**Methods S1**

*Detailed description assay regorafenib, M-2 and M-5*

Regorafenib and the metabolites M-2- and M-5 were simultaneously quantitated by a validated liquid chromatography tandem triple quadrupole mass spectrometry (UPLC-MS/MS) assay. Aliquots of 25 µL of human lithium heparinized plasma samples for the quantitation of regorafenib and its metabolites were deproteinized, after the addition of 100 µL of Internal Standard (sunitinib-d10). After vigorously mixing for 5 seconds and centrifugation for 10 min at 18,000**g*, aliquots of 1 µL were injected into the UPLC-MS/MS-system. Peak area ratios of analytes versus the Internal Standard were a function of the concentration from 20.0 to 5,000 ng/mL. For regorafenib, the within and between-run precisions at five tested concentrations, including the LLQ, were ≤ 5.94 and ≤ 9.99%, respectively, while the average accuracy ranged from 101.4 to 112.5%. For regorafenib-M2, the within and between-run precisions at five tested concentrations, including the LLQ, were ≤ 5.18 and ≤ 11.4%, respectively, while the average accuracy ranged from 91.0 to 96.7% and for regorafenib-M5, the within and between-run precisions at five tested concentrations, including the LLQ, were ≤ 6.47 and ≤ 11.2%, respectively, while the average accuracy ranged from 92.8 to 99.4%.