Original Article

Bevacizumab and the Risk of Arterial and Venous Thromboembolism in Patients With Metastatic, Castration-Resistant Prostate Cancer Treated on Cancer and Leukemia Group B (CALGB) 90401 (Alliance)

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BACKGROUND: Bevacizumab is associated with an increased risk of arterial thromboembolism (ATE); however, its effect on venous thromboembolism (VTE) remains controversial. Scant data exist on the factors that increase the risk of ATE/VTE in patients with prostate cancer. The authors investigated the association of bevacizumab treatment and clinical factors with ATE/VTE risk in patients who were treated on Cancer and Leukemia Group B (CALGB) trial 90401. **METHODS:** Patients with metastatic, castration-resistant prostate cancer were randomized to receive docetaxel and prednisone with or without bevacizumab once every 21 days. Cycle-to-event Cox regression models were used to investigate the association of bevacizumab with the incidence of grade 3 or greater ($\geq$3) ATE and VTE. Age, prior ATE/VTE, baseline antiplatelet/anticoagulant use, and VTE risk score (based on leukocyte count, hemoglobin, platelet count, body mass index, and tumor location) were evaluated in univariate and multivariable analyses. **RESULTS:** Of 1008 randomized patients, the odds of experiencing grade $\geq$3 ATE were significantly greater in those who received bevacizumab compared with those who received placebo (odds ratio, 2.79; P = .02), whereas an opposite trend was noted for grade $\geq$3 VTE (odds ratio, 0.60; P = .08). In the multivariable analysis, bevacizumab treatment (hazard ratio [HR], 3.00; P = .01) and age (HR, 1.06; P = .02) were significantly associated with the risk of ATE; whereas age (HR, 1.05; P = .01) and VTE risk score (HR, 1.83; P = .03) were significantly associated with the risk of VTE. **CONCLUSIONS:** Bevacizumab was significantly associated with a greater risk of ATE in patients with metastatic, castration-resistant prostate cancer, but it was not significantly associated with the risk of VTE. Understanding clinical factors that increase the risk for experiencing ATE/VTE is essential to mitigate the risks and reduce the burden of these prevalent complications in cancer care. ***Cancer*** **2015;121:1025-31**. © *2014 American Cancer Society.*

KEYWORDS: arterial, venous, thromboembolism, bevacizumab, prostate, cancer, risk.

INTRODUCTION

Bevacizumab is a humanized monoclonal antibody that targets the vascular endothelial growth factor (VEGF) and is currently approved to treat metastatic colorectal cancer, glioblastoma, metastatic renal cell carcinoma, and nonsquamous nonsmall cell lung cancer.[1-5] Although bevacizumab is generally well tolerated, common adverse drug events include hypertension and proteinuria, whereas rarer, more serious events include hemorrhaging and gastrointestinal (GI) perforation.[6-10]

Patients with cancer are approximately 4 times more likely to experience a thromboembolism than those without cancer.[11] Clinical manifestations comprise arterial thromboembolism (ATE), including cardiac and cerebrovascular ischemia, and venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. The risk factors

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for ATE and VTE are distinct. Whereas the risk of ATE is increased by treatment with certain chemotherapeutic agents,[12] the risk of VTE may be increased by a variety of factors, such as chemotherapy and specific tumor types, including prostate cancer,[13] and by several patient-specific factors, including prior history, age, mobility, and diet.[14] Attesting to the array of influences on VTE is a predictive VTE risk score proposed and validated by Khorana et al that incorporates cancer site, hemoglobin, platelet count, leukocyte count, and body mass index (BMI) to stratify patients into low-risk, intermediate-risk, or high-risk categories for developing a VTE.[15]

Bevacizumab has been associated with an increased risk of ATE. However, its effect on VTE remains controversial.[8,9,16-19] A meta-analysis reporting an increased VTE risk with bevacizumab treatment[17] was refuted by 2 subsequent large pooled analyses.[8,19]

The objective our current report was to elucidate the influence of bevacizumab treatment and patient-specific factors on the risk of grade 3 or greater ($\geq$3) ATE and VTE through Cancer and Leukemia Group B (CALGB) (Alliance) trial 90401,[20] a previously reported, large, randomized phase 3 study in patients with metastatic, castration-resistant prostate cancer who received docetaxel and prednisone with or without bevacizumab. Summary incidence rates from that trial suggested an increased rate of grade $\geq$3 ATE and a decreased rate of grade $\geq$3 VTE in bevacizumab-treated patients.

MATERIALS AND METHODS

Patient Selection

CALGB 90401 was a double-blinded phase 3 trial that randomized men with castration-resistant prostate cancer 1:1 to docetaxel and prednisone with and without bevacizumab.[20] All eligible patients were enrolled and treated on the CALGB 90401 study and provided institutional review board-approved, protocol-specific informed consent in accordance with federal and institutional guidelines. Briefly, patient eligibility included histologically documented, castration-resistant, progressive adenocarcinoma of the prostate. Relevant exclusion criteria included prior chemotherapy or antiangiogenic therapy, an Eastern Cooperative Oncology Group performance status >2, evidence of brain metastasis, congestive heart failure, uncontrolled hypertension, a GI bleed within the past 6 months, a GI perforation within the past 12 months, history of an ATE within the past 12 months, serious nonhealing ulcers or wounds, or grade $\geq$2 peripheral neuropathy.

Treatment

All patients received docetaxel 75 mg/m^2 as an intravenous infusion over 1 hour on day 1 of each 21-day cycle with oral dexamethasone before the docetaxel infusion plus oral prednisone 5 mg twice daily. Patients were equally randomized to receive bevacizumab 15 mg/kg or placebo as an intravenous infusion on day 1 of each 21-day cycle and were treated until disease progression, death, or a treatment-terminating adverse event occurred, for up to a maximum of 2 years of treatment. Stable doses of anticoagulants or antiplatelet therapy, including aspirin, were allowed. Bevacizumab or placebo was immediately discontinued for grade 4 hypertension, reversible leukoencephalopathy syndrome, recurrent ATE, grade $\geq$2 ATE, grade 3 hemorrhages or bleeding from any cause, GI perforation, wound dehiscence, or nephrotic syndrome.

Toxicity and Risk Factor Data Collection

Toxicity data were collected prospectively by the Alliance Statistics and Data Center at each treatment cycle on standardized forms that mandated reporting of all grade $\geq$3 toxicities as defined by the National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 3.0. For this analysis, an ATE included any grade $\geq$3 *cardiac ischemia/infarction* or *central nervous system ischemia*, whereas VTE included any grade $\geq$3 *thrombosis/thrombus/embolism*. Medical history was collected on standardized prestudy forms that included documentation of prior ATE (myocardial infarction, angina pectoris, peripheral vascular disease, arterial thrombosis, transient ischemic disease, and cerebrovascular accident) and prior VTE. Baseline antiplatelet/anticoagulant use was recorded along with dose and frequency. A validated predictive risk score for the incidence of VTE developed by Khorana et al[15] based on site of cancer (prostate, categorized as low risk), baseline platelet count ($\geq$350,000/μL), hemoglobin (<10 g/dL), leukocyte count (>11,000/μL), and BMI ($\geq$35 kg/m^2; all of which were collected prospectively) was used to classify patients into low-risk (zero risk factors), intermediate-risk (1-2 risk factors), or high-risk ($\geq$3 risk factors) categories for developing a VTE.

Statistical Analysis

The primary endpoint was time (cycle) to the event of interest (ATE or VTE). The analyses for this endpoint were carried out under a competing-risks model in which the event of interest was subject to 3 dependent, informative censoring mechanisms: progression/death, other treatment-terminating adverse events, or "other reasons," such as loss to follow-up, withdrawal for reasons other

TABLE 1. Number of Patients Experiencing Each Competing-Risk Event

Event of Interest	No. of Patients	
	ATE, N = 26	VTE, N = 58
Completed treatment	35	34
Competing-risk events		
Death/progression	418	424
Other treatment-terminating adverse event	351	318
Withdrawal for reasons other than toxicity	178	174

Abbreviations: ATE, arterial thromboembolism; VTE, venous thromboembolism.

than toxicity, or incomplete information (Table 1). Patients who did not complete 2 years of therapy because of any of these competing risks before they experienced the event of interest were informatively censored at the cumulative bevacizumab cycles received. Given the competing risks, the time-to-event analyses were conducted on the basis of a cause-specific hazard for the influence of each covariate on the event of interest (VTE or ATE). A multivariable Cox regression model[21] was used to adjust for baseline covariates, including age (continuous, per year), prior ATE or VTE (yes vs no), baseline antiplatelet/anticoagulant use (yes vs no), and VTE risk score (VTE analysis only; low risk vs intermediate/high risk according to the Khorana model[15]). Cumulative incidence plots were constructed to observe the influence of bevacizumab treatment on the risk of ATE and VTE. Fisher exact tests[22] were used to assess baseline differences between bevacizumab-treated and placebo-treated patients. No adjustment for multiplicity testing was performed. Statistical analyses were conducted by the Alliance Statistics and Data Center on a data set that was locked on January 28, 2014.

RESULTS

Patients

The CALGB 90401 study randomized a total of 1050 patients, of whom 1008 received treatment (503 men received docetaxel, prednisone, and bevacizumab; 505 men received docetaxel, prednisone, and placebo). The median duration of therapy for both arms was 8 cycles. The median age for the entire cohort was 69 years. Approximately 68.2%, 31.1%, and 0.5% of patients were categorized as low risk, intermediate risk, and high risk based on the validated VTE risk score. The *intermediate-risk* and *high-risk* categories were collapsed for the univariate and multivariable analysis because of the low number of *high-risk* patients. At study entry, most patients (59.5%) were using aspirin, a different antiplatelet, or an anticoagulant,

TABLE 2. Baseline Patient Demographics Stratified By Treatment Arm

Baseline Demographics	No. of Patients (%)	
	Bevacizumab, N = 503	Placebo, N = 505
Self-reported race		
White	447 (88.9)	440 (87.1)
African American	48 (9.5)	58 (11.5)
Other	8 (1.6)	7 (1.4)
ECOG performance status		
0	284 (56.5)	281 (55.6)
1	199 (39.6)	203 (40.2)
2	20 (4)	21 (4.2)
Age: Median [range], y	68.7 [41.7–92.9]	69.2 [41.7–93.5]
Prior thromboembolism		
ATE[a]	65 (12.9)	64 (12.7)
VTE	17 (3.4)	21 (4.2)
Baseline antiplatelet/ anticoagulant use		
Yes	293 (58.3)	307 (60.8)
No	210 (41.7)	195 (38.6)
Khorana risk score category[b]		
Low	341 (67.8)	346 (68.5)
Intermediate	159 (31.6)	154 (30.5)
High	2 (0.4)	3 (0.6)

Abbreviations: ATE, arterial thromboembolism; ECOG, Eastern Cooperative Oncology Group; VTE, venous thromboembolism.
[a] Prior ATE includes any previous history of myocardial infarction, angina pectoris, peripheral vascular disease, arterial thrombosis, transient ischemic disease, and cerebrovascular accident, including stroke.
[b] Three patients were unable to be categorized according to the Khorana risk score because of missing data (1 bevacizumab-treated patient and 2 placebo-treated patients).

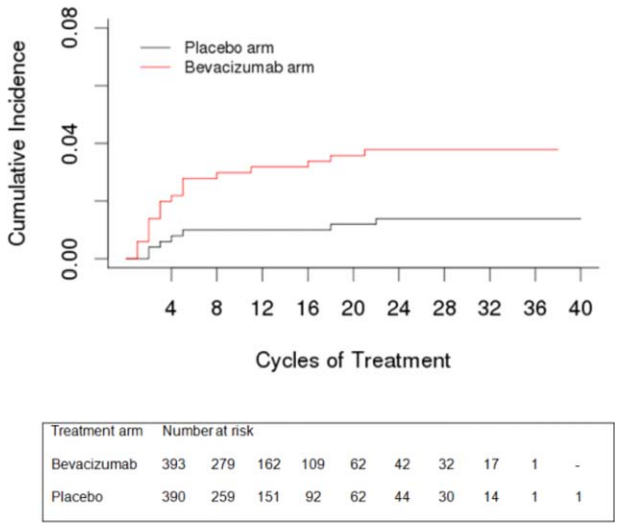
whereas 12.8% and 3.8% of patients had a positive history of a prior ATE and VTE, respectively. The baseline factors between bevacizumab-treated and placebo-treated patients were similar (Table 2). Of the total population, 26 patients experienced grade $\geq$3 ATE, and 58 patients experienced grade $\geq$3 VTE. Table 1 describes the number of patients who experienced each competing-risk event.

Influence of Bevacizumab on the Risk of ATE

The cause-specific univariate analysis of the cycle-to-event Cox regression model confirmed previous reports that bevacizumab treatment significantly increased the risk of ATE compared with placebo (cause-specific hazard ratio [HR], 2.70; 95% confidence interval [CI], 1.14-6.43; $P = .02$). Figure 1 illustrates the cumulative incidence of grade $\geq$3 ATE by treatment cycle stratified according to treatment arm. The incidence of grade $\geq$3 ATE in the bevacizumab-treated and placebo-treated patients was 3.8% and 1.4%, respectively (odds ratio [OR], 2.79; $P = .02$).

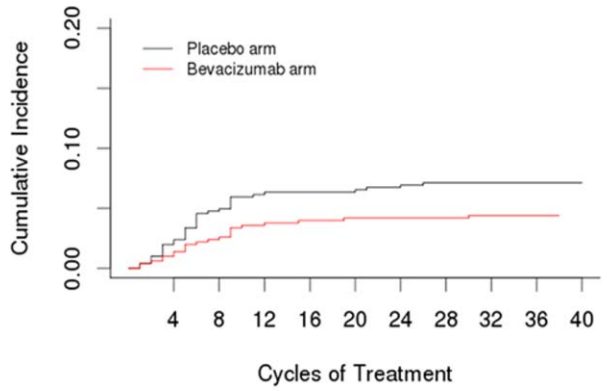
Influence of Bevacizumab on the Risk of VTE

The cause-specific univariate analysis of the cycle-to-event Cox regression model demonstrated a trend toward a



Treatment arm	Number at risk									
Bevacizumab	393	279	162	109	62	42	32	17	1	-
Placebo	390	259	151	92	62	44	30	14	1	1

Figure 1. This is a cumulative incidence curve for grade 3 or greater (≥3) arterial thromboembolism (ATE) stratified by treatment arm. There were 19 events among 503 patients (3.78%) in the bevacizumab arm and 7 events among 505 patients (1.39%) in the placebo arm. The hazard ratio for the cumulative incidence of grade ≥3 ATE in the patients who received bevacizumab was 2.76 (95% confidence interval, 1.16-6.55; $P = .021$).



Treatment arm	Number at risk									
Bevacizumab	392	276	158	104	60	40	30	16	1	-
Placebo	387	252	143	89	61	43	29	14	1	1

Figure 2. This is a cumulative incidence curve for grade 3 or greater (≥3) venous thromboembolism (VTE) stratified by treatment arm. There were 22 events among 503 patients (4.37%) in the bevacizumab arm and 36 events among 505 patients (7.13%) in the placebo arm. The hazard ratio for the cumulative incidence of grade ≥3 VTE in the patients who received bevacizumab was 0.60 (95% confidence interval, 0.35-1.02; $P = .059$).

decreased risk of VTE in bevacizumab-treated patients compared with placebo-treated patients (HR, 0.60; 95% CI, 0.35-1.02; $P = .06$). Figure 2 illustrates the cumulative incidence of grade ≥3 VTE by treatment cycle stratified according to treatment arm. The incidence of grade ≥3 VTE in bevacizumab-treated and placebo-treated patients was 4.4% and 7.1%, respectively (odds ratio, 0.6; $P = .08$).

Covariate Analysis

In the cause-specific univariate analysis, prior ATE (HR, 2.95; 95% CI, 1.23-7.06; $P = .02$) and increasing age (HR, 1.06; 95% CI, 1.01-1.11; $P = .02$) were significantly associated with grade ≥3 ATE, whereas only increasing age (HR, 1.04; 95% CI, 1.01-1.07; $P = .01$) was significantly associated with grade ≥3 VTE. A trend was noted between the VTE risk score and increased VTE risk (HR, 1.67; 95% CI, 0.99-2.82; $P = .054$) in the univariate analysis. It is noteworthy that prior VTE was not associated with the risk of developing grade ≥3 VTE (HR, 0.91; 95% CI, 0.22-3.73; $P = .89$), and baseline antiplatelet/anticoagulant use was not associated with the risk of developing grade ≥3 ATE (HR, 1.31; 95% CI, 0.58-2.94; $P = .51$) or VTE (HR, 0.77; 95% CI, 0.46-1.3; $P = .33$).

The cause-specific multivariable analysis of grade ≥3 ATE and VTE with bevacizumab treatment and each covariate is reported in Table 3. Both treatment with bevacizumab (HR, 3.00; 95% CI, 1.25-7.19; $P = .01$) and increasing age (HR, 1.06; 95% CI, 1.01-1.12; $P = .02$) remained significant for an association with increased risk of grade ≥3 ATE, whereas prior ATE no longer met statistical significance (HR, 2.29; 95% CI, 0.93-5.68; $P = .07$). Both increasing age (HR, 1.05; 95% CI, 1.01-1.08; $P = .01$) and VTE risk score (HR, 1.83; 95% CI, 1.07-3.14; $P = .03$), but not bevacizumab treatment (HR, 0.66; 95% CI, 0.38-1.12; $P = .13$), were significantly associated with the risk of grade ≥3 VTE in the multivariable model.

DISCUSSION

Our analyses confirmed previous data indicating that patients who received bevacizumab were at a significantly greater risk of experiencing grade ≥3 ATE compared with patients who received placebo. The incidence of grade ≥3 ATE among patients who did and did not receive bevacizumab (3.8% and 1.4%, respectively) is consistent with the rates from a previously reported pooled analysis of 1745 patients with metastatic cancer (data for bevacizumab-treated patients with prostate cancer were not previously available) of 3.8% and 1.7% in the bevacizumab and control populations, respectively.[8]

In univariate analysis, a potential protective effect of bevacizumab on the risk of VTE was identified. The VTE incidence rates in this study, 4.4% and 7.1% for

TABLE 3. Multivariable Analysis for the Risk of Arterial Thromboembolism and Venous Thromboembolism by Treatment Arm and Clinical Risk Factors

Risk Factor	Cause-Specific HR (95% CI)[a]	
	ATE Risk	VTE Risk
Bevacizumab treatment	**3.00 (1.25–7.19)**	0.66 (0.38–1.12)
P	**.01**	.13
Age[b]	**1.06 (1.01–1.12)**	**1.05 (1.01–1.08)**
P	**.02**	**.01**
Prior thrombosis[c]	2.29 (0.93–5.68)	0.92 (0.23–3.80)
P	.07	.91
Baseline antiplatelet/ anticoagulant	1.08 (0.47–2.46)	0.67 (0.39–1.13)
P	.86	.13
VTE risk score[d]	NA	**1.83 (1.07–3.14)**
P	—	**.03**

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; HR, hazard ratio; NA, not applicable; VTE, venous thromboembolism.
[a] Values in boldface indicate a statistically significant difference.
[b] Age was included as a continuous variable.
[c] Prior thrombosis for ATE includes prior myocardial infarction, angina pectoris, peripheral vascular disease, arterial thrombosis, transient ischemic disease, and cerebrovascular accident, including stroke. Prior thrombosis for VTE includes venous thrombosis only.
[d] The validated risk score was developed by Khorana et al[15] for VTE analysis only. Patients were categorized as either low risk, intermediate risk, or high risk if they had 0, 1 to 2, or ≥3 risk factors (hemoglobin <10 g/dL, platelet count ≥350,000/μL, leukocyte count >11,000/μL, body mass index ≥35 kg/m2), respectively. Prostate as the site of cancer was categorized as low risk (zero points). Because there were only 5 high-risk patients, the intermediate-risk and high-risk categories were collapsed.

bevacizumab-treated and placebo-treated patients, respectively, are lower than those reported (10.9% and 9.8%, respectively) in a prior pooled analysis; however, the incidence rates of grade ≥3 VTE vary greatly across tumor types and treatment regimens (range, 1.2%-13.6%).[19] A prior analysis of 6055 patients reported lower rates of VTE in bevacizumab-treated patients when adjusted by exposure and proposed that patients who receive bevacizumab may experience better tumor control, resulting in decreased tumor-related complications, such as VTE. In CALGB 90401, the patients who received bevacizumab had superior progression-free survival, prostate-specific antigen response, and objective response but did not have superior overall survival.[20] Because VTE is a well documented tumor-related complication,[14] it is possible that the tumor control benefit of bevacizumab treatment partially explains the suggested protective effect on VTE.

Given the lack of data on clinical risk factors associated with ATE and VTE in patients with prostate cancer, we assessed the influence of baseline covariates on the risk of ATE and VTE.

In multivariable analysis, bevacizumab treatment and increasing age were statistically significant predictors of increased ATE risk, whereas there was a trend toward an increased risk in patients with prior ATE. These data are consistent with a previously reported pooled analysis by Scappaticci et al.[8]

Alternatively, both increasing age and VTE risk score had statistically significant associations with an increased risk of VTE. A previously published pooled analysis by Hurwitz et al[19] demonstrated that age, prior VTE, and coumarin use at baseline were associated with increased VTE risk. It is possible that the relatively low number of patients with prior VTE events reported in our population prevented the replication of this finding. Only a minority of baseline antiplatelet/anticoagulant users were receiving coumarins, which also may have prevented the replication of similar findings. However, to our knowledge, our report is the first to validate the VTE risk score[15] in a homogenous cohort of patients with 1 tumor type from a randomized phase 3 study using a competing-risks model. It is noteworthy that accounting for age and VTE risk score further abrogated the apparent protective effect of bevacizumab on the risk of VTE.

Our approach of using a competing-risks model accounted for informative intervening events that may interfere with the observed event of interest. By definition, the informative censoring approach and removal of patients from being subject to the event of interest (ie, ATE/VTE) will result in a lower cumulative incidence.[23] Failure to account for informative censoring may result in a falsely overestimated cumulative incidence, which may be substantial when the competing-risk event is related to the underlying disease.[24] Use of this method allowed for a more principled interpretation of ATE and VTE risk compared with previous studies, which generally have used the traditional Kaplan-Meier approach and may have overestimated the risk.

Although bevacizumab does not have a standard role in current prostate cancer treatment paradigms,[20] these findings still have clinical applicability both within and beyond this tumor type. Bevacizumab is used in the first-line setting for many other tumor types, underscoring the need to understand the adverse event profile of this agent, in particular its influence on rates of rare but severe adverse events like ATE. In addition, our report provides the first known analysis of the covariates that influence VTE risk in patients receiving docetaxel and prednisone, a standard first-line chemotherapy regimen for metastatic, castration-resistant prostate cancer. Recognizing patients with prostate cancer who are at high risk for developing VTE (eg, older patients and those with a higher VTE risk score) is vital for improving patient safety and identifying patients for thromboprophylaxis.

American Society of Clinical Oncology practice guidelines for VTE prophylaxis[14] support the VTE risk score proposed by Khorana et al[15] to identify *high-risk* patients in the outpatient setting. Although routine thromboprophylaxis is not currently recommended in this setting, the balance of benefit and harm with thromboprophylaxis for high-risk patients identified by the model is currently under study (national clinical trials NCT00876915 and NCT02048865). Nevertheless, it is critical that clinicians actively engage patients in discussion about the signs and symptoms of VTE, particularly those who are at higher risk.

In conclusion, our analysis from a large, prospective cohort of patients with metastatic, castration-resistant prostate cancer who received docetaxel and prednisone with or without bevacizumab confirms the increased risk of grade $\geq$3 ATE from bevacizumab treatment. We observed that increasing age was significantly associated with an increased risk of experiencing grade $\geq$3 ATE; whereas increasing age and VTE risk score, but not treatment with bevacizumab, were significantly associated with an increased risk of experiencing grade $\geq$3 VTE. Understanding the risk factors for ATE and VTE is essential to mitigate the risks and reduce the burden of these prevalent complications in cancer care.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Ratain reports grants from PharmaMar, Dicerna, OncoTherapy Science, and Bristol-Myers Squibb; reports personal fees from AbbVie, Biscayne Pharmaceuticals, Cantex Pharmaceuticals, Cyclacel, Genentech, Sanofi-Aventis, Fresenius Kabi, Teva, USV, Kinex Pharmaceuticals, Onconova Therapeutics, Apotex, Shionogi, and Xspray; owns stock options in Biscayne Pharmaceuticals; and has a patent pending for "System and Methods for Providing Customized Medical Services" outside the submitted work. Dr. Morris serves without compensation on the advisory boards of Astellas and Janssen; reports institutional research funding from Bayer, Sanofi-Aventis, Astellas, and Takeda; and reports personal fees for service on the advisory boards of Bayer and Millennium outside the submitted work. Dr. McLeod serves as a Scientific Advisor to Cancer Genetics Inc. outside the submitted work.

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