INCONTRI DI AGGIORNAMENTO - DIPARTIMENTO ONCOLOGICO
Strategie terapeutiche nel carcinoma del colon-retto metastatico
Negrar, 11 Febbraio 2014

Caratterizzazione biomolecolare e strategie terapeutiche nel paziente con metastasi non resecabili

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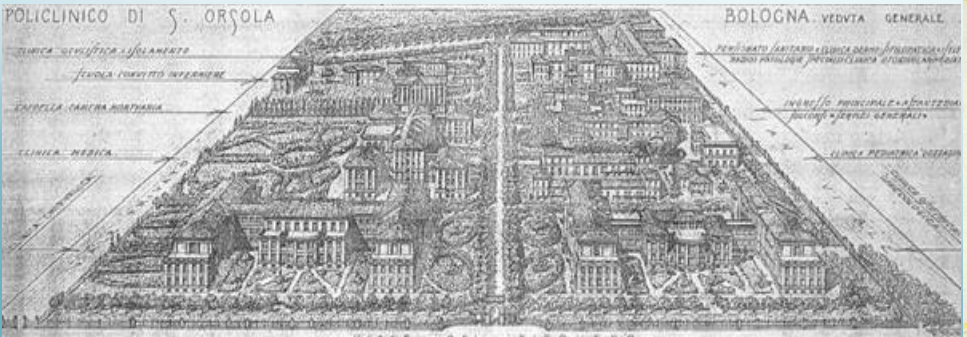
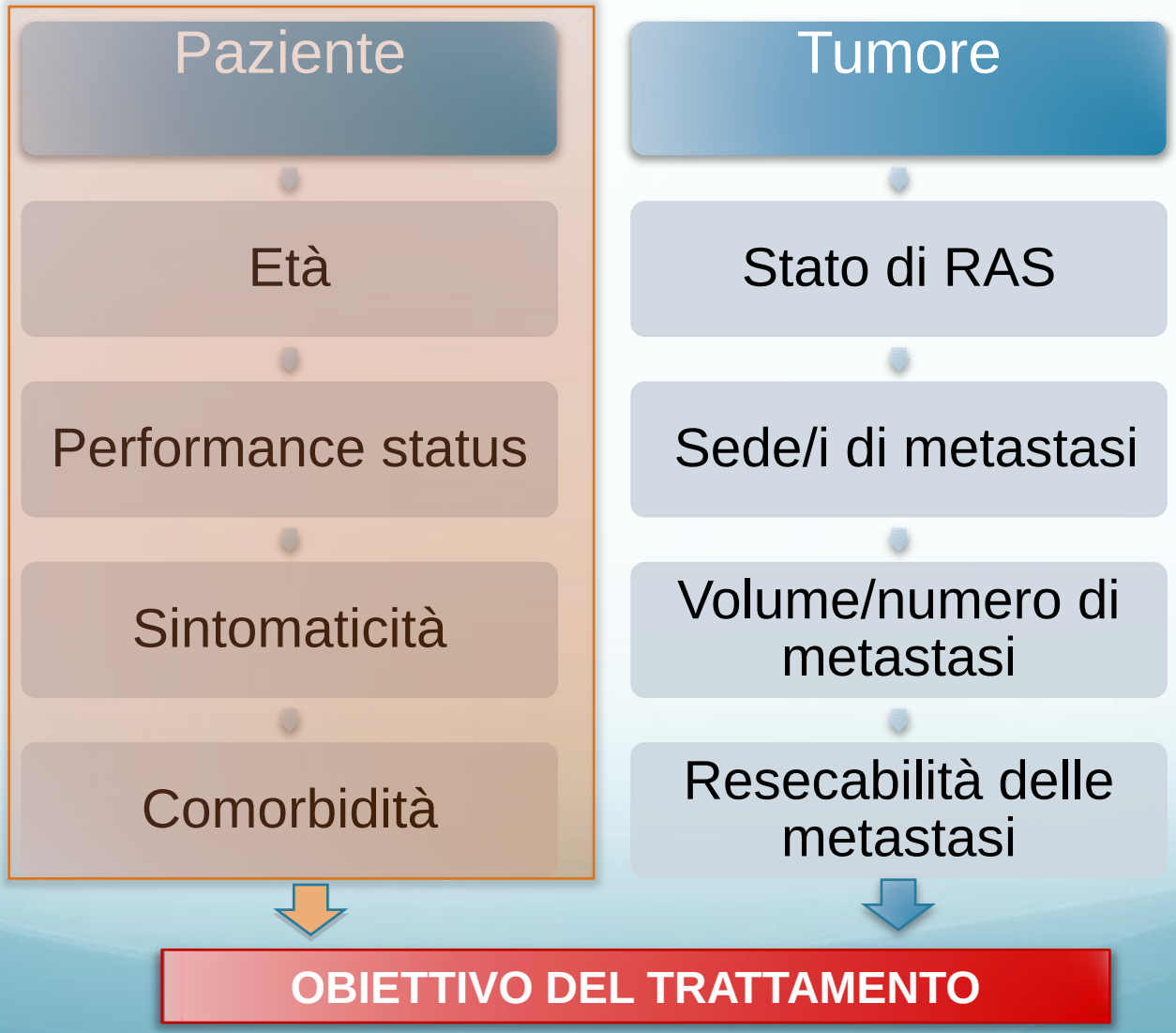
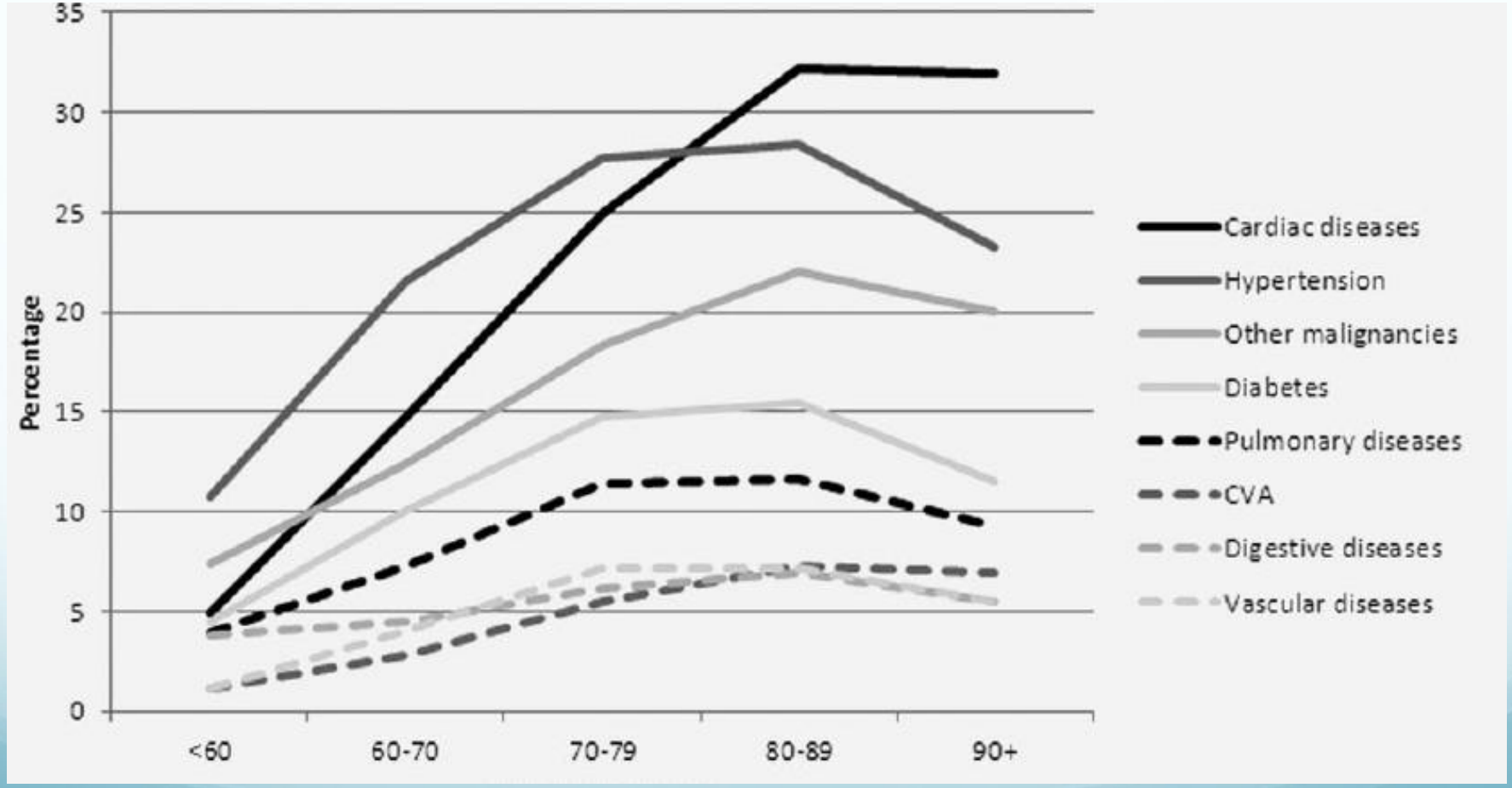


Terapia personalizzata nel CCRM



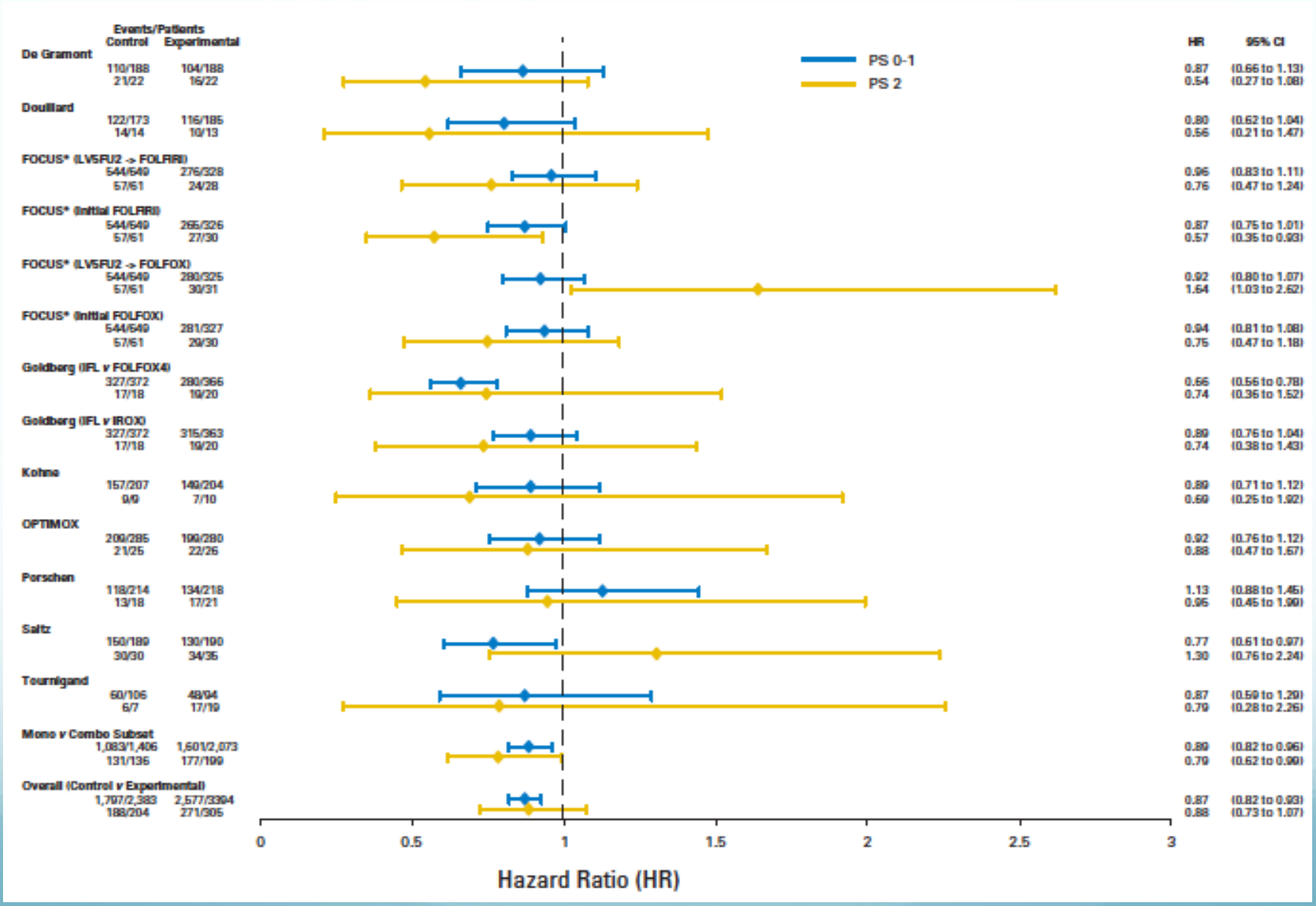
Multimorbidità in pazienti con CCR

27.339 pazienti con CCR, Registro Tumori di Eindhoven (NL), periodo 1995-2010



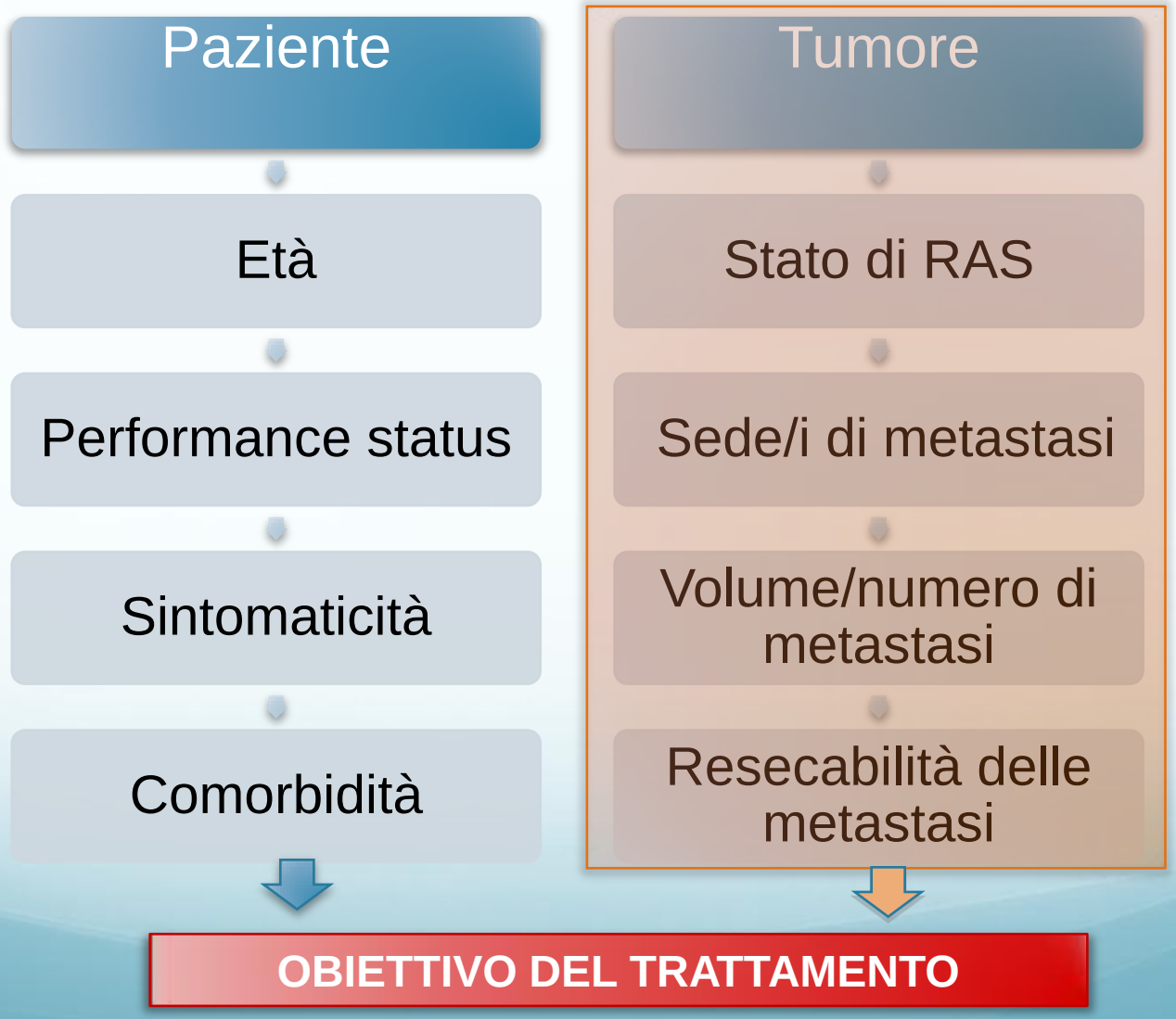
Van Leersum et al , Int J Cancer 2012

Performance status e OS nel CCRM



Sargent et al, J Clin Oncol 2009

Terapia personalizzata nel CCRM



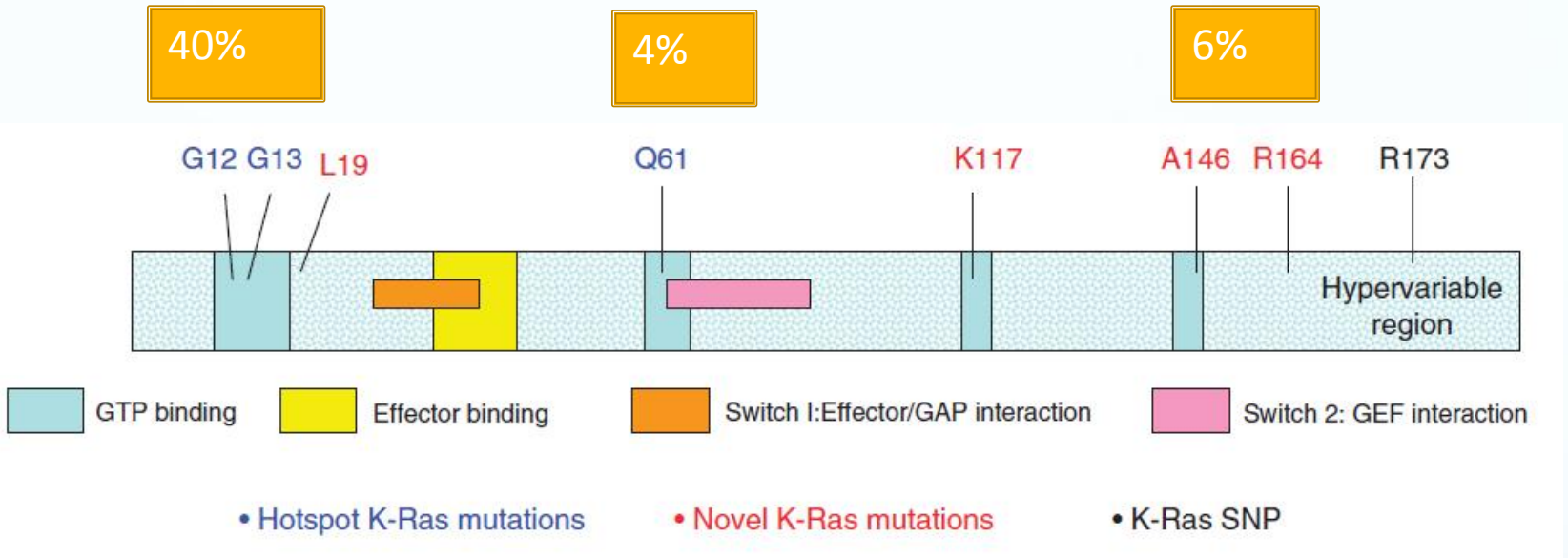
CCR con metastasi non resecabili

- Caratterizzazione e selezione dei pazienti
- La I linea e la scelta della sequenza
- La terapia di mantenimento
- La sostenibilità delle scelte

Caratterizzazione e selezione dei pazienti

- Da KRAS a all RAS
- Indicazioni registrative
- L’impatto di BRAF
- Accessibilità al test

Exon 2, 3 and 4 KRAS and NRAS mutations



KRAS wild type ≈ 60%

All RAS wild type ≈ 45%

Smith et al, Br J Cancer 2010

PRIME study: OS According to RAS Mutation Status

Variable	Panitumumab FOLFOX4 (months)	FOLFOX4 (months)	HR	p
No KRAS mutation in exon 2	23.9	19.7	0.83	0.07
KRAS mutation in exon 2	15.5	19.3	1.24	0.07
No RAS mutation	26.0	20.2	0.78	0.04
RAS mutation	15.6	19.2	1.25	0.03
No RAS or BRAF mutations	28.3	20.9	0.74	0.02
BRAF mutation	10.5	9.2	0.90	0.76

Douillard et al, JCO 2010, NEJM 2013

FIRE 3 study: OS According to RAS Mutation Status

	FOLFIRI + cetuximab (months)	FOLFIRI + bevacizumab (months)	HR	p
KRAS wild type ITT (n. 592)	28.7	25.0	0.77	0,017
All RAS wt (n. 342)	33,1	25.6	0,69	0.011
New RAS mt (n. 65)	16.4	20,6	1.20	0.57
All RAS mt (n. 178)	20.3	20.6	1.09	0.60
BRAF mt (n. 43)	12.9	11.0		0,448

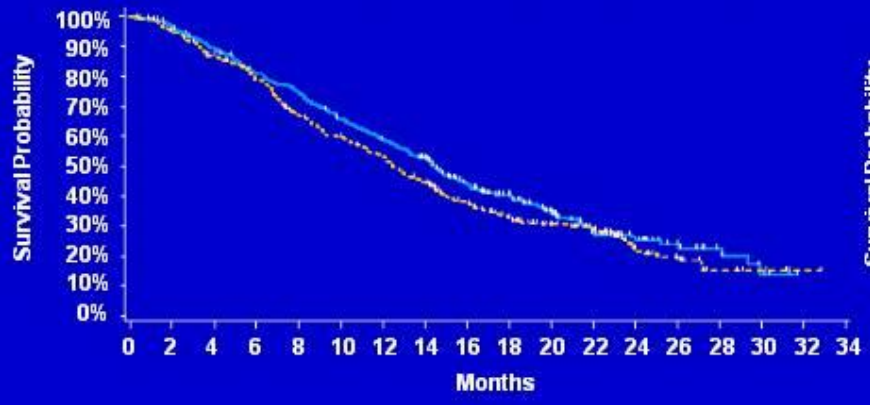
Stintzing et al, ECCO-ESMO 2013

Study 20050181

OS by WT *KRAS* Exon 2 And WT *RAS*

Primary Analysis WT *KRAS* Exon 2*

HR = 0.85 (95% CI: 0.70, 1.04)
Log-rank p-value = 0.12



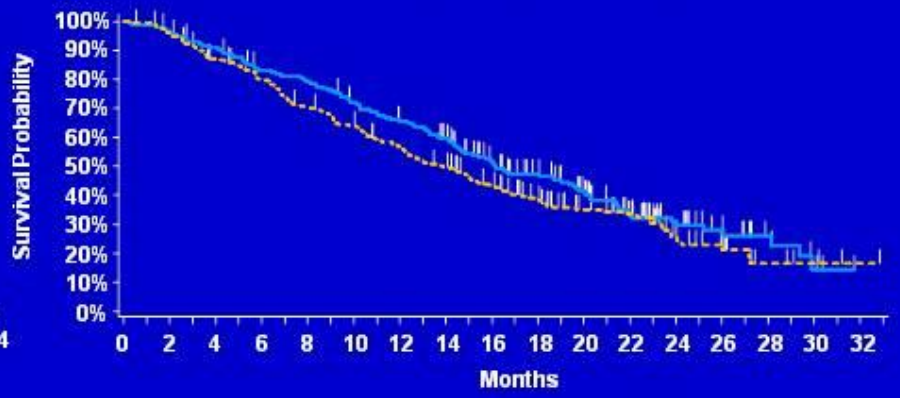
Panitumumab Plus FOLFIRI	303	288	264	235	217	189	168	147	111	89	65	43	29	18	9	4	0	0
FOLFIRI alone	294	278	249	223	187	166	146	121	93	74	58	46	26	16	7	5	1	0

	Events n/N (%)	Median months (95% CI)
Panitumumab + FOLFIRI	200/303 (66)	14.5 (13.0, 16.0)
FOLFIRI	207/294 (70)	12.5 (11.2, 14.2)

Ascertainment rate: 91%

Extended WT *RAS*

HR = 0.803 (95% CI: 0.629, 1.024)
Log-rank p-value = 0.08



Panitumumab + FOLFIRI	204	194	182	163	156	139	126	112	88	70	54	36	25	16	8	3	0
FOLFIRI	211	201	179	162	142	128	112	97	77	61	46	38	20	12	5	3	1

	Events n/N (%)	Median months (95% CI)
Panitumumab + FOLFIRI	127/204 (62)	16.2 (14.5, 19.7)
FOLFIRI	141/211 (67)	13.9 (11.9, 16.1)

Ascertainment rate: 85%

*Adapted from Peeters M, et al. *J Clin Oncol* 2010;28:4706-13.

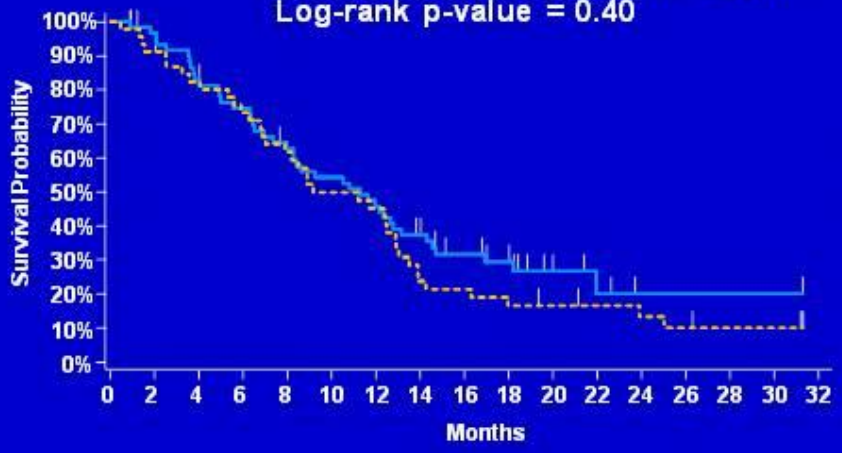
Presented By Marc Peeters, MD, PhD at 2014 Gastrointestinal Cancers Symposium

Study 20050181

OS of MT *RAS* Groups

WT *KRAS* Exon 2/ MT Other *RAS*

HR = 0.825 (95% CI: 0.527, 1.293)
Log-rank p-value = 0.40

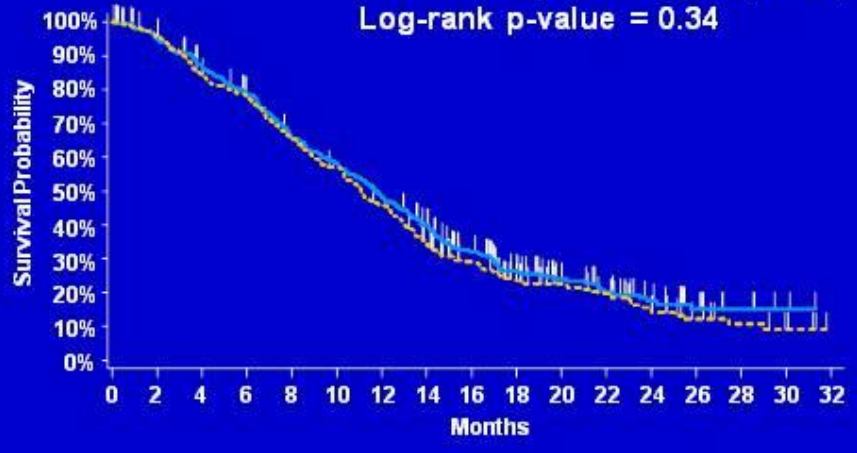


Panitumumab Plus FOLFIRI	61	57	49	44	37	32	27	21	15	12	6	3	1	1	1	1	0
FOLFIRI alone	46	42	37	32	26	21	19	10	9	7	6	5	4	3	2	2	0

	Events n/N (%)	Median months (95% CI)
Panitumumab + FOLFIRI	43/61 (70)	11.3 (8.3, 13.1)
FOLFIRI	38/46 (83)	9.2 (7.0, 12.9)

MT *RAS*

HR = 0.914 (95% CI: 0.759,1.101)
Log-rank p-value = 0.34



Panitumumab Plus FOLFIRI	299	281	256	228	190	168	139	111	80	57	40	29	20	10	5	2	0
FOLFIRI alone	294	277	240	221	185	160	127	92	70	50	39	32	20	11	7	4	0

	Events n/N (%)	Median months (95% CI)
Panitumumab + FOLFIRI	224/299 (75)	11.8 (10.4, 13.1)
FOLFIRI	231/294 (79)	11.1 (10.2, 12.4)

Presented By Marc Peeters, MD, PhD at 2014 Gastrointestinal Cancers Symposium

BRAF status – CRYSTAL Study

	BRAF wt	BRAF mt
	FOLFIRI (n= 289)	FOLFIRI (n=33)
ORR (%) [95% CI]	42.6 [36.8–48.5]	15.2 [5.1–31.9]
PFS (moths) [95% CI]	8.8 [7.6–9.4]	5.6 [3.5–8.1]
OS (months) [95% CI]	21.6 [20.0–24.9]	10.3 [8.4–14.9]

Van Cutsem et al, ASCO GI 2010, ASCO 2010; J Clin Oncol 2011

BRAF status – OPUS Study

	BRAF wt	BRAF mt
	FOLFOX4 (n= 92)	FOLFOX4 (n=5)
ORR (%) [95% CI]	35.9 [26.1–46.5]	0 [0.0–52.2]
Median PFS (months) [95% CI]	7.2 [5.6–7.4]	1.7 [0.9–7.9]
Median OS (months) [95% CI]	19.5 [17.0–23.8]	4.4 [0.9–10.1]

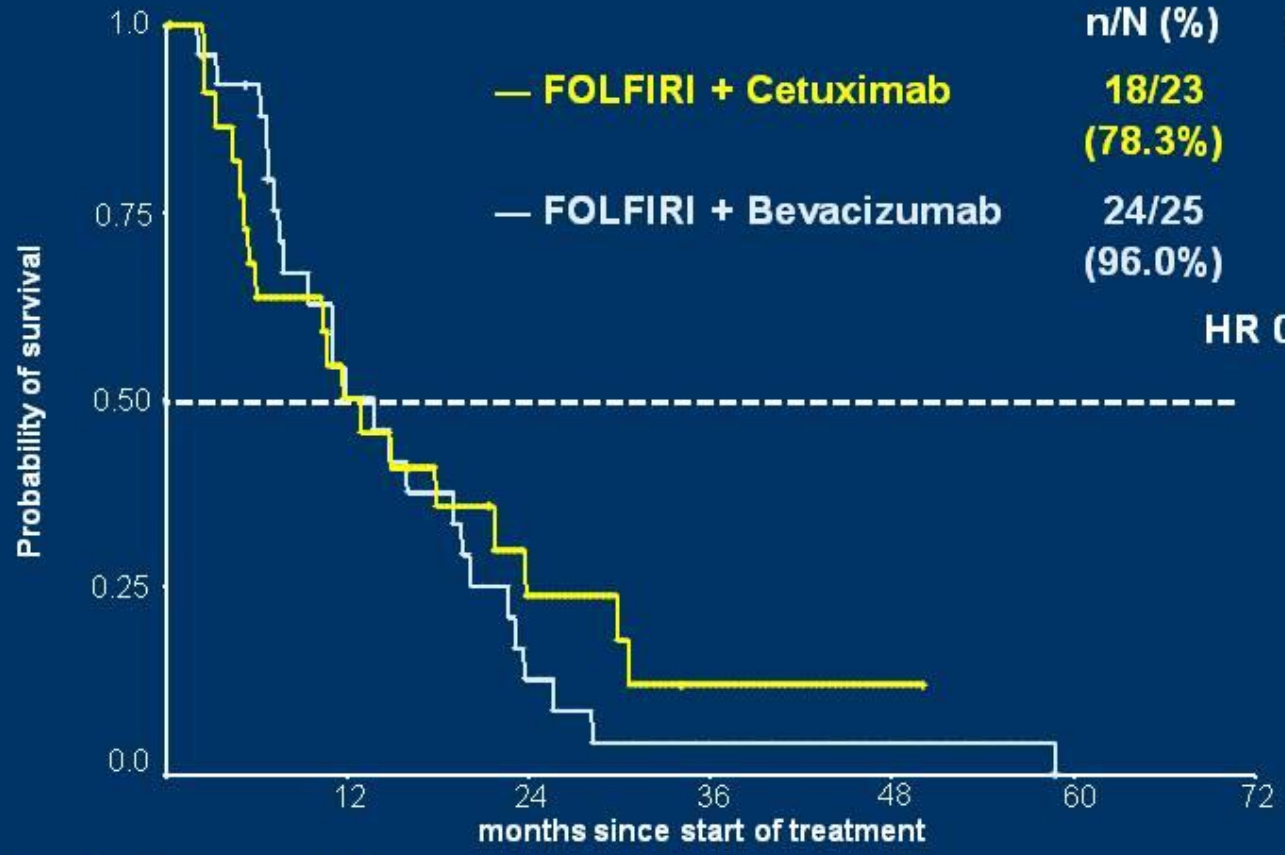
Bokemeyer et al, ASCO GI 2010, ASCO 2010

BRAF status – CAIRO 2 Study

	BRAF wt	BRAF mt	P
Patients No.			
XELOX/BEVA	243	17	
XELOX/BEVA + CET	231	28	
PFS (months)			
XELOX/BEVA	12.2	5.9	0.003
XELOX/BEVA + CET	10.4	6.6	0.010
OS (months)			
XELOX/BEVA	24.6	15.0	0.002
XELOX/BEVA + CET	21.5	15.2	0.001
RR (%)			
XELOX/BEVA	50	35	0.32
XELOX/BEVA + CET	48	39	0.43

Tol et al, NEJM 2009

Overall survival
BRAF mutant population

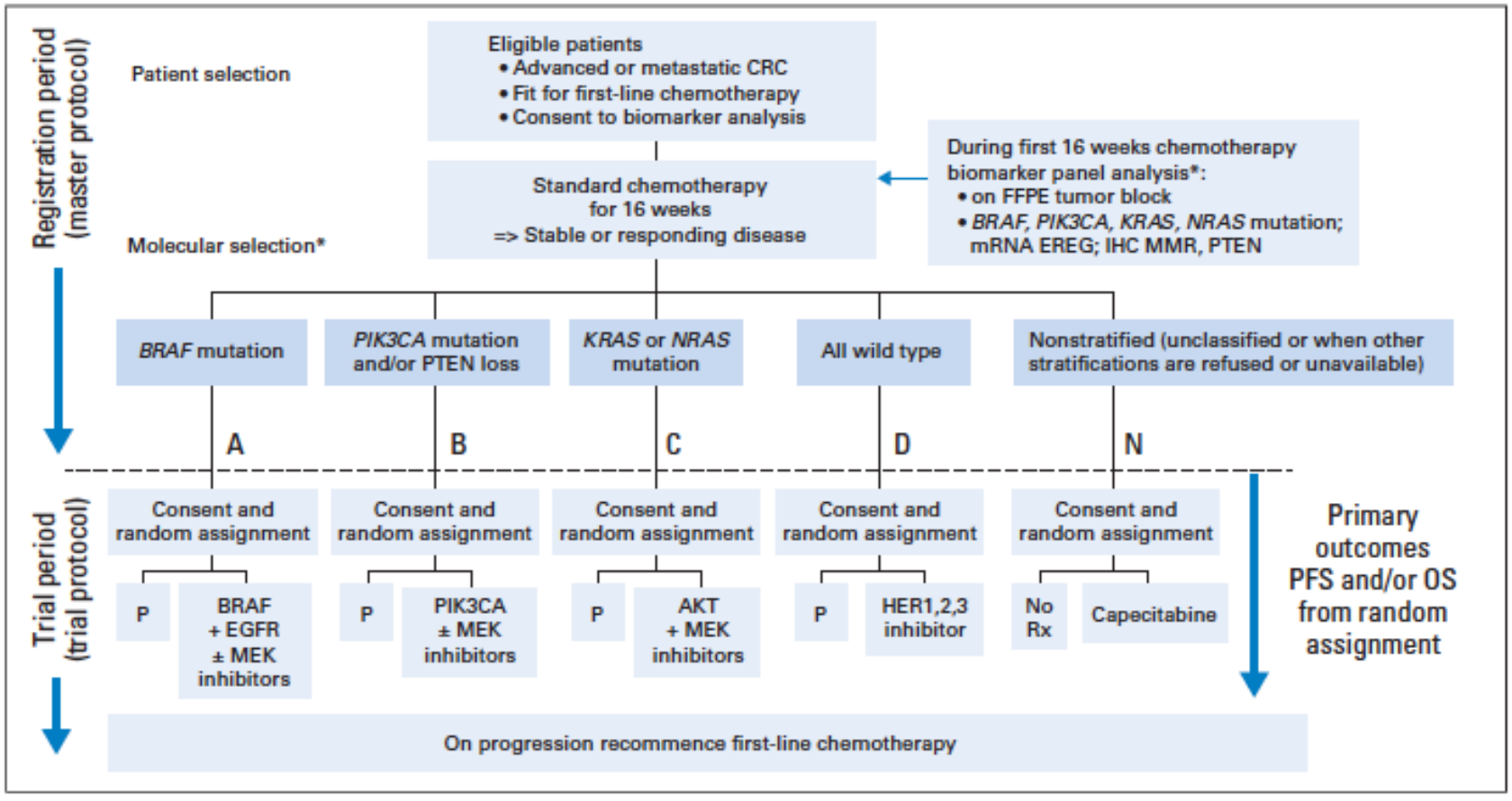


	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	18/23 (78.3%)	12.3	5.5 – 21.7
— FOLFIRI + Bevacizumab	24/25 (96.0%)	13.7	7.8 – 19.5

HR 0.87 (95% CI: 0.47 – 1.61)
p (log-rank)= 0.65

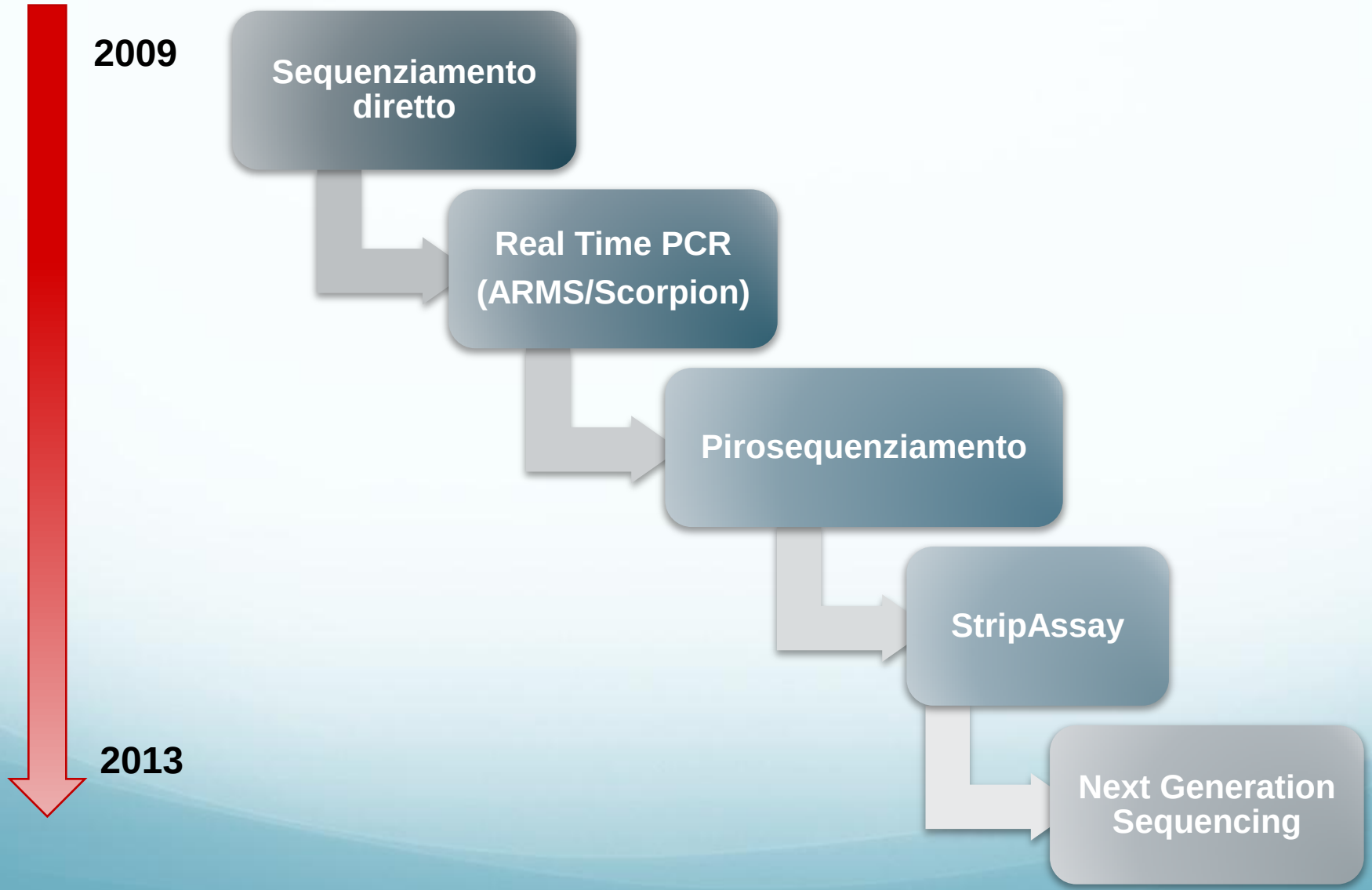
No. at risk	23	11	4	1	1
	25	12	3	1	

FOCUS-4 Study

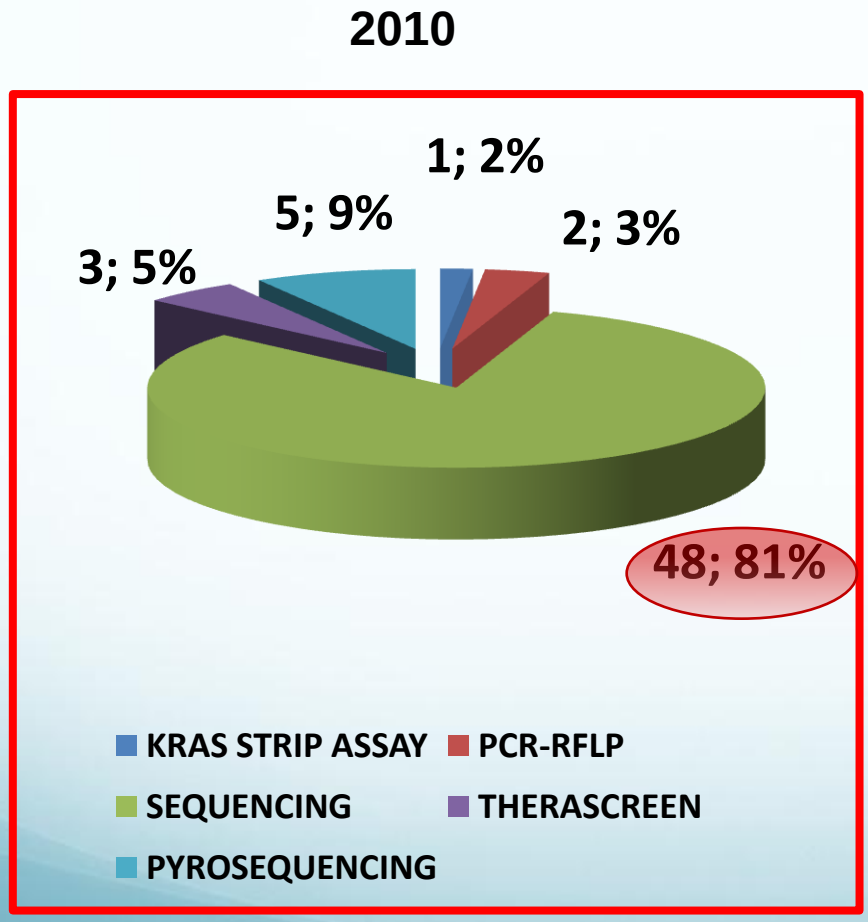


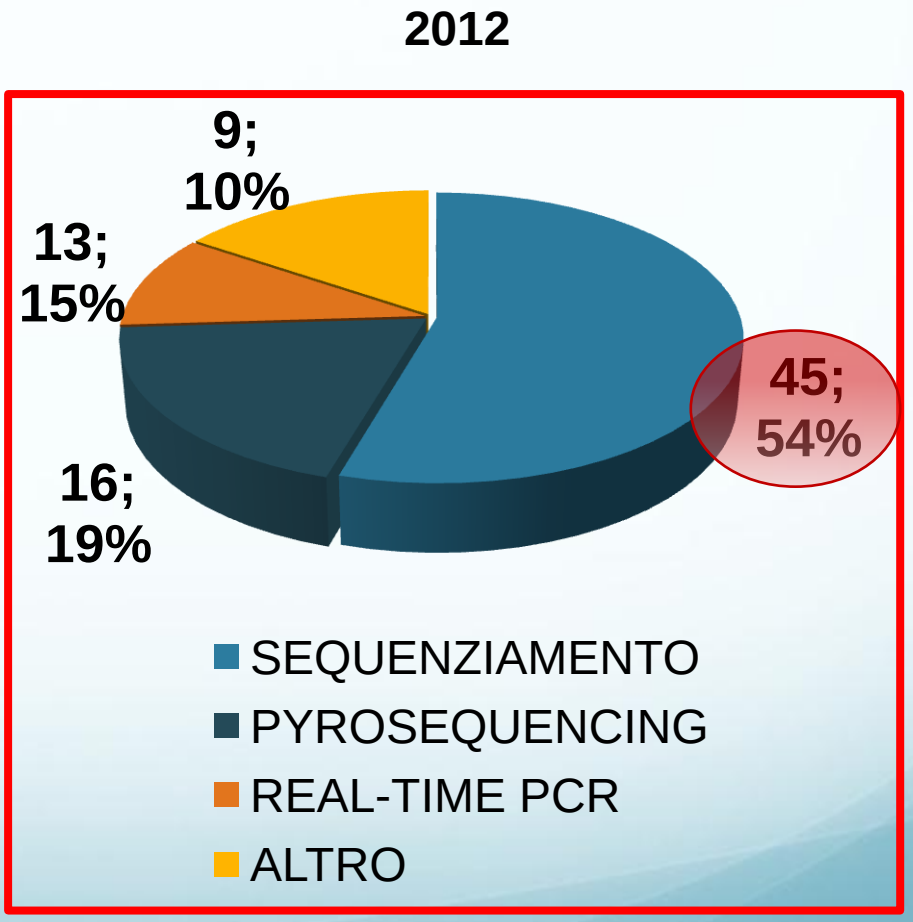
Maughan et al, ASCO 2001; Kaplan et al, JCO 2013

Quali tecnologie per KRAS e NRAS



Methods used for KRAS testing in Italy



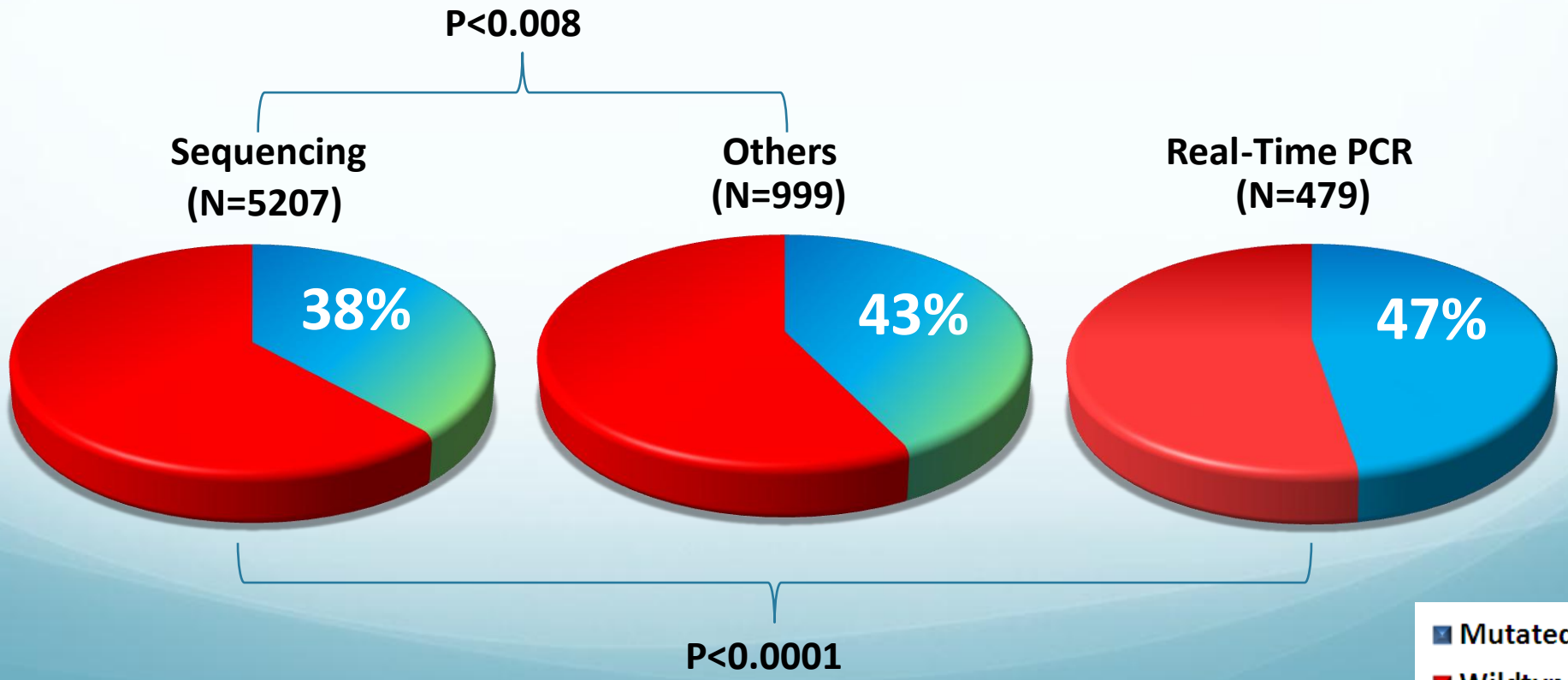


Marchetti et al, AIOM 2011

KRAS αKtive

Mutations by Techniques

KRAS mutation analysis was performed by PCR-Sanger sequencing, real time PCR or other techniques (Pyrosequencing, Strip Assay).



Marchetti et al. AIOM 2011

Sensitivity methods KRAS mutations

Table 6 | Laboratory analysis of *KRAS* mutations

Method for assessing gene status	Sensitivity (%)*
Direct dideoxy sequencing	20–30
Direct pyrosequencing	5
Allele specific probes	10
High-resolution melting analysis	5
ARMS/scorpion probes	1

*The lowest level of mutant DNA that can be detected, expressed as a percentage of total DNA in the tumor sample analyzed. Abbreviation: ARMS, amplification refractory mutation system.

Normanno et al, Nat Rev Clin Oncol 2009

CAPRI Study *(Ciardiello et al, ECCO ESMO 2013)*

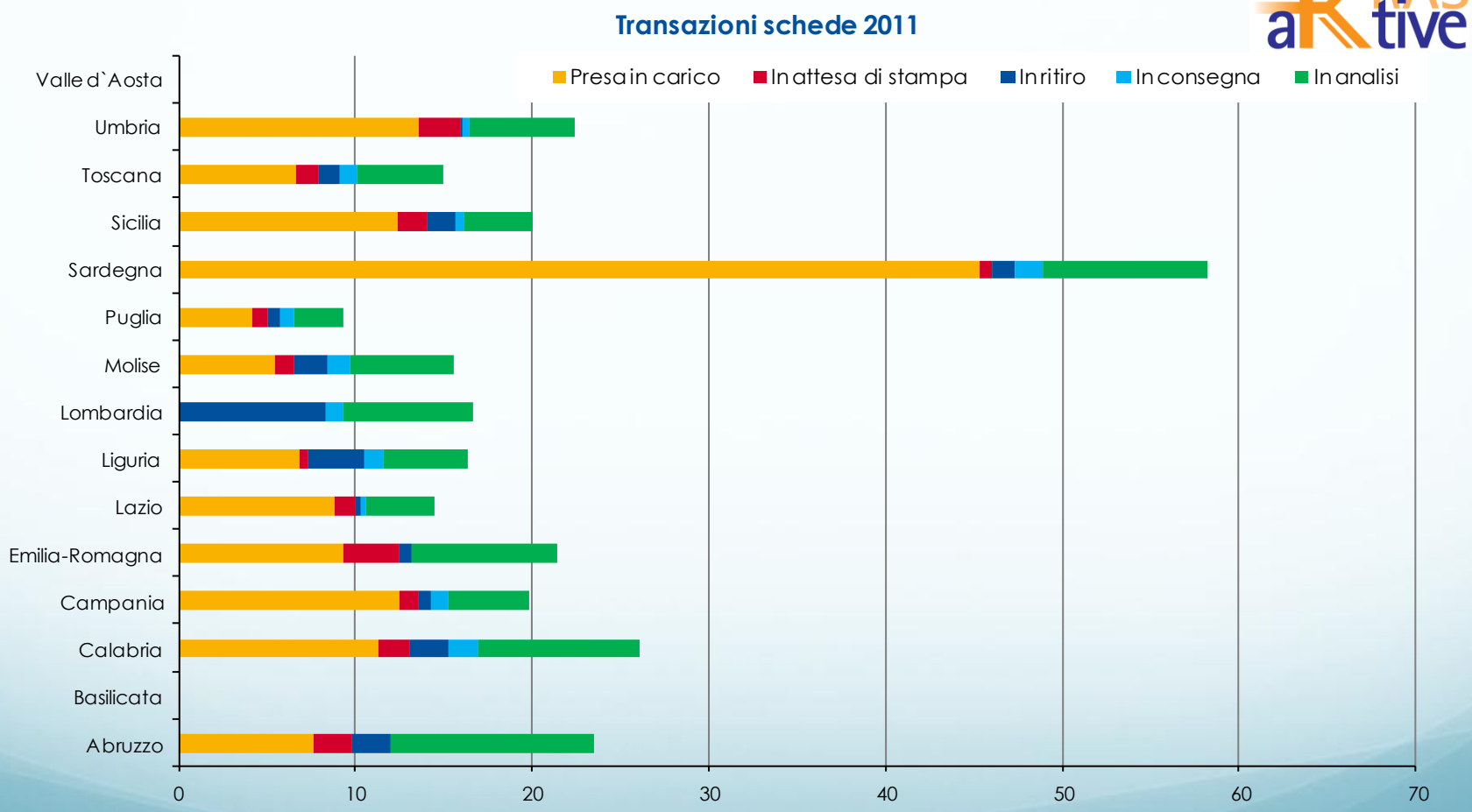
22 multiple gene mutation analysis in mCRC treated with FOLFIRI + cetuximab (2)

Gene	Number of cases (>2%) with mutations, n (%) (N=182 analyzed)	
TP53	72* (39.5%)	
KRAS	45^ (24.7%)	30 at codon 12 or 13 (16.5%); 16 at other (8.8%)
PIK3CA	24 § (13.2%)	16 at exon 9 (8.8%); 10 at exon 20 (5.5%)
BRAF	15 (8.2%)	10 at codon 600 (5.5%); 5 at other (2.7%)
NRAS	13 (7.1%)	
MET	7 (3.8%)	
FBXW7	9 (4.9%)	

- Mutations in genes EGFR, CTNNB1, FGFR3, SMAD4 occurred in 2 cases each (1.1%); mutations in genes ERBB2, FGFR2, PTEN occurred in 1 case each (0.55%)

*7 cases with double TP53 mutation; ^1 case with double KRAS mutation; § 2 cases with double PIK3CA mutation

Tempo globale dalla richiesta alla determinazione delle mutazioni

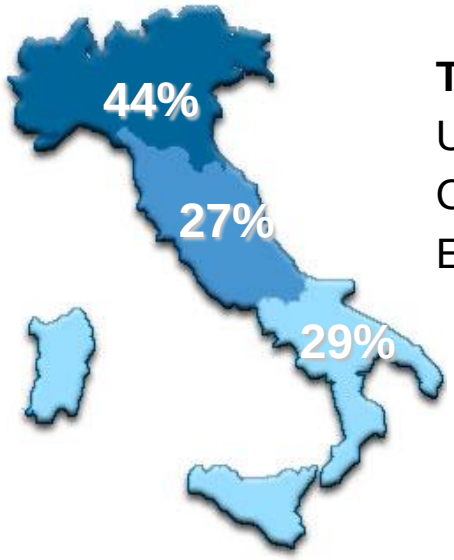


Consensus KRAS early testing

Major findings

Advisory Board: C. Barone, L. Capussotti, F. Cognetti, A. Falcone, L.G. Mantovani, N. Normanno, C. Pinto

Expert Panel: 140 experts



Tipo di centro:

Universitario	11,46%
Ospedaliero	53,13%
Entrambi	35,42%

Per il 74% dei responder la determinazione dello stato di KRAS è un elemento fondamentale per decidere la strategia terapeutica del paziente con carcinoma del colon-retto metastatico

Un intervallo di tempo superiore a 15 gg per la risposta del test KRAS limita le scelte terapeutiche per il 75% dei responder

Tempo massimo di attesa dei risultati del test KRAS per procedere con una terapia:

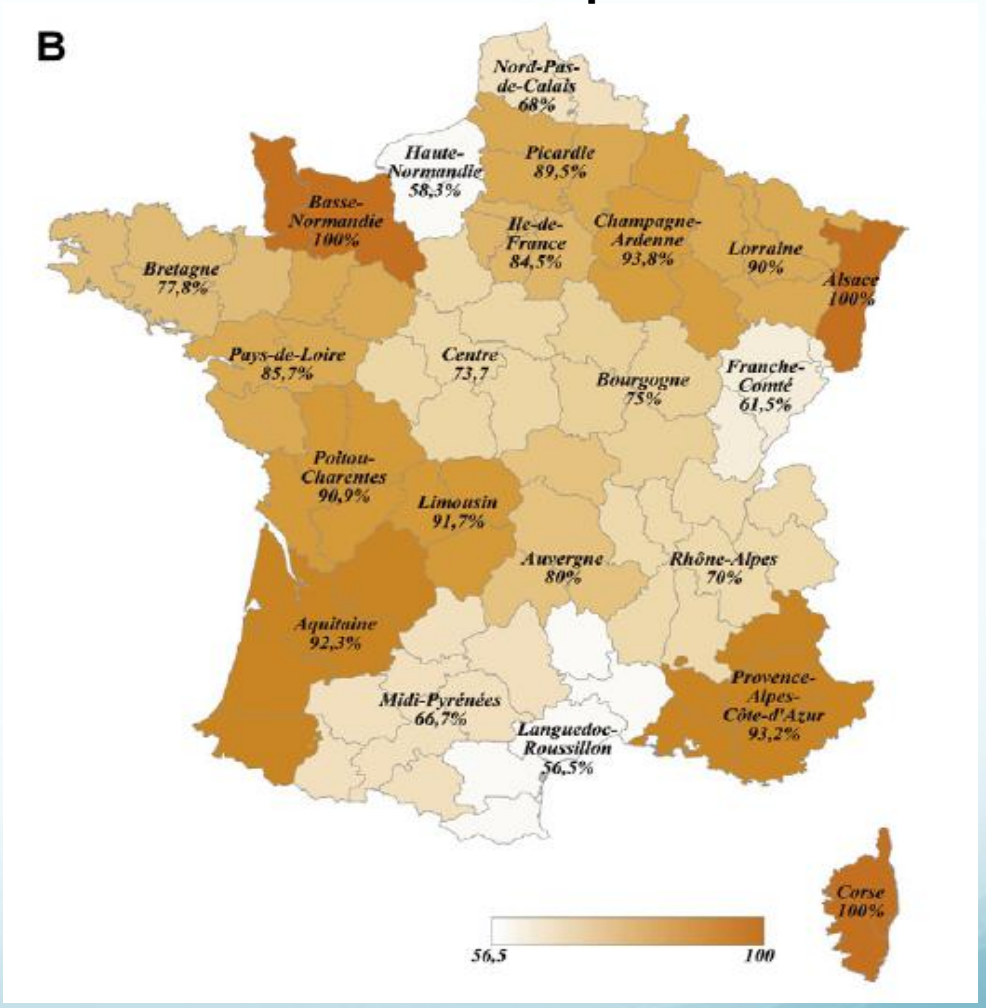
15 giorni

Per il 72% dei responder è utile anticipare il test KRAS nei pazienti ad alto rischio

FLASH KRAS Study

- Studio osservazionale retrospettivo
- 160 Centri in Francia richiesta di test KRAS per scelta 1ª linea CHT nel CCRM
- Periodo considerato di 2 settimane (28/03/11-08/07/11)
- N. pazienti 538
- N. test KRAS richiesti 433 (81,1%)

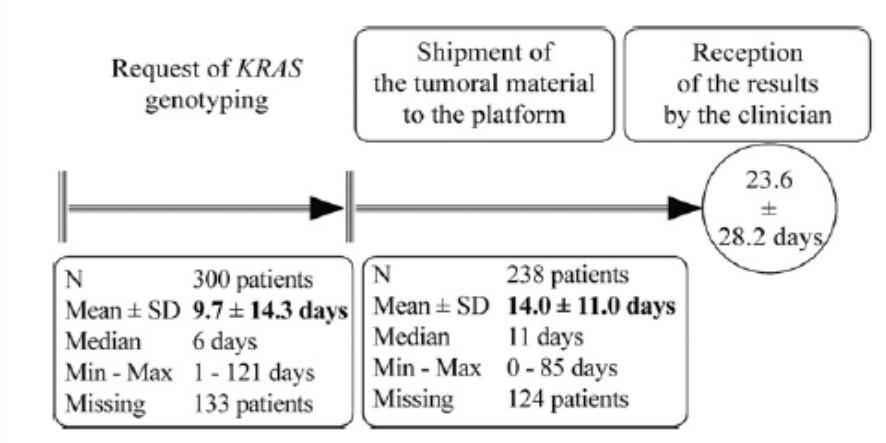
Prescrizione test per KRAS

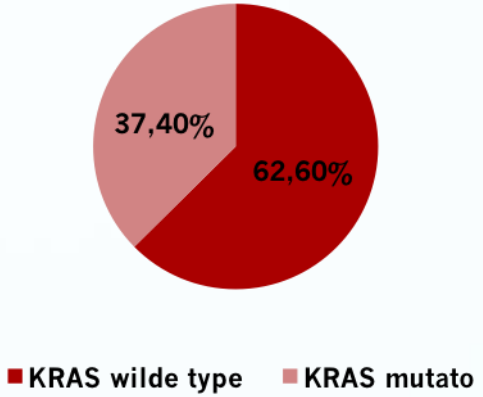


Lièvre et al, Eur J Cancer 2013

FLASH KRAS Study

Duration of the whole process of KRAS testing





- **Tempo di prescrizione dalla diagnosi di CCRM : 40% entro il I mese; mediana 15 gg**
- **Tempo tra prescrizione e invio dei campioni in laboratorio: mediana 6 gg**
- **Tempo tra la spedizione e la recezione dei risultati: mediana 11 gg**
- **Tempo globale del processo: mediana 19 gg**
- **Risultato KRAS noto prima della scelta della I linea di CT nel 43,4% dei pazienti**

Lièvre et al, Eur J Cancer 2013

Quali criticità per KRAS e NRAS

Parametro	Criticità
Quantità di tessuto disponibile	Pezzo operatorio >80%
Conservazione del tessuto	Solitamente adeguata (CQ)
Dissezione del tessuto	Macrodissezione (patologo/biologo molecolare)
Estrazione DNA	Limitate problematiche (CQ)
Sensibilità metodica	**Disponibilità di più tecnologie**
Qualità del referto	Interpretazione immediata per il clinico secondo registrazione del farmaco (Raccomandazioni)
Tempo di refertazione	**≤ 15 giorni**
Organizzazione del percorso	**Patologia/Biologia molecolare Centralizzazione in rete**
Costo	**600-800 Euro**

Potenzialità delle diverse metodiche

	Sequenziamento diretto	CRC RAScan Transgenomics	Sequenom Myriapod Colon	Pyro Qiagen	Ion Torrent Colon & Lung panel	Illumina Cancer Panel
KRAS esone 2	X	X	X	X	X	X
KRAS esone 3	X	X	X	X	X	X
KRAS esone 4	X	X	X	X	X	X
NRAS esone 2	X	X	X	X	X	X
NRAS esone 3	X	X	X	X	X	X
NRAS esone 4	X	X	X	X	**	-
Sensibilità	10-25%	~5%	~1%	~5%	~2%	<5%
Tempo richiesto totale (giorni)	5-10	7-10	3	3	4-5	4-5
Costo reagenti (euro)	210	200*	400	235	200***	250****
Costo apparecchiatura (euro)	Da 130.000 a 210.000	~100.000	250.000	~60.000	~100.000	~100.000

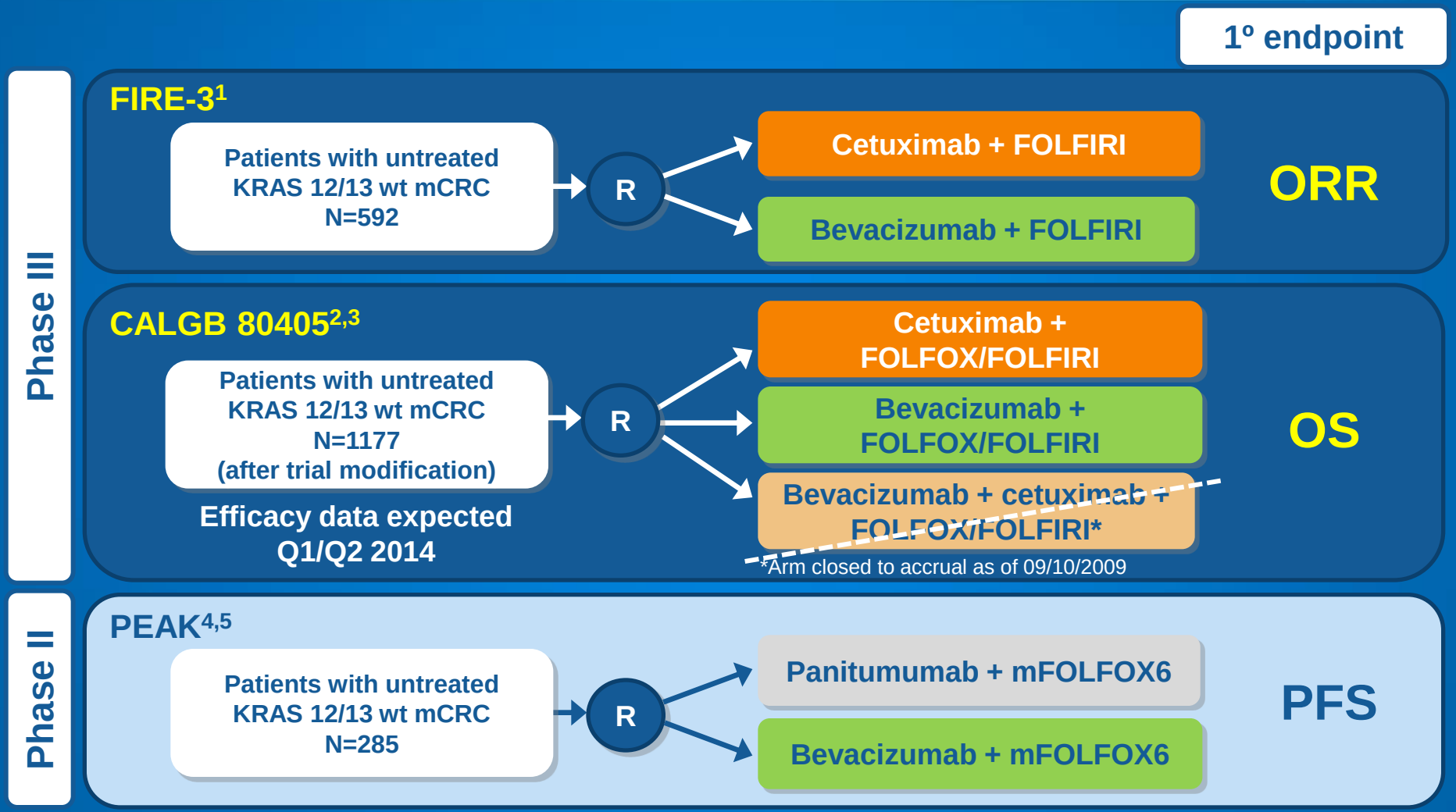
***almeno 5 pazienti analizzati per run; ** in fase di rielaborazione; ***8 pazienti per run; ****6 pazienti run**

Courtesy of N. Normanno

La I linea e la scelta delle sequenze

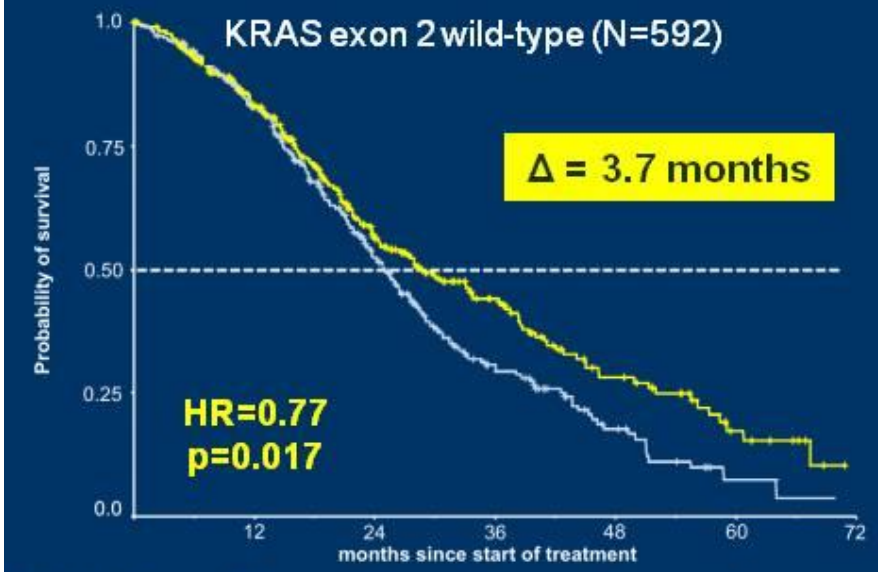
- OS in I linea del regime FOLFIRI + cetuximab (seguito da CT + bevacizumab in ≈ 40%) nella popolazione RAS wt (FIRE 3)
- Selezione clinica dei pazienti
  - Fluoropirimidina + bevacizumab un opzione in pazienti non suscettibili di regimi di CHT a due farmaci
  - FOLFOXIRI + bevacizumab in pazienti “fit”

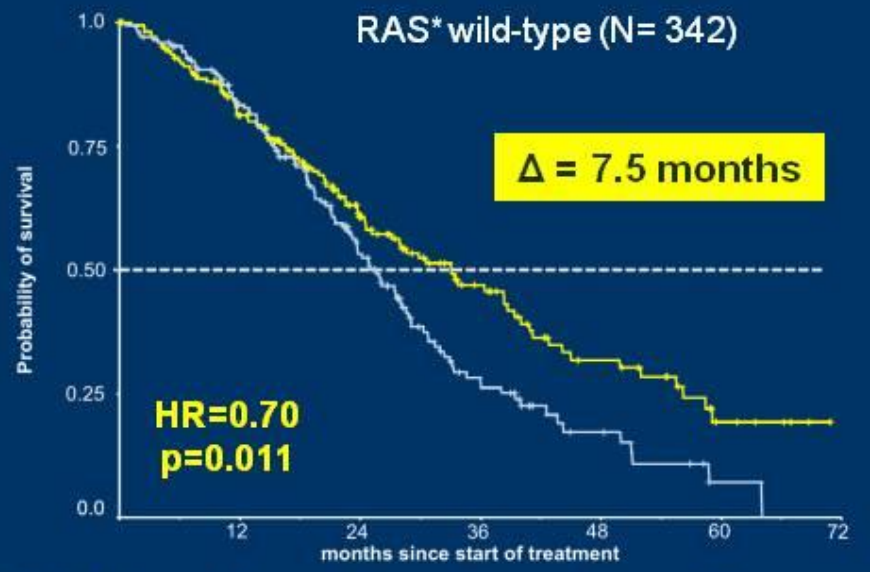
Head-to-head trials of targeted agents in 1st line treatment of mCRC



1. Heinemann V, et al. ASCO 2013 (Abstract No. LBA3506); 2. Naughton MJ, et al. ASCO 2013 (Abstract No. 3611); 3. NCT00265850; 4. Schwartzberg LS, et al. ASCO GI 2013 (Abstract No. 446); 5. Schwartzberg LS, et al. ASCO 2013 (Abstract No. 3631)

Evaluation of OS





	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	191/171 (53.2%)	33.1	24.5 – 39.4
— FOLFIRI + Bevacizumab	110/171 (64.3%)	25.6	22.7 – 28.6

HR 0.70 (95% CI: 0.53 – 0.92)
p (log-rank)= 0.011

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

Possible explanations for the FIRE-3 results

Differences in subsequent treatment lines (2nd/3rd line)

- Distribution of treatment regimen
- Differences in 2nd/3rd line efficacy

Real difference in 1st line, which is not captured by ‘standard’ criteria

-e.g. deepness of response

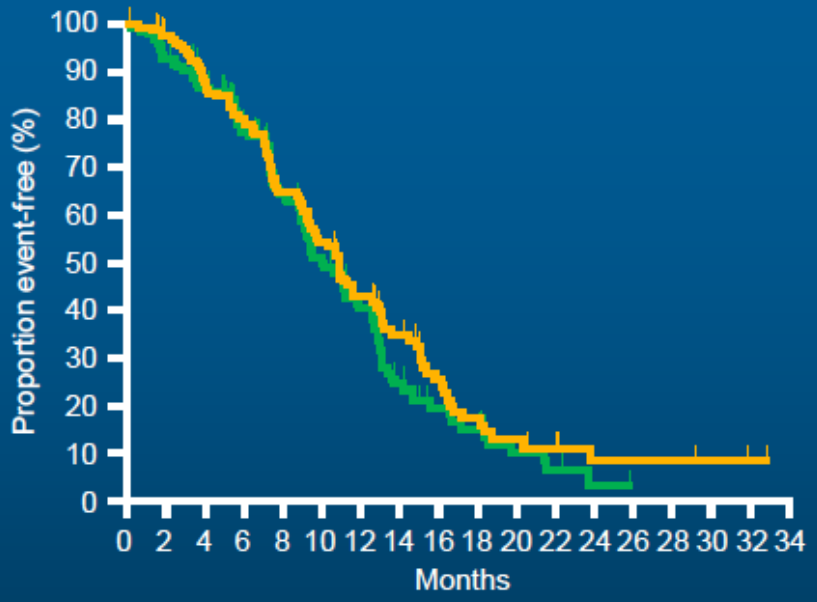
Alteration of tumour biology by treating with an EGFR inhibitor

- Sensitizing for further treatment lines

PEAK Trial Biomarker Analysis

PFS in Patients with WT *KRAS* exon 2 and WT *RAS* mCRC Treated with Panitumumab + mFOLFOX6#

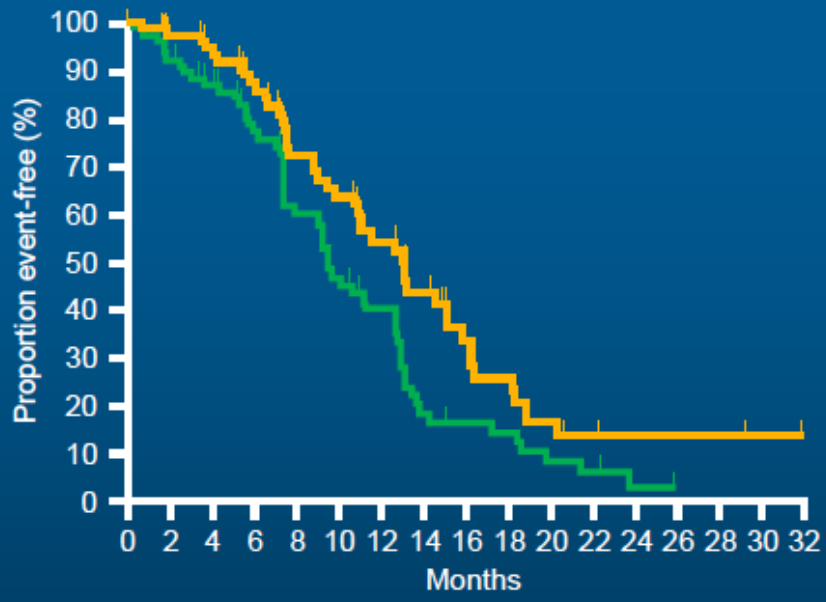
Original WT *KRAS* exon 2 (ITT set)



	Events n (%)	Median (95% CI) months
Panitumumab + mFOLFOX6 (n=142)	90 (63)	10.9 (9.4–13.0)
Bevacizumab + mFOLFOX6 (n=143)	94 (66)	10.1 (9.0–12.6)

HR*=0.87 (95% CI: 0.65–1.17)
p=0.35

WT *RAS* (exons 2,3,4 of *KRAS/NRAS*)



	Events n (%)	Median (95% CI) months
Panitumumab + mFOLFOX6 (n=88)	50 (57)	13.0 (10.9–15.1)
Bevacizumab + mFOLFOX6 (n=82)	60 (73)	9.5 (9.0–12.7)

HR*=0.65 (95% CI: 0.44–0.96)
p=0.03

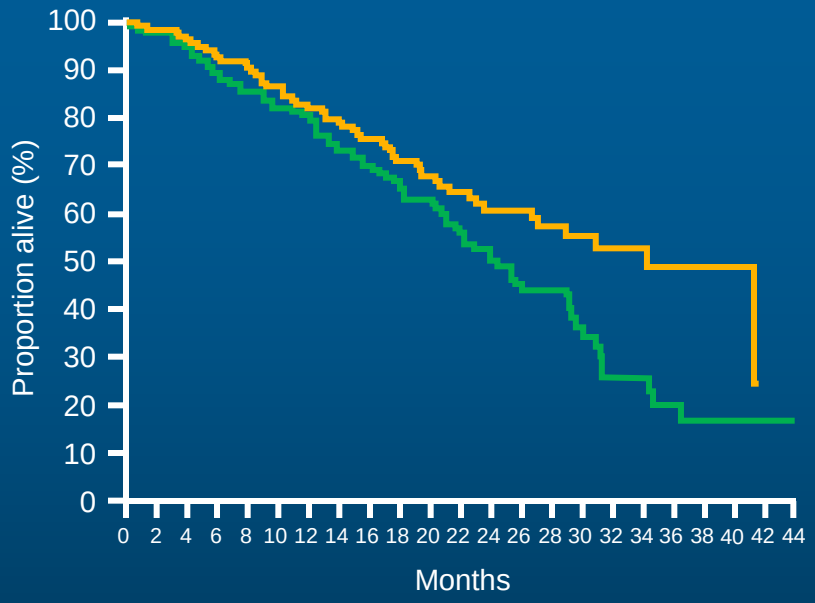
#Data cutoff 30 May 2012; *Stratified Cox proportional hazards model

Schwartzberg L, et al. J Clin Oncol 31, 2013 (suppl; abstr 3631).

PEAK Trial Biomarker Analysis

OS in Patients with WT *KRAS* exon 2 and WT *RAS* mCRC Treated with Panitumumab + mFOLFOX6 with Longer Follow-Up Time[#]

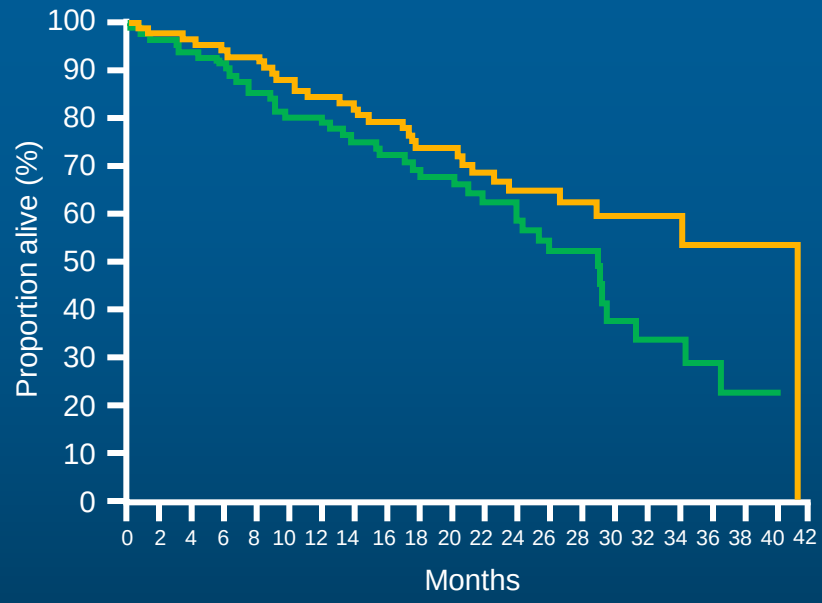
WT *KRAS* exon 2 (ITT set)



	Events n (%)	Median (95% CI) Months
Panitumumab + mFOLFOX6 (n=142)	52 (37)	34.2 (26.6–NR)
Bevacizumab + mFOLFOX6 (n=143)	78 (55)	24.3 (21.0–29.2)

HR*=0.62 (95% CI: 0.44–0.89)
p=0.009

WT *RAS* (exons 2,3,4 of *KRAS/NRAS*)



	Events n (%)	Median (95% CI) months
Panitumumab + mFOLFOX6 (n=88)	30 (34)	41.3 (28.8–41.3)
Bevacizumab + mFOLFOX6 (n=82)	40 (49)	28.9 (23.9–31.3)

HR*=0.63 (95% CI: 0.39–1.02)
p=0.058

[#]Data cutoff 3 Jan 2013; *Stratified Cox proportional hazards model; NR, not reached

Schwartzberg L, et al. J Clin Oncol 31, 2013 (suppl; abstr 3631).

VOLUME 26 · NUMBER 33 · NOVEMBER 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

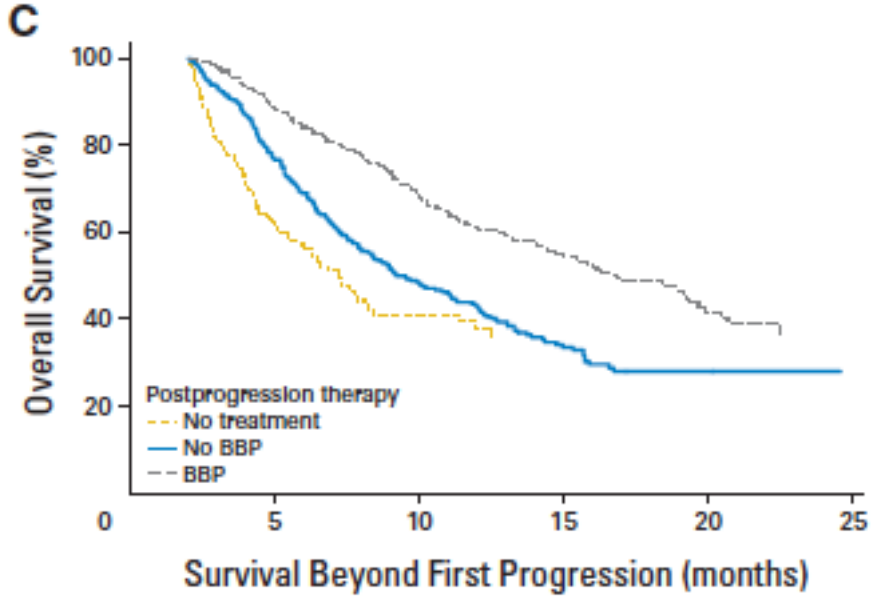
Obervational BRiTe Study

Bevacizumab Beyond First Progression Is Associated With Prolonged Overall Survival in Metastatic Colorectal Cancer: Results From a Large Observational Cohort Study (BRiTE)

Axel Grothey, Mary M. Sugrue, David M. Purdie, Wei Dong, Daniel Sargent, Eric Hedrick, and Mark Kozloff

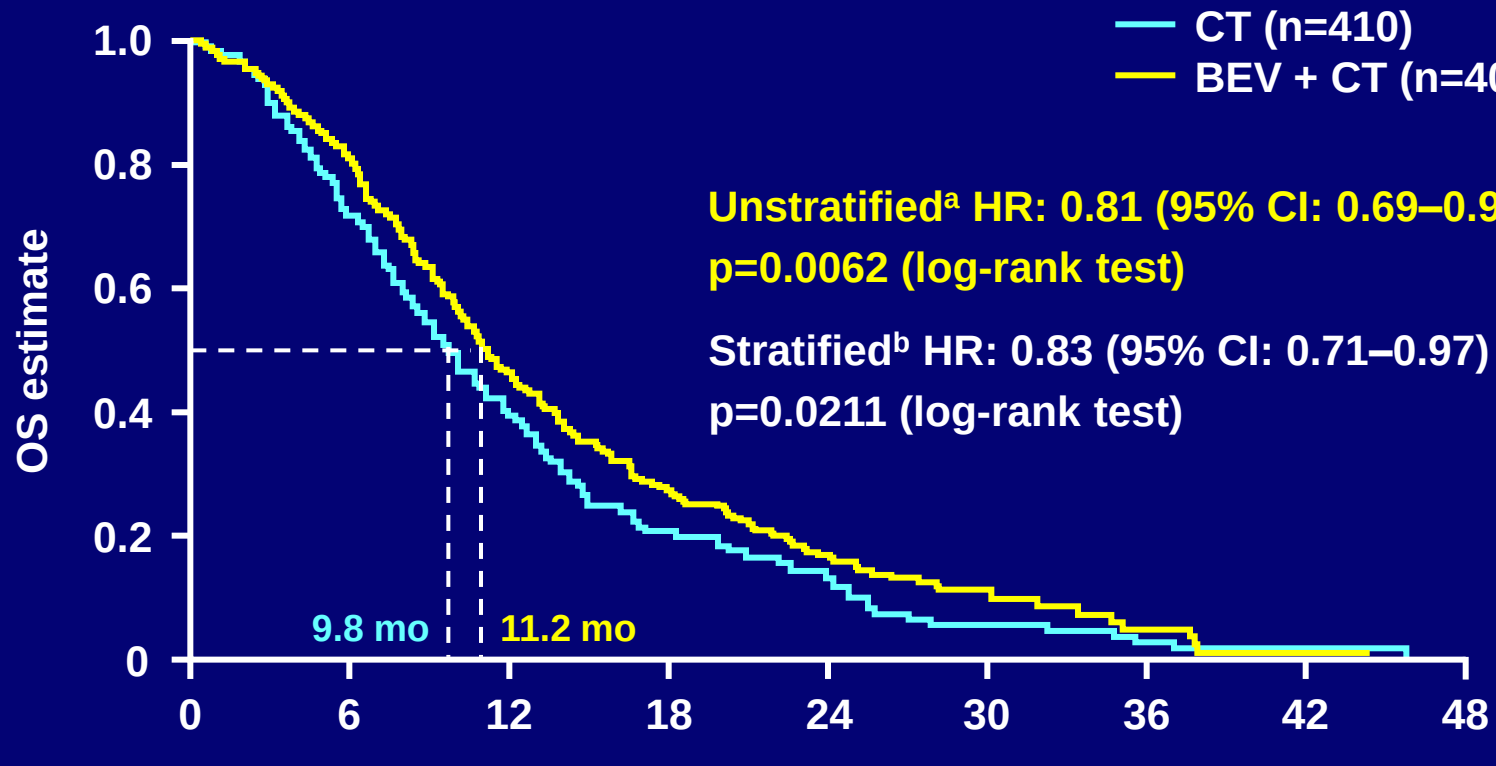
- **248 centers in USA**
- **Total patients No. 1,953**
  - No treatment No. 253
  - No BBP No.531
  - BBP No.642

	All patients (N = 1,953)	No post-progression treatment (n = 253)	No BBP (n = 531)	BBP (n = 642)
Number of deaths	932	168	305	260
Percent	47.7	66.4	57.8	40.5
1-year survival rate, %	74.7	52.5	77.3	87.7
95% CI	72.7 to 76.7	46.2 to 58.8	73.7 to 80.9	85.2 to 90.3
Median survival beyond first progression, months	12.0	3.6	9.5	19.2
95% CI	11.1 to 13.3	2.7 to 4.3	8.4 to 11.2	16.8 to 20.7



ML18147 study

OS: ITT population



Unstratified[a] HR: 0.81 (95% CI: 0.69–0.94)
p=0.0062 (log-rank test)

Stratified[b] HR: 0.83 (95% CI: 0.71–0.97)
p=0.0211 (log-rank test)

No. at risk								
CT	410	293	162	51	24	7	3	2
	0							
BEV + CT	409	328	188	64	29	13	4	1
	0							

Median follow-up: CT, 9.6 months (range 0–45.5); BEV + CT, 11.1 months (range 0.3–44.0)

Arnold et al, ASCO 2012

AVEX Study

Select baseline patient characteristics

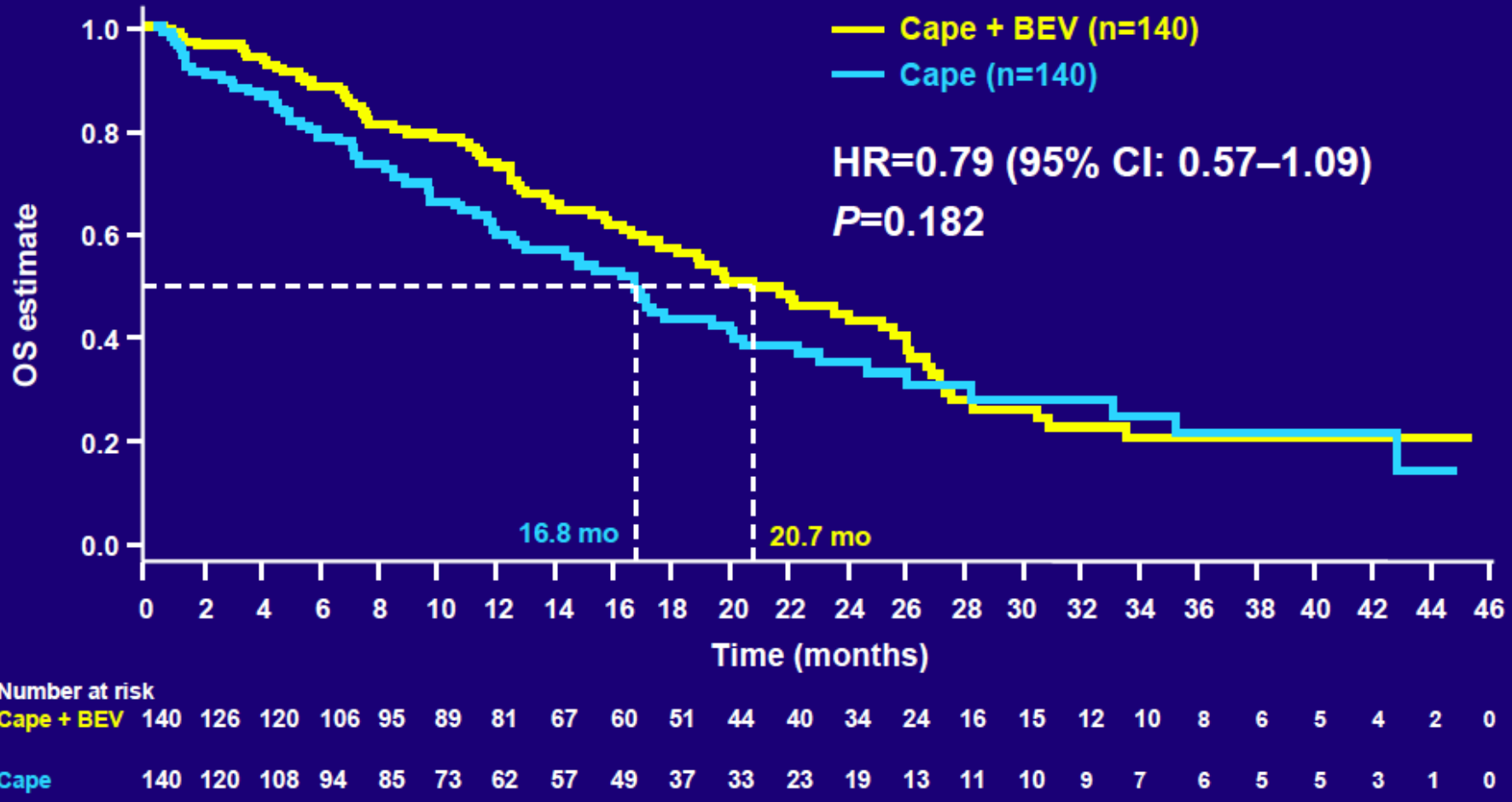
		Cape + BEV (n=140)	Cape (n=140)
Sex, %	Female	40.0	40.0
Median age, years (range)		76 (70–87)	77 (70–87)
	<75 years, %	39.3	32.9
	≥75 years, %	60.7	67.1
ECOG performance status, %	0	50.0	42.9
	1	41.4	47.9
	2	7.1	7.9
Prior adjuvant therapy, %	Yes	32.1	18.6
Site of metastatic disease, %	Liver	62.9	67.9
	Lung	35.7	40.7
	Other	35.0	22.9
	Liver only	37.1	38.6
Surgical resection, %	Yes	73.6	63.6
Location of primary disease, %	Colon only	57.9	54.3
	Rectum	31.4	25.0
	Colon and rectum	10.7	19.3

ITT population. Cape = capecitabine; ECOG PS = Eastern Cooperative Group performance status.

Cunningham et al, ASCO GI 2013

Overall survival

AVEX Study

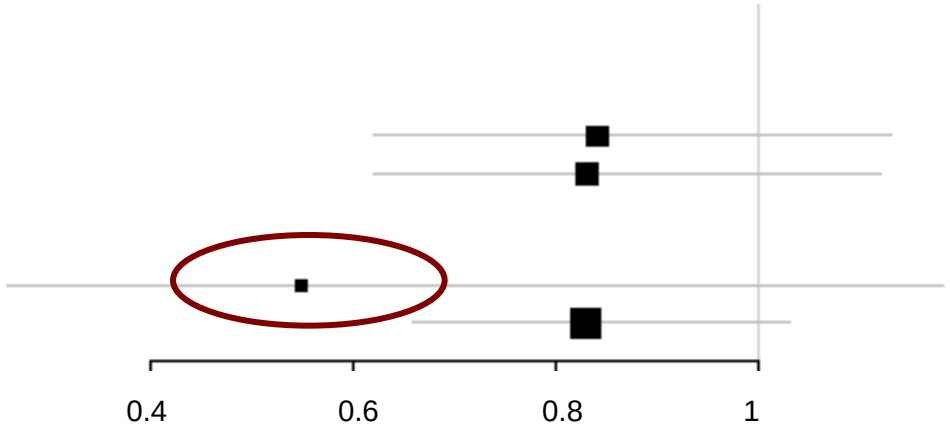


ITT population. 75 OS events in each treatment arm.

Cunningham et al, ASCO GI 2013

Subgroup analyses of PFS – molecular and clinical characteristics

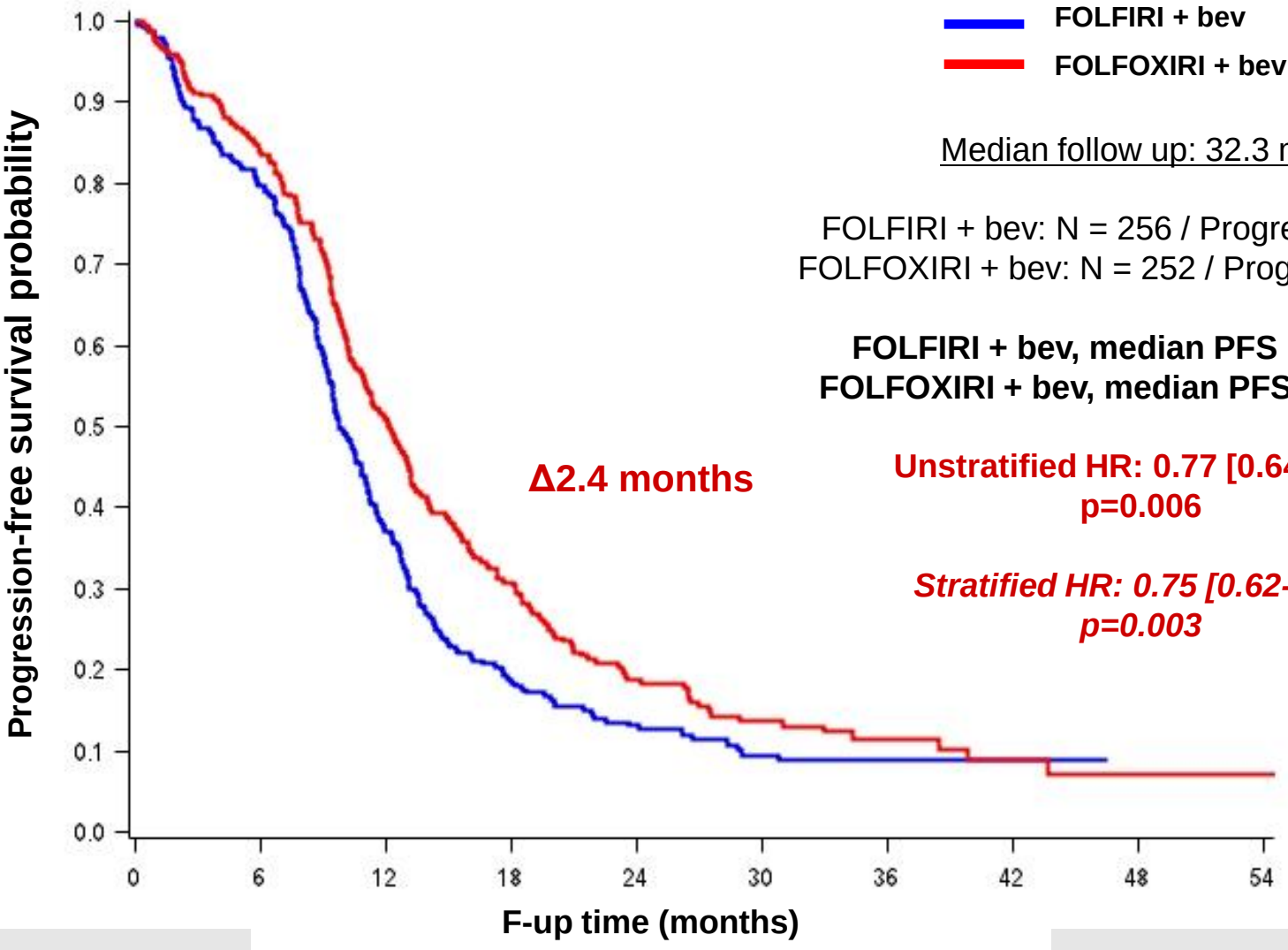
Factor	N	HR	p
KRAS status			
mut	200	0.84	0.973
wt	193	0.83	
BRAF status			
mut	28	0.55	0.323
wt	365	0.83	



Characteristic, % patients	FOLFIRI + bev N = 256	FOLFOXIRI + bev N = 252
Median Age (range)	60 (29 – 75)	61 (29 – 75)
ECOG PS (0 / 1-2)	89 / 11	90 / 10
Synchronous Metastases (Y / N)	81 / 19	79 / 21
Prior Adjuvant CT (Y / N)	13 / 87	13 / 87

TRIBE Study
Primary endpoint: PFS (updated) – ITT population

Falcone et al, ASCO 2013



Median follow up: 32.3 mos

FOLFIRI + bev: N = 256 / Progressed = 226
FOLFOXIRI + bev: N = 252 / Progressed = 213

FOLFIRI + bev, median PFS : 9.7 mos
FOLFOXIRI + bev, median PFS : 12.1 mos

Unstratified HR: 0.77 [0.64-0.93]
p=0.006

Stratified HR: 0.75 [0.62-0.90]
p=0.003

FOLFIRI/bev	256	203	94	46	26	14	7	3	0	0
FOLFOXIRI/bev	252	208	125	74	35	21	11	5	2	1

Studi di fase III con regimi di CT a due/tre farmaci +/- bevacizumab nel CCRM

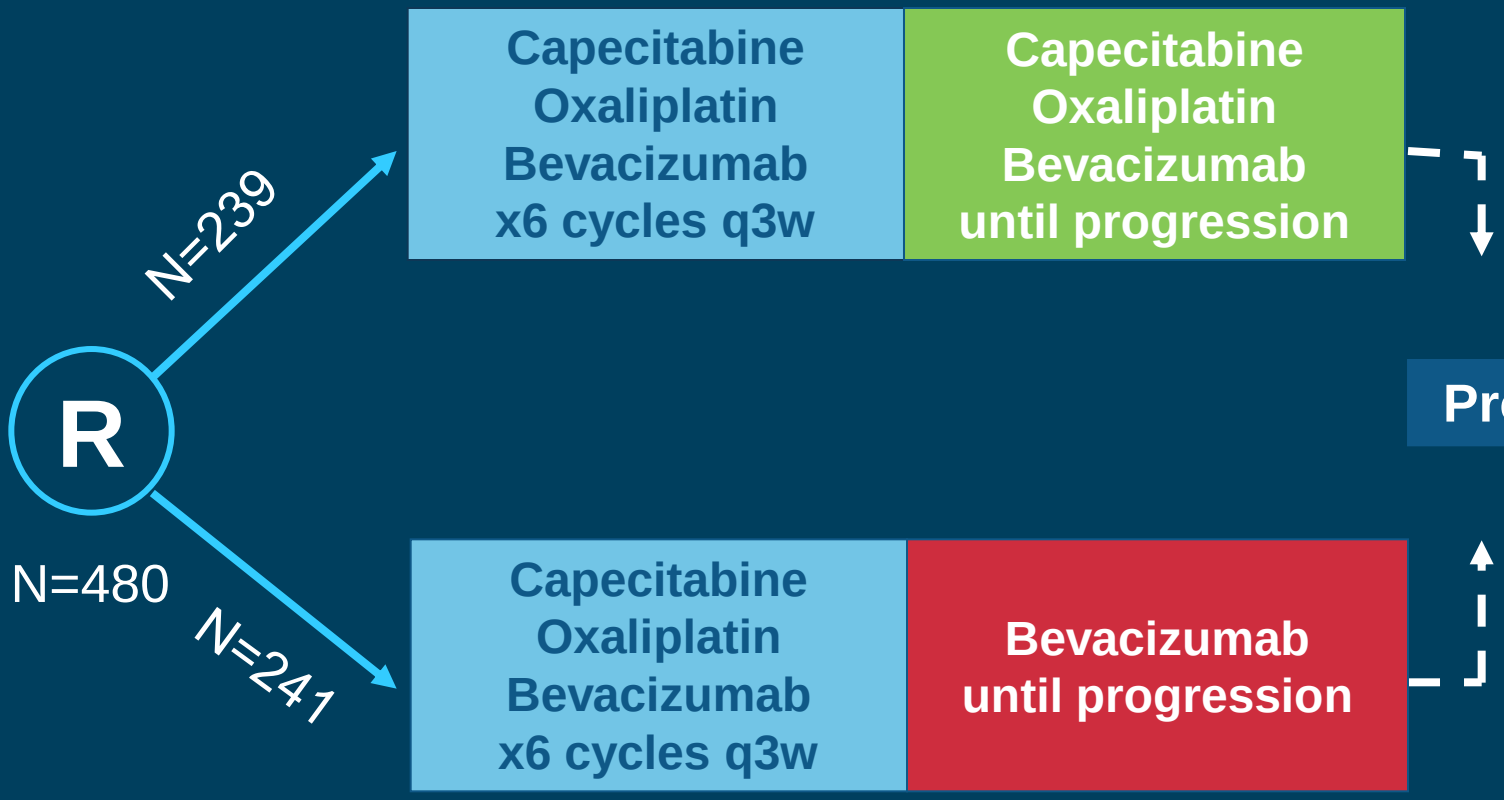
Regime	N.	RR (%)	PFS (mesi)	OS (mesi)	Autore
FOLFIRI FOLFOXIRI	122 122	41 66*	6,9 9,8* HR 0,63 (0,47-0,81)	16,7 22,6* HR 0,70 (0,50-0,96)	Falcone, 2007
FOLFIRI + Bevacizumab FOLFOXIRI + Bevacizumab	254 250	53 65*	9,7 12,1* HR 0,77 (0.64-0.93)		Falcone, 2013

La terapia di mantenimento

- OS con detensificazione della chemioterapia/mantenimento con bevacizumb in combinazione con capecitabina

Study Design

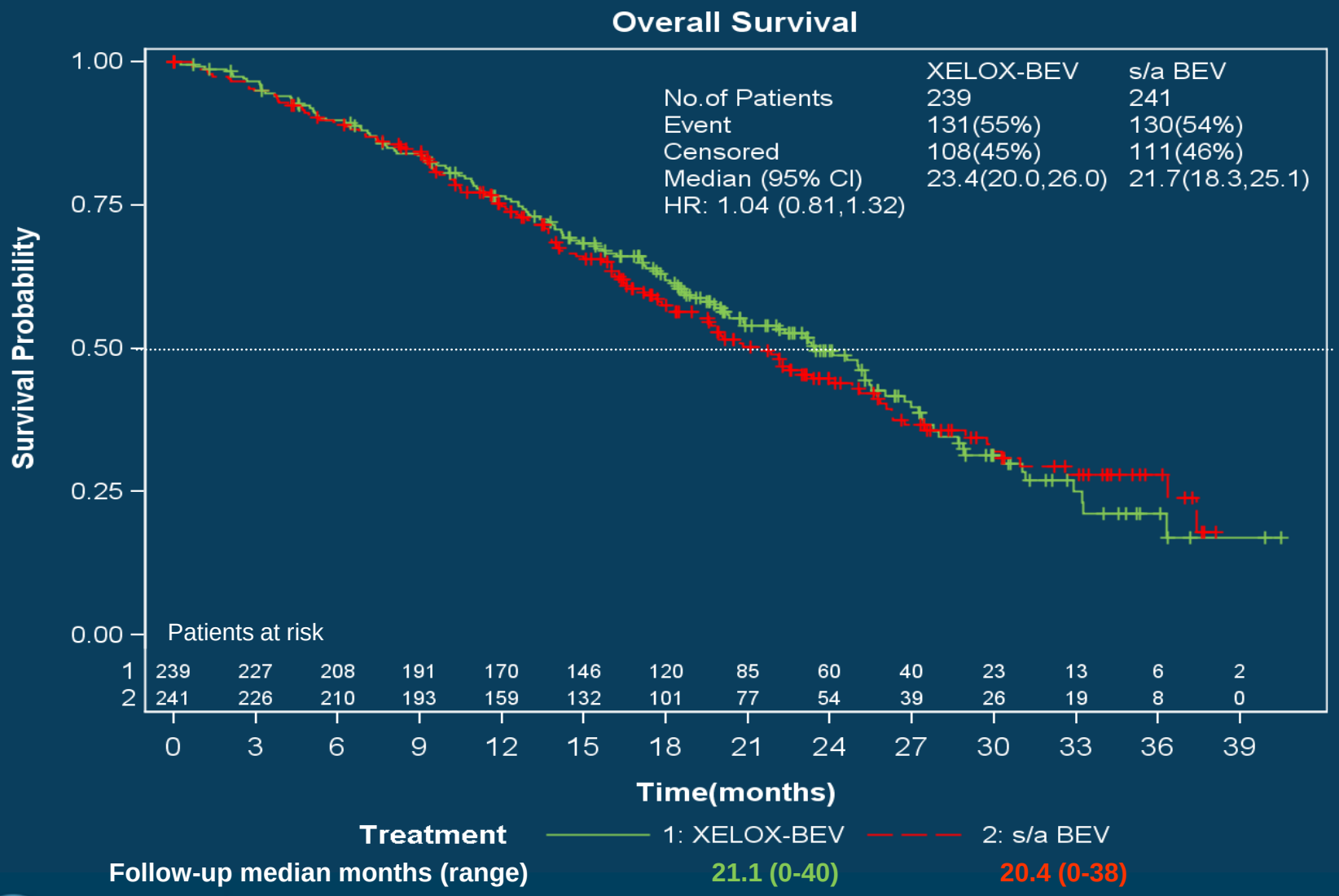
MACRO Study



ASCO Annual '10 Meeting

Tabernero et al, ASCO 2010

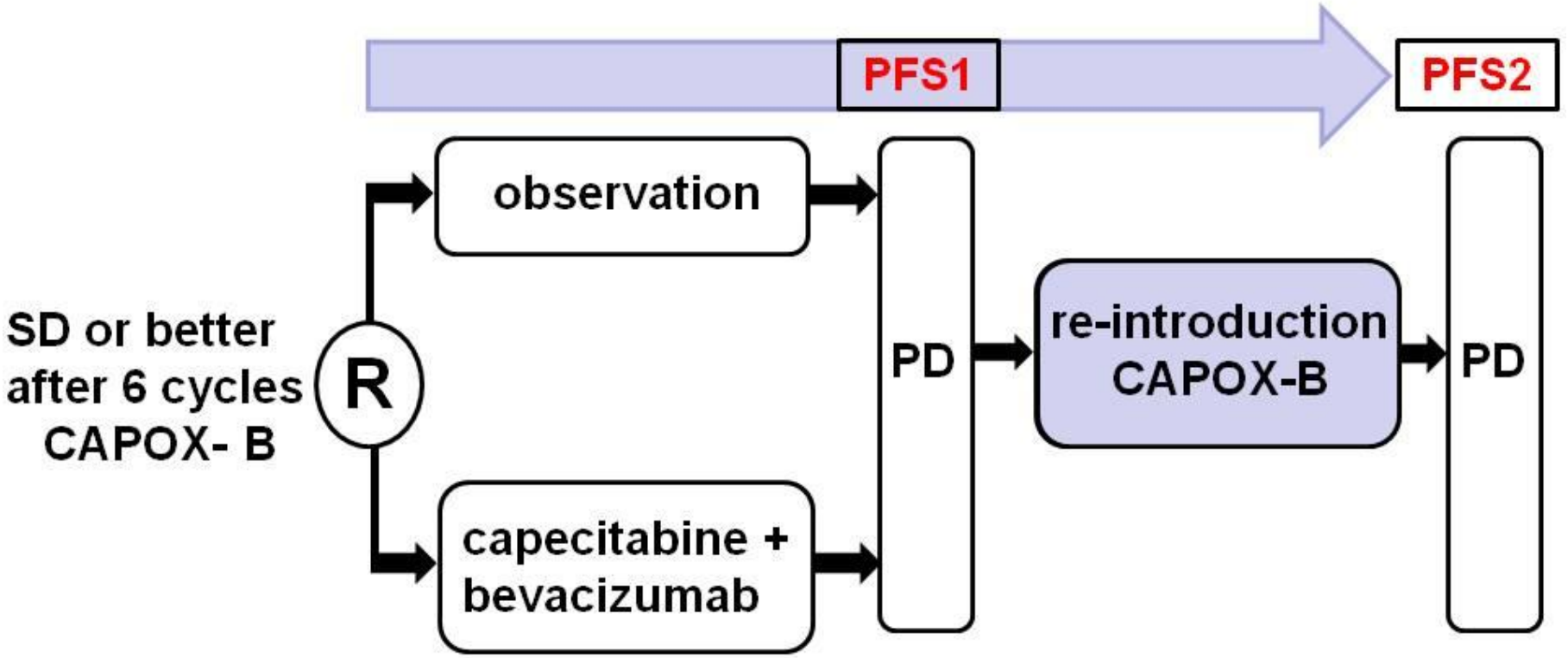
Overall Survival ITT



ASCO Annual '10 Meeting

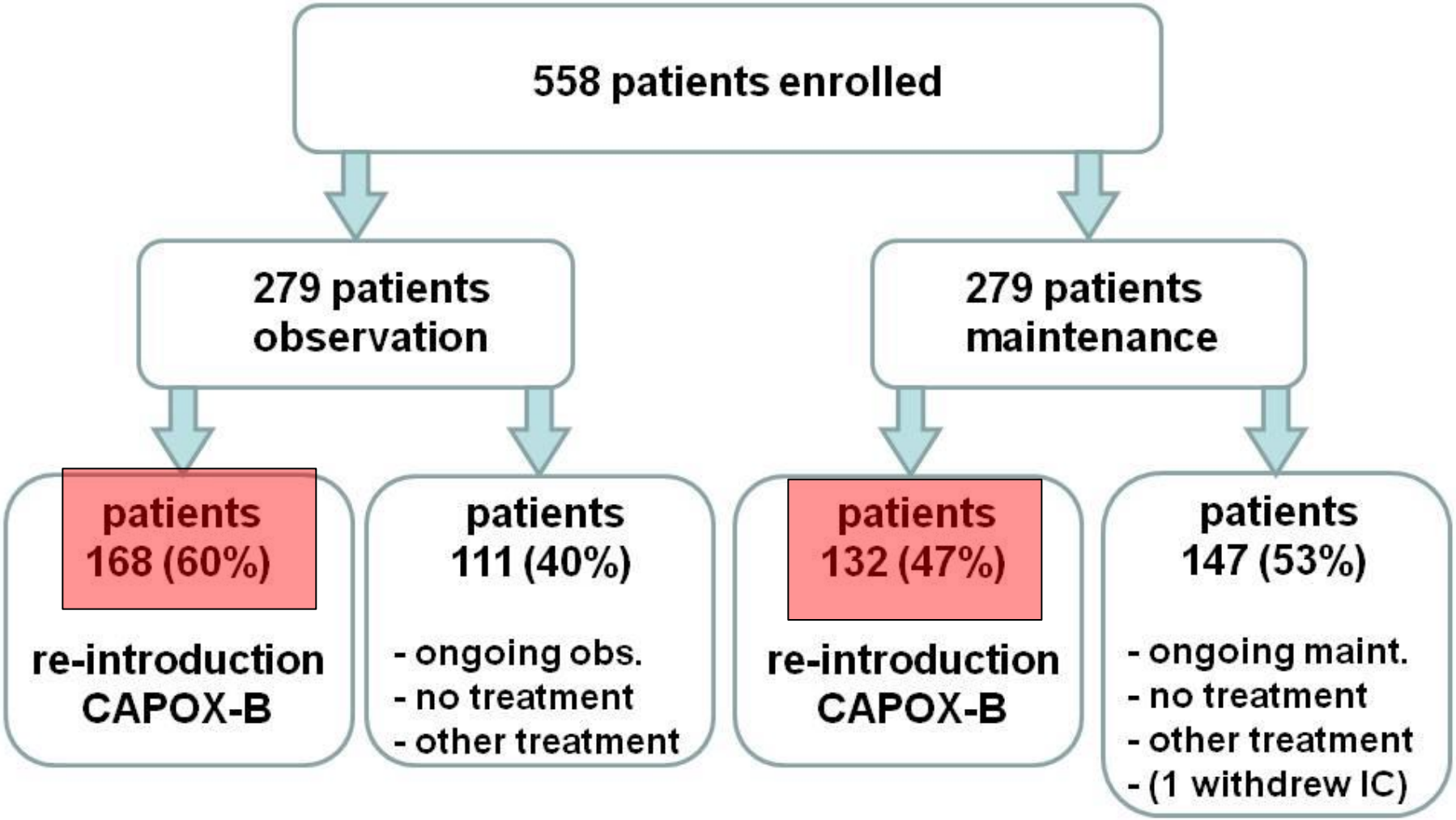
Tabernero et al, ASCO 2010

Study design

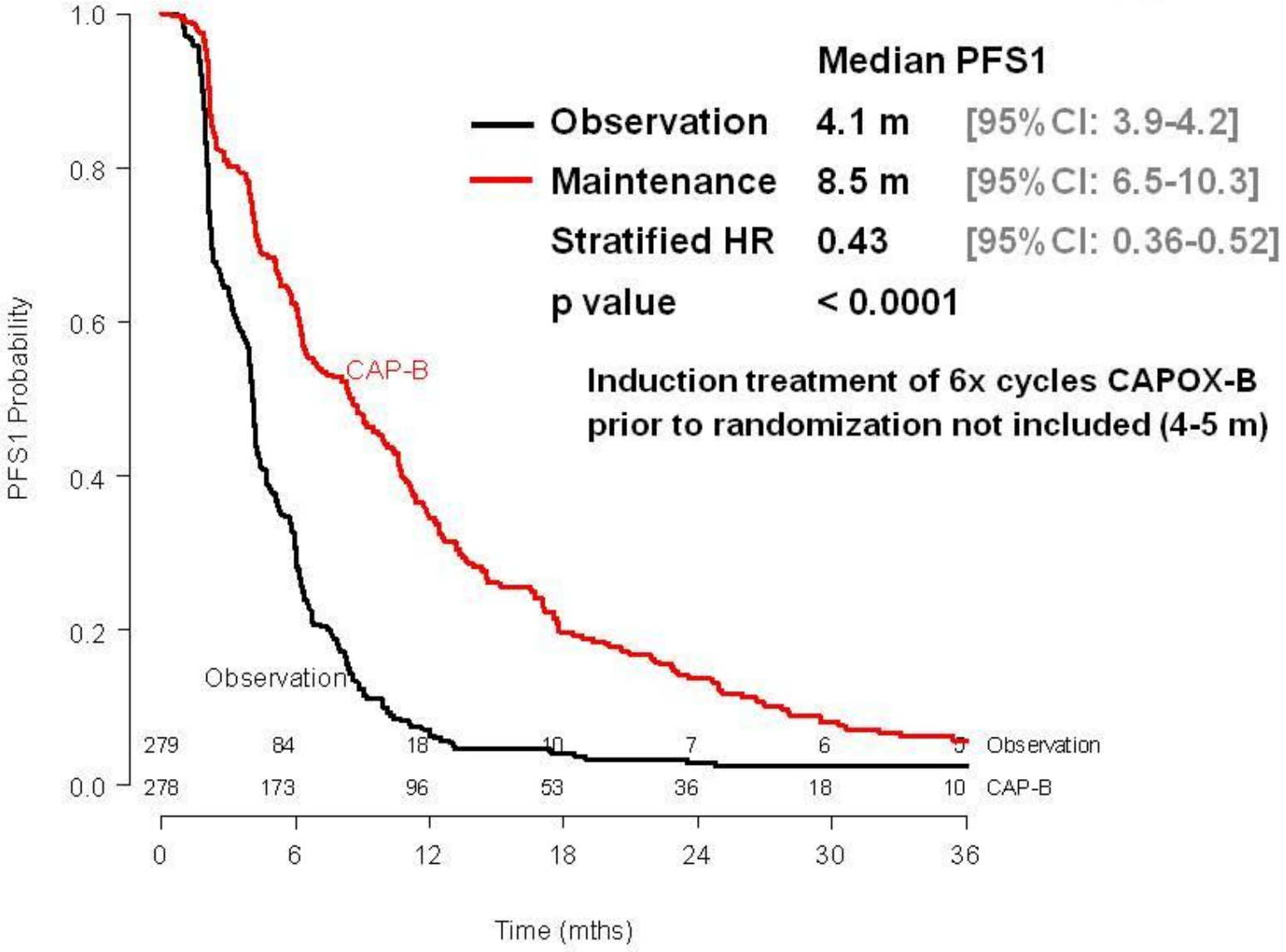


- Stratification factors: prior adjuvant therapy, serum LDH, response to induction treatment, WHO PS, institution
- Primary endpoint: PFS2
- PFS2 is considered to be equal to PFS1 for patients in whom CAPOX- B is not reintroduced after PFS1 for any reason

CAIRO3 study profile

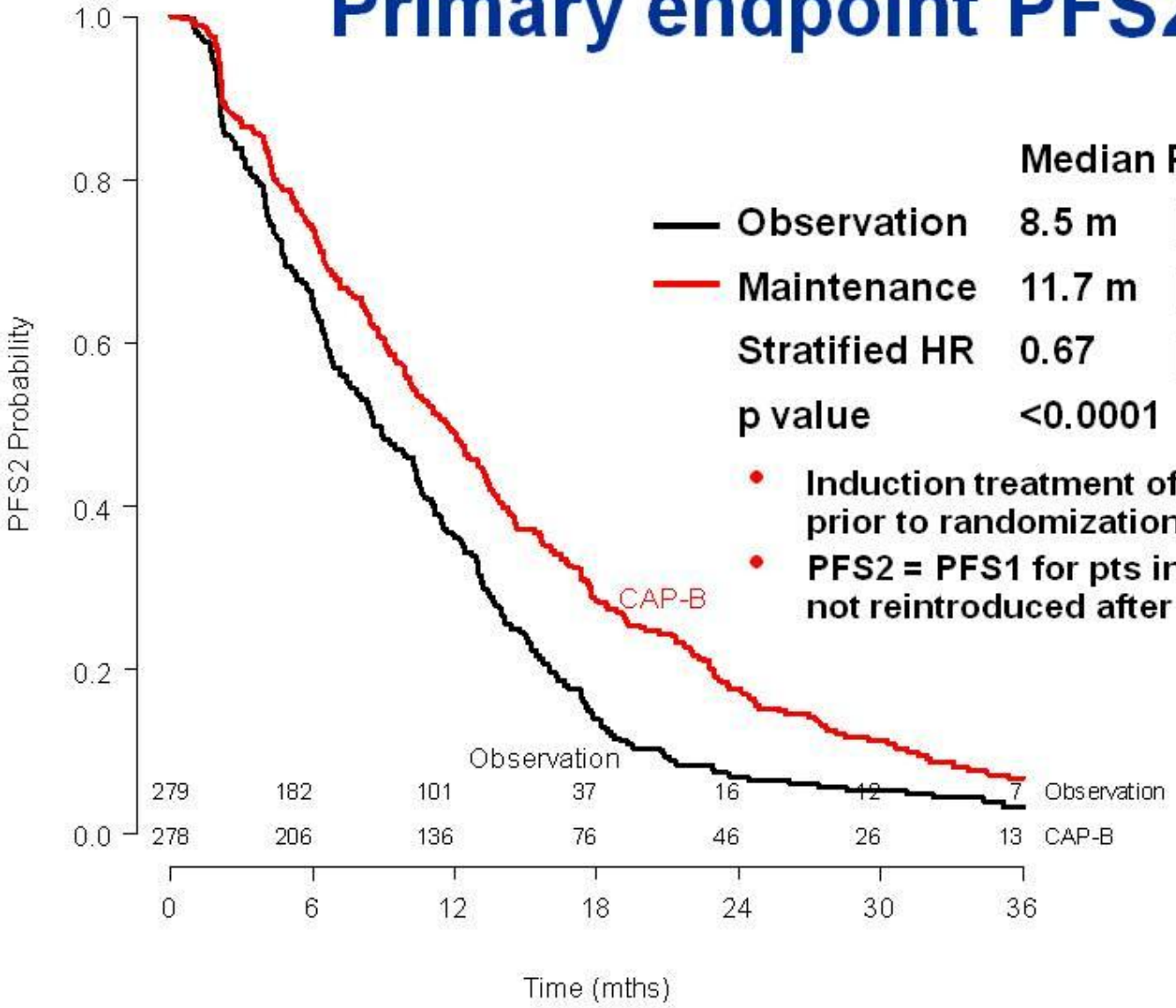


PFS1



Presented By Miriam Koopman, MD, PhD at 2014 Gastrointestinal Cancers Symposium

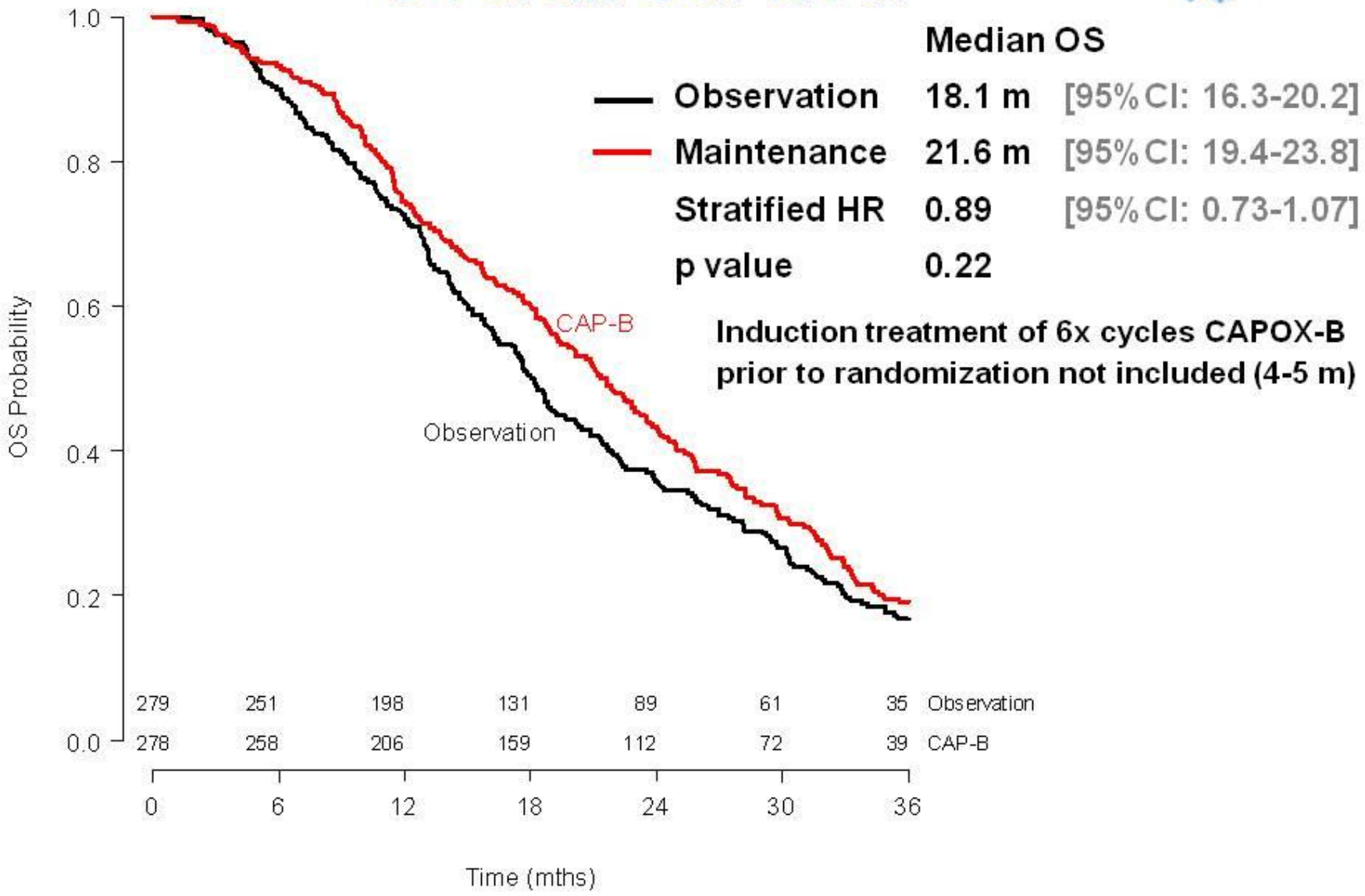
Primary endpoint PFS2



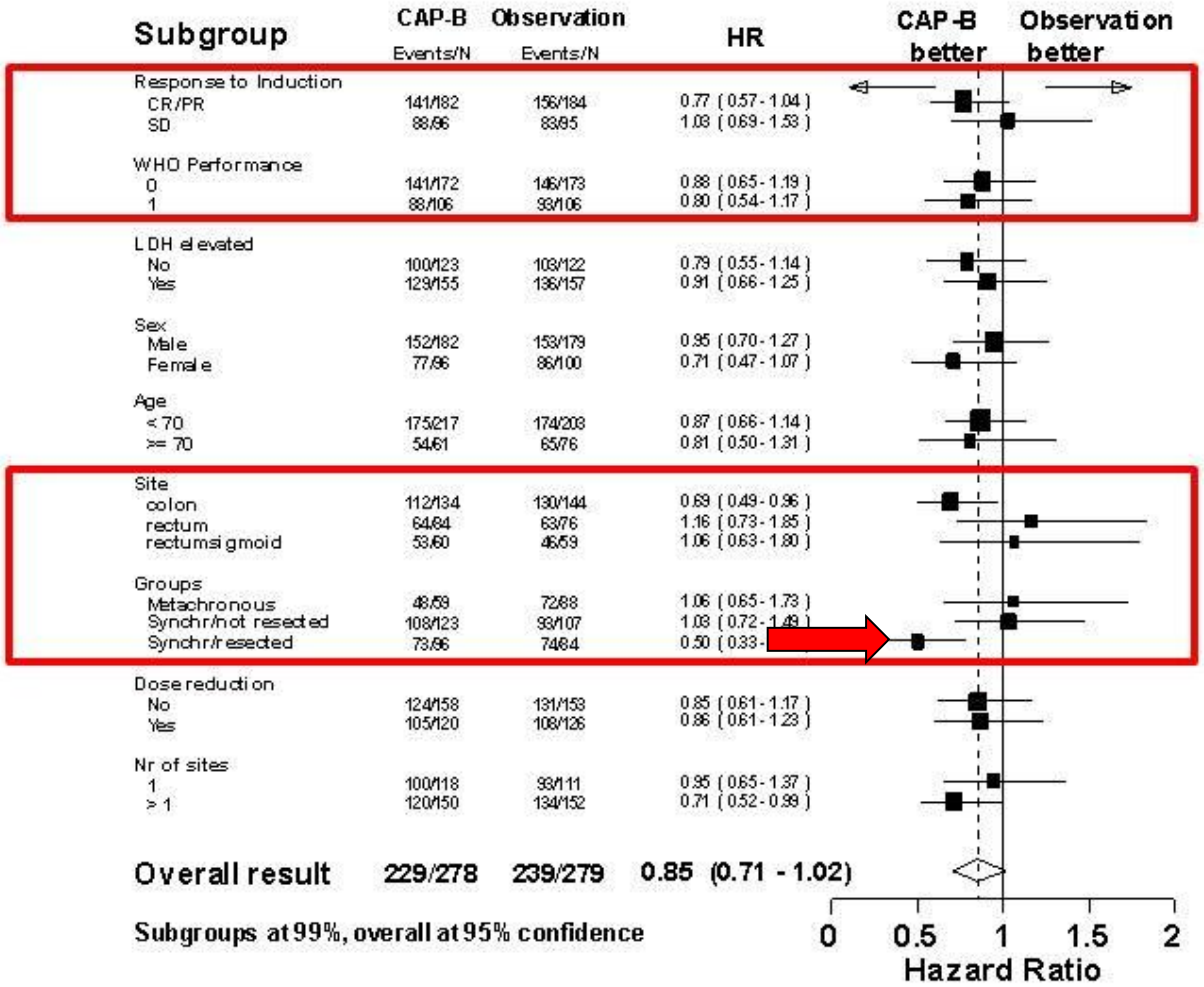
	Median PFS2	
Observation	8.5 m	[95% CI: 7.4-10.4]
Maintenance	11.7 m	[95% CI: 10.1-13.3]
Stratified HR	0.67	[95% CI: 0.56-0.81]
p value	<0.0001	

- Induction treatment of 6x cycles CAPOX-B prior to randomization not included (4-5 m)
- PFS2 = PFS1 for pts in whom CAPOX- B is not reintroduced after PFS1 for any reason

Overall Survival



Subgroup analysis OS

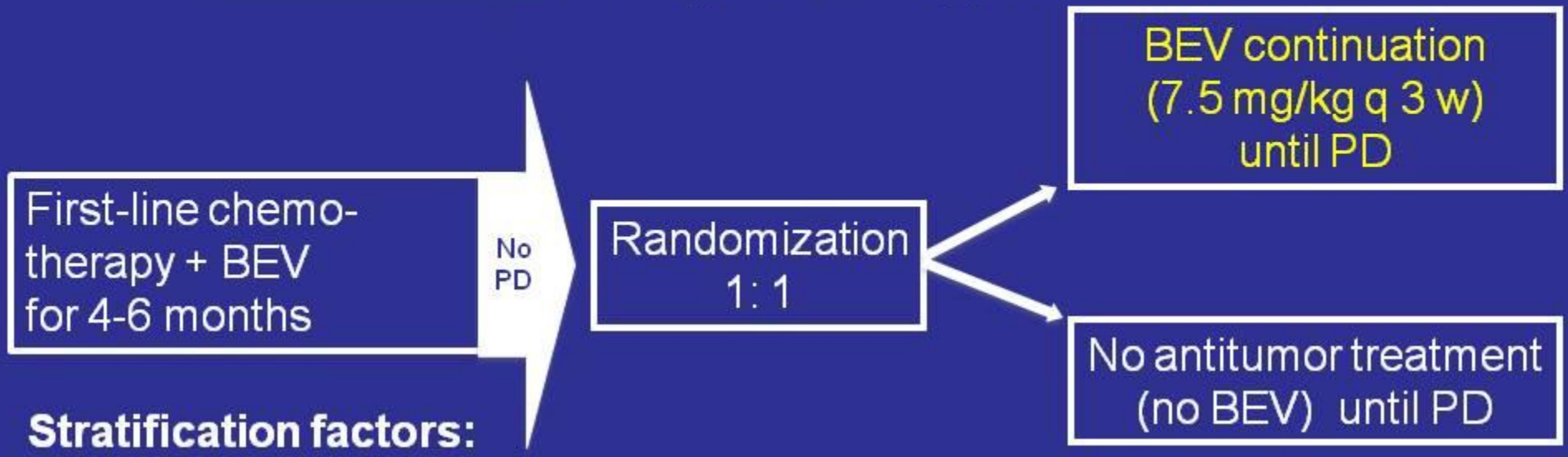


Significant factors in multivariable model: treatment arm, response to induction treatment, WHO performance status, site of primary tumor, and metachronous vs. synchronous with/without resection of primary tumor

Presented By Miriam Koopman, MD, PhD at 2014 Gastrointestinal Cancers Symposium

Stratified phase III non-inferiority trial

SAKK Swiss Group for Clinical Cancer Reseach



Stratification factors:

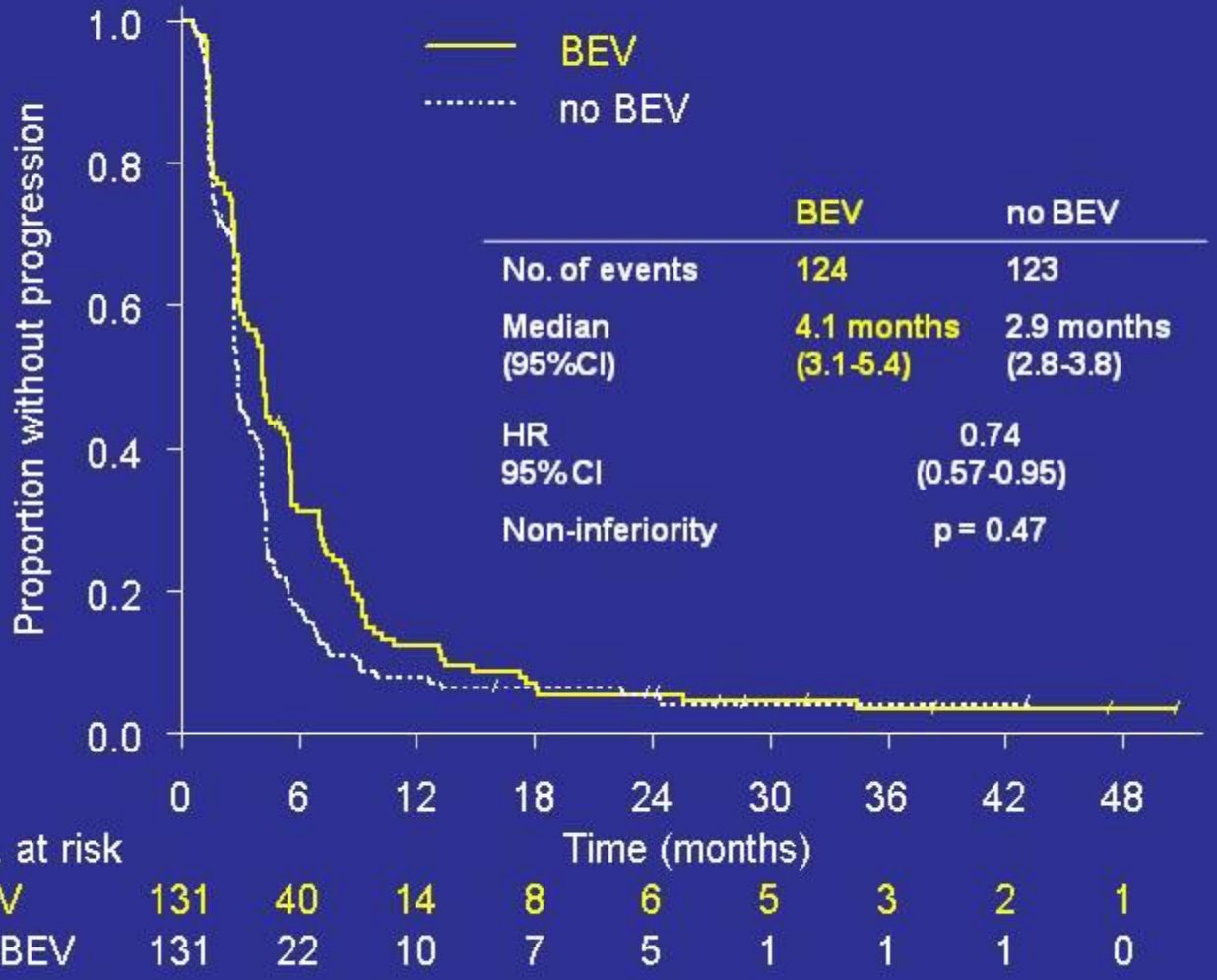
- Best response during first-line chemotherapy + BEV (CR/PR vs SD)
- Duration of first-line chemotherapy + BEV (16-20 vs 21-24 weeks)
- Type of chemotherapy (Irinotecan + 5-FU vs Oxalipaltin + 5-FU vs Fluoropyrimidine mono)
- Disease burden (metastases in one organ vs multiple organs)
- Center

Study conducted in 26 sites in Switzerland (accrual period 2007-2012)

Median FU time: 30.1 months

TTP

(from randomization)

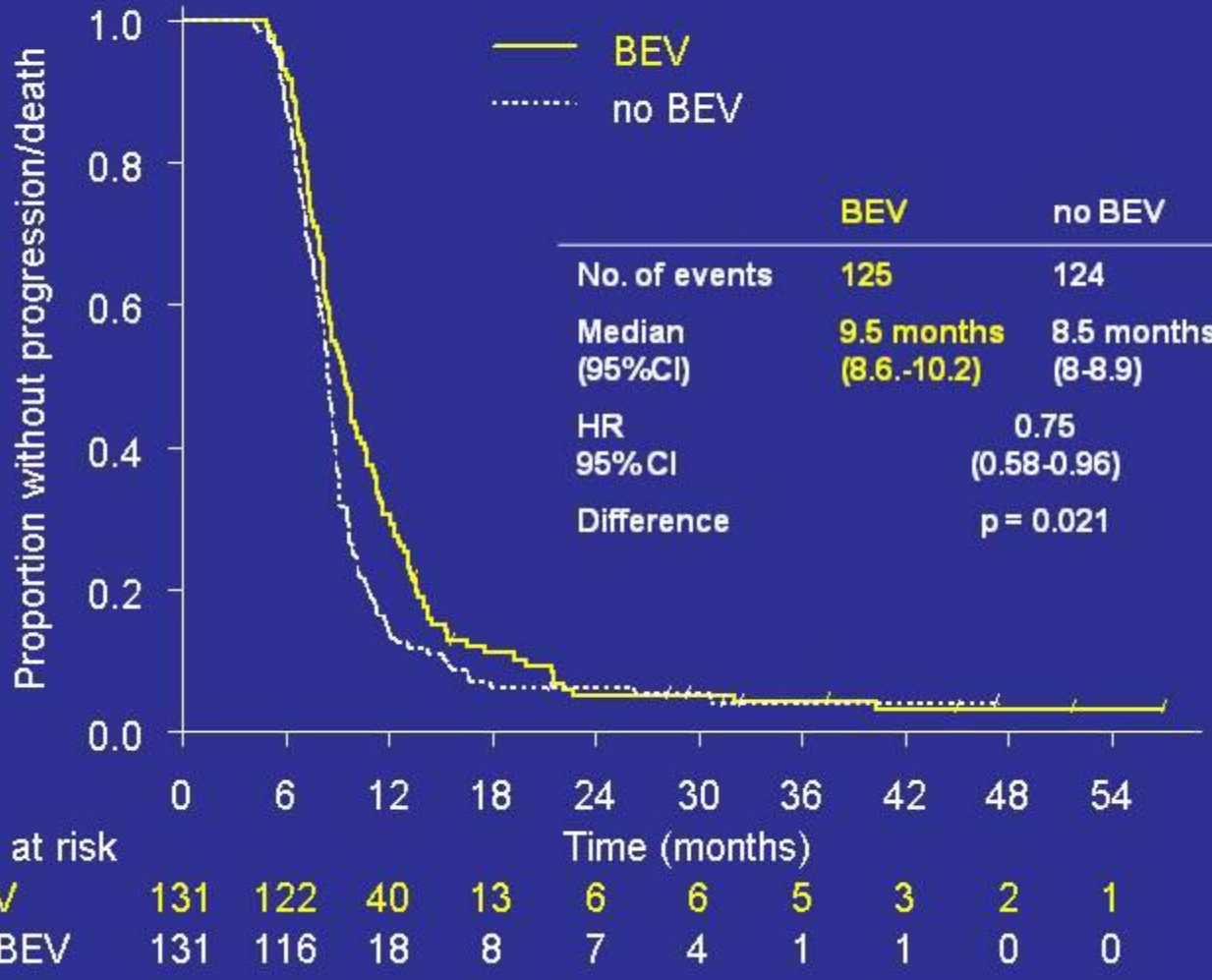


	BEV	no BEV
No. of events	124	123
Median (95%CI)	4.1 months (3.1-5.4)	2.9 months (2.8-3.8)
HR	0.74	
95% CI	(0.57-0.95)	
Non-inferiority	p = 0.47	

No. at risk									
BEV	131	40	14	8	6	5	3	2	1
no BEV	131	22	10	7	5	1	1	1	0

PFS

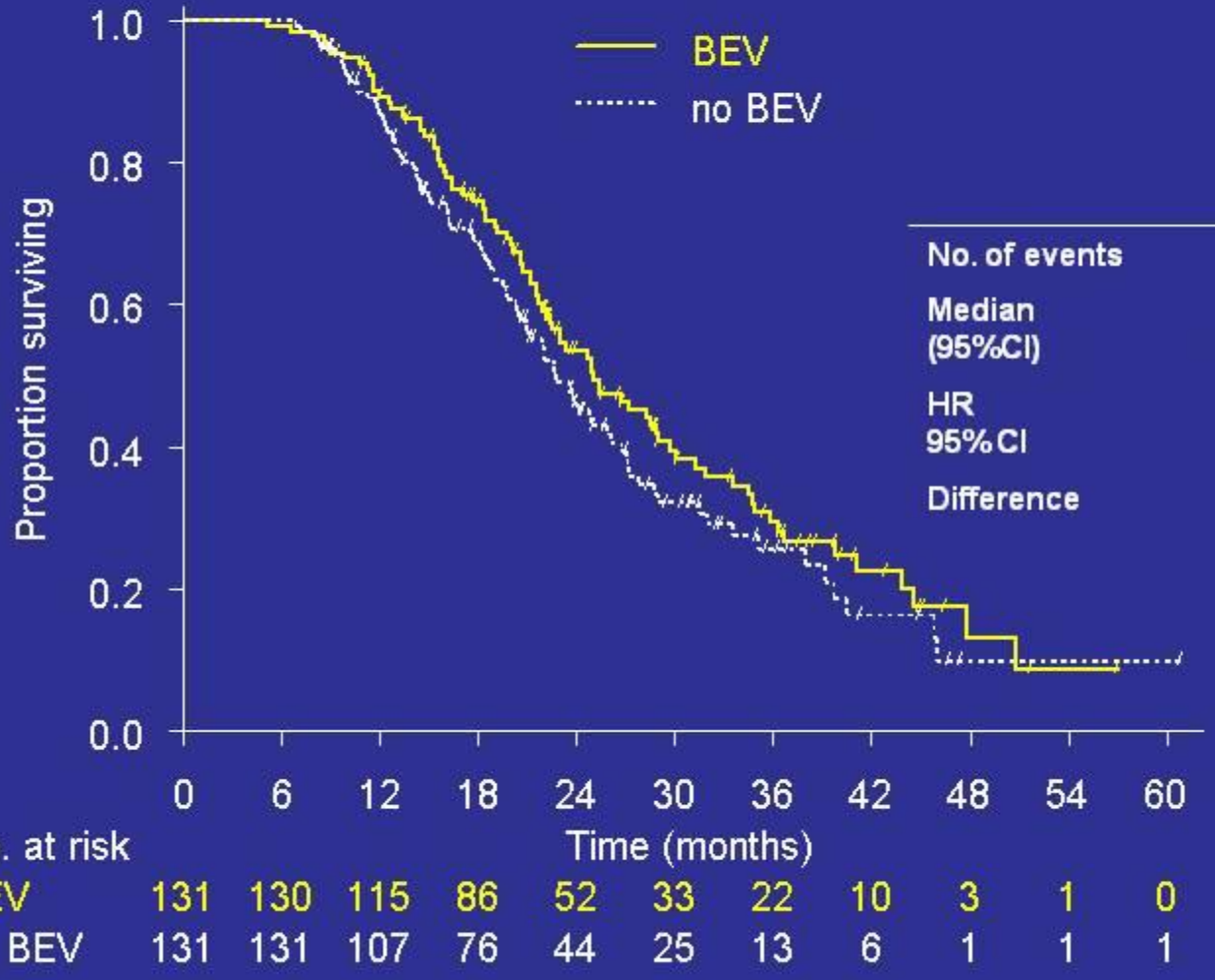
(from start of first-line therapy)



	BEV	no BEV
No. of events	125	124
Median (95%CI)	9.5 months (8.6.-10.2)	8.5 months (8-8.9)
HR 95% CI	0.75 (0.58-0.96)	
Difference	p = 0.021	

Overall Survival

(from start of first-line therapy)



No. at risk											
BEV	131	130	115	86	52	33	22	10	3	1	0
no BEV	131	131	107	76	44	25	13	6	1	1	1

	BEV	no BEV
No. of events	84	84
Median (95%CI)	25.1 months (22-28.9)	22.8 months (20.3-26.1)
HR 95% CI	0.83 (0.61-1.12)	
Difference	p = 0.218	

La sostenibilità delle scelte

- Proposta di raccomandazioni ASCO per OS nei clinical trials
- Impatto dei successivi vantaggi incrementali in OS
- Valore della strategia terapeutica

Colon Cancer

Recommendation: Clinical trials should aim to improve overall survival (OS) by approximately 3-5 months with minimal increases in toxicity compared to current regimens/drugs utilized in this setting. Table 1 details recommendations for patients who have progressed on all standard therapies.

Table 1: Summary of recommended targets for meaningful clinical trial goals.

Cancer Type	Patient Population	Current Baseline Median OS	Improvement Over Current OS That Would be Clinically Meaningful	Target Hazard Ratios	1 Yr Survival Rate (Current/ Target)
Pancreatic Cancer	FOLFIRONOX Eligible Patients	10 – 11 months	4-5 months	0.67 – 0.69	48% / 56%
Pancreatic Cancer	Gemcitabine Eligible Patients	6 - 8 months	3-4 months	0.6 – 0.679	21% / 24%
Lung Cancer	Non-squamous cell carcinoma	13 months	3.25-4 months	0.76-0.8	53% / 61%
Lung Cancer	Squamous cell carcinoma	10 months	2.5-3 months	0.77-0.8	44% / 53%
Breast Cancer	Metastatic triple negative, previously untreated for metastatic disease	18 months	4.5-6 months	0.75-0.8	63% / 69%
Colon Cancer	disease progression on all prior therapies (or not a candidate for standard 2nd or 3rd line options)	4-6 months	3-5 months	0.44 – 0.67*	N/A

*Hazard ratios represent a 5 month improvement on a baseline of 4 month median OS and a 3 month improvement on a baseline of 6 month median OS

Studi di fase III in I linea con regimi di combinazione 5FU/AF + Irinotecan o Oxaliplatino

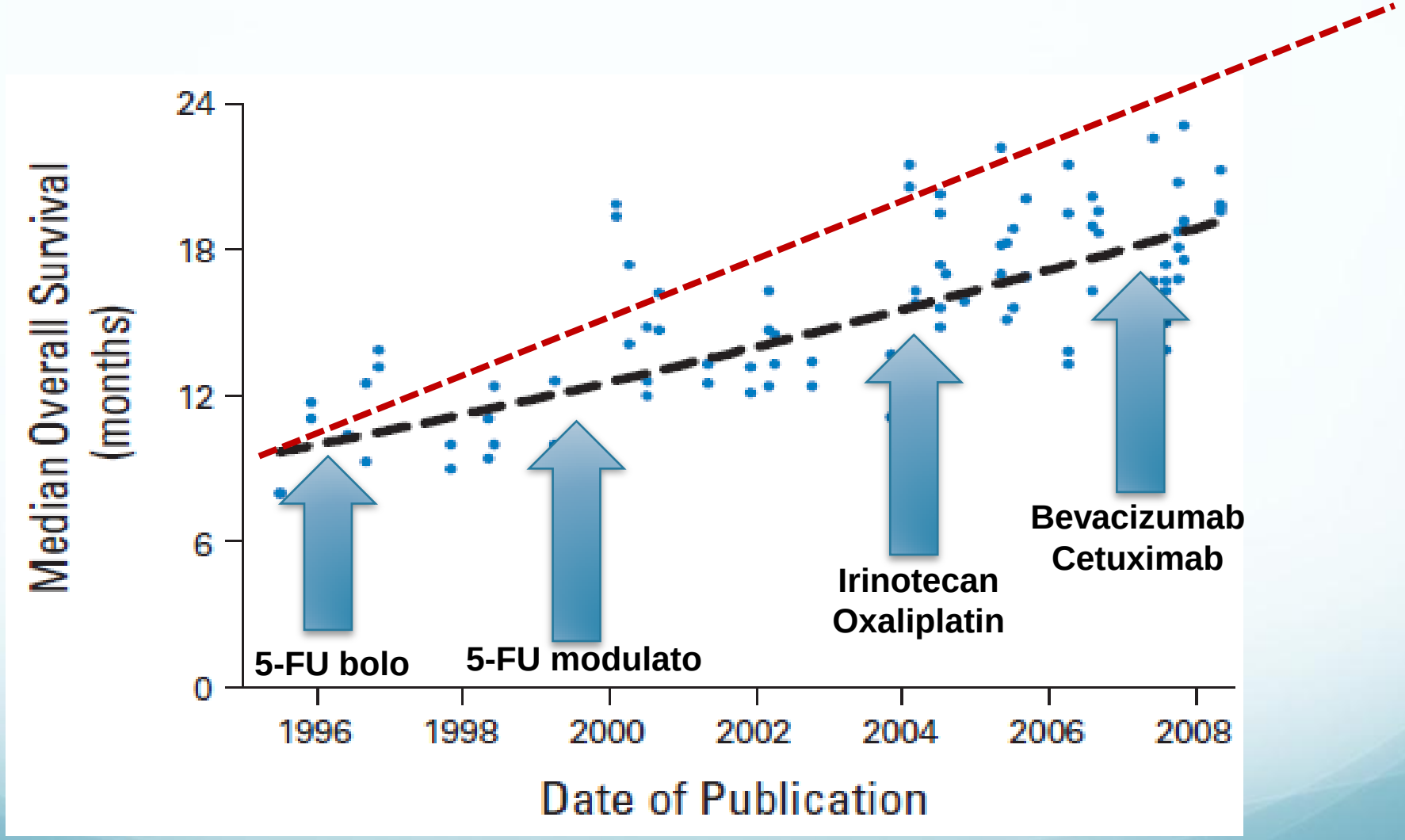
Studio	Paz	Regime	OS esi)	Δ (mesi)
Saltz et al, 2000			2,6 14,8	+ 2,2
Douillard et, 2000	338		14,1 17,4	+3,3
Kohne et al, 2005	4	(A	16,9 1	+3,2
De Gramont et al, 2000	4	5FU/AF in 5FU/AF inf.+ OX	14,7 16,2	+ 1,5

Non approvato

OS negli studi di fase III nel CCRM

Studio	Regime	OS (mesi)	
I linea			
CRYSTAL	FOLFIRI vs FOLFIRI cetuximab	20,0 vs 23,5	+ 3,5
AVF2107g	IFL vs IFL + bevacizumab	15,5 vs 20,3	+ 4,8
PRIME	FOLFOX + FOLFOX + panitumumab	20,2 vs 26,,0	+ 5,8
FIRE 3	FOLFIRI + bevacizumab vs FOLFIRI + cetuximab	25,6 vs 33,1	+ 7,5
II linea			
ECOG E3200	FOLFOX vs FOLFOX + bevacizumab	2,6 vs 4,7	+ 2,1
ML18147	OXA/IRI CT + vs OXA/IRI + bevacizumab	9,8 vs 11,2	+ 1,4
VELOUR	FOLFIRI vs FOLFIRI + aflibercept	12,06 vs 13,50	+ 1,4
20050181	FOLFIRI vs FOLFIRI + panitumumab	12,5 vs 14,5	+ 2,0*
≥ III linea			
CORRECT	Placebo vs regorafenib	5,0 vs 6,4	+ 1,4

Sopravvivenza in studi di fase III di I linea nel CCRM



Kopetzt al, J Clin Oncol 2009

Spesa per antiblastici nel 2012

Sottogruppi e sostanze	Spesa lorda pro capite	%	Δ % 12-11	DDD/1000 ab die	%	Δ % 12-11
Pemetrexed disodico	1,28	23,6	24,7	0,0	2,2	12,9
Altri antimetaboliti	0,82	15,2	28,7	0,3	23,0	46,1
Taxani	0,69	12,7	59,1	0,1	9,8	22,4
Capecitabina	0,66	12,2	8,9	0,1	4,4	3,2
Antracicline e sostanze correlate	0,39	7,2	0,9	0,1	8,9	-0,4
Altre sostanze alchilanti	0,29	5,4	89,2	0,3	22,0	-10,7
Oxaliplatino	0,23	4,2	173,4	0,1	5,8	4,5
Altri citostatici	0,2	3,7	7,0	0,0	2,8	0,7
Temozolomide	0,19	3,4	-2,9	0,0	0,4	-2,9
Vinorelbina	0,14	2,5	16,8	0,0	1,6	-3,4
Altri composti del platino	0,12	2,3	265,4	0,1	9,1	3,2
Gemcitabina	0,12	2,1	34,0	0,0	2,7	-2,1
Altri antibiotici citotossici	0,09	1,7	21,6	0,0	3,4	16,4
Altri prodotti di derivazione naturale	0,08	1,5	47,1	0,0	2,2	-0,5
Irinotecan	0,06	1,0	-14,9	0,0	2,1	0,6
Topotecan	0,04	0,8	-22,6	0,0	0,4	-3,2
Fludarabina	0,02	0,4	-23,6	0,0	0,1	-28,4
Tegafur/uracile	0,00	0,0	-69,6	0,0	0,0	-69,7
Antineoplastici citostatici	**5,42**	**100,0**	**28,1**	**1,5**	**100,0**	**8,1**

Rapporto OsMed 2012

Andamento della spesa per farmaci biologici (2007-2012)

Medicinale	Principio Attivo	2007	2008	2009	2010	2011	2012	Totale	%
AVASTIN	BEVACIZUMAB		273.243	721.944	16.925.478	13.108.208	16.390.675	47.419.548	39,0%
TARCEVA	ERLOTINIB	1.715.223	4.318.385	3.104.668	4.626.634	5.892.029	5.369.538	25.026.477	20,6%
NEXAVAR	SORAFENIB		256.464	306.332	242.216	3.458.694	4.942.629	11.206.335	9,2%
SUTENT	SUNITINIB	2.925	2.925		2.925	7.580.130	2.190.864	9.779.791	8,0%
ERBITUX	CETUXIMAB			65.580	144.852	1.795.254	1.991.632	3.997.318	3,3%
VELCADE	BORTEZOMIB			14.950	201.500	1.512.106	2.001.602	3.730.158	3,1%
HALAVEN	ERIBULINA						3.713.984	3.713.984	3,1%
AFINITOR	EVEROLIMUS				81.060	1.229.280	1.893.480	3.203.820	2,6%
TYVERB	LAPATINIB			49.000	456.925	939.943	826.261	2.272.128	1,9%
IRESSA	GEFITINIB				75.237	876.147	986.333	1.937.717	1,6%
VECTIBIX	PANITUMUMAB			20.400	525.508	616.514	633.675	1.796.097	1,5%
ARZERRA	OFATUMUMAB					103.431	1.322.950	1.426.381	1,2%
YONDELIS	TRABECTEDINA			45.180	36.876	601.800	598.053	1.281.909	1,1%
JAVLOR	VINFLUNINA					293.020	647.351	940.371	0,8%
VIDAZA	AZACITIDINA				3.582	236.171	612.552	852.305	0,7%
VOTRIENT	PAZOPANIB					12.944	759.396	772.340	0,6%
TORISEL	TEMSIROLIMUS			47.328	12.818	399.330	146.914	606.390	0,5%
SPRYCEL	DASATINIB		8.264	16.907	78.979	53.998	356.917	515.065	0,4%
MOZOBIL	PLERIXAFOR						422.620	422.620	0,3%
HERCEPTIN	TRASTUZUMAB					73.111	347.577	420.688	0,3%
TASIGNA	NILOTINIB			8.288	24.864	41.440	93.634	168.226	0,1%
REMOVAB	CATUMAXOMAB						10.696	10.696	0,0%
ITALIA		1.718.149	4.859.281	4.400.576	23.439.456	40.823.569	46.259.333	121.500.364	100,0%

Rapporto OsMed 2012

Spesa per farmaci biologici nel 2012

Sottogruppi e sostanze	Spesa lorda pro capite	%	Δ % 12-11	DDD/1000 ab die	%	Δ % 12-11
Anticorpi monoclonali (uso prevalentemente onco-ematologico)	10,24	34,0	11,8	0,6	33,9	4,2
Anti TNF alfa + abatacept	9,48	31,5	26,4	0,8	45,4	6,5
Inibitori della tirosin chinasi (esclusivo uso onco-ematologico)	7,59	25,2	15,7	0,2	10,4	3,5
Altri immunosoppressori biologici	0,88	2,9	29,1	0,0	0,1	29,2
Natalizumab	0,83	2,7	-1,0	0,0	2,6	6,5
Inibitori dell'Interleuchina	0,82	2,7	50,7	0,1	3,5	55,7
Omalizumab	0,24	0,8	21,1	0,0	1,1	20,8
Denosumab	0,02	0,1	1.290,3	0,1	2,9	1.279,5
Biologici	**30,10**	**100,0**	**18,1**	**1,8**	**100,0**	**9,7**
trastuzumab	4,01	13,3	12,8	0,1	7,2	5,9
etanercept	3,72	12,3	13,0	0,3	15,5	4,8
adalimumab	3,38	11,2	3,3	0,2	13,8	7,3
imatinib	3,03	10,1	3,9	0,1	5,0	3,9
rituximab	2,99	9,9	8,7	0,4	21,0	3,6
bevacizumab	2,07	6,9	5,7	0,1	4,2	4,2
infliximab	1,61	5,3	150,9	0,2	12,6	-2,7
cetuximab	0,96	3,2	39,3	0,0	1,2	15,3
eculizumab	0,88	2,9	29,1	0,0	0,1	29,3
sunitinib	0,83	2,8	5,7	0,0	0,8	-0,4

Rapporto OsMed 2012

Riflessioni su presente e sul futuro sostenible

- Sostenibilità e appropriatezza vanno correlati alla riorganizzazione del sistema sanitario e del **percorso assistenziale**
- In fase di disegno di uno studio clinico e di interpretazione dei risultati da parte delle autorità regolatorie considerare la **rilevanza clinica** e non solo statistica dei risultati
- Rivisitazione dei **sistemi di rimborso** (a bassa compliance) e costi sulla base dell'**effectiveness** nella pratica clinica
- Vantaggi dell'introduzione di un farmaco considerati nell'ambito di una **strategia terapeutica** (vantaggi relativi incrementali)