

Supplementary material

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Methods

Multiple imputation

Imputation under missing at random (MAR) assumption was undertaken using chained equations and predictive mean matching. Fifty imputed datasets were estimated, including in the equation OS, PFS, World Health Organisation performance status, EQ-5D-3L utility (US) and cognitive functioning scores at baseline. A correction factor (delta) was applied to the imputed values of the pre-specified outcomes and EQ-5D-3L utility-scores at ≤ 3 months to explore the impact of missing at random (MNAR) assumption on our conclusions.

Adverse Events

The safety analysis included the adverse events (AEs) with grade severity ≥ 3 observed between randomisation and 7 months after randomisation. We used the available cases of the as-treated population (507 received SIRT+FOLFOX, 571 received FOLFOX) at ≤ 3 months, 6 month and 12 month time-points. The Appendix 14 reports the results of longitudinal OLS model by the trial arms (i.e. columns 'FOLFOX' and 'SIRT + FOLFOX'), the results based on full sample (column 'Full model') and the results based on the full sample including an interaction term 'SIRT received x Number of AEs' (column 'Full model + interaction term'). The results of the 'Full model + interaction term' were plotted in Appendix figure 2.

Time-points of HRQOL data collection between randomisation and 6 months

At the 6 month follow-up, FFrG administered the QLQ-C30 and EQ-5D, SF the EQ-5D, and FFr the QLQ-C30, QLQ-LMC21, and EQ-5D following a protocol amendment mid-trial. HRQOL at disease progression was collected in FFr and FFrG only, resulting in smaller sample sizes at the 6 month and disease progression time-points. Administration of questionnaires during treatment also differed between trials: EQ-5D at 2 months in FFr and at 3 months post-randomisation in FFrG and SF, and EORTC QLQ-C30 at 1-month (FFrG, SF) and 2-month (FFr) post-randomisation. The EORTC QLQ-LMC21 was administered only to FFr patients.

Sensitivity analyses

EQ-5D-3L utility-scores (UK tariffs)

Appendix 1. Mean scores (standard error) [number of patients] for the EQ-5D-3L utility-scores (UK), differences adjusted for respective baseline scores and cognitive functioning score at baseline (p-value; 95% confidence interval). [online only]

	Baseline	≤ 3 months*	12 months	24 months
FOLFOX	0.796 (0.009) [507]	0.806 (0.01) [417]	0.799 (0.014) [215]	0.757 (0.031) [74]
SIRT+FOLFOX	0.790 (0.009) [510]	0.778 (0.011) [431]	0.78 (0.014) [253]	0.751 (0.026) [85]
Difference	-0.006 (0.648; -0.031 to 0.019)	-0.034 (p=0.022; -0.062 to -0.005)	-0.041 (p=0.034; -0.079 to -0.003)	-0.026 (0.535; -0.11 to 0.057)

* ≤ 3 months time-point includes cycle 4 and 3 months.

Multiple imputation: Missing At Random

Appendix 2. Mean scores (standard error) [number of patients] for the imputed EORTC QLQ-C30 scores, differences adjusted for respective baseline scores and cognitive functioning score at baseline (p-value; 95% confidence interval). [online only]

	≤3 months*	12 months	24 months
Physical functioning			
FOLFOX	81.44 (0.89) [541]	78.85 (1.33) [449]	74.12 (2.09) [285]
SIRT+FOLFOX	79.25 (0.91) [538]	77.65 (1.44) [430]	77.17 (2.06) [270]
Difference	-2.62 (p=0.019; -4.81 to -0.43)	-2.02 (0.31; -5.93 to 1.89)	2.85 (0.35; -3.13 to 8.82)
Role functioning			
FOLFOX	72.59 (1.33) [541]	72.45 (1.78) [449]	67.65 (3.21) [285]
SIRT+FOLFOX	69.1 (1.29) [538]	70.19 (1.95) [430]	79.15 (2.76) [270]
Difference	-3.48 (p=0.039; -6.78 to -0.18)	-2.86 (0.3; -8.27 to 2.55)	11.8 (p=0.008; 3.14 to 20.45)
Emotional functioning			
FOLFOX	80.95 (0.94) [541]	79.39 (1.37) [449]	83.68 (1.21) [285]
SIRT+FOLFOX	83.28 (0.88) [538]	81.62 (1.32) [430]	77.13 (1.68) [270]
Difference	1.3 (0.27; -0.99 to 3.59)	1.24 (0.51; -2.49 to 4.97)	-6.55 (p=0.003; -10.76 to -2.33)
Cognitive functioning			
FOLFOX	86.15 (0.93) [541]	83.14 (1.4) [449]	80.52 (1.89) [285]
SIRT+FOLFOX	86.37 (0.88) [538]	83.39 (1.21) [430]	84.32 (1.71) [270]
Difference	-1.08 (0.36; -3.4 to 1.23)	-1.39 (0.44; -4.95 to 2.18)	3.66 (0.16; -1.47 to 8.79)
Social functioning			
FOLFOX	74.64 (1.25) [541]	76.62 (1.69) [449]	75.69 (3.31) [285]
SIRT+FOLFOX	74.47 (1.25) [538]	73.19 (1.8) [430]	73.42 (2.47) [270]
Difference	.04 (0.98; -3.21 to 3.29)	-4.08 (0.11; -9.07 to 0.91)	-2.19 (0.6; -10.52 to 6.14)
Global health status			
FOLFOX	68.91 (0.98) [541]	68.45 (1.34) [449]	68.88 (1.68) [285]
SIRT+FOLFOX	65.64 (0.97) [538]	66.8 (1.63) [430]	72.67 (1.69) [270]
Difference	-3.25 (p=0.01; -5.7 to -0.79)	-2.32 (0.27; -6.45 to 1.8)	3.8 (0.13; -1.2 to 8.8)
Fatigue			
FOLFOX	34.42 (1.15) [541]	33.07 (1.56) [449]	30.69 (2.44) [285]
SIRT+FOLFOX	38.65 (1.12) [538]	35.38 (1.69) [430]	36.27 (2.09) [270]
Difference	4.05 (p=0.005; 1.23 to 6.88)	2.85 (0.21; -1.65 to 7.36)	5.33 (0.1; -1 to 11.66)
Nausea and vomiting			
FOLFOX	8.97 (0.72) [541]	8.99 (0.97) [449]	6.95 (1.22) [285]
SIRT+FOLFOX	10.75 (0.81) [538]	8.34 (0.91) [430]	13.39 (1.86) [270]
Difference	1.68 (0.11; -0.41 to 3.78)	-0.47 (0.73; -3.18 to 2.23)	6.43 (p=0.005; 1.95 to 10.91)
Pain			
FOLFOX	17.7 (1.1) [541]	19.83 (1.55) [449]	17.19 (2.38) [285]
SIRT+FOLFOX	17.69 (1.1) [538]	25.02 (1.71) [430]	20.16 (2.39) [270]
Difference	-0.02 (0.99; -2.88 to 2.84)	6.12 (p=0.006; 1.76 to 10.47)	3.05 (0.38; -3.77 to 9.87)

Dyspnea			
FOLFOX	13.35 (1.07) [541]	16.04 (1.52) [449]	26.02 (3.27) [285]
SIRT+FOLFOX	14.86 (1.04) [538]	15.4 (1.61) [430]	17.99 (2.52) [270]
Difference	1.41 (0.31; -1.32 to 4.14)	-0.73 (0.75; -5.35 to 3.88)	-8.28 (0.06; -16.86 to 0.29)
Insomnia			
FOLFOX	27.98 (1.42) [541]	22.46 (1.59) [449]	27.3 (2.94) [285]
SIRT+FOLFOX	29.58 (1.37) [538]	27.7 (1.95) [430]	26.02 (2.65) [270]
Difference	1.56 (0.4; -2.05 to 5.16)	5.85 (p=0.02; 0.92 to 10.78)	-1.28 (0.76; -9.53 to 6.97)
Appetite loss			
FOLFOX	17.51 (1.21) [541]	20.21 (1.77) [449]	16.91 (2.74) [285]
SIRT+FOLFOX	21.59 (1.31) [538]	21.55 (1.73) [430]	23.09 (2.02) [270]
Difference	4.36 (p=0.011; 1.01 to 7.72)	1.79 (0.48; -3.18 to 6.76)	6.14 (0.07; -0.61 to 12.89)
Constipation			
FOLFOX	17.41 (1.21) [541]	16.09 (1.74) [449]	11.24 (2.06) [285]
SIRT+FOLFOX	19.74 (1.32) [538]	15.63 (1.6) [430]	15.49 (2.05) [270]
Difference	2.3 (0.19; -1.11 to 5.72)	0.23 (0.92; -4.1 to 4.56)	4.35 (0.13; -1.3 to 10)
Diarrhea			
FOLFOX	16.71 (1.21) [541]	15.6 (1.63) [449]	7.14 (1.6) [285]
SIRT+FOLFOX	11.06 (0.97) [538]	14.52 (1.56) [430]	12.96 (2.19) [270]
Difference	-5.13 (p<0.001; -8.1 to -2.15)	-0.55 (0.81; -5.08 to 3.98)	6.19 (p=0.017; 1.12 to 11.25)
Financial difficulties			
FOLFOX	18.21 (1.46) [541]	16.43 (1.79) [449]	11.28 (1.87) [285]
SIRT+FOLFOX	17.95 (1.31) [538]	19.54 (1.83) [430]	13.29 (1.88) [270]
Difference	-0.41 (0.82; -3.9 to 3.08)	2.69 (0.29; -2.27 to 7.65)	2.12 (0.46; -3.57 to 7.81)

* ≤3 months time-point includes 1 month and cycle 4.

Appendix 3. Mean scores (standard error) [number of patients] for the imputed EORTC QLQ-LMC21 symptom scales, adjusted differences for respective baseline and ‘contact with friends’ baseline scores (p-value; 95% confidence interval). [online only]

	≤3 months*	12 months ⁺
Nutritional problems		
FOLFOX	12.58 (1.49) [179]	28.73 (3.87) [141]
SIRT+FOLFOX	17.01 (1.8) [176]	26.28 (3.4) [132]
Difference	3.95 (0.08; -0.5 to 8.4)[355]	-2.69 (0.6; -12.76 to 7.39)[273]
Fatigue		
FOLFOX	38.91 (2.12) [179]	47.69 (3.32) [141]
SIRT+FOLFOX	46.47 (2.16) [176]	49.08 (3.15) [132]
Difference	7.25 (p=0.012; 1.62 to 12.87)[355]	2.05 (0.65; -6.94 to 11.04)[273]
Pain		
FOLFOX	17.42 (1.6) [179]	33.17 (3.71) [141]
SIRT+FOLFOX	18.1 (1.72) [176]	31.02 (3.36) [132]
Difference	1.43 (0.52; -2.94 to 5.79)[355]	-0.84 (0.87; -10.74 to 9.06)[273]
Emotional problems		
FOLFOX	32.05 (1.84) [179]	45.93 (3.17) [141]
SIRT+FOLFOX	33.59 (2.22) [176]	43.44 (3) [132]
Difference	1.81 (0.5; -3.45 to 7.07)[355]	-1.73 (0.69; -10.18 to 6.71)[273]
Weight loss		
FOLFOX	17.18 (2.07) [179]	26.73 (4.04) [141]
SIRT+FOLFOX	20.36 (2.2) [176]	25.13 (3.43) [132]
Difference	2.43 (0.42; -3.46 to 8.31)[355]	-1.77 (0.74; -12.15 to 8.62)[273]
Taste		
FOLFOX	32.73 (2.6) [179]	31.85 (4.19) [141]
SIRT+FOLFOX	28.78 (2.49) [176]	23.6 (3.34) [132]
Difference	-3.96 (0.27; -10.94 to 3.03)[355]	-7.61 (0.15; -17.89 to 2.68)[273]
Dry mouth		
FOLFOX	30.07 (2.54) [179]	29.69 (3.93) [141]
SIRT+FOLFOX	27.04 (2.51) [176]	30.46 (3.9) [132]
Difference	-3.43 (0.34; -10.44 to 3.58)[355]	1.47 (0.79; -9.42 to 12.37)[273]
Sore mouth/tongue		
FOLFOX	27.91 (2.65) [179]	26.51 (4.16) [141]
SIRT+FOLFOX	16.12 (1.96) [176]	21.62 (3.61) [132]
Difference	-11.59 (p<0.001; -18.16 to -5.02)[355]	-4.3 (0.43; -15.14 to 6.54)[273]
Peripheral neuropathy		
FOLFOX	47.88 (2.39) [179]	59.74 (3.74) [141]

SIRT+FOLFOX	32.6 (1.97) [176]	48.33 (4.38) [132]
Difference	-15.88 (p<0.001; -22.24 to -9.52)[355]	-11.01 (0.06; -22.52 to 0.49)[273]
Jaundice		
FOLFOX	3.22 (0.95) [179]	20.23 (4.26) [141]
SIRT+FOLFOX	2.39 (0.88) [176]	12.04 (3.35) [132]
Difference	-0.65 (0.63; -3.25 to 1.96)[355]	-7.58 (0.15; -18.03 to 2.86)[273]
Contact with friends		
FOLFOX	11.3 (1.69) [179]	26.95 (4.14) [141]
SIRT+FOLFOX	19.19 (2.46) [176]	24.7 (3.64) [132]
Difference	6.02 (p=0.037; 0.36 to 11.68)[355]	-2.58 (0.64; -13.62 to 8.46)[273]
Talking about feelings		
FOLFOX	9.08 (1.66) [179]	26.35 (4.03) [141]
SIRT+FOLFOX	10.69 (1.94) [176]	21.18 (3.46) [132]
Difference	1.23 (0.61; -3.55 to 6.02)[355]	-5.06 (0.33; -15.32 to 5.21)[273]
Sex life		
FOLFOX	19.39 (2.5) [179]	33.15 (4.05) [141]
SIRT+FOLFOX	16.21 (2.31) [176]	32.52 (4.15) [132]
Difference	-2.34 (0.48; -8.9 to 4.22)[355]	0.38 (0.95; -11.12 to 11.89)[273]

* ≤3 months time-point includes cycle 4.

+ The multiple imputation model did not converge including data points beyond 12 months.

Appendix 4. Mean scores (standard error) [number of patients] for the imputed EQ-5D-3L utility-scores (US and UK), differences adjusted for respective baseline scores and cognitive functioning score at baseline (p-value; 95% confidence interval). [online only]

	≤3 months*	12 months	24 months
Utility (US Tariffs)			
FOLFOX	0.844 (0.007) [541]	0.833 (0.008) [449]	0.799 (0.012) [285]
SIRT+FOLFOX	0.828 (0.007) [538]	0.821 (0.01) [430]	0.797 (0.014) [270]
Difference	-0.016 (0.093; -0.036 to 0.003)[1079]	-0.017 (0.204; -0.043 to 0.009)[879]	-0.001 (0.939; -0.039 to 0.036)[555]
Utility (UK Tariffs)			
FOLFOX	0.802 (0.009) [541]	0.789 (0.011) [449]	0.738 (0.018) [285]
SIRT+FOLFOX	0.778 (0.011) [538]	0.764 (0.014) [430]	0.739 (0.02) [270]
Difference	-0.024 (0.085; -0.052 to 0.003)[1079]	-0.03 (0.095; -0.066 to 0.005)[879]	0.003 (0.926; -0.051 to 0.057)[555]

* ≤3 months time-point includes cycle 4 and 3 months.

Multiple imputation: Missing Not At Random

Appendix 5. Sensitivity analysis of imputed values in EORTC QLQC-30 global health status (12 months): between arms adjusted differences (p-value; 95%CI). [online only]

Delta units	EORTC-QLQC30 Global Health Status (12 months)		
	Delta only in FOLFOX patients imputed observation	Delta only in FOLFOX+SIRT patients imputed observation	Delta in both arms patients imputed observation
-20	6.73 (p=0.002; 2.61 to 10.84)	-9.92 (p<0.001; -13.95 to -5.90)	-0.87 (0.67; -4.89 to 3.15)
-17.5	5.61 (p=0.01; 1.50 to 9.72)	-9.00 (p<0.001; -13.041 to -4.96)	-1.07 (0.60; -5.09 to 2.96)
-15	4.48 (p=0.03; 0.38 to 8.58)	-8.060 (p<0.001; -12.11 to -4.013)	-1.25 (0.54; -5.28 to 2.77)
-12.5	3.35 (0.11; -0.75 to 7.45)	-7.11 (p<0.001; -11.16 to -3.055)	-1.43 (0.48; -5.46 to 2.59)
-10	2.22 (0.29; -1.88 to 6.32)	-6.16 (p=0.003; -10.22 to -2.092)	-1.61 (0.43; -5.65 to 2.42)
-7.5	1.09 (0.6; -3.02 to 5.19)	-5.20 (p=0.01; -9.28 to -1.13)	-1.79 (0.38; -5.84 to 2.26)
-5	-0.051 (0.98; -4.16 to 4.055)	-4.24 (p=0.04; -8.33 to -0.15)	-1.97 (0.34; -6.04 to 2.10)
-2.5	-1.19 (0.57; -5.30 to 2.93)	-3.28 (0.12; -7.39 to 0.82)	-2.15 (0.30; -6.24 to 1.95)
0 ⁺	-2.33 (0.27; -6.45 to 1.80)	-2.32 (0.27; -6.45 to 1.80)	-2.32 (0.27; -6.45 to 1.80)
2.5	-3.43 (0.1; -7.55 to 0.68)	-1.35 (0.52; -5.46 to 2.76)	-2.46 (0.24; -6.56 to 1.64)
5	-4.54 (p=0.03; -8.65 to -0.44)	-0.37 (0.86; -4.47 to 3.73)	-2.59 (0.21; -6.67 to 1.49)
7.5	-5.65 (p=0.01; -9.75 to -1.55)	0.60 (0.77; -3.49 to 4.69)	-2.72 (0.19; -6.79 to 1.34)
10	-6.71 (p=0.001; -10.80 to -2.61)	1.55 (0.45; -2.53 to 5.63)	-2.83 (0.17; -6.88 to 1.21)
12.5	-7.74 (p<0.001; -11.82 to -3.65)	2.49 (0.23; -1.58 to 6.56)	-2.92 (0.15; -6.95 to 1.10)
15	-8.77 (p<0.001; -12.85 to -4.69)	3.43 (0.10; -0.67 to 7.49)	-3.02 (0.14; -7.03 to 1.00)
17.5	-9.68 (p<0.001; -13.75 to -5.62)	4.26 (p=0.040; 0.22 to 8.30)	-3.10 (0.13; -7.08 to 0.88)
20	-10.38 (p<0.001; -14.42 to -6.34)	4.90 (p=0.020; 0.91 to 8.90)	-3.16 (0.11; -7.05 to 0.74)

⁺ Results assuming missing at random

Appendix 6. Sensitivity analysis of imputed values in EORTC QLQ-LMC21 fatigue (≤3 months): adjusted differences (p-value; 95%CI). [online only]

Delta units	EORTC-LMC21 fatigue (≤ 3 months)		
	Delta only in FOLFOX patients imputed observation	Delta only in FOLFOX+SIRT patients imputed observation	Delta in both arms patients imputed observation
-20	12.14 (p<0.001; 6.54 to 17.75)	2.79 (0.33; -2.86 to 8.45)	7.69 (p=0.008; 2.06 to 13.33)
-17.5	11.55 (p<0.001; 5.96 to 17.14)	3.34 (0.24; -2.3 to 8.98)	7.65 (p=0.008; 2.04 to 13.25)
-15	10.96 (p<0.001; 5.38 to 16.55)	3.88 (0.18; -1.75 to 9.51)	7.6 (p=0.008; 2.01 to 13.19)
-12.5	10.37 (p<0.001; 4.78 to 15.96)	4.42 (0.12; -1.2 to 10.05)	7.55 (p=0.008; 1.97 to 13.13)
-10	9.76 (p<0.001; 4.17 to 15.35)	4.98 (0.08; -0.64 to 10.59)	7.49 (p=0.009; 1.91 to 13.07)
-7.5	9.13 (p=0.001; 3.54 to 14.72)	5.54 (0.05; -0.07 to 11.16)	7.43 (p=0.009; 1.86 to 13.01)
-5	8.5 (p=0.003; 2.91 to 14.1)	6.11 (p=0.033; 0.5 to 11.72)	7.37 (p=0.01; 1.79 to 12.95)
-2.5	7.87 (p=0.006; 2.27 to 13.48)	6.68 (p=0.02; 1.06 to 12.3)	7.31 (p=0.011; 1.71 to 12.91)
0	7.25 (p=0.012; 1.62 to 12.87)	7.25 (p=0.012; 1.62 to 12.87)	7.25 (p=0.012; 1.62 to 12.87)
2.5	6.59 (p=0.022; 0.97 to 12.2)	7.8 (p=0.007; 2.19 to 13.42)	7.14 (p=0.013; 1.54 to 12.74)
5	5.93 (p=0.038; 0.32 to 11.53)	8.36 (p=0.004; 2.75 to 13.97)	7.04 (p=0.014; 1.46 to 12.63)
7.5	5.27 (0.07; -0.33 to 10.87)	8.92 (p=0.002; 3.31 to 14.52)	6.94 (p=0.015; 1.36 to 12.52)
10	4.61 (0.11; -0.99 to 10.21)	9.48 (p=0.001; 3.87 to 15.08)	6.84 (p=0.017; 1.26 to 12.42)
12.5	3.95 (0.17; -1.65 to 9.56)	10.03 (p<0.001; 4.41 to 15.64)	6.74 (p=0.018; 1.15 to 12.33)
15	3.3 (0.25; -2.31 to 8.91)	10.57 (p<0.001; 4.95 to 16.19)	6.63 (p=0.021; 1.02 to 12.23)
17.5	2.65 (0.35; -2.98 to 8.27)	11.11 (p<0.001; 5.48 to 16.75)	6.52 (p=0.023; 0.89 to 12.14)
20	1.99 (0.49; -3.65 to 7.64)	11.66 (p<0.001; 6.01 to 17.31)	6.41 (p=0.027; 0.75 to 12.07)

+ Results assuming missing at random

Appendix 7. Sensitivity analysis of imputed values in EQ-5D-3L (≤ 3 months) (US tariffs): adjusted differences (p-value; 95%CI). [online only]

EQ-5D-3L (≤ 3 months)

Delta units	Delta only in FOLFOX patients imputed observation	Delta only in FOLFOX+SIRT patients imputed observation	Delta in both arms patients imputed observation
-0.2	0.029 (p=0.01; 0.009 to 0.05)	-0.056 (p<0.001; -0.076 to -0.036)	-0.011 (0.33; -0.032 to 0.011)
-0.17	0.024 (p=0.02; 0.003 to 0.044)	-0.051 (p<0.001; -0.071 to -0.031)	-0.011 (0.29; -0.032 to 0.01)
-0.15	0.018 (0.08; -0.002 to 0.038)	-0.046 (p<0.001; -0.066 to -0.027)	-0.012 (0.25; -0.033 to 0.008)
-0.13	0.012 (0.23; -0.008 to 0.032)	-0.041 (p<0.001; -0.061 to -0.022)	-0.013 (0.21; -0.033 to 0.007)
-0.1	0.006 (0.52; -0.013 to 0.026)	-0.036 (p<0.001; -0.056 to -0.017)	-0.014 (0.18; -0.033 to 0.006)
-0.08	0.001 (0.94; -0.019 to 0.02)	-0.031 (p=0.001; -0.051 to -0.012)	-0.014 (0.15; -0.034 to 0.005)
-0.05	-0.005 (0.61; -0.024 to 0.014)	-0.026 (p=0.01; -0.046 to -0.007)	-0.015 (0.13; -0.034 to 0.004)
-0.03	-0.011 (0.27; -0.03 to 0.008)	-0.021 (p=0.03; -0.041 to -0.002)	-0.016 (0.11; -0.035 to 0.004)
0	-0.016 (0.09; -0.036 to 0.003)	-0.016 (0.09; -0.036 to 0.003)	-0.016 (0.09; -0.036 to 0.003)
0.03	-0.021 (p=0.03; -0.04 to -0.002)	-0.013 (0.18; -0.032 to 0.006)	-0.017 (0.07; -0.036 to 0.002)
0.05	-0.025 (p=0.01; -0.044 to -0.006)	-0.009 (0.33; -0.028 to 0.009)	-0.018 (0.06; -0.036 to 0.001)
0.08	-0.029 (p=0.002; -0.048 to -0.01)	-0.006 (0.54; -0.025 to 0.013)	-0.018 (p=0.05; -0.037 to -0.0002)
0.1	-0.033 (p<0.001; -0.052 to -0.015)	-0.002 (0.81; -0.021 to 0.016)	-0.019 (p=0.04; -0.037 to -0.001)
0.13	-0.037 (p<0.001; -0.056 to -0.019)	0.001 (0.89; -0.017 to 0.02)	-0.02 (p=0.03; -0.038 to -0.002)
0.15	-0.041 (p<0.001; -0.06 to -0.023)	0.005 (0.62; -0.014 to 0.023)	-0.02 (p=0.03; -0.038 to -0.002)
0.17	-0.045 (p<0.001; -0.063 to -0.026)	0.007 (0.43; -0.011 to 0.026)	-0.021 (p=0.02; -0.039 to -0.003)
0.2	-0.047 (p<0.001; -0.065 to -0.028)	0.009 (0.33; -0.009 to 0.028)	-0.021 (p=0.02; -0.039 to -0.003)

+ Results assuming missing at random

Additional time-points

EQ-5D-3 utility-scores

Appendix 8. Mean scores (standard error) [number of patients] for the EQ-5D-3L utility-scores (US and UK), differences adjusted for respective baseline scores and cognitive functioning score at baseline (p-value; 95% confidence interval). [online only]

	6 months	36 months	48 months	60 months
Utility (US Tariffs)				
FOLFOX	0.836 (0.009) [247]	0.873 (0.036) [17]	0.811 (0.108) [5]	1 (.) [1]
SIRT+FOLFOX	0.823 (0.01) [260]	0.858 (0.033) [18]	0.876 (0.041) [4]	1 (0) [2]
Difference	-0.019 (0.144; -0.045 to 0.007)	-0.01 (0.837; -0.11 to 0.09)	-0.006 (0.942; -0.215 to 0.203)	0 (N/A)
Utility (UK Tariffs)				
FOLFOX	0.79 (0.013) [247]	0.847 (0.052) [17]	0.729 (0.167) [5]	1 (.) [1]

SIRT+FOLFOX	0.77 (0.014) [260]	0.816 (0.048) [18]	0.864 (0.047) [4]	1 (0) [2]
Difference	-0.028 (0.127; -0.065 to 0.008)	-0.024 (0.752; -0.175 to 0.128)	0.017 (0.87; -0.261 to 0.296)	0 (N/A)

N/A: Not Applicable

EORTC QLQ-C30

Appendix 9. Mean scores (standard error) [number of patients] for the EORTC QLQ-C30 scores, differences adjusted for respective baseline scores and cognitive functioning score at baseline (p-value; 95% confidence interval). [online only]

	6 months	36 months	48 months	60 months
Physical functioning				
FOLFOX	75.16 (2.48) [83]	83.33 (6.85) [9]	100 (.) [1]	. (.) [0]
SIRT+FOLFOX	81.76 (1.94) [88]	76.67 (8.21) [6]	100 (.) [1]	93.33 (.) [1]
Difference	3.84 (0.19; -1.88 to 9.56)	-7.22 (0.51; -30.67 to 16.23)	0 (N/A)	N/A
Role functioning				
FOLFOX	66.06 (3.31) [83]	83.33 (6.8) [9]	100 (.) [1]	. (.) [0]
SIRT+FOLFOX	77.27 (2.81) [88]	75 (11.98) [6]	100 (.) [1]	100 (.) [1]
Difference	7.22 (0.09; -1.07 to 15.52)	-15.79 (0.24; -43.67 to 12.09)	0 (N/A)	N/A
Emotional functioning				
FOLFOX	80.62 (2.47) [83]	89.58 (4.38) [8]	41.67 (.) [1]	. (.) [0]
SIRT+FOLFOX	83.07 (2.24) [86]	83.33 (10.54) [6]	100 (.) [1]	100 (.) [1]
Difference	1.14 (0.71; -4.8 to 7.07)	-9.16 (0.49; -37.71 to 19.39)	0 (N/A)	N/A
Cognitive functioning				
FOLFOX	79.12 (2.63) [83]	89.58 (4.38) [8]	100 (.) [1]	. (.) [0]
SIRT+FOLFOX	84.88 (2.06) [86]	75 (11.18) [6]	100 (.) [1]	83.33 (.) [1]

Difference	1.82 (0.58; -4.61 to 8.26)	-14.47 (0.23; -39.66 to 10.72)	0 (N/A)	N/A
Social functioning				
FOLFOX	74.7 (3.12) [83]	85.42 (6.63) [8]	66.67 (.) [1]	. (.) [0]
SIRT+FOLFOX	76.36 (2.68) [86]	61.11 (11.11) [6]	100 (.) [1]	100 (.) [1]
Difference	0.19 (0.96; -7.59 to 7.98)	-23.49 (0.11; -53.16 to 6.18)	33.33 (N/A)	N/A
Global health status				
FOLFOX	67.47 (2.3) [83]	64.58 (9.93) [8]	83.33 (.) [1]	. (.) [0]
SIRT+FOLFOX	69.19 (2.23) [86]	62.5 (13.39) [6]	100 (.) [1]	100 (.) [1]
Difference	0.68 (0.83; -5.44 to 6.8)	-7.16 (0.72; -49.9 to 35.59)	0 (N/A)	N/A
Fatigue				
FOLFOX	40.09 (2.94) [83]	25.93 (10.14) [9]	0 (.) [1]	. (.) [0]
SIRT+FOLFOX	32.89 (2.09) [88]	38.89 (13.98) [6]	0 (.) [1]	11.11 (.) [1]
Difference	-5.85 (0.09; -12.58 to 0.88)	20.94 (0.25; -17.09 to 58.97)	0 (N/A)	N/A
Nausea and vomiting				
FOLFOX	9.04 (1.7) [83]	5.56 (3.93) [9]	0 (.) [1]	. (.) [0]
SIRT+FOLFOX	6.25 (1.15) [88]	8.33 (3.73) [6]	0 (.) [1]	0 (.) [1]
Difference	-3.09 (0.13; -7.15 to 0.97)	5.93 (0.33; -7.01 to 18.86)	0 (N/A)	N/A
Pain				
FOLFOX	22.02 (3.12) [84]	20.37 (9.12) [9]	0 (.) [1]	. (.) [0]
SIRT+FOLFOX	18.54 (2.55) [89]	33.33 (8.61) [6]	16.67 (.) [1]	0 (.) [1]
Difference	-0.86 (0.82; -8.44 to 6.72)	10.56 (0.43; -17.71 to 38.83)	0 (N/A)	N/A
Dyspnea				
FOLFOX	19.28 (2.29) [83]	18.52 (11.26) [9]	0 (.) [1]	. (.) [0]
SIRT+FOLFOX	11.36 (2.08) [88]	33.33 (12.17) [6]	0 (.) [1]	0 (.) [1]
Difference	-6.47 (p=0.03; -12.3 to -0.65)	14.58 (0.45; -26.47 to 55.64)	0 (N/A)	N/A

Insomnia				
FOLFOX	28.11 (3.15) [83]	29.63 (8.69) [9]	0 (.) [1]	. (.) [0]
SIRT+FOLFOX	22.35 (2.73) [88]	38.89 (20.03) [6]	0 (.) [1]	0 (.) [1]
Difference	-2.75 (0.5; -10.72 to 5.23)	18.67 (0.43; -31.1 to 68.45)	0 (N/A)	N/A
Appetite loss				
FOLFOX	21.69 (3.4) [83]	7.41 (7.41) [9]	0 (.) [1]	. (.) [0]
SIRT+FOLFOX	25.38 (3.28) [88]	27.78 (15.91) [6]	0 (.) [1]	0 (.) [1]
Difference	2.96 (0.53; -6.23 to 12.14)	21.25 (0.24; -16.16 to 58.65)	0 (N/A)	N/A
Constipation				
FOLFOX	13.65 (2.74) [83]	16.67 (8.91) [8]	0 (.) [1]	. (.) [0]
SIRT+FOLFOX	17.24 (2.72) [87]	5.56 (5.56) [6]	0 (.) [1]	0 (.) [1]
Difference	2.46 (0.53; -5.22 to 10.14)	-0.1 (0.99; -20.14 to 19.93)	0 (N/A)	N/A
Diarrhea				
FOLFOX	18.07 (2.82) [83]	12.5 (6.1) [8]	66.67 (.) [1]	. (.) [0]
SIRT+FOLFOX	12.79 (2.54) [86]	27.78 (13.38) [6]	0 (.) [1]	0 (.) [1]
Difference	-4.39 (0.24; -11.69 to 2.9)	21.25 (0.2; -13.62 to 56.12)	-66.67 (N/A)	N/A
Financial difficulties				
FOLFOX	16.67 (2.67) [82]	4.17 (4.17) [8]	0 (.) [1]	. (.) [0]
SIRT+FOLFOX	16.47 (2.93) [85]	16.67 (16.67) [6]	0 (.) [1]	0 (.) [1]
Difference	0.53 (0.89; -7.02 to 8.07)	16.79 (0.32; -19.08 to 52.65)	0 (N/A)	N/A

N/A: Not Applicable

EORTC QLQ-LMC21

Appendix 10. Mean scores (standard error) [number of patients] for the EORTC QLQ-LMC21 symptom scales, adjusted differences for respective baseline and ‘contact with friends’ baseline scores (p-value; 95% confidence interval). [online only]

	6 months	36 months	48 months	60 months
Fatigue				
FOLFOX	55.56 (7.67) [7]	41.67 (16.59) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	38.89 (7.92) [12]	51.11 (16.7) [5]	0 (0) [2]	11.11 (.) [1]
Difference	-14.38 (0.25; -40.18 to 11.42)	6.97 (0.83; -74.33 to 88.28)	N/A	N/A
Pain				
FOLFOX	14.81 (6.83) [6]	22.22 (13.61) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	19.44 (6.72) [12]	31.11 (4.16) [5]	22.22 (11.11) [2]	0 (.) [1]
Difference	7.83 (0.48; -15.46 to 31.13)	20.2 (0.06; -1.46 to 41.86)	N/A	N/A
Dry mouth				
FOLFOX	23.81 (14.02) [7]	33.33 (23.57) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	38.89 (9.02) [12]	46.67 (20) [5]	0 (0) [2]	0 (.) [1]
Difference	14.12 (0.41; -20.88 to 49.11)	22.22 (0.56; -70.48 to 100)	N/A	N/A
Sore mouth/tongue				
FOLFOX	14.29 (6.73) [7]	33.33 (23.57) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	8.33 (4.35) [12]	33.33 (18.26) [5]	0 (0) [2]	0 (.) [1]
Difference	-5.19 (0.52; -22.05 to 11.66)	-16.67 (0.53; -80.21 to 46.88)	N/A	N/A
Peripheral neuropathy				
FOLFOX	76.19 (15.79) [7]	16.67 (9.62) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	61.11 (9.02) [12]	73.33 (12.47) [5]	33.33 (33.33) [2]	100 (.) [1]
Difference	-26.85 (0.15; -64.06 to 10.37)	53.85 (p=0.029; 8.04 to 99.65)	N/A	N/A
Contact with friends				

FOLFOX	4.76 (4.76) [7]	11.11 (11.11) [3]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	19.44 (8.66) [12]	26.67 (12.47) [5]	0 (0) [2]	0 (.) [1]
Difference	14.6 (0.25; -11.3 to 40.5)	15.15 (0.49; -37.45 to 67.75)	N/A	N/A
Talking about feelings				
FOLFOX	4.76 (4.76) [7]	0 (0) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	19.44 (6.43) [12]	13.33 (8.16) [5]	0 (0) [2]	0 (.) [1]
Difference	14.06 (0.13; -4.44 to 32.57)	14.2 (0.24; -13 to 41.4)	N/A	N/A
Nutritional problems				
FOLFOX	14.29 (7.65) [7]	12.5 (12.5) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	23.61 (5.97) [12]	20 (13.33) [5]	0 (0) [2]	0 (.) [1]
Difference	7.06 (0.4; -10.16 to 24.27)	12.79 (0.51; -34.11 to 59.69)	N/A	N/A
Emotional problems				
FOLFOX	31.94 (5.86) [6]	25 (6.8) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	33.33 (6.8) [12]	43.33 (15.23) [5]	16.67 (16.67) [2]	0 (.) [1]
Difference	1.74 (0.85; -16.98 to 20.45)	17.94 (0.39; -31.07 to 66.96)	N/A	N/A
Weight loss				
FOLFOX	4.76 (4.76) [7]	0 (0) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	25 (8.33) [12]	20 (13.33) [5]	0 (0) [2]	0 (.) [1]
Difference	19.75 (0.12; -5.66 to 45.16)	11.11 (0.6; -40.14 to 62.36)	N/A	N/A
Taste				
FOLFOX	42.86 (9.52) [7]	25 (25) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	41.67 (8.33) [12]	46.67 (22.61) [5]	0 (0) [2]	0 (.) [1]
Difference	1.12 (0.93; -27.47 to 29.7)	22.58 (0.55; -65.47 to 100)	N/A	N/A
Jaundice				
FOLFOX	0 (0) [7]	0 (0) [4]	. (.) [0]	. (.) [0]

SIRT+FOLFOX	0 (0) [12]	13.33 (8.16) [5]	0 (0) [2]	0 (.) [1]
Difference	0 (N/A)	12.9 (0.23; -10.53 to 36.34)	N/A	N/A
Sex life				
FOLFOX	22.22 (16.48) [6]	0 (0) [4]	. (.) [0]	. (.) [0]
SIRT+FOLFOX	21.21 (10.32) [11]	16.67 (16.67) [4]	0 (0) [2]	0 (.) [1]
Difference	19.66 (0.26; -16.01 to 55.34)	22.22 (0.37; -39.48 to 83.92)	N/A	N/A

N/A: Not Applicable

* 95% CIs have been constrained where relevant to be bounded by the 0-100 range of the instrument.

EORTC QLQ-LMC21 not significant scales

Appendix 11. Mean scores (standard error) [number of patients] for the EORTC QLQ-LMC21 symptom scales, adjusted (not significant) differences for respective baseline and ‘contact with friends’ baseline scores (p-value; 95% confidence interval). [online only]

	Baseline	≤ 3 months*	12 months	24 months
Nutritional problems				
FOLFOX	14.91 (1.72) [161]	12.47 (1.53) [135]	14.84 (2.53) [73]	14.1 (5.92) [13]
SIRT+FOLFOX	17.08 (1.75) [161]	16.79 (1.86) [136]	18.29 (2.74) [82]	19.05 (5.49) [14]
Difference	2.17 (0.38; -2.66 to 7)	4.54 (0.06; -0.14 to 9.23)	3.92 (0.33; -3.94 to 11.78)	4.8 (0.56; -11.94 to 21.54)
Emotional problems				
FOLFOX	38.87 (1.96) [158]	32.44 (2.01) [130]	34.4 (2.69) [70]	32.69 (8.97) [13]
SIRT+FOLFOX	38.31 (1.99) [159]	33.84 (2.28) [131]	37.03 (2.58) [79]	32.14 (7.41) [14]
Difference	-0.56 (0.84; -6.06 to 4.94)	2.49 (0.33; -2.53 to 7.52)	4.54 (0.21; -2.56 to 11.64)	2.13 (0.86; -22.99 to 27.25)
Weight loss				
FOLFOX	17.39 (1.93) [161]	16.91 (2.09) [136]	12.5 (2.75) [72]	5.13 (5.13) [13]
SIRT+FOLFOX	17.81 (2.18) [161]	20.59 (2.36) [136]	16.26 (2.73) [82]	9.52 (4.18) [14]
Difference	0.41 (0.89; -5.31 to 6.14)	2.23 (0.45; -3.56 to 8.03)	5.65 (0.16; -2.31 to 13.6)	-1.88 (0.77; -15.32 to 11.56)
Taste				
FOLFOX	9.79 (1.69) [160]	32.12 (2.57) [137]	19.37 (3.33) [74]	10.26 (4.44) [13]
SIRT+FOLFOX	9.26 (1.71) [162]	28.64 (2.46) [135]	14.63 (2.32) [82]	9.52 (4.18) [14]
Difference	-0.53 (0.82; -5.26 to 4.19)	-3.61 (0.31; -10.55 to 3.33)	-2.06 (0.63; -10.46 to 6.35)	-1.17 (0.87; -15.46 to 13.12)
Jaundice				
FOLFOX	2.94 (1.05) [159]	3.21 (1.04) [135]	3.76 (1.58) [71]	2.56 (2.56) [13]
SIRT+FOLFOX	1.86 (0.84) [161]	1.96 (0.68) [136]	1.65 (1) [81]	7.14 (7.14) [14]
Difference	-1.07 (0.43; -3.71 to 1.57)	-1.43 (0.29; -4.07 to 1.2)	-0.92 (0.62; -4.53 to 2.69)	5.56 (0.54; -13.04 to 24.16)
Sex life				
FOLFOX	18.38 (2.33) [156]	19.34 (2.53) [131]	18.78 (3.19) [71]	23.08 (8.76) [13]
SIRT+FOLFOX	16.35 (2.18) [159]	15.5 (2.35) [129]	25.32 (3.76) [79]	12.82 (8.04) [13]
Difference	-2.02 (0.53; -8.31 to 4.26)	-1.65 (0.62; -8.28 to 4.98)	9.66 (0.08; -1.14 to 20.47)	-1.47 (0.91; -29.5 to 26.56)

* ≤3 months time-point includes cycle 4.

Disease progression

Appendix 12. Mean scores (standard error) [number of patients] for the EORTC-QLQ-C30 scores and EQ-5D-3L utility-scores (US) at progression and at previous follow-up time-point: differences between progression score and the previous time-point (p-value; 95% confidence interval). [online only]

	Progression between:			
	Baseline to 3 months	≤3 to 12 month*	12 to 24 months	Total
	EORTC QLQ-C30 Global health status			
Scores at progression				
FOLFOX	75.0 (5.3) [5]	57.7 (3.3) [27]	67.9 (6.3) [14]	63.0 (2.8) [48]
SIRT+FOLFOX	76.4 (7.6) [6]	65.1 (3.7) [27]	78.7 (3.5) [18]	71.8 (2.5) [54]
Difference**	1.4 (0.89; -20.4 to 23.2)	7.6 (0.12; -2.0 to 17.3)	11.0 (0.10; -2.3 to 24.3)	9.0 (p=0.010; 2.2 to 15.7)
Score at previous follow-up point				
FOLFOX	76.7 (8.1) [5]	72.2 (2.7) [27]	73.8 (5.2) [14]	73.4 (2.3) [47]
SIRT+FOLFOX	70.8 (6.4) [6]	64.8 (4.1) [27]	83.8 (2.9) [18]	73.0 (2.6) [54]
Change in score from previous time-point to disease progression				
FOLFOX	-1.7 (8.5) [5]	-14.5 (3.0) [27]	-6.0 (4.8) [14]	-10.4 (2.4) [48]
SIRT+FOLFOX	5.6 (5.1) [6]	0.3 (3.7) [27]	-5.1 (3.3) [18]	-1.2 (2.2) [54]
Difference between arms in change**	7.2 (0.47; -14.4 to 28.8)	14.1 (p=0.005; 4.4 to 23.9)	2.8 (0.61; -8.2 to 13.7)	9.5 (p=0.006; 2.8 to 16.2)
	EQ-5D-3L Utility-scores (US tariff)			
Scores at progression				
FOLFOX	0.828 (0.04) [21]	0.793 (0.02) [110]	0.866 (0.03) [40]	0.814 (0.01) [174]
SIRT+FOLFOX	0.793 (0.03) [28]	0.782 (0.02) [83]	0.874 (0.02) [41]	0.813 (0.01) [158]
Difference**	-0.035 (0.47; -0.13 to 0.06)	0 (01; -0.05 to 0.05)	0.004 (0.91; -0.07 to 0.08)	-0.006 (0.74; -0.04 to 0.03)
Score at previous follow-up point				
FOLFOX	0.774 (0.04) [21]	0.846 (0.01) [110]	0.895 (0.02) [40]	0.848 (0.01) [174]
SIRT+FOLFOX	0.852 (0.03) [28]	0.812 (0.02) [83]	0.859 (0.02) [41]	0.837 (0.01) [158]
Change in score from previous time-point to disease progression				
FOLFOX	0.054 (0.04) [21]	-0.053 (0.02) [110]	-0.029 (0.02) [40]	-0.034 (0.01) [174]
SIRT+FOLFOX	-0.059 (0.03) [28]	-0.029 (0.02) [83]	0.015 (0.02) [41]	-0.024 (0.01) [158]
Difference between arms in change**	-0.11 (p=0.028; -0.21 to -0.01)	0.015 (0.53; -0.03 to 0.06)	0.044 (0.22; -0.03 to 0.12)	-0.001 (0.97; -0.04 to 0.03)

* ≤3 months time-point includes cycle 4 and 3 months.

** Differences adjusted for respective baseline scores and cognitive functioning at baseline.

Appendix 13. Mean scores (standard error) [number of patients] for the EORTC-QLQ-C30 scores and EQ-5D-3L utility-scores (US) at progression and at previous follow-up time-point: differences between progression score and the previous time-point (p-value; 95% confidence interval).

	Progression between:				
	Baseline to 3 months	≤3 to 12 month*	12 to 24 months	after 24 months	Total
	Physical functioning				
Scores at progression					
FOLFOX	84 (8.59) [5]	67.6 (5.66) [27]	78.6 (5.77) [14]	66.7 (20) [2]	72.5 (3.81) [48]
SIRT+FOLFOX	86.7 (5.96) [6]	77.9 (4.55) [28]	90 (2.36) [18]	93.3 (3.85) [3]	83.6 (2.63) [55]
Difference**	2.7 (0.8; -20.36 to 25.69)	5.2 (0.39; -6.93 to 17.37)	11 (0.06; -0.54 to 22.5)	46.7 (p=0.049; 1.39 to 91.95)	7.6 (0.05; -0.11 to 15.3)
Score at previous follow-up point					
FOLFOX	86.7 (7.6) [5]	80.7 (3.46) [27]	86.7 (4.36) [14]	83.3 (3.33) [2]	83.2 (2.44) [48]
SIRT+FOLFOX	94.4 (2.05) [6]	79.3 (3) [28]	90.3 (2.17) [18]	86.7 (7.7) [3]	84.9 (1.89) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	-2.7 (8.06) [5]	-13.1 (3.46) [27]	-8.1 (2) [14]	-16.7 (16.67) [2]	-10.7 (2.27) [48]
SIRT+FOLFOX	-7.8 (6.31) [6]	-1.4 (3.73) [28]	-0.3 (3.26) [18]	6.7 (6.67) [3]	-1.3 (2.3) [55]
Difference between arms in change**	-5.1 (0.62; -27.9 to 17.67)	10.3 (0.05; -0.05 to 20.59)	7.4 (0.1; -1.39 to 16.14)	40 (0.27; -186.39 to 266.39)	8.3 (p=0.013; 1.83 to 14.85)
	Role functioning				
Scores at progression					
FOLFOX	83.3 (7.45) [5]	60.5 (6.17) [27]	70.2 (7.85) [14]	100 (.) [1]	66.7 (4.45) [47]
SIRT+FOLFOX	75 (8.33) [6]	70.8 (5.04) [28]	86.1 (4.52) [18]	100 (0) [3]	77.9 (3.27) [55]
Difference**	-8.3 (0.48; -34.14 to 17.47)	9.4 (0.18; -4.63 to 23.43)	13.5 (0.13; -4.01 to 30.99)	N/A	8.9 (0.07; -0.89 to 18.61)
Score at previous follow-up point					
FOLFOX	83.3 (12.91) [5]	74.7 (4.74) [27]	76.2 (6.47) [14]	100 (.) [1]	76.6 (3.57) [47]

SIRT+FOLFOX	77.8 (11.11) [6]	66.1 (4.65) [28]	85.2 (3.27) [18]	100 (0) [3]	75.5 (3.14) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	0 (10.54) [5]	-14.2 (3.41) [27]	-6 (8.49) [14]	0 (.) [1]	-9.9 (3.39) [47]
SIRT+FOLFOX	-2.8 (9.04) [6]	4.8 (4.6) [28]	.9 (5.3) [18]	0 (0) [3]	2.4 (3.04) [55]
Difference between arms in change**	-2.8 (0.84; -34.0 to 28.44)	19.2 (p=0.002; 7.47 to 30.98)	4.6 (0.66; -16.64 to 25.9)	N/A	12.1 (p=0.011; 2.85 to 21.4)
	Emotional functioning				
Scores at progression					
FOLFOX	81.1 (10.22) [5]	74.1 (4.27) [27]	83.3 (6.71) [14]	75 (.) [1]	77.6 (3.33) [47]
SIRT+FOLFOX	94.4 (2.78) [6]	83.9 (4.2) [28]	88.4 (3.02) [18]	94.4 (5.56) [3]	87.1 (2.42) [55]
Difference**	13.3 (0.2; -8.66 to 35.33)	8.7 (0.1; -1.76 to 19.15)	3 (0.65; -10.36 to 16.41)	N/A	7.4 (p=0.044; 0.2 to 14.62)
Score at previous follow-up point					
FOLFOX	72.2 (7.81) [5]	80.9 (3.47) [27]	87.3 (4.51) [14]	83.3 (.) [1]	81.9 (2.57) [47]
SIRT+FOLFOX	88.9 (4.12) [6]	83.9 (3.09) [28]	92.1 (2.65) [18]	91.7 (4.81) [3]	87.6 (1.91) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	8.9 (14.68) [5]	-6.8 (3.72) [27]	-4.0 (4.03) [14]	-8.3 (.) [1]	-4.3 (2.89) [47]
SIRT+FOLFOX	5.6 (4.12) [6]	0 (3.59) [28]	-3.7 (2.63) [18]	2.8 (2.78) [3]	-0.5 (2.08) [55]
Difference between arms in change**	-3.3 (0.82; -35.04 to 28.37)	5.1 (0.32; -5.24 to 15.51)	0 (01; -10.05 to 10.08)	N/A	3.2 (0.36; -3.73 to 10.23)
	Cognitive functioning				
Scores at progression					
FOLFOX	83.3 (5.27) [5]	79 (4.04) [27]	86.9 (6.34) [14]	83.3 (.) [1]	81.9 (3.03) [47]

SIRT+FOLFOX	80.6 (16.34) [6]	85.1 (3.13) [28]	90.7 (3.36) [18]	88.9 (5.56) [3]	86.7 (2.57) [55]
Difference**	-2.8 (0.89; -45.03 to 39.48)	4.3 (0.37; -5.34 to 14.01)	3.4 (0.64; -11.27 to 18.03)	N/A	3.3 (0.4; -4.39 to 10.98)
Score at previous follow-up point					
FOLFOX	90 (4.08) [5]	84.6 (3.77) [27]	89.3 (3.75) [14]	83.3 (.) [1]	86.5 (2.46) [47]
SIRT+FOLFOX	88.9 (8.24) [6]	86.9 (2.76) [28]	93.5 (2.39) [18]	100 (0) [3]	90 (1.87) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	-6.7 (4.08) [5]	-5.6 (4.45) [27]	-2.4 (4.23) [14]	0 (.) [1]	-4.6 (2.85) [47]
SIRT+FOLFOX	-8.3 (15.96) [6]	-1.8 (3.01) [28]	-2.8 (3.37) [18]	-11.1 (5.56) [3]	-3.3 (2.5) [55]
Difference between arms in change**	-1.7 (0.93; -42.44 to 39.1)	4.1 (0.45; -6.77 to 14.99)	0 (01; -11.52 to 11.56)	N/A	1.8 (0.64; -5.82 to 9.47)
	Social functioning				
Scores at progression					
FOLFOX	83.3 (7.45) [5]	64.8 (6.31) [27]	83.3 (7.41) [14]	100 (.) [1]	73 (4.49) [47]
SIRT+FOLFOX	86.1 (7.95) [6]	75.6 (4.65) [28]	89.8 (3.84) [18]	100 (0) [3]	82.7 (2.96) [55]
Difference**	2.8 (0.81; -22.27 to 27.83)	11.5 (0.1; -2.08 to 25.09)	8.1 (0.26; -6.36 to 22.51)	N/A	9.7 (p=0.038;0.53 to 18.83)
Score at previous follow-up point					
FOLFOX	83.3 (7.45) [5]	81.5 (4.01) [27]	89.3 (3.75) [14]	100 (.) [1]	84.4 (2.7) [47]
SIRT+FOLFOX	91.7 (5.69) [6]	75.6 (4.06) [28]	88.9 (3.01) [18]	100 (0) [3]	83 (2.58) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	0 (5.27) [5]	-16.7 (4.71) [27]	-6 (5.69) [14]	0 (.) [1]	-11.3 (3.33) [47]
SIRT+FOLFOX	-5.6 (7.03) [6]	0 (4.7) [28]	.9 (4.15) [18]	0 (0) [3]	-0.3 (2.82) [55]
Difference between arms in change**	-5.6 (0.56; -26.16 to 15.05)	16.5 (p=0.018; 2.98 to 30.02)	7.7 (0.24; -5.47 to 20.79)	N/A	11.1 (p=0.013; 2.4 to 19.75)

Global health status					
Scores at progression					
FOLFOX	75 (5.27) [5]	57.7 (3.33) [27]	67.9 (6.29) [14]	70.8 (4.17) [2]	63.0 (2.78) [48]
SIRT+FOLFOX	76.4 (7.58) [6]	65.1 (3.78) [27]	78.7 (3.45) [18]	80.6 (2.78) [3]	71.8 (2.5) [54]
Difference**	1.4 (0.89; -20.41 to 23.19)	7.7 (0.1; -1.66 to 17.13)	11 (0.1; -2.29 to 24.26)	17.9 (0.1; -19.19 to 54.91)	9.0 (p=0.01; 2.21 to 15.71)
Score at previous follow-up point					
FOLFOX	76.7 (8.08) [5]	72.2 (2.71) [27]	73.8 (5.23) [14]	75 (8.33) [2]	73.3 (2.27) [48]
SIRT+FOLFOX	70.8 (6.36) [6]	64.8 (4.08) [27]	83.8 (2.9) [18]	86.1 (2.78) [3]	73 (2.64) [54]
Change in score from previous time-point to disease progression:					
FOLFOX	-1.7 (8.5) [5]	-14.5 (2.97) [27]	-6 (4.82) [14]	-4.2 (4.17) [2]	-10.2 (2.41) [48]
SIRT+FOLFOX	5.6 (5.12) [6]	0.3 (3.68) [27]	-5.1 (3.31) [18]	-5.6 (2.78) [3]	-1.2 (2.24) [54]
Difference between arms in change**	7.2 (0.47; -14.35 to 28.79)	14.1 (p=0.005; 4.36 to 23.89)	2.8 (0.61; -8.19 to 13.73)	-2.4 (0.75; -76.48 to 71.72)	9.5 (p=0.006; 2.84 to 16.22)
Fatigue					
Scores at progression					
FOLFOX	22.2 (6.09) [5]	47.3 (5.58) [27]	36.5 (7.41) [14]	50 (16.67) [2]	41.7 (4.02) [48]
SIRT+FOLFOX	24.1 (8.8) [6]	35.9 (4.93) [28]	21 (4.11) [18]	22.2 (6.42) [3]	29 (3.12) [55]
Difference**	1.9 (0.87; -23.43 to 27.13)	-10.1 (0.12; -22.92 to 2.78)	-12 (0.12; -27.3 to 3.3)	-42.9 (0.25; -268.35 to 182.63)	-9.7 (p=0.026; -18.16 to -1.19)
Score at previous follow-up point					
FOLFOX	20 (10.77) [5]	34.2 (3.5) [27]	25.4 (5.39) [14]	25 (8.33) [2]	29.7 (2.8) [48]
SIRT+FOLFOX	16.7 (6.25) [6]	40.9 (4.75) [28]	18.5 (3.59) [18]	18.5 (9.8) [3]	29.7 (3.17) [55]

Change in score from previous time-point to disease progression:					
FOLFOX	2.2 (8.89) [5]	13.2 (5.07) [27]	11.1 (4.2) [14]	25 (25) [2]	11.9 (3.32) [48]
SIRT+FOLFOX	7.4 (5.49) [6]	-5 (5.75) [28]	2.5 (3.43) [18]	3.7 (14.81) [3]	-0.7 (3.28) [55]
Difference between arms in change**	5.2 (0.62; -17.58 to 27.95)	-18.3 (p=0.023; -33.92 to -2.68)	-6.9 (0.19; -17.48 to 3.72)	-48.4 (0.46; -589.59 to 492.77)	-12.2 (p=0.012; -21.65 to -2.7)
	Nausea and vomiting				
Scores at progression					
FOLFOX	10 (4.08) [5]	9.3 (3.48) [27]	6.0 (3.32) [14]	0 (0) [2]	8 (2.22) [48]
SIRT+FOLFOX	2.8 (2.78) [6]	11.3 (2.72) [28]	3.7 (1.68) [18]	0 (0) [3]	7.3 (1.6) [55]
Difference**	-7.2 (0.17; -18.07 to 3.63)	.8 (0.85; -8.08 to 9.71)	-2.7 (0.47; -10.4 to 4.95)	N/A	-1.2 (0.65; -6.53 to 4.12)
Score at previous follow-up point					
FOLFOX	6.7 (4.08) [5]	10.5 (2.97) [27]	4.8 (2.72) [14]	0 (0) [2]	8 (1.92) [48]
SIRT+FOLFOX	5.6 (3.51) [6]	10.7 (2.87) [28]	5.6 (1.91) [18]	0 (0) [3]	7.9 (1.67) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	3.3 (3.33) [5]	-1.2 (4.07) [27]	1.2 (4.08) [14]	0 (0) [2]	0 (2.58) [48]
SIRT+FOLFOX	-2.8 (5.12) [6]	0.6 (2.64) [28]	-1.9 (1.85) [18]	0 (0) [3]	-0.6 (1.56) [55]
Difference between arms in change**	-6.1 (0.37; -20.62 to 8.39)	0.9 (0.86; -9.04 to 10.8)	-3.1 (0.48; -11.93 to 5.8)	N/A	-0.9 (0.77; -6.81 to 5.07)
	Pain				
Scores at progression					
FOLFOX	6.7 (4.08) [5]	23.5 (4.97) [27]	26.2 (8.86) [14]	25.0 (8.33) [2]	22.6 (3.86) [48]
SIRT+FOLFOX	8.3 (5.69) [6]	25.6 (4.65) [28]	9.3 (2.77) [18]	5.6 (5.56) [3]	17.3 (2.83) [55]
Difference**	1.7 (0.82; -14.83 to 18.16)	2.4 (0.72; -10.91 to 15.77)	-13.7 (0.1; -30.33 to 2.92)	-16.7 (N/A)	-4.7 (0.31; -13.7 to 4.33)

Score at previous follow-up point					
FOLFOX	20.8 (7.98) [4]	13.6 (2.82) [27]	17.9 (6.17) [14]	8.3 (8.33) [2]	15.2 (2.53) [47]
SIRT+FOLFOX	22.2 (14.05) [6]	23.2 (4.72) [28]	7.4 (3.36) [18]	11.1 (5.56) [3]	17.3 (3.15) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	-16.7 (6.8) [4]	9.9 (4.64) [27]	8.3 (3.81) [14]	16.7 (0) [2]	7.4 (3.12) [47]
SIRT+FOLFOX	-13.9 (12.48) [6]	2.4 (5.67) [28]	1.9 (4.02) [18]	-5.6 (5.56) [3]	0 (3.46) [55]
Difference between arms in change**	2.8 (0.87; -35.29 to 40.84)	-5.8 (0.45; -20.9 to 9.33)	-3.9 (0.47; -14.92 to 7.1)	-25 (0.33; -208.4 to 158.4)	-6.7 (0.17; -16.35 to 2.88)
	Dyspnea				
Scores at progression					
FOLFOX	13.3 (8.16) [5]	29.6 (5.72) [27]	21.4 (7.5) [14]	33.3 (.) [1]	25.5 (4.08) [47]
SIRT+FOLFOX	5.6 (5.56) [6]	14.3 (3.99) [28]	14.8 (4.84) [18]	0 (0) [3]	12.7 (2.66) [55]
Difference**	-7.8 (0.44; -29.48 to 13.93)	-12.3 (0.07; -25.52 to 0.82)	-6.4 (0.36; -20.68 to 7.83)	N/A	-10.6 (p=0.019; -19.4 to -1.76)
Score at previous follow-up point					
FOLFOX	6.7 (6.67) [5]	19.8 (5.41) [27]	4.8 (3.24) [14]	33.3 (.) [1]	14.2 (3.47) [47]
SIRT+FOLFOX	0 (0) [6]	14.3 (4.98) [28]	5.6 (3.01) [18]	0 (0) [3]	9.1 (2.8) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	6.7 (6.67) [5]	9.9 (6.12) [27]	16.7 (5.79) [14]	0 (.) [1]	11.3 (3.96) [47]
SIRT+FOLFOX	5.6 (5.56) [6]	0 (5.69) [28]	9.3 (4.51) [18]	0 (0) [3]	3.6 (3.31) [55]
Difference between arms in change**	-1.1 (0.9; -20.56 to 18.34)	-9.9 (0.25; -27 to 7.15)	-6.9 (0.21; -18.06 to 4.2)	N/A	-7.9 (0.14; -18.34 to 2.62)
	Insomnia				

Scores at progression					
FOLFOX	33.3 (0) [5]	35.8 (6.64) [27]	26.2 (7.95) [14]	16.7 (16.67) [2]	31.9 (4.43) [48]
SIRT+FOLFOX	0 (0) [6]	27.4 (5.16) [28]	20.4 (5.48) [18]	33.3 (0) [3]	22.4 (3.36) [55]
Difference**	-33.3 (N/A)	-7.6 (0.38; -24.75 to 9.59)	-3.7 (0.69; -22.89 to 15.47)	33.3 (N/A)	-8.4 (0.13; -19.37 to 2.62)
Score at previous follow-up point					
FOLFOX	13.3 (8.16) [5]	38.3 (5.82) [27]	21.4 (5.64) [14]	16.7 (16.67) [2]	29.9 (4) [48]
SIRT+FOLFOX	16.7 (11.39) [6]	41.7 (6.56) [28]	14.8 (4.02) [18]	11.1 (11.11) [3]	28.5 (4.19) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	20 (8.16) [5]	-2.5 (5.88) [27]	4.8 (6.86) [14]	0 (0) [2]	2.1 (4.02) [48]
SIRT+FOLFOX	-16.7 (11.39) [6]	-14.3 (7.56) [28]	5.6 (4.86) [18]	22.2 (11.11) [3]	-6.1 (4.58) [55]
Difference between arms in change**	-36.7 (p=0.033; -69.66 to -3.67)	-13 (0.18; -32.05 to 6.02)	0.7 (0.94; -17.43 to 18.75)	16.7 (0.67; -350.13 to 383.46)	-10.4 (0.09; -22.5 to 1.72)
	Appetite loss				
Scores at progression					
FOLFOX	25.0 (8.33) [4]	23.5 (4.97) [27]	21.4 (8.27) [14]	16.7 (16.67) [2]	22.7 (3.81) [47]
SIRT+FOLFOX	11.1 (11.11) [6]	35.7 (6.4) [28]	1.9 (1.85) [18]	0 (0) [3]	20 (4.11) [55]
Difference**	-13.9 (0.39; -49.34 to 21.56)	11.9 (0.15; -4.5 to 28.38)	-19 (p=0.021; -34.96 to -3.1)	N/A	-2 (0.72; -13.09 to 9.04)
Score at previous follow-up point					
FOLFOX	16.7 (9.62) [4]	21.0 (4.76) [27]	9.5 (4.18) [14]	16.7 (16.67) [2]	17 (3.19) [47]
SIRT+FOLFOX	11.1 (7.03) [6]	23.8 (5.38) [28]	7.4 (4.31) [18]	11.1 (11.11) [3]	16.4 (3.34) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	8.3 (8.33) [4]	2.5 (5.61) [27]	11.9 (8.27) [14]	0 (0) [2]	5.7 (4.1) [47]

SIRT+FOLFOX	0 (8.61) [6]	11.9 (7.11) [28]	-5.6 (4.04) [18]	-11.1 (11.11) [3]	3.6 (4.12) [55]
Difference between arms in change**	-8.3 (0.53; -37.42 to 20.76)	8.5 (0.36; -10.12 to 27.21)	-18.3 (0.05; -36.84 to 0.23)	-16.7 (0.67; -383.46 to 350.13)	-2.4 (0.69; -14.32 to 9.52)
	Constipation				
Scores at progression					
FOLFOX	6.7 (6.67) [5]	23.5 (5.85) [27]	11.9 (6.64) [14]	0 (.) [1]	17.7 (4.04) [47]
SIRT+FOLFOX	0 (0) [6]	9.5 (3.37) [28]	5.6 (4.04) [18]	11.1 (11.11) [3]	7.3 (2.24) [55]
Difference**	-6.7 (0.3; -20.28 to 6.95)	-13.3 (0.06; -27.44 to 0.79)	-1.9 (0.8; -17.52 to 13.71)	N/A	-9.7 (p=0.037; -18.73 to -0.6)
Score at previous follow-up point					
FOLFOX	0 (0) [5]	19.8 (4.79) [27]	14.3 (6.73) [14]	0 (.) [1]	15.6 (3.49) [47]
SIRT+FOLFOX	22.2 (16.48) [6]	20.2 (6.02) [28]	9.3 (5.26) [18]	0 (0) [3]	15.8 (3.95) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	6.7 (6.67) [5]	3.7 (6.74) [27]	-2.4 (2.38) [14]	0 (.) [1]	2.1 (3.98) [47]
SIRT+FOLFOX	-22.2 (16.48) [6]	-10.7 (7.08) [28]	-3.7 (2.54) [18]	11.1 (11.11) [3]	-8.5 (4.17) [55]
Difference between arms in change**	-28.9 (0.17; -72.29 to 14.52)	-8.3 (0.4; -27.91 to 11.37)	-3.3 (0.28; -9.27 to 2.77)	N/A	-6.1 (0.3; -17.72 to 5.55)
	Diarrhea				
Scores at progression					
FOLFOX	20 (8.16) [5]	17.3 (5.15) [27]	19 (6.73) [14]	0 (.) [1]	17.7 (3.63) [47]
SIRT+FOLFOX	11.1 (7.03) [6]	11.9 (3.07) [28]	11.1 (3.81) [18]	11.1 (11.11) [3]	11.5 (2.16) [55]
Difference**	-8.9 (0.43; -33.11 to 15.34)	-4.5 (0.46; -16.4 to 7.49)	-9.1 (0.25; -24.95 to 6.73)	N/A	-5.9 (0.16; -14.15 to 2.36)
Score at previous follow-up point					
FOLFOX	6.7 (6.67) [5]	16 (4.12) [27]	7.1 (3.79) [14]	33.3 (.) [1]	12.8 (2.79) [47]
SIRT+FOLFOX	22.2 (16.48) [6]	15.5 (4.69) [28]	13 (5.48) [18]	0 (0) [3]	14.5 (3.43) [55]

Change in score from previous time-point to disease progression:					
FOLFOX	13.3 (8.16) [5]	1.2 (7) [27]	11.9 (6.64) [14]	-33.3 (.) [1]	5 (4.64) [47]
SIRT+FOLFOX	-11.1 (20.49) [6]	-3.6 (4.95) [28]	-1.9 (6.86) [18]	11.1 (11.11) [3]	-3 (3.99) [55]
Difference between arms in change**	-24.4 (0.33; -78.33 to 29.44)	-6.3 (0.45; -22.88 to 10.26)	-15.4 (0.15; -36.42 to 5.67)	N/A	-9.3 (0.11; -20.73 to 2.18)
	Financial difficulties				
Scores at progression					
FOLFOX	8.3 (8.33) [4]	14.8 (4.82) [27]	9.5 (6.47) [14]	33.3 (.) [1]	13 (3.51) [46]
SIRT+FOLFOX	16.7 (7.45) [6]	13.1 (5.24) [28]	13 (5.48) [18]	11.1 (11.11) [3]	13.3 (3.31) [55]
Difference**	8.3 (0.49; -17.98 to 34.65)	4.1 (0.47; -7.11 to 15.34)	1 (0.9; -14.28 to 16.2)	N/A	2.5 (0.54; -5.73 to 10.82)
Score at previous follow-up point					
FOLFOX	16.7 (9.62) [4]	12.3 (5.38) [27]	11.9 (5.64) [14]	33.3 (.) [1]	13 (3.66) [46]
SIRT+FOLFOX	5.6 (5.56) [6]	21.4 (5.74) [28]	9.3 (5.26) [18]	0 (0) [3]	14.5 (3.54) [55]
Change in score from previous time-point to disease progression:					
FOLFOX	-8.3 (8.33) [4]	2.5 (3.04) [27]	-2.4 (6.5) [14]	0 (.) [1]	0 (2.74) [46]
SIRT+FOLFOX	11.1 (7.03) [6]	-8.3 (6.09) [28]	3.7 (3.7) [18]	11.1 (11.11) [3]	-1.2 (3.56) [55]
Difference between arms in change**	19.4 (0.11; -5.88 to 44.76)	-11.1 (0.12; -25.46 to 3.19)	6 (0.44; -9.67 to 21.72)	N/A	-1.6 (0.74; -11.09 to 7.92)

* ≤3 months time-point includes cycle 4 and 3 months.

** Differences adjusted for respective baseline scores and cognitive functioning at baseline

Adverse events (Safety analysis)

The number of AEs had a statistically significant adverse impact on EQ-5D-3L utility-scores and EORTC QLQ-C30 global health status in both trial arms. However, the 95% CI of AEs coefficients suggested this difference is not substantial between FOLFOX and FOLFOX+SIRT arms in none of the HRQOL scores tested. Introducing the interaction term (column IV) did not provide evidence on the adverse effect of AEs being smaller amongst SIRT+FOLFOX and confirmed the treatment effect on HRQOL is not clinically important.

Appendix 14. EQ-5D-3L utility-scores, EORTC QLQ-C30 global health status and EORTC QLQ-LMC21 fatigue scale adjusted for numbers of adverse events (grade≥3). [online only]

	FOLFOX	SIRT+FOLFOX	Full model	Full model + interaction term
Utility (US)*				
Number of AEs (grade≥3)	-0.0109(p<0.001; -0.017 to -0.0047)	-0.0055(p=0.011; -0.0098 to -0.0013)	-0.0071(p<0.001; -0.0107 to -0.0034)	-0.0107(p<0.001; -0.017 to -0.0045)
Cognitive Functioning (baseline)	0.0012(p<0.001; 0.0005 to 0.0019)	0.0014(p=0.0069; 0.00037 to 0.0023)	0.0013(p<0.001; 0.00069 to 0.0018)	0.0012(p<0.001; 0.00067 to 0.0018)
Utility (baseline)	0.27(p<0.001; 0.16 to 0.38)	0.33(p<0.001; 0.22 to 0.44)	0.3(p<0.001; 0.22 to 0.38)	0.3(p<0.001; 0.22 to 0.38)
SIRT received	-	-	-0.018(p=0.0348; -0.035 to -0.0013)	-0.028(p=0.0103; -0.049 to -0.0065)
Number of AEs (grade≥3) X SIRT received	-	-	-	0.005(0.18; -0.002 to 0.0126)
Constant	0.53(p<0.001; 0.42 to 0.63)	0.43(p<0.001; 0.32 to 0.54)	0.49(p<0.001; 0.41 to 0.56)	0.5(p<0.001; 0.42 to 0.57)
Global health *				
Number of AEs (grade≥3)	-1.5(p<0.001; -2.09 to -0.92)	-0.63(p=0.0135; -1.12 to -0.13)	-0.91(p<0.001; -1.33 to -0.496)	-1.49(p<0.001; -2.07 to -0.91)
Cognitive Functioning (baseline)	0.088(0.07; -0.01 to 0.18)	0.17(p=0.0052; 0.05 to 0.297)	0.13(p=0.0012; 0.05 to 0.202)	0.12(p=0.0015; 0.05 to 0.2)
Global health (baseline)	0.43(p<0.001; 0.36 to 0.5)	0.38(p<0.001; 0.28 to 0.47)	0.41(p<0.001; 0.35 to 0.47)	0.41(p<0.001; 0.35 to 0.47)
SIRT received	-	-	-1.92(0.08; -4.08 to 0.25)	-3.54(p=0.009; -6.19 to -0.89)
Number of AEs (grade≥3) X SIRT received	-	-	-	0.857(p=0.028; 0.09 to 1.62)
Constant	34.03(p<0.001; 25.03 to 43.02)	26.58(p<0.001; 14.78 to 38.37)	31.27(p<0.001; 24.12 to 38.41)	32.67(p<0.001; 25.43 to 39.91)
Fatigue*				
Number of AEs (grade≥3)	1.19(0.14; -0.4 to 2.78)	0.98(0.18; -0.44 to 2.4)	1.04(0.053; -0.01 to 2.1)	1.19(0.13; -0.37 to 2.76)
Contact with friends (baseline)	-0.00113(0.99; -0.17 to 0.17)	-0.082(0.43; -0.28 to 0.12)	-0.054(0.45; -0.19 to 0.087)	-0.053(0.46; -0.19 to 0.088)
Fatigue (baseline)	0.45(p<0.001; 0.29 to 0.61)	0.46(p<0.001; 0.28 to 0.65)	0.46(p<0.001; 0.34 to 0.57)	0.46(p<0.001; 0.34 to 0.57)
SIRT received	-	-	6.33(p=0.0150; 1.24 to 11.43)	6.75(0.050; -0.01 to 13.51)
Number of AEs (grade≥3) X SIRT received	-	-	-	-0.24(0.83; -2.37 to 1.89)
Constant	22.81(p<0.001; 17.37 to 28.24)	29.9(p<0.001; 23.23 to 36.56)	23.24(p<0.001; 18.72 to 27.76)	23.06(p<0.001; 18.2 to 27.92)

*Includes complete cases at ≤3 months, 6 months and 12 months time-points.

Subgroups analysis

Appendix 15. EORTC QLQ-C30 global health status at 12 months adjusted for subgroups.

	FOLFOX	SIRT + FOLFOX	Full model	Full model + interaction term
Liver involvement >25%	3.1(0.261; -2.3 to 8.4)	-0.9(0.772; -7.1 to 5.2)	1.1(0.582; -2.9 to 5.2)	2.4(0.418; -3.5 to 8.3)
Cognitive functioning (baseline)	0.3(p<0.001; 0.1 to 0.4)	0.2(p=0.036; 0 to 0.4)	0.3(p<0.001; 0.1 to 0.4)	0.3(p<0.001; 0.1 to 0.4)
Global health status (baseline)	0.4(p<0.001; 0.2 to 0.5)	0.2(p=0.004; 0.1 to 0.4)	0.3(p<0.001; 0.2 to 0.4)	0.3(p<0.001; 0.2 to 0.4)
SIRT received	-	-	-2.1(0.249; -5.6 to 1.5)	-1.4(0.492; -5.6 to 2.7)
SIRT received X Liver involvement >25%	-	-	-	-2.4(0.552; -10.4 to 5.6)
Constant	18.8(p=0.006; 5.4 to 32.2)	34(p<0.001; 15.6 to 52.4)	26.8(p<0.001; 15.6 to 37.9)	26.6(p<0.001; 15.4 to 37.8)
Bevacizumab given	-3.8(0.107; -8.4 to 0.8)	-0.6(0.817; -6 to 4.8)	-2.4(0.184; -5.9 to 1.1)	-3.9(0.132; -9 to 1.2)
Cognitive functioning (baseline)	0.3(p<0.001; 0.2 to 0.5)	0.2(p=0.035; 0 to 0.4)	0.3(p<0.001; 0.1 to 0.4)	0.3(p<0.001; 0.1 to 0.4)
Global health status (baseline)	0.3(p<0.001; 0.2 to 0.5)	0.2(p=0.002; 0.1 to 0.4)	0.3(p<0.001; 0.2 to 0.4)	0.3(p<0.001; 0.2 to 0.4)
SIRT received	-	-	-2.3(0.197; -5.9 to 1.2)	-3.7(0.135; -8.7 to 1.2)
SIRT received X Bevacizumab given	-	-	-	2.9(0.415; -4.2 to 10)
Constant	22.0(p=0.001; 8.7 to 35.4)	33.3(p<0.001; 15.5 to 51.1)	28.2(p<0.001; 17.2 to 39.1)	29.2(p<0.001; 18 to 40.3)
Age ≥ 65years	-2.1(0.367; -6.7 to 2.5)	-2.2(0.422; -7.7 to 3.2)	-2.1(0.254; -5.6 to 1.5)	-1.9(0.47; -7 to 3.2)
Cognitive functioning (baseline)	0.3(p<0.001; 0.1 to 0.4)	0.2(p=0.044; 0 to 0.4)	0.3(p<0.001; 0.1 to 0.4)	0.3(p<0.001; 0.1 to 0.4)
Global health status (baseline)	0.3(p<0.001; 0.2 to 0.5)	0.2(p=0.002; 0.1 to 0.4)	0.3(p<0.001; 0.2 to 0.4)	0.3(p<0.001; 0.2 to 0.4)
SIRT received	-	-	-2.2(0.223; -5.7 to 1.3)	-2(0.395; -6.7 to 2.7)
SIRT received X Age ≥ 65years	-	-	-	-0.4(0.915; -7.5 to 6.7)
Constant	21.0(p=0.002; 7.7 to 34.3)	34.5(p<0.001; 16.5 to 52.5)	28.4(p<0.001; 17.4 to 39.4)	28.3(p<0.001; 17.2 to 39.4)
Extra-hepatic metastases	-0.2(0.952; -5.1 to 4.8)	-5.2(0.06; -10.7 to 0.2)	-2.9(0.127; -6.6 to 0.8)	-0.2(0.943; -5.7 to 5.3)
Cognitive functioning (baseline)	0.3(p<0.001; 0.1 to 0.4)	0.2(0.05; 0 to 0.4)	0.3(p<0.001; 0.1 to 0.4)	0.3(p<0.001; 0.1 to 0.4)
Global health status (baseline)	0.3(p<0.001; 0.2 to 0.5)	0.2(p=0.002; 0.1 to 0.4)	0.3(p<0.001; 0.2 to 0.4)	0.3(p<0.001; 0.2 to 0.4)
SIRT received	-	-	-1.9(0.299; -5.4 to 1.7)	-0.2(0.922; -4.5 to 4.1)
SIRT received X Extra-hepatic metastases	-	-	-	-4.9(0.194; -12.4 to 2.5)
Constant	20.3(p=0.003; 7 to 33.6)	36.3(p<0.001; 18.4 to 54.3)	28.6(p<0.001; 17.6 to 39.6)	28(p<0.001; 16.9 to 39)

Primary tumour in situ	0.5(0.832; -4.1 to 5.1)	-1.8(0.501; -7.1 to 3.5)	-0.8(0.636; -4.4 to 2.7)	0.2(0.954; -4.9 to 5.2)
Cognitive functioning (baseline)	0.3(p<0.001; 0.1 to 0.4)	0.2(p=0.034; 0 to 0.4)	0.3(p<0.001; 0.1 to 0.4)	0.3(p<0.001; 0.1 to 0.4)
Global health status (baseline)	0.3(p<0.001; 0.2 to 0.5)	0.2(p=0.003; 0.1 to 0.4)	0.3(p<0.001; 0.2 to 0.4)	0.3(p<0.001; 0.2 to 0.4)
SIRT received	-	-	-2.1(0.244; -5.6 to 1.4)	-1.2(0.64; -6.1 to 3.8)
SIRT received X Primary tumour in situ	-	-	-	-1.9(0.594; -9 to 5.1)
Constant	19.9(p=0.005; 6.2 to 33.6)	34.1(p<0.001; 16.1 to 52)	28.0(p<0.001; 16.9 to 39.1)	27.3(p<0.001; 15.9 to 38.7)
Female	-0.3(0.913; -5.2 to 4.7)	5.0(0.077; -0.5 to 10.5)	2.7(0.158; -1 to 6.4)	-0.3(0.925; -5.8 to 5.2)
Cognitive functioning (baseline)	0.3(p<0.001; 0.1 to 0.4)	0.2(p=0.039; 0 to 0.4)	0.3(p<0.001; 0.1 to 0.4)	0.3(p<0.001; 0.1 to 0.4)
Global health status (baseline)	0.3(p<0.001; 0.2 to 0.5)	0.2(p=0.001; 0.1 to 0.4)	0.3(p<0.001; 0.2 to 0.4)	0.3(p<0.001; 0.2 to 0.4)
SIRT received	-	-	-2.2(0.223; -5.7 to 1.3)	-4.0(0.07; -8.3 to 0.3)
SIRT received X Female	-	-	-	5.4(0.154; -2 to 12.9)
Constant	20.3(p=0.003; 7 to 33.7)	31(p=0.001; 13.1 to 48.9)	26.4(p<0.001; 15.4 to 37.4)	27.2(p<0.001; 16.2 to 38.2)
Synchronous disease	0.8(0.817; -5.9 to 7.5)	-2.2(0.592; -10.2 to 5.8)	-1.0(0.703; -6.3 to 4.2)	0.2(0.951; -7.2 to 7.7)
Cognitive functioning (baseline)	0.3(p<0.001; 0.1 to 0.4)	0.2(p=0.035; 0 to 0.4)	0.3(p<0.001; 0.1 to 0.4)	0.3(p<0.001; 0.1 to 0.4)
Global health status (baseline)	0.3(p<0.001; 0.2 to 0.5)	0.2(p=0.002; 0.1 to 0.4)	0.3(p<0.001; 0.2 to 0.4)	0.3(p<0.001; 0.2 to 0.4)
SIRT received	-	-	-2.2(0.221; -5.8 to 1.3)	-0.1(0.99; -9.8 to 9.7)
SIRT received X Synchronous disease	-	-	-	-2.5(0.642; -12.9 to 8)
Constant	19.2(p=0.012; 4.3 to 34)	34.8(p<0.001; 16.1 to 53.5)	28.2(p<0.001; 16.4 to 40)	26.9(p<0.001; 14 to 39.8)
Primary tumour location, right	-4.5(0.219; -11.8 to 2.7)	-2.9(0.425; -9.9 to 4.2)	-3.5(0.176; -8.5 to 1.6)	-4.2(0.285; -12 to 3.6)
Cognitive functioning (baseline)	0.3(p=0.001; 0.1 to 0.5)	0.3(p=0.026; 0 to 0.6)	0.3(p<0.001; 0.2 to 0.5)	0.3(p<0.001; 0.2 to 0.5)
Global health status (baseline)	0.3(p<0.001; 0.2 to 0.5)	0.2(0.071; 0 to 0.3)	0.2(p<0.001; 0.1 to 0.3)	0.2(p<0.001; 0.1 to 0.3)
SIRT received	-	-	-0.1(0.95; -4.4 to 4.2)	-0.4(0.863; -5.3 to 4.4)
SIRT received X Primary tumour location, right	-	-	-	1.3(0.8; -8.9 to 11.6)
Constant	18.9(p=0.037; 1.2 to 36.6)	32.2(p=0.009; 8.2 to 56.2)	26.0(p<0.001; 11.8 to 40.2)	26.2(p<0.001; 11.9 to 40.5)
WHO performance status	-4.6(0.065; -9.5 to 0.3)	-1.4(0.653; -7.3 to 4.6)	-2.7(0.169; -6.5 to 1.1)	-4.9(0.079; -10.3 to 0.6)
Cognitive functioning (baseline)	0.3(p<0.001; 0.1 to 0.4)	0.2(p=0.035; 0 to 0.4)	0.3(p<0.001; 0.1 to 0.4)	0.2(p<0.001; 0.1 to 0.4)
Global health status (baseline)	0.3(p<0.001; 0.2 to 0.5)	0.2(p=0.005; 0.1 to 0.4)	0.3(p<0.001; 0.2 to 0.4)	0.3(p<0.001; 0.2 to 0.4)
SIRT received	-	-	-2.1(0.245; -5.6 to 1.4)	-3.4(0.113; -7.7 to 0.8)

SIRT received X WHO performance status	-	-	-	4.3(0.266; -3.3 to 11.9)
Constant	23.6(p=0.001; 10 to 37.2)	34.3(p<0.001; 16 to 52.7)	29.5(p<0.001; 18.3 to 40.8)	30.3(p<0.001; 18.9 to 41.6)
Intention to Treat biological agents	-2.9(0.306; -8.4 to 2.6)	1.3(0.683; -4.9 to 7.4)	-0.9(0.655; -5.1 to 3.2)	-3.1(0.307; -9.1 to 2.9)
Cognitive functioning (baseline)	0.3(p=0.001; 0.1 to 0.5)	0.2(0.063; 0 to 0.4)	0.3(p<0.001; 0.1 to 0.4)	0.3(p<0.001; 0.1 to 0.4)
Global health status (baseline)	0.3(p<0.001; 0.2 to 0.5)	0.2(p=0.023; 0 to 0.3)	0.3(p<0.001; 0.2 to 0.4)	0.3(p<0.001; 0.2 to 0.4)
SIRT received	-	-	-1.4(0.463; -5.3 to 2.4)	-4.3(0.219; -11.1 to 2.6)
SIRT received X Intention to Treat biological agents	-	-	-	4.2(0.323; -4.1 to 12.4)
Constant	21.6(p=0.007; 6.1 to 37)	36.9(p<0.001; 17.3 to 56.5)	29.3(p<0.001; 17 to 41.7)	30.9(p<0.001; 18.2 to 43.7)

Appendix 16. EQ-5D-3L utility-scores at 12 months adjusted for subgroups.

	FOLFOX	SIRT + FOLFOX	Full model	Full model + interaction term
Liver involvement >25%	0.02(0.357; -0.022 to 0.062)	0.004(0.85; -0.041 to 0.049)	0.012(0.43; -0.019 to 0.043)	0.019(0.403; -0.026 to 0.065)
Cognitive functioning (baseline)	0.003(p<0.001; 0.001 to 0.004)	0.001(0.084; 0 to 0.003)	0.002(p<0.001; 0.001 to 0.003)	0.002(p<0.001; 0.001 to 0.003)
Utility-scores (baseline)	0.217(p=0.002; 0.079 to 0.355)	0.251(p=0.002; 0.093 to 0.41)	0.234(p<0.001; 0.129 to 0.34)	0.234(p<0.001; 0.129 to 0.34)
SIRT received	-	-	-0.029(p=0.038; -0.056 to -0.002)	-0.025(0.116; -0.057 to 0.006)
SIRT received X Liver involvement >25%	-	-	-	-0.013(0.681; -0.074 to 0.048)
Constant	0.435(p<0.001; 0.307 to 0.563)	0.485(p<0.001; 0.317 to 0.653)	0.465(p<0.001; 0.362 to 0.569)	0.464(p<0.001; 0.36 to 0.568)
Bevacizumab given	-0.032(0.084; -0.068 to 0.004)	0.002(0.916; -0.038 to 0.042)	-0.015(0.288; -0.042 to 0.012)	-0.031(0.122; -0.071 to 0.008)
Cognitive functioning (baseline)	0.003(p<0.001; 0.001 to 0.004)	0.001(0.091; 0 to 0.003)	0.002(p<0.001; 0.001 to 0.003)	0.002(p<0.001; 0.001 to 0.003)
Utility-scores (baseline)	0.215(p=0.002; 0.079 to 0.351)	0.248(p=0.002; 0.091 to 0.405)	0.232(p<0.001; 0.127 to 0.336)	0.231(p<0.001; 0.127 to 0.336)
SIRT received	-	-	-0.03(p=0.03; -0.058 to -0.003)	-0.045(p=0.019; -0.083 to -0.007)
SIRT received X Bevacizumab given	-	-	-	0.031(0.262; -0.023 to 0.085)
Constant	0.456(p<0.001; 0.332 to 0.581)	0.491(p<0.001; 0.329 to 0.652)	0.477(p<0.001; 0.376 to 0.577)	0.487(p<0.001; 0.385 to 0.589)
Age ≥ 65years	-0.003(0.854; -0.04 to 0.033)	0.022(0.284; -0.018 to 0.062)	0.011(0.44; -0.017 to 0.038)	-0.004(0.858; -0.043 to 0.036)
Cognitive functioning (baseline)	0.003(p<0.001; 0.001 to 0.004)	0.001(0.07; 0 to 0.003)	0.002(p<0.001; 0.001 to 0.003)	0.002(p<0.001; 0.001 to 0.003)
Utility-scores (baseline)	0.21(p=0.003; 0.072 to 0.348)	0.245(p=0.002; 0.088 to 0.401)	0.225(p<0.001; 0.12 to 0.329)	0.227(p<0.001; 0.122 to 0.331)
SIRT received	-	-	-0.028(p=0.045; -0.055 to -0.001)	-0.039(p=0.032; -0.076 to -0.003)
SIRT received X Age ≥ 65years	-	-	-	0.027(0.333; -0.028 to 0.081)
Constant	0.449(p<0.001; 0.323 to 0.574)	0.478(p<0.001; 0.316 to 0.64)	0.472(p<0.001; 0.371 to 0.572)	0.475(p<0.001; 0.374 to 0.576)
Extra-hepatic metastases	0.007(0.716; -0.033 to 0.047)	0.008(0.694; -0.033 to 0.049)	0.009(0.549; -0.02 to 0.037)	0.008(0.729; -0.036 to 0.051)
Cognitive functioning (baseline)	0.002(p<0.001; 0.001 to 0.004)	0.001(0.081; 0 to 0.003)	0.002(p<0.001; 0.001 to 0.003)	0.002(p<0.001; 0.001 to 0.003)
Utility-scores (baseline)	0.21(p=0.003; 0.073 to 0.348)	0.247(p=0.002; 0.09 to 0.404)	0.228(p<0.001; 0.124 to 0.332)	0.228(p<0.001; 0.123 to 0.333)
SIRT received	-	-	-0.029(p=0.038; -0.056 to -0.002)	-0.029(0.08; -0.062 to 0.003)
SIRT received X Extra-hepatic metastases	-	-	-	0.002(0.948; -0.056 to 0.06)
Constant	0.445(p<0.001; 0.318 to 0.571)	0.487(p<0.001; 0.325 to 0.648)	0.472(p<0.001; 0.371 to 0.573)	0.472(p<0.001; 0.371 to 0.574)
Primary tumour in situ	-0.01(0.589; -0.046 to 0.026)	-0.026(0.184; -0.066 to 0.013)	-0.019(0.167; -0.046 to 0.008)	-0.01(0.62; -0.05 to 0.03)

Cognitive functioning (baseline)	0.003(p<0.001; 0.001 to 0.004)	0.001(0.083; 0 to 0.003)	0.002(p<0.001; 0.001 to 0.003)	0.002(p<0.001; 0.001 to 0.003)
Utility-scores (baseline)	0.207(p=0.003; 0.07 to 0.344)	0.244(p=0.002; 0.088 to 0.4)	0.225(p<0.001; 0.121 to 0.33)	0.225(p<0.001; 0.121 to 0.329)
SIRT received	-	-	-0.029(p=0.034; -0.056 to -0.002)	-0.021(0.268; -0.059 to 0.016)
SIRT received X Primary tumour in situ	-	-	-	-0.017(0.546; -0.07 to 0.037)
Constant	0.454(p<0.001; 0.327 to 0.581)	0.505(p<0.001; 0.344 to 0.667)	0.487(p<0.001; 0.386 to 0.589)	0.483(p<0.001; 0.38 to 0.585)
Female	0.023(0.254; -0.017 to 0.062)	0.023(0.263; -0.018 to 0.065)	0.022(0.124; -0.006 to 0.051)	0.022(0.313; -0.021 to 0.065)
Cognitive functioning (baseline)	0.003(p<0.001; 0.001 to 0.004)	0.001(0.093; 0 to 0.003)	0.002(p<0.001; 0.001 to 0.003)	0.002(p<0.001; 0.001 to 0.003)
Utility-scores (baseline)	0.21(p=0.003; 0.073 to 0.346)	0.26(p=0.001; 0.103 to 0.418)	0.234(p<0.001; 0.13 to 0.339)	0.234(p<0.001; 0.13 to 0.339)
SIRT received	-	-	-0.029(p=0.033; -0.056 to -0.002)	-0.03(0.077; -0.062 to 0.003)
SIRT received X Female	-	-	-	0.001(0.983; -0.057 to 0.058)
Constant	0.437(p<0.001; 0.311 to 0.563)	0.475(p<0.001; 0.313 to 0.637)	0.463(p<0.001; 0.362 to 0.564)	0.463(p<0.001; 0.361 to 0.565)
Synchronous disease	-0.013(0.627; -0.064 to 0.039)	-0.006(0.835; -0.065 to 0.052)	-0.011(0.579; -0.05 to 0.028)	-0.014(0.617; -0.07 to 0.042)
Cognitive functioning (baseline)	0.002(p<0.001; 0.001 to 0.004)	0.001(0.076; 0 to 0.003)	0.002(p<0.001; 0.001 to 0.003)	0.002(p<0.001; 0.001 to 0.003)
Utility-scores (baseline)	0.211(p=0.003; 0.074 to 0.349)	0.249(p=0.002; 0.091 to 0.406)	0.229(p<0.001; 0.124 to 0.333)	0.23(p<0.001; 0.125 to 0.335)
SIRT received	-	-	-0.029(p=0.036; -0.056 to -0.002)	-0.034(0.352; -0.107 to 0.038)
SIRT received X Synchronous disease	-	-	-	0.006(0.873; -0.072 to 0.085)
Constant	0.458(p<0.001; 0.327 to 0.59)	0.49(p<0.001; 0.32 to 0.66)	0.483(p<0.001; 0.377 to 0.589)	0.485(p<0.001; 0.375 to 0.596)
Primary tumour location, right	0.01(0.736; -0.048 to 0.067)	-0.007(0.811; -0.06 to 0.047)	0(0.993; -0.039 to 0.039)	0.009(0.764; -0.052 to 0.07)
Cognitive functioning (baseline)	0.002(p=0.007; 0.001 to 0.004)	0.002(0.147; -0.001 to 0.004)	0.002(p=0.003; 0.001 to 0.003)	0.002(p=0.003; 0.001 to 0.003)
Utility-scores (baseline)	0.2(p=0.026; 0.025 to 0.376)	0.244(p=0.016; 0.045 to 0.444)	0.224(p=0.001; 0.092 to 0.356)	0.223(p=0.001; 0.091 to 0.355)
SIRT received	-	-	-0.027(0.123; -0.06 to 0.007)	-0.023(0.236; -0.061 to 0.015)
SIRT received X Primary tumour location, right	-	-	-	-0.016(0.691; -0.095 to 0.063)
Constant	0.497(p<0.001; 0.341 to 0.653)	0.477(p<0.001; 0.234 to 0.721)	0.497(p<0.001; 0.365 to 0.629)	0.494(p<0.001; 0.362 to 0.627)
WHO performance status	-0.011(0.601; -0.051 to 0.029)	-0.011(0.616; -0.055 to 0.033)	-0.012(0.447; -0.041 to 0.018)	-0.013(0.558; -0.056 to 0.03)
Cognitive functioning (baseline)	0.002(p<0.001; 0.001 to 0.004)	0.001(0.089; 0 to 0.003)	0.002(p<0.001; 0.001 to 0.003)	0.002(p<0.001; 0.001 to 0.003)
Utility-scores (baseline)	0.202(p=0.005; 0.062 to 0.341)	0.238(p=0.004; 0.075 to 0.4)	0.219(p<0.001; 0.112 to 0.326)	0.219(p<0.001; 0.112 to 0.326)
SIRT received	-	-	-0.028(p=0.041; -0.055 to -0.001)	-0.029(0.083; -0.062 to 0.004)
SIRT received X WHO performance status	-	-	-	0.002(0.935; -0.055 to 0.06)

Constant	0.46(p<0.001; 0.327 to 0.594)	0.504(p<0.001; 0.334 to 0.674)	0.49(p<0.001; 0.383 to 0.596)	0.49(p<0.001; 0.383 to 0.597)
Intention to Treat biological agents	-0.045(p=0.044; -0.088 to -0.001)	0.025(0.276; -0.02 to 0.07)	-0.009(0.592; -0.04 to 0.023)	-0.044(0.06; -0.091 to 0.002)
Cognitive functioning (baseline)	0.002(p<0.001; 0.001 to 0.004)	0.001(0.283; -0.001 to 0.003)	0.002(p<0.001; 0.001 to 0.003)	0.002(p=0.001; 0.001 to 0.003)
Utility-scores (baseline)	0.185(p=0.015; 0.037 to 0.334)	0.209(p=0.011; 0.049 to 0.369)	0.19(p=0.001; 0.08 to 0.3)	0.194(p=0.001; 0.085 to 0.303)
SIRT received	-	-	-0.023(0.119; -0.053 to 0.006)	-0.069(p=0.01; -0.121 to -0.017)
SIRT received X Intention to Treat biological agents	-	-	-	0.066(p=0.038; 0.004 to 0.129)
Constant	0.499(p<0.001; 0.355 to 0.644)	0.553(p<0.001; 0.384 to 0.722)	0.527(p<0.001; 0.416 to 0.638)	0.553(p<0.001; 0.44 to 0.666)

Appendix 17. EORTC LMC-21 fatigue at ≤3 months adjusted for subgroups.

	FOLFOX	SIRT + FOLFOX	Full model	Full model + interaction term
Liver involvement >25%	2.2(0.624; -6.7 to 11.1)	-7.5(0.094; -16.4 to 1.3)	-2.7(0.393; -8.9 to 3.5)	1.6(0.711; -7.1 to 10.3)
Contact with friends (baseline)	0.0(0.773; -0.3 to 0.2)	0.1(0.392; -0.1 to 0.3)	0.0(0.622; -0.1 to 0.2)	0.1(0.48; -0.1 to 0.2)
Fatigue (baseline)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.7)	0.5(p<0.001; 0.4 to 0.6)	0.5(p<0.001; 0.3 to 0.6)
SIRT received	-	-	8.2(p=0.006; 2.4 to 14.1)	11.1(p=0.002; 4 to 18.2)
SIRT received X Liver involvement >25%	-	-	-	-8.6(0.165; -20.7 to 3.5)
Constant	23.2(p<0.001; 16.8 to 29.7)	32.8(p<0.001; 26 to 39.6)	23.7(p<0.001; 18.2 to 29.2)	22.4(p<0.001; 16.6 to 28.2)
Bevacizumab given	-6(0.23; -15.8 to 3.8)	-1.5(0.878; -20.7 to 17.8)	-4.7(0.284; -13.4 to 4)	-5.6(0.266; -15.4 to 4.3)
Contact with friends (baseline)	-0.1(0.648; -0.3 to 0.2)	0.1(0.562; -0.1 to 0.2)	0.0(0.738; -0.1 to 0.2)	0.0(0.749; -0.1 to 0.2)
Fatigue (baseline)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.7)	0.5(p<0.001; 0.4 to 0.6)	0.5(p<0.001; 0.4 to 0.6)
SIRT received	-	-	7.6(p=0.014; 1.6 to 13.5)	7.2(p=0.024; 1 to 13.5)
SIRT received X Bevacizumab given	-	-	-	3.8(0.721; -17.3 to 24.9)
Constant	24.9(p<0.001; 18.4 to 31.4)	31.1(p<0.001; 24.3 to 37.9)	24.2(p<0.001; 18.5 to 29.9)	24.3(p<0.001; 18.6 to 30)
Age ≥ 65years	0.1(0.977; -8.3 to 8.5)	-3.6(0.389; -11.9 to 4.7)	-1.9(0.514; -7.8 to 3.9)	0.1(0.991; -8.3 to 8.4)
Contact with friends (baseline)	0.0(0.776; -0.3 to 0.2)	0.1(0.589; -0.1 to 0.2)	0.0(0.672; -0.1 to 0.2)	0.0(0.717; -0.1 to 0.2)
Fatigue (baseline)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.7)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.6)
SIRT received	-	-	8.5(p=0.005; 2.6 to 14.3)	10.1(p=0.011; 2.4 to 17.8)
SIRT received X Age ≥ 65years	-	-	-	-3.8(0.519; -15.4 to 7.8)
Constant	23.6(p<0.001; 16.3 to 30.9)	32.9(p<0.001; 25 to 40.8)	24(p<0.001; 18 to 30)	23.2(p<0.001; 16.7 to 29.7)
Extra-hepatic metastases	2.1(0.637; -6.6 to 10.8)	8.3(0.062; -0.4 to 17.1)	5.1(0.1; -1 to 11.2)	1.8(0.683; -6.8 to 10.4)
Contact with friends (baseline)	0.0(0.735; -0.3 to 0.2)	0.1(0.586; -0.1 to 0.2)	0.0(0.762; -0.1 to 0.2)	0.0(0.749; -0.1 to 0.2)
Fatigue (baseline)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.6)
SIRT received	-	-	8.5(p=0.004; 2.7 to 14.3)	6.4(0.075; -0.6 to 13.4)
SIRT received X Extra-hepatic metastases	-	-	-	6.7(0.282; -5.5 to 18.8)
Constant	23(p<0.001; 16.2 to 29.8)	28.9(p<0.001; 22.2 to 35.7)	21.5(p<0.001; 15.9 to 27.2)	22.7(p<0.001; 16.7 to 28.8)
Primary tumour in situ	3.5(0.41; -4.9 to 12)	7.3(0.083; -1 to 15.5)	5.3(0.076; -0.6 to 11.1)	3.2(0.457; -5.2 to 11.6)
Contact with friends (baseline)	0.0(0.718; -0.3 to 0.2)	0.1(0.495; -0.1 to 0.3)	0.0(0.664; -0.1 to 0.2)	0.0(0.639; -0.1 to 0.2)

Fatigue (baseline)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.7)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.6)
SIRT received	-	-	8.5(p=0.004; 2.7 to 14.3)	6.1(0.199; -3.2 to 15.3)
SIRT received X Primary tumour in situ	-	-	-	4.0(0.5; -7.7 to 15.7)
Constant	21.6(p<0.001; 13.7 to 29.5)	26.8(p<0.001; 18.9 to 34.8)	19.9(p<0.001; 13.6 to 26.3)	21.2(p<0.001; 13.8 to 28.6)
Female	1.3(0.779; -7.6 to 10.1)	5.8(0.187; -2.8 to 14.4)	3.7(0.23; -2.4 to 9.8)	1.3(0.768; -7.6 to 10.2)
Contact with friends (baseline)	0.0(0.784; -0.3 to 0.2)	0.1(0.594; -0.1 to 0.2)	0.0(0.693; -0.1 to 0.2)	0.0(0.718; -0.1 to 0.2)
Fatigue (baseline)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.7)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.6)
SIRT received	-	-	8.2(p=0.006; 2.4 to 14)	6.7(0.059; -0.3 to 13.7)
SIRT received X Female	-	-	-	4.5(0.465; -7.7 to 16.8)
Constant	23.3(p<0.001; 16.5 to 30.1)	29.3(p<0.001; 22.4 to 36.2)	22.1(p<0.001; 16.5 to 27.7)	22.8(p<0.001; 16.9 to 28.8)
Synchronous disease	-2.1(0.717; -13.4 to 9.2)	-2.2(0.685; -13 to 8.6)	-2.3(0.549; -10 to 5.4)	-2.6(0.649; -13.6 to 8.5)
Contact with friends (baseline)	0.0(0.786; -0.3 to 0.2)	0.0(0.707; -0.2 to 0.2)	0.0(0.8; -0.1 to 0.2)	0.0(0.801; -0.1 to 0.2)
Fatigue (baseline)	0.5(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.7)	0.5(p<0.001; 0.4 to 0.6)	0.5(p<0.001; 0.4 to 0.6)
SIRT received	-	-	8.9(p=0.003; 3.1 to 14.7)	8.6(0.223; -5.2 to 22.4)
SIRT received X Synchronous disease	-	-	-	0.4(0.958; -14.7 to 15.6)
Constant	25.1(p<0.001; 15 to 35.2)	33.1(p<0.001; 22.6 to 43.6)	24.7(p<0.001; 17 to 32.5)	24.9(p<0.001; 15 to 34.9)
WHO performance status	4.8(0.313; -4.6 to 14.1)	7.1(0.115; -1.8 to 15.9)	6.1(0.058; -0.2 to 12.4)	4.7(0.313; -4.5 to 13.9)
Contact with friends (baseline)	0.0(0.878; -0.3 to 0.2)	0.0(0.646; -0.1 to 0.2)	0.0(0.648; -0.1 to 0.2)	0.0(0.699; -0.1 to 0.2)
Fatigue (baseline)	0.4(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.6)	0.4(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.6)
SIRT received	-	-	8.1(p=0.006; 2.3 to 13.9)	7.4(p=0.036; 0.5 to 14.2)
SIRT received X WHO performance status	-	-	-	2.6(0.682; -9.9 to 15.1)
Constant	22.9(p<0.001; 16.6 to 29.3)	29.4(p<0.001; 22.6 to 36.1)	22.1(p<0.001; 16.7 to 27.5)	22.4(p<0.001; 16.8 to 28.1)
Intention to Treat biological agents	2.4(0.601; -6.6 to 11.3)	4.0(0.369; -4.8 to 12.8)	3.5(0.263; -2.7 to 9.7)	3.0(0.503; -5.8 to 11.8)
Contact with friends (baseline)	-0.1(0.649; -0.3 to 0.2)	0.1(0.296; -0.1 to 0.3)	0.1(0.431; -0.1 to 0.2)	0.1(0.444; -0.1 to 0.2)
Fatigue (baseline)	0.4(p<0.001; 0.3 to 0.6)	0.5(p<0.001; 0.3 to 0.6)	0.4(p<0.001; 0.3 to 0.6)	0.4(p<0.001; 0.3 to 0.6)
SIRT received	-	-	8.7(0.006; 2.5 to 14.9)	8.2(p=0.048; 0.1 to 16.4)
SIRT received X Intention to Treat biological agents	-	-	-	1.0(0.872; -11.4 to 13.4)
Constant	23.7(p<0.001; 16.1 to 31.3)	29.3(p<0.001; 21.3 to 37.2)	22.0(p<0.001; 15.7 to 28.2)	22.2(p<0.001; 15.4 to 28.9)

Response rates

Appendix 18. Questionnaire response rates (number responding/number alive, percentage) for each quality of life questionnaire at each follow-up point.

	EORTC QLQ-C30 ⁺		EORTC QLQ-LMC21*		EQ-5D	
	FOLFOX	SIRT+FOLFOX	FOLFOX	SIRT+FOLFOX	FOLFOX	SIRT+FOLFOX
Baseline	503/549 (91.6)	513/554 (92.6)	161/182 (88.5)	162/182 (89.0)	507/549 (92.3)	510/554 (92.1)
≤3 months	446/541 (82.4)	456/538 (84.8)	137/179 (76.5)	136/176 (77.3)	417/541 (77.1)	431/538 (80.1)
6 months	84/517 (16.2)	89/502 (17.7)	7/171 (4.1)	12/162 (7.4)	247/517 (47.8)	260/502 (51.8)
12 months	240/449 (53.5)	262/430 (60.9)	74/141 (52.5)	82/132 (62.1)	215/449 (47.9)	253/430 (58.8)
24 months	33/285 (11.6)	29/270 (10.7)	13/80 (16.3)	14/73 (19.2)	74/285 (26.0)	85/270 (31.5)
36 months	9/175 (5.1)	6/165 (3.6)	4/46 (8.7)	5/44 (11.4)	17/175 (9.7)	18/165 (10.9)
48 months	1/148 (0.7)	1/136 (0.7)	0/38 (0)	2/36 (5.6)	5/148 (3.4)	4/136 (2.9)
60 months	0/142 (0)	1/129 (0.8)	0/37 (0)	1/32 (3.1)	1/142 (0.7)	2/129 (1.6)
Disease progression	48/467 (10.3)	55/474 (11.6)	3/156 (1.9)	2/148 (1.4)	174/467 (37.3)	158/474 (33.3)

⁺ EORTC QLQ-C30 was not collected in SF trial at 6 months and after 12 months.

* EORTC QLQ-LMC21 was collected only in FFr trial.

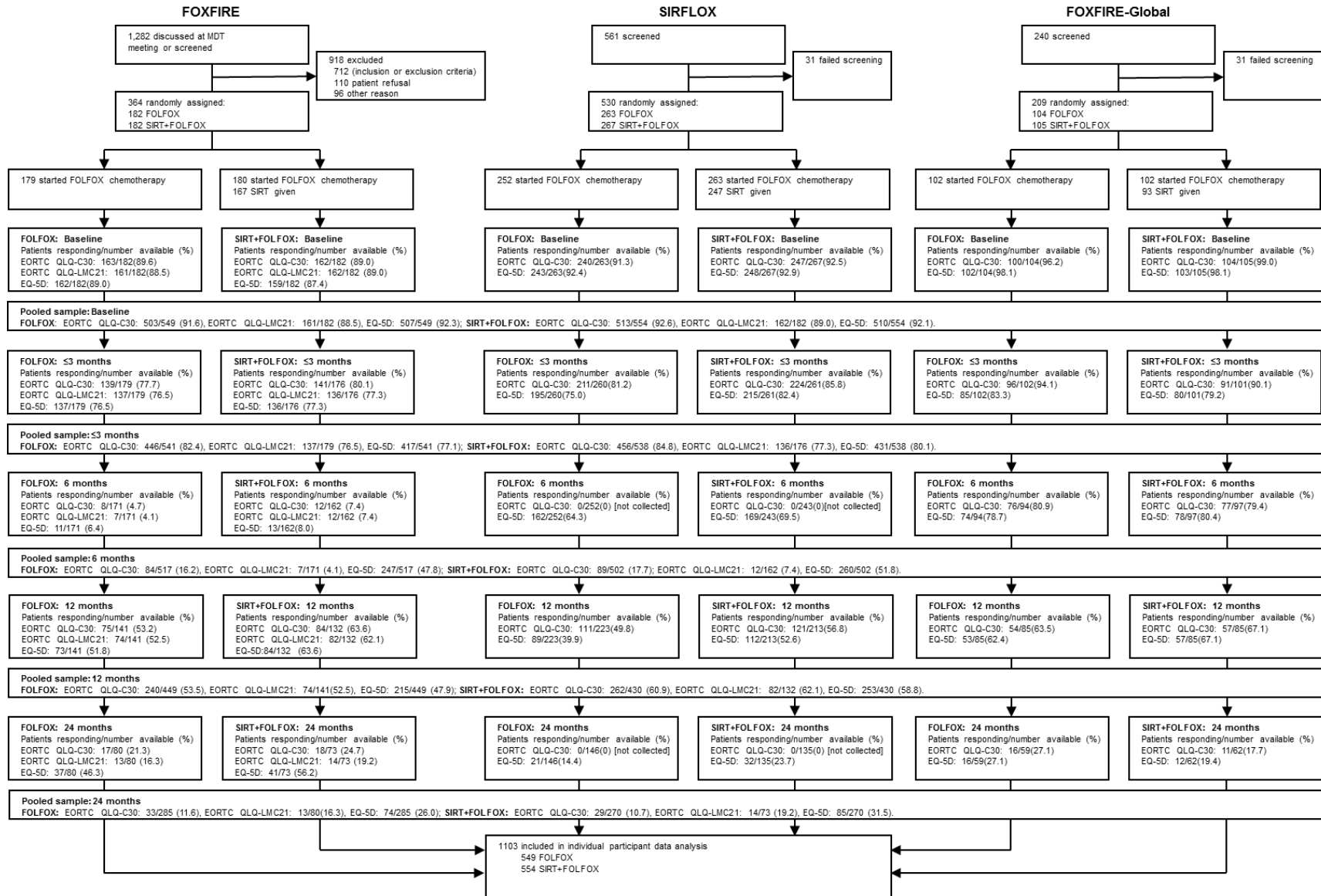
EORTC QLQ-LMC21 significant scales

Appendix 19. Mean scores (standard error) [number of patients] for the EORTC QLQ-LMC21 symptom scales+, adjusted differences (p-value; 95% confidence interval) for respective baseline and ‘contact with friends’ baseline scores.

	Baseline	≤ 3 months [#]	12 months	24 months
Fatigue				
FOLFOX	34.0 (2.3) [158]	38.5 (2.2) [131]	36.4 (3.3) [72]	41.0 (11.0) [13]
SIRT+FOLFOX	34.9 (2.1) [161]	46.3 (2.3) [134]	43.1 (3.2) [81]	42.7 (8.5) [13]
Difference	1.0 (0.76; -5.1 to 7.1)	8.3 (0.0050; 2.5 to 14.1)**	9.6 (0.039; 0.5 to 18.7)*	7.8 (0.59; -22.2 to 37.9)
Pain				
FOLFOX	20.7 (1.8) [158]	17.5 (1.7) [135]	19.1 (2.2) [72]	10.1 (5.3) [11]
SIRT+FOLFOX	18.4 (1.5) [158]	17.4 (1.7) [134]	23.1 (2.8) [81]	29.4 (6.0) [14]
Difference	-2.3 (0.31; -6.8 to 2.2)	0.3 (0.89; -4.1 to 4.7)	5.8 (0.14; -2.0 to 13.5)	22.2 (0.039; 1.3 to 43.2)*
Dry mouth				
FOLFOX	15.1 (2.0) [161]	29.9 (2.7) [135]	15.5 (2.7) [73]	18.0 (8.1) [13]
SIRT+FOLFOX	14.4 (1.9) [162]	27.4 (2.6) [135]	22.4 (3.4) [82]	14.3 (5.8) [14]
Difference	-0.7 (0.79; -6.1 to 4.7)	-2.9 (0.44; -10.3 to 4.5)	10.1 (0.038; 0.6 to 19.7)*	4.8 (0.59; -13.6 to 23.3)
Sore mouth/tongue				
FOLFOX	4.2 (1.0) [160]	27.1 (2.7) [134]	11.7 (2.7) [74]	12.8 (8.0) [13]
SIRT+FOLFOX	3.5 (1.1) [161]	16.3 (2.1) [133]	12.2 (2.7) [82]	4.8 (3.2) [14]
Difference	-0.7 (0.67; -3.6 to 2.3)	-11.0 (0.0020; -17.9 to -4.1)**	-1.0 (0.82; -9.3 to 7.4)	-9.4 (0.34; -29.5 to 10.8)
Peripheral neuropathy				
FOLFOX	5.6 (1.2) [160]	48.0 (2.4) [136]	50.9 (4.0) [74]	66.7 (11.9) [13]
SIRT+FOLFOX	6.8 (1.4) [161]	32.8 (2.0) [136]	41.5 (4.4) [82]	31.0 (10.8) [14]
Difference	1.2 (0.51; -2.4 to 4.8)	-16.9 (0.001; -23.5 to -10.4)**	-7.8 (0.23; -20.5 to 4.9)	-36.2 (0.06; -73.4 to 1.1)
Contact with friends				
FOLFOX	9.6 (1.7) [159]	11.4 (1.8) [135]	13.2 (3.2) [73]	15.4 (8.1) [13]
SIRT+FOLFOX	15.7 (2.1) [161]	19.2 (2.5) [134]	16.7 (2.9) [82]	14.3 (7.6) [14]
Difference	6.1 (0.028; 0.7 to 11.5)*	5.2 (0.080; -0.7 to 11.1)	5.2 (0.25; -3.8 to 14.2)	0.01 (0.10; -26.2 to 26.2)
Talking about feelings				
FOLFOX	11.1 (1.5) [159]	9.1 (1.8) [135]	11.4 (2.5) [73]	5.1 (3.5) [13]
SIRT+FOLFOX	10.4 (1.7) [161]	10.3 (1.9) [136]	11.8 (2.3) [82]	19.1 (8.4) [14]
Difference	-0.8 (0.74; -5.3 to 3.8)	0.5 (0.83; -4.4 to 5.5)	2.2 (0.54; -5.0 to 9.5)	19.1 (0.036; 1.3 to 36.9)
[#] ≤3 months time-point includes cycle 4. * p<0.05 ** p<0.01				
+ The table reports symptoms scales registering at least one statistically significant difference. The remaining scales are shown in the supplementary table 11.				

Figures

Appendix figure 1. Consort diagram: number of patients' response rate for EORTC QLQ-C30, EORTC QLQ-LMC21 and EQ-5D-3L by time-points and trial.



Appendix figure 1 legend

MDT: multidisciplinary team.

FOLFOX: leucovorin-oxaliplatin-fluorouracil chemotherapy.

SIRT: selective internal radiotherapy.

Patients responding: valid cases (i.e. non-missing).

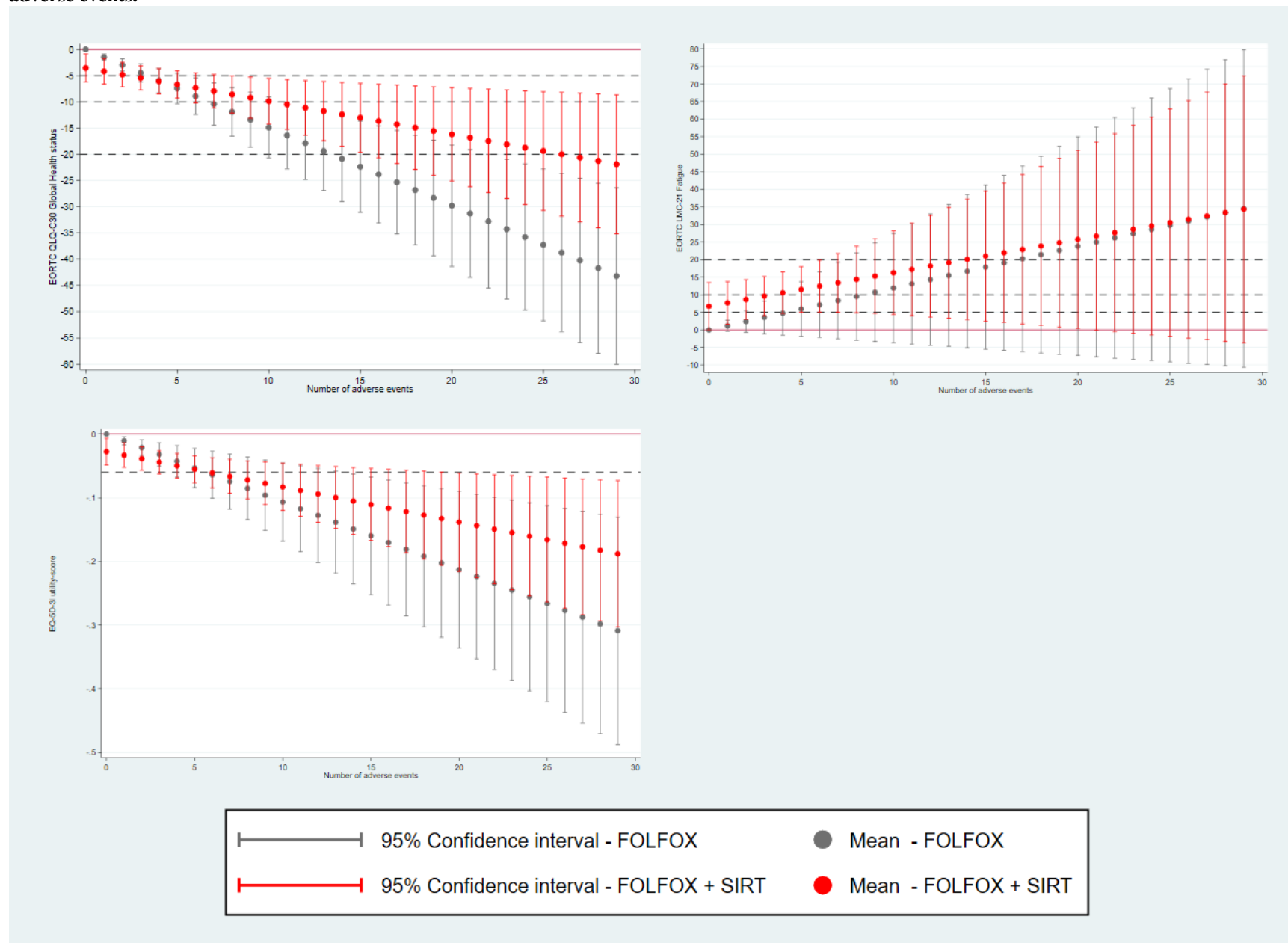
Number available: Patients alive at the time-point.

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of Life cancer generic questionnaire.

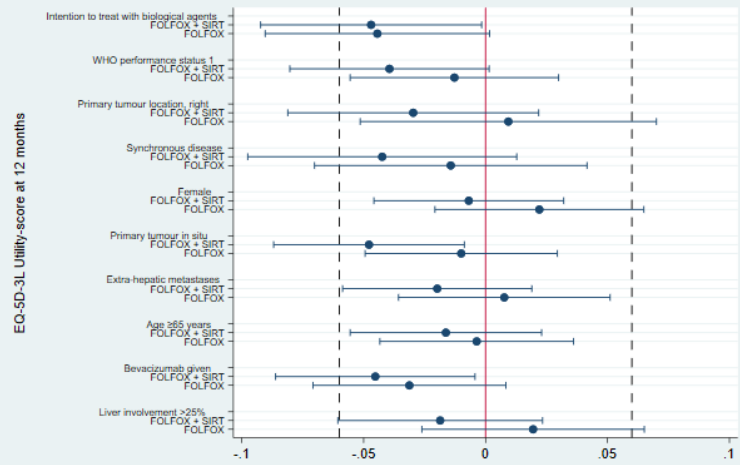
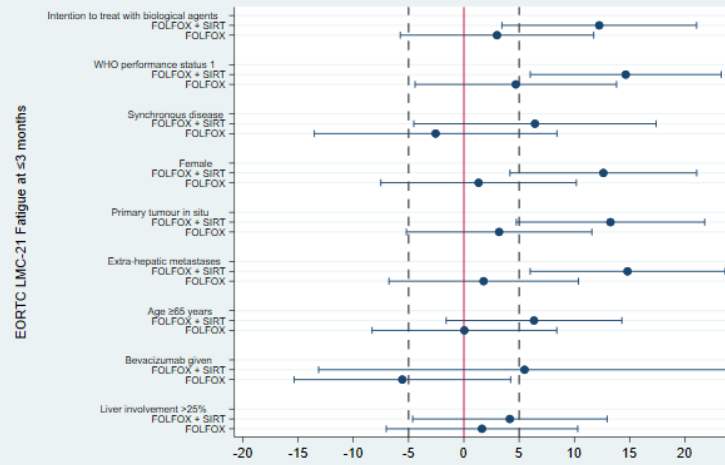
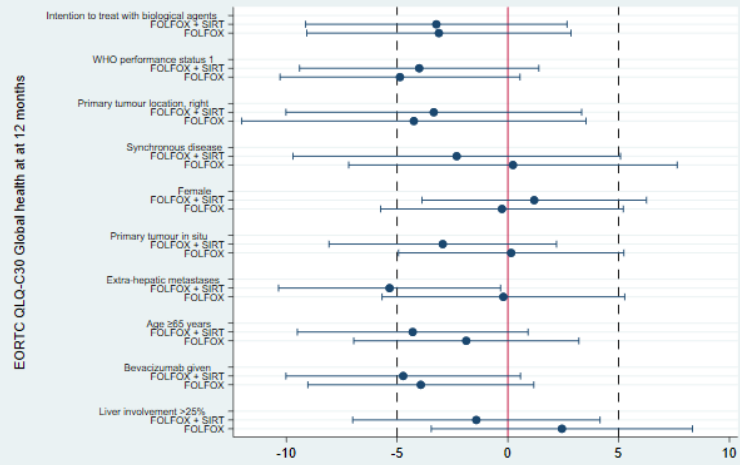
EORTC QLQ-LMC21: European Organisation for Research and Treatment of Cancer colorectal liver cancer quality of life module.

EQ-5D-3L: EQ-5D generic Health Related Quality of Life questionnaire (three-level version).

Appendix figure 2. EORTC QLQ-C30 global health, EQ-5D-3L utility-score and EORTC QLQ-LMC21 fatigue at ≤ 3 months, 6 months and 12 months by trial arm and number of adverse events.

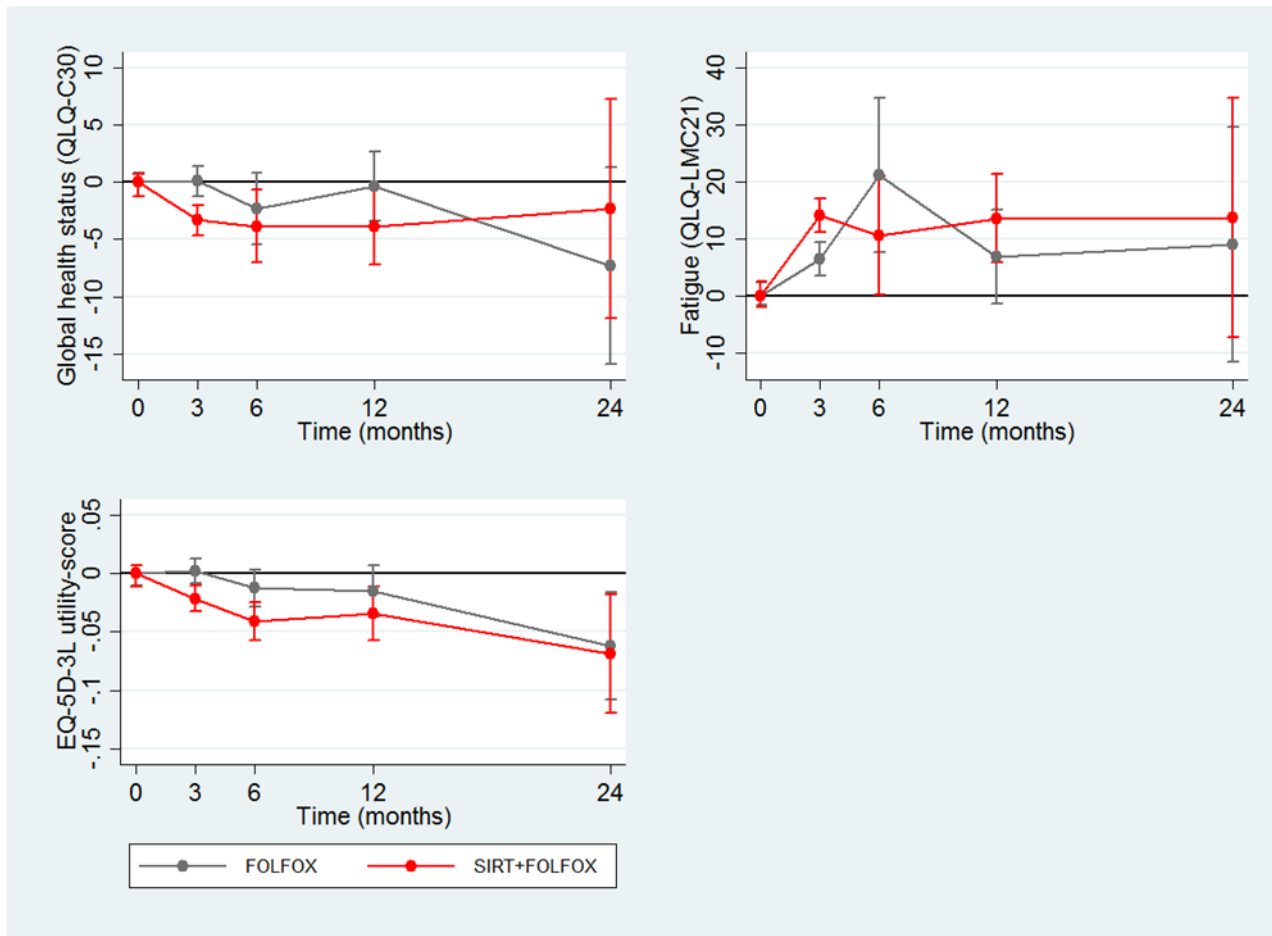


Appendix figure 3. EORTC QLQ-C30 global health at 12 months, EQ-5D-3L utility-score at 12 months and EORTC QLQ-LMC21 fatigue at ≤3 months by subgroups.



— 95% Confidence interval ● Mean

Appendix figure 4. Mean difference (95% confidence interval error bars) in EQ-5D-3L utility, global health status (EORTC QLQ-C30) and fatigue (EORTC QLQ-LMC21) score from baseline adjusted for the respective baseline scores, cognitive functioning (on in EQ-5D utility-scores and global health status) and ‘contact with friends’ (only in fatigue symptom scale (EORTC QLQ-LMC21)).



Appendix Figure 4 legend:

Global health status (QLQ-C30): EORTC QLQ-C30 global health status scale.

Fatigue (QLQ-LMC21): EORTC QLQ-LMC21 fatigue symptom scale.

EQ-5D-3L utility-score: EQ-5D-3L utility-score calculated using US EQ-5D tariff.

SIRT: selective internal radiotherapy.

FOLFOX: leucovorin-oxaliplatin-fluorouracil chemotherapy.

