ASX/MEDIA RELEASE **3 JULY 2017**

Right-Side Survival Data from SIRFLOX/FOXFIRE Global Studies Presented at WCGIC

Sydney, Australia

Sirtex Medical Limited (ASX:SRX) today announces the presentation of the SIRFLOX/FOXFIRE Global right-side survival data in metastatic colorectal cancer (mCRC) at the 19th European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer (WCGIC) in Barcelona, Spain.

Professor Guy van Hazel, Clinical Professor of Medicine at the University of Western Australia and Co-Principal Investigator on the SIRFLOX study presented the study data. The combined SIRFLOX and FOXFIRE Global studies (n=530 and n=209, respectively) showed that for patients with a right-sided primary tumour, median Overall Survival (OS) was significantly improved with the addition of SIR-Spheres® Y-90 resin microspheres to standard chemotherapy versus chemotherapy alone [22.0 *vs*. 17.1 months, respectively; p=0.007; Hazard Ratio (HR): 0.64 (95% CI: 0.46-0.89)], but not for patients with a left-sided primary tumour [24.6 *vs*. 26.6 months; p=0.279; HR: 1.12 (95% CI: 0.92-1.36)][1].

Importantly, Professor van Hazel also presented the baseline characteristics of the combined patient data set between the two arms of the study for both left-sided and right-sided patients. There was no statistically significant difference in the baseline characteristics of patients who received SIR-Spheres microspheres plus chemotherapy versus chemotherapy alone. Patients with a right-sided primary tumour were older (mean: 64.4 *vs.* 61.6 years) and a higher proportion were female (42.5% *vs.* 32.0%), compared to those with a left-sided primary tumour.

Mr Andrew McLean, Chief Executive Officer of Sirtex Medical said "There is now solid scientific evidence to support the observation that for patients whose primary cancer is located on the right-side of the bowel, their prognosis is demonstrably worse, with fewer treatment options and a lower overall life expectancy. The statistically significant 4.9 month OS benefit observed in patients who received SIR-Spheres microspheres is clinically meaningful and subject to further confirmatory analyses, coupled with additional supporting evidence of this OS benefit from the FOXFIRE study. Collectively, this may support consideration of right-sided liver-only or liver-dominant mCRC patients for SIR-Spheres microspheres treatment."

"This striking and essentially unexpected finding may bring new hope to mCRC patients with liver-only or liver-dominant tumours that have spread from the right side of the bowel or colon. These cancers are genetically and structurally different from tumours that start on the left side of the colon. Patients with right-sided primary tumours have a worse prognosis for survival and fewer treatment options. They do not respond well to such biological therapies as cetuximab or panitumumab," said Professor van Hazel.

A copy of Professor van Hazel's presentation on 1 July is attached to this release.

A further two oral abstracts were also presented at the WCGIC meeting relating to the combined SIRFLOX/FOXFIRE/FOXFIRE Global and SARAH clinical studies, the outcomes of which have been previously announced to the ASX.

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Dr Harpreet Wasan - *Overall survival analysis of the FOXFIRE, SIRFLOX and FOXFIRE-Global prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer.*

Dr Mohamed Bouattour - *Efficacy, tolerability and impact on quality of life of selective internal radiation therapy (with yttrium 90 resin microspheres) or sorafenib in patients with locally advanced hepatocellular carcinoma: the SARAH trial.*

https://academic.oup.com/annonc/issue/28/suppl_3

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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 medical device company with global market coverage. Its core revenue producing technology, which has regulatory approvals, is a selective internal radiation therapy (SIRT), with clinically proven applications for liver cancer with over 73,000 doses supplied and administered at 1,060 medical centres in more than 40 countries.

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[1] van Hazel G, Heinemann V, Sharma N *et al.* Impact of primary tumour location on survival in patients with metastatic colorectal cancer receiving selective internal radiation therapy and chemotherapy as first-line therapy. *ESMO 19th World Congress on Gastrointestinal Cancer, Ann Oncol* 2017; Abs. LBA-006.
[2] World Cancer Report, 2014; Geneva, WHO: 2014; 1.1.

Sirtex Medical Limited

Impact of Primary Tumour Location on Survival Benefit - SIRFLOX/FOXFIRE Global Combined Clinical Study

WCGIC Oral Abstract Presentation

1 July 2017

Columbus [Colón] Set Sail from Barcelona

Unexpectedly, he discovered a New World

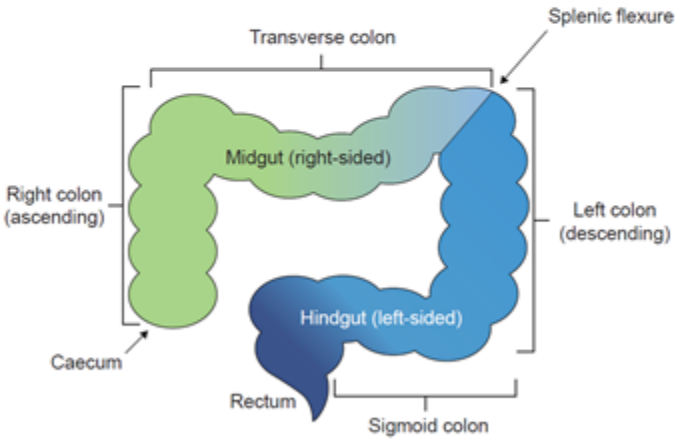
Impact of primary tumour location on survival benefit in patients with metastatic colorectal cancer receiving selective internal radiation therapy and chemotherapy as first-line therapy

Guy van Hazel[1], Volker Heinemann, Navesh Sharma, Julien Taieb, Jens Ricke, Marc Peeters, Michael Findlay, Peter Gibbs, SIRFLOX and FOXFIRE-Global trial investigators

[1]University of Western Australia, Perth, Western Australia, Australia

Background

- The location of the primary tumour in metastatic colorectal cancer (mCRC) is emerging as a major prognostic factor and predictor of response to treatment



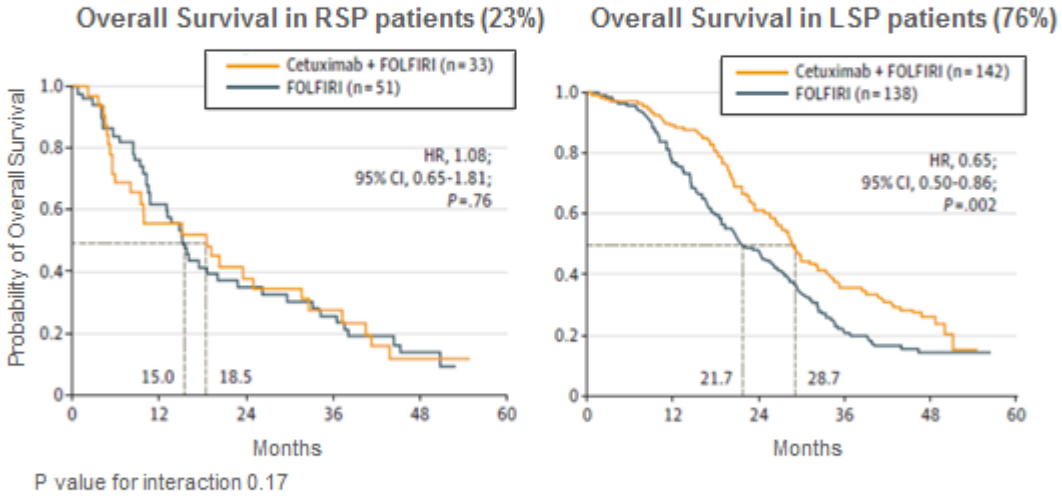
Background

- The location of the primary tumour in metastatic colorectal cancer (mCRC) is emerging as a major prognostic factor and predictor of response to treatment
- Patients with right-sided primary (RSP) tumours have an inferior response to treatment and a worse prognosis compared with those with left-sided primary (LSP) tumours [1]
- Patients with RSP tumours have fewer treatment options [2]

1. Petrelli F *et al. JAMA Oncol.* 2017; 3(2): 211–219.
2. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. Version 1.2017.

Patients with right-sided tumours display worse outcomes

OS in Right versus Left-Sided Primary Tumours: CRYSTAL Study

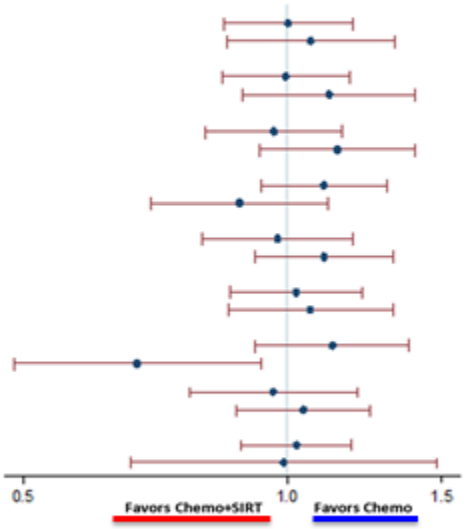


P value for interaction 0.17

Tejpar *et al.* JAMA Oncol 2017; 3: 194–201.

FOXFIRE Combined Analysis: 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)



Impact of the primary tumour location in the SIRFLOX and FOXFIRE Global cohorts

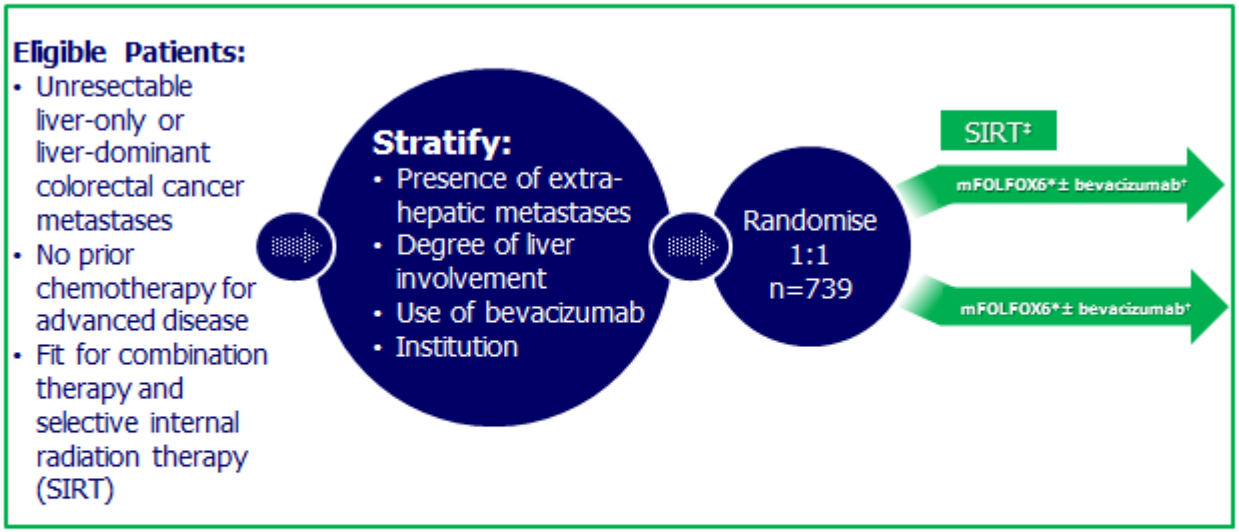
- The impact of primary tumour location on outcomes after SIRT in patients with mCRC has not previously been examined, but a survival benefit in patients with RSP tumours was recently suggested in an exploratory analysis of the FOXFIRE studies [1]
  - Data on primary tumour location was only available for 719 of 1103 patients in the FOXFIRE studies, comprising those in the SIRFLOX and FOXFIRE Global cohorts
- We report in more detail the data from the SIRFLOX and FOXFIRE Global trials cohorts on the impact of the primary tumour location on survival and other outcomes

1. Sharma R *et al. 2017 ASCO Annual Meeting, J Clin Oncol* 2017; 35 (suppl; abstr 3507)

Methods

- SIRFLOX and FOXFIRE Global evaluated the efficacy of combining SIRT using Y-90 resin microspheres with 1st-line FOLFOX-based chemotherapy in patients with liver-only or liver-dominant mCRC
- Primary tumour location was captured prospectively on the case report form in both studies:
  - RSP tumours were defined as any primary tumour proximal to the splenic flexure
  - LSP tumours included any primary tumour at the splenic flexure, the more distal colon or the rectum
- Overall survival (OS) and progression-free survival (PFS) data were examined independently for patients with RSP and LSP
- Tumour response was determined according to RECIST version 1.0
- Analyses were performed on the intention-to-treat population

Methods



‡ Y-90 resin microspheres (SIR-Spheres) were implanted on Days 3–4 of Cycle 1

* oxaliplatin was administered at 60 mg/m^2 for Cycles 1–3 in the FOLFOX + SIRT arm

† at the investigator's discretion, bevacizumab may commence at Cycle 4 in the test arm and at Cycle 1 (or per institutional protocol) in the control arm

1. van Hazel GA *et al. J Clin Oncol* 2016; 34: 1723–1731.

Patients Baseline and Treatment Characteristics

Parameter	RSP tumour			LSP tumour		
	mFOLFOX6 (n=81)	mFOLFOX6+SIRT (n=98)	P-value	mFOLFOX6 (n=276)	mFOLFOX6+SIRT (n=264)	P-value
Age, years mean (SD)	65.1 (10.1)	63.7 (10.7)	NS	61.5 (11.1)	61.6 (10.4)	NS
Sex, n (%) Female Male	39 (48.1) 42 (51.9)	37 (37.8) 61 (61.2)	NS	90 (32.6) 186 (67.4)	83 (31.4) 181 (68.6)	NS
WHO performance status, n (%) 0 1	 47 (58.0) 34 (42.0)	 64 (65.3) 34 (34.7)	NS	 178 (64.5) 97 (35.1)	 168 (63.6) 95 (36.0)	NS
Mean liver tumour burden, % (SD)	18.4 (15.4)	20.2 (19.4)	NS	17.4 (15.8)	18.0 (16.5)	NS
Primary tumour *in situ*, n (%)	37 (45.7)	40 (40.8)	NS	140 (50.7)	125 (47.3)	NS
EHM at randomisation, n (%)	28 (34.6)	41 (41.8)	NS	99 (35.9)	94 (35.6)	NS
Synchronous disease, n (%)	78 (96.3)	88 (89.8)	NS	247 (89.5)	233 (88.3)	NS
ITT with bevacizumab, n (%)	55 (67.2)	60 (61.2)	NS	172 (62.3)	166 (62.9)	NS
Treatment characteristics						
Did not receive SIRT, n (%)	NA	6 (6.1)	NA	NA	27 (10.2)	NA
Received bevacizumab, n (%)	53 (65.4)	53 (54.1)	0.125	170 (61.6)	135 (51.1)	0.014

EHM, extrahepatic metastases; ITT, intention-to-treat; NA, not applicable; SD, standard deviation; WHO, World Health Organization

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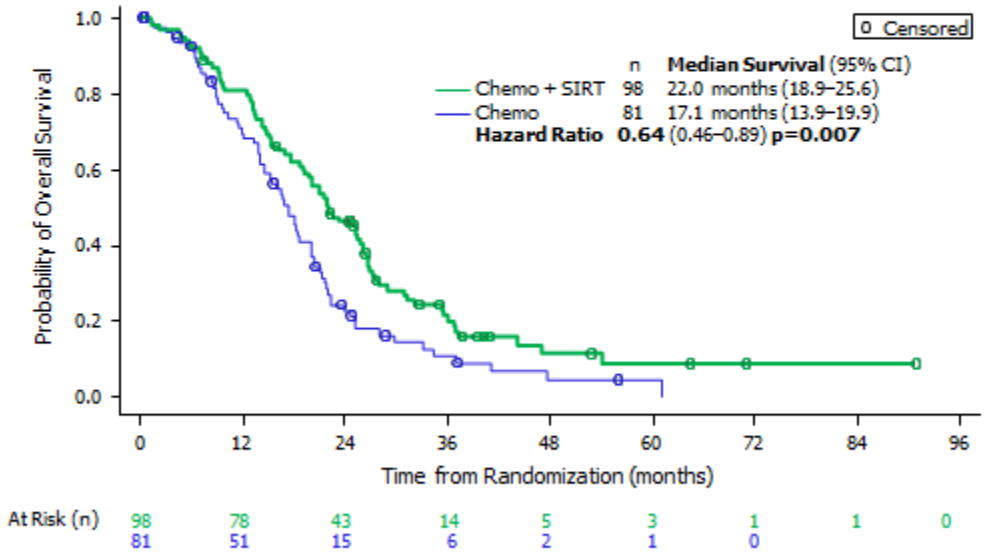
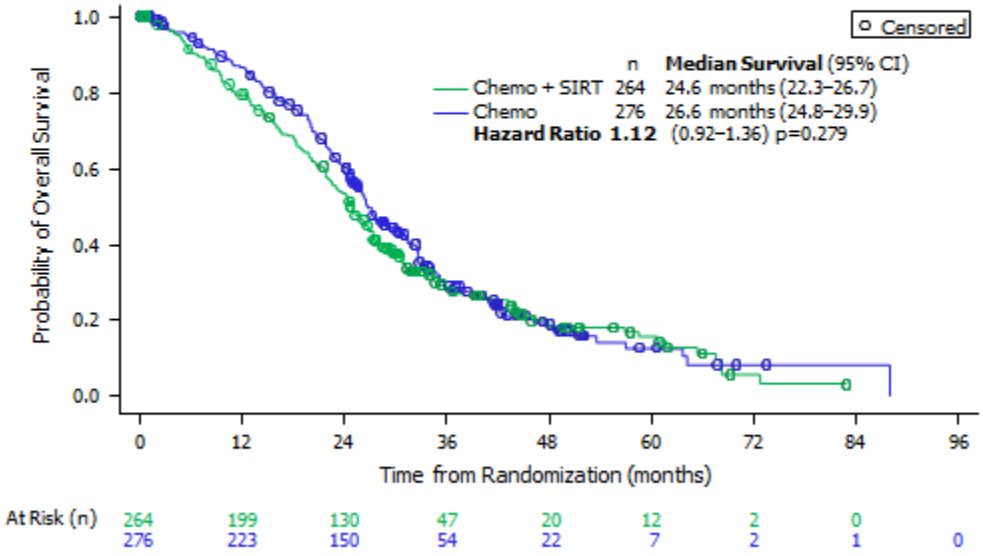
Overall Survival for mCRC Patients with Right-Sided Primary Tumours



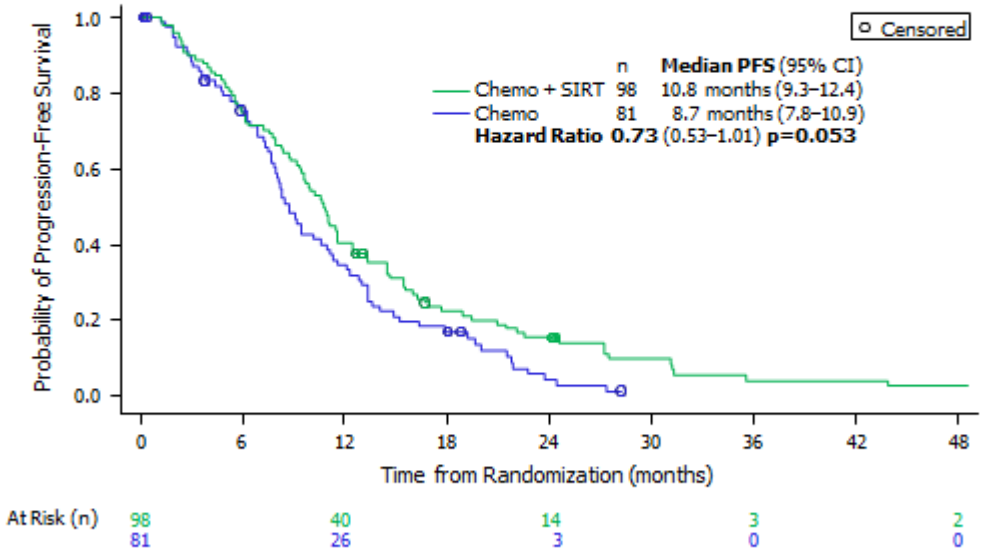
Overall Survival for mCRC Patients with Left-Sided Primary Tumours



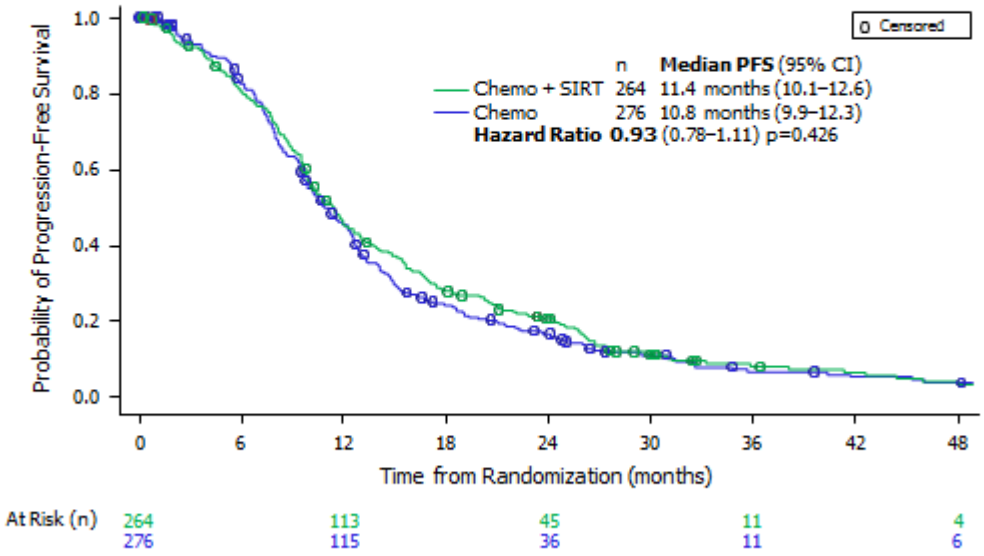
Test for Interaction

- The treatment interaction by location for Overall Survival was highly significant (Chi-square: 9.49; p=0.002; HR: 0.548 [0.37–0.80])

Progression-Free Survival for mCRC Patients with Right-Sided Primary Tumours



Progression-Free Survival for mCRC Patients with Left-Sided Primary Tumours



Best Response

Patients (%) with complete or partial response

	mFOLFOX6	mFOLFOX6+SIRT	P-value
All patients, n (%)	**(n=367)**	**(n=372)**	
Overall response	248 (67.6)	267 (71.8)	0.456
Hepatic response	251 (68.4)	293 (78.8)	0.004
Patients with RSP tumours	**(n=81)**	**(n=98)**	
Overall response	49 (60.5)	70 (71.4)	0.286
Hepatic response	52 (64.2)	76 (77.6)	0.143
Patients with LSP tumours	**(n=276)**	**(n=264)**	
Overall response	193 (69.9)	188 (71.2)	0.859
Hepatic response	193 (69.9)	208 (78.8)	0.013

LSP, left-sided primary; RSP, right-sided primary; SIRT, selective internal radiation therapy

There was a higher hepatic response rate in the whole group in favour of the combination treatment

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Safety and Tolerability

Parameter, n (%)	RSP tumour			LSP tumour		
	mFOLFOX6 (n=84)	mFOLFOX6+SIRT (n=92)	Total (n=176)	mFOLFOX6 (n=289)	mFOLFOX6+SIRT (n=237)	Total (n=526)
All patients, any grade	84 (100%)	92 (100%)	176 (100%)	288 (99.7%)	237 (100%)	525 (99.8%)
Haematological (any grade)						
Neutropenia	28 (33.3%)	45 (48.9%)	73 (41.5%)	105 (36.3%)	115 (48.5%)	220 (41.8%)
Thrombocytopenia	11 (13.1%)	34 (37.0%)	45 (25.6%)	44 (15.2%)	99 (41.8)	143 (27.7%)
Leukopenia	8 (9.5%)	11 (12.0%)	19 (10.8%)	23 (8.0%)	33 (13.9%)	56 (10.6%)
Non-haematological (any grade)						
Fatigue	40 (47.6%)	58 (63.0%)	98 (55.7%)	137 (47.4%)	133 (56.1%)	270 (51.3%)
Abdominal pain	18 (21.4%)	35 (38.0%)	53 (30.1%)	56 (19.4%)	97 (40.9%)	153 (29.1%)
Diarrhoea	43 (51.2%)	41 (44.6%)	84 (47.7%)	143 (49.5%)	96 (40.5%)	239 (45.4%)
Peripheral sensory neuropathy	19 (22.6%)	14 (15.2%)	33 (18.8%)	50 (17.3%)	41 (17.3%)	91 (17.3%)
AEs associated with SIRT (any grade)						
Gastric ulcer	0	7 (7.6%)	7 (4.0%)	1 (0.3%)	8 (3.4%)	9 (1.7%)
Duodenal ulcer	0	1 (1.1%)	1 (0.6%)	1 (0.3%)	6 (2.5%)	7 (1.3%)
Ascites	2 (2.4%)	6 (6.5%)	8 (4.5%)	3 (1.0%)	23 (9.7%)	26 (4.9)
Hepatic failure	0	1 (1.1%)	1 (0.6%)	0	4 (1.7%)	4 (0.8%)
Radiation hepatitis	0	0	0	0	3 (1.3%)	3 (0.6%)

There were no significant differences in the incidence of AEs between the RSP and LSP groups

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Summary and Conclusions

- Treatment with FOLFOX-based chemotherapy + SIRT using Y-90 resin microspheres in mCRC patients with primary tumours originating in the right colon results in a statistically significant ($p<0.007$) and clinically meaningful (HR=0.64) improvement in overall survival compared with chemotherapy alone
- The significant treatment interaction by location provides further evidence that the observed benefit was not a chance finding
- The observed improvement in overall survival represents a potentially significant clinical outcome for a sub-group of mCRC patients relatively resistant to standard-of-care systemic chemotherapy regimens and may support a side-based approach to 1st-line selection for SIRT
- The drivers of the observed side-based differences in treatment impact remain to be elucidated

Thank you

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