Ospedale S. Cuore Don Calabria

Gestione del paziente con carcinoma del colon retto metastatico

Massimo Cirillo
Oncologia Medica – Negrar
26-10-2022

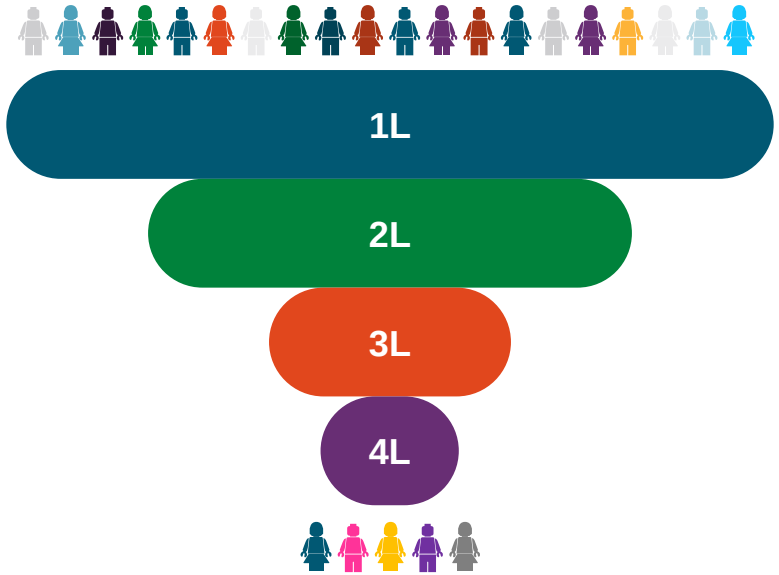
What Influences Treatment Choices in mCRC?

Patient characteristics

- Comorbidities
- Prior adjuvant treatment
- Age
- Performance status

Tumor characteristics

- Tumor burden
- Resectability
- Tumor location



Molecular characteristics

- RAS
- BRAF
- MSI-high

Patient preference

- Quality of life
- Toxicity profile

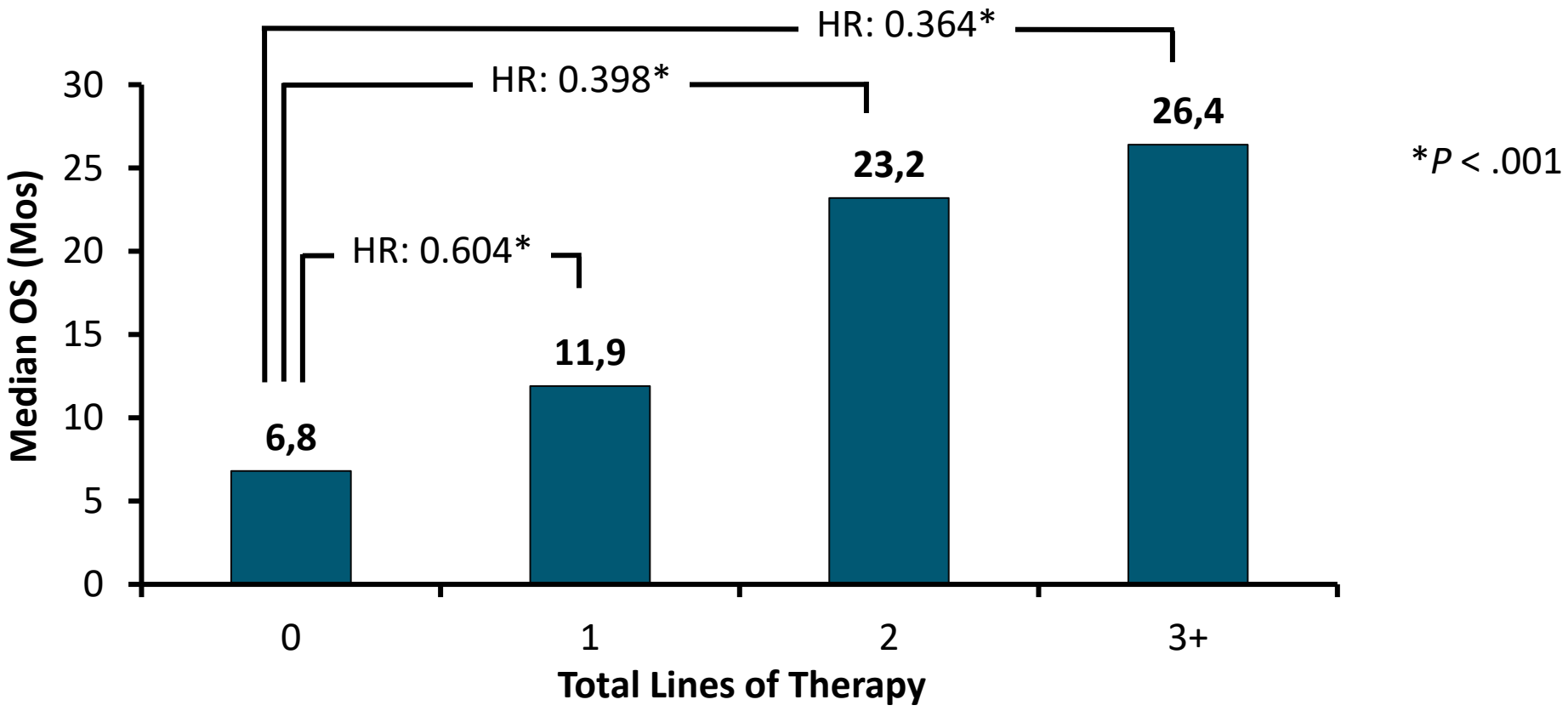
Therapy tailored according to individual patient needs

Median Survival Increases With Increased Lines of Therapy

Grothey A et al JCO 2004; Hanna et al ASCO GI 2014. Abstr 559, .

- **Patients should be exposed to all active and approved agents during treatment**
- **OS not associated with the order in which drugs were received**

SEER Medicare Database Analysis for mCRC (2003-2007; N = 5129)



*P < .001

Sequencis and timing of therapies

FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study

Christophe Tournigand, Thierry André, Emmanuel Achille, Gérard Lledo, Michel Flesh, Dominique Mery-Mignard, Emmanuel Quinaux, Corinne Couteau, Marc Buyse, Gérard Ganem, Bruno Landi, Philippe Colin, Christophe Louvet, and Aimery de Gramont

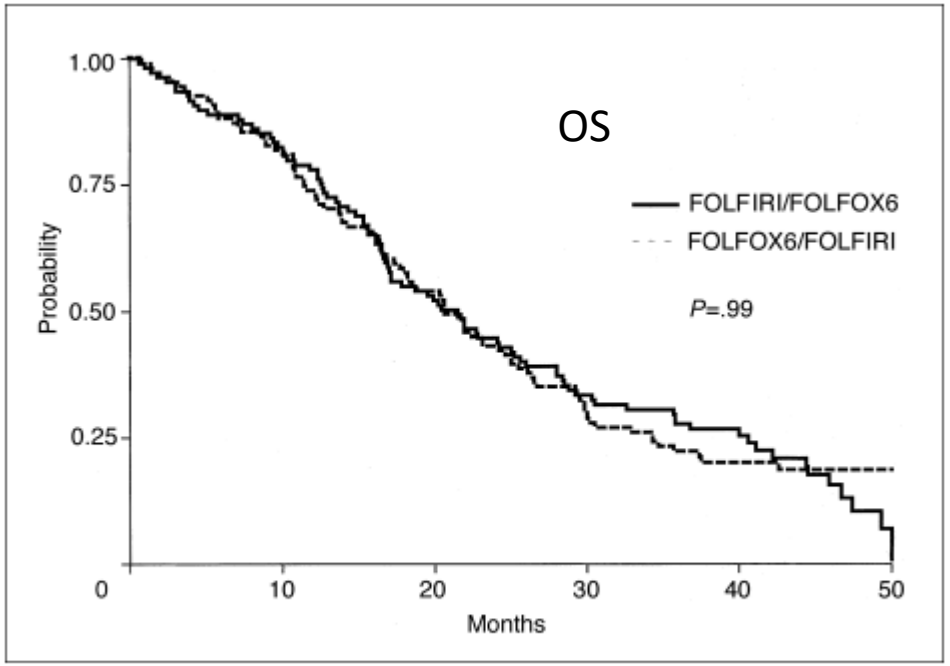


Fig 4. Overall survival curves. FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin.

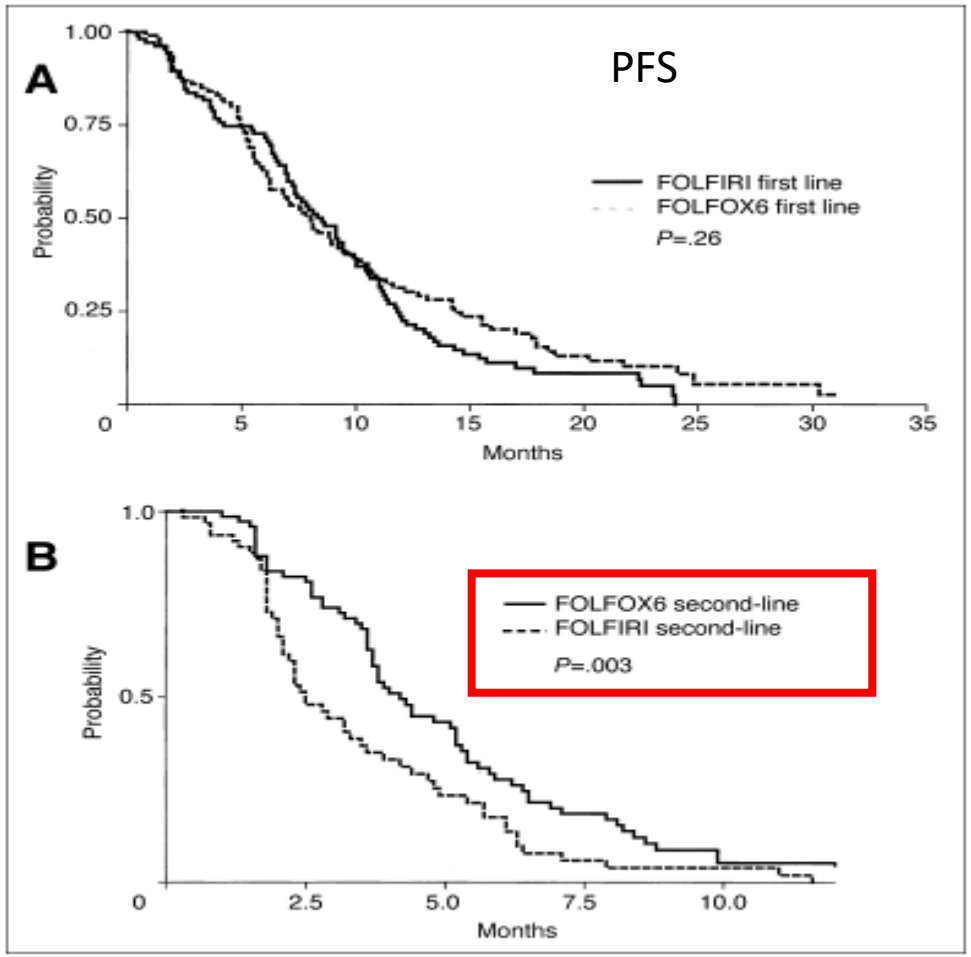
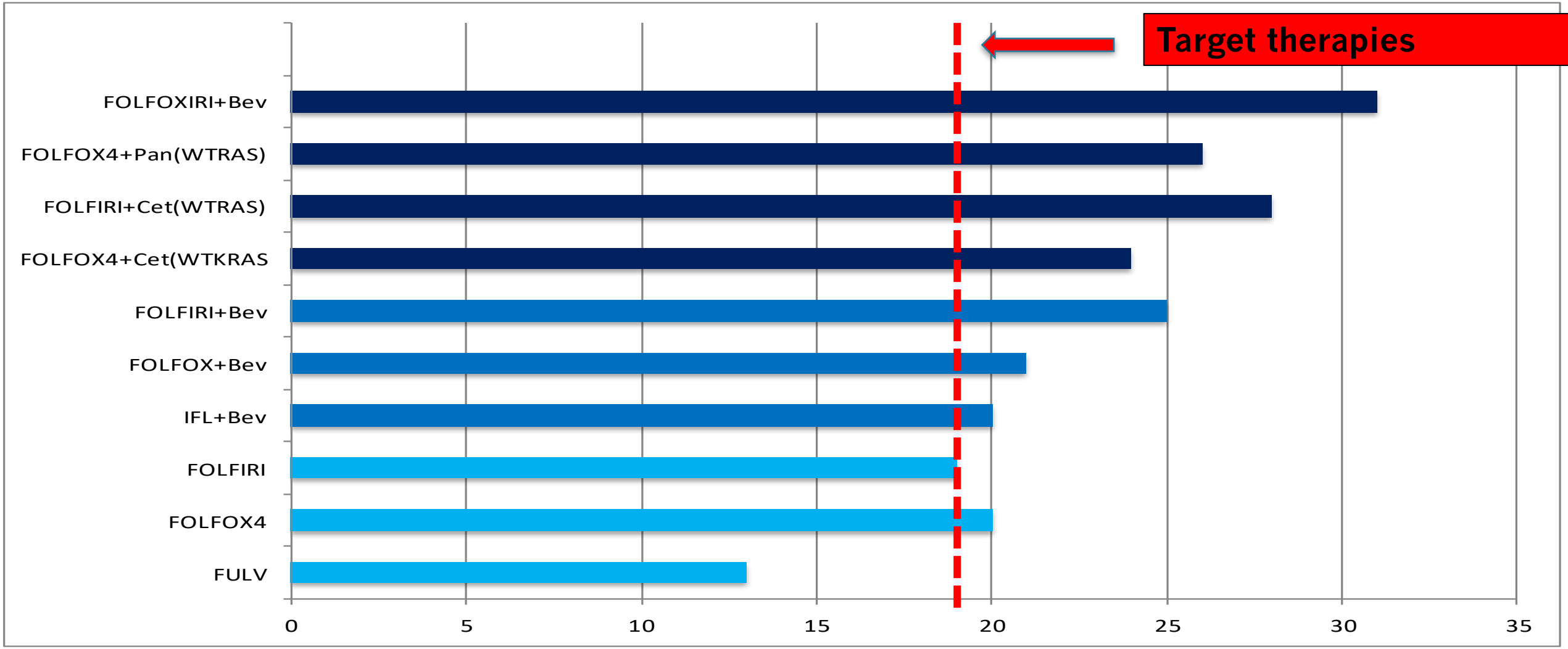


Fig 2. Progression-free survival in (A) first-line therapy and (B) second-line therapy. FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin.

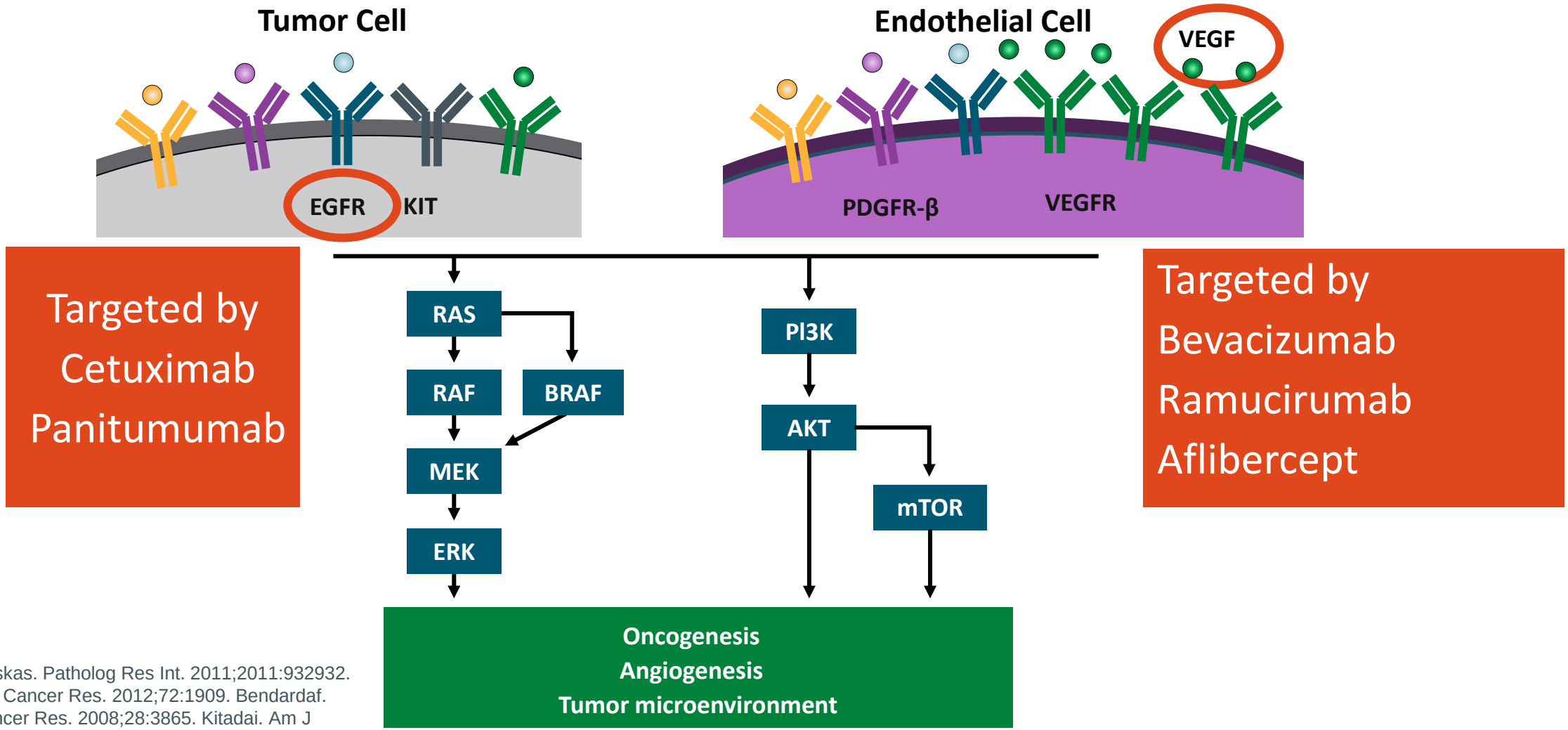
Tournigand C et al JCO 2004

Overall Survival in first-line stage IV colorectal cancer



Van Cutsem et al, NEJM 2009, JCO 2011; Bokemeyer et al, JCO 2009; Maughan et al, ASCO 2010; Douillard et al, NEJM 2013; Hurwitz et al, NEJM 2004; Saltz et al, JCO 2008; Tabernero et al, 2010; Falcone ASCO 2013; Heinemann et al, ASCO 2013

EGFR and VEGFR Growth Signaling Pathways

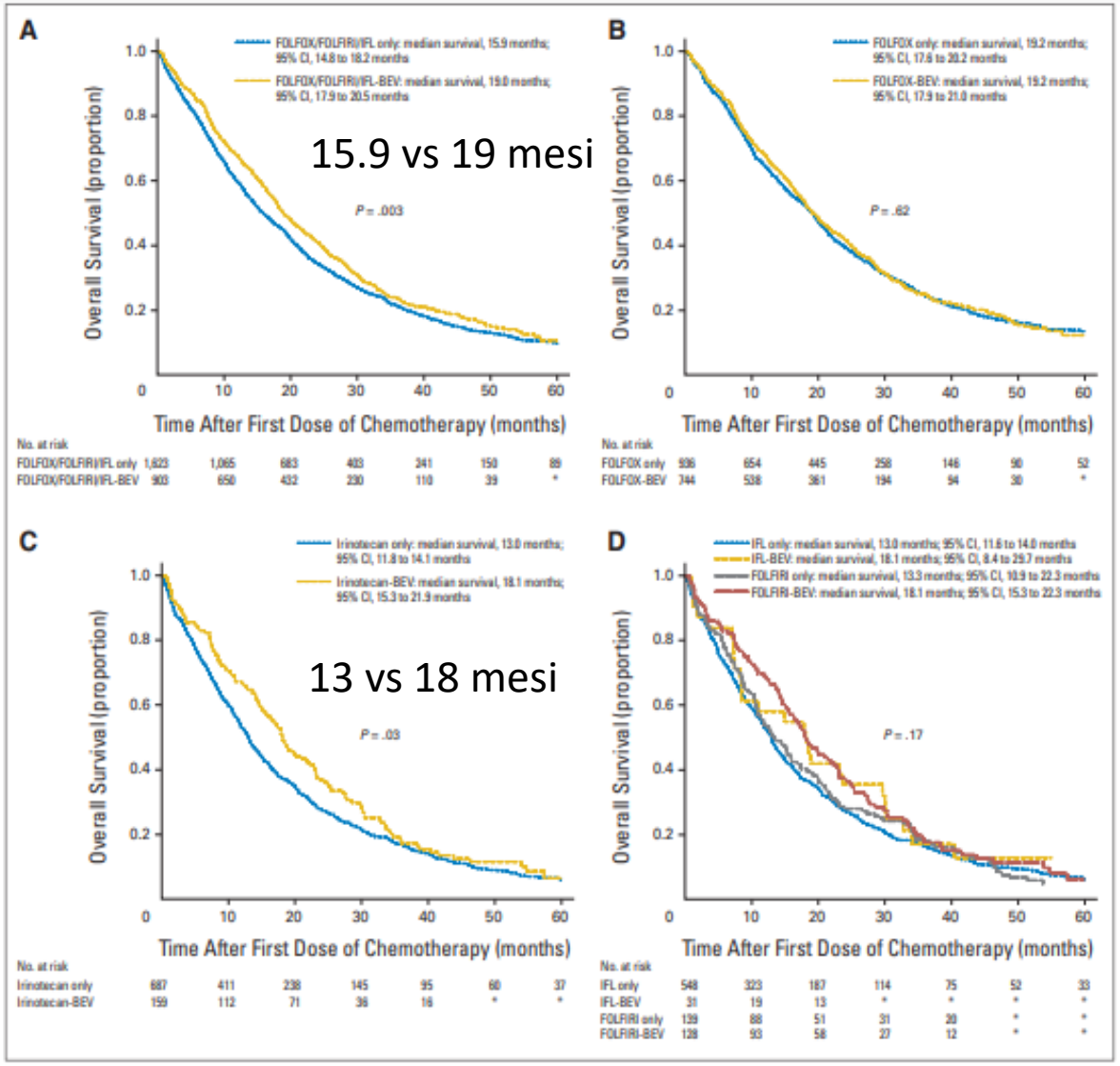


Krasinskas. Patholog Res Int. 2011;2011:932932. Sitohy. Cancer Res. 2012;72:1909. Bendardaf. Anticancer Res. 2008;28:3865. Kitadai. Am J Pathol. 2006;169:2054. Jayson. JCO. 2005;23:973.

VOLUME 30 · NUMBER 6 · FEBRUARY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



Effectiveness of Bevacizumab With First-Line Combination Chemotherapy for Medicare Patients With Stage IV Colorectal Cancer

Jeffrey A. Meyerhardt, Ling Li, Hanna K. Sanoff, William Carpenter IV, and Deborah Schrag

Analysis of the SEER- Medicare database (2526 pts since 2002-2007)

- Bevacizumab added to Irinotecan-based chemotherapy offered advantage in OS vs chemotherapy alone (figura C)

- No advantage if Bevacizumab was added to Oxaliplatin based chemotherapy (figura B)

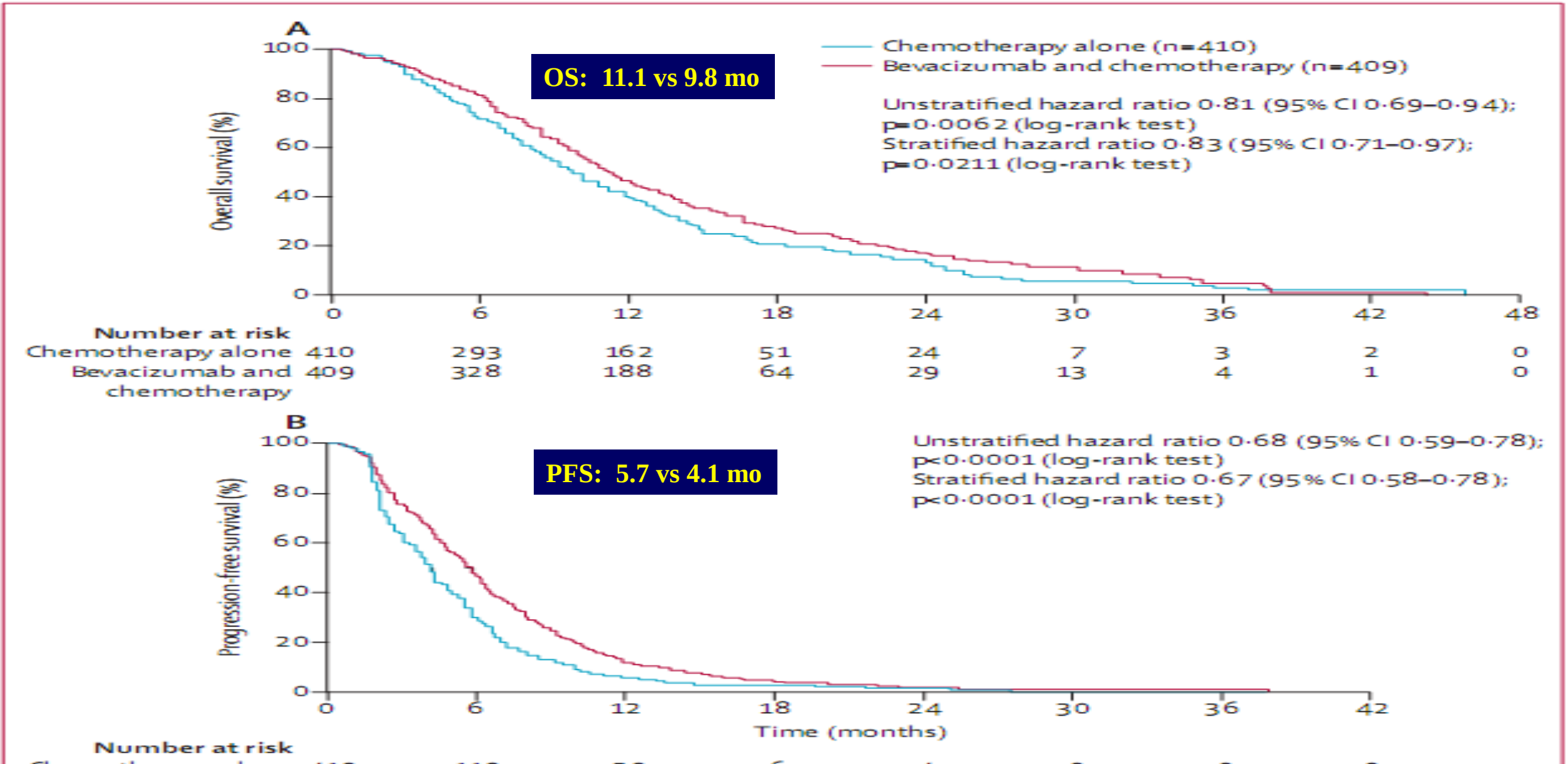
Terapia di mantenimento con Bevacizumab dopo induzione con chemioterapia di prima linea

- **Bevacizumab da solo non inferiore a CT + Bevacizumab in PFS ma nessun vantaggio in OS** *(Diaz Rubio E et al The Oncologist 2012)*
- **Bevacizumab/FP da vantaggio in PFS1-PFS2 vs non mantenimento ma nessun vantaggio in OS** *(CAIRO3 Simkens LH et al Lancet 2015; AIO-KRK 02/07 Arnold D et al ASCO 2014)*
- **Bevacizumab da solo non da vantaggi in OS e PFS vs non mantenimento** (SAKK-41/06 Koeberle D et al ASCO 2014; PRODIGE 9 Aparicio T et al JCO 2018)
- **Vantaggio nel mantenimento con Bevacizumab in PFS non in OS** (Lisa et al Cancer Treat Rev 2021)

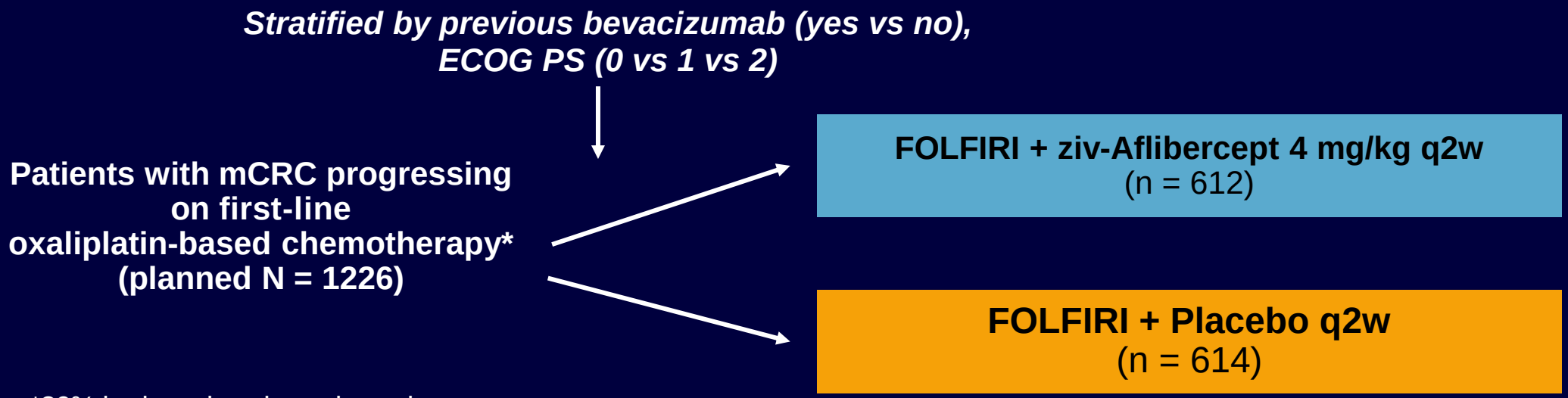
il mantenimento con Bevacizumab dopo induzione con chemioterapia di prima linea rappresenta una valida opzione in termini di PFS1 e PFS2 ma solo in associazione a CT depotenziata mentre non ci sono vantaggi in OS

Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial

Bennouna J et al Lancet Oncol 2013



Phase III VELOUR Study: FOLFIRI ± ziv-Aflibercept as Second-line Therapy in mCRC

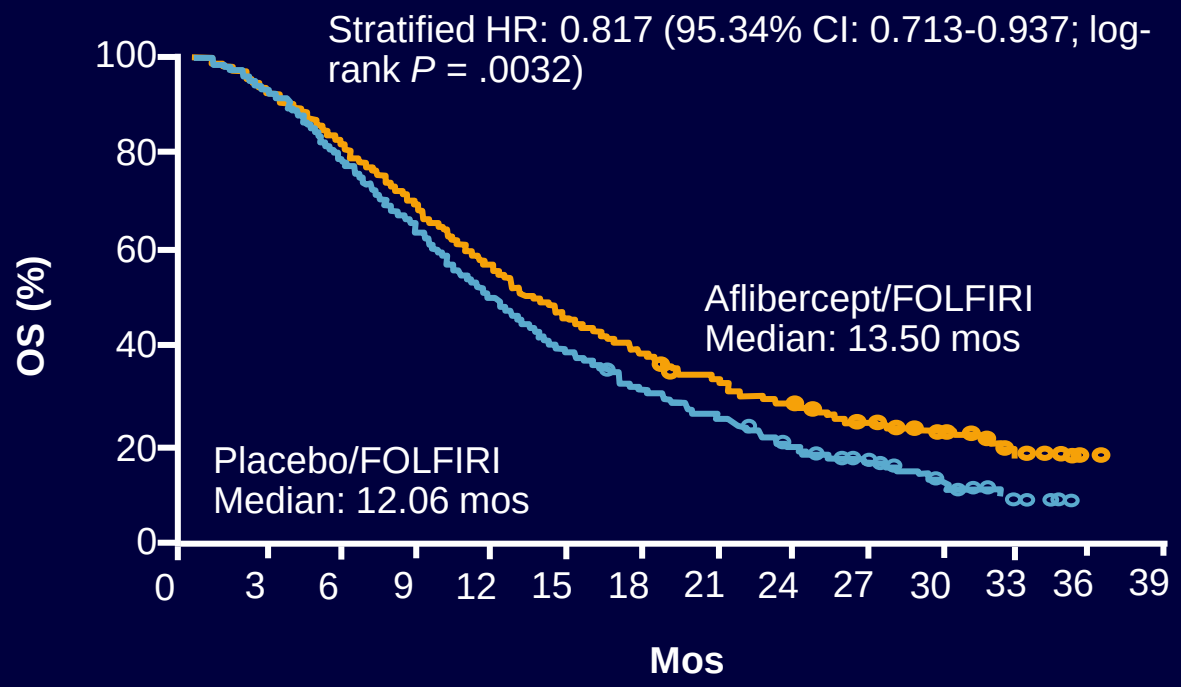


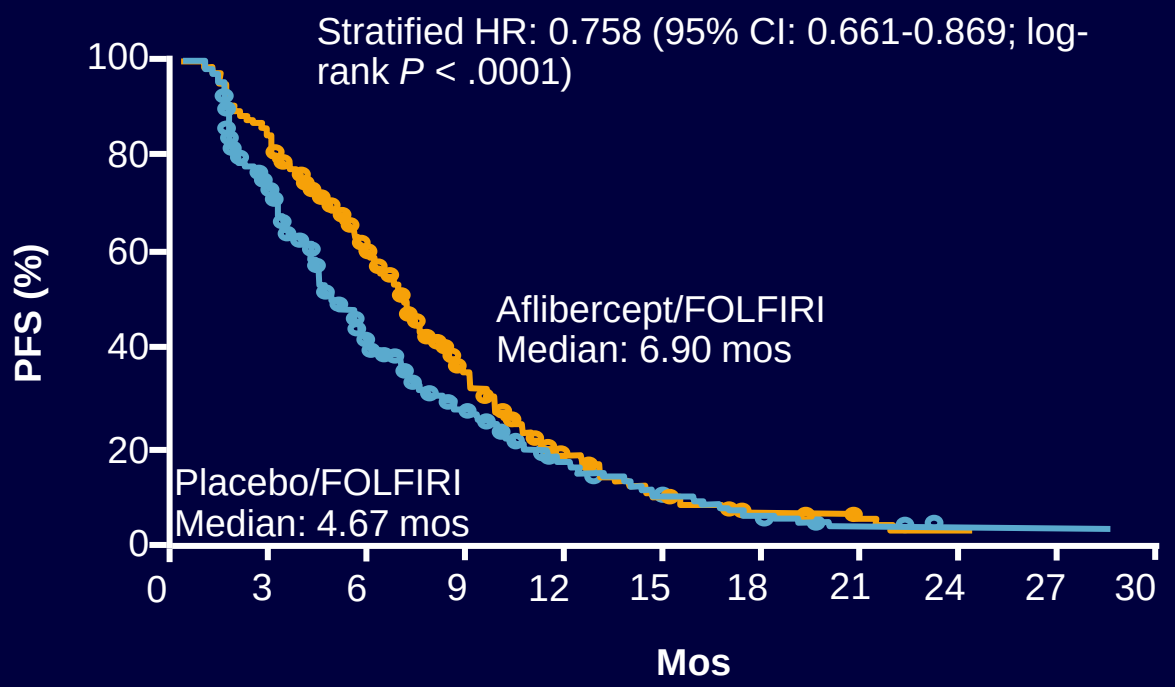
*30% had previous bevacizumab.

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, safety, immunogenicity
- No correlatives

Van Cutsem E, et al. J Clin Oncol. 2012;30:3499-3506..

VELOUR Study: Survival Results





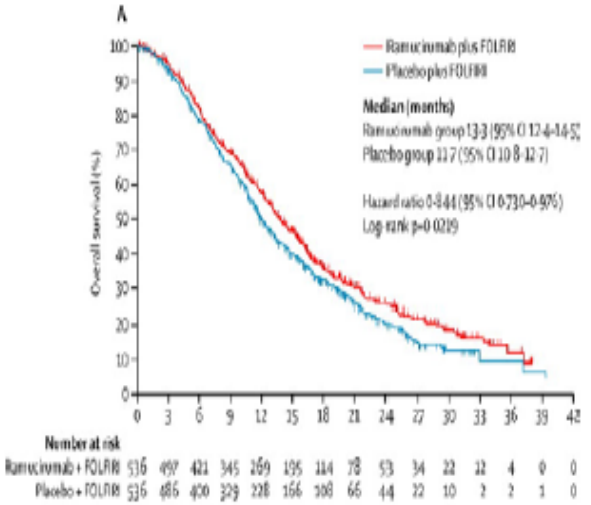
Van Cutsem E, et al. J Clin Oncol. 2012

1072 mCRC patients Progressed on 1st line therapy with FOLFOX + bevacizumab

1:1

FOLFIRI + placebo

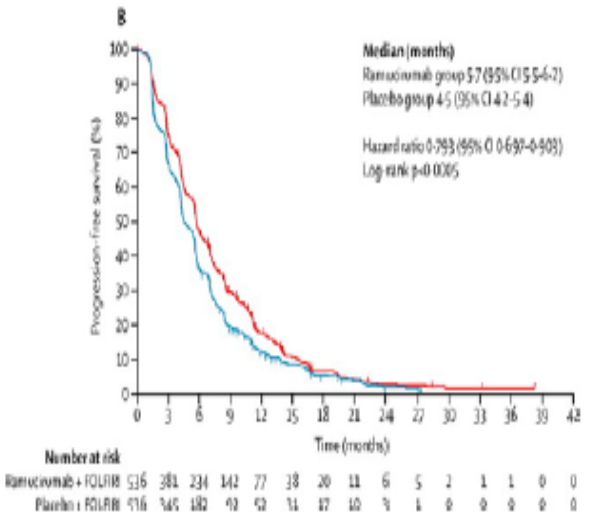
FOLFIRI + ramucirumab (8mg/kg)



Overall survival: 13.3 vs 11.7 months
HR 0.844 (95% CI 0.730-0.976)
log rank p=0.0219

Tabernero et al, Lancet Oncol 2015;16:499-508.

End point primario: Overall Survival



Progression-free survival: 5.7 vs 4.5 months
HR 0.793 (95% CI 0.697-0.903)
log rank p <0.0005

CRYSTAL trial: Folfiri + Cetuximab vs Folfiri Efficacy: *RAS* subgroups

Subgroup	FOLFIRI + cetuximab n	FOLFIRI n	PFS time Hazard ratio 95% CI p-value	OS time Hazard ratio 95% CI p-value	ORR Odds ratio 95% CI p-value
RAS* evaluable	210	220	11.3 vs 7.7† 0.58 0.44–0.77 p=0.0001	26.1 vs 20.2† 0.75 0.60–0.93 p=0.0080	61.4 vs 38.2‡ 2.64 1.78–3.92 p<0.0001
***RAS* wild-type**	178	189	11.4 vs 8.4† 0.56 0.41–0.76 p=0.0002	28.4 vs 20.2† 0.69 0.54–0.88 p=0.0024	66.3 vs 38.6‡ 3.11 2.03–4.78 p<0.0001

*Patients with *KRAS* codon 12/13 wild-type tumors for which tumor DNA samples were evaluable for other *RAS* mutations
†Median, months; ‡%

Presented by: Eric Van Cutsem

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Fortunato Ciardiello at 2014 ASCO Annual Meeting

PRIME trial: Folfox + Panitumumab vs Folfox

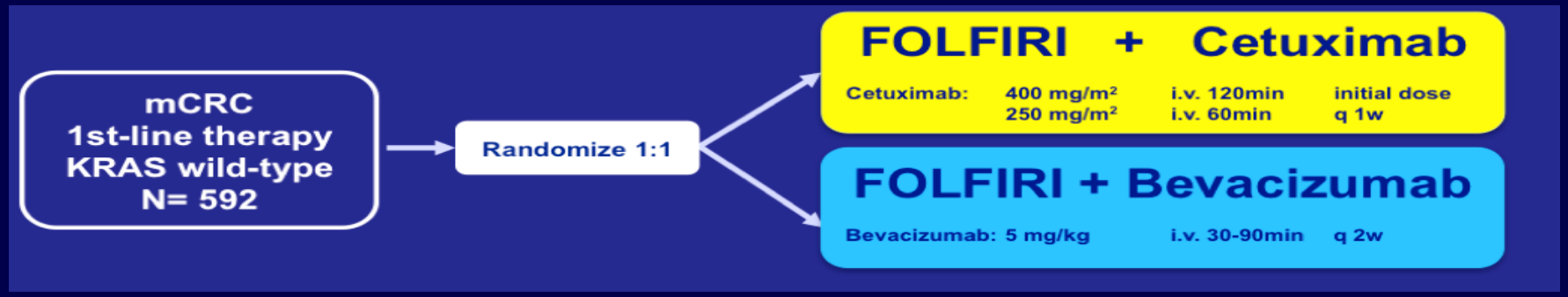
Variable	Panitumumab–FOLFOX4	FOLFOX4 Alone	Hazard Ratio (95% CI)	P Value
No *RAS* or *BRAF* mutations				
No. of patients	228	218		
Months of progression-free survival — median (95% CI)	10.8 (9.4–12.4)	9.2 (7.4–9.6)	0.68 (0.54–0.87)	0.002
Months of overall survival — median (95% CI)	28.3 (23.7–NE)	20.9 (18.4–23.8)	0.74 (0.57–0.96)	0.02
No *RAS* mutation, *BRAF* mutation				
No. of patients	24	29		
Months of progression-free survival — median (95% CI)	6.1 (3.7–10.7)	5.4 (3.3–6.2)	0.58 (0.29–1.15)	0.12
Months of overall survival — median (95% CI)	10.5 (6.4–18.9)	9.2 (8.0–15.7)	0.90 (0.46–1.76)	0.76
***RAS* or *BRAF* mutation**				
No. of patients	296	305		
Months of progression-free survival — median (95% CI)	7.3 (6.3–7.7)	8.0 (7.5–9.0)	1.24 (1.02–1.49)	0.03
Months of overall survival — median (95% CI)	15.3 (12.7–17.6)	18.0 (15.9–20.8)	1.21 (0.99–1.47)	0.06
No *KRAS* mutation in exon 2, other *RAS* or *BRAF* mutation				
No. of patients	75	86		
Months of progression-free survival — median (95% CI)	6.7 (5.3–8.2)	7.3 (5.7–8.0)	1.05 (0.73–1.52)	0.80
Months of overall survival — median (95% CI)	14.5 (10.4–18.5)	15.8 (11.9–18.8)	1.14 (0.78–1.66)	0.51

* NE denotes not evaluated.

Douillard J, et al. NEJM 2013 -

Studio FIRE-3 Bevacizumab vs Cetuximab

FIRE-3



Primary endpoint : Objective Response Rate

	FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab		Odds ratio	p
ORR	%	95%-CI	%	95%-CI		
KRAS exon 2 WT 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	0.32**

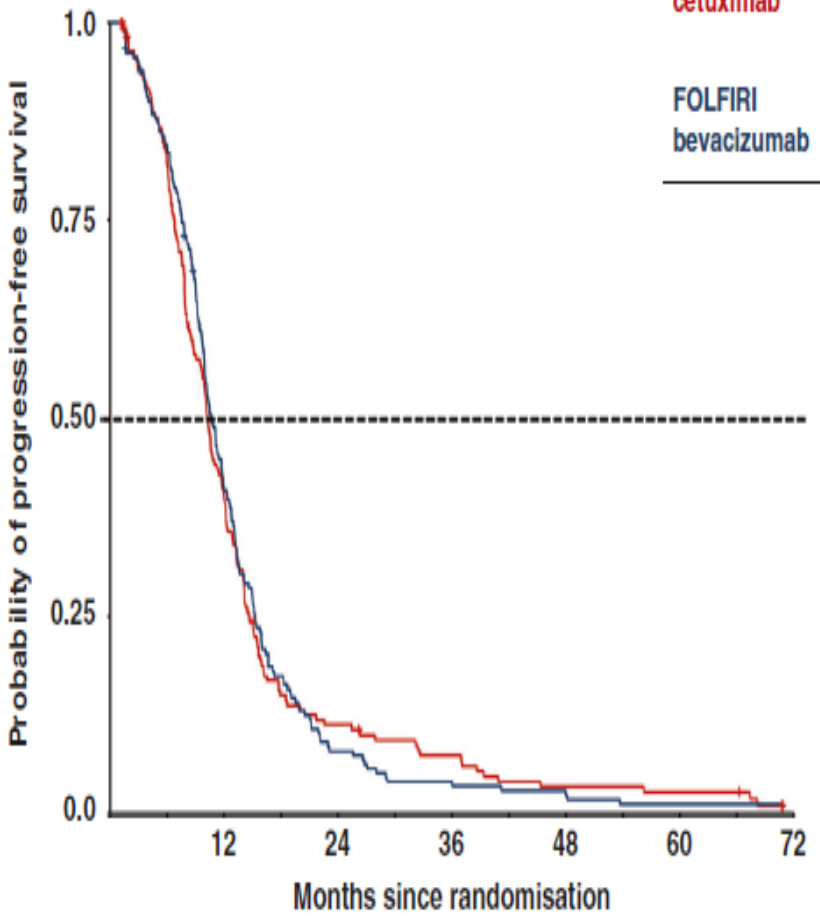
Heinemann et al, ECC2013
Stintzing et al, ASCO GI 2014

FIRE-3: final analysis in RAS wt population

- Heinemann V. et al BJC 2020 -

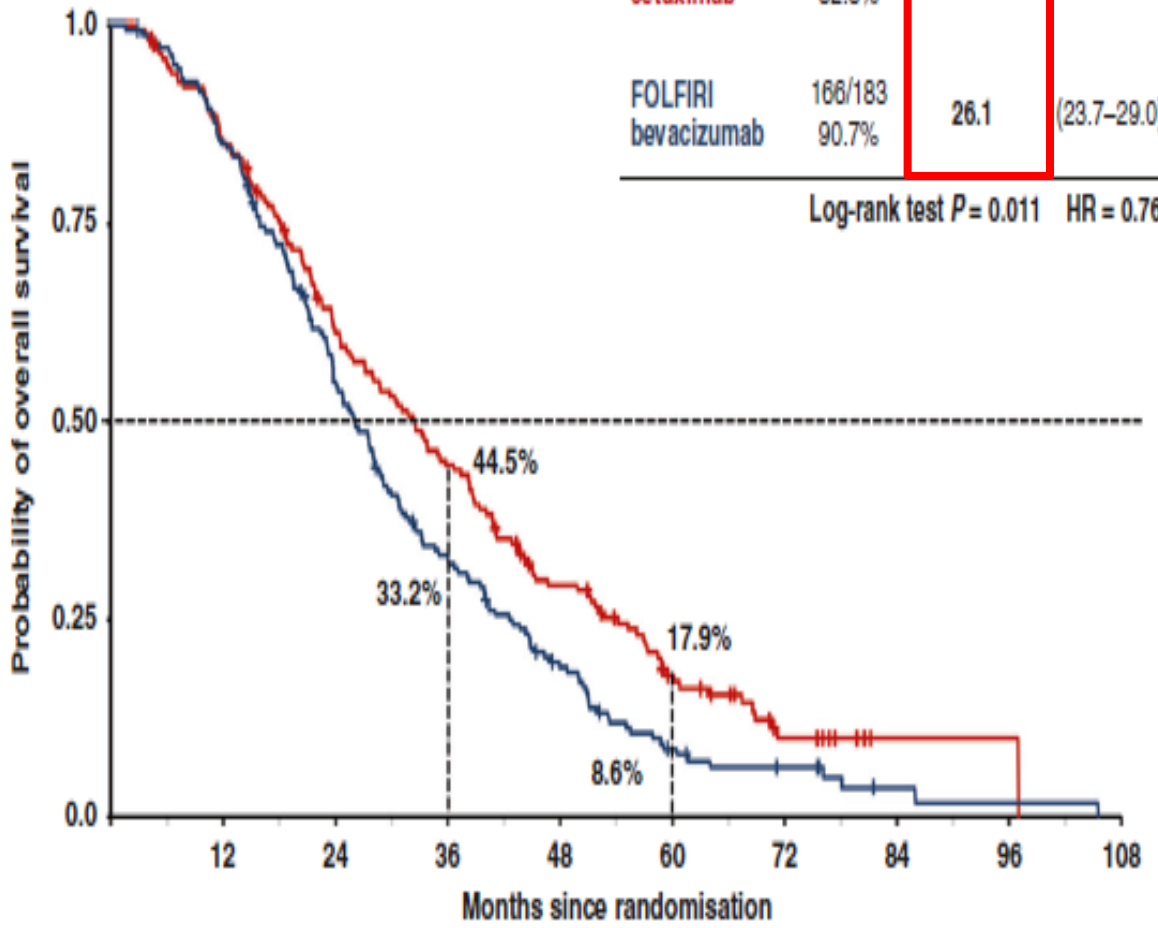
Progression Free survival

	Events (*n*/*N*)	Median PFS	95% CI
FOLFIRI cetuximab	161/169 95.3%	10.3	(9.5–11.8)
FOLFIRI bevacizumab	178/183 97.3%	10.7	(9.9–11.8)
	Log-rank test *P* = 0.99	HR = 1.00	



Overall survival

	Events (*n*/*N*)	Median OS	95% CI
FOLFIRI cetuximab	140/169 82.8%	32.5	(25.9–38.3)
FOLFIRI bevacizumab	166/183 90.7%	26.1	(23.7–29.0)
	Log-rank test *P* = 0.011	HR = 0.76	

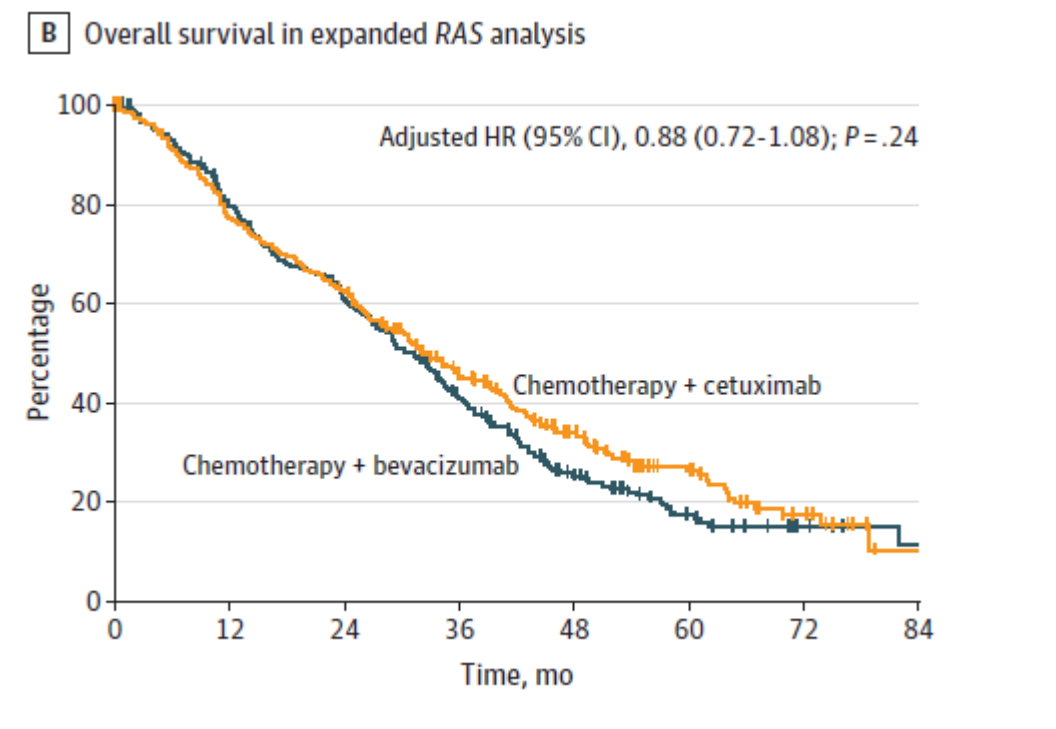


CALGB/SWOG 80405: Study Design and Survival

- **Randomized, open-label phase III trial (primary end point: OS)**

Pts with *KRAS* wild-type (Codons 12, 13) metastatic/advanced CRC no previous therapy for advanced disease (N = 1137)

	OS, Mos	PFS, Mos
Cetuximab + Chemotherapy* (n = 578)	29.9	10.4
Bevacizumab + Chemotherapy* (n = 559)	29.0	10.8

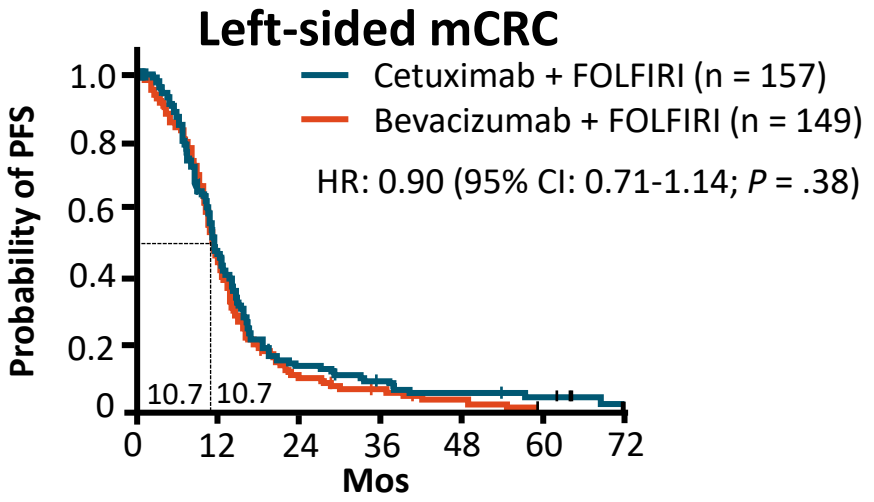


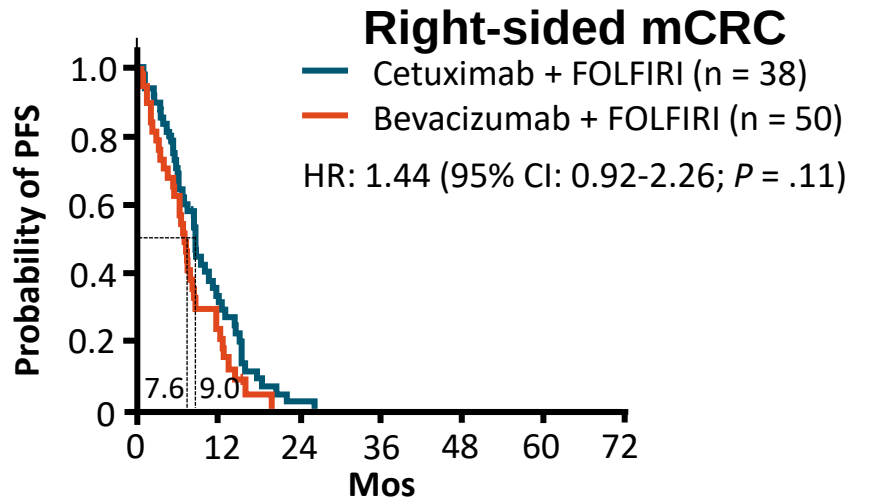
***Physician choice of FOLFIRI or FOLFOX.**

1. Venook A, et al. JAMA. 2017

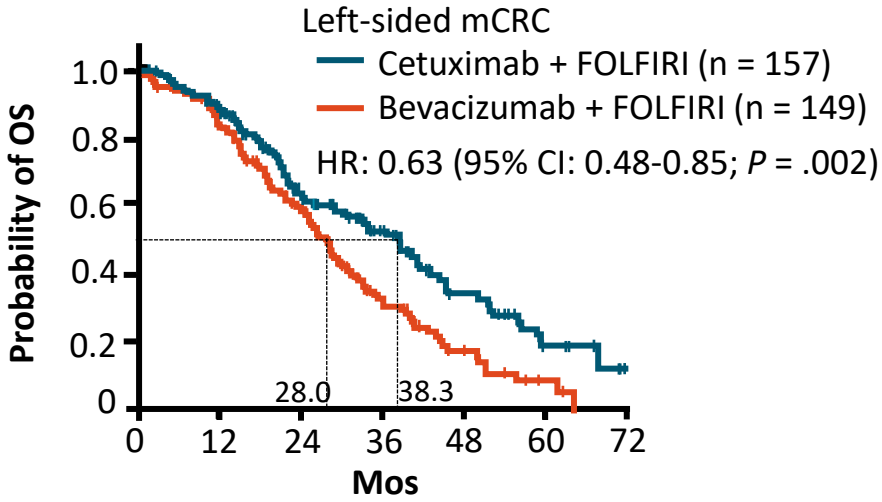
FIRE-3 and CRYSTAL (FOLFIRI + Bevacizumab or Cetuximab): PFS and OS by Tumor Location

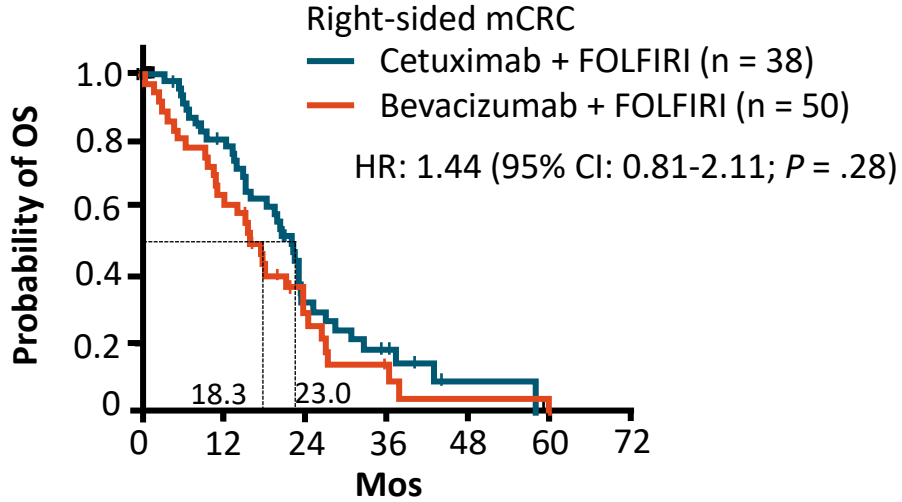
PFS





OS





Tejpar S et al . JAMA 2016

Anti-EGFR Efficacy by Tumor Location (*RAS* WT)

Biologic	Panitumumab						Cetuximab	
Study	PRIME[1] (First Line)		PEAK[1] (First Line)		181[2] (Second Line)		CRYSTAL[3] (First Line)	
Treatment	FOLFOX vs Pmab/FOLFOX		Bev/FOLFOX vs Pmab/FOLFOX		FOLFIRI vs Pmab/FOLFIRI		FOLFIRI vs Cetux/FOLFIRI	
Location	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
n	**156 vs 168**	**46 vs 38**	**54 vs 53**	**14 vs 22**	**148 vs 150**	**39 vs 31**	**138 vs 142**	**51 vs 33**
PFS, mos	9.2 vs 12.9	7.0 vs 7.5	11.5 vs 14.6	12.6 vs 8.7	5.8 vs 8.0	2.4 vs 4.8	8.9 vs 12.0	7.1 vs 8.1
HR (95% CI)	0.72 (0.57-0.90)	0.80 (0.50-1.26)	0.68 (0.45-1.04)	1.04 (0.50-2.18)	0.88 (0.69-1.12)	0.75 (0.45-1.27)	0.50 (0.34-0.72)	0.87 (0.47-1.62)
***P* value**	NR		NR		NR		.0001	.66
Interaction *P* value	NR		NR		NR		0.11	
OS, mos	23.6 vs 30.3	15.4 vs 11.1	32.0 vs 43.4	21.0 vs 17.5	16.6 vs 20.1	8.1 vs 10.3	21.7 vs 28.7	15.0 vs 18.5
HR (95% CI)	0.73 (0.57-0.93)	0.87 (0.55-1.37)	0.77 (0.46-1.28)	0.67 (0.30-1.50)	0.96 (0.74-1.23)	1.14 (0.68-1.89)	0.65 (0.50-0.86)	1.08 (0.65-1.81)
***P* value**	NR		NR		NR		.002	.76
Interaction *P* value	NR		NR		NR		.17	
ORR, %	52.6 vs 67.9	34.8 vs 42.1	57.4 vs 64.2	50.0 vs 63.6	13 vs 50	3 vs 13	40.6 vs 72.5	33.3 vs 42.4
OR (95% CI)	NR		NR		NR		3.99 (2.40-6.62)	1.45 (0.58-3.64)
***P* value**	NR		NR		NR		< .001	.43
Interaction *P* value	NR		NR		NR		.07	

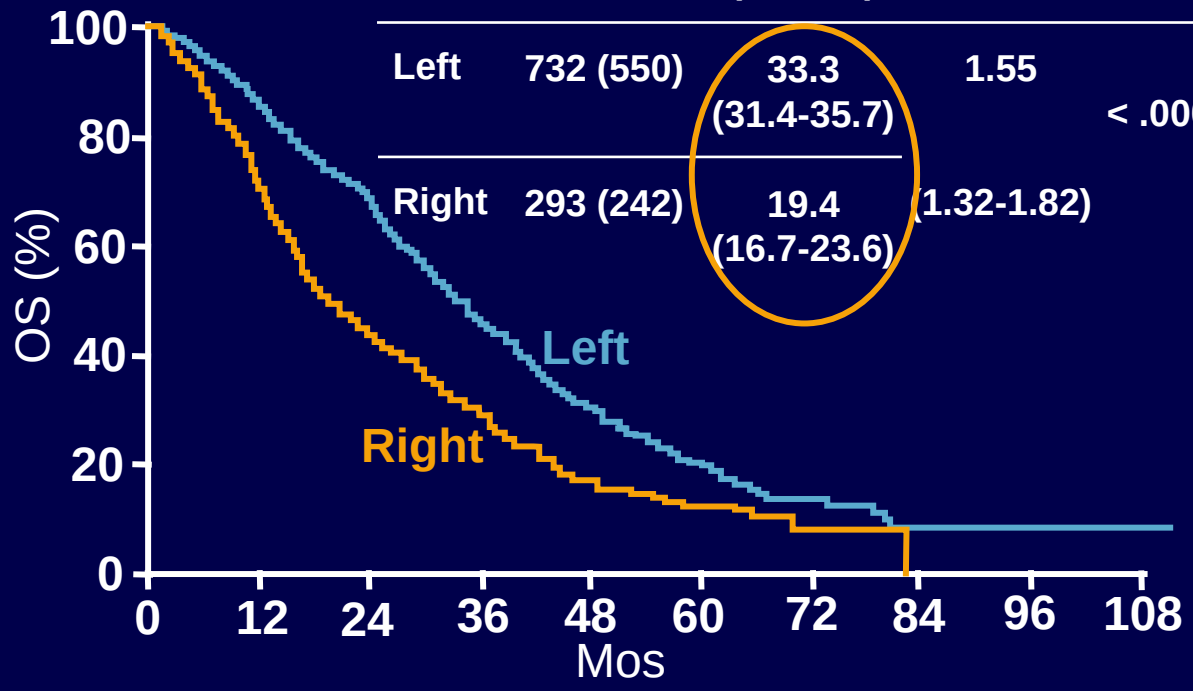
1. Boeckx N, et al. Ann Oncol. 2017;. 2. Boeckx N, et al. ESMO 2016.
3. Tejpar S, et al. JAMA Oncol. 2016;

CALGB/SWOG 80405 Prognostic Factors: OS by Side of Tumor and Biologic Treatment

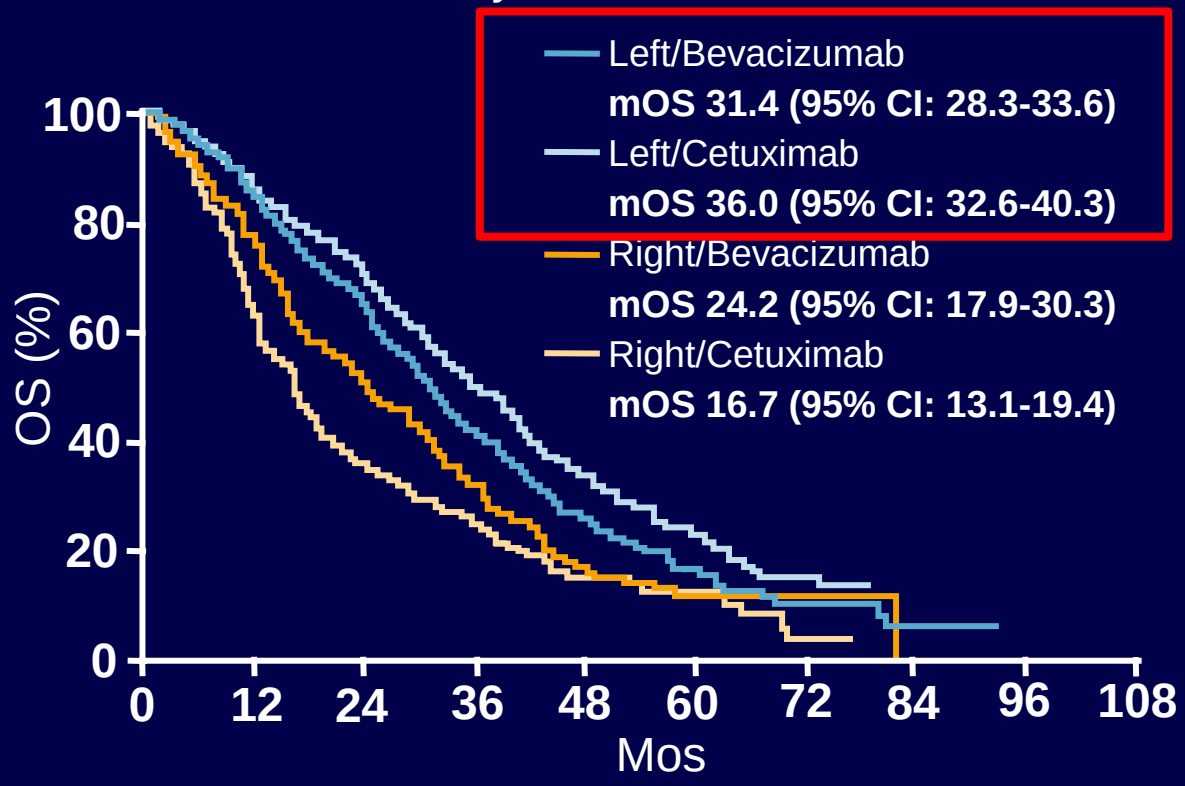
- **Pts with right-sided tumor, n = 293 (27%); left-sided, n = 732 (68%)**
  - **Pts with transverse colon tumors excluded from analysis (n = 66)**

OS by Sidedness

Side	N (Events)	mOS (95% CI)	HR (95% CI)	*P* Value
Left	732 (550)	33.3 (31.4-35.7)	1.55	< .0001
Right	293 (242)	19.4 (16.7-23.6)	(1.32-1.82)	



OS by Side and Treatment



Venook A, et al. JAMA 2017

mCRC Is a Molecularly Heterogeneous Disease

BRAF V600E mutation

BRAF-like signature

PIK3CA mutations

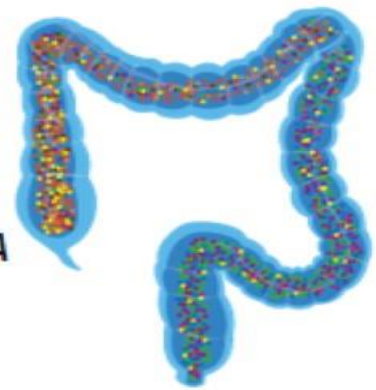
dMMR

CIMP-high

Low *AREG-EREG* expression

CMS1 (immune)

- *KRAS*
- *RAS*
- *MSI*
- *BRAF*
- *PIK3CA*
- *PTEN*



- *RAS*
- *KRAS*
- *PIK3CA*
- *APC*
- *TP53*

HER2 overexpression
RAS mutations

High *AREG-EREG* expression

EGFR amplification

TP53 mutation

APC

Salem M, et al. *J Clin Oncol.* 2017;35(suppl 4S). Abstract 530.
Lee GH, et al. *Eur J Surg Oncol.* 2015;41:300-308.
Lee MS, et al. *Br J Cancer.* 2016;114:1352-1361.

Impact of Consensus Molecular Subtype on Survival in Patients With Metastatic Colorectal Cancer: Results From CALGB/SWOG 80405 (Alliance)

- Lenz Heinz-Joseph et al JCO 2019 -

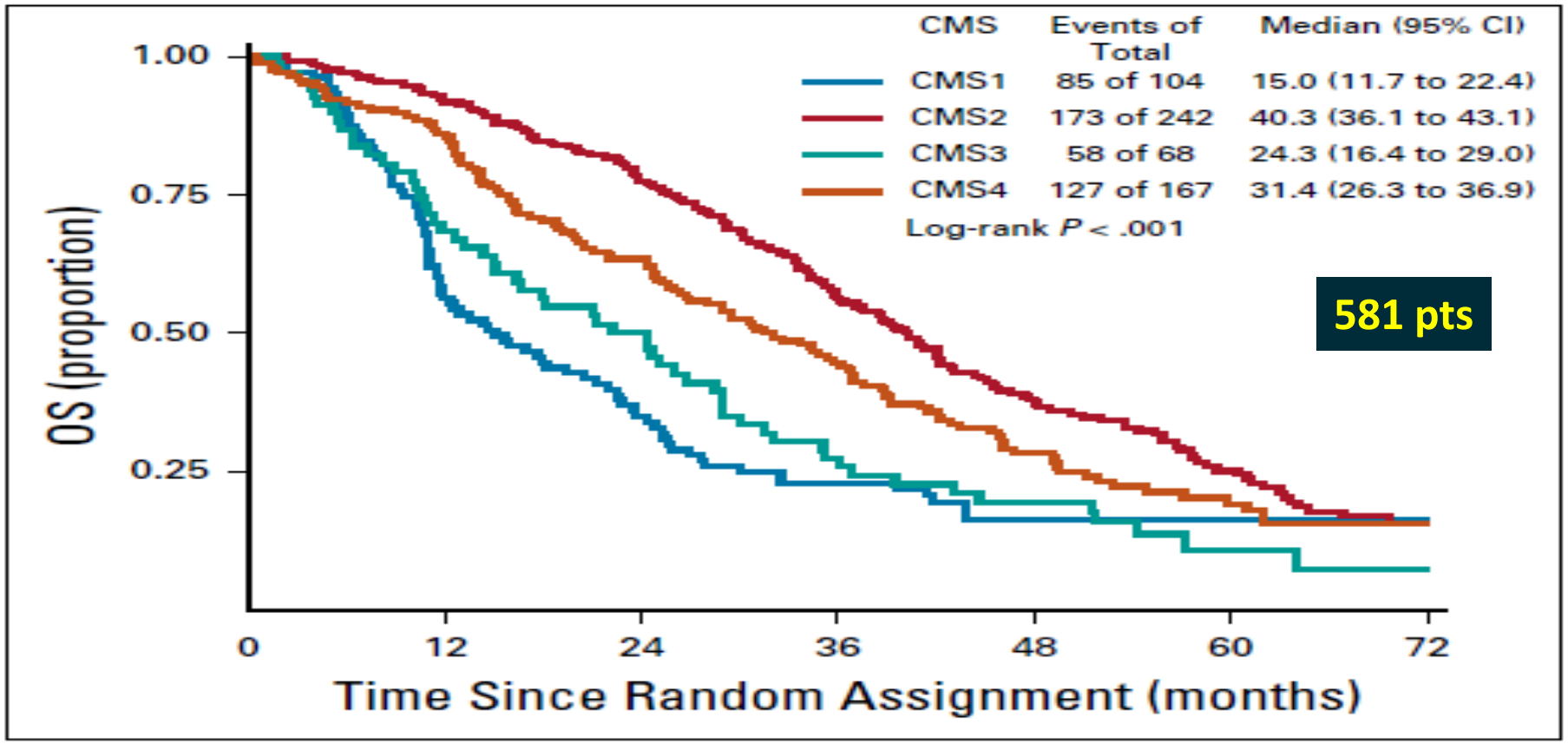
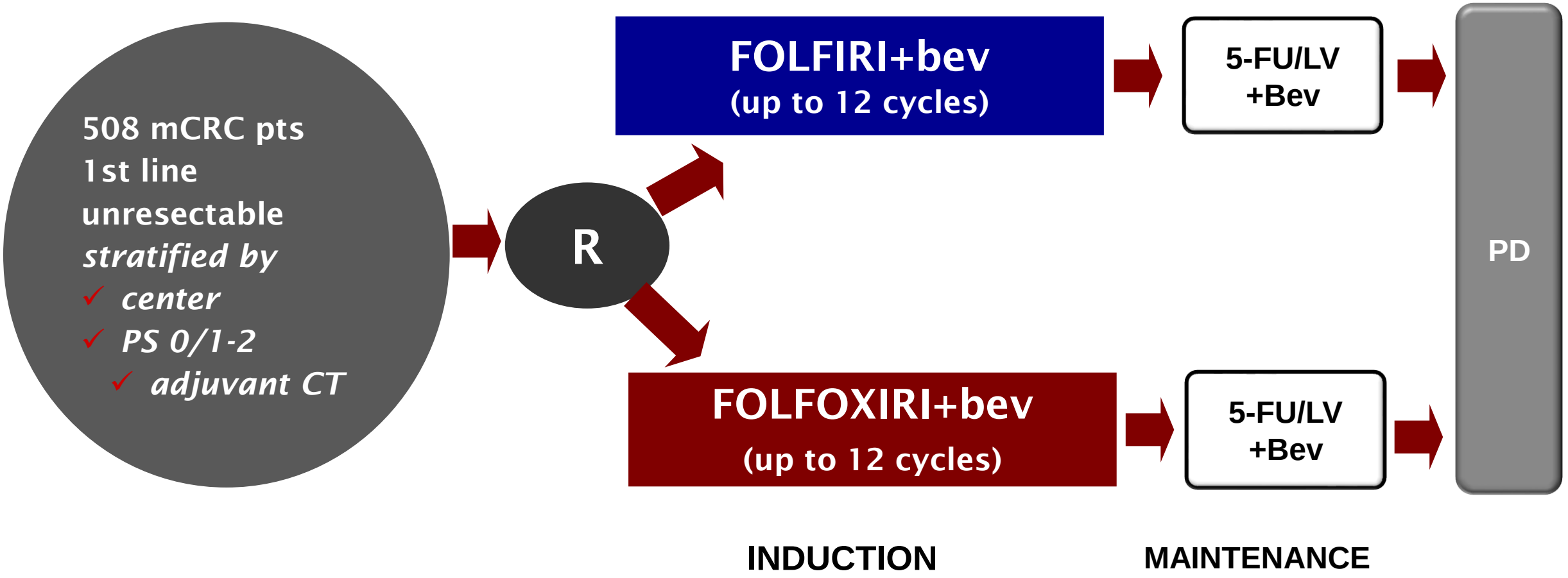


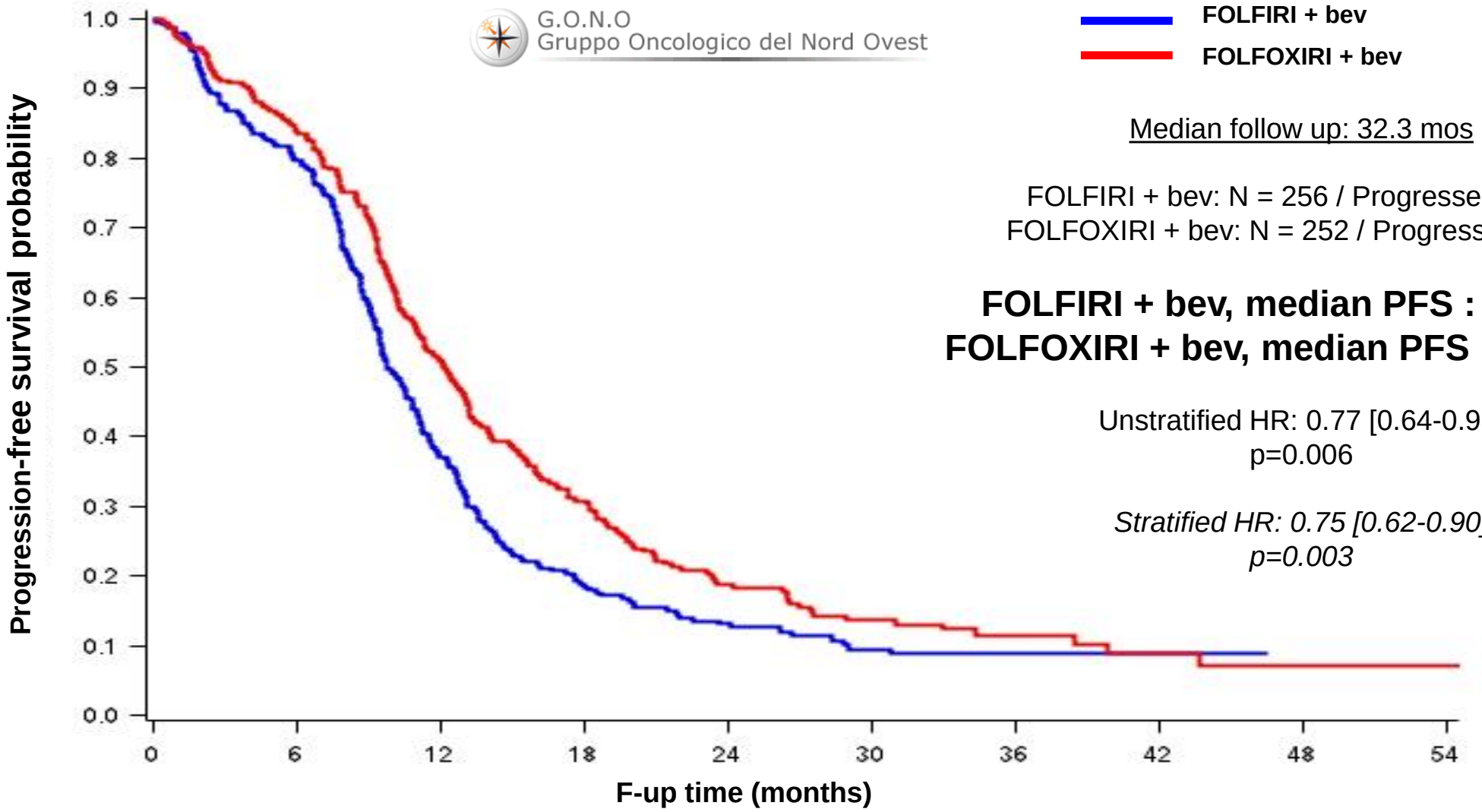
FIG 3. Overall survival (OS) among patients included in this analysis.

TRIBE Study Design



G.O.N.O
Gruppo Oncologico del Nord Ovest

Primary endpoint: PFS – ITT population
- Cremolini C et al Lancet Oncol 2015-



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

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 : 12.3 mos

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

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

Secondary endpoint: Response rate - ITT population

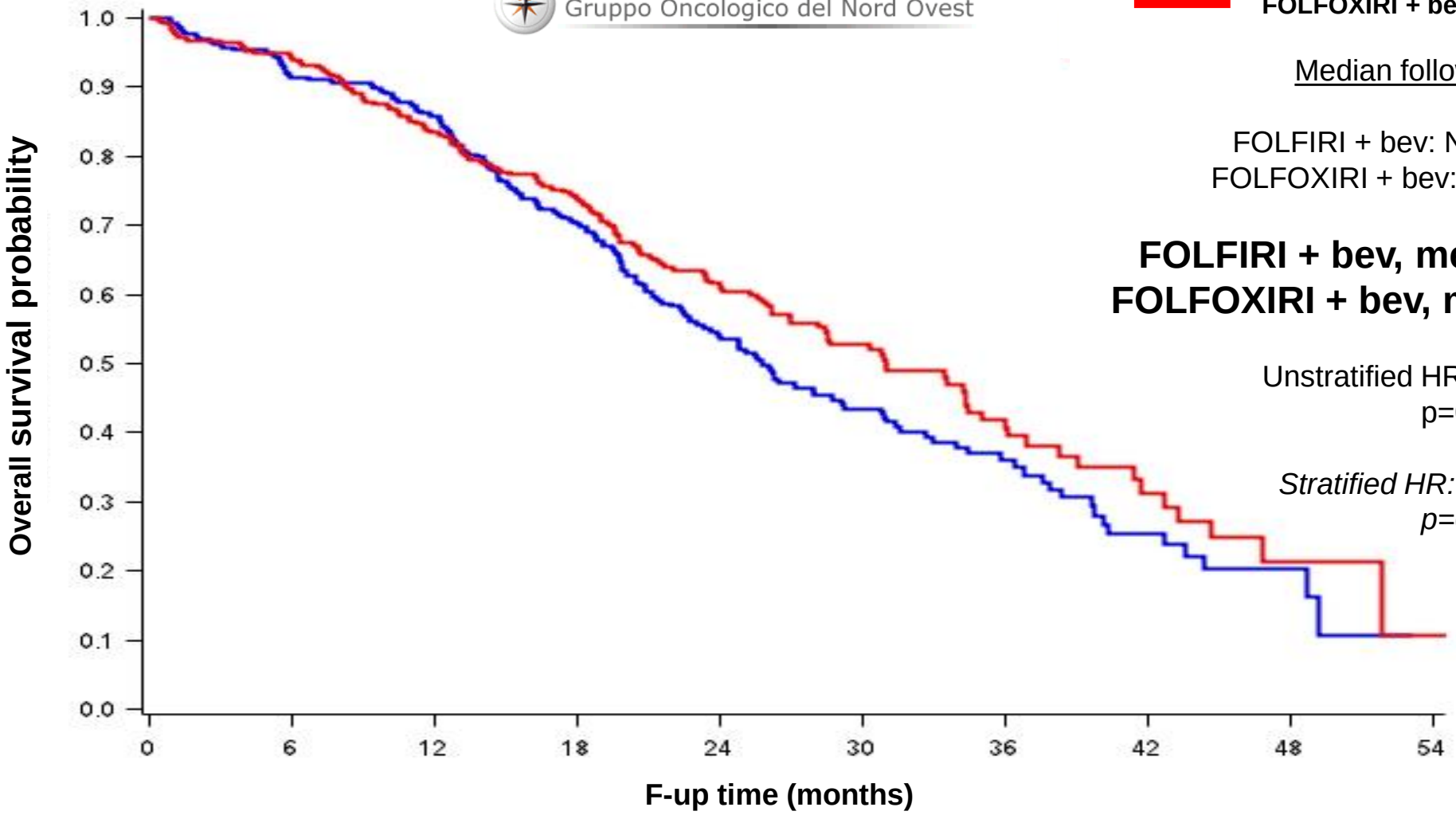
Best Response, %	FOLFIRI + bev N = 256	FOLFOXIRI + bev N = 252	*p*
Complete Response	3%	5%	
Partial Response	50%	60%	
Response Rate	**53%**	**65%**	***0.006***
Stable Disease	32%	25%	
Progressive Disease	11%	6%	
Not Assessed	4%	4%	

Cremolini et al, Lancet Oncol 2015

	FOLFIRI + bev Arm A N = 256	FOLFOXIRI + bev Arm B N = 252	p
Secondary surgery with radical intent	21%	26%	0.2
R0 secondary surgery	12%	15%	0.3
Liver-only subgroup	**N = 46**	**N = 59**	
Secondary surgery with radical intent	41%	39%	1.0
R0 secondary surgery	28%	32%	0.8

Secondary endpoint: OS – ITT population

Cremolini et al, Lancet Oncol 2015



FOLFIRI/bev	256	233	216	172	109	69	36	15	5	0
FOLFOXIRI/bev	252	234	205	175	119	70	35	15	4	0

Median follow up: 48.1 mos

FOLFIRI + bev: N = 256 / Died = 155
FOLFOXIRI + bev: N = 252 / Died = 131

FOLFIRI + bev, median OS : 25.8 mos
FOLFOXIRI + bev, median OS : 29.8 mos

Unstratified HR: 0.83 [0.66-1.05]
p=0.125

Stratified HR: 0.79 [0.63-1.00]
p=0.054

FOLFOXIRI+Bev in *BRAF* mut

Subgroup analysis of phase III TRIBE trial

	N	FOLFIRI + bev Arm A Median PFS	FOLFOXIRI + bev Arm B Median PFS	HR [95% CI]
ITT population	508	9.7	12.1	0.75 [0.62-0.90]
***RAS* mutated**	218	9.5	12.0	0.82 [0.61-1.09]
***BRAF* mutated**	28	5.5	7.5	0.55 [0.26-1.18]
All wt patients	129	11.3	13.3	0.75 [0.52-1.10]

	N	FOLFIRI + bev Arm A Median OS	FOLFOXIRI + bev Arm B Median OS	HR [95% CI]
ITT population	508	25.8	31.0	0.79 [0.63-1.00]
***RAS* mutated**	218	23.1	30.8	0.86 [0.60-1.22]
***BRAF* mutated**	28	10.8	19.1	0.55 [0.24-1.23]
All wt patients	129	34.4	41.7	0.85 [0.52-1.39]

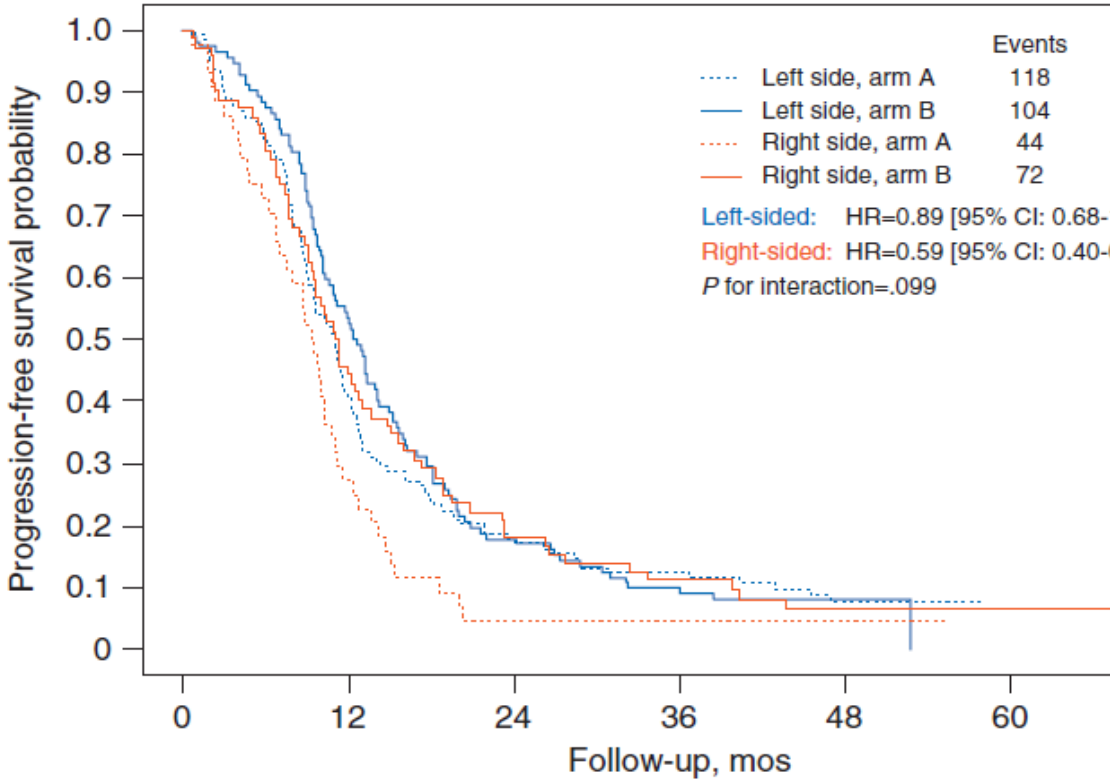
Cremolini et al, Lancet Oncol 2015

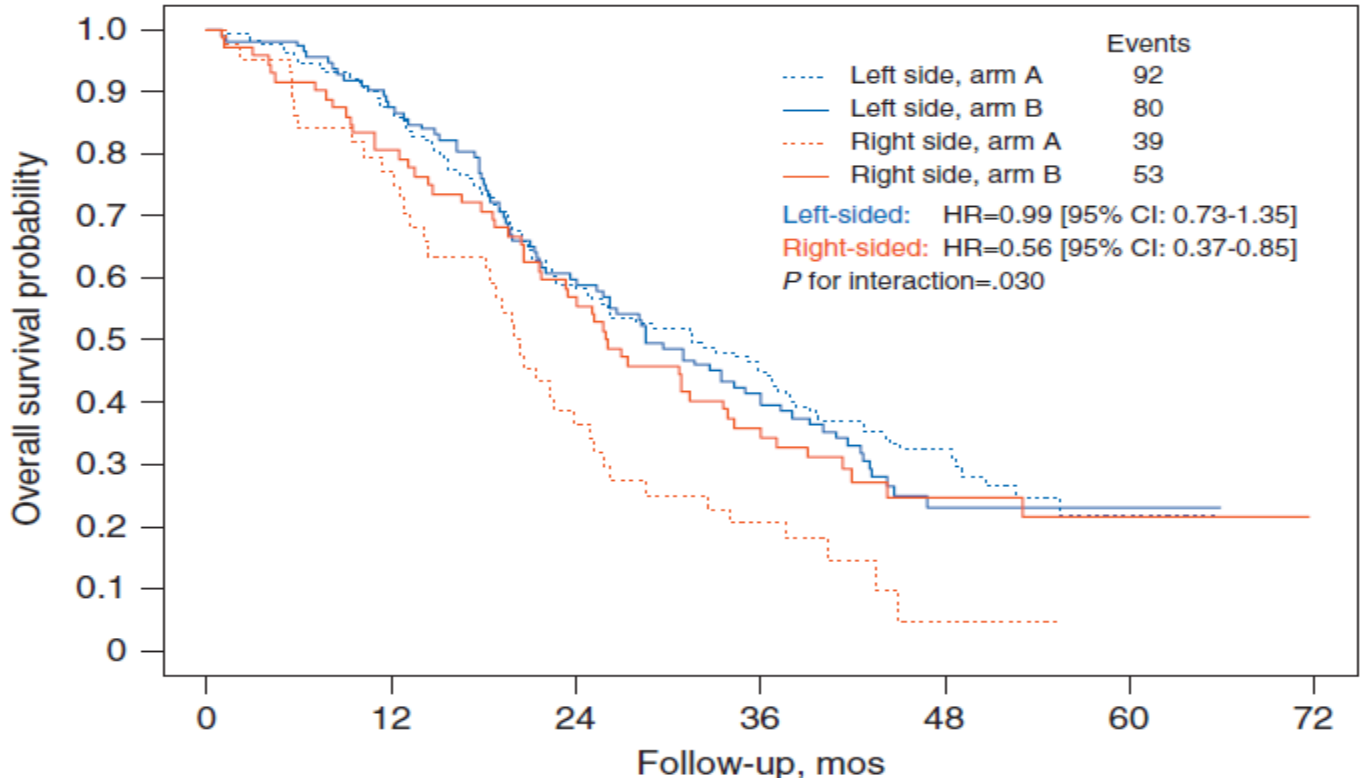
Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer. Retrospective analysis of the TRIBE trial by GONO

Vantaggio della tripletta in OS e PFS nei tumori a dx vs sx indipendente dallo stato RAS/BRAF

C. Cremolini[1,2*], C. Antoniotti[1,2], S. Lonardi[3], F. Bergamo[3], E. Cortesi[4], G. Tomasello[5], R. Moretto[1,2], M. Ronzoni[6], P. Racca[7], F. Loupakis[1,3], A. Zaniboni[8], G. Tonini[9], A. Buonadonna[10], F. Marmorino[1,2], G. Allegrini[11], C. Granetto[12], G. Masi[1,2], V. Zagonel[3], E. Sensi[13], G. Fontanini[14], L. Boni[15] & A. Falcone[1,2]

Annals of Oncology 29: 1528–1534, 2018



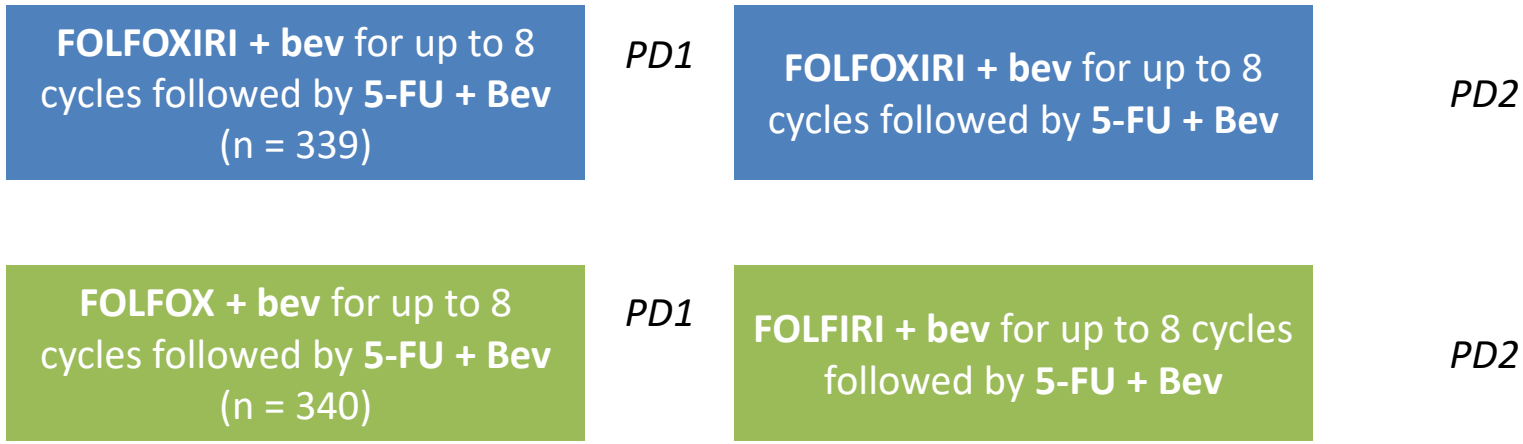


TRIBE2: Study Design

It is unknown whether first-line treatment with FOLFOXIRI + bev limits efficacy of subsequent lines of therapy or whether it is more beneficial vs preplanned, sequential exposure to all cytotoxics

- Multicenter, open-label, randomized phase III trial

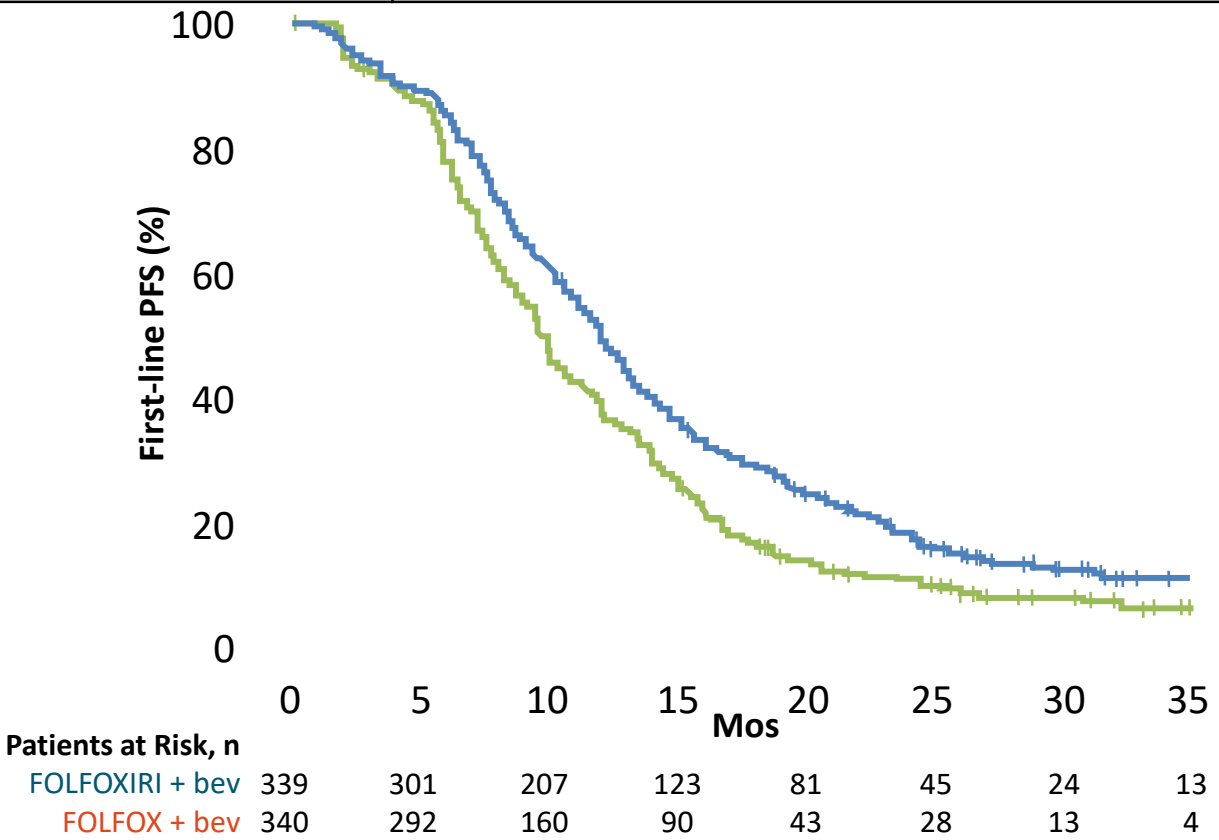
Patients with unresectable mCRC; not previously treated for metastatic disease; histologically demonstrated adenocarcinoma; age 18-75 yrs; ECOG PS ≤ 2 (0 if age 71-75 yrs); no prior adjuvant CT containing oxaliplatin; adjuvant 5-FU permitted if > 6 mos from EOT to first relapse; adequate BM, liver, renal function
(N = 679)



- Primary endpoint: PFS2 (time from randomization to PD2 or death on any treatment given after PD1)
  - Powered to detect HR for PFS2 of 0.77 with overall 2-sided $\alpha = 0.05$ requiring 466 events (2-sided α level: interim analysis, 0.0131; final analysis, 0.0455)
- Secondary endpoints: first and second PFS, response rate, OS and safety

TRIBE2: First-line PFS and Response

	FOLFOXIRI + Bev (n = 339)	FOLFOX + Bev (n = 340)
Events, n (%)	291 (86)	303 (89)
First-line mPFS, mos	**12.0**	**9.8**
	HR: 0.75 (95% CI: 0.63-0.88; *P* < .001)	



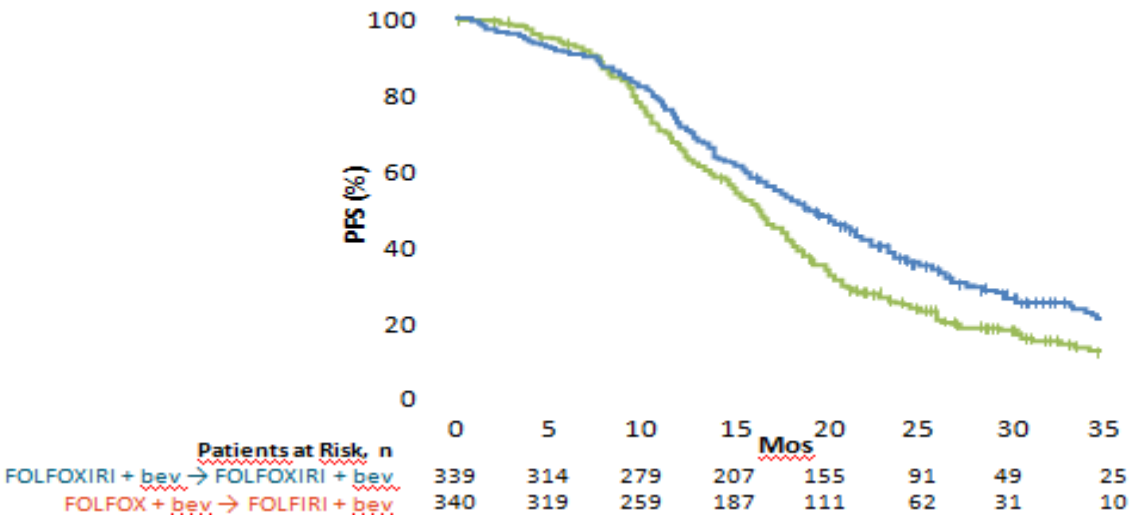
- First-line response rate higher with FOLFOXIRI + bev vs FOLFOX + bev
  - OR: 1.61 (95% CI: 1.19-2.18; *P* = .002)

Response, %	FOLFOXIRI + Bev (n = 339)	FOLFOX + Bev (n = 340)
ORR	62	50
▪ CR	3	4
▪ PR	59	46
SD	29	40
PD	4	7
Not assessed	5	3

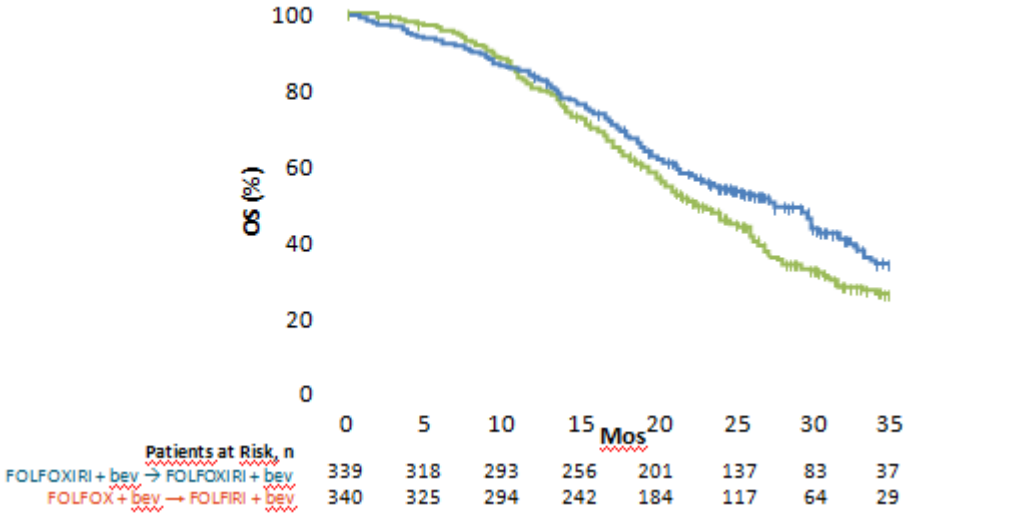
- Cremolini C et al Lancet Oncol 2020 -

TRIBE2: PFS2 (Primary Endpoint) & mOS (follow up 30 mos)

	FOLFOXIRI + Bev → FOLFOXIRI + Bev (n = 339)	FOLFOX + Bev → FOLFIRI + Bev (n = 340)
Events, n (%)	242 (71)	272 (80)
mPFS2, mos	**19.1**	**17.5**
	HR: 0.74 (95% CI: 0.62-0.88; *p* < .001)	



	FOLFOXIRI + Bev → FOLFOXIRI + Bev (n = 339)	FOLFOX + Bev → FOLFIRI + Bev (n = 340)
Events, n (%)	191 (56)	217 (64)
mOS	**27.4**	**22.5**
	HR: 0.81 (95% CI: 0.67-0.98; *p* = .033)	



- Cremolini C et al Lancet Oncol 2020 -

CAIRO5: Study Design

- Prospective, randomized phase III trial

Stratified by potentially vs permanently unresectable, serum LDH (normal vs abnormal), BRAF^{V600E} mutation status, choice of oxaliplatin vs irinotecan

Patients aged ≥18 yr with mCRC with previously untreated liver-only mets; initial unresectability confirmed by a liver expert panel; WHO PS 0-1; primary tumor resectable if in situ
(N = 564)

This analysis

Up to 12 Cycles

Patients with *RAS/BRAFV^{600E}* mutated and/or right-sided primary
(N = 291)

- **FOLFOX/FOLFIRI*† + Bev‡** (n = 147)
- **FOLFOXIRI§ + Bev‡** (n = 144)

Patients with *RAS/BRAFV^{600E}* wild-type and left-sided primary

- **FOLFOX/FOLFIRI + Bev**
- **FOLFOX/FOLFOXIRI + Pani**

Maintenance
5-FU + LV + bevacizumab

Until PD; panel evaluation every 2 mo for resectability assessment

*FOLFOX or FOLFIRI by patient preference; all patients could receive local treatments and up to 12 cycles of systemic tx without bev after local tx.
†Oxaliplatin 85 mg/m^2 or irinotecan 180 mg/m^2 with LV 400 mg/m^2 in 120 min; bolus 5-FU 400 mg/m^2, infusional 5-FU 2400 mg/m^2 in 46h Q2W.
‡5 mg/kg IV in 15-30 min.
§Oxaliplatin 85 mg/m^2, irinotecan 165 mg/m^2 with LV 400 mg/m^2 in 120 min; infusional 5-FU 3200 mg/m^2 in 46h.

- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR, toxicity, rates of R0/1 resection, postoperative morbidity

NCT02162563. Punt. ASCO 2022. Abstr LBA35(

- At a median follow-up of 41 mo, OS data not yet mature
- PFS subgroup analyses showed no significant interaction between baseline unresectability or mutation status (*RAS*, *BRAF*^{V600E}, WT, and right-sided) and PFS

Parameter	FOLFOX/FOLFIRI + Bevacizumab (n = 147)	FOLFOXIRI + Bevacizumab (n = 144)	HR (95% CI)	*P* Value
Median PFS, mo	9.0	10.6	0.77 (0.60-0.99)	.038
Median no. of cycles,* n (range)	8 (1-16)	8 (1-15)	--	
ORR, %	33.3	53.5	--	<.001

Parameter	FOLFOX/FOLFIRI + Bevacizumab (n = 147)	FOLFOXIRI + Bevacizumab (n = 144)	*P* Value
Resection with or without ablation, %	46	57	.08
Rate of R0/1 resection ± ablation, % ▪ Any ▪ 2-stage surgery ± PVE	 37 16	 51 32	 .02 .04

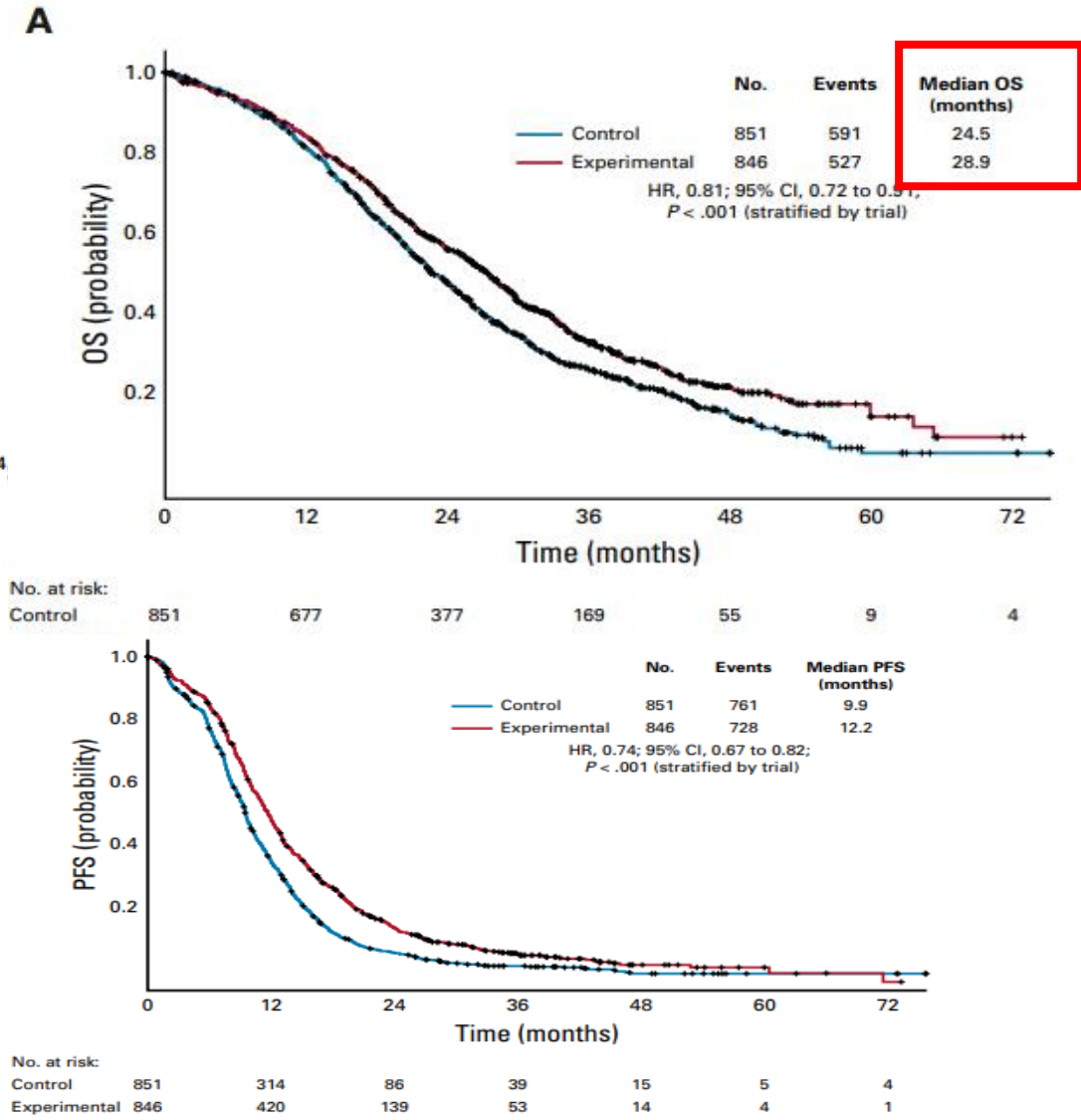
Individual Patient Data Meta-Analysis of FOLFOXIRI Plus Bevacizumab Versus Doublets Plus Bevacizumab as Initial Therapy of Unresectable Metastatic Colorectal Cancer

Chiara Cremolini, MD, PhD[1]; Carlotta Antoniotti, MD[1]; Alexander Stein, MD[2]; Johanna Bendell, MD[3]; Thomas Gruenberger, MD[4]
Daniele Rossini, MD[1]; Gianluca Masi, MD[1]; Elena Ongaro, MD[1,5]; Herbert Hurwitz, MD[6]; Alfredo Falcone, MD[1];
Hans-Joachim Schmoll, MD, PhD[7]; and Massimo Di Maio, MD[8]

J Clin Oncol 2020

TABLE 1. Characteristics of the Five Randomized Trials Included in the Meta-Analysis

Characteristic	TRIBE	OLIVIA	CHARTA	STEAM	TRIBE2
Phase of the study	III	II	II	II	III
Country	Italy	Austria, France, Spain, and United Kingdom	Germany	United States	Italy
Treatment of control arm	FOLFIRI + Bev	FOLFOX + Bev	FOLFOX + Bev	FOLFOX + Bev	FOLFOX + Bev
Primary end point	PFS	Overall resection rate	PFR at 9 months	ORR and PFS	PFS2
Planned No. of participants	(n = 450)	(n = 80)	(n = 250)	(n = 280)[a]	(n = 654)
Actual No. of participants	(N = 508)	(N = 80)	(N = 242)	(N = 280)[a]	(N = 679)



Vantaggio significativo della tripletta + Bevacizumab se confrontata con doppietta (Oxaliplatino/Irinotecan) + Bevacizumab in termini di OS (28.9 vs 24.5 mesi) e di PFS (12.2 vs 9.9 mesi)

ORR: 64.5% vs 53.6% ($p < 0.001$) resezioni R0 16.4% vs 11.8% ($p < 0.007$)

TRIPLETE: Study Design

- Randomized, open-label phase III trial conducted at 57 centers in Italy

Stratification by ECOG PS, primary tumor location, metastatic spread

Patients aged 18-75 yr with unresectable *RAS* and *BRAF* WT mCRC; no previous treatment for metastatic disease*; ECOG PS 0-2
(N = 435)
88% left sided tumours

mFOLFOXIRI + Panitumumab
for up to 12 cycles
(n = 218)

5-FU/LV + Panitumumab
Until PD

mFOLFOX6 + Panitumumab
for up to 12 cycles
(n = 217)

5-FU/LV + Panitumumab
Until PD

mFOLFOXIRI dosing: LV 200 mg/m^2, 5-FU 2400 mg/m^2, oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2. Panitumumab dosed at 6 mg/kg.
*Adjuvant oxaliplatin-containing chemotherapy not allowed; adjuvant fluoropyrimidine monotherapy allowed if >6 mo between end of therapy and relapse.

- **Primary endpoint:** ORR
- **Key secondary endpoints:** depth of response, early tumor shrinkage, R0 resection rate, PFS, OS

Cremolini. ASCO 2022. Abstr LBA3505. Rossini. JCO. 2022;[Epub].

TRIPLETE: Efficacy

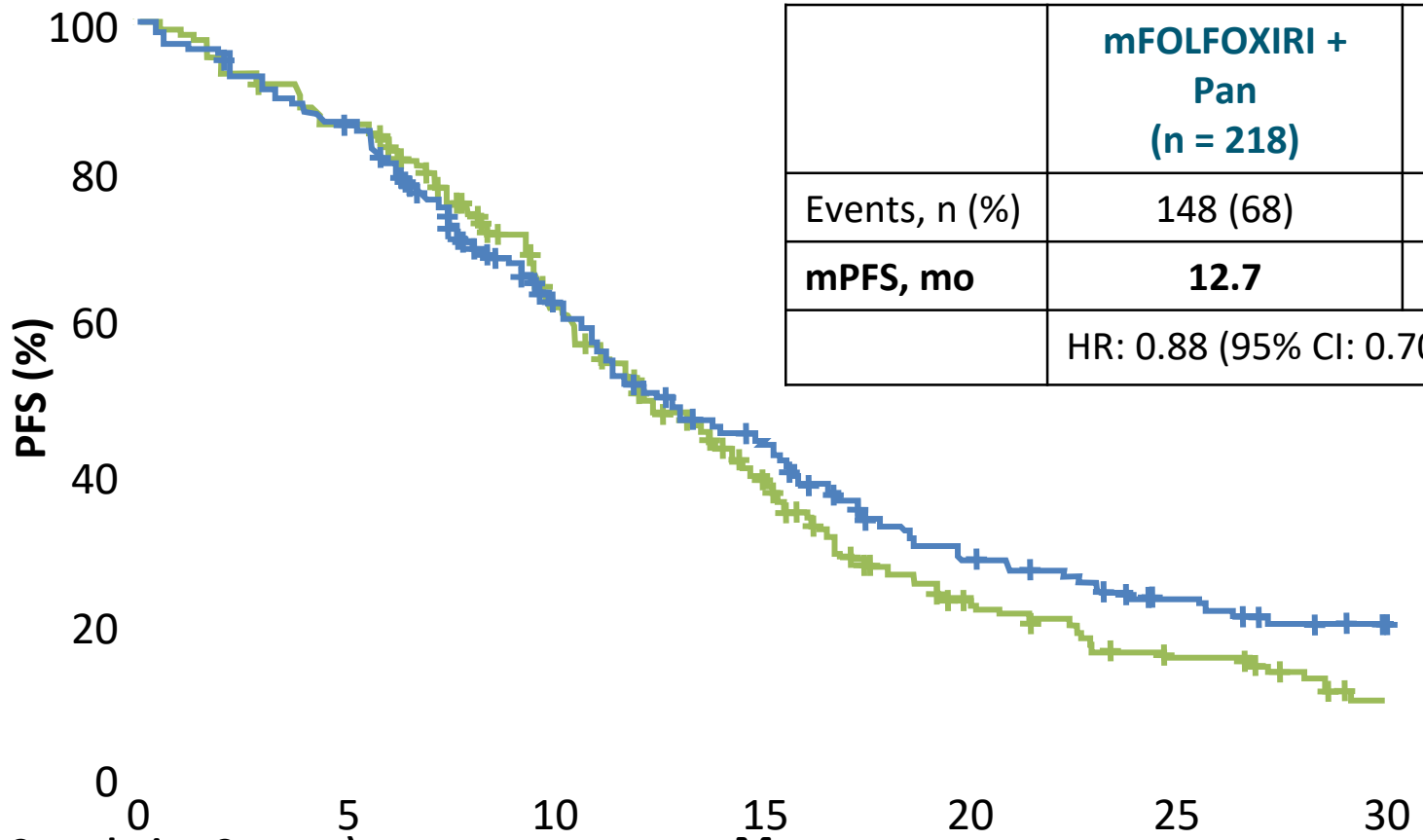
Nessun vantaggio in OR nella tripletta + Pan vs FOLFOX + Pan

Efficacy Outcome	mFOLFOXIRI + Panitumumab (n = 218)	mFOLFOX6 + Panitumumab (n = 217)	OR (95% CI)	*P* Value
ORR, %	73	76	0.87 (0.56-1.34)	.526
Best response, % ▪ CR ▪ PR ▪ SD ▪ PD ▪ Not assessed	 7 66 18 5 4	 7 69 17 5 2		
Median depth of response,* %	48	47		.845
Early tumor shrinkage,† %	57	58	0.97 (0.66-1.42)	.878
R0 resection, %	25	29	0.81 (0.53-1.23)	.317

*Relative change in the sum of the longest diameters of target lesions at the nadir in the absence of new lesions or progression of nontarget lesions.
†≥20% decrease in the sum of the diameters of RECIST target lesions after 8 wk.

Cremolini. ASCO 2022. Abstr LBA3505. Rossini. JCO. 2022;[Epub].

TRIPLETE: Progression-Free Survival



	mFOLFOXIRI + Pan (n = 218)	mFOLFOX6 + Pan (n = 217)
Events, n (%)	148 (68)	157 (72)
mPFS, mo	**12.7**	**12.3**
	HR: 0.88 (95% CI: 0.70-1.11; *P* = .277)	

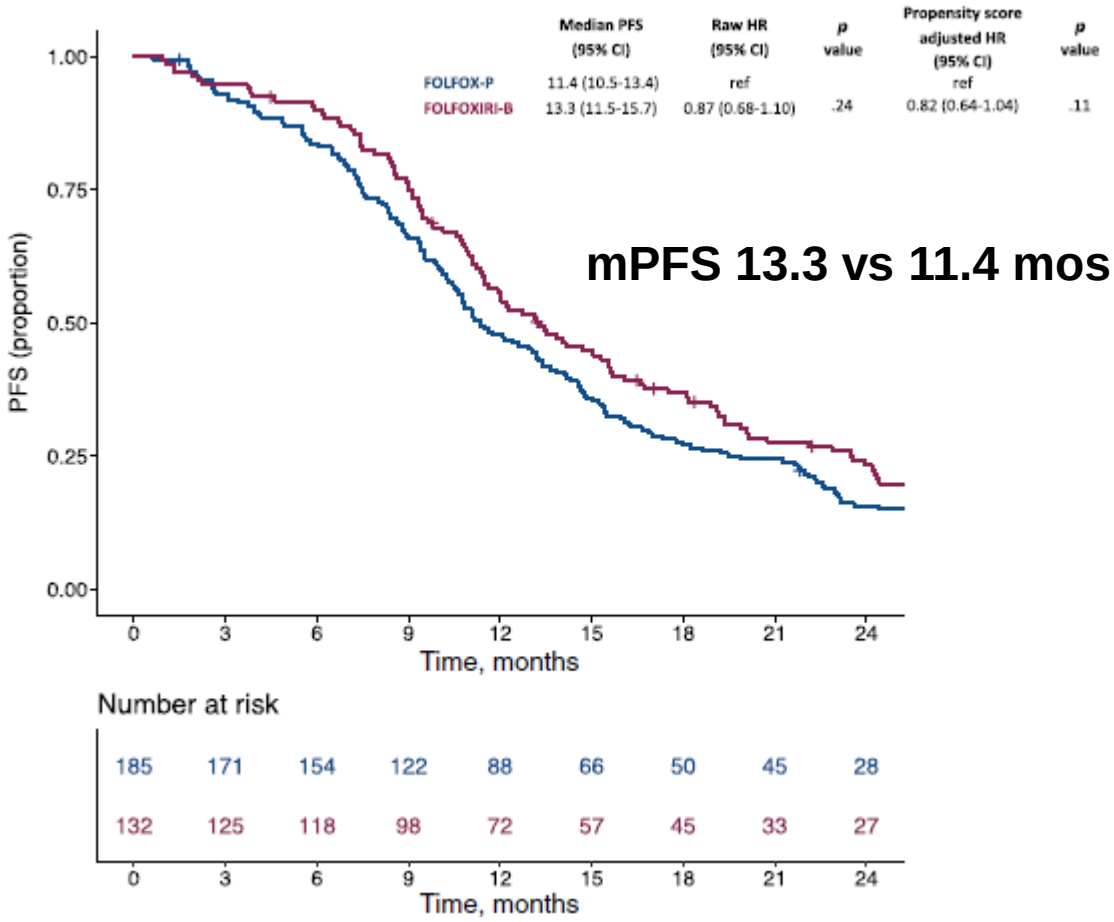
No. at Risk (No. Cumulative Censors)							
Control Group	217 (0)	183 (5)	117 (24)	67 (34)	31 (45)	18 (48)	8 (53)
Experimental Group	218 (0)	181 (7)	114 (28)	73 (38)	43 (43)	30 (49)	20 (55)

Cremolini. ASCO 2022. Abstr LBA3505. Rossini. JCO. 2022;[Epub].

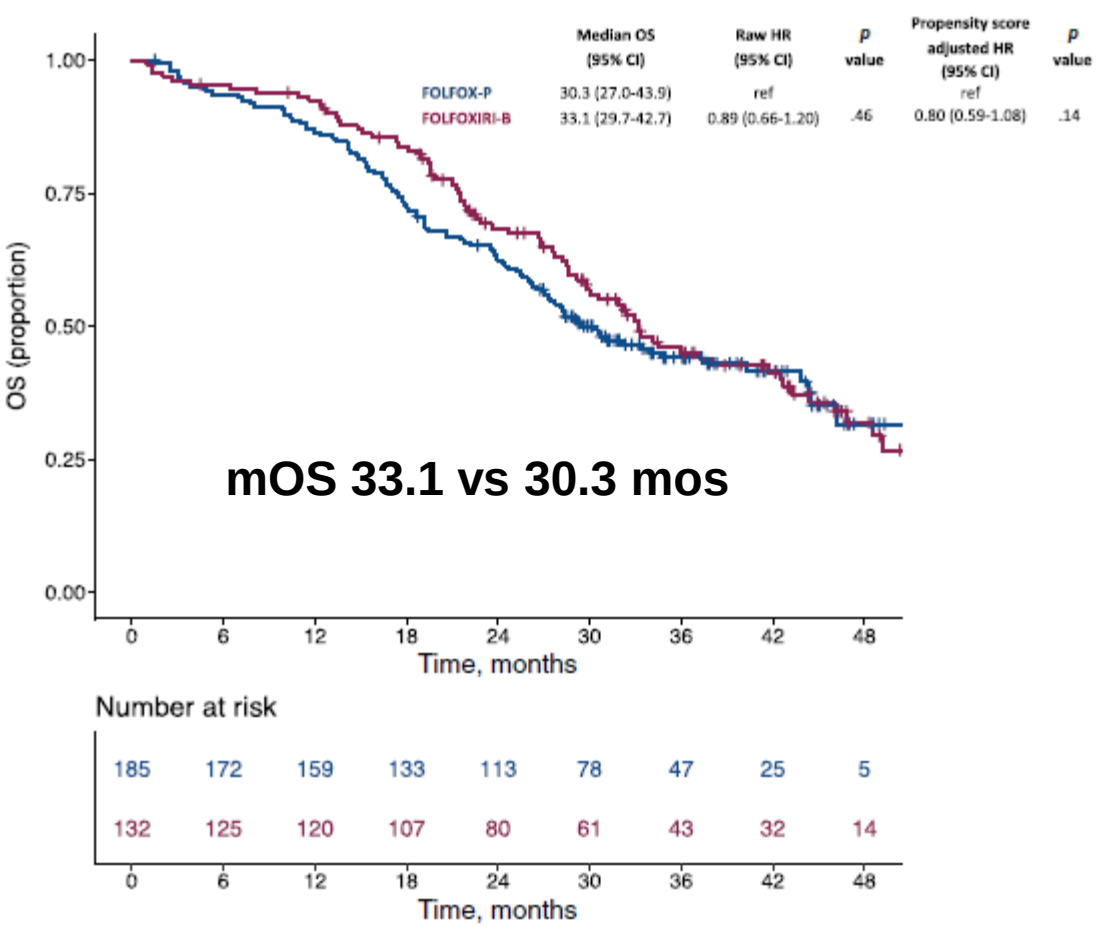
FOLFOXIRI-Bevacizumab or FOLFOX-Panitumumab in Patients with Left-Sided *RAS*/*BRAF* Wild-Type Metastatic Colorectal Cancer: A Propensity Score-Based Analysis

- The Oncologist 2020 -

Filippo Pietrantonio,[a,b,†] Giovanni Fucà,[a,†] Daniele Rossini,[c,d] Hans-Joachim Schmoll,[e] Johanna C. Bendell,[f] Federica Morano,[a] Carlotta Antoniotti,[c,d] Salvatore Corallo,[a] Beatrice Borelli,[c,d] Alessandra Raimondi,[a] Federica Marmorino,[c,d] Monica Niger,[a] Alessandra Boccaccino,[c,d] Gianluca Masi,[c,d] Sara Lonardi,[g] Luca Boni,[h] Filippo de Braud,[a,b] Maria Di Bartolomeo,[a] Alfredo Falcone,[c,d] Chiara Cremolini[c,d]



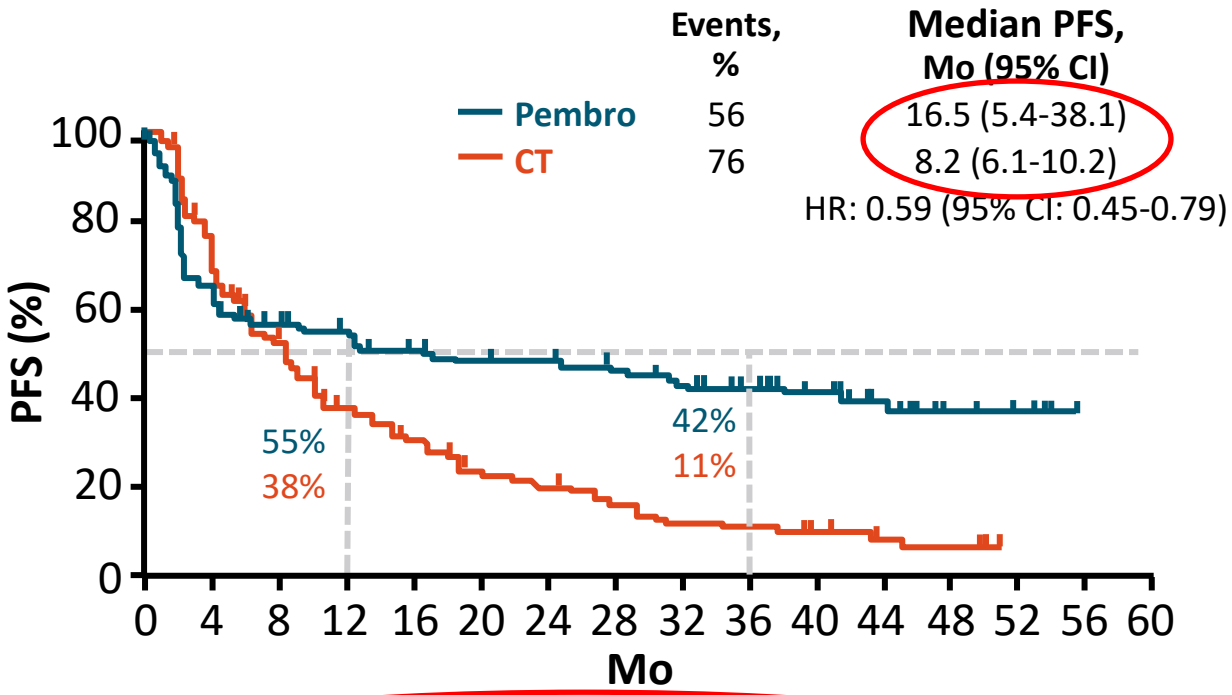
mPFS 13.3 vs 11.4 mos

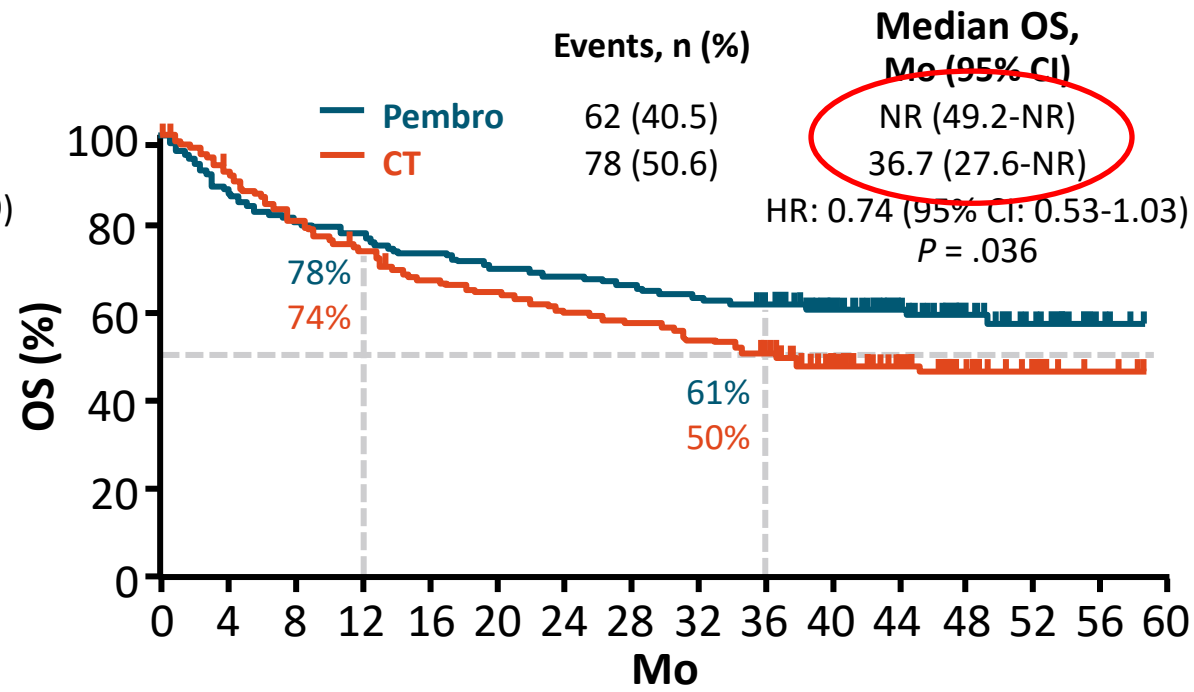


mOS 33.1 vs 30.3 mos

KEYNOTE-177: First-line Pembrolizumab vs Chemotherapy in MSI-H/dMMR Metastatic CRC

- Randomized, open-label phase III study of pembrolizumab vs CT* for patients with treatment-naive MSI-H/dMMR mCRC (N = 307)





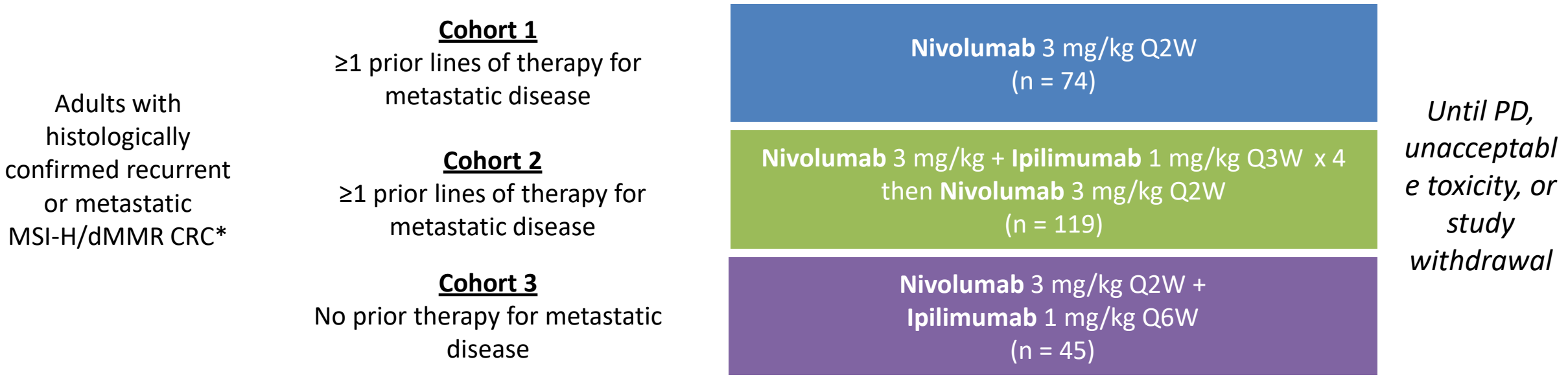
- ORR: pembrolizumab, 45%; CT, 33%

*mFOLFOX-6 ± bevacizumab or cetuximab or FOLFIRI ± bevacizumab or cetuximab.

André. ASCO 2021. Abstr 3500.

CheckMate 142 Extended Follow-up: Study Design

- Ongoing, multicohort, nonrandomized phase II study



- **Primary endpoint:** ORR per investigator assessment (RECIST v1.1)
- **Secondary endpoints:** DCR, DoR, PFS per investigator and BICR, safety

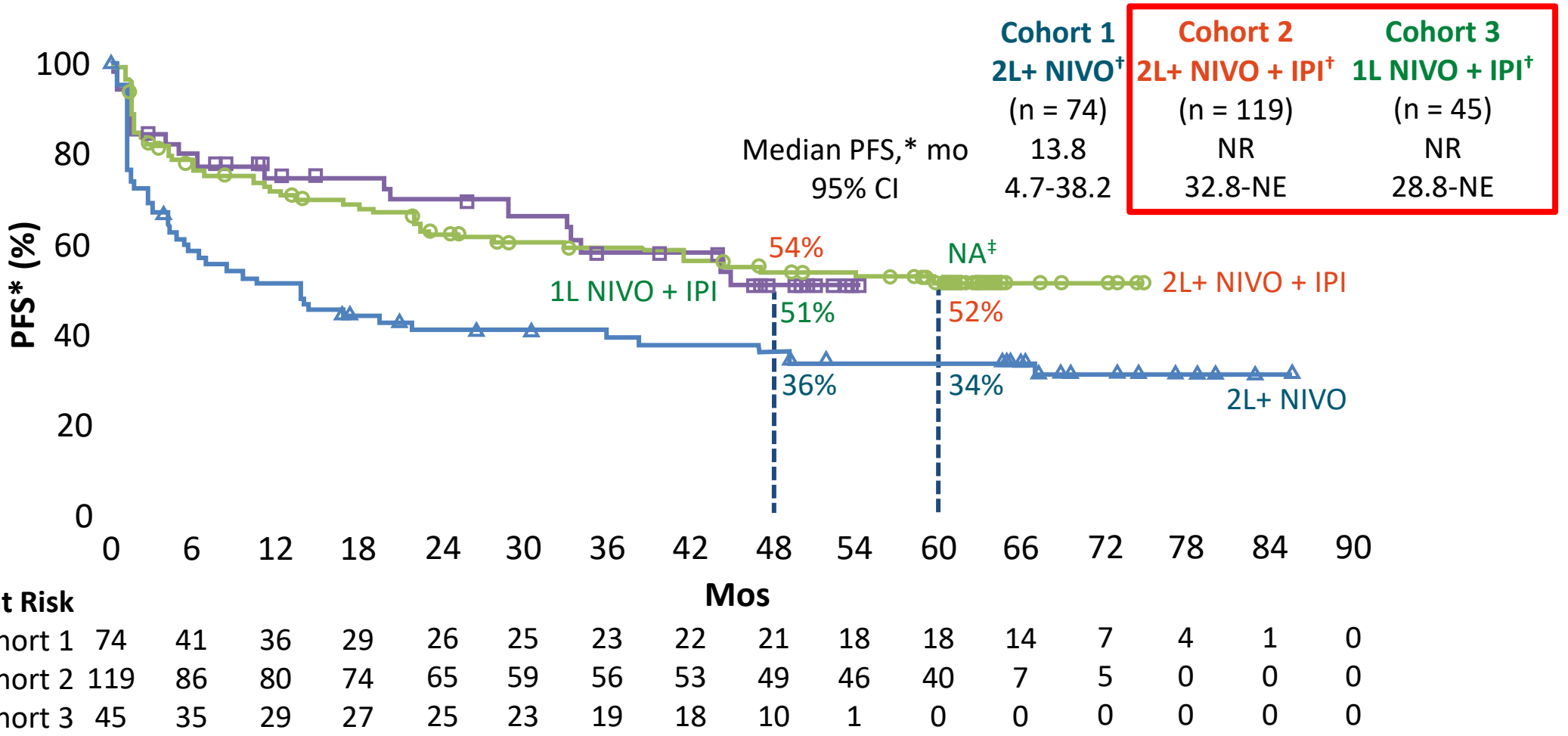
CheckMate 142 Extended Follow-up: Response (238 pts)

Outcome	Cohort 1 (n = 74)	Cohort 2 (n = 119)	Cohort 3 (n = 45)
ORR, n (%) ▪ 95% CI	29 (39) 28-51	77 (65) 55-73	32 (71) 56-84
Best overall response, n (%) ▪ CR ▪ PR ▪ SD ▪ PD ▪ ND	 12 (16) 17 (23) 22 (30) 19 (26) 4 (5)	 20 (17) 57 (48) 25 (21) 14 (12) 3 (3)	 9 (20) 23 (51) 6 (13) 7 (16) 0
DCR,* n (%) ▪ 95% CI	51 (69) 57-79	96 (81) 72-87	38 (84) 71-94
Median TTR, mo (range)	2.8 (1.2-46.3)	2.8 (1.1-37.1)	2.7 (1.2-27.7)
Median DoR, mo (95% CI) ▪ 36-mo rate, % (95% CI) ▪ 42-mo rate, % (95% CI) ▪ 60-mo rate, % (95% CI)	NR (NE) 81 (60-92) 77 (55-89) 77 (55-89)	NR (NE) 79 (67-87) 75 (63-84) 73 (60-82)	NR (41.5-NE) 75 (52-88) 69 (44-84) NA

*CR, PR, or SD for ≥12 wk.

Overman. ASCO 2022. Abstr 3510.

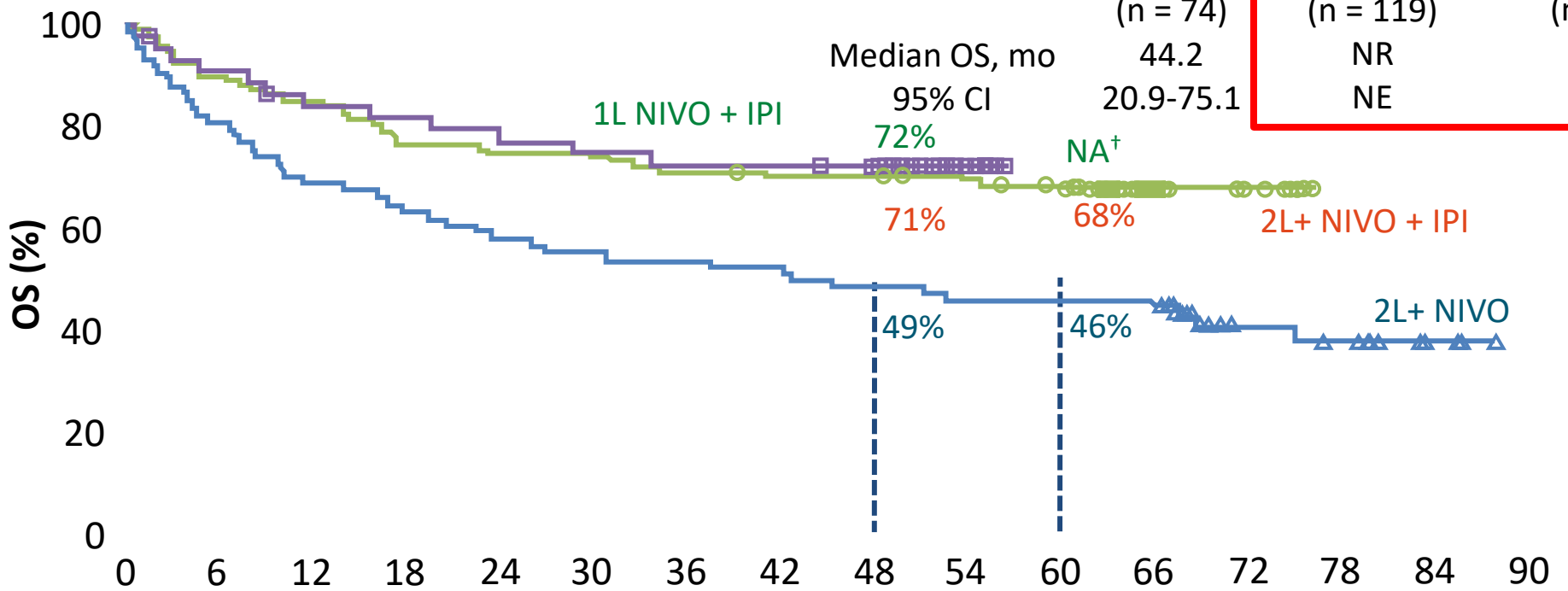
CheckMate 142 Extended Follow-up: PFS



*Per investigator. †Cohorts not randomized, nor was trial designed for formal comparison. ‡Median follow-up for cohort 3: 47.6 mo.

Overman ASCO 2022. Abstr 3510.

CheckMate 142 Extended Follow-up: OS



No. at Risk

Cohort 1	74	60	51	48	43	41	40	39	36	34	34	34	1	11	4	0
Cohort 2	119	107	101	92	89	89	85	83	83	80	76	23	14	0	0	0
Cohort 3	45	40	36	35	34	32	31	31	29	11	0	0	0	0	0	0

*Cohorts not randomized, nor was trial designed for formal comparison. †Median follow-up for cohort 3: 47.6 mo.

Overman ASCO 2022. Abstr 3510.