



18^{as} Jornadas HITOS
ONCOLÓGICOS: LO MEJOR DE 2023

Madrid, 22 y 23 de noviembre de 2023

Tratamiento de tercera línea del CCRm: ¿hay un estándar?

Dra. Cristina Grávalos

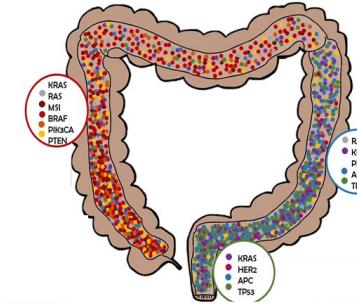
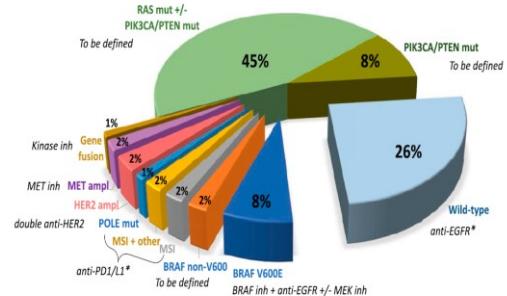


Conflictos de intereses

-Amgen, Merck, Servier

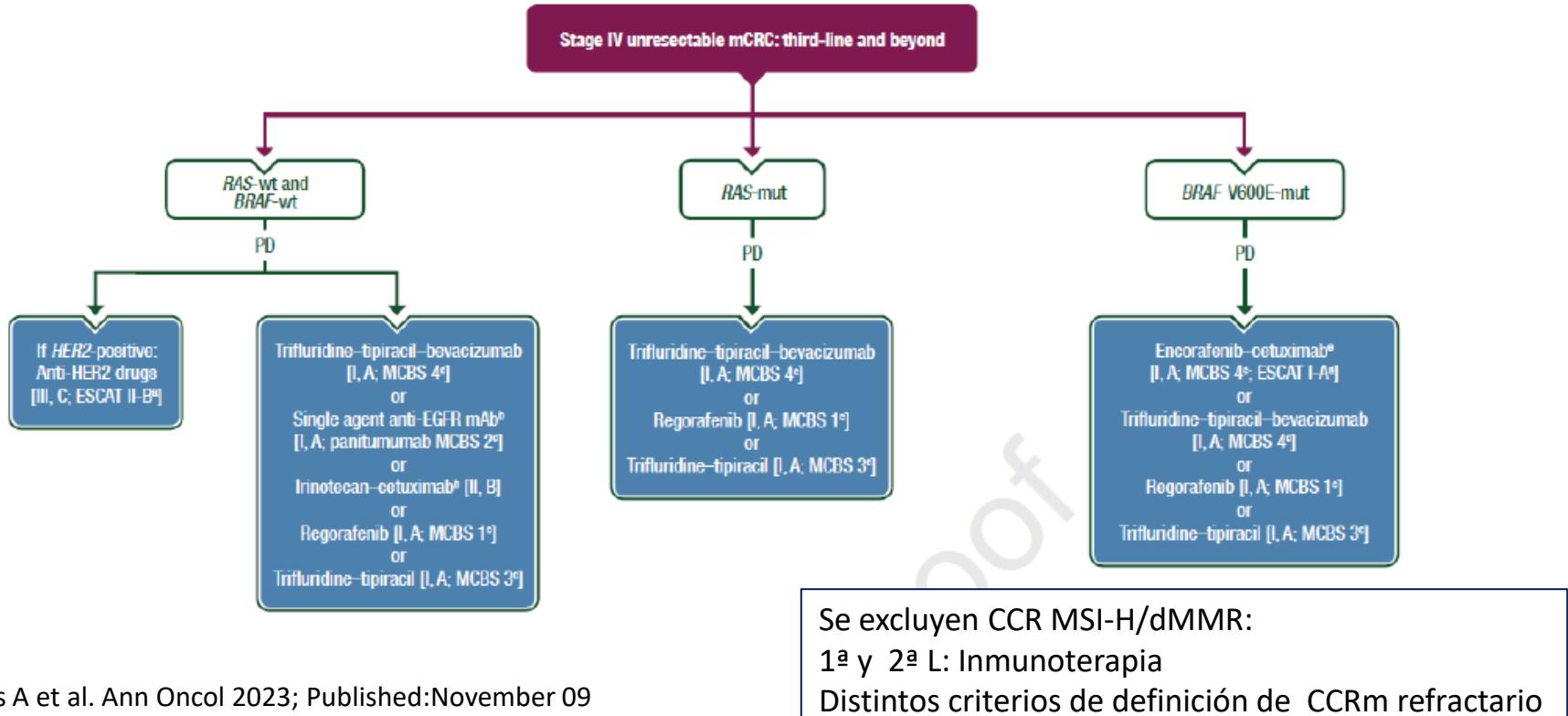
Introducción

- En 1^a y 2^a líneas de CCRm MSS/pMMR, el oxaliplatino, irinotecan, fluoropirimidinas, generalmente asociados a antiangiogénicos o anti-EGFR (RAS/BRAF wt), son los tratamientos sistémicos estándares
- Sin embargo, la mayoría de los pacientes desarrollan intolerancia o progresan a estos fármacos (CCRm refractario), y es necesario disponer de esquemas de $\geq 3^{\text{a}}$ línea que **prolonguen la supervivencia**
- Por otro lado, el CCRm es una enfermedad heterogénea, con distintos subtipos moleculares, y el perfil mutacional de RAS/BRAF puede modificarse con el tiempo en ciertos pacientes



ESMO Guidelines 2023

Stage IV unresectable mCRC: third-line treatment and beyond.



> 3^a línea para CCRm MSS/pMMR

SIN SELECCIÓN POR BIOMARCADORES

- Trifluridina/tipiracilo ± bevacizumab
- Regorafenib
- Fruquintinib

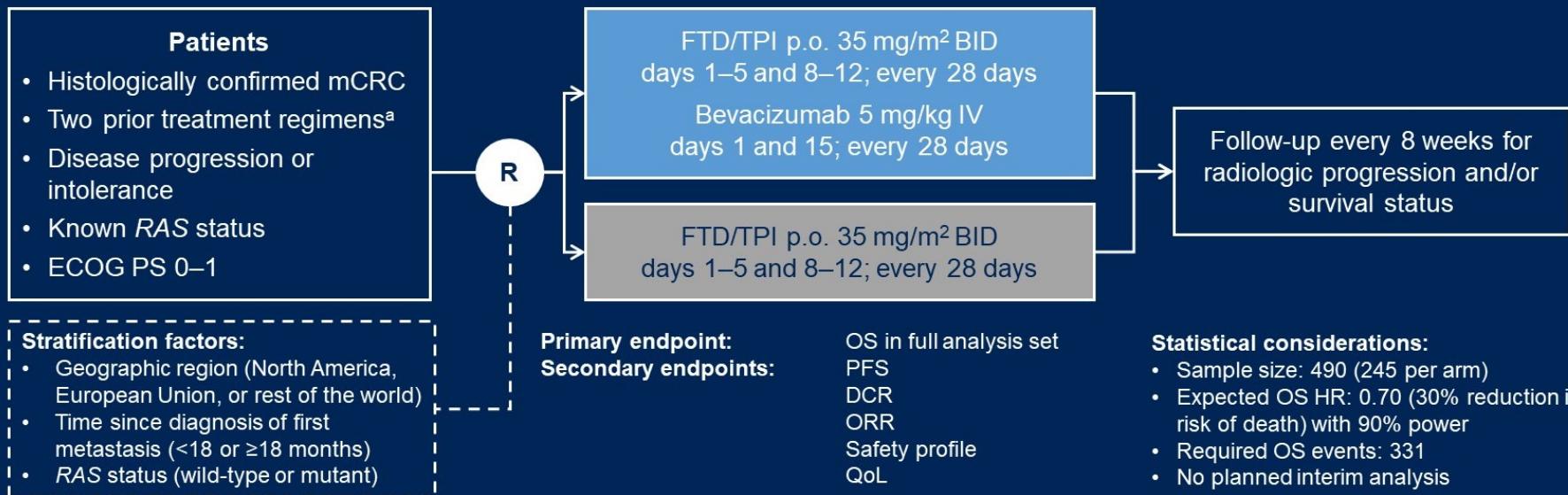
CON SELECCIÓN POR BIOMARCADORES

- Combinaciones con iBRAF (BRAF v600E mt)
- Inhibidores orales KRAS^{G12C} +/- AcMo antiEGFR (KRAS 12^C mt)
- Terapias anti-HER2 (HER2+)
- AcMo Anti-EFGR (RAS wt) (biopsia líquida)
- Otros

ALGUNOS COMERCIALIZADOS Y OTROS EN ENSAYO CLÍNICO

3^a línea sin selección molecular: SUNLIGHT

- An open-label, randomized, phase 3 study in patients with refractory mCRC (NCT04737187)

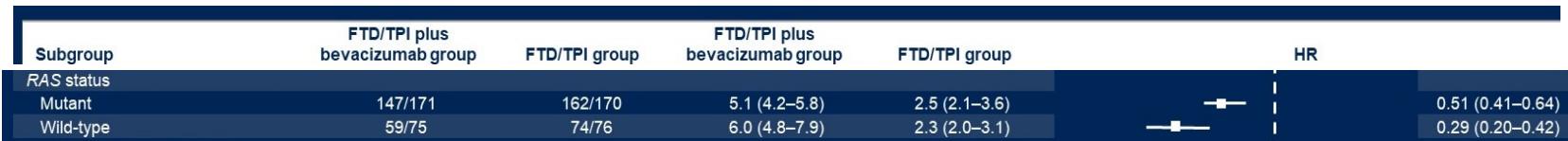
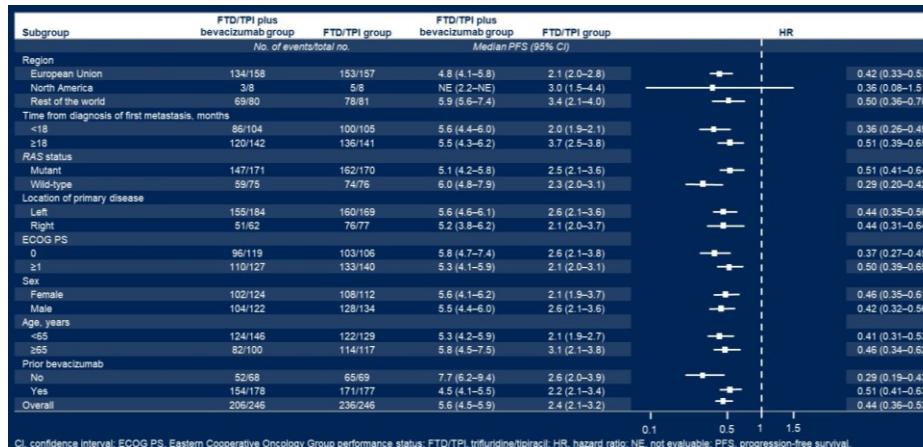
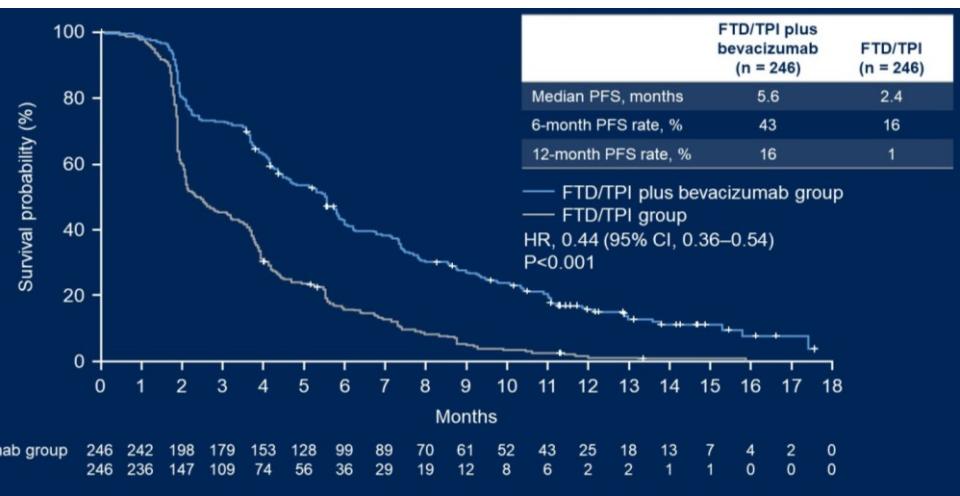


SUNLIGHT: RR, DCR, SLP y análisis por subgrupos

RR 6.3% vs 1%; p=0.004

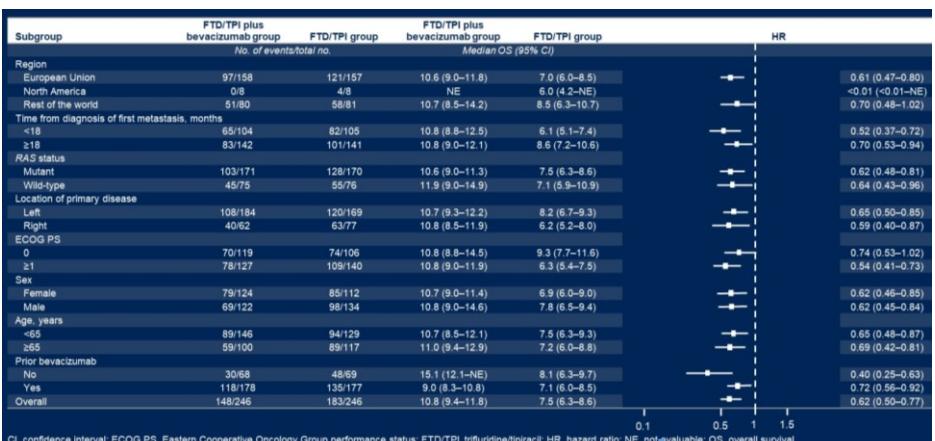
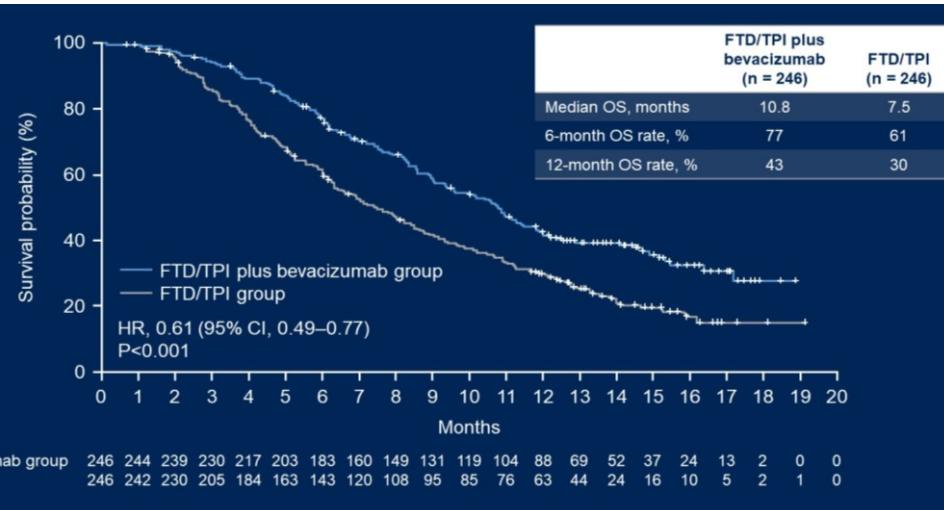
DCR 76.6% vs 47%; p<0.001

SLPm 5.6 vs 2.4 m



SUNLIGHT: SG y análisis por subgrupos

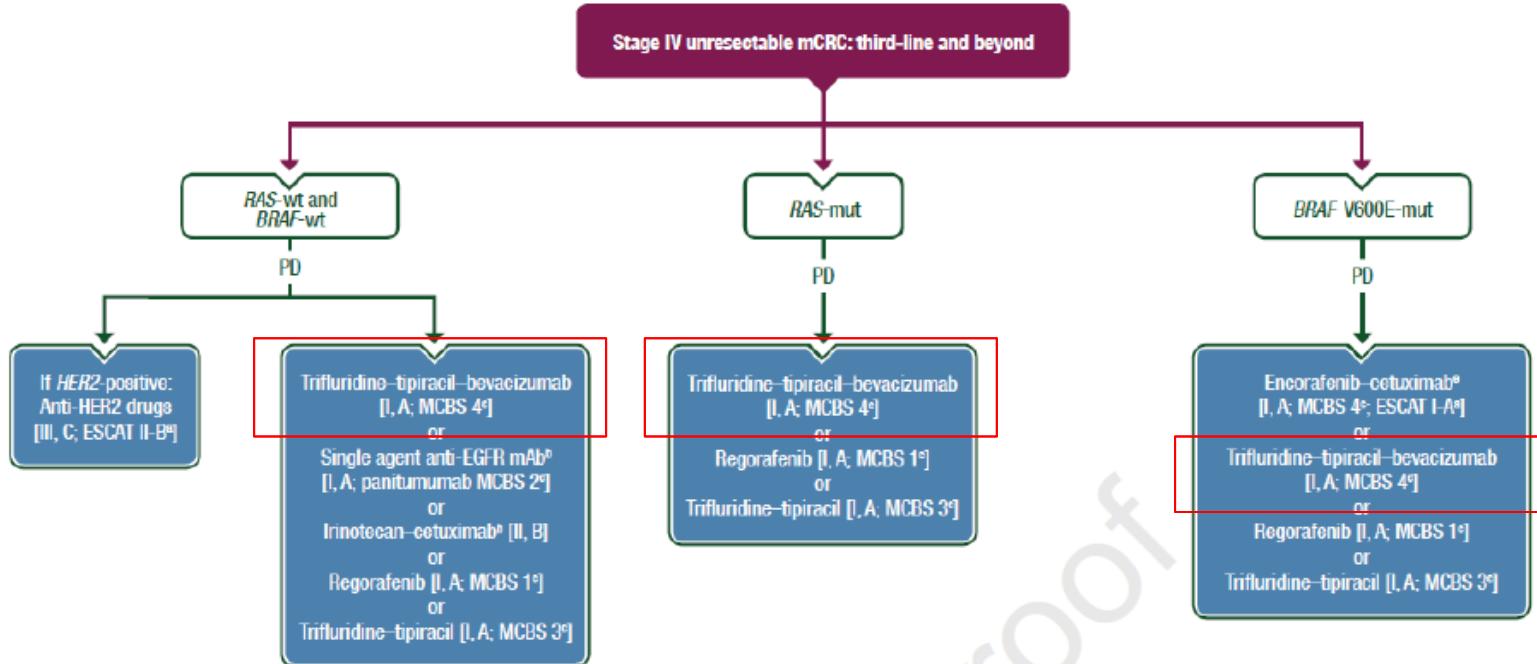
SGm 10.8 vs 7.5 m



Subgroup	FTD/TPI plus bevacizumab group	FTD/TPI group	FTD/TPI plus bevacizumab group	FTD/TPI group	HR
RAS status					
Mutant	103/171	128/170	10.6 (9.0–11.3)	7.5 (6.3–8.6)	0.62 (0.48–0.81)
Wild-type	45/75	55/76	11.9 (9.0–14.9)	7.1 (5.9–10.9)	0.64 (0.43–0.96)

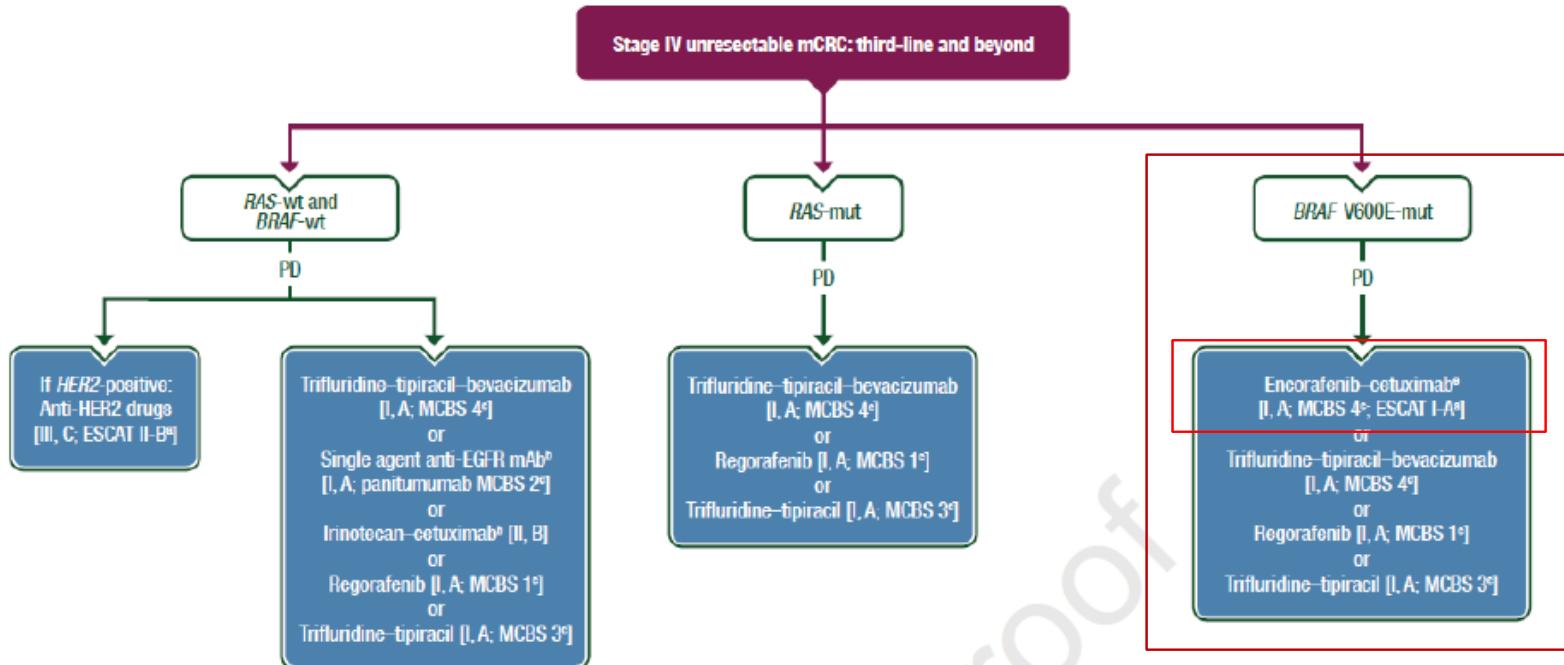
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Stage IV unresectable mCRC: third-line treatment and beyond.



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Stage IV unresectable mCRC: third-line treatment and beyond.

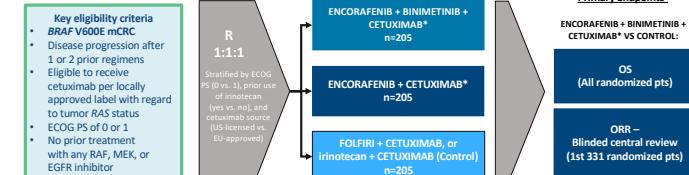


Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated BRAF V600E-Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study

Jain Salterman, MD, PhD¹; Anil Gishley, MD¹; Eric Van Cutsem, MD, PhD²; Rosa Vergier, MD³; Hapreet Wassan, MD⁴; Takayuki Kubono, MD, PhD⁵; Jayash Desai, MBBS⁶; Fernando Cardoso, MD, PhD⁷; Fabio Lanza, MD, PhD⁸; Yong Sung Hong, MD, PhD⁹; Heetic Steeghs, MD, PhD¹⁰; Tommo Kyra Gunes, MD, PhD¹¹; Hendrik-Tobias Arenzus, MD, PhD¹²; Pilar Garcia-Alfaro, MD¹³; Elena Ezer, MD, PhD¹⁴; Ashwin Golombok, MD¹⁵; Kelli Maharry, PhD¹⁶; Anna Chiriboga-Hel, MSN¹⁷; and Scott Kopetz, MD, PhD¹⁸

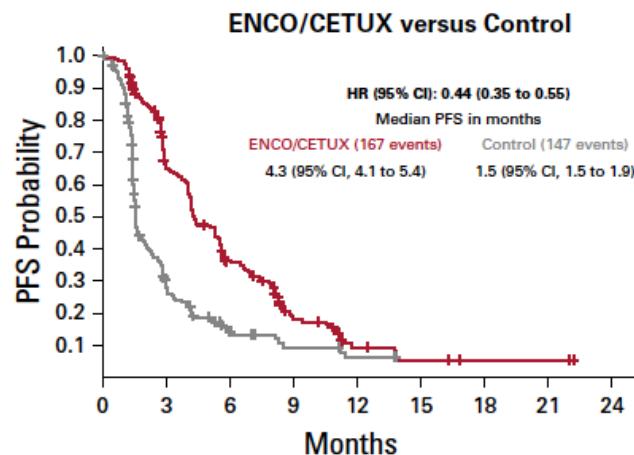
J Clin Oncol 39:273-284. © 2021

BRAF v600E mt

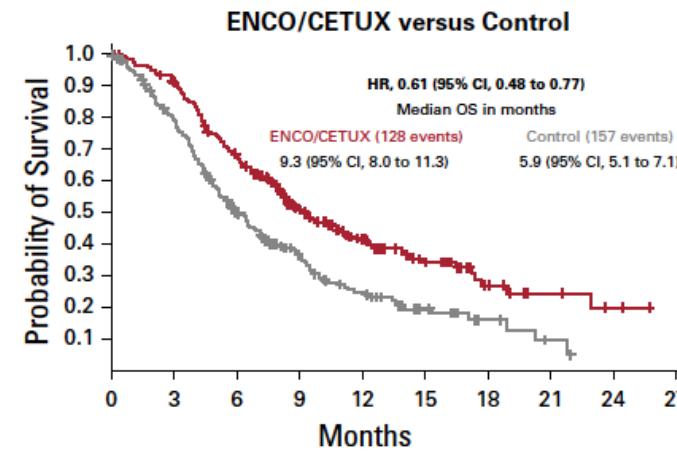


Encorafenib + Cetuximab RR 20%. SLP 4.3 m. SG 9.3 m.

B



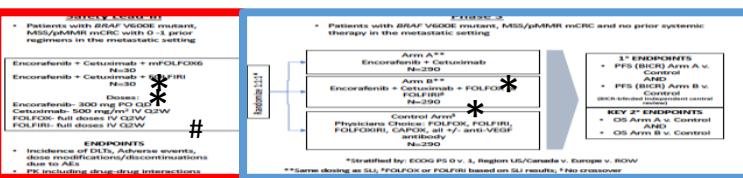
B



Encorafenib + Cetuximab: nuevo estándar para CCRm BRAF^{V600E} mt (2^a o 3^a línea)

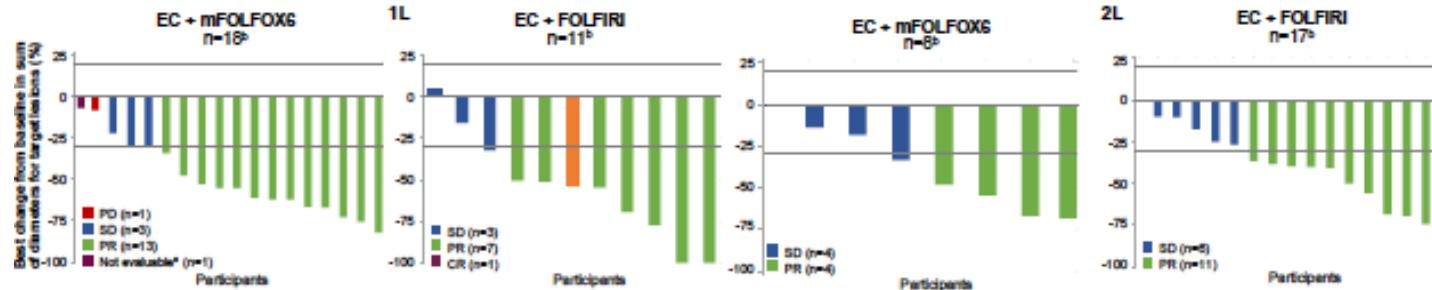
1^a LINEA: Fase III BREAKWATER parte de safety lead-in (SLI)

BRAF v600E mt



1L ORR		2L ORR	
EC + mFOLFOX6	EC + FOLFIRI	EC + mFOLFOX6	EC + FOLFIRI
n=19	n=12	n=8	n=18
68.4%	66.7%	50.0%	61.1%
68.4%	75%	37.5%	44.4%

ASCO-GI 2023

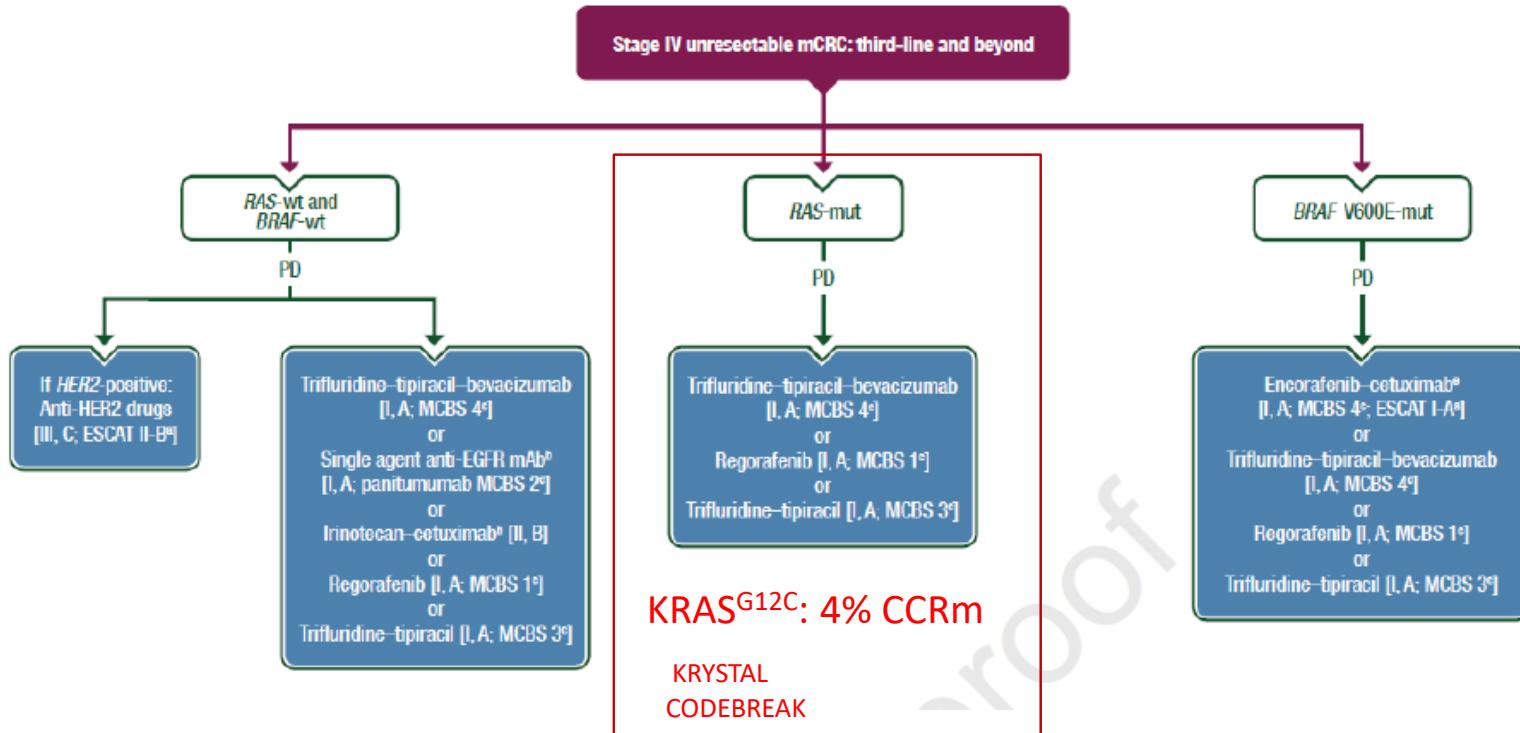


1L OPFS		2L PFS	
EC + mFOLFOX6	EC + FOLFIRI	EC + mFOLFOX6	EC + FOLFIRI
n=19	n=12	n=8	n=18
9.9 mos	NR	9.7 mos	NR
11.1 m	NE	10.8 m	12.6 m

ASCO-GI 2023

ESMO Guidelines 2023

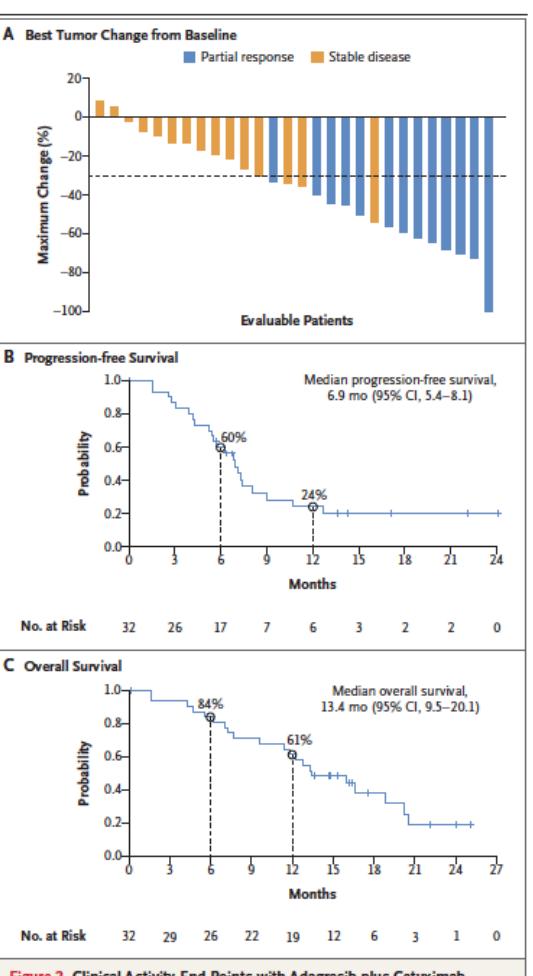
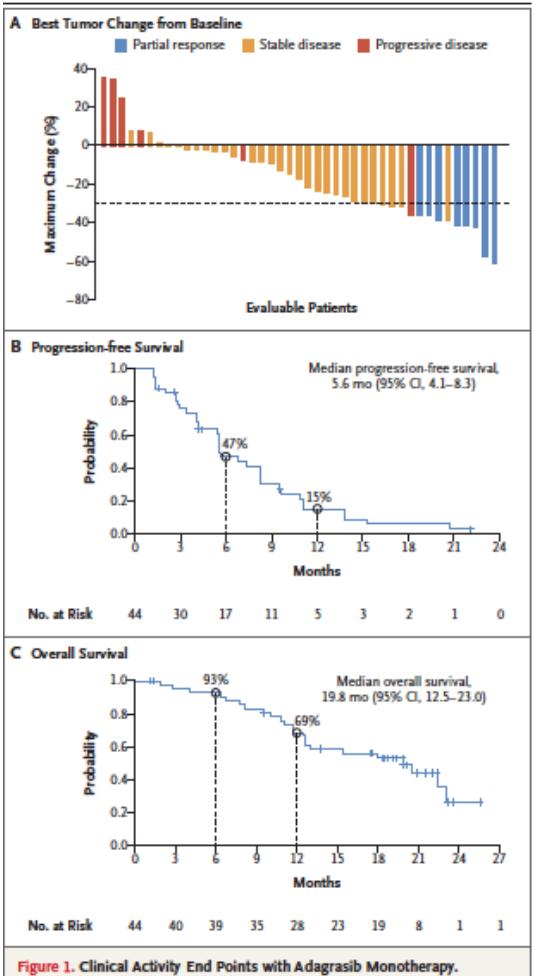
Stage IV unresectable mCRC: third-line treatment and beyond.



> 2^a LINEA: Fase I-II KRYSTAL 1

Adagrasib Monoterapia

N= 44
RR 19%
DCR 86%
SLPm 5.6 m
SGm 19.8 m



Adagrasib + Cetuximab

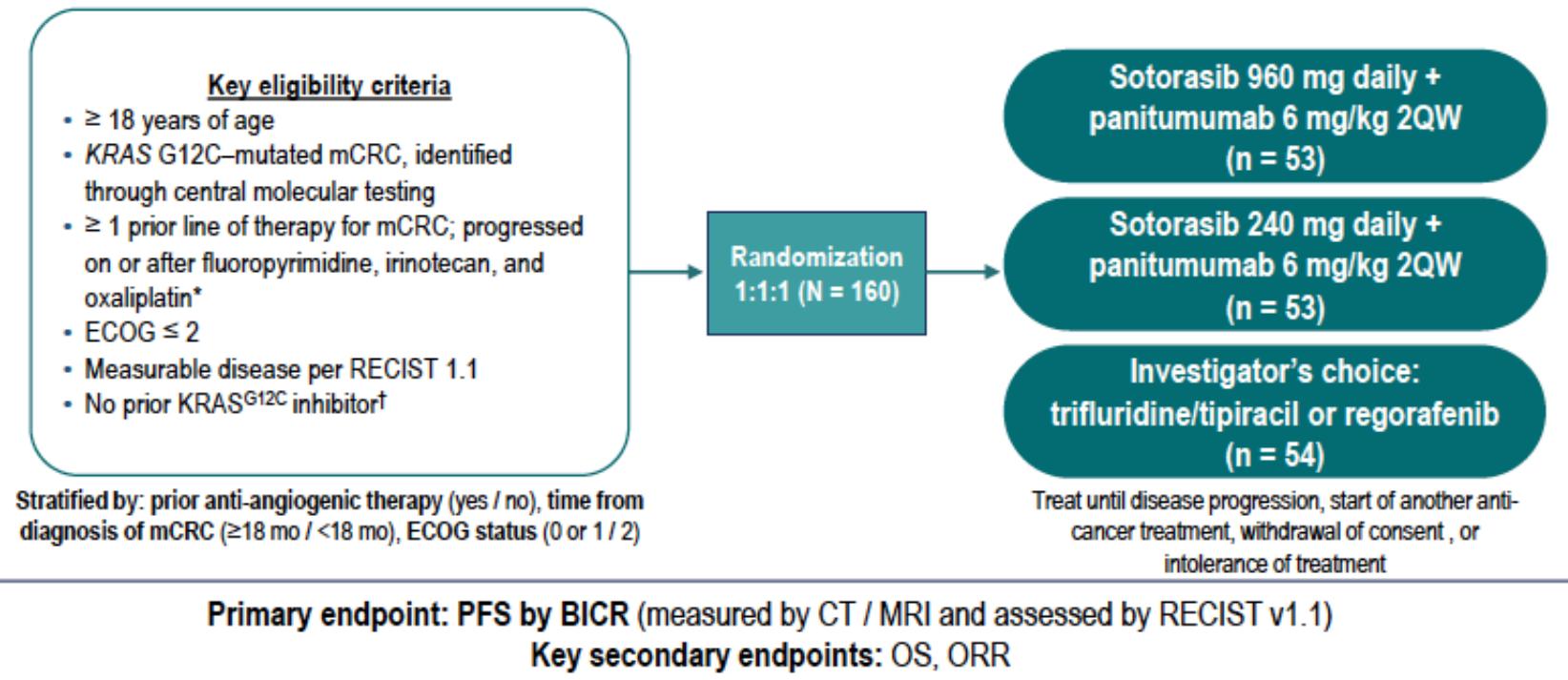
N= 32
RR 46%
DCR 100%
SLPm 6.9 m
SGm 13.4 m

Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated KRAS G12C

Rona Yaeger, M.D., Jared Weiss, M.D., Meredith S. Peltier, M.D., Alexander I. Spirra, M.D., Ph.D., Michael Barone, M.D., Shih-Chieh Ou, M.D., Tigran Ghosh, M.D., Thomas S. Bruck-Sabb, M.D., Michael P. Pannier, Ph.D., Grace A. Hesvey, B.S., James G. Christensen, Ph.D., Karen Velasquez, B.Sc., Tianan Kheoh, Ph.D., Hirak Der-Torossian, M.D., and Samuel J. Klempner, M.D.

> 2ª LINEA: Fase III CodeBreak 300

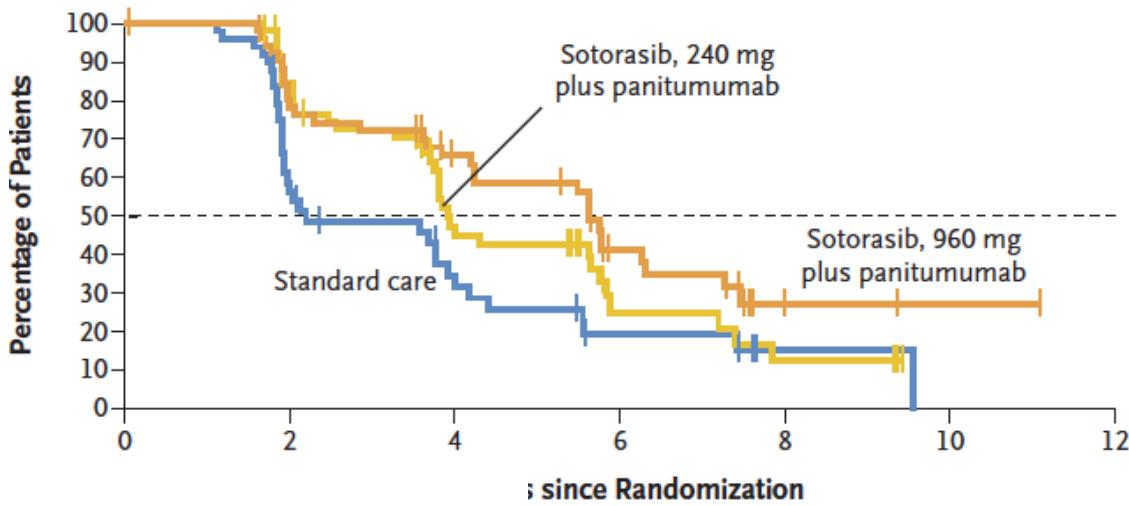
Global, randomized, open-label, active-controlled study of sotorasib + panitumumab in mCRC (NCT05198934)



Progression-free Survival (Intention-to-Treat Population)

ORR: 26.4% vs 5.7% vs 0%

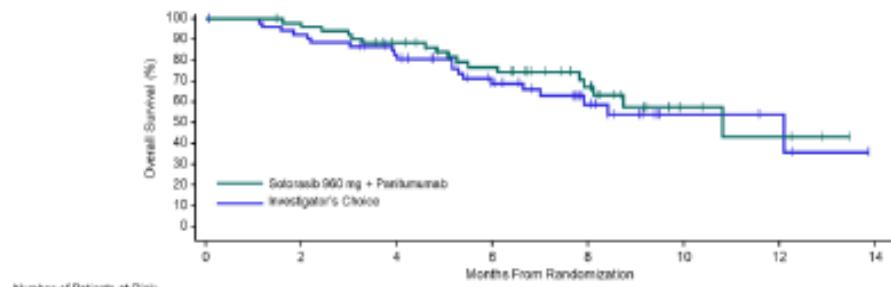
Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated KRAS G12C
M.G. Fakih, L. Salvatore, T. Esaki, D.P. Modest, D.P. Lopez-Bravo, J. Taleb,
M.V. Karamouzi, E. Ruiz-Garcia, T.-W. Kim, Y. Kuboki, F. Merigli,
D. Cunningham, K.-H. Yeh, E. Chan, J. Chao, Y. Sapotatos, Q. Tran,
C. Cremolini, and F. Petrelli



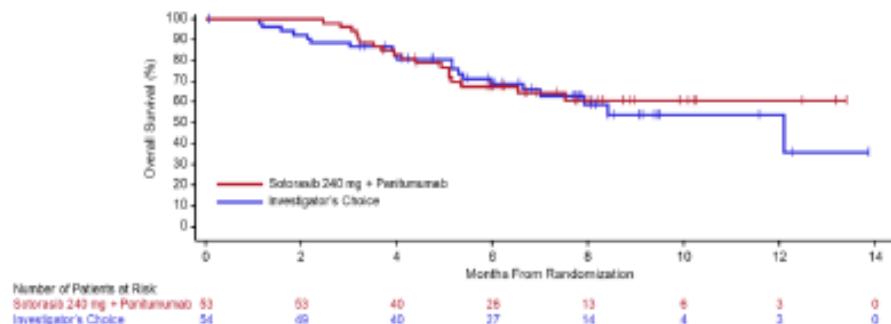
	Median Progression-free Survival mo	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
Sotorasib, 960 mg plus Panitumumab	5.62	0.49 (0.30–0.80)	0.006
Sotorasib, 240 mg plus Panitumumab	3.91	0.58 (0.36–0.93)	0.03
Standard Care	2.20		

B Subgroup Analysis for Progression-free Survival — Sotorasib, 960 mg plus Panitumumab				
Subgroup	Sotorasib, 960 mg plus Panitumumab no. of patients	Standard Care no. of patients	Hazard Ratio for Disease Progression or Death (95% CI)	P value
All patients	53	54	0.49 (0.30–0.80)	
Age				
<65 yr	32	27	0.52 (0.36–1.04)	
≥65 yr	21	27	0.43 (0.20–0.92)	
Sex				
Male	29	24	0.59 (0.30–1.15)	
Female	24	30	0.35 (0.17–0.73)	
Time from initial diagnosis of metastatic disease to randomization				
≤18 mo	29	31	0.42 (0.20–0.84)	
>18 mo	24	23	0.31 (0.24–1.07)	
Location of tumor				
Right side	24	16	0.41 (0.19–0.90)	
Left side	28	37	0.62 (0.32–1.20)	
Body site at initial diagnosis				
Colon	37	37	0.45 (0.25–0.80)	
Rectum	16	17	0.57 (0.24–1.31)	
No. of lines of previous therapy for metastatic disease				
1–2	37	28	0.39 (0.21–0.72)	
≥3	16	26	0.58 (0.22–1.47)	
Liver metastasis				
Yes	38	38	0.35 (0.20–0.61)	
No	15	16	0.82 (0.30–2.21)	
C Subgroup Analysis for Progression-free Survival — Sotorasib, 240 mg plus Panitumumab				
Subgroup	Sotorasib, 240 mg plus Panitumumab no. of patients	Standard Care no. of patients	Hazard Ratio for Disease Progression or Death (95% CI)	P value
All patients	53	54	0.58 (0.36–0.92)	
Age				
<65 yr	39	27	0.63 (0.32–1.23)	
≥65 yr	14	27	0.36 (0.14–0.91)	
Sex				
Male	26	24	0.71 (0.37–1.37)	
Female	27	30	0.63 (0.31–1.02)	
Time from initial diagnosis of metastatic disease to randomization				
≤18 mo	29	31	0.49 (0.25–0.97)	
>18 mo	22	23	0.78 (0.40–1.52)	
Location of tumor				
Right side	17	16	0.59 (0.27–1.32)	
Left side	36	37	0.58 (0.33–1.03)	
Body site at initial diagnosis				
Colon	32	37	0.53 (0.30–0.95)	
Rectum	21	17	0.47 (0.21–1.02)	
No. of lines of previous therapy for metastatic disease				
1–2	29	28	0.56 (0.31–1.02)	
≥3	24	26	0.58 (0.27–1.26)	
Liver metastasis				
Yes	36	38	0.47 (0.28–0.80)	
No	17	16	0.56 (0.20–1.31)	
Sotorasib, 960 mg plus Panitumumab Better Standard Care Better				
Sotorasib, 240 mg plus Panitumumab Better Standard Care Better				
Sotorasib, 240 mg plus Panitumumab Better Standard Care Better				

Overall Survival



	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
HR (95% CI)*	0.77 (0.41, 1.45)	0.91 (0.48, 1.71)	–
Deaths, n (%)	17 (32)	18 (34)	20 (37)
Median follow-up, months (95% CI)	8.1 (6.7, 8.7)	7.7 (6.2, 8.3)	7.8 (6.5, 8.5)



Overall survival data were not mature at data cutoff, with 55 (34%) deaths observed

Sotorasib (Soto) plus panitumumab (Pmab) and FOLFIRI for previously treated KRAS G12C-mutated metastatic colorectal cancer (mCRC): CodeBreak 101 phase 1b safety and efficacy.

David S. Hong, Yasutoshi Kuboki, John H Strickler, Marwan Fakih, Hélène Houssiau, Timothy Jay Price, Elena Elez, Salvatore Siena, Emily Chan, Jane Nolte-Hippenmeyer, Panli Cardona, Qui Tran, Toshiki Masuishi; University of Texas MD Anderson Cancer Center, Houston,

N= 33 tratados previamente con ≥ 2 líneas



1ª LINEA: Fase III

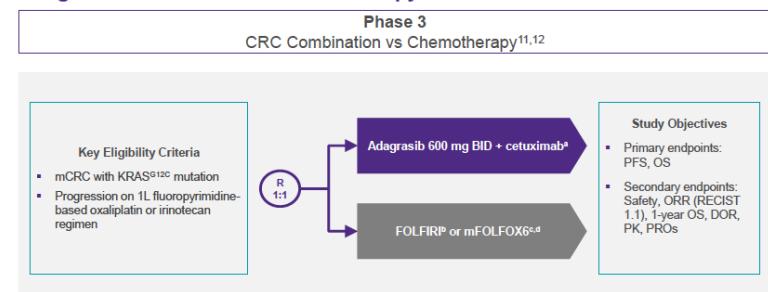
ORR: 58%

DCR: 93.5%

SLP y SG: no maduros

2ª LINEA: Fase III KRYSTAL-10

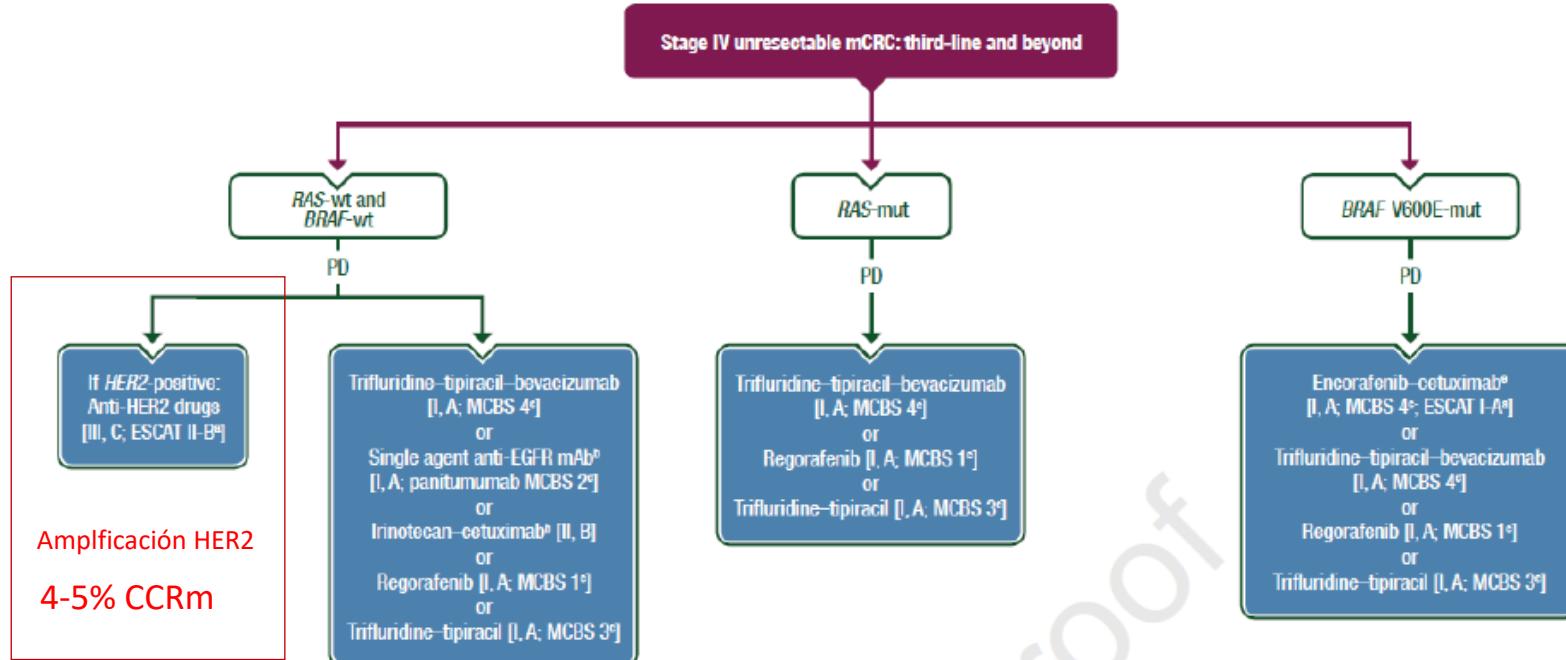
KRYSTAL-10 (849-010) Global, Phase 3, Randomized, Open-Label Trial of 2L Adagrasib + Cetuximab vs Chemotherapy in mCRC With KRAS^{G12C} Mutation



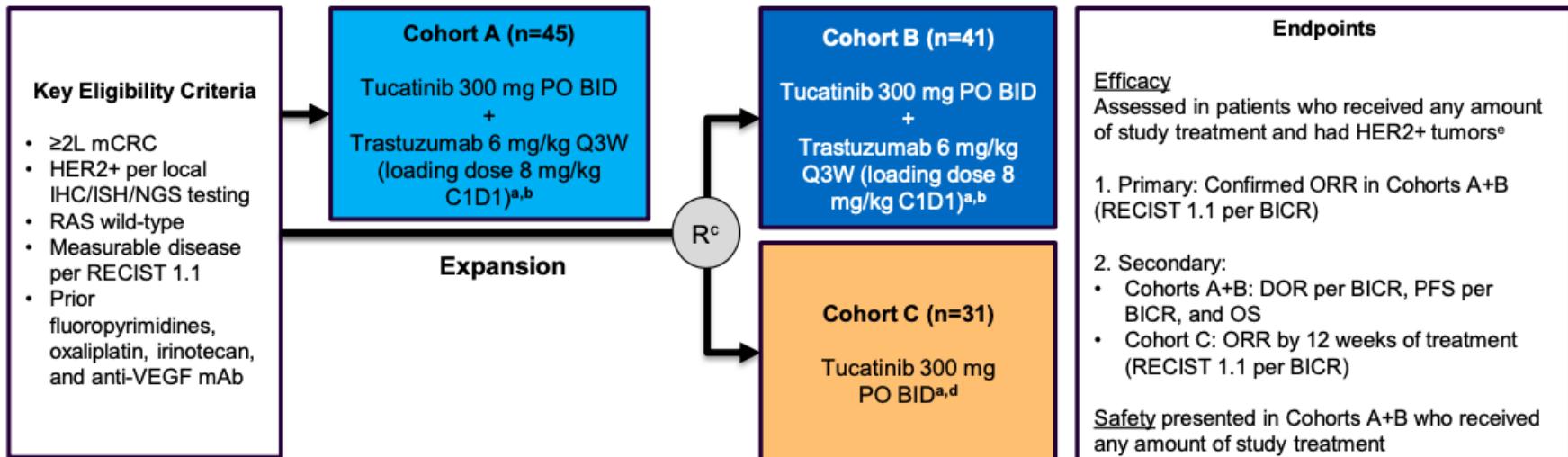
Cerrado reclutamiento oct 2023

ESMO Guidelines 2023

Stage IV unresectable mCRC: third-line treatment and beyond.



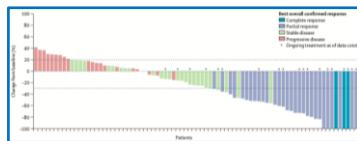
EC MOUNTAINEER



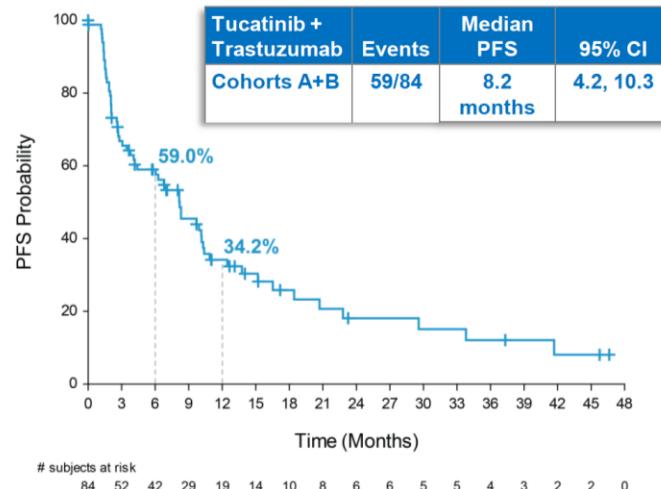
MOUNTAINEER began as a US Investigator-Sponsored Trial and initially consisted of a single cohort (Cohort A) and was expanded globally to include patients randomised to receive tucatinib + trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C)

Tucatinib + Trastuzumab: ORR, Change in Tumor Size, PFS, OS

ORR 38.1%
DORm 12.4 m

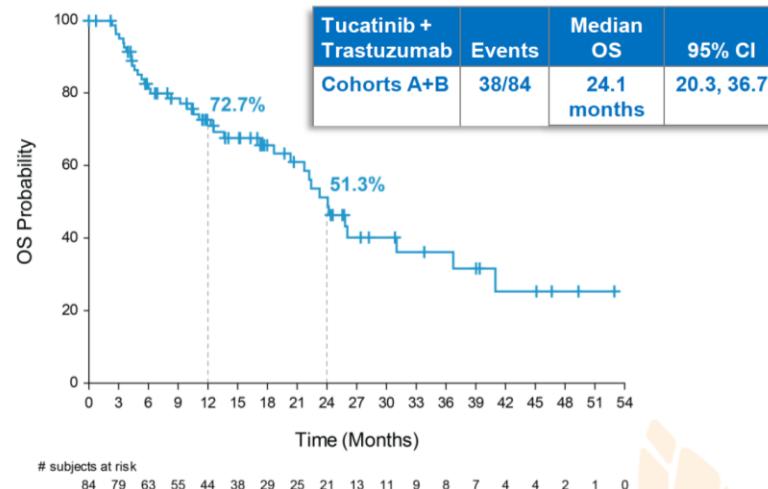


Progression-free Survival per BICR



Median follow-up for Cohorts A+B was 20.7 months (IQR, 11.7, 39.0)

Overall Survival



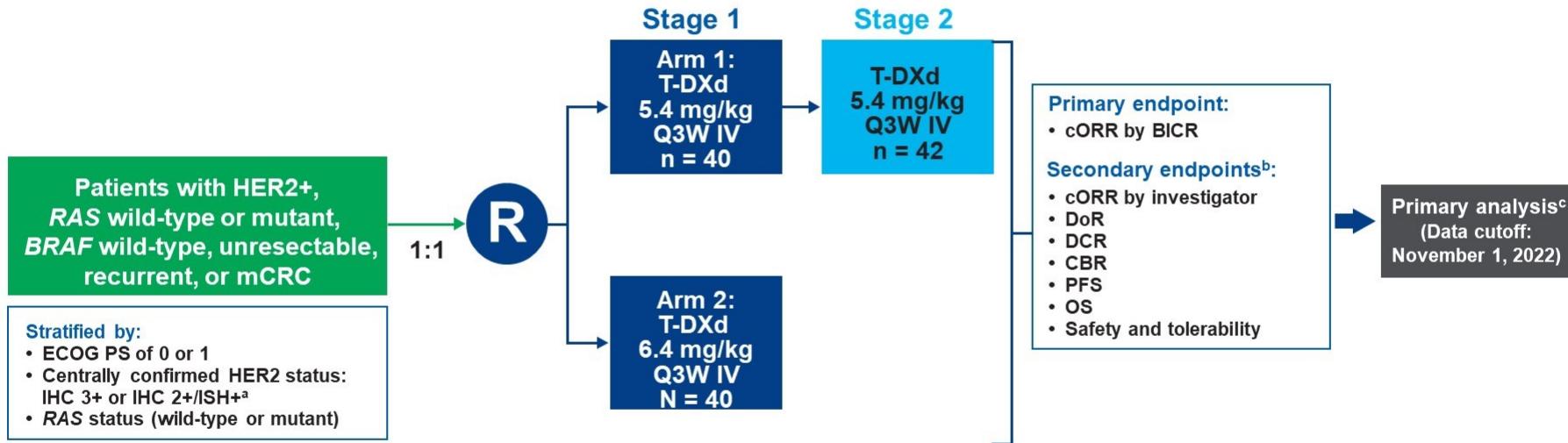
BICR, blinded independent central review; IQR, interquartile range; OS, overall survival; PFS, progression-free survival.



DESTINY-CRC02 Study Design

A randomized, blinded, 2-stage, 2-arm, multicenter, global, phase 2 study (NCT04744831)

- Stage 1 (randomized) was followed by Stage 2 (nonrandomized), which enrolled an additional 42 patients



This study was not powered to statistically compare the two arms.

BICR, blinded independent central review; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate; cORR, confirmed objective response rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RAS, rat sarcoma; T-DXd, trastuzumab deruxtecan.

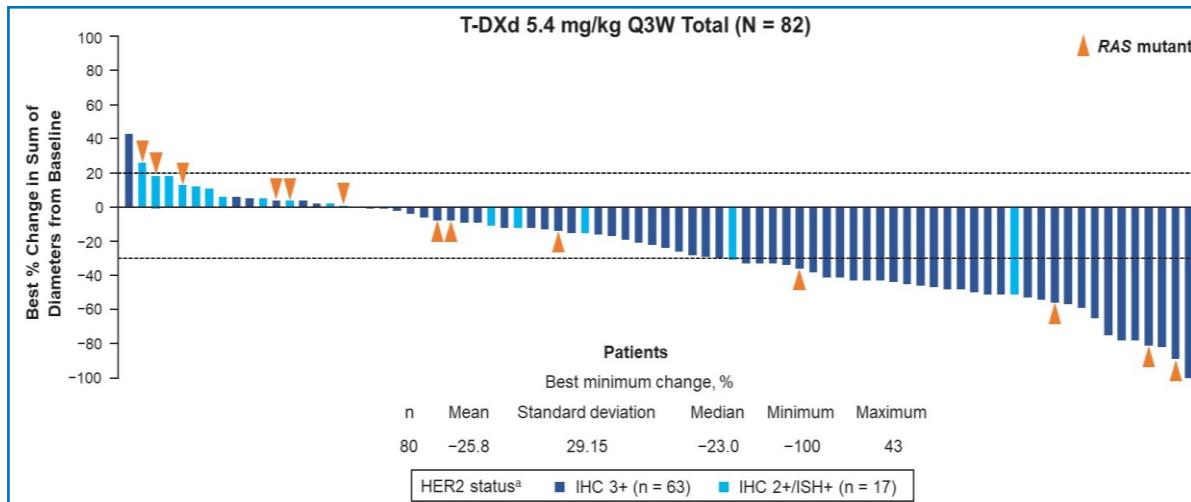
Both investigators and patients were blind to treatments.

^aHER2 status was assessed with the Roche VENTANA HER2 Dual ISH DNA probe cocktail assay (ILO). ^bExploratory endpoints included best percent change in the sum of diameters of measurable tumors based on BICR and investigator. ^cPrimary analysis occurred ≥6 months after the last patient had been enrolled or when all patients discontinued from the study, whichever was earlier.

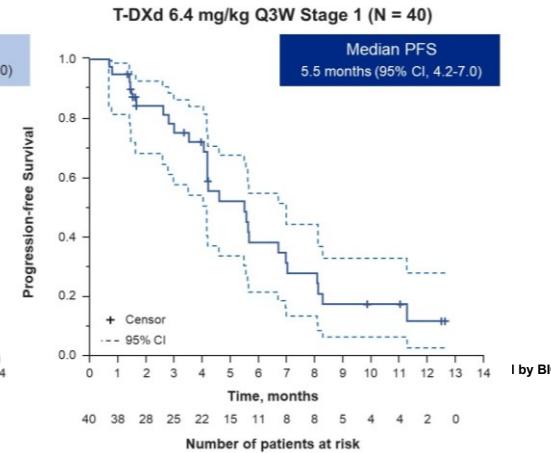
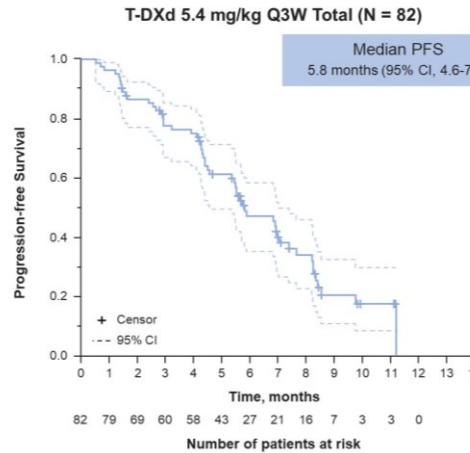
Efficacy Results

20-25% habían recibido tto antiHER2 previo

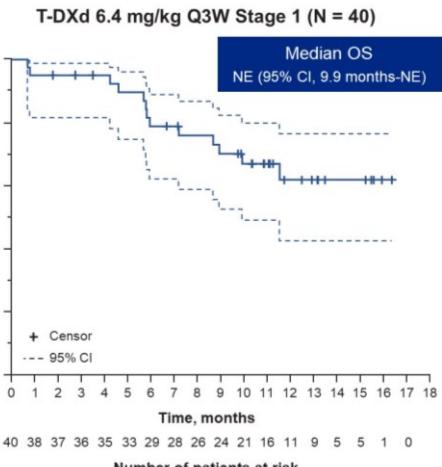
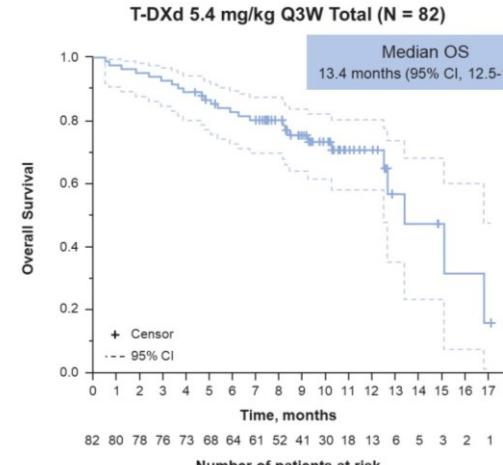
	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
cORR, n (%) [95% CI]	18 (45.0) [29.3-61.5]	13 (31.0) [17.6-47.1]	31 (37.8) [27.3-49.2]	11 (27.5) [14.6-43.9]
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)



Median Progression-Free Survival by BICR



Median Overall Survival

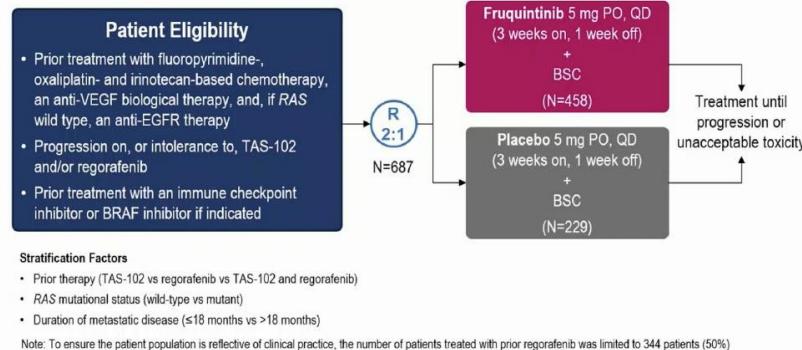


Principales estudios fase III en marcha en CCRm HER2+

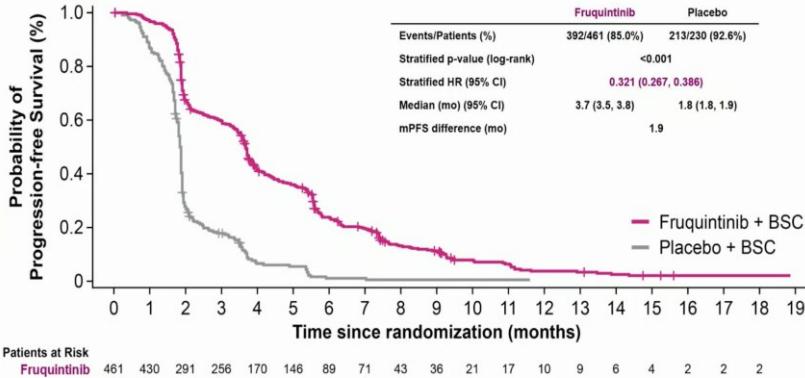
Trial	Phase	Line	Endpoint	Treatment
MOUNTAINEER-03 (NCT05253651)	III	1st	PFS	mFOLFOX6+tucatinib+trastuzumab vs mFOLFOX6+bevacizumab or +cetuximab
SWOG-1613 (NCT03365882)	III	2 nd - 3 rd	PFS	Cetuximab+irinotecan vs trastuzumab+pertuzumab

Mas allá de 3^a línea sin selección molecular: FRESCO-2

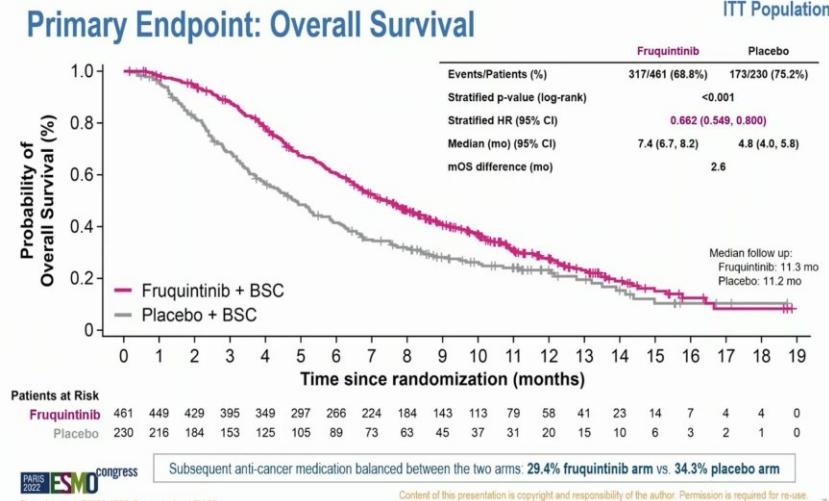
FRESCO-2 Study Design



Progression-Free Survival



Primary Endpoint: Overall Survival



Conclusiones

- TAS 102 + bevacizumab es superior a TAS 102 en 3^a L en CCRm sin selección molecular
- Regorafenib y fruquintinib son superiores a placebo en CCRm refractario sin selección molecular
- Otras opciones para subgrupos moleculares
 - $BRAF^{V600E}$ mt: encorafenib + cetuximab
 - $KRAS^{G12C}$ mt: adagrasib+ cetuximab o sotorasib + panitumumab
 - Amplificación HER2: trastuzumab + lapatinib, trastuzumab + tucatinib, trastuzumab + pertuzumab o trastuzumab deruxtecan
 - Los ensayos clínicos en marcha establecerán el papel de estas terapias en líneas previas y las secuencias
- Retratamiento para RAS/BRAF wt