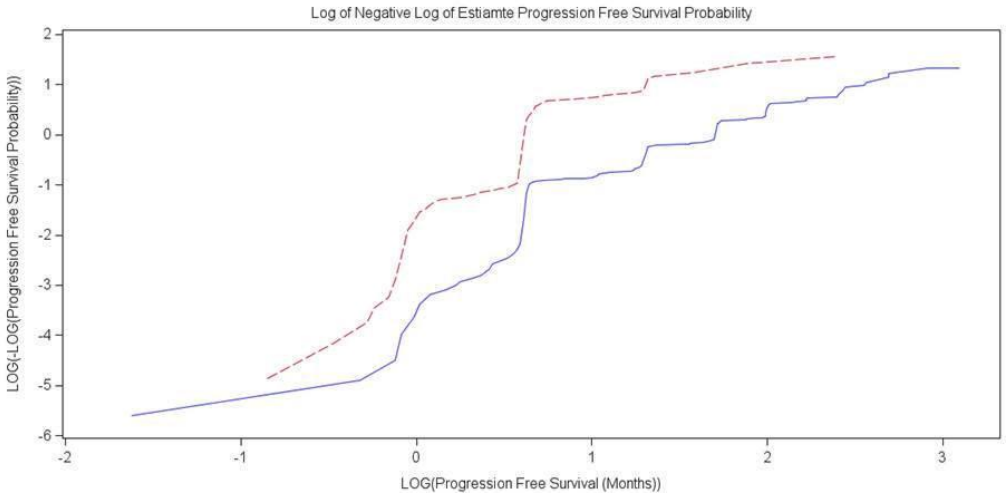
Tests for the proportional hazards assumption:

Methodology: The method was added to the Statistical Methods (line 209): Post-hoc tests for interaction of treatment by each covariate were performed by fitting Cox models including treatment, covariate, and covariate by treatment interaction term. The significance level for interaction test was set to two-sided 0.10.

The assumption of proportionality was assessed firstly by examining plots of complementary log-log (event times) versus log (time) and, if this raised concerns, by adding interaction of treatment with time to the stratified Cox model to assess the extent to which this represented random variation. If a lack of proportionality was evident, the variation in treatment effect would be described by presenting piecewise hazard ratio calculated over distinct time-periods from a post-hoc analysis. In such circumstances, the hazard ratio can still be meaningfully interpreted as an average hazard ratio over time.[1,2]

The proportionality check for PFS: As shown in the plot of complementary log-log (event times) versus log (time), a concern was raised on the proportional hazards assumption. Therefore, the assumption was furthered tested by adding treatment by time interaction term to the stratified Cox model. The result showed that the p-value for the interaction is 0.0029. Therefore the piecewise HRs were explored for two periods: 0 to 1.85 months post-randomization, and 1.85 months post-randomization to thereafter). The cutoff 1.85 months post-randomization was the time point where the two PFS curves were getting to the closest.

Figure1 Plot of Negative Log of Estimate Progression Free Survival Probability



[1] Borucka, Jadwiga. Extensions of Cox Model For Non-Proportional Hazards Purpose. Ekonometria 2014;3(45): 85-101.
[2] Allison, Paul D. 2010. Survival Analysis Using SAS®:A Practical Guide, Second Edition. Cary, NC: SAS Institute Inc

Table 1. Testing of Treatment-by-Time Interaction Using Stratified Cox Model

Parameter	Degree of Freedom	Parameter Estimate	Standard Error	Chi-Square	p-vlue
Treatment	1	-1.98435	0.24602	65.0601	<.0001
Treatment*Progression Free Survival	1	-0.27557	0.09266	8.8444	0.0029

Note: The stratified cox model included treatment and interaction of treatment by progression free survival time (continuous variable). Stratified factors included use of VEGF inhibitor (yes vs. no) and KRAS gene state (wild type vs. mutated).

Table2. Piecewise Hazard Ratios (Fruquintinib vs Placebo) from Stratified Cox Model

Time from Randomization (Months)	Hazard Ratio	95% Confidence Interval
(0, 1.85]	0.20	(0.14,0.29)
(1.85,∞)	0.12	(0.05, 0.26)

Note: The stratified cox model included treatment and interaction of treatment by progression free survival time (≤18.5 months or >18.5 months). Stratified factors included use of VEGF inhibitor (yes vs. no) and KRAS gene state (wild type vs. mutated).