Supplementary Table 4. Dose-limiting toxicities

Cohort, n	Patients evaluable for DLT	Patients with a DLT	DLT events (all grade 3)
Regorafenib 72 mg/m^2 concomitant with VI (n=2)	2	2	Peripheral sensory neuropathy; hepatic pain; ALT increased; AST increased; DILI[a]
			Abdominal pain; vomiting; febrile bone marrow aplasia[b]
Regorafenib 72 mg/m^2 sequential with VI (n=6)	6	1	Maculopapular rash; AST increased
Regorafenib 82 mg/m^2 sequential with VI (n=13)	12[c]	1	Thrombocytopenia > 7days

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; DLT, dose-limiting toxicity; VI, vincristine and irinotecan.

[a]Hepatic pain, drug-induced liver injury, and peripheral sensory neuropathy occurred on day 3 of concomitant treatment ,and elevated ALT and AST occurred on day 4 of treatment. Irinotecan was interrupted on day 5 (the fifth dose of five daily doses was omitted); regorafenib was interrupted on day 4, and both drug doses were reduced at the next cycle. Vincristine was discontinued due to neuropathy.

[b]Vomiting started on day 8 of concomitant treatment, whereas abdominal pain and febrile bone marrow aplasia occurred on day 10. Regorafenib was interrupted on day 10, whereas irinotecan and vincristine had already been given for cycle 1 and the DLTs delayed cycle 2 by 1 week.

[c]One patient received <80% of the planned dose of regorafenib during cycle 1, and so was not evaluable for DLT.