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Primary Results of ROSE/TRIO-12, a Randomized Placebo-Controlled Phase III Trial Evaluating the Addition of Ramucirumab to First-Line Docetaxel Chemotherapy in Metastatic Breast Cancer

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See accompanying editorial on page 133

ABSTRACT

Purpose

Currently, antiangiogenic strategies in metastatic breast cancer have demonstrated modest improvements in progression-free survival (PFS) but not improved quality or duration of survival, warranting evaluation of new agents in a placebo-controlled setting. Ramucirumab is a human immunoglobulin G1 antibody that binds vascular endothelial growth factor receptor-2 and blocks ligand-stimulated activation. The ROSE/TRIO-012 trial evaluated ramucirumab with docetaxel in unresectable, locally recurrent, or metastatic breast cancer.

Patients and Methods

In this double-blind, placebo-controlled, randomized, multinational phase III trial, 1,144 patients with human epidermal growth factor receptor 2 (HER2) –negative breast cancer who had not received cytotoxic chemotherapy in the advanced setting were randomly assigned at a two-to-one ratio to receive docetaxel 75 mg/m² plus ramucirumab 10 mg/kg or docetaxel 75 mg/m² plus placebo once every 3 weeks. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria. Patients were stratified by previous taxane therapy, visceral metastasis, hormone receptor status, and geographic region. An independent data monitoring committee oversaw the trial. The primary end point was investigator-assessed PFS.

Results

Median PFS in patients treated with ramucirumab plus docetaxel was 9.5 months, compared with 8.2 months in patients who received placebo plus docetaxel (hazard ratio [HR], 0.88; *P* = .077). Median overall survival was 27.3 months in patients who received ramucirumab plus docetaxel, compared with 27.2 months in patients who received placebo plus docetaxel (HR, 1.01; *P* = .915). Toxicities seen at significantly higher rates in patients receiving ramucirumab included fatigue, hypertension, febrile neutropenia, palmar-plantar erythrodysesthesia syndrome, and stomatitis.

Conclusion

Addition of ramucirumab to docetaxel in HER2-negative advanced breast cancer did not meaningfully improve important clinical outcomes.

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INTRODUCTION

Treatment of cancer using antiangiogenic agents is based on several hypotheses: first, there is a continuously expanding network of blood vessel capillaries supplying nutrients and oxygen to support tumor growth; second, the process of **angiogenesis** can be blocked therapeutically without causing excessive host toxicity; and third, such interventions will be therapeutic by either inducing

a state of tumor dormancy or conferring increased chemosensitivity.

Discovery of the **vascular endothelial growth factor (VEGF)** family of angiogenesis stimulators (VEGF-A, -B, -C, and -D and placental growth factor) and development of several VEGF pathway-targeting agents have permitted these hypotheses to be tested in clinical studies. Although the clinical benefits of antiangiogenic agents have been established in colorectal cancer,¹ renal cell carcinoma,^{2,3}

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cervical cancer,⁴ epithelial ovarian cancer,⁵⁻⁷ and non-small-cell lung carcinoma,^{8,9} they have not yet been shown to improve quality or duration of life in metastatic breast cancer.¹⁰

VEGF receptor-2 (VEGFR-2) is associated with breast cancer metastasis and poor prognosis and is believed to be the principal mediator of angiogenesis, endothelial proliferation, permeability, and survival in breast cancer.¹¹⁻¹⁴ Ramucirumab (IMC-1121B; ImClone Systems, Branchburg, NJ) is a fully human immunoglobulin G1 monoclonal antibody that binds the extracellular domain of VEGFR-2, blocking interaction between VEGF and VEGFR-2.¹⁵ Clinical studies have shown safety across a wide range of ramucirumab doses, and early studies have suggested activity in a variety of tumor types.^{8,16,17} Randomized studies with ramucirumab have demonstrated improvements in overall survival (OS) in metastatic gastric cancer¹⁶ and advanced non-small-cell lung cancer.^{8,12} We sought to evaluate whether ramucirumab plus docetaxel treatment would prolong progression-free survival (PFS) or OS in patients with human epidermal growth factor receptor 2 (HER2)–negative breast cancer when compared with placebo plus docetaxel treatment.

PATIENTS AND METHODS

Patient Eligibility

Patients eligible for enrollment were women age ≥ 18 years with HER2-negative recurrent or metastatic carcinoma of the breast who had not received cytotoxic chemotherapy or biologic therapy in the advanced setting. Additional inclusion criteria included completion of neoadjuvant taxane therapy ≥ 6 months, adjuvant biologic therapy ≥ 6 weeks, or radiotherapy ≥ 3 weeks before random assignment; measurable and/or nonmeasurable disease; left ventricular ejection fraction within normal institutional ranges; adequate hematologic functions; adequate hepatic function; adequate coagulation function; urinary protein $\leq 1+$ on dipstick or routine urinalysis; serum creatinine $\leq 1.5\times$ upper limit of normal; resolution to grade ≤ 1 by National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0)¹⁸ of all clinically significant toxicities resulting from prior chemotherapy, surgery, radiotherapy, or hormonal therapy, with the exception of peripheral neuropathy, which must have resolved to grade ≤ 2 ; and Eastern Cooperative Oncology Group performance status of 0 to 1 (Table 1).

Patients were excluded from the study if they had a concurrent active malignancy other than breast adenocarcinoma; brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis or new evidence of brain or leptomeningeal disease; known sensitivity to drugs formulated with polysorbate 80 or agents of biologic composition similar to that of IMC-1121B; uncontrolled hereditary or acquired bleeding or thrombotic disorders or active, high-risk bleeding; ongoing or active infection requiring parenteral antibiotic, antifungal, or antiviral therapy; serious uncontrolled medical disorders including but not limited to hypertension, symptomatic congestive heart failure, psychiatric illness, and HIV infection or AIDS-related illness; or chronic diarrheal disease within 6 months of study enrollment.

Study Design and Conduct

The study was designed by academic investigators in collaboration with Eli Lilly/ImClone Systems. Translational Research in Oncology (TRIO), an academically led international clinical trial network, conducted this Eli Lilly/ImClone Systems–sponsored trial.

In this multicenter, double-blind phase III trial—ROSE (Ramucirumab Overall Survival Evaluation)/TRIO-012—1,144 patients with HER2-negative, unresectable, locally recurrent, or metastatic breast cancer were randomly assigned at a ratio of two-to-one to receive docetaxel 75 mg/m² plus ramucirumab 10 mg/kg intravenously (IV) on day 1 of every 3-week cycle or docetaxel 75 mg/m² plus placebo IV on day 1 of every 3-week cycle (IV infusion time was 1 hour per agent; Fig 1). Randomization was stratified by prior taxane therapy, visceral metastasis status, hormone receptor status, and geographic region.

Table 1. ITT Population Baseline Demographic and Clinical Characteristics

Characteristic	RAM Plus DOC Arm (%)	PBO Plus DOC Arm (%)
Total No. of patients	759	385
Age, years		
Median	54	54
Range	24-82	29-81
ECOG PS		
0	58	62
1	42	37
No. of metastatic sites		
< 3	48	52
≥ 3	52	48
Visceral involvement	71	72
Prior adjuvant taxane therapy		
Yes	26	27
No	74	73
Geographic region		
North or South America	24	24
Europe, Australia, or New Zealand	64	64
Asia, Middle East, or Africa	12	13
Hormone receptor status		
ER positive	72	75
ER negative or unknown	28*	25*
PR positive	53	61
PR negative or unknown	47†	39†
HER2 negative (IHC 0-1+ or ISH negative)	100	99.7‡
Triple negative		
Yes	25	22
No	75	78

Abbreviations: DOC, docetaxel; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intent to treat; PBO, placebo; PR, progesterone receptor; PS, performance status; RAM, ramucirumab.

*In RAM group, three patients (0.4%) had unknown ER status.

†In RAM group, 19 patients (2.5%), and in PBO group, 10 patients (2.6%) had unknown PR status at study initiation.

‡One patient had unknown HER2 status at study initiation.

Every patient or patient representative signed an ethics committee–approved informed consent form before any study-specific procedures were performed.

Study Assessments

Treatment continued until investigator-determined evidence of disease progression using RECIST criteria,¹⁹ unacceptable toxicity, or other withdrawal criteria were met. All patients were assessed at regularly scheduled intervals (every 6 weeks until disease progression and every 6 months thereafter) until death or for at least 36 months after the end of the study treatment. Progression was also examined by an independent review committee. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).¹⁸ The Functional Assessment of Cancer Therapy–Breast questionnaire (version 4.0)²⁰ was completed by patients for quality-of-life assessment; validated translations were used when required.

Statistical Analyses

An independent data monitoring committee oversaw conduct of the trial, the efficacy database resided with TRIO, and primary statistical analysis was performed by a statistical office (International Drug Development Institute) independent of the sponsors. The primary end point was investigator-assessed PFS.

The minimum sample size of 1,113 patients was determined using a group sequential analysis methodology (as implemented in East software [version 5.2]; Cytel, Cambridge, MA). Median PFS in the control group (placebo plus docetaxel) was assumed to be 6 months, and a 2-month (33%) improvement in median PFS was deemed of clinical interest; although the

Fig 1. ROSE/TRIO-12 CONSORT diagram and study design. Patients with recurrent or metastatic human epidermal growth factor receptor 2–negative breast cancer who had not received cytotoxic chemotherapy in advanced setting were randomly assigned at two-to-one ratio to treatment or placebo group and assessed for progression-free and overall survival (OS). IV, intravenously; PD, progressive disease. (*) One patient in placebo group received ramucirumab plus docetaxel in cycle one and therefore is included in treatment safety population.

primary hypothesis was tested with an overall two-tailed significance level of .05, sample size was determined with a two-tailed significance level of .01, and the power of the trial was set to 86% for a PFS hazard ratio (HR) of 0.75.

Statistical tests were performed using a two-sided .05 significance level. Time-to-event end points were analyzed using stratified Kaplan-Meier methods, and stratified Cox regression was used to estimate HRs and 95% CIs. For categorical end points, such as response, the stratified Mantel-Haenszel test was used. Fisher's exact test was used to compare adverse events (all grades and grades ≥ 3).

RESULTS

Between August 2008 and December 2011, a total of 1,144 patients were randomly assigned. After a median follow-up of 18.6 months, there were sufficient events to trigger this analysis. The pri-

mary end point was investigator-assessed PFS. Secondary end points included OS, time to progression (TTP), overall response metrics, safety, and quality of life. At baseline, 76% of patients had hormone receptor–positive and 24% had triple-negative breast cancers (Table 1). Patients in the ramucirumab group received a median of nine cycles of ramucirumab (range, zero to 58 cycles) and eight cycles of docetaxel (range, one to 40 cycles); those in the placebo arm received a median of nine cycles of placebo (range, one to 52 cycles) and eight cycles of docetaxel (range, one to 52 cycles; Table 2).

There was no significant difference in the protocol-specified primary end point of investigator-assessed PFS between the ramucirumab and placebo arms. Investigator-assessed median PFS in the ramucirumab group was 9.5 months (95% CI, 8.3 to 9.8 months), compared with 8.2 months in the placebo group (95% CI, 7.1 to 8.5

Table 2. Treatment Administration in Safety Population

Characteristic	RAM Plus DOC Arm (n = 752)		PBO Plus DOC Arm (n = 382)	
	RAM	DOC	PBO	DOC
Duration of treatment, weeks				
Median	28	24	27	24
Range	3-181	3-137	3-170	3-170
No. of cycles*				
Median	9	8	9	8
Range	0-58†	1-40	1-52	1-52
Relative dose-intensity, %				
Median	97	97	97	98
Range	30-114	54-107	74-107	61-103

Abbreviations: DOC, docetaxel; PBO, placebo; RAM, ramucirumab.
 *Cycle consisted of 21 days.
 †One patient in RAM plus DOC arm started docetaxel treatment but did not receive RAM.

months), resulting in an HR of 0.88 (95% CI, 0.75 to 1.01; $P = .077$; Fig 2A). Efficacy results in clinical subgroups were consistent with overall PFS results (Fig 3). As per protocol, a sensitivity analysis using PFS determined by independent radiologic review demonstrated a median PFS of 11.1 months (95% CI, 9.9 to 11.8 months) in the ramucirumab group, compared with 8.5 months (95% CI, 7.9 to 9.8 months) in the placebo group (HR, 0.79; 95% CI, 0.67 to 0.94; $P = .008$; Fig 2B).

At the interim analysis, there was no significant difference in OS between the treatment arms. Median OS was 27.3 months (95% CI, 23.6 to 29.1 months) in the ramucirumab group, compared with 27.2 months (95% CI, 24.3 to 32.2 months) in the placebo group (HR, 1.01; 95% CI, 0.83 to 1.23; $P = .915$; Fig 2C).

Other secondary efficacy end points, including TTP, objective response rate (ORR), and disease control rate based on investigator assessment, were higher in the ramucirumab arm, whereas a similar duration of response was observed between treatment arms. Median TTP was 9.7 months (95% CI, 8.5 to 10.3 months) in the ramucirumab arm and 8.2 months (95% CI, 7.1 to 9.0 months) in the placebo arm (HR, 0.85; $P = .033$). ORR was 44.7% (95% CI, 41.1% to 48.3%) in the ramucirumab arm and 37.9% (95% CI, 33.1% to 43.0%) in the placebo arm ($P = .027$). Disease control rate was 86.4% (95% CI, 83.8% to 88.8%) in the ramucirumab arm and 81.3% (95% CI, 77.0% to 85.1%) in the placebo arm ($P = .022$; Table 3). In the subset of patients with a best response of complete or partial response, median duration of response was 8.4 months (95% CI, 8.0 to 9.7 months) in the ramucirumab arm and 8.1 months (95% CI, 6.8 to 8.9 months) in the placebo arm (HR, 0.84; $P = .150$).

Quality of life seemed to be similar between treatment arms during the study period, as determined by Functional Assessment of Cancer Therapy–Breast scores and subscores, suggesting that patient-reported quality of life was not negatively affected by treatment with ramucirumab plus docetaxel relative to placebo plus docetaxel (data not shown).

Several treatment-emergent adverse events that occurred more frequently in the ramucirumab group included stomatitis, epistaxis, increased lacrimation, hypertension, decreased appetite, decrease in body weight, palmar-plantar erythrodysesthesia syndrome, insomnia, febrile neutropenia, and fatigue (grade ≥ 3 only, as assessed by $P < .05$). The most common hematologic adverse event was neutropenia, and

Fig 2. (A) Investigator-assessed probability of progression-free survival (PFS) was not significantly different between ramucirumab (RAM) and placebo (PBO) arms (hazard ratio [HR], 0.88; 95% CI, 0.75 to 1.01; $P = .077$). (B) Independently assessed probability of PFS for RAM and PBO arms (HR, 0.79; 95% CI, 0.67 to 0.94; $P = .008$). (C) Probability of overall survival for RAM and PBO arms (HR, 1.01; 95% CI, 0.83 to 1.23; $P = .915$). DOC, docetaxel.

grade 3 to 4 neutropenia occurred in 15.2% and 13.1% of patients in the ramucirumab and placebo arms, respectively. Bleeding or hemorrhage of any grade occurred in 48% of patients who received ramucirumab, compared with 22.3% of patients who received placebo (Table 4).

Fig 3. Forest plot of patient subgroups. Progression-free survival results were consistent across clinically defined patient subgroups. DOC, docetaxel; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IWRS, interactive-voice Web response system; PBO, placebo; PS, performance status; RAM, ramucirumab.

DISCUSSION

Breast cancer is a heterogeneous disease characterized by deregulation of multiple cellular pathways, different morphologies, and

varying sensitivities to therapy. Given the balance of preclinical and clinical data suggesting antiangiogenic therapy might benefit women with metastatic breast cancer, we designed a study to examine the effects of adding a specific VEGFR-2–directed monoclonal antibody to a standard taxane chemotherapy regimen (ie, docetaxel every 3 weeks).

In this large, multinational, double-blind registration study, we evaluated a first-in-class antiangiogenic agent in combination with standard cytotoxic therapy for the first-line treatment of HER2-negative advanced or metastatic breast cancer. This study has several strengths, including a placebo-controlled design, reducing biases in PFS and safety assessment; sufficient power to detect OS effects; and academic involvement in trial design, conduct, and statistical analysis. This study was conducted according to strict good clinical practice guidelines. Baseline patient and disease characteristics were balanced between the study arms and were typical of the population of patients typically enrolled onto first-line systemic therapy studies; the majority of patients randomly assigned in ROSE were age < 65 years, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and had measurable disease (82%). Given the relatively nonspecific nature of ramucirumab-associated toxicities, blinding was effectively maintained throughout the study, minimizing investigator bias and allowing for a robust assessment of PFS.

Table 3. Overall Response

Outcome	RAM Plus DOC Arm (%)	PBO Plus DOC Arm (%)	P [*]
Total No. of patients	752	382	
Best overall response			
CR	2.4	1.8	
PR	42.3	36.1	
SD	41.8	43.4	
PD	7.6	13.0	
Inevaluable	5.9	5.7	
Objective response rate (CR + PR)	44.7	37.9	.027
Disease control rate (CR + PR + SD)	86.4	81.3	.022

Abbreviations: CR, complete response; DOC, docetaxel; PBO, placebo; PD, progressive disease; PR, partial response; RAM, ramucirumab; SD, stable disease; *Cochran-Mantel-Haenszel *P* value, stratified by prior use of taxane therapy, visceral metastasis, hormone receptor status, and geographic region. Because primary end point analysis did not reach statistical significance, this sensitivity analysis is considered not statistically significant.

Table 4. Treatment-Emergent AEs With High Occurrence or of Special Interest

AE*	RAM Plus DOC Arm (n = 752)		PBO Plus DOC Arm (n = 382)	
	Any Grade (%)	Grade ≥ 3 (%)	Any Grade (%)	Grade ≥ 3 (%)
Any AE	98.7	61.7†	98.2	52.4
Fatigue‡	68.4	16.4†	66.0	9.7
Stomatitis	50.7†	6.1†	30.6	1.0
Bleeding/hemorrhage event§	48.0†	0.9	22.3	1.8
Epistaxis	39.9†	0.1	16.8	0.0
Lacrimation increase	31.1†	0.8	17.0	0.5
Hypertension§	27.0†	6.8†	11.5	1.8
Weight decrease	21.9†	1.3	10.5	0.5
Decreased appetite	21.7†	0.7	16.2	0.0
Neutropenia†	17.6	15.2	16.0	13.1
Palmar-plantar erythrodysesthesia syndrome	14.2†	3.9†	8.6	1.0
Insomnia	13.0†	0.0	8.4	0.0
Infusion-related reaction§	11.4	1.9	11.5	1.8
Anemia‡	10.1	2.3	7.3	1.8
Febrile neutropenia	8.1†	7.8†	4.2	3.9
Proteinuria§	5.1†	0.4	1.3	0.0
Venous thromboembolic event§	2.4	1.3†	4.2	3.1
GI perforation§	1.2†	1.1	0.0	0.0
Arterial thromboembolic event§	1.1	0.7	1.3	0.3
Congestive heart failure§	1.1	0.3	0.8	0.3

Abbreviations: AE, adverse event; DOC, docetaxel; PBO, placebo; RAM, ramucirumab.
 *As defined by MedDRA (version 16.0) and Common Terminology Criteria for Adverse Events (version 3.0).
 †P value < .05 using Fisher's exact test comparing RAM with PBO.
 ‡Consolidated AE category comprising synonymous MedDRA preferred terms.
 §AE of special interest defined by set of MedDRA preferred terms.

This study did not meet the primary end point of investigator-assessed PFS; median PFS was 9.5 months (95% CI, 8.3 to 9.8 months) in the ramucirumab arm and 8.2 months (95% CI, 7.1 to 8.5 months) in the placebo arm. Although PFS numerically favored the ramucirumab group, this difference was not statistically significant (HR, 0.88; $P = .077$). Prespecified sensitivity analyses, including an independent radiologic review for PFS, supported the results of the primary analysis. Furthermore, interim OS analyses demonstrated similar survival in both treatment arms of approximately 27 months. Although the final OS analysis is anticipated in 2015, there is no suggestion of a treatment effect that would be likely to influence final OS. There were no clinically meaningful differences observed in quality-of-life parameters when the two arms were compared. Although secondary end points, including TTP and ORR, provided evidence of anticancer activity with ramucirumab, the clinical benefits were insufficient to warrant its use in breast cancer outside the setting of a clinical trial.

Although this study did not improve key clinical outcomes in this patient population, the placebo-controlled design and large sample size permitted a relatively unbiased assessment of the safety signals arising from the combination of ramucirumab plus docetaxel. Ramucirumab was generally well tolerated in this patient population, as demonstrated by similar rates for most adverse events between the ramucirumab and placebo arms. As expected,

grade ≥ 3 treatment-emergent adverse events occurred at a significantly higher rate in the ramucirumab group compared with the placebo group and included fatigue, hypertension, febrile neutropenia, palmar-plantar erythrodysesthesia syndrome, and stomatitis. There were no unexpected toxicities observed with ramucirumab; the anticipated antiangiogenic class effects of hypertension, proteinuria, and epistaxis were evident.

Nonetheless, this represents another antiangiogenic trial in the setting of breast cancer that has failed to meaningfully improve important clinical outcomes. It is helpful to evaluate potential reasons for this lack of robust efficacy in the metastatic breast cancer setting. It is unlikely this result is simply a statistical artifact, because the ROSE/TRIO-012 trial was well powered to demonstrate PFS effects. Ramucirumab is an effective anticancer agent, as demonstrated by survival advantages in other reported phase III trials in the settings of advanced gastric^{16,21,22} and non-small-cell lung carcinomas.⁸ In general, it does not seem that a high breast cancer tumor burden represents the critical barrier to efficacy of antiangiogenic agents, because two well-powered and well-conducted adjuvant bevacizumab studies targeting residual micrometastatic disease also failed to improve outcomes.^{23,24}

The results of antiangiogenic therapy in metastatic and adjuvant breast cancer settings are in contrast with the experience of neoadjuvant bevacizumab for treatment of primary breast cancer, where clear improvements in pathologic complete response (pCR) rates have been identified.²⁵⁻²⁷ This discordance between improved pCR rates and lack of adjuvant disease-free survival suggests that the stromal milieu of primary breast cancer may be more sensitive to VEGF-based antiangiogenic strategies, whereas micrometastases and clinically evident metastatic disease in highly vascular organs, such as liver, bone marrow, and lung parenchyma, may be less sensitive to angiogenesis inhibitors. Long-term follow-up will be required to determine whether increased rates of pCR produced by bevacizumab will improve disease-free survival and OS in the neoadjuvant setting.

The larger question remains why antiangiogenic strategies in breast cancer have failed to improve OS, whereas similar studies with these agents in other solid tumors have shown clear survival improvements.¹⁻⁹ One possibility is that normal breast vasculature undergoes repeated cycles of expansion and regression during menstrual cycling, pregnancy, and lactation²⁸ and that consequently, breast cancers exhibit a lower sensitivity than solid tumors arising from organs without cycling vasculatures. In addition, although VEGF is the pre-eminent mediator of tumor angiogenesis, it is increasingly apparent that other known molecular mediators of angiogenesis may circumvent VEGF pathway inhibition.²⁹ By targeting VEGFR-2, ramucirumab would be expected to reduce tumor oxygenation and thereby upregulate hypoxia-inducible factor-1, a key transcription factor known to induce expression of multiple proangiogenic mediators, including VEGFR-1, platelet-derived growth factor-B, fibroblast growth factor-2, and angiopoietins.^{30,31}

Although PFS and OS were similar across predefined clinical subgroups, protocol-specified correlative assessments are under way to identify molecularly defined populations with ramucirumab-sensitive disease. Ultimately, a better understanding of breast cancer responses to available antiangiogenic therapies and assays to identify relevant biomarkers and sensitive patients are needed for antiangiogenic therapy for breast cancer to fulfill its original promise.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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Provision of study materials or patients: John R. Mackey, Oleg Lipatov, Karen A. Gelmon, Marc Webster, Miguel Martin

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GLOSSARY TERMS

angiogenesis: the process involved in the generation of new blood vessels. Although this is a normal process that naturally occurs and is controlled by so-called on and off switches, blocking tumor angiogenesis (antiangiogenesis) disrupts the blood supply to tumors, thereby preventing tumor growth.

monoclonal antibody: an antibody that is secreted from a single clone of an antibody-forming cell. Large quantities of monoclonal antibodies are produced from hybridomas, which are produced by fusing single antibody-forming cells to tumor cells. The process is initiated with initial immunization against a particular antigen, stimulating the production of antibodies targeted to different epitopes of the antigen. Antibody-forming cells are subsequently isolated from the spleen. By fusing each antibody-forming cell to tumor cells, hybridomas can each be generated with a different specificity and targeted against a different epitope of the antigen.

vascular endothelial growth factor (VEGF): a cytokine that mediates numerous functions of endothelial cells including proliferation, migration, invasion, survival, and permeability. VEGF is also known as vascular permeability factor. VEGF naturally occurs as a glycoprotein and is critical for angiogenesis. Many tumors overexpress VEGF, which correlates with poor prognosis. VEGF-A, -B, -C, -D, and -E are members of the larger family of VEGF-related proteins.

You've Guided Them Through Treatment: What Next?

As a supplement to the guidance ASCO offers on survivorship care, the **ASCO Cancer Survivorship Compendium** serves as a repository of tools and resources to enable oncology providers to implement or improve survivorship care within their practices. Delivering high-quality survivorship care can enhance patients' long-term health by complementing efforts to manage concerns related to cancer treatment and survivorship.

To view the Compendium's online resources to support your own survivorship care efforts, visit asco.org/survivorship.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Primary Results of ROSE/TRIO-12, a Randomized

Placebo-Controlled Phase III Trial Evaluating the Addition of Ramucirumab to First-Line Docetaxel Chemotherapy in Metastatic Breast Cancer

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