Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients

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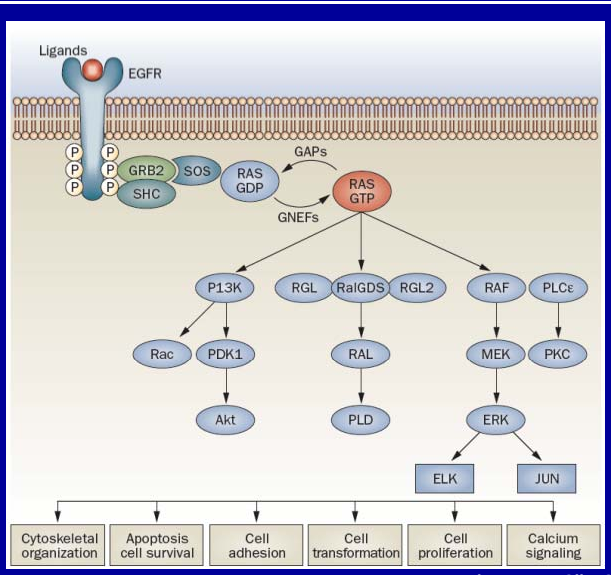
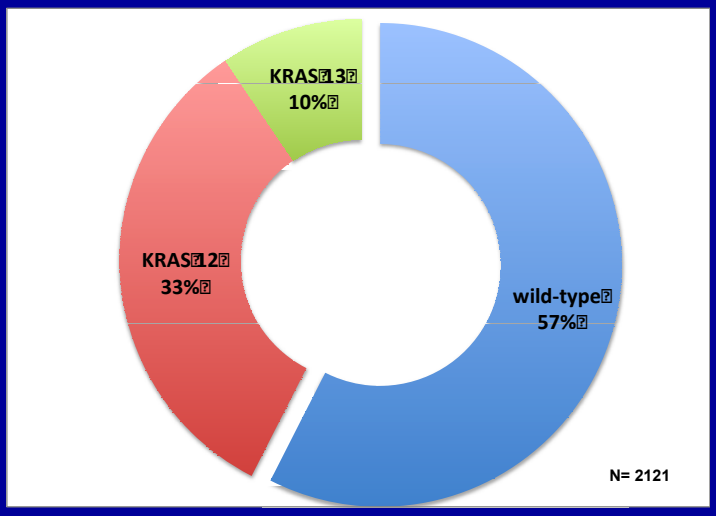
RAS Mutations



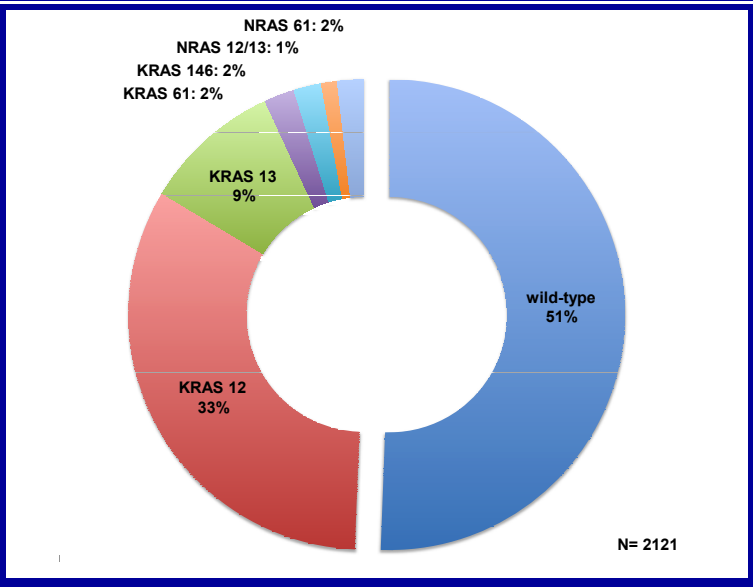
Normanno, N. et al. Nat. Rev, Clin. Oncol. 6, 519-527 (2009)

KRAS – NRAS – mutation frequency in CRC



adapted from: Vaughn et al GENES, CHROMOSOMES & CANCER 50:307–312 (2011)

KRAS – NRAS – mutation frequency in CRC



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FIRE-3 study design

mCRC
1st-line therapy
KRAS wild-type

→ Randomize 1:1

FOLFIRI + Cetuximab

Cetuximab: 400 mg/m² i.v. 120min initial dose
250 mg/m² i.v. 60min q 1w

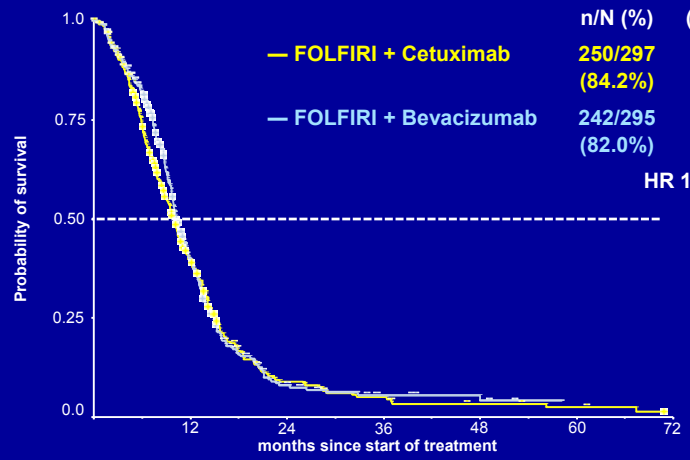
FOLFIRI + Bevacizumab

Bevacizumab: 5 mg/kg i.v. 30-90min q 2w

FOLFIRI q2w: 5-FU: 400 mg/m² (i.v. bolus);
folinic acid: 400mg/m²
irinotecan: 180 mg/m²
5-FU: 2,400 mg/m² (i.v. 46h)

- **Key inclusion criteria**
  - Patients ≥18 years with histologically confirmed diagnosis of mCRC
  - ECOG PS 0-2
  - prior adjuvant chemotherapy allowed if completed >6 month before inclusion
- **Amendment in October 2008** to include only KRAS wildtype patients
- 150 active centers in Germany and Austria

Progression-free survival

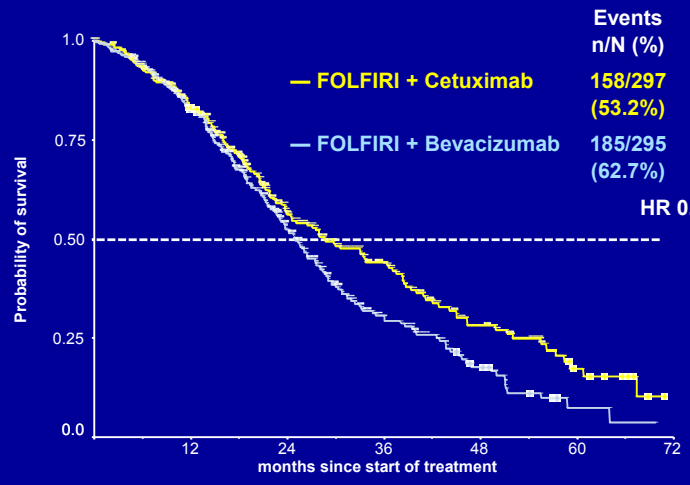


	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	250/297 (84.2%)	10.0	8.8 – 10.8
— FOLFIRI + Bevacizumab	242/295 (82.0%)	10.3	9.8 – 11.3

HR 1.06 (95% CI: 0.88 – 1.26)
p (log-rank)= 0.547

No. at risk						
	297	100	19	10	5	3
	295	99	15	6	4	

Overall survival



	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	158/297 (53.2%)	28.7	24.0 – 36.6
— FOLFIRI + Bevacizumab	185/295 (62.7%)	25.0	22.7 – 27.6

HR 0.77 (95% CI: 0.62 – 0.96)
p (log-rank)= 0.017

No. at risk						
	297	218	111	60	29	9
	295	214	111	47	18	2

Median-follow-up-time: 35.2 months, 95%CI (30.9-39.6)

Tumor samples

N= 637
tumor samples

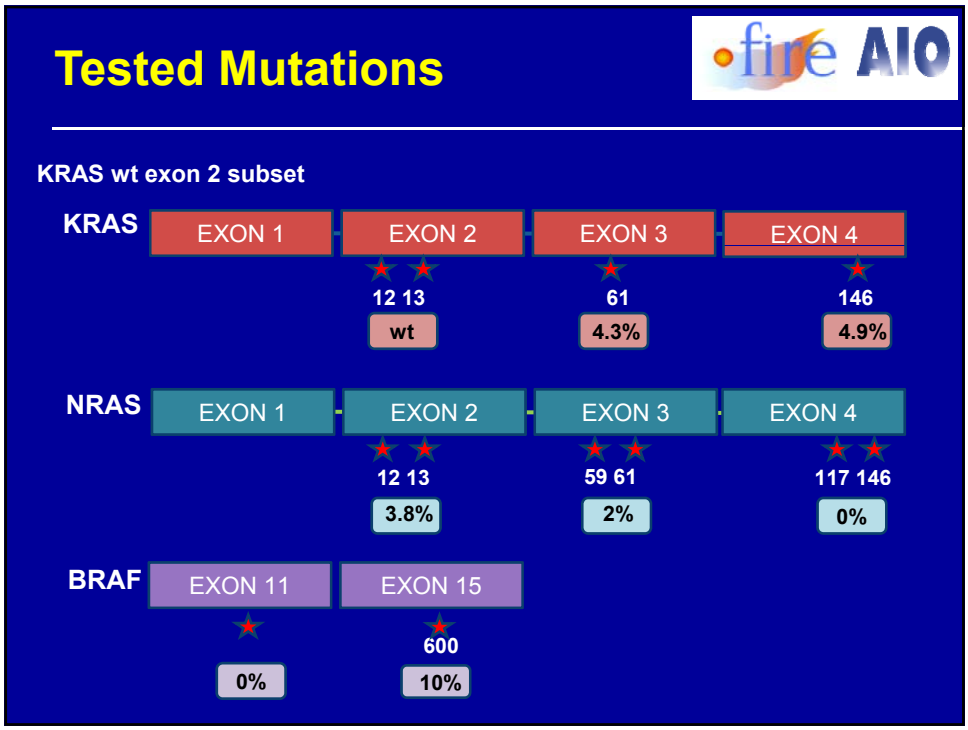
- not KRAS wild-type ITT: 115
- redundant tumor samples: 14
- no tumor on block: 20

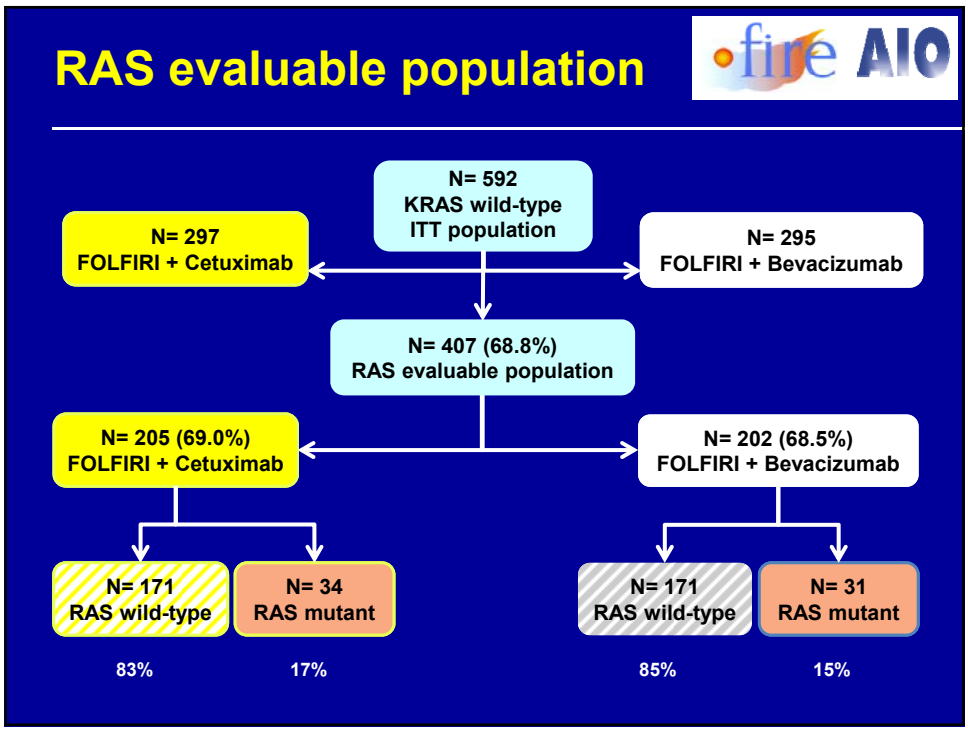
N= 488 (82.4%)
tumor material available of
KRAS wild-type ITT

successful mutational analysis:

- KRAS 61: 431
- KRAS 146: 458
- NRAS exon 2: 464
- NRAS exon 3: 468

N= 407 (69.8%)
RAS mutational analyses
successful in all RAS locations


Tested Mutations
KRAS wt exon 2 subset
KRAS
EXON 1
EXON 2
EXON 3
EXON 4
12 13
wt
61
4.3%
146
4.9%
NRAS
EXON 1
EXON 2
EXON 3
EXON 4
12 13
3.8%
59 61
2%
117 146
0%
BRAF
EXON 11
EXON 15
0%
600
10%


RAS evaluable population
N= 592
KRAS wild-type
ITT population
N= 297
FOLFIRI + Cetuximab
N= 295
FOLFIRI + Bevacizumab
N= 407 (68.8%)
RAS evaluable population
N= 205 (69.0%)
FOLFIRI + Cetuximab
N= 202 (68.5%)
FOLFIRI + Bevacizumab
N= 171
RAS wild-type
N= 34
RAS mutant
N= 171
RAS wild-type
N= 31
RAS mutant
83%
17%
85%
15%

Comparability of Evaluated Groups
Baseline Parameters of Patients

Characteristic	wild-type ITT N=592	RAS population N= 407
Sex, male, %	69.3	68.3
Age, median, years	64.0	64.0
Age < 65, %	53.7	50.6
Age ≥ 65, %	46.3	49.4
Age > 70, %	26.9	23.3
ECOG Performance Status, %		
0	52.7	49.9
1	45,4	48.2
2	1.9	2.0
Leukocyte count		
≥ 8,000/µl, %	41.7	41.5
Alkaline Phosphatase		
≥ 300 U/L, %	13.3	12.0

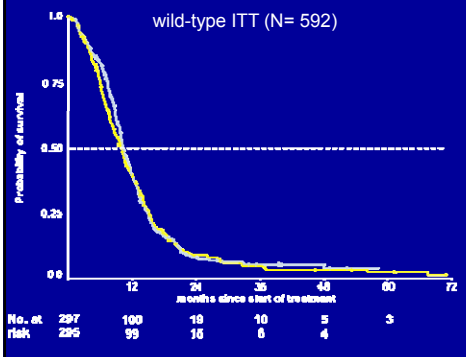
Comparability of Evaluated Groups
Tumor-Related Characteristics

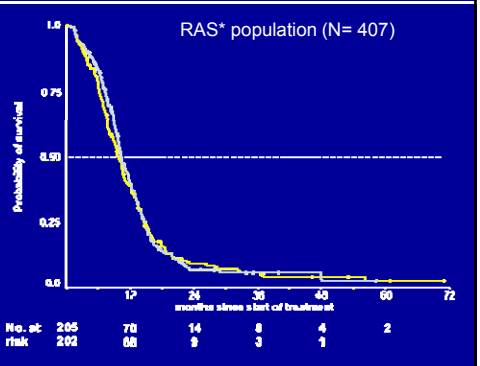
Characteristic	wild-type ITT N=592	RAS population N= 407
Site of primary tumor		
Colon	58.3	59.2
Rectum	37.2	36.4
Colon + Rectum	3.5	3.7
Liver metastasis only		
Yes	31.6	35.4
Prior treatment		
Surgery	82.6	85.5
Adjuvant chemotherapy	20.6	18.7
Radiotherapy pretreatment	13.4	11.6
Number of metastatic sites		
1 site	42.9	44.7
≥ 2 sites	57.1	55.3

Comparability of Evaluated Groups
Response Parameters

	KRAS (exon-2) wt ITT N= 592		RAS analysis population N= 407	
	FOLFIRI Cetuximab N= 297	FOLFIRI Bevacizumab N= 295	FOLFIRI Cetuximab N= 205	FOLFIRI Bevacizumab N= 202
ORR	62%	58%	61%	59.4%
Progression-free survival (median, months)	10.0	10.3	9.9	10.3
Overall survival (median, months)	28.7	25.0	28.7	24.9

Comparability of Evaluated Groups
Progression-free survival





	Events n/N (%)	Median (months)	95% CI
— FOLFIRI Cetuximab	250/297 (84.2%)	10.0	8.8 – 10.8
— FOLFIRI Bevacizumab	242/295 (82.0%)	10.3	9.8 – 11.3

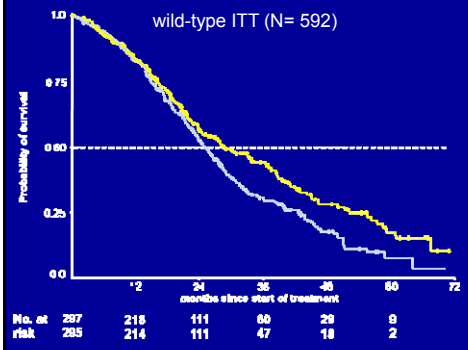
HR 1.06 (95% CI: 0.88 – 1.26)
p (log-rank)= 0.547

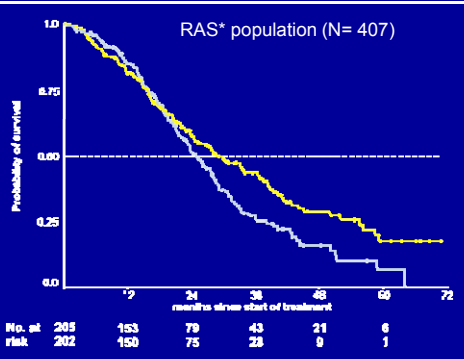
	Events n/N (%)	Median (months)	95% CI
— FOLFIRI Cetuximab	175/205 (85.4%)	9.9	8.8 – 10.8
— FOLFIRI Bevacizumab	165/202 (81.7%)	10.3	9.7 – 11.7

HR 1.05 (95% CI: 0.84 – 1.26)
p (log-rank)= 0.68

RAS* wild-type: KRAS61/146; NRAS Exon2, NRAS Exon3

Comparability of Evaluated Groups
Overall survival





	Events n/N (%)	Median (months)	95% CI
— FOLFIRI Cetuximab	158/297 (53.2%)	28.7	24.0 – 36.6
— FOLFIRI Bevacizumab	185/295 (62.7%)	25.0	22.7 – 27.6

HR 0.77 (95% CI: 0.62 – 0.96)
p (log-rank)= 0.017

	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	113/205 (55.1%)	28.7	24.4 – 36.6
— FOLFIRI + Bevacizumab	127/202 (62.9%)	24.8	21.9 – 28.0

HR 0.76 (95% CI: 0.59 – 0.98)
p (log-rank)= 0.033

RAS* wild-type: KRAS61/146; NRAS Exon2, NRAS Exon3

Evaluation of ORR

ORR	FOLFIRI + Cetuximab %	FOLFIRI + Cetuximab 95%-CI	FOLFIRI + Bevacizumab %	FOLFIRI + Bevacizumab 95%-CI	Odds ratio	p
ITT population* (N= 592)	62.0	56.2 – 67.5	58.0	52.1 – 63.7	1.18 0.85-1.64	0.183
RAS WT (N= 342)	65.5	57.9 – 72.6	59.6	51.9 – 67.1	1.28 0.83-1.99	0.157
RAS MT (N= 65)	38.2	22.2 – 56.4	58.1	39.1 – 75.5	0.45 0.17-1.21	0.97
BRAF MT (N= 48)	52.2	30.6– 73.2	40.0	21.1 – 61.3	1.64 0.52-5.14	0.29

p = one-sided Fisher´s exact test

*KRAS exon-2 wild-type

Evaluation of ORR assessable for response population

ORR	FOLFIRI + Cetuximab %	FOLFIRI + Cetuximab 95%-CI	FOLFIRI + Bevacizumab %	FOLFIRI + Bevacizumab 95%-CI	Odds ratio	p
Assessable for response* (N= 526)	72.2	66.2 – 77.6	63.1	57.1 – 68.9	1.52 1.05-2.19	0.017
RAS WT (N= 307)	75.7	67.9 82.3	64.2	56.2 – 71.6	1.73 1.06-2.86	0.019
RAS MT (N=57)	44.8	26.6 – 64.3	64.3	44.1 – 81.4	0.45 0.16-1.31	0.96
BRAF MT (N= 44)	60.0	36.1 – 80.9	41.7	22.1 – 63.4	2.10 0.63-7.03	0.18

*KRAS exon-2 wild-type

p = one-sided Fisher´s exact test

Evaluation of PFS

PFS	FOLFIRI + Cetuximab months	FOLFIRI + Cetuximab 95%-CI	FOLFIRI + Bevacizumab months	FOLFIRI + Bevacizumab 95%-CI	Hazard ratio	p
ITT population (N= 592)	10.0	8.8 – 10.8	10.3	9.8 – 11.3	1.06 (0.88 – 1.26)	0.547
RAS WT (N= 342)	10.4	9.5 – 12.2	10.2	9.3 – 11.5	0.93 (0.74 – 1.17)	0.54
RAS MT (N= 65)	6.1	5.3 – 8.5	12.2	9.7 – 13.9	2.22 (1.28 – 3.86)	0.004
BRAF MT (N= 48)	4.9	2.4 – 8.8	6.0	4.3 – 7.8	0.87 (0.49 – 1.57)	0.65

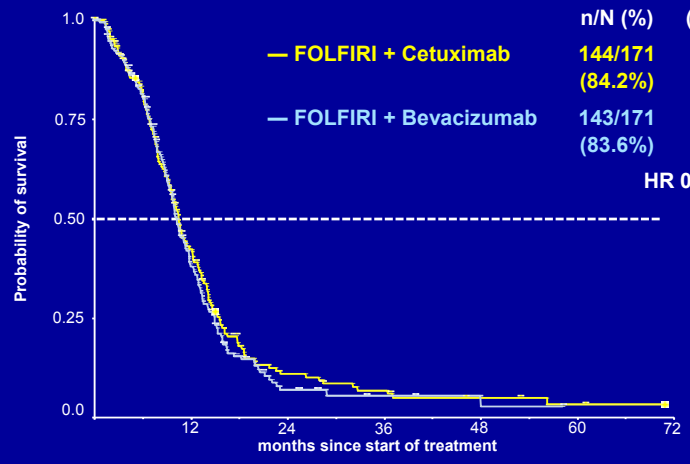
p = one-sided Fisher´s exact test

Evaluation of OS

PFS	FOLFIRI + Cetuximab months	FOLFIRI + Cetuximab 95%-CI	FOLFIRI + Bevacizumab months	FOLFIRI + Bevacizumab 95%-CI	Hazard ratio	p
ITT population (N= 592)	28.7	24.0 – 36.6	25.0	22.7 – 27.6	0.77 (0.62 – 0.96)	0.017
RAS WT (N= 342)	33.1	24.5 – 39.4	25.6	22.7 – 28.6	0.70 (0.53 – 0.92)	0.011
RAS MT (N= 65)	16.4	15.9 – 27.6	20.6	17.0 – 28.4	1.20 (0.64 – 2.28)	0.57
BRAF MT (N= 48)	12.3	5.5 – 21.7	13.7	7.8 – 19.5	0.87 (0.47 – 1.61)	0.65

p = one-sided Fisher´s exact test

Progression-free survival RAS* wild-type

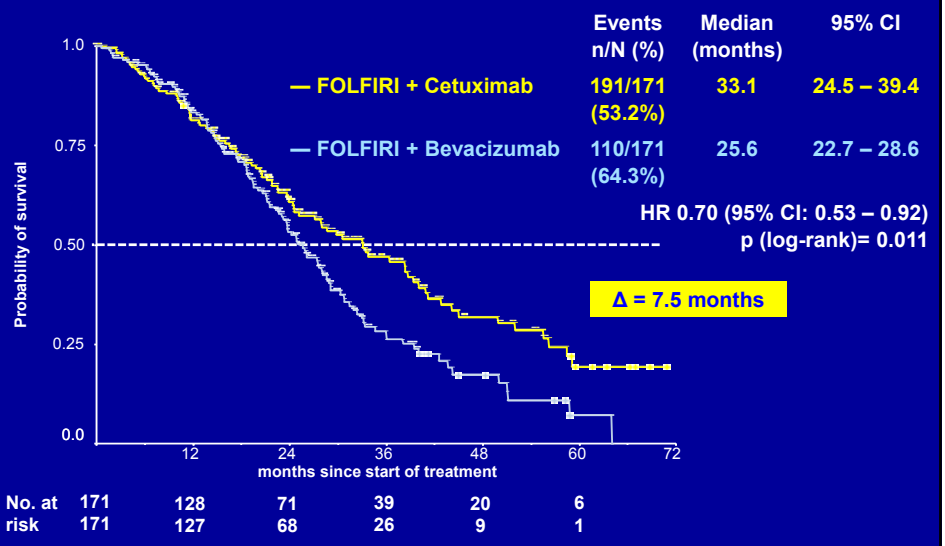


	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	144/171 (84.2%)	10.4	9.5 – 12.2
— FOLFIRI + Bevacizumab	143/171 (83.6%)	10.2	9.3 – 11.5

HR 0.93 (95% CI: 0.74 – 1.17)
p (log-rank)= 0.54

RAS* wild-type: KRAS61/146; NRAS Exon2, NRAS Exon3

Overall survival RAS* wild-type



RAS* wild-type: KRAS61/146; NRAS Exon2, NRAS Exon3

Summary

- **FIRE-3 is the first study** to compare cetuximab plus FOLFIRI to bevacizumab plus FOLFIRI in 1st-line treatment of mCRC
- The RAS evaluable population was in all respects comparable to the ITT population
- In patients with all-RAS wild-type tumors ORR and PFS were not significantly different between treatment arms
- **OS was markedly superior (Δ = 7.5 months)** in all-RAS wild-type patients receiving 1st-line therapy with cetuximab
- **Inferior outcome** was observed when patients with Ras-mutant tumors were treated with FOLFIRI plus cetuximab as compared to FOLFIRI plus bevacizumab

Conclusions

- **Upfront determination of RAS mutation** status appears highly recommendable in patients with metastatic disease
- Patients with all-RAS wild-type tumors have a clinically relevant **survival benefit** when first-line treatment with cetuximab is offered
- Patients with **RAS mutated tumors** appear to have a disadvantage from cetuximab and should not receive ant-EGFR-based therapy
- **BRAF mutation** mainly has a prognostic importance