Supplementary Methods

DNA Extraction and Genotyping

Genomic DNA was extracted from peripheral whole blood in patients of both cohorts, with the exception of 21 patients' formalin-fixed paraffin-embedded tissues from the evaluation cohort using the QIAmp Kit (Qiagen, Germantown, MD), according to the manufacturer's protocol. The candidate SNPs were tested with PCR-based direct DNA sequence analysis using the ABI 3100A Capillary Genetic Analyzer and Sequencing Scanner v1.0 (Thermo Fisher Scientific, Waltham, MA). The forward and reverse primers used for amplification of extracted DNA are listed in Supplemental Table 1. For quality control purposes, a randomly selected 10% of the samples was analyzed by direct DNA sequencing for each SNP, resulting in a genotype concordance rate of 99% or more. The investigators analyzing the SNPs were blinded to the clinical data.

Analysis of Serum VEGF-A and CCL5 *Levels*

Separated serum was stored at −80°C. The serum levels of VEGF-A and *CCL5* were measured using Quantikine ELISA kits (R&D Systems, Minneapolis, MN). A portion of the data has been previously reported, showing associations between serum cytokine levels and efficacy as well as toxicity of regorafenib.[5] In the current study, the genetic functionality of the candidate SNPs was first analyzed retrospectively to investigate the relationship between serum cytokine levels and genotypes during regorafenib treatment.

Statistical Analysis

PFS was defined as the interval between the date of starting treatment and the date of confirmed disease progression or death. The data of patients without disease progression or death were censored at the date of last follow-up. OS was calculated from the date of starting treatment until the date of death from any cause. In patients who were lost to follow-up, data were censored at the date of last follow-up. Disease control rate was defined as the proportion of patients who achieved a complete response, partial response, or stable disease according to Response Evaluation Criteria in Solid Tumors v1.1. The chi-square test or Wilcoxon test was used to examine the differences in baseline patient characteristics between the 2 cohorts. The allelic distribution of polymorphisms was tested for deviation from the Hardy-Weinberg equilibrium using the exact test, linkage disequilibrium among SNPs was assessed using D' and r^2 values, and haplotype frequencies of the genes were inferred using HaploView version 4.2 (http://www.broad.mit.edu/mpg/haploview). Fisher's exact test was applied to examine the associations between SNPs and disease control rate or toxicity. The Kaplan-Meier method and the log-rank test were performed to evaluate the association between candidate SNPs and PFS or OS. The baseline demographic and clinical characteristics that remained statistically significantly associated with PFS and OS in multivariable analyses were included in the final models to reevaluate the independent effect of candidate SNPs. Because the true modes for candidate SNPs were not yet established, the analyses used a codominant, dominant, or recessive genetic model as appropriate. Serum VEGF-A and *CCL5* levels at baseline and at day 21 and level changes during treatment were compared between the genetic variants of candidate SNPs using Student's unpaired *t* test and 1-way analysis of variance.

Supplemental Table 1 Candidate SNPs in *CCL5/CCR5* Pathway

Gene and rs No.	Allele Location	Base Exchange	MAF (W/JPN)[a]	Function of Polymorphism	Primer (5′-3′)
CCL5 rs2280789	Intron Chromosome 17:35879999	A > G	0.11/0.31	Transcriptional regulation	F: ATCTCCCCAACATGAGTCCA R: CCATATGTCCTGTTGTCCTTGA
CCL5 rs3817655	Intron Chromosome 17:35872637	A > T	015/0.31	Transcriptional regulation	F: TGATATCGGGGTAGGGCATA R: GGCGATTAAAATGCACACAA
CCL3 rs1130371	Synonymous Chromosome 17:36089191	G > A	0.31/0.31	Protein coding, splicing regulation, posttranslation, conserved	F: GCCTTTCCAGGATAGCCTTC R: CTTTGAGACGAGCAGCCAGT
CCL4 rs1634517	Intron Chromosome 17:36105010	C > A	0.33/0.22	Tagging SNP	F: CCGATTCCTTAAACCGTGCT R: TTCCACCCACTGGATTTAGC
CCR5 rs1799988	5′ prime UTR Chromosome 3:46370768	C > T	0.47/0.48	Transcriptional regulation	F: TGGGATGAGCAGAGAACAAA R: GGCGAAAAGAATCAGAGAACA
PRCKD rs1483185	Intron Chromosome 3:53164998	T > G	0.18/0.13	Transcriptional regulation	F: ACAAATAGTGGTGCCCAGGA R: AACAGGCTCTCCCCGTCTAC
PRCKD rs2306574	Synonymous Chromosome 3:53188745	C > T	0.23/0.15	Protein coding, splicing regulation, transcriptional regulation, conserved	F: GAAGAAATGTCCCCTGCTGA R: TTCTCTTTGCACATCCCAAA
KLF13 rs2241779	Intron Chromosome 15:31348049	C > A	0.42/0.42	Transcriptional regulation	F: CGTTCCAGATCTCAGGCTTC R: TTTCCACTTTCCTCCACCAG
HIF1A rs12434438	Intron Chromosome 14:61730580	A > G	0.16/0.23	Transcriptional regulation	F: CCTGCACCATGTTAAGCATTT R: CCATGCAAAGGAATGGTAGAA

Abbreviations: F = forward primer; JPN = Japanese; MAF = minor allele frequency; R = reverse primer; SNP = single nucleotide polymorphism; W = white.
[a]In W and JPN from Ensembl Genome Browser (http://uswest.ensembl.org/index.html).

Supplemental Table 2 Baseline Patient and Tumor Characteristics

Characteristic	Evaluation Cohort (N = 79)		Validation Cohort (N = 150)		*P*
	N	%	N	%	
Sex					.30
Male	37	46.8	81	54.0	
Female	42	53.2	69	46.0	
Age (y)					
Median (range)	62 (34-83)		62 (33-81)		.48
≤65	48	60.8	90	60.0	
>65	31	39.2	60	40.0	
ECOG PS					<.001[b]
0	44	55.7	117	78.0	
1-2	35	44.3	33	22.0	
Primary Tumor Site					.54
Right	23	29.1	49	32.7	
Left	56	70.9	99	66.0	
Unknown[a]	—	—	2	1.3	
Liver Metastasis					.031[b]
Yes	53	67.1	120	80.0	
No	26	32.9	30	20.0	
Lung Metastasis					.026[b]
Yes	46	58.2	109	72.7	
No	33	41.8	41	27.3	
Lymph Node Metastasis					.93
Yes	40	50.6	75	50.0	
No	39	49.4	75	50.0	
Peritoneal Metastasis					.59
Yes	20	25.3	43	28.7	
No	59	74.7	107	71.3	
No. of Metastases					<.001[b]
1	24	30.4	16	10.7	
>1	55	69.6	134	89.3	
Primary Tumor Resected					.58
Yes	69	87.3	127	84.7	
No	10	12.7	23	15.3	
History of Adjuvant Therapy					.19
Yes	26	32.9	37	24.7	
No	53	67.1	112	74.7	
Unknown[a]	—	—	1	0.6	

Abbreviation: ECOG PS = Eastern Cooperative Oncology Group performance status.
[a]Not included in analysis.
[b]Statistically significant ($P < .05$) by *P* chi-square test or by Wilcoxon test when appropriate.

Supplemental Table 3 Association of Baseline Characteristics With Clinical Outcome in Evaluation Cohort

Characteristic	N	Progression-Free Survival			Overall Survival		
		Median (95% CI) (mo)	Univariate HR (95% CI)	*P*	Median (95% CI) (mo)	Univariate HR (95% CI)	*P*
Age (y)				.41			.87
≤65	49	2.0 (1.8, 2.5)	1 (Reference)		8.1 (5.2, 12.0)	1 (Reference)	
>65	31	2.0 (1.7, 3.3)	0.83 (0.52, 1.33)		8.7 (5.1, 13.6)	0.95 (0.55, 1.66)	
Gender				.12			.57
Male	38	2.3 (2.0, 3.3)	1 (Reference)		8.7 (5.1, 13.6)	1 (Reference)	
Female	42	1.8 (1.7, 2.0)	1.40 (0.89, 2.20)		8.1 (5.8, 12.6)	1.17 (0.68, 2.02)	
Primary Tumor Site				.80			.25
Right	23	2.0 (1.8, 4.2)	1 (Reference)		12.9 (5.8, 27.2)	1 (Reference)	
Left	57	2.0 (1.8, 2.5)	1.06 (0.65, 1.74)		7.8 (5.1, 10.8)	1.44 (0.77, 2.70)	
Primary Tumor Resected				.85			.030[a]
Yes	70	2.0 (1.8, 2.3)	1 (Reference)		10.3 (6.5, 12.9)	1 (Reference)	
No	10	3.0 (1.7, 4.5)	0.94 (0.48, 1.84)		4.9 (2.8, 7.9)	2.16 (1.04, 4.46)	
Adjuvant Treatment				.94			.21
Yes	27	2.3 (1.8, 4.5)	1 (Reference)		12.0 (7.6, 15.3)	1 (Reference)	
No	53	2.0 (1.8, 2.7)	0.98 (0.61, 1.58)		6.3 (4.6, 9.6)	1.44 (0.81, 2.57)	
Histology				.12			.19
Moderate to poor	62	1.8 (1.8, 2.3)	1 (Reference)		8.1 (5.8, 11.8)	1 (Reference)	
Well	17	3.2 (2.0, 6.2)	0.66 (0.39, 1.14)		13.6 (4.6, 27.7)	0.63 (0.31, 1.28)	
Liver Metastasis				<.001[a]			<.001[a]
Yes	54	1.9 (1.8, 2.3)	1 (Reference)		6.1 (4.6, 8.7)	1 (Reference)	
No	26	4.1 (1.8, 6.6)	0.45 (0.26, 0.76)		13.9 (10.8, 29.9)	0.34 (0.18, 0.65)	
Lung Metastasis				.35			.22
Yes	47	2.0 (1.8, 3.2)	1 (Reference)		10.8 (5.9, 15.3)	1 (Reference)	
No	33	2.0 (1.7, 2.5)	1.23 (0.78, 1.94)		7.6 (4.6, 11.8)	1.40 (0.81, 2.39)	
Lymph Node Metastasis				.079			.017[a]
Yes	41	1.9 (1.7, 2.3)	1 (Reference)		6.3 (4.1, 8.1)	1 (Reference)	
No	39	3.0 (1.8, 4.5)	0.69 (0.44, 1.07)		12.9 (7.6, 15.5)	0.52 (0.30, 0.90)	
Peritoneal Involved				.63			.86
Yes	20	1.8 (1.3, 4.5)	1 (Reference)		9.4 (4.0, 12.9)	1 (Reference)	
No	60	2.2 (1.8, 2.7)	0.88 (0.53, 1.48)		7.9 (5.9, 12.6)	0.95 (0.52, 1.72)	
No. of Metastases				.005[a]			.043[a]
1	24	3.8 (1.8, 4.8)	1 (Reference)		12.6 (7.6, 27.2)	1 (Reference)	
>1	56	1.9 (1.8, 2.3)	1.91 (1.16, 3.16)		6.5 (4.6, 10.8)	1.84 (1.00, 3.41)	
No. of Prior Treatment Regimens				.75			.20
<3	24	2.0 (1.6, 2.7)	1 (Reference)		12.6 (5.0, 29.9)	1 (Reference)	
≥3	56	2.2 (1.8, 3.0)	1.08 (0.66, 1.77)		7.6 (5.2, 10.8)	1.49 (0.80, 2.80)	
ECOG PS				.84			.30
0	45	2.3 (1.8, 3.2)	1 (Reference)		9.6 (6.3, 12.9)	1 (Reference)	
1	35	1.8 (1.7, 2.7)	1.05 (0.67, 1.64)		7.6 (4.0, 12.9)	1.33 (0.77, 2.28)	

Supplemental Table 3 Continued

Characteristic	N	Progression-Free Survival			Overall Survival		
		Median (95% CI) (mo)	Univariate HR (95% CI)	*P*	Median (95% CI) (mo)	Univariate HR (95% CI)	*P*
KRAS				.26			.11
Wild type	50	2.0 (1.8, 2.5)	1 (Reference)		7.6 (5.8, 10.3)	1 (Reference)	
Mutant	28	2.0 (1.7, 3.0)	0.77 (0.48, 1.25)		13.6 (3.7, 29.9)	0.61 (0.33, 1.14)	

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio.
[a]Statistically significant ($P < .05$) by log-rank test for progression-free survival and overall survival in univariate analysis.

Supplemental Table 4 Association of Baseline Characteristics With Clinical Outcome in Validation Cohort

Characteristic	N	Progression-Free Survival			Overall Survival		
		Median (95% CI) (mo)	Univariate HR (95% CI)	*P*	Median (95% CI) (mo)	Univariate HR (95% CI)	*P*
Age (y)				.17			.42
≤65	90	2.0 (1.8, 2.3)	1 (Reference)		6.4 (5.4, 8.8)	1 (Reference)	
>65	60	2.2 (1.8, 3.4)	0.80 (0.57, 1.12)		5.9 (4.0, 9.5)	0.87 (0.62, 1.23)	
Gender				.067			.22
Male	81	2.3 (2.0, 3.4)	1 (Reference)		7.8 (5.4, 9.6)	1 (Reference)	
Female	69	1.9 (1.8, 2.1)	1.34 (0.97, 1.86)		5.8 (4.1, 7.6)	1.23 (0.88, 1.73)	
Time to Regorafenib Initiation (mo)				.039[a]			.37
<18	20	1.8 (0.9, 2.0)	1 (Reference)		3.9 (1.7, 7.8)	1 (Reference)	
≥18	130	2.1 (1.9, 2.7)	0.62 (0.37, 1.01)		6.5 (5.6, 8.7)	0.79 (0.48, 1.32)	
Primary Tumor Site				.10			.21
Right	49	1.9 (1.7, 2.1)	1 (Reference)		4.7 (3.5, 7.1)	1 (Reference)	
Left	54	1.9 (1.8, 2.8)	1.11 (0.74, 1.67)		5.6 (3.5, 8.8)	1.19 (0.79, 1.79)	
Rectum	45	2.7 (2.1, 4.1)	0.74 (0.49, 1.11)		9.1 (6.5, 10.7)	0.83 (0.54, 1.27)	
Primary Tumor Resected				.21			.008[a]
Yes	127	2.1 (1.9, 2.3)	1 (Reference)		7.0 (5.6, 8.7)	1 (Reference)	
No	23	2.1 (1.8, 2.3)	1.32 (0.84, 2.06)		3.7 (2.4, 6.0)	1.81 (1.14, 2.86)	
Adjuvant Treatment				.23			.49
Yes	37	2.8 (1.9, 4.1)	1 (Reference)		6.3 (4.3, 10.6)	1 (Reference)	
No	112	2.0 (1.8, 2.2)	1.25 (0.86, 1.83)		6.2 (5.1, 7.9)	1.15 (0.77, 1.73)	
Synchronous				.42			.22
Yes	101	2.0 (1.8, 2.2)	1 (Reference)		6.0 (4.7, 8.0)	1 (Reference)	
No	49	2.3 (1.9, 3.1)	0.87 (0.62, 1.23)		6.3 (4.4, 10.2)	0.80 (0.56, 1.16)	
Liver Metastasis				.064			.008[a]
Yes	120	2.0 (1.8, 2.2)	1 (Reference)		5.6 (4.4, 7.8)	1 (Reference)	
No	30	2.4 (2.0, 4.7)	0.69 (0.46, 1.04)		10.1 (6.3, 12.5)	0.57 (0.37, 0.89)	
Lung Metastasis				.99			.56
Yes	109	2.1 (1.9, 2.7)	1 (Reference)		7.0 (5.6, 8.8)	1 (Reference)	
No	41	1.8 (1.7, 2.3)	1.00 (0.68, 1.46)		4.3 (2.6, 9.6)	1.12 (0.76, 1.63)	
Lymph Node Metastasis				.12			.11
Yes	75	1.9 (1.8, 2.2)	1 (Reference)		5.4 (3.5, 7.8)	1 (Reference)	
No	75	2.3 (2.0, 3.4)	0.78 (0.56, 1.08)		7.6 (5.8, 9.6)	0.76 (0.54, 1.07)	
Peritoneum Involved				.012[a]			.11
Yes	43	1.9 (1.8, 2.2)	1 (Reference)		5.1 (2.6, 7.8)	1 (Reference)	
No	107	2.2 (1.9, 2.8)	0.64 (0.45, 0.92)		6.5 (5.5, 9.1)	0.74 (0.51, 1.08)	
No. of Metastasis Sites				.26			.17
1	16	2.3 (1.8, 4.7)	1 (Reference)		6.4 (3.5, 21.2)	1 (Reference)	
>1	134	2.1 (1.8, 2.2)	1.35 (0.79, 2.30)		6.0 (5.3, 8.0)	1.43 (0.82, 2.49)	
No. of Treatment Lines Before Regorafenib Initiation				.74			.37
≤3	108	2.1 (1.9, 2.3)	1 (Reference)		6.5 (5.7, 8.7)	1 (Reference)	
>3	42	2.0 (1.8, 2.7)	1.06 (0.74, 1.52)		5.2 (3.3, 9.0)	1.19 (0.81, 1.73)	
Kohne Score				<.001[a]			<.001[a]
Low to intermediate	119	2.2 (2.0, 2.8)	1 (Reference)		8.0 (6.0, 9.6)	1 (Reference)	
High	31	1.6 (0.9, 1.8)	2.22 (1.48, 3.33)		2.6 (1.8, 3.5)	3.17 (2.06, 4.88)	

Supplemental Table 4 Continued

Characteristic	N	Progression-Free Survival			Overall Survival		
		Median (95% CI) (mo)	Univariate HR (95% CI)	*P*	Median (95% CI) (mo)	Univariate HR (95% CI)	*P*
ECOG PS				<.001[a]			<.001[a]
0	117	2.2 (2.0, 2.8)	1 (Reference)		7.9 (6.0, 9.5)	1 (Reference)	
1-2	33	1.7 (1.0, 2.1)	2.11 (1.41, 3.15)		3.1 (2.0, 4.0)	2.46 (1.62, 3.75)	
***RAS* Status**				.12			.31
Wild type	52	2.4 (1.8, 3.7)	1 (Reference)		7.0 (5.4, 8.9)	1 (Reference)	
Mutant	93	2.1 (1.8, 2.3)	1.30 (0.92, 1.84)		5.9 (4.4, 8.7)	1.20 (0.84, 1.72)	

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio.
[a]Statistically significant ($P < .05$) by log-rank test for progression-free survival and overall survival in univariate analysis.

Supplemental Table 5 Association Between Gene Polymorphism and Clinical Outcome

Characteristic	N	Disease Control			Progression-Free Survival					Overall Survival				
		PR + SD	PD	*P*	Median (95% CI) (mo)	Univariate HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*	Median (95% CI) (mo)	Univariate HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Evaluation Cohort														
PRKCD rs1483185				.17			.39		.11 (.60)			.59		.076 (.51)
G/G	55	24 (53%)	21 (47%)		2.0 (1.8, 2.7)	1 (Reference)		1 (Reference)		8.1 (6.1, 12.6)	1 (Reference)		1 (Reference)	
G/T[a]	22	6 (33%)	12 (67%)		2.3 (1.8, 3.3)	0.81 (0.49, 1.34)		0.66 (0.40, 1.10)		12.0 (5.1, 15.3)	0.85 (0.46, 1.56)		0.56 (0.29, 1.06)	
T/T[a]	1	1 (100%)	0											
PRKCD rs2306574				1.00			.29		.72 (1.00)			.15		.71 (1.00)
T/T	56	23 (49%)	24 (51%)		2.0 (1.8, 3.2)	1 (Reference)		1 (Reference)		9.6 (6.1, 13.6)	1 (Reference)		1 (Reference)	
T/C	22	8 (47%)	9 (53%)		1.9 (1.7, 2.7)	1.30 (0.78, 2.15)		0.91 (0.53, 1.55)		6.5 (3.6, 12.0)	1.52 (0.85, 2.70)		0.89 (0.47, 1.68)	
HIF1A rs12434438				.20			.37		.47 (.89)			.96		.72 (1.00)
A/A	51	18 (43%)	24 (57%)		2.0 (1.8, 3.0)	1 (Reference)		1 (Reference)		7.6 (5.8, 12.9)	1 (Reference)		1 (Reference)	
A/G[a]	23	12 (67%)	6 (33%)		2.0 (1.6, 3.3)	1.22 (0.75, 1.99)		1.20 (0.73, 1.96)		8.7 (5.0, 15.5)	0.99 (0.55, 1.77)		0.90 (0.49, 1.63)	
G/G[a]	4	1 (25%)	3 (75%)											
Validation Cohort														
HIF1A rs12434438				.22			.11		.66 (1.00)			.40		.69 (1.00)
A/A	71	29 (42%)	40 (58%)		2.3 (2.0, 3.1)	1 (Reference)		1 (Reference)		7.0 (5.4, 9.1)	1 (Reference)		1 (Reference)	
A/G	60	15 (27%)	40 (73%)		1.9 (1.7, 2.1)	1.43 (1.01, 2.03)		1.18 (0.81, 1.71)		5.4 (2.9, 7.8)	1.24 (0.87, 1.77)		1.01 (0.69, 1.48)	
G/G	19	6 (32%)	13 (68%)		1.9 (1.7, 3.9)	1.15 (0.69, 1.92)		1.00 (0.60, 1.69)		8.7 (4.5, 13.9)	0.93 (0.53, 1.63)		0.79 (0.45, 1.40)	
				.11			.059[b]		.49 (.61)			.38		.78 (1.00)
A/A	71	29 (42%)	40 (58%)		2.3 (2.0, 3.1)	1 (Reference)		1 (Reference)		7.0 (5.4, 9.1)	1 (Reference)		1 (Reference)	
Any G	79	21 (28%)	53 (72%)		1.9 (1.8, 2.1)	1.35 (0.98, 1.87)		1.13 (0.80, 1.59)		5.7 (4.0, 7.8)	1.16 (0.83, 1.62)		0.95 (0.66, 1.36)	

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; PD = progressive disease; PR = partial response; SD = stable disease.

[a]Grouped together for estimate of HR.

[b]Statistically significant ($P < .05$). *P* values after p-act multiple testing adjustment are shown in parentheses. *P* was based on Fisher's exact test for response, log-rank test in univariate analysis, and Wald test in multivariable analysis within Cox regression model adjusted for liver metastasis and lymph node metastasis in evaluation cohort; and for time to regorafenib initiation (< 18 vs. ≥ 18 months), ECOG PS (0 vs. 1 or 2), primary tumor resection (yes vs. no), and Kohne score (low-intermediate vs. high) in validation cohort.

Supplemental Table 6 Association Between Toxicities and Clinical Outcome

Characteristic	N	Progression-Free Survival			Overall Survival		
		Median (mo) (95% CI)	HR (95% CI)	*P*	Median (mo) (95% CI)	HR (95% CI)	*P*
Evaluation Cohort							
HFSR				.24			.80
<3	53	1.8 (1.6, 2.7)	1 (Reference)		8.1 (5.8, 12.6)	1 (Reference)	
≥3	26	2.3 (1.8, 3.2)	0.76 (0.48, 1.22)		10.8 (5.0, 13.9)	0.93 (0.53, 1.63)	
Hypertension				.042[a]			.090
<3	72	2.0 (1.8, 2.4)	1 (Reference)		7.6 (5.8, 10.8)	1 (Reference)	
≥3	7	4.8 (1.3, 12.0)	0.45 (0.19, 1.03)		13.9 (8.7, 26.7)	0.43 (0.16, 1.20)	
Rash				.035[a]			.016[a]
<3	69	1.8 (0.5, 2.3)	1 (Reference)		5.2 (1.5, 8.7)	1 (Reference)	
≥3	10	2.2 (1.8, 2.7)	0.51 (0.25, 1.01)		9.6 (6.3, 12.9)	0.43 (0.20, 0.90)	
Diarrhea				.71			.92
<3	77	2.5 (0.5, 4.5)	1 (Reference)		5.2 (3.6, 14.5)	1 (Reference)	
≥3	3	2.0 (1.8, 2.7)	0.81 (0.25, 2.58)		8.7 (6.3, 12.0)	0.93 (0.23, 3.83)	
AST/ALT				.059			.048[a]
<3	75	2.2 (1.8, 2.7)	1 (Reference)		8.7 (6.3, 12.6)	1 (Reference)	
≥3	4	1.5 (1.1, 2.0)	2.48 (0.87, 7.08)		5.1 (1.9, 9.6)	2.66 (0.94, 7.55)	
Validation Cohort							
HFSR				.035[a]			.096
<3	126	1.9 (1.8, 2.2)	1 (Reference)		5.9 (5.0, 7.8)	1 (Reference)	
≥3	24	4.0 (2.1, 5.8)	0.64 (0.41, 0.99)		11.6 (4.4, 13.9)	0.67 (0.41, 1.09)	
Hypertension				.004[a]			.15
<3	114	2.0 (1.8, 2.2)	1 (Reference)		5.9 (4.7, 7.8)	1 (Reference)	
≥3	36	3.9 (1.8, 5.3)	0.59 (0.40, 0.88)		9.2 (4.5, 12.5)	0.75 (0.50, 1.11)	
Rash				.074			.034[a]
<3	128	2.0 (1.8, 2.2)	1 (Reference)		5.8 (4.5, 7.6)	1 (Reference)	
≥3	22	2.5 (1.8, 4.2)	0.68 (0.42, 1.08)		9.9 (5.1, 18.8)	0.62 (0.38, 0.99)	
Diarrhea				.36			.47
<3	139	2.1 (1.8, 2.3)	1 (Reference)		5.9 (5.0, 7.8)	1 (Reference)	
≥3	11	3.7 (2.0, 4.3)	0.76 (0.41, 1.40)		10.6 (4.5, 12.5)	0.79 (0.41, 1.51)	
AST/ALT				.41			.16
<3	140	2.1 (1.9, 2.3)	1 (Reference)		6.5 (5.5, 8.7)	1 (Reference)	
≥3	10	1.8 (0.9, 2.3)	1.30 (0.68, 2.50)		4.4 (1.0, 8.0)	1.65 (0.80, 3.42)	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; HFSR = hand–foot skin reaction; HR = hazard ratio.
[a]Statistically significant ($P < .05$) by log-rank test in univariate analysis.