	Trametinib group (n=128)				Standard-of-care group (n=127)			
	Any grade	Grade 1	Grade 2	Grade ≥3	Any grade	Grade 1	Grade 2	Grade ≥3
General disorders								
Fatigue	93 (73%)	47 (37%)	36 (28%)	10 (8%)	74 (58%)	44 (35%)	25 (20%)	5 (4%)
Peripheral oedema	62 (49%)	44 (34%)	18 (14%)	0	15 (12%)	9 (7%)	5 (4%)	1 (1%)
Gastrointestinal disorders								
Abdominal pain	57 (45%)	37 (29%)	13 (10%)	7 (6%)	60 (47%)	27 (21%)	11 (9%)	22 (17%)
Constipation	54 (42%)	43 (34%)	8 (6%)	3 (2%)	49 (39%)	38 (30%)	8 (6%)	3 (2%)
Diarrhoea	93 (73%)	57 (45%)	23 (18%)	13 (10%)	43 (34%)	29 (23%)	10 (8%)	4 (3%)
Oral mucositis	45 (35%)	34 (27%)	8 (6%)	3 (2%)	23 (18%)	13 (10%)	8 (6%)	2 (2%)
Nausea	78 (61%)	43 (34%)	23 (18%)	12 (9%)	65 (51%)	39 (31%)	12 (9%)	14 (11%)
Vomiting	59 (46%)	40 (31%)	10 (8%)	10 (7%)	44 (35%)	24 (19%)	10 (8%)	10 (8%)
Skin and subcutaneous tissue disorders								
Dry skin	56 (44%)	46 (36%)	9 (7%)	1 (1%)	17 (13%)	16 (13%)	1 (1%)	0
Acneiform rash	81 (63%)	52 (41%)	21 (16%)	8 (6%)	13 (10%)	10 (8%)	2 (2%)	1 (1%)
Maculopapular rash	54 (42%)	30 (23%)	15 (12%)	9 (7%)	28 (22%)	21 (17%)	7 (6%)	0
Blood and lymphatic system disorders								
Anaemia	67 (52%)	30 (23%)	21 (16%)	16 (13%)	54 (43%)	23 (18%)	19 (15%)	12 (10%)
White blood cell count decreased	28 (22%)	19 (15%)	8 (6%)	1 (1%)	21 (17%)	13 (10%)	5 (4%)	3 (2%)
Injury, poisoning, and procedural complications								
Alkaline phosphatase increased	32 (25%)	29 (23%)	1 (1%)	2 (2%)	11 (9%)	11 (9%)	0	0
Aspartate aminotransferase increased	47 (37%)	43 (34%)	3 (2%)	1 (1%)	15 (12%)	13 (10%)	1 (1%)	1 (1%)
Alanine aminotransferase increased	28 (22%)	24 (19%)	2 (2%)	2 (2%)	13 (10%)	11 (9%)	2 (2%)	0
Creatinine increased	26 (20%)	21 (16%)	4 (3%)	1 (1%)	10 (8%)	7 (6%)	3 (2%)	0
Metabolism and nutrition disorders								
Anorexia	34 (27%)	22 (17%)	10 (8%)	2 (2%)	24 (19%)	15 (12%)	8 (6%)	1 (1%)
Hyperglycaemia	32 (25%)	26 (20%)	6 (5%)	0	25 (20%)	20 (16%)	3 (2%)	2 (2%)
Hypokalaemia	26 (20%)	21 (16%)	0	5 (4%)	16 (13%)	11 (9%)	2 (2%)	3 (2%)
Hypomagnesemia	41 (32%)	34 (27%)	6 (5%)	1 (1%)	29 (23%)	27 (21%)	2 (2%)	0
Hypoalbuminemia	43 (34%)	19 (15%)	20 (16%)	4 (3%)	16 (13%)	8 (6%)	7 (6%)	1 (1%)
Nervous system disorders								
Headache	27 (21%)	22 (17%)	5 (4%)	0	24 (19%)	19 (15%)	4 (3%)	1 (1%)
Peripheral sensory neuropathy	36 (28%)	31 (24%)	4 (3%)	1 (1%)	28 (22%)	23 (18%)	4 (3%)	1 (1%)
Vascular disorders								
Hypertension	50 (39%)	7 (6%)	28 (22%)	15 (12%)	27 (21%)	8 (6%)	13 (10%)	6 (5%)
Respiratory, thoracic, and mediastinal disorders								
Dyspnoea	45 (35%)	31 (24%)	10 (8%)	4 (3%)	28 (22%)	20 (16%)	5 (4%)	3 (2%)
Infections and infestations								
Urinary tract infection	29 (23%)	0	20 (16%)	9 (7%)	18 (14%)	0	12 (9%)	6 (5%)

Data are n (%). Adverse events occurring in more than 20% of patients according to system organ class are shown.

Table 2: **Treatment-emergent adverse events in the safety analysis population**

of 127 patients in the standard-of-care group. Small intestine obstruction occurred in nine (7%) patients in the standard-of-care group and in 16 (13%) patients in the trametinib group, and colon obstruction occurred in six (5%) patients in the standard-of-care group and in one (1%) patient in the trametinib group.

The compliance rates of quality-of-life assessments in patients were 88% (227 of 259 patients) at baseline and 77% (194 of 253) at 12 weeks, 63% (153 of 244) at 24 weeks, 60% (139 of 233) at 36 weeks, and 56% (125 of 222) at 52 weeks after cycle 1. No significant difference in quality-of-life assessment compliance rates between the two groups was observed (p=0·57). A total of 198 evaluable patients (98 in the standard-of-care group and 100 in the trametinib group) who completed the baseline assessment and at least one follow-up assessment were evaluable for quality-of-life analysis. The patient-reported FACT-O TOI scores are presented in the appendix (p 13).