RAISE: A Randomized, Double-Blind, Multicenter Phase III Study of Irinotecan, Folinic Acid, and 5-Fluorouracil (FOLFIRI) Plus Ramucirumab or Placebo in Patients With Metastatic Colorectal Carcinoma Progression During or Following First-Line Combination Therapy With Bevacizumab, Oxaliplatin, and a Fluoropyrimidine

Abstract 512

Tabernero J, Cohn AL, Obermannova R, Garcia-Carbonero R, Ciuleanu T-E, Portnoy DC, Van Cutsem E, Grothey A, Prausová J, Garcia-Alfonso P, Yamazaki K, Clingan PR, Zagonel V, Kim TW, Simms L, Change S-C, Nasroulah F, Yoshino T, The RAISE Study Investigators

Introduction

- Colorectal carcinoma (CRC) is the fourth most common cause of cancer death worldwide.
- VEGF and VEGFR-2 mediated signaling and angiogenesis are important in CRC tumor growth and are established therapeutic targets.
- Ramucirumab is a recombinant human IgG1 monoclonal antibody that binds to the extracellular domain of VEGFR-2, preventing ligand binding and receptor activation.
- The RAISE study evaluated the efficacy and safety of adding ramucirumab to the standard second-line treatment FOLFIRI following progression after first-line bevacizumab, oxaliplatin, and a fluoropyrimidine.

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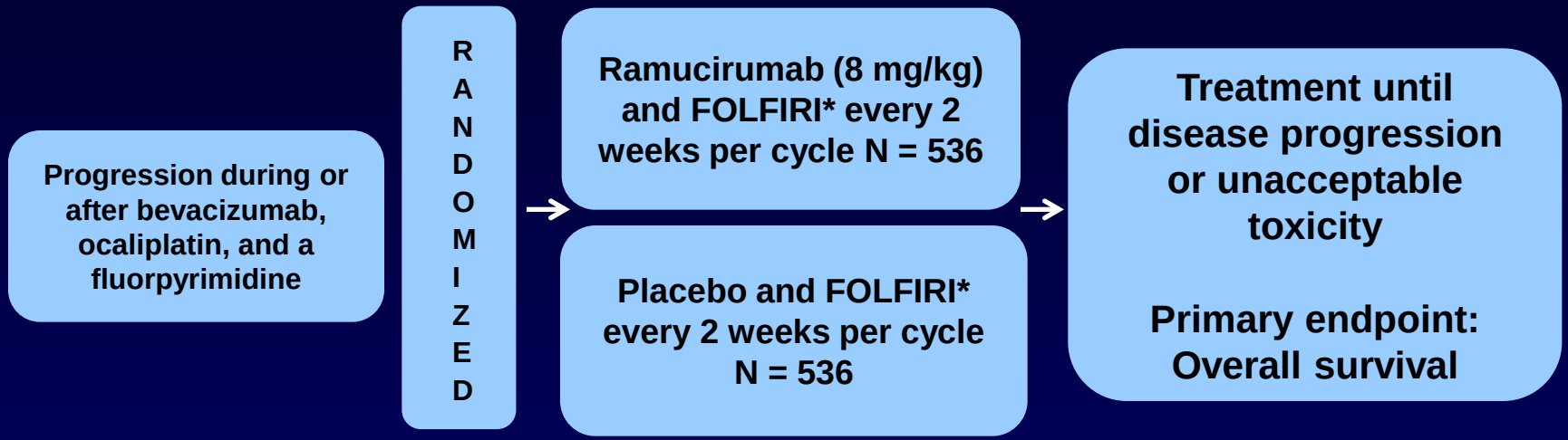
Trial Design



*Irinotecan: 180 mg/m2; Folinic acid: 400 mg/m2; 5-Fluorouracil 400 mg/m2 bolus, followed by 2400 mg/m2 administered intraveniously over 46 to 48 hours (continuously)

Stratification factors:

- Geographic regions
- *KRAS* mutation status
- Time to disease progression after beginning first-line therapy

Sample size assumptions:

- Hazard ratio of 0.8
- Median overall survival of 10 months in the control arm vs 12.5 months with ramuciruman with a 2-sided α level of 0.05
- Enrollment of 1050 patients with 756 events for 85% power
- Gatekeeping from OS to PFS to ORR

IG, immunogenicity; PFS, prorgession-free survival; PK, pharmacokinetics; OS, overall survival; ORR, objective response rate

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Key Inclusion Criteria

- Diagnosis of metastatic CRC (histological or cytological confirmation)
- Known *KRAS* mutation status
- Eastern Cooperative Oncology Group performance status score of 0 or 1
- Documented progressive disease during or after a first-line combination therapy of bevacizumab, oxaliplatin, and a fluoropyrimidine
- At least two doses of bevacizumab in first-line therapy
- Disease progression ≤6 months after the last dose of first-line therapy
- Adequate hematologic and biochemical parameters

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Key Exclusion Criteria

- Previous first-line systemic therapy, other than a combination of bevacizumab, oxaliplatin, and a fluoropyrimidine
- Uncontrolled hypertension
- Arterial thrombotic event within 12 months
- Received bevacizumab ≤28 days or chemotherapy ≤21 days prior to randomization
- Known brain metastasis
- Grade 3 or higher bleeding event ≤3 months prior to randomization

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Baseline Characteristics

	Ramucirumab + FOLFIRI (N = 536)	Placebo + FOLFIRI (N = 536)
Median age (range), years	62 (21-83)	62 (33-87)
Age group, n (%) ≥65 years	212 (39.6)	215 (40.1)
Male, n (%)	289 (53.9)	326 (60.8)
Race, n (%)		
Caucasian	405 (75.6)	410 (76.5)
Asian	111 (20.7)	103 (19.2)
ECOG PS, n (%)		
0	263 (49.1)	259 (48.3)
1	268 (50.0)	273 (50.9)
Number of metastatic sites, n (%)		
1	171 (31.9)	157 (29.3)
2	205 (38.2)	194 (36.2)
≥3	157 (29.3)	182 (34.0)
Liver only metastasis, n(%) Yes	92 (17.2)	95 (17.7)
Carcinoembryonic antigen, n (%)		
<200 µg/L	389 (72.6)	393 (73.3)
≥200 µg/L	108 (20.1)	107 (20.0)

Some patients may be missing from some categories

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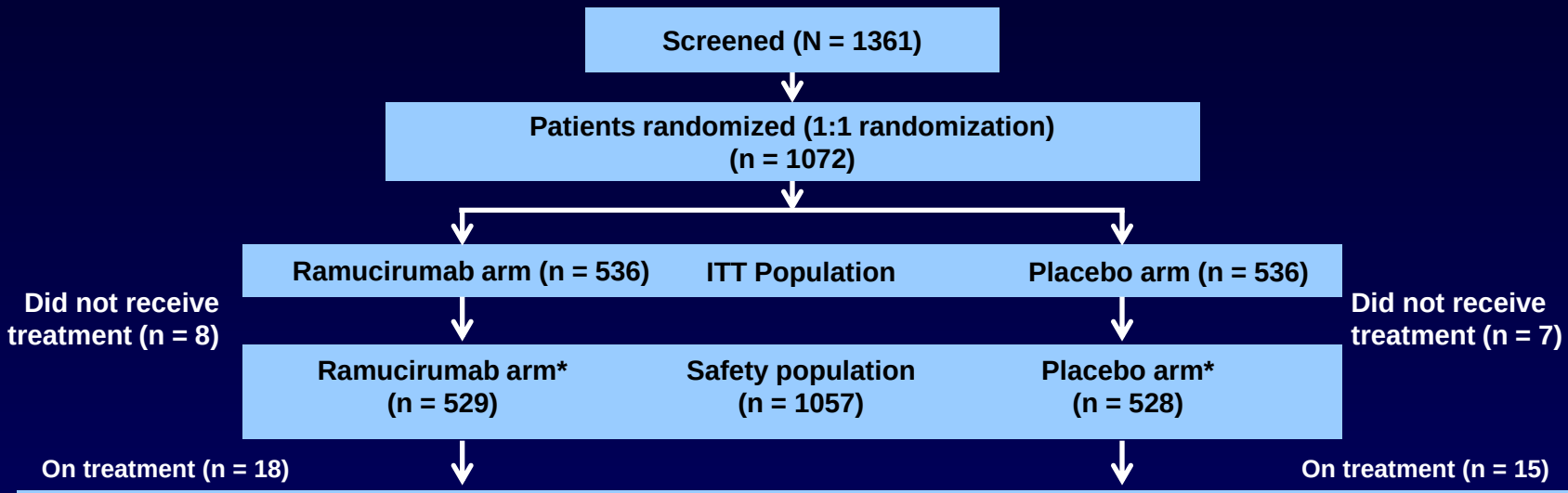
Patient Disposition



Treatment discontinuation

	n	%
Progressive disease	338	63
Subject decision	49	9
Death	18	3
Withdrawel of consent	8	1
Lost to follow-up	0	0
Adverse event	59	11
Other	4	<1
Investigator decision	35	7
Total	511	95

	n	%
Progressive disease	417	78
Subject decision	26	5
Death	13	2
Withdrawel of consent	4	<1
Lost to follow-up	0	0
Adverse event	23	4
Other	5	<1
Investigator decision	25	5
Total	513	96

ITT, intent-to-treat; N, number of patients in category; One patient was randomized to the placebo group but received ramucirumab

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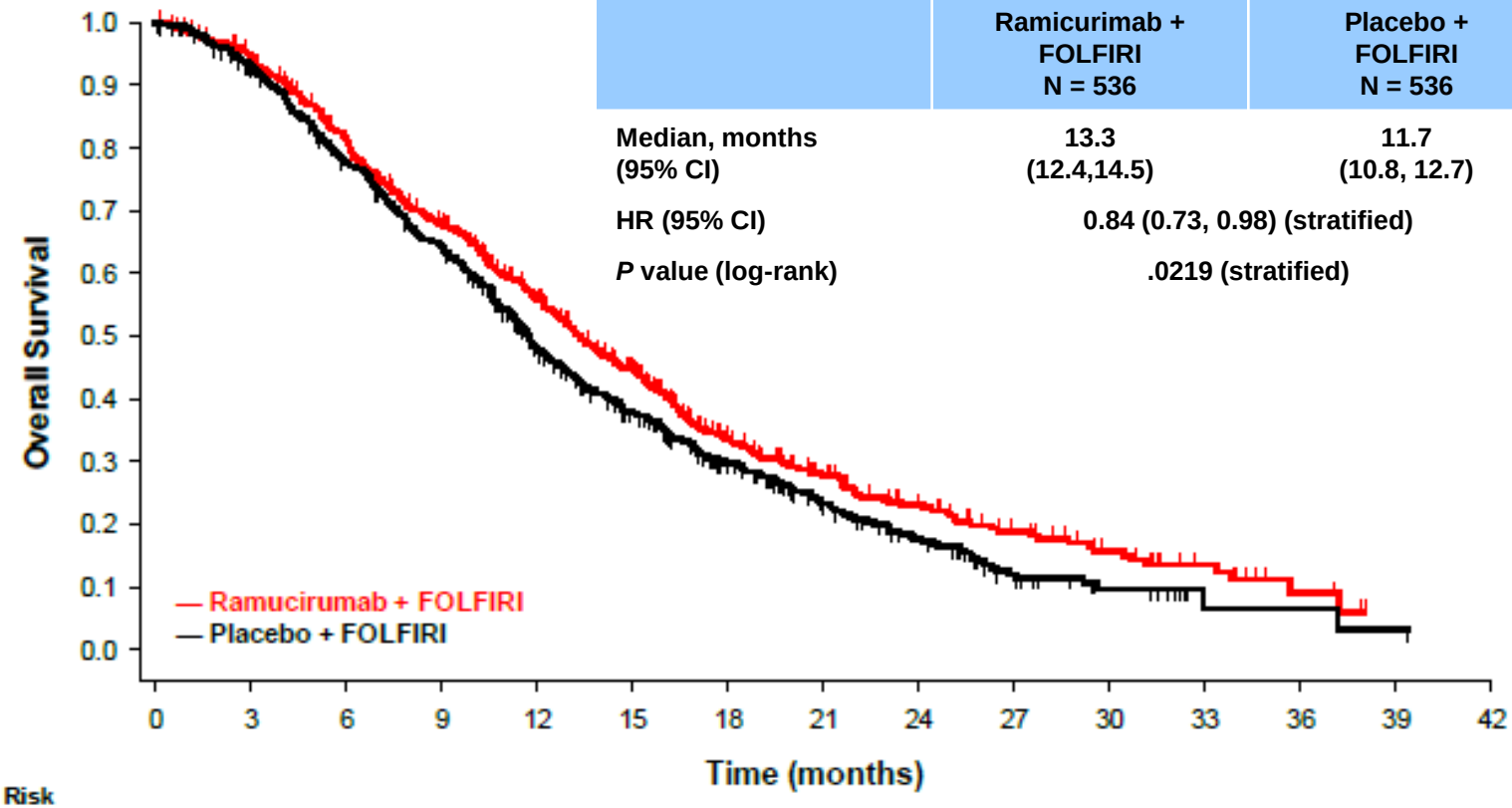
Overall Survival



	Ramicurimab + FOLFIRI N = 536	Placebo + FOLFIRI N = 536
Median, months (95% CI)	13.3 (12.4,14.5)	11.7 (10.8, 12.7)
HR (95% CI)	0.84 (0.73, 0.98) (stratified)	
P value (log-rank)	.0219 (stratified)	

Patients at Risk

Ram + FOLFIRI	536	497	421	345	269	195	114	78	53	34	22	12	4	0	0
Placebo + FOLFIRI	536	486	400	329	228	166	108	66	44	22	10	2	2	1	0

CI, confidential interval; HR, hazard ratio; Ram, ramicurimab

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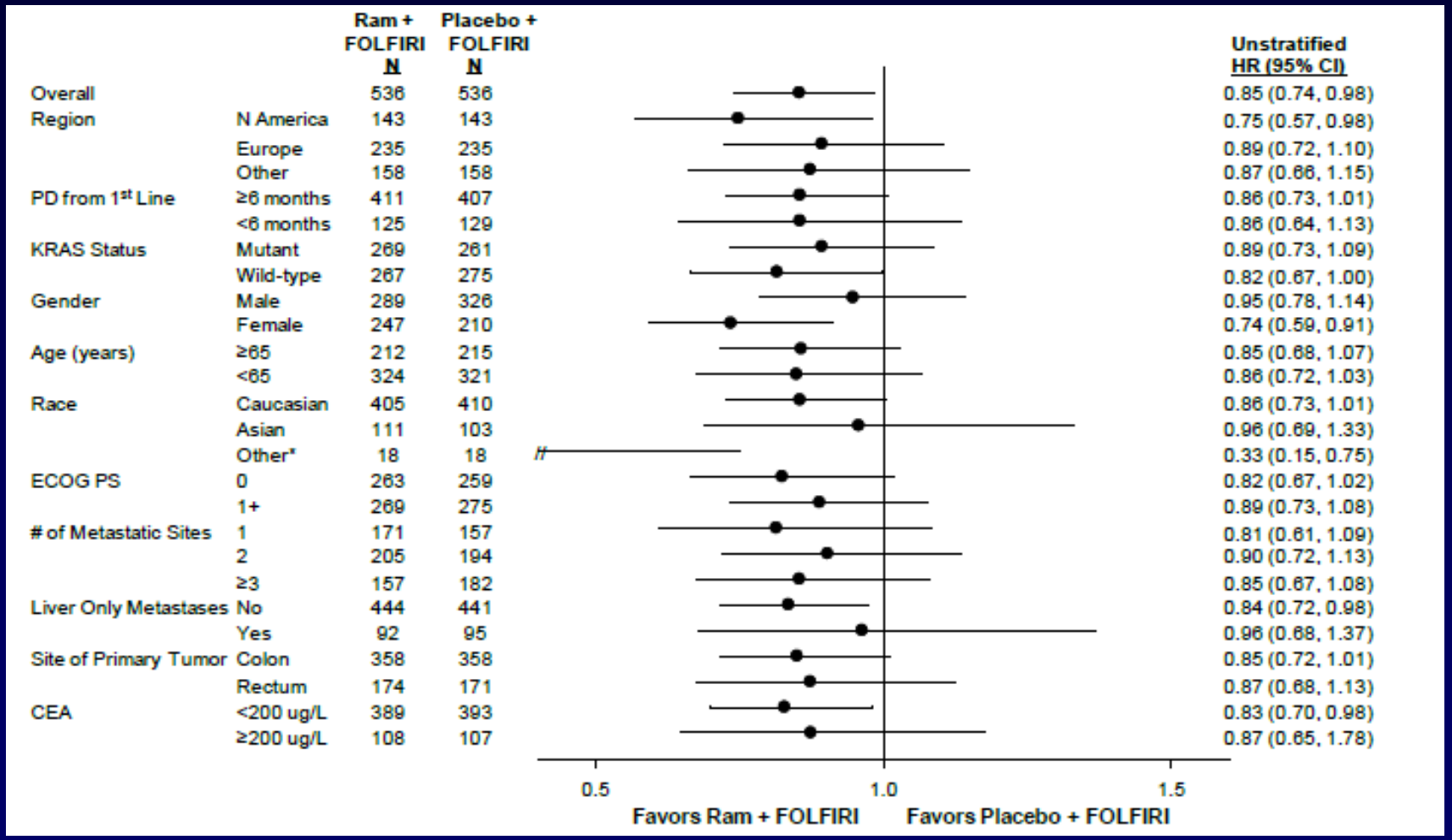
Overall Survival by Subgroup



CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; N, number of patients; PD, progressive disease

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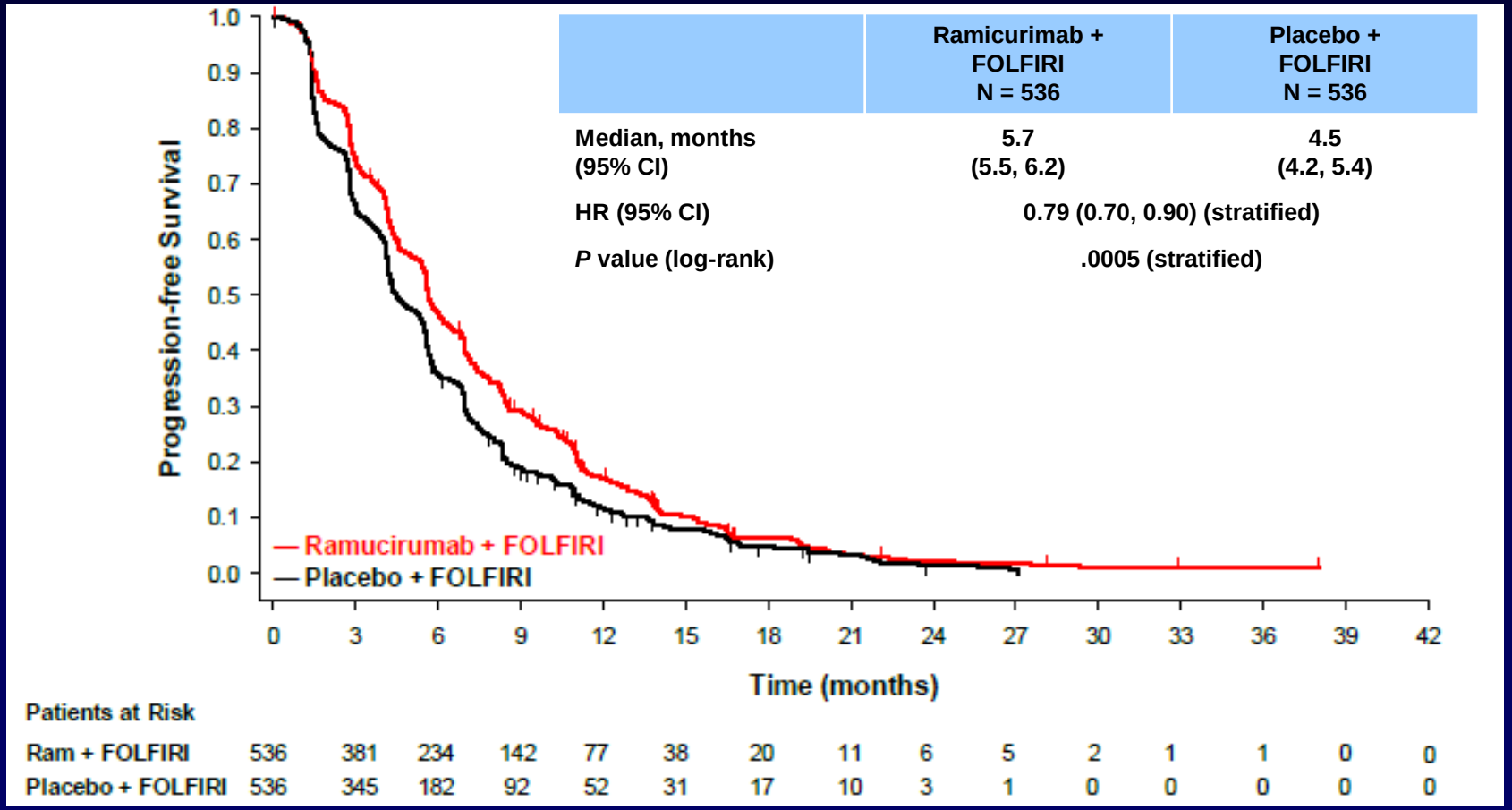
Progression-Free Survival



	Ramicurimab + FOLFIRI N = 536	Placebo + FOLFIRI N = 536
Median, months (95% CI)	5.7 (5.5, 6.2)	4.5 (4.2, 5.4)
HR (95% CI)	0.79 (0.70, 0.90) (stratified)	
P value (log-rank)	.0005 (stratified)	

Patients at Risk

Ram + FOLFIRI	536	381	234	142	77	38	20	11	6	5	2	1	1	0	0
Placebo + FOLFIRI	536	345	182	92	52	31	17	10	3	1	0	0	0	0	0

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Tumor Response

	Ramicurimab + FOLFIRI N = 536 %	Placebo + FOLFIRI N = 536 %	*P*-value
Response rate (CR+PR)	13.4	12.5	.6336
Disease control rate (CR+PR+SD)	74.1	68.8	.0587
Complete response	0	0.4	
Partial response (PR)	13.4	12.1	
Stable disease (SD)	60.6	56.3	
Progressive disease (PD)	16.2	25	
Not done or unknown	9.7	6.2	

Tumor assessments based on RECIST 1.1

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Post-Treatment Anticancer Therapy

	Ramicurimab + FOLFIRI N = 536 %	Placebo + FOLFIRI N = 536 %
Systemic anticancer therapy	54.1	56.0
Fluoropyrimidines	33.4	34.0
Irinotecan	30.6	28.7
Anti-EGFR antibody (cetuximab or panitumumab)	25.6	28.5
Anti-angiogenic agents (bevacizumab or aflibercept)	12.7	13.1
Regorafenib	10.4	10.8
Platinum	9.0	10.8

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Treatment-Emergent Adverse Events

Preferred Term	Any Grade				Grade ≥3			
	Ramucirumab + FOLFIRI N=529		Placebo + FOLFIRI N=528		Ramucirumab + FOLFIRI N=529		Placebo + FOLFIRI N=528	
	n	%	n	%	n	%	n	%
Any TEAE	522	98.7	519	98.3	418	79.0	329	62.3
Neutropenia	*311*	*58.8*	*241*	*45.6*	*203*	*38.4*	*123*	*23.3*
Fatigue	*305*	*57.7*	*275*	*52.1*	*61*	*11.5*	*41*	*7.8*
Diarrhea	316	59.7	271	51.3	57	10.8	51	9.7
Hypertension	136	25.7	45	8.5	57	10.8	15	2.8
Stomatitis	163	30.8	110	20.8	20	3.8	12	2.3
Abdominal pain	*140*	*26.5*	*139*	*26.3*	*18*	*3.4*	*19*	*3.6*
Thrombocytopenia	*150*	*28.4*	*72*	*13.6*	*16*	*3.0*	*4*	*0.8*
Vomiting	154	29.1	144	27.3	15	2.8	13	2.5
Nausea	262	49.5	271	51.3	13	2.5	14	2.7
Decreased appetite	198	37.4	144	27.3	13	2.5	10	1.9
Anemia	*86*	*16.3*	*110*	*20.8*	*8*	*1.5*	*19*	*3.6*
Constipation	151	28.5	120	22.7	5	0.9	8	1.5
Peripheral edema	108	20.4	48	9.1	1	0.2	0	
Epistaxis	177	33.5	79	15.0	0		0	
Alopecia	155	29.3	165	31.3	0		0	

Italicized terms are consolidated adverse event category comprising synonymous MedDRA preferred terms.

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Adverse Events of Special Interest

	Any Grade				Grade ≥3			
	Ramucirumab + FOLFIRI N=529		Placebo + FOLFIRI N=528		Ramucirumab + FOLFIRI N=529		Placebo + FOLFIRI N=528	
	n	%	n	%	n	%	n	%
Bleeding/hemorrhage event	232	43.9	120	22.7	13	2.5	9	1.7
Hypertension	138	26.1	45	8.5	59	11.2	15	2.8
Proteinuria	90	17.0	24	4.5	16	3.0	1	0.2
GI hemorrhage	65	12.3	36	6.8	10	1.9	6	1.1
Venous thromboembolic events	44	8.3	34	6.4	22	4.2	11	2.1
Infusion-related reaction	31	5.9	16	3.0	4	0.8	2	0.4
Renal failure	18	3.4	18	3.4	7	1.3	5	0.9
GI perforation	9	1.7	3	0.6	9	1.7	3	0.6
Arterial thromboembolic event	8	1.5	13	2.5	4	0.8	6	1.1
Pulmonary hemorrhage events	7	1.3	3	0.6	0		0	
Healing complication	6	1.1	1	0.2	1	0.2	0	
Congestive heart failure	4	0.8	3	0.6	4	0.8	3	0.6
Fistula	4	0.8	2	0.4	0		0	
RPLS	1	0.2	1	0.2	0		0	
Thrombotic microangiopathy	1	0.2	0		1	0.2	0	
Hepatic hemorrhage event	0		1	0.2	0		1	0.2

Abbreviations: GI=gastrointestinal; RPLS=reversible posterior leukoencephalopathy syndrome.

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Conclusions

- RAISE met its primary endpoint.
  - Demonstrated a statistically significant improvement in overall survival for ramucirumab and FOLFIRI vs placebo and FOLFIRI
  - In second-line metastatic CRC patients who progressed after first-line treatment with bevacizumab, oxaliplatin, and a fluoropyrimidine
- Consistent survival benefits were observed across subgroups
- Ramucirumab in combination with FOLFIRI was well tolerated in patients with mCRC; overall, the adverse events were considered manageable

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