

Table S1. Toxicity

Toxicity^a	Regorafenib N (%)	Regorafenib + Esomeprazole Concomitant N (%)	Regorafenib + Esomeprazole 3h prior N (%)	Overall^b N (%)
Gastrointestinal				
Anorexia All grades Grade ≥3	6 (43) 1 (7)	5 (36) 1 (7)	5 (36) 1 (7)	10 (71) 2 (14)
Constipation All grades Grade ≥3	2 (14) 0	2 (14) 0	1 (7) 0	4 (29) 0
Diarrhea All grades Grade ≥3	0	1 (7) 0	2 (14) 0	2 (14) 0
Nausea All grades Grade ≥3	2 (14) 0	5 (36) 0	3 (21) 0	7 (50) 0
Reflux All grades Grade ≥3	1 (7) 0	0 0	1 (7) 0	2 (14) 0
Stomatitis All grades Grade ≥3	5 (36) 0	6 (43) 0	5 (36) 0	8 (57) 0
Vomiting All grades Grade ≥3	2 (14) 0	2 (14) 0	3 (21) 0	5 (36) 0
Respiratory				
Cough All grades Grade ≥3	0	2 (14) 0	1 (7) 0	2 (14) 0
Dry mouth All grades Grade ≥3	0	1 (7) 0	3 (21) 0	3 (21) 0
Dyspnea All grades Grade ≥3	3 (21) 0	3 (21) 0	4 (29) 1 (7)	6 (43) 1 (7)
Ear pain All grades Grade ≥3	1 (7) 0	2 (14) 0	1 (7) 0	3 (21) 0
Hoarseness All grades Grade ≥3	8 (57) 0	11 (79) 0	9 (64) 0	11 (79) 0
Vascular				
Cardiac events ^c All grades Grade ≥3	0	2 (14) 0	0	2 (14) 0
Hypertension All grades Grade ≥3	4 (29) 3 (21)	4 (29) 3 (21)	5 (36) 5 (36)	10 (71) 9 (64)
Skin & Hair				
Erythema All grades Grade ≥3	1 (7) 0	2 (14) 0	1 (7) 0	4 (29) 0
Hand foot skin reaction All grades Grade ≥3	6 (43) 0	9 (64) 1 (7)	7 (50) 1 (7)	9 (64) 2 (14)

Hypertrichosis <i>All grades</i> <i>Grade ≥3</i>	0	1 (7) 0	1 (7) 0	1 (7) 0
General disorders				
Fatigue <i>All grades</i> <i>Grade ≥3</i>	6 (43) 1 (7)	7 (50) 0	7 (50) 1 (7)	10 (71) 1 (7)
Blood value disorders				
AST/ALT increase <i>All grades</i> <i>Grade ≥3</i>	7 (50) 0	6 (43) 1 (7)	5 (36) 0	11 (79) 1 (7)
Bilirubin increase <i>All grades</i> <i>Grade ≥3</i>	4 (29) 0	3 (21) 0	2 (14) 0	7 (50) 0
Hypophosphatemia <i>All grades</i> <i>Grade ≥3</i>	2 (14) 0	1 (7) 0	1 (7) 1 (7)	4 (29) 1 (7)
Platelet count decreased <i>All grades</i> <i>Grade ≥3</i>	0	1 (7) 0	0	1 (7) 0

Number of patients is scored as individual patients per phase.

^a Toxicity was graded according to the NCI CTC-AE classification (version 4.03)

^b Overall toxicity was defined as the number of patients during the whole study period (i.e. all three phases)

^c Cardiac events included atrial fibrillation and myocardial infarction

Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; N = number of patients