Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population

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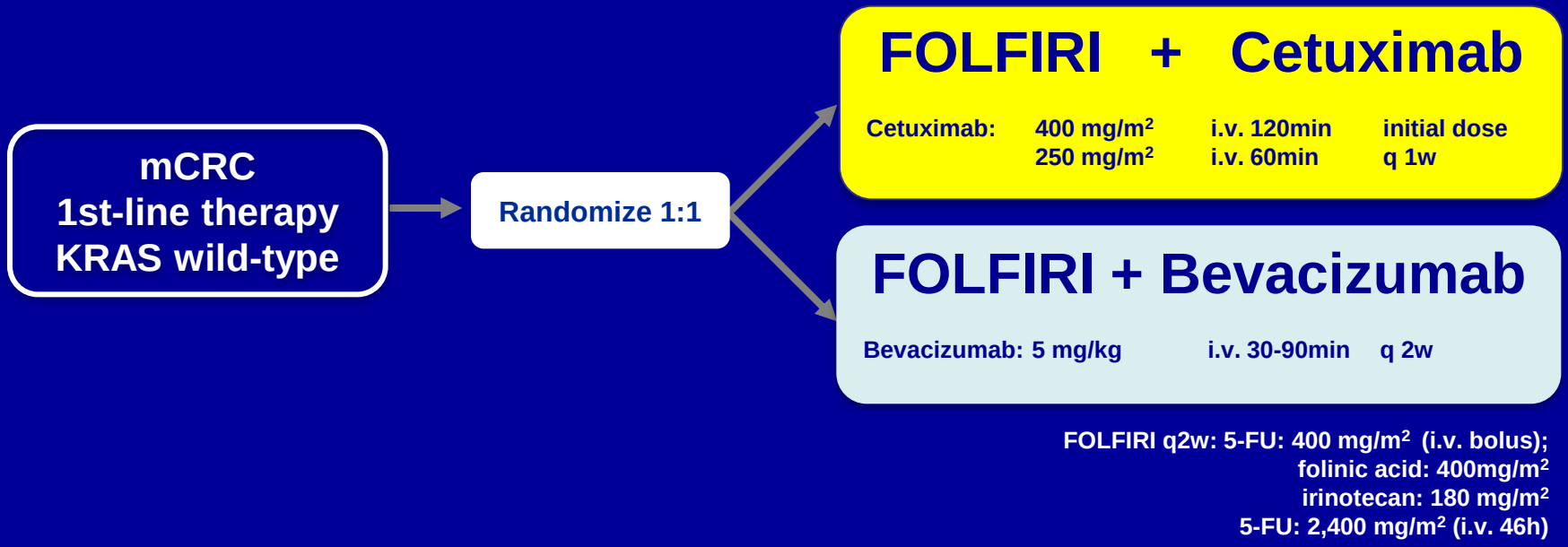
Disclosures

- Research funding / advisory boards
  - Merck KGaA
  - Roche
  - Amgen
  - Sanofi-Aventis

FIRE-3 study design

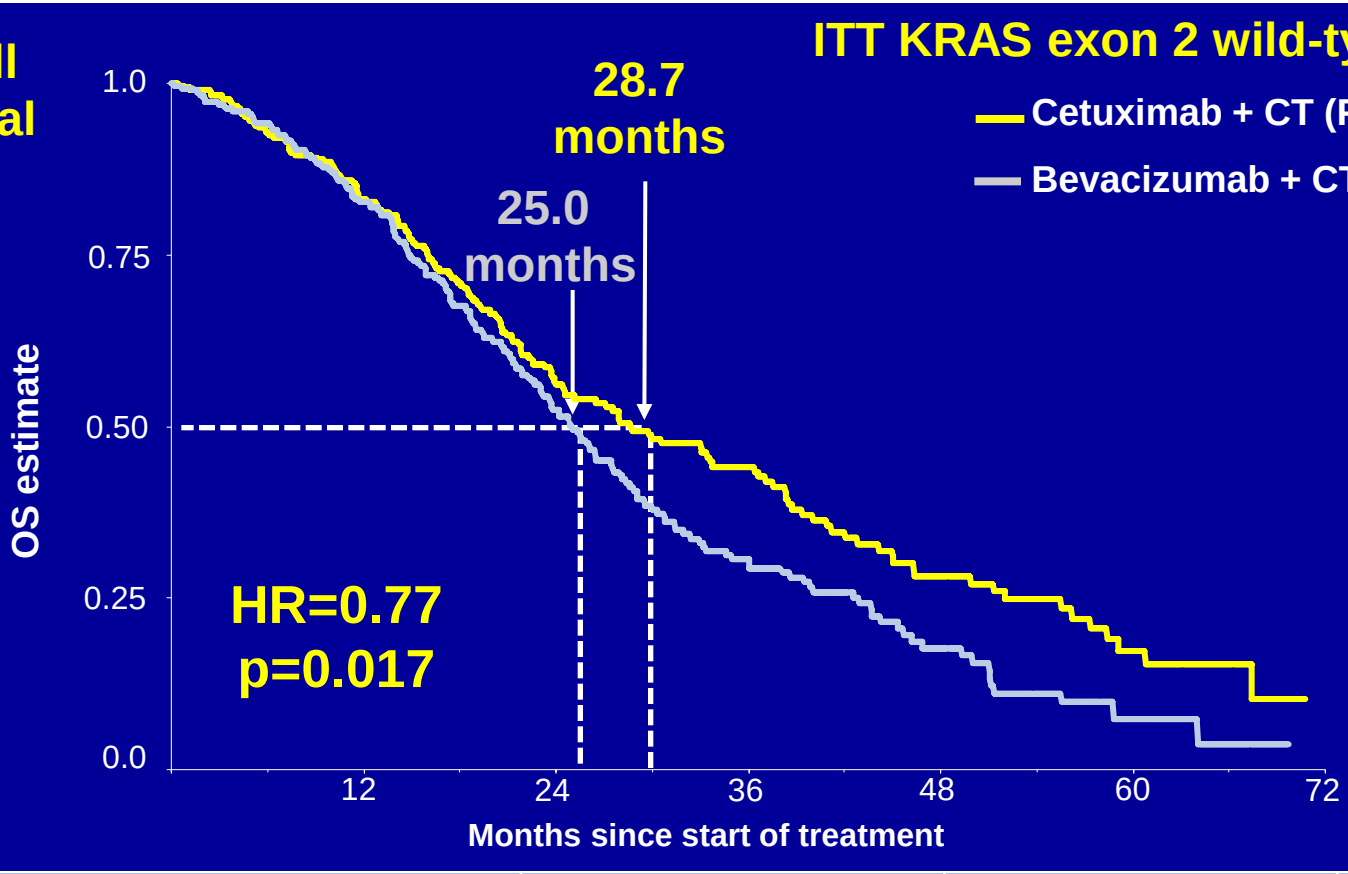


FOLFIRI q2w: 5-FU: 400 mg/m² (i.v. bolus);
folinic acid: 400mg/m²
irinotecan: 180 mg/m²
5-FU: 2,400 mg/m² (i.v. 46h)

- **Primary endpoint: Overall response rate (RECIST 1.0)**
- **Amendment in October 2008** to include only KRAS wild-type patients
- 150 active centers in Germany and Austria

FIRE-3 study results

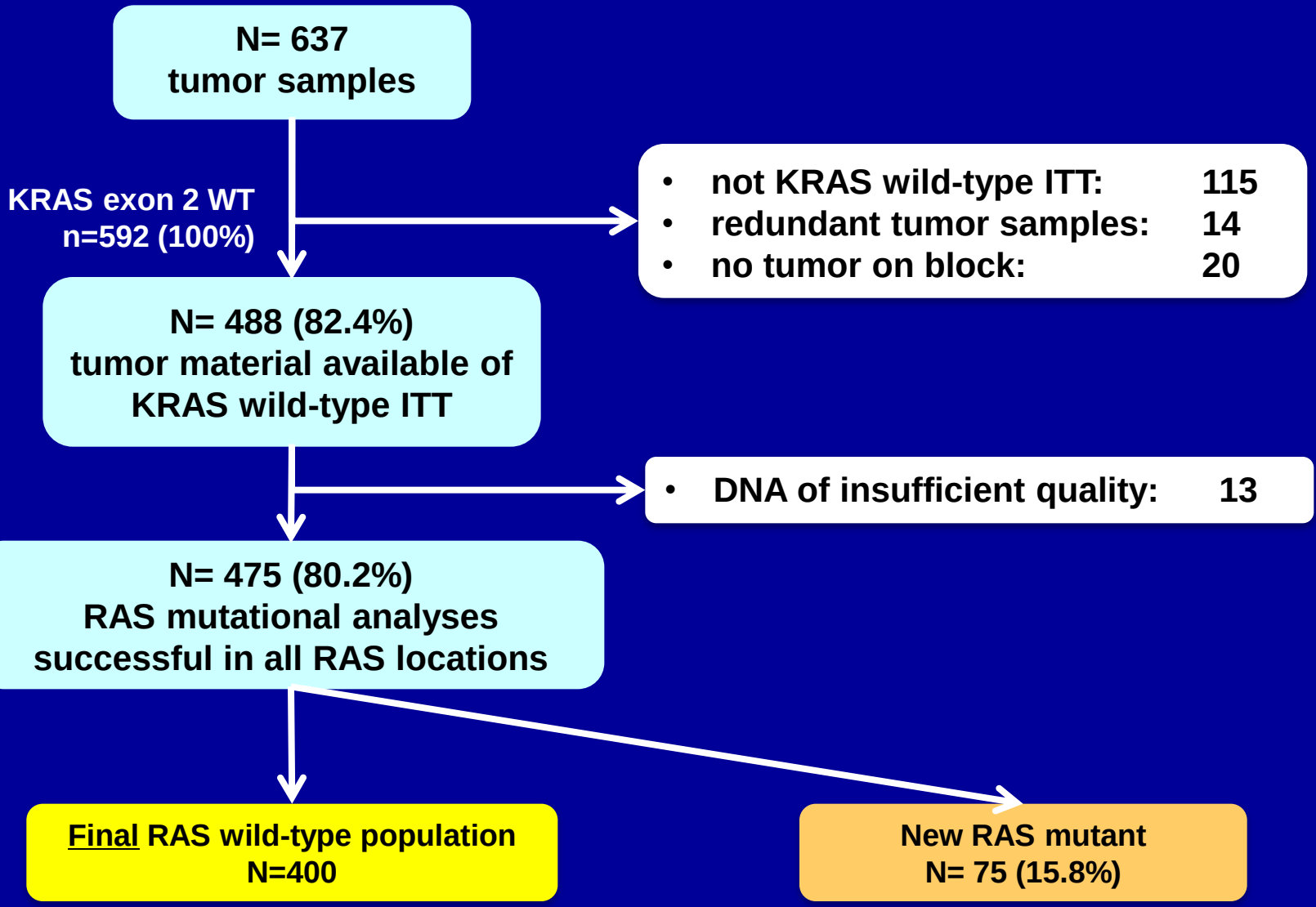
Overall survival



	Cetuximab + CT	Bevacizumab + CT	p value
Overall response rate (primary endpoint not met)	62%	58%	0.183
Progression-free survival	10.0 months	10.3 months	0.547

Heinemann V, et al. Lancet Oncol Lancet Oncol. 2014 Sep;15(10):1065-75

Tumor samples

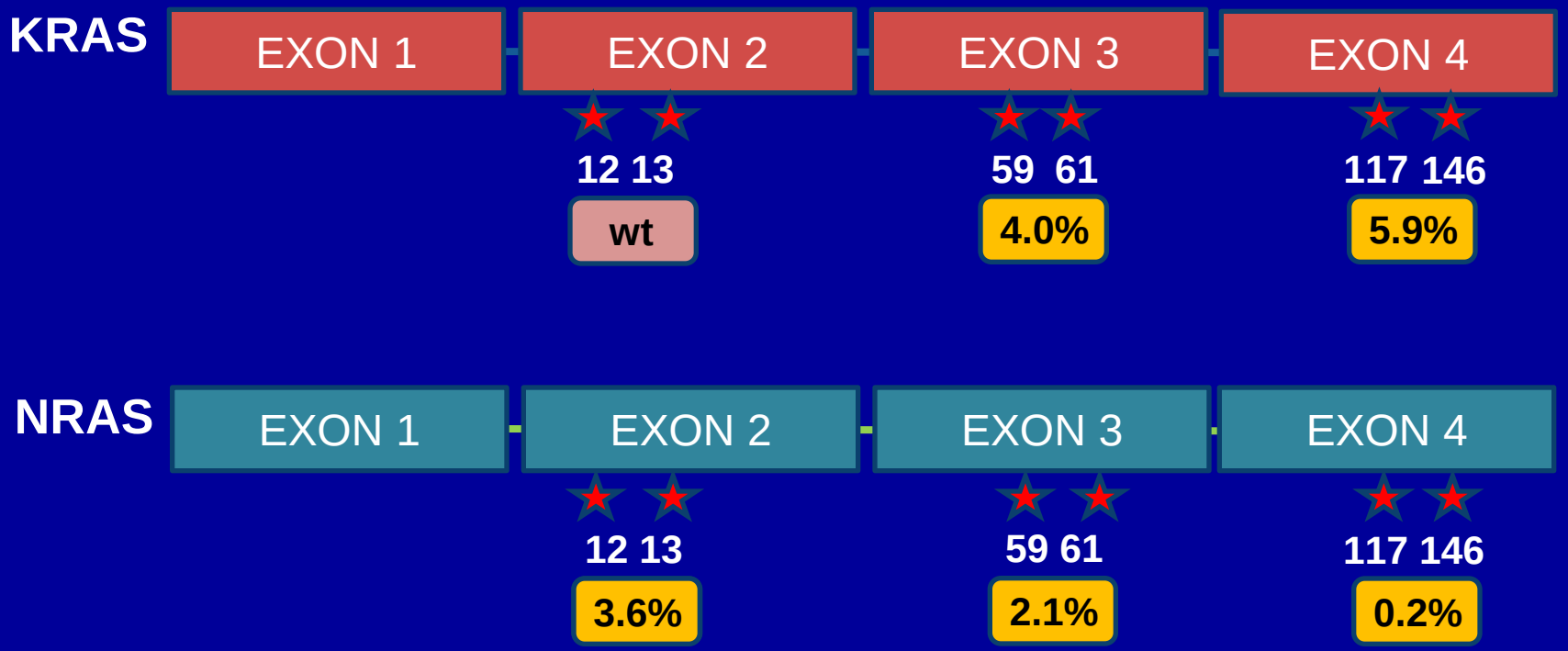


Comparability of Evaluated Groups
Efficacy Parameters

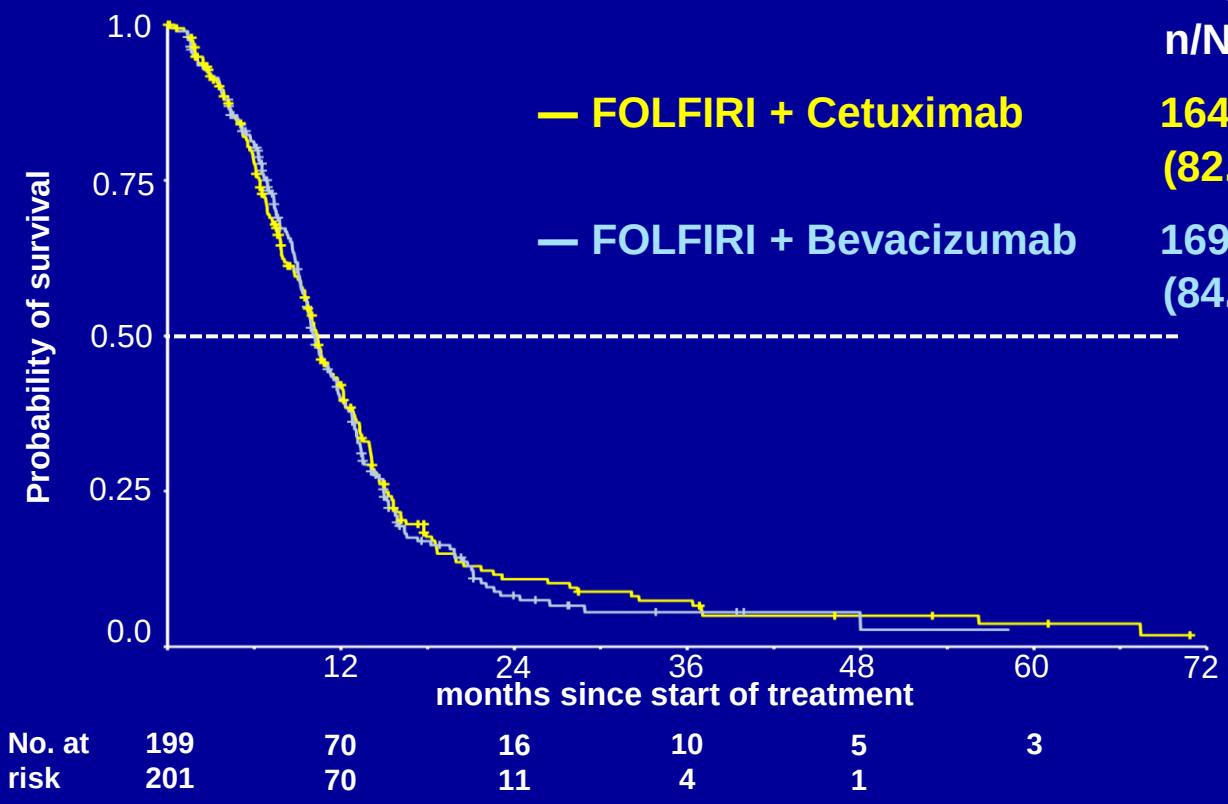
	ITT, KRAS wt exon 2 population N=592		Final RAS evaluable population N= 475	
	FOLFIRI Cetuximab N= 297	FOLFIRI Bevacizumab N= 295	FOLFIRI Cetuximab N= 238	FOLFIRI Bevacizumab N= 237
ORR	62%	58%	61.3%	58.2%
Progression-free survival (median, months)	10.0	10.3	9.7	10.3
Overall survival (median, months)	28.7	25.0	28.0	24.7

Tested Mutations

KRAS exon 2 wild-type subset



ORR and PFS
Final RAS* wild-type population



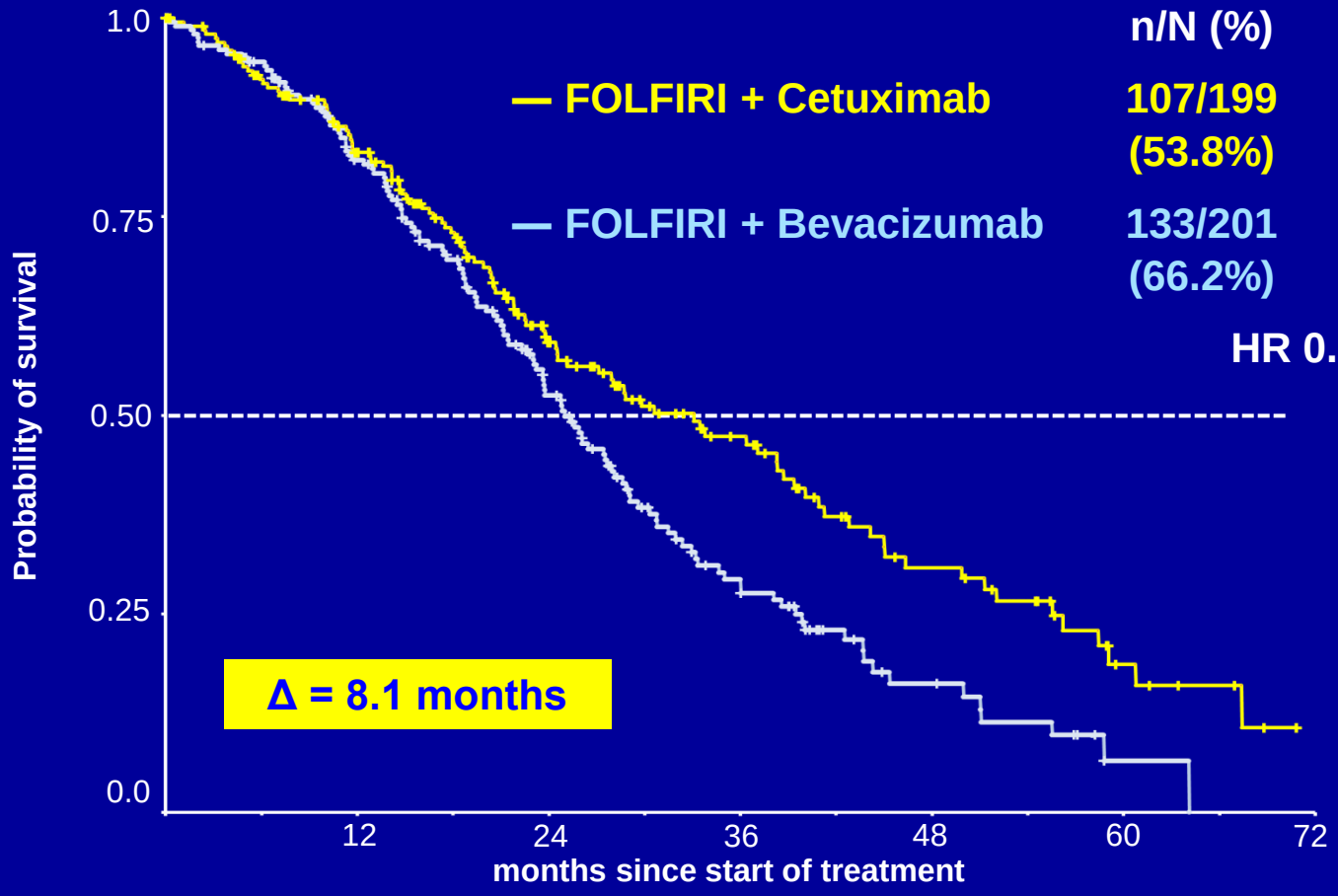
	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	164/199 (82.4%)	10.3	9.5 – 11.8
— FOLFIRI + Bevacizumab	169/201 (84.1%)	10.2	9.3 – 11.7

HR 0.97 (95% CI: 0.78 – 1.20)
p (log-rank)= 0.77

N=400	Cetuximab + FOLFIRI (N=199)	Bevacizumab + FOLFIRI (N=201)	OR/ (95% CI)	p-value
ORR, % (95% CI)	**65.3** (58.3–51.6)	**58.7** (51.6–65.6)	1.33 (0.88–1.99)	0.18

*** KRAS and NRAS exon 2, 3 and 4 wild-type**

Overall survival
Final RAS* wild-type population



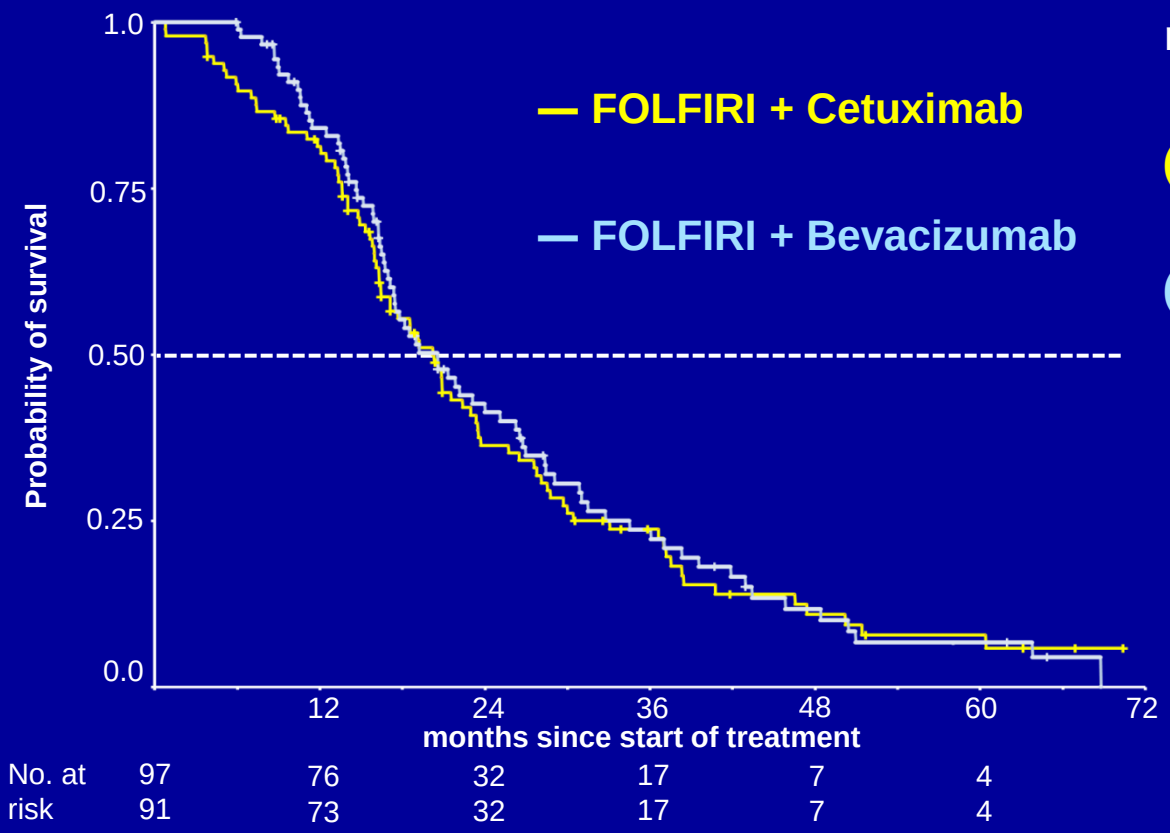
	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	107/199 (53.8%)	33.1	24.5 – 39.4
— FOLFIRI + Bevacizumab	133/201 (66.2%)	25.0	23.0 – 28.1

HR 0.697 (95% CI: 0.54 – 0.90)
p (log-rank)= 0.0059

No. at risk						
	199	147	79	46	23	7
	201	147	82	34	11	1

* KRAS and NRAS exon 2, 3 and 4 wild-type

Final RAS mutant population



	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	82/97 (84.5%)	20.2	16.4 – 23.4
— FOLFIRI + Bevacizumab	75/91 (82.4%)	20.6	17.1 – 26.3

HR 1.05 (95% CI: 0.77 – 1.44)
p (log-rank)= 0.75

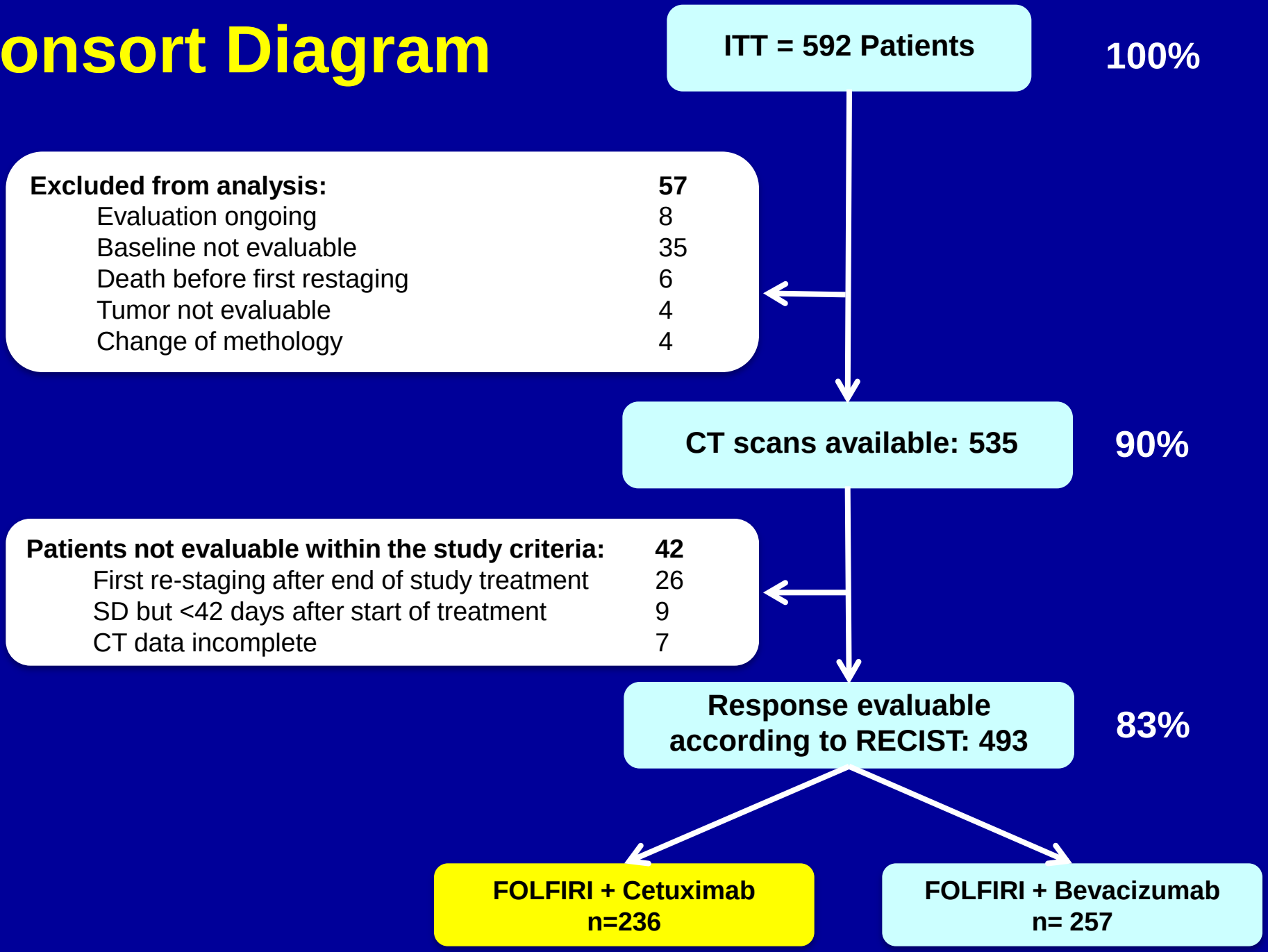
n=188	Cetuximab + FOLFIRI	Bevacizumab + FOLFIRI	OR/HR (95% CI)	p-value
ORR, % (95% CI)	**38.1** (28.5–48.6)	**50.5** (39.9–61.2)	0.60 (0.34–1.08)	0.11
Median PFS, months (95% CI)	**7.5** (5.7–8.5)	**9.6** (8.5–10.9)	1.25 (0.93–1.68)	0.14

Independent radiological review

An independent, centralized radiological review (blinded to treatment arms) was performed to evaluate:

- **Tumor response** according to RECIST 1.1
- **Early tumor shrinkage** (ETS) (-20% diameter change) measured at 1st CT after baseline (6 weeks)
- **Depth of response** defined as the percentage of maximal tumor shrinkage observed at the nadir compared with baseline

Consort Diagram



Independent radiological review

ITT, KRAS exon 2 wt population
n= 592 patients

100%

FOLFIRI + Cetuximab (n= 296)
FOLFIRI + Bevacizumab (n= 295)

KRAS exon 2 wt CT evaluable population
n= 493 patients

83%

FOLFIRI + Cetuximab (n= 236)
FOLFIRI + Bevacizumab (n= 257)

Final RAS wt population
n= 400 patients

100%

FOLFIRI + Cetuximab (n= 199)
FOLFIRI + Bevacizumab(n=201)

RAS wt CT evaluable population
n= 330 patients

83%

FOLFIRI + Cetuximab (n= 157)
FOLFIRI + Bevacizumab (n=173)

Evaluation of ORR
Primary analysis

	FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab		Odds ratio	p
ORR	%	95%-CI	%	95%-CI		
ITT population (N= 592)	62.0	56.2 – 67.5	58.0	52.1 – 63.7	1.18 0.85-1.64	0.183
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

p = Fisher´s exact test (one-sided)

Heinemann V- et al J Clin Oncol 31, 2013 (suppl; abstr LBA3506)

Independent evaluation of response

CT evaluable population	FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab			
ORR	%	95%-CI	%	95%-CI	Odds ratio	p
KRAS exon 2 wt n= 493	66.5	60.1 – 72.5	55.6	49.3 – 61.8	1.58 (1.10-2.28)	0.016
Final RAS wt n= 330	72.0	64.3 – 78.8	56.1	48.3 – 63.6	2.01 (1.27-3.19)	0.003

p = Fisher´s exact test (two-sided)

Evaluation of ETS Rate

(Early Tumor Shrinkage)

Rate of Early Tumor Shrinkage*

CT evaluable population	FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab		Odds ratio	p
	%	95%-CI	%	95%-CI		
KRAS exon 2 wt n= 493	62.3	55.8 – 68.5	47.9	41.6 – 54.2	1.80 (1.26-2.58)	0.0015
Final RAS wt n= 330	68.2	60.3 – 75.4	49.1	41.5 – 56.8	2.22 (1.41-3.47)	0.0005

*ETS: early tumor shrinkage ≥20% at 6 weeks

p = Fisher´s exact test (two-sided)

Association of ETS* and Survival

Final RAS wt population

Final RAS wild-type population (n= 330)

	FOLFIRI + Cetuximab (n= 157)				FOLFIRI + Bevacizumab (n= 173)				
Patients with	PFS (mo)	p HR	OS (mo)	p HR	Patients with	PFS (mo)	p HR	OS (mo)	p HR
ETS (n=107)	9.7	0.0037 0.59	38.3	0.0023 0.52	ETS (n=85)	11.7	0.03 0.71	31.9	0.0001 0.48
no ETS (n=50)	5.8		20.5		no ETS (n=88)	8.3		21.2	

*ETS: early tumor shrinkage ≥20% at 6 weeks

p = log-rank test p (two-sided)

Evaluation of Depth of Response (DpR*)

median DpR	FOLFIRI + Cetuximab %	FOLFIRI + Cetuximab SE	FOLFIRI + Bevacizumab %	FOLFIRI + Bevacizumab SE	p
KRAS exon 2 wt n= 493	- 44.1	(±54.6%)	- 32.9	(± 44.3%)	0.0003
Final RAS wt n= 330	- 48.9	(±54.8%)	- 32.3%	(± 42.3%)	<0.0001

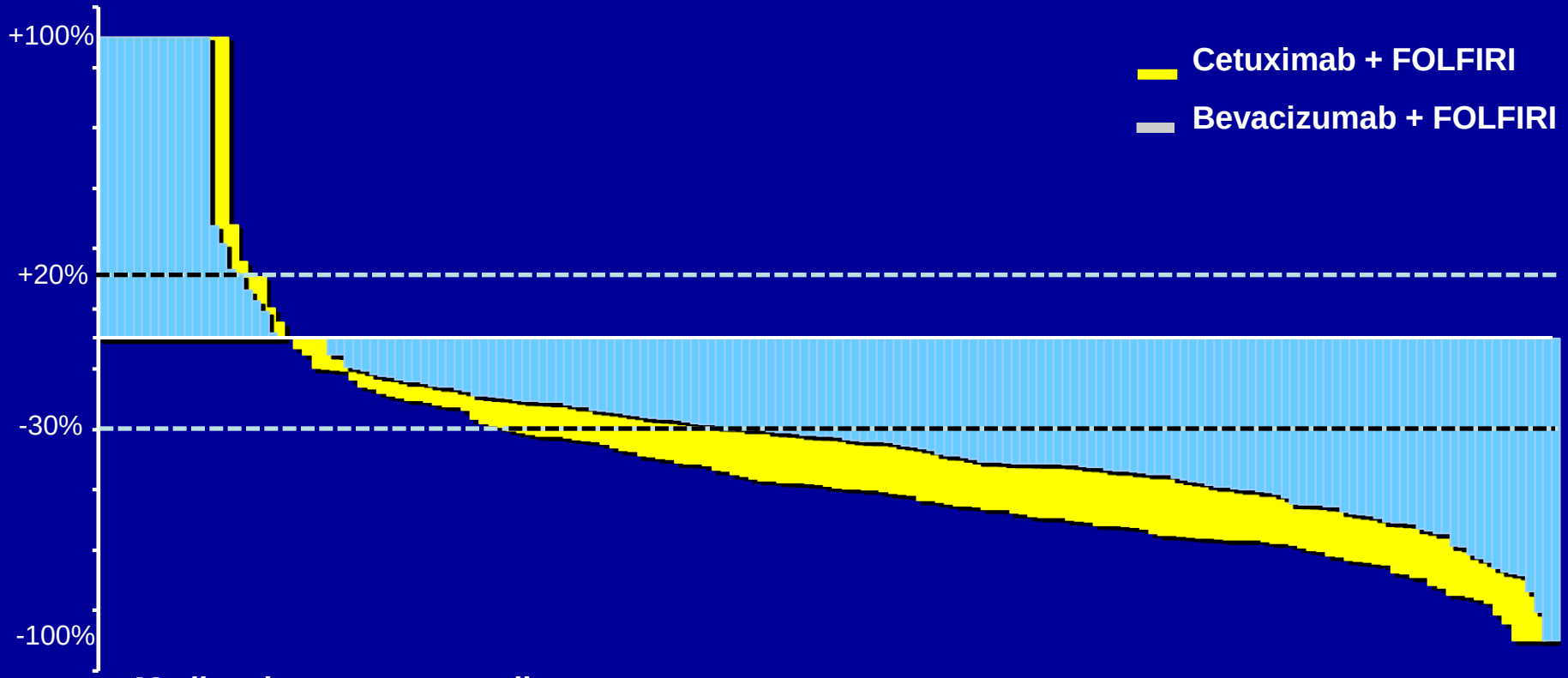
Depth of response correlated significantly with OS and PFS (two-sided Bravais Pearson test)

***DpR:** percentage of maximal tumor shrinkage observed at the nadir compared with baseline

SE = standard error; p = two-sided Wilcoxon test p

Waterfall-Plot

- Tumor response in final **RAS wild-type** population (n=330)

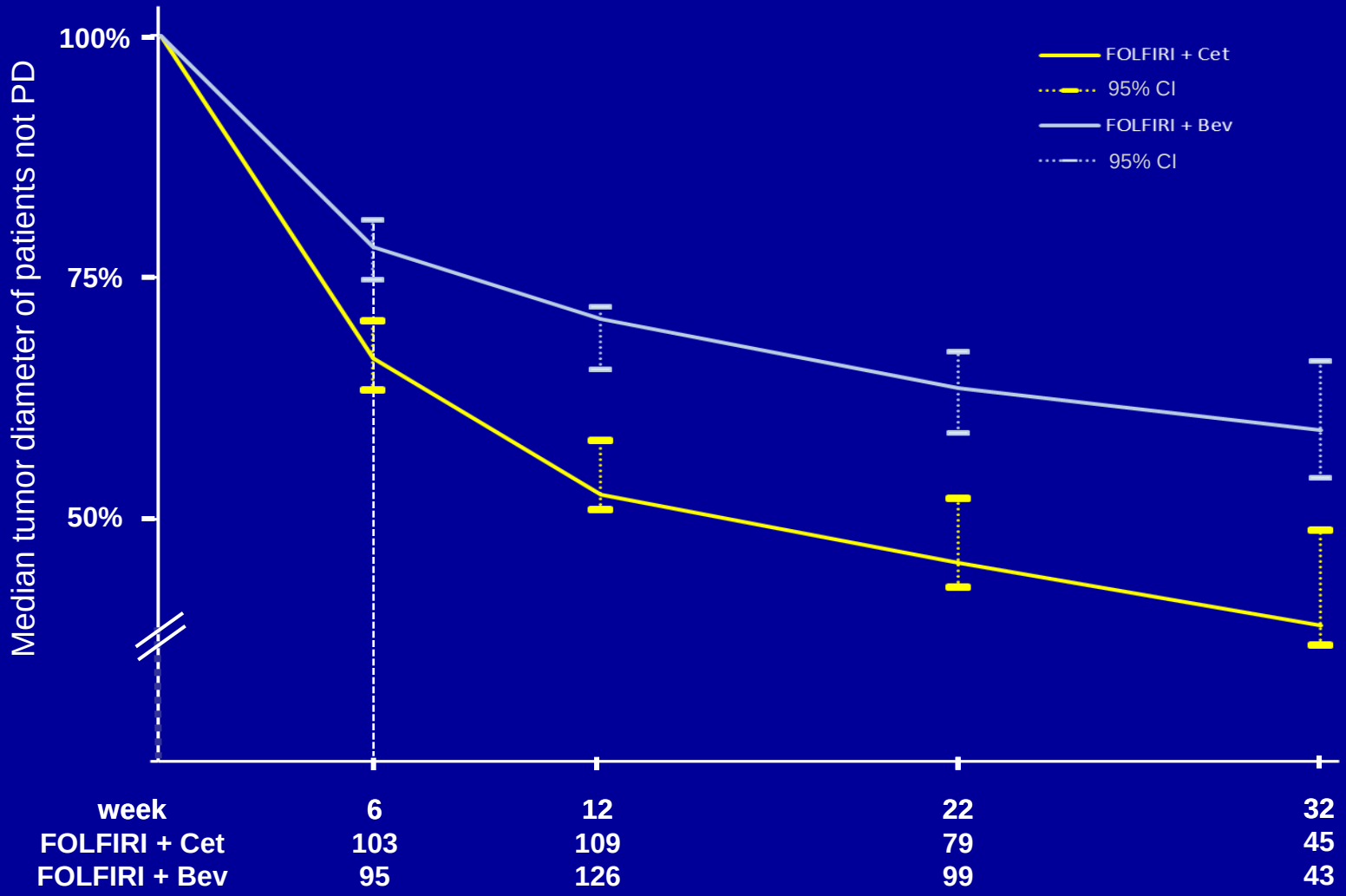


Median time to tumor nadir:

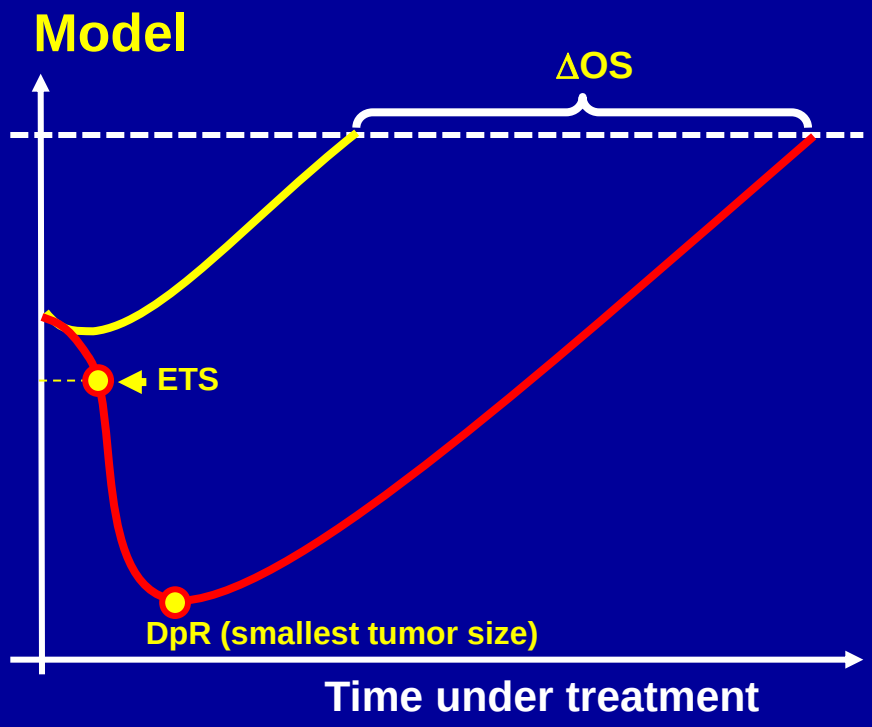
FOLFIRI + Cet: **15.0 weeks**

FOLFIRI + Bev: **15.7 weeks**

Median tumor diameter by treatment time (final RAS)



Depth of response correlates with overall survival

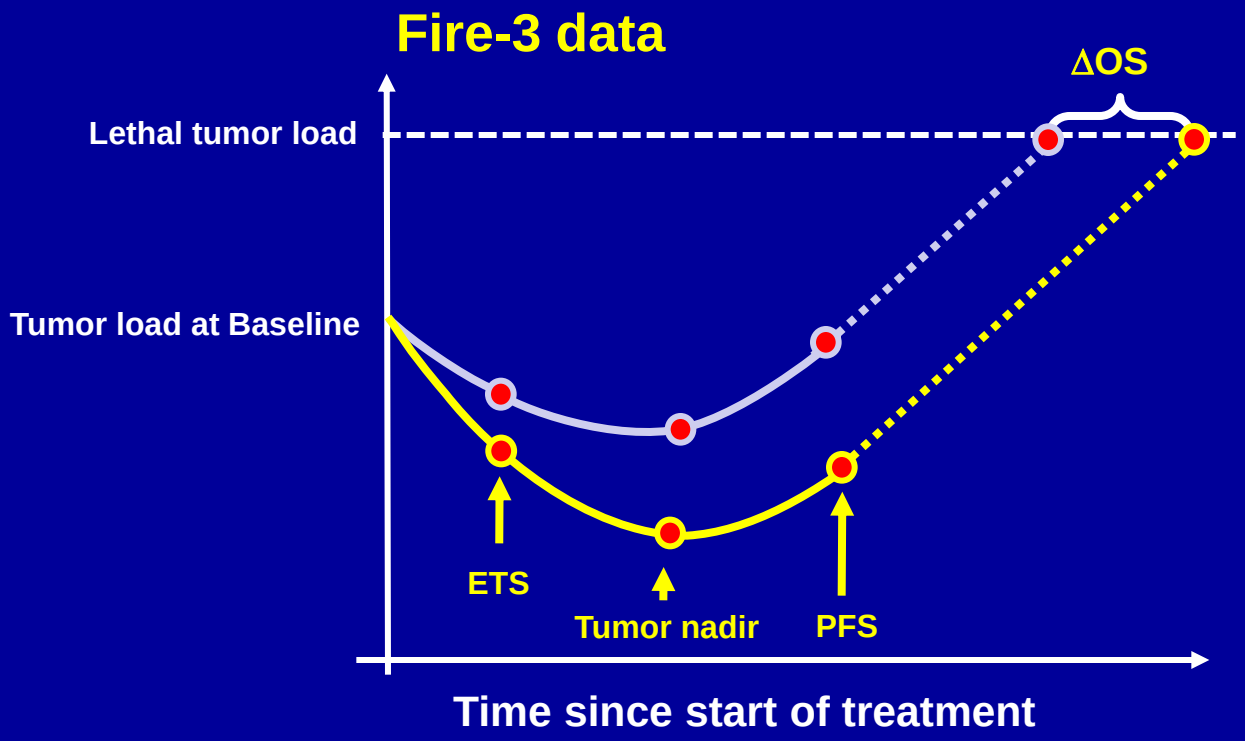


- ETS predicts sensitivity to treatment
- ETS predicts the potential DpR
- DpR predicts OS

CRYSTAL study	Cetuximab + FOLFIRI (n=315)	FOLFIRI (n=348)	p
Median DpR (95% CI)	**50.9**	**33.3**	**p<0.0001**
Median OS (95% CI)	**23.5** (21.2 - 26.3)	**20.0** (17.4 - 21.7)	**P<0.0093**

adopted from Mansmann et al, ASCO GI 2013 abstract #427

Depth of response correlates with overall survival



- ETS predicts sensitivity to treatment
- DpR predicts OS

FIRE-3 Study (AIO KRK-0306)	Cetuximab + FOLFIRI (n=157)	Bevacizumab + FOLFIRI (n=173)	p
Median DpR (95% CI)	**48.9**	**32.2**	**p<0.0001**
Median OS (95% CI)	**33.1** (24.5 – 39.4)	**25.0** (23.0 – 28.1)	**P=0.0056**

Summary of RAS analyses

- Extended RAS testing was possible in **>80% of FIRE-3 ITT.**
- 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
- **Median OS was markedly superior (Δ = 8.1 months, HR 0.70)** in all-RAS wild-type patients receiving 1st-line therapy with cetuximab

Summary of central independent radiological evaluation

- Independent evaluation of CT-scans was possible in **>80% of FIRE-3 ITT** population.
- The independent CT review demonstrates a **significantly higher ORR in FOLFIRI plus cetuximab** treated patients compared to those receiving FOLFIRI plus bevacizumab
- ETS was significantly **more frequent in the cetuximab arm** (68.2% vs. 49.1%; p=0.0005)
- **ETS was significantly associated with prolonged survival**, independent of the treatment arm
- **Median DpR** was significantly greater in the cetuximab arm (48.9% vs 32.2%; p <0.0001) and correlated with survival

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