Supplementary Material

Population Pharmacokinetics and Exposure-Response Analysis for the Phase 3 COSMIC-311 Trial of Cabozantinib for Radioiodine-Refractory Differentiated Thyroid Cancer

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Population Pharmacokinetics Base Model Equations

$$\frac{CL}{F_i} = 1.99 \cdot exp\left(\eta_i^{CL/F}\right) \quad \text{Eq.1}$$

Where *CL/F* is the apparent oral clearance of cabozantinib for the i^{th} individual, 1.99 L/hr is the population estimate for cabozantinib apparent oral clearance, and $\eta_i^{CL/F}$ is the interindividual variability (IIV) in *CL/F* for the i^{th} subject.

$$\frac{Vc}{F} = 111 \cdot exp\left(\eta_i^{Vc/F}\right) \quad \text{Eq.2}$$

Where *Vc/F* is the apparent distribution volume of the plasma compartment of cabozantinib for the i^{th} individual, 111 L is the population estimate for cabozantinib apparent distribution volume of the plasma compartment, and $\eta_i^{Vc/F}$ is the IIV in *Vc/F* for the i^{th} subject.

$$Ka = 3.38 \cdot exp(\eta_i^{Ka}) \quad \text{Eq.3}$$

Where *Ka* is the first-order absorption rate constant of cabozantinib for the i^{th} individual, 3.38 hr^{-1} is the population estimate for the cabozantinib absorption rate constant, and η_i^{Ka} is the IIV in *Ka* for the i^{th} subject.

$$F4 = 1 - 0.736 \quad \text{Eq.4}$$

Where *F4* is the fraction of dose undergoing delayed absorption and 0.736 is the fraction of dose being absorbed via the transit absorption process, assuming an oral bioavailability of 1 in the model.

Explanation for choice of covariates included in Pharmacokinetics full model

Clinical judgment, mechanistic plausibility, and prior modeling experience were used to determine which covariates should be tested and on which model parameters they should be evaluated. Among the demographic covariates that were evaluated in a previous PopPK model developed from data in 11 clinical trials (data courtesy of Exelixis), female sex had a significant effect on CL/F (24% lower than males) which resulted in moderately increased exposure (26% higher maximum steady state plasma concentration [$C_{max,ss}$], 34% higher minimum steady state plasma concentration [$C_{min,ss}$], and 30% higher steady state 24-hour area under the concentration time curve [$AUC_{0-24,ss}$]). Body weight was selected in consideration of cabozantinib exposure prediction in adolescent patients and due to its association with effects on Vc/F: (~40% increase in Vc/F with high body weight [109 kg] and ~40% decrease in Vc/F with low body weight [54 kg], relative to reference body weight [80 kg]), though this did not appear to impact cabozantinib exposure.

Population Pharmacokinetics full model equations

Equations for the PK full model are identical to the base model with the addition of the following parameters:

$$\frac{CL}{F} = \theta_{CL} \cdot \left(\frac{WT}{70}\right)^{\theta WT,CL} \cdot (1 + SEX \cdot \theta_{SEX}) \quad \text{Eq.5}$$

where terms are defined as indicated for base model in Supplementary Material (page 2) and in addition, θWT,CL is the exponent describing the relationship between cabozantinib oral clearance and baseline body weight (WT) centered on a body weight of 70 kg, SEX is an indicator variable (1 for females and 0 for males) and θSEX is the fractional change in cabozantinib oral clearance for females

$$\frac{Vc}{F} = \theta_{Vc} \cdot \left(\frac{WT}{70}\right)^{\theta WT,Vc} \quad \text{Eq.6}$$

where $\theta_{WT,Vc}$ is the exponent describing the relationship between cabozantinib apparent distribution volume (Vc/F) for the plasma compartment and baseline body weight (*WT*) centered on a body weight of 70 kg

Adolescent simulation (allometric scaling) equations

$$CL_{adolescent} = CL_{adult} \cdot \left(\frac{WT}{70}\right)^{0.75} \quad \text{Eq.7}$$

$$Vc_{adolescent} = Vc_{adult} \cdot \left(\frac{WT}{70}\right)^{1} \quad \text{Eq.8}$$

CL clearance, *Vc* central distribution volume, *WT* body weight in kilograms (with a reference weight of 70 kg)

Table S1 Summary of studies of cabozantinib tablet formulation included in the cabozantinib population pharmacokinetic analysis

Study	Design	Subject Type	Nominal Doses	Planned PK Sampling
XL184-020[a]	Phase 1 pharmacokinetic study of cabozantinib (XL184) tablet formulation in healthy adult volunteers	Healthy volunteers	20, 40, 60 mg, single dose	Pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 14, 24, 48, 72, 120, 168, 240, 288, 336, 408, and, 504 hours post-dose
XL184-306	Phase 3, randomized, double-blind, controlled trial of cabozantinib (XL184) vs. mitoxantrone plus prednisone in men with previously treated symptomatic CRPC	Patients with CRPC	60 mg QD	Week 1 Day 1, Week 4 Day 1, Week 7 Day 1, and Week 13 Day 1
XL184-307	Phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs. prednisone in patients with metastatic castration-resistant prostate cancer who have received prior docetaxel and prior abiraterone or MDV3100	Patients with CRPC	60 mg QD	End of Week 3 and end of Week 12
XL184-308	Phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in patients with metastatic renal cell carcinoma (RCC) that has progressed after prior VEGFR tyrosine kinase inhibitor therapy	Patients with RCC	60 mg cabozantinib tablets PO QD	~8 or more hours after the prior evening dose on the W5D1 (Day 29) and W9D1 (Day 57) visits
XL184-309	Phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs placebo in patients with HCC who have received prior sorafenib	Patients with HCC	60 mg cabozantinib tablets PO QD	~8 or more hours after the previous dose of study treatment on the W3D1, W5D1, and W9D1 visits
XL184-311	Phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) in patients with radioiodine-refractory differentiated thyroid cancer (DTC) who have progressed after prior VEGFR-targeted therapy	Patients with DTC	60 mg cabozantinib tablets PO QD	~8 or more hours after the previous dose of study treatment on the W3D1, W5D1, and W9D1 visits
CheckMate 9ER	Phase 3, randomized, open-label study of nivolumab combined with cabozantinib versus sunitinib in patients with previously untreated advanced or metastatic RCC	Patients with RCC	40 mg cabozantinib tablets PO QD with nivolumab combination therapy	Pre-dose (Cycle 1, Day 1) and on Day 1 of Cycles 3, 4 and 7 (cycle = 2 weeks), ~8 or more hours after the prior evening dose

[a]XL184-020 was the only study to have morning dosing and serial PK sampling; other studies had evening dosing and sparse PK sampling

C cycle, *CRPC* castration-resistant prostate cancer, *D* day, *DTC* differentiated thyroid cancer,, *HCC* hepatocellular carcinoma, *hr* hour, *MDV3100* enzalutamide, *PK* pharmacokinetic, *PO* oral, *QD* once daily, *RCC* renal cell carcinoma, *VEGFR* vascular endothelial growth factor receptor, *W* week

Table S2 Summary of covariate information for studies included in population pharmacokinetic model

Study	**XL184 -020**	**XL184 -306**	**XL184 -307**	**XL184 -308**	**XL184 -309**	**XL184 -311**	**CheckMate 9ER**	**Total (%)**
N (%) of subjects	63 (3.6)	41 (2.4)	498 (28.5)	282 (16.2)	452 (25.9)	101 (5.8)	308 (17.7)	1745
Sex								
Male	33	41	498	222	365	45	237	1441 (82.6)
Female	30	0	0	60	87	56	71	304 (17.4)
Race								
Unknown	0	0	105	11	31	6	0	153 (8.8)
White	62	34	380	231	253	74	253	1287 (73.8)
Black	1	4	9	5	8	0	1	28 (1.6)
Asian	0	1	1	19	152	17	26[a]	216 (12.4)
Native American/Alaskan	0	0	0	0	0	2	3	5 (0.3)
Other	0	2	3	16	8	2	25	56 (3.2)
Population								
Healthy	63	0	0	0	0	0	0	63 (3.6)
RCC	0	0	0	282	0	0	308	590 (33.8)
CRPC	0	41	498	0	0	0	0	539 (30.9)
HCC	0	0	0	0	452	0	0	452 (25.9)
DTC	0	0	0	0	0	101	0	101 (5.8)
Age (yr)								
No.	63	41	498	282	452	101	308	1745
Mean	36.9	64.83	68.79	61.56	63.05	63.22	61.33	63.25
Median	38	65	69	62	64	66	62	65
SD	8.61	6.42	7.61	9.45	10.88	11.07	10.26	11.21
Minimum	19	48	35	32	22	32	29	19
Maximum	54	79	87	86	86	85	90	90
Body weight (kg)								
No.	63	41	492	282	451	101	308	1738
Mean	76.42	89.3	83.35	81.94	70.78	71.00	81.61	78.72
Median	76.5	84.8	82.3	80.4	68.94	70.0	80.15	77.55
SD	11.8	23.06	14.08	16.97	14.97	16.95	17.95	16.83
Minimum	58.1	57.5	49.7	48.1	35	41	36	35

Maximum	113.5	190.7	140	155.7	130	117	160.4	190.7
ALT (U/L)								
No.	63	41	498	282	452	101	307	1744
Mean	23.25	19.78	19.75	21.29	46.39	20.46	22.6	27.57
Median	23	16	16	17	37	16	18	20
SD	10.55	10.96	14.88	15.69	33.46	15.02	14.89	24.00
Minimum	9	7	4	5	6	6	5	4
Maximum	59	49	162	115	279	134	102	279
AST (U/L)								
No.	63	41	498	282	452	101	307	1744
Mean	21.08	29.66	27.22	22.19	62.21	21.70	21.11	33.92
Median	20	25	23	20	51	20	19	24
SD	6.36	18.14	15.47	10.43	39.95	9.37	9.76	28.57
Minimum	11	11	9	7	13	11	6	6
Maximum	43	94	123	70	286	71	69	286
Bilirubin (umol/L)								
No.	63	41	498	269	448	101	307	1727
Mean	10.15	6.54	6.89	7.67	12.75	7.71	8.93	9.05
Median	10.26	5	6	7	11	7	8.55	7.87
SD	5.05	3.35	3.23	3.21	7.57	3.92	4.26	5.50
Minimum	3.42	3	3	3	3	2.97	2.57	2.57
Maximum	30.78	17	28	21	82	21	39.33	82
CRCL (mL/min)[b]								
No.	63	41	491	282	451	101	307	1736
Mean	137.73	110.03	96.92	77.95	93.01	88.53	77.74	90.73
Median	135.7	112.3	92.9	74.4	90.0	83.4	72.2	85.95
SD	26.58	31.60	31.85	28.06	31.36	33.50	27.82	32.81
Minimum	86.5	48.6	27.5	29.7	34.3	26.6	27.2	26.6
Maximum	247.1	179.2	216.0	183.6	230.2	182.1	196.5	247.1

[a]Of the 26 Asian patients in Study CheckMate 9ER, 22 patients were Japanese
[b]Creatinine clearance was estimated using the Cockcroft-Gault equation

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CRCL* creatinine clearance, *CRPC* castration-resistant prostate cancer, *DTC* differentiated thyroid cancer, *HCC* hepatocellular carcinoma, *No.* number, *RCC* renal cell carcinoma, *SD* standard deviation

Table S3 Summary of predicted exposure measures in adults at steady state following 60 mg cabozantinib once daily

	Mean (SD) Exposure Parameter						
	Healthy Volunteers XL184-020	**CRPC Patients XL184-306**	**CRPC Patients XL184-307**	**RCC Patients Study XL184-308**	**HCC Patients Study XL184-309**	**DTC Patients Study XL184-311**	**RCC Patients Study CheckMate 9ER**
N	63	41	498	282	452	101	308
$C_{min,\ ss}$[a], ng/mL	1206 (484)	997 (356)	1190 (386)	1243 (429)	1301 (539)	1421 (455)	1290 (481)
$C_{max,\ ss,}$ ng/mL	1488 (640)	1230 (348)	1435 (390)	1503 (455)	1636 (566)	1771 (512)	1559 (510)
$AUC_{,ss,}$ ng·h/mL	30441 (12224)	25328 (8545)	30042 (9302)	31359 (10395)	32957 (13017)	35915 (11099)	32496 (11659)

[a]C_{min} concentrations are the pre-dose concentrations at steady state

$AUC_{,ss}$ steady state area under the concentration-time profile, *$C_{max,ss}$* steady state maximum plasma drug concentration, *$C_{min,ss}$* steady state minimum plasma drug concentration, *CRPC* castration-resistant prostate cancer, *DTC* differentiated thyroid cancer, *HCC* hepatocellular carcinoma; *SD* standard deviation, *RCC* renal cell carcinoma

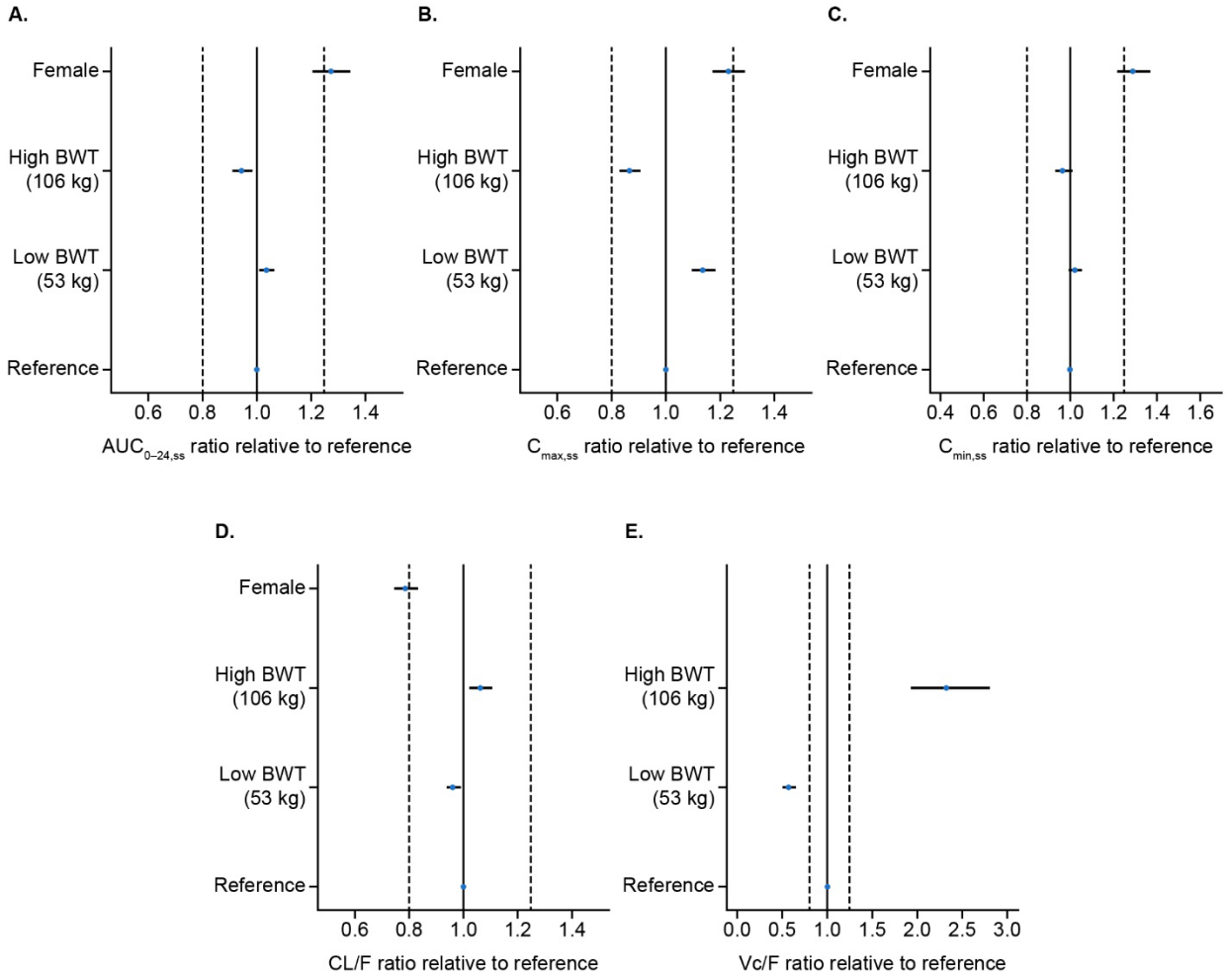
Table S4 Summary of number of events and number of patients at risk for time-to-event endpoints in COSMIC-311

Endpoint	Patients receiving at least one dose of cabozantinib and with at least one measurable cabozantinib concentration	
	Number of events[a]	Total Number of Patients at Risk
Progression-free survival[b]	29	98[g]
Cabozantinib dose modification[c]	92	114[h]
Palmar-plantar erythrodysesthesia (Grade ≥1)	55	115
Diarrhea (Grade ≥3)	9	115
Hypertension[d] (VS source data) (Grade ≥3)	24	115
Hypertension[e] (MedDRA terms) (Grade ≥3)	11	115
Fatigue/asthenia (Grade ≥3)	13	115
Nausea/vomiting (Grade ≥3)	5	115
Oral mucositis/stomatitis (Grade ≥3)	6	115
ALT/AST Elevation[f] (CTCAE v5) (Grade ≥3)	1	110[i]

[a]One event counted per endpoint per patient (data cut-off: August 19, 2020)
[b]For the endpoint of progression free survival, an event is defined as disease progression or death
[c]Dose reductions or holds
[d]Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg, based on VS source data
[e]Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg, based on MedDRA terms
[f]Per CTCAEv5 criteria for ALT/AST elevation
[g]For the analysis of progression free survival, patients were also required to have a valid baseline tumor assessment and at least one evaluable post-baseline tumor assessment
[h]Of the total 115 patients, one patient had a dose modification in the first week post dose and was excluded
[i]Of the total 115 patients with at least one measurable PK concentration, 110 had valid post-baseline ALT/AST measurements

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BP* blood pressure, *CTCAE* common terminology criteria for adverse events, *MedDRA* medical dictionary for regulatory activities, *VS* vital signs

Fig. S1 Impact of covariates on $AUC_{0\text{-}24,ss}$ (**A**), $C_{max,ss}$ (**B**), $C_{min,ss}$ (**C**), CL/F (**D**), and Vc/F (**E**)

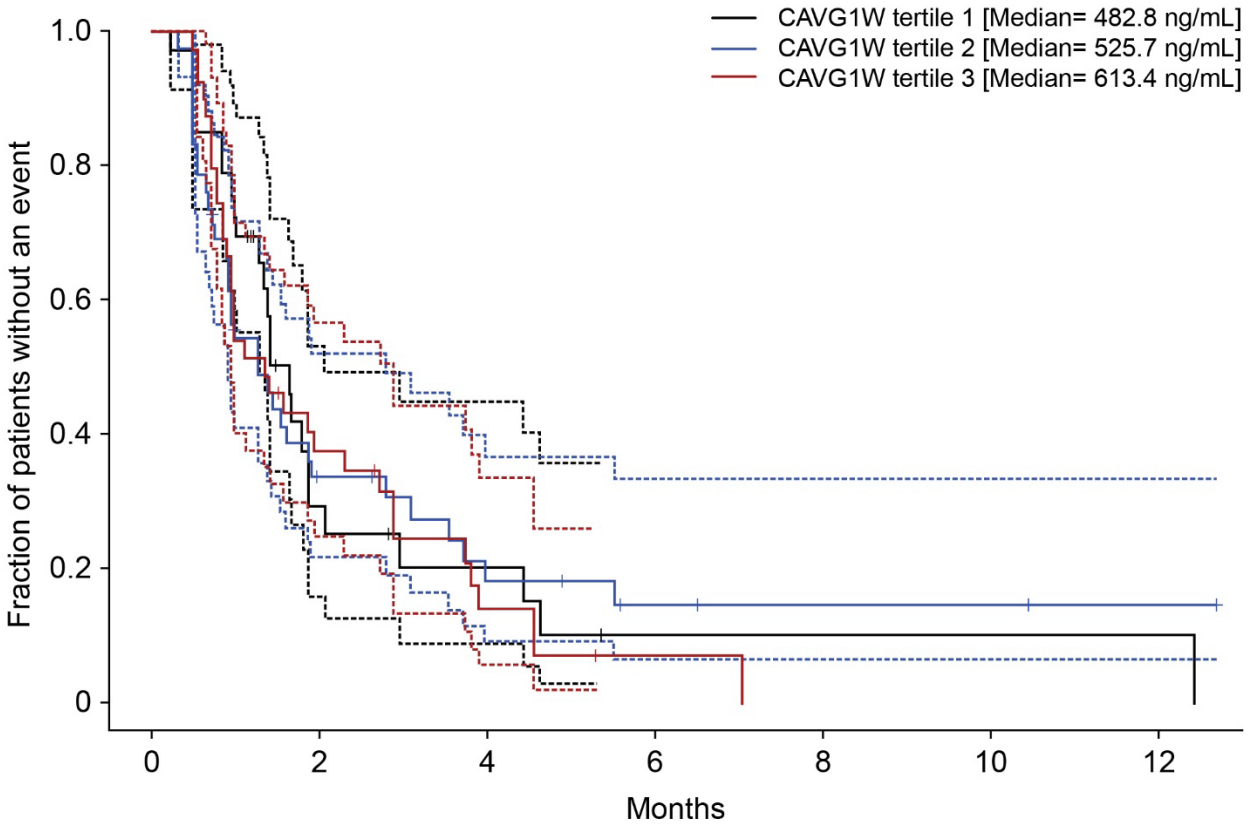


Note: A reference patient (Reference) was defined as a male patient with DTC and a BWT of 70 kg. other test conditions are defined as follows: Low BWT: a patient with BWT of 53 kg. High BWT: a patient with BWT of 106 kg

Blue solid circles show the ratio of the typical parameter value under the test conditions compared to the reference patient, and the line segments represent the corresponding 90% CI. Vertical dashed lines indicate the interval between ratios of 0.8 to 1.25

$AUC_{0\text{-}24,ss}$ steady state area under the concentration-time profile during one dosing interval (ng·hr/mL), *BWT* body weight, *CI* confidence interval, *$C_{max,ss}$* steady state maximum plasma drug concentration (ng/mL), *$C_{min,ss}$* pre-dose plasma drug concentrations at steady state (ng/mL)

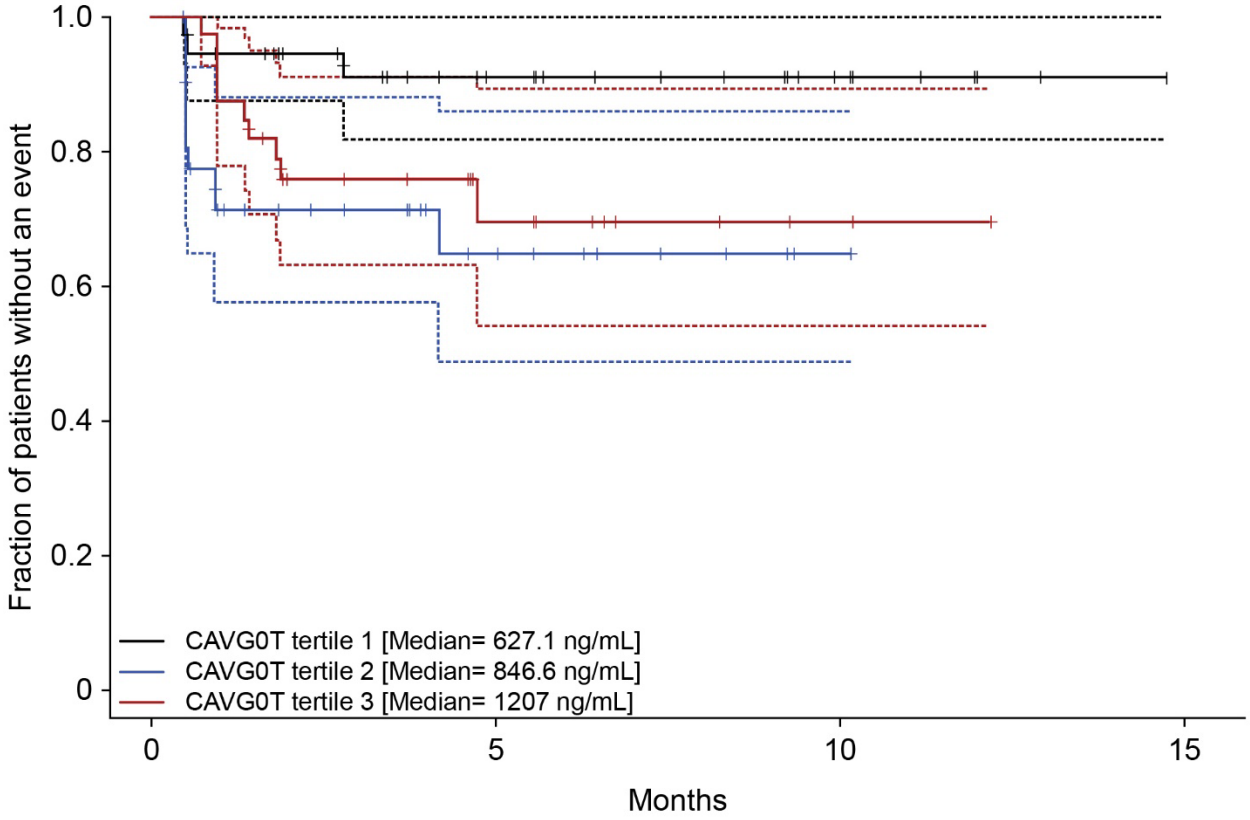
Fig. S2 Kaplan-Meier plot for cabozantinib dose modification using CAVG1W



Data derived from 114 patients with at least one measurable cabozantinib concentration and dose modification after the first week of treatment in COSMIC-311

Note: Dashed lines represent 95% confidence intervals for each exposure tertile. One patient had a dose modification event before Day 7 and was excluded from the analysis
CAVG1W predicted average cabozantinib concentration for the first week of treatment

Fig. S3 Kaplan-Meier plot for hypertension (BP data, Grade ≥3) by average exposure tertile

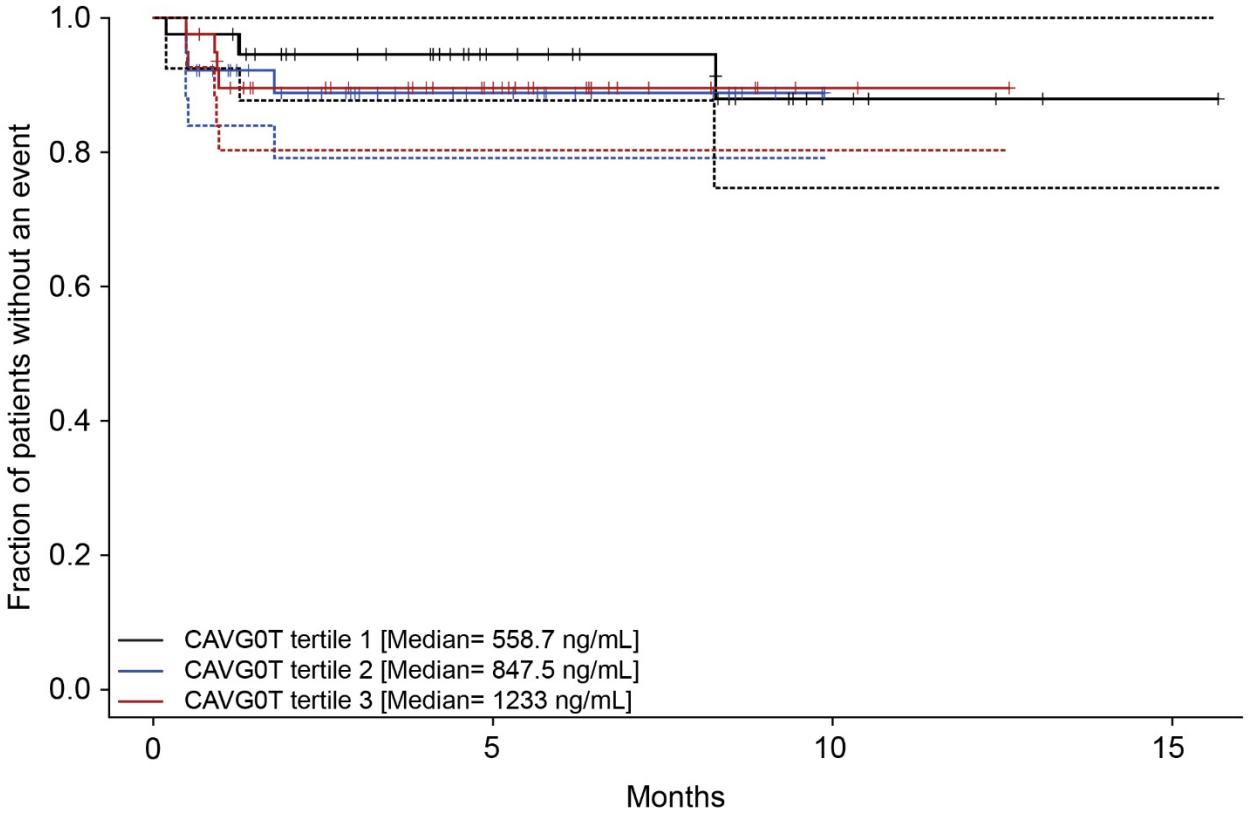


Data derived from 115 patients with at least one measurable cabozantinib concentration in COSMIC-311

Note: Dashed lines represent 95% confidence intervals for each exposure tertile

BP blood pressure, *CAVG0T* predicted average cabozantinib concentration from time zero to the event or censoring time

Fig. S4 Kaplan-Meier plot for hypertension (MedDRA, Grade ≥3) by average exposure tertile

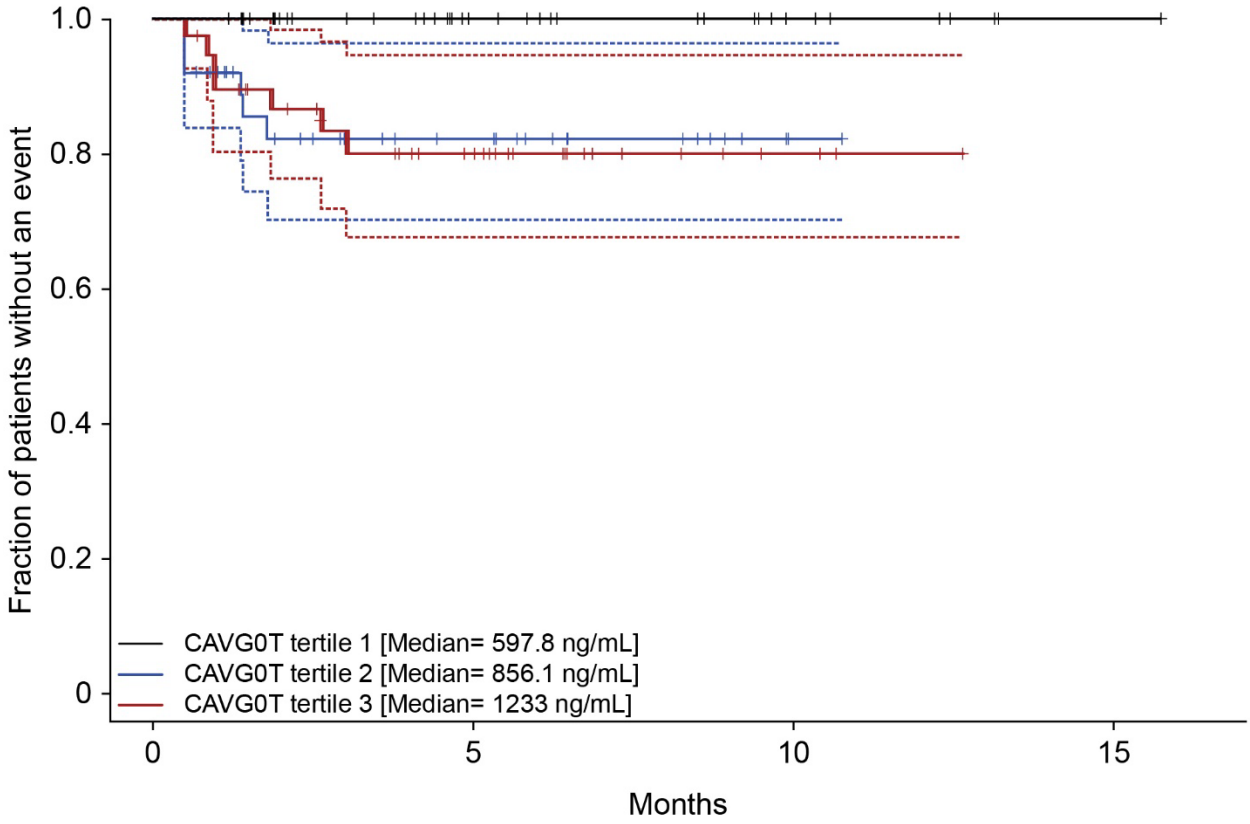


Data derived from 115 patients with at least one measurable cabozantinib concentration in COSMIC-311

Note: Dashed lines represent 95% confidence intervals for each exposure tertile

CAVG0T predicted average cabozantinib concentration from time zero to the event or censoring time, *MedDRA* Medical Dictionary for Regulatory Activities

Fig. S5 Kaplan-Meier plot for fatigue/asthenia (Grade ≥3) by average exposure tertile

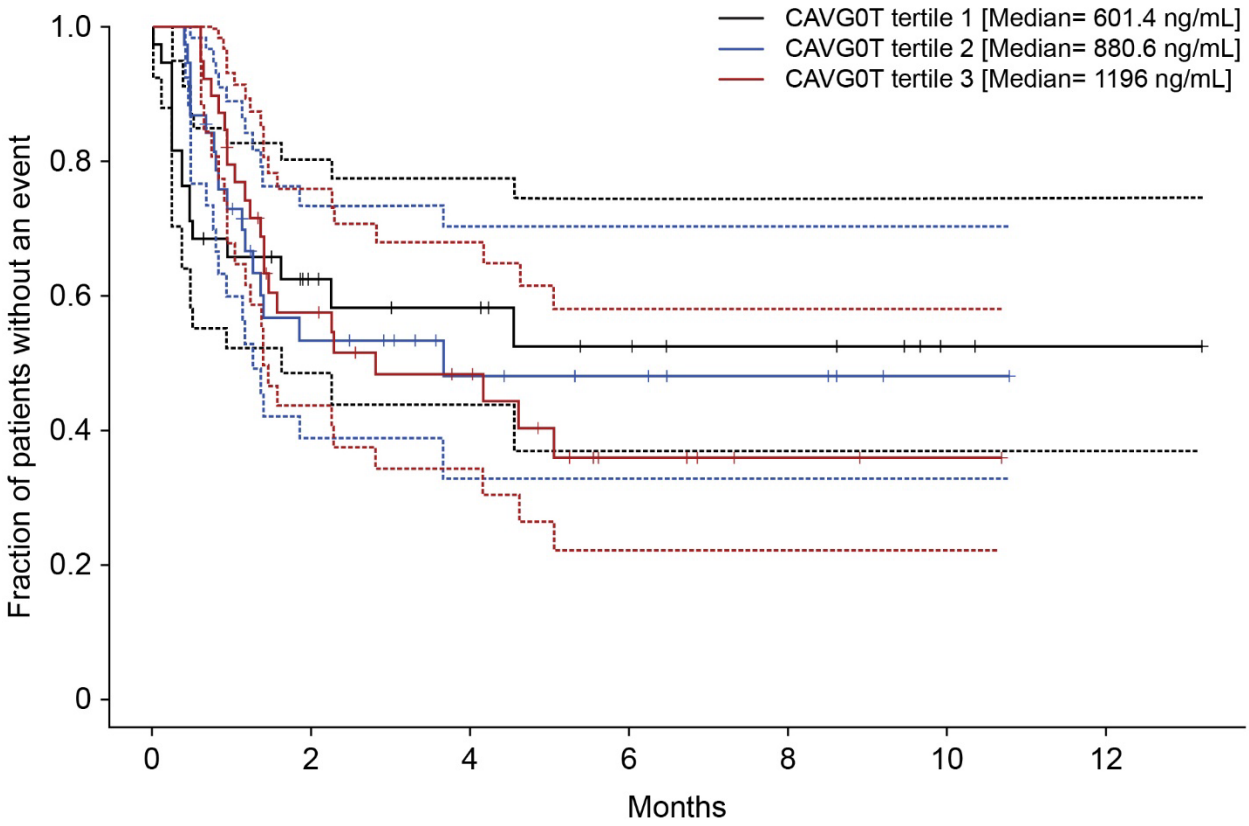


Data derived from 115 patients with at least one measurable cabozantinib concentration in COSMIC-311

Note: Dashed lines represent 95% confidence intervals for each exposure tertile

CAVG0T predicted average cabozantinib concentration from time zero to the event or censoring time

Fig. S6 Kaplan-Meier plot for PPE (Grade ≥1) by average exposure tertile

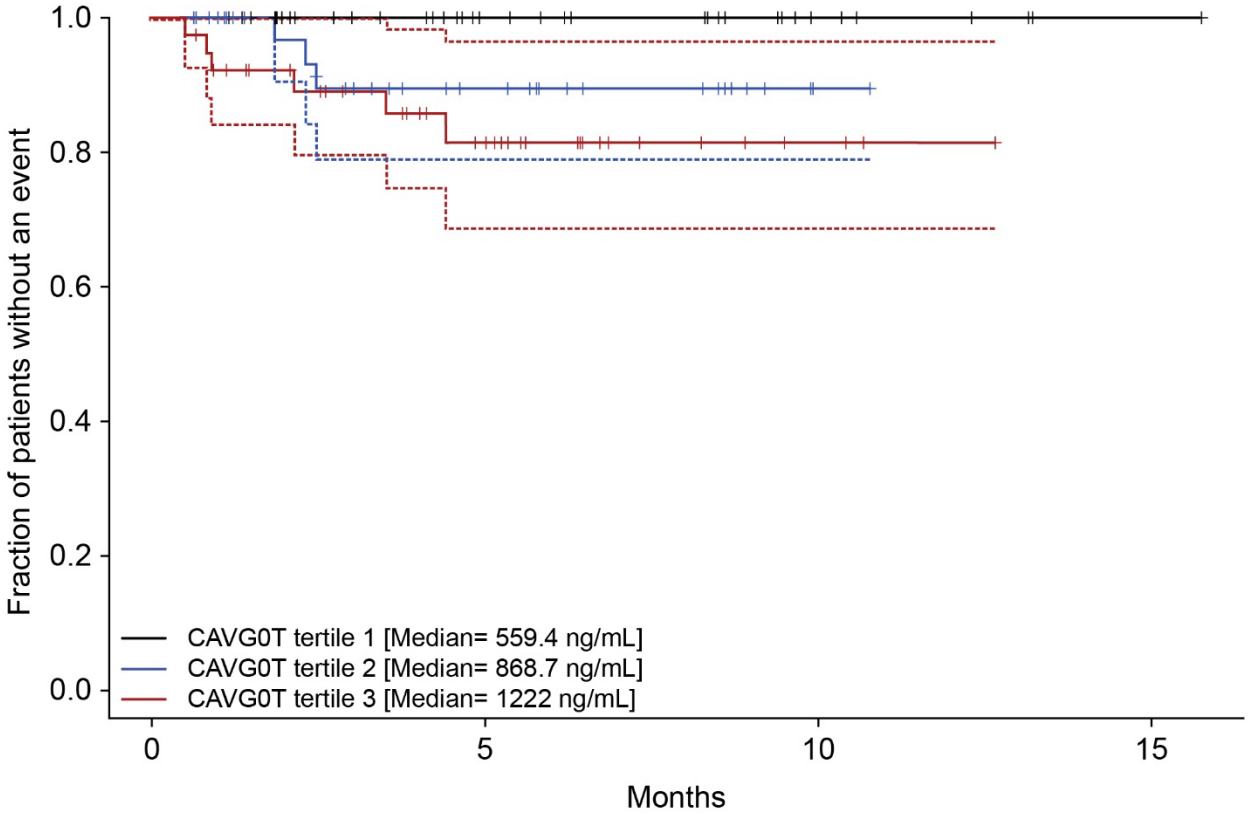


Data derived from 115 patients with at least one measurable cabozantinib concentration in COSMIC-311

Note: Dashed lines represent 95% confidence intervals for each exposure tertile

CAVG0T predicted average cabozantinib concentration from time zero to the event or censoring time, *PPE* palmar-plantar erythrodysesthesia

Fig. S7 Kaplan-Meier plot for diarrhea (Grade ≥3) by average exposure tertile

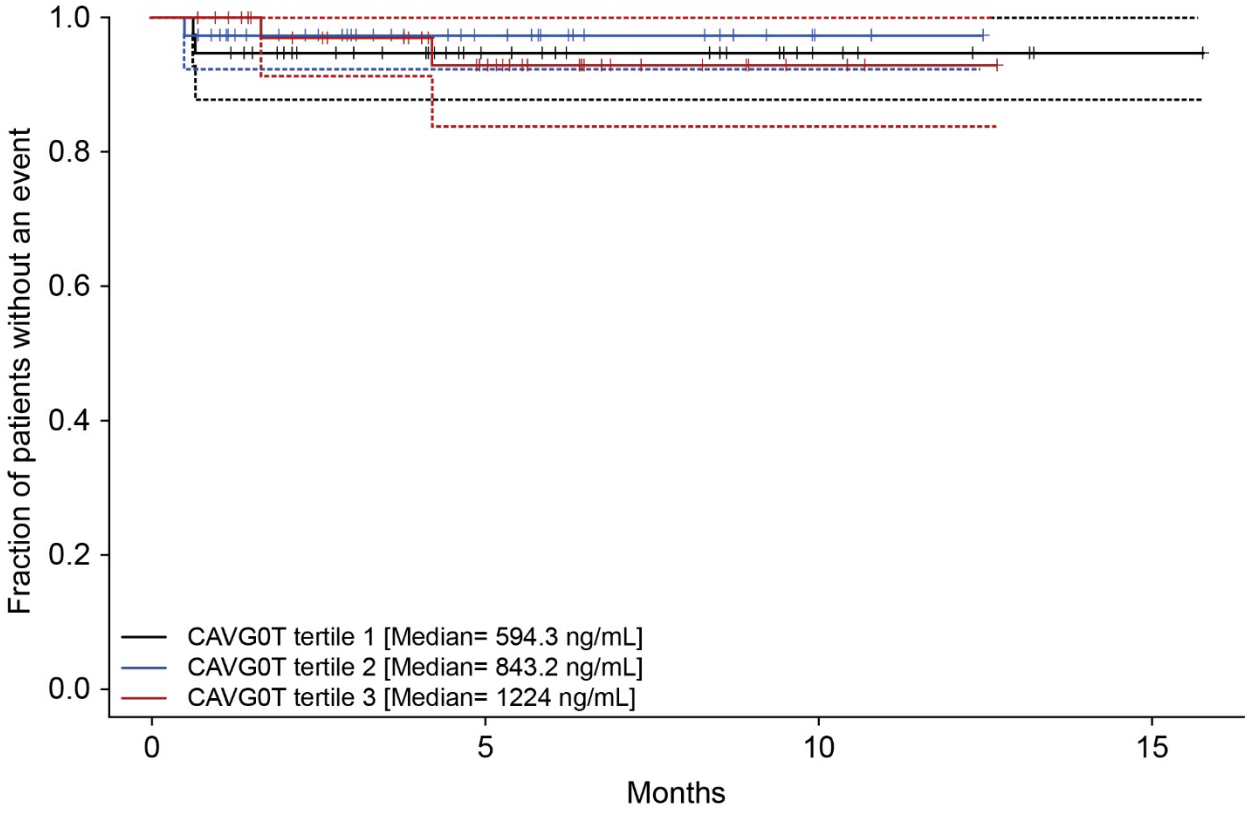


Data derived from 115 patients with at least one measurable cabozantinib concentration in COSMIC-311

Note: Dashed lines represent 95% confidence intervals for each exposure tertile

CAVG0T predicted average cabozantinib concentration from time zero to the event or censoring time

Fig. S8 Kaplan-Meier plot for nausea/vomiting (Grade ≥3) by average exposure tertile

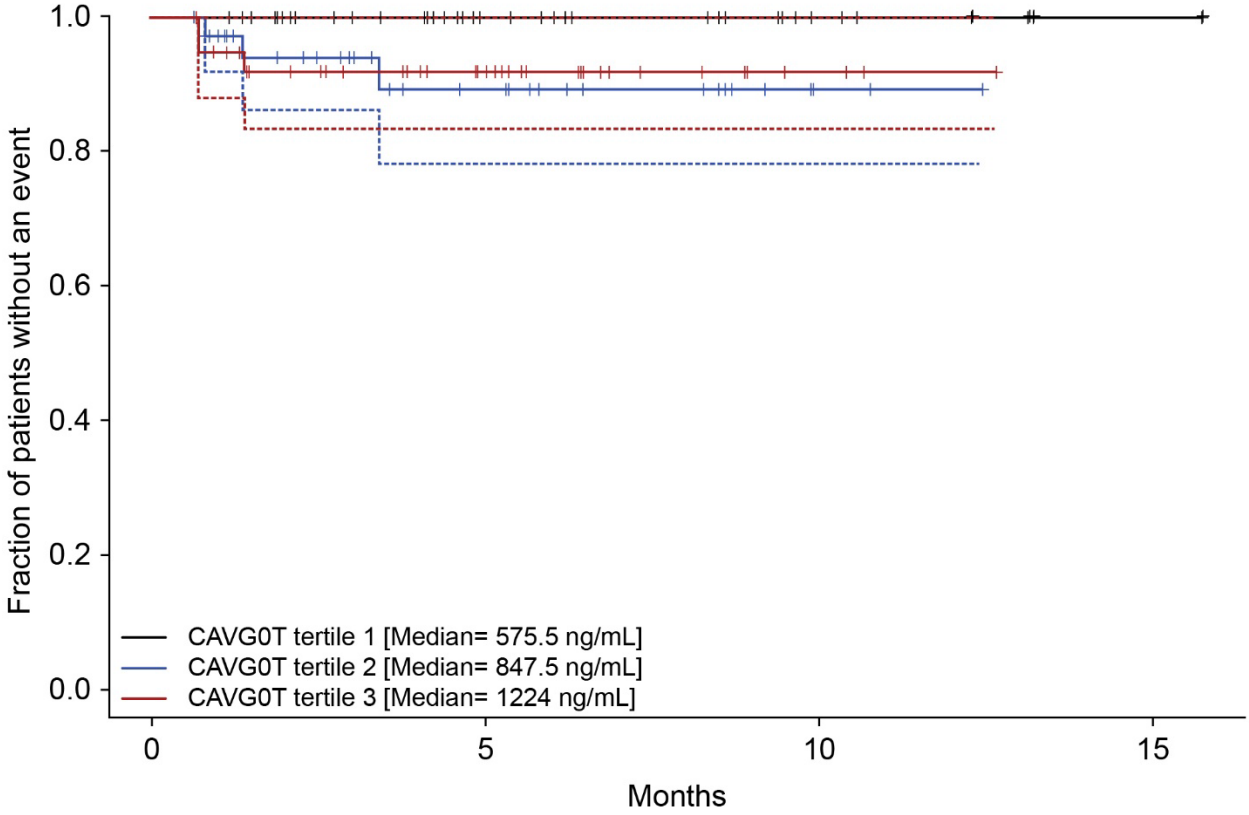


Data derived from 115 patients with at least one measurable cabozantinib concentration in COSMIC-311

Note: Dashed lines represent 95% confidence intervals for each exposure tertile

CAVG0T predicted average cabozantinib concentration from time zero to the event or censoring time

Fig. S9 Kaplan-Meier plot for mucositis/stomatitis (Grade ≥3) by average exposure tertile

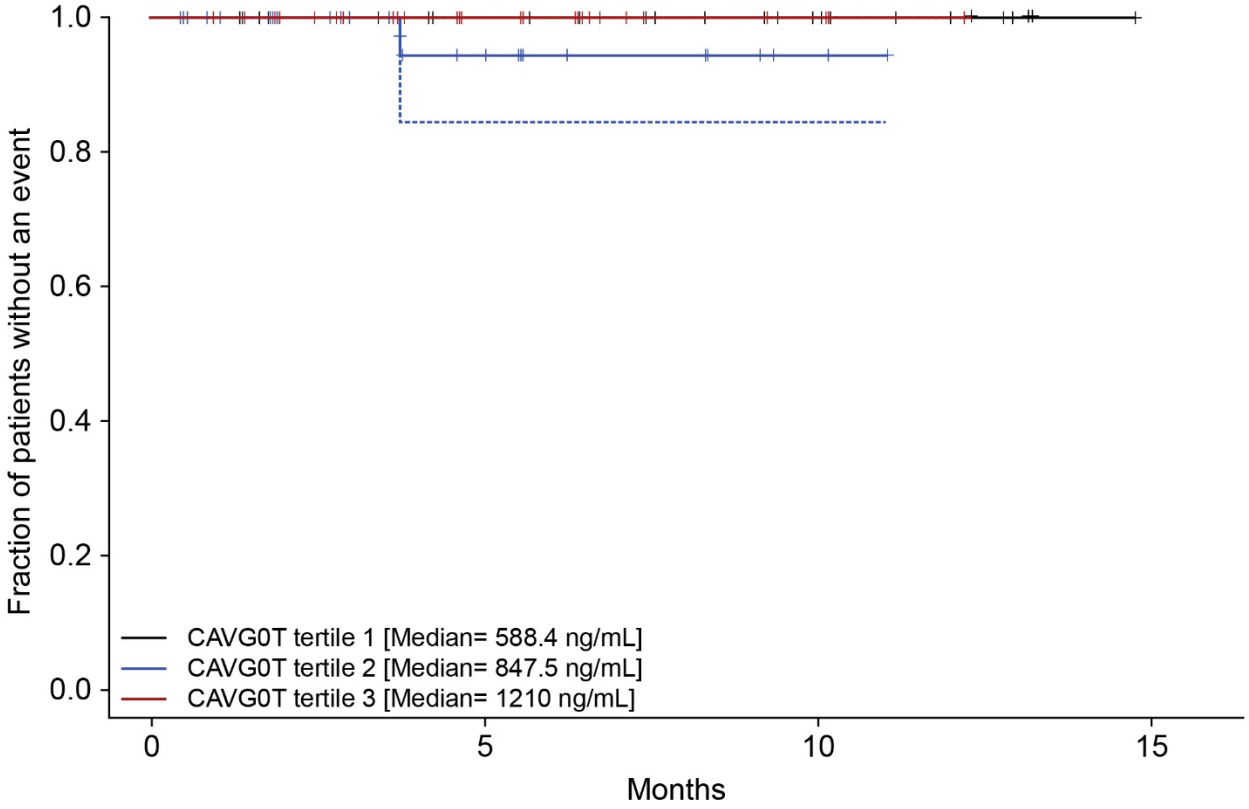


Data derived from 115 patients with at least one measurable cabozantinib concentration in COSMIC-311

Note: Dashed lines represent 95% confidence intervals for each exposure tertile

CAVG0T predicted average cabozantinib concentration from time zero to the event or censoring time

Fig. S10 Kaplan-Meier plot for ALT/AST elevation (Grade ≥3) by average exposure tertile



Data derived from 110 patients with at least one measurable cabozantinib concentration and valid post-baseline ALT/AST measurements in COSMIC-311

Note: Dashed lines represent 95% confidence intervals for each exposure tertile

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CAVG0T* predicted average cabozantinib concentration from time zero to the event or censoring time