Supplementary Material

Drugs – Real World Outcomes

Title: Post-marketing safety study of ramucirumab plus FOLFIRI: Analysis of age and initial dose of irinotecan in patients with metastatic colorectal cancer

Running title: Ramucirumab plus FOLFIRI treatment for metastatic colorectal cancer in clinical practice

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Table S1: Patient demographics and baseline clinical characteristics by age

Characteristic		Age			
		<65 years N=144	**≥65 years N=218**	**<70 years N=232**	**≥70 years N=130**
Sex	Male	74 (51.4)	126 (57.8)	122 (52.6)	78 (60.0)
	Female	70 (48.6)	92 (42.2)	110 (47.4)	52 (40.0)
Age, years, mean (SD)		53.2 (8.3)	71.4 (4.5)	58.5 (9.4)	74.3 (3.5)
Age, median (minimum – maximum)		55.0 (32-64)	70.0 (65-83)	61.0 (32-69)	74.0 (70-83)
Body mass index, $kg/m^{2,}$ mean (SD)		22.6 (4.4)	22.2 (3.6)	22.6 (4.2)	22.0 (3.3)
RAS (K/NRAS) gene mutation	No	60 (41.7)	91 (41.7)	93 (40.1)	58 (44.6)
	Yes	82 (56.9)	120 (55.1)	136 (58.6)	66 (50.8)
	Unknown	2 (1.4)	7 (3.2)	3 (1.3)	6 (4.6)
Primary tumor site[a]	Ascending colon	25 (17.4)	54 (24.8)	44 (19.0)	35 (26.9)
	Transverse colon	9 (6.3)	17 (7.8)	15 (6.5)	11 (8.5)
	Descending colon	10 (6.9)	10 (4.6)	15 (6.5)	5 (3.9)
	Sigmoid colon	38 (26.4)	43 (19.7)	57 (24.6)	24 (18.5)
	Rectal	65 (45.1)	101 (46.3)	106 (45.7)	60 (46.2)
Metastasis and recurrent sites[a]	Liver	86 (59.7)	142 (65.1)	144 (62.1)	84 (64.6)
	Lung	68 (47.2)	114 (52.3)	118 (50.9)	64 (49.2)
	Local	8 (5.6)	14 (6.4)	13 (5.6)	9 (6.9)

	Peritoneal (with ascites)	19 (13.2)	18 (8.3)	25 (10.8)	12 (9.2)
	Peritoneal (without ascites)	24 (16.7)	29 (13.3)	35 (15.1)	18 (13.9)
	Bone	14 (9.7)	18 (8.3)	22 (9.5)	10 (7.7)
	Brain	1 (0.7)	2 (0.9)	2 (0.9)	1 (0.8)
	Lymph nodes (intraperitoneally)	55 (38.2)	67 (30.7)	91 (39.2)	31 (23.9)
	Lymph nodes (other)	18 (12.5)	18 (8.3)	25 (10.8)	11 (8.5)
	Other	7 (4.9)	8 (3.7)	9 (3.9)	6 (4.6)
Eastern Cooperative Oncology Group performance status	0	91 (63.2)	137 (62.8)	150 (64.7)	78 (60.0)
	1	49 (34.0)	72 (33.0)	76 (32.8)	45 (34.6)
	2	4 (2.8)	9 (4.1)	6 (2.6)	7 (5.4)

Data are n (%) unless otherwise indicated.

[a]Patients could have more than one site.

SD, standard deviation.

Table S2. Use of ramucirumab by age

Parameter	Age <65 years N=144	Age ≥65 years N=215	Age <70 years N=232	Age ≥70 years N=127
Number of cycles (1 cycle = 14 days)	8.0 (1-32)	8.0 (1-34)	8.5 (1-32)	7.0 (1-34)
Duration of treatment (weeks)	17.4 (2-65)	16.0 (2-68)	17.9 (2-65)	14.0 (2-68)
Cumulative dose (mg/kg)	44.8 (5-247)	39.0 (6-199)	44.6 (5-247)	32.0 (7-199)
Dose intensity (mg/kg/week)	3.0 (1.0-4.4)	2.8 (0.9-4.4)	3.0 (0.9-4.4)	2.8 (1.1-4.3)
Relative dose intensity (%)	76.1 (21.5-109.6)	70.4 (21.5-109.5)	74.5 (21.5-109.6)	70.3 (26.1-106.2)

Data presented as median (minimum-maximum).

Table S3. Use of FOLFIRI/Levofolinate by age

Parameter	Age <65 years N=144	Age ≥65 years N=218	Age <70 years N=232	Age ≥70 years N=130
Number of cycles (1 cycle = 14 days)	8.0 (1-32)	8.0 (1-34)	8.0 (1-32)	7.0 (1-34)
Duration of treatment (weeks)	17.0 (2-65)	16.0 (2-68)	17.9 (2-65)	14.0 (2-68)
Cumulative dose (mg/m^2)	1325.0 (194-6720)	1000.0 (0-8125)	1232.0 (160-6720)	960.0 (0-8125)
Dose intensity (mg/m^2/week)	84.2 (11.8-191.3)	76.5 (0-170.0)	80.5 (11.8-191.3)	75.0 (0-170.0)
Relative dose intensity (%)	84.2 (11.8-191.3)	76.5 (0-170.0)	80.5 (11.8-191.3)	75.0 (0-170.0)

Data presented as median (minimum-maximum).

FOLFIRI, fluorouracil, levofolinate, and irinotecan.

Table S4. Use of FOLFIRI/irinotecan by age

Parameter	**Age <65 years N=144**	**Age ≥65 years N=218**	**Age <70 years N=232**	**Age ≥70 years N=130**
Number of cycles (1 cycle = 14 days)	8.0 (1-32)	8.0 (1-34)	8.0 (1-32)	7.0 (1-34)
Duration of treatment (weeks)	17.0 (2-65)	16.0 (2-68)	17.9 (2-65)	14.0 (2-68)
Cumulative dose (mg/m^2)	840.0 (77-5760)	696.5 (95-5320)	826.0 (77-5760)	640.0 (1000-5320)
Dose intensity (mg/m^2/week)	58.0 (18.0-140.0)	50.2 (14.4-143.6)	56.3 (14.4-143.6)	48.0 (16.0-125.0)
Relative dose intensity (%)	77.8 (25.7-103.8)	69.4 (24.0-114.7)	74.7 (24.0-113.5)	69.6 (24.6-114.7)

Data presented as median (minimum-maximum).

FOLFIRI, fluorouracil, levofolinate, and irinotecan.

Table S5. Use of FOLFIRI/Fluorouracil by age

Parameter	Age <65 years N=144	Age ≥65 years N=218	Age <70 years N=232	Age ≥70 years N=130
Number of cycles (1 cycle = 14 days)	8.0 (1-32)	8.0 (1-34)	8.0 (1-32)	7.0 (1-34)
Duration of treatment (weeks)	17.0 (2-65)	16.0 (2-68)	17.9 (2-65)	14.0 (2-68)
Cumulative dose (mg/m^2)	15050.0 (1593-108000)	12380.0 (0-87000)	14400.0 (1536-108000)	11760.0 (0-87000)
Dose intensity (mg/m^2/week)	1067.7 (117.7-2837.0)	863.2 (0-2290.0)	1021.0 (117.7-2837.0)	822.2 (0-2050.0)
Relative dose intensity (%)	76.3 (8.4-202.6)	61.7 (0-163.6)	72.9 (8.4-202.6)	58.7 (0-146.4)

Data presented as median (minimum-maximum).

FOLFIRI, fluorouracil, levofolinate, and irinotecan.

Table S6. Notable adverse events by age

	Age <65 years N=144		Age ≥65 years N=218		Age <70 years N=232		Age ≥70 years N=130	
Any AE, n (%)	120 (83.3)		185 (84.9)		195 (84.1)		110 (84.6)	
Grade ≥3 AE, n (%)	70 (48.6)		115 (52.8)		114 (49.1)		71 (54.6)	
SAE, n (%)	22 (15.3)		50 (22.9)		38 (16.4)		34 (26.2)	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Neutropenia	57 (39.6)	39 (27.1)	93 (42.7)	62 (28.4)	97 (41.8)	64 (27.6)	53 (40.8)	37 (28.5)
Proteinuria	28 (19.4)	8 (5.6)	36 (16.5)	15 (6.9)	46 (19.8)	15 (6.5)	18 (13.9)	8 (6.2)
Hypertension	29 (20.1)	15 (10.4)	30 (13.8)	20 (9.2)	40 (17.2)	21 (9.1)	19 (14.6)	14 (10.8)
Leukopenia	16 (11.1)	3 (2.1)	21 (9.6)	6 (2.8)	27 (11.6)	5 (2.2)	10 (7.7)	4 (3.1)
Liver injury/failure	18 (12.5)	10 (6.9)	10 (4.6)	5 (2.3)	25 (10.8)	14 (6.0)	3 (2.3)	1 (0.8)
Bleeding/haemorrhagic events	10 (6.9)	2 (1.4)	14 (6.4)	1 (0.5)	15 (6.5)	2 (0.9)	9 (6.9)	1 (0.8)
Febrile neutropenia	3 (2.1)	3 (2.1)	7 (3.2)	7 (3.2)	7 (3.0)	7 (3.0)	3 (2.3)	3 (2.3)
Venous thromboembolic events	2 (1.4)	1 (0.7)	6 (2.8)	2 (0.9)	3 (1.3)	2 (0.9)	5 (3.9)	1 (0.8)
Interstitial lung disease	2 (1.4)	1 (0.7)	3 (1.4)	1 (0.5)	4 (1.7)	1 (0.4)	1 (0.8)	1 (0.8)
Infusion-related reaction	2 (1.4)	0 (0.0)	2 (0.9)	0 (0.0)	3 (1.3)	0 (0.0)	1 (0.8)	0 (0.0)
Gastrointestinal perforation	2 (1.4)	2 (1.4)	1 (0.5)	1 (0.5)	2 (0.9)	2 (0.9)	1 (0.8)	1 (0.8)
Arterial thromboembolic events	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.5)	1 (0.8)
Congestive heart failure	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)

Healing complications	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

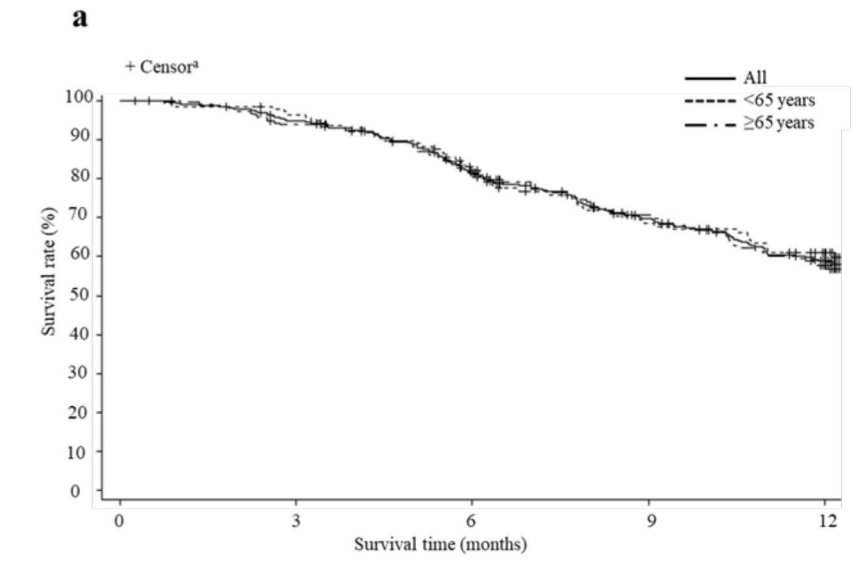
MedDRA version 23.0.

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

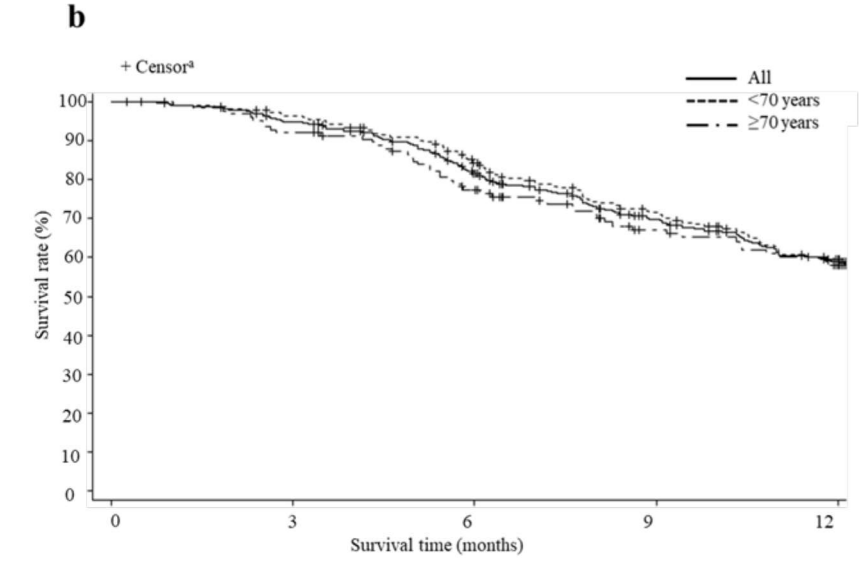
Fig. S1 Survival analysis generated using the Kaplan-Meier method by **a.** patients aged <65 and ≥65 years and **b.** patients aged <70 and ≥70 years

The number of deaths/censored are presented as n (%). Survival time is presented as point estimate (95% CI).

[a]Censored at the last date when the survival status was confirmed. CI, confidence interval.



	All patients	Age <65	Age ≥65
Number of patients	355	140	215
Number of deaths	141 (39.7)	52 (37.1)	89 (41.4)
Number censored	214 (60.3)	88 (62.9)	126 (58.6)
Survival rate: 3 months	94.9 (92.6, 97.2)	96.4 (93.3, 99.5)	93.9 (90.6, 97.1)
6 months	81.7 (77.6, 85.8)	82.3 (75.9, 88.7)	81.3 (76.0, 86.6)
9 months	69.9 (64.9, 74.9)	68.6 (60.6, 76.6)	70.8 (64.4, 77.1)
12 months	59.0 (53.5, 64.4)	60.9 (52.4, 69.5)	57.7 (50.6, 64.7)



	All patients	Age <70	Age ≥70
Number of patients	355	227	128
Number of deaths	141 (39.7)	91 (40.1)	50 (39.1)
Number censored	214 (60.3)	136 (59.9)	78 (60.9)
Survival rate: 3 months	94.9 (92.6, 97.2)	96.4 (94.0, 98.9)	92.1 (87.3, 96.8)
6 months	81.7 (77.6, 85.8)	84.1 (79.3, 89.0)	77.3 (69.9, 84.7)
9 months	69.9 (64.9, 74.9)	71.4 (65.4, 77.5)	67.1 (58.6, 75.7)
12 months	59.0 (53.5, 64.4)	59.6 (52.9, 66.4)	57.9 (48.7, 67.2)