18as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2023
Madrid, 22 y 23 de noviembre de 2023

Anti-EGFR en primera línea de CCRm: entre la lateralidad y la selección molecular

Ana Mª López Muñoz
Hospital Universitario de Burgos

FIRST LINE

Selecting an appropriate upfront treatment is a cornerstone in the therapeutic pathway of mCRC patients

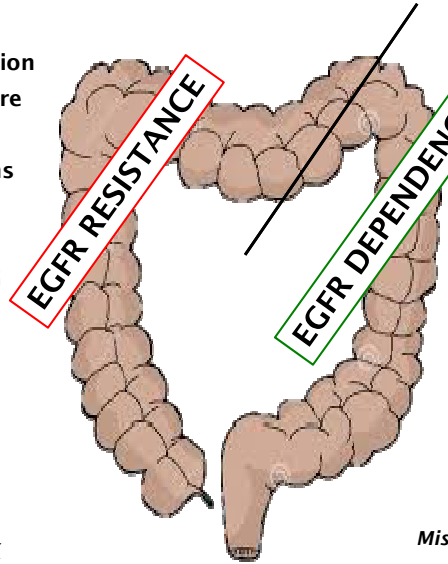
The «best» chemotherapy

The «best» targeted agent

Anti-EGFR vs -VEGF mAb in first-line treatment for patients with RAS WT mCRC

	RAS WT population (n)	ETS (%)	Median DpR (%)	ORR (%)	Median PFS months	Median OS months
FIRE-3[14]						
Cetuximab + FOLFIRI	199	68.2	48.9	65	10.3	33.1
Bevacizumab + FOLFIRI	201	49.1	32.3	58.7	10.2	25
HR or OR (95% CI)		2.22 (1.41–3.47) *P*=0.0005	NA; *P*<0.001	1.33 (0.88–1.99) *P*=0.18	0.97 (0.78–1.20) *P*=0.77	0.70 (0.54–0.90) *P*=0.0059
CALGB/SWOG 80405[17,20]						
Cetuximab + chemotherapy	270	NR	NR	69	11.2	32
Bevacizumab + chemotherapy	256	NR	NR	54	11.0	31.2
HR or OR (95% CI)				NR; *P*<0.01	1.03 (0.86–1.24) *P*=0.71	0.88 (0.72–1.08) *P*=0.24
PEAK[21]						
Panitumumab + FOLFOX	88	64	65	65	12.8	36.9
Bevacizumab + FOLFOX	82	45	46.3	60	10.1	28.9
HR or OR (95% CI)		1.99 (0.99–4.10); *P*=0.052	NA; *P*=0.0018	1.12 (0.56–2.22); *P*=0.86	0.68 (0.48–0.96); *P*=0.029	0.76 (0.53–1.11); *P*=0.15

Right versus Left: Molecular make-up



BRAF V600E mutation
BRAF-like signature
RAS mutations
PIK3CA mutations
dMMR
CIMP-high
Low AREG-EREG expression

CMS1(Immune)

miR-31-3p high

EGFR promoter methylation

ALK/ROS1/NTRK rearrangements

HER-2 overexpression

High AREG-EREG expression

EGFR amplification

miR-31-3p low

Lee et al., Br J Can '16
Missiaglia et al., Ann Oncol '14
Guinney et al., Nat Med '15
Laurent-Puig et al., ESMO '16
Puzzoni et al, ASCO GI '17
Pietrantonio et al, JNCI '17

Primary Tumour Location

WT *RAS* (pooled)	Total LEFT	Total RIGHT
OS HR (95% CI), right vs left P-value	0.75 (0.67–0.84) < 0.001 Favours CTx + anti-EGFR	1.12 (0.87–1.45) 0.381 Favours CTx ± bevacizumab
$HR_{Interaction}$ (95% CI) P-value $HR_{Interaction}$†	1.50 (1.19–1.88) P < 0.001	
PFS HR (95% CI), right vs left P-value	0.76 (0.70–0.87) < 0.001 Favours CTx + anti-EGFR	1.12 (0.87–1.44) 0.365 Favours CTx ± bevacizumab
$HR_{Interaction}$ (95% CI) P-value $HR_{Interaction}$†	1.43 (1.14–1.80) P = 0.002	
ORR OR (95% CI), right vs left P-value	2.12 (1.77–2.55) < 0.001 Favours CTx + anti-EGFR	1.47 (0.94–2.29) 0.089 Favours CTx + anti-EGFR
$OR_{Interaction}$ (95% CI) P-value $OR_{Interaction}$†	0.69 (0.46–1.04) P = 0.07	

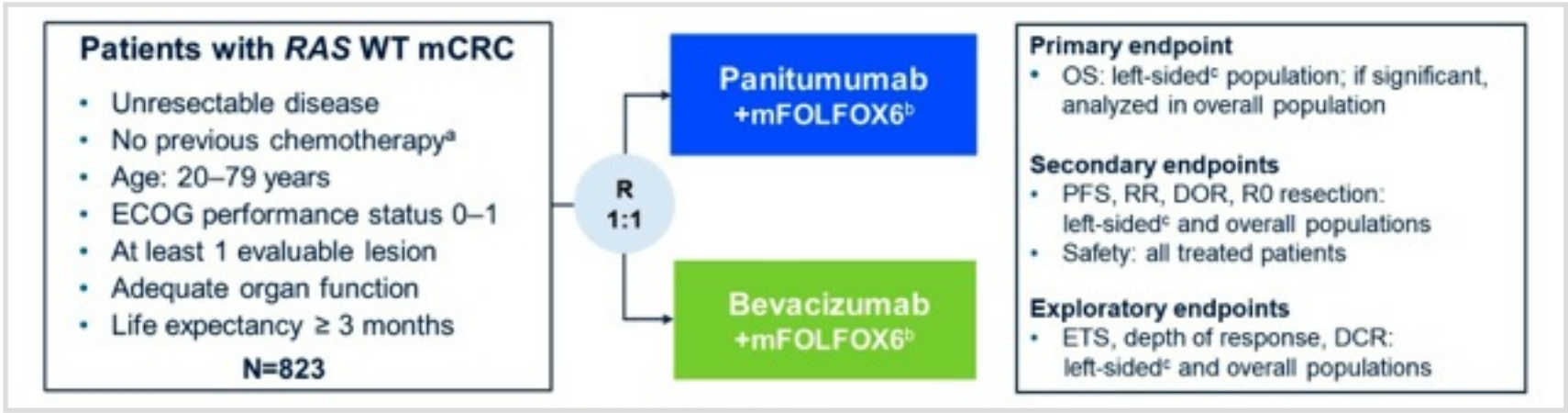
HR < 1 favours CTx + anti-EGFR; HR > 1 favours CTx ± bevacizumab;
OR > 1 favours CTx + anti-EGFR; OR < 1 favours CTx ± bevacizumab.

D. Arnold. Annals of Oncology 2017

2022 ASCO ANNUAL MEETING

Panitumumab plus mFOLFOX6 versus Bevacizumab plus mFOLFOX6 as first-line treatment in patients with *RAS* wild-type metastatic colorectal cancer: results from the phase 3 PARADIGM trial

Panitumumab vs Bevacizumab Added to Standard First-line Chemotherapy and Overall Survival Among Patients With *RAS* Wild-type, Left-Sided Metastatic Colorectal Cancer
A Randomized Clinical Trial

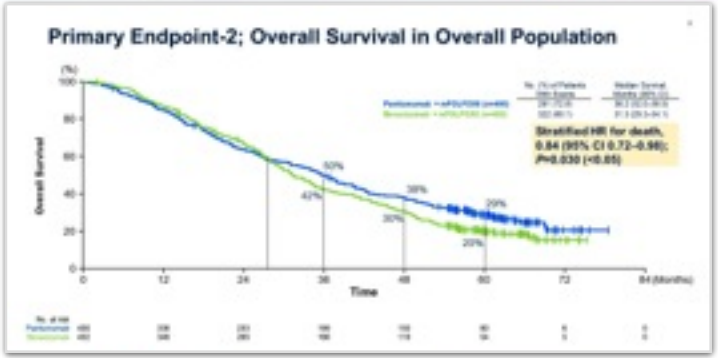


Takayuki Yoshino. ASCO 2022

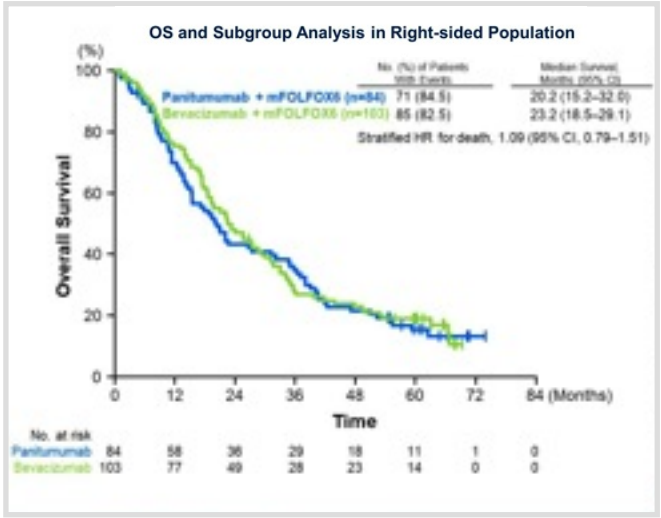
Jun Watanabe et al. JAMA 2023; 329(15):1271-1282.

Primary Endpoint-1; Overall Survival in Left-sided Population

Primary Endpoint-2; Overall Survival in Overall Population



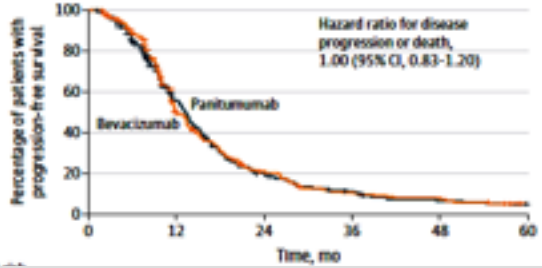
OS and Subgroup Analysis in Right-sided Population



Takayuki Yoshino. ASCO 2022

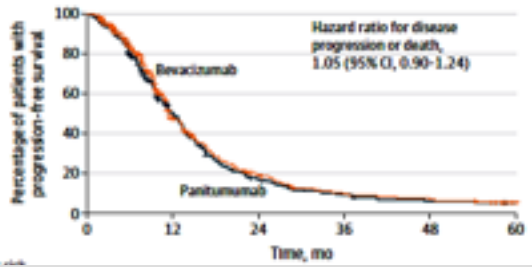
Participants with left-sided tumors

	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 312)	217 (69.6)	13.1 (11.6-14.5)
Bevacizumab plus mFOLFOX6 (n = 292)	224 (76.7)	11.9 (11.3-13.5)



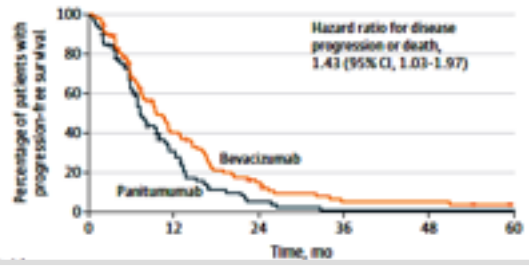
Overall study population

	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 400)	294 (73.5)	12.2 (10.8-13.2)
Bevacizumab plus mFOLFOX6 (n = 402)	316 (78.6)	11.4 (11.2-13.2)



Participants with right-sided tumors

	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 84)	73 (86.9)	7.2 (6.6-9.9)
Bevacizumab plus mFOLFOX6 (n = 103)	85 (82.5)	9.4 (7.6-13.0)



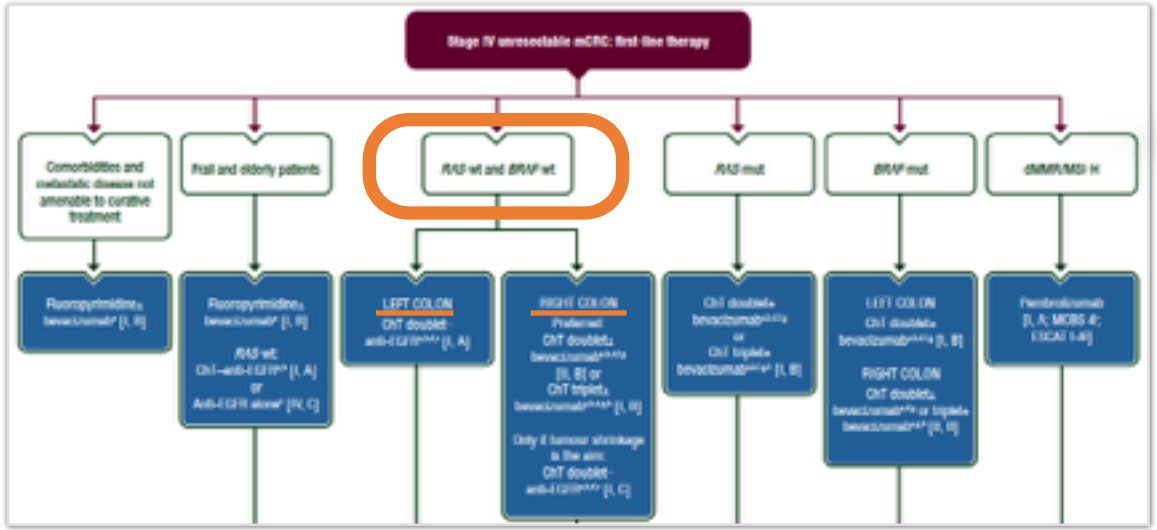
Outcomes	Panitumumab plus mFOLFOX6	Bevacizumab plus mFOLFOX6
Participants with left-sided primary tumors	n = 312	n = 292
Response rate, No./total (%) [95% CI]	247/308 (80.2) [75.3-84.5]	197/287 (68.6) [62.9-74.0]
Overall population[b]	n = 400	n = 402
Response rate, No./total (%) [95% CI]	295/394 (74.9) [70.3-79.1]	267/397 (67.3) [62.4-71.9]
Participants with right-sided primary tumors	n = 84	n = 103
Response rate, No./total (%) [95% CI]	45/82 (54.9) [43.5-65.9]	65/103 (63.1) [53.0-72.4]

Jun Watanabe et al. JAMA 2023; 329(15):1271-1282.

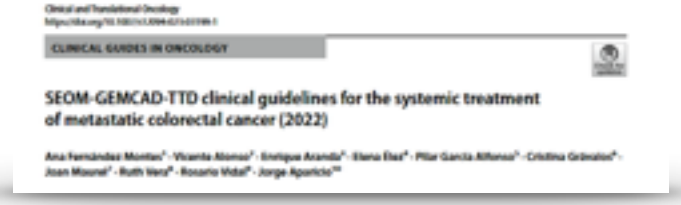
ESMO
ANNALS OF ONCOLOGY

SPECIAL ARTICLE

Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

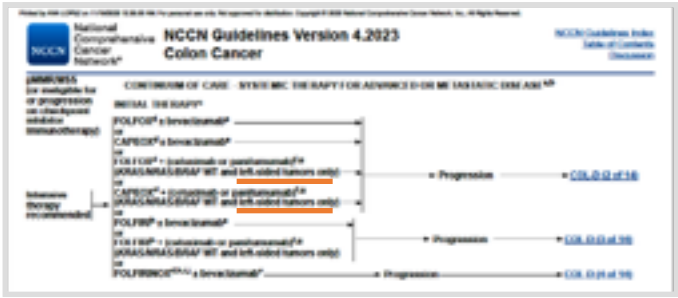


A. Cervantes. Annals of Oncology 2023; 34: 10-32



CLINICAL GUIDES IN ONCOLOGY

SEOM-GEMCAD-TTD clinical guidelines for the systemic treatment of metastatic colorectal cancer (2022)



Primary **tumour location** has emerged as a crucial driver in the treatment algorithm of **mCRC**

Primary tumour side as a driver for treatment choice in *RAS* wild-type metastatic colorectal cancer patients: a systematic review and pooled analysis of randomised trials

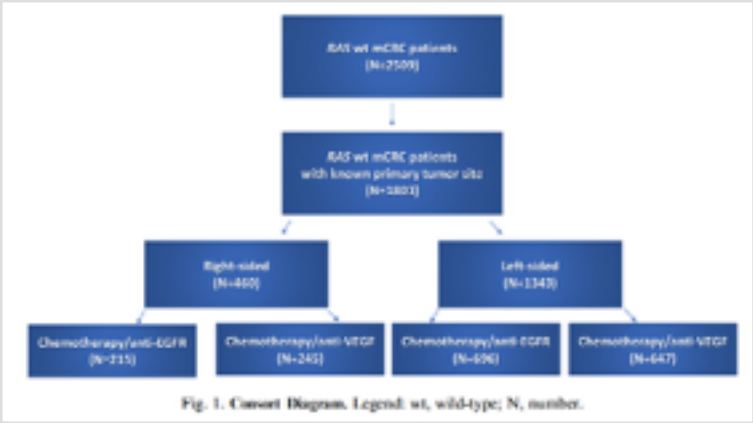


Fig. 1. Consort Diagram. Legend: wt, wild-type; N, number.

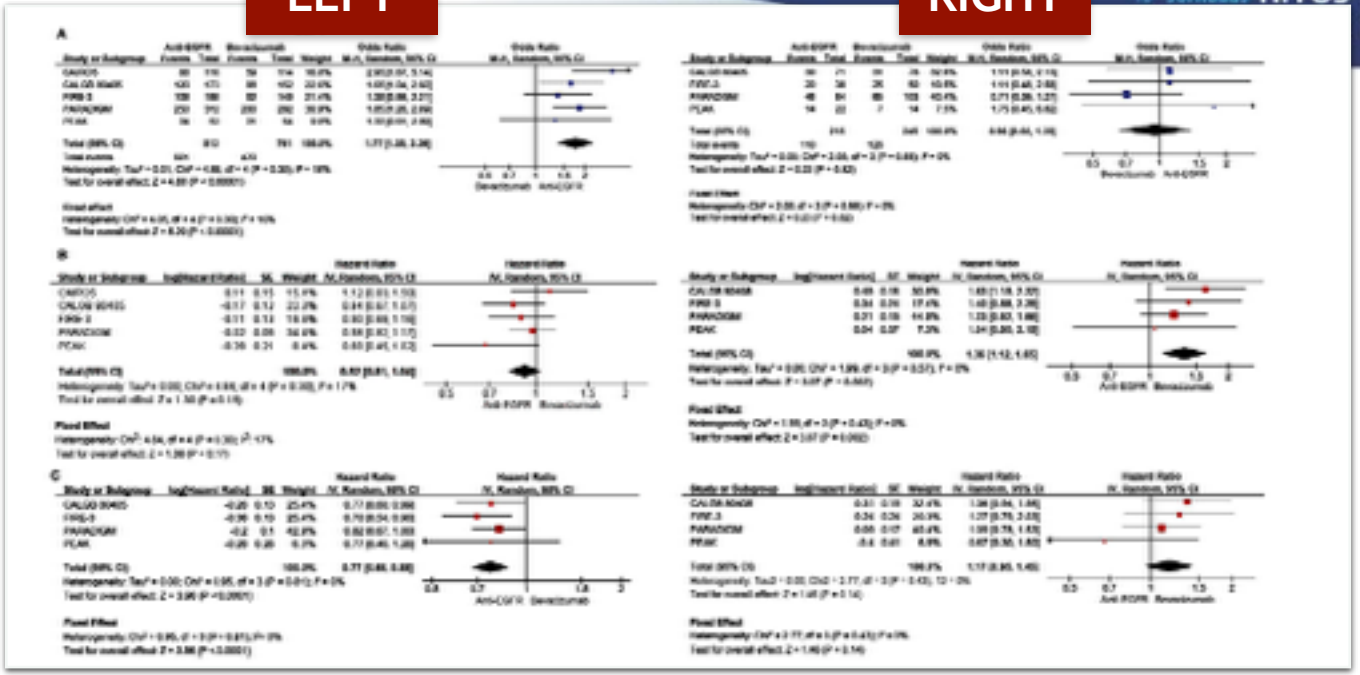
Table 1
Distribution of patients by the treatment arm and primary tumour site among the selected trials.

Trials	Overall Population N = 2739		Left-sided N = 1562		Right-sided N = 471		Unknown primary location N = 706
	Anti-EGFR *N* = 1381 (50%)	Bevacizumab *N* = 1358 (50%)	Anti-EGFR *N* = 806 (52%)	Bevacizumab *N* = 756 (48%)	Anti-EGFR *N* = 221 (47%)	Bevacizumab *N* = 250 (53%)	Anti-EGFR + Bevacizumab *N* = 706 (100%)
CALGB/SWOG 80405	578	559	173	152	71	78	663
FIRE-3	199	201	158	149	38	50	5
PEAK	88	82	53	54	22	14	27
PARADIGM	400	402	312	292	84	103	11
CAIRO5	116	114	110	109	6	5	0

D. Rossini. European Journal of Cancer 2023 (184): 106-116

LEFT

RIGHT



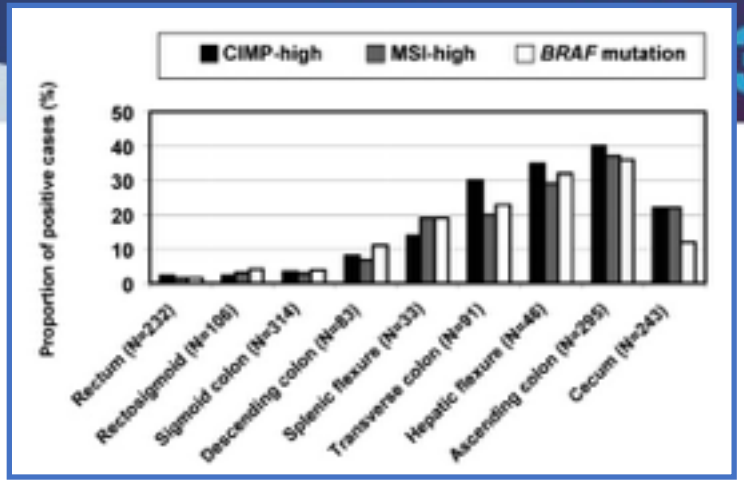
Corroborates the role of the primary tumour location in the choice of the upfront therapy for RAS wt mCRC patients, leading to strongly recommend anti-EGFRs in left-sided tumours and to prefer bevacizumab in the right-sided

In terms of ORR: the suboptimal activity of anti-EGFRs in right-sided patients.

¿¿¿These results challenge the recommendation provided by the latest version of the ESMO guidelines ???

Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal versus distal colorectum

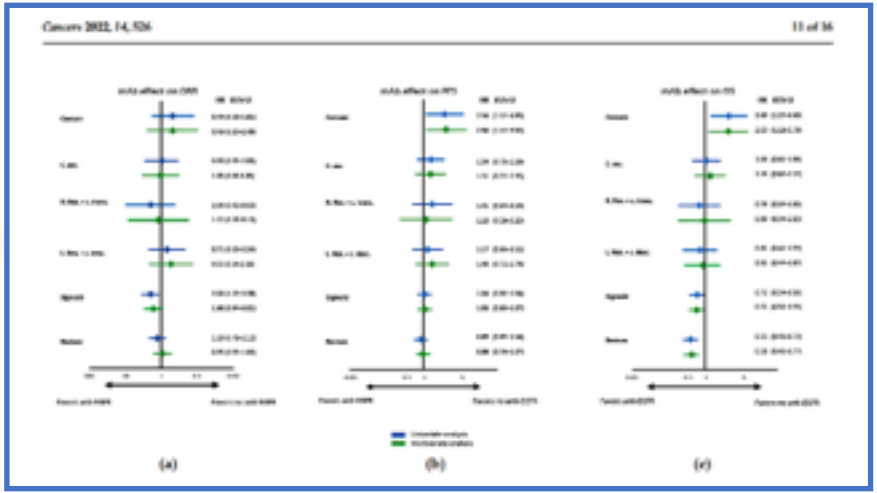
Mai Yamauchi. Gut 2012



Article

Exact Primary Tumor Location in mCRC: Prognostic Value and Predictive Impact on Anti-EGFR mAb Efficacy

Annabel H.S. Alig. Cancers 2022

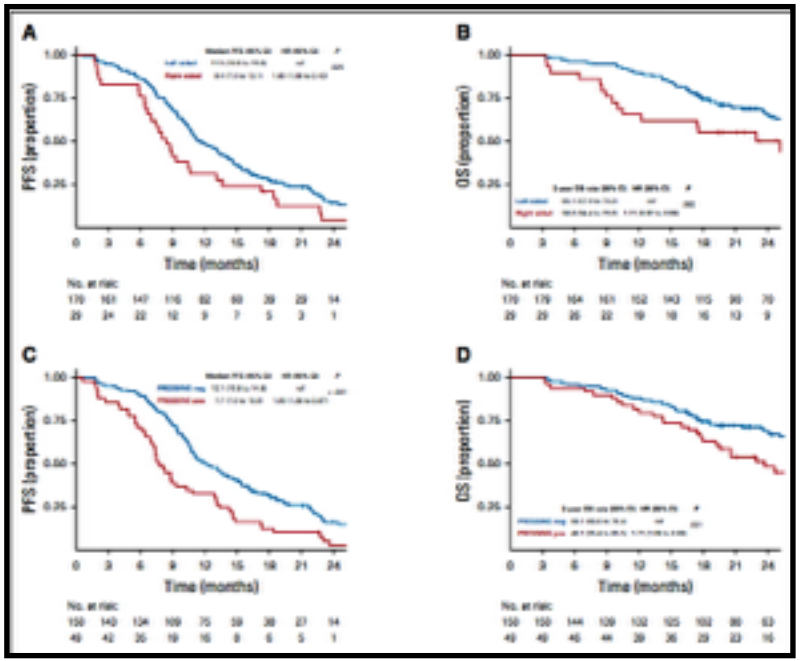


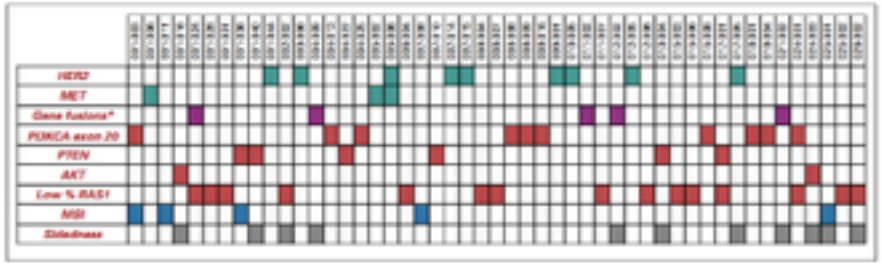
Patients with RAS and BRAF wild-type mCRC and a primary tumor located in the left colon are considered suitable candidates for first-line anti-EGFR treatment in combination with chemotherapy

Despite this SELECTION of patients, resistance to anti-EGFR agents still exists…..

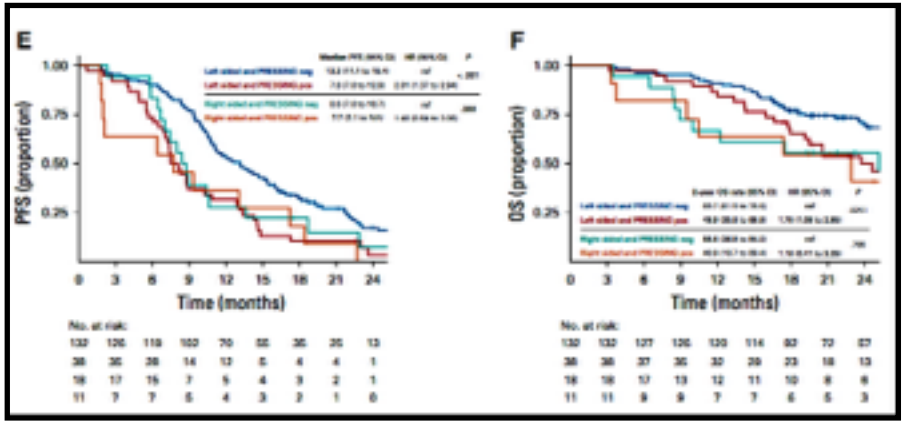
Valentino study

Negative Hyperselection of Patients With *RAS* and *BRAF* Wild-Type Metastatic Colorectal Cancer Who Received Panitumumab-Based Maintenance Therapy



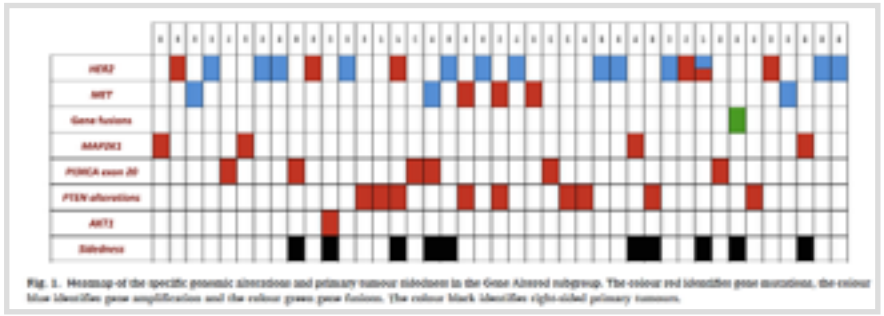


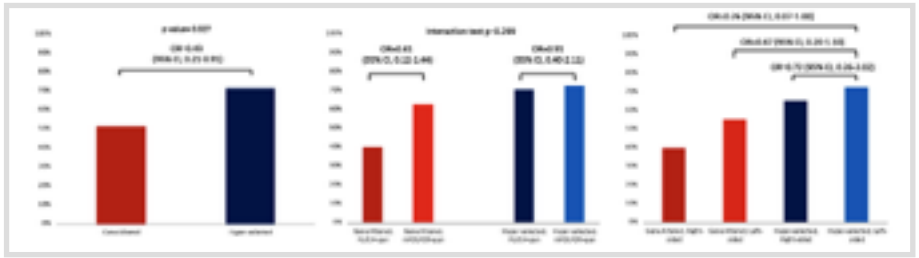
Higher rate of PRESSING positivity in right-sided tumors (37.9%) versus left-sided ones (22.3%; p =.07).

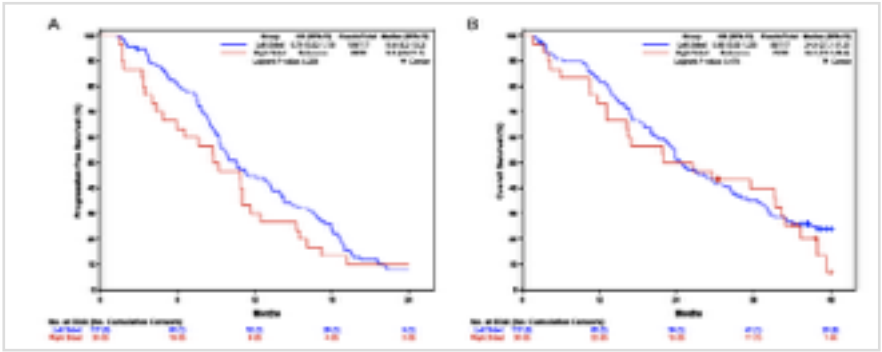


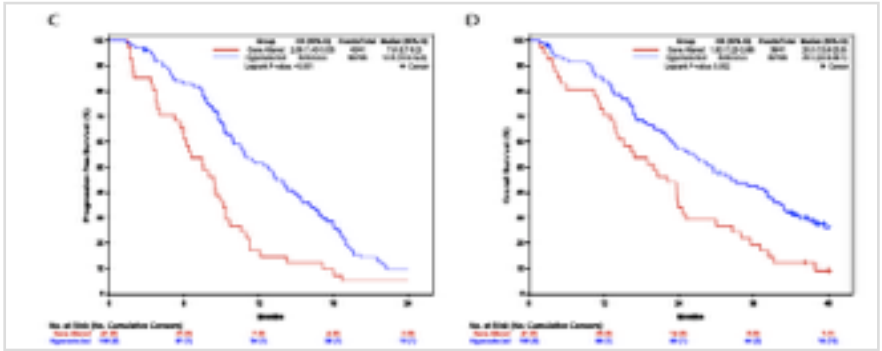
F. Morano. J Clin Oncol 2019; 37:3099-3110.

Negative hyperselection of elderly patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer receiving initial panitumumab plus FOLFOX or 5-FU/LV









F. Pietrantonio. European Journal of Cancer 2023 (195)

SELECTION

HYPERSELECTION

ULTRASELECTION

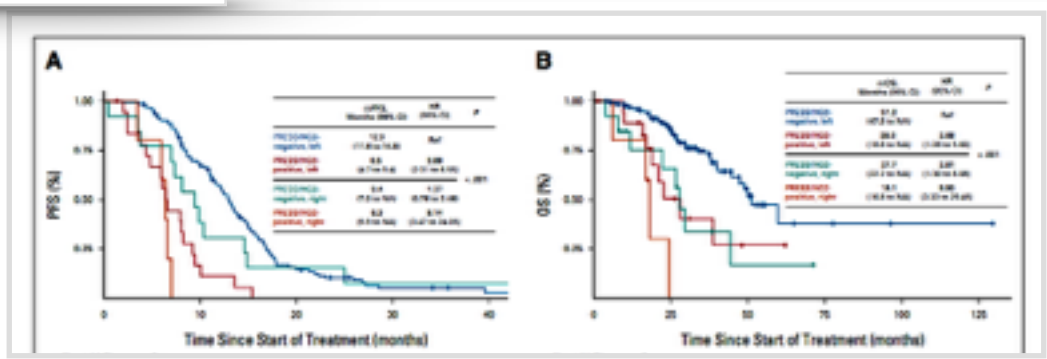
BIOMARKERS

Negative Ultraselection of Patients With *RAS/BRAF* Wild-Type, Microsatellite-Stable Metastatic Colorectal Cancer Receiving Anti–EGFR-Based Therapy

A modest proportion of hyperselected mCRC has intrinsic resistance potentially driven by even rarer genomic alterations

15% (28% R-13% I)

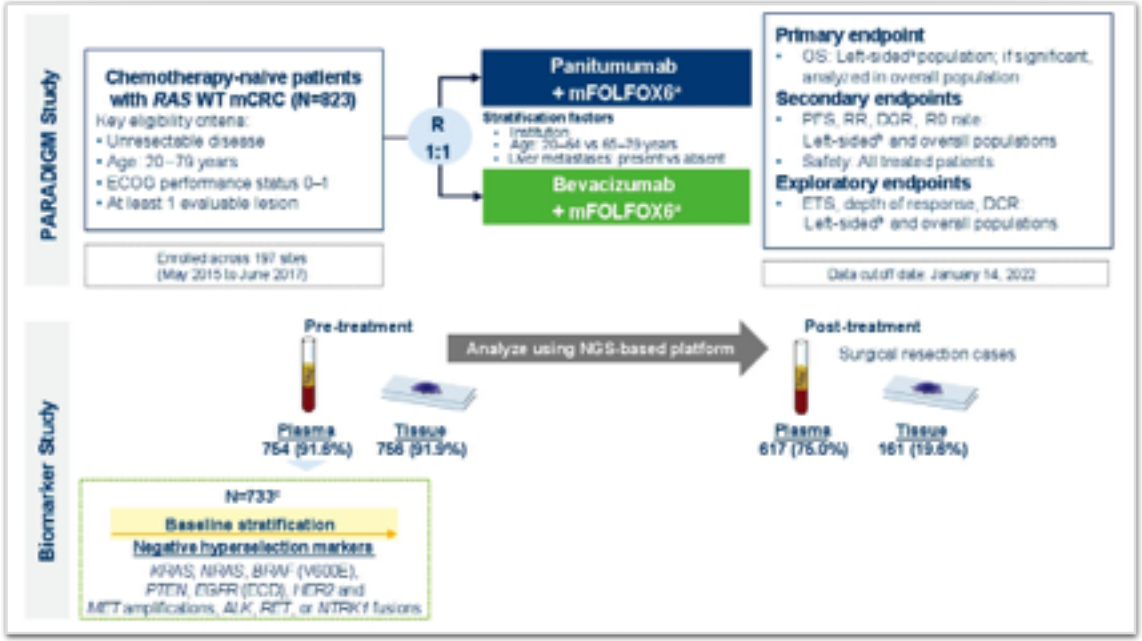
MAP2K4
EGFR
MAP2K1
NF1
PTEN
ARAF
IGF1R
AKT2
ERBB3
FGFR2
KRAS
MAP2K2
NTRK2
TP53
APC
MYC
BCL2L1
FBXW7
PIK3CA
SMAD4
SOX9
SRC
CCND2
AURKA
FGF23
FGF6
ZNF217
ARFRP1
ATM
FLT3
GNAS
RAD21
WWSCL1
KDM5A
CCND1
FGFR1
ATR
PARK2
LYN
MLL2
MUTYH
RBM10
RICTOR
RNF43
ZNF703
ARID1A
ASXL1
BRCA1
PAX5



Patient Subgroup	PFS			OS		
	mPFS, Months (95% CI)	HR (95%CI)	*P*	mOS, Months (95% CI)	HR (95%CI)	*P*
Left-sided/PRESSING2-negative	12.9 (11.6 to 14.5)	Ref	< .001	51.2 (47.3 to NA)	Ref	< .001
Left-sided/PRESSING2-positive	6.5 (4.7 to 9.4)	3.89 (2.31 to 6.55)		28.0 (18.8 to NA)	2.68 (1.28 to 5.60)	
Right-sided/PRESSING2-negative	9.4 (7.0 to NA)	1.37 (0.76 to 2.46)		27.7 (22.2 to NA)	2.81 (1.30 to 6.08)	
Right-sided/PRESSING2-positive	6.3 (5.9 to NA)	9.14 (3.47 to 24.05)		18.1 (16.8 to NA)	9.90 (3.33 to 29.45)	

Giovanni Randon. JCO Precis Oncol 2022 (6)

Negative hyperselection of patients with *RAS* wild-type metastatic colorectal cancer for panitumumab: A biomarker study of the phase III PARADIGM trial



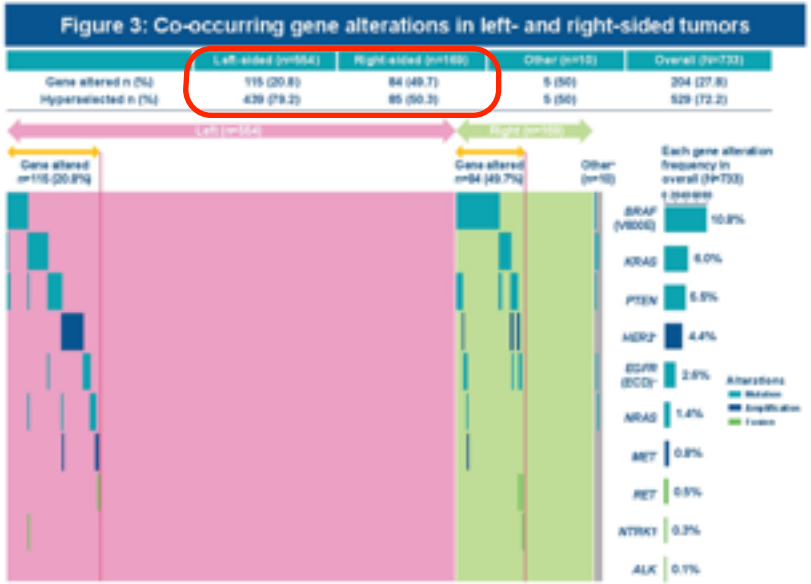
- Hyperselection status (all negative vs gene altered [any positive biomarker]) was correlated with OS, PFS, and RR in the PARADIGM study population

K. Shitara. ASCO-GI 2023

- ctDNA status was evaluable in 91% (733/802) of patients (**Figure 2**; **Figure 3**)
  - 28% of patients had at least 1 gene alteration
  - 72% of patients had no gene alterations and were classified as hyperselected patients
- When stratified by primary tumor sidedness, any gene alteration was detected in 21% of patients with left-sided mCRC and 50% of patients with right-sided mCRC

Number of genetic alterations ctDNA

Gene alteration, n (%)	Overall population (N=733)		Left-sided mCRC (n=554)		Right-sided mCRC (n=169)	
	Panitumumab (n=368)	Bevacizumab (n=365)	Panitumumab (n=287)	Bevacizumab (n=267)	Panitumumab (n=78)	Bevacizumab (n=91)
BRAF (V600E)	43 (11.7)	36 (9.9)	17 (5.9)	8 (3.0)	26 (33.3)	27 (29.7)
KRAS	22 (6.0)	23 (6.3)	11 (3.8)	15 (5.6)	9 (11.5)	6 (6.6)
PTEN	23 (6.3)	17 (4.7)	12 (4.2)	8 (3.0)	10 (12.8)	9 (9.9)
HER2 amplification	19 (5.2)	14 (3.8)	16 (5.6)	11 (4.1)	3 (3.8)	2 (2.2)
EGFR (ECD)	12 (3.3)	7 (1.9)	7 (2.4)	3 (1.1)	5 (6.4)	3 (3.3)
NRAS	10 (2.7)	3 (0.8)	6 (2.1)	2 (0.7)	1 (1.3)	0
MET amplification	3 (0.8)	2 (0.5)	3 (1.0)	2 (0.7)	0	0
RET fusion	2 (0.5)	2 (0.5)	0	2 (0.7)	2 (2.6)	0
NTRK1 fusion	1 (0.3)	1 (0.3)	0	1 (0.4)	1 (1.3)	0
ALK fusion	0	1 (0.3)	0	0	0	1 (1.1)



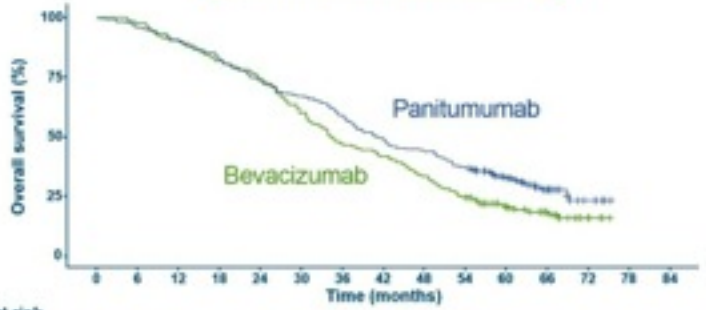
K. Shitara. ASCO-GI 2023

Survival outcomes in the overall population analyzed for ctDNA

Hyperselected

	mOS, months (95% CI)
Panitumumab	41.3 (37.1–48.1)
Bevacizumab	34.4 (31.3–40.3)

HR 0.75 (95% CI, 0.62–0.92)



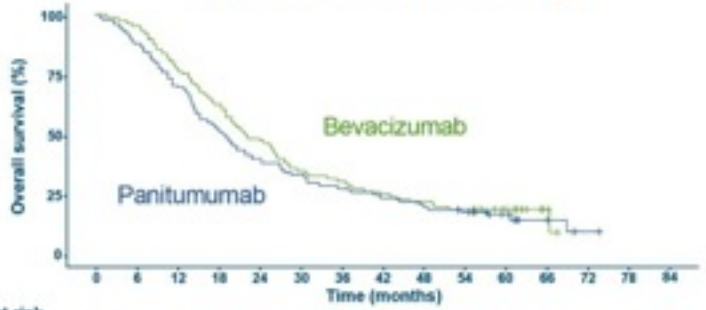
No. at risk

Panitumumab	258	247	232	211	188	172	151	127	113	96	62	23	4	0	0
Bevacizumab	271	263	242	217	196	158	123	109	88	65	36	18	5	0	0

Gene Altered

	mOS, months (95% CI)
Panitumumab	19.0 (14.8–23.0)
Bevacizumab	22.2 (19.1–27.7)

HR 1.14 (95% CI, 0.84–1.54)



No. at risk

Panitumumab	110	97	78	58	44	37	31	26	23	19	11	4	1	0	0
Bevacizumab	94	90	73	59	46	33	29	24	21	18	12	3	0	0	0

Subgroup	N	Panitumumab + mFOLFOX6	Bevacizumab + mFOFLFOX6	Hazard ratio (95% CI)	Log-rank P value	P value for interaction
Overall population	733	368	365	0.87 (0.73–1.02)	0.089	0.029
Hyperselected	529	258	271	0.75 (0.62–0.92)	0.005	
Gene altered	204	110	94	1.14 (0.84–1.54)	0.399	

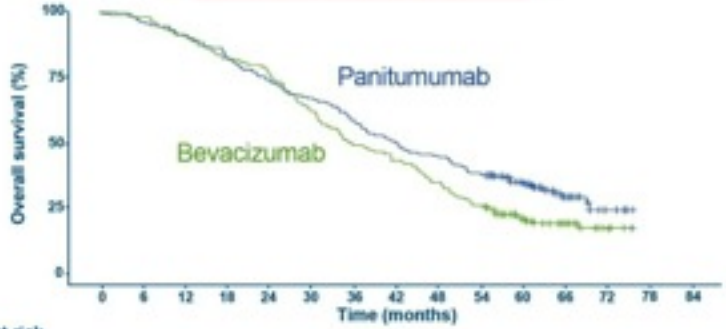
K. Shitara. ASCO-GI 2023

Survival outcomes in the left-sided population analyzed for ctDNA

Hyperselected

	mOS, months (95% CI)
Panitumumab	42.1 (36.9–49.6)
Bevacizumab	35.5 (31.6–41.4)

HR 0.76 (95% CI, 0.61–0.94)



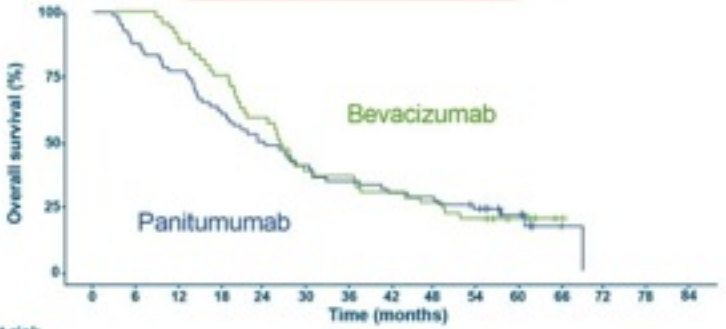
No. at risk

Panitumumab	221	213	201	182	162	147	129	111	98	84	54	20	4	0	0
Bevacizumab	218	214	198	177	163	132	104	92	73	54	28	14	5	0	0

Gene Altered

	mOS, months (95% CI)
Panitumumab	23.6 (17.5–30.9)
Bevacizumab	26.4 (20.8–30.9)

HR 1.10 (95% CI, 0.72–1.66)



No. at risk

Panitumumab	66	58	51	41	33	27	23	20	19	15	8	2	0	0	0
Bevacizumab	49	49	44	37	29	19	18	15	13	10	6	1	0	0	0

Subgroup		N	Panitumumab + mFOLFOX6	Bevacizumab + mFOFLFOX6	Hazard ratio (95% CI)	Log-rank *P* value	*P* value for interaction
Left-sided	Overall	554	287	267	0.83 (0.69–1.01)	0.062	
	Hyperselected	439	221	218	0.76 (0.61–0.94)	0.012	0.139
	Gene altered	115	66	49	1.10 (0.72–1.66)	0.661	

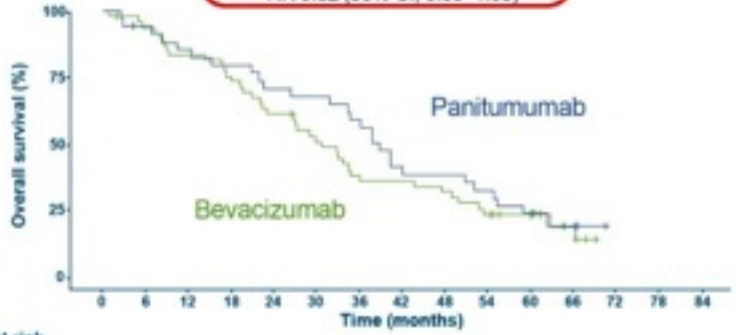
K. Shitara. ASCO-GI 2023

Survival outcomes in the right-sided population analyzed for ctDNA

Hyperselected

	mOS, months (95% CI)
Panitumumab	38.9 (26.5–52.2)
Bevacizumab	30.9 (22.4–36.1)

HR 0.82 (95% CI, 0.50–1.35)



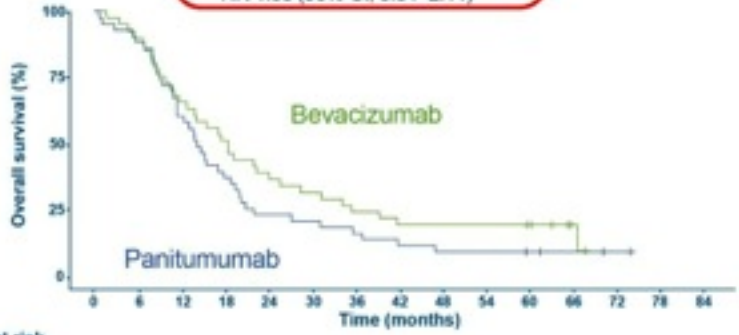
No. at risk

Panitumumab	35	32	29	27	24	23	20	14	13	11	8	3	0	0	0
Bevacizumab	50	46	41	37	30	24	18	17	15	11	8	4	0	0	0

Gene Altered

	mOS, months (95% CI)
Panitumumab	14.1 (11.3–18.7)
Bevacizumab	18.5 (11.6–25.5)

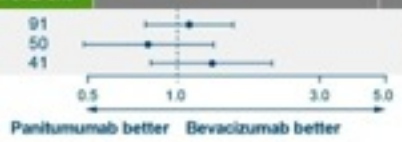
HR 1.33 (95% CI, 0.84–2.11)



No. at risk

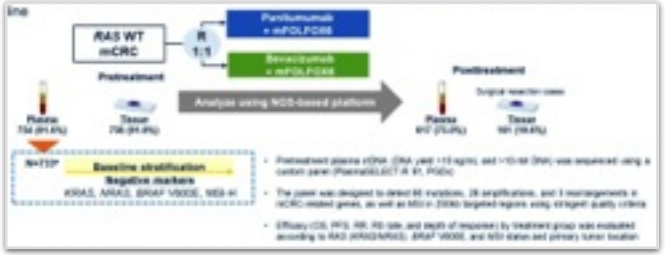
Panitumumab	43	38	26	16	10	9	7	5	4	4	3	2	1	0	0
Bevacizumab	41	37	27	21	16	13	10	8	8	8	6	2	0	0	0

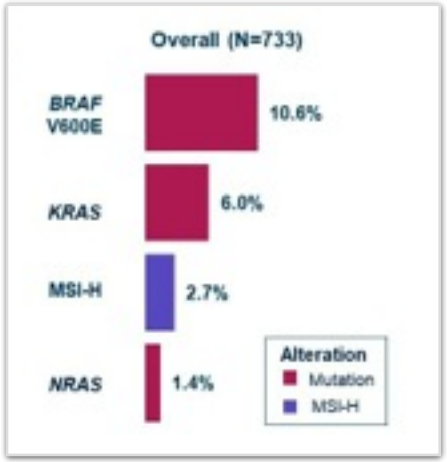
	Subgroup	N	Panitumumab + mFOLFOX6	Bevacizumab + mFOFLFOX6	Hazard ratio (95% CI)	Log-rank *P*-value	*P*-value for interaction
Right-sided	Overall	169	78	91	1.12 (0.80–1.56)	0.504	
	Hyperselected	85	35	50	0.82 (0.50–1.35)	0.431	0.145
	Gene altered	84	43	41	1.33 (0.84–2.11)	0.228	



K. Shitara. ASCO-GI 2023

Efficacy of panitumumab in left-sided patients with MSS/MSI-L and *RAS/BRAF* WT: a biomarker study of the phase III PARADIGM trial





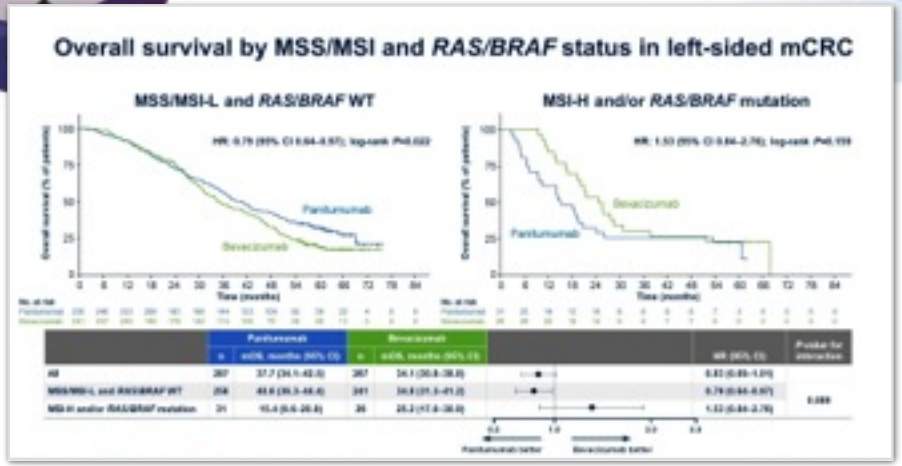
Co-occurring gene alterations by tumor sidedness

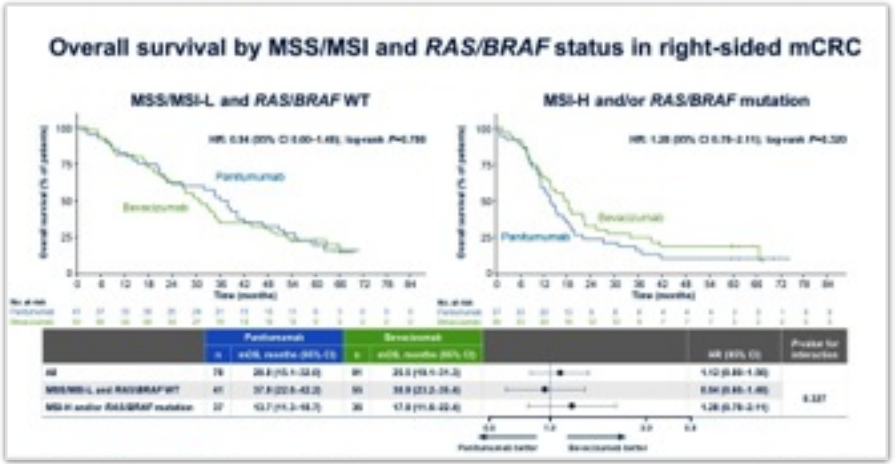
Gene alteration status, n (%)	Left-sided mCRC (n=554)	Right-sided mCRC (n=169)	Other[a] (n=10)	Overall (n=733)
MSI-H or *RAS*/*BRAF* mutation	57 (10.3)	73 (43.2)	5 (50%)	135 (18.4)
MSS/MSI-L and *RAS*/*BRAF* WT	497 (89.7)	96 (56.8)	5 (50%)	598 (81.6)

Incidence of gene alterations in baseline ctDNA

Gene alteration, n (%)	Left-sided mCRC (n=554)		Right-sided mCRC (n=169)		Overall population (N=733)	
	Panitumumab + mFOLFOX6 (n=287)	Bevacizumab + mFOLFOX6 (n=267)	Panitumumab + mFOLFOX6 (n=75)	Bevacizumab + mFOLFOX6 (n=91)	Panitumumab + mFOLFOX6 (n=366)	Bevacizumab + mFOLFOX6 (n=367)
BRAF V600E	16 (5.6)	8 (3.0)	25 (33.3)	27 (29.7)	42 (11.4)	36 (9.8)
KRAS	11 (3.8)	16 (6.0)	9 (11.8)	6 (6.6)	21 (5.7)	23 (6.3)
NRAS	6 (2.1)	2 (0.7)	1 (1.3)	0	7 (1.9)	2 (0.5)
MSI-H	1 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	9 (2.4)	11 (3.0)

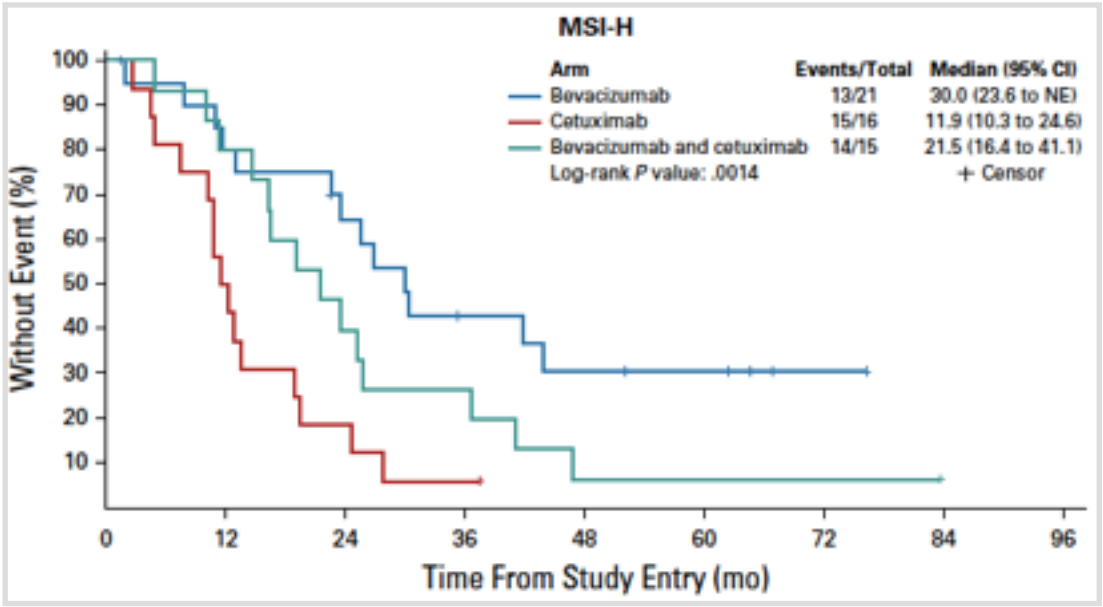
Kentaro Yamazaki. ASCO 2023 # 3508





Kentaro Yamazaki. ASCO 2023 # 3508

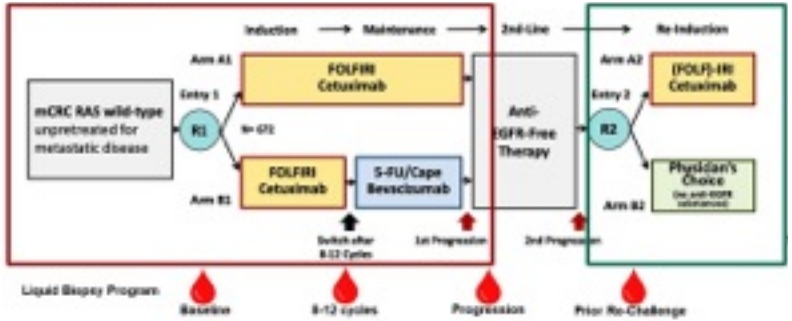
Mutational Analysis of Patients With Colorectal Cancer in CALGB/SWOG 80405 Identifies New Roles of Microsatellite Instability and Tumor Mutational Burden for Patient Outcome



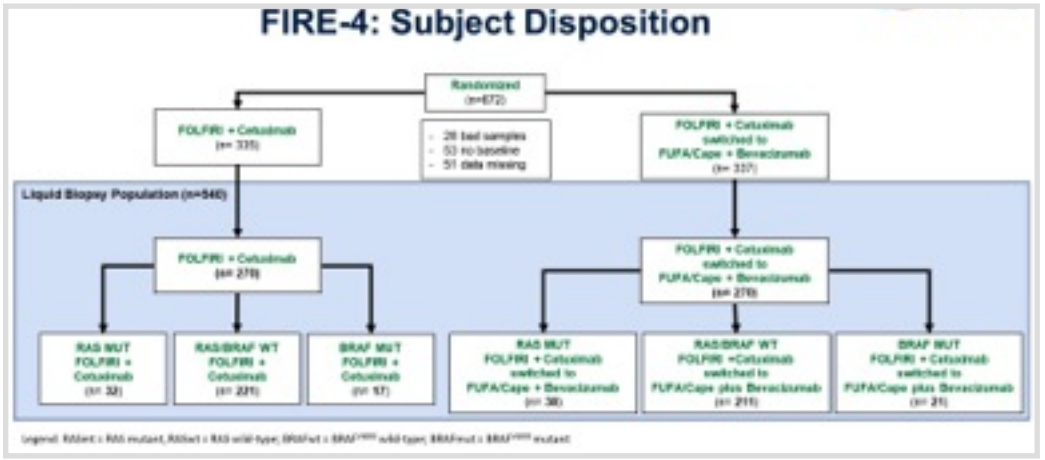
F. Innocenti. JCO 2019; 37:1217-1227.

Influence of baseline liquid biopsy results on first-line treatment efficacy of FOLFIRI plus Cetuximab in patients with tissue RAS-WT mCRC

Data of the phase III FIRE-4 study (AIO KRK-0114):



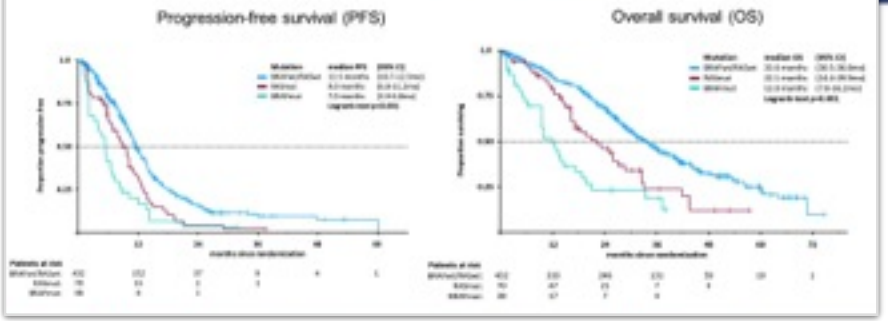
Primary Endpoint:
Overall Survival (OS) after randomisation 2



13% RAS mut
7% BRAF V600E mut

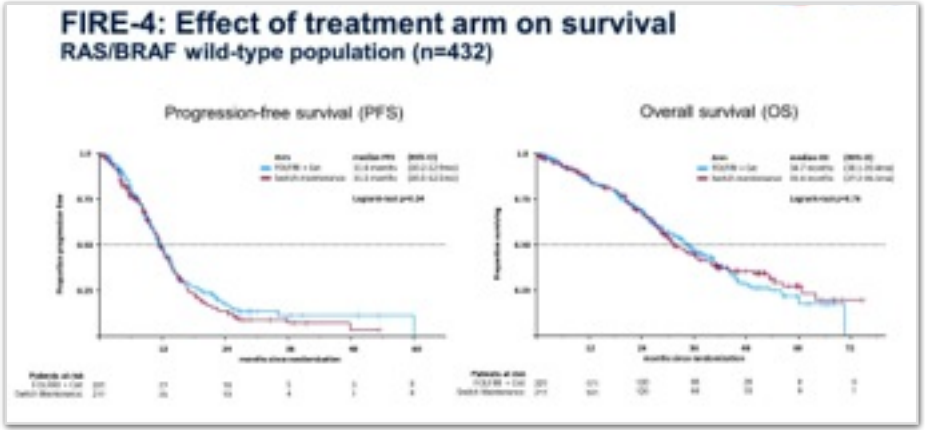
S. Stintzing. ASCO 2023 # 3507

FIRE-4: Effect of baseline liquid biopsy result on survival

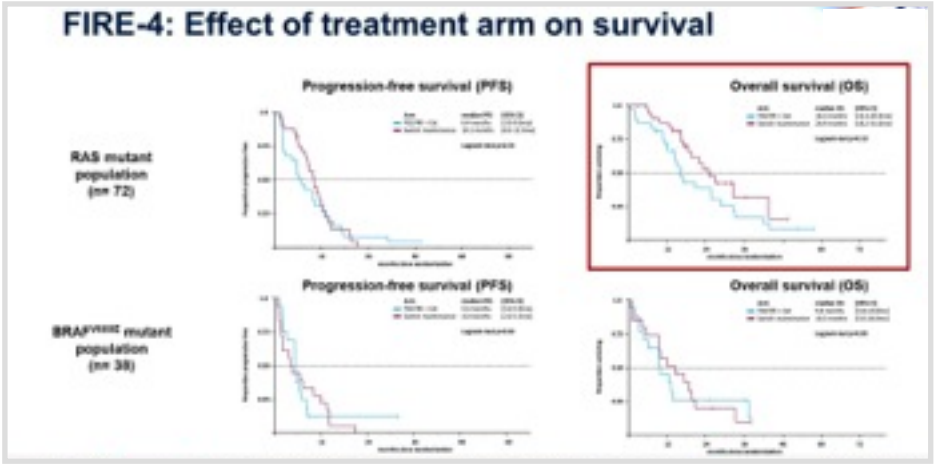


FIRE-4: Effect of treatment arm on survival

RAS/BRAF wild-type population (n=432)



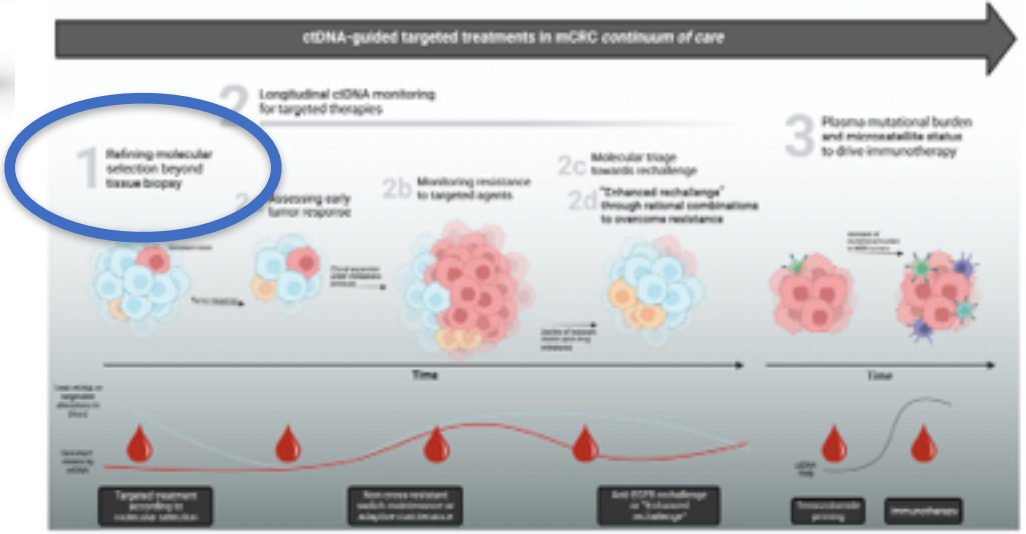
FIRE-4: Effect of treatment arm on survival



S. Stintzing. ASCO 2023 # 3507

CLINICAL CANCER RESEARCH | REVIEW

Circulating Tumor DNA to Drive Treatment in Metastatic Colorectal Cancer



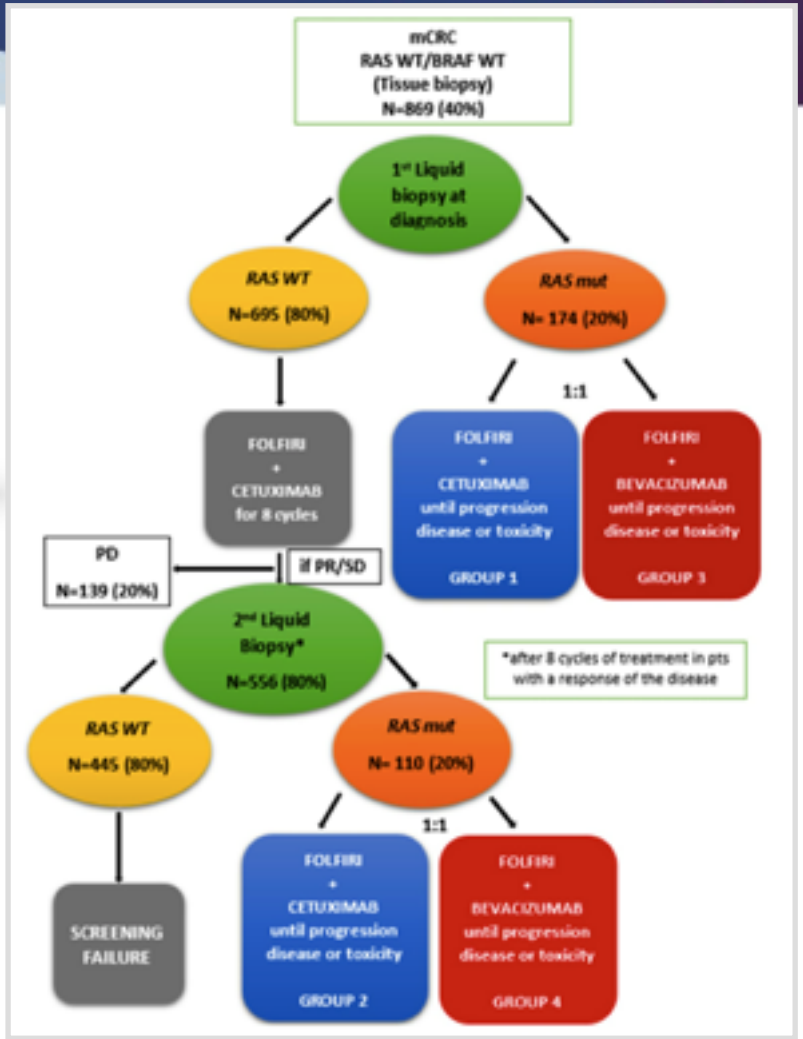
ctDNA is regarded as an exquisite tool for the detection of these additional biomarkers of resistance, by comprehensively capturing heterogeneity together with a higher sensitivity for minor clones

ctDNA characterization might improve selection for anti-EGFR.

Giorgio Patelli. Clin Cancer Res 2023;29:4530–9

TPS3636 **Poster Session**

Phase III study to compare bevacizumab or cetuximab plus FOLFIRI in patients with advanced colorectal cancer RAS/BRAF wild type (wt) on tumor tissue and RAS mutated (mut) in liquid biopsy: LIBImAb Study.

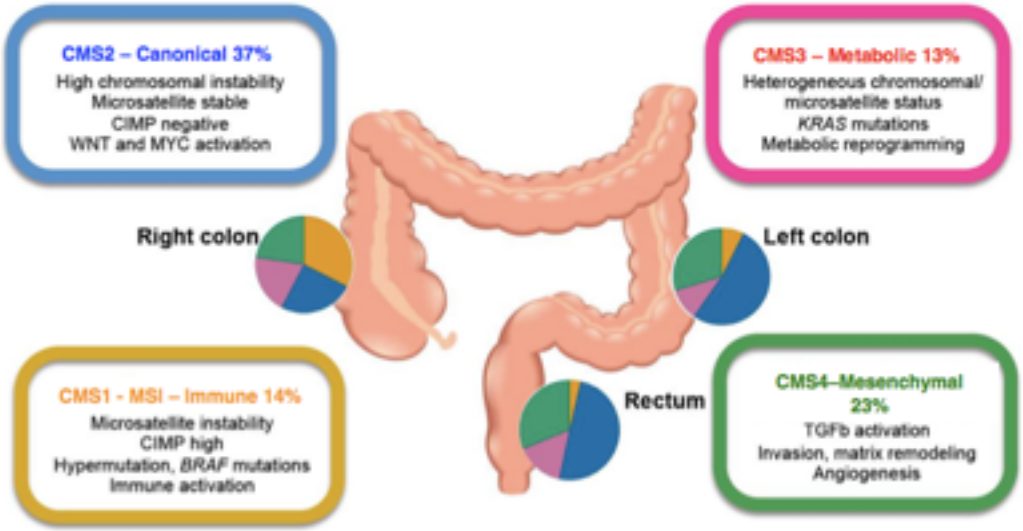


Angela Damato. ASCO 2022

Hyperselection rather than tumor sidedness may identify appropriate patients for first-line antiEGFR

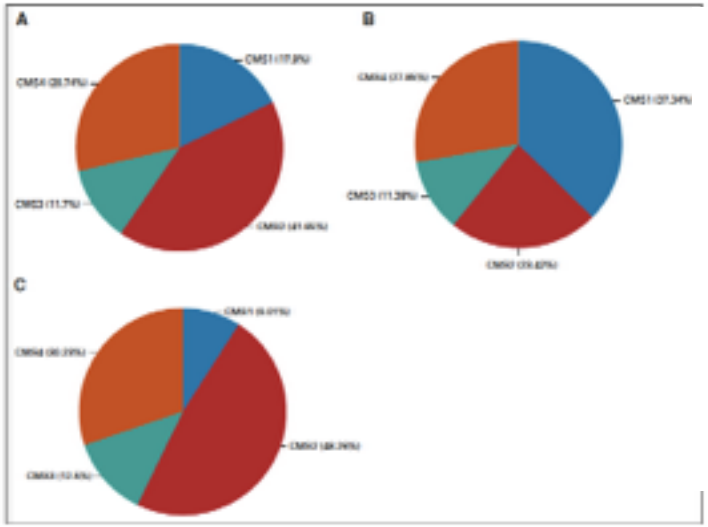
Liquid biopsy performed at baseline, may refine the molecular selection of patients with highest likelihood of benefit from EGFR blockade as compared with tumor tissue profiling alone

CMS classification may provide a path toward identifying patients with metastatic CRC who are most likely to benefit from specific targeted therapy as part of the initial treatment



Guinney J, Dienstmann R et al. Nat Med 2015

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



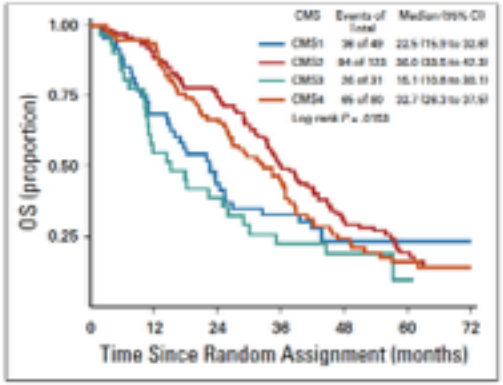


FIG 4. Overall survival (OS) among patients who received bevacizumab. CMS, consensus molecular subtype.

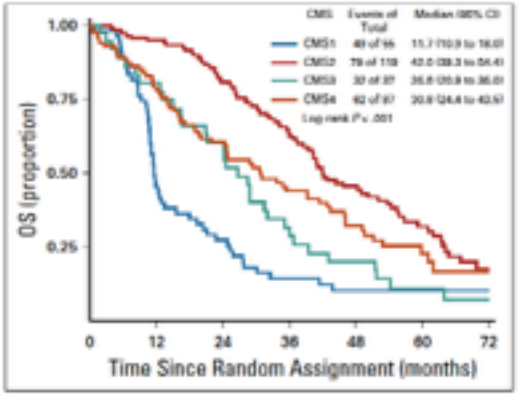
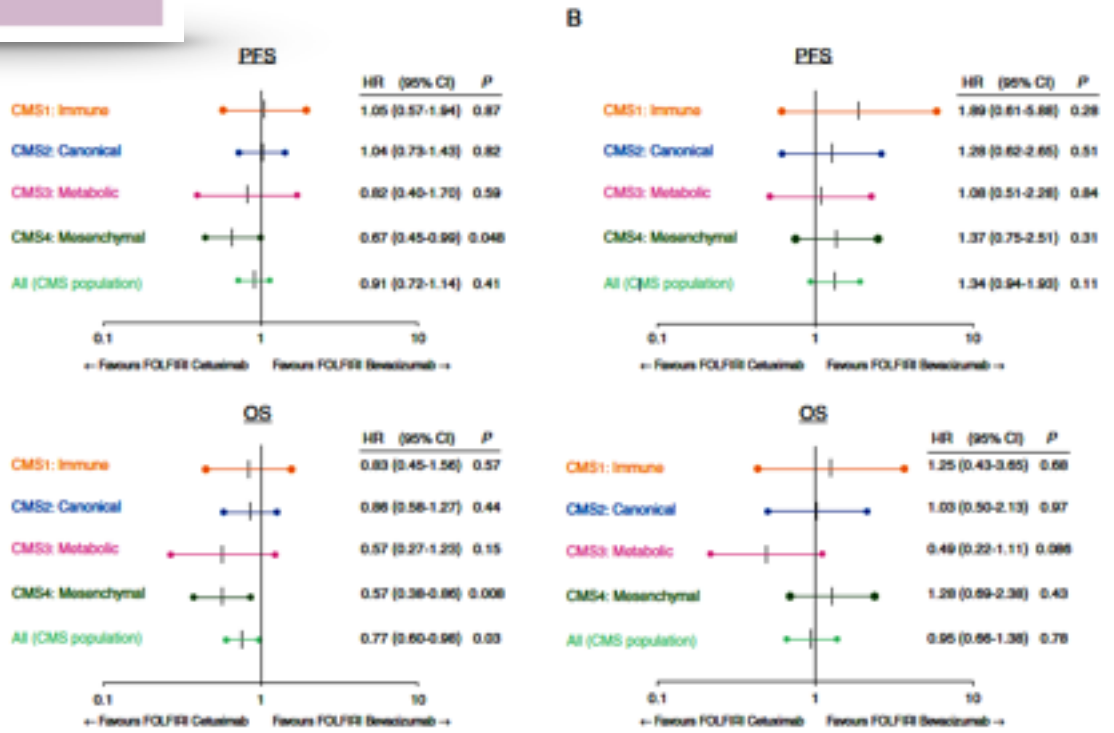


FIG 5. Overall survival (OS) among patients who received cetuximab. CMS, consensus molecular subtype.

Heinz-Josef Lenz,. J Clin Oncol 2019; 37:1876-1885.

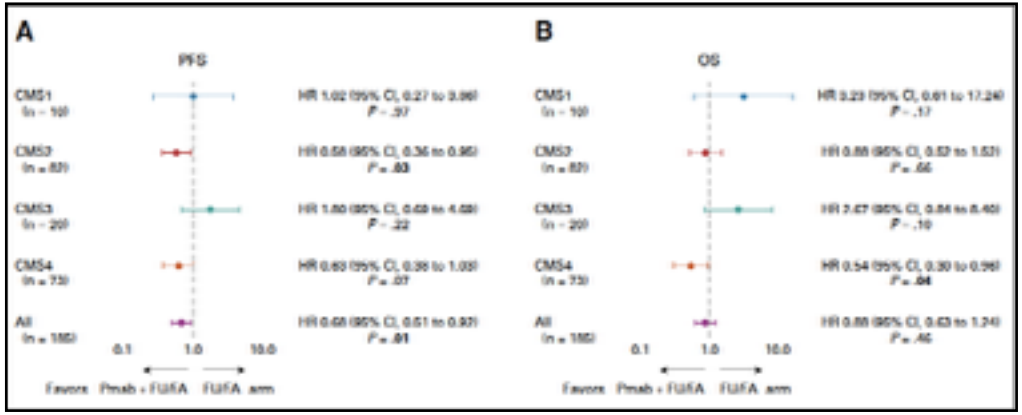
Consensus molecular subgroups (CMS) of colorectal cancer (CRC) and first-line efficacy of FOLFIRI plus cetuximab or bevacizumab in the FIRE3 (AIO KRK-0306) trial

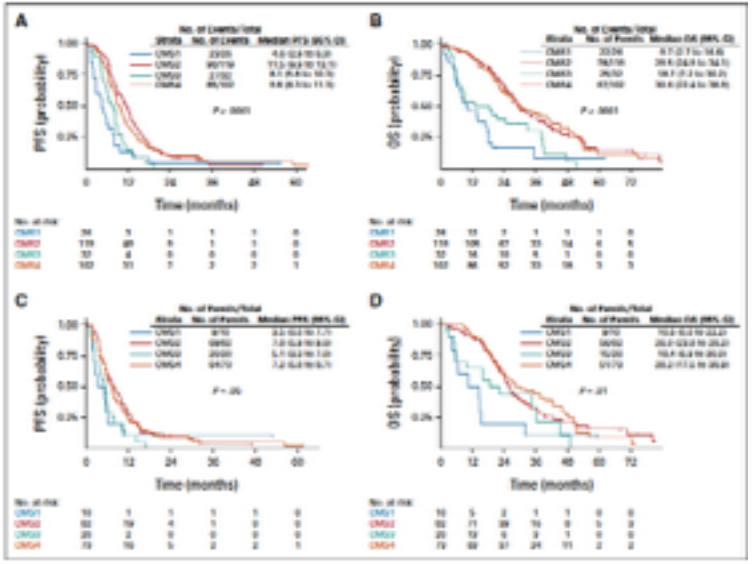
Right-sided RASwt tumors showed a higher prevalence of CMS1 (27% versus 11%) and a lower prevalence of CMS2 (28% versus 45%) than left-sided RASwt tumors



S. Stintzing Annals of Oncology 2019; 30: 1796–1803.

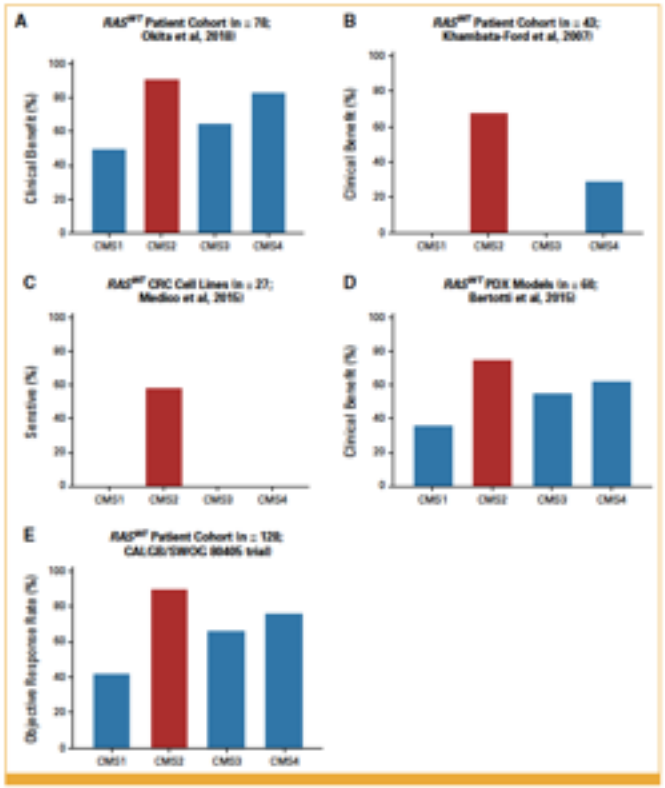
Consensus Molecular Subtypes as Biomarkers of Fluorouracil and Folinic Acid Maintenance Therapy With or Without Panitumumab in *RAS* Wild-Type Metastatic Colorectal Cancer (PanaMa, AIO KRK 0212)

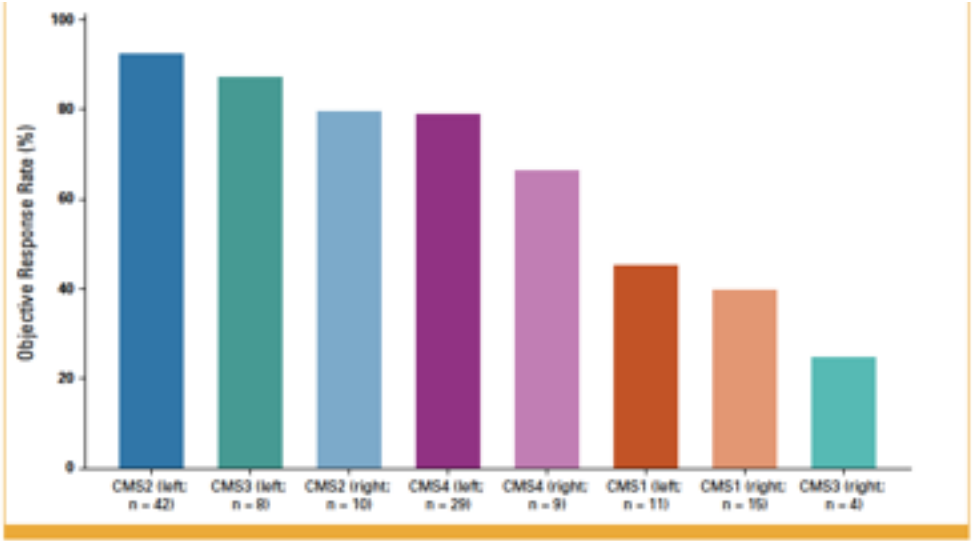




J Clin Oncol 2023; 41:2975-2987

Transcriptional Profiling and Consensus Molecular Subtype Assignment to Understand Response and Resistance to Anti–Epidermal Growth Factor Receptor Therapy in Colorectal Cancer





Saikat Chowdhury. JCO Precis Oncol 2023 (7)

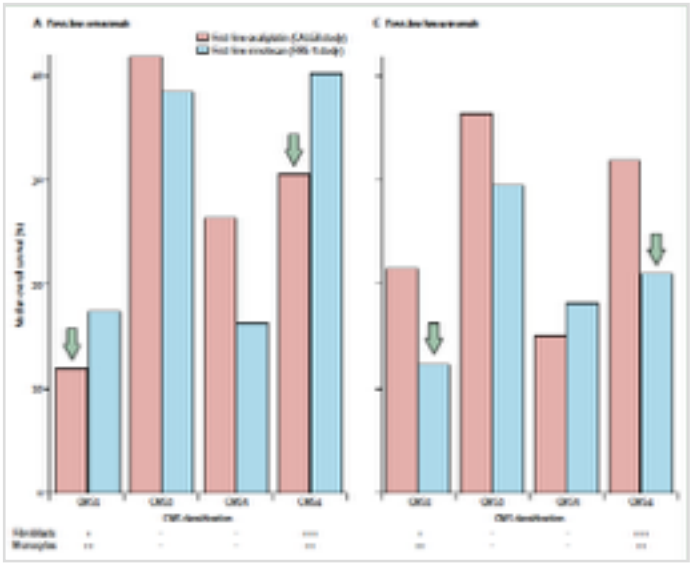
Explaining the unexplainable: discrepancies in results from the CALGB/SWOG 80405 and FIRE-3 studies

Dan Arnika, Sebastian Stintzing, Volker Heinemann

Lancet Oncol 2019; 20: e274-83

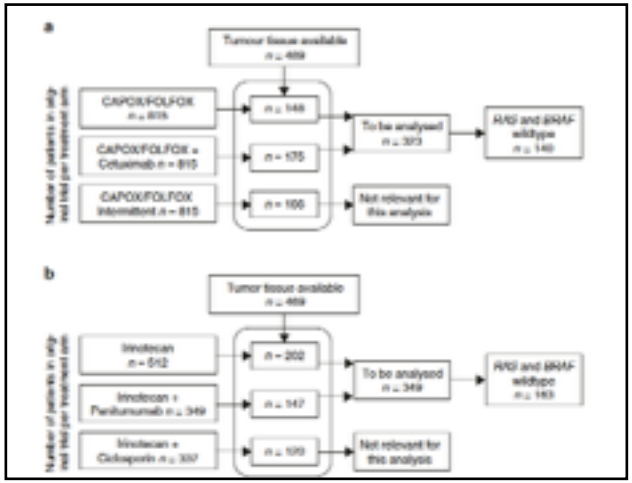
Proper interpretation of the CALGB/SWOG 80405 and FIRE-3 results requires an in-depth examination of the complex interplay, not only between the targeted biological agents and chemotherapeutic drugs, but also between therapies and the tumour biology and microenvironment, for each line of treatment.

	CALGB/SWOG 80405 Oxaliplatin (75% of patients) Median (95% CI) overall survival (months)		FIRE-3 Irinotecan (100% of patients) Median (95% CI) overall survival (months)		Most effective first-line combinations	Least effective first-line combinations
	Cetuximab	Bevacizumab	Cetuximab	Bevacizumab		
CMS1	11·7 (10·9–18·0)	22·5 (15·9–32·6)	17·9 (7·1–28·7)	13·1 (8·5–17·6)	Oxaliplatin-bevacizumab	Oxaliplatin-cetuximab
CMS2	47·0 (39·3–54·4)	36·0 (33·5–43·3)	28·3 (23·9–47·8)	29·1 (25·0–33·3)	Irinotecan/oxaliplatin-cetuximab	Irinotecan-bevacizumab
CMS3	26·8 (20·9–36·0)	15·1 (10·8–30·1)	16·6 (0·0–42·3)	18·6 (13·0–24·1)	Oxaliplatin-cetuximab	Oxaliplatin-bevacizumab
CMS4	10·8 (24·4–43·5)	12·7 (25·1–37·5)	40·1 (20·1–59·6)	25·1 (14·8–27·1)	Irinotecan-cetuximab	Irinotecan-bevacizumab



Clinical Studies

Molecular subtype-specific efficacy of anti-EGFR therapy in colorectal cancer is dependent on the chemotherapy backbone



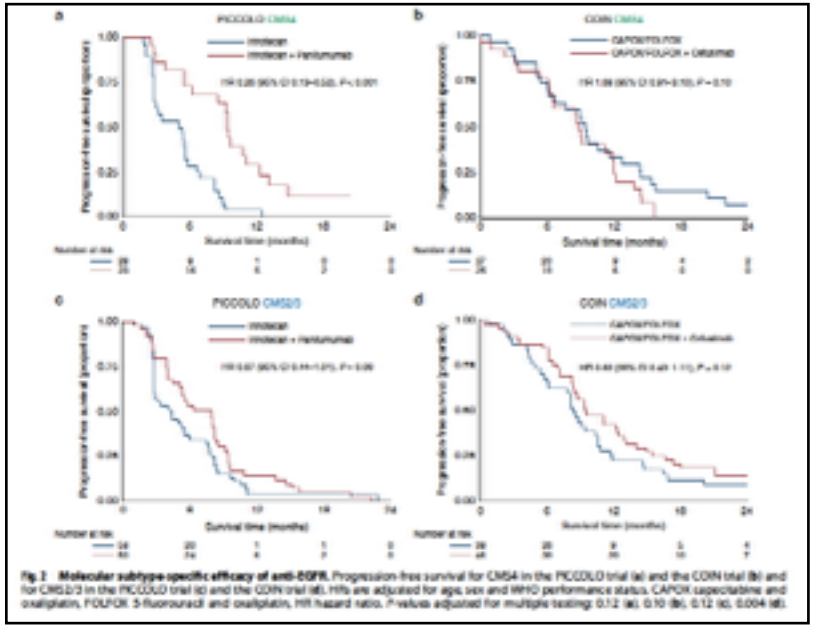


Table 2. Best response[a] for subtype-specific anti-EGFR efficacy

Trial	Treatment	CMS2/3				CMS4			
		CR or PR No. (%)		OR (95% CI)	P value	CR or PR No. (%)		OR (95% CI)	P value
		Yes	No			Yes	No		
COIN	CAPOX/FOLFOX	23 (65.7)	12 (34.3)	1.00	0.31	19 (70.4)	8 (29.6)	1.00	0.95
	CAPOX/FOLFOX	35 (77.8)	10 (22.2)	1.72		17 (70.8)	7 (29.2)	1.05	
	+ Cetuximab			(0.60–4.95)				(0.28–3.96)	
PICCOLO	Irinotecan	9 (15.5)	49 (84.5)	1.00	0.003	3 (10.7)	25 (89.3)	1.00	0.01
	Irinotecan	20 (40.8)	29 (59.2)	4.27		10 (43.5)	13 (56.5)	8.52	
	+ Panitumumab			(1.66–11.00)				(1.69–43.05)	

Fig. 2 Molecular subtype-specific efficacy of anti-EGFR. Progression-free survival for CMS4 in the PICCOLO trial (a) and the COIN trial (b) and for CMS2/3 in the PICCOLO trial (c) and the COIN trial (d). HRs are adjusted for age, sex and WHO performance status. CAPOX capecitabine and oxaliplatin, FOLFOX 5-fluorouracil and oxaliplatin, HR hazard ratio. *P* values adjusted for multiple testing: 0.12 (a), 0.10 (b), 0.12 (c), 0.004 (d).

Sanne ten Hoorn. British Journal of Cancer (2021) 125:1080–1088

Associations between AI-Assisted Tumor Amphiregulin and Epiregulin IHC and Outcomes from Anti-EGFR Therapy in the Routine Management of Metastatic Colorectal Cancer

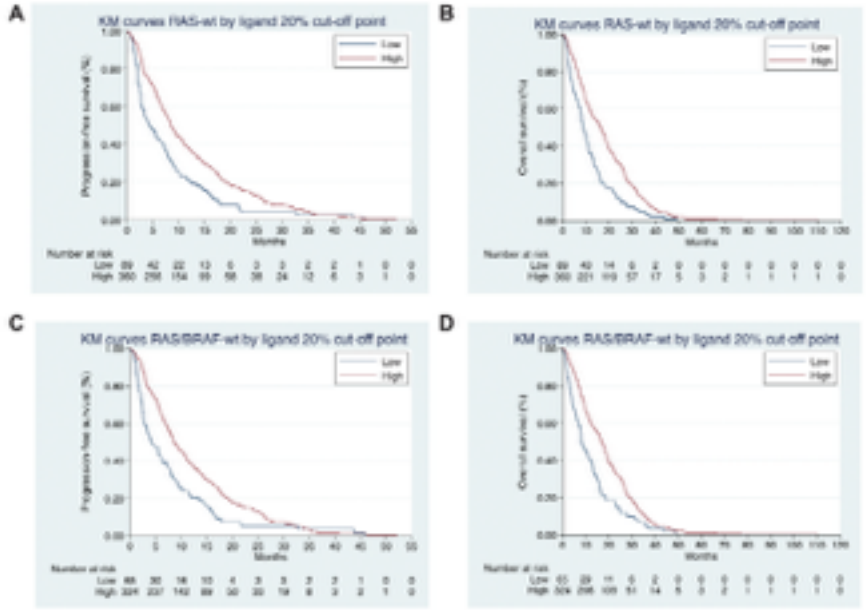
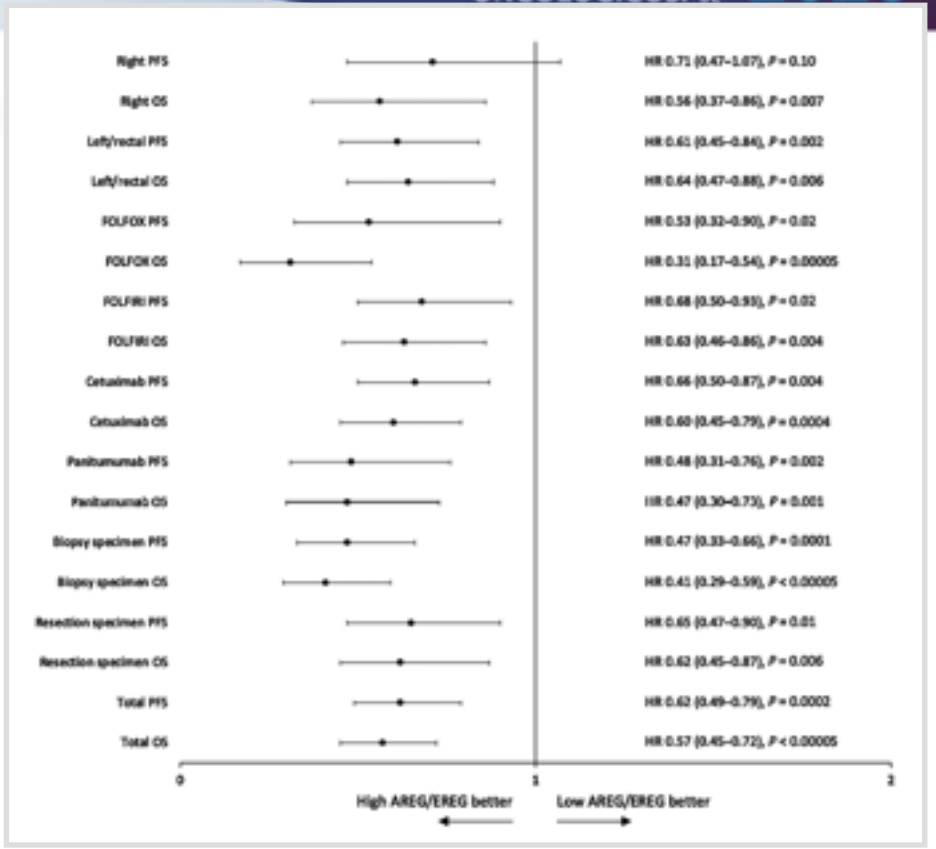


Figure 1.

PFS (**A**) and OS (**B**) Kaplan–Meier (KM) curves for RAS-wt patients and PFS (**C**) and OS (**D**) for RAS- and BRAF-wt patients with low (blue line) and high (red line) AREG/EREG expression (AREG and EREG <20% vs. AREG or EREG >20%).

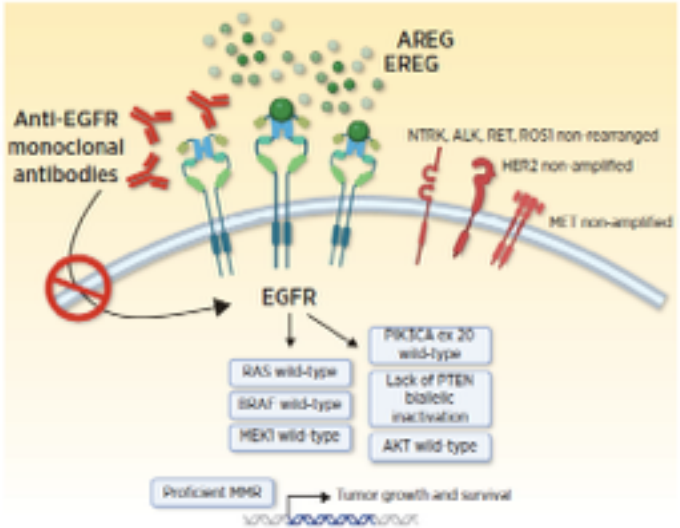


Christopher J.M. Williams. Clin Cancer Res 2023;29:4153–65

CLINICAL CANCER RESEARCH | CCR TRANSLATIONS

Towards Multiomics-Based Dissection of Anti-EGFR Sensitivity in Colorectal Cancer

Giovanni Randon and Filippo Pietrantonio



Both AREG/EREG overexpression and molecular hyperselection are emerging as the most promising biomarker-enrichment strategies to further refine the personalization of EGFR inhibition in mCRC

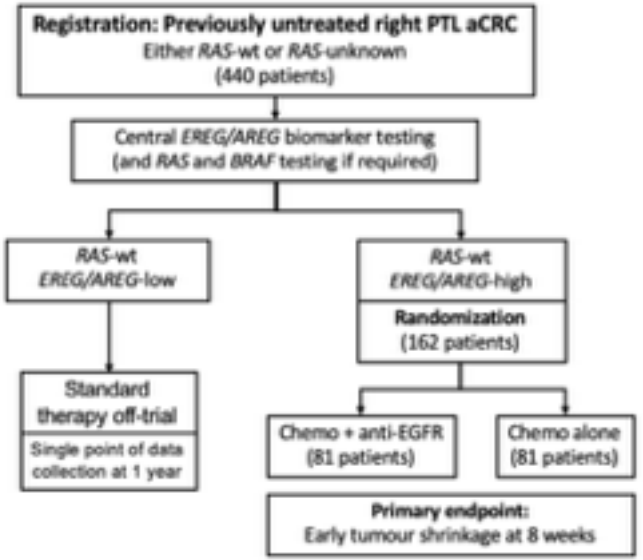
Patients with right-sided and high AREG/EREG expression do exist and represent a relatively small molecular subgroup at risk of being neglected and who may still derive a benefit from the upfront use of anti–EGFR-based therapies.

Giovanni Randon and Filippo Pietrantonio. Clin Cancer Res 2023;29:4021–3

TPS3633: A biomarker enrichment trial of anti-EGFR agents in right primary tumor location, *RAS* wild-type advanced colorectal cancer – ARIEL ISRCTN 11061442

ARIEL

Selecting patients with RAS wild-type **advanced colorectal cancer** and right primary tumour location for effective anti-EGFR treatment



Christopher Williams. ASCO 2022

MOLECULAR SELECTION:
RAS-BRAF wt and MSS

MOLECULAR HYPERSELECTION

MOLECULAR ULTRASELECTION

CMS

AREG/EREG

PRIMARY TUMOR LOCALITATION

ctDNA