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ORIGINAL REPORT

Double-Blind Phase III Trial of Adjuvant Chemotherapy With and Without Bevacizumab in Patients With Lymph Node–Positive and High-Risk Lymph Node–Negative Breast Cancer (E5103)

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ABSTRACT

Purpose

Bevacizumab improves progression-free survival but not overall survival in patients with metastatic breast cancer. E5103 tested the effect of bevacizumab in the adjuvant setting in patients with human epidermal growth factor receptor 2–negative disease.

Patients and Methods

Patients were assigned 1:2:2 to receive placebo with doxorubicin and cyclophosphamide (AC) followed by weekly paclitaxel (arm A), bevacizumab only during AC and paclitaxel (arm B), or bevacizumab during AC and paclitaxel followed by bevacizumab monotherapy for 10 cycles (arm C). Random assignment was stratified and bevacizumab dose adjusted for choice of AC schedule. Radiation and hormonal therapy were administered concurrently with bevacizumab in arm C. The primary end point was invasive disease–free survival (IDFS).

Results

Four thousand nine hundred ninety-four patients were enrolled. Median age was 52 years; 64% of patients were estrogen receptor positive, 27% were lymph node negative, and 78% received dose-dense AC. Chemotherapy-associated adverse events including myelosuppression and neuropathy were similar across all arms. Grade ≥ 3 hypertension was more common in bevacizumab-treated patients, but thrombosis, proteinuria, and hemorrhage were not. The cumulative incidence of clinical congestive heart failure at 15 months was 1.0%, 1.9%, and 3.0% in arms A, B, and C, respectively. Bevacizumab exposure was less than anticipated, with approximately 24% of patients in arm B and approximately 55% of patients in arm C discontinuing bevacizumab before completing planned therapy. Five-year IDFS was 77% (95% CI, 71% to 81%) in arm A, 76% (95% CI, 72% to 80%) in arm B, and 80% (95% CI, 77% to 83%) in arm C.

Conclusion

Incorporation of bevacizumab into sequential anthracycline- and taxane-containing adjuvant therapy does not improve IDFS or overall survival in patients with high-risk human epidermal growth factor receptor 2–negative breast cancer. Longer duration bevacizumab therapy is unlikely to be feasible given the high rate of early discontinuation.

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INTRODUCTION

Over the past three decades, substantial laboratory and indirect clinical evidence has accumulated to support the central role of angiogenesis in breast cancer progression.[1] This nascent vascular network provides a novel opportunity for therapy. The vascular endothelial growth factor (VEGF) is a potent stimulator of angiogenesis[2] and is inversely correlated with overall survival (OS).[3,4] Bevacizumab, a monoclonal antibody that recognizes all isoforms of VEGF-A, improves response rate and progression-free survival, although not OS, when combined with chemotherapy in patients with metastatic breast cancer lacking overexpression of the human epidermal growth factor 2 (HER2).[5-8]

As tumors progress, the number of proangiogenic peptides produced increases.[9] We hypothesized that the most successful clinical application of angiogenesis inhibitors would be in patients with

ASSOCIATED CONTENT

Appendix
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micrometastatic rather than macrometastatic disease, which is to say in the adjuvant setting. We designed E5103 to test that hypothesis, incorporating bevacizumab into sequential anthracycline- and taxane-containing adjuvant therapy.

PATIENTS AND METHODS

Patient Eligibility

Patients must have had adenocarcinoma of the breast with a substantial risk of systemic recurrence on the basis of at least one of the following factors: involvement of at least one axillary or internal mammary lymph node on routine hematoxylin and eosin staining; estrogen receptor (ER)–negative tumor $>$ 1 cm; ER-positive tumor $>$ 5 cm; or ER-positive tumor $>$ 2 cm with an Oncotype DX Recurrence Score (Genomic Health, Redwood City, CA) $\geq$ 11. Patients had to have completed definitive breast surgery $>$ 28 days and $\leq$ 84 days from the start of protocol therapy; axillary dissection was encouraged but not required for patients with an involved sentinel node. Patients with synchronous bilateral breast cancer were eligible if the higher TNM stage tumor met the eligibility criteria. All patients had to have adequate renal, hepatic, and hematologic function. Left ventricular ejection fraction (LVEF) greater than the institutional lower limit of normal (LLN) was required.

Patients with HER2-positive disease, defined as 3+ by immunohistochemistry or gene amplification by fluorescence in situ hybridization that would support treatment with HER2-targeted therapy (ie, HER2:CEP17 ratio $\geq$ 2.0), were excluded. Patients could not have received prior cytotoxic chemotherapy or hormonal therapy for this breast cancer. Prior treatment with an anthracycline, anthracenedione, or taxane for any condition was not allowed. In addition, patients were excluded if they had a major surgery within 4 weeks, nonhealing wound or fracture, infection requiring parenteral antibiotics, or clinically significant cardiovascular disease. Therapeutic anticoagulation, regular nonsteroidal anti-inflammatory medication, and aspirin ($>$ 325 mg/d) were prohibited, but prophylactic low-dose anticoagulants were permitted.

The Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN) Cancer Research Group coordinated the study in collaboration with the North Central Cancer Treatment Group and Cancer and Leukemia Group B. Local institutional review boards approved the protocol, and patients provided written informed consent before screening.

Treatment Plan

All patients received doxorubicin and cyclophosphamide (AC) followed by paclitaxel weekly for 12 weeks as in the prior E1199 trial.[10] AC could be administered in a classic (every 3 weeks) or a dose-dense (every 2 weeks) schedule[11] on the basis of investigator discretion; bevacizumab dose was adjusted for choice of AC schedule (patients receiving classic AC received bevacizumab 15 mg/kg; patients receiving dose-dense AC received bevacizumab 10 mg/kg). Placebo (arm A) or bevacizumab (arms B and C) was administered concurrently with chemotherapy. All patients were unblinded at week 10 of paclitaxel therapy. Patients in arm C continued bevacizumab monotherapy (15 mg/kg every 3 weeks) for an additional 10 cycles. Radiation therapy (RT) was required for all patients treated with breast-conserving surgery (BCS); postmastectomy RT was required for patients with primary tumors $>$ 5 cm or involvement of four or more axillary lymph nodes and was allowed at the discretion of the treating physician for all other patients. Hormonal therapy was recommended for all patients with tumors expressing ER and/or progesterone receptors. When indicated, RT and hormonal therapy were to commence within 6 weeks of completion of chemotherapy and were administered concurrently with bevacizumab for patients in arm C.

Chemotherapy dose modifications were mandated for hematologic and nonhematologic toxicity as in E1199.[10] Bevacizumab therapy was interrupted for uncontrolled hypertension or proteinuria $\geq$ 3,500 mg in 24 hours. Bevacizumab was permanently discontinued for symptomatic hypertension, nephrotic syndrome, venous thrombosis requiring anticoagulation, arterial thrombosis, serious bleeding, bowel perforation, or wound dehiscence. Chemotherapy dose reduction did not affect bevacizumab treatment. However, if a chemotherapy cycle was delayed, bevacizumab therapy was delayed to maintain concurrent administration. If chemotherapy was permanently discontinued, patients could complete the planned therapy with bevacizumab alone.

Safety Assessments

CBCs were assessed before each chemotherapy infusion. Serum chemistry was required every other treatment cycle; urine protein-to-creatinine ratio was assessed approximately every four cycles.

Bevacizumab was held and cardiac evaluation repeated in 4 weeks in patients with an absolute decrease in LVEF $\geq$ 16% or a decrease of 10% to 15% to a value less than LLN. Bevacizumab was continued but cardiac evaluation repeated in 4 weeks in patients with an LVEF decrease $<$ 10% to less than LLN. Bevacizumab was permanently discontinued in all patients with symptomatic congestive heart failure (CHF) and those with cardiac assessments requiring bevacizumab to be held at two consecutive or three intermittent time points.

Definition and Assessment of Clinical CHF

Cardiac assessment with either multigated acquisition scan or echocardiography was performed within 8 weeks before registration, on day 1 of cycle 5, within 2 weeks of completing chemotherapy, 1 year from study entry in all arms, and on day 1 of cycle 15 in arm C patients. A physician-directed cardiac symptom evaluation was conducted 2 years from entry. Clinical CHF was defined as a decline in LVEF to less than LLN or diastolic dysfunction occurring concurrently with any of the following: grade $\geq$ 2 lower extremity edema, grade $\geq$ 2 dyspnea, or grade 1 dyspnea associated with an LVEF $<$ 40%. Auscultation of an S_3 gallop, bibasilar rales, and documented cardiomegaly also constituted signs of clinical CHF. All potential instances of clinical CHF were adjudicated by the study primary investigator and two independent cardiologists, who were all blinded to the treatment assignment.

Statistical Design and Monitoring

The primary end point was invasive disease–free survival (IDFS).[12] A total accrual of 4,950 patients across three arms was planned; blinded treatment assignments were made in permuted blocks in a 1:2:2 fashion to arm A (n = 990), arm B (n = 1,980), and arm C (n = 1,980). Random assignment was stratified by the following: ER-positive tumor (yes or no), lymph node involvement (negative, one to three nodes, or four or more nodes), type of surgery and RT (BCS plus RT, BCS plus accelerated partial breast irradiation, mastectomy and no RT, or mastectomy plus RT), and AC schedule (classic or dose dense). A two-step hierarchical approach was used, first testing arm C with arm A. Assuming a 5-year IDFS of 80% for arm A (based on E1199[10]), 2,970 patients accrued to arms A and C over 2.06 years and observed for an additional 3.14 years with 426 IDFS events provided 80% power to detect a 25% reduction in the failure hazard rate using a one-sided $P = .025$ test. Only if arm C significantly improved IDFS relative to arm A was a comparison of arm B to arm A to be performed. Only if both arms C and B significantly improved IDFS relative to arm A was a comparison of arm C to arm B to be performed. O'Brien-Fleming boundaries[13] and the Jennison-Turnbull repeated CI method[14] were used to monitor for early stopping. The ECOG-ACRIN Data Safety Monitoring Committee reviewed three planned interim outcome analyses without stopping criteria being met. Taking these into account, the threshold for significance for this final analysis is $P < .02$ (nominal, one-sided).

The Data Safety Monitoring Committee continuously monitored safety. One of two prespecified stopping rules was met and accrual was suspended on September 24, 2009 (six of the first 200 patients randomly

assigned to the combined arms B and C experienced clinical CHF). After review of safety data by ECOG-ACRIN, the Cancer Therapy Evaluation Program, and the US Food and Drug Administration and revision of clinical CHF risk in the consent form, accrual reopened on December 18, 2009.

Comparisons between arms were intent-to-treat analyses among all patients. The Kaplan-Meier method was used to estimate distributions for IDFS and OS. Cox proportional hazards models, stratified by the factors at random assignment, were used to estimate hazard ratios and to test for significance in outcome. Cumulative incidence curves for development of clinical CHF and time to treatment discontinuation were generated. Two-sided *P* values and 95% CIs are reported.

Role of the Sponsor

E5103 was conducted under a corporate research and development agreement between Genentech (South San Francisco, CA) and the National Cancer Institute (Bethesda, MD). Genentech provided bevacizumab and partial funding but did not participate in data collection. ECOG-ACRIN statisticians independently conducted the analyses. The lead author made the decision to publish and wrote the article, which was then reviewed by all authors and submitted to NCI and Genentech for comment. The authors vouch for the completeness and accuracy of the data.

RESULTS

Four thousand nine hundred ninety-four patients were enrolled between November 2007 and February 2011 (Fig 1). The study arms were well balanced (Table 1). The majority had poorly differentiated tumors larger than 2 cm with involvement of at least one axillary lymph node. Nearly two thirds of patients had ER-positive disease. Seventy-eight percent of patients received AC in the dose-dense schedule.

Efficacy

In arms A, B, and C, 5-year IDFS rates were 77% (95% CI, 71% to 81%), 76% (95% CI, 72% to 80%), and 80% (95% CI, 77% to 83%), respectively, and 5-year OS rates were 90% (95% CI, 87% to 92%), 86% (95% CI, 83% to 88%), and 90% (95% CI, 88% to 92%), respectively (Table 2 and Figs 2A and 2B) Longer duration bevacizumab therapy led to a favorable but nonsignificant difference in IDFS among patients with hormone receptor–negative tumors (Fig 2C). No other clinical factors identified subsets of patients who benefited from bevacizumab.

Adverse Events

Noncardiac chemotherapy-related toxicities were comparable to those reported in the E1199[10] and C9741[11] trials (Table 3). Eight percent of bevacizumab-treated patients experienced grade 3 hypertension (Table 3). The increase in minor mucosal bleeding reported in the prior adjuvant pilot trial[15] was not detected in E5103. Grade 3 or 4 hemorrhage, thromboembolic events, GI perforation, and wound complications were uncommon adverse events and similar across treatment arms. Bevacizumab monotherapy was associated with an ongoing risk of toxicity, particularly hypertension (Table 3). The risk of treatment-related death during or within 30 days of protocol treatment (n = 14, 0.3%) was similar across study arms; causes included acute myelogenous leukemia (n = 3), infection (n = 2), CNS ischemia or hemorrhage (n = 2), pulmonary hemorrhage or fibrosis (n = 2), liver failure (n = 1), thrombosis or embolism (n = 1), colitis (n = 1), sudden death (n = 1), and hypotension (n = 1).

As expected from previous trials,[5,15] the addition of bevacizumab led to a small but real increase in cardiac toxicity. At 15 months, the cumulative incidence of clinical CHF was 1.0%, 1.9%, and 3% in arms A, B, and C, respectively (Appendix Fig A1, online only) and was not clearly related to RT or clinical risk factors. Most patients with changes in LVEF remained asymptomatic (Appendix Table A1, online only).

Drug Exposure and Discontinuation

The addition of bevacizumab reduced the ability to complete chemotherapy, with more patients in arms B and C discontinuing

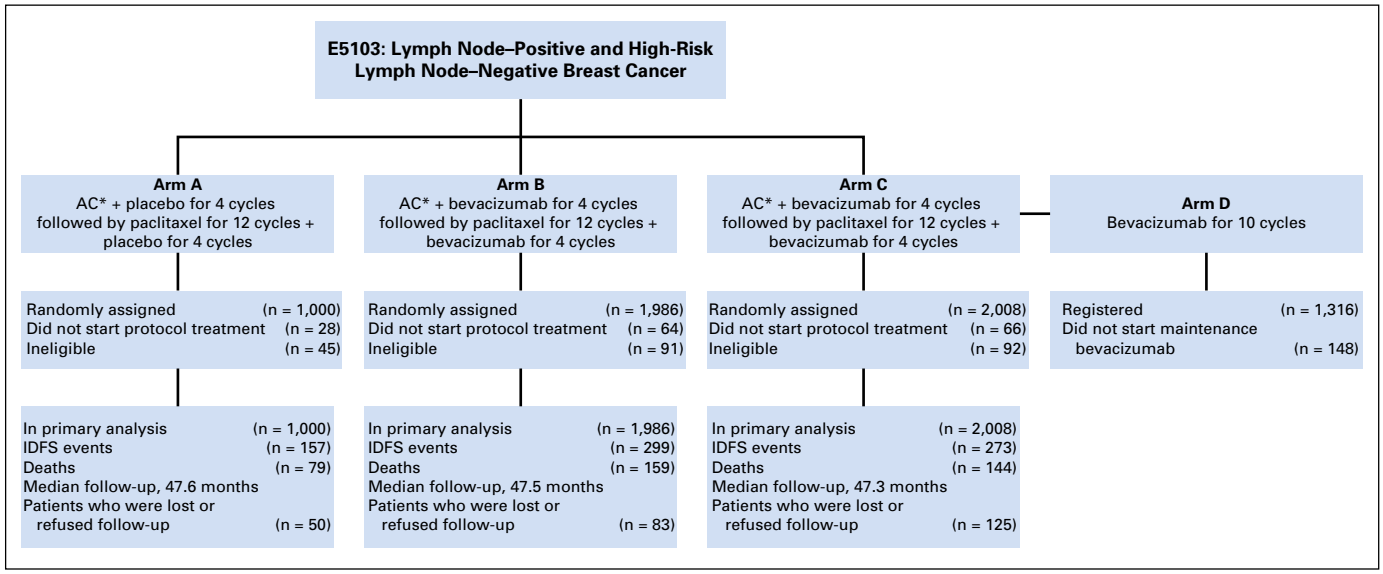

Fig 1. CONSORT diagram. All patients enrolled (N = 4,994) were included in efficacy analyses. All treated patients (n = 4,836) were evaluated for toxicity. AC, doxorubicin and cyclophosphamide; IDFS, invasive disease–free survival. (*) Every 14 or 21 days per physician and patient choice.

Table 1. Patient Characteristics

Characteristic	No. of Patients (%)			
	Arm A (n = 1,000)	Arm B (n = 1,986)	Arm C (n = 2,008)	Total (N = 4,994)
Median age, years (range)	51.8 (25.4-77.7)	51.7 (21.2-85.0)	51.6 (21.5-82.5)	51.7 (21.2-85.0)
ECOG PS				
0	860 (86)	1,714 (86)	1,700 (85)	4,274 (86)
1	138 (14)	272 (14)	307 (15)	717 (14)
Missing	2	—	1	3
Sex				
Male	5 (< 1)	10 (< 1)	8 (< 1)	23 (< 1)
Female	995 (99.5)	1,976 (99.5)	2,000 (99.5)	4,971 (99.5)
Race				
White	848 (85)	1,687 (85)	1,686 (84)	4,221 (85)
African American	101 (10)	224 (11)	240 (12)	565 (11)
Asian	43 (4)	56 (3)	59 (3)	158 (3)
Other	7 (1)	11 (1)	15 (1)	33 (1)
Missing	1	8	8	17
Primary tumor size, cm				
≤ 2	376 (38)	782 (39)	775 (39)	1,933 (39)
> 2 to ≤ 5	521 (52)	1,007 (51)	1,024 (51)	2,552 (51)
> 5	102 (10)	194 (10)	207 (10)	503 (10)
Missing	1	3	2	6
LN involvement				
Negative	259 (26)	541 (27)	563 (28)	1,363 (27)
Positive	740 (74)	1,443 (73)	1,444 (72)	3,627 (73)
Missing	1	2	1	4
Histologic grade				
1	74 (8)	174 (9)	174 (9)	422 (9)
2	354 (36)	641 (33)	633 (32)	1,628 (33)
3	551 (56)	1,124 (58)	1,158 (59)	2,833 (58)
Missing	21	47	43	111
ER and PgR status				
ER and PgR negative	350 (35)	717 (36)	729 (36)	1,796 (36)
ER and/or PgR positive	649 (65)	1,269 (64)	1,276 (64)	3,194 (64)
Missing	1	—	3	4
Local therapy				
BCS + WBRT	395 (40)	791 (41)	789 (40)	1,975 (40)
BCS + APBI	7 (1)	19 (1)	22 (1)	48 (1)
Mastectomy	178 (18)	385 (20)	393 (20)	956 (20)
Mastectomy + RT	342 (35)	648 (33)	632 (32)	1,622 (33)
BCS/no RT	35 (3)	48 (2)	57 (3)	140 (3)
Missing	15	31	49	95
Did not start protocol therapy	28 (3)	64 (3)	66 (4)	158 (3)

Abbreviations: APBI, accelerated partial breast irradiation; BCS, breast-conserving surgery; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; LN, lymph node; PgR, progesterone receptor; RT, radiation therapy; WBRT, whole-breast radiation therapy.

chemotherapy before completing the planned treatment (18.3% in arm A *v* 26.3% in arm B and 28% in arm C). Forty percent of patients (774 of 1,942 patients) who began treatment on arm C did not proceed to bevacizumab maintenance therapy, most commonly as a result of patient withdrawal or refusal or treatment-related toxicity (Fig 1 and Appendix Fig A2, online only).

DISCUSSION

The addition of bevacizumab to sequential anthracycline and taxane adjuvant therapy did not improve IDFS or OS in this high-risk, HER2-negative population. Although subset analyses pointed to a potential benefit for longer duration bevacizumab in patients with ER-negative disease, the Adjuvant Bevacizumab-Containing Therapy in Triple-Negative Breast Cancer (BEATRICE) trial found no benefit to adding bevacizumab to adjuvant chemotherapy in patients with triple-negative (ER, progesterone receptor, and HER2 negative) disease,[16,17] suggesting that this association is spurious.

E5103 may have been a negative study for many reasons. First, delivery of both chemotherapy and bevacizumab may have been inadequate. The addition of bevacizumab attenuated delivery of chemotherapy, and early drug discontinuation severely limited bevacizumab exposure. The overall rate of bevacizumab discontinuation, particularly in patients randomly assigned to arm C (approximately 70%), was predicted by the E2104 pilot trial.[15] Although the withdrawal of US Food and Drug Administration approval for bevacizumab in the metastatic setting may have led some patients to discontinue therapy, most stopped as a result of an adverse event. No single adverse event predominated, and toxicity rarely reached grade 3 severity. In comparison, approximately 25% to 30% of patients in the adjuvant trastuzumab trials discontinued treatment early,[18,19] whereas < 20% of patients stopped anastrozole during the first year of therapy.[20] This may reflect less

Table 2. IDFS and OS

Survival	Arm A (n = 1,000)	Arm B (n = 1,986)	Arm C (n = 2,008)
IDFS			
No. of events	157	299	273
5-year IDFS, % (95% CI)	77 (71 to 81)	76 (72 to 80)	80 (77 to 83)
HR (95% CI)*			
Univariate	0.87† (0.71 to 1.06)	0.95‡ (0.78 to 1.16)	0.91§ (0.77 to 1.07)
P	.17	.62	.25
Multivariate‖	0.84† (0.69 to 1.02)	0.93‡ (0.77 to 1.13)	0.89§ (0.76 to 1.06)
P	.08	.47	.19
ER/PgR negative	0.77† (0.58 to 1.03)	1.00‡ (0.76 to 1.33)	0.77§ (0.61 to 0.98)
OS			
Median follow-up, months	47.6	47.5	47.3
No. of events	79	159	144
5-year OS, % (95% CI)	90 (87 to 92)	86 (83 to 88)	90 (88 to 92)
HR (95% CI)*			
Univariate	0.89† (0.68 to 1.17)	1.01‡ (0.77 to 1.33)	0.90§ (0.72 to 1.13)
P	.41	.92	.36
Multivariate‖	0.86† (0.66 to 1.14)	0.99‡ (0.75 to 1.30)	0.90§ (0.72 to 1.13)
P	.30	.93	.36
ER/PgR negative	0.77† (0.53 to 1.12)	0.99‡ (0.69 to 1.41)	0.79§ (0.58 to 1.06)

Abbreviations: ER, estrogen receptor; HR, hazard ratio; IDFS, invasive disease–free survival; OS, overall survival; PgR, progesterone receptor.
**P* values are two-sided and are based on stratified test using stratification factors at random assignment.
†Arm C *v* arm A: Values < 1 indicate better outcome for arm C.
‡Arm B *v* arm A: Values < 1 indicate better outcome for arm B.
§Arm C *v* arm B: Values < 1 indicate better outcome for arm C.
‖Adjusted for age, ER and PgR status, nodal status, tumor size, and grade (to preserve sample size, dummy variables were included for missing disease status values). Stratification variables for this model included type of surgery or radiotherapy and doxorubicin and cyclophosphamide schedule (classic or dose dense) but excluded ER and nodal status because these were covariates in the model.

willingness of patients and treating physicians to accept bevacizumab-specific toxicities. Because many of the bevacizumab-specific toxicities have a constant, cumulative risk over time,[21] we cannot recommend trials exploring a longer duration of therapy.

Second, although bevacizumab targets VEGF-A, the study population was not enriched for VEGF-A expression or any other molecular feature. Despite repeated efforts, we lack a way to identify patients more or less likely to benefit from bevacizumab. We have interrogated samples collected in metastatic trials at both the genomic and proteomic levels. Potential predictors on the basis of expression of VEGF or its ligands, inherited polymorphisms in the VEGF-A gene, circulating pro- and antiangiogenic peptides, and oncogene expression have been put forth.[8,22-30] Although isolated associations have been found, overall the results have been inconsistent, lacked correction for multiple testing, or failed in confirmatory trials. In sum, bevacizumab has remained stubbornly undifferentiated.

When viewed within the context of similar negative trials in patients with HER2-positive breast cancer,[31] colon cancer,[32,33] melanoma,[34,35] and lung cancer,[36] we have no choice but to conclude that the underlying hypothesis, namely that inhibiting VEGF would be most effective in the adjuvant setting, is simply wrong. How could such compelling biology and generally positive results in the metastatic setting give way to such uniformly negative adjuvant trials?

Microscopic disease does not have an established vasculature and thus may be inherently resistant to anti-VEGF therapy. For example, vascular normalization, a reduction in tumor interstitial pressure leading to improved delivery of cytotoxic therapy,[37,38] does not apply to micrometastatic disease. We have learned that tumors establish a vasculature in at least six different ways, each with varying sensitivity to VEGF inhibition (reviewed by Carmeliet and Jain[39]). The predominant mode of vascularization and, therefore, sensitivity to VEGF inhibition may differ in micrometastatic versus macrometastatic disease. Although VEGF plays an important role in establishing the premetastatic niche (an event that occurs before clinical diagnosis), once established, avascular micrometastatic deposits (equivalent to the adjuvant setting) may persist despite VEGF inhibition.[40]

Early enthusiasm for antiangiogenic therapy was buoyed by claims that this was a therapy resistant to resistance.[41] Multiple mechanisms of resistance to anti-VEGF therapy have been identified, including induction of alternative angiogenic pathways, hypoxia-mediated increases in aggressiveness, cancer stem cells and autophagy, and compensatory recruitment of vascular progenitors.[42-47] Recent preclinical models suggested an increase in metastasis with VEGF inhibition. Thankfully, that has not been apparent clinically. Although bevacizumab has been ineffective in the adjuvant setting, none of the reported trials suggested a deleterious effect.

Multiple lessons can be learned from this negative clinical trial. First, our preclinical models were, and likely still are, inadequate to model the complex biology at play before the development of overt metastases. No matter how persuasive the biology and how convincing the results in the metastatic setting, adjuvant trials are the final clinical laboratory.

Second, we should have taken the concerns about early discontinuation in the adjuvant setting more seriously. Calculating the effect of early discontinuation on overall benefit requires knowledge of both the treatment effect and the impact of duration of therapy on that effect—factors that were unknowable when E5103 began. If future studies proceed despite concerns about feasibility, strategies to mitigate toxicity and enhance adherence will be crucial. Early termination of such trials if the discontinuation

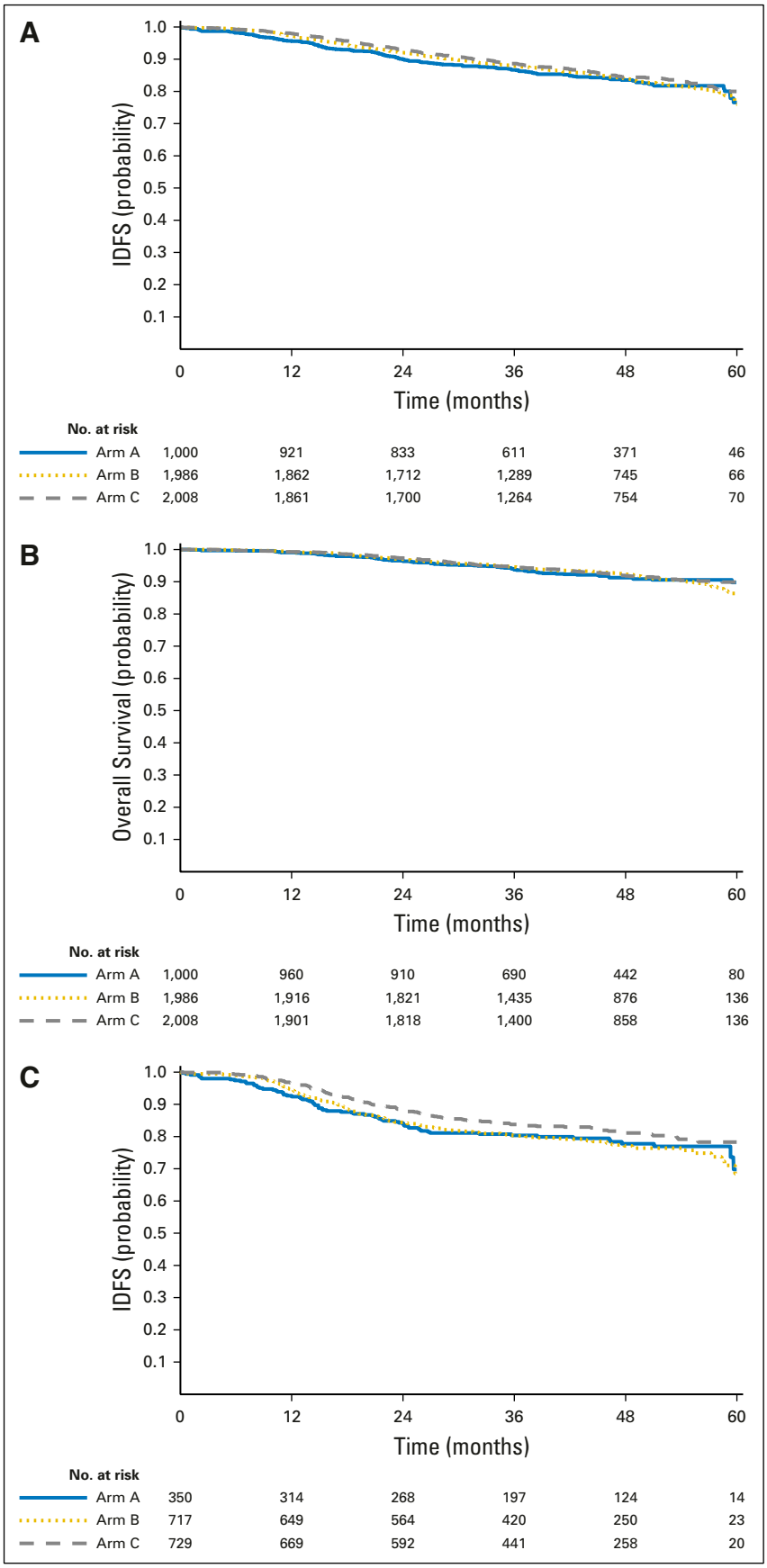

Fig 2. Five-year (A) invasive disease–free survival (IDFS) and (B) overall survival rates were similar across all treatment arms. (C) IDFS in patients with estrogen receptor– and progesterone receptor–negative disease. Hazard ratios for IDFS favored bevacizumab in patients with hormone receptor–negative tumors receiving longer duration bevacizumab therapy, but this difference did not reach significance.

Table 3. Select Adverse Events

Adverse Event	% of Patients															
	Arm A (n = 972)				Arm B (n = 1,922)				Arm C (bevacizumab cycles 1 to 8; n = 1,942)				Arm D (bevacizumab cycles 9 to 18 of arm C; n = 1,168)			
	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	NA	NA	1	—	NA	NA	2	—	NA	NA	1	—	NA	NA	< 1	—
Neutropenia	NA	NA	17	—	NA	NA	20	—	NA	NA	20	—	NA	NA	1	—
Febrile neutropenia	NA	3	< 1	—	NA	4	< 1	—	NA	4	1	—	NA	NA	—	—
Thrombocytopenia	NA	NA	< 1	—	NA	NA	1	—	NA	NA	1	—	NA	NA	—	—
Nausea	NA	3	—	—	NA	3	—	—	NA	3	—	—	NA	< 1	—	—
Mucositis (oral)	NA	1	< 1	—	NA	3	—	—	NA	3	< 1	—	NA	—	—	—
Increased AST/ALT	NA	NA	< 1	—	NA	NA	< 1	—	NA	NA	< 1	—	NA	NA	< 1	—
Fatigue	NA	7	< 1	—	NA	10	< 1	—	NA	10	< 1	—	NA	3	—	—
Sensory neuropathy	19	8	< 1	—	19	8	< 1	—	17	9	< 1	—	16	4	< 1	—
Arthralgia/joint pain	NA	3	—	—	NA	2	< 1	—	NA	2	< 1	—	NA	3	< 1	—
Myalgia/muscle pain	NA	2	< 1	—	NA	2	< 1	—	NA	1	< 1	—	NA	2	—	—
Dyspnea	5	3	< 1	—	6	3	1	—	6	3	< 1	—	2	1	< 1	—
Pneumonitis	NA	1	—	—	NA	1	< 1	—	NA	1	< 1	—	NA	—	—	—
Hypertension	NA	2	< 1	—	NA	8	< 1	—	NA	7	< 1	—	NA	11	< 1	—
Headache	NA	2	—	—	NA	4	< 1	—	NA	3	< 1	—	NA	2	< 1	—
Left ventricular diastolic dysfunction	< 1	< 1	—	—	1	< 1	—	—	1	< 1	—	—	1	< 1	—	—
Left ventricular systolic dysfunction*	4	1	—	—	5	2	< 1	—	4	2	< 1	—	5	3	< 1	—
Proteinuria	1	—	—	—	1	< 1	—	—	1	< 1	—	—	3	2	—	—
Thrombosis/embolism	1	3	1	—	1	2	1	< 1	1	2	1	—	1	1	< 1	< 1
Hemorrhage (nose)	< 1	—	—	—	1	< 1	—	—	2	< 1	—	—	1	< 1	—	—
Hemorrhage (rectal)	< 1	< 1	—	—	< 1	< 1	—	—	1	< 1	—	—	< 1	< 1	—	—
Colon/appendix perforation	—	< 1	—	—	—	—	< 1	—	—	< 1	< 1	—	—	—	< 1	—
Wound dehiscence, noninfectious	NA	< 1	—	—	NA	1	—	—	NA	1	—	—	NA	1	—	—
Allergic reaction	NA	1	< 1	—	NA	1	—	—	NA	1	< 1	—	NA	< 1	—	—
CNS ischemia	—	—	< 1	< 1	—	< 1	< 1	—	—	< 1	< 1	—	—	< 1	< 1	—
CNS hemorrhage	< 1	—	—	—	< 1	—	—	—	< 1	< 1	—	< 1	—	—	< 1	—
Leukoencephalopathy	—	—	—	—	—	—	< 1	—	—	—	—	—	—	—	—	—

NOTE. Worst adverse event reported per patient based on Common Terminology Criteria for Adverse Events (version 3.0). Only patients who began protocol treatment in each arm are included in this summary. Adverse event reporting in the trial was limited to ≥ grade 4 hematologic events, ≥ grade 2 nonhematologic events for a group of specific adverse events, and ≥ grade 3 nonhematologic events otherwise. All attributions were included.

Abbreviation: NA, not applicable (grade not collected for that adverse event and only appears in the table when events are present for the other reportable grades).

*Common Terminology Criteria for Adverse Events grade 3 left ventricular systolic dysfunction includes decreases in left ventricular ejection fraction to an absolute value between 20% and 40% and/or symptoms of congestive heart failure.

rate reaches a critical, albeit arbitrary, threshold should be considered.

Some may argue that E5103 was started prematurely and that we should have demanded more data in the metastatic setting before embarking on such a large adjuvant trial. At the time E5103 was designed, early survival data from E2100[5] were quite promising, but the data were not final and would not have reached a threshold for early stopping had OS been the primary end point. Preliminary results from the Avastin Plus Docetaxel Chemotherapy (AVADO) trial[6] reported a positive but less striking improvement in progression-free survival. Of course, once negative results are in hand, it is easy to argue that the basis was not strong enough to support a trial of this magnitude. In reality, we have started adjuvant trials with much less supporting data (eg, studying trastuzumab or pembrolizumab). Even when the supporting data are stronger and OS in the metastatic is improved, adjuvant results may be disappointing (eg, as with lapatinib or pertuzumab). E5103 reminds us that adjuvant trials will always entail risk.

E5103 adds another cautionary note to those who have embraced an improvement in pathologic complete response (pCR) as predictive of longer term benefit. Four neoadjuvant trials found that adding bevacizumab to chemotherapy in patients with HER2-negative disease improved pCR,[48-51] and with longer follow-up, one[52] reported a survival benefit. Yet, the adjuvant trials have been resolutely negative. Is this discordance between neoadjuvant and adjuvant results an aberration? A similar discordance was seen in trials of lapatanib[53,54] and, some would argue, pertuzumab, where the striking improvement in pCR[55] barely reached significance in the adjuvant setting.[56] Indeed, an analysis across trials did not find an association between increases in pCR and improvements in event-free survival.[57]

Finally, E5103 reminds us of the importance of publically funded research and the resulting public and private partnership. Some may question whether public support should be granted to a trial with registration intent. However, E5103 generated a richly annotated biospecimen bank that, combined with ongoing follow-up, will support important studies. Analyses embedded within E5103 have already taught us the effect of unblinding and random assignment to placebo in clinical trial participants[58] and studied biomarkers predictive of amenorrhea.[59] Germline DNA analyses have identified single nucleotide polymorphisms associated with

increased risk of common chemotherapy-related toxicities including peripheral sensory neuropathy[60,61] and anthracycline-induced cardiotoxicity,[62] whereas companion studies have quantified the effect of such biomarkers on physician recommendation and patient preference for different treatments.[63,64] An associated biobank identified a marker for late relapse, paving the way for trials of delayed intervention.[65] These correlative studies, unlikely to have been supported in a trial funded exclusively by industry, expand the effect of E5103 far beyond disproving the original clinical hypothesis.

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Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Double-Blind Phase III Trial of Adjuvant Chemotherapy With and Without Bevacizumab in Patients With Lymph Node–Positive and High-Risk Lymph Node–Negative Breast Cancer (E5103)

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Appendix

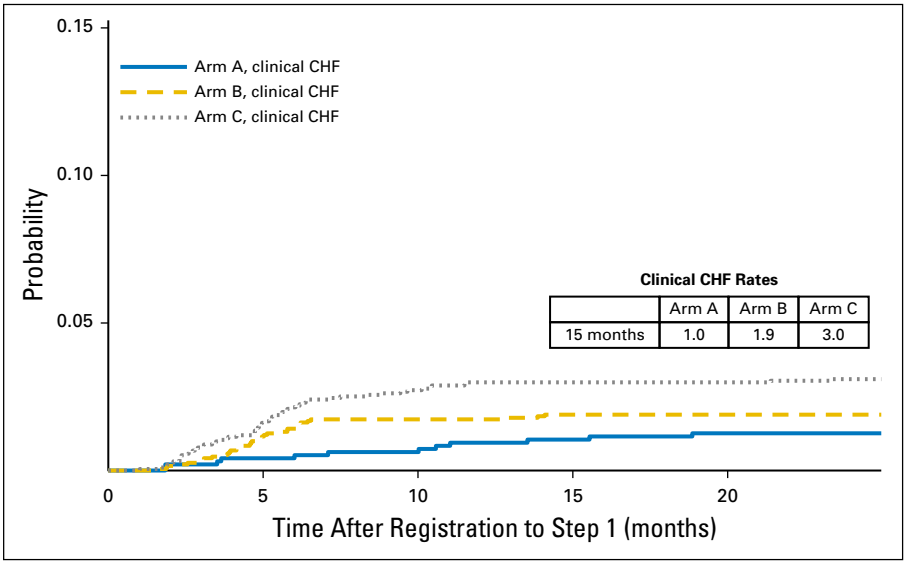

Fig A1. Cumulative incidence of clinical congestive heart failure (CHF). Bevacizumab increased the risk of clinical CHF in a time- and exposure-dependent manner. Most events occurred during bevacizumab therapy.

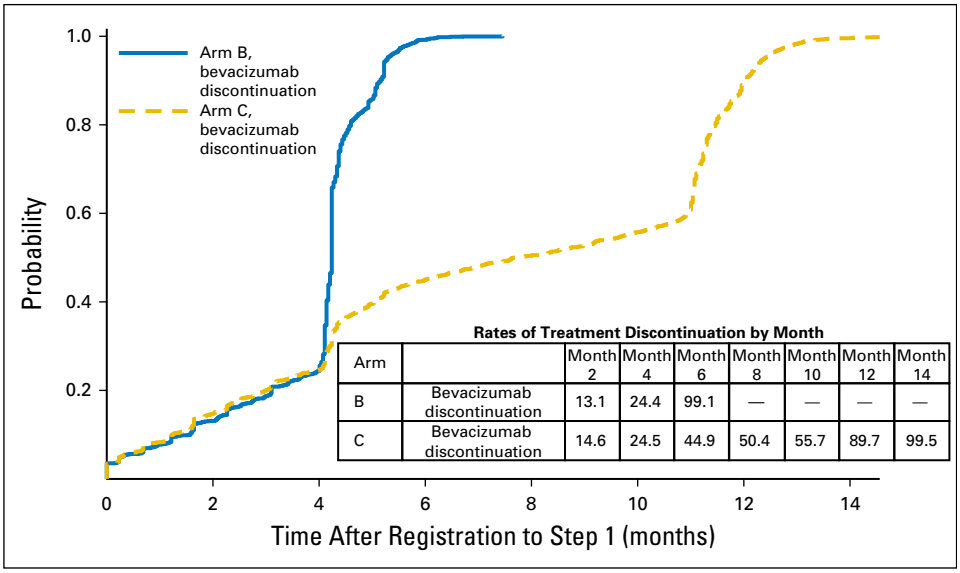

Fig A2. Timing of bevacizumab discontinuation. Early discontinuation of bevacizumab is common, with > 25% of patients stopping therapy before completing chemotherapy. Only 29% of patients (585 of 2,008 patients) randomly assigned to arm C completed all prescribed bevacizumab therapy.

Table A1. Sequential Assessment of LVEF

LVEF	Arm A	Arm B	Arm C	Arm D*
Baseline and cycle 5†				
No. of patients	909	1,728	1,744	
Median baseline LVEF, % (95% CI)	64 (49 to 87)	64 (50 to 89)	64 (50 to 85)	
Median LVEF at cycle 5, % (95% CI)	63 (37 to 89)	62 (27 to 89)	62 (30 to 87)	
LVEF decrease > 10%, No. (%)	69 (8)	152 (9)	172 (10)	
LVEF decrease > 10% to < LLN, No. (%)	8 (1)	28 (2)	39 (2)	
Baseline and EOC/cycle 9				
No. of patients	865	1,715	553‡	1,148
Median LVEF at EOC/cycle 9, % (95% CI)	61 (35 to 90)	60 (10 to 94)	60 (18 to 83)	60 (25 to 90)
LVEF decrease > 10%, No. (%)	99 (12)	306 (18)	125 (23)	168 (15)
LVEF decrease > 10% to < LLN, No. (%)	21 (2)	107 (6)	64 (12)	40 (3)
Baseline and cycle 15				
No. of patients				899
Median LVEF at cycle 15, % (95% CI)				60 (30 to 83)
LVEF decrease > 10%, No. (%)				148 (16)
LVEF decrease > 10% to < LLN, No. (%)				27 (3)
Baseline and 12 months/EOB				
No. of patients	683	1,382	444‡	1,029
Median LVEF at 12 months/EOB, % (95% CI)	60 (25 to 82)	61 (35 to 85)	61 (20 to 84)	60 (23 to 84)
LVEF decrease > 10%, No. (%)	88 (13)	183 (13)	86 (19)	184 (18)
LVEF decrease > 10% to < LLN, No. (%)	21 (3)	42 (3)	36 (8)	52 (5)

Abbreviations: EOB, end of bevacizumab; EOC, end of chemotherapy; LLN, lower limit of normal; LVEF, left ventricular ejection fraction.
*Arm D includes patients randomly assigned to arm C who proceeded to bevacizumab monotherapy.
†A prespecified stopping rule that monitored for difference at cycle 5 among the first 300 patients who received protocol therapy between arms A and C or between arms A and B plus C with respect to proportion of patients with an absolute decrease in LVEF > 10% to less than LLN was not met.
‡Patients randomly assigned to arm C who did not proceed to bevacizumab monotherapy.