Systemic Treatment for Peritoneal Carcinomatosis

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Disclosures

- Grant/Research Support from Genentech.
- Consultant for AbbVie, AstraZeneca, Eisai, Merck, and Pfizer.

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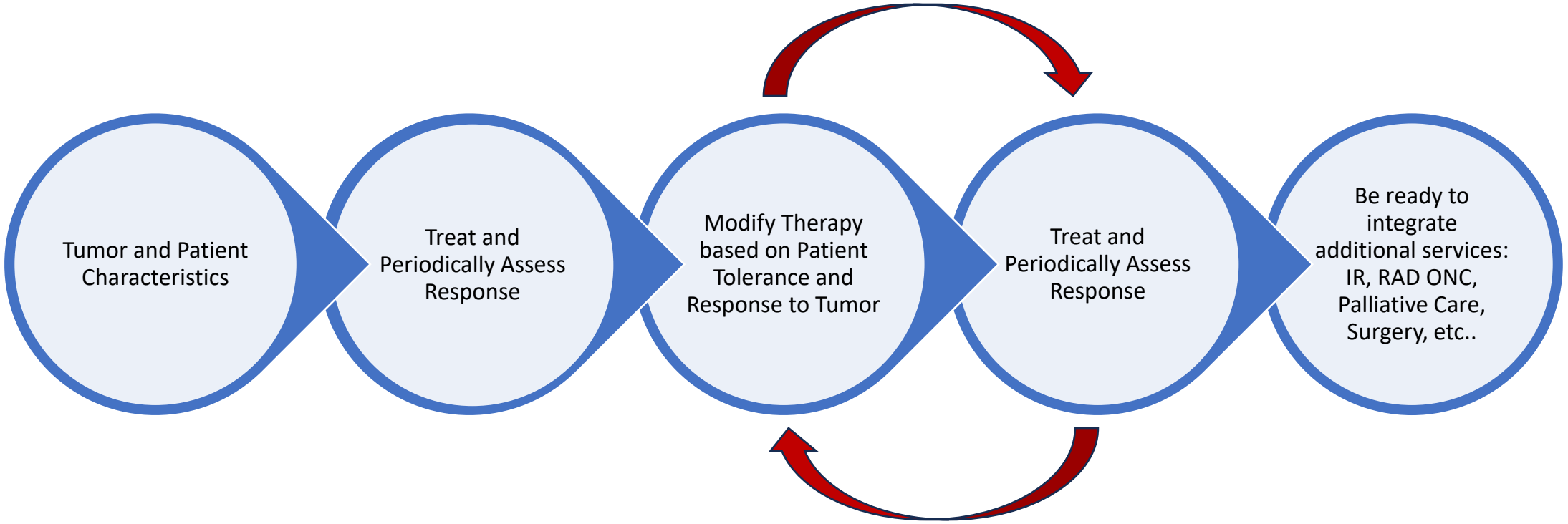
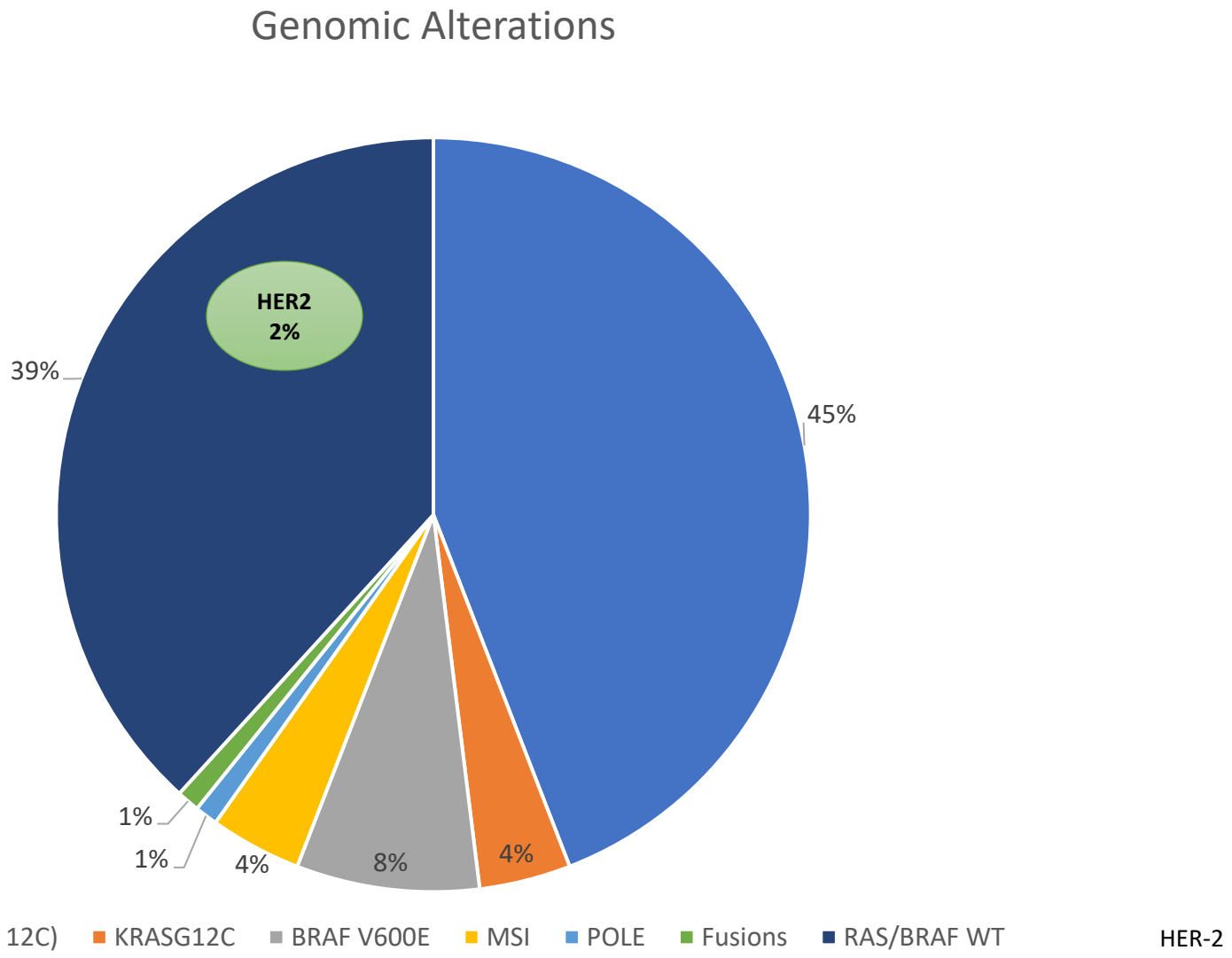
This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

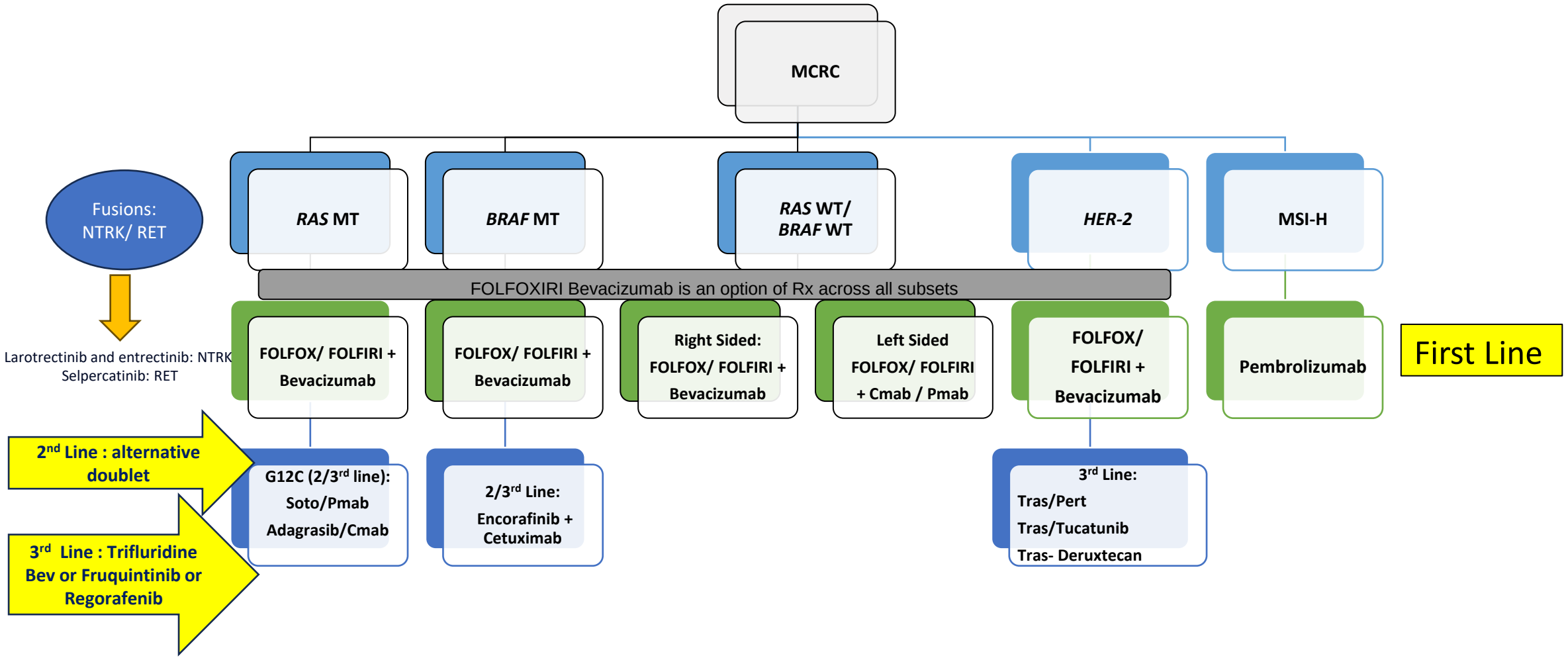
Unresectable Metastatic Colorectal Cancer



Metastatic Colorectal Cancer Pertinent Genomics

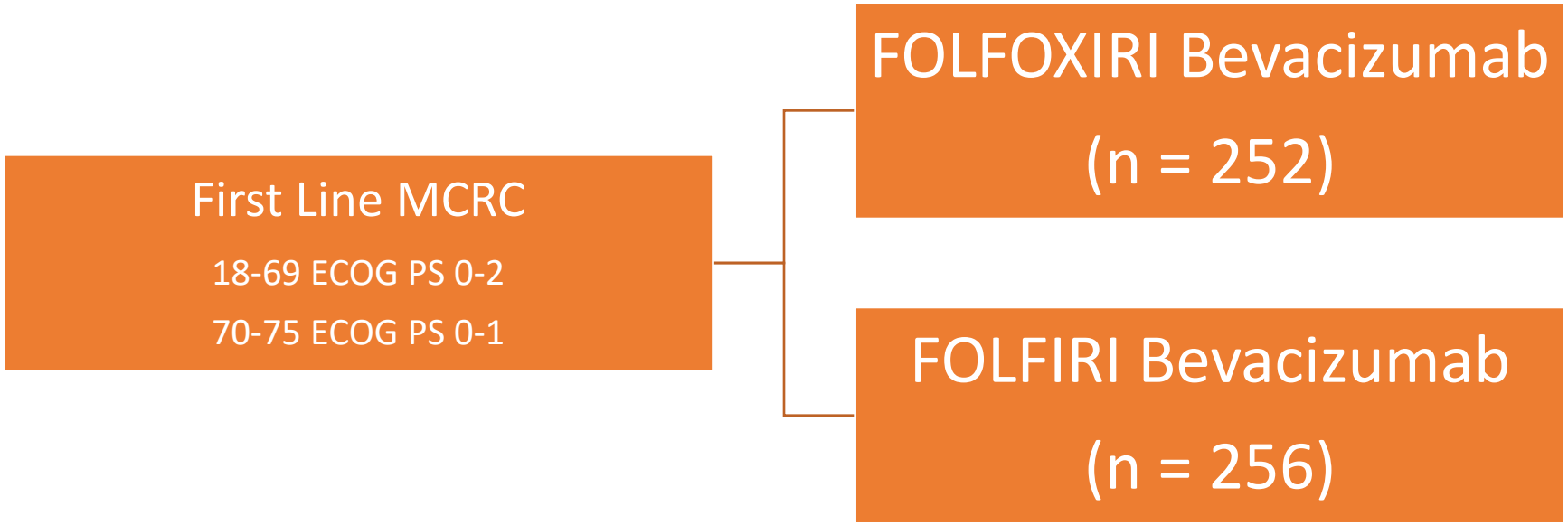


Optimal Outcomes are Dictated by Drug + Molecular Signature Matching



RAS and BRAF (especially) Mutant MCRC Patients Represent Populations with Poor Prognosis

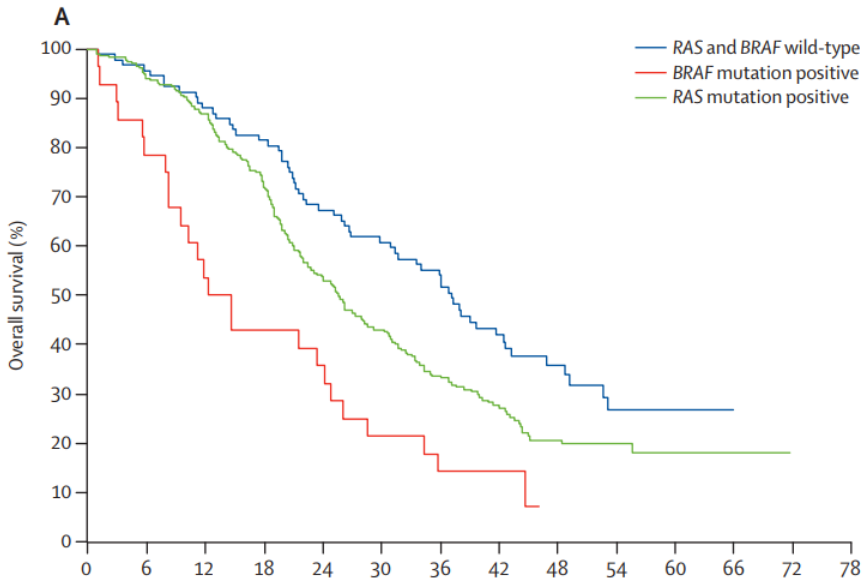
TRIBE Trial: FOLFOXIRI Bev vs FOLFIRI BEV

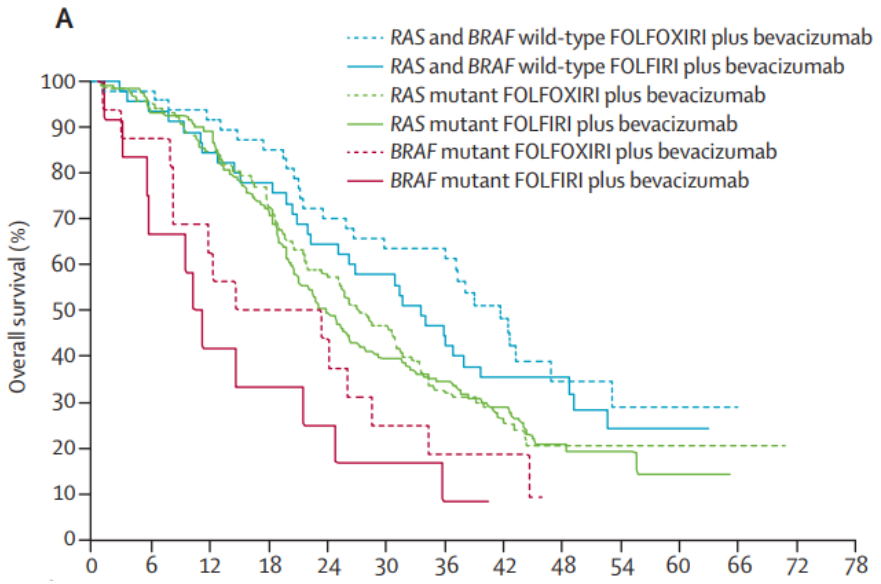


FOLFOXIRI Bev mOS 29·8 months (95% CI 26·0–34·3) compared with FOLFIRI Bev mOS 25·8 months (22·5–29·1) - (hazard ratio [HR] 0·80, 95% CI 0·65–0·98; p=0·03)

C Cermolini, Lancet Oncol 2015

RAS Mutations are associated with worse OS





mOS 37·1 months (95% CI 29·7–42·7) in the RAS/BRAF wild-type subgroup compared with 25·6 months (22·4–28·6) in the RAS-MT subgroup (HR 1·49, 95% CI 1·11–1·99), and 13·4 months (8·2–24·1) in the BRAF-MT subgroup (2·79, 1·75–4·46).

Inferior survival in RAS-MT compared to RAS/BRAF-WT is seen irrespective of the treatment arm.
FOLFOXIRI BEV resulted in better OS irrespective of the molecular subgroup

C Cermolini, Lancet Oncol 2015

PARADIGM Trial

PARADIGM Trial Design

Phase 3, randomized, open-label, multicenter study (NCT02394795)

Patients with *RAS* WT mCRC

- Unresectable disease
- No previous chemotherapy[a]
- Age: 20–79 years
- ECOG performance status 0–1
- At least 1 evaluable lesion
- Adequate organ function
- Life expectancy ≥ 3 months

N=823

R 1:1

Panitumumab +mFOLFOX6[b]

Bevacizumab +mFOLFOX6[b]

Primary endpoint
- OS: left-sided[c] population; if significant, analyzed in overall population

Secondary endpoints
- PFS, RR, DOR, R0 resection: left-sided[c] and overall populations
- Safety: all treated patients

Exploratory endpoints
- ETS, depth of response, DCR: left-sided[c] and overall populations

Stratification factors
- Institution
- Age: 20–64 vs 65–79 years
- Liver metastases: present vs absent

DCR, disease control rate; DOR; duration of response; ECOG, Eastern Cooperative Oncology Group; ETS, early tumor shrinkage; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; RR, response rate; R0, curative resection; WT, wild type.
[a]Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment. [b]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection.
[c]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum.

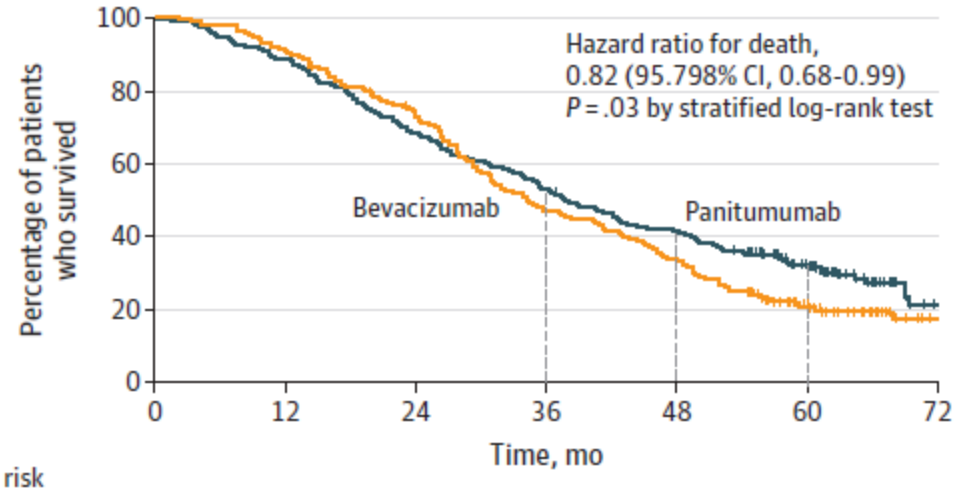
Primary Endpoints: 1) OS in left-sided RAS WT population; OS in overall population

Anti-EGFR is Superior to Bevacizumab in Left Sided Tumors

A Overall survival

Participants with left-sided tumors

	No. (%) of patients with events	Median survival, mo (95.798% CI)
Panitumumab plus mFOLFOX6 (n = 312)	218 (69.9)	37.9 (34.1-42.6)
Bevacizumab plus mFOLFOX6 (n = 292)	230 (78.7)	34.3 (30.9-40.3)



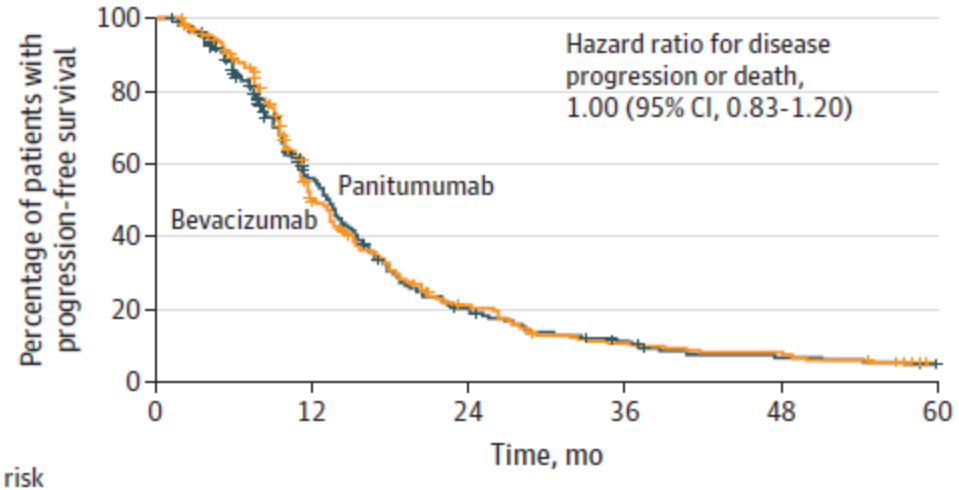
No. at risk

Panitumumab	312	276	213	166	129	68	5
Bevacizumab	292	266	212	136	96	40	5

B Progression-free survival

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)

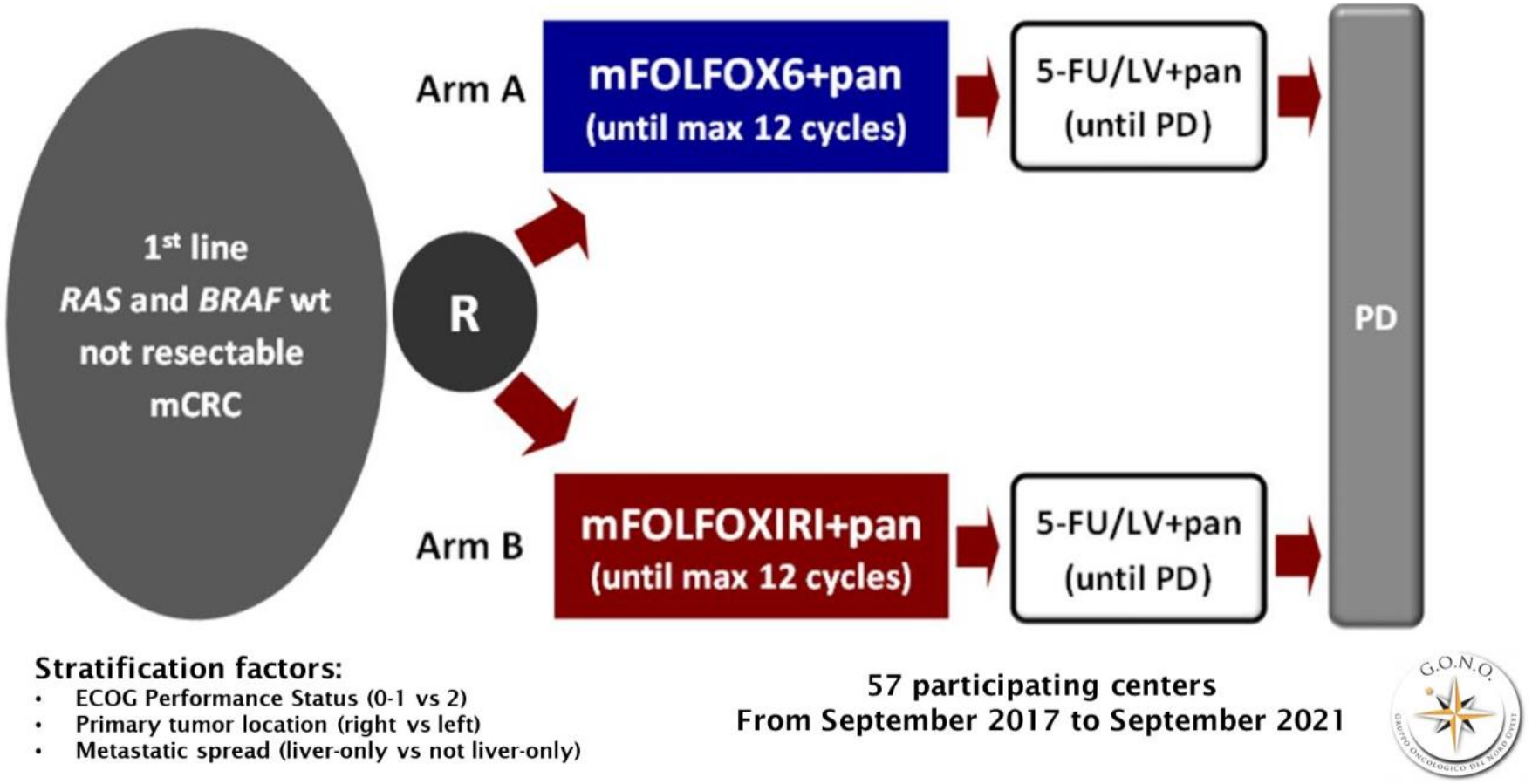


No. at risk

Panitumumab	312	123	40	21	12	7
Bevacizumab	292	115	43	22	15	5

Watanabe, J. JAMA 2023

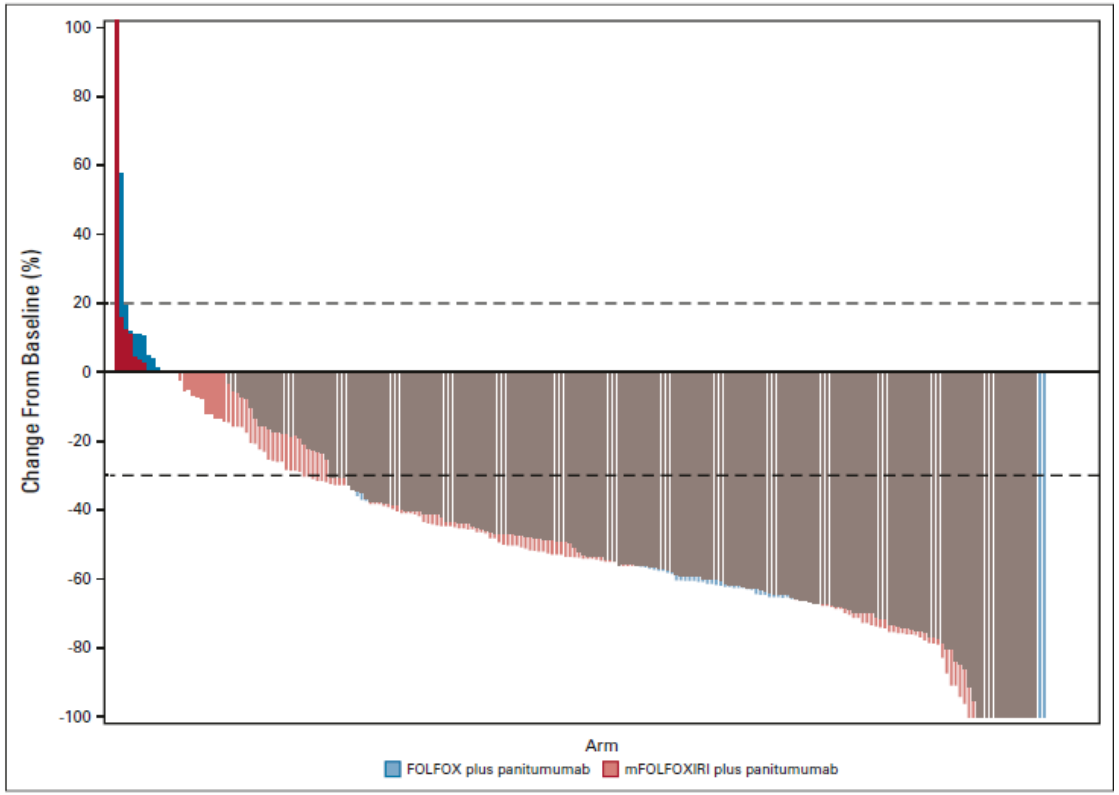
TRIPLETE Trial (GONO)

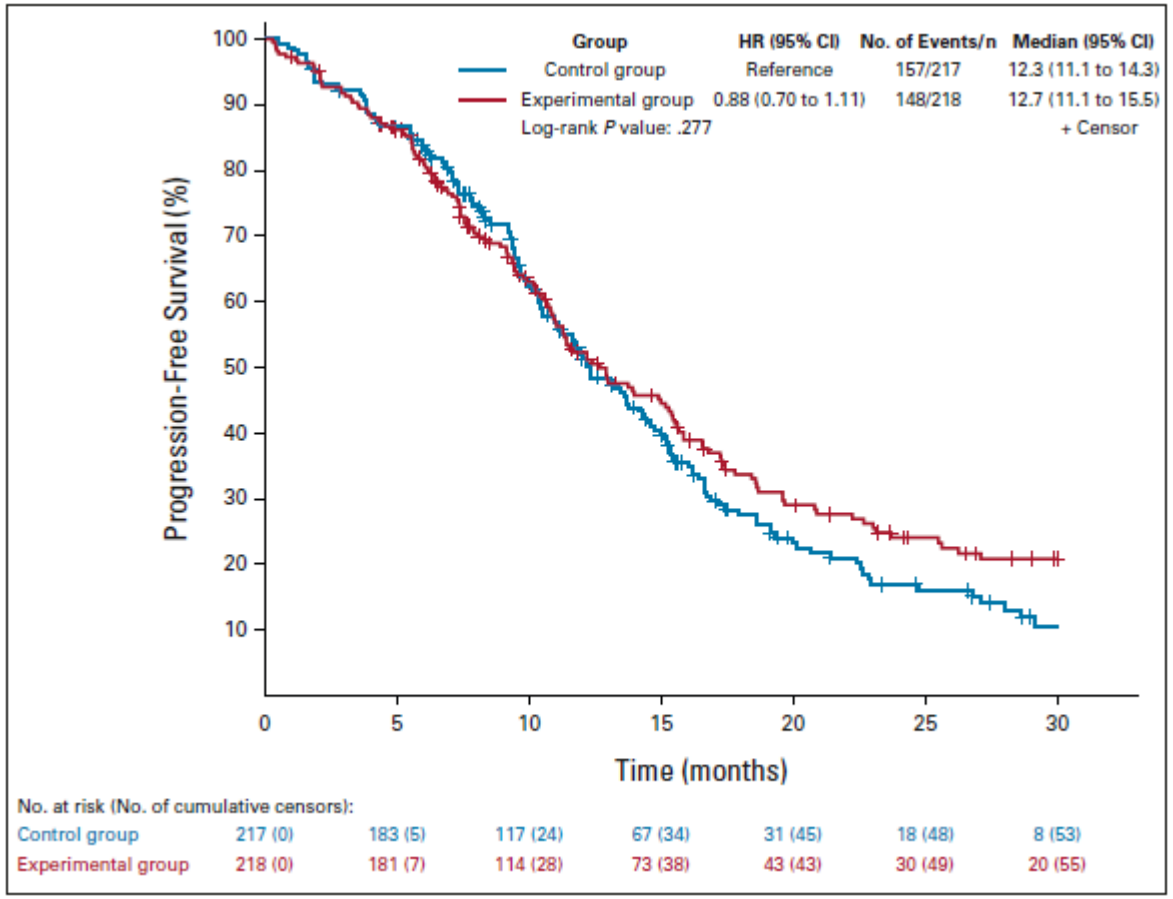


Primary Endpoint: ORR (to detect 15% increase in experimental arm)

Chiara Cremolini, MD. ASCO 2022

FOLFOXIRI Panitumumab no better than FOLFOX Panitumumab





Rossini, D. JCO 2022

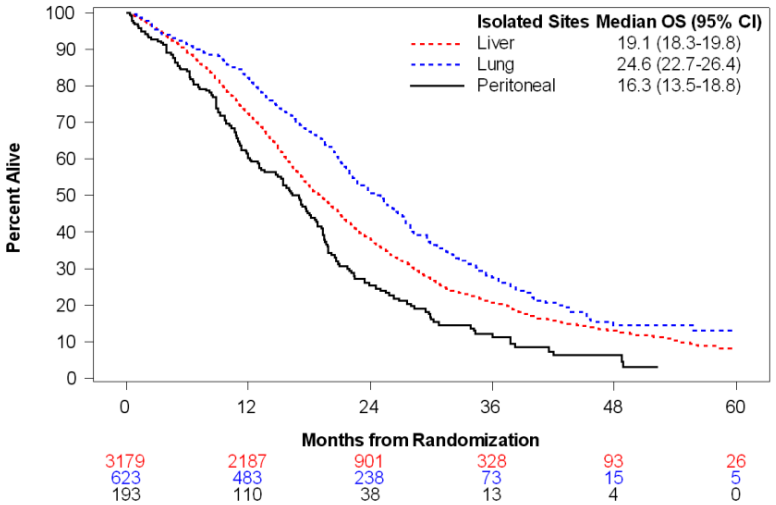
Progress in MCRC

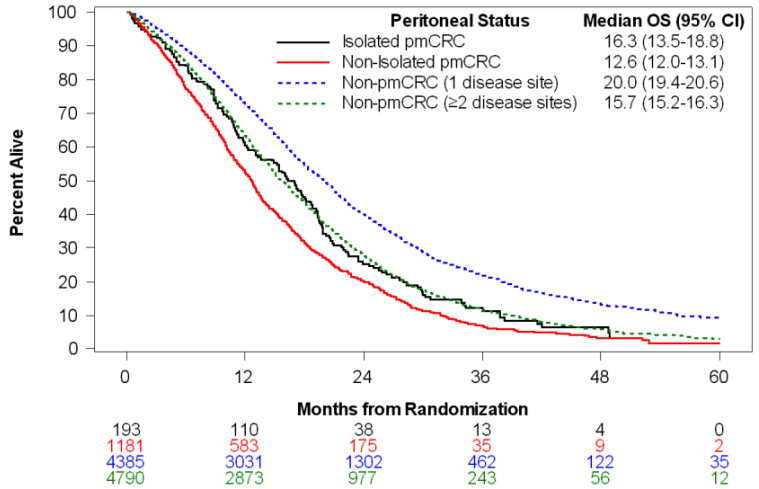
- Median OS for Left Sided RAS-WT MCRC is ~ 3+ years, doublet + anti-EGFR is associated with the best outcome
- Median OS for RAS-MT populations and Rt-Sided RAS/BRAF-WT is ~2+ years, with FOLFOXIRI bevacizumab being favored (in fit individuals)
- Median OS for BRAF-MT is poor and marginally exceeds 1 years and current data does not favor conclusively triplet + bev vs. doublet + bev
- **Where are we with peritoneal metastatic disease?**

Systemic Chemotherapy has Activity in Peritoneal Carcinomatosis: ARCAD 1st Line Experience

Study	Accrual Period
N016966	02/2004-02/2005
OPTIMOX1	01/2000-06/2002
OPTIMOX2	12/2002-06/2003
C97-3	12/1997-12/1999
CAIRO	01/2003-12/2004
CAIRO2	06/2005-12/2006
COIN	03/2005-05/2008
FOCUS	05/2000-12/2003
FOCUS2	01/2004-07/2006
03-TTD-01	04/2002-08/2004
AGITG MAX	07/2005-06/2007
HORG 99.30	10/2000-12/2004
GONO	11/2001-04/2005
FIRE II	09/2004-12/2006

	Events/Total	Median OS [months] (95% CI)†	Hazard Ratio (95% CI)‡	P-value
All patients with isolated organ/disease site Disease Sites				<.0001#
Liver-only	2269/3179	19.1 (18.3-19.8)	0.75 (0.63-0.88)	0.0004+
Lung-only	391/623	24.6 (22.7-26.4)	0.53 (0.44-0.64)	<.0001+
Peritoneal-only	159/193$	16.3 (13.5-18.8)	Reference	--
Distant Lymph Nodes-only	281/405	19.4 (17.0-21.9)	0.69 (0.57-0.84)	0.0003+
Other Isolated Organ/Site	127/178	18.0 (14.4-20.5)	0.85 (0.67-1.07)	0.1707+
Multiple Organs/Sites‡	4757/5971	15.0 (14.6-15.3)	1.02 (0.87-1.20)	0.8058+
All Arms with Only Cytotoxic Agents Disease Sites				<.0001#
Liver-only	1907/2543	18.3 (17.7-19.2)	0.78 (0.65-0.93)	0.0047+
Lung-only	332/511	23.8 (22.0-26.0)	0.55 (0.45-0.67)	<.0001+
Peritoneal-only	137/163	16.3 (12.9-19.2)	Reference	--
Distant Lymph Nodes-only	228/320	18.2 (16.5-21.3)	0.72 (0.58-0.89)	0.0025+
Other Isolated Organ/Site	107/147	18.4 (13.6-20.7)	0.84 (0.65-1.08)	0.1705+
Multiple Organs/Sites‡	3719/4498	14.5 (14.1-15.0)	1.04 (0.87-1.23)	0.6856+
All Arms with at Least One Targeted Agent Disease Sites				<.0001#
Liver-only	362/636	22.2 (20.5-25.7)	0.58 (0.38-0.90)	0.0157+
Lung-only	59/112	27.4 (23.8-33.5)	0.42 (0.26-0.69)	0.0006+
Peritoneal-only	22/30	17.1 (13.0-22.1)	Reference	--





Franko J. Lancet Oncol. 2016 Dec;17(12):1709-1719

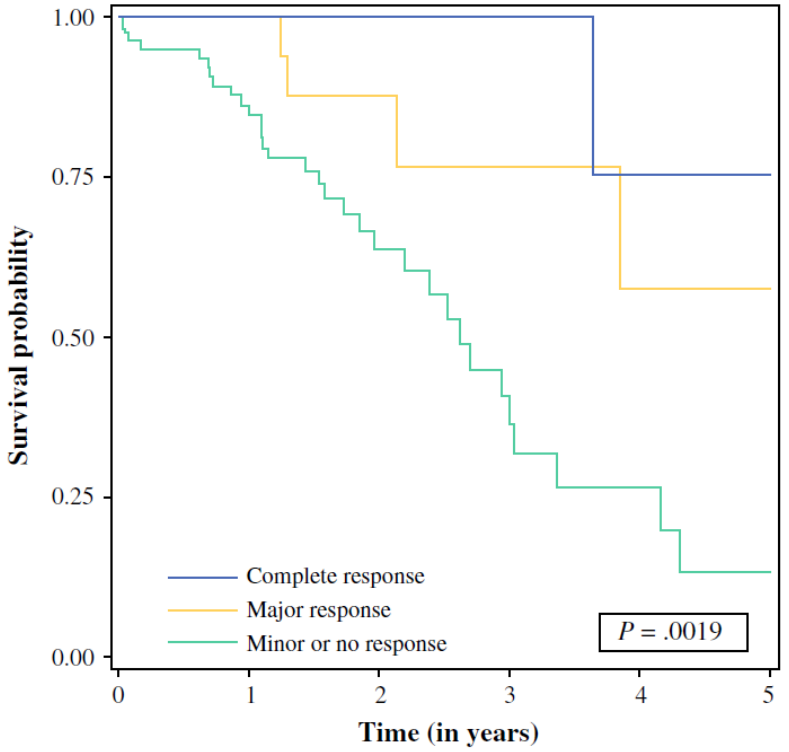
Pathological Responses to Systemic Chemotherapy in Patients with MCRC to the Peritoneum are Associated with Better Outcome

Lyon Sud Experience 2005-2012

TABLE 1 Regimen used for the last line of neoadjuvant chemotherapy

	Number of patients	Number of cycles (median)
FOLFIRI	20	4.0
FOLFIRI+beva	27	5.0
FOLFIRI+cetux	7	5.0
FOLFOX	33	4.0
FOLFOX+beva	16	6.0
FOLFOX+cetux	5	4.0
Others regimens	7	6.0
Total	115	–
Overall median	–	5.0

FOLFIRI leucovorin+fluorouracil+irinotecan, *FOLFOX* leucovorin+fluorouracil+oxaliplatin, *beva* bevacizumab, *cetux* cetuximab



Patients at risk	0	1	2	3	4	5
Complete response	12	10	7	5	2	2
Major response	23	16	11	5	3	2
Minor or no response	80	54	21	9	4	1

FIG. 2 Overall survival according to pathological response

- **pCR: defined as no residual cancer cells in all specimens: 9.7% of patients**
- **major responses (1 to 49 % residual cancer cells): 20.2% of pts**
- **minor or no responses (>50 % residual cancer cells): 70.1 % of pts**

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Passot G. Ann Surg Oncol 2014

Histological Response to Chemotherapy is Associated with OS in patients MCRC with PC

- Paired comparison of pre-chemotherapy samples from peritoneal carcinomatosis and post-chemo at the time of CRS was performed in 23 patients

- PRGS 1 corresponds to a complete regression with absence of tumor cells
- PRGS 2 to major regression features with only a few residual tumor cells
- PRGS 3 to minor regression with predominance of residual tumor cells and only few regressive features
- PRGS 4 to no response to therapy where the tumor cells are not accompanied by any regressive feature

- TRG1 corresponds to the absence of tumour cells and their replacement by abundant fibrosis
- TRG2, residual tumour cells are rare and are scattered throughout abundant fibrosis
- TRG3 there are more residual tumour cells throughout a predominantly fibrotic area
- TRG4 tumour cells predominate over the fibrosis.
- TRG5, tumour cells are present exclusively, i.e. without fibrosis.

Histological response according to the Peritoneal Regression Grading Score (PRGS) and to the Tumour Regression Grade (TRG).

Residual tumour cells	TRG	HR	n (%)	PRGS	HR	n (%)
0%	**1**	**Major**	14 (61%)	**1**	**Complete**	4 (17,5%)
< 5–10%	**2**			**2**	**Major**	12 (52%)
< 50%	**3**	**Partial**	2 (9%)			
> 50%	**4**	**No**	7 (30%)	**3**	**Minor**	3 (13%)
100%	**5**			**4**	**No**	4 (17,5%)

HR: Histological response, n = number of patients, Partial pathological response (PHR), R: Response TRG: Tumor regression grade, PRGS: Peritoneal regression grading score; % percentage.

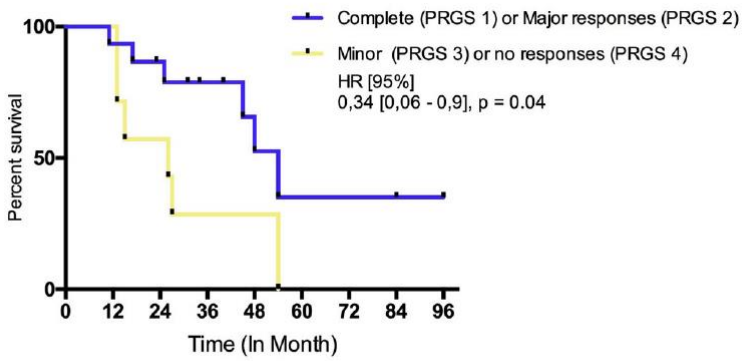


Fig. 1. Overall survival according to the histological response using the Peritoneal Regression Grading Score. *HR:* Hazard ratio, *CI*: Confidence interval, *PRGS:* Peritoneal Regression Grading Score.

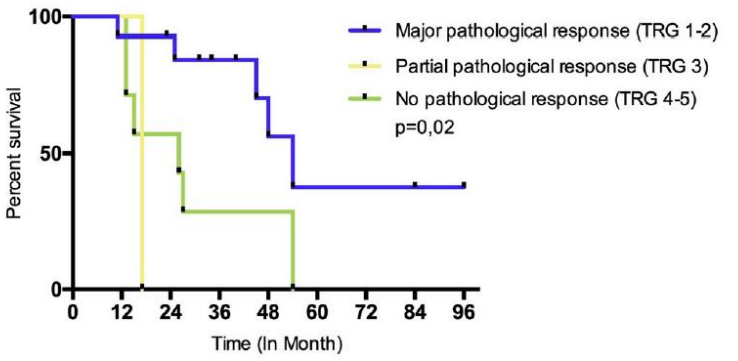
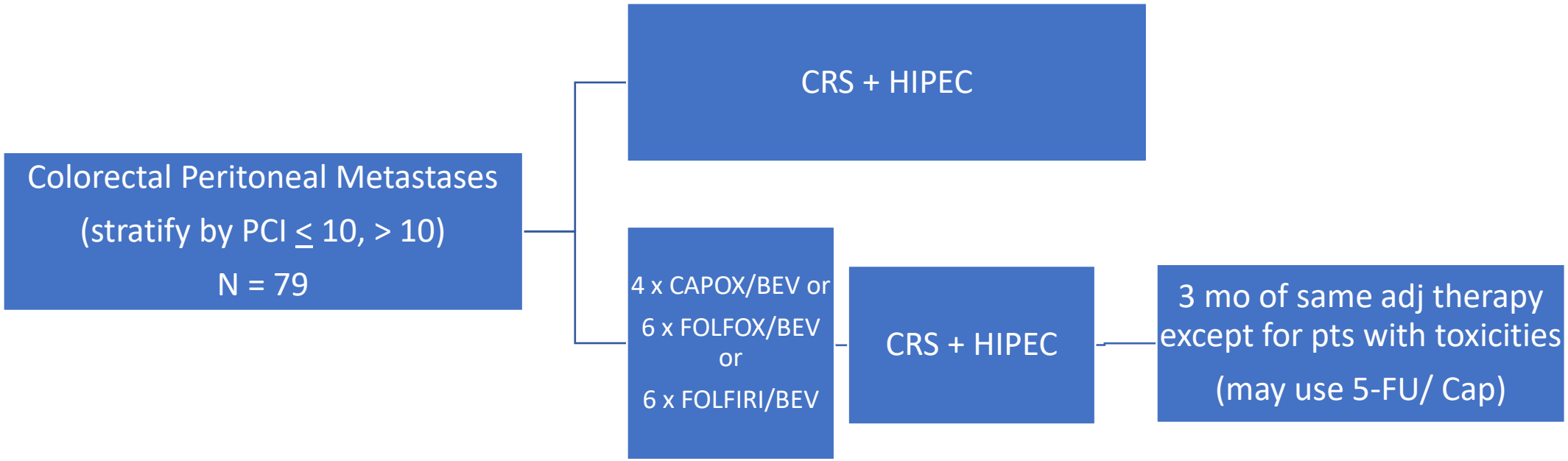


Fig. 2. Overall survival according to the histological response using the Tumor Regression Grade, *TRG:* Tumor Regression Grade.

Taibi, A. Surg Oncol. 2020

CAIRO-6 Trial: Perioperative Chemo in CRC with PC



Primary outcome: safety and feasibility (complete cytoreduction and post-op complications)
Secondary: ORR (radiological peritoneal cancer index and RECIST) and path response (TRG and Peritoneal Regression Grading Score)

Rovers, K. JAMA Surgery, 2021

Response to Neoadjuvant Therapy

Table 4. Centrally Assessed Pathologic Response to Neoadjuvant Treatment

Category	Classification system, No. (%)[a]	
	Mandard TRG	PRGS
Peritoneal metastases, evaluable, No.[b]	34	34
Grade 1	8 (24)	8 (24)
Grade 2	5 (15)	16 (47)
Grade 3	11 (32)	5 (15)
Grade 4	5 (15)	5 (15)
Grade 5	5 (15)	NA
Primary tumor, evaluable, No.[b]	8	8
Grade 1	1 (13)	1 (13)
Grade 2	1 (13)	5 (63)
Grade 3	4 (50)	2 (25)
Grade 4	2 (25)	0 (0)
Grade 5	0	NA
Locoregional lymph nodes, evaluable, No.[b]	8	8
Grade 1	1 (13)	1 (13)
Grade 2	0	4 (50)
Grade 3	4 (50)	3 (38)
Grade 4	3 (38)	0
Grade 5	0	NA
Overall, evaluable, No.[b]	35	35
Grade 1	9 (26)	9 (26)
Grade 2	4 (11)	16 (46)
Grade 3	12 (34)	6 (17)
Grade 4	6 (17)	4 (11)
Grade 5	4 (11)	NA

Abbreviations: NA, not applicable; PRGS, peritoneal regression grading score; TRG, tumor regression grade.

38% TRG1-2

	RECIST RESPONSE (13 evaluable)	Radiologic Peritoneal Cancer Index (32 evaluable)
CR	1 (8%)	1 (3%)
PR	1 (8%)	8 (25%)
SD	11 (85%)	23 (72%)
PD	0	2 (6%)

No increase in risk of operative complications

Rovers, K. JAMA Surgery, 2021

Role of Bevacizumab in Patients with Metastatic Peritoneal Carcinomatosis

Retrospective Analysis of Patients with Peritoneal Disease and Not Candidate for CRS

Erasmus Medical Center Cancer Institute Experience

TABLE 2 Main reasons of ineligibility for CRS-HIPEC with corresponding overall survival

Main reason	Total (n = 227) n (%)	Median PCI (IQR)	Median OS Months (IQR)
Extensive PM[a]	96 (42.3)	25 (23–28)[f]	11 (5–18)
Distant lymph node metastases[b]	26 (11.5)	4 (3–16)[g]	14 (4–25)
(Rapid) progression[c]	25 (11.0)	12 (8–15)[h]	7 (5–24)
Extensive liver metastases[d]	20 (8.8)	10 (8–15)[i]	22 (8–27)
Patient's preference	19 (8.4)	6 (5–14)[j]	13 (9–37)
Performance status	17 (7.5)	18 (2–NA)[k]	10 (3–14)
Lung metastases	17 (7.5)	6 (3–14)[l]	24 (12–29)
Irresectable PM [e]	7 (3.1)	7 (4–NA)[m]	23 (12–48)

CRS-HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; PCI, peritoneal cancer index; IQR, interquartile range; OS, overall survival; PM, peritoneal metastasis

[a]PCI of 20 or higher

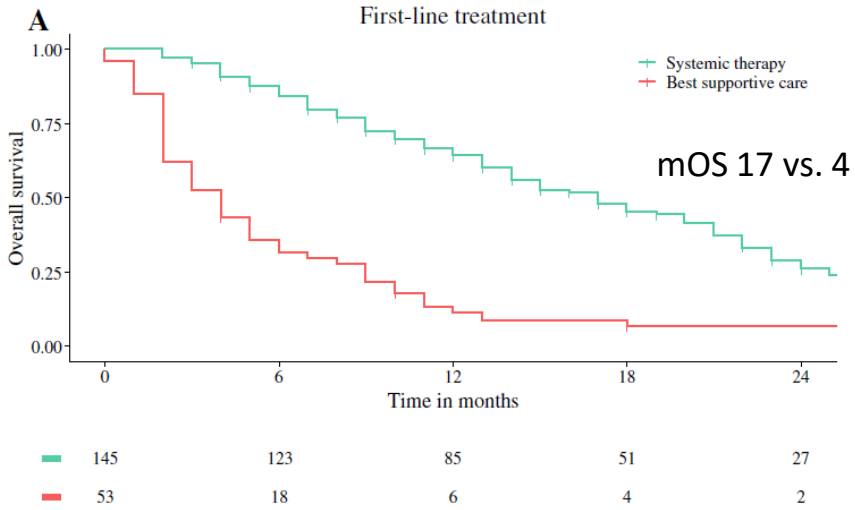
[b]Retroperitoneal, mediastinal or inguinal lymph node metastases

[c]That is, rapid progression during workup for CRS-HIPEC or during treatment with chemotherapy, based on radiologic or surgical assessment

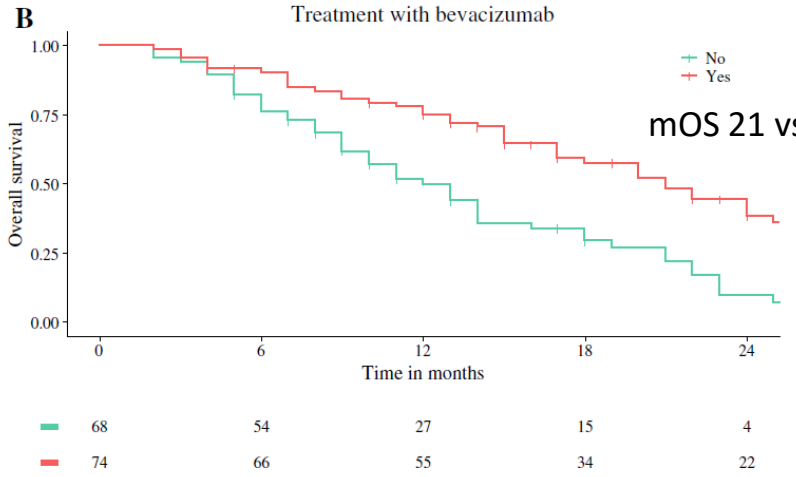
[d]Presence of more than three liver metastases

[e]Radical resection of PM deemed impossible

Median PCI available for [f]79, [g]5, [l]10, [l]5, [j]8, [k]3, [l]4, and [m]2 patients



mOS 17 vs. 4 months



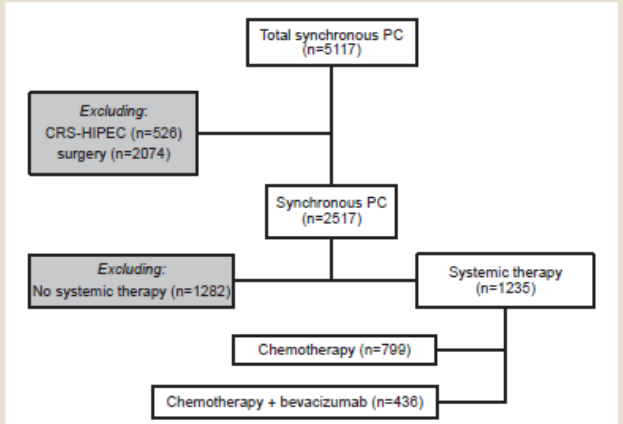
mOS 21 vs. 12 months

Dietz, M. Ann Surg Oncol. 2023

More Evidence to the Benefit from Bevacizumab

Netherlands Registry: Outcome with Systemic Therapy +/- Bevacizumab in the 1st Line Treatment of MCRC with PC

Figure 1 An Overview of the Patients Diagnosed With Synchronous Peritoneal Carcinomatosis (PC) From Colorectal Cancer (CRC) From 2007 to 2014 in the Netherlands



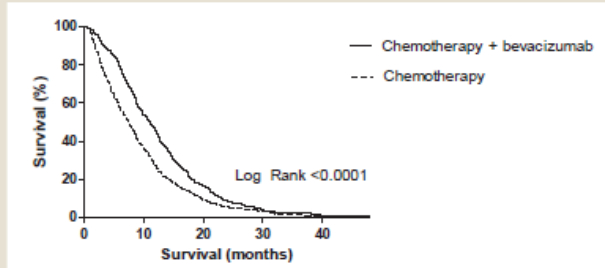
Abbreviation: CRS-HIPEC = cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Table 1 Clinicopathologic Patient Characteristics Stratified by Palliative Systemic Treatment (n = 1235)

Characteristic	Chemotherapy + Bevacizumab (n = 436)	Chemotherapy Alone (n = 799)	*P* Value
Gender			.66
Male	255 (58)	457 (57)	
Female	181 (42)	342 (43)	
Age (years)			<.0001
<60	139 (32)	190 (24)	
60-75	246 (56)	413 (52)	
≥75	51 (12)	196 (24)	
Tumor localization			<.01
Rectum	86 (20)	115 (14)	
Colon	350 (80)	684 (86)	
Histologic subtype			.23
Adenocarcinoma	329 (75)	564 (71)	
Mucinous carcinoma	71 (16)	144 (18)	
Signet ring cell carcinoma	25 (6)	67 (8)	
Other	11 (3)	24 (3)	
Tumor grade			.73
Well/moderate	72 (17)	138 (15)	
Poor/undifferentiated	71 (15)	117 (16)	
Unknown	293 (68)	544 (70)	
Extent of metastases			.06
PC only	121 (28)	263 (33)	
PC other	315 (72)	536 (67)	
Radiotherapy	15 (3)	39 (5)	.24

Data presented as n (%).
Abbreviations: PC only = isolated peritoneal carcinomatosis; PC other = peritoneal carcinomatosis with concomitant extraperitoneal metastases.

Figure 3 Overall Survival of Patients With Synchronous Peritoneal Carcinomatosis From Colorectal Origin According to Treatment Received (n = 1235)



HR = 0.7; median OS 11 mo vs 7.5 m

Razenberg, L. Clinical Colorectal Cancer, 2015

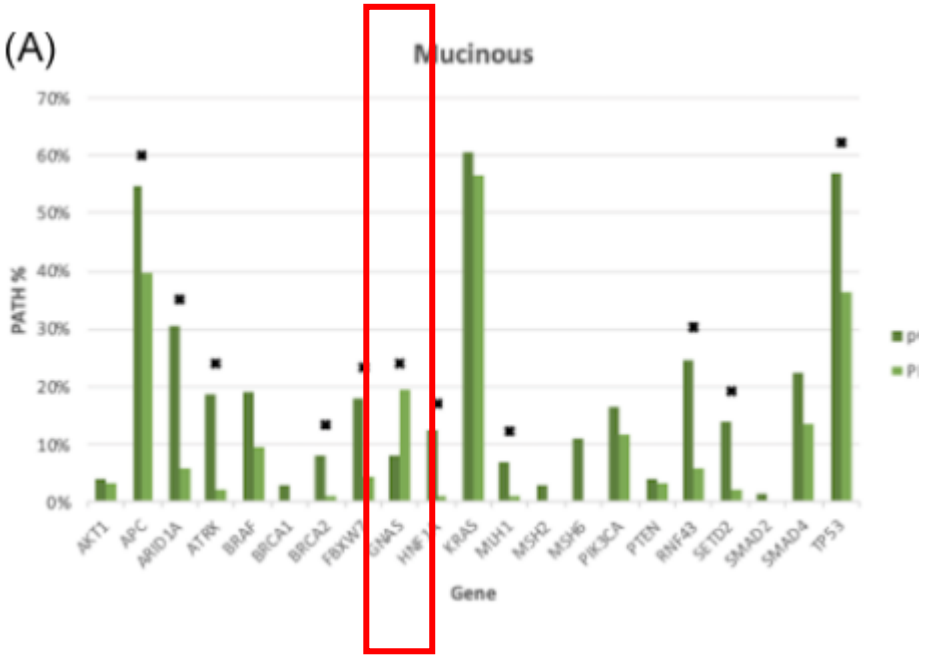
Role of anti-EGFR in Patients with Metastatic Peritoneal Carcinomatosis

Comprehensive tumor profiling reveals unique molecular differences between peritoneal metastases and primary colorectal adenocarcinoma

NGS testing of primary vs peritoneal MCRC from CARIS (NGS)

Variable	pCRC N = 617	PM N = 348
Gender		
Male	339	190
Female	281	158
Age, y	59 (16-91)	59 (20-93)
Primary site		
Right colon	189	45
Left colon	232	29
Rectum	147	22
NOS	49	252
Histology		
Mucinous	74	126
Signet ring cell	14	36
Goblet cell	1	1
Grade		
Low	110	34
Moderate	303	44
High	49	11

Note: Data presented as N (range).
Abbreviations: pCRC, primary colorectal tumor; PM, peritoneal metastases; NOS, not otherwise specified.



Mucinous tumors are particularly enriched with NGAS mutations in peritoneal metastases (more than mucinous primary)

Stein M. Journal of Surgical Oncology, Volume: 121, Issue: 8, Pages: 1320-1328

What is the Impact of Mucinous Left Sided MCRC on Response to anti-EGFR Therapy in Left Sided RAS/BRAF WT MCRC?

Table 1. Characteristics of patients with mucinous and nonmucinous left-sided *RAS/BRAF* wild-type metastatic CRC.

Characteristics	Total (n = 118)	Mucinous 16.9% (n = 20)	Non-mucinous 83.1% (n = 9 8)	P-value
Age at diagnosis				
Median (range)	52 (19-88)	48 (19-88)	54 (20-84)	.02
Gender				
Female	35.6% (42)	50% (10)	32.7% (32)	.2
Male	64.4% (76)	50% (10)	67.3%% (66)	
Stage at diagnosis				
II/III	22% (26)	15% (3)	23.5% (23)	.6
IV	78% (92)	85% (17)	76.5% (75)	
APC				
Mutated	73.7% (87)	20% (4)	84.7% (83)	<.0001
Nonmutated	31.3% (31)	80% (16)	15.3% (15)	
TP53				
Mutated	86.4% (102)	60% (12)	91.8% (90)	.001
Nonmutated	13.6% (16)	40% (8)	8.2% (8)	
GNAS				
Mutated	3.4% (4)	20% (4)	0 (0)	.0006
Nonmutated	96.6% (114)	80% (16)	100% (98)	
SMAD4				
Mutated	11.9% (14)	25% (5)	10.2% (10)	.13
Nonmutated	88.1% (104)	75% (15)	89.8% (88)	
SMAD2				
Mutated	5.1% (6)	10% (2)	4.1% (4)	.27
Nonmutated	94.9% (112)	90% (18)	95.9% (94)	
PIK3CA				
Mutated	8.5% (10)	10% (2)	8.2% (8)	.68
Nonmutated	91.5% (108)	90% (18)	91.8% (90)	
TMB[a]				
Median (range)	5 (0-13)	5.5 (1-11)	5 (0-13)	.32

[a]Data not available, 4 in mucinous group, 4 in nonmucinous group.

Table 2. Patients with left-sided *RAS/BRAF* wild-type mucinous metastatic colorectal cancer treated with anti-EGFR.

Patients	Lines of therapy	Best response	PFS
01	First line	PD	1.4
02	First line	PD	4.0
03	First line	SD	4.6
04	First line	PD	3.8
05	First line	PD	4.0
06	First line	SD	5.1
07	First line	PR	6.1
08	Second line	SD	3.7
09	Second line	SD	3.7
10	Second line	SD	2.8
11	Second line	SD	3.2
12	Fifth line	SD	3.0

PD, progressive disease; SD, stable disease; PR, partial response; PFS, progression-free survival.

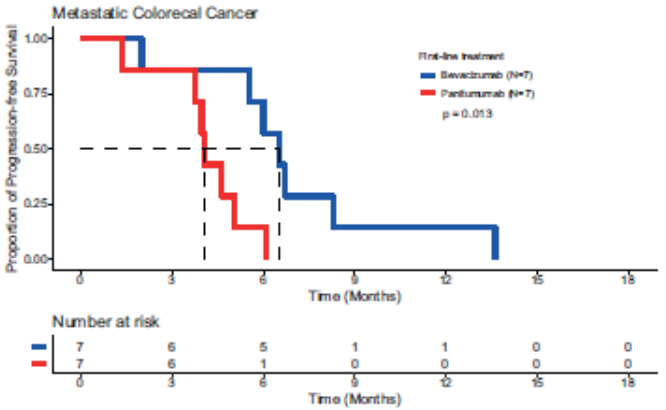


Figure 1. Kaplan-Meier curves for PFS of patients with left-sided, *RAS/BRAF* wild-type mucinous metastatic colorectal cancer treated with first-line panitumumab versus first-line bevacizumab.

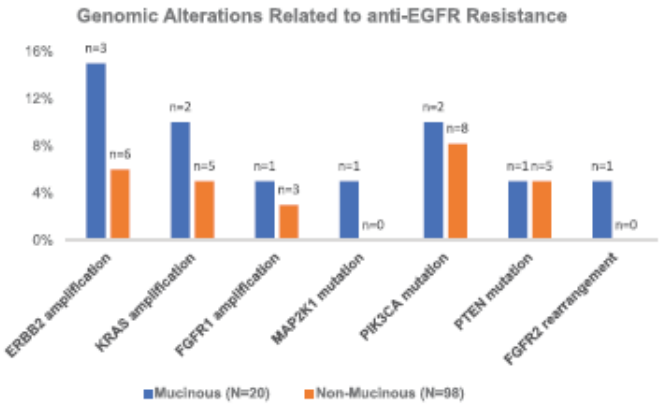


Figure 2. Bar chart of genomic alterations associated with resistance to anti-EGFR therapy in patients with mucinous and non-mucinous left-sided *RAS/BRAF* wild-type metastatic colorectal cancer.

Fakih et al. The Oncologist, 2022

Special Considerations: MSI-H Metastatic CRC with Peritoneal Carcinomatosis

Does Peritoneal Carcinomatosis Impact Response to CPI in the Setting of MSI-H Metastatic Colorectal Cancer- COH Experience

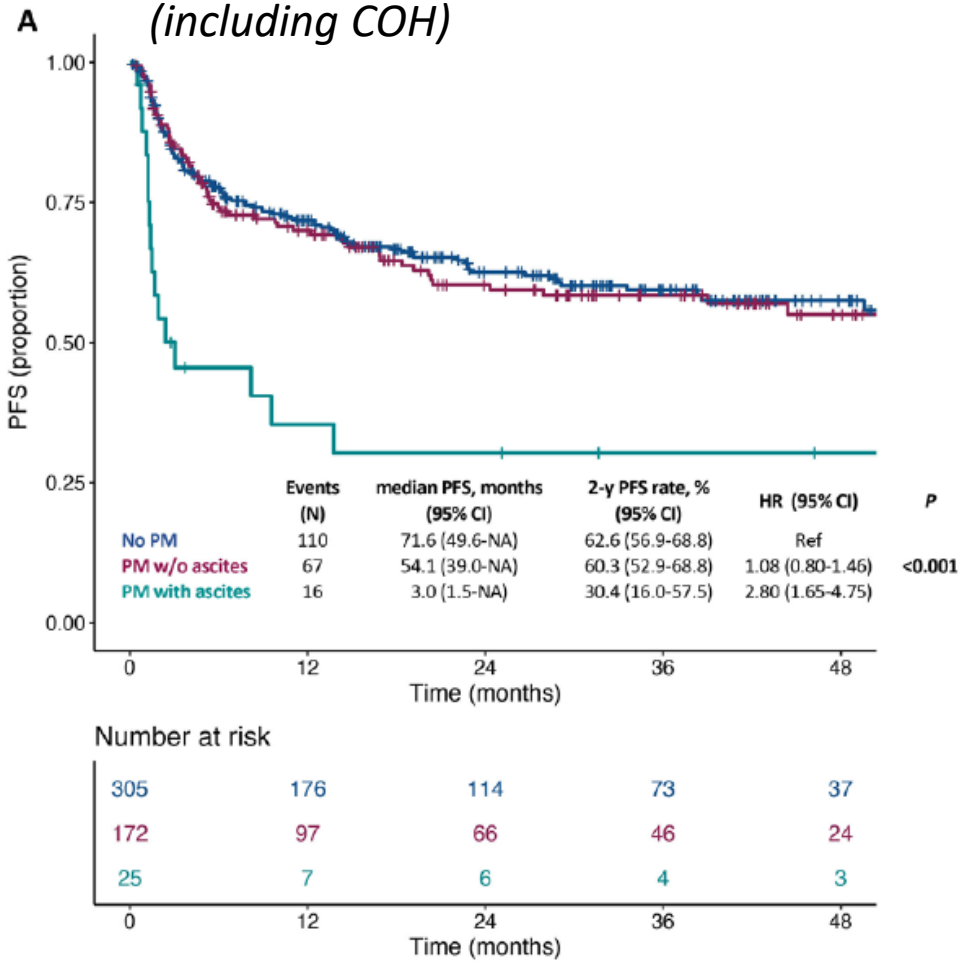
Metastatic pattern and responses in patients with MSI-H metastatic colorectal cancer treated with ICIs

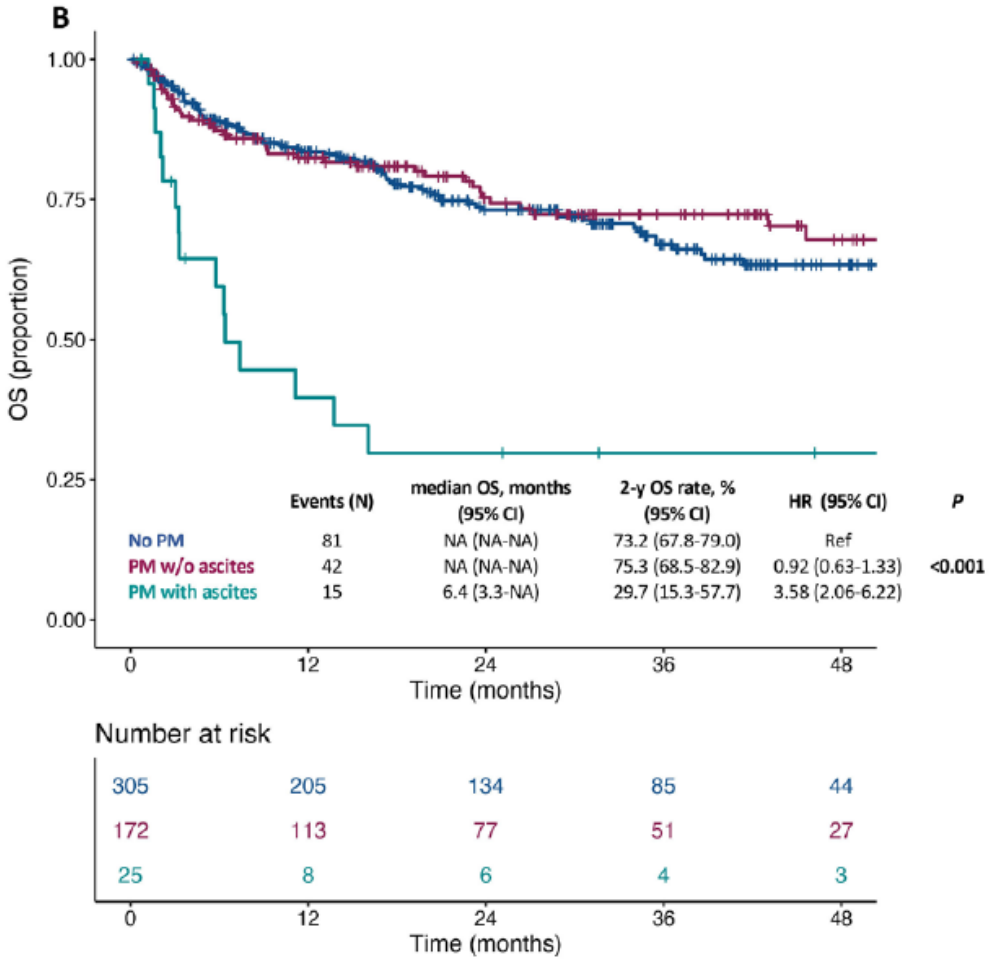
Metastatic Pattern at the start of IO	N	ORR (CR/ PR)	ORR + SDcPR	SD excluding SDcPR	PD	Median PFS (Months)	Median OS (Months)
LM	12	(5/2) (58%)	8 (66.6%)	0 (%)	4 (33%)	23.0 [3, NE]*	NR Median OS ≥ 52.0
PM	8	(0/2) (25%)	2 (25%)	2 (25%)	4 (50%)	4.5 [2, NE]	35 [8.36, NE]
Non-LM/PM	15	(8/4) (80%)	12 (80%)	1 (6.7%)	2 (13.3%)	NR Median PFS ≥ 54	NR Median OS ≥ 54
Overall Population	35	(13/8) (60%)	22 (62.9%)	3 (8.6%)	10 (28.6%)	30.0 [18, NE]	NR Median OS ≥ 52.0

***NE: not estimable, NR: not reached, LM: liver metastases; PM: peritoneal metastases; No overlap between LM and PM**

Only MSI-H Peritoneal Metastatic Disease with Ascites are Associated with Poor Response to CPI

Analysis of 502 patients with MSI-H mCRC treated with IO across multiple sites/ countries (including COH)





Fuca, G. J Immuno Cancer. 2022

Conclusions:

- Patients with metastatic colorectal cancer and peritoneal carcinomatosis carry a worse prognosis than lung and liver metastases
- Patients with peritoneal carcinomatosis that are amenable to CRS can be particularly responsive to chemotherapy with 38% achieving a TRG1-2
- Pathological responses to chemotherapy predict for the best clinical outcome in CRC with peritoneal carcinomatosis
- The addition of bevacizumab to systemic chemotherapy is associated with improved outcome compared to systemic chemotherapy
- The benefits from anti-EGFR therapy in peritoneal carcinomatosis is not adequately defined with small series suggesting a low response rate and a short PFS in mucinous carcinomatosis of CRC origin
- Like metastatic disease to other sites, MSI-H colorectal cancer with peritoneal carcinomatosis derive an excellent outcome with CPI, except for patients with malignant ascites where short PFS and OS have been noted