Supplementary Table S8. Adverse events leading to dose reduction and drug discontinuation by CTCAE grade during the phase II portion				
Adverse Event	**Adverse Event Grade by Treatment Group**			
	Nintedanib, 200 mg bid (n = 62)		Sorafenib, 400 mg bid (n = 31)	
AEs Leading to Dose Reduction	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Patients with AEs leading to dose reduction of trial drug	12 (19.4)	9 (14.5)	13 (41.9)	12 (38.7)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	2 (6.5)	2 (6.5)
Neutropenia	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)
Gastrointestinal disorders	4 (6.5)	2 (3.2)	1 (3.2)	1 (3.2)
Diarrhoea	2 (3.2)	1 (1.6)	1 (3.2)	1 (3.2)
Gastric ulcer	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Nausea	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	2 (3.2)	1 (1.6)	1 (3.2)	1 (3.2)
Fatigue	2 (3.2)	1 (1.6)	0 (0.0)	0 (0.0)
General physical health deterioration	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)
Investigations	5 (8.1)	5 (8.1)	1 (3.2)	1 (3.2)
ALT increased	1 (1.6)	1 (1.6)	1 (3.2)	1 (3.2)
AST increased	2 (3.2)	2 (3.2)	1 (3.2)	0 (0.0)
Amylase increased	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Blood alkaline phosphatase increased	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Lipase increased	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)

Nervous system disorders	0 (0.0)	0 (0.0)	3 (9.7)	2 (6.5)
Hepatic encephalopathy	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)
Lethargy	0 (0.0)	0 (0.0)	2 (6.5)	1 (3.2)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	9 (29.0)	7 (22.6)
Palmar-plantar erythrodysesthesia syndrome	0 (0.0)	0 (0.0)	6 (19.4)	5 (16.1)
Rash	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)
Skin reaction	0 (0.0)	0 (0.0)	2 (6.5)	2 (6.5)
Vascular disorders	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Essential hypertension	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Hypertension	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Patients with AEs leading to discontinuation of trial drug	28 (45.2)	18 (29.0)	7 (22.6)	5 (16.1)
Blood and lymphatic system disorders	1 (1.6)	1 (1.6)	1 (3.2)	1 (3.2)
Anaemia	1 (1.6)	1 (1.6)	1 (3.2)	1 (3.2)
Cardiac disorders	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	10 (16.1)	6 (9.7)	1 (3.2)	1 (3.2)
Upper gastrointestinal haemorrhage	2 (3.2)	1 (1.6)	0 (0.0)	0 (0.0)
Vomiting	2 (3.2)	1 (1.6)	0 (0.0)	0 (0.0)
Abdominal pain upper	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Ascites	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)

Gastric varices haemorrhage	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Nausea	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Oesophageal varices haemorrhage	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Varices oesophageal	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Mouth ulceration	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)
General disorders and administration site conditions	9 (14.5)	8 (12.9)	0 (0.0)	0 (0.0)
Fatigue	4 (6.5)	4 (6.5)	0 (0.0)	0 (0.0)
General physical health deterioration	3 (4.8)	2 (3.2)	0 (0.0)	0 (0.0)
Asthenia	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Disease progression	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Performance status decreased	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	1 (1.6)	1 (1.6)	1 (3.2)	0 (0.0)
Hyperbilirubinemia	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Hepatotoxicity	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)
Infections and infestations	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	3 (4.8)	1 (1.6)	2 (6.5)	1 (3.2)
Blood alkaline phosphatase increased	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	2 (3.2)	1 (1.6)	0 (0.0)	0 (0.0)
ALT increased	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic enzyme increased	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Electrocardiogram QT prolongation	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)
Transaminases increased	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)

Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Malignant neoplasm progression	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Nervous system disorders	2 (3.2)	1 (1.6)	0 (0.0)	0 (0.0)
Hepatic encephalopathy	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Lethargy	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Depressed mood	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Nephrotic syndrome	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	4 (12.9)	3 (9.7)
Palmar-plantar erythrodysesthesia syndrome	0 (0.0)	0 (0.0)	2 (6.5)	1 (3.2)
Rash	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)
Stevens–Johnson syndrome	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)
Surgical and medical procedures	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Hepatectomy	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Vascular disorders	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Hypertensive crisis	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.
NOTE. Percentages are calculated using total number of patients per treatment as the denominator. MedDRA v17.0 was used for reporting. Only AEs with CTCAE grades equal to 1 to 5 are included. On-treatment AEs include the 28-day post-treatment period. AEs are sorted by frequency in the nintedanib 200 mg group.
[a]One patient had one AE “metastases to central nervous system” with missing CTCAE grade.