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Target therapy e neoplasie apparato gastroenterico: quali reali novità per la pratica clinica

Carcinoma Gastrico

TRASTUZUMAB: Preclinica

HER2: Espressione variabile

Con valutazione uguale al K. mammario = 7-43% ¹

Con valutazione uguale allo score pre-TOGA = 22% ¹

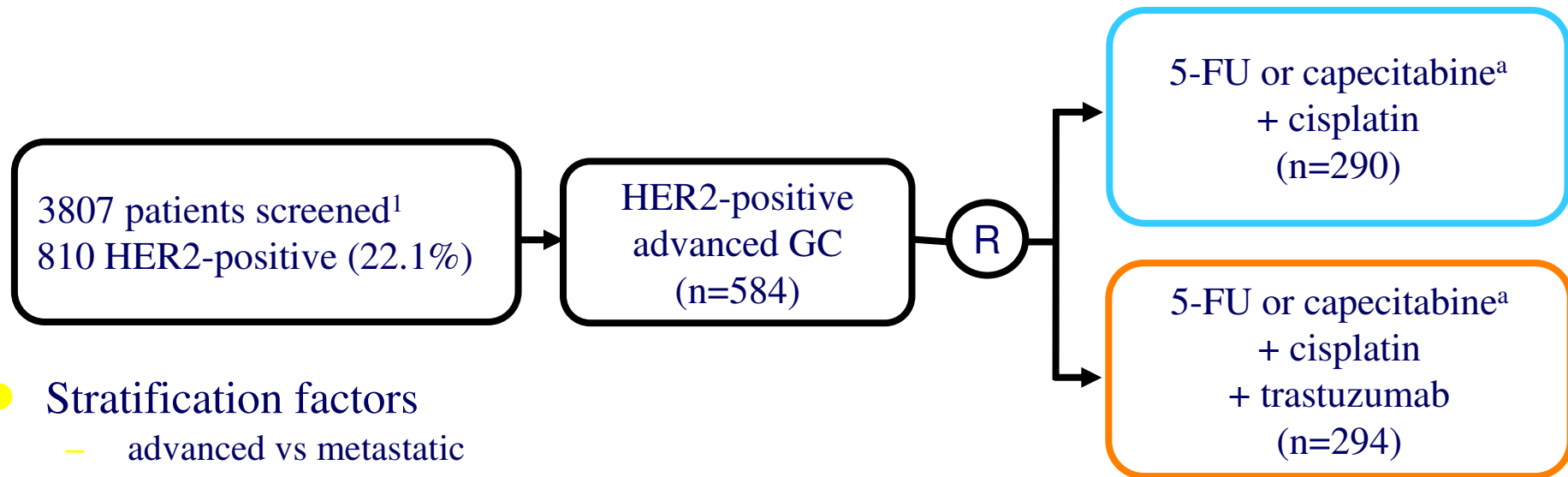
Espressione ICH = Amplificazione FISH ²

Espressione correlata con istotipo (Diffusi -), sede (GEG ++),
altre mutazioni (E-cadherina --) ²

¹ Hofmann M, Histopathology 2008 52:797–805

² Marx AH, Hum Pathol. 2009 Jun;40(6):769-77

TOGA trial: Disegno dello studio



● Stratification factors

- advanced vs metastatic
- GC vs GEJ
- measurable vs non-measurable
- ECOG PS 0-1 vs 2
- capecitabine vs 5-FU

^aChosen at investigator's discretion
GEJ, gastroesophageal junction

Primary end point:

overall survival

Secondary end points

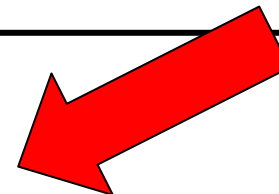
PFS, TTP, ORR, Clinical Benefit Rate, Duration of Response, QoL

¹Bang et al; Abstract 4556, ASCO 2009

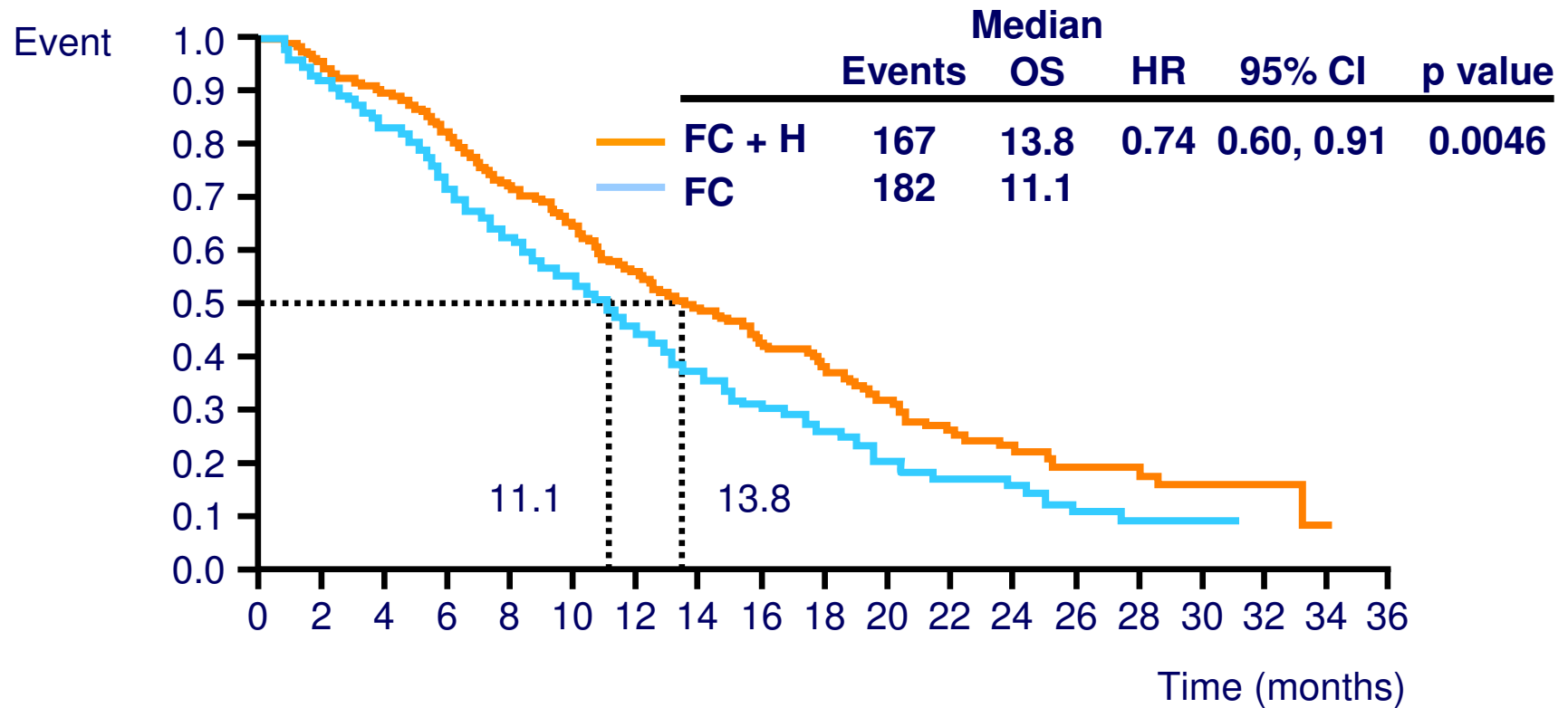
Demografica e caratteristiche dei pazienti

Characteristic	F+C n=290	F+C + trastuzumab n=294
Sex, %		
Male / Female	75 / 25	77 / 23
Age, median (range) years	59.0 (21-82)	61.0 (23-83)
Weight, median (range) kg	60.3 (28-105)	61.5 (35-110)
Region, n (%)		
Asia	166 (56)	158 (53)
C/S America	26 (9)	27 (9)
Europe	95 (32)	99 (33)
Other	9 (3)	14 (5)
Type of GC (central assessment)		
Intestinal	74.2 ^a	76.8 ^b
Diffuse	8.7 ^a	8.9 ^b
Mixed	17.1 ^a	14.3 ^b
Prior gastrectomy	21.4	24.1

Highest recruitment was from Korea, Japan, China and Russia
 F, fluoropyrimidine; C, cisplatin ^an=287; ^bn=293



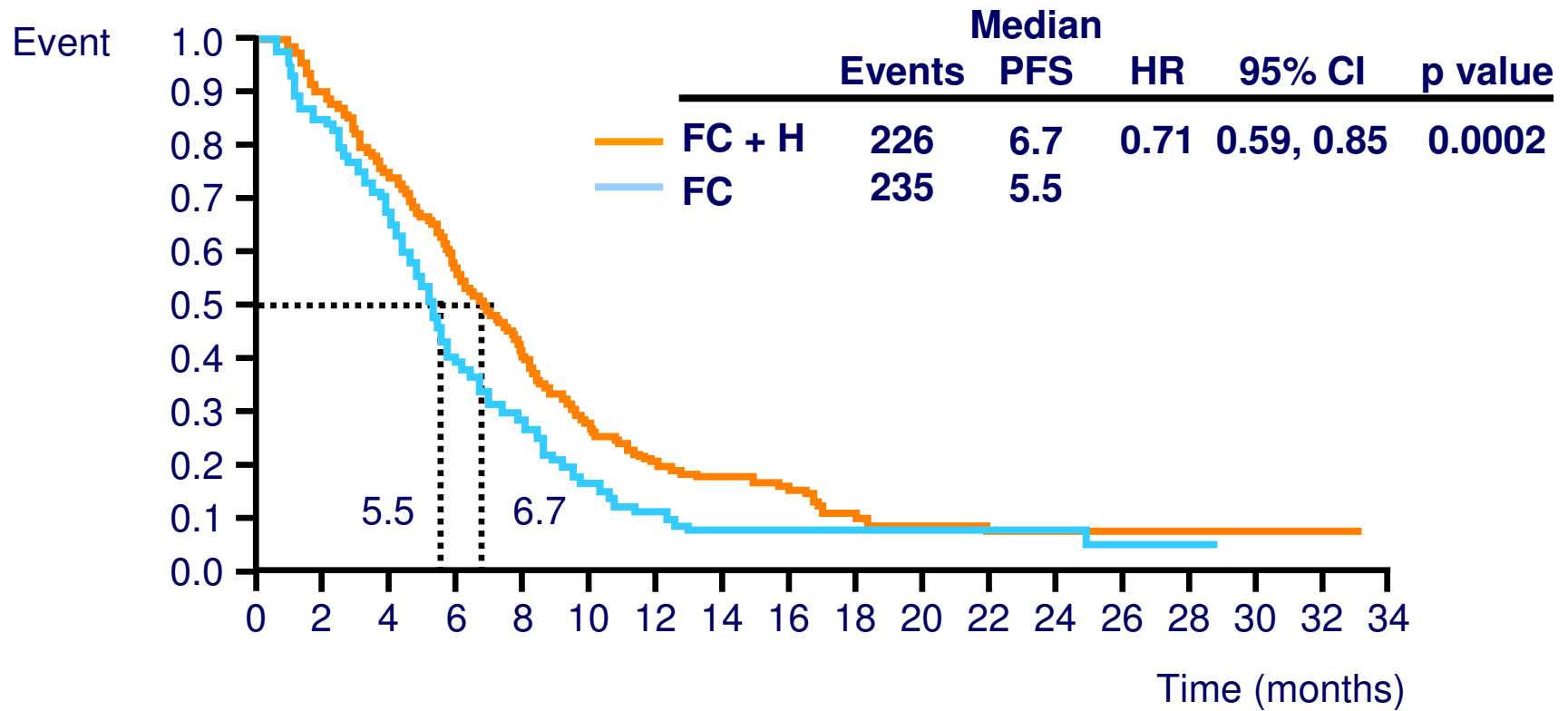
Primary end point: OS



No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
FC + H	294	277	246	209	173	147	113	90	71	56	43	30	21	13	12	6	4	1	0
FC	290	266	223	185	143	117	90	64	47	32	24	16	14	7	6	5	0	0	0

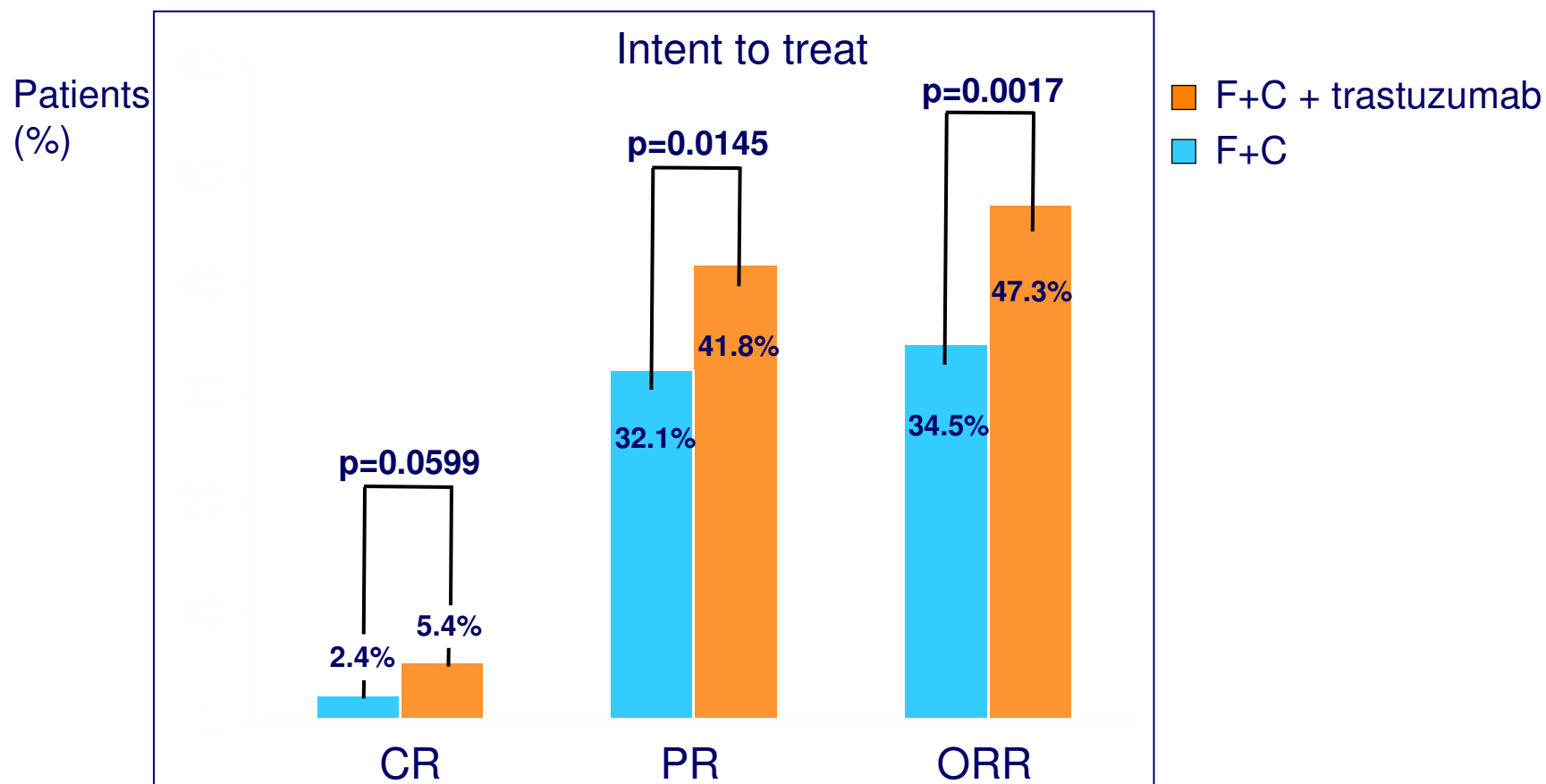
CI, confidence interval; H, trastuzumab

Secondary end point: PFS



No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
FC + H	294	258	201	141	95	60	41	28	21	13	9	8	6	6	6	4	2	0
FC	290	238	182	99	62	33	17	7	5	3	3	2	2	1	1	0	0	0

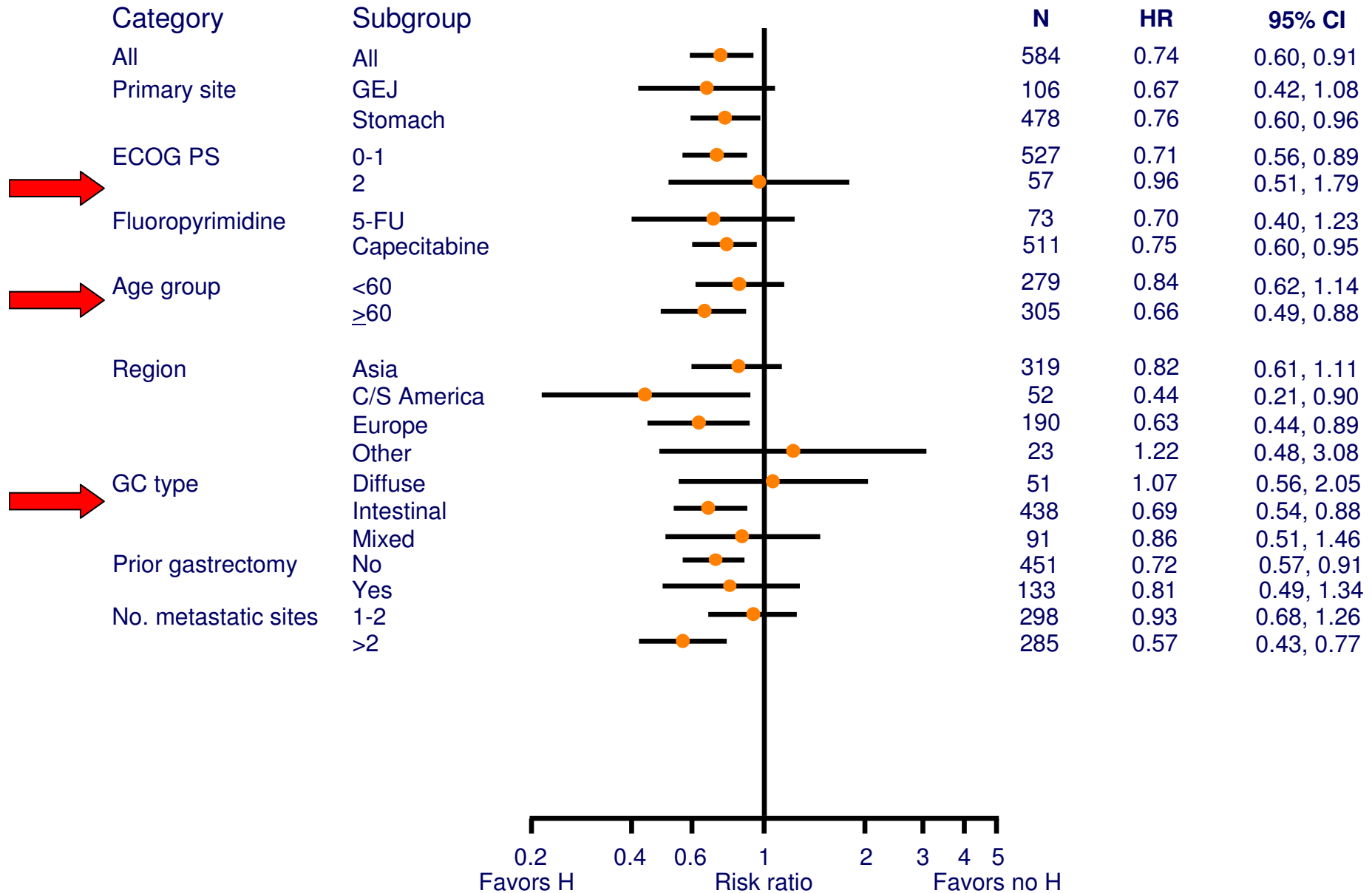
Secondary end point: tumor response rate



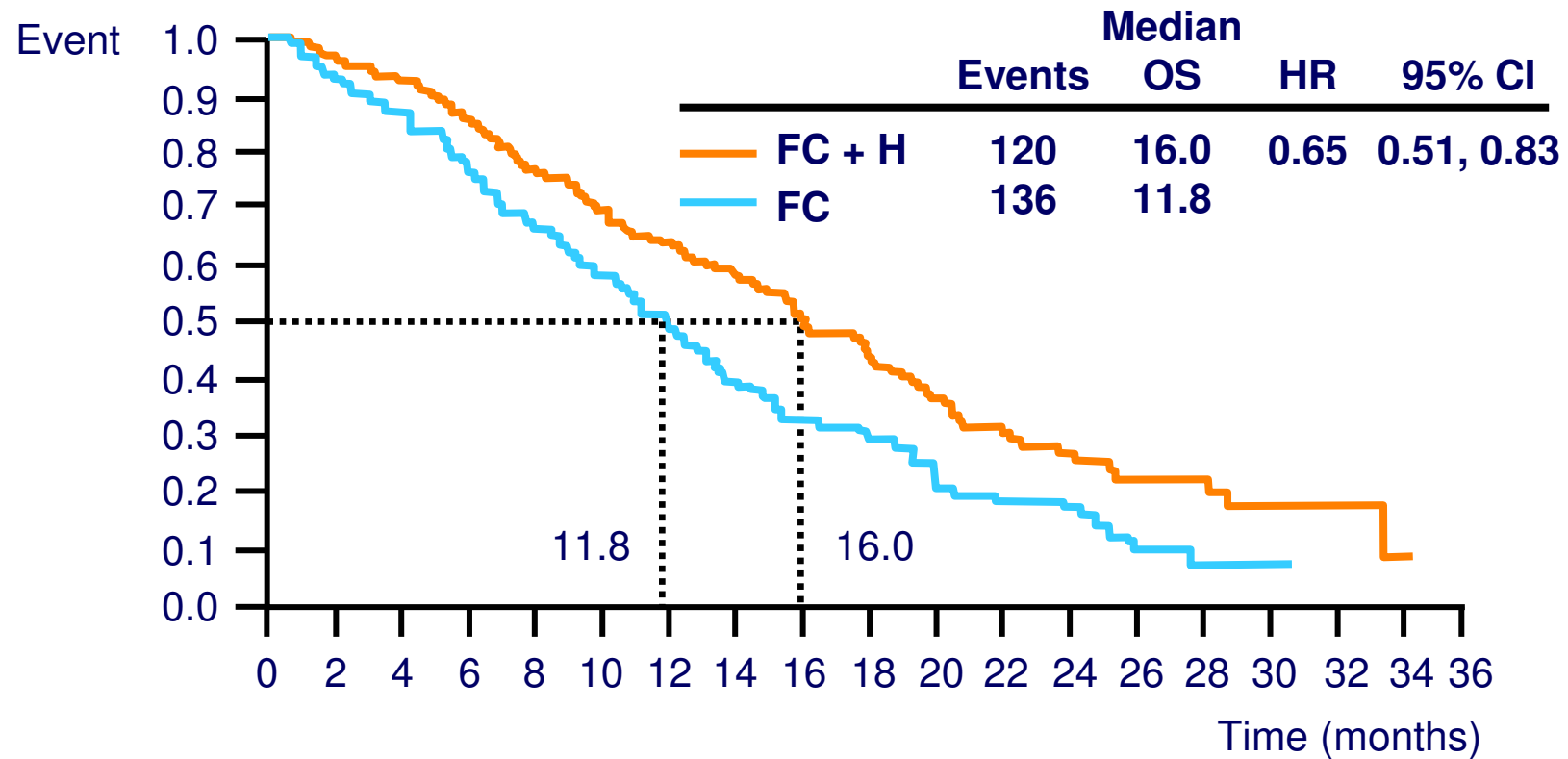
ORR= CR + PR

CR, complete response; PR, partial response

Efficacy: OS subgroup analysis



OS in IHC2+/FISH+ or IHC3+ (exploratory analysis)



No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
FC + H	228	218	196	170	142	122	100	84	65	51	39	28	20	12	11	5	4	1	0
FC	218	198	170	141	112	96	75	53	39	28	20	13	11	4	3	3	0	0	0

2nd-line treatment received after progression

Treatment, n (%)	F+C n=290	F+C + trastuzumab n=294
Patients receiving any therapy	131 (45)	122 (42)
Chemotherapy	124 (43)	113 (38)
Cytotoxic therapy received by >5% of patients		
Docetaxel	40 (14)	38 (13)
Paclitaxel	35 (12)	38 (13)
5-FU	52 (18)	53 (18)
Irinotecan	56 (19)	47 (16)
Cisplatin	21 (7)	21 (7)
Oxaliplatin	20 (7)	14 (5)
S-1	21 (7)	22 (7)
HER2 targeting therapy		
Lapatinib	3 (1)	4 (1)
Trastuzumab	2 (<1)	3 (1)
Radiotherapy	17 (6)	17 (6)
Surgery	13 (4)	8 (3)

Conclusioni Herceptin

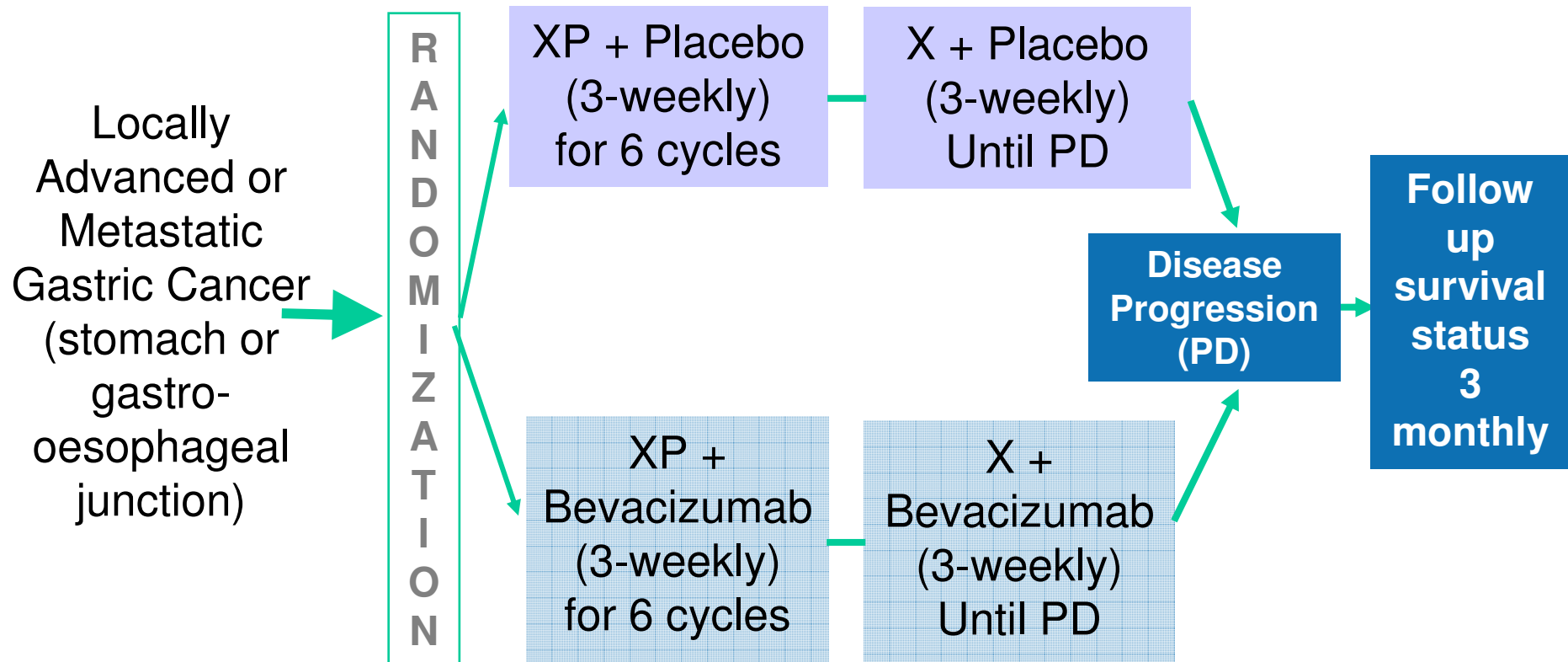
Opzione terapeutica in pazienti con HER2 espresso
in associazione a chemioterapia a base di X/F+Platino

Valutazione HER2 gastrico \neq valutazione HER2 mammella

Anche con nuovo score, concordanza tra vari patologi > 90% ¹

Nei pazienti con HER2+ si è raggiunta un OS mediana di
16 mesi

Avagast: disegno dello studio



XP = capecitabine + cisplatin

AVAGAST: Caratteristiche dei pazienti

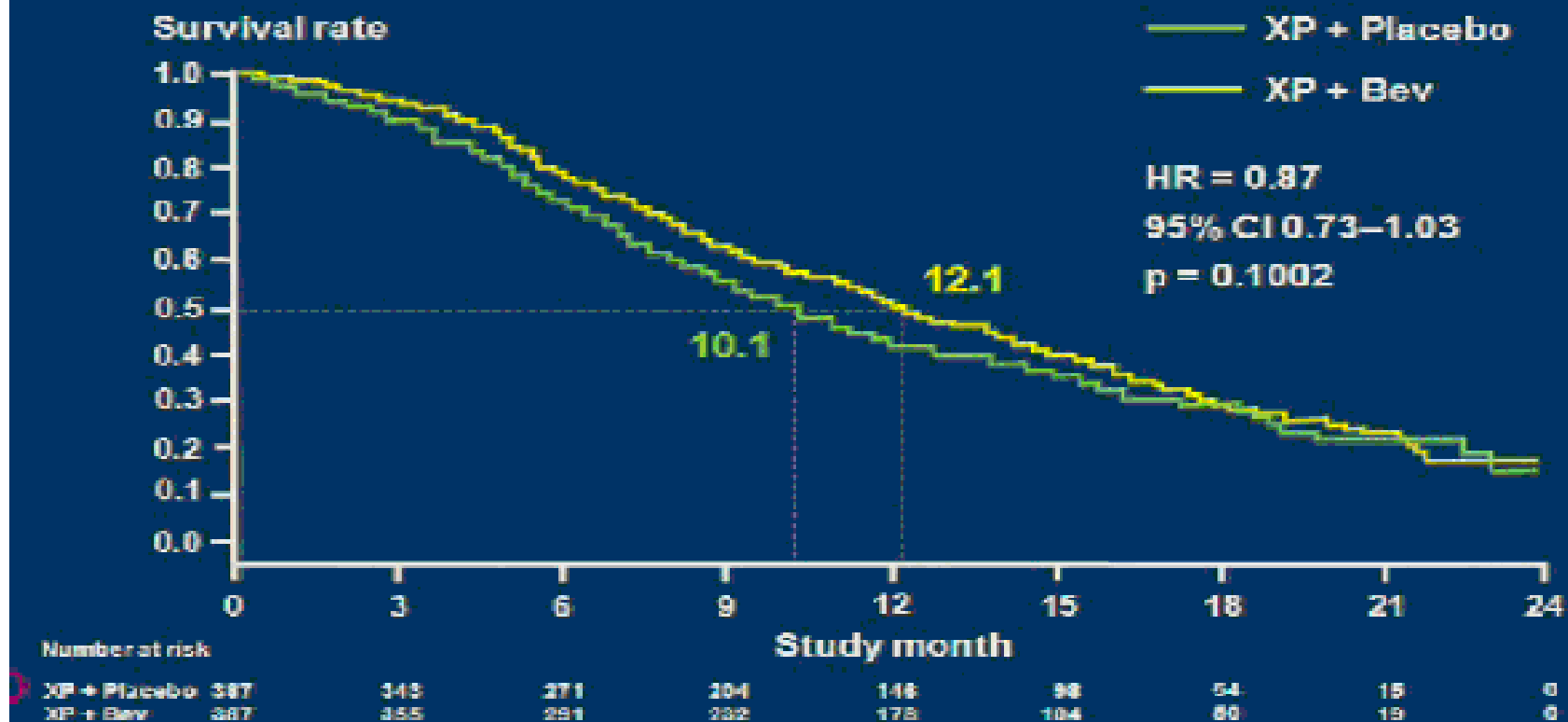
Number of patients N=774 (%)		XP + Placebo N=387	XP + Bev N=387
Gender	Male	258 (67)	257 (66)
Age, years	Median (range)	59 (22–82)	58 (22–81)
ECOG PS	0–1	367 (95)	365 (94)
	≥2	20 (5)	22* (6)
Region	Asia	188 (49)	188 (49)
	Europe	124 (32)	125 (32)
	Pan-America	75 (19)	74 (19)
Fluoropyrimidine	Capecitabine	365 (94)	364 (94)
	5-FU	22 (6)	23 (6)
Disease status	Locally advanced	9 (2)	20 (5)
	Metastatic	378 (98)	367 (95)

AVAGAST: Caratteristiche dei pazienti

Number of patients N=774 (%)		XP + Placebo N=387	XP + Bev N=387
Primary site	Stomach	338 (87)	333 (86)
	GEJ	49 (13)	54 (14)
Histologic type	Intestinal	135 (35)	155 (40)
	Diffuse	206 (53)	176 (46)
	Mixed	26 (7)	35 (9)
Disease measurability	Measurable	297 (77)	311 (80)
	Evaluable	90 (23)	76 (20)
Metastatic sites, n	0	8 (2)	8 (2)
	1	131 (34)	131 (34)
	≥2	247 (64)	247 (64)
Prior gastrectomy	Yes	107 (28)	110 (28)
Liver metastasis	Yes	126 (33)	130 (34)

Obiettivo Primario: OS

Overall Survival



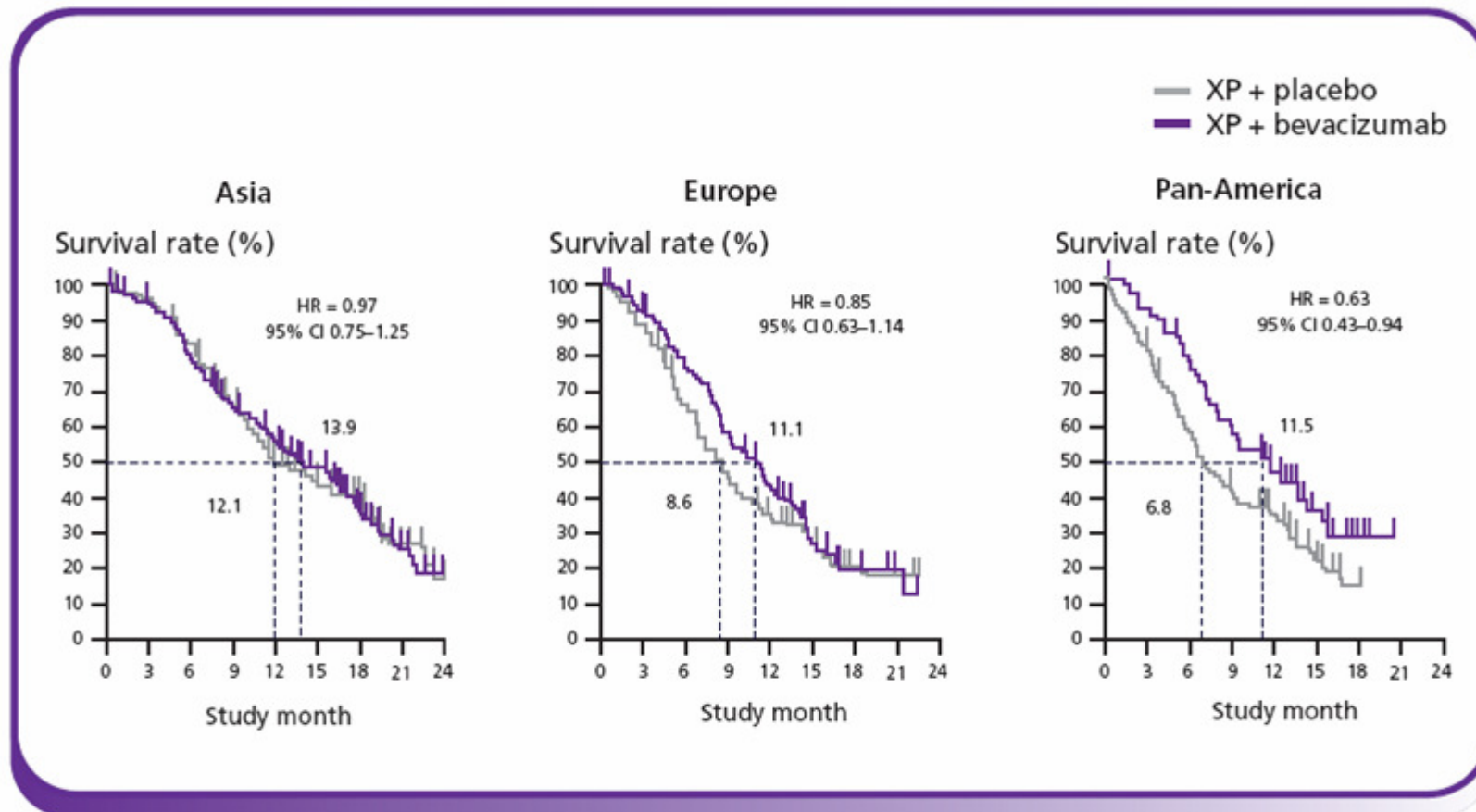
Differenze tra varie OS

Regional Differences in Efficacy

	Region	XP + Placebo Median, mo	XP + Bev Median, mo	Delta, mo	Hazard Ratio	95% CI
OS	Asia	12.1	13.9	1.8	0.97	0.75–1.25
	Europe	8.6	11.1	2.5	0.85	0.63–1.14
	America	6.8	11.5	4.7	0.63	0.43–0.94
PFS	Asia	5.6	6.7	1.1	0.92	0.74–1.14
	Europe	4.4	6.9	2.5	0.71	0.54–0.93
	America	4.4	5.9	1.5	0.65	0.46–0.93

Differenze geografiche = diversa efficacia?

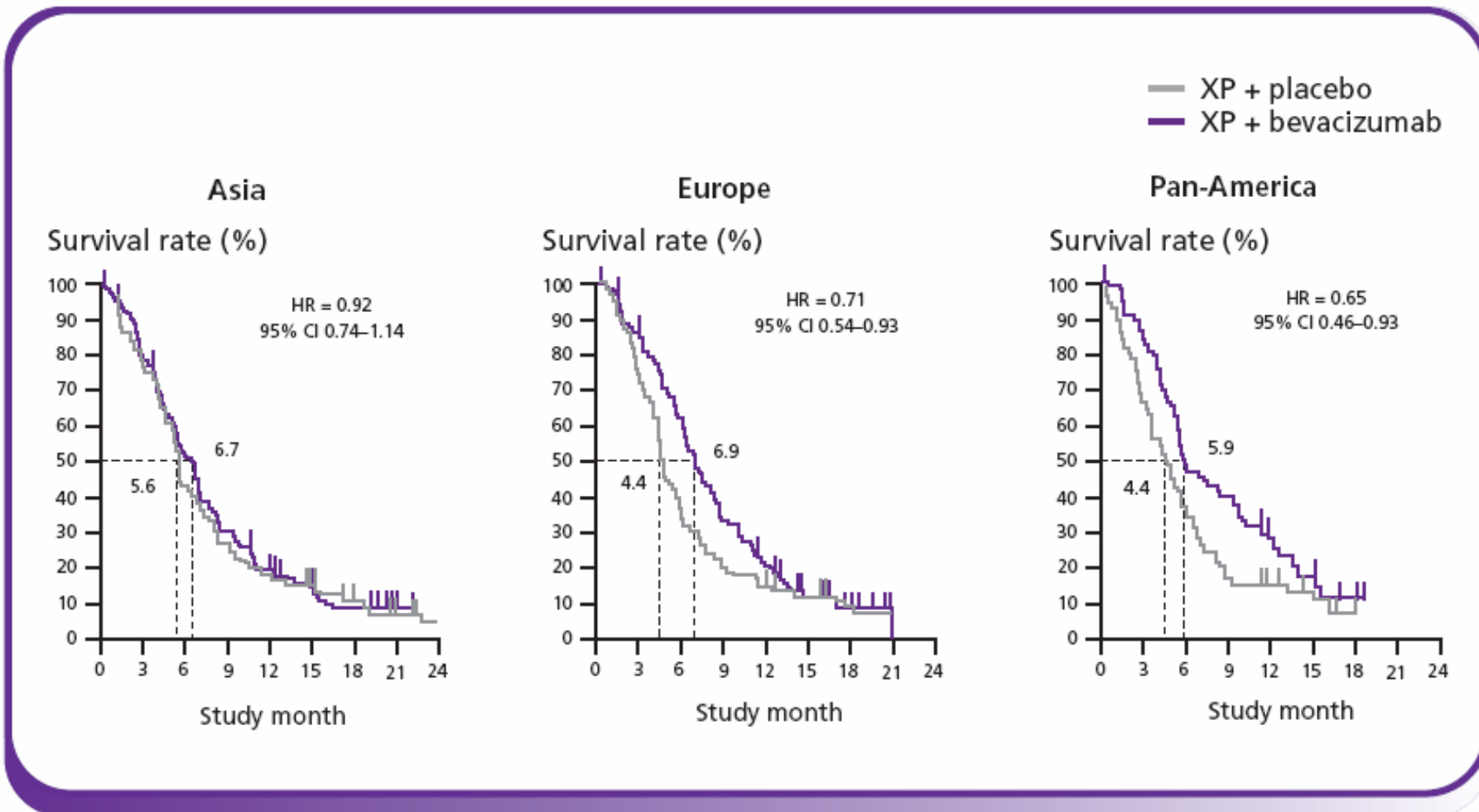
OS by region



- Analysis of OS by region found that the largest difference in OS was observed in the Pan-American patient population.

Differenze geografiche = diversa efficacia?

PFS by region



Differenze geografiche = diversa efficacia?

Best ORR by region

	Asia		Europe		Pan-America	
	XP + placebo (n=132)	XP + bev (n=142)	XP + placebo (n=110)	XP + bev (n=109)	XP + placebo (n=55)	XP + bev (n=60)
ORR, %	45.5	47.9	28.2	41.3	36.4	50.0
Odds ratio (95% CI)	1.10 (0.69–1.77)		1.79 (1.02–3.15)		1.75 (0.83–1.97)	

- The differences in ORR between the treatment groups in the European and Pan-American patient populations were greater than the Asian patient population.

Differenze geografiche = diversa gestione del paziente?

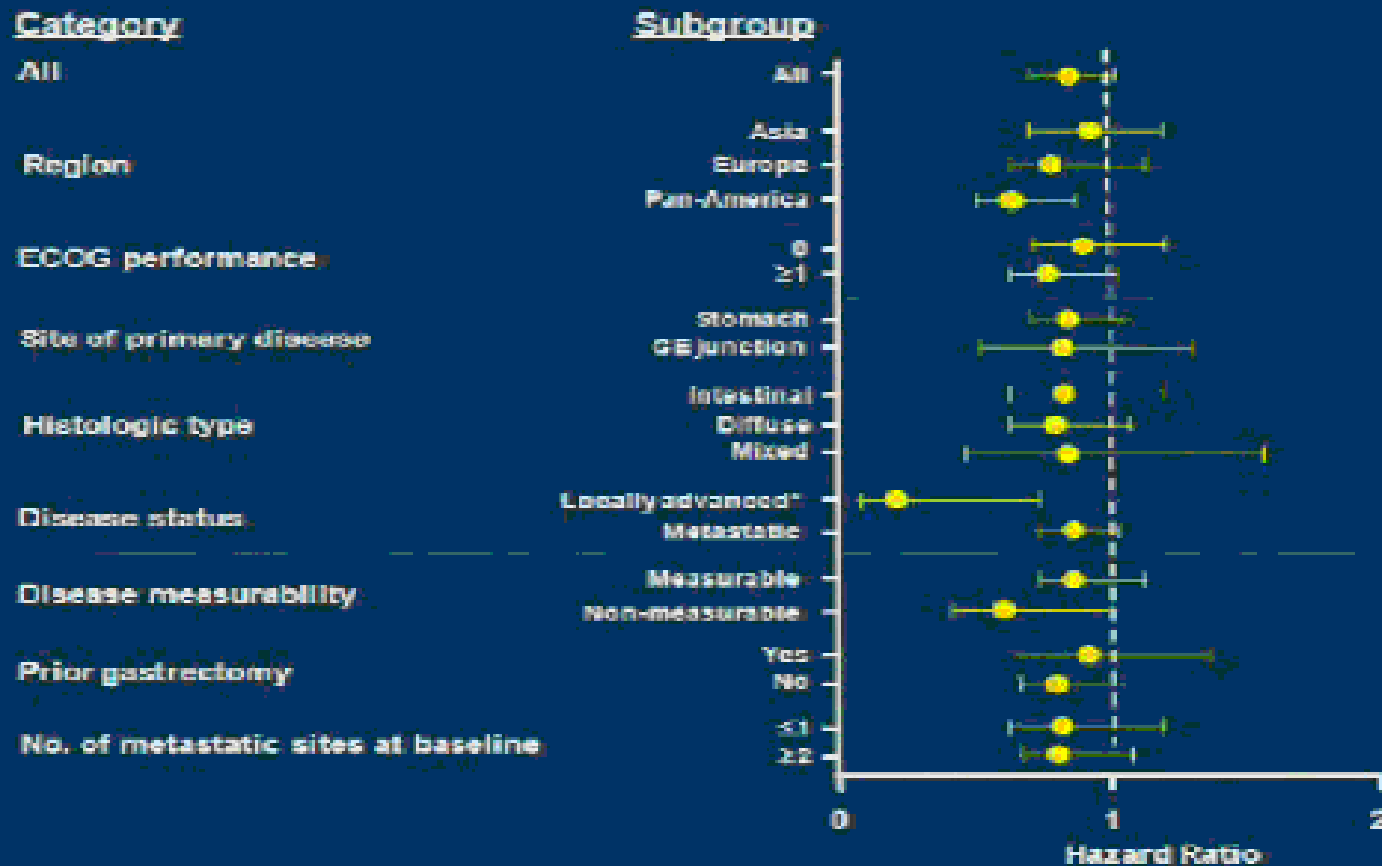
Subsequent lines of therapy by region

Region	Patients entered	Patients receiving second-line treatment	%
Asia	376	248	66
Europe	249	78	31
Pan-America	149	32	21

- The extensive use of second-line therapy in the Asian region might explain the higher OS compared with the other regions.

Analisi per sottogruppi

Overall Survival: Subgroup Analysis



BEVACIZUMAB PERIOPERATORIO



Preliminary safety data from a randomised trial of perioperative epirubicin, cisplatin + capecitabine (ECX) +/- bevacizumab in patients with gastric or oesophagogastric junction adenocarcinoma

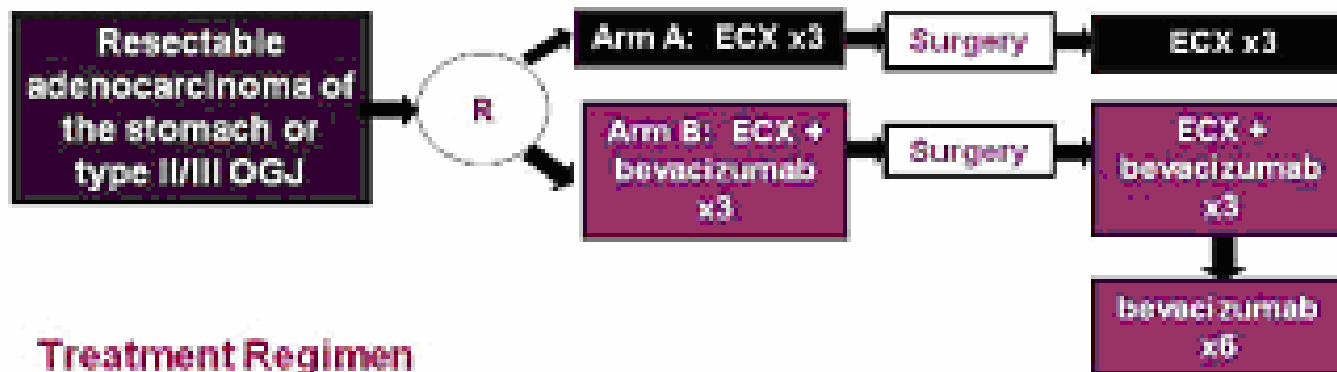
Alicia Okines¹, Ruth Langley², Fay Cafferty², Sally Stenning³, Stephen Falk⁴, Matt Seymour⁴, David Smith⁵, Gary Middleton⁶, Fareeda Coxon⁷ & David Cunningham¹

1. The Royal Marsden (MRC) Foundation Trust, London & Surrey 2. The Medical Research Council, London 3. Bristol Oncology and Haematology Centre, Bristol 4. Cancer Research UK Clinical Centre, University of Leeds 5. Gastrointestinal Cancer Research Unit, Royal Surrey County Hospital, Guildford 6. Wolfson Centre for Cancer Care, Newcastle

BEVACIZUMAB PERIOPERATORIO



Trial Design



Treatment Regimen

- Epirubicin 50mg/m² day 1 every 21 days
- Cisplatin 60mg/m² day 1 every 21 days
- Capecitabine 1250mg/m²/day, continuous dosing
- Bevacizumab 7.5mg/kg day 1 every 21 days (Arm B only)

Conclusioni Bevacizumab

OS nello studio AVAGAST non raggiunta

Tutti gli altri end-point secondari raggiunti

Notevoli differenze tra I pazienti trattati per area geografica e per sottogruppi

Non ancora “scartata” definitivamente l’ipotesi di un ruolo del Bevacizumab nel carcinoma gastrico (es. Studio MAGIC-2)

Carcinoma Colon-rettale

Terapia con farmaci anti-EGFR

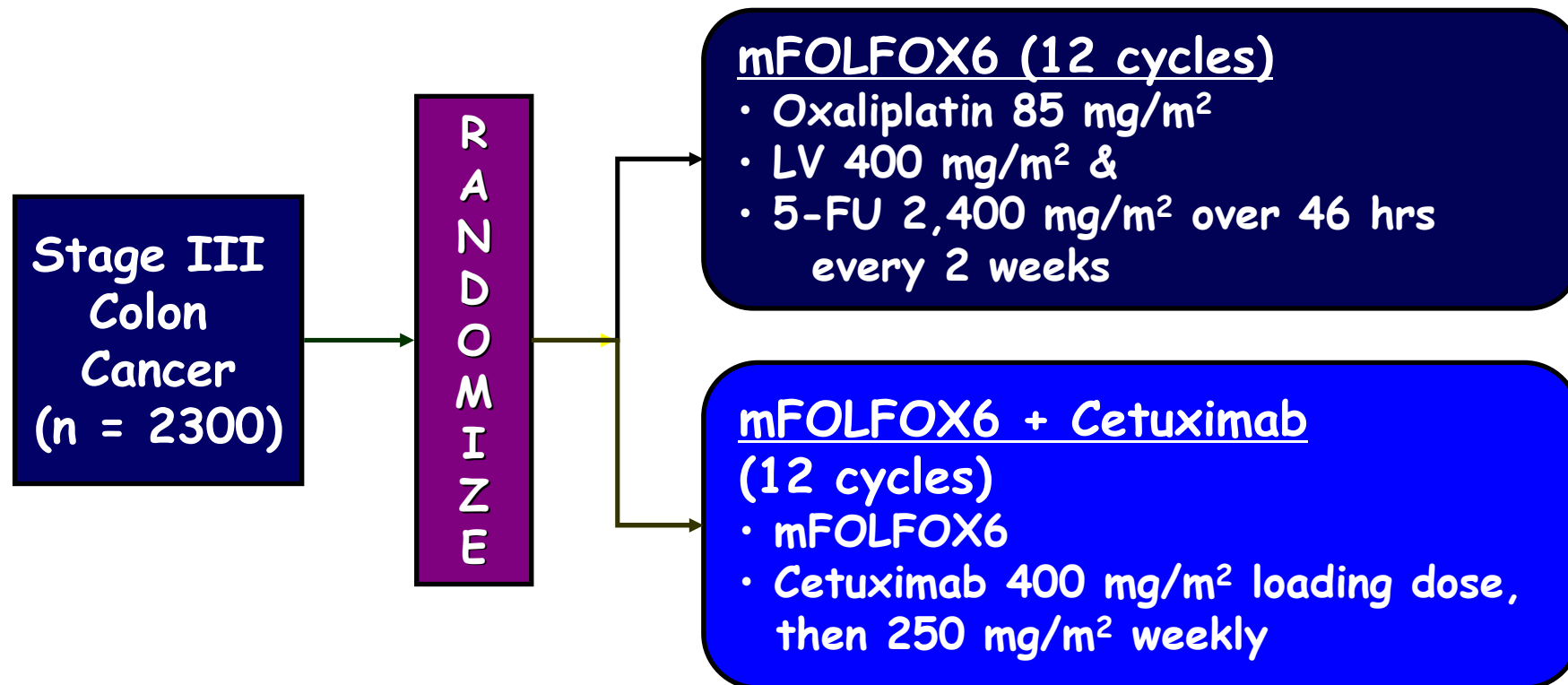
Adiuvante con farmaci anti-EGFR?

Il migliore farmaco di accompagnamento al Cetuximab?

Fattori biomolecolari predittivi?

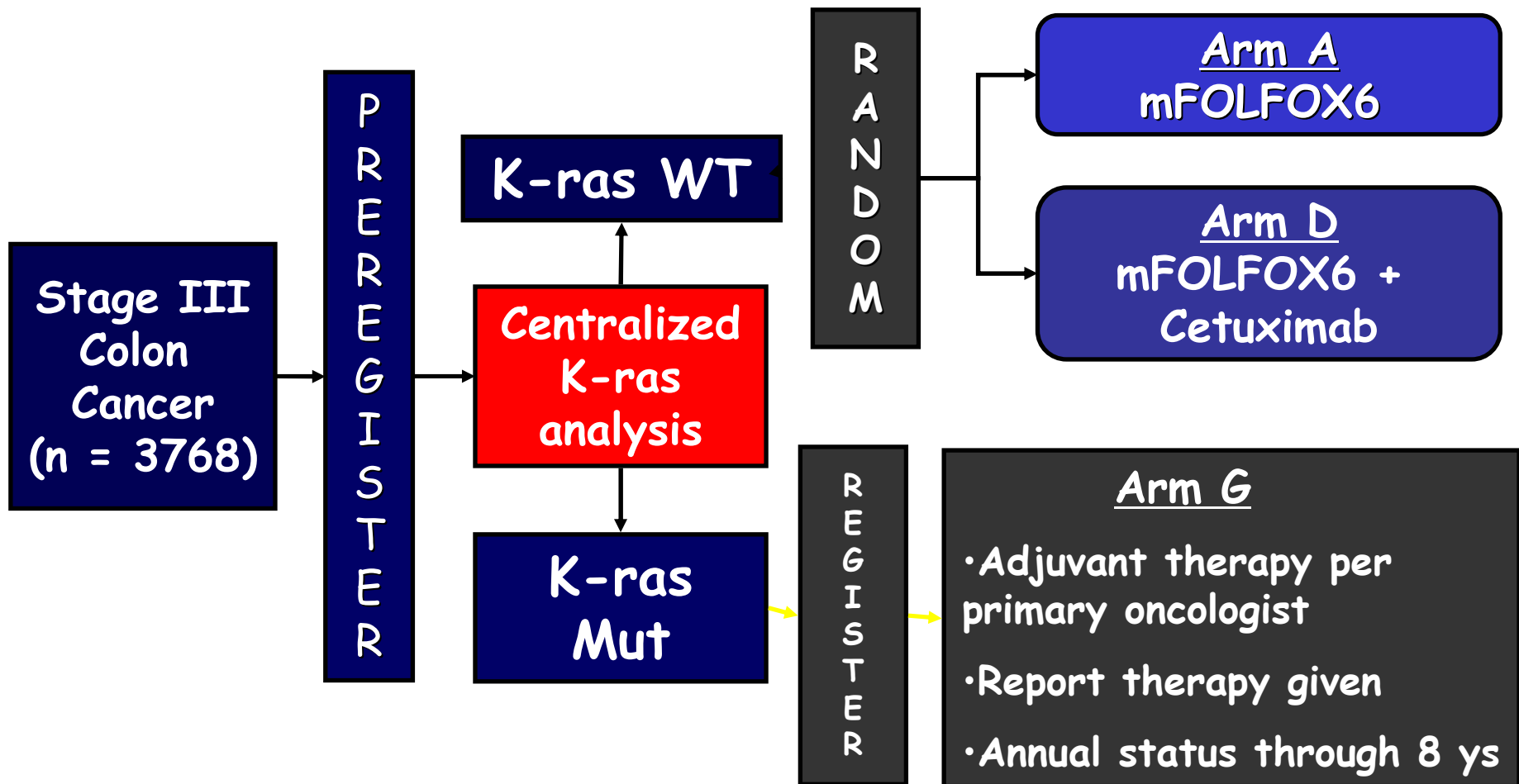
Adiuvante con Cetuximab

Studio N0147-Disegno dello studio



Goldberg RM et al. ASCO 2010;#3508

Studio N0147-Emendamento per K-ras



Goldberg RM et al. ASCO 2010;#3508

Studio N0147-Outcome

Wild-Type KRAS

Mutant KRAS

	mFOLFOX6 (n = 902)	mFOLFOX6 + Cetuximab (n = 945)	mFOLFOX6 (n = 374)	mFOLFOX6 + Cetuximab (n = 343)
3-yr DFS, %	75.8	72.3	67.2	64.2
▪ HR (95% CI)	1.2 (0.96-1.5)		1.2 (0.9-1.6)	
▪ P value	.22		.13	
3-yr OS, %	87.8	83.9	88.0	80.4
▪ HR (95% CI)	1.3 (0.96-1.8)		1.5 (0.9-2.3)	
▪ P value	.13		.12	

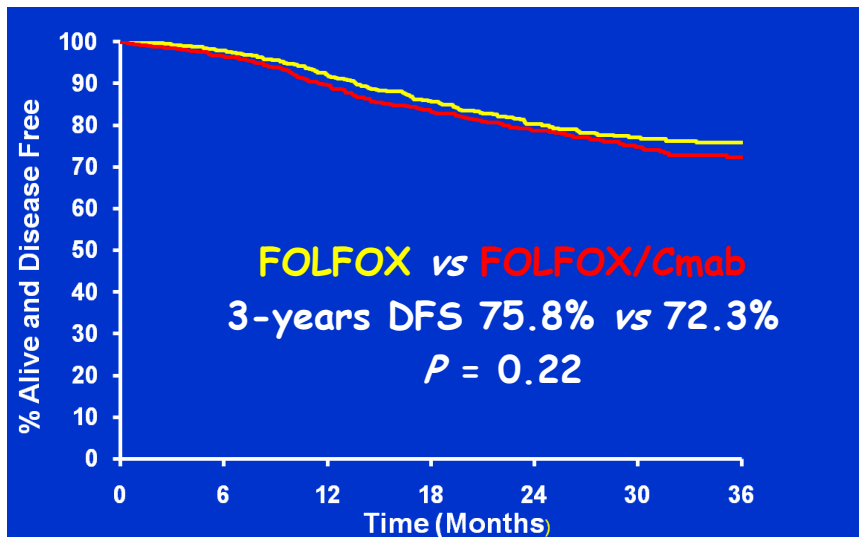
Goldberg RM et al. ASCO 2010;#3508

Studio N0147-Valore del K-ras

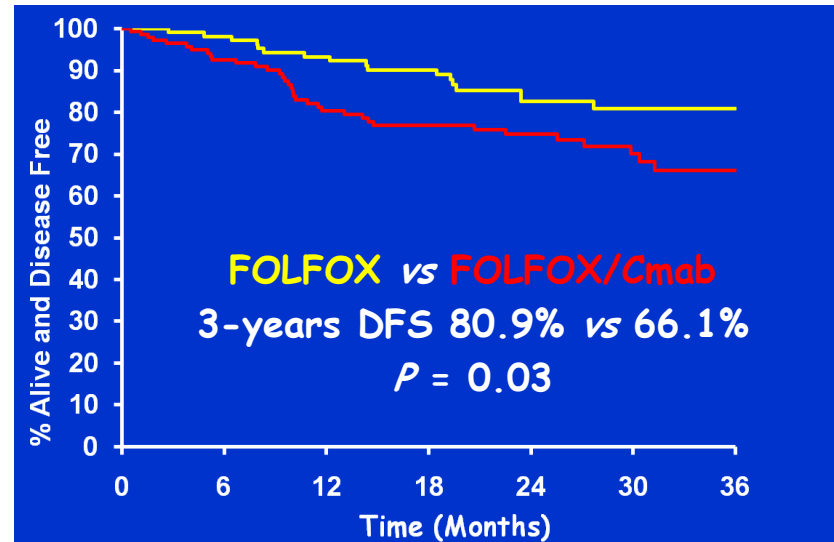
	mFOLFOX6		mFOLFOX6 + Cetuximab	
	<i>KRAS</i> wt (n = 902)	<i>KRAS</i> mut (n = 374)	<i>KRAS</i> wt (n = 945)	<i>KRAS</i> mut (n = 343)
Alive and disease free at 3 yrs, %	75.8	67.2	72.3	64.2
▪ HR (95% CI)	0.7 (0.5-0.9)		0.7 (0.5-0.9)	
▪ <i>P</i> value	.04		.004	

Goldberg RM et al. ASCO 2010;#3508

Studio N0147-DFS



Popolazione Generale



Pazienti > 70 anni

Cetuximab Adjuvante?

Lo studio N0147 mostra assenza beneficio aggiunta
Cetuximab allo standard di trattamento chemioterapico
adiuvante

In attesa dei risultati del PETACC8...

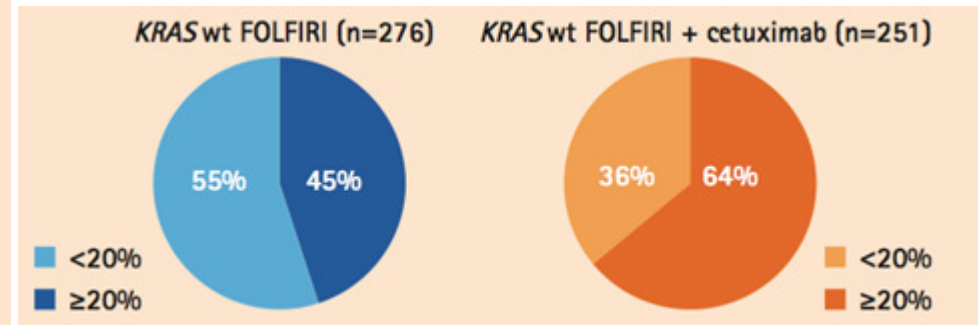
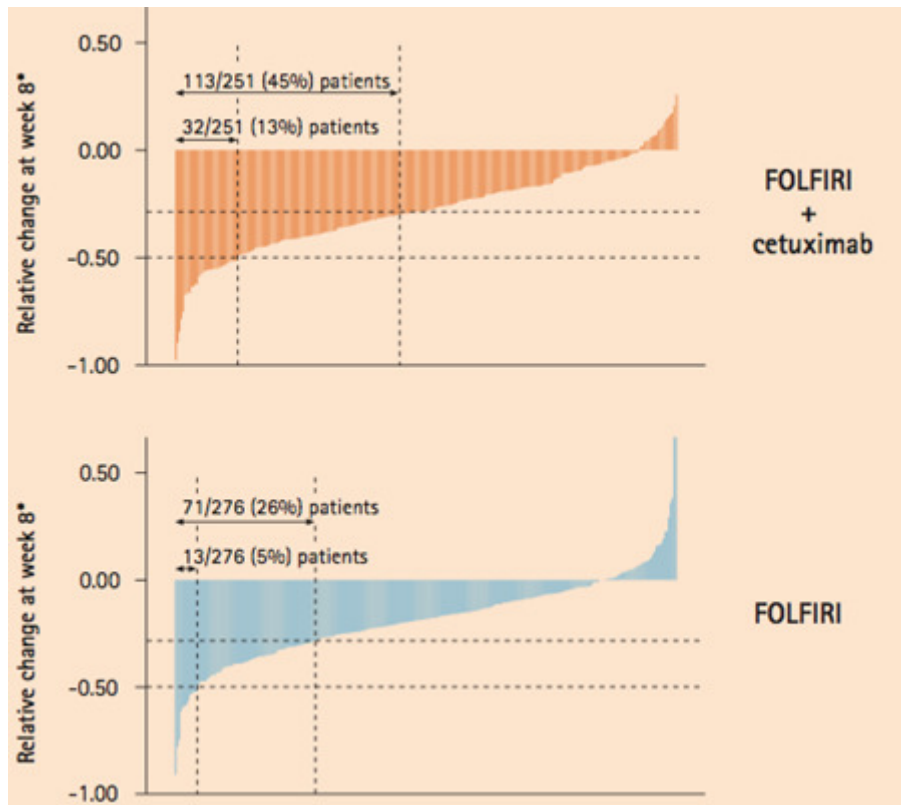
**Quale è il partner migliore per
Cetuximab?**

Quale migliore partner per Cetuximab?

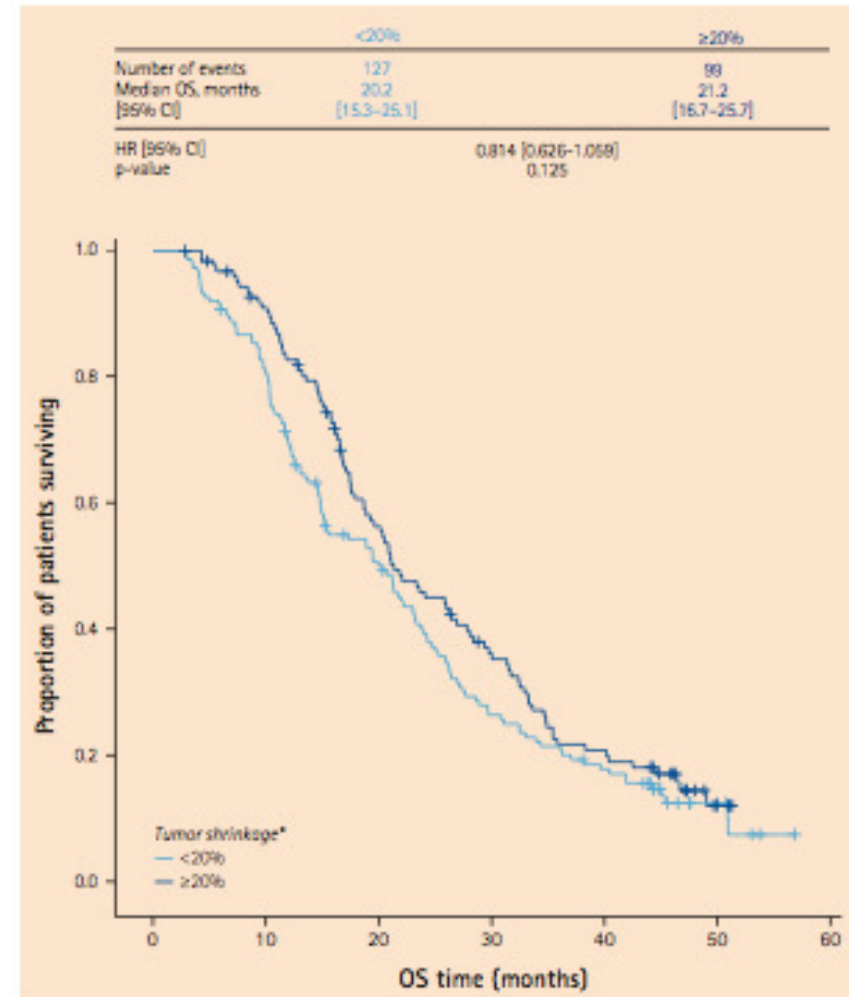
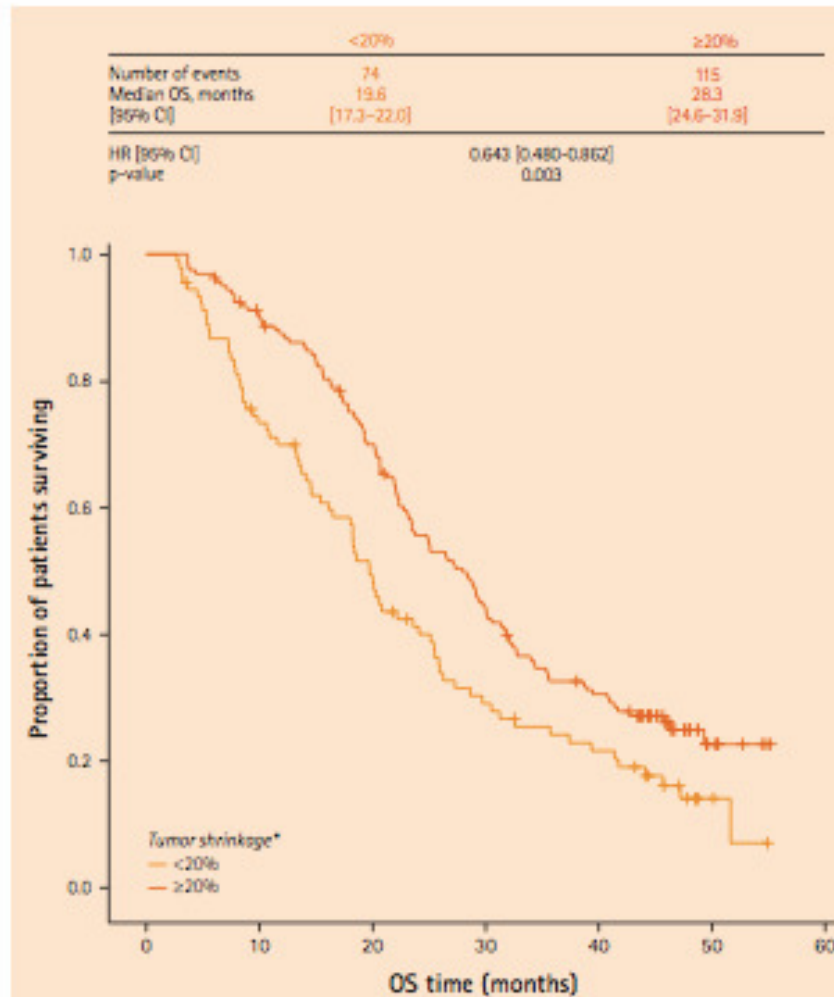
	CRYSTAL¹	COIN²	NORDIC VII³
Chemotherapy	FOLFIRI	XELOX/FOLFOX	FLOX
n	666	729	498
OS, months	23.5 vs 20.0	17.0 vs 17.9	20.1 vs 22.0
HR	0.796	1.038	1.14
p value	0.0093	0.68	0.66
PFS, months	9.9 vs 8.4	8.6 vs 8.6	7.9 vs 8.7
HR	0.696	0.959	1.07
p value	0.0012	0.60	0.66
ORR (%)	57 vs 40	64 vs 57	46 vs 47
p value	<0.0001	0.049	0.87

1. Van Cutsem, et al. ASCO GI 2010;
2. Maughan, et al. ASCO 2010
3. Tveit, et al. ESMO 2010

FOLFIRI+Cetuximab: risultati aggiornati del CRYSTAL, ORR



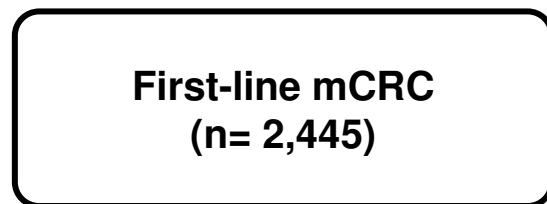
Studio CRYSTAL: Risposte precoci (>20% in <8 settimane)



Studio COIN: Disegno dello studio

MRC Sponsored study
supported by Merck

109 UK and Irish Hospitals



Continuous* XELOX
or FOLFOX

Arm A

Continuous XELOX
or FOLFOX +
cetuximab

Arm B

Intermittent‡ XELOX
or FOLFOX

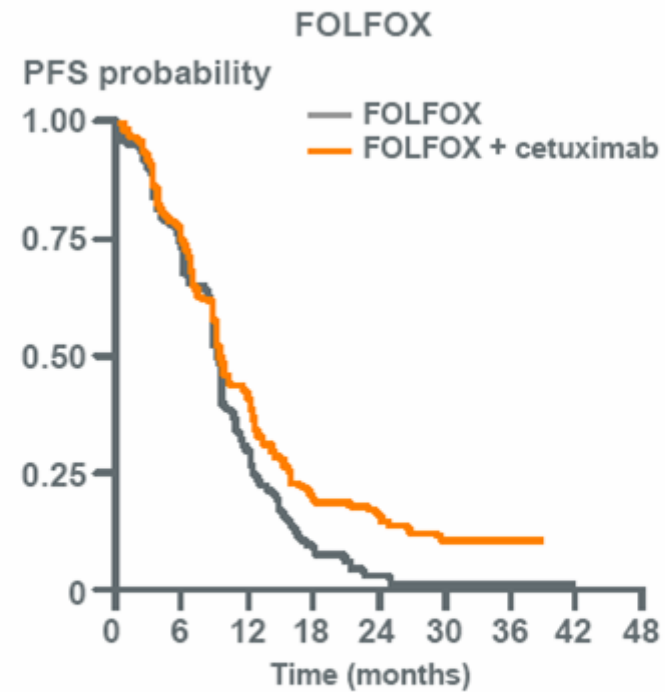
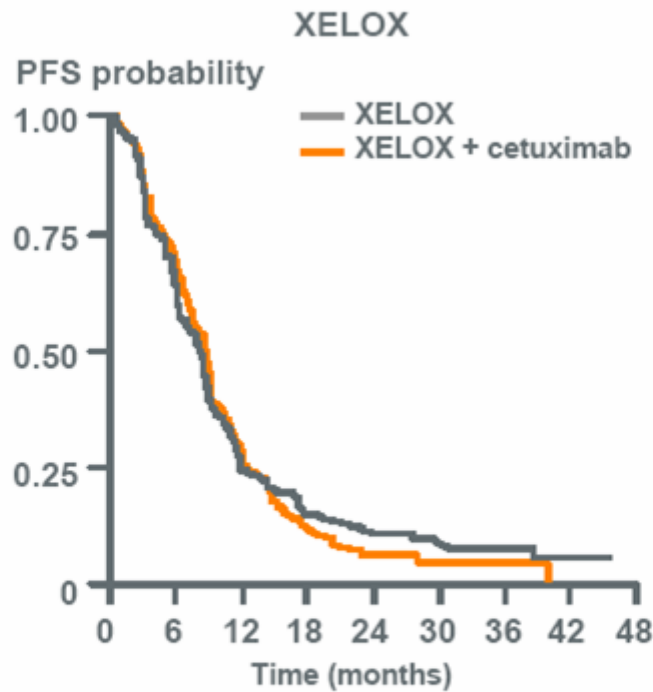
Arm C

65% XELOX; 35% FOLFOX
(patient/physician choice)

*Treatment until disease progression or unacceptable toxicity
‡Stop and Go treatment (12 weeks then restart at progression)

Studio COIN: Sopravvivenza

HR for interaction (FOLFOX vs XELOX) p=0.07



No. at risk:

XELOX or FOLFOX	240	151	58	32	15	9	5	1	0
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Cetuximab+

XELOX/FOLOX	245	162	60	23	10	10	2	0	0
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FOLFOX	127	94	34	9	3	2	1	0	0
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FOLFOX + cetuximab	117	87	43	19	12	5	4	0	0
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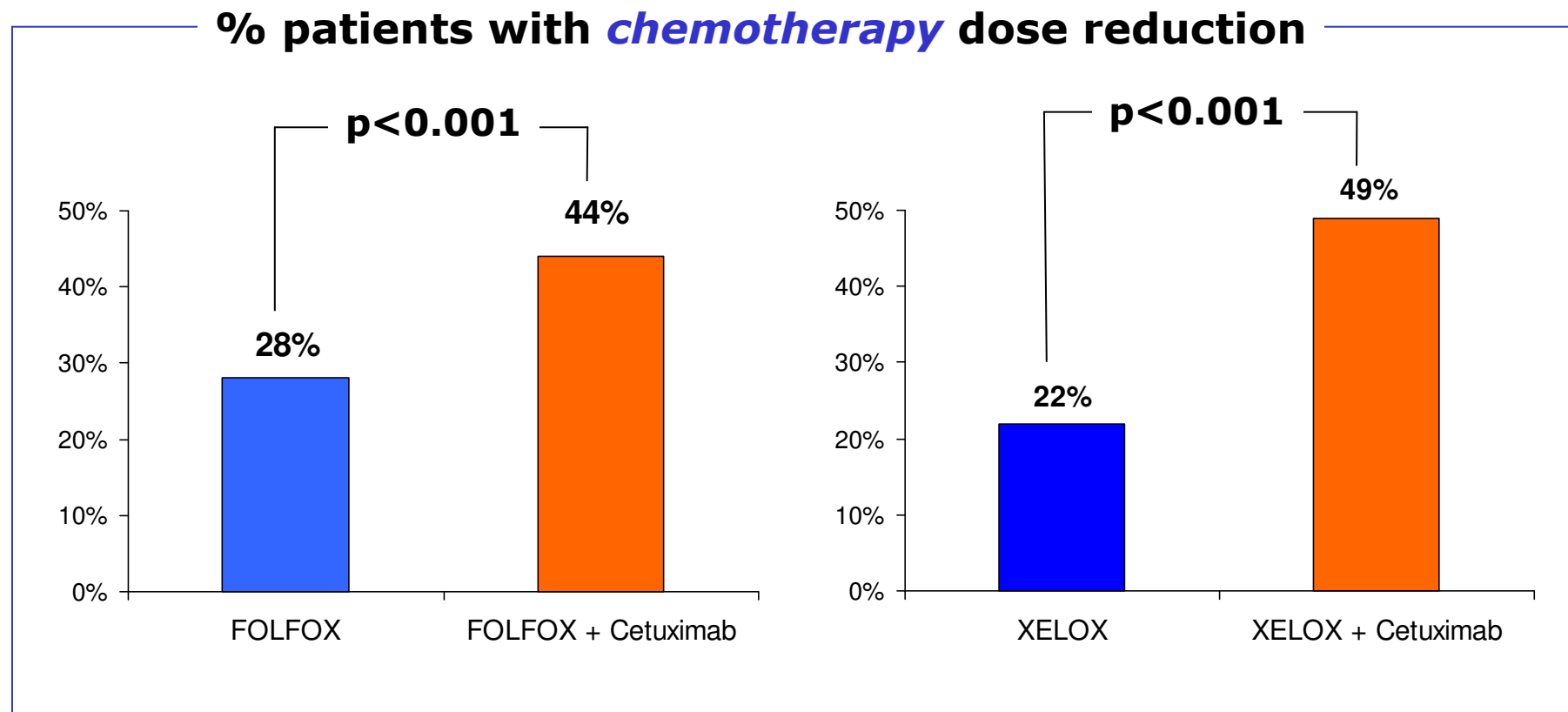
Maughan, et al. ECCO-ESMO 2009

Studio COIN: ORR

- Improved response rate in *KRAS* WT patients overall and at 12 weeks

	All patients		<i>KRAS</i> WT		<i>KRAS</i> MT	
	FOLFOX/ XELOX (n=815)	Cetuximab + FOLFOX/ XELOX (n=815)	FOLFOX/ XELOX (n=367)	Cetuximab + FOLFOX/ XELOX (n=362)	FOLFOX/ XELOX (n=268)	Cetuximab + FOLFOX/ XELOX (n=297)
ORR at 12 weeks (%)	45	49	50	59	41	40
Odds ratio	1.17 (p=0.124)		1.44 (p=0.015)		0.97 (p=0.877)	
Best overall response (%)	51	53	57	64	46	43
Odds ratio	1.08 (p=0.428)		OR=1.35 (p=0.049)		OR=0.88 (p=0.449)	

Studio COIN: Ridotta compliance braccio sperimentale

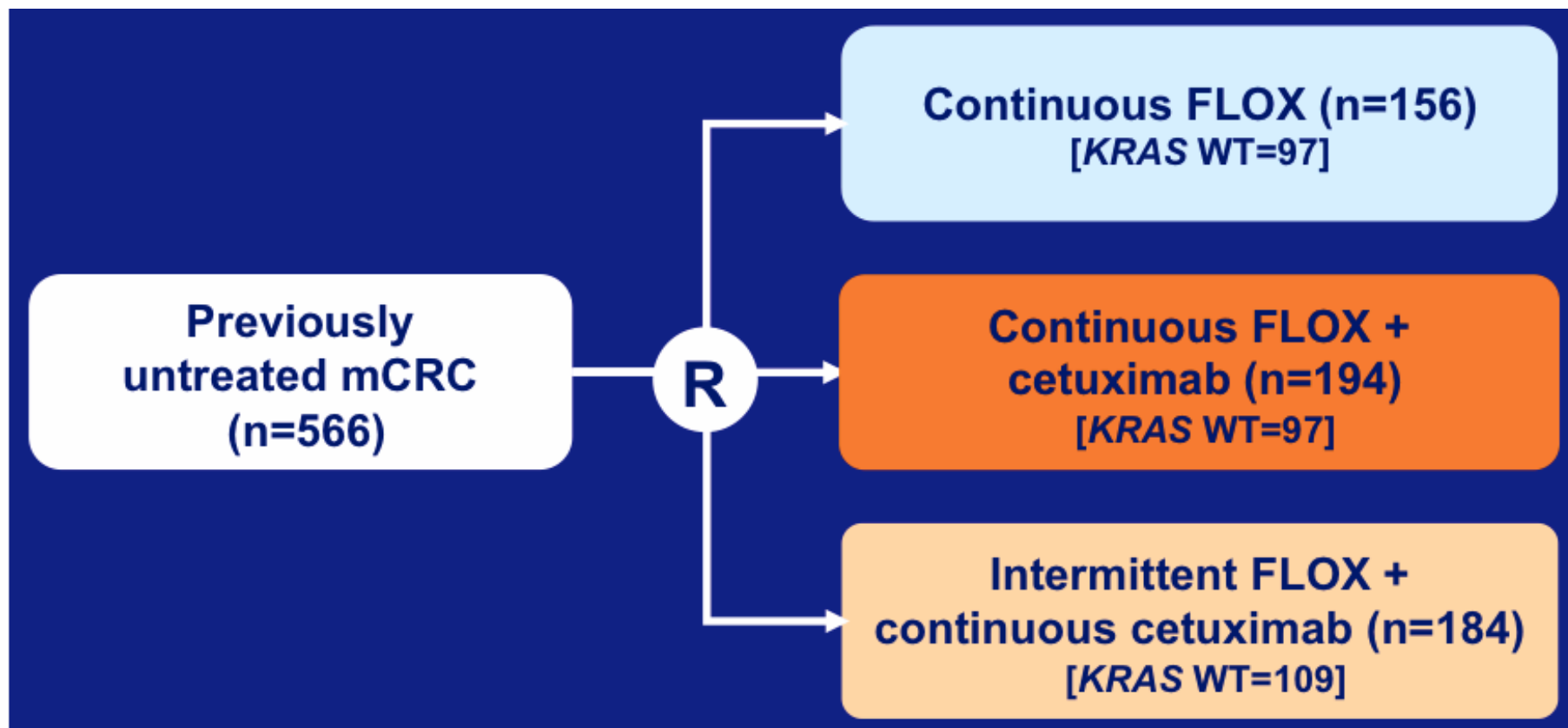


* Adams et al, BJC (2009), 100(2), 251-258, Analysis of first 805 pts of the COIN trial

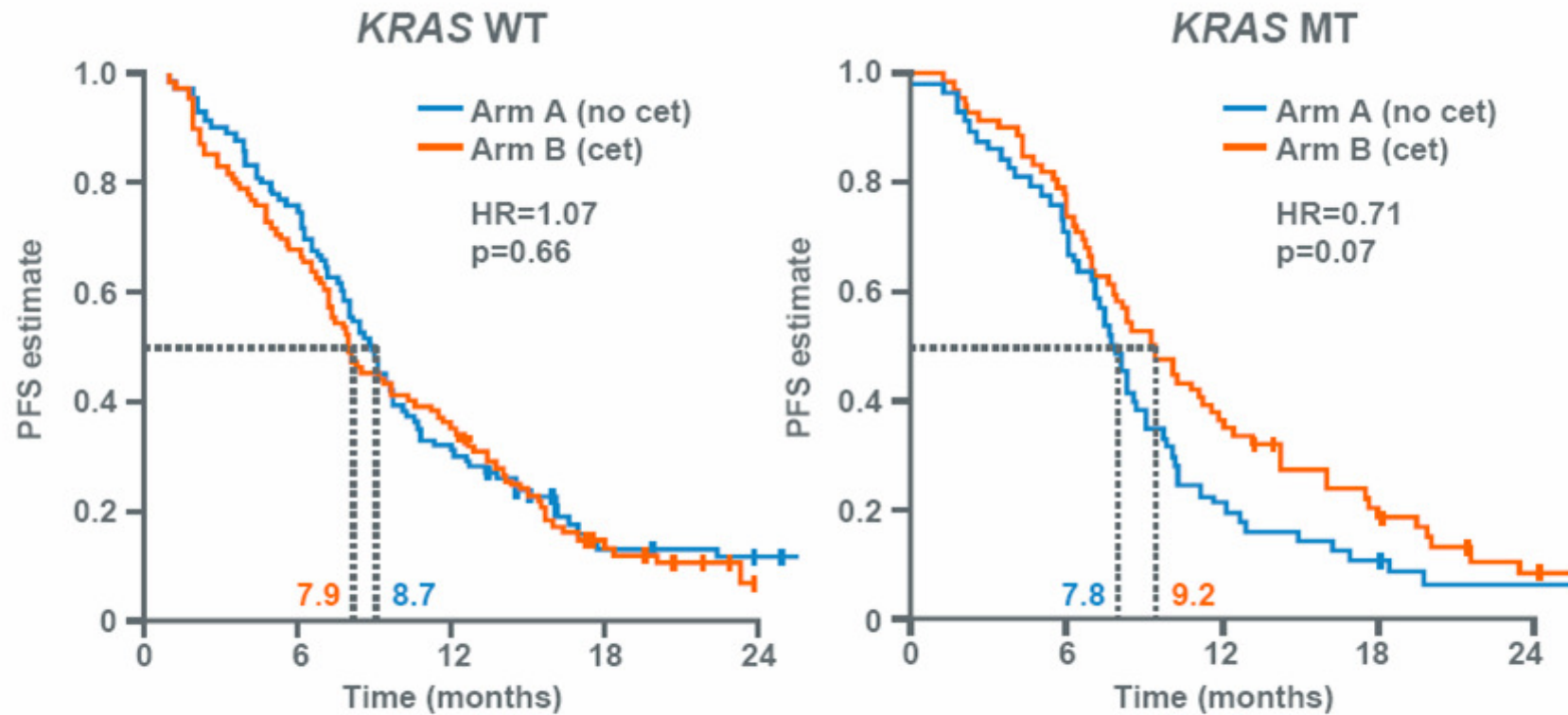
Studio COIN: Minore percentuale di pazienti trattati in seconda linea

	All pts		<u>KRAS^{wt}</u>	
	Arm A	Arm B	Arm A	Arm B
	N (%)	N (%)	N (%)	N (%)
Eligible for 2nd-line therapy	724	695	323	311
Any 2 nd -line therapy	449 (62%)	386 (56%)	210 (65%)	169 (54%)
	p=0.014		p=0.006	
<u>Irinotecan</u>	361 (50%)	306 (44%)	171 (53%)	132 (42%)
	p=0.030		p=0.008	
5FU	218 (30%)	170 (24%)	105 (33%)	67 (22%)
	p=0.018		p=0.002	
<u>Capecitabine</u>	150 (21%)	131 (19%)	78 (24%)	67 (22%)
Oxaliplatin	123 (17%)	105 (15%)	60 (19%)	46 (15%)
EGFR-targeted therapy	42 (6%)	41 (6%)	15 (5%)	20 (6%)
Cetuximab	16 (2%)	23 (3%)	5 (2%)	10 (3%)
Other therapy	18 (2%)	18 (3%)	10 (3%)	8 (3%)

Studio NORDIC VII: Disegno dello studio

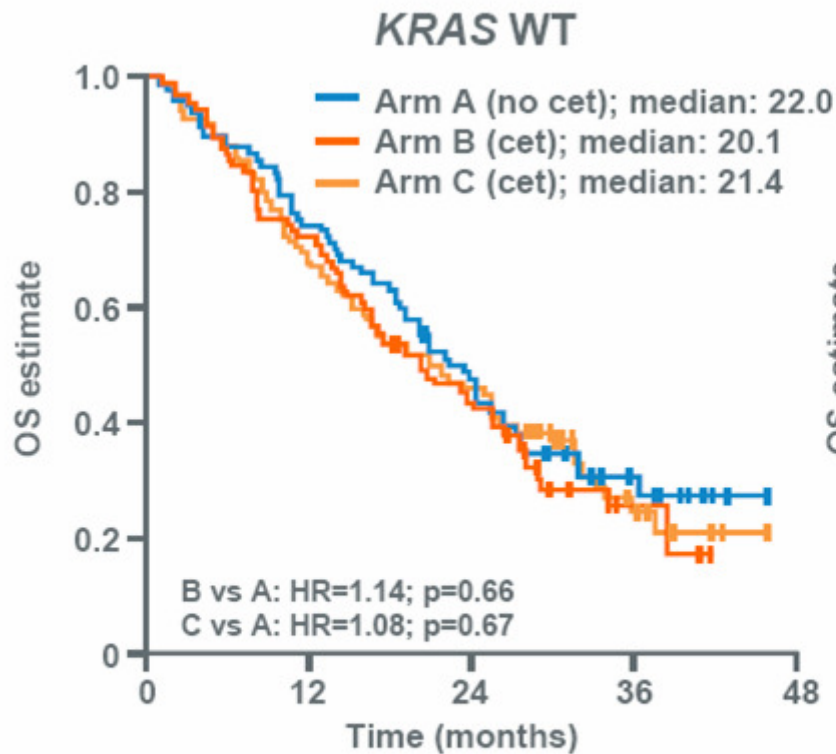


Studio NORDIC VII: PFS in base a K-ras

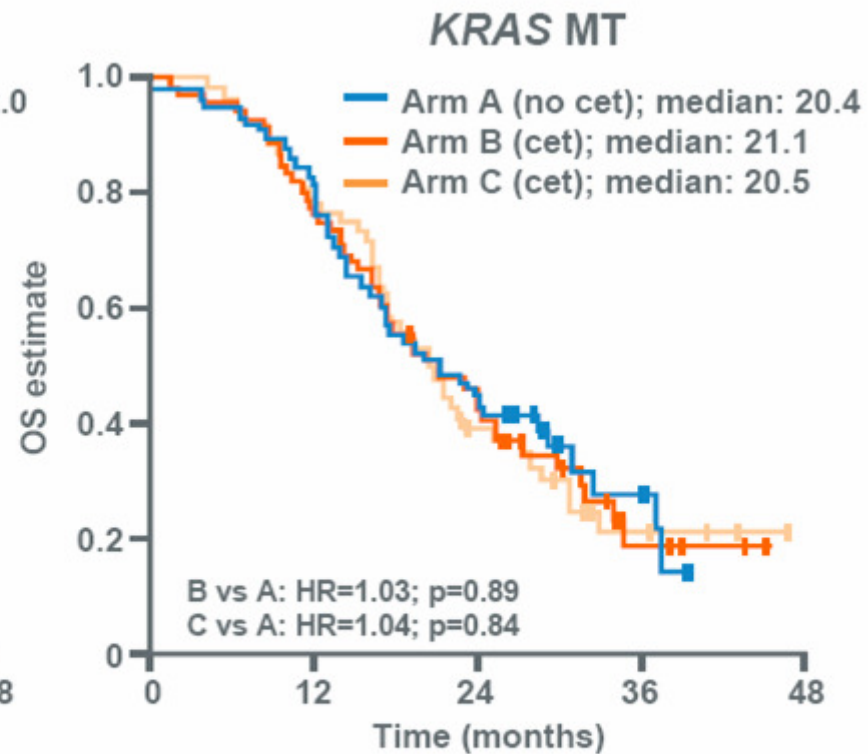


97	70	29	9	6	58	41	12	6	3
97	65	34	9	0	72	55	26	11	2

Studio NORDIC VII: OS in base a K-ras



97	72	38	9
97	70	29	7
109	73	44	9



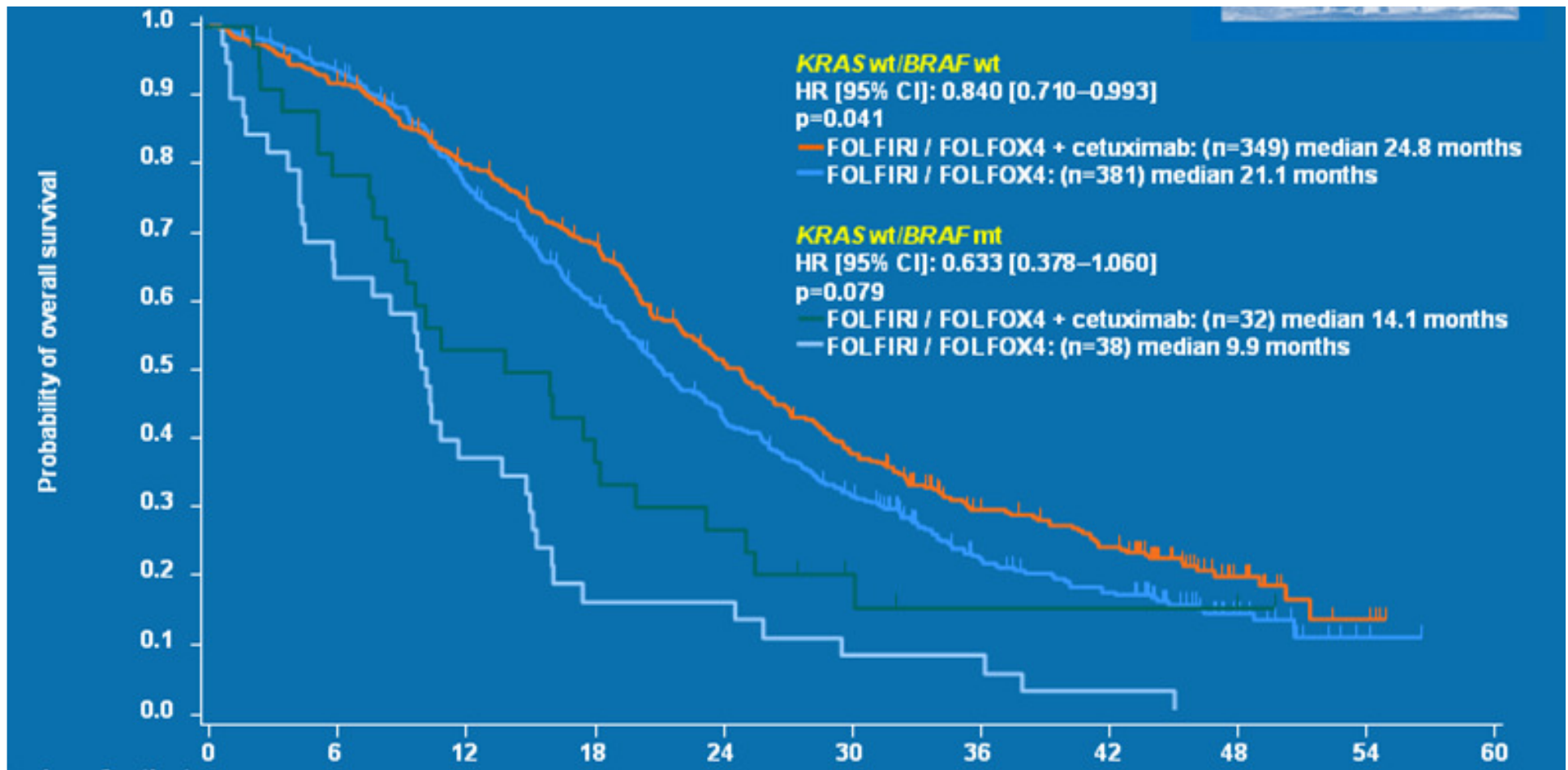
58	47	23	5
72	55	23	4
65	51	20	5

B-raf? Prognostico o predittivo?

B-raf come fattore prognostico più che predittivo...

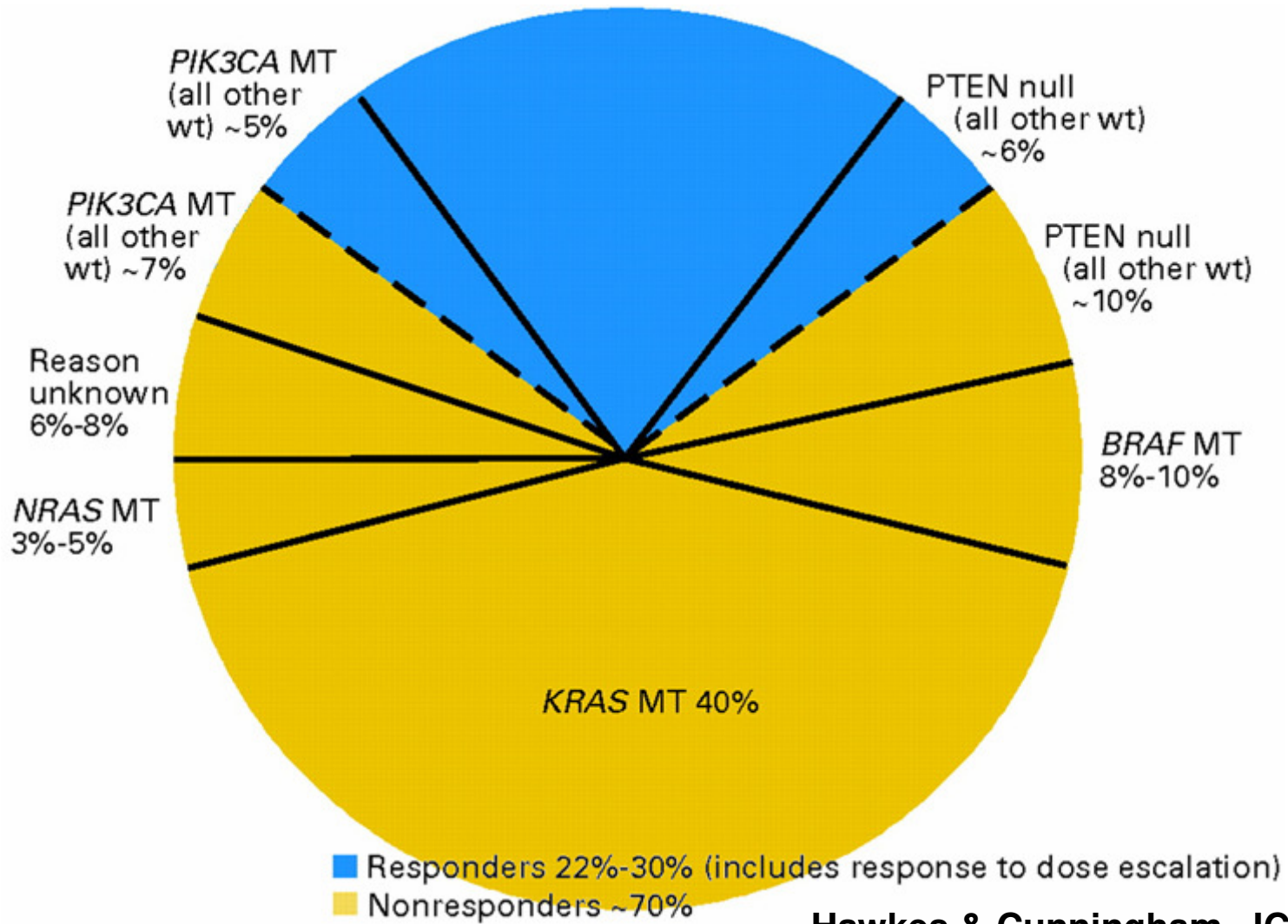
	<i>KRAS</i> WT / <i>BRAF</i> WT (n=730)		<i>KRAS</i> WT / <i>BRAF</i> MT (n=70)	
	Chemotherapy (n=381)	Chemotherapy + cetuximab (n=349)	Chemotherapy (n=38)	Chemotherapy + cetuximab (n=32)
Median OS, months (95% CI)	21.1 (19.5–23.6)	24.8 (22.1–27.0)	9.9 (5.7–13.6)	14.1 (8.8–18.5)
HR		0.84		0.62
p value		0.0479		0.0764
Median PFS, months (95% CI)	7.7 (7.4–9.0)	10.9 (9.2–11.9)	3.7 (2.1–7.9)	7.1 (3.7–9.1)
HR		0.64		0.67
p value		<0.0001		0.2301
ORR, %	40.9	60.7	13.2	21.9
Odds ratio		2.27		1.60
p value		<0.0001		0.4606

B-raf come fattore prognostico più che predittivo... (2)



Bokemeyer, ASCO 2010 (abstr. 3506)

Non solo K-ras...



Hawkes & Cunningham, JCO 2010

Terapia con farmaci anti-VEGF

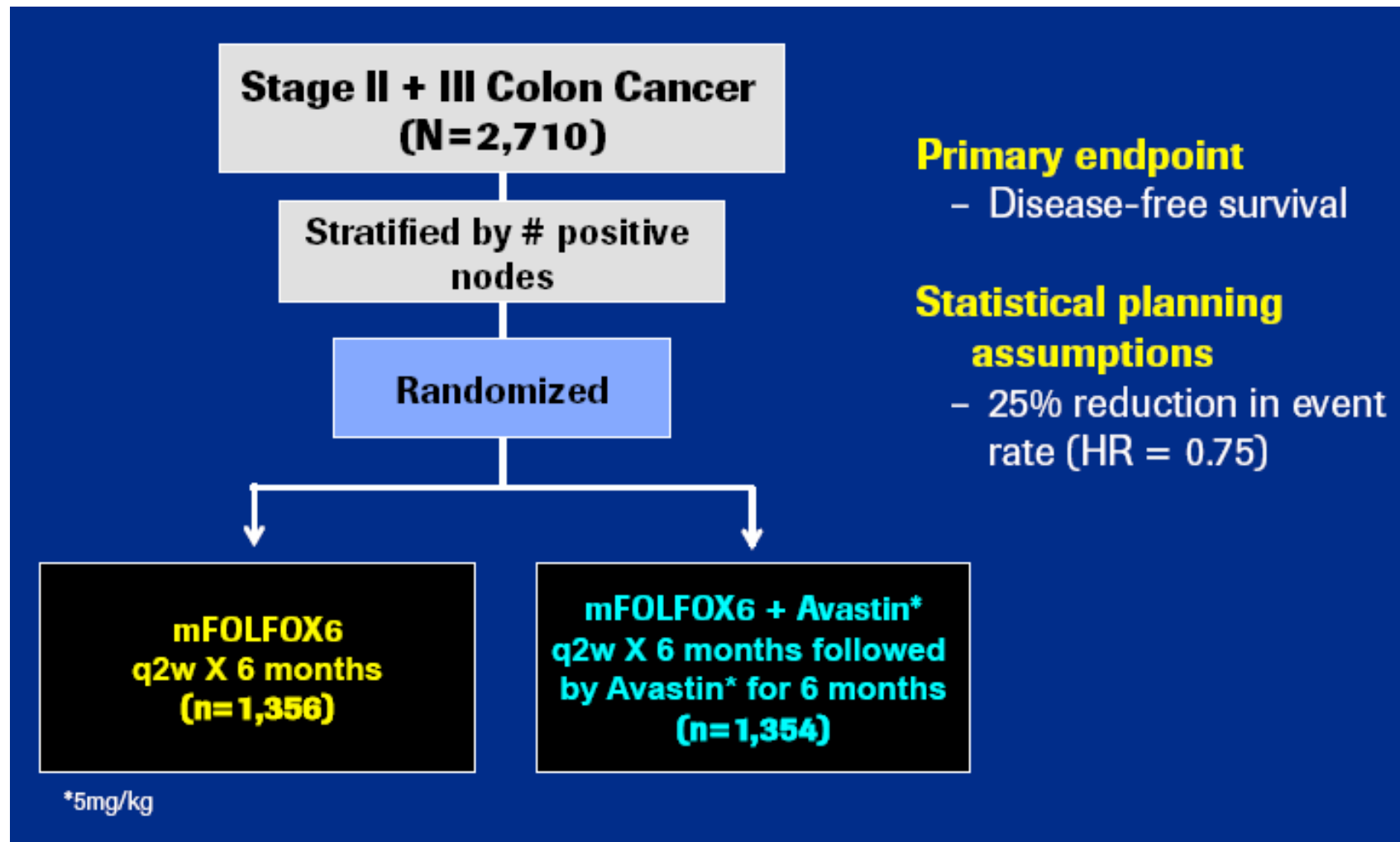
Adiuvante con farmaci anti-VEGF?

Mantenimento?

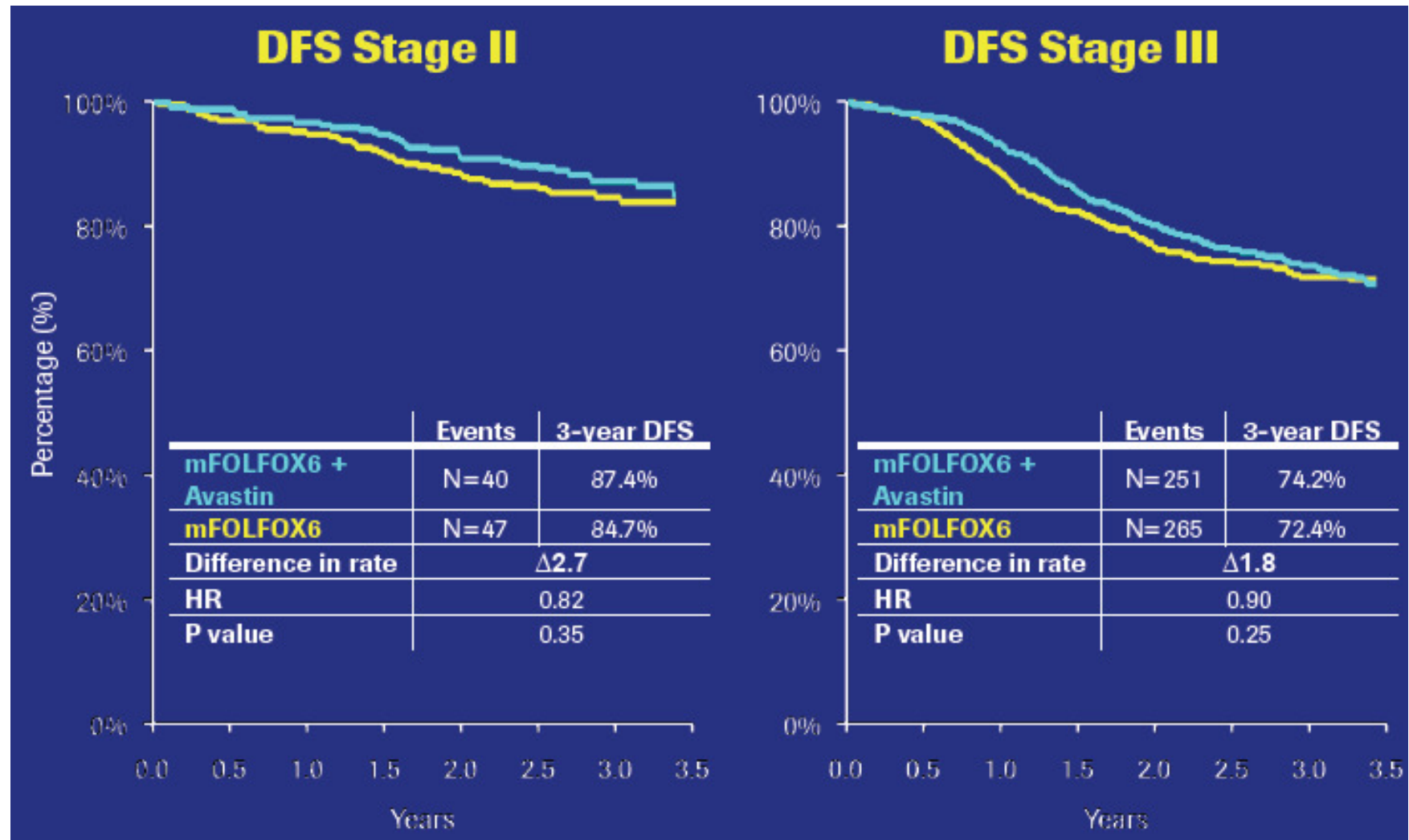
Bevacizumab post-progressione?

Bevacizumab adiuvante: studio C-08

Disegno dello studio



C-08: DFS



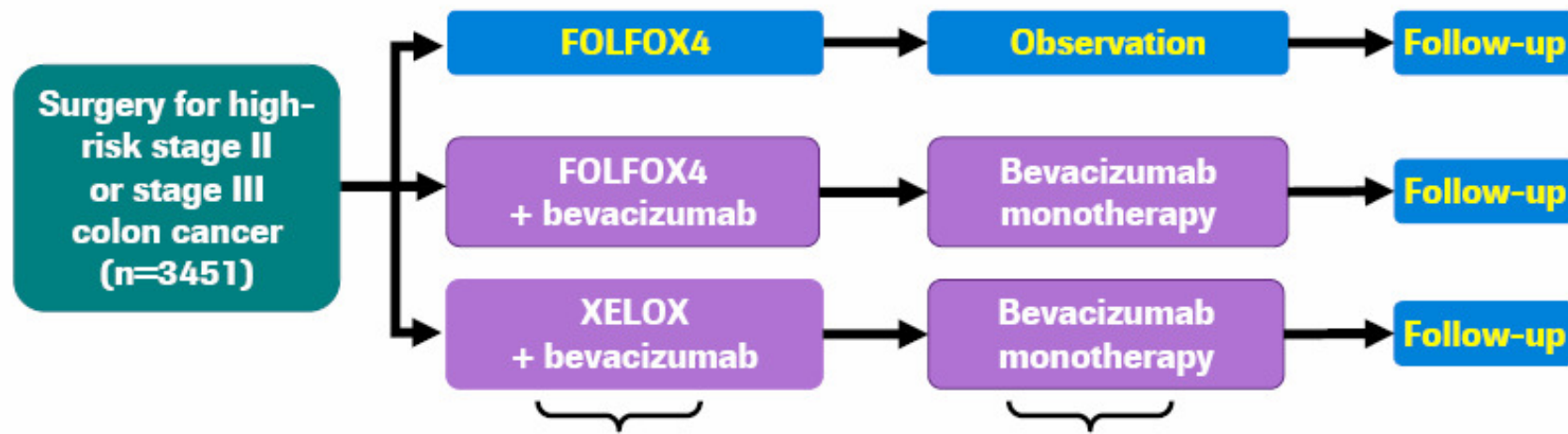
C-08: Riassunto

Status at 36 Months Median Follow-up

	mFOLFOX6	mFOLFOX6 + Avastin	P value
Recurrence (N)	248	227	NS
Death (N)	146	132	NS
Second Cancer (N)	46	47	NS
2-year Survival Post Recurrence (%)	41	37	NS
Recurrence Multiple Sites (%)	18	18	NS
Sites of Recurrence	–	–	NS

AVANT: Disegno dello studio

AVANT (BO17920) study design



Duration of treatment phase: 24 weeks (5.5 months)

24 weeks (5.5 months)

- FOLFOX4 (oxaliplatin 85 mg/m², LV 200 mg/m², 5-FU 400 mg/m² bolus + 600 mg/m² continuous infusion, Days 1 + 2) every 2 weeks
- FOLFOX4 + bevacizumab 5 mg/kg every 2 weeks
- XELOX (oxaliplatin 130 mg/m² Day 1, capecitabine 2 x 1000 mg/m² Days 1–14) + bevacizumab 7.5 mg/kg every 3 weeks
- Bevacizumab monotherapy: 7.5 mg/kg every 3 weeks

Bevacizumab mantenimiento?

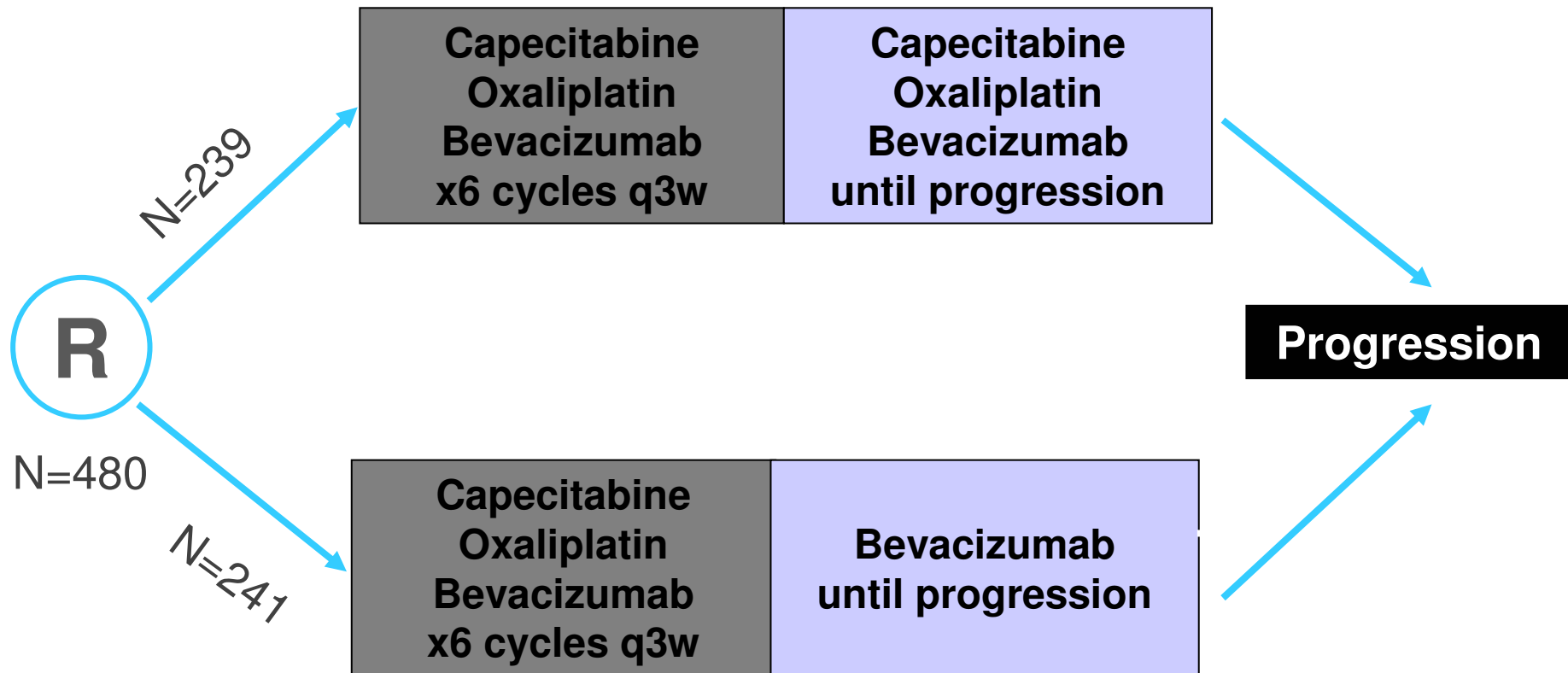
Mantenimiento?

Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single agent (s/a) BEV as **maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC) the **MACRO** trial**

J. Tabernero

E. Aranda, A. Gomez, B. Massutí, J. Sastre, A. Abad,
M. Valladares, F. Rivera, M^a J. Safont, E. Diaz-Rubio
On behalf of the Spanish Cooperative Group for the
Treatment of Digestive Tumors (TTD)

MACRO: Disegno dello studio



Obiettivo primario:
Progression free survival
(PFS)

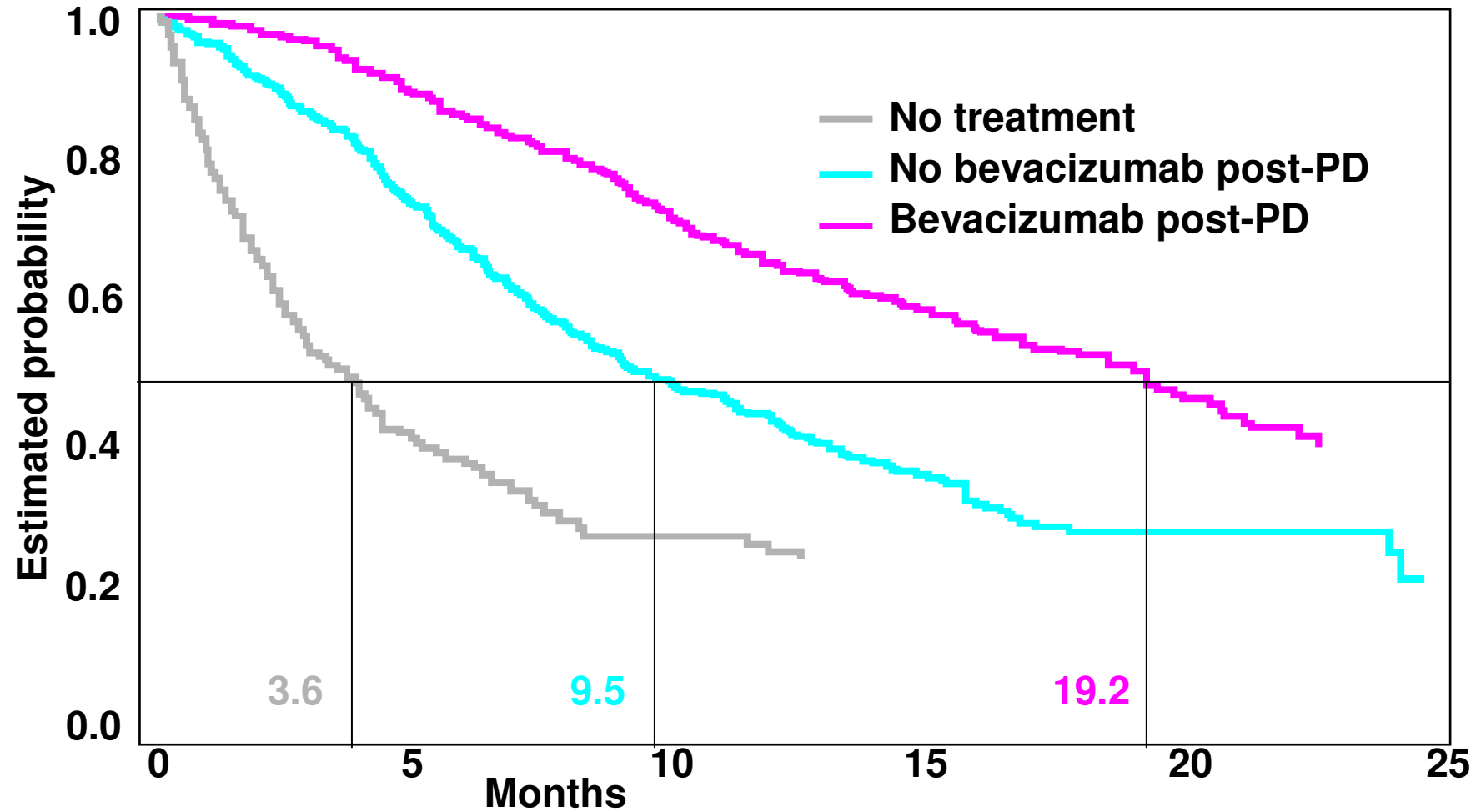
MACRO: Risultati

Efficacy	Arm A	Arm B	p value
mPFS, months	11.0	10.3	0.59
mOS, months	25.3	20.7	0.63
ORR, %	60	57	0.51

There were not statistically significant differences in ORR, PFS, and OS between the 2 arms

Bevacizumab post-progression?

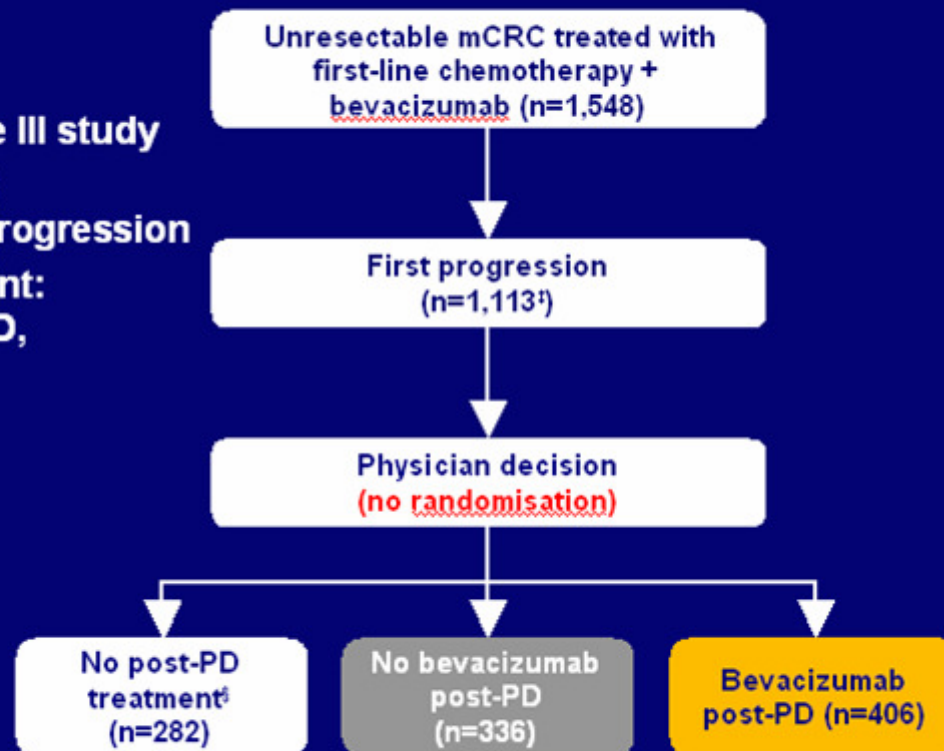
Studio BRITE



Studio ARIES: disegno

ARIES: post-progression observation of bevacizumab treatment

- ARIES*
 - total n=1,548
 - prospective phase III study
 - primary endpoint: survival beyond progression
 - secondary endpoint: OS, time to first PD, OS, safety



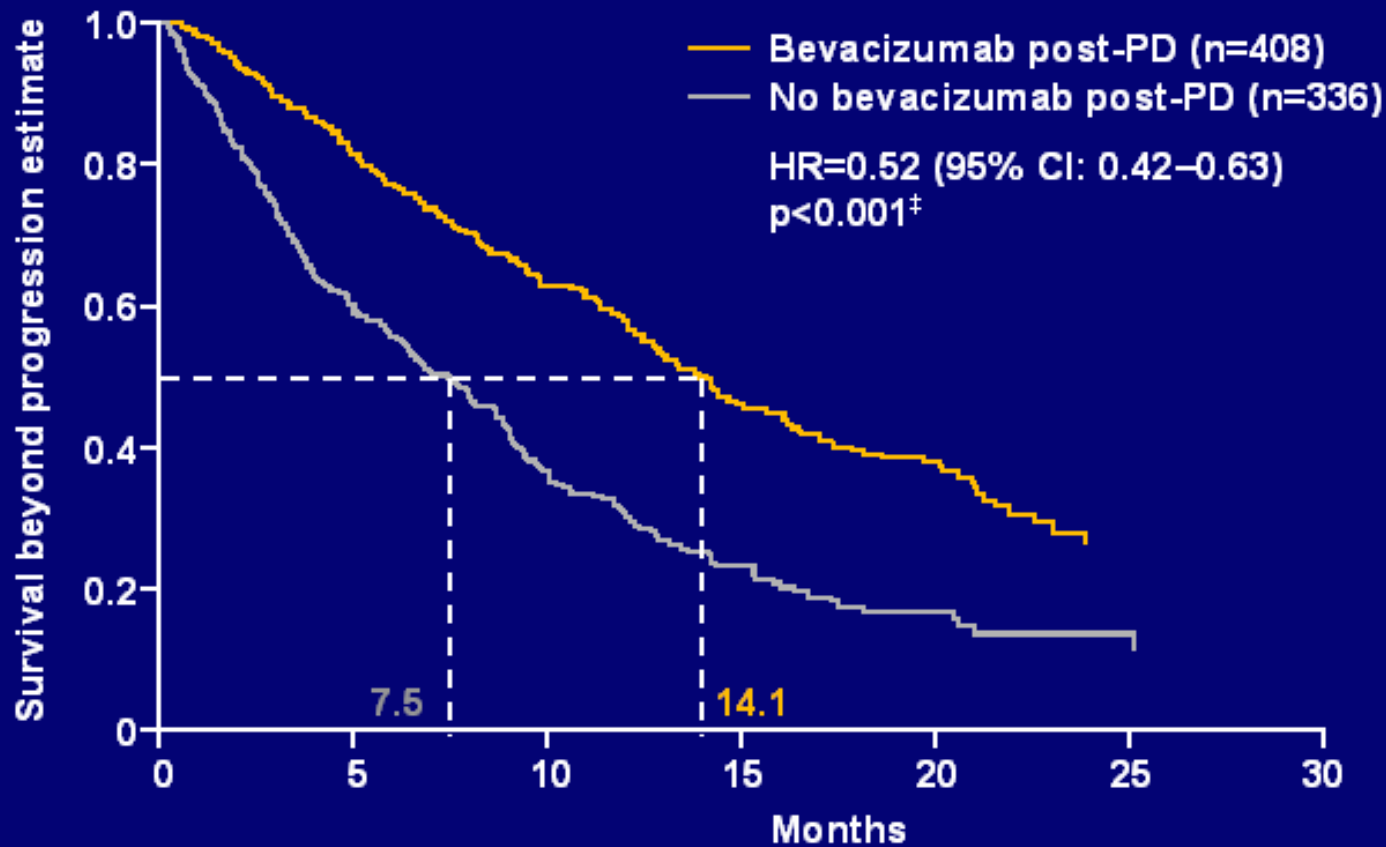
*Non-randomised, observational study

¹1,026 patients were alive 2 months after first PD

²No treatment ever or bevacizumab and/or chemotherapy ≥ 2 months after PD

Cohn, et al. ASCO 2010

Studio ARIES: risultati

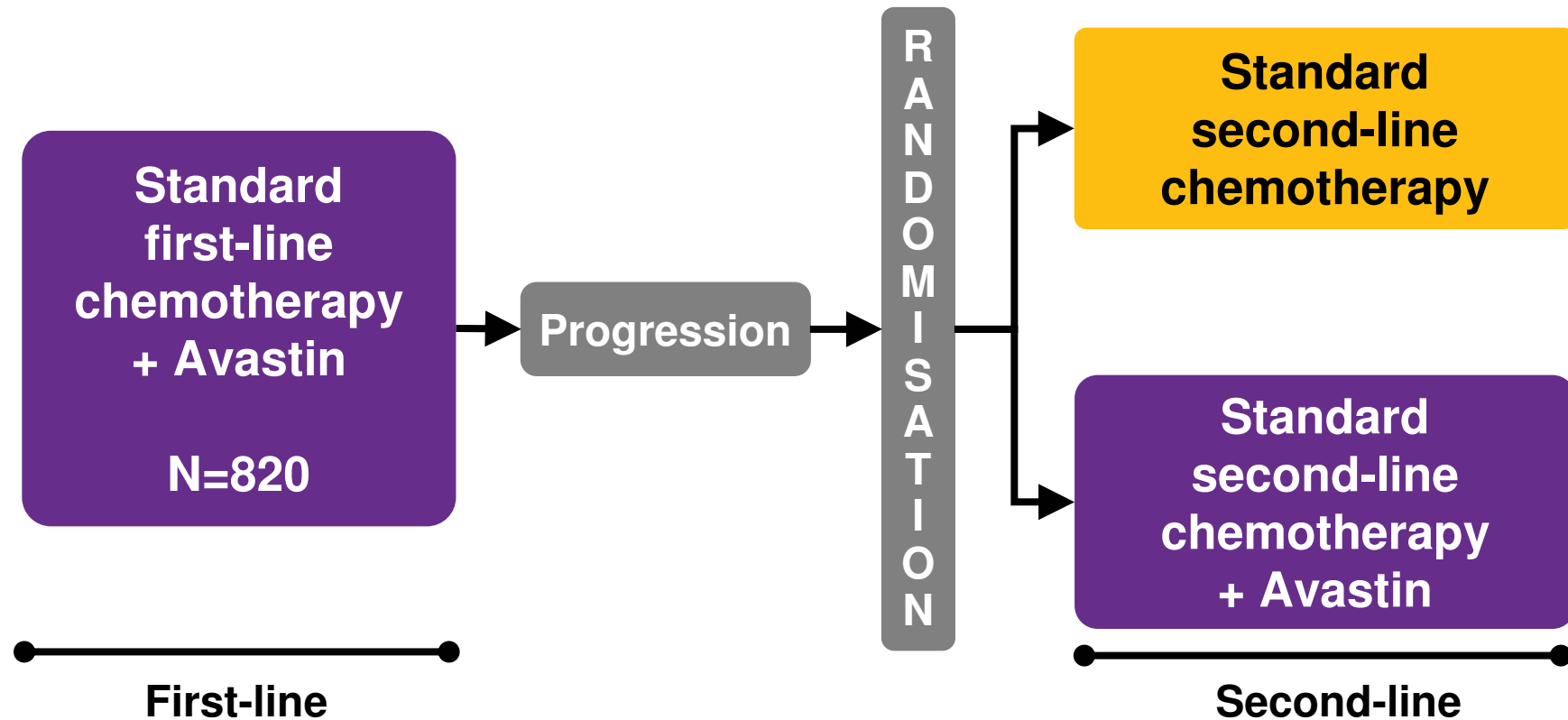


*Non-randomised, observational study

[‡]Post-progression bevacizumab versus no bevacizumab study

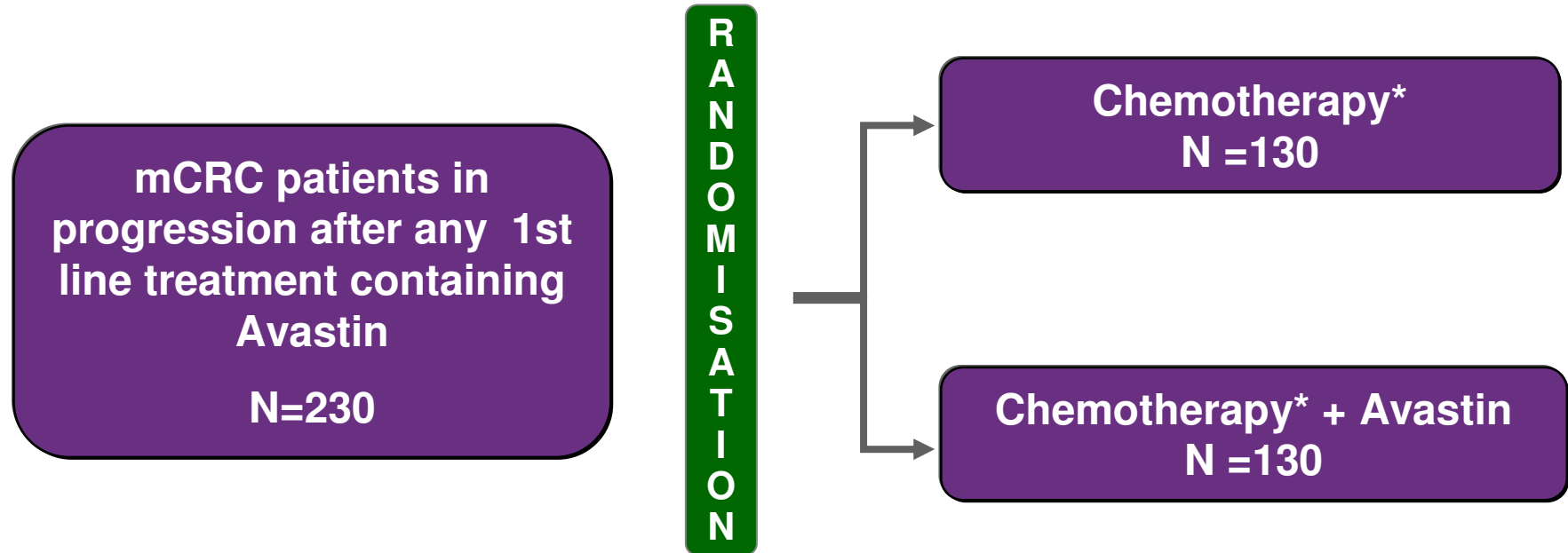
Cohn, et al. ASCO 2010

Valutazione prospettica: Disegno studio AIO 0504



Primary endpoint: OS
PI: Stefan Kubicka

Valutazione prospettica: Disegno studio BeByp



Primary endpoint: PFS superiority

PI: A. Falcone

C'è dell'altro?

Panitumumab dove lo mettiamo?

STUDIO PRIME (1° linea):

1183 mCRC pazienti trattati con PMAB+FOLFOX4 vs FOLFOX4

Aumento significativo PFS in pazienti con tumori WT KRAS (9.6 vs 8.0 mos, $p=0.02$)

Aumento (non statisticamente significativo) dell' OS

Douillard, JCO 2010

STUDIO 181 (2° linea):

1186 mCRC pazienti trattati con PMAB+FOLFIRI vs FOLFIRI

Aumento significativo PFS in pazienti con tumori WT KRAS (5.9 vs 3.9 mos, $p=0.004$)

Aumento (non statisticamente significativo) dell'OS

Peeters, JCO 2010

STUDIO PANERB (Dopo progressione a Cetuximab):

32 mCRC pazienti trattati con PMAB monoterapia dopo P a CPT11 e Cetuximab

Pazienti in progressione dopo precedente risposta a Cetuximab hanno clinical benefit del 74%

Pazienti che non avevano risposto precedentemente a Cetuximab hanno clinical benefit del 15%

Metges, ASCO 2010 (abstr. E14000)

W le ammucchiate!

STUDIO FOIB (Folfoxiri+Bevacizumab , fase II):

PFS mediana: 13.1 mesi

OS mediana: 30.9 mesi

ORR: 77% + SD 23% = Disease control rate 100% (!)

23% resezioni R0

Masi, Lancet Oncology 2010

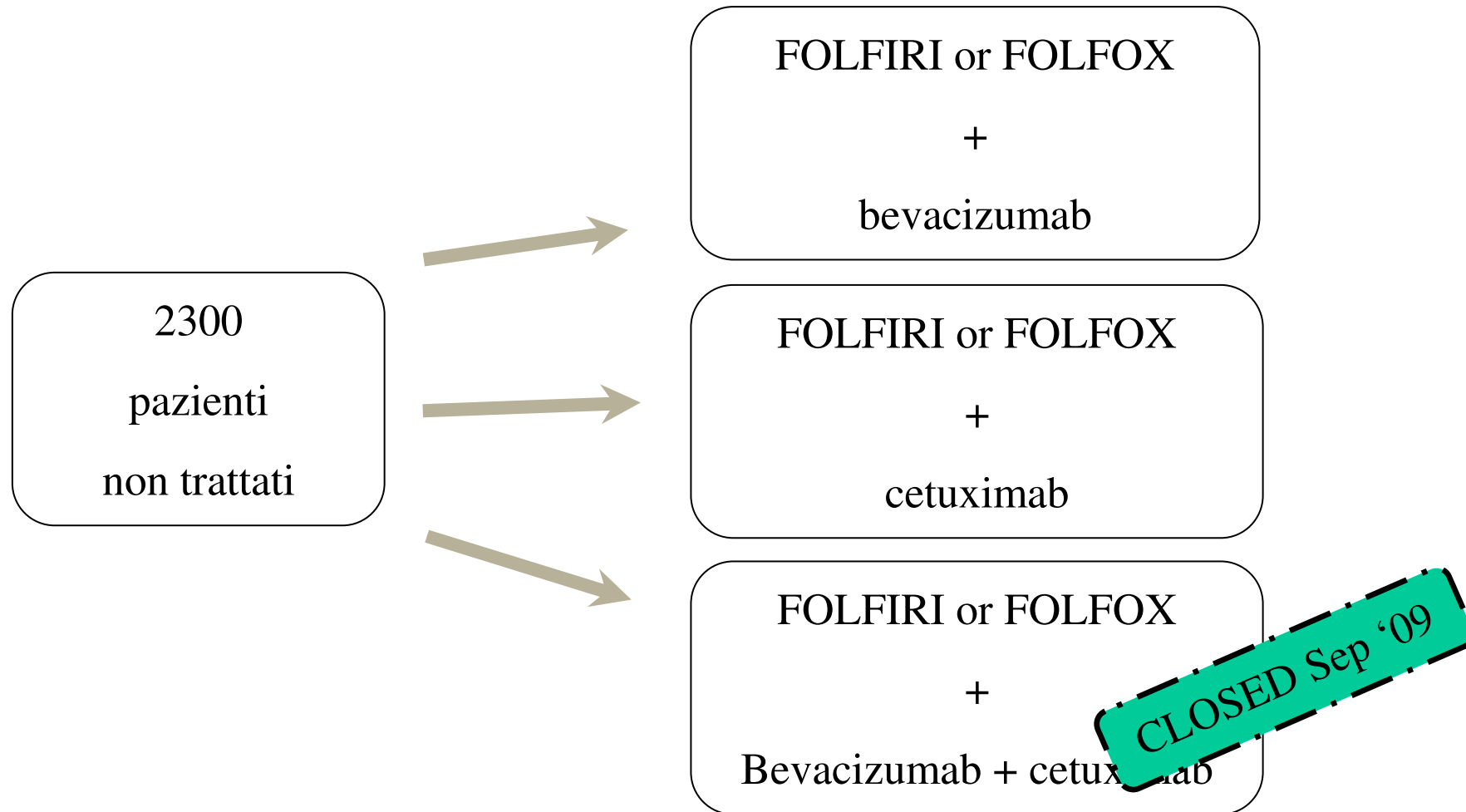
STUDIO POCHER (Chrono-CPT11 + FF + Oxaliplatino + Cetuximab) in pazienti con malattia limitata al fegato:

79% ORR (!)

Garufi, Br J Cancer 2010

La tempesta perfetta...

STUDIO CALGB C80405



Grazie per l'attenzione!