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ORIGINAL ARTICLE

Simulations to Predict Clinical Trial Outcome of Bevacizumab Plus Chemotherapy vs. Chemotherapy Alone in Patients With First-Line Gastric Cancer and Elevated Plasma VEGF-A

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To simulate clinical trials to assess overall survival (OS) benefit of bevacizumab in combination with chemotherapy in selected patients with gastric cancer (GC), a modeling framework linking OS with tumor growth inhibition (TGI) metrics and baseline patient characteristics was developed. Various TGI metrics were estimated using TGI models and data from two phase III studies comparing bevacizumab plus chemotherapy vs. chemotherapy as first-line therapy in 976 GC patients. Time-to-tumor-growth (TTG) was the best TGI metric to predict OS. TTG, Eastern Cooperative Oncology Group (ECOG) score, albumin level, and Asian ethnicity were significant covariates in the final OS model. The model correctly predicted a decreased hazard ratio favorable to bevacizumab in patients with high baseline plasma VEGF-A above the median of 113.4 ng/L. Based on trial simulations, in trials enrolling patients with elevated baseline plasma VEGF-A (500 patients per arm), the expected hazard ratio was 0.82 (95% prediction interval: 0.70–0.95), independent of ethnicity.
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Modeling and simulation approaches may be used to provide quantitative support for study design and development decisions in oncology.

• WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What would be the probability to success of future phase III studies of bevacizumab in combination of chemotherapy in selected patients with gastric cancer (GC) stratified by baseline biomarkers?

• WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ A model that uses tumor growth inhibition metrics to capture the treatment effect of bevacizumab was developed to simulate overall survival in first-line GC. Time-to-tumor-growth captured bevacizumab effect in GC and explained bevacizumab benefit in patients with elevated baseline plasma VEGF-A. The phase III study enrolling patients with elevated baseline plasma VEGF-A (500 patients per arm) has a good chance of success, independent of ethnicity.

• HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

☑ Model-based simulations could be used more systematically to support phase III trial designs and decisions.

Drug-independent models have been proposed to link tumor size response (based on model-based tumor growth inhibition (TGI) metrics estimates) and baseline prognostic factors to overall survival (OS) in a number of cancers: colorectal cancer,[1,2] non-small cell lung cancer (NSCLC),[3] and multiple myeloma (using M-protein as a marker of tumor size).[4]

Models for longitudinal tumor size data are used to estimate TGI metrics predictive of treatment effect.[1–3,5,6] A number of tumor size metrics have been proposed so far to capture treatment effect and predict OS: ratio of tumor size at end-of-cycle 2 (week 6 or 8) to baseline tumor size (TSratio),[1–4] tumor growth rate,[5] and time to tumor growth (TTG).[6] Some of these models have been prospectively used to successfully predict OS outcome based on early tumor growth inhibition data in both multiple myeloma[4] and NSCLC,[7] and recently reviewed.[8]

Bevacizumab (Avastin, Genentech, South San Francisco, CA) is a humanized monoclonal immunoglobulin G (IgG) 1 antibody that specifically binds and neutralizes the biological activity of vascular endothelial growth factor A (VEGF-A), a key isoform of VEGF involved in angiogenesis, and a well-characterized proangiogenic factor. Bevacizumab causes inhibition of tumor angiogenesis by blocking VEGF-A from binding to its receptors and leads to tumor growth inhibition. Two recently conducted studies (AVAGAST[9] and AVATAR[10]) failed to show OS benefit of the addition of bevacizumab to chemotherapy in first-line advanced gastric cancer. However, a number of baseline biomarkers may be predictive of bevacizumab

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benefit, meaning that patients with a biomarker level above or below a certain threshold may be more likely to benefit from bevacizumab treatment than other patients (i.e., the predictive value of the biomarker for treatment effect).[11]

The objectives of this study were to (1) assess metrics of tumor size response to predict OS in gastric cancer, (2) examine prognostic and predictive values of biomarkers, (3) test for any ethnic differences in tumor size response to OS relationship, and (4) perform clinical trial simulations to assess OS benefit of bevacizumab treatment in selected patients.

METHODS

Data

Individual patient data were collected from two double-blind randomized phase III studies comparing bevacizumab (7.5 mg/kg every 3 weeks) vs. placebo with chemotherapy (fluoropyrimidine and cisplatin) as the first-line treatment of advanced gastric cancer (AVAGAST[9] and AVATAR[10]). AVAGAST enrolled 774 patients including 376 patients from Asian countries (Japan and Korea) and 398 patients from Western countries (North America, Latin America, and Europe). The primary endpoint OS was reached in the Western patient population including patients enrolled in North America and Latin America (hazard ratio (HR): 0.63; 95% confidence interval (CI): 0.43 to 0.94) and patients enrolled in Europe (HR: 0.85; 95% CI: 0.63 to 1.14), but not reached in the overall population (HR: 0.87; 95% CI: 0.73 to 1.03) or patients enrolled in Asian regions (HR: 0.97; 95% CI: 0.75 to 1.25). Furthermore, a trend toward improved OS favorable to bevacizumab was observed in patients with high baseline plasma VEGF-A above the median of 111 ng/L (HR: 0.72; 95% CI: 0.57 to 0.93) and low expression of tumor neuropilin-1 (HR: 0.75; 95% CI: 0.59 to 0.97).[11] AVATAR enrolled 202 patients in China, but failed to show significant improvement in OS by bevacizumab (HR: 1.11, 95% CI: 0.79 to 1.56).

Tumor size models and metrics

A simplified version of the previously developed semimechanistic exposure-driven TGI model[2,6] was fit to the tumor size data with a nonlinear mixed effect approach (NONMEM, v. 7) using the first-order conditional estimation algorithm with interaction.[12] As previously discussed,[6] the simplified TGI model does not account for exposure to the treatment drugs, and it is not meant to be used in simulations. In this analysis, the TGI model should be seen as an analysis model to fit tumor size data, interpolate data, and estimate TGI metrics. Given this goal and since this model was not meant to perform simulations, the model was evaluated with standard diagnostic plots. Two TGI metrics were obtained for each patient using the TGI model: ratio of tumor size to baseline (TSratio) at weeks 8, 12, and 14, and the theoretical time to tumor growth (TTG), i.e., the model predicted time to tumor size nadir. Details of model equations, implementation and estimation are presented in the **Supplementary Materials**.

Survival model development

Overall survival data were explored using Kaplan-Meier and Cox regression analyses using *survfit* and *coxph* functions, respectively in R version 2.13.1. All baseline patient characteristics including ethnicity, baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS), gastrectomy, tumor size, number of metastatic sites, albumin, lactate dehydrogenase (LDH), and other laboratory tests, baseline biomarkers (plasma VEGF-A, tumor protein expression of epidermal growth factor receptor (EGFR), neuropilin-1, human epithelial growth factor receptor 2 (HER2), and VEGF receptors-1 and -2) and tumor size metrics (TSratio and TTG) were tested to explain variability in OS.

A parametric survival regression model was developed using the *survreg* function in R v. 2.13.1 that describes OS distribution as a function of covariates. The probability density function that best describes the observed survival time was selected among normal, lognormal, Weibull, logistic, log-logistic, and exponential by using difference in Akaike Information Criterion (AIC) and goodness of fit plots of the alternative models.

A "full" model was built by including all significant covariates from the Cox univariate analysis ($P < 0.05$ per the log-likelihood ratio test where the difference in -2*log-likelihood (deviance) between alternative models follows a χ^2 distribution). Then a backward stepwise elimination was carried out. At each elimination step, the relative influence of each remaining covariate on the model was reevaluated by deleting it from the reduced model on an individual basis using a cutoff of $P < 0.01$. Interactions between different covariates of interest were also examined in the final model.

The model simulation performances were evaluated using posterior predictive checks (PPC). OS distributions were simulated 1,000 times for the patients with same characteristics as in the original studies. Model parameters were sampled from the estimated mean values and uncertainty in parameter estimates for each of the simulated study replicate. Censoring was simulated in sampling patient study duration, assumed to be independent of death, in a uniform distribution from 10 to 23 months, consistent with the minimum and the maximum time period the patient stayed in the study without a death event. Simulated survival distribution, HR, and their respective 95% prediction intervals were estimated and compared with observed.

Survival model simulations

The model was then used to simulate expected survival HR in patient subpopulations in an attempt to inform patient selection for future studies. Patient characteristics as well as estimated TGI metrics were sampled from observed with replacement. Simulations were conducted as described for the PPC. Multiple replicates (1,000) of virtual randomized studies (500 patients per arm) of bevacizumab plus chemotherapy vs. chemotherapy alone were simulated. HR and 95% predictions intervals were reported in the different populations of interest.

RESULTS

Data explorations and tumor size model

Patients needed to have at least two tumor size measurements (one at baseline and one post treatment) to be evaluable in the tumor size analysis. Over 709 patients (559 in AVAGAST and 150 in AVATAR) out of 976 (73%)

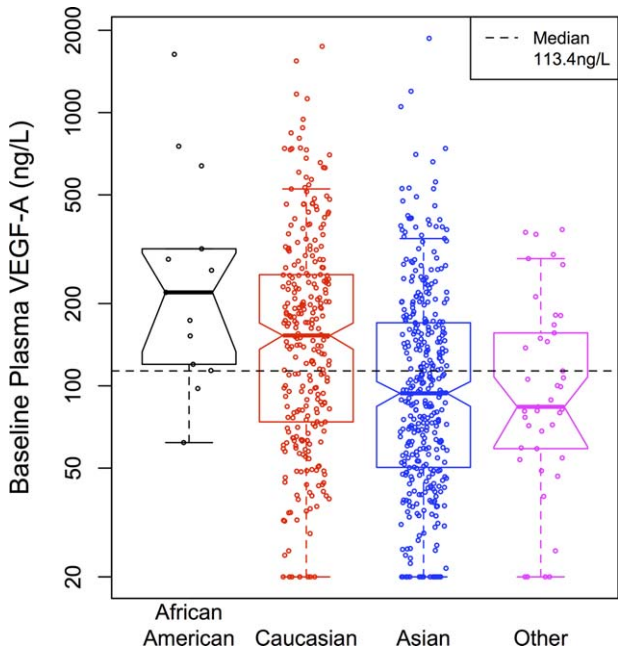

Figure 1 Baseline plasma VEGF-A in different ethnic groups.

were evaluable. Evaluable patients correspond to 91% of the patients with measurable disease. Baseline plasma VEGF-A level was significantly higher in Caucasian than that in Asian patients (**Figure 1**). Biomarker data were only available in the AVAGAST study.

The simplified TGI model provided a good fit of the data (**Supplementary Figure 1**). Model parameter estimates (**Supplementary Table 1**) were used to calculate the tumor size metrics to be tested as predictors of OS.

Individual tumor size metrics estimates are summarized in **Supplementary Table 2**. Most of the patients experienced tumor shrinkage (TSratio <1) with a trend to more shrinkage later in time (week 14 compared to weeks 12 or 8). TTG was highly variable, with a median of 16.4 weeks. An illustration of the fit to individual data is presented on a random sample of patients together with TTG estimates and the observed time to minimum tumor size in **Supplementary Figure 2**.

Overall survival model

In univariate Cox analysis, several baseline prognostic factors were highly significant (ranked by order of significance, **Table 1**): albumin, ECOG PS (0 vs. >0), prior gastrectomy, LDH, number of metastatic sites (≤2 vs. >2), and tumor size (all at $P < 0.0001$, deviance ranging from 16 to 9). Among the biomarkers only baseline plasma VEGF-A (taken as the log) was significant ($P < 0.0001$, deviance 12). Asian patients had a significantly longer survival than others ($P < 0.0001$, deviance 10). All the tumor size metrics were highly significant too ($P < 0.0001$, deviance ranging from 97 to 38) with TTG (taken as log) being the most significant (deviance 97) (**Figure 2**).

A lognormal distribution best described the OS distribution (AIC: 6,676 vs. >6,688 for the other distributions).

Table 1 Univariate Cox regression analysis to assess the association between OS and each factor alone (ordered by significance)

	Deviance	*P*	*N*	Sign
Log(TTG)	96.5	<0.0001	709	–
Baseline albumin (g/L)	15.3	<0.0001	952	–
ECOG score (0 vs. >0)	14.7	<0.0001	976	+
Prior gastrectomy (No vs. Yes)	14.6	<0.0001	976	–
Lactate dehydrogenase (U/L)	12.3	<0.0001	938	+
Log(baseline plasma VEGF-A)	12	<0.0001	712	+
Asian ethnicity	10.3	<0.0001	976	–
Baseline number of metastatic sites (<2 vs. ≥2)	8.9	<0.0001	948	+
Baseline tumor size (cm)	8.8	<0.0001	767	+
Site in Japan or not	6	0.0006	976	–
Study (AVAGAST vs. AVATAR)	0.1	0.5902	976	–

Deviance: the difference in −2*log-likelihood between alternative models following a χ^2 distribution; *P*: *P* value calculated by log-likelihood ratio test; Sign: hazard increases (+) or decreases (–) with the increased value of the covariate; TTG: time to tumor growth (weeks) with 6 weeks added to avoid negative value (see **Supplementary Material**).

Backward elimination of the above covariates significant in the Cox univariate analysis (using TTG as the tumor size metrics) selected (by order of significance) log(TTG), Asian

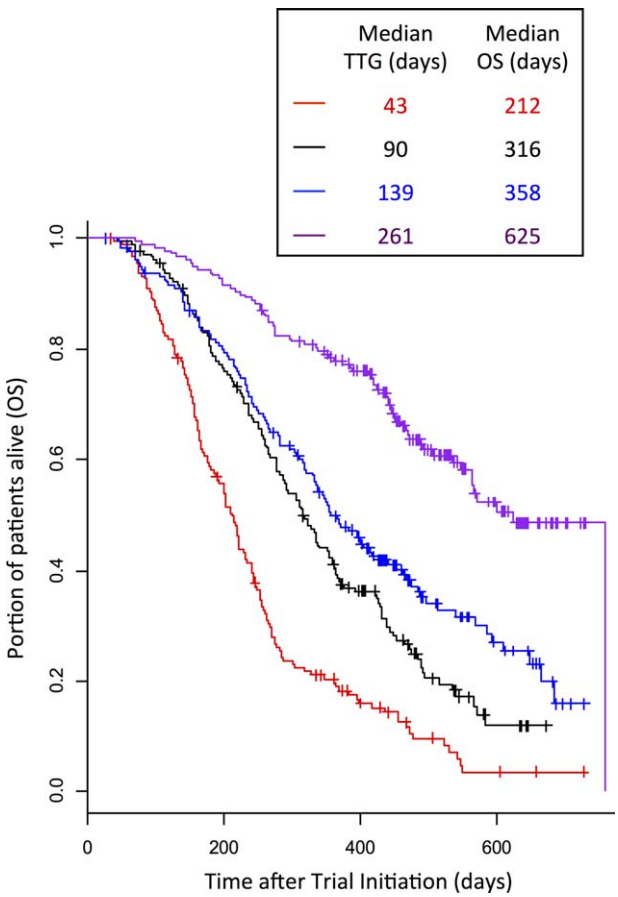

Figure 2 Survival distribution by quartiles of time to tumor growth (each group represents 25% of the patients). TTG, time to tumor growth; OS, overall survival.

Table 2 Parameter estimates of the final overall survival model

	Estimate	SE	z	*P*
Intercept	3.1358	0.31696	9.89	<0.00001
Log (TTG)	0.6198	0.05622	11.02	<0.00001
ECOG score>0	−0.2759	0.06789	−4.06	<0.00001
Asian	0.2078	0.06811	3.05	0.00023
Albumin (g/L)	0.0208	0.00703	2.96	0.00031
Log(scale)	−0.4358	0.04316	−10.1	<0.00001

Survival times were modeled by lognormal distribution in days; *P*: obtained from Wald test (χ^2); z: Wald statistic; SE, standard error; TTG, time to growth (weeks) with 6 weeks added to avoid negative value (see **Supplementary Material**).

ethnicity, albumin, and ECOG PS to enter the final model. Log(baseline plasma VEGF-A) did not enter in the model after adjusting for the other effects. There was no interaction between TTG effect and Asian ethnicity. All parameters of the final survival model are adequately estimated (**Table 2**). According to this model, the probability to survive decreases when ECOG PS is greater than 0, in patients with low albumin, and increases in Asian patients and when TTG increases (drug effect).

The model was qualified by simulating survival distributions and HRs in both arms in Asian and Western patients (**Figure 3**). The observed HRs of bevacizumab plus chemotherapy vs. chemotherapy alone are within the 95% prediction intervals (PI) of the predicted HR. The observed vs. predicted HR was 0.74 vs. 0.82 (PI: 0.63–1.07) in patients with high baseline plasma VEGF-A above 113.4 ng/L (i.e., the median of evaluable patients), and 1.17 vs. 0.98 (PI: 0.75–1.29) in patients with low baseline plasma VEGF-A below 113.4 ng/L, respectively.

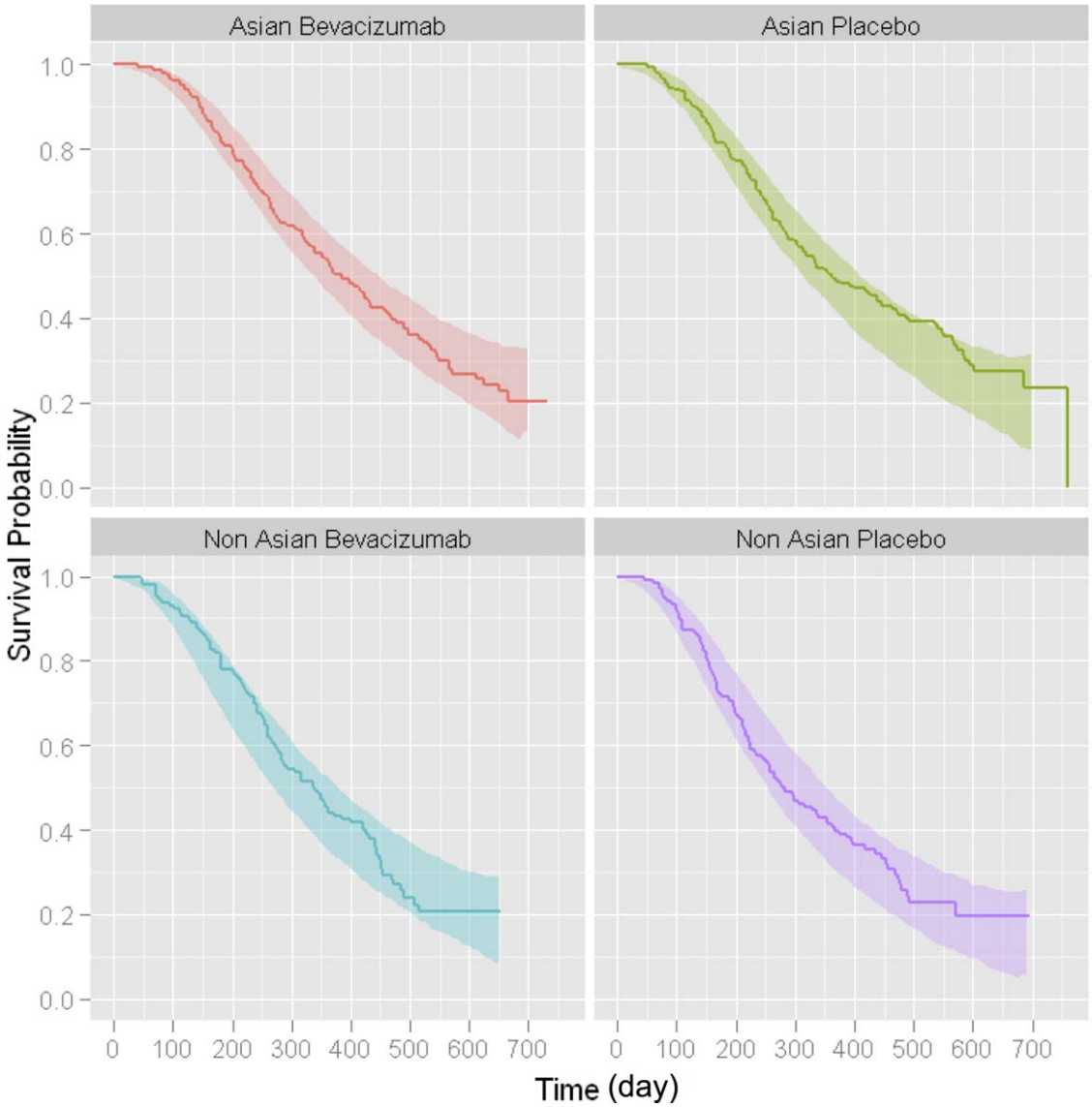

Figure 3 Posterior predictive check of the survival model in various subpopulations. Solid line: observed OS. Band: 95% prediction interval of OS. OS, overall survival.

Table 3 Simulation of 1,000 virtual trials of bevacizumab plus chemotherapy vs. chemotherapy (500 patients per arm)

Population	HR	95% PI
Asian	0.91	0.78–1.06
Non-Asian	0.91	0.79–1.06
Elevated VEGF-A*	0.82	0.70–0.95

*Baseline plasma VEGF-A above the median in evaluable patients of 113.4 ng/L. PI, prediction interval.

Simulations

Model qualification showed that even if baseline plasma VEGF-A did not enter the model, the model was able to predict an HR favorable to bevacizumab in patients with high baseline plasma VEGF-A in both Asian and Western populations, generating the hypothesis that these patients may benefit from bevacizumab. This hypothesis was tested in clinical trial simulations. These simulations showed an expected HR of 0.82 (95% PI: 0.70–0.95, 500 patients per arm, **Table 3**) favorable to bevacizumab plus chemotherapy in patients with elevated plasma VEGF-A (>113.4 ng/L), independently of ethnicity.

DISCUSSION

This is an analysis of individual patient data with gastric cancer (GC) using a model-based approach involving longitudinal tumor size and survival modeling as previously proposed in other tumor types.[1,7] A model-based estimate of time to growth, i.e., the nadir of the tumor size vs. time profile,[6] was the best tumor size metrics to predict OS in the combined databases of two phase III studies in GC.[9,10] As previously observed in colorectal cancer,[6] TTG was a better predictor than weeks 8, 12, or 14 tumor responses (TSratio). We performed a two-stage analysis, meaning that we first estimated TGI metrics and then developed the OS model, and we thereby ignored time-dependent hazard driven by time-dependent tumor size. In a typical clinical trial setting, tumor size is only observed until disease progression when treatment is stopped. Median time of last tumor size observation was 4–5 months while median OS was twice as long (10–11 months) in our dataset. Accounting for tumor size-dependent hazard would have implied an extrapolation substantially beyond last tumor size observation, leading to unrealistically large tumor sizes, as the model assumes exponential growth after end of treatment. We also used a simplified TGI model as an analysis model to estimate TGI metrics. This model ignored drug exposure and covariates and was not used in simulations, particularly for simulating TGI profiles for alternative drug dose or schedules. Another limitation of our analysis is that patients needed to have measurable disease (about 21% did not) and at least two tumor size measurements to be evaluable in the TGI model because the TGI parameters were unidentifiable with only one tumor size measurement. These excluded patients who died or dropped out of the study early before the first tumor size measurement may have rapidly growing tumors. Ninety-one percent of the patients with measurable disease were evaluable in our database. In addition, missing data in baseline biomarker may also incur possible bias.

Our analysis demonstrated and confirmed significant baseline prognostic factors for OS in GC patients: albumin, ECOG PS, prior gastrectomy, LDH, plasma VEGF-A, Asian ethnicity, number of metastatic sites, and baseline tumor size. Low albumin levels, high ECOG PS, and high LDH generally indicate poor health status. Prior gastrectomy, smaller number of metastatic sites, and smaller baseline tumor size indicate lower patient tumor burden. In addition

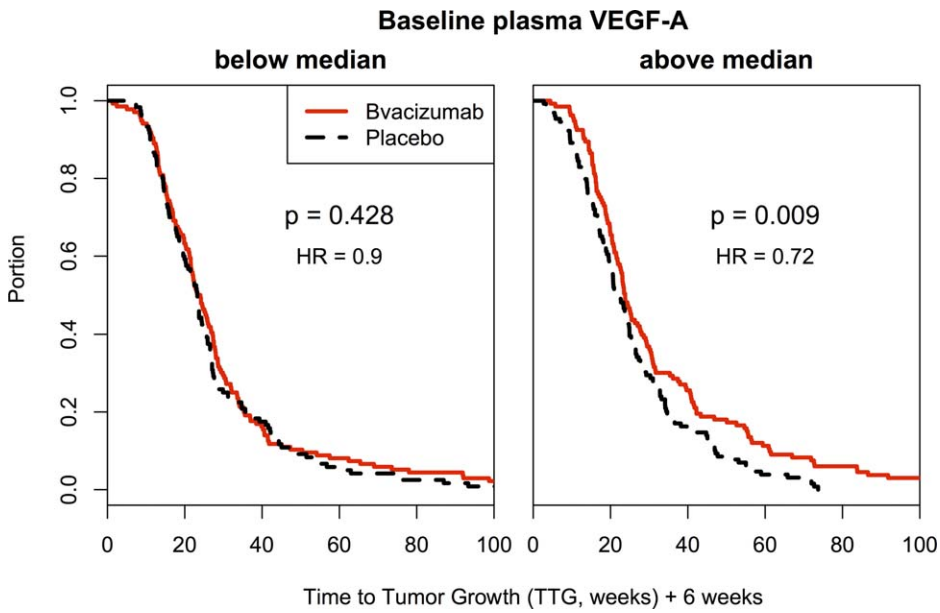

Figure 4 Distribution of TTG (weeks) in the bevacizumab arm (red solid line) and in the placebo arm (black dash line) for the two groups of patients with different baseline plasma VEGF-A levels (below and above median of 113.4 ng/L). The *P* value was calculated using the log-rank test. Six weeks were added to TTG to avoid negative values.

to the baseline prognostic factors, the final OS model incorporates an ethnicity component to account for the longer survival observed in Asian patients. There was no interaction between TTG-OS relationship and ethnicity. This indicates that the proposed model can be used to predict expected OS based on longitudinal tumor size and support drug development decisions in Asian patients as well as in Western patients. Baseline biomarkers (plasma VEGF-A, tumor protein expression of EGFR, neuropilin-1, HER2, and VEGF receptors-1 and -2) were not prognostic in the final OS model. However, simulations showed that patients with high baseline plasma VEGF-A may benefit from bevacizumab treatment independent of ethnicity. The HR of bevacizumab plus chemotherapy vs. chemotherapy alone in patients with baseline plasma VEGF-A exceeding the median value in our population (113.4 ng/mL) would be 0.82 (0.70–0.95) assuming a trial with 500 patients per arm. Bevacizumab effect and benefit over placebo seems to be conditioned on plasma VEGF-A level and this effect is captured by a longer TTG in these patients. As described in **Figure 4,** the TTG distributions in the two arms only separate in the elevated plasma VEGF-A patients explaining the favorable HR in these patients. Western patients also tend to have higher plasma VEGF-A than Asian patients in the AVAGAST study (**Figure 1**), again explaining the more favorable outcome observed in Western patients.[9]

The application of results in GC from our analysis to other cancer types may need further evaluation. Studies investigating baseline VEGF-A as a predictive biomarker for bevacizumab treatment effect on OS outcomes in different types of cancers have shown mixed results. Studies showed that baseline VEGF-A was predictive in GC,[11] but not in metastatic colorectal cancer,[13–16] non-small cell lung cancer,[15,17] small cell lung cancer,[18] pancreatic cancer,[19] ovarian cancer,[20] and metastatic renal cell carcinoma.[15] In patients with metastatic breast cancer, some studies showed that baseline VEGF-A was not predictive for objective response rate,[21] progression-free survival (PFS),[22] and OS,[23] but other studies showed that baseline VEGF-A was predictive for both PFS and OS.[24] Recently, another monoclonal antibody targeting the VEGF pathway, ramucirumab, was approved to treat second-line GC. Further research may be warranted to investigate the predictive value of baseline VEGF-A for the treatment effect of ramucirumab in gastric cancer.

In conclusion, the proposed model and associated simulations support (1) the use of longitudinal tumor size data and TTG as endpoints in early clinical oncology studies,[25–28] (2) the use of Western data to inform design of studies in Asian patients, and (3) the incorporation of prognostic and predictive biomarkers in future study design. Estimation of TGI metrics will likely benefit from optimized tumor size sampling (e.g., more pretreatment and postprogression samples), and further research in this area is warranted.

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Conflict of Interest. Disclosure: Kelong Han, Priti Hegde, Amita Joshi, and Jin Jin are employees of Genentech, receive salary from Genentech, and hold stock of F. Hoffmann-La Roche; Laurent Claret and Rene Bruno receive salary from Pharsight Consulting Services and have acted as a consultant for F. Hoffmann-La Roche; Yongzhe Piao is an employee of Roche Product Development in Asia Pacific, Shanghai, China, and receives salary from Roche Product Development in Asia Pacific; Bob Powell was an employee of Roche Pharmaceutical Research and Early Development (pRED), Beijing, China at the time of writing the article. In addition, Jin Jin holds stock in Eli Lilly.

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Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (http://www.wileyonlinelibrary.com/psp4)