19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
MADRID 20 - 21 NOVIEMBRE 2024

Hiperselección molecular en el tratamiento con anti-EGFR en el cáncer colorrectal

Nuria Rodríguez Salas, MD, PhD
Hospital Universitario La Paz, Madrid

Hospital Universitario La Paz 60 años

UAM Universidad Autónoma de Madrid

Actionability

	Matched treatment	ESCAT score[126–128]	OncoKb level
RAS mutation	..	..	..
KRAS Gly12Cys mutation	Adagrasib or sotorasib with or without cetuximab	..	3A
BRAF^{V600E} (ie, Val600Glu) mutation	Encorafenib plus cetuximab	I-A	1
dMMR or microsatellite instability high	Pembrolizumab or dostarlimab (dMMR)	I-A	1
dMMR or microsatellite instability high	Nivolumab plus ipilimumab	I-A	1
BRAF$^{non\text{-}V600E}$ mutation	BRAF blockade (eg, PLX8394)	..	4
MET amplification or fusion	MET blockade	IIIA*	4†
HER2 or *ERBB2* amplification	HER2 blockade‡	II-B	2
NTRK gene fusion	Entrectinib	I-C	1
NTRK gene fusion	Larotrectinib	I-C	1
ATM mutation	Olaparib	IIIA	..
PIK3CA mutation	Alpelisib	IIIA	4
POLE mutation	Anti-PD1 or anti-PD-L1	IIIA	..
RET or ALK fusions	Selpercatinib§	IIIA	1
RET or ALK fusions	ALK blockade¶	IIIA	..
No genomic alterations	..	..	..

subtypes of CRC

Lancet Vol 404 , 2024

Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group

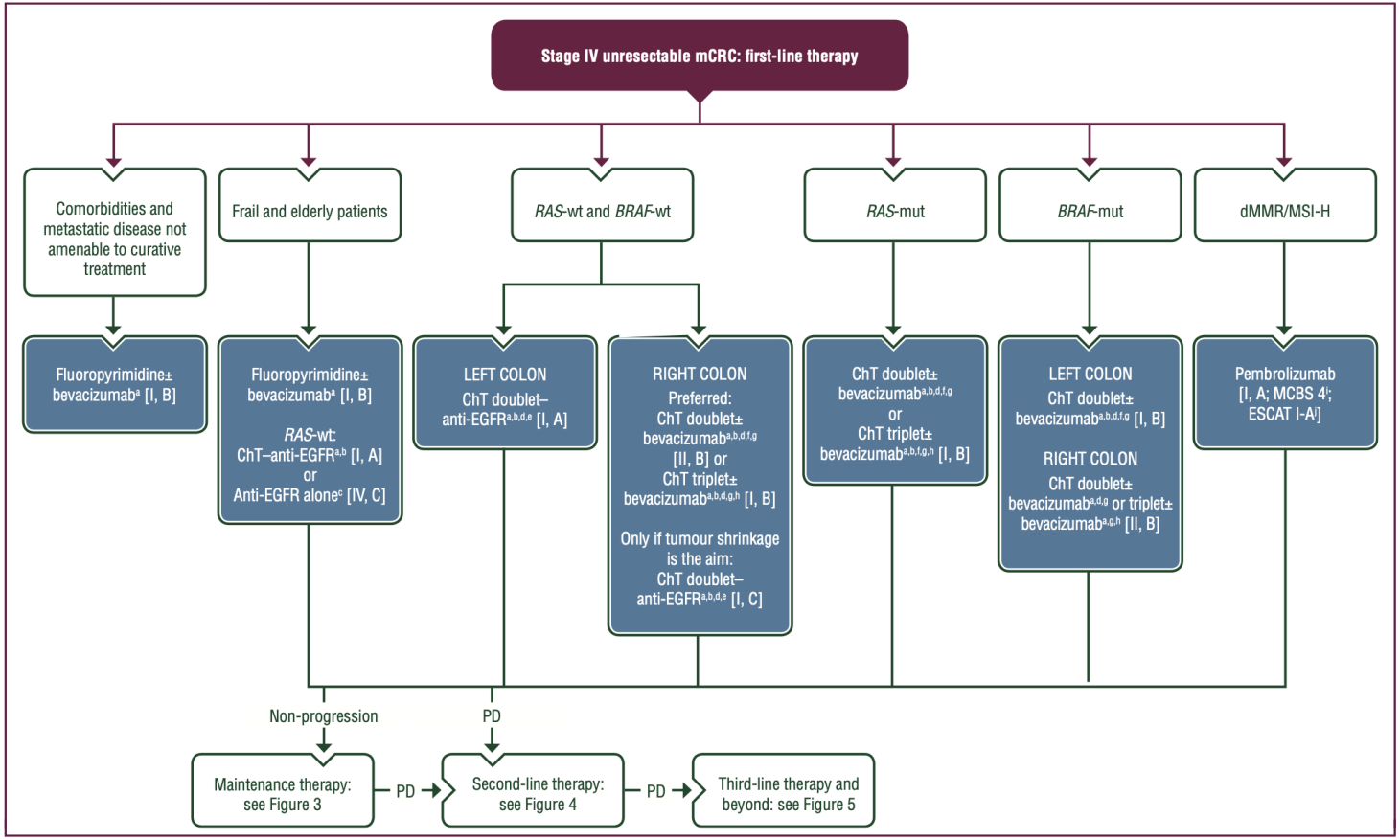
F. Mosele[1], J. Remon[2], J. Mateo[3], C. B. Westphalen[4], F. Barlesi[1], M. P. Lolkema[5], N. Normanno[6], A. Scarpa[7], M. Robson[8], F. Meric-Bernstam[9], N. Wagle[10], A. Stenzinger[11], J. Bonastre[12,13], A. Bayle[1,12,13], S. Michiels[12,13], I. Bièche[14], E. Rouleau[15], S. Jezdic[16], J-Y. Douillard[16], J. S. Reis-Filho[17], R. Dienstmann[18] & F. André[1,19,20*]

List of genomic alterations level I/II/III according to ESMO- ESCAT in metastatic colorectal cancer (mCRC)

Ann Oncol 2020

Gene	Alteration	Prevalence	ESCAT	References
KRAS *NRAS*	Mutations (resistance biomarker)	44% 4%	Not applicable	Van Cutsem E, et al. *J Clin Oncol.* 2015[79] Douillard J-Y, et al. *N Engl J Med.* 2013[80] Sorich M, et al. *Ann Oncol.* 2015[81]
BRAF^{V600E}	Mutations	8.5%	IA	https://doi.org/10.1093/annonc/mdw235 Kopetz S, et al. *N Engl J Med.* 2019[82]
	MSI-H	4%—5%	IA	Overman M, et al. *Lancet Oncol.* 2017[83] Le DT, et al. *J Clin Oncol.* 2020[84]
NTRK1	Fusions	0.5%	IC	Demetri G, et al. *Ann Oncol.* 2018[85] Doebele RC, et al. *Lancet Oncol.* 2020[50]
ERBB2	Amplifications	2%	IIB	Meric-Bernstam F, et al. *Lancet Oncol.* 2019[86] Sartore-Bianchi A, et al. *Lancet Oncol.* 2016[87]
PIK3CA	Hotspot mutations	17%	IIIA	Juric D, et al. *J Clin Oncol.* 2018[90]
ATM	Mutations	5%	IIIA	Wang C, et al. *Transl Oncol.* 2017[92] De Bono J, et al. *N Engl J Med.* 2020[93]
MET	Amplifications	1.7%	IIIA	https://clinicaltrials.gov/ct2/show/NCT03592641[94]
AKT1^{E17K}	Mutations	1%	IIIA	Hyman D, et al. *J Clin Oncol.* 2017[76]
	TMB-high in MSS	1%	IIIA	Fabrizio D, et al. *J Gastrointest Oncol.* 2018[89]
RET	Fusions	0.3%	IIIA	Drilon A, et al. *J Clin Oncol.* 2018[91]
ALK	Fusions	0.2%	IIIA	Yakirevich E, et al. Clin Cancer Res 2016[88]

Management of stage IV unresectable mCRC in first-line therapy



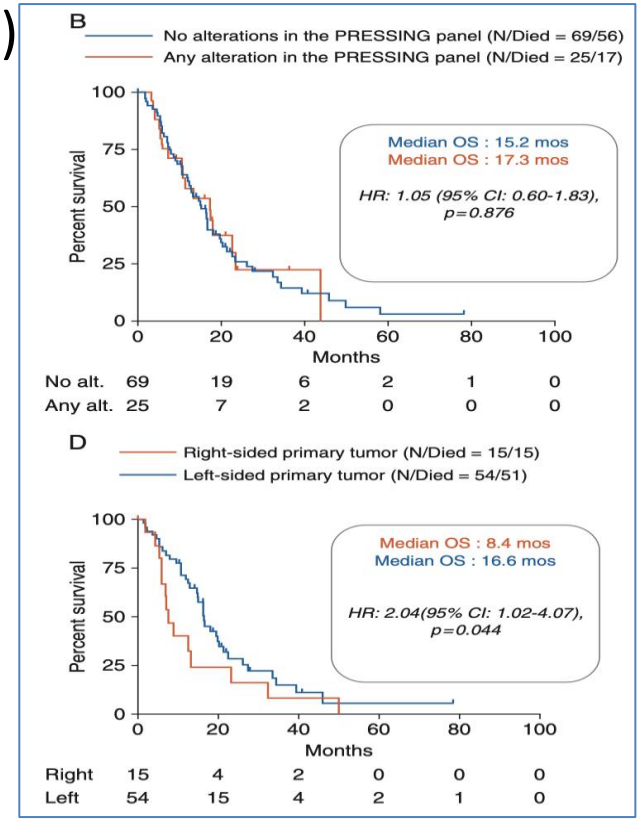
Ann Oncol 2023

Several genomic alterations beyond RAS and BRAFV600E mutations drive primary resistance to EGFR monoclonal antibodies in metastatic colorectal cancer (mCRC)

Negative hyper-selection of metastatic colorectal cancer patients for anti-EGFR monoclonal antibodies: the PRESSING case–control study

C. Cremolini[1*], F. Morano[2], R. Moretto[1], R. Berenato[2], E. Tamborini[3], F. Perrone[3], D. Rossini[1], A. Gloghini[3], A. Busico[3], G. Zucchelli[1], C. Baratelli[4], E. Tamburini[5], M. Tampellini[6], E. Sensi[7], G. Fucà[2], C. Volpi[3], M. Milione[3], M. Di Maio[4], G. Fontanini[7], F. De Braud[2,8], A. Falcone[1] & F. Pietrantonio[2]

PRESSING panel:
-HER2/MET amplifications
-ALK/ROS1/NTRK1-3/RET fusions -
-PIK3CA mutations

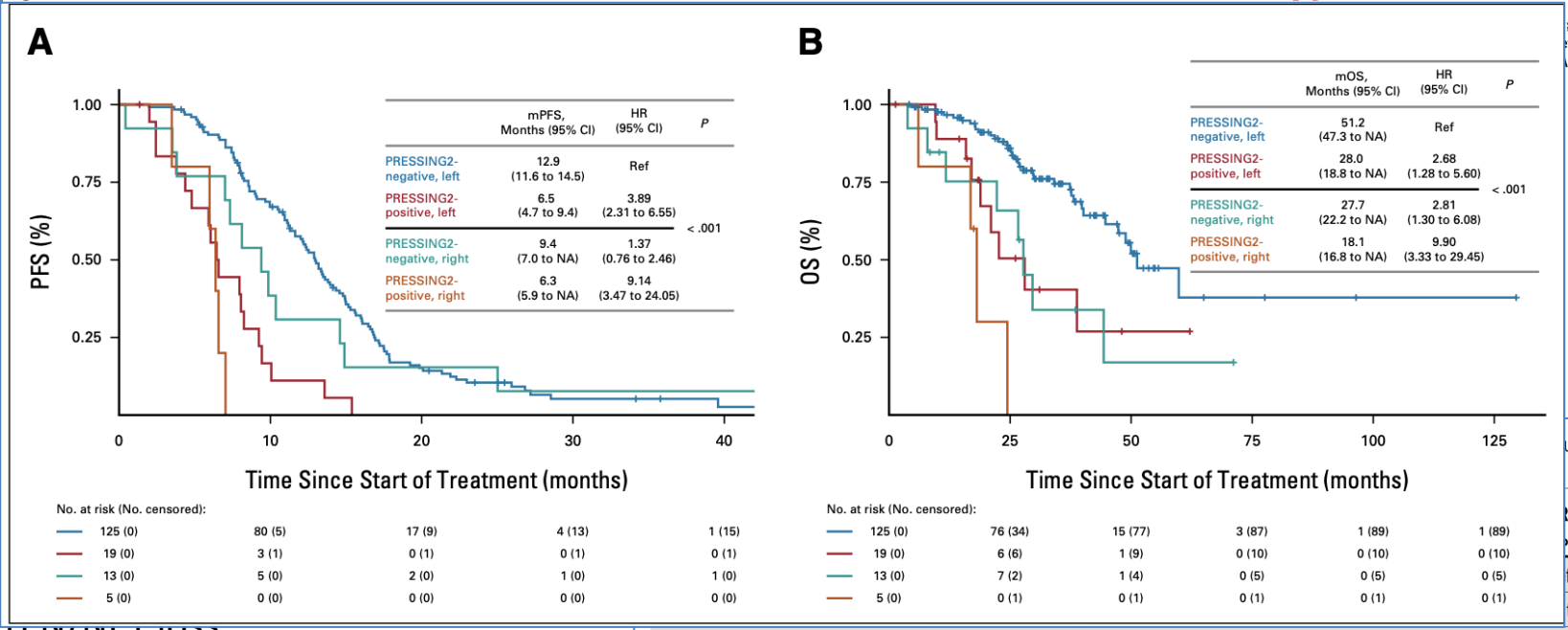


Ann Oncol 2017

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

; Paolo Manca, MD
tere, MD[4,5];
mbrosini, MD[1];

C D



PR
-N
Al
-P
-ERBB3, FGFR2, IGF1R, KRAS, ARAF, and AKT1-2 amplification; and
-EGFR rearrangements.

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)

JCO Precision Oncology 2022

¿¿Puede la hiperselección molecular ayudar en la decisión terapéutica más allá de la lateralidad??

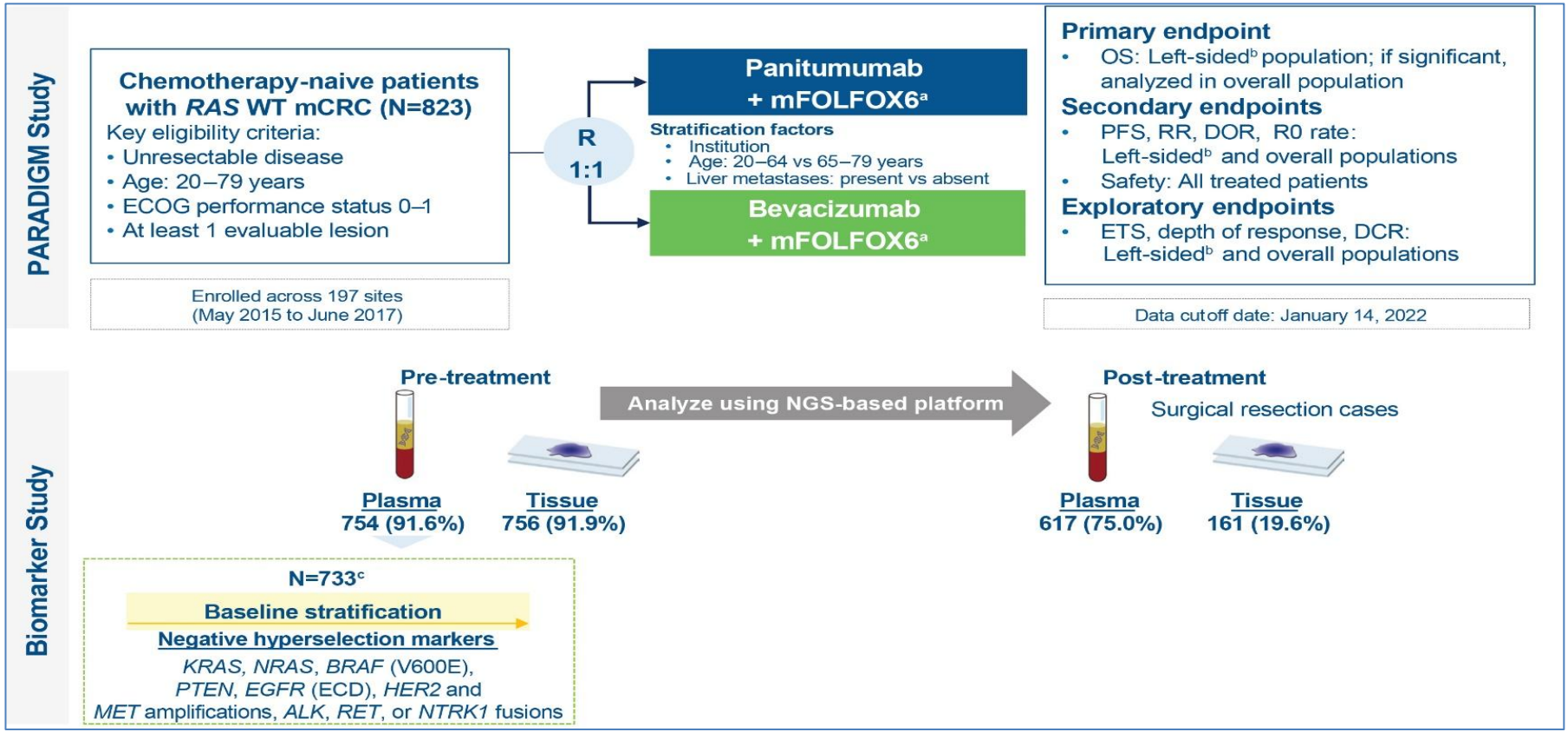
Negative hyperselection of patients with *RAS* wild-type metastatic colorectal cancer for panitumumab: A biomarker study of the phase III **PARADIGM trial**

Kohei Shitara[1], Kei Muro[2], Jun Watanabe[3], Kentaro Yamazaki[4], Hisatsugu Ohori[5], Manabu Shiozawa[6], Hirofumi Yasui[4], Eiji Oki[7], Takeo Sato[8], Takeshi Naito[9], Yoshito Komatsu[10], Takeshi Kato[11], Kazunori Yamanaka[12], Junpei Soeda[13], Ikuo Mori[13], Masamitsu Hihara[13], Kouji Yamamoto[14], Riu Yamashita[15], Kiwamu Akagi[16], Atsushi Ochiai[17], Hiroyuki Uetake[18], Katsuya Tsuchihara[15], Takayuki Yoshino[1]

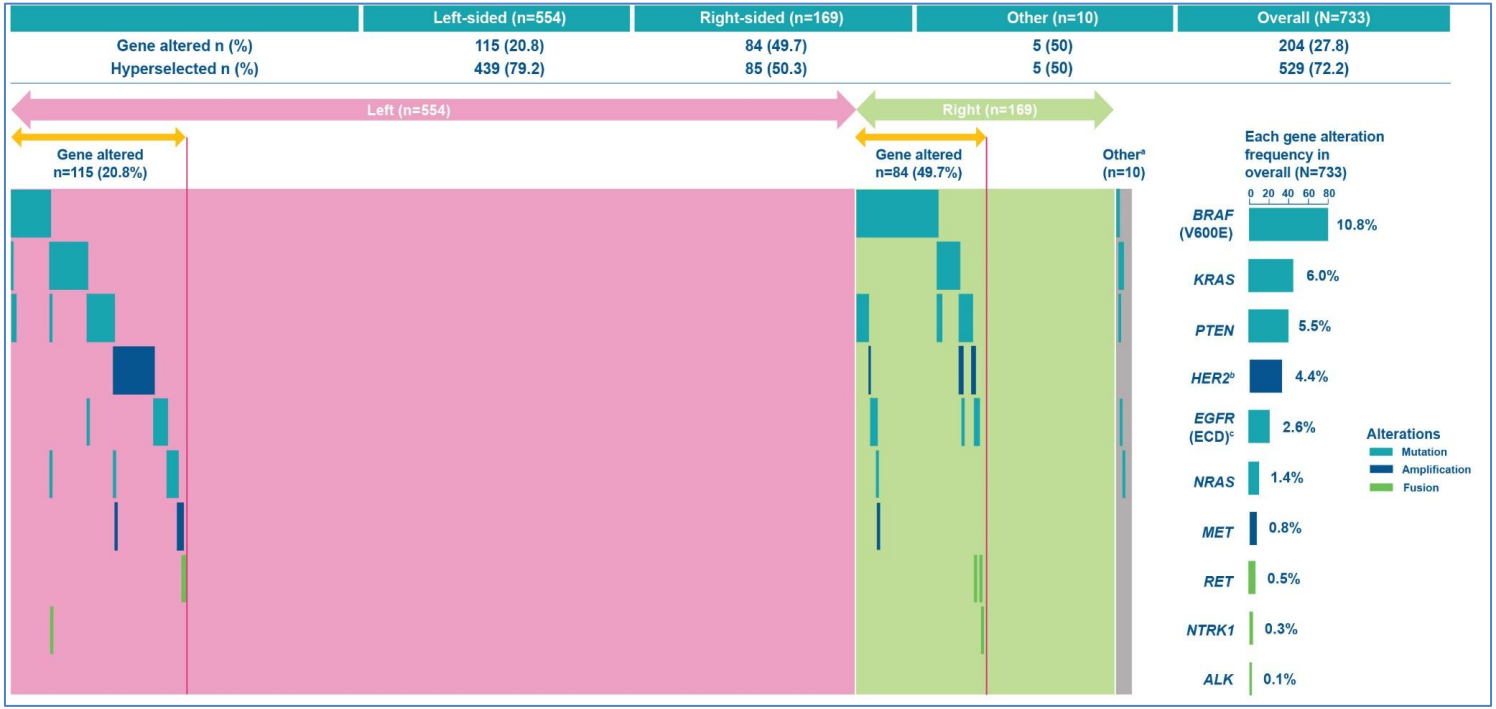
[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [2]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [3]Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan; [4]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [5]Division of Medical Oncology, Japanese Red Cross Ishinomaki Hospital, Miyagi, Japan; [6]Division of Gastrointestinal Surgery, Kanagawa Cancer Center, Kanagawa, Japan; [7]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [8]Research and Development Center for Medical Education, Department of Clinical Skills Education, Kitasato University School of Medicine, Sagamihara, Japan; [9]Department of Lower Gastrointestinal Surgery, Kitasato University School of Medicine, Sagamihara, Japan; [10]Division of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Japan; [11]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan; [12]Pharmaceutical Research Division, Takeda Pharmaceutical Company Ltd, Tokyo, Japan; [13]Japan Medical Affairs, Japan Oncology Business Unit, Takeda Pharmaceutical Company Ltd, Tokyo, Japan; [14]Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan; [15]Division of Translational Informatics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan; [16]Division of Molecular Diagnosis and Cancer Prevention, Saitama Cancer Center, Saitama, Japan; [17]Research Institute for Biomedical Sciences, Tokyo University of Science, Tokyo, Japan; [18]National Hospital Organization, Disaster Medical Center, Tokyo, Japan

Presented at ASCO GI 2023 in San Francisco, CA

Study Design



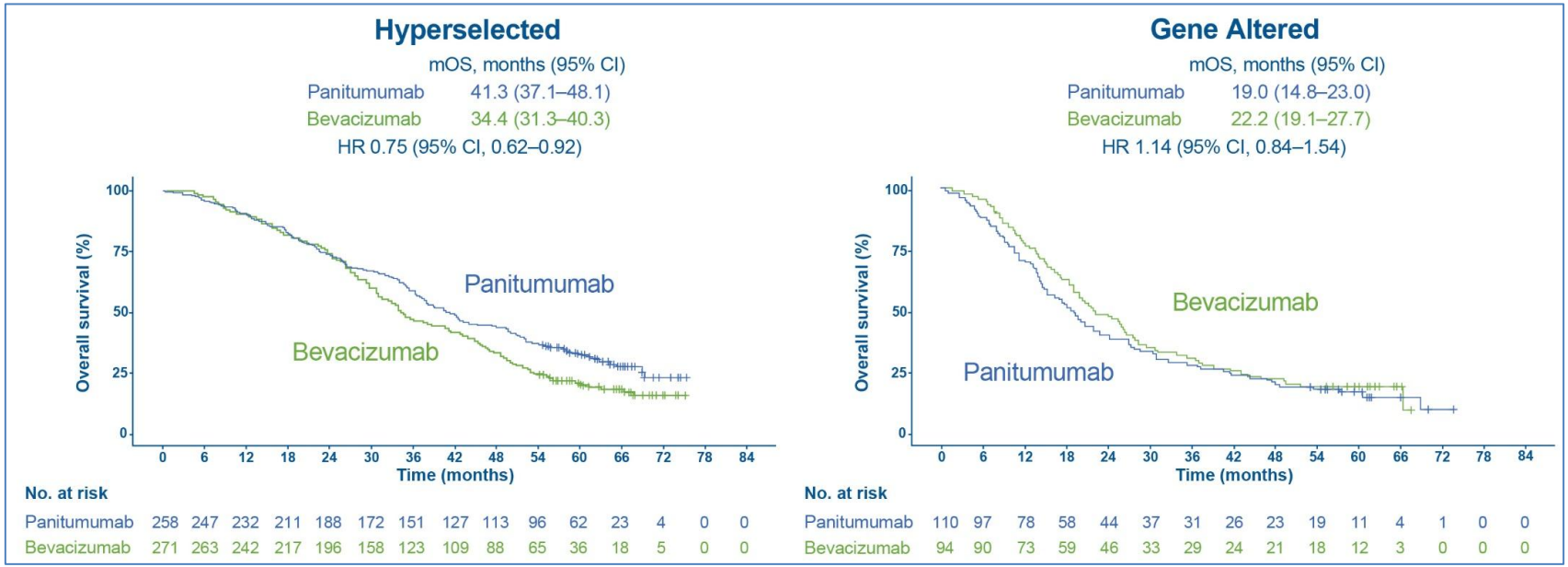
Co-occurring gene alterations in left- and right-sided tumors



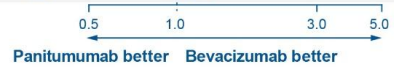
Number of genetic alterations ctDNA

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)

Survival outcomes in the overall population

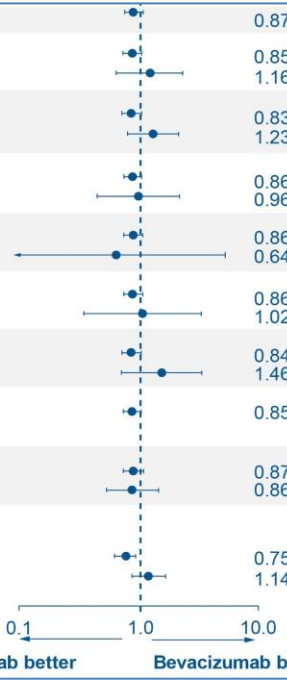


Subgroup	N	Panitumumab + mFOLFOX6	Bevacizumab + mFOFLFOX6	Hazard ratio (95% CI)	Log-rank *P*-value	*P*-value for interaction
Overall population	733	368	365	0.87 (0.73–1.02)	0.089	0.029
Hyperselected	529	258	271	0.75 (0.62–0.92)	0.005	
Gene altered	204	110	94	1.14 (0.84–1.54)	0.399	

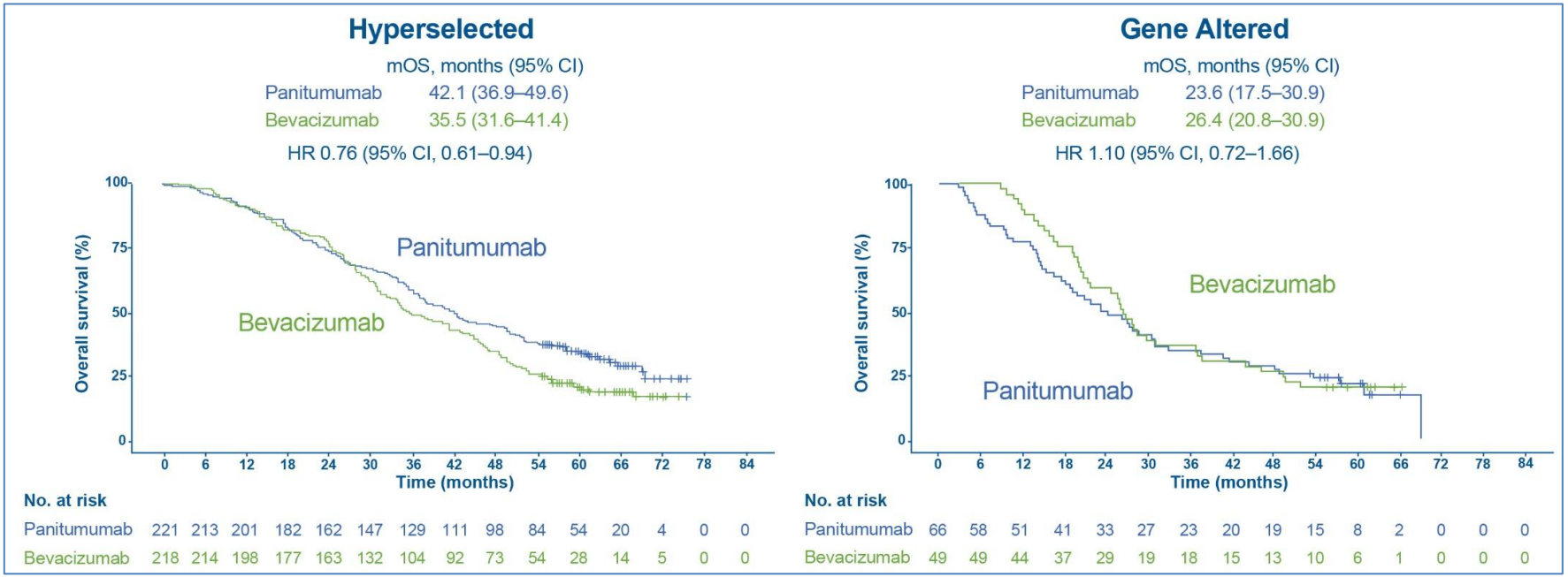


Subgroup analysis of overall survival by gene alteration in the overall population

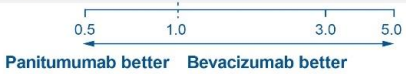
Subgroup	Median OS, month (95% CI)				Hazard ratio (95% CI)	Log-rank *P*-value	*P*-value for interaction
	N	Panitumumab + mFOLFOX6	N	Bevacizumab + mFOFLFOX6			
Overall	368	35.6 (31.1–38.9)	365	31.6 (29.3–34.5)	0.87 (0.73–1.02)	0.077	
RAS							
Wild type	341	36.3 (32.9–40.4)	339	32.4 (29.8–34.8)	0.85 (0.71–1.00)	0.046	0.337
Gene altered	27	20.9 (14.0–41.8)	26	25.7 (17.0–37.7)	1.16 (0.63–2.14)	0.576	
***BRAF* (V600E)**							
Wild type	325	38.0 (35.3–42.3)	329	34.0 (30.9–37.1)	0.83 (0.69–0.98)	0.025	0.198
Gene altered	43	12.3 (9.6–15.4)	36	14.8 (11.5–19.4)	1.23 (0.77–1.97)	0.453	
***HER2* (Amp)**							
Wild type	349	36.3 (32.9–40.4)	352	31.6 (29.6–34.5)	0.86 (0.72–1.01)	0.063	0.703
Gene altered	19	23.0 (16.5–30.6)	13	26.7 (15.0–37.1)	0.96 (0.45–2.04)	0.948	
***MET* (Amp)**							
Wild type	364	36.2 (32.0–38.9)	363	31.6 (29.6–34.6)	0.86 (0.73–1.02)	0.068	0.765
Gene altered	4	19.6 (4.1–NE)	2	27.0 (26.2–NE)	0.64 (0.09–4.62)	0.225	
***EGFR* (ECD)**							
Wild type	356	35.6 (31.1–38.9)	358	31.6 (29.6–34.5)	0.86 (0.73–1.02)	0.066	0.670
Gene altered	12	37.3 (9.3–48.1)	7	20.0 (5.4–NE)	1.02 (0.35–3.00)	0.864	
PTEN							
Wild type	345	36.3 (32.9–40.4)	348	31.6 (29.3–34.6)	0.84 (0.71–0.99)	0.036	0.138
Gene altered	23	19.9 (13.7–37.5)	17	30.9 (20.1–66.6)	1.46 (0.70–3.04)	0.398	
***ALK/RET/NTRK1* (Fusion)**							
Wild type	365	36.2 (32.0–38.9)	361	31.3 (29.3–34.4)	0.85 (0.72–1.00)	0.049	<0.001
Gene altered	3	5.3 (2.7–NE)	4	55.9 (17.0–NE)		0.117	
PIK3CA							
Wild type	328	36.2 (32.0–40.4)	323	33.1 (29.8–35.7)	0.87 (0.73–1.03)	0.098	0.945
Gene altered	40	31.0 (22.5–40.4)	42	22.4 (15.8–32.9)	0.86 (0.53–1.39)	0.756	
***RAS*, *BRAF* (V600E), *HER2* (Amp), *MET* (Amp), *EGFR* (ECD), *PTEN*, *ALK/RET/NTRK1* (Fusion)**							
Hyperselected (Wild type)	258	41.3 (37.1–48.1)	271	34.4 (31.3–40.3)	0.75 (0.62–0.92)	0.004	0.029
Gene altered	110	19.0 (14.8–23.0)	94	22.2 (19.1–27.7)	1.14 (0.84–1.54)	0.396	



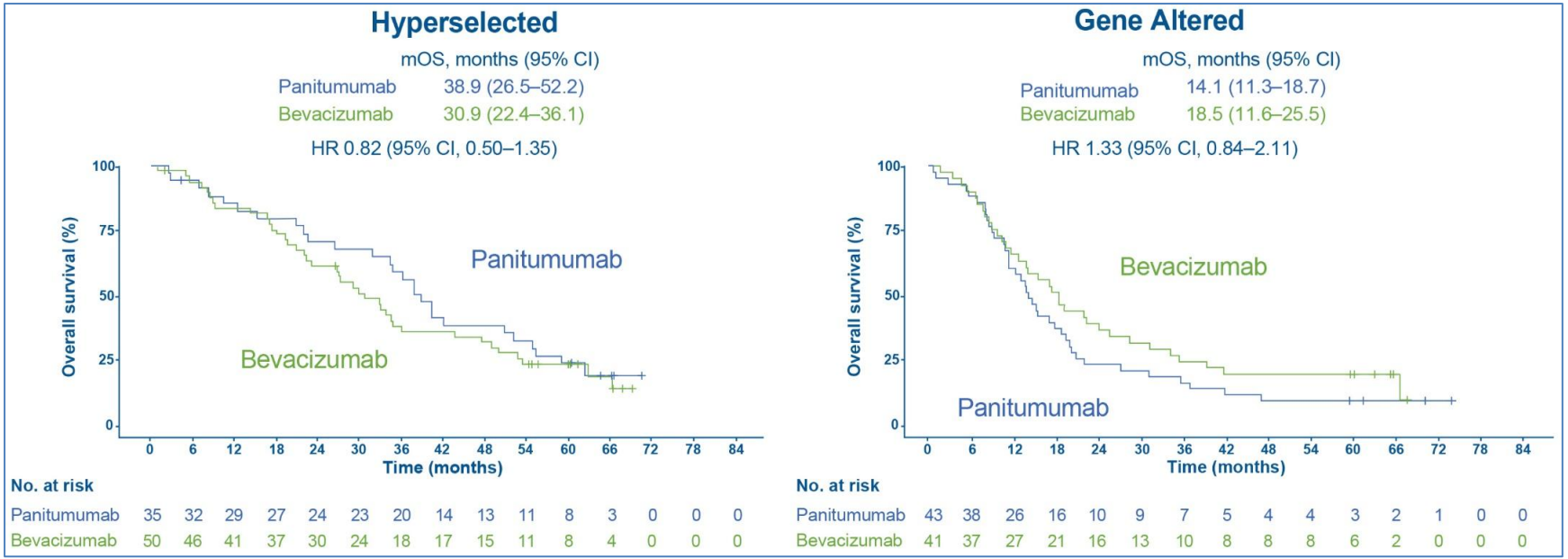
Survival outcomes in the left-sided population



Subgroup		N	Panitumumab + mFOLFOX6	Bevacizumab + mFOFLFOX6	Hazard ratio (95% CI)	Log-rank *P*-value	*P*-value for interaction
sided	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	



Survival outcomes in the right-sided population



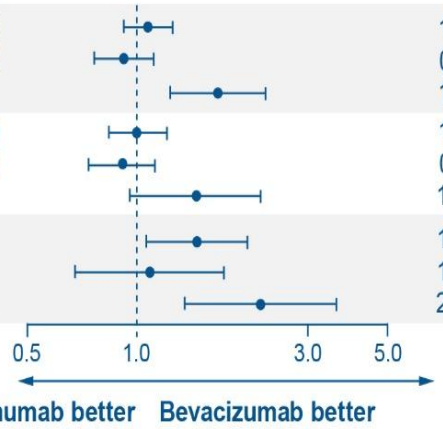
Subgroup		N	Panitumumab + mFOLFOX6	Bevacizumab + mFOLFOX6	Hazard ratio (95% CI)	Log-rank *P*-value	*P*-value for interaction
sided	Hyperselected	85	35	50	0.82 (0.50–1.35)	0.431	0.145
	Gene altered	84	43	41	1.33 (0.84–2.11)	0.228	

0.5 1.0 3.0 5.0

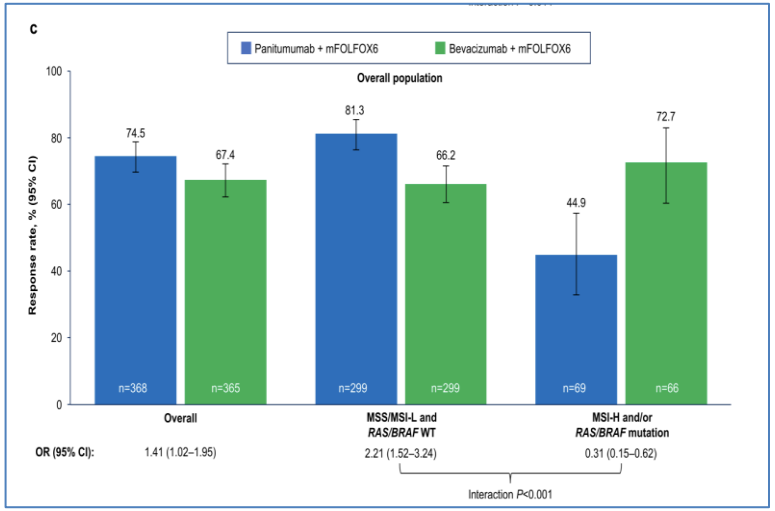
Panitumumab better Bevacizumab better

Progression-free survival in ctDNA-analyzed population

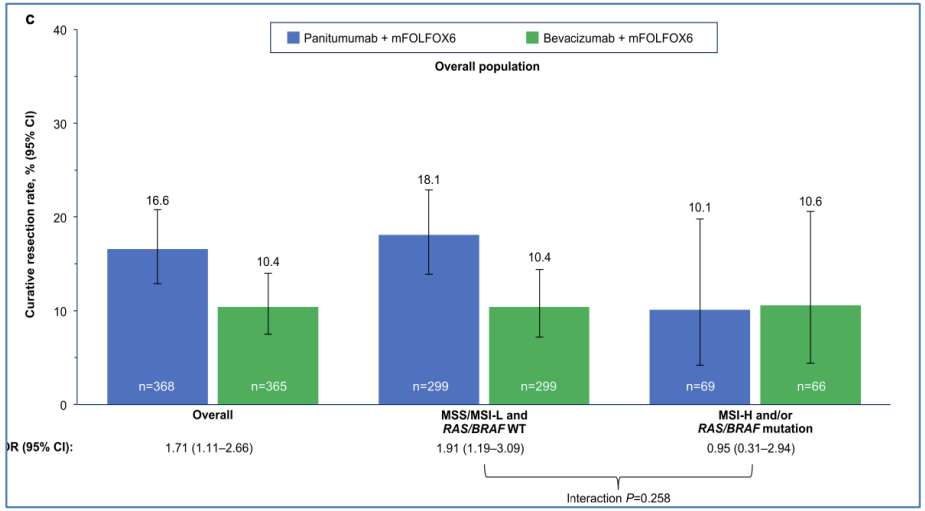
Subgroup		N	Median PFS, month (95% CI) Panitumumab + mFOLFOX6	Median PFS, month (95% CI) Bevacizumab + mFOFLFOX6	Hazard ratio (95% CI)	Log-rank *P*-value	*P*-value for interaction
Overall population		733	12.2 (10.8–13.3)	11.5 (11.2–13.3)	1.07 (0.91–1.26)	0.429	
	Hyperselected	529	13.6 (12.7–15.7)	12.8 (11.3–14.1)	0.91 (0.75–1.12)	0.379	<0.001
	Gene altered	204	7.8 (6.8–9.3)	9.8 (8.4–11.5)	1.69 (1.24–2.31)	<0.001	
Left-sided	Overall	554	13.2 (11.8–14.3)	12.0 (11.8–14.3)	1.00 (0.82–1.21)	0.991	
	Hyperselected	439	14.0 (12.7–16.2)	12.8 (11.3–14.1)	0.90 (0.72–1.12)	0.360	0.037
	Gene altered	115	9.2 (7.8–12.2)	9.9 (9.4–14.8)	1.47 (0.96–2.26)	0.078	
Right-sided	Overall	169	7.7 (6.8–9.9)	10.6 (7.7–14.3)	1.48 (1.06–2.07)	0.021	
	Hyperselected	85	13.2 (8.0–15.1)	11.3 (7.2–16.7)	1.08 (0.66–1.77)	0.749	0.025
	Gene altered	84	6.3 (4.6–7.2)	10.3 (5.9–12.7)	2.25 (1.36–3.70)	0.001	



Response rates



Curative resection rates



Conclusions Paradigm

-In hyperselected patients with no gene alterations, OS tended to be longer with panitumumab than with bevacizumab regardless of primary tumor sidedness.

Overall: mOS 41.3 vs 34.4 months, HR, 0.75 (95% CI: 0.62–0.92)

Left-sided: mOS 42.1 vs 35.5 months, HR, 0.76 (95% CI: 0.61–0.94)

Right-sided: mOS 38.9 vs 30.9 months, HR, 0.82 (95% CI: 0.50–1.35)

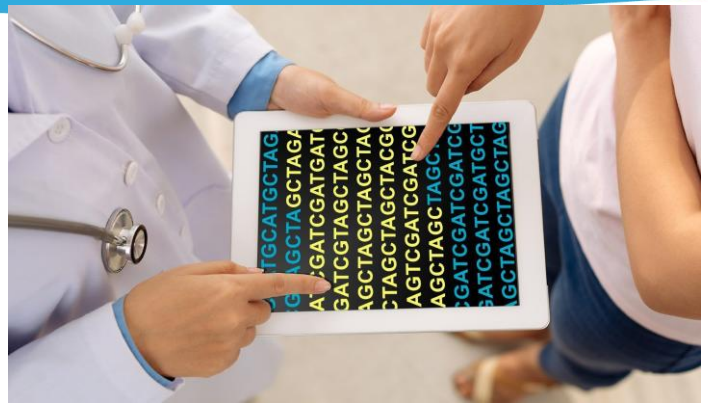
-OS was similar or inferior with panitumumab vs bevacizumab irrespective of the primary tumor sidedness in patients with any of these gene alterations

-Negative hyperselection using ctDNA analysis rather than tumor sidedness may identify appropriate patients for first-line panitumumab over bevacizumab

-Response rates and curative resection rates are both better in hyperselected cohort

These results warrant further validation in additional cohorts

Nat Med. 2024; 30(3): 730–739.



CONCLUSIONES

-Debemos avanzar en ofrecer estudios de caracterización molecular de los pacientes de mCRC mas allá de RAS/RAF

-La biopsia liquida es un método validado para su implementación en la practica clínica

-La mejor selección molecular de los pacientes nos aporta una valor añadido para optimizar la selección del tratamiento y redunda en mejoras de PFS, OS, RR y resecciones curativas de nuestros pacientes.