QUASAR2

A Multicentre, International, Randomised Phase III trial of Capecitabine +/- Bevacizumab in the Adjuvant Setting of Stage II/III Colorectal Cancer

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Background

- Bevacizumab has an established role in advanced CRC, increasing efficacy when added to single or doublet chemotherapy

- Two previous trials adding bevacizumab to *doublet* chemotherapy in the *adjuvant* setting of colon cancer failed to demonstrate any benefit from its addition

- The C-08 trial post hoc translational analysis suggested patients with MMRd (MSI) tumours may be a subgroup potentially benefitting from the addition of bevacizumab in the adjuvant setting (overall survival HR 0.52; 95%CI = 0.29-0.94; p=0.02)

- Studies have shown that a high Tumour Stroma Ratio (TSR) in CRC predicts for worse prognosis, and we postulated that this subset of patients may specifically benefit from therapy with bevacizumab

Study Schema

Stage III and high risk stage II* CRC (post R0 resection)

Eligibility Screening

R

**ARM A
Standard Arm**
Capecitabine 1250mg/m^2
twice daily d1-14
q3 weeks for 8 cycles
(24 weeks)

**ARM B
Experimental Arm**
Capecitabine 1250mg/m^2
twice daily d1-14
q3 weeks for 8 cycles
(24 weeks) **PLUS**
Bevacizumab 7.5 mg/kg
d1: 30-60 min IV infusion
q3 weeks for 16 cycles
(48 weeks)

High risk stage II*: T4, Ly1, V1, obstruction, perforation

Objectives & Stratification

- **Objectives**
  - **Primary Endpoint:**
    - **DFS (all patients - 3 year)**
      Final recruitment of 1941 patients delivered approximately 80% power to detect a 6% difference in 3-year disease-free survival (66- to 72%)

  - **Secondary Endpoints:**
    - **DFS (Stage III patients - 3 year)**
    - **OS**
    - **Toxicity**
    - **Translational Science**

- **Stratification factors**
  - **Age, Site (colon vs rectum), Stage, Country**

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Demographics

Stage	Arm A (968)	Arm B (973)	TOTAL (1941)
II	373	371	**744 (38.3%)**
III	595	602	**1197(61.7%)**
Gender			
Female	414	418	**832 (42.9%)**
Male	554	555	**1109 (57.1%)**
Disease Site			
Colon	854	861	**1715 (88.4%)**
Rectum	114	112	**226 (11.6%)**
Age Band			
<50	93	96	**189 (9.7%)**
50-59	197	192	**389 (20.0%)**
60-69	394	388	**782 (40.3%)**
70+	284	297	**581 (30.0%)**

Frequency of CTCAE*

Worst grade suffered cycles 1-8	Cap Total=963 N (%)	CapBev Total=959 N (%)	RR (95%CI)	P value

Hypertension
Grade 1 or 2
Grade 3 or 4
	69 (7.2)
	6 (0.6)
		284 (29.6)
		36 (3.8)
			All grades
			    4.3 (3.4 - 5.4)
			Grade 3 and 4
			    6.0 (2.6 - 14.2)
				<0.001
				
				<0.001

Proteinuria **Grade 1 or 2** **Grade 3 or 4**	48 (5.0) 1 (0.1)	188 (19.6) 9 (0.9)	All grades 4.0 (3.0 - 5.4)	**<0.001**
Poor Wound Healing **Grade 1 or 2** **Grade 3 or 4**	17 (1.8) 0 (0.0)	28 (2.9) 2 (0.2)	All grades 1.8 (1.0 - 3.2)	**0.05**

*number of patients

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Frequency of CTCAE

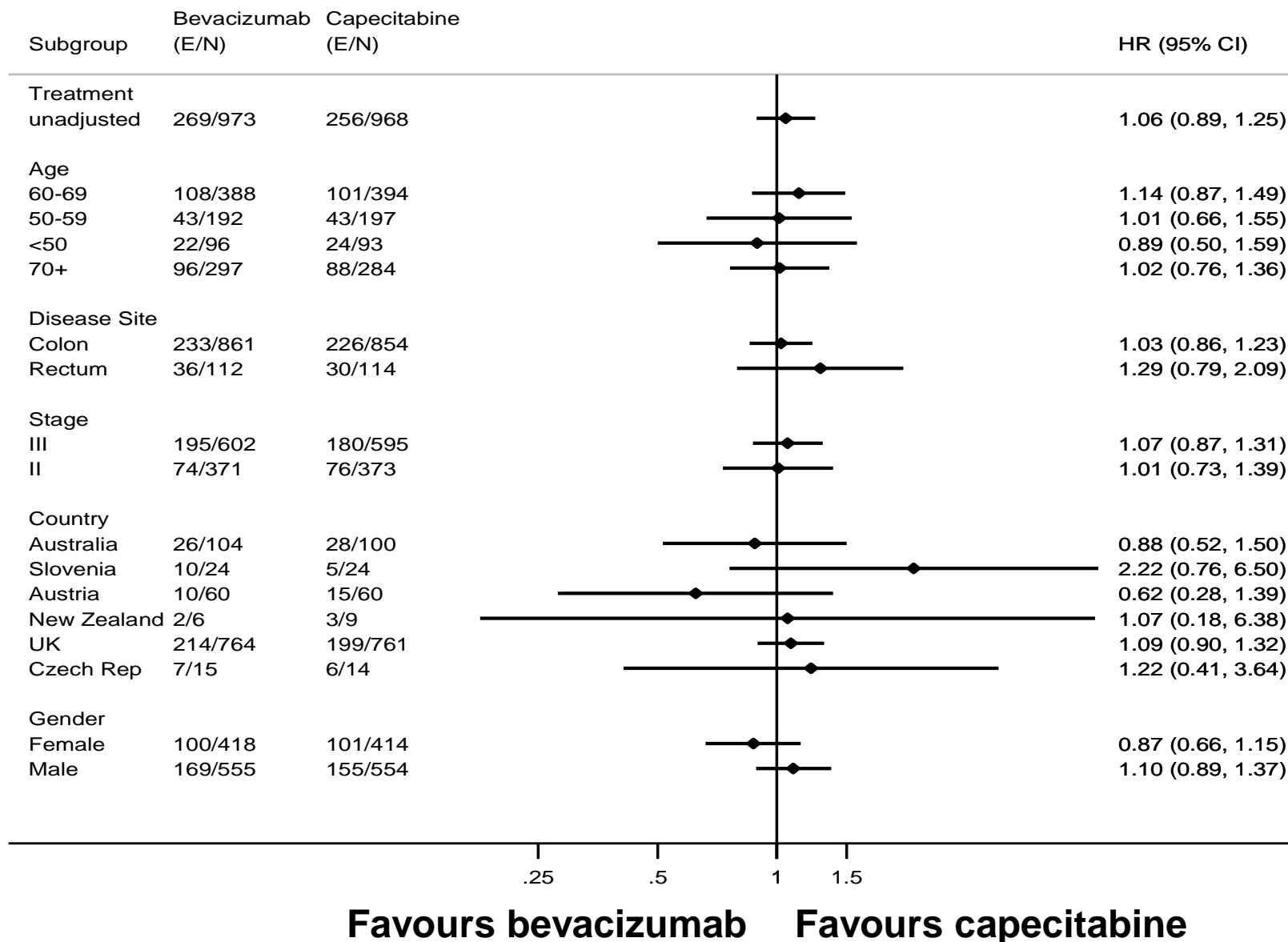| Worst grade suffered cycles 1-8	Arm A Total=963 N (%)	Arm B Total=959 N (%)	RR (95%CI)	P value
Diarrhoea **Grade 1 or 2** **Grade 3 or 4**	476 (49.4) 102 (10.6)	484 (50.5) 104 (10.8)	Grade 3 and 4 1.0 (0.8-1.3)	0.9
Hand-Foot syndrome **Grade 1 or 2** **Grade 3 or 4**	555 (57.6) 201 (20.9)	526 (54.8) 257 (26.8)	Grade 3 and 4 1.3 (1.1-1.5)	**0.002**
Epistaxis **All Grades**	13 (1.3)	132 (13.8)	All grades 10.2 (5.8-17.9)	**<0.001**

An excess of 'possibly treatment-related' deaths was found in patients receiving Bev (1.9% vs 0.9%: RR2.3: CI 1.0-5.2) and this just reached significance (p=0.05)

DFS by randomised treatment

3 year DFS
CAP   78.4%
CAPBEV 75.4%

HR=1.06
Logrank p=0.5

Proportion Disease Free (y-axis)

Disease Free Survival (years) (x-axis)

Number at risk

	0	1	2	3	4	5
CAP	967	872	779	700	543	293
CAPBEV	972	871	767	671	537	299

CAP — CAPBEV

Hazard Ratios: Year 1 = 0.83; year 2 = 0.87; year 3 = 1.32
Relapse-free survival curves mirror DFS curves

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DFS: Exploratory Subgroup Analysis

Subgroup	Bevacizumab (E/N)	Capecitabine (E/N)	HR (95% CI)
Treatment unadjusted	269/973	256/968	1.06 (0.89, 1.25)
Age			
60-69	108/388	101/394	1.14 (0.87, 1.49)
50-59	43/192	43/197	1.01 (0.66, 1.55)
<50	22/96	24/93	0.89 (0.50, 1.59)
70+	96/297	88/284	1.02 (0.76, 1.36)
Disease Site			
Colon	233/861	226/854	1.03 (0.86, 1.23)
Rectum	36/112	30/114	1.29 (0.79, 2.09)
Stage			
III	195/602	180/595	1.07 (0.87, 1.31)
II	74/371	76/373	1.01 (0.73, 1.39)
Country			
Australia	26/104	28/100	0.88 (0.52, 1.50)
Slovenia	10/24	5/24	2.22 (0.76, 6.50)
Austria	10/60	15/60	0.62 (0.28, 1.39)
New Zealand	2/6	3/9	1.07 (0.18, 6.38)
UK	214/764	199/761	1.09 (0.90, 1.32)
Czech Rep	7/15	6/14	1.22 (0.41, 3.64)
Gender			
Female	100/418	101/414	0.87 (0.66, 1.15)
Male	169/555	155/554	1.10 (0.89, 1.37)

.25   .5   1   1.5

Favours bevacizumab   Favours capecitabine

OS by randomised treatment

Translational Analyses

Tumour DNA (extracted from FFPE, n=1028)

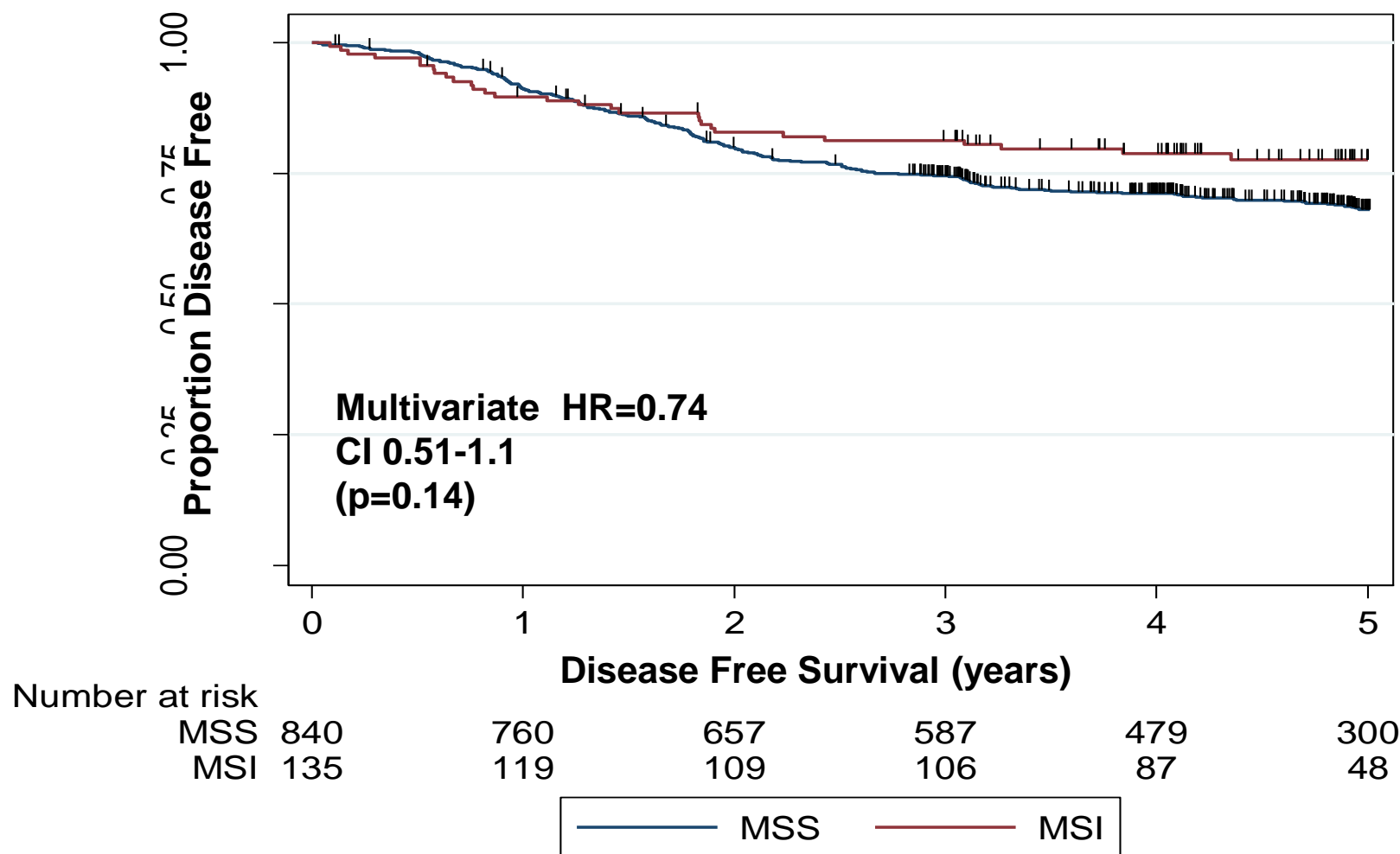| Assay	Number positive / Number tested	Frequency
CIN+	252 / 391	65%
KrasMut	199 / 617	32%
BrafMut	86 / 709	12%
POLEmut	4 / 307	1.3%

None of these were prognostic or predictive

MSI+: 135/975 (14%)

Tumour IHC (FFPE)

TSR High: 344 / 1038 (33%)

PROGNOSIS: DFS according to MSI status (treatment arms combined)

Multivariate HR=0.74
CI 0.51-1.1
(p=0.14)

Number at risk

MSS	840	760	657	587	479	300
MSI	135	119	109	106	87	48

MSS — MSI

PREDICTION: DFS by treatment arm and according to MSI status

MSS (n=840)

Proportion Disease Free

Multivariate HR=1.43
95% CI 1.12 − 1.84
p=0.005

Disease Free Survival (years)

Number at risk

	0	1	2	3	4	5
CAP	405	375	332	294	238	142
CAPBEV	435	385	326	293	239	157

— CAP   — CAPBEV

MSI (n=135)

Proportion Disease Free

Multivariate HR=0.74
95% CI 0.35 − 1.56
p=0.42

Disease Free Survival (years)

Number at risk

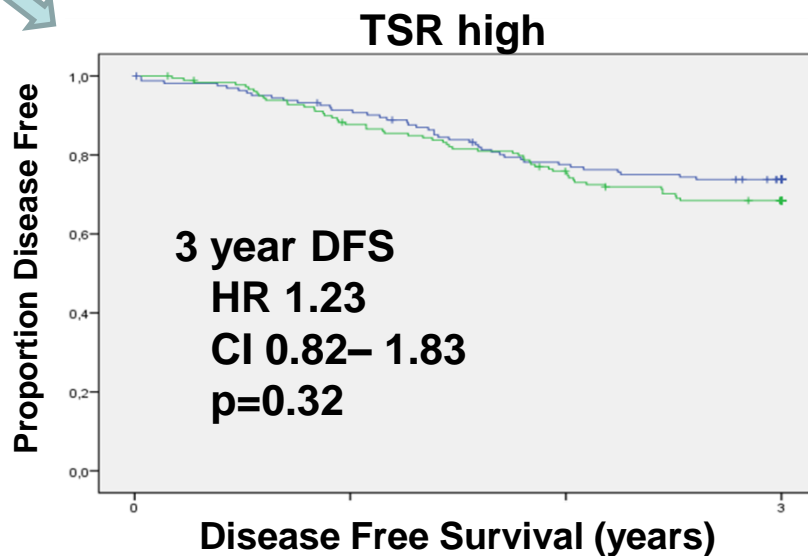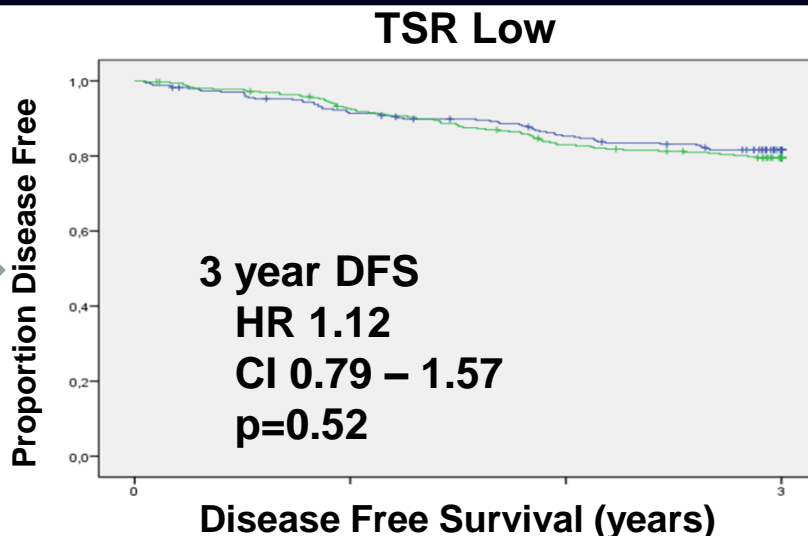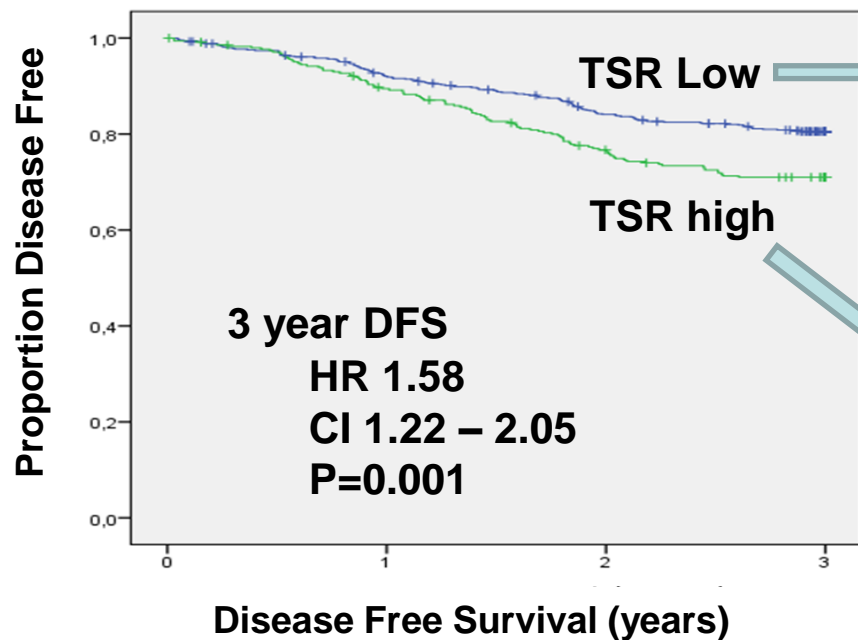|	0	1	2	3	4	5
CAP	69	60	55	55	43	23
CAPBEV	66	59	54	51	44	26

— CAP   — CAPBEV

$P_{interaction} = 0.18$

C-08: n=1668; HR = 1.03; CI 0.84-1.27; p = 0.78   C-08: n=237; HR = 0.52; CI 0.29-0.94; P = 0.02

C08: $P_{interaction}$ = 0 .04

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PROGNOSIS and PREDICTION: DFS by Tumour Stromal Ratio

TSR Low

3 year DFS
HR 1.12
CI 0.79 – 1.57
p=0.52

Proportion Disease Free

Disease Free Survival (years)

— CAP — CAPBEV

TSR high

3 year DFS
HR 1.23
CI 0.82– 1.83
p=0.32

Proportion Disease Free

Disease Free Survival (years)

TSR Low

TSR high

3 year DFS
HR 1.58
CI 1.22 – 2.05
P=0.001

Proportion Disease Free

Disease Free Survival (years)

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CONCLUSIONS

- There is no role for bevacizumab in combination with capecitabine in the adjuvant treatment of CRC

- Subgroup analysis did not reveal a specific subpopulation (defined by stage / subsite / gender / age) that benefits from bevacizumab therapy

- Results suggest that MSS patients suffer a reduced DFS when bevacizumab is added to single agent capecitabine

- Although we were able to confirm a prognostic effect of TSR, there was no evidence this marker determined responsiveness to bevacizumab

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Acknowledgements

Clinical / Scientific / Statistical Team

Rachel Kerr, Sharon Love, Andrew Weaver, Eva Segelov, John Zalcberg, David Ferry, Elaine Johnstone, Enric Domingo, Anouck Hujbers, Rob Tollenaar, Gabi van Pelt, Wilma Mesker, Francesco Pezella, Jianting Hu, Haitao Wang, David Church, Ian Tomlinson and David Kerr

Administrative Team

Claire Scudder, Barbara Searle, Aimi Swift, Sarah Pearson and the team at OCTO

Top 30 recruiting Hospitals

Russells Hall (Dudley), Churchill Hospital (Oxford), City Hospital (Nottingham), Royal Shrewsbury, Institute of Oncology, Ljubliana (Slovenia), Royal United (Bath), City General (Stoke-on-Trent), Mount Vernon, Musgrove Park, Bristol, Clatterbridge, Yeovil, University Hospital (Walsgrave), Queen's (Burton-on-Trent), New Cross (Wolverhampton), LKH Salzburg (Austria), Lincoln County, Leicester Royal Infirmary, Royal Bournemouth, Christie (Manchester), Maidstone, Norfolk & Norwich, Tweed Hospital (Australia), Bulovce (Czech Republic), St James's (Leeds), Essex County, Broomfield (Chelmsford), Wycombe, St John of God, Subiaco (Australia), Royal Hobart (Australia)

Unrestricted Educational Grant

Kindly provided by Roche