Biomarker Analyses of Clinical Outcomes in Patients With Advanced Hepatocellular Carcinoma Treated With Sorafenib With or Without Erlotinib in the SEARCH Trial

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Disclosures

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Statement of Translational Relevance:

Validated biomarkers of prognosis and response to sorafenib have not yet been identified in patients with advanced HCC. We assessed whether baseline concentrations of 15 plasma biomarkers and various combinations of these biomarkers, as well as mutations in 19 oncogenes, could predict prognosis or treatment response in patients with advanced HCC enrolled in SEARCH, a phase 3 trial of sorafenib with or without erlotinib. We found that high baseline plasma HGF and VEGF-A correlated significantly with shorter OS, , and high KIT with longer OS. In addition, high VEGF-C correlated significantly with better TTP and DCR. Two multimarker signatures, one consisting of 2 markers (HGF and VEGF-A) and the other of 5 markers (HGF, VEGF-A, KIT, VEGF-C, and epigen), showed significant correlations with OS. These findings, if confirmed, could potentially guide clinicians on how to predict patient prognosis or response to treatment.

ABSTRACT

Purpose: Sorafenib is the current standard therapy for advanced HCC, but validated biomarkers predicting clinical outcomes are lacking. This study aimed to identify biomarkers predicting prognosis and/or response to sorafenib, with or without erlotinib, in HCC patients from the phase 3 SEARCH trial.

Experimental Design: 720 patients were randomized to receive oral sorafenib 400 mg BID plus erlotinib 150 mg QD or placebo. Fifteen growth factors relevant to the treatment regimen and/or to HCC were measured in baseline plasma samples.

Results: Baseline plasma biomarkers were measured in 494 (69%) patients (sorafenib plus erlotinib, n=243; sorafenib plus placebo, n=251). Treatment arm–independent analyses showed that elevated HGF (HR, 1.687 [high vs low expression]; endpoint multiplicity adjusted [e-adj] *P*=0.0001) and elevated plasma VEGF-A (HR, 1.386; e-adj *P*=0..0377) were significantly associated with poor OS in multivariate analyses, and low plasma KIT (HR, 0.75 [high vs low]; *P*=0.0233; e-adj *P*=0.2793) tended to correlate with poorer OS. High plasma VEGF-C independently correlated with longer TTP (HR, 0.633; e-adj *P*=0.0010) and trended toward associating with improved disease control rate (univariate:OR, 2.047; *P*=0.030; e-adj *P*=0.420). In 67% of evaluable patients (339/494), a multimarker signature of HGF, VEGF-A, KIT, epigen, and VEGF-C correlated with improved median OS in multivariate analysis (HR, 0.150; *P*<0.00001). No biomarker predicted efficacy from erlotinib.

Conclusions: Baseline plasma HGF, VEGF-A, KIT, and VEGF-C correlated with clinical outcomes in HCC patients treated with sorafenib with or without erlotinib. These biomarkers plus epigen constituted a multimarker signature for improved OS.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second most frequent cause of cancer deaths worldwide.(1) Most patients are diagnosed with advanced stage disease, when curative treatments, including resection, liver transplantation, and ablation, are no longer an option.(2,3) The oral multikinase inhibitor sorafenib, which targets Raf-1, VEGFR1-3, PDGFR, KIT, RET, and other tyrosine kinases, has both antiproliferative and antiangiogenic effects.(4) Sorafenib has demonstrated survival benefits in patients with advanced unresectable HCC and remains the standard of care for this disease based on two phase 3 trials.(5,6)

Erlotinib is a potent, orally active inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase approved to treat patients with advanced non–small-cell lung and pancreatic cancers.(7-9) In two single-arm phase 2 trials, erlotinib showed modest prolonged progression-free survival and promising disease control in patients with unresectable HCC.(10,11) Moreover, a phase 2 trial of the combination of erlotinib and the antiangiogenic monoclonal antibody bevacizumab, which binds to and inhibits vascular endothelial growth factor (VEGF), found that this combination led to clinically meaningful progression-free survival and response rates in patients with advanced HCC.(12)

Based on these findings, the SEARCH trial was designed to compare the efficacy and safety of sorafenib plus erlotinib with sorafenib plus placebo as first-line treatment in patients with advanced/unresectable HCC.(13) In this trial, 720 patients were randomized to sorafenib plus erlotinib (n=362) or sorafenib plus placebo (n=358), with a primary endpoint of overall survival (OS).(13) The trial did not meet the primary endpoint; median OS was similar in the sorafenib plus erlotinib and sorafenib plus placebo groups (hazard ratio [HR], 0.929; *P*=0.204; 9.5 vs 8.5 months, respectively), as was median time to progression (TTP; HR, 1.135; *P*=0.091; 3.2 vs 4.0 months).(13) Of note, the overall response rate (ORR) with sorafenib plus erlotinib was almost

twice as high as the ORR with sorafenib plus placebo (7% vs 4%).(13) In contrast, the disease control rate (DCR) was significantly lower (43.9% vs 52.5%, *P*=0.010) in the sorafenib plus erlotinib group compared with sorafenib plus placebo, perhaps due to the shorter treatment duration in the sorafenib plus erlotinib group.(13)

Despite this trial not demonstrating a benefit for the addition of erlotinib to sorafenib, much can be learned by assessing biomarkers that may predict prognosis and/or benefit from treatment. A previous prospective study demonstrated that lower baseline plasma levels of insulin-like growth factor-1 and higher plasma VEGF levels correlated with advanced clinicopathologic parameters and poor OS in patients with HCC.(14) In addition, an analysis of the 602 patients in the phase 3 Sorafenib HCC Assessment Randomized Protocol (SHARP) trial randomized to receive oral sorafenib or placebo found that baseline plasma concentrations of angiopoietin 2 and VEGF-A were independent prognostic predictors of patient survival in the entire patient population and the placebo cohort.(15) Also in SHARP, trends toward enhanced survival benefit from sorafenib treatment were seen in patients with high plasma KIT and/or low hepatocyte growth factor (HGF) concentrations at baseline (*P* of interaction = 0.081 and 0.073, respectively). The goal of the present exploratory biomarker analysis of patients in SEARCH was to identify biomarkers that may predict prognosis and/or benefit from sorafenib, with or without erlotinib, in patients with advanced HCC. In this biomarker study 15 candidate mechanistic plasma biomarkers – proteins with known or hypothesized relevance to sorafenib's and/or erlotinib's mechanism of action or to HCC outcome – were examined. Analytes selected for plasma biomarker analysis are either molecular targets of sorafenib or ligands of those targeted receptors (VEGF-A, VEGF-C, soluble KIT, and PDGF-BB), or are ligands of the EGFR targeted by erlotinib (amphiregulin, betacellulin, EGF, epigen, epiregulin, heregulin, heparin binding EGF (hbEGF), and TGF-α), or have been implicated in the pathogenesis of HCC and were found to correlate with measures of outcome in SHARP (bFGF, IGF-2, and HGF).(15) In addition, the mutational status of 19 genes

was analyzed in available tumor samples; the hotspot mutation panel utilized includes genes targeted by sorafenib and erlotinib as well as genes reported to be mutated in HCC (16), though most at low prevalence.

PATIENTS AND METHODS

Patients and Samples

The SEARCH trial has been described in detail.(13) Eligible patients with histologically or radiologically confirmed advanced/metastatic HCC not amenable to local therapies, an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, and Child-Pugh class A (determined during screening; n=720) were randomized to treatment with sorafenib 400 mg twice daily plus either erlotinib 150 mg once daily (n=362) or matching placebo (n=358), stratified by ECOG performance score (0 vs 1), macrovascular invasion and/or extrahepatic spread (yes vs no), smoking status (current vs former vs never), and geographic region (North America/South America vs Europe/South Africa vs Asia-Pacific). The primary endpoint was OS. Secondary endpoints included TTP by independent radiologic review, DCR, ORR, and safety.

Blood samples were collected before treatment (during screening or predose on day 1 of cycle 1) into tubes containing ethylenediamine tetraacetic acid as anticoagulant. Plasma was prepared by centrifugation and removed to a separate tube. The tubes were stored at –70°C (although storage at –20°C was acceptable if no –70°C freezer was available) and shipped on dry ice every 6 weeks (4–5 weeks if stored at –20°C) to the central laboratory.

Formalin-fixed paraffin-embedded archival tumor biopsy samples or unstained slides were collected at screening.

Submission of biomarker samples and consent for tumor genetics were optional per the SEARCH protocol; all plasma samples received were assayed for plasma biomarkers, and all usable tumor samples received from patients who gave genetic consent were assayed for tumor mutations.

Biomarker Assays

Candidate plasma biomarkers were chosen based on their known or hypothesized relevance to the mechanisms of action of sorafenib and/or erlotinib and/or their relevance to HCC, and the planned analyses were prespecified at study design.(15) All plasma biomarkers were measured by AssayGate Laboratories (Ijamsville, MD, USA). Plasma concentrations of VEGF-C, heregulin, soluble KIT (R&D Systems, Minneapolis, MN, USA), epigen (USCN Life Science Inc, Wuhan City, China), and IGF2 (Mediagnost GmbH, Reutlingen, Germany) were measured by commercially available enzyme-linked immunosorbent assay kits; and plasma concentrations of VEGF-A, HGF, amphiregulin, betacellulin, EGF, epiregulin, HbEGF, TGF-α, bFGF, and PDGF-BB were measured using multiplex Luminex bead assays (Thermo Fisher Scientific Inc., Waltham, MA USA), according to the manufacturer's instructions. Mutations in 19 oncogenes (ABL1, AKT1, AKT2, BRAF, CDK4, EGFR, ERBB2, FGFR1, FGFR3, FLT3, HRAS, JAK-2, KIT, KRAS, MET, NRAS, PDGFA, PIK3CA, RET) were analyzed in tumor DNA by Quintiles Laboratories (Marietta, GA, USA) using the Sequenom OncoCarta 1.0 multiplex assay system, according to the manufacturer's instructions (the list of mutations assayed is shown in **Supplementary Figure 2**). All personnel associated with the laboratories performing the assays were blinded to treatment group assignments and all clinical data, including outcome.

Statistical Methods and Analyses

Statistical analyses were performed using SAS and R software version 9.2 (SAS Institute Inc, Riyadh, Saudi Arabia). Clinical outcome measures included in the biomarker analyses were OS,

TTP, and DCR. Each biomarker was analyzed as a continuous variable and a dichotomized variable (dichotomized using the median and an optimized cutoff point determined using the maximum chi-square method, which tests all possible cutoff points between the 25th and 75th percentiles and selects the optimal cutoff value), as well as being included in multimarker models.

For multimarker models, feature selection methods were used to identify a subset of biomarkers to be used in developing multimarker signatures associated with clinical outcomes.(17) The 14 plasma biomarkers tested on a continuous scale (excluding Heregulin, for which a large proportion of values were BLQ) were included in feature selection and were analyzed as log2 transformed continuous variables, utilizing a model adjusting for treatment. Penalized Cox regression using a bootstrap elastic net (BELNET) was used to investigate the stability of feature selection. This procedure repeatedly performs feature selection on bootstrap samples (n=50) drawn from the observed data to calculate a selection probability for each feature (ie, the proportion of times each of the 14 biomarkers was selected across all bootstrap samples). Selection probability thresholds of 0.9 and 0.8 were considered to identify sets of features of interest. A composite score was generated using the selected biomarkers from each analysis, and optimal cutoffs were identified using the maximum chi-square method.

For each biomarker associated with prognosis (including both single biomarkers and multimarker signatures), multivariable analyses were performed which included clinical variables identified as associated with prognosis. Cox regression models were used to identify the clinical variables prognostic for OS, TTP and DCR in HCC. The clinical variables tested for prognostic significance were as follows: age, ECOG PS, gender, geographic region, race, stage at randomization, ascites, macroscopic vascular invasion, extrahepatic spread, cirrhosis, smoking status, Child-Pugh score, BCLC score, hepatitis B and hepatitis C. Multivariable models were

then run which included the biomarkers of interest and the identified prognostic clinical covariates.

RESULTS

Populations of Patients Evaluated for Biomarkers

A total of 720 patients were randomized in the SEARCH trial, 362 to sorafenib plus erlotinib and 358 to sorafenib plus placebo.(13) Plasma samples were obtained from 494 patients (68.6%) at baseline, 243 (67.1%) in the sorafenib plus erlotinib group and 251 (70.1%) in the sorafenib plus placebo group. Baseline demographic and disease characteristics of patients in the biomarker subpopulations were similar to those in the overall SEARCH population **(Table 1)**. Clinical outcomes were also similar in the SEARCH biomarker and SEARCH overall populations. In the biomarker population, OS in the sorafenib plus erlotinib and in the sorafenib plus placebo groups was 9.7 and 8.9 months, respectively (HR, 0.922; 95% CI, 0.749–1.133), and TTP was 3.2 and 3.9 months (HR, 1.166; 95% CI, 0.937–1.450). In the overall SEARCH population, OS of the sorafenib plus erlotinib and sorafenib plus placebo groups was 9.5 and 8.5 months (HR, 0.929; 95% CI, 0.781–1.106), respectively, and TTP was 3.2 and 4.0 months (HR, 1.135; 95% CI, 0.944–1.366; **Table 2**).

Plasma Biomarkers Correlating With Clinical Outcomes in the Full Biomarker Population

Median, mean, range, and 25^{th}/75^{th} percentiles are shown for key biomarkers in **Supplementary Table 3**. In the first set of analyses, the treatment arms were combined into one group because all patients had been treated with sorafenib, making this a treatment arm–independent analysis **(Table 3)**. Plasma biomarkers were first assayed for their ability to predict

OS. When dichotomized using the maximum chi-square method, high baseline HGF correlated significantly with shorter OS (HR, 1.672; 95% CI, 1.352–2.074; max chi-square *P*=0.00005; endpoint multiplicity adjusted [e-adj] *P*=0.0007; **Figure 1A**). High baseline HGF also correlated significantly with shorter OS when dichotomized at the median (HR, 1.595; 95% CI, 1.294–1.967; max chi-square *P*=0.00001; e-adj *P*=0.0002), when analyzed as a continuous variable (HR, 1.148; 95% CI, 1.070–1.233; max chi-square *P*=0.0001; e-adj *P*=0.0015; **Table 3**), as well as when analyzed among only those patients with Stage IV disease (HR, 1.708; 95% CI, 1.295–2.254). High baseline VEGF-A showed a trend toward correlation with shorter OS when dichotomized at the optimized cutoff (HR, 1.385; 95% CI, 1.124–1.704; max chi-square *P*=0.03; e-adj *P*=0.39; **Figure 1B**), when dichotomized at the median, or analyzed as a continuous variable **(Table 3)**, as well as when analyzed among only those patients with Stage IV disease (HR, 1.480; 95% CI, 1.126–1.946). High baseline KIT showed a trend toward correlation with longer OS (analysis using optimized cutoff: HR, 0.713; 95% CI, 0.562–0.897; max chi-square *P*=0.05; e-adj *P*=0.60; **Figure 1C**; analysis as a continuous variable, **Table 3**). In multivariate analyses including known prognostic clinical variables, HGF was independently prognostic for OS whether analyzed as a dichotomized (e-adj *P*=0.0001) or continuous (e-adj *P*=0.0108) variable (**Table 3**). VEGF-A was also indpendently prognostic for OS (dichotomized, e-adj *P*=0.0377; continuous, e-adj *P*=0.0457), and both HGF and VEGF-A remained independently prognostic when included in the same multivariable model together (**Table 3**). While the *P*-values for the association between KIT and OS in multivariate analyses were 0.0233 and 0.0323 for dichotomized and continuous analyses, respectively, the adjusted *P*-values did not reach <0.05, and thus this association is not statistically significant.

All plasma biomarkers were also assessed for correlation with other efficacy outcomes (TTP and DCR). High baseline VEGF-C correlated with longer TTP when dichotomized using the max

chi-square method (HR, 0.615; 95% CI, 0.493–0.767; max chi-square *P*=0.0003; e-adj *P*=0.0042; **Figure 1D**), when dichotomized at the median (HR, 0.679; 95% CI, 0.544–0.846; max chi-square *P*=0.0006; e-adj *P*=0.0078), and when analyzed as a continuous variable (HR, 0.877; 95% CI, 0.806–0.957; max chi-square *P*=0.0032; e-adj *P*=0.0486). High baseline VEGF-C also correlated with higher DCR when dichotomized at the median (odds ratio, 1.819; 95% CI, 1.225–2.714; max chi-square *P*=0.003; e-adj *P*=0.0421), and showed similar trends when dichotomized using an optimized cutoff or when analyzed as a continuous variable. VEGF-C remained independently prognostic for TTP in multivariable models when analyzed as either a dichotomized (e-adj *P*=0.0010) or as a continuous (e-adj *P*=0.0195) variable (**Table 3**). None of the other plasma biomarkers assayed was associated with any efficacy outcome.

Analysis of Plasma Biomarkers as Predictors of Treatment Benefit

In the second, "predictive" set of analyses, differences in clinical outcome between treatment arms were analyzed in biomarker subgroups. Because one arm received sorafenib plus erlotinib and the other received sorafenib plus placebo, the biomarker data could be analyzed for correlations between biomarkers and erlotinib treatment effect, thus attempting to identify biomarkers predicting benefit from one treatment regimen over the other. For example, neither patients with low (ie, <195.365 pg/mL) nor high (ie, ≥195.365 pg/mL) baseline betacellulin showed significant survival benefit from the addition of erlotinib to sorafenib treatment compared with sorafenib plus placebo (unadjusted interaction *P*-value=0.357), though a trend toward benefit from the addition of erlotinib was seen in the high betacellulin group (HR, 0.725; 95% CI, 0.522–1.004; *P*=0.0531) (**Figure 2**). Likewise, none of the other plasma biomarkers showed a significant relationship with treatment effect, suggesting that none of the candidate

biomarkers significantly predict benefit from one treatment arm over the other (**Supplementary Tables 1** and **2**, and **Supplementary Figure 1**).

Multimarker Signatures

In the third set of analyses, feature-selection methods were used to identify multimarker signatures associated with clinical outcomes including generation of a composite score. The multimarker signature analysis was performed for both treatment arm–independent and predictive analyses. Two biomarkers, HGF and VEGF-A, met the stringent BELNET threshold of 0.9 in the treatment arm–independent analysis. When patients were divided into those with (n=270) and without (n=224) this signature based on a composite score, median OS was significantly longer in the former group (11.7 vs 6.8 months; HR, 0.573; 95% CI, 0.465–0.705; *P*<0.00001; **Figure 3A**). Five markers (KIT, epigen, HGF, VEGF-A, and VEGF-C) met the relaxed BELNET threshold of 0.8, with 339 patients with and 155 without the signature. A multimarker composite score defined by these 5 markers also showed a statistically significant association with OS in treatment arm–independent analysis (11.5 vs 6.0 months; HR, 0.505; 95% CI, 0.407–0.627; *P*<0.0001; **Figure 3B**). Both the 2 marker (HR, 0.050; 95% CI, 0.016–0.151; *P*<0.00001) and the 5 marker (HR, 0.150; 95% CI, 0.078–0.287; *P*<0.00001) sets remained independently prognostic of OS in multivariable models including the clinical covariates identified as prognostic for OS (see footnote of **Table 3**). No predictive multimarker signature correlating with treatment effect (ie, in a predictive analysis as described above) could be identified (data not shown).

Mutations in Tumor Samples

Only 33 tumor samples were evaluable for oncogene mutations. Of these, 30 were negative for mutations in the 19 oncogenes assessed. Tumors of 3 patients were positive for gene mutations. One patient, with both H-RAS and PDGFRA mutations, was in the sorafenib plus erlotinib treatment group and had a best response of stable disease. The second patient, with an EGFR T790M mutation, was treated with sorafenib plus erlotinib, and had a best response of progressive disease. The third patient had a mutation in MET, although this T992I mutation is at best a weak activating mutation and its presence in healthy individuals suggests it may be a nononcogenic single-nucleotide polymorphism (18); this patient was in the sorafenib plus placebo treatment group and had a best response of progressive disease.

DISCUSSION

This study, conducted in the setting of the phase 3 SEARCH trial (13), is one of the largest studies to date to attempt to identify biomarkers predictive of prognosis and/or treatment benefit of erlotinib over placebo in addition to sorafenib in patients with advanced HCC. Of the 720 patients in the overall SEARCH population, 494 (68.6%) were included in the SEARCH biomarker population. Demographic characteristics and clinical outcomes (OS and TTP) were similar in the biomarker and overall populations, indicating that the biomarker population was representative of the full study population.

In treatment arm–independent analyses of the SEARCH biomarker population, high baseline levels of plasma HGF showed a significant correlation with poorer OS. HGF is the ligand for the receptor tyrosine kinase c-MET. The HGF-MET cascade is associated with hepatocarcinogenesis.(19) Elevated HGF levels have been associated with poor prognosis in patients with HCC,(15) and high expression of c-MET has been associated with poor outcomes

in patients with HCC treated with sorafenib.(20) The present clinical results, showing that elevated HGF levels at baseline were associated with significantly shorter OS in patients with advanced HCC, are consistent with these earlier findings. The present study also indicated that high KIT levels tended to correlate with better OS.

Because of the study design, in which both arms were treated with sorafenib, it could not be determined whether correlation with outcome in these treatment arm–independent analyses was due to a biomarker's indication of prognosis or due to a biomarker's correlation with sorafenib benefit (or both); such a clear distinction would only be possible to achieve with the inclusion of an additional arm without sorafenib treatment. In the phase 3 SHARP trial, high HGF (in univariate analysis) and high VEGF-A (in both univariate and multivariate analyses) correlated with poor prognosis, whereas KIT was not prognostic.(13) These findings suggest that the correlations of HGF and VEGF-A with OS observed in the SEARCH trial were due, at least in part, to the prognostic effects of these biomarkers in HCC. In addition, in SHARP, high KIT and low HGF showed a trend toward predicting greater benefit from sorafenib treatment, whereas VEGF-A was clearly not predictive. These results suggest that in SEARCH, at least part of the correlation observed between KIT or HGF and OS in the treatment arm–independent analyses may be due to a role in predicting benefit from sorafenib treatment.

In the present study, in which all patients were treated with sorafenib, high baseline VEGF-A, which promotes vascular angiogenesis through activation of endothelial cell associated VEGFR-1 and VEGFR-2 (21), tended to correlate with poorer OS in univariate analysis and correlated significantly in multivariate analysis; since the placebo-controlled SHARP trial showed that elevated VEGF-A was prognostic of poor outcome but not predictive of sorafenib benefit, the observation in the present study that elevated VEGF-A correlates with shorter survival in the full study population (all treated with sorafenib) is consistent with VEGF-A having a prognostic role in HCC. In contrast to the VEGF-A results, those with high baseline VEGF-C, a ligand for

VEGFR-2 and VEGFR-3 which promotes angiogenesis and lymphangiogenesis (21), had longer TTP in the present study, though no similar relationship was observed with OS. Though the absence of a non-sorafenib arm in the present study precludes decisive determination of whether the VEGF-C result is due to a prognostic effect or is predictive of treatment benefit from sorafenib, it has been shown in previous studies that elevated tumor levels of VEGF-C or peritumoral levels of VEGF-C in combination with VEGFR-1 and VEGFR-3 correlate with poor prognosis in HCC, including shorter disease free survival, time to recurrence, and overall survival.(22-24) While these studies examined VEGF-C protein levels in tissue and not in circulation, these published findings suggest that VEGF-C, like VEGF-A, is an indicator of poor prognosis in HCC. In contrast, a phase 2 study of advanced HCC patients treated with the VEGFR inhibitor sunitinib showed that elevated plasma VEGF-C concentrations correlated with improved outcomes, including longer TTP and OS and increased DCR (25). This finding in combination with the VEGF-C result from the present study suggests that elevated circulating VEGF-C levels may enhance the antitumor activity of therapies targeting the VEGFR pathway in HCC, though the role of circulating VEGF-C in HCC as compared to tumor or peritumor VEGF-C is not well studied. In addition, the present study demonstrated that two multimarker signatures correlated with OS in treatment arm–independent analyses. One signature included two biomarkers, HGF and VEGF-A, and the other included 5 markers, HGF, VEGF-A, KIT, VEGF-C, and epigen.

These biomarkers were also tested in predictive analyses to determine whether their baseline concentrations correlated with treatment benefit in one treatment arm versus the other. However, none of these biomarkers, either individually or in multimarker analyses, significantly predicted differences in benefit from sorafenib plus erlotinib versus sorafenib plus placebo.

The biomarker analyses in SEARCH were exploratory and hypothesis generating. Although several potentially prognostic and predictive biomarkers were identified in the advanced HCC

setting, further investigations are needed to confirm and validate their predictive and/or prognostic value.

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TABLES

Table 1. Baseline Patient Characteristics in the Biomarker and Full-Analysis Sets

	Biomarker Population			Full Analysis Set		
Characteristic	**Overall**	**Sorafenib + Placebo**	**Sorafenib + Erlotinib**	**Overall**	**Sorafenib + Placebo**	**Sorafenib + Erlotinib**
n (%)	494 (68.6)	251 (70.1)	243 (67.1)	720	358	362
Median age, y	61.0	62.0	61.0	—	60.0	60.5
Sex						
Male	414 (83.8)	210 (83.7)	204 (84.0)	581 (80.7)	286 (79.9)	295 (81.5)
Female	80 (16.2)	41 (16.3)	39 (16.0)	139 (19.3)	72 (20.1)	67 (18.5)
Liver cirrhosis	338 (68.4)	176 (70.1)	162 (66.7)	491 (68.2)	251 (70.1)	240 (66.3)
Ascites	46 (9.3)	23 (9.2)	23 (9.5)	76 (10.6)	36 (10.1)	40 (11.0)
Macroscopic vascular invasion	210 (42.5)	111 (44.2)	99 (40.7)	291 (40.4)	153 (42.7)	138 (38.1)
Extrahepatic spread	290 (58.7)	160 (63.7)	130 (53.5)	424 (58.9)	219 (61.2)	205 (56.6)
Etiology						
Hepatitis B	159 (32.2)	79 (31.5)	80 (32.9)	255 (35.4)	133 (37.2)	122 (33.7)
Hepatitis C	130 (26.3)	57 (22.7)	73 (30.0)	191 (26.5)	84 (23.5)	107 (29.6)
BCLC stage						
B	75 (15.2)	33 (13.1)	42 (17.3)	108 (15.0)	48 (13.4)	60 (16.6)
C	419 (84.8)	218 (86.9)	201 (82.7)	612 (85.0)	310 (86.6)	302 (83.4)
Child-Pugh score						
5	353 (71.5)	185 (73.7)	168 (69.1)	498 (69.2)	252 (70.4)	246 (68.0)
6	128 (25.9)	59 (23.5)	69 (28.4)	203 (28.2)	93 (26.0)	110 (30.4)
ECOG PS*						
0	307 (62.1)	153 (61.0)	154 (63.4)	439 (61.0)	215 (60.1)	224 (61.9)
1	184 (37.2)	97 (38.6)	87 (35.8)	278 (38.6)	142 (39.7)	136 (37.6)
2	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	1 (0.3)
Missing	2 (0.4)	1 (0.4)	1 (0.4)	2 (0.3)	1 (0.3)	1 (0.3)
Geographic region						

Americas	88 (17.8)	46 (18.3)	42 (17.3)	173 (24.0)	85 (23.7)	88 (24.3)
Europe	295 (59.7)	146 (58.2)	149 (61.3)	369 (51.3)	183 (51.1)	186 (51.4)
Asia-Pacific	111 (22.5)	59 (23.5)	52 (21.4)	178 (24.7)	90 (25.1)	88 (24.3)
Stage at randomization						
I	6 (1.2)	4 (1.6)	2 (0.8)	10 (1.4)	5 (1.4)	5 (1.4)
II	44 (8.9)	22 (8.8)	22 (9.1)	58 (8.1)	29 (8.1)	29 (8.0)
IIIA	123 (24.9)	56 (22.3)	67 (27.6)	182 (25.3)	90 (25.1)	92 (25.4)
IIIB	31 (6.3)	10 (4.0)	21 (8.6)	46 (6.4)	16 (4.5)	30 (8.3)
IIIC	20 (4.0)	12 (4.8)	8 (3.3)	27 (3.8)	16 (4.5)	11 (3.0)
IV	269 (54.6)	147 (58.6)	122 (50.2)	396 (55.0)	202 (56.4)	194 (53.6)
Missing	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	1 (0.3)
Smoking status						
Never	142 (28.7)	71 (28.3)	71 (29.2)	219 (30.4)	107 (29.9)	112 (30.9)
Former	191 (38.7)	97 (38.6)	94 (38.7)	260 (36.1)	128 (35.8)	132 (36.5)
Current	161 (32.6)	83 (33.1)	78 (32.1)	241 (33.5)	123 (34.4)	118 (32.6)

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; ECOG PS=Eastern Cooperative Oncology Group performance status.
All values n (%) except where noted.
* ECOG PS based on clinical database

Table 2. OS and TTP in the Biomarker Population and Full Analysis Set

	Biomarker Population		**Full Analysis Set**	
	Sorafenib + Placebo	**Sorafenib + Erlotinib**	**Sorafenib + Placebo**	**Sorafenib + Erlotinib**
OS, months				
Median	8.9	9.7	8.5	9.5
95% CI	7.4–10.8	8.0–11.0	7.4–10.6	8.2–10.5
HR	0.922		0.929	
95% CI	0.749–1.133		0.781–1.106	
TTP, months				
Median	3.9	3.2	4.0	3.2
95% CI	2.9–4.5	2.6–4.1	2.9–4.5	2.7–4.1
HR	1.166		1.135	
95% CI	0.937–1.450		0.944–1.366	
Best Resonse, %				
ORR (CR+PR)	3.6	6.2	3.9	6.6
DCR (CR+PR+SD)	51.8	42.4	52.5	43.9

Abbreviations: HR=hazard ratio; OS=overall survival; TTP=time to progression; ORR=objective response rate; DCR=disease control rate; CR=complete response; PR=partial response; SD=stable disease.

Table 3. Summary of Plasma Biomarker Treatment arm–independent Analyses of Interest, Including Both Univariate and Multivariate Analyses

Marker	Dichotomized Using Max Chi-Square Analysis				Dichotomized at the Median			Continuous Variable		
	Percentile for Dichotomization	HR (95% CI)	Max Chi-Square *P* Value	Adjusted *P* Value[a]	HR (95% CI)	*P* Value	Adjusted *P* Value[a]	HR (95% CI)	*P* Value	Adjusted *P* Value[a]

OS – Univariate analyses										
VEGF-A	57.5	1.385 (1.124–1.704)	0.0300[b]	0.3900	1.280 (1.040–1.575)	0.0196[b]	0.2549	1.172 (1.045–1.313)	0.0070[b]	0.0976
VEGF-C	48.4	0.829 (0.674–1.020)	0.4000	1.0000	0.876 (0.712–1.078)	0.2105	1.0000	0.973 (0.900–1.054)	0.5039	1.0000
HGF	42.9	1.672 (1.352–2.074)	0.00005[b]	0.0007[b]	1.595 (1.294–1.967)	0.00001[b]	0.0002[b]	1.148 (1.070–1.233)	0.0001[b]	0.0015[b]
KIT	68.6	0.713 (0.562–0.897)	0.0500[b]	0.6000	0.878 (0.714–1.080)	0.2188	1.0000	0.756 (0.607–0.941)	0.0122[b]	0.1586
TTP – Univariate analyses										
VEGF-C	48.4	0.615 (0.493–0.767)	0.0003[b]	0.0042[b]	0.679 (0.544–0.846)	0.0006[b]	0.0078[b]	0.877 (0.806–0.957)	0.0032[b]	0.0486[b]
DCR – Univariate analyses										
VEGF-C	47.7	2.047[c] (1.376–3.059)	0.0300[b]	0.4200	1.819[c] (1.225–2.714)	0.0030[b]	0.0421[b]	1.251[c] (1.068–1.473)	0.0053[b]	0.0789
OS – Multivariate analyses[d]										
VEGF-A	57.5	1.386 (1.119–1.715)	0.0029[b]	0.0377[b]	ND	ND	ND	1.196 (1.061–1.347)	0.0035[b]	0.0457[b]
HGF	42.9	1.687 (1.340–2.131)	<0.00001[b]	0.0001[b]	ND	ND	ND	1.135 (1.053–1.225)	0.0008[b]	0.0108[b]
KIT	68.6	0.754 (0.586–0.963)	0.0233[b]	0.2793	ND	ND	ND	0.772 (0.610–0.978)	0.0323[b]	0.3875
VEGF-A, with HGF in model	57.5	1.419 (1.144–1.758)	0.0014[b]	ND	ND	ND	ND	1.194 (1.060–1.343)	0.0033[b]	ND
HGF, with VEGF-A in model	42.9	1.706 (1.357–2.151)	<0.0001[b]	ND	ND	ND	ND	1.135 (1.053–1.224)	0.0010[b]	ND
TTP – Multivariate analyses[e]										

VEGF-C	48.4	0.633 (0.505–0.793)	0.0001[b]	0.0010[b]	ND	ND	ND	0.864 (0.791–0.945)	0.0014[b]	0.0195[b]
DCR – Multivariate analyses[f]										
VEGF-C	47.7	2.156[c] (1.414–3.309)	0.0724	1.0000	ND	ND	ND	1.183[c] (0.976–1.137)	0.0871	1.0000

Abbreviations: DCR=disease control rate; HR=hazard ratio; HGF=hepatocyte growth factor; OS=overall survival; TTP=time to progression; VEGF=vascular endothelial growth factor; ND=not done.

[a]Endpoint multiplicity adjusted *P* value.

[b]*P*<0.05.

[c]Odds ratio.

[d]OS model included the following clinical covariates identified as prognostic for OS in the SEARCH biomarker population: ECOG PS, stage, macroscopic vascular invasion, extrahepatic spread, Child-Pugh status, BCLC score, and hepatitis B, and the individual biomarker unless multiple biomarkers noted.

[e]TTP model included the following clinical covariates identified as prognostic for TTP in the SEARCH biomarker population: age, gender, geographic region, stage, extrahepatic spread, and hepatitis B.

[f]DCR model included the following clinical covariates identified as prognostic for DCR in the SEARCH biomarker population: age, stage, extrahepatic spread, smoking status, BCLC score, and hepatitis B.

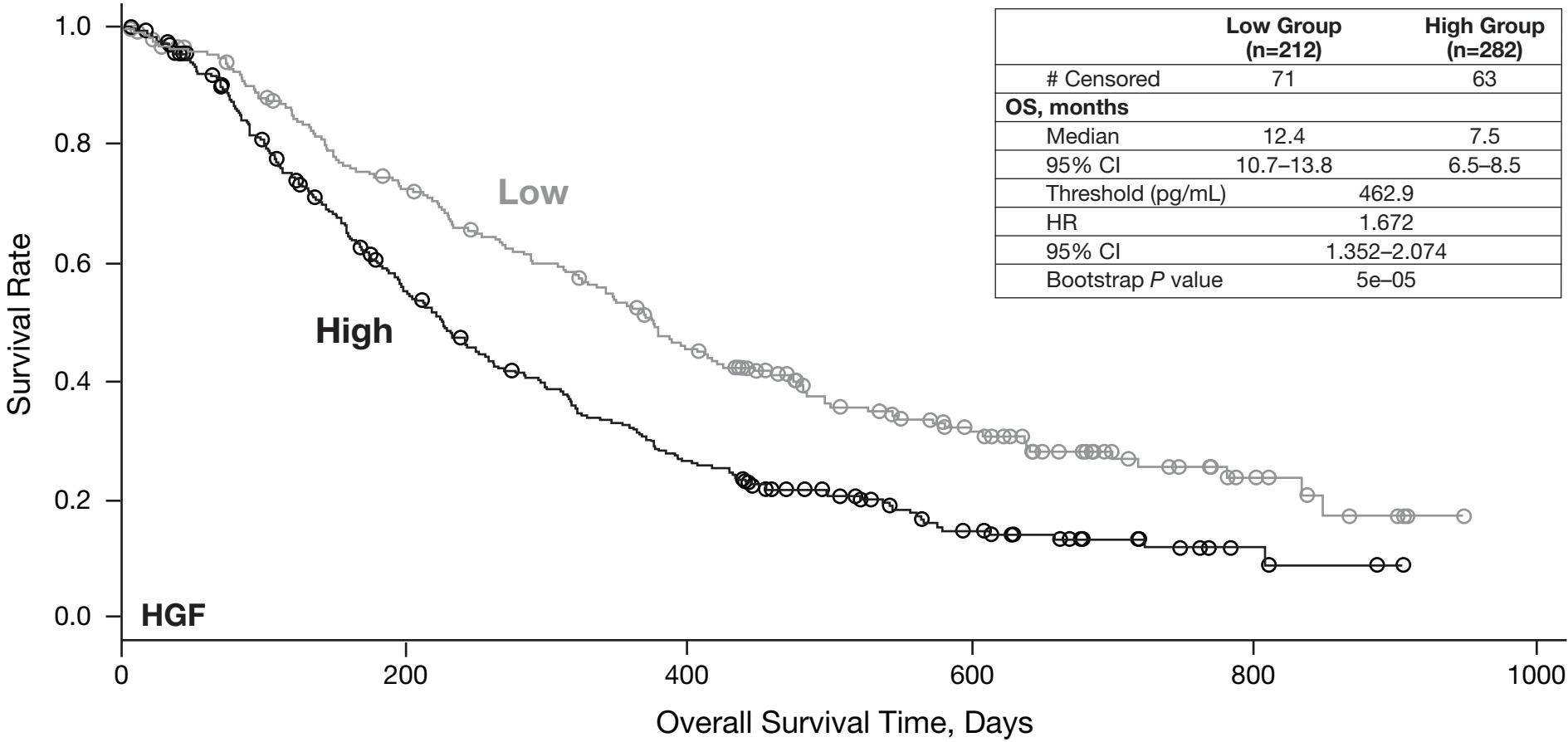
FIGURES

Figure 1. Kaplan-Meier survival curves showing correlations between optimized dichotomization thresholds of baseline biomarker concentrations and clinical outcomes in patients in the SEARCH trial treated with sorafenib plus placebo or sorafenib plus erlotinib. (A–C) Correlations between OS and (A) HGF, (B) VEGF-A and (C) KIT concentrations. (D) Correlation between TTP and VEGF-C concentration.

Figure 2. Kaplan-Meier survival curves of treatment effect on OS in patients with low (left panel) and high (right panel) baseline betacellulin (max chi-square interaction *P*=0.357). Betacellulin was dichotomized using the max chi-square optimized cutoff. BL=baseline; Erlot=erlotinib; Sor=sorafenib.

Figure 3. Kaplan-Meier survival curves of OS in (A) patients with (n=270) and without (n=224) a 2-marker signature (HGF, VEGF-A) and (B) patients with (n=339) and without (n=155) a 5-marker signature (HGF, VEGF-A, KIT, epigen, VEGF-C) who were treated with sorafenib plus placebo or sorafenib plus erlotinib.

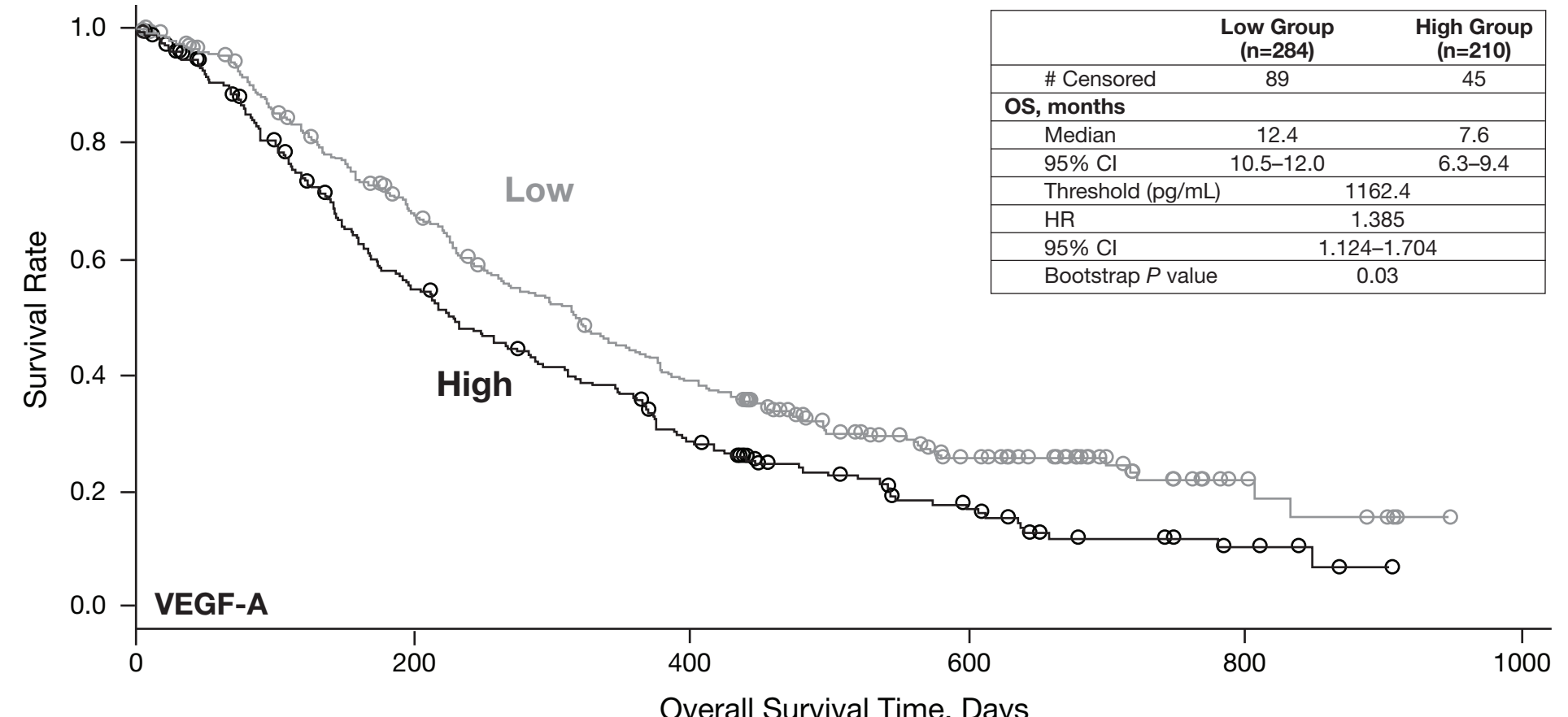
Figure 1a



	Low Group (n=212)	High Group (n=282)
# Censored	71	63
OS, months		
Median	12.4	7.5
95% CI	10.7–13.8	6.5–8.5
Threshold (pg/mL)	462.9	
HR	1.672	
95% CI	1.352–2.074	
Bootstrap *P* value	5e–05	

High (n)	282	141	66	23	4	0
Low (n)	212	145	87	43	10	0

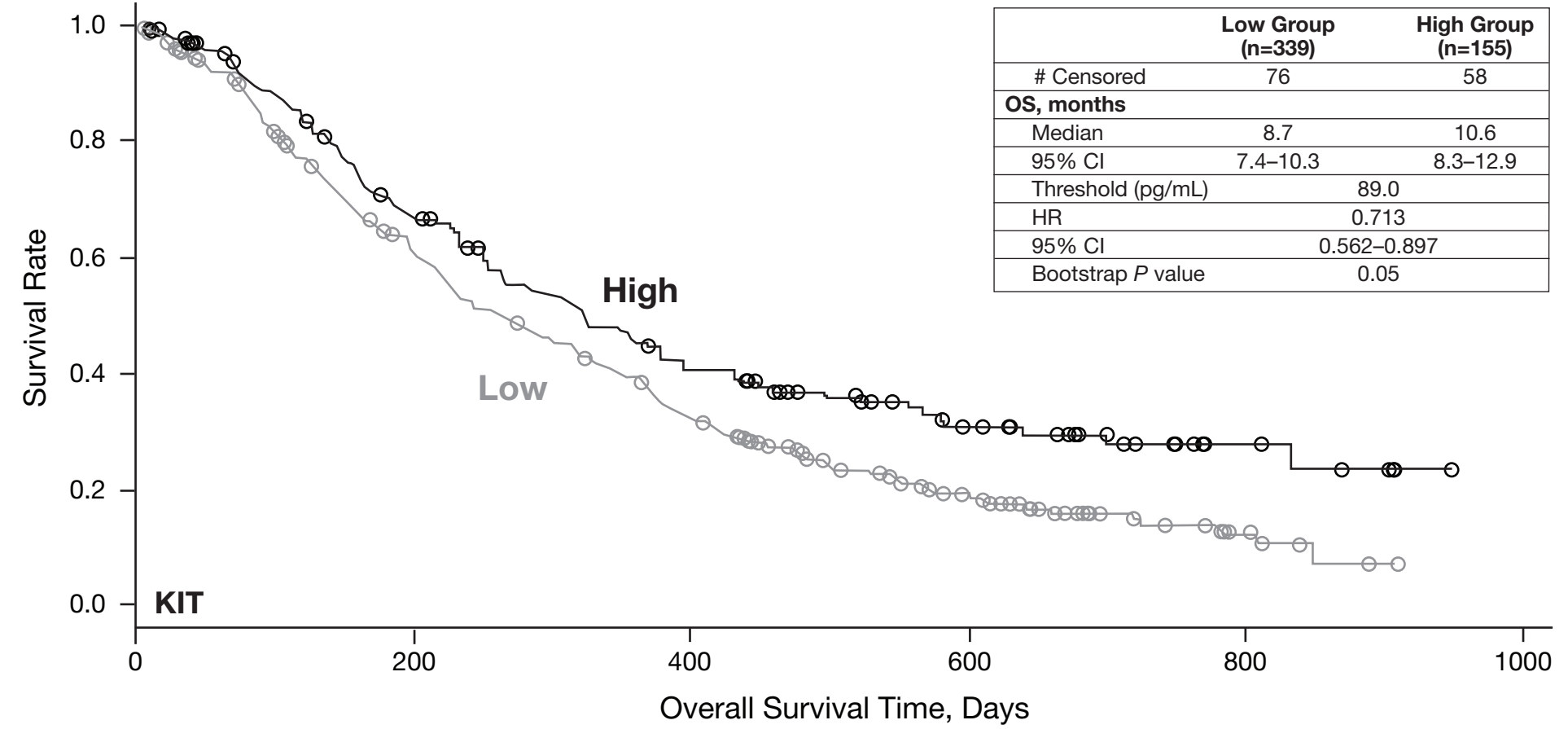
Figure 1b



	Low Group (n=284)	High Group (n=210)
# Censored	89	45
OS, months		
Median	12.4	7.6
95% CI	10.5–12.0	6.3–9.4
Threshold (pg/mL)	1162.4	
HR	1.385	
95% CI	1.124–1.704	
Bootstrap *P* value	0.03	

High (n)	210	107	53	23	6	0
Low (n)	284	179	100	43	8	0

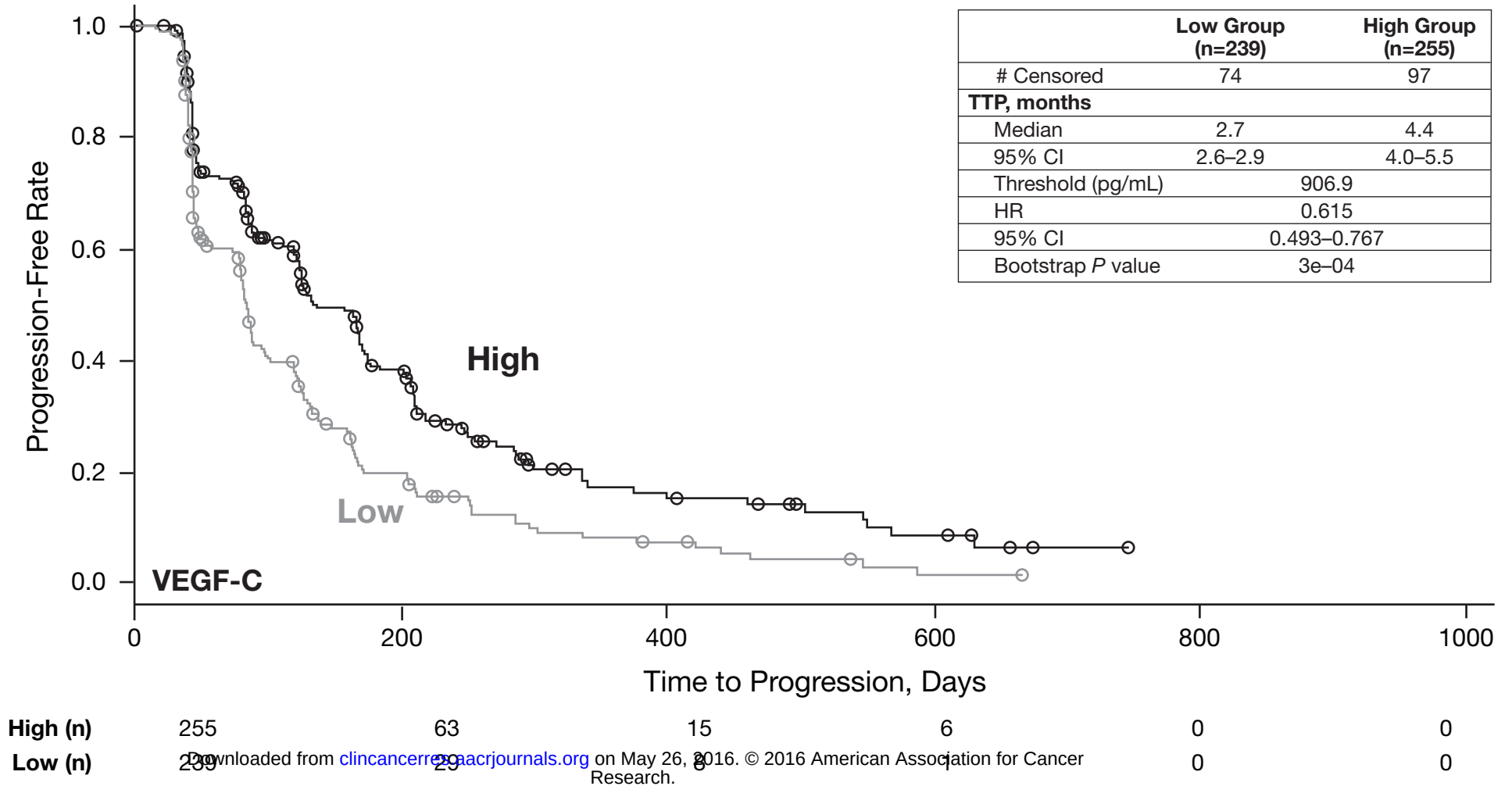
Figure 1c



	Low Group (n=339)	High Group (n=155)
# Censored	76	58
OS, months		
Median	8.7	10.6
95% CI	7.4–10.3	8.3–12.9
Threshold (pg/mL)	89.0	
HR	0.713	
95% CI	0.562–0.897	
Bootstrap *P* value	0.05	

High (n)	155	94	54	27	7	0
Low (n)	339	192	99	39	7	0

Figure 1d



	Low Group (n=239)	High Group (n=255)
# Censored	74	97
TTP, months		
Median	2.7	4.4
95% CI	2.6–2.9	4.0–5.5
Threshold (pg/mL)	906.9	
HR	0.615	
95% CI	0.493–0.767	
Bootstrap *P* value	3e–04	

Figure 2

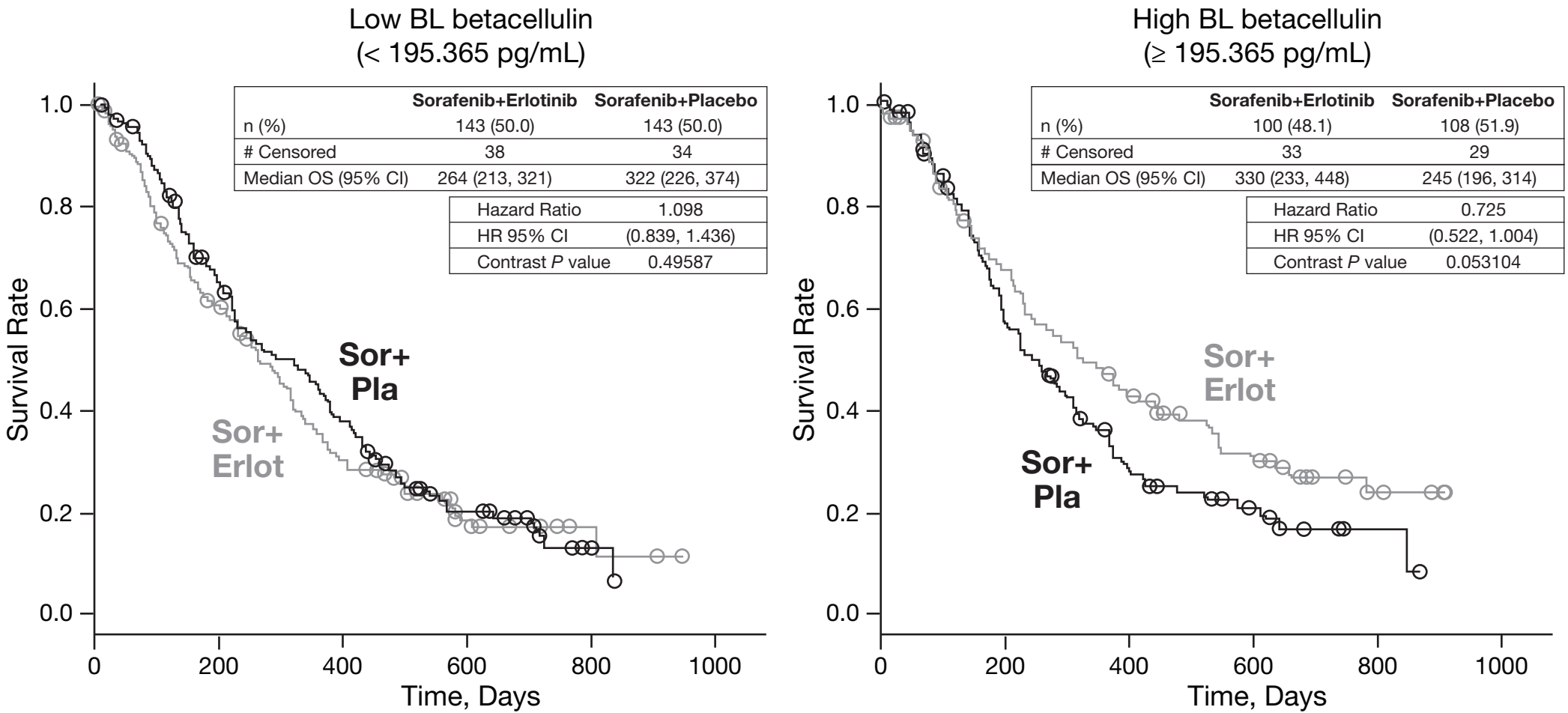
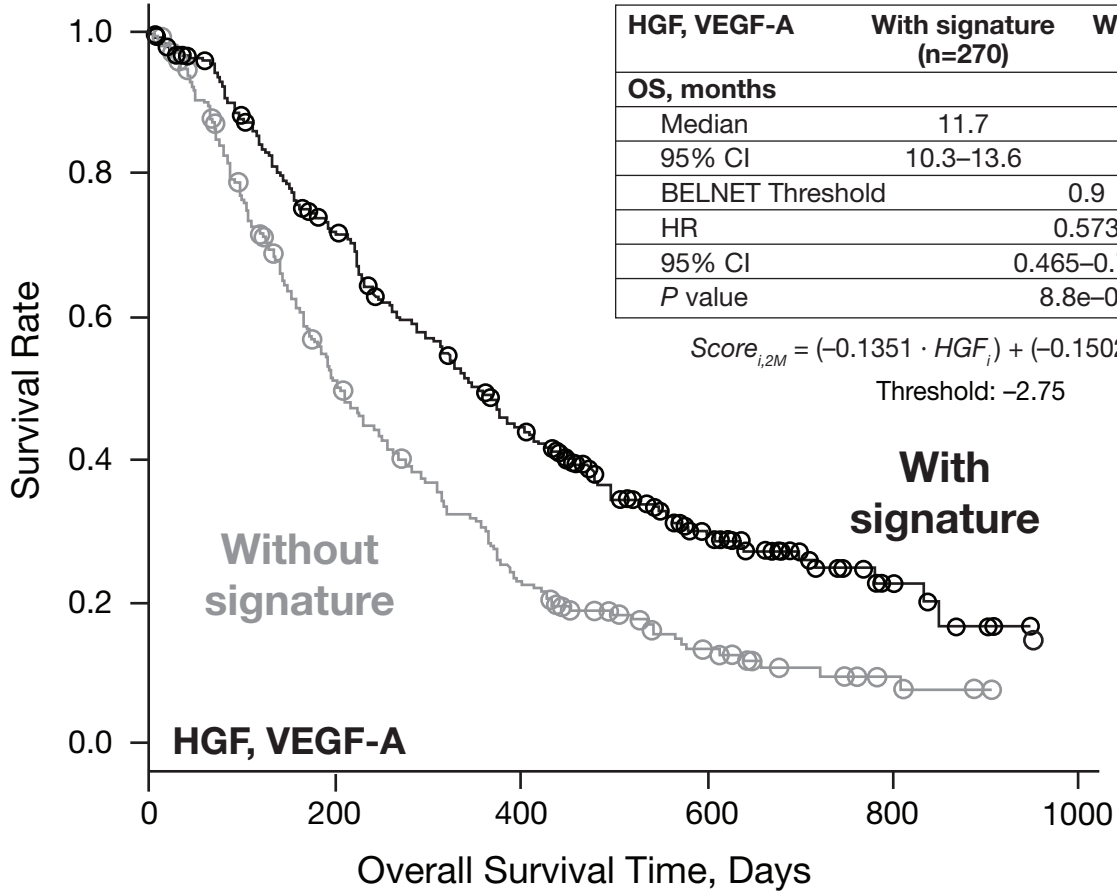


Figure 3a



HGF, VEGF-A	With signature (n=270)	Without signature (n=224)
OS, months		
Median	11.7	6.8
95% CI	10.3–13.6	6.0–8.3
BELNET Threshold	0.9	
HR	0.573	
95% CI	0.465–0.705	
P value	8.8e–07	

$Score_{i,2M} = (-0.1351 \cdot HGF_i) + (-0.1502 \cdot VEGFA_i)$.

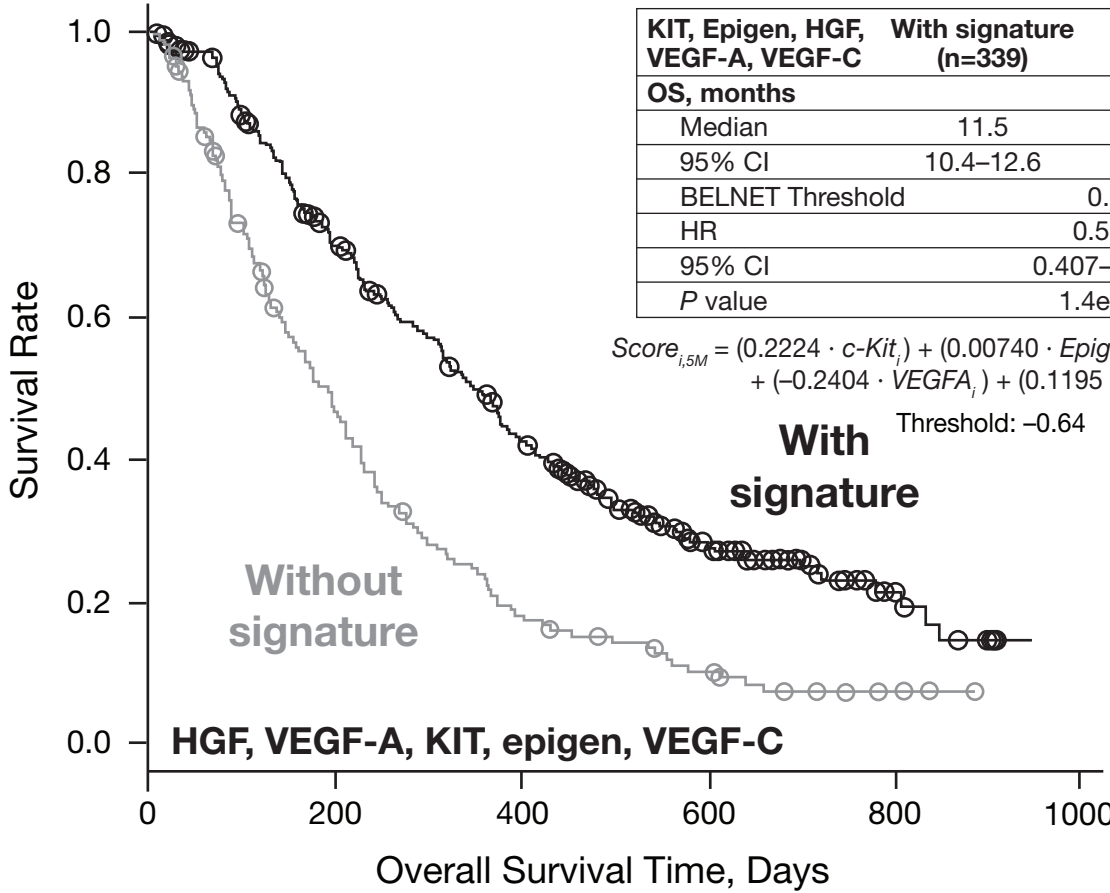
Threshold: –2.75

Figure 3b

KIT, Epigen, HGF, VEGF-A, VEGF-C	With signature (n=339)	Without signature (n=155)
OS, months		
Median	11.5	6.0
95% CI	10.4–12.6	5.0–7.5
BELNET Threshold	0.8	
HR	0.505	
95% CI	0.407–0.627	
P value	1.4e–08	

$Score_{i,5M} = (0.2224 \cdot c\text{-}Kit_i) + (0.00740 \cdot Epigen_i) + (-0.1552 \cdot HGF_i) + (-0.2404 \cdot VEGFA_i) + (0.1195 \cdot VEGFC_i)$.

Threshold: –0.64



With signature (n)	339	219	128	54	11	0
Without signature (n)	155	87	25	12	3	0

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Biomarker Analyses of Clinical Outcomes in Patients With Advanced Hepatocellular Carcinoma Treated With Sorafenib With or Without Erlotinib in the SEARCH Trial

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