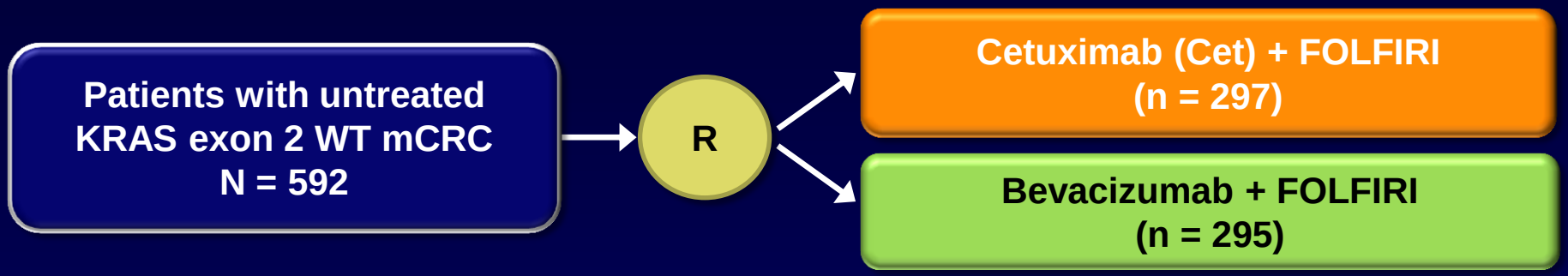
Influence of Adjuvant Pretreatment on Outcome of FIRE-3 (AIO KRK-0306): A Randomized Phase III Study of FOLFIRI Plus Cetuximab as First-Line Treatment for Wild-Type (WT) KRAS (Exon 2) Metastatic Coloreactal Cancer (mCRC) Patients

Abstract 515

Stintzing S, Modest DP, Fischer von Weikersthal L, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran S-E, Heintges T, Lerchenmuller CA, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Held S, Giessen CA, Moehler MH, Jung A, Kirchner T, Heinemann V

FIRE-3: Head-to-Head Study of Erbitux + FOLFIRI vs Bevacizumab (Bev) + FOLFIRI in First-Line mCRC[1]

Open-label, randomized, multicenter, phase III investigator sponsored trial (IST)

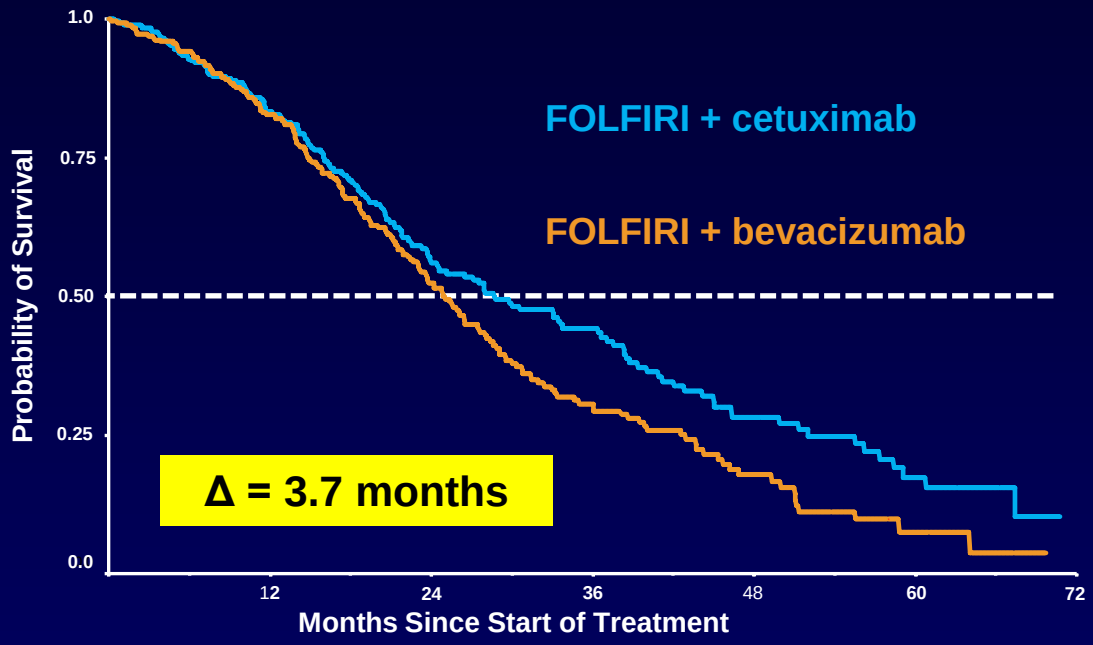


- **Primary endpoint: Investigator-assessed overall response rate (ORR)**
- **Secondary endpoints: Progression-free survival (PFS), overall survival (OS), time to failure of strategy, depth of response, independent read of ORR, secondary resection rate, and safety**
- **Amended October 2008 to include only patients with KRAS exon 2 WT mCRC**
  - **113 patients with KRAS exon 2 mutated mCRC were enrolled before the amendment**
- **Retrospective RAS subgroup analysis (RAS-evaluable population, including both RAS WT and new RAS mutated: n = 407)**

Heinemann V, et al. *Lancet Oncol.* 2014;15(10):1065-1075.

Stintzing S, et al. *J Clin Oncol.* 2015;33(suppl 3): Abstract 515.

KRAS Exon 2 WT (Intent-to-Treat [ITT]; n = 592)



Events n/N (%)	Median (months)	95% CI
158/297 (53.2%)	28.7	24.0-36.6
185/295 (62.7%)	25.0	22.7-27.6

HR 0.77 (0.62-0.96)
P = .017

	ITT population, KRAS exon 2 WT	
	Cet + chemo (n = 297)	Bev + chemo (n = 295)
ORR, %	62.0	58.0
Odds ratio *P* value	1.18, *P* = .183*	
PFS, months	10.0	10.3
HR, *P* value	1.06, *P* = .547	

Heinemann V, et al. *Lancet Oncol.* 2014;15(10):1065-1075.
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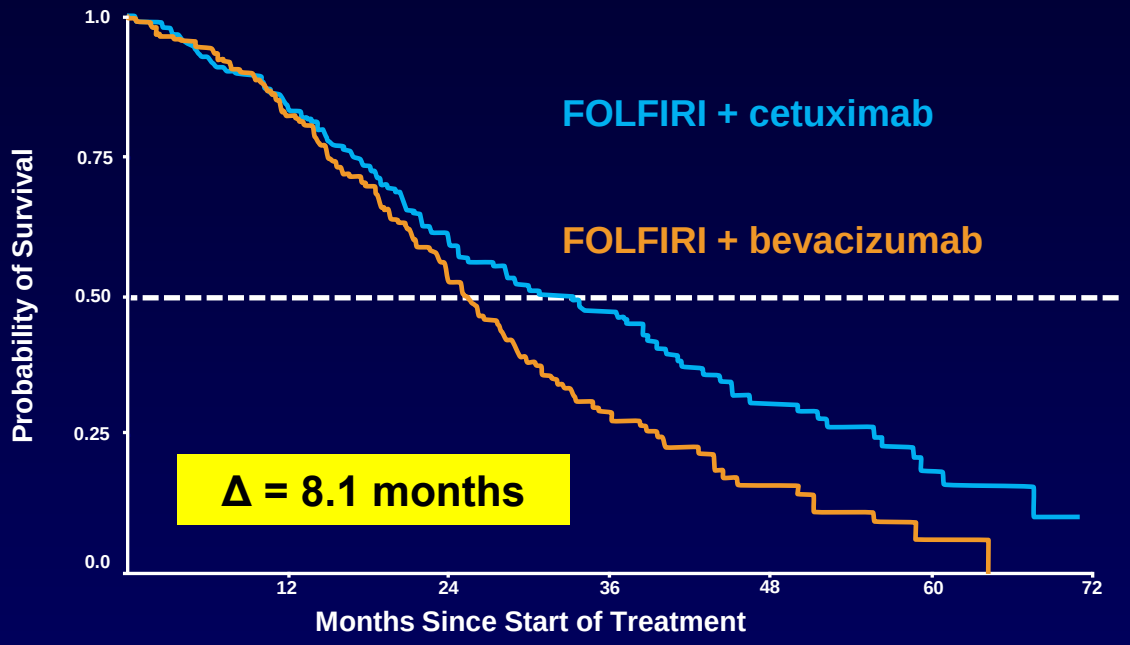
RAS WT (n = 400)



Events n/N (%)	Median (months)	95% CI
107/199 (53.8%)	33.1	24.5-39.4
133/201 (66.2%)	25.0	23.0-28.1

HR 0.697 (0.54-0.90)
***P* = .0059**

	ITT population, KRAS exon 2 WT	
	Cet + chemo (n = 297)	Bev + chemo (n = 295)
ORR*, %	65.3	58.7
Odds ratio, *P* value	1.33, *P* = .18*	
PFS, months	10.3	10.2
HR, *P* value	0.97, *P* = .77	

P, logrank test; *P**, one-sided Fisher's exact test

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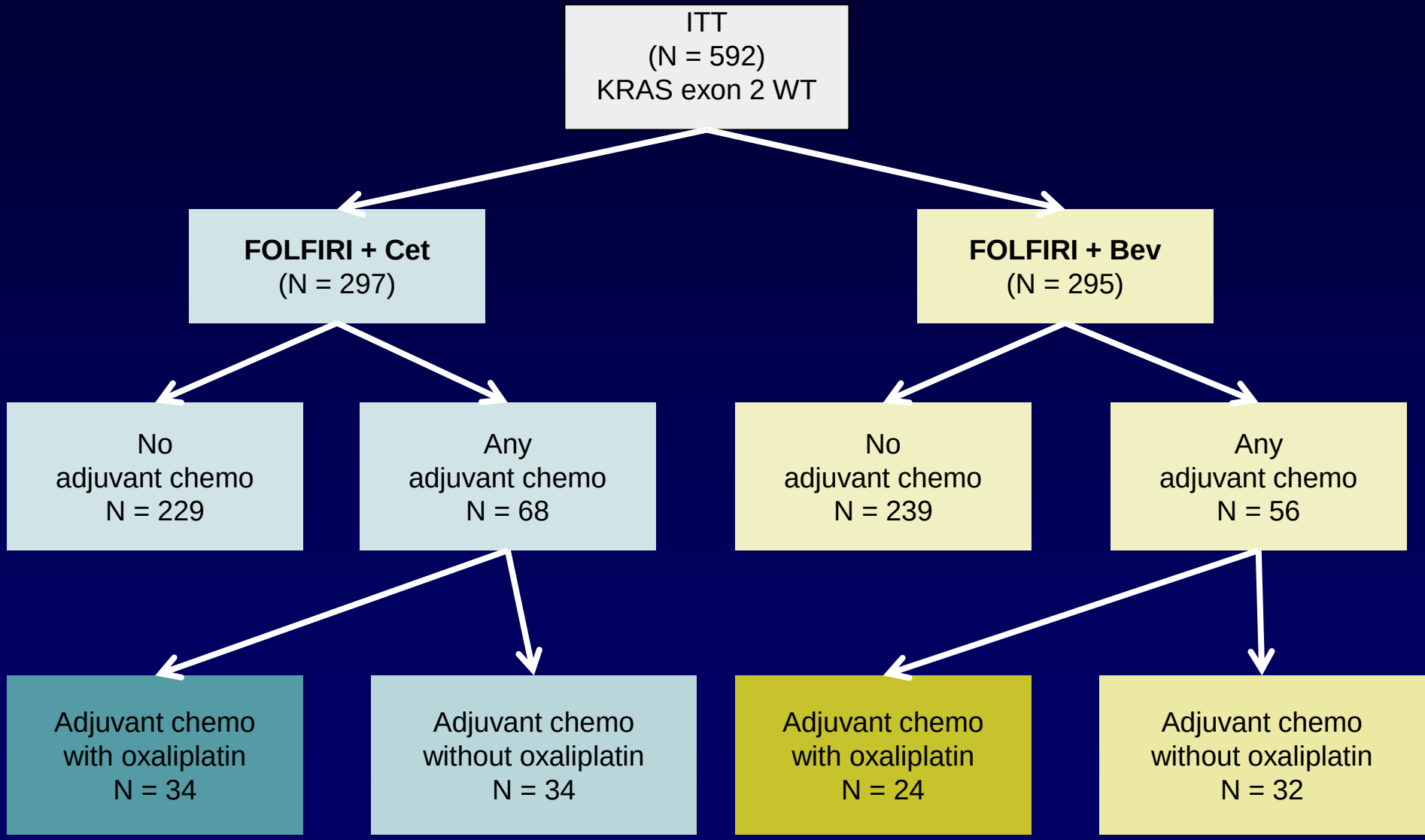
Populations



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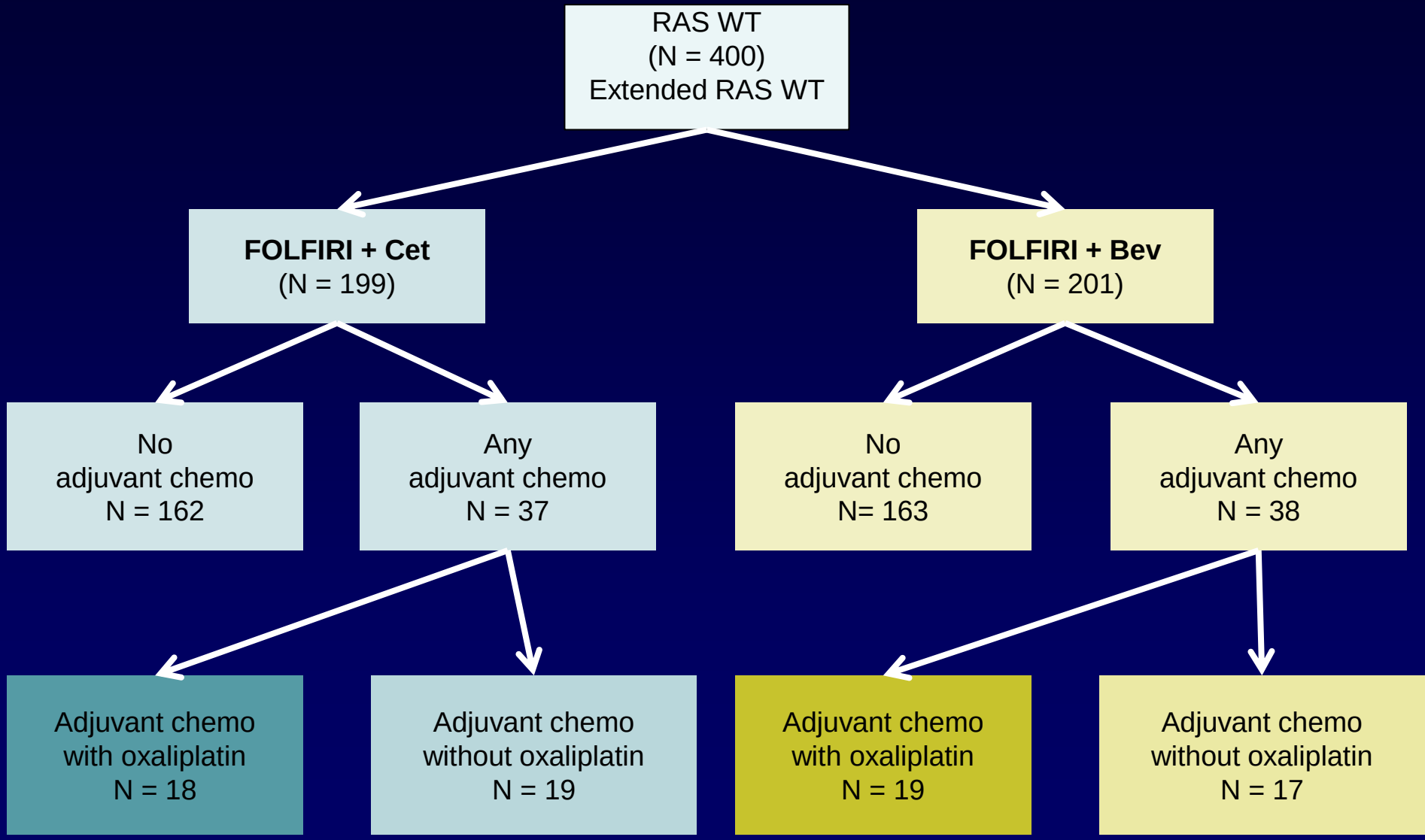
Populations



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Baseline Characteristics (KRAS Exon 2 WT)

Characteristic	Adjuvant treatment without oxaliplatin		Adjuvant treatment with oxaliplatin		Total (n = 124)
	FOLFIRI cetuximab (n = 34)	FOLFIRI bevacizumab (n = 32)	FOLFIRI cetuximab (n = 34)	FOLFIRI bevacizumab (n = 24)	
Sex					
Male, % (n)	71% (24)	81% (26)	59% (20)	58% (14)	68% (84)
Female, % (n)	29% (10)	19% (6)	41% (14)	42% (10)	32% (40)
Age					
Median, years	68	64	62	68	65
Categories, % (n)					
≤65 years	41% (14)	63% (20)	65% (22)	33% (8)	52% (64)
>65 years	59% (20)	37% (12)	35% (12)	67% (16)	48% (60)
≥70 years	35% (12)	19% (6)	21% (7)	46% (11)	29% (36)
ECOG % (n)					
0	59% (20)	56% (18)	68% (23)	46% (11)	58% (72)
1	41% (14)	41% (13)	29% (10)	54% (13)	40% (50)
2	0% (0)	3% (1)	3% (1)	0% (0)	2% (2)
Lab values, % (n)					
Leukocytes ≥8000/µl	18% (6)	16% (5)	27% (9)	13% (3)	19% (23)
AP ≥300/µl	6% (2)	6% (2)	3% (1)	0% (0)	4% (5)

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Baseline Characteristics (KRAS Exon 2 WT) Cont

Characteristic	Adjuvant treatment without oxaliplatin		Adjuvant treatment with oxaliplatin		Total (n = 124)
	FOLFIRI cetuximab (n = 34)	FOLFIRI bevacizumab (n = 32)	FOLFIRI cetuximab (n = 34)	FOLFIRI bevacizumab (n = 24)	
Site of primary, % (n)					
Right colon	6% (2)	6% (2)	32% (11)	29% (7)	18% (22)
Left colon	94% (32)	94% (30)	68% (23)	71% (17)	82% (102)
Rectum	77% (26)	78% (25)	29% (10)	46% (11)	58% (72)
Metastatic sites, % (n)					
1 site	44% (15)	47% (15)	35% (12)	42% (10)	42% (52)
≥2 sites	56% (19)	53% (17)	65% (22)	58% (14)	58% (72)
Unknown	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Metastatic sites, % (n)					
Liver	59% (20)	50% (16)	47% (16)	54% (13)	52% (65)
Liver only	27% (9)	19% (6)	6% (2)	8% (2)	15% (19)
Liver not affected	41% (14)	50% (16)	53% (18)	46% (1)	48% (59)
Unknown	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Prior treatment, % (n)					
Surgery	100% (34)	94% (30)	100% (34)	100% (24)	98% (122)
Radiotherapy	74% (25)	72% (23)	32% (11)	38% (9)	55% (68)

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Primary Outcome Measurements (KRAS Exon 2 WT)

	No adjuvant treatment		*P*	Any adjuvant treatment		*P*
	FOLFIRI cetuximab (n = 229)	FOLFIRI bevacizumab (n = 239)		FOLFIRI cetuximab (n = 68)	FOLFIRI bevacizumab (n = 56)	
ORR %, (n)	62 (143)	61 (145)	0.71	60 (41)	48 (27)	0.21
PFS, months (95% CI)	10.0 (8.8-11.1)	10.5 (9.9-11.6)	0.91	9.4 (7.4-12.3)	9.7 (8.8-10.8)	0.36

	Adjuvant treatment without oxaliplatin		*P*	Adjuvant treatment with oxaliplatin		*P*
	FOLFIRI cetuximab (n = 34)	FOLFIRI bevacizumab (n = 32)		FOLFIRI cetuximab (n = 34)	FOLFIRI bevacizumab (n = 24)	
ORR %, (n)	62% (21)	47% (15)	0.32	58.8 (20)	50 (12)	0.60
PFS, months (95% CI)	8.6 (6.4-12.9)	9.4 (7.8-10.8)	0.69	10.2 (6.8-12.8)	10.3 (8.8-12.0)	0.30

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Primary Outcome Measurements (RAS WT)

	No adjuvant treatment		*P*	Any adjuvant treatment		*P*
	FOLFIRI cetuximab (n = 162)	FOLFIRI bevacizumab (n = 163)		FOLFIRI cetuximab (n = 37)	FOLFIRI bevacizumab (n = 38)	
ORR %, (n)	64 (103)	63 (102)	0.91	73 (27)	42 (16)	0.01
PFS, months (95% CI)	10.5 (9.3-11.8)	11.1 (9.8-12.3)	0.55	10.2 (7.2-13-3)	9.9 (8.6-11.9)	0.59

	Adjuvant treatment without oxaliplatin		*P*	Adjuvant treatment with oxaliplatin		*P*
	FOLFIRI cetuximab (n = 18)	FOLFIRI bevacizumab (n = 21)		FOLFIRI cetuximab (n = 19)	FOLFIRI bevacizumab (n = 17)	
ORR %, (n)	72 (14)	38 (8)	0.05	74 (13)	47 (8)	0.17
PFS, months (95% CI)	8.5 (5.5-12.2)	9.3 (6.9-10.3)	0.91	10.2 (7.2-13-3)	9.9 (8.6-11.9)	0.59

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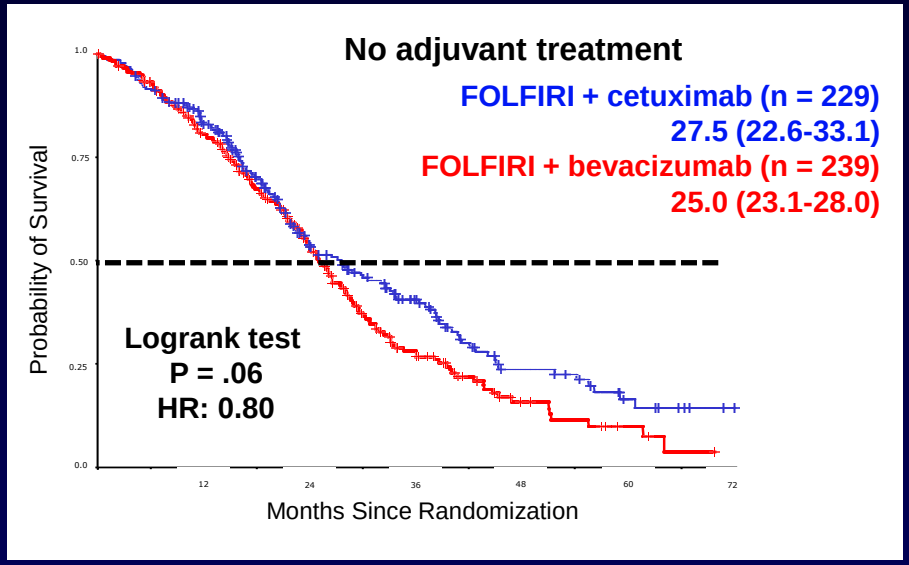
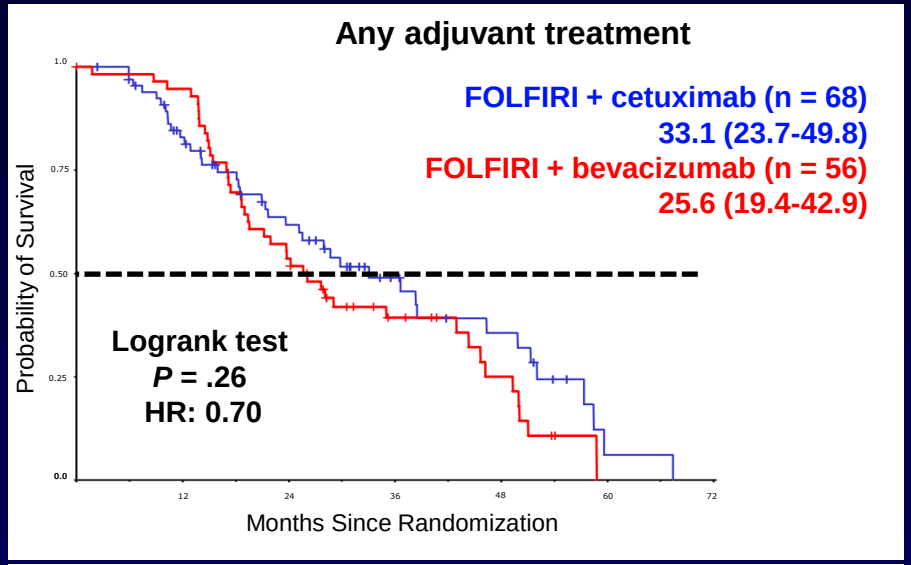
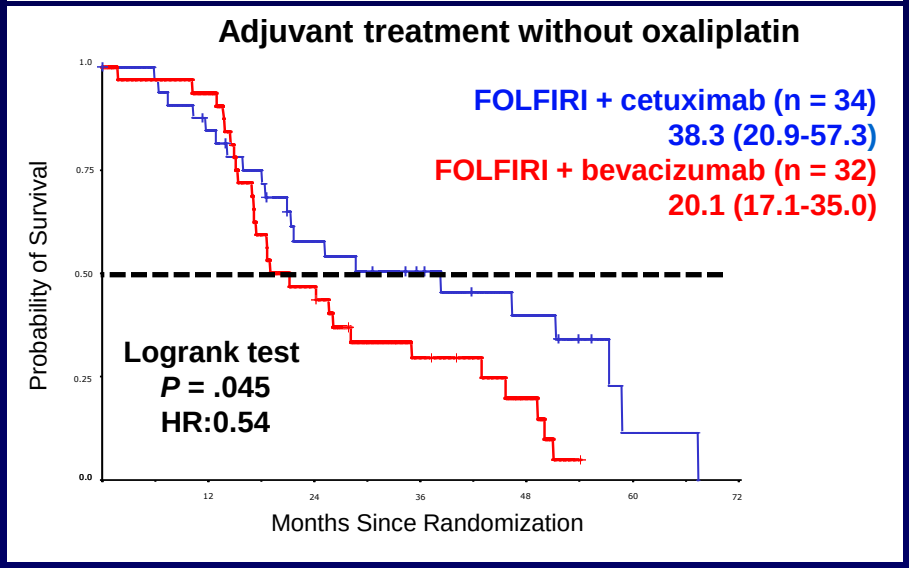
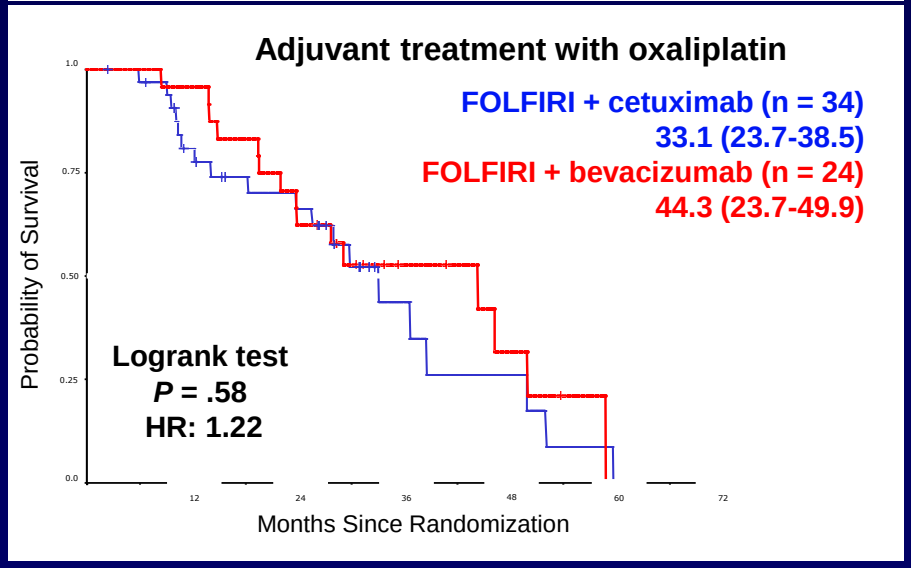
Overall Survival According to Adjuvant Pretreatment (KRAS Exon 2 WT)









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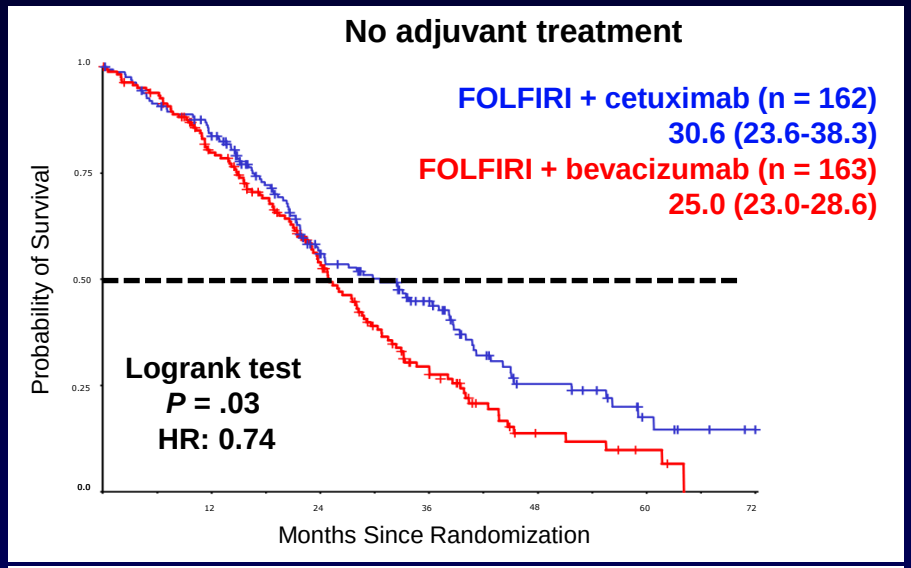
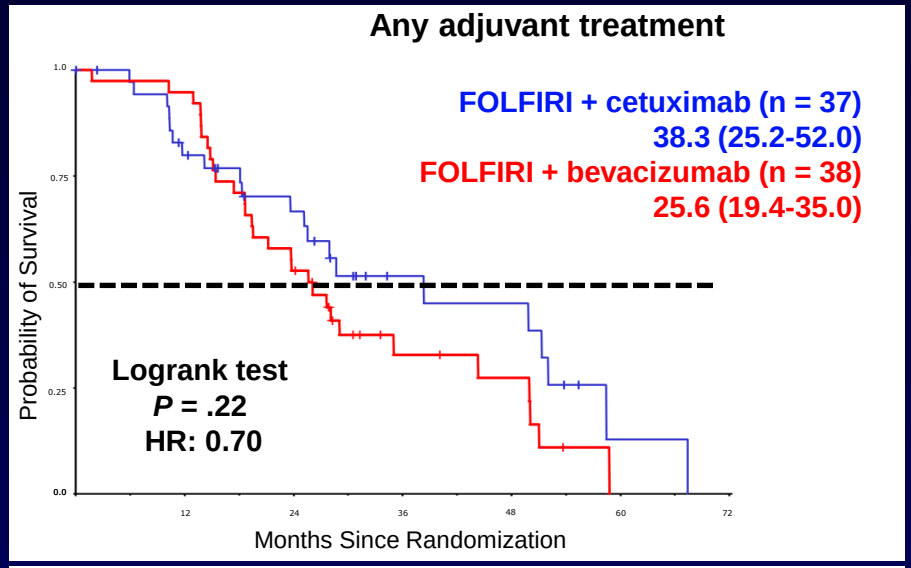
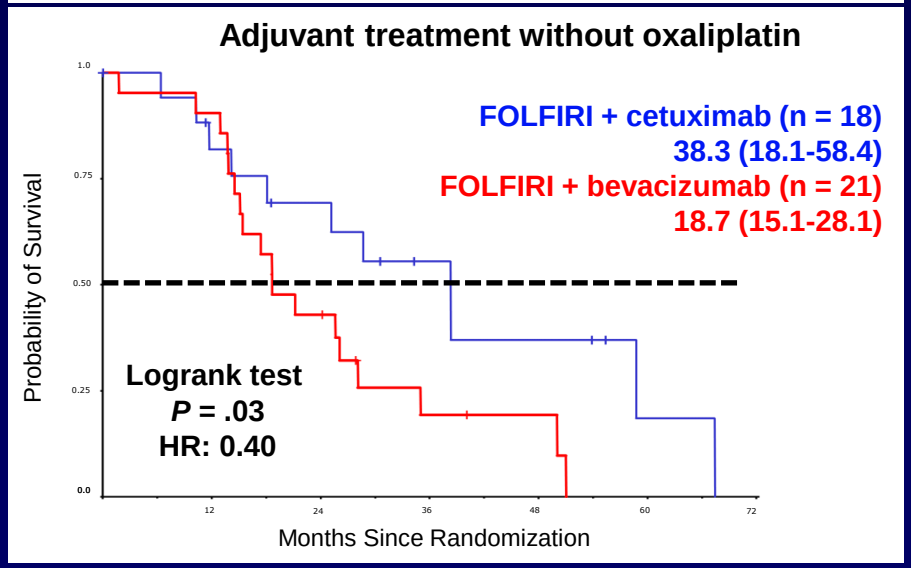
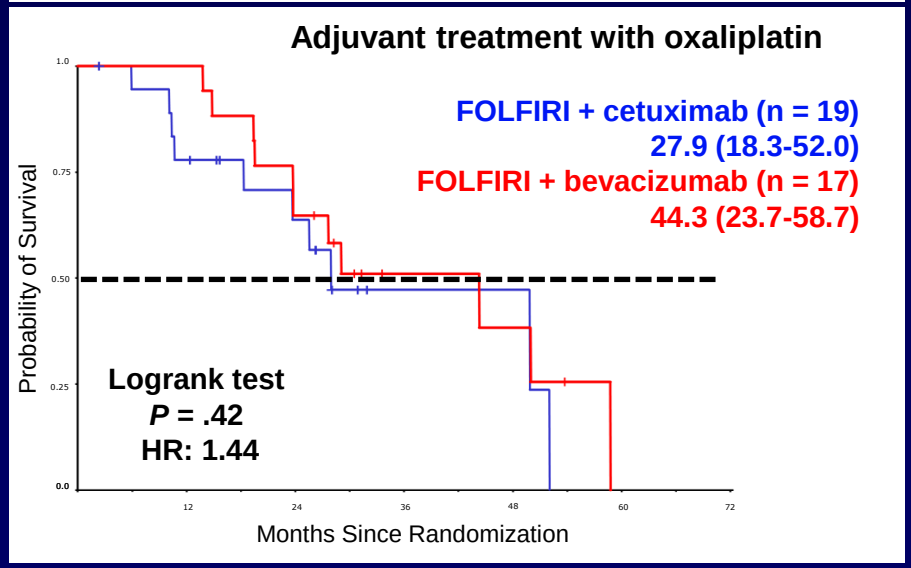
Overall Survival According to Adjuvant Pretreatment (RAS WT)









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Conclusions

- Results in patients treated with adjuvant chemotherapy mirrored those in the whole study population
- In adjuvant pretreated RAS WT patients, a significantly higher ORR was reached in the cetuximab arm when compared to the bevacizumab arm (*P* = .01)
- The role of adjuvant treatment on efficacy of first-line therapy remains to be further evaluated

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