Analysis of Early Hypertension and Clinical Outcome With Bevacizumab: Results From Seven Phase III Studies

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Key Words. Bevacizumab • Hypertension • Clinical outcome • Prognostic factor • Predictive factor

ABSTRACT

Background. Hypertension is associated with antivasculature endothelial growth factor treatment, but the clinical implications of hypertension are uncertain. To assess the prognostic and predictive value of bevacizumab-related hypertension, a comprehensive analysis of whether hypertension and efficacy outcomes are associated was conducted on seven company-sponsored placebo-controlled phase III studies of bevacizumab.

Methods. Patient-specific data were available from 6,486 patients with metastatic colorectal, breast, non-small cell lung, pancreatic, and renal cell cancers. Primary hypertension endpoint was a blood pressure (BP) increase of >20 mmHg systolic or >10 mmHg diastolic within the first 60 days of treatment. Additional endpoints included other predefined thresholds of change in BP and severity of hypertension graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events. To analyze the general

prognostic importance of an early BP increase, multivariate Cox regression models were used to assess the correlation between BP changes and progression-free (PFS) and overall survival (OS) outcomes in the control groups. To analyze whether early BP increases could predict for benefit from bevacizumab, similar analyses were conducted in the bevacizumab-treated and control groups.

Results. In six of seven studies, early BP increase was neither predictive of clinical benefit from bevacizumab nor prognostic for the course of the disease. For study AVF2107g, early increased BP was associated with longer PFS and OS times in the bevacizumab group but shorter OS time in the control group.

Conclusions. Early treatment-related BP increases do not predict clinical benefit from bevacizumab based on PFS or OS outcomes. BP increases do not appear to have general prognostic importance for patients with advanced cancer. *The Oncologist* 2013;18:273–280

Implications for Practice: Treatment-related hypertension has been seen with multiple inhibitors of vascular endothelial growth factor (VEGF), including bevacizumab, when treating colorectal, non-small cell lung, renal cell, and brain cancers. Approximately 10%–20% of patients treated with bevacizumab develop grade 3 hypertension. While a qualitative association between hypertension and anti-VEGF therapy has been described, the clinical implications of this association have not been well studied. Current practice has no guidance on strategies related to maximizing hypertension as a strategy to increase patient benefit. There have been many speculations that patients should have their anticancer treatment adjusted to maximally increase blood pressure and/or that blood pressure should be left untreated. Here, a comprehensive analysis of hypertension and efficacy outcomes in seven large clinical studies involving 6,486 patients was performed to evaluate the prognostic and predictive value of bevacizumab-related hypertension. It was found that early treatment-related blood pressure increases do not predict clinical benefit from bevacizumab based on progression-free and overall survival. Blood pressure increases do not appear to have general prognostic importance in patients with advanced cancer. Blood pressure increase should not be used to individualize anticancer therapy; significant hypertension should not be left untreated.

INTRODUCTION

Treatment-related hypertension has been seen with multiple inhibitors of vascular endothelial growth factor (VEGF). Bevacizumab is an anti-VEGF monoclonal antibody approved for

the treatment of colorectal cancer, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and glioblastoma cancer [1–6]. Approximately 10%–20% of patients treated with bev-

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Table 1. Comparison of National Cancer Institute grading for hypertension

Adverse event	Grade					
	0	1	2	3	4	5
Common Toxicity Criteria (version 2.0, published 1999)	None	Asymptomatic, transient increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; not requiring treatment	Recurrent or persistent or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; not requiring treatment	Requiring therapy or more intensive therapy than previously	Hypertensive crisis	Not applicable
Common Terminology Criteria for Adverse Events (version 3.0, published 2003)		Asymptomatic, transient (<24 h) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated	Recurrent or persistent (≥24 h) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g., hypertensive crisis)	Death

Abbreviation: WNL, within normal limits.

acizumab develop grade 3 hypertension, which is defined as requiring the initiation or adjustment of antihypertensive medications [3, 7–8]. Elevations of blood pressure (BP) are usually easily managed with standard antihypertensive medications; in the context of the underlying malignant illnesses, hypertension is rarely clinically significant. The mechanism of anti-VEGF-induced hypertension appears primarily to be related to alterations in endothelial cell nitric oxide signaling [9]. Although a qualitative association between hypertension and anti-VEGF therapy has been described since the earliest trials of anti-VEGF therapies [3, 7–8, 10–11], the clinical implications of this association have not been well studied.

Most oncology trials report BP findings based upon the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTC) (Table 1). Blood pressure values and concomitant antihypertensive medications are not routinely recorded or monitored, which precludes analyses that would use BP values directly. Thus, in many clinical trials, the evaluation of treatment-related hypertension is driven primarily by the treating oncologist's judgment that their patient's BP required intervention. The possible predictive importance of elevations in BP that emerge with exposure to anti-VEGF treatment and their possible prognostic importance in the oncology clinical setting have not been well studied.

To evaluate the prognostic and predictive importance of bevacizumab-associated hypertension, we undertook a systematic and comprehensive review of all placebo-controlled phase III studies with bevacizumab conducted by Genentech or Roche that were completed by June 2009. Data from these studies were consistently collected and monitored, including BP values and all concomitant medications. The primary analysis was based on a documented patient-specific early in-

crease in BP by >20 mmHg for systolic (SBP) or >10 mmHg for diastolic (DBP). Additional analyses were performed to explore alternative definitions of hypertension, including incremental thresholds for increases in BP and the NCI-CTC grade of a hypertension adverse event.

METHODS

Patients and Study Designs

All seven selected phase III studies were company-sponsored, placebo-controlled studies. Complete BP data sets were available for 6,486 patients. All data entries were monitored prior to database lock. The eligibility criteria, treatment regimens, statistical methods, and outcomes for all seven studies have previously been reported in the individual study reports [2, 4–6, 12–14]. The treatment regimens studied, progression-free survival (PFS) and overall survival (OS) outcomes, and incidences of hypertension are summarized in Table 2 [2, 4–6, 12–14].

Studies were conducted in patients with metastatic colorectal cancer (AVF2107g [2], NO16966 [4]), metastatic breast cancer (AVADO [13], RIBBON-1 [12]), metastatic NSCLC (AVAIL [6]), metastatic pancreatic cancer (AVITA [14]), and metastatic RCC (AVOREN [5]). In six of the seven studies, the primary endpoint of either OS time (AVF2107g, AVOREN) or PFS time (NO16966, AVADO, RIBBON-1, AVAIL) was met; in one study with OS time as the primary endpoint (AVITA), only the secondary endpoint of PFS was met.

Blood Pressure Assessments

In all studies, BP measurements were specified to be performed on day 1 of each cycle before the administration of bevacizumab with cycle durations of 2 or 3 weeks. In study AVF2107g [2], BP measurements were specified to be per-

Table 2. Summary of studies: Efficacy and incidence of hypertension

Study name	Disease	Bevacizumab dose	Chemotherapy	Hazard ratio (<i>p</i> value)		n of patients with hypertension (%)	
				PFS	OS	Grade 1/2	Grade 3/4
AVF2107g	Metastatic colorectal cancer	5 mg/kg every 2 wks	IFL + bevacizumab	0.54 (<.0001)	0.66 (<.0001)	24 (6.1) 45 (11.5)	9 (2.3) 43 (11.0)
NO16966	Metastatic colorectal cancer	7.5 mg/kg every 3 wks	(CapeOX)/FOLFOX-4	0.83 (.0023)	0.89 (.192)	35 (5.2)	8 (1.2)
		5 mg/kg every 2 wks	(FOLFOX-4) + bevacizumab			105 (15.1)	26 (3.7)
AVADO	Metastatic breast cancer	7.5 mg/kg every 3 wks	Docetaxel + bevacizumab	0.80 (.045)	1.05 (.72)	21 (9.1) 45 (17.9)	3 (1.3) 2 (0.8)
		15 mg/kg every 3 wks	Docetaxel + bevacizumab	0.67 (<.001)	1.03 (.85)	21 (9.1) 68 (27.5)	3 (1.3) 11 (4.5)
RIBBON-1	Metastatic breast cancer	15 mg/kg every 3 wks	Taxane/anthracycline + bevacizumab	0.64 (<.001)	1.03 (.83)	NR	2 (1.0) 40 (9.9)
			Capecitabine + bevacizumab	0.69 (<.001)	0.85 (.27)	NR	2 (1.0) 41 (10.1)
AVOREN	Metastatic renal cell carcinoma	10 mg/kg every 2 wks	IFN alfa2A + bevacizumab	0.60 (<.0001)	0.75 (.027)	27 (8.9) 77 (22.8)	2 (0.7) 19 (5.6)
AVAL	Advanced or recurrent NSCLC	7.5 mg/kg every 3 wks	Cisplatin and gemcitabine + bevacizumab	0.75 (0.003)	0.92 (.366)	32 (9) 63 (19)	7 (2) 23 (7)
		15 mg/kg every 3 wks	Cisplatin and gemcitabine + bevacizumab	0.85 (0.46)	1.02 (.842)	32 (9) 83 (25)	7 (2) 29 (9)
AVITA	Metastatic pancreatic cancer	7.5 mg/kg every 3 wks	Gemcitabine and erlotinib + bevacizumab	0.68 (<.0001)	0.86 (.1366)	23 (8.1) 47 (15.9)	3 (1.0) 10 (3.4)

Hazard ratios calculated from stratified Cox regression; *p* values calculated from log-rank test.

Abbreviations: CapeOX, capecitabine + oxaliplatin; FOLFOX-4, oxaliplatin + folinic acid + 5-FU; 5-FU, 5-fluorouracil; IFL, irinotecan + bolus 5-FU/leucovorin; IFN, interferon; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

formed weekly. Timing of BP measurements and administration of treatment regimens were recorded in the case report forms. The method for measurement of BP was left to the discretion of the investigators and measurements were taken in accordance with the local standard of care. In patients with SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, a repeat measurement was requested for confirmation at unscheduled visits. In those cases, the maximum value was used for this analysis. Measurements taken at visits not prespecified were not used for analysis because BP was generally not recorded. Only individual patient data from the locked efficacy and safety data sets for regulatory purposes were used for this analysis. Efficacy outcomes were PFS (determined using Response Evaluation Criteria in Solid Tumors) and OS times. Adverse events were graded according to the NCI-CTC (version 2 for AVF2107g and version 3 for all other studies; see Table 1).

Statistical Analyses

Initial exploratory analyses with scatter plots (data not shown) led to selection of an increase in SBP of >20 mmHg or DBP of >10 mmHg during the first 60 days of bevacizumab treatment as the primary endpoint. This threshold

of BP increase was selected to minimize confounding due to diurnal changes in BP. The 60-day time frame was selected to minimize confounding related to duration of therapy, tumor response, modifications in BP medications, and variable surveillance times. Incremental changes in BP based on other thresholds (SBP >10 , >30 , >40 mmHg; DBP >5 , >15 , >20 mmHg, respectively) and by NCI-CTC grade were selected as secondary endpoints following precedents in hypertension and oncology literature.

Treatment-associated changes in BP were compared among dose groups using Fisher's exact test for categorical data and Student's *t* test for continuous data. The prognostic importance of early hypertension was evaluated by correlating BP changes with PFS and OS in the control group. The medians for PFS and OS were estimated by the Kaplan-Meier method. Hazard ratios (HRs) with 95% confidence intervals and *p* values were derived by multivariate Cox regression models. Multivariate models included age (<65 vs. ≥ 65 years), sex, race (white vs. nonwhite), and predefined study-specific stratification factors in each study. The importance of early treatment-associated BP changes in predicting benefit from bevacizumab was then evaluated

Table 3. Percentage of patients with early blood pressure increases

	Percentage of patients with blood pressure increase				Difference between high-dose group and low-dose group	<i>p</i> value ^b
	+ 10/5 mmHg	+ 20/10 mmHg	+ 30/15 mmHg	+ 40/20 mmHg		
AVAIL [6]						
Low-dose group	63.2	37.4	22.3	7.2		
High-dose group	59.7	30.0	19.5	7.7		
<i>p</i> value ^a	.4133	.0531	.4337	.8802		
SBP					−1.57	.2419
DBP					0.11	.8940
AVADO [13]						
Low-dose group	55.6	29.5	16.6	7.9		
High-dose group	58.2	32.6	18.4	10.0		
<i>p</i> value ^a	.5815	.4902	.6321	.4284		
SBP					0.96	.5555
DBP					1.55	.1344

Data show the percentage of patients with early blood pressure increases in high-dose and low-dose bevacizumab groups in AVAIL and AVADO studies and the difference between high-dose and low-dose bevacizumab groups in mean blood pressure in AVAIL and AVADO studies within first 60 days.

^aFisher's exact test for 2×2 table.

^bStudent's *t* test.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

using similar methods; multivariate models included a BP increase-by-treatment interaction test. The presence of hypertension at baseline was defined as SBP $\geq$ 160 mmHg or DBP $\geq$ 100 mmHg.

Role of the Funding Source

The funding source contributed to the design, conduct, data collection, and data analysis. All authors had full access to the study data. H.I.H., on behalf of the authors, had final responsibility for the decision to submit the paper for publication.

RESULTS

Demographic and baseline disease characteristics of patients with and without an early increase in BP were well balanced at the lower cutpoints (increase in SBP >10/DBP >5 mmHg, or SBP >20/DBP >10 mmHg) such that the data distribution for cohorts of patients with and without an early increase in BP were similar (data not shown). Particularly at the highest cutpoint (increase in SBP >40/DBP >20 mmHg), there was an uneven data distribution for cohorts with versus without an early increase in BP (supplemental online data). The rates of on-study death from any cause and of study discontinuation due to an adverse event were comparable for patients with and without an early increase in BP in all studies for all BP thresholds (data not shown).

The median treatment-associated change in SBP/DBP within the first 60 days of treatment was 10/6 mmHg for the bevacizumab groups and 8/5 mmHg for the control groups. Approximately 55% of patients had an increase in SBP >10 mmHg and/or DBP >5 mmHg at any time during the trials. Increases in SBP >40/DBP >20 mmHg occurred in 495 of the 6,486 patients (7.6%) included in this analysis. Hypertensive crises (NCI-CTC grade 4) were observed in eight patients in the bevacizumab groups and one patient in the control groups.

In two of the seven studies (AVADO [13] and AVAIL [6]), patients were randomized between two different bevacizumab doses. No dose effect on the presence or severity of BP increase was noted in either study, with the exception of the BP threshold of 20/10 mmHg in AVAIL only (Table 3). In that study, the lower dose of bevacizumab was associated with a slightly higher incidence of increased BP (37.4% vs. 30.0%; *p* = .0531).

The role of an early increase in BP as a general prognostic factor across cancer types was evaluated by Kaplan-Meier estimates and as an independent prognostic factor by multivariate Cox regression models. These analyses were performed in the control groups of all studies for all BP thresholds. In six studies, HRs for PFS and OS were not significant at any cutoff point (Table 4). However, in study AVF2107g [2], early increased BP was associated with shorter OS; in the Cox regression model, this association was statistically significant for cutoff points of >20/10 mmHg (HR: 1.36; *p* = .02) and >30/15 mmHg (HR: 1.58; *p* = 0.002). Results of the multivariate Cox models are presented in Table 5.

To evaluate the role of an early increase in BP in predicting benefit from bevacizumab treatment, tests for interaction between early changes in BP and bevacizumab treatment with PFS and OS times were performed in a multivariate Cox model. The *p* values for early BP increase by treatment interaction for the primary cutpoint (increase in SBP >20/DBP >10 mmHg) and secondary cutpoints were not significant for the majority of the studies (Table 6). Study AVF2107g [2] was the only study with a significant interaction between early hypertension and PFS and OS outcomes. For PFS, the HR was 0.55 (*p* = .0008) for patients with an early increase in SBP >20/DBP >10 mmHg; for OS, which was the primary endpoint of the study, the HR was 0.43 (*p* < .0001).

Analyses using an early increase in BP as an incrementally increased threshold and using an early increase in BP by NCI-

Table 4. Univariate analysis: Hazard ratios (*p* values) for prognostic impact of treatment-related early increase in blood pressure

	AVF2107g [2]	NO16966 [4]	AVADO [13]	RIBBON-1 [12]	AVAIL [6]	AVOREN [5]	AVITA [14]
SBP/DBP increase >20/10 mmHg							
PFS	1.18 (.1883)	0.97 (.7726)	1.24 (.2439)	1.19 (.2671)	1.00 (.9918)	0.99 (.9398)	0.92 (.5469)
OS	1.29 (.0683)	0.84 (.3587)	1.12 (.6508)	1.40 (.0999)	0.95 (.7749)	0.87 (.4751)	1.17 (.2532)
SBP/DBP increase >10/5 mmHg							
PFS	1.06 (.6567)	0.93 (.4709)	1.26 (.1365)	0.96 (.6945)	0.98 (.8728)	0.81 (.1312)	0.86 (.2302)
OS	0.99 (.9294)	0.84 (.2581)	1.13 (.5719)	1.00 (.9993)	0.89 (.4325)	0.80 (.2223)	0.97 (.8050)
SBP/DBP increase >30/15 mmHg							
PFS	1.45 (.0067)	1.18 (.3015)	1.06 (.8143)	1.18 (.4360)	1.01 (.9599)	1.10 (.6113)	0.98 (.8870)
OS	1.56 (.0037)	1.34 (.1903)	1.22 (.5210)	1.20 (.5335)	0.95 (.7921)	0.97 (.8976)	1.11 (.5190)
SBP/DBP increase >40/20 mmHg							
PFS	1.63 (.0121)	0.90 (.6756)	1.24 (.5959)	1.04 (.8948)	1.07 (.8151)	1.06 (.8213)	1.30 (.2544)
OS	2.07 (.0003)	0.82 (.6428)	1.67 (.2518)	1.44 (.3216)	0.75 (.4560)	0.88 (.7286)	1.44 (.1113)

Hazard ratios were calculated from stratified Cox model; *p* values were calculated from stratified log-rank test.

Abbreviations: DBP, diastolic blood pressure; OS, overall survival; PFS, progression-free survival; SBP, systolic blood pressure.

Table 5. Multivariate analysis: Hazard ratios (*p* values) for prognostic impact of treatment-related early increase in blood pressure

	AVF2107g [2]	NO16966 [4]	AVADO [13]	RIBBON-1 [12]	AVAIL [6]	AVOREN [5]	AVITA [14]
SBP/DBP increase >20/10 mmHg							
PFS	1.20 (.1416)	1.00 (.9970)	1.30 (.1179)	1.16 (.3448)	0.95 (.6898)	1.11 (.4486)	0.91 (.4831)
OS	1.36 (.0233)	0.89 (.4860)	1.21 (.4149)	1.40 (.1064)	0.85 (.3269)	0.87 (.4517)	1.10 (.4777)
SBP/DBP increase >10/5 mmHg							
PFS	1.03 (.8372)	0.91 (.3512)	1.31 (.0526)	0.98 (.8772)	0.92 (.4657)	0.88 (.3364)	0.83 (.1221)
OS	1.02 (.8688)	0.84 (.2301)	1.07 (.7383)	0.99 (.9357)	0.85 (.2101)	0.78 (.1633)	0.95 (.6494)
SBP/DBP increase >30/15 mmHg							
PFS	1.43 (.0083)	1.20 (.2026)	1.22 (.3632)	1.10 (.6561)	0.98 (.8966)	1.21 (.2850)	0.95 (.7339)
OS	1.58 (.0024)	1.37 (.1366)	1.21 (.5102)	1.14 (.6452)	0.90 (.5905)	0.97 (.8802)	1.05 (.7669)
SBP/DBP increase >40/20 mmHg							
PFS	1.60 (.0161)	0.89 (.6378)	2.29 (.0173)	0.98 (.9307)	0.97 (.9238)	1.19 (.4524)	1.21 (.4107)
OS	2.04 (.0004)	0.83 (.6466)	2.51 (.0213)	1.48 (.2954)	0.68 (.3130)	0.92 (.8014)	1.29 (.2697)

Hazard ratios were calculated from stratified Cox model; *p* values were calculated from Wald test.

Abbreviations: DBP, diastolic blood pressure; OS, overall survival; PFS, progression-free survival; SBP, systolic blood pressure.

CTC grade yielded results similar to the primary analyses (data not shown). Stratified univariate Cox regression models were used to assess whether hypertension at baseline would result in an improved general prognosis or a differential benefit from bevacizumab treatment. These stratified Cox analyses also found no association between early BP increase and clinical benefit from bevacizumab (data not shown). The incidences of selected adverse events of known association with bevacizumab are shown for each of the individual studies in the supplemental online data.

DISCUSSION

This analysis of 6,486 patients from seven phase III studies across multiple tumor types is the largest analysis to date evaluating the predictive significance of an early BP increase on clinical outcome in patients with cancer treated with a VEGF inhibitor and in patients with cancer in general. This analysis has the additional advantage of using data from large random-

ized controlled trials with similar study designs and consistent data collection, including patient-specific BP values. In six out of seven studies, there was no indication that early hypertension was a general prognostic factor. Study AVF2107g—one of two studies in patients with metastatic colorectal cancer—was an exception: patients in the control arm with an early BP increase had significantly shorter OS times.

Early treatment-related hypertension did not predict benefit from bevacizumab. This lack of predictive value was seen across all indications and at all cutpoints of early increases of BP, with one exception. Study AVF2107g [2] did show a significant interaction for PFS and OS outcomes for all cutpoints. This was the only study offering any indication that an early increase in BP might predict clinical benefit from bevacizumab.

Our combined analysis of seven phase III studies to explore the association between bevacizumab, an early increase in BP, and clinical outcomes in patients with cancer was performed ac-

Table 6. Multivariate analysis: Hazard ratios (*p* values) for predictive impact of treatment-related early increase in blood pressure

	AVF2107g [2]	NO16966 [4]	AVADO ^a [13]	RIBBON-1 [12]	AVAIL ^a [6]	AVOREN [5]	AVITA [14]
SBP/DBP increase >20/10 mmHg							
PFS	0.55 (.0008)	0.81 (.1791)	0.68 (.0823)	0.82 (.2597)	1.04 (.8332)	0.81 (.2927)	0.94 (.7381)
OS	0.43 (<.0001)	0.80 (.3629)	0.72 (.2800)	0.62 (.0505)	1.32 (.2051)	0.98 (.9467)	0.86 (.4271)
SBP/DBP increase >10/5 mmHg							
PFS	0.69 (.0705)	0.79 (.1028)	0.70 (.0641)	0.99 (.9461)	0.96 (.7770)	1.16 (.4628)	1.05 (.7648)
OS	0.63 (.0373)	0.82 (.3618)	0.96 (.8811)	0.64 (.0317)	0.97 (.8696)	1.38 (.2366)	0.94 (.7285)
SBP/DBP >30/15 mmHg							
PFS	0.50 (.0006)	0.81 (.2630)	0.61 (.0921)	0.85 (.4992)	0.94 (.7831)	0.80 (.3480)	0.83 (.4062)
OS	0.38 (<.0001)	0.60 (.0766)	0.78 (.5175)	0.71 (.2892)	1.04 (.8881)	0.96 (.9044)	0.84 (.4273)
SBP/DBP increase >40/20 mmHg							
PFS	0.51 (.0110)	1.36 (.3154)	0.25 (.0013)	0.89 (.7320)	0.81 (.5466)	0.91 (.7505)	0.71 (.2677)
OS	0.30 (.0001)	1.18 (.7408)	0.35 (.0361)	0.49 (.1138)	1.61 (.3078)	0.71 (.4641)	0.63 (.1297)

Hazard ratios were calculated from Cox model; *p* values were calculated from Wald test.

^a5 mg/kg/wk.

Abbreviations: DBP, diastolic blood pressure; OS, overall survival; PFS, progression-free survival; SBP, systolic blood pressure.

cording to a prospectively defined analysis plan and used individual patient BP and outcome data. However, the current analysis has several limitations. Although study endpoints were formally prespecified before analysis, this study remains retrospective, as the original studies were not designed to address BP-related questions. BP measurements were captured systematically before each dose of bevacizumab or placebo and these data were monitored. However, there is the potential for variability in several factors known to affect BP measurements, including the time of day, diet, volume status, disease burden, comfort and anxiety, and use of concomitant medications, including antihypertensive medications. Because the primary studies were large randomized controlled trials, most of these factors are likely to have been similarly distributed between the bevacizumab and control groups, although imbalances due to chance are possible. Use of BP medications was recorded on the case report forms; however, the dose used and frequency of administration were not recorded.

Analysis of treatment-related changes in BP is subject to several confounders, including diurnal variation in BP and the effect of treatment on the tumor, which may in turn affect many modifiers of BP. To account for these issues and to ensure clinical relevance, the primary endpoint for this analysis was predetermined to be a change in SBP >20 mmHg or DBP >10 mmHg within the first 60 days of exposure to bevacizumab. In populations of patients without cancer, the recorded BP can vary by 10%–15% or more from visit to visit [15]. The reasons for this variability, approaches to minimize it, and its clinical implications have been extensively reviewed [15, 16]. The time frame of <60 days was intended to minimize confounding related to potential changes in BP medications and the effect of tumor response or progression, as well as variable observation times.

Hypertension is a complex medical condition that may be affected by many patient-related factors (e.g., age, diet, stress, activity, comorbid conditions, concomitant medications), and most of these factors can also be affected by cancer and anticancer treatments [17–21]. BP physiology is also com-

plex, involving multiple organs and multiple effectors, such as renin, angiotensin, aldosterone, prostanoids, alpha- and beta-adrenergic receptors, and nitric oxide [17, 19–21]. Polymorphisms in several genes have been reported to potentially modify the risk of hypertension [22, 23]. Preclinical and clinical evidence suggests a primary role for endothelial nitric oxide synthase in anti-VEGF-related hypertension [9]. Polymorphisms in VEGF and VEGF receptor 2 have been implicated as potential candidate biomarkers to predict for benefit and/or the development of hypertension with bevacizumab [24]. The current analysis did not include pharmacogenomic or other biomarker analyses.

In the current analysis, there was no bevacizumab dose effect on BP within the dose ranges studied; that is, 2.5 and 5.0 mg/kg per week. The lack of dose effect is consistent with both doses being bioactive and being outside the linear range for any potential dose-response relationship. These limitations apply to many pharmacodynamic biomarkers. Another limitation is that single-timepoint, nonstandardized measurements based upon local clinical standards were used in this analysis for pragmatic reasons and for clinical relevance.

The primary goal of this study was to determine whether bevacizumab-related early increases in BP were associated with clinical outcome measured as PFS and OS. This analysis found that early treatment-related increases in BP were not of general prognostic importance. In addition, early treatment-associated increases in BP did not predict for greater benefit from bevacizumab. These results were consistent across six of the seven phase III trials in five disease settings and across all primary and additional endpoints. In addition, these results were consistent when early BP change was analyzed using NCI-CTC grade. A favorable effect of increased BP in the bevacizumab group and an unfavorable effect in the control group were seen only in study AVF2107g. Because NO16966 was also conducted in the setting of first-line metastatic colorectal cancer with 5-fluorouracil based regimens, this finding most likely reflects statistical variability across the studies.

The current analysis has the advantage of using BP values directly rather than NCI-CTC grade only. Our primary analysis used a cutpoint approach—that is, a predefined early increase from any baseline value—to ensure categories of hypertension would reflect precedents in the hypertension field and would be clinically applicable. The use of a maximum increase in BP during the first 60 days in our analysis—in contrast to a landmark assessment at day 60—reduces the potential for confounding related to changes in disease status and changes in antihypertensive medications and other concomitant medications. Importantly, our secondary analyses using BP as an incrementally changing variable were consistent with the primary analysis. Nevertheless, a predictive relationship between changes in BP and clinical outcomes cannot be excluded by our analysis. It is possible such an effect could be noted with more precise BP evaluations, in other disease settings, or with other VEGF inhibitors.

The lack of predictive importance for hypertension with bevacizumab in our report is at odds with other reports in the literature [25–31]. Recently, reports of retrospective analyses in two phase III studies—the E4599 study of carboplatin and paclitaxel with or without bevacizumab in NSCLC, and the CALGB 90206 study of interferon with or without bevacizumab in RCC—indicated an association between increased BP and clinical benefit from bevacizumab [25, 31]. These cooperative group studies used NCI-CTC grade of hypertension and not patient-specific BP values. In the current report, no association between change in BP and clinical outcome was seen in either the NSCLC study [6] or the RCC study [5], including when NCI-CTC grading was used in the analysis. These differences may be explained by trial-to-trial variability and by differences in the levels of data capture and monitoring, which were more intensive in the current analysis.

The lack of correlation between increased BP and clinical benefit suggest that BP should be regularly monitored and carefully managed, particularly if patients have other risk factors for cardiovascular or cerebrovascular disease [32, 33]. Multiple classes of antihypertensive agents have been used successfully for the treatment of bevacizumab-related hypertension. Our data argue against strategies that individualize

patient dosing of bevacizumab based upon treatment-related hypertension [34].

In conclusion, in this large retrospective analysis, treatment-related increases in BP were not associated with an improved general prognosis nor with a predicted benefit from bevacizumab. These findings also highlight the limitations of using BP as a pharmacodynamic marker of anti-VEGF therapy and the importance of using patient-specific BP values in analyses of treatment-related hypertension. Lastly, bevacizumab has the tendency to increase BP and significant increases should be clinically managed.

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DISCLOSURES

Herbert I. Hurwitz: Genentech, Roche, Sanofi (C/A); Roche (H); Genentech, Roche, Sanofi, Pfizer, Bristol-Myers Squibb (RF); **Pamela S. Douglas:** CardioDX, Universal Oncology (OI); **John P. Middleton:** Amgen, Paragon (C/A); Eli Lilly, Amgen, Mitsubishi, Questcor, Keryx, Reata (RF); **David H. Johnson:** miRNA Therapeutics, Peloton (C/A); **David A. Reardon:** Roche/Genentech, Merck/Schering, EMD Serono, Abbott (C/A); **Dafeng Chen:** Roche/Genentech (C/A); **Oliver Rosen:** Genentech (E). The other author reported no financial relationships. (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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