ASX/MEDIA RELEASE **6th June 2017**

Combined FOXFIRE Study Data Presented at ASCO Annual Meeting

Sydney, Australia; 6th June 2017 – Sirtex Medical Limited (ASX:SRX) announces the oral abstract of the combined SIRFLOX/FOXFIRE/FOXFIRE Global studies comparing SIR-Spheres® Y-90 resin microspheres plus standard of care systemic chemotherapy versus systemic chemotherapy alone in non-resectable, first-line metastatic colorectal cancer (mCRC) patients, was presented at the gastrointestinal (colorectal) cancer session at the American Society of Clinical Oncology (ASCO) Annual Meeting today[1].

Dr David N. Cade, Chief Medical Officer of Sirtex Medical said "The presentation of the combined FOXFIRE analysis by Professor Sharma at ASCO now confirms that while SIR-Spheres plus systemic chemotherapy did not meet the primary endpoint of an overall survival advantage over chemotherapy alone, a statistically significant benefit was observed in objective response rates and liver-specific progression. Also, the initial data presented from the SIRFLOX and FOXFIRE Global analyses, did confirm a statistically significant reduction in the risk of death for those patients who received SIR-Spheres plus chemotherapy with a right-sided primary colon cancer. Across both studies, the incidence of a right-sided primary colon cancer was 24%. We eagerly await further data presentation on all three studies and clinician feedback on this interesting finding at future medical conferences."

Professor Ricky Sharma, the Principal Investigator of the FOXFIRE study and Chair of Radiation Oncology at University College London said "Although overall survival is the gold standard for randomised phase III clinical trials, it is often difficult to see statistically significant results since patients have multiple lines of therapy after they receive the new treatment and there is no way of controlling cross-over to the new treatment after the patient has completed protocol therapy. Even in a very large phase III study, it is difficult to control for all biological factors since researchers are still discovering previously unknown factors that drive cancer, for example recent studies that show that right-sided colorectal cancer is a different disease from left-sided colorectal cancer whereas we classified them as a single disease when we planned the FOXFIRE and SIRFLOX studies over a decade ago."

Dr Andrew Kennedy, Physician in Chief, Radiation Oncology and Director, Radiation Oncology Research at the Sarah Cannon Research Institute commented "The results in first line patients reported in this abstract do not alter the established benefit of radioembolisation for patients beyond first line therapy. It is very encouraging that a potential benefit in survival for right-sided colon cancer patients receiving chemotherapy plus hepatic radiation is suggested by these data as it is already established that many patients derive benefit from liver-directed radiotherapy to treat metastases as proven with level I and II medical evidence of efficacy and safety."

The combined SIRFLOX/FOXFIRE/FOXFIRE Global study was the largest ever interventional oncology study with a liver-directed therapy, namely SIR-Spheres microspheres, to examine OS in the first-line mCRC setting with standard of care systemic chemotherapy with or without biologic therapy. A total of 1,103 patients were enrolled across all three studies.

Further data on the impact of primary tumour location on overall survival will be presented at the 19th European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer (WCGIC) in Barcelona, Spain from 28th June to 1st July. Unless embargoed by the scientific committee of the meeting, the abstract release date will be 4pm AEST on Wednesday 28th June.

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Professor Sharma's ASCO presentation is attached.

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About SIRFLOX/FOXFIRE/FOXFIRE Global

The aim of the SIRFLOX/FOXFIRE/FOXFIRE Global studies is to prospectively combine clinical data from the three similarly designed individual trials to allow adequate power to evaluate the impact of chemotherapy with Selective Internal Radiation Therapy (SIRT) using SIR-Spheres® Y-90 resin microspheres on overall survival in first-line metastatic colorectal cancer, in over 1,100 patients. Efficacy and safety estimates derived using individual participant data (IPD) from SIRFLOX, FOXFIRE, and FOXFIRE Global will be pooled using 2-stage prospective meta-analysis. Secondary outcome measures include progression-free survival (PFS), liver-specific PFS, health-related quality of life, response rate, resection rate, and adverse event profile. The potential treatment benefit in those patients who present with disease confined to the liver will be also be investigated.

About Colorectal Cancer

Colorectal cancer (CRC or bowel cancer) occurs when cancerous cells develop in the patient's colon or rectum. CRC is the third most common form of cancer worldwide, making up about 10% of all cancers. In 2012, an estimated 1.4 million new cases were diagnosed globally and 694,000 cancer deaths were attributed to CRC.[2]

About SIR-Spheres® Y-90 Resin Microspheres

SIR-Spheres Y-90 resin microspheres are a medical device used in interventional oncology and delivered via Selective Internal Radiation Therapy (SIRT), also known as radioembolisation, directly to liver tumours. SIR-Spheres Y-90 resin microspheres are approved for supply in key markets, such as the United States, European Union and Australia.

About Sirtex Medical

Sirtex Medical Limited (ASX:SRX) is an Australian-based global healthcare business working to improve outcomes in people with cancer. Our current lead product is a targeted radiation therapy for liver cancer. Over 73,000 doses have been supplied to treat patients with liver cancer at 1,060 medical centres in over 40 countries. For more information please visit www.sirtex.com.

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[1] Sharma RA et al. Overall survival analysis of the FOXFIRE prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer. *2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.

[2] World Cancer Report, 2014; Geneva, WHO: 2014; 1.1.

Sirtex Medical Limited

SIRFLOX/FOXFIRE/FOXFIRE Global

Combined Clinical Study

ASCO Oral Abstract Presentation

6 June 2017

Overall survival analysis of the FOXFIRE prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer

Professor Ricky Sharma

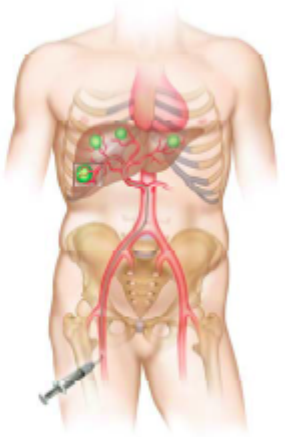
Chair of Radiation Oncology, University College London, United Kingdom

on behalf of the FOXFIRE, SIRFLOX and FOXFIRE-Global Investigators

Sharma RA *et al. Presented at 2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.

Selective Internal Radiation Therapy (SIRT)

- SIRT involves injection of millions of yttrium-90 labelled resin microspheres directly in to the blood supply of primary or secondary liver tumors
  - A single large radiation dose
  - FDA approved in 2002 for unresectable liver tumors
  - Supported by NCCN Guidelines (Category 2A) and ESMO Guidelines (II,B)
  - Commissioned in several countries for mCRC patients refractory to chemotherapy



Hendlisz A et al. *J Clin Oncol* 28: 3687-3694, 2010.
NCCN Guidelines: Rectal Cancer v1.2017.

NCCN Guidelines: Colon Cancer v1.2017
Van Cutsem E et al. *Ann Oncol* 27: 1386-1422, 2016

Sharma RA *et al. Presented at 2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.

Liver metastases from colorectal cancer

- >1 million diagnoses of CRC every year
- 40-50% of patients develop liver metastases

- SIRT plus FOLFOX has an acceptable safety profile
- SIRT plus FOLFOX as first-line therapy improves local control of liver metastases

Sharma RA et al. *J Clin Oncol* 25: 1099-1106, 2007 Van Hazel G et al. *J Clin Oncol* 34: 1723-1731, 2016

Sharma RA *et al. Presented at 2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.

SIRTeX

Three prospective randomized studies planned for combined analysis of overall survival

Study name	Geographic region	Recruitment completed	Patients recruited
SIRFLOX	ANZ, EME, USA	2013	530
FOXFIRE	UK	2014	364
FOXFIRE Global	ANZ, AP, EME, USA	2014	209
		Total recruitment	1,103

Virdee PS et al. *JMIR Res Protocol* 28: e43, 2017

Sharma RA *et al. Presented at 2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.

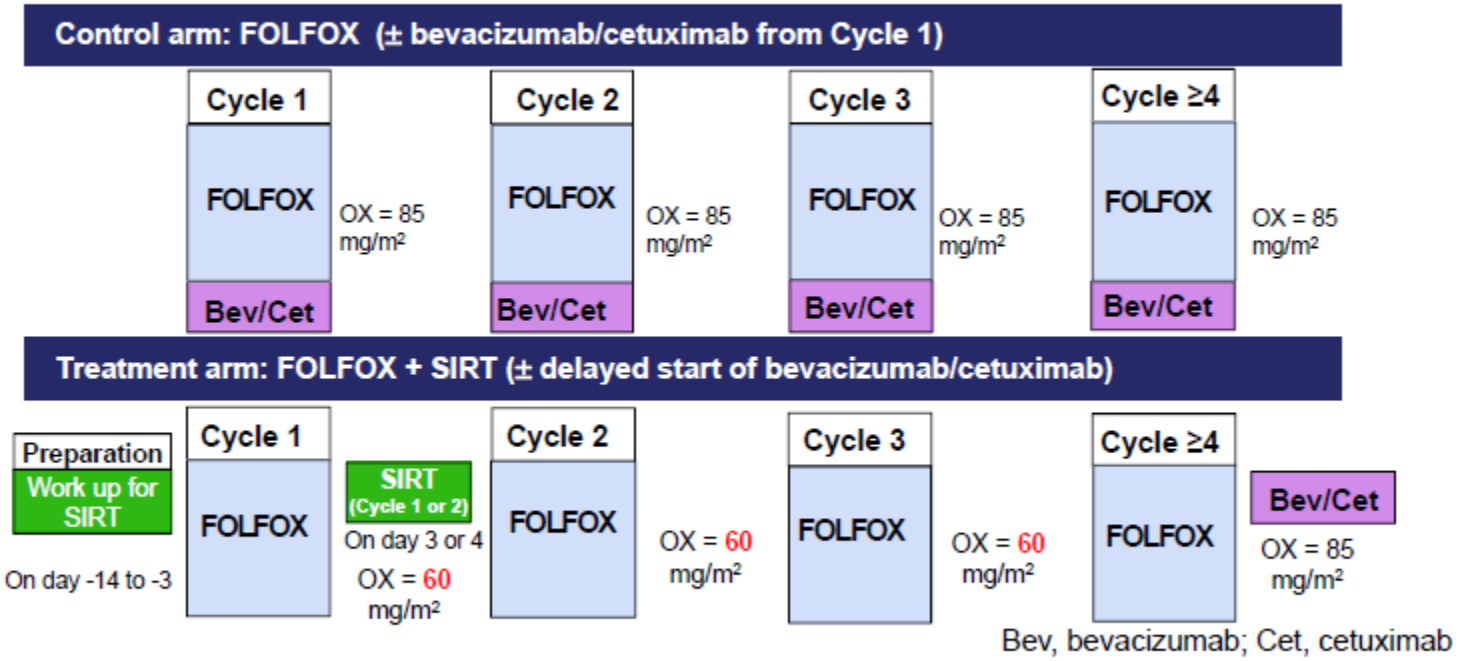
SIRTeX

Key eligibility criteria

- Adenocarcinoma of the colon or rectum
- Liver metastases not surgically resectable or ablatable
- Eligible for systemic chemotherapy as first-line treatment for metastatic CRC
- WHO Performance Status 0 – 1
- Limited extra-hepatic metastases
- Permitted to have primary tumor in situ
- No evidence of ascites, cirrhosis, portal hypertension

Sharma RA *et al. Presented at 2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.

Treatment schedule



Bev, bevacizumab; Cet, cetuximab

Sharma RA *et al. Presented at 2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.

Study endpoints

Primary endpoint

- Overall survival *(time from randomization to all-cause death)*

Secondary endpoints

- PFS at any site (independent central imaging review)
- Liver-specific PFS (independent central imaging review)
- Objective tumor response rate at any site (RECIST v1.0)
- Hepatic resection rate
- Toxicity & safety (NCI CTCAE v3.0)
- Health-related quality of life

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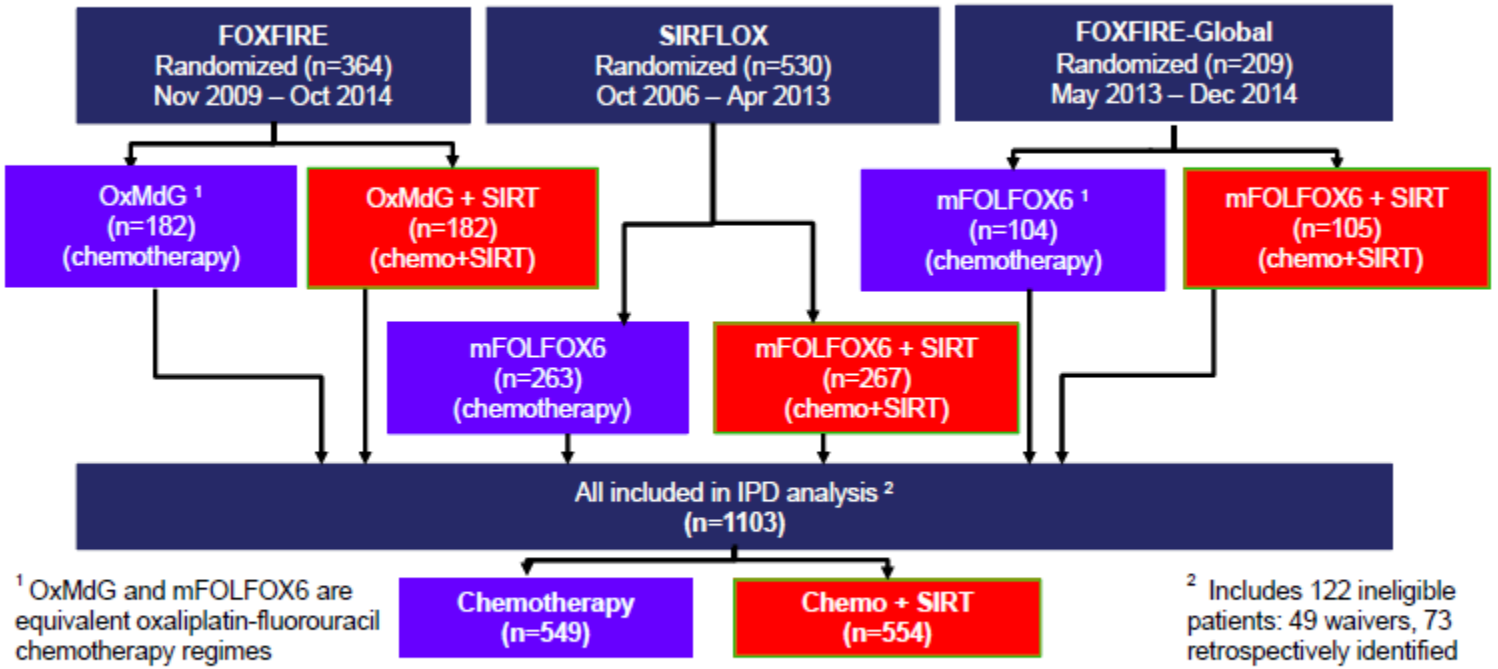
Statistics

- Specified in protocol:
  - Hazard Ratio 0.8, 80% power, 2-sided 5% alpha
  - 710 OS events to detect increase in median OS from 19.7 months (control arm) to 24.6 months (experimental arm)
- Statistical methods (all Intention-to-Treat, except for safety):
  - OS and PFS analyzed by Cox regression and 2-stage meta-analysis using individual patient data (IPD)
  - Liver-specific PFS analyzed by Competing Risk regression and 1-stage meta-analysis to account for competing risks: First site of progression not involving the liver; death without radiological progression documented

Virdee PS et al. *JMIR Res Protocol* 28: e43, 2017 Fine J & Gray RJ. *Am Stat Assoc* 94: 496-508, 1999

Sharma RA *et al. Presented at 2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.

Study flow chart



[1] OxMdG and mFOLFOX6 are equivalent oxaliplatin-fluorouracil chemotherapy regimes

[2] Includes 122 ineligible patients: 49 waivers, 73 retrospectively identified

Sharma RA *et al. Presented at 2017 ASCO Annual Meeting; J Clin Oncol* 2017; **35** (Suppl): Abs 3507.

Patient characteristics

Characteristic	Chemo (n = 549)	Chemo+SIRT (n = 554)
Median age in years (range)	63 (23 – 89)	63 (28 – 90)
Male	65.8%	65.5%
WHO performance status 0	63.2%	63.9%
1	36.4%	35.7%
Extra-hepatic metastases	34.8%	35.9%
>25% liver involvement	30.6%	32.3%
Intent to treat with biologicals	54.5%	53.8%
Synchronous presentation with liver mets	86.5%	87.2%
Primary tumor in situ	55.0%	50.2%

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SIRTeX

Treatment characteristics

Characteristic	Chemo (n = 549)	Chemo+SIRT (n = 554)
Did not receive SIRT: Total Reasons in FOXFIRE: • Clinical deterioration • Aberrant vascular anatomy/lung shunting • Withdrew consent to SIRT	-	**8.5%** - - -	 (33.3%) (40.0%) (20.0%)
Cycles of oxaliplatin received at full protocol dose	49.1%	43.8%
Median (IQR) number of cycles of FOLFOX chemotherapy	12 (7-13)	12 (7-15)
Patients receiving bevacizumab	**46.6%**	**35.6%**
Patients receiving cetuximab	1.6%	0.7%

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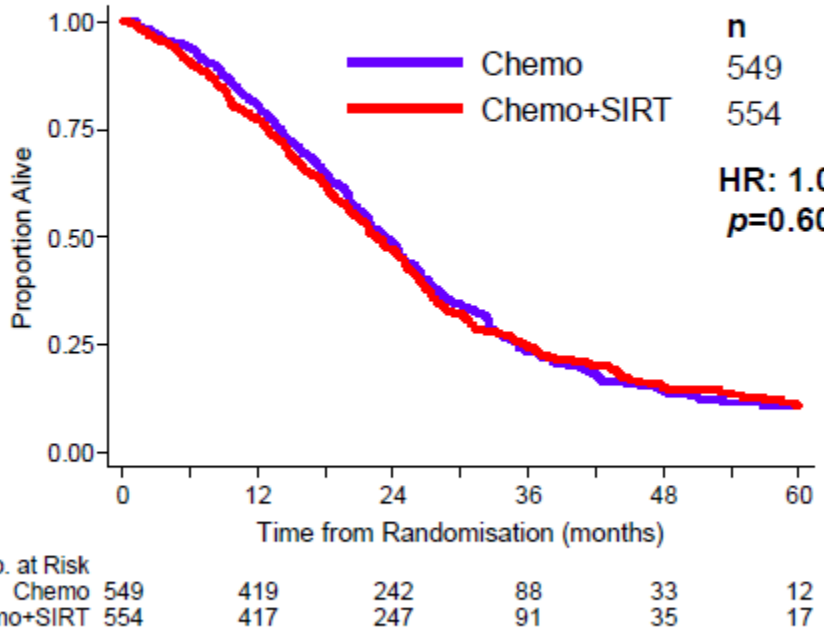
Overall survival (n=1103)



	n	Events	Median
Chemo	549	411	23.3 months
Chemo+SIRT	554	433	22.6 months

HR: 1.04 (95% CI: 0.90–1.19)
***p*=0.609**

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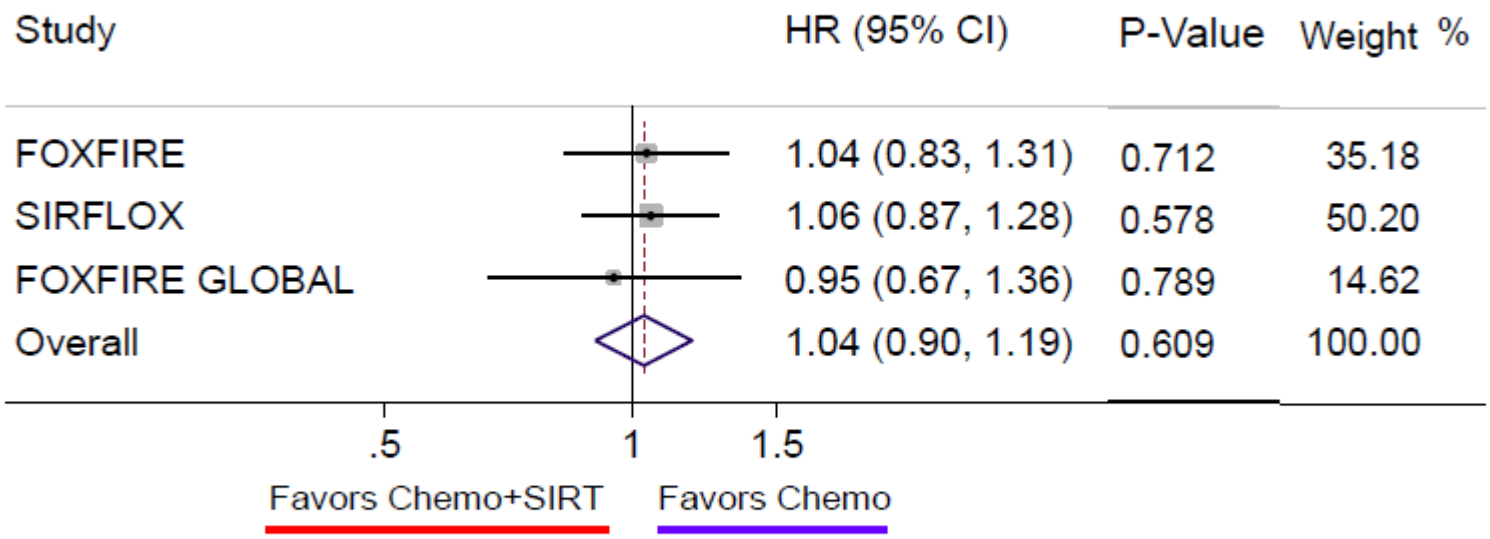
Overall survival by study



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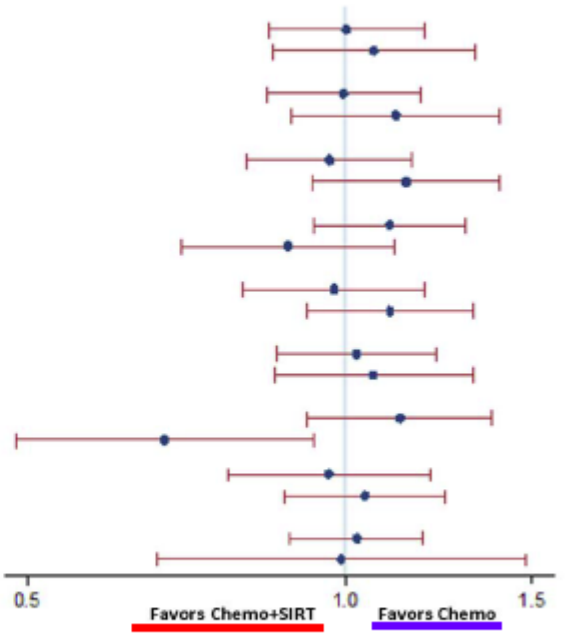
Treatment effect on OS within subgroups

Subgroup	n	Events	HR (95% CI)
Liver-only	713	525	1.00 (0.85 - 1.19)
Liver-dominant	390	319	1.07 (0.85 - 1.33)
Liver involvement ≤ 25%	754	545	1.00 (0.84 - 1.18)
Liver involvement > 25%	347	297	1.12 (0.89 - 1.41)
Age < 65 years	623	470	0.97 (0.81 - 1.16)
Age ≥ 65 years	479	374	1.14 (0.93 - 1.41)
Male	724	556	1.11 (0.94 - 1.31)
Female	378	288	0.88 (0.70 - 1.12)
No primary tumor in situ	521	390	0.98 (0.80 - 1.19)
Primary tumor in situ	580	453	1.10 (0.92 - 1.33)
WHO performance status 0	701	514	1.03 (0.86 - 1.22)
WHO performance status 1	398	328	1.07 (0.86 - 1.32)
Primary tumor location - left	540	389	1.14 (0.93 - 1.39)
Primary tumor location - right	179	147	0.67 (0.48 - 0.92)
Bevacizumab received	465	336	0.97 (0.78 - 1.20)
Bevacizumab not received	638	508	1.04 (0.87 - 1.24)
Synchronous disease	958	739	1.02 (0.89 - 1.18)
Metachronous disease	139	101	0.99 (0.66 - 1.48)



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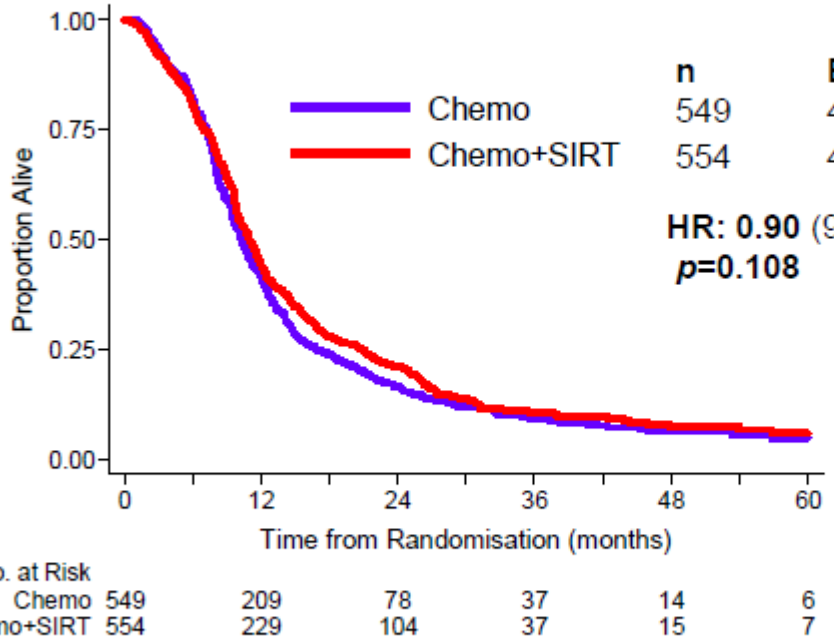
Progression-free survival



	n	Events	Median
Chemo	549	467	10.3 months
Chemo+SIRT	554	474	11.0 months

HR: 0.90 (95% CI: 0.79–1.02)
***p*=0.108**

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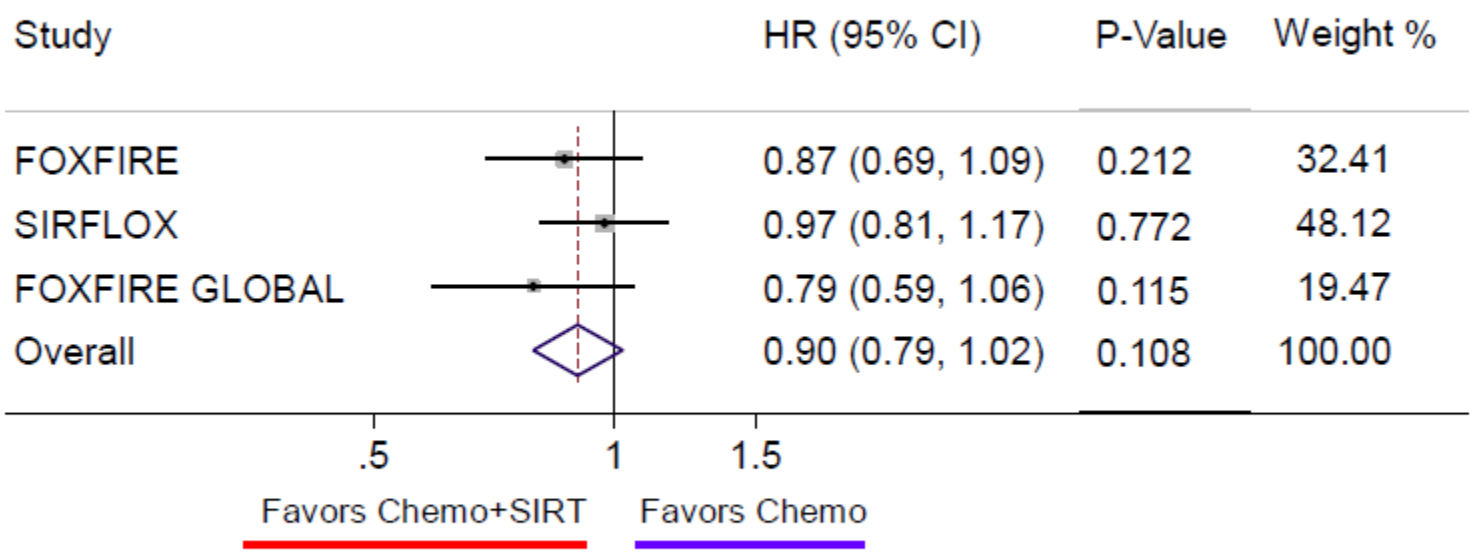
Progression-free survival by study



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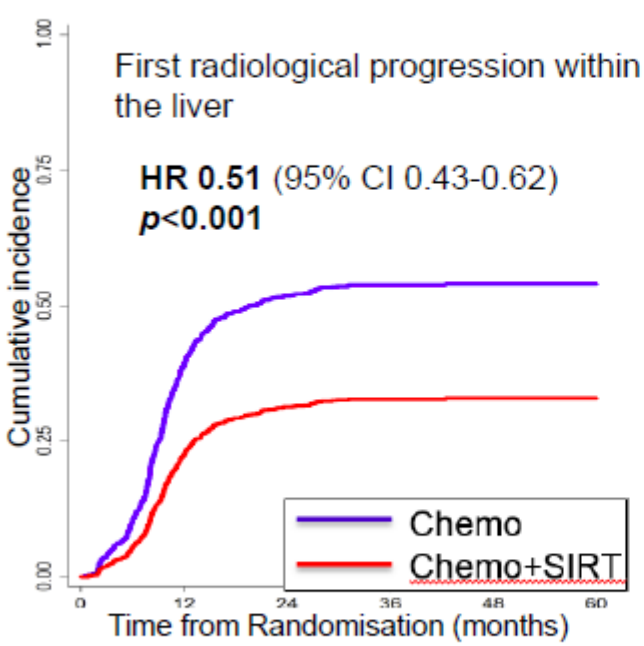
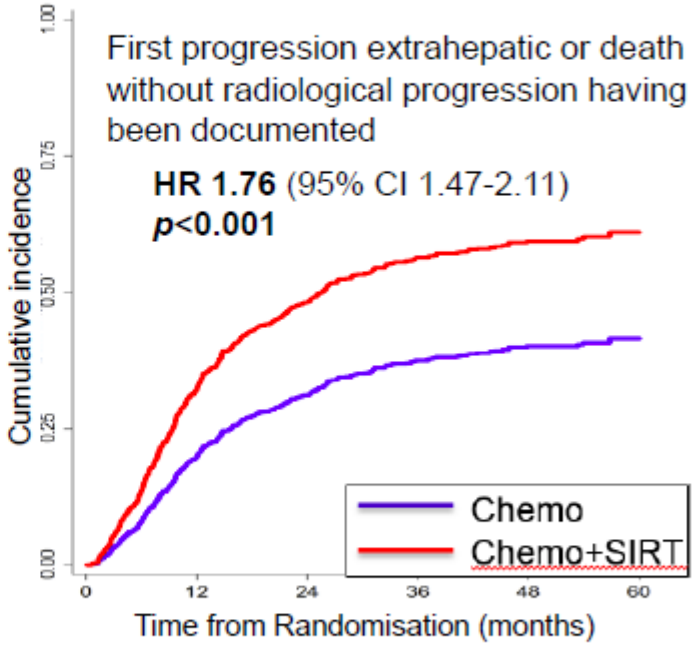
Liver-specific Progression-Free Survival





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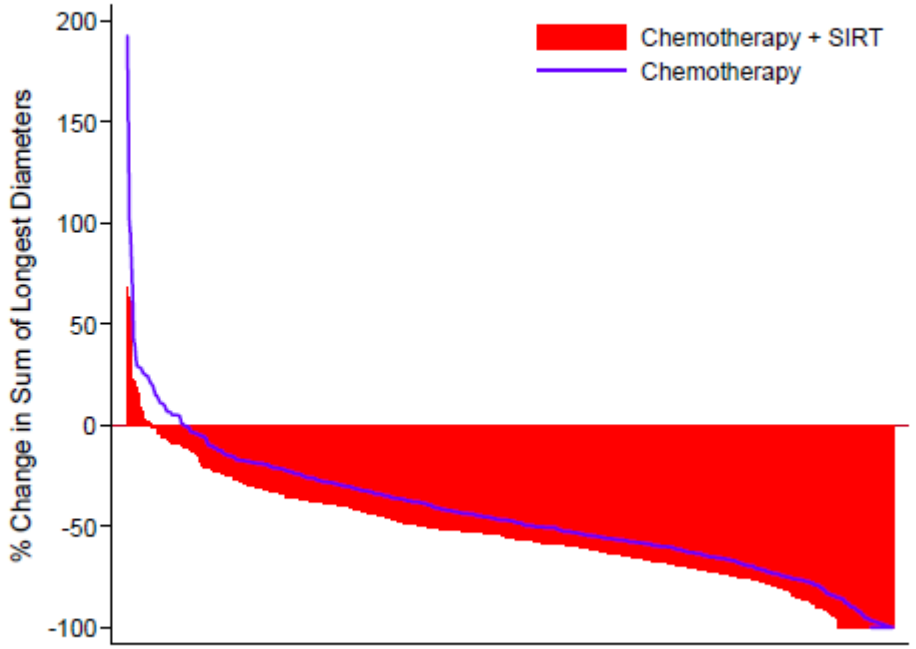
Waterfall plot of best radiological response



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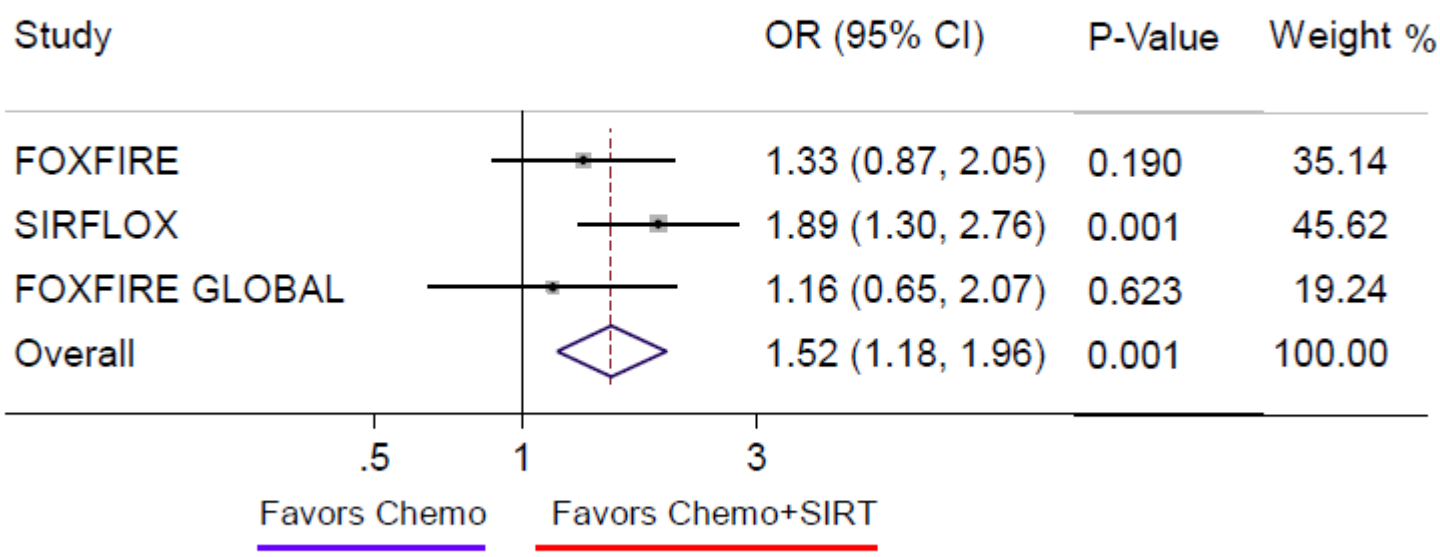
Best radiological response by study



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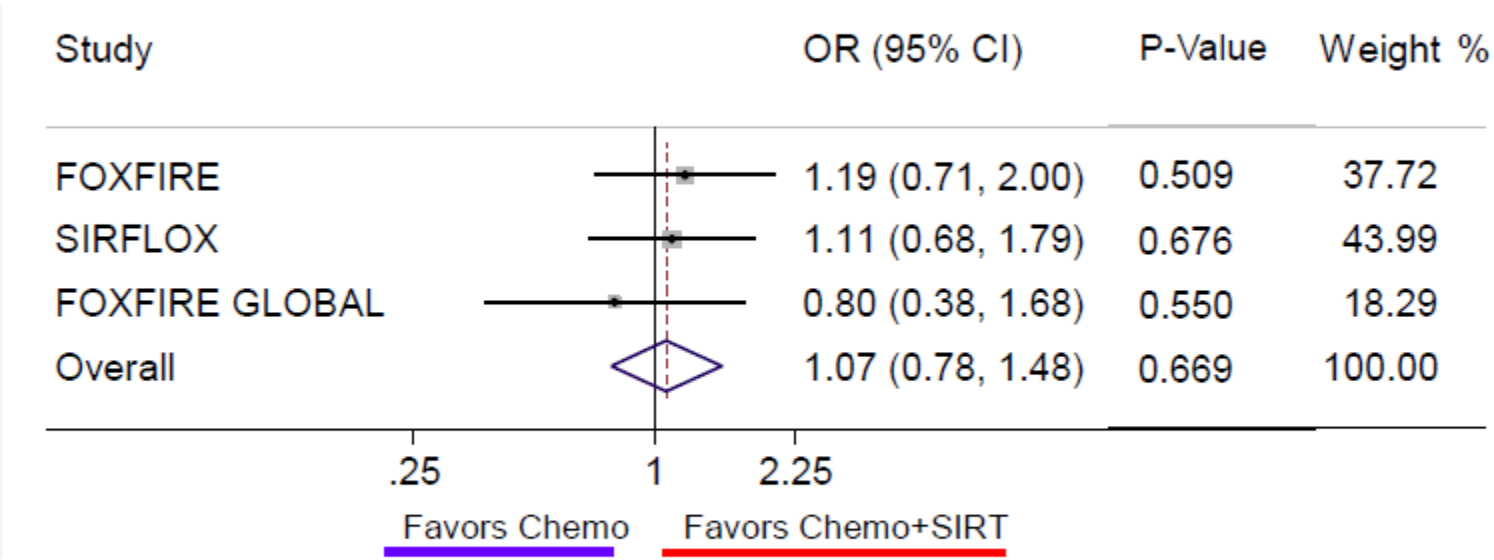
Resection rate



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Selected all-cause adverse events (safety population)

Adverse events	Chemo (n = 571)	Chemo+SIRT (n = 507)
All patients any grade	99.6%	99.8%
All patients grade ≥3	**66.5%**	**74.0%**
All patients grade 5	1.9%	2.0%
Hematological (grade ≥3)		
Neutropenia	**24.2%**	**36.7%**
Febrile neutropenia	**2.8%**	**6.5%**
Thrombocytopenia	**1.2%**	**7.7%**
Leukopenia	**2.3%**	**5.9%**
Non-hematological (grade ≥3)		
Fatigue	**4.9%**	**8.5%**
Abdominal pain	**2.3%**	**6.1%**
Diarrhea	6.5%	6.7%
Peripheral neuropathy	**5.8%**	**3.6%**
Radiation hepatitis	-	0.8%

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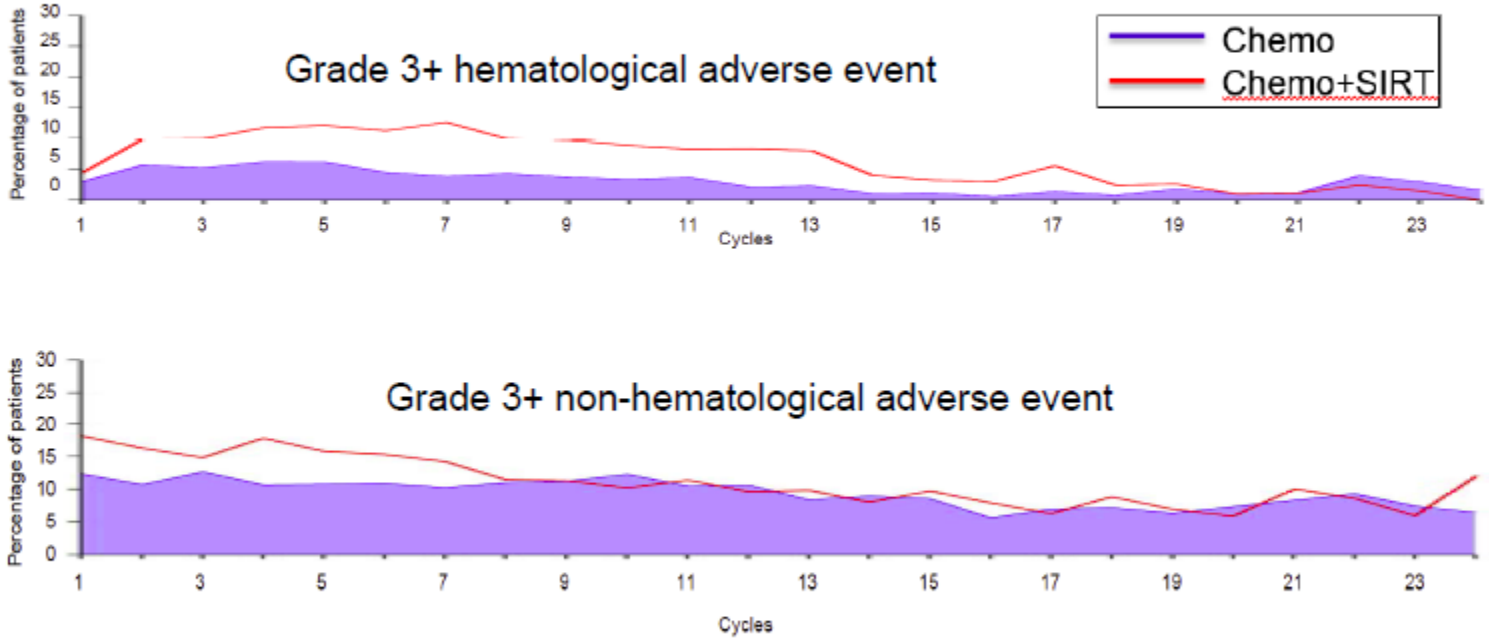
Grade 3+ adverse events per cycle of chemotherapy



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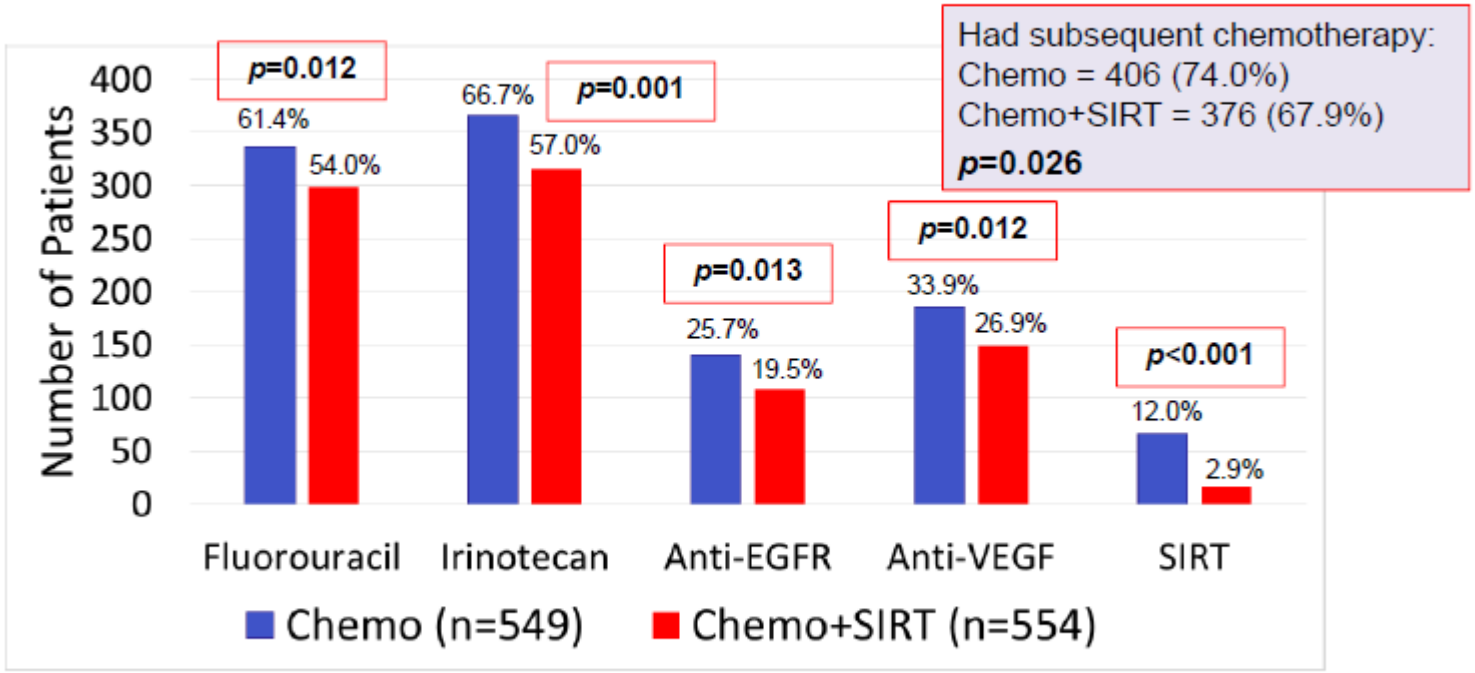
Post-protocol systemic treatment or SIRT



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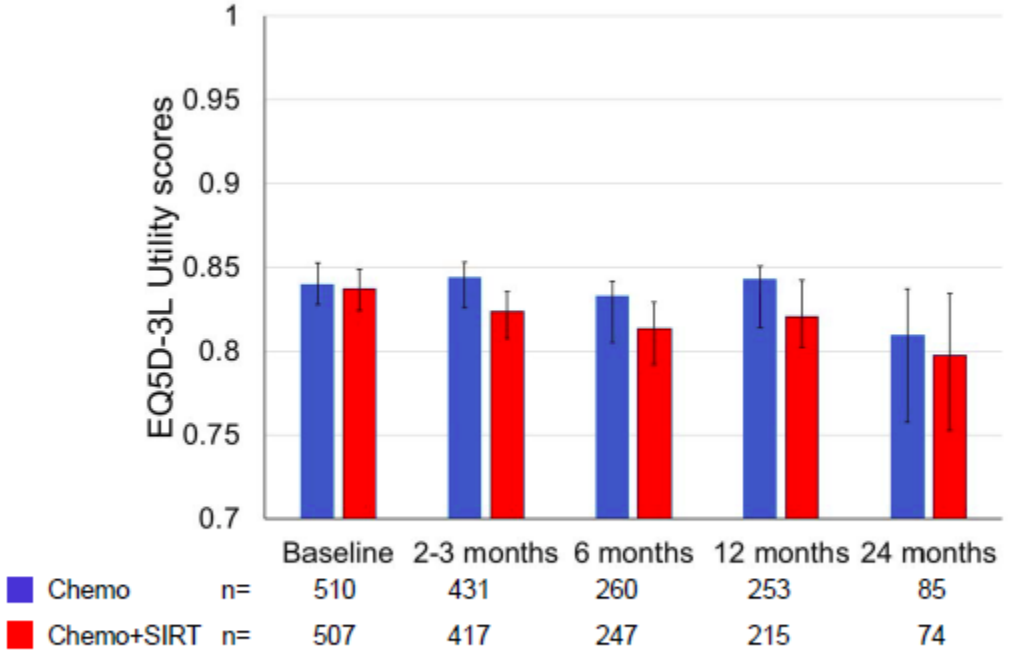
Health Related Quality of Life: EQ5D (US tariff)



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Conclusions

- Addition of SIRT to FOLFOX first-line chemotherapy in patients with liver-only or liver-dominant mCRC did not improve OS or PFS
- Significant benefit in liver-specific PFS and radiological response rate was achieved by the addition of SIRT
- Toxicity was higher in FOLFOX+SIRT group, particularly hematological
- FOLFOX+SIRT patients were less likely to receive bevacizumab and to receive subsequent post-protocol systemic therapy
- Liver metastases from right-sided primary merit evaluation in other datasets as a subgroup who may derive additional clinical benefit from SIRT

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Acknowledgements

- Trial participants and their families
- Investigators
- NCRI Colorectal Clinical Study Group
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- Oxford Clinical Trials Research Unit, University of Oxford

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Thank you