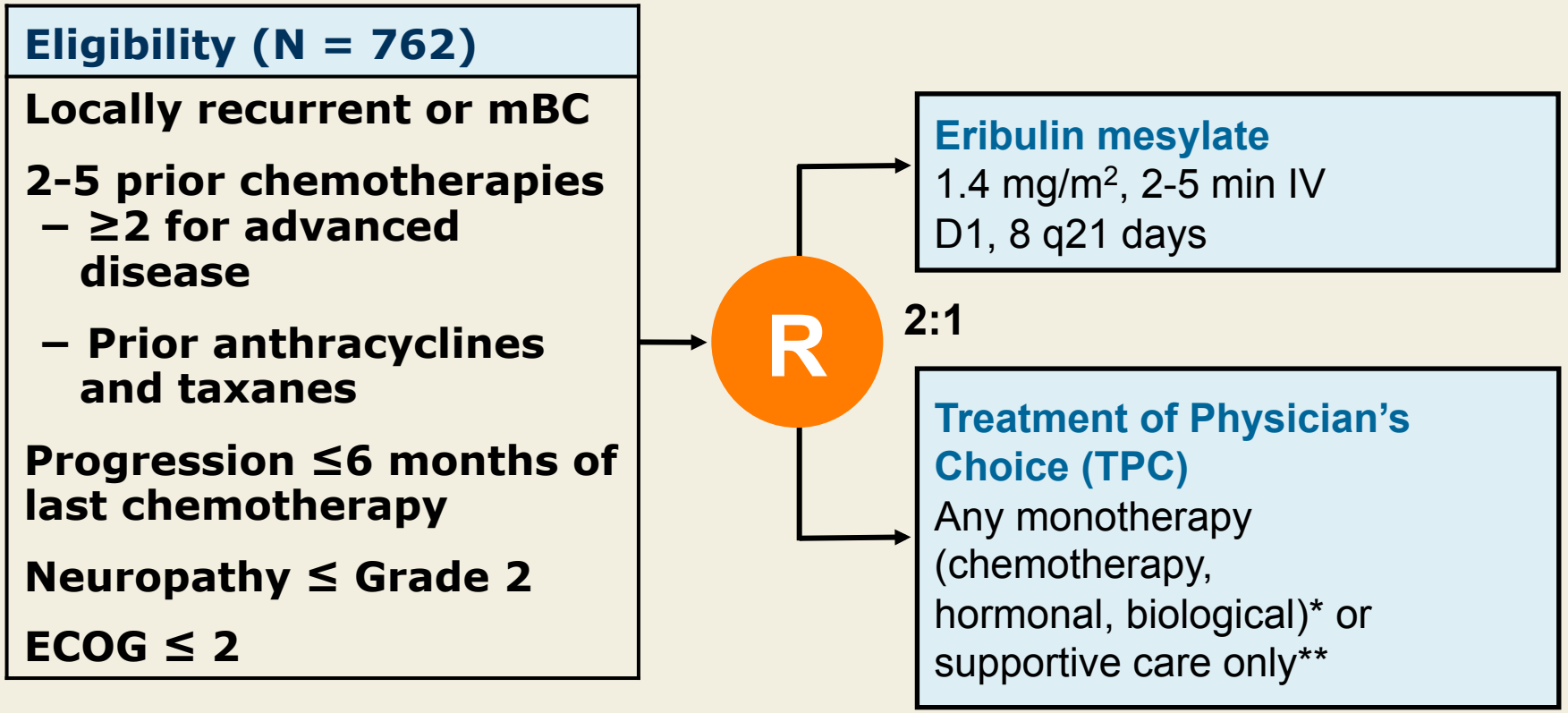
Proc ASCO 2010;Abstract CRA1004.

Introduction

- No single standard of care treatment exists for heavily pretreated metastatic breast cancer (mBC) and no single agent has demonstrated an overall survival benefit.
- Eribulin mesylate is a synthetic analog of halichondrin B, a natural marine sponge product.
  - Non-taxane microtubule dynamics inhibitor with a novel mode of action
  - Potent anti-proliferative agent in vitro and in vivo
  - Active against β-tubulin mutated cell lines
  - Wide therapeutic window and induces less neuropathy in mice than paclitaxel
  - Overall response rate in heavily pretreated mBC (median prior treatments = 4): 9-12% (ASCO 2008;Abstract 1084; *JCO* 2009;27:2954)
- **Current study objective:**
  - Evaluate eribulin versus treatment of physician's choice in patients with mBC previously treated with an anthracycline and taxane.

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

EMBRACE Study Design



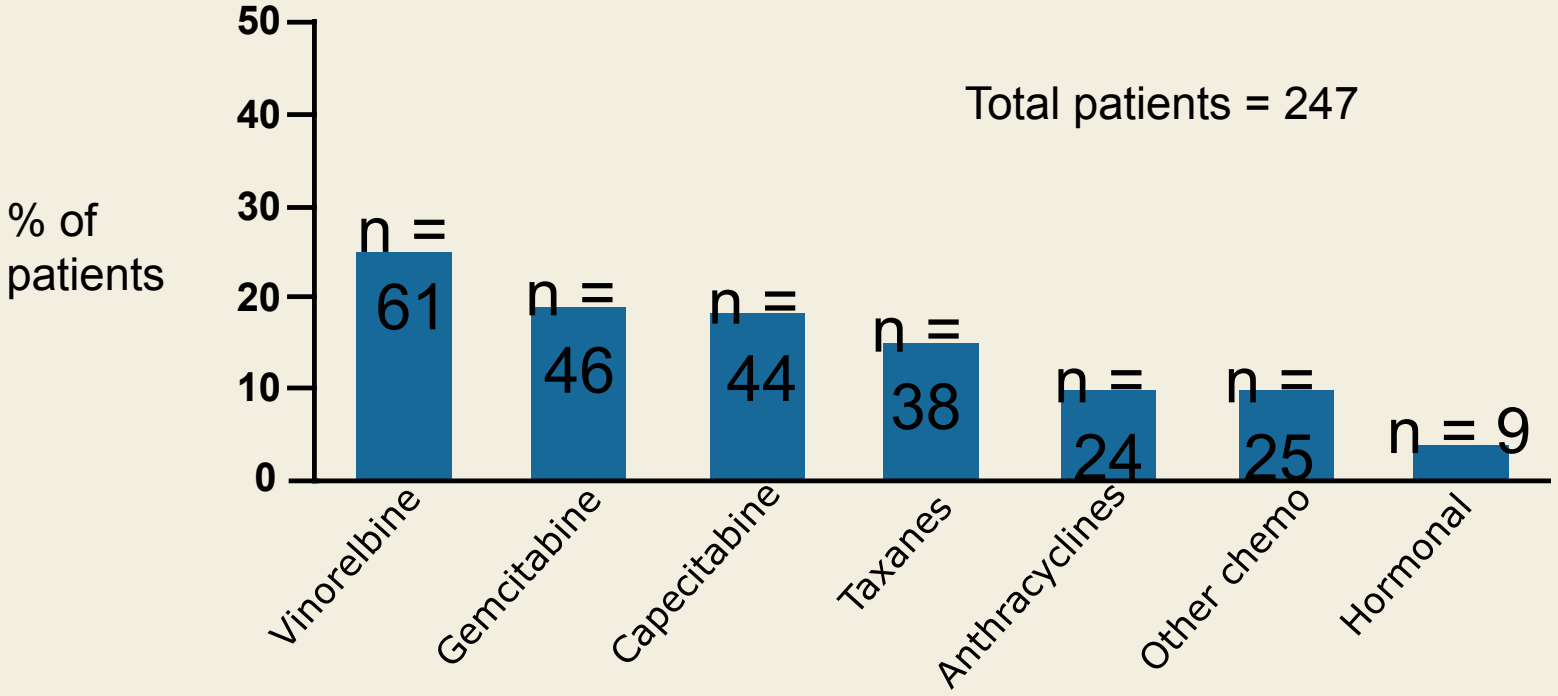
* Approved for cancer treatment

** Or palliative treatment or radiotherapy according to local practice

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

TPC Treatment Received
ITT Population

96% of patients treated with chemotherapy



No patient received best supportive care or “biological” therapies only

Taxanes: paclitaxel, docetaxel, nanoparticle albumin-bound (*nab*) paclitaxel; Anthracyclines: doxorubicin, liposomal doxorubicin, mitoxantrone

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

Summary of Efficacy

Endpoint	Eribulin	TPC	Hazard ratio	*p*-value
OS (n = 508, 254)	13.12 mo	10.65 mo	0.81	0.041
PFS* (n = 508, 254) Independent review (ITT) Investigator review (ITT)	 3.7 mo 3.6 mo	 2.2 mo 2.2 mo	 0.87 0.76	 0.14 0.002
ORR (CR+PR) (n = 468, 214) Independent review (ITT) Investigator review (ITT)	 12.2% 13.2%	 4.7% 7.5%	 — —	 0.002 0.028
CBR (CR+PR+SD) (n = 468, 214) Independent review (ITT) Investigator review (ITT)	 22.6% 27.8%	 16.8% 20.1%	 — —	 — —

* PFS in per-protocol population was significant for independent ($p = 0.02$) and investigator ($p < 0.001$) reviews

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

Overall Incidence of Adverse Events

Adverse Event (AE)	Eribulin (n = 503)	TPC (n = 247)
All AEs	98.8%	93.1%
Serious AEs	25.0%	25.9%
AEs leading to		
Interruption	5.0%	10.1%
Discontinuation	13.3%	15.4%
Dose reduction	16.9%	15.8%
Dose delay	35.2%	32.4%
Fatal AEs	4.0%	7.3%
Fatal AEs (treatment-related)	1.0%	0.8%

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

Grade 3 and 4 Adverse Events

	Grade 3		Grade 4	
	Eribulin (n = 503)	TPC (n = 247)	Eribulin (n = 503)	TPC (n = 247)
Hematologic events				
Neutropenia	21.1%	14.2%	24.1%	6.9%
Leukopenia	11.7%	4.9%	2.2%	0.8%
Anemia	1.8%	3.2%	0.2%	0.4%
Febrile neutropenia	3.0%	0.8%	1.2%	0.4%
Non-hematologic events				
Asthenia/fatigue	8.2%	10.1%	0.6%	0
Peripheral neuropathy	7.8%	2.0%	0.4%	0
Nausea	1.2%	2.4%	0	0
Dyspnea	3.6%	2.4%	0	0.4%
Mucosal inflammation	1.4%	2.0%	0	0
Hand-foot syndrome	0.4%	3.6%	0	0

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

Conclusions

- EMBRACE met its primary endpoint of prolonged overall survival.
  - Improvement of median overall survival was 2.5 months (23%) with eribulin versus TPC.
  - Clinically meaningful in heavily pretreated patients
    - Median # of prior chemotherapy regimens (range): 4 (1-7)
- Overall response rate and progression-free survival also favored eribulin.
- Clinical benefits were achieved with a manageable safety profile.
- These results potentially establish eribulin as a new option for women with heavily pre-treated mBC.

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

Investigator comment on the results of the EMBRACE trial: Eribulin versus treatment of physician's choice

EMBRACE is a nice trial, which took women who were multiply refractory — having received between two and seven prior chemotherapy regimens (median of four) — and randomly assigned them to eribulin versus physician's choice of treatment. At the fourth or fifth line of therapy, there is no right choice and it's difficult to mandate a particular therapy, so this was a great study design. Almost all of the patients had a performance status of 2 or better — in fact, the majority were PS 0 or 1. A major criticism frequently heard is that women receiving late-line therapy will die quickly and have a terrible performance status. That's not true and it's an important take-home message from this trial.

Another important message is that these heavily refractory patients had a statistically significant survival benefit to eribulin of about 20 percent — more than 13 months versus

Investigator comment on the results of the EMBRACE trial: Eribulin versus treatment of physician's choice

In EMBRACE almost 800 patients who had received between two and five prior regimens for metastatic breast cancer were randomized in a two-to-one ratio to eribulin versus physician's choice monotherapy.

This was a high-risk study design with overall survival as the endpoint, but it was reasonable because patients were not going to be receiving much therapy, if any, thereafter. Eribulin is the first single-agent chemotherapy treatment that has been shown to improve survival in late-line metastatic breast cancer.

Eribulin is a good drug for breast cancer. It's well tolerated and has a good side-effect profile. Not everybody loses their hair. It can cause some neutropenia but febrile neutropenia is fairly low. It doesn't affect hemoglobin or the platelets too much, and the nonhematologic toxicity profile is also quite favorable, in that Grade 3/4 peripheral neuropathy is about eight percent. I've seen great responses with eribulin.

Interview with Linda T Vahdat, MD, June 5, 2010