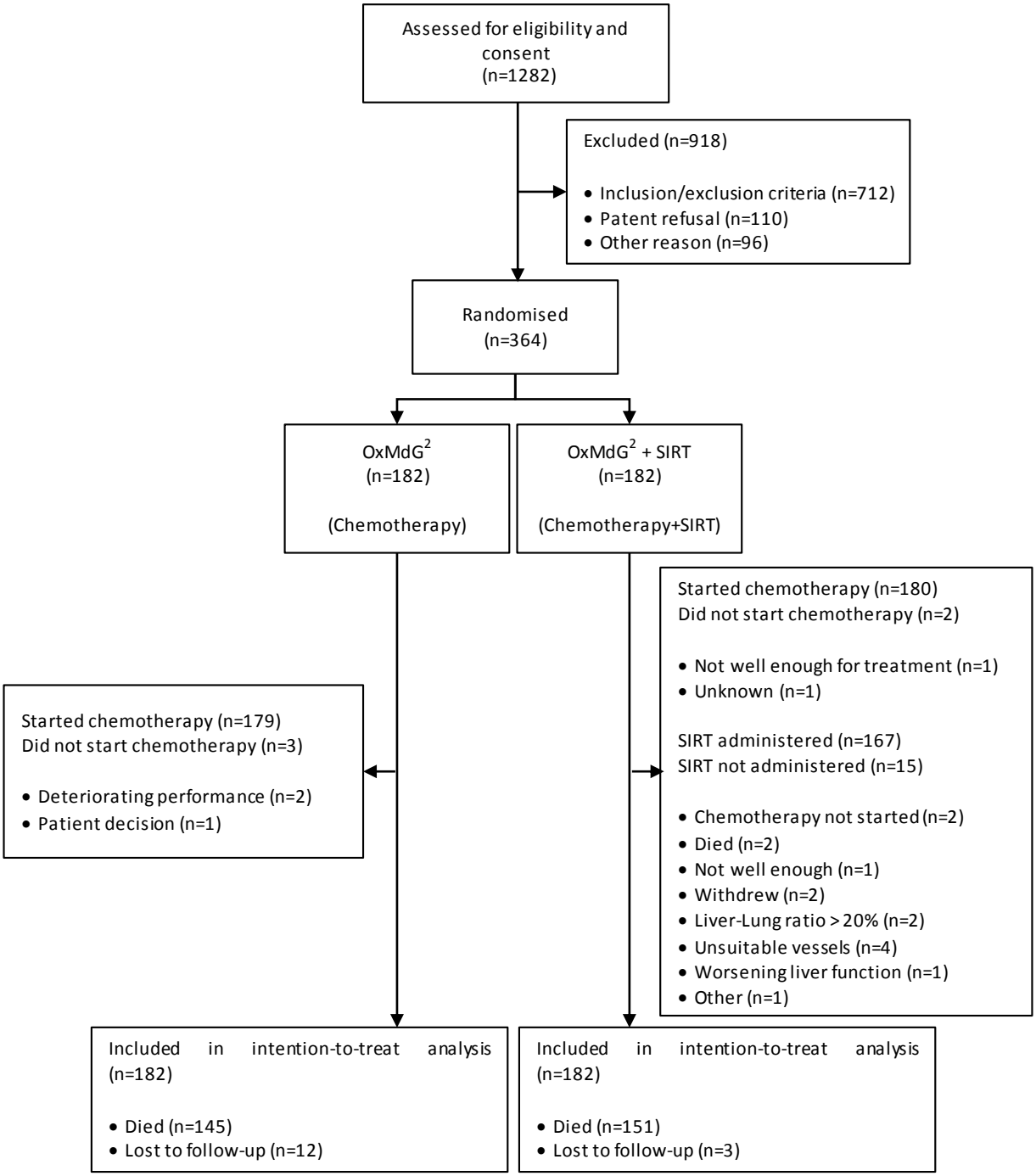
Participant Flow



Baseline Characteristics

		FOXFIRE		
		Chemotherapy (n=182)	Chemotherapy + SIRT (n=182)	Overall (n=364)
Extra-hepatic metastases status	No	122 (67.0%)	121 (66.5%)	243 (66.8%)
	Yes	60 (33.0%)	61 (33.5%)	121 (33.2%)
Extra-hepatic metastases sites[2]	Lungs	26 (43.3%)	19 (31.1%)	45 (37.2%)
	Lungs & lymph nodes	4 (6.7%)	4 (6.6%)	8 (6.6%)
	Lungs & Other	1 (1.7%)		1 (0.8%)
	Lymph nodes	18 (30.0%)	21 (34.4%)	39 (32.2%)
	Lymph nodes & Other	2 (3.3%)		2 (1.7%)
	Other	5 (8.3%)	5 (8.2%)	10 (8.3%)
	Missing	4 (6.7%)	12 (19.7%)	16 (13.2%)
Degree of liver involvement	<=25%	114 (62.6%)	115 (63.2%)	229 (62.9%)
	>25%	68 (37.4%)	67 (36.8%)	135 (37.1%)
	Missing			
Intention to treat with biological agents	Yes	65 (35.7%)	65 (35.7%)	130 (35.7%)
	No	96 (52.7%)	95 (52.2%)	191 (52.5%)
	Not applicable[3]	21 (11.5%)	22 (12.1%)	43 (11.8%)
Age at randomisation (years)[4]		62.0 (30.0,84.0)	63.5 (30.0,83.0)	62.5 (30.0,84.0)
Time since diagnosis of primary tumour to randomisation (months)[5]		1.5 (1.0,2.6)	1.5 (1.1,2.7)	1.5 (1.0,2.7)
Time since diagnosis of liver metastases to randomisation (months)[5]		1.2 (0.9,1.9)	1.3 (0.9,1.9)	1.3 (0.9,1.9)
Gender	Male	127 (69.8%)	117 (64.3%)	244 (67.0%)
	Female	55 (30.2%)	65 (35.7%)	120 (33.0%)
	Missing			
WHO performance status	0	119 (65.4%)	117 (64.3%)	236 (64.8%)
	1	63 (34.6%)	64 (35.2%)	127 (34.9%)
	Missing		1 (0.5%)	1 (0.3%)
Primary tumour site	Colon	127 (69.8%)	134 (73.6%)	261 (71.7%)
	Rectum	55 (30.2%)	48 (26.4%)	103 (28.3%)
	Not Categorisable[6]			
	Missing			
Primary tumour in situ?	Yes	122 (67.0%)	109 (59.9%)	231 (63.5%)
	No	60 (33.0%)	72 (39.6%)	132 (36.3%)
	Missing		1 (0.5%)	1 (0.3%)
KRAS status	Mutation	30 (16.5%)	23 (12.6%)	53 (14.6%)
	Wild Type	32 (17.6%)	33 (18.1%)	65 (17.9%)
	Missing	120 (65.9%)	126 (69.2%)	246 (67.6%)
Prior adjuvant chemotherapy?	Yes	9 (4.9%)	14 (7.7%)	23 (6.3%)
	No	173 (95.1%)	168 (92.3%)	341 (93.7%)
	Missing			
Prior radiotherapy (non-liver)?	Yes	10 (5.5%)	15 (8.2%)	25 (6.9%)
	No	172 (94.5%)	167 (91.8%)	339 (93.1%)
	Missing			
Metastases present at initial diagnosis?	Yes - Synchronous	154 (84.6%)	150 (82.4%)	304 (83.5%)
	No - Metachronous	27 (14.8%)	30 (16.5%)	57 (15.7%)
	Missing	1 (0.5%)	2 (1.1%)	3 (0.8%)

[1] Centre was also a minimisation factor (26 centres in total in FOXFIRE)

[2] Site of metastases was not a stratification factor

[3] Intention to treat with a biological agent was not a stratification variable for these patients as it was introduced after these patients entered the study

[4] Median (min-max)

[5] Median (interquartile range)

[6] Patient's site of primary tumour recorded as being both colon and rectum. Note: only options for FOXFIRE were colon or rectum.

Outcome Measures

Primary Outcome: Overall Survival[1]	FOXFIRE		SIRFLOX		FOXFIRE-Global	
	Chemo (n=182)	Chemo+SIRT (n=182)	Chemo (n=263)	Chemo+SIRT (n=267)	Chemo (n=104)	Chemo+SIRT (n=105)
No. (%) of events	145 (80%)	151 (83%)	202 (77%)	222 (83%)	64 (62%)	60 (57%)
Median survival time (months)	20.4	18.8	24.5	22.6	25.0	25.9
95% CI for median	17.6 - 23.9	17.2 – 23.0	21.8 - 26.4	21.5 - 25.6	22.1 – 28.5	23.1 – 28.9
Trial-specific HR[2] (95% CI)	**1.08 (0.85 – 1.37)**		**1.00 (0.81 – 1.23)**		**0.90 (0.62 – 1.31)**	
Overall pooled HR[2] (95% CI)	**1.04 (0.88 – 1.17)**					

[1] The primary analysis was performed on data from the FOXFIRE, SIRFLOX and FOXFIRE-Global clinical trials
[2] The reference group for statistical comparisons is the chemotherapy alone group

Secondary Outcomes	Chemo (n=182)	Chemo+SIRT (n=182)
Progression-free survival		
No. (%) of events	156 (86%)	148 (81%)
Median survival time (months) (95% CI)	9.5 (8.3 – 10.3)	9.9 (9.3 – 11.3)
HR[1] (95% CI)	0.87 (0.69 – 1.09)	
Liver-specific progression-free survival		
First event of liver progression:		
No. (%) of events	84 (46%)	47 (26%)
Sub-distribution HR[1] (95% CI)	0.45 (0.32 – 0.65)	
Cause-specific HR[1] (95% CI)	0.51 (0.36 – 0.73)	
First event of non-liver progression/death:		
No. (%) of events	72 (40%)	101 (55%)
Sub-distribution HR[1] (95% CI)	1.69 (1.25 – 2.28)	
Cause-specific HR[1] (95% CI)	1.28 (0.95 – 1.73)	
Response rate		
No (%) achieving an objective response (CR + PR)	111 (61.0%)	123 (67.6%)
OR (95% CI)	1.33 (0.87 – 2.05)	
Resection rate		
No (%) undergoing a hepatic resection	33 (18.1%)	38 (20.9%)
OR (95% CI)	1.19 (0.71 – 2.00)	
Safety and toxicity		
No (%) with grade 3-5 adverse event	119 (62.0%)	117 (70.1%)
OR (95% CI)	1.44 (0.92 – 2.23)	
Percentage of patients receiving second line treatment		
No (%) receiving second line chemotherapy	127 (69.8%)	105 (57.7%)
OR (95% CI)	0.59 (0.38 – 0.91)	
Interval from randomisation to start of second line treatment		
First event of commencing second line treatment:		
No. (%) of events	127 (69.8%)	105 (57.7%)
Sub-distribution HR[1] (95% CI)	0.67 (0.52 – 0.87)	
Cause-specific HR[1] (95% CI)	0.73 (0.56 – 0.94)	
First event of death:		
No. (%) of events	41 (22.5%)	64 (35.2%)
Sub-distribution HR[1] (95% CI)	1.67 (1.13 – 2.48)	
Cause-specific HR[1] (95% CI)	1.38 (0.93 – 2.04)	

[1] The reference group for statistical comparisons is the chemotherapy alone group

Adverse Events

n (%) experiencing grade 3+ adverse events[1]	Chemo (n=182)	Chemo + SIRT (n=182)
Neutropenia	28 (15%)	48 (29%)
Fatigue	13 (7%)	17 (10%)
Diarrhoea	10 (5%)	12 (7%)
Pain	2 (1%)	16 (10%)
Febrile neutropenia	8 (4%)	9 (5%)
Neutropenic sepsis	6 (3%)	10 (6%)
Infection	10 (5%)	5 (3%)
Pulmonary embolism	8 (4%)	7 (4%)
Abdominal pain	5 (3%)	8 (5%)
Thrombocytopenia	1 (1%)	11 (7%)
Ascites	4 (2%)	7 (4%)
Neuropathy peripheral	7 (4%)	4 (2%)
Lethargy	6 (3%)	4 (2%)
Constipation	5 (3%)	4 (2%)
Intestinal obstruction	5 (3%)	3 (2%)
Vomiting	2 (1%)	6 (4%)
Chest pain	3 (2%)	5 (3%)
Pyrexia	3 (2%)	5 (3%)
Neutrophil count	2 (1%)	5 (3%)
Leukopenia	2 (1%)	4 (2%)
Lower respiratory tract infection	5 (3%)	1 (1%)
Radiation hepatitis	0	5 (3%)
Decreased appetite	2 (1%)	3 (2%)
Dehydration	2 (1%)	3 (2%)
Deep vein thrombosis	2 (1%)	3 (2%)
Myocardial infarction	2 (1%)	2 (1%)
Intestinal perforation	3 (2%)	1 (1%)
Large intestinal obstruction	4 (2%)	0
Device related infection	2 (1%)	2 (1%)
Hyperglycaemia	2 (1%)	2 (1%)
Back pain	3 (2%)	1 (1%)
Dyspnoea	1 (1%)	3 (2%)
Hypotension	2 (1%)	2 (1%)
Anaemia	1 (1%)	2 (1%)
Acute myocardial infarction	1 (1%)	2 (1%)
Angina pectoris	2 (1%)	1 (1%)
Mucosal inflammation	3 (2%)	0
Sepsis	2 (1%)	1 (1%)
Hypokalaemia	0	3 (2%)
Embolism	1 (1%)	2 (1%)
Arteriospasm coronary	0	2 (1%)

Abdominal pain upper	0	2 (1%)
Duodenal ulcer	0	2 (1%)
Faecal volume increased	2 (1%)	0
Large intestine perforation	1 (1%)	1 (1%)
Nausea	0	2 (1%)
Stomatitis	1 (1%)	1 (1%)
Oedema peripheral	1 (1%)	1 (1%)
Hyperbilirubinaemia	2 (1%)	0
Anaphylactic reaction	1 (1%)	1 (1%)
Peritonitis	0	2 (1%)
Pneumonia	0	2 (1%)
Urinary tract infection	1 (1%)	1 (1%)
Administration related reaction	0	2 (1%)
Blood bilirubin increased	2 (1%)	0
Blood glucose increased	1 (1%)	1 (1%)
Blood phosphorus decreased	1 (1%)	1 (1%)
Blood potassium decreased	1 (1%)	1 (1%)
Gamma-glutamyltransferase increased	1 (1%)	1 (1%)
Pain in extremity	2 (1%)	0
Paraesthesia	1 (1%)	1 (1%)
Presyncope	0	2 (1%)
Syncope	0	2 (1%)
Lymphopenia	0	1 (1%)
Neutropenic sepsis	0	1 (1%)
Atrial tachycardia	0	1 (1%)
Cardiac failure	0	1 (1%)
Left ventricular dysfunction	0	1 (1%)
Myocardial ischaemia	0	1 (1%)
Tachycardia	1 (1%)	0
Visual impairment	0	1 (1%)
Abdominal distension	0	1 (1%)
Abdominal strangulated hernia	1 (1%)	0
Colitis	0	1 (1%)
Faecaloma	1 (1%)	0
Gastrointestinal perforation	0	1 (1%)
Intestinal ischaemia	0	1 (1%)
Oedema mouth	1 (1%)	0
Small intestinal obstruction	0	1 (1%)
Hernia pain	1 (1%)	0
Infusion site thrombosis	1 (1%)	0
Medical device complication	1 (1%)	0
Obstruction	0	1 (1%)
Thrombosis in device	0	1 (1%)
Vessel puncture site thrombosis	1 (1%)	0
Cholangitis	1 (1%)	0

Hepatic function abnormal	0	1 (1%)
Portal vein thrombosis	0	1 (1%)
Hypersensitivity	0	1 (1%)
Biliary tract infection	0	1 (1%)
Cellulitis	1 (1%)	0
Colonic abscess	1 (1%)	0
Device related sepsis	1 (1%)	0
Herpes zoster	1 (1%)	0
Lower respiratory tract infection viral	1 (1%)	0
Lung infection	0	1 (1%)
Neutropenic infection	0	1 (1%)
Ophthalmic herpes zoster	1 (1%)	0
Orchitis	1 (1%)	0
Parainfluenzae virus infection	0	1 (1%)
Pyelonephritis	1 (1%)	0
Staphylococcal bacteraemia	1 (1%)	0
Deep vein thrombosis postoperative	0	1 (1%)
Documented hypersensitivity to administered drug	1 (1%)	0
Fall	0	1 (1%)
Infusion related reaction	1 (1%)	0
Muscle strain	0	1 (1%)
Spinal fracture	0	1 (1%)
Toxicity to various agents	0	1 (1%)
Alanine aminotransferase increased	1 (1%)	0
Aspartate aminotransferase increased	1 (1%)	0
Blood urea increased	1 (1%)	0
C-reactive protein increased	0	1 (1%)
General physical condition abnormal	0	1 (1%)
Liver function test abnormal	0	1 (1%)
Liver function tests abnormal	0	1 (1%)
White blood cell count	0	1 (1%)
Diabetes mellitus inadequate control	0	1 (1%)
Hypoalbuminaemia	0	1 (1%)
Hypochloraemia	1 (1%)	0
Hypophosphataemia	1 (1%)	0
Groin pain	1 (1%)	0
Metastatic pain	1 (1%)	0
Tumour pain	0	1 (1%)
Cerebellar syndrome	0	1 (1%)
Cerebral haemorrhage	1 (1%)	0
Cerebrovascular accident	0	1 (1%)
Dizziness	1 (1%)	0
Dysgeusia	1 (1%)	0
Dyskinesia	1 (1%)	0
Headache	1 (1%)	0

Peripheral motor neuropathy	1 (1%)	0
Peripheral sensory neuropathy	1 (1%)	0
Peroneal nerve palsy	1 (1%)	0
Speech disorder	0	1 (1%)
Transient ischaemic attack	1 (1%)	0
Tremor	1 (1%)	0
Depression	1 (1%)	0
Suicidal ideation	1 (1%)	0
Suicide attempt	1 (1%)	0
Asthma	1 (1%)	0
Cough	1 (1%)	0
Dysaesthesia pharynx	1 (1%)	0
Pulmonary oedema	0	1 (1%)
Erythema multiforme	1 (1%)	0
Rash	1 (1%)	0
Arterial spasm	0	1 (1%)
Hypertension	1 (1%)	0
Jugular vein thrombosis	1 (1%)	0
Orthostatic hypotension	1 (1%)	0
Thrombosis	1 (1%)	0
Venous thrombosis limb	1 (1%)	0

[1] Sorted by prevalence

n (%) experiencing grade 1+ serious adverse events[1]	**Chemo (n=182)**	**Chemo + SIRT (n=182)**
Febrile neutropenia	8 (4%)	9 (5%)
Neutropenia	7 (4%)	5 (3%)
Neutropenic sepsis	6 (3%)	6 (4%)
Infection	7 (4%)	4 (2%)
Intestinal obstruction	5 (3%)	3 (2%)
Diarrhoea	3 (2%)	4 (2%)
Pyrexia	2 (1%)	3 (2%)
Radiation hepatitis	0	5 (3%)
Intestinal perforation	3 (2%)	1 (1%)
Large intestinal obstruction	4 (2%)	0
Lower respiratory tract infection	3 (2%)	1 (1%)
Pulmonary embolism	1 (1%)	3 (2%)
Angina pectoris	2 (1%)	1 (1%)
Constipation	1 (1%)	2 (1%)
Device related infection	2 (1%)	1 (1%)
Sepsis	2 (1%)	1 (1%)
Embolism	1 (1%)	2 (1%)
Acute myocardial infarction	1 (1%)	1 (1%)

Arteriospasm coronary	0	2 (1%)
Myocardial infarction	1 (1%)	1 (1%)
Abdominal pain	1 (1%)	1 (1%)
Duodenal ulcer	0	2 (1%)
Faecal volume increased	2 (1%)	0
Large intestine perforation	1 (1%)	1 (1%)
Vomiting	0	2 (1%)
Chest pain	1 (1%)	1 (1%)
Mucosal inflammation	2 (1%)	0
Pain	0	2 (1%)
Peritonitis	0	2 (1%)
Pneumonia	0	2 (1%)
Urinary tract infection	1 (1%)	1 (1%)
Administration related reaction	0	2 (1%)
Blood glucose increased	1 (1%)	1 (1%)
Presyncope	0	2 (1%)
Syncope	0	2 (1%)
Leukopenia	1 (1%)	0
Neutropenic sepsis	0	1 (1%)
Thrombocytopenia	0	1 (1%)
Atrial tachycardia	0	1 (1%)
Cardiac failure	0	1 (1%)
Myocardial ischaemia	0	1 (1%)
Abdominal pain upper	0	1 (1%)
Abdominal strangulated hernia	1 (1%)	0
Ascites	0	1 (1%)
Colitis	0	1 (1%)
Gastrointestinal perforation	0	1 (1%)
Intestinal ischaemia	0	1 (1%)
Nausea	0	1 (1%)
Oedema mouth	1 (1%)	0
Small intestinal obstruction	0	1 (1%)
Infusion site thrombosis	1 (1%)	0
Thrombosis in device	0	1 (1%)
Cholangitis	1 (1%)	0
Hyperbilirubinaemia	1 (1%)	0
Portal vein thrombosis	0	1 (1%)
Biliary tract infection	0	1 (1%)
Colonic abscess	1 (1%)	0
Device related sepsis	1 (1%)	0
Herpes zoster	1 (1%)	0
Lower respiratory tract infection viral	1 (1%)	0
Lung infection	0	1 (1%)
Neutropenic infection	0	1 (1%)
Orchitis	1 (1%)	0

Pyelonephritis	1 (1%)	0
Staphylococcal bacteraemia	1 (1%)	0
Muscle strain	0	1 (1%)
Spinal fracture	0	1 (1%)
Blood bilirubin increased	1 (1%)	0
Blood potassium decreased	0	1 (1%)
Blood urea increased	1 (1%)	0
General physical condition abnormal	0	1 (1%)
Dehydration	0	1 (1%)
Diabetes mellitus inadequate control	0	1 (1%)
Hyperglycaemia	0	1 (1%)
Hypokalaemia	0	1 (1%)
Metastatic pain	1 (1%)	0
Tumour pain	0	1 (1%)
Cerebral haemorrhage	1 (1%)	0
Cerebrovascular accident	0	1 (1%)
Transient ischaemic attack	1 (1%)	0
Tremor	1 (1%)	0
Suicide attempt	1 (1%)	0
Asthma	1 (1%)	0
Cough	1 (1%)	0
Dysaesthesia pharynx	1 (1%)	0
Dyspnoea	0	1 (1%)
Hypotension	0	1 (1%)
Jugular vein thrombosis	1 (1%)	0

[1] Sorted by prevalence