biomarkers that can predict response means a commitment to conducting correlative studies in large clinical trials.

It is likely that novel drugs for cancer coming to market will continue to have stratospheric price tags.[10] It is also likely that novel agents will achieve, at best, incremental improvements in PFS that often will not translate into improvements in overall survival. We will serve our patients best by designing trials that permit us to identify which patients have the highest likelihood of deriving a meaningful survival benefit from a novel agent. Correlative science for effective patient selection may be the key to cost-effective treatment of cancer in the biologic therapy era.

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Bevacizumab for Advanced Breast Cancer: All Tied Up With a RIBBON?

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See accompanying editorial on page 1230 and articles on pages 1247 and 1252

It has been more than 5 years since Eastern Cooperative Oncology Group (ECOG) 2100 showed that adding bevacizumab to paclitaxel as first-line treatment for metastatic breast cancer nearly doubled the tumor response rates and time to progression (TTP).[1,2] Since then, there have been more questions than answers regarding the role of bevacizumab in advanced breast cancer. Did ECOG E2100 establish a general principle regarding chemotherapy and bevacizumab, or were the findings unique to once-a-week paclitaxel? Who was most likely to benefit from bevacizumab? How safe would this agent be in advanced breast cancer? Was there a survival advantage and why or why not? Was bevacizumab *an* option or *the* option for initial treatment of metastatic breast cancer? With results now available from multiple trials of chemotherapy with or without bevacizumab for metastatic breast cancer, it seems reasonable to reassess the lessons from and role for this drug in patients with breast cancer.

Two placebo-controlled, randomized phase III trials of first-line chemotherapy (Avastin and Docetaxel [AVADO][3] and Regimens in Bevacizumab for Breast Oncology [RIBBON] -1[4]) were designed to validate the findings of ECOG E2100 while exploring the use of bevacizumab with chemotherapy backbones that differed from weekly paclitaxel. AVADO paired bevacizumab with docetaxel given every 3 weeks. RIBBON-1 offered investigators the choice of capecitabine, once every three weeks taxane (docetaxel or nab-paclitaxel), or anthracycline-cyclophosphamide combinations—each given with or without bevacizumab. These trials demonstrated statistically significant improvement in progression-free survival (PFS), their primary end point, and in response rates with the addition of bevacizumab to chemotherapy.

But sequels are rarely as good as the original, and so it is with bevacizumab in advanced breast cancer. Although the AVADO and RIBBON-1 trials produced *P* values that were statistically significant, the outcomes were arguably not clinically compelling (Table 1). Improvements in PFS and response rates, which are standard if imperfect measures of antitumor activity, were qualitatively and quantitatively smaller in the later trials than in ECOG E2100. Of course, comparing results among individual studies is fraught with problems because of differences in agents and schemas, patient populations, and prior therapies. Nonetheless, these results fell short of the high expectations created by ECOG E2100, and combined with the lack of overall survival advantage in any of the reported trials of bevacizumab in breast cancer, the results generated yet more uncertainty about how to use bevacizumab in advanced breast cancer.

RIBBON-1 clarifies many aspects of the toxicity of bevacizumab in breast cancer regimens. There is a greater risk of hypertension with any bevacizumab regimen, and adverse effects such as headache and nasal congestion, although rarely scored as grade 3 or 4, are also more frequent with bevacizumab. When bevacizumab is paired with taxanes taken once every three weeks, there is a greater chance of neutropenia. Altogether, between 34% and 57% of patients receiving bevacizumab-based treatment in RIBBON-1 experienced toxicity ≥ grade 3, which suggests that there may be limitations for adding extra therapy to these combinations. For instance, attempts to add sunitinib,

Table 1. Randomized Trials of Chemotherapy With or Without Bevacizumab in First-Line Treatment of Metastatic Breast Cancer

Study	Agent	PFS Hazard Ratio*	Chemotherapy		Chemotherapy Plus Bevacizumab	
			Median PFS (months)	Response Rate (%)	Median PFS (months)	Response Rate (%)
ECOG E2100 (N = 722)	Paclitaxel weekly with or without bevacizumab†	0.48	5.8	22	11.3	49
AVADO (N = 736)	Docetaxel with or without bevacizumab‡	0.67	8.2	46	10.1	64
RIBBON-1 (N = 1,237)	Capecitabine with or without bevacizumab‡	0.69	5.7	24	8.6	35
	Taxane (docetaxel or nab-paclitaxel) or anthracycline with or without bevacizumab‡	0.64	8.0	38	9.2	51

Abbreviations: PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; AVADO, Avastin and Docetaxel; RIBBON, Regimens in Bevacizumab for Breast Oncology.
*All hazard ratio *P* values were < .001.
†Bevacizumab dosed at 10 mg/kg every 2 weeks; data from reference 2.
‡Bevacizumab dosed at 15 mg/kg every 3 weeks.

the multitargeted tyrosine kinase inhibitor, to chemotherapy with bevacizumab have proven unsuccessful as a result of extensive toxicity in patients with breast cancer.[5]

Because of vascular-related adverse effects of bevacizumab, congestive heart failure remains a potential concern. Regardless of bevacizumab administration, patients treated with anthracyclines in RIBBON-1 had a 6% risk of congestive heart failure (CHF), a rate that precludes serious consideration of anthracyclines and bevacizumab in metastatic disease, especially given the negligible clinical benefit. Of more subtle concern is the increased risk of CHF among patients receiving bevacizumab with either taxanes taken once every three weeks or with capecitabine treatment. A recent meta-analysis has confirmed a bevacizumab-associated increased risk of CHF on the order of 1% to 2% compared with chemotherapy alone in metastatic breast cancer.[6]

To date, subset analyses have failed to convincingly identify which patients or tumor types warrant, or could be spared, bevacizumab-based treatment, although there are no meaningful data for use of the agent in HER2-overexpressing breast cancers. In all three randomized trials, hazard ratios for TTP among patients with triple-negative breast cancers were similar to those for patients with hormone-receptor positive tumors, although the absolute gains were smaller because of the more rapid growth rates of triple-negative cancers. Patients enrolled onto RIBBON-1 who were offered capecitabine were more likely to have previously had adjuvant chemotherapy (including anthracyclines and taxanes) than were those patients who were offered the anthracycline- or taxane-based treatments. Such patient selection on the basis of prior therapy likely accounts for the shorter overall PFS among the capecitabine cohort. In RIBBON-1, bevacizumab was able to add to the response rates and TTP seen with capecitabine. In a separate randomized study in which all the patients had previously received anthracyclines and taxanes, bevacizumab did not yield any benefit beyond that seen with capecitabine alone.[7] It is unclear how these considerations of prior therapy contributed to different results when bevacizumab has been paired with capecitabine. In summary, it seems that neither prior adjuvant therapy nor tumor subtype will serve as selection factors for bevacizumab-based treatment. Despite being a targeted therapy, bevacizumab lacks a robust, predictive, biologic, or clinical marker of activity.

Bevacizumab has not enhanced survival in advanced breast cancer. Crossover likely confounds survival analyses from RIBBON-1, but it was not a major issue in other studies. The lack of a survival difference is more likely rooted in the poorly correlated and weak relationship between PFS and overall survival in most studies of advanced breast cancer[8] as well as in the efficacy of subsequent lines of chemotherapy, the implicit development of resistance to bevacizumab plus chemotherapy, and the modest clinical effects of bevacizumab. In a world in which patients with breast cancer average between three and six lines of chemotherapy for metastatic disease, it is unclear that overall survival is a fair benchmark for establishing the clinical activity of new agents. Conversely, the current treatment paradigm, which includes multiple lines of therapy, suggests that TTP in the first-line treatment may not be a very important end point for evaluating novel regimens in the absence of strong considerations of toxicity and quality of life.

As has been widely discussed in the popular press,[9] bevacizumab is an expensive drug, even by the standards of oncology treatments and particularly in the absence of a survival advantage. A careful economic analysis in 2009 that was based on efficacy data from ECOG E2100 and cost estimates from Zurich, Switzerland, suggested an incremental cost-effectiveness ratio of 189,427 € per quality-adjusted life-year—well in excess of $200,000 per quality-adjusted life-year in dollar terms.[10] Because the dominant cost-item in this model is bevacizumab itself and because the clinical benefits seen in the AVADO and RIBBON-1 trials are of lower absolute magnitude than in ECOG E2100 with comparable or greater rates of toxicity, it is unlikely that any of the chemotherapy regimens used with bevacizumab in AVADO or RIBBON-1 would have a lower cost-effectiveness ratio. Clear norms for cost-effectiveness and treatment recommendation do not exist, and willingness-to-pay thresholds vary from country to country and within health care systems. Nonetheless, the cost of bevacizumab is likely to be a consideration in its use for many patients worldwide.

A dilemma in assessing the role of bevacizumab lies in the value placed on different end points in clinical studies. Given the relatively weak relationships between response, PFS, and overall survival, the multiple treatment agents and lines of therapy offered to patients, and the different trajectories of tumor progression in different tumor subsets, it seems likely that there are different end points that are of interest to clinicians, patients, and regulators, respectively. End points most critical to patients include survival, but they also include tolerability, symptom relief, convenience, and time until initiation of next

treatment. None of these latter end points are routinely quantified in clinical trials, which makes it challenging to ascertain the real worthiness of new agents and regimens.

Which is the true bevacizumab result in first-line treatment of metastatic breast cancer: the leap of ECOG E2100 or the narrow steps forward of AVADO and RIBBON-1? If bevacizumab does improve response rates and TTP, how best should the drug be used? At present, weekly paclitaxel plus bevacizumab as delivered in ECOG E2100 is *an* option for first-line treatment of advanced breast cancer, and this seems preferred to other bevacizumab-based treatment options on the basis of its tolerability and superior performance in that study. In this regard, AVADO and RIBBON-1 have been valuable in demonstrating that the benefits for adding bevacizumab to every 3 week docetaxel or nab-paclitaxel therapy or to anthracycline-based chemotherapy are rather minimal and are associated with greater toxicity than is seen using paclitaxel once per week. There may be modest gain, at best, in adding bevacizumab to capecitabine, but the existence of a previous negative study makes this a less appealing option. Real-world performance data on bevacizumab-chemotherapy combinations would be helpful and may be found in the Avastin Therapy for Advanced Breast Cancer (ATHENA) study, a prospective registry of 2,251 patients receiving various first-line chemotherapy regimens with bevacizumab.[11] The results from such registry studies are subject to the uncharacterized vagaries of patient and treatment selection and need to be interpreted cautiously. However, a back-of-the-envelope comparative effectiveness analysis that considers TTP, the incidence of grade 3 or greater toxicity, and response rates suggests that paclitaxel would be the chemotherapy of choice with bevacizumab, striking a better balance of efficacy and tolerability than docetaxel, capecitabine, or vinorelbine do (Table 2). Collectively, ECOG E2100, AVADO, RIBBON-1, and ATHENA underscore the principle that, if given, bevacizumab should not be an off-the-shelf addition to any established chemotherapy regimens; it needs to be administered in the context of specific agents, doses, and schedules.

It is a cliché to end a clinical editorial with the admonishment that the current study underscores the need for more research, and that call seems particularly hollow when five randomized trials (three in the first-line setting), a large prospective treatment registry, and extensive reviews by American, British, and European regulatory agencies are available. But as a clinical and research community, we need to determine whether bevacizumab plus chemotherapy is a genuine advance for metastatic breast cancer as well as in whom, at what cost, and whether or not bevacizumab-based treatment can serve as a practical foundation for subsequent developments in the field. These assessments will require judgment and perspective as much as data, because the metrics for gauging success may be defined differently by various stakeholders. Recent discordant recommendations from various expert panels and regulatory agencies, including evolving use of vague definitions of substantial benefit or risk, underscore the inconsistencies in interpreting bevacizumab data. The US Food and Drug Administration, having granted accelerated approval based on the magnitude of improvement in PFS in E2100, found that the AVADO and RIBBON1 trials "failed to confirm the magnitude of benefit" and that the "modest benefit observed in breast cancer trials to-date with the substantial adverse reactions observed in breast cancer trials fail to provide a favorable risk-benefit profile to support continuing marketing."[12] The European Medicines Agency (EMA), having previously approved bevacizumab in combination with taxane-based chemotherapy, changed their recommendations based on the AVADO and RIBBON1 data. The EMA noted that docetaxel and bevacizumab "produced a much smaller increase in progression-free survival" when compared across different trials to paclitaxel plus bevacizumab. With regard to capecitabine, which EMA considered a drug aimed at patients for whom a relatively mild treatment is appropriate and thus where "increased toxicity" was also considered important, the agency noted that although adding bevacizumab "produced a modest improvement in progression-free survival . . . no meaningful effects were observed for other measurements such as overall survival or health-related quality of life." EMA stated that paclitaxel plus bevacizumab "convincingly" prolonged PFS without negative effects on overall survival and "concluded that the benefit-risk balance for this combination remains positive."[13] The National Comprehensive Cancer Network "affirmed its existing recommendation of bevacizumab in combination with paclitaxel" as a preferred combination, a designation reflecting a "balance of efficacy, toxicity, and treatment schedules of the drugs."[14] Finally, the National Institute for Health and Clinical Excellence in the United Kingdom found it "likely that bevacizumab plus paclitaxel improved progression-free survival relative to weekly paclitaxel, but that there was no robust evidence that bevacizumab plus paclitaxel improved overall survival" and, citing a "most plausible" cost estimate of bevacizumab plus paclitaxel versus paclitaxel alone of £110,000 to £259,000 per quality-adjusted life-year, concluded that the regimen was "not a cost effective use of NHS (National Health Service) resources."[15] These differing verdicts exemplify how varying perspectives on endpoints and costs can affect treatment recommendations. Ideally, these regulatory and expert panel decisions should stimulate important discussions between clinicians, patients, investigators, regulators, and third-party payers. Without greater clarity on these pressing questions, bevacizumab may prove to be an expensive cul-de-sac for advanced breast cancer.

Table 2. Clinical Outcomes in ATHENA Registry of First-Line Chemotherapy and Bevacizumab

Agent Paired With Bevacizumab	No. of Patients	SAE (any grade; %)	AE Grade ≥ 3 (%)	Response Rate (%)	Median TTP (months)
Paclitaxel	777	24	48	49	9.8
Docetaxel	742	35	60	59	8.8
Capecitabine	102	22	45	36	7.0
Vinorelbine	57	37	58	28	8.4

NOTE. Data adapted.[11]
Abbreviations: ATHENA, Avastin Therapy for Advanced Breast Cancer; SAE, serious adverse event; AE, adverse event; TTP, time to progression.

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