Colorectal and Anal Cancer

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Disclosures

I have no disclosures to report.

Permission was obtained from ASCO to use the following slides from its 2022 Annual Meeting in this presentation.

What We'll Cover:

Major practice –affirming and –changing updates in:

- Metastatic colon cancer trials
  - *PARADIGM*
  - *TRIPLETE*
  - *CAIRO5*
  - *SYNCHRONOUS-CCRe-IV*
- Rectal cancer management
  - *Cercek et al 2022*

Metastatic Colon Cancer Updates

Practice-Changing:

Anti-EGFR antibodies constitute the preferred first-line therapy in RAS wildtype left sided metastatic colorectal cancer: **PARADIGM**

The optimal debulking strategy for metastatic left or right sided metastatic colorectal cancer: **TRIPLETE** and **CAIRO5**

Practice-affirming:

Whether to resect the primary site before starting palliative chemotherapy in metastatic colorectal cancer: **SYNCHRONOUS and CCRe-IV** trial

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Colon Cancer

NCCN Guidelines Index
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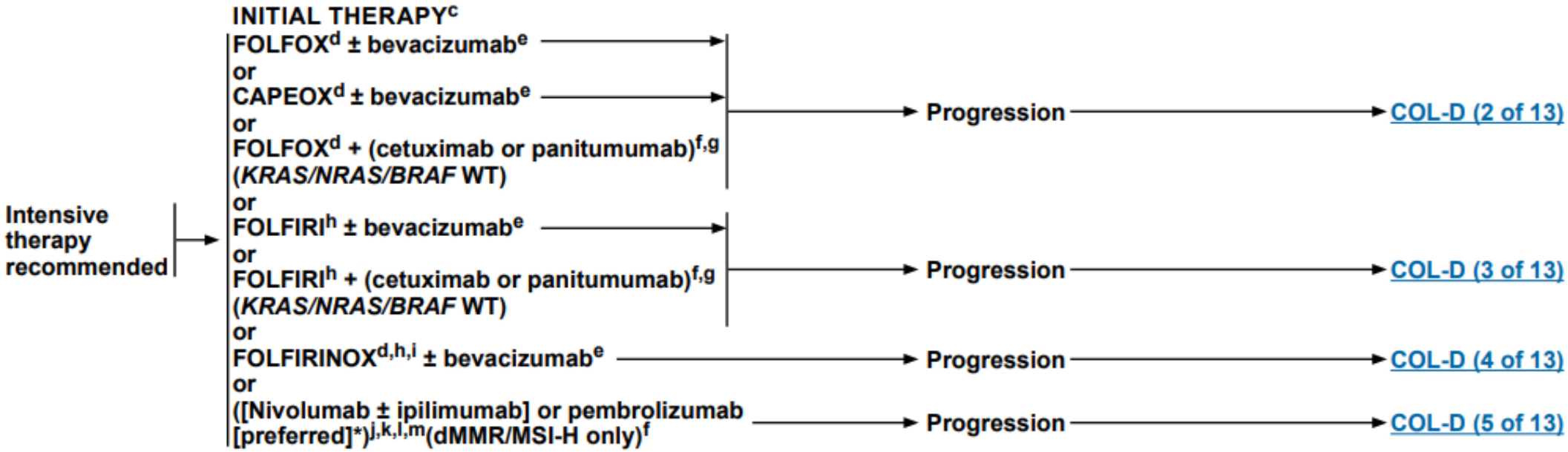
Discussion

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]



National Comprehensive Cancer Network. Colon Cancer (Version 1.2022). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 19, 2022.

Anti-EGFR therapy is the preferred first-line chemo adjunct for RAS wildtype, metastatic left-sided colorectal cancer: the **PARADIGM** trial.

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

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

[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [2]Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan; [3]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [4]Division of Medical Oncology, Japanese Red Cross Ishinomaki Hospital, Miyagi, Japan; [5]Division of Gastrointestinal Surgery, Kanagawa Cancer Center, Kanagawa, Japan; [6]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka,

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.

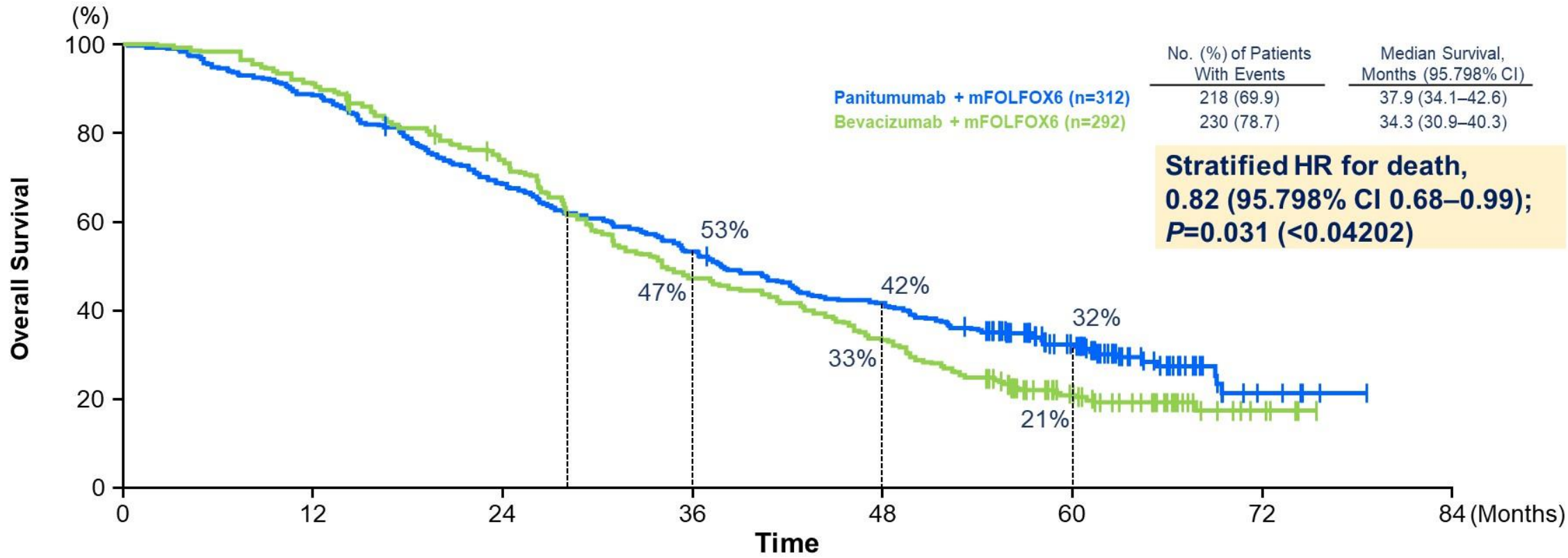
[a]Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment. [b]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection. [c]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum.

Baseline Patient Characteristics

Characteristic	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=312)	Bevacizumab + mFOLFOX6 (n=292)	Panitumumab + mFOLFOX6 (n=400)	Bevacizumab + mFOLFOX6 (n=402)
Age category, n (%)				
20–64 years	138 (44.2)	127 (43.5)	164 (41.0)	168 (41.8)
65–79 years	174 (55.8)	165 (56.5)	236 (59.0)	234 (58.2)
Sex, female, n (%)	104 (33.3)	91 (31.2)	148 (37.0)	134 (33.3)
ECOG performance status, n (%)				
0	261 (83.7)	231 (79.1)	328 (82.0)	319 (79.4)
1	51 (16.3)	61 (20.9)	71 (17.8)	83 (20.6)
Primary tumor location, n (%)[a]				
Left-sided	312 (100.0)	292 (100.0)	312 (78.0)	292 (72.6)
Right-sided	0	0	84 (21.0)	103 (25.6)
Number of metastatic organs, n (%)				
1	155 (49.7)	147 (50.3)	196 (49.0)	194 (48.3)
≥2	157 (50.3)	145 (49.7)	204 (51.0)	208 (51.7)
Metastatic site, n (%)				
Liver	225 (72.1)	206 (70.5)	275 (68.8)	278 (69.2)
Liver as only site of metastasis	90 (28.8)	89 (30.5)	105 (26.3)	113 (28.1)
Prior treatment, n (%)				
Primary tumor resection	185 (59.3)	193 (66.1)	239 (59.8)	272 (67.7)
Radiotherapy	2 (0.6)	2 (0.7)	2 (0.5)	3 (0.7)
Adjuvant chemotherapy[b]	17 (5.4)	16 (5.5)	22 (5.5)	20 (5.0)

[a] 4 patients receiving panitumumab and 7 patients receiving bevacizumab had multiple primary lesions in both the left-sided and right-sided. [b] Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment.

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

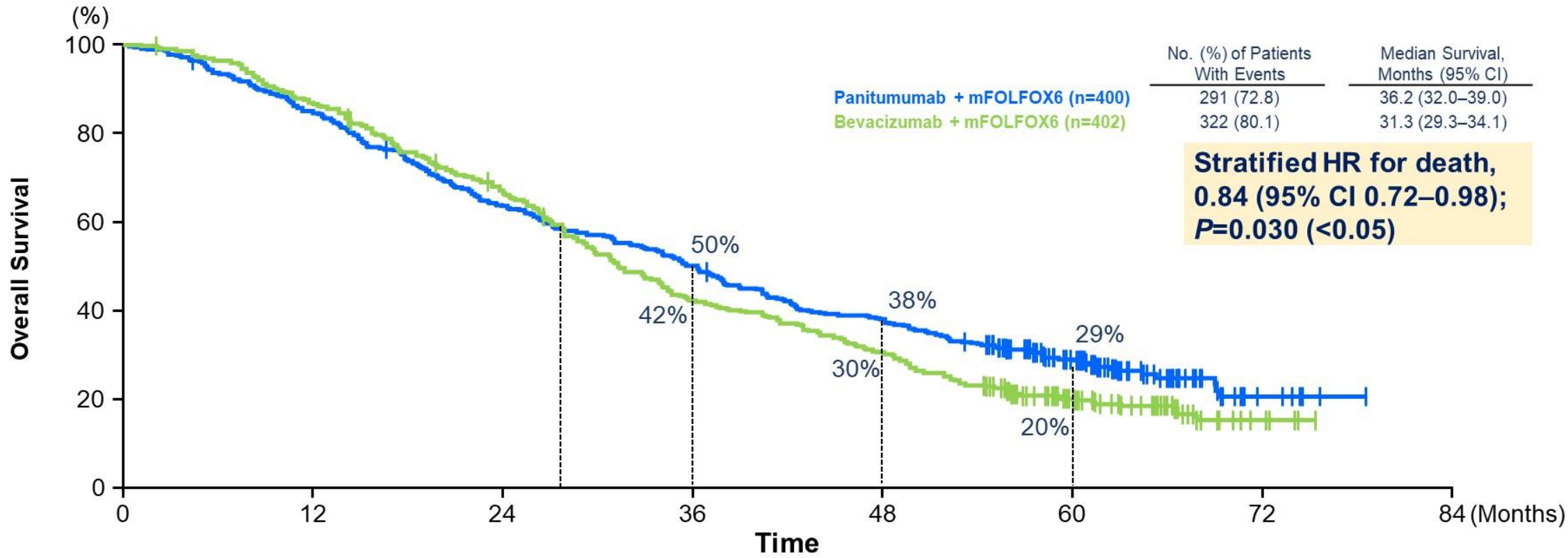


	No. (%) of Patients With Events	Median Survival, Months (95.798% CI)
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	37.9 (34.1–42.6)
Bevacizumab + mFOLFOX6 (n=292)	230 (78.7)	34.3 (30.9–40.3)

Stratified HR for death, 0.82 (95.798% CI 0.68–0.99); *P*=0.031 (<0.04202)

No. at risk							
Panitumumab	312	276	213	166	129	68	5	0
Bevacizumab	292	266	212	136	96	40	5	0

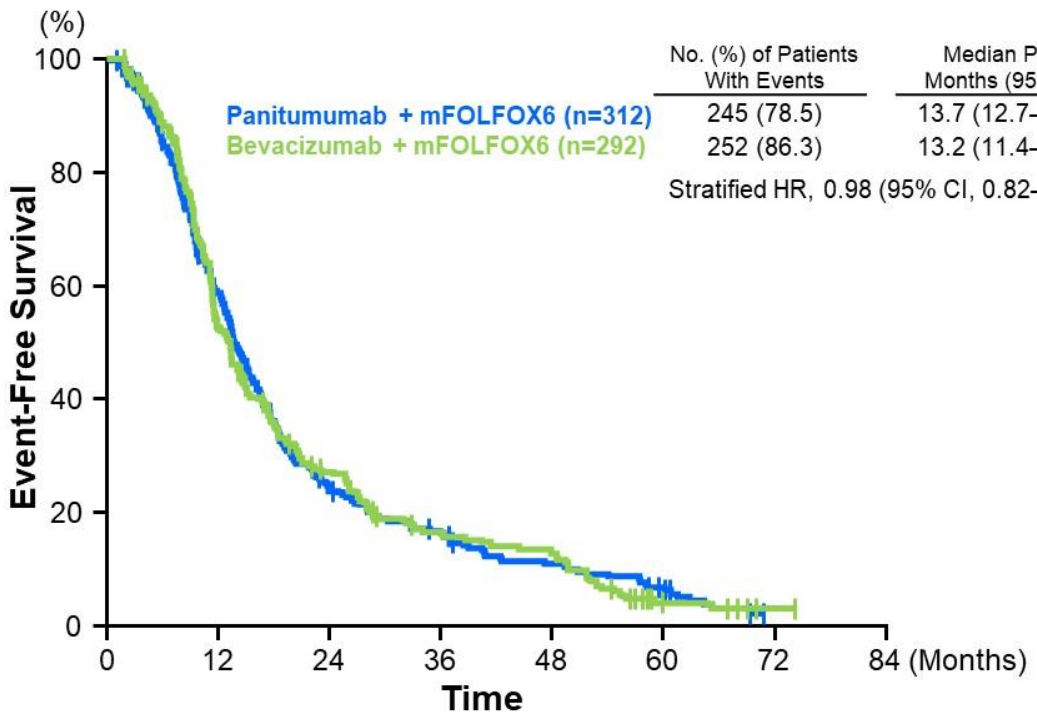
Primary Endpoint-2; Overall Survival in Overall Population



No. at risk							
Panitumumab	400	338	253	199	150	80	6	0
Bevacizumab	402	348	265	166	119	54	5	0

Progression-free Survival[a]

Left-sided Population

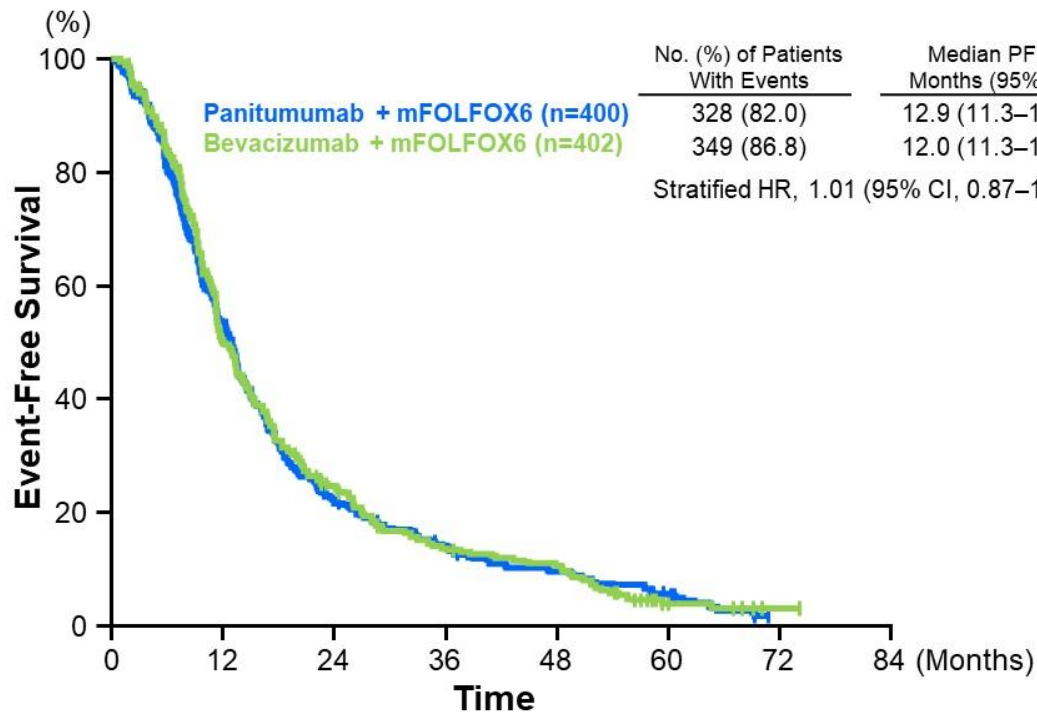


	No. (%) of Patients With Events	Median PFS, Months (95% CI)
Panitumumab + mFOLFOX6 (n=312)	245 (78.5)	13.7 (12.7–15.3)
Bevacizumab + mFOLFOX6 (n=292)	252 (86.3)	13.2 (11.4–14.5)

Stratified HR, 0.98 (95% CI, 0.82–1.17)

No. at risk								
Panitumumab	312	149	59	38	24	13	0	0
Bevacizumab	292	139	67	40	31	5	1	0

Overall Population



	No. (%) of Patients With Events	Median PFS, Months (95% CI)
Panitumumab + mFOLFOX6 (n=400)	328 (82.0)	12.9 (11.3–13.6)
Bevacizumab + mFOLFOX6 (n=402)	349 (86.8)	12.0 (11.3–13.5)

Stratified HR, 1.01 (95% CI, 0.87–1.18)

No. at risk								
Panitumumab	400	179	71	43	28	15	0	0
Bevacizumab	402	182	83	45	35	6	1	0

[a]Patients who underwent curative-intent resection were censored at the last tumor evaluable assessment date before the resection.

Other Efficacy Outcomes

Parameter	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=308)	Bevacizumab + mFOLFOX6 (n=287)	Panitumumab + mFOLFOX6 (n=394)	Bevacizumab + mFOLFOX6 (n=397)
Response rate, % (95% CI)	80.2 (75.3–84.5)	68.6 (62.9–74.0)	74.9 (70.3–79.1)	67.3 (62.4–71.9)
Difference, % (95% CI)	11.2 (4.4–17.9)		7.7 (1.5–13.8)	
DCR, % (95% CI)	97.4 (94.9–98.9)	96.5 (93.7–98.3)	94.9 (92.3–96.9)	95.5 (92.9–97.3)
Median DOR,[a] months (95% CI)	13.1 (11.1–14.8)	11.2 (9.6–13.1)	11.9 (10.5–13.4)	10.7 (9.5–12.2)
R0 rate,[b] % (95% CI)	18.3 (14.1–23.0)	11.6 (8.2–15.9]	16.5 (13.0–20.5)	10.9 (8.1–17.1)

RR, response rate; DCR, disease control rate; DOR, duration of response; R0, curative resection.
[a] DOR was evaluated in patients with complete or partial response.
[b] R0 rate was evaluated in all the patients of efficacy analysis population (left-sided: n=312 for panitumumab and n=292 for bevacizumab; overall: n=400 and 402, respectively).

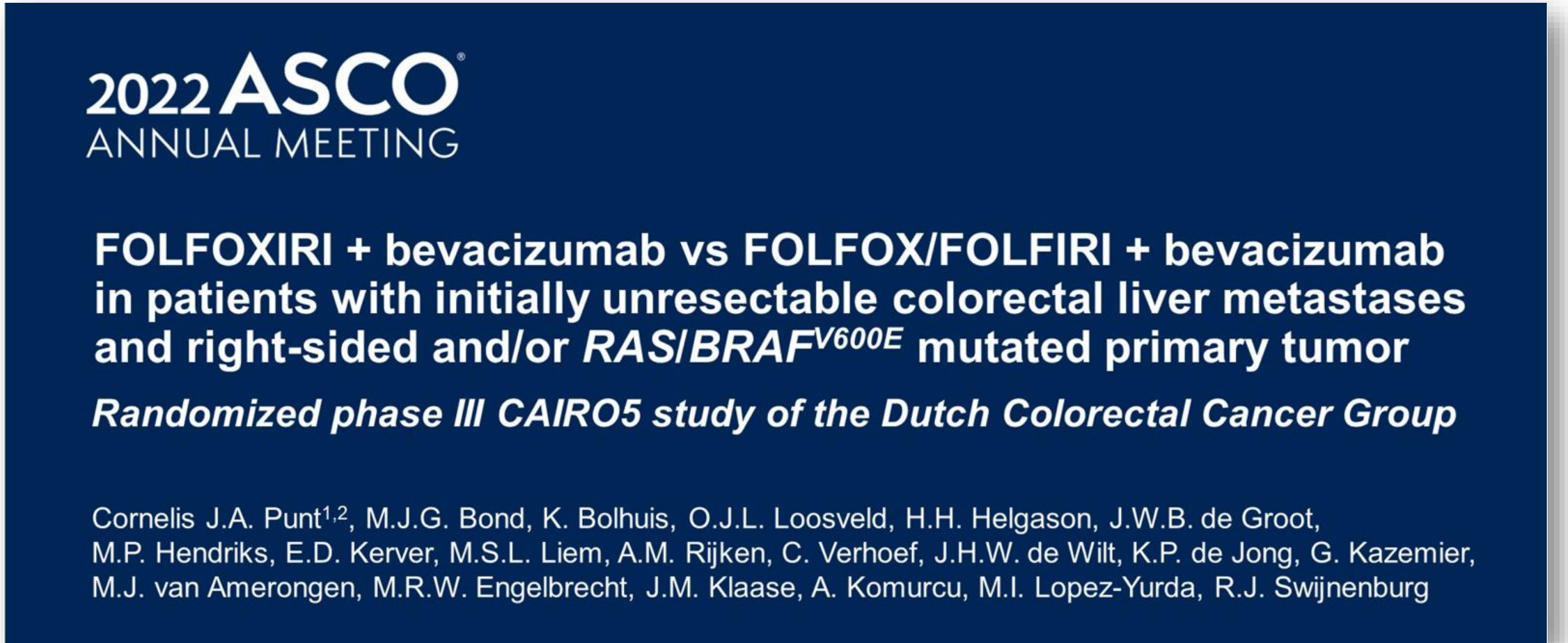
Anti-EGFR therapy is the preferred first-line chemo adjunct for RAS/RAF wildtype, metastatic colorectal cancer: the **PARADIGM** trial.

…but significant non-hematologic toxicities may limit our ability to give anti-EGFR therapy

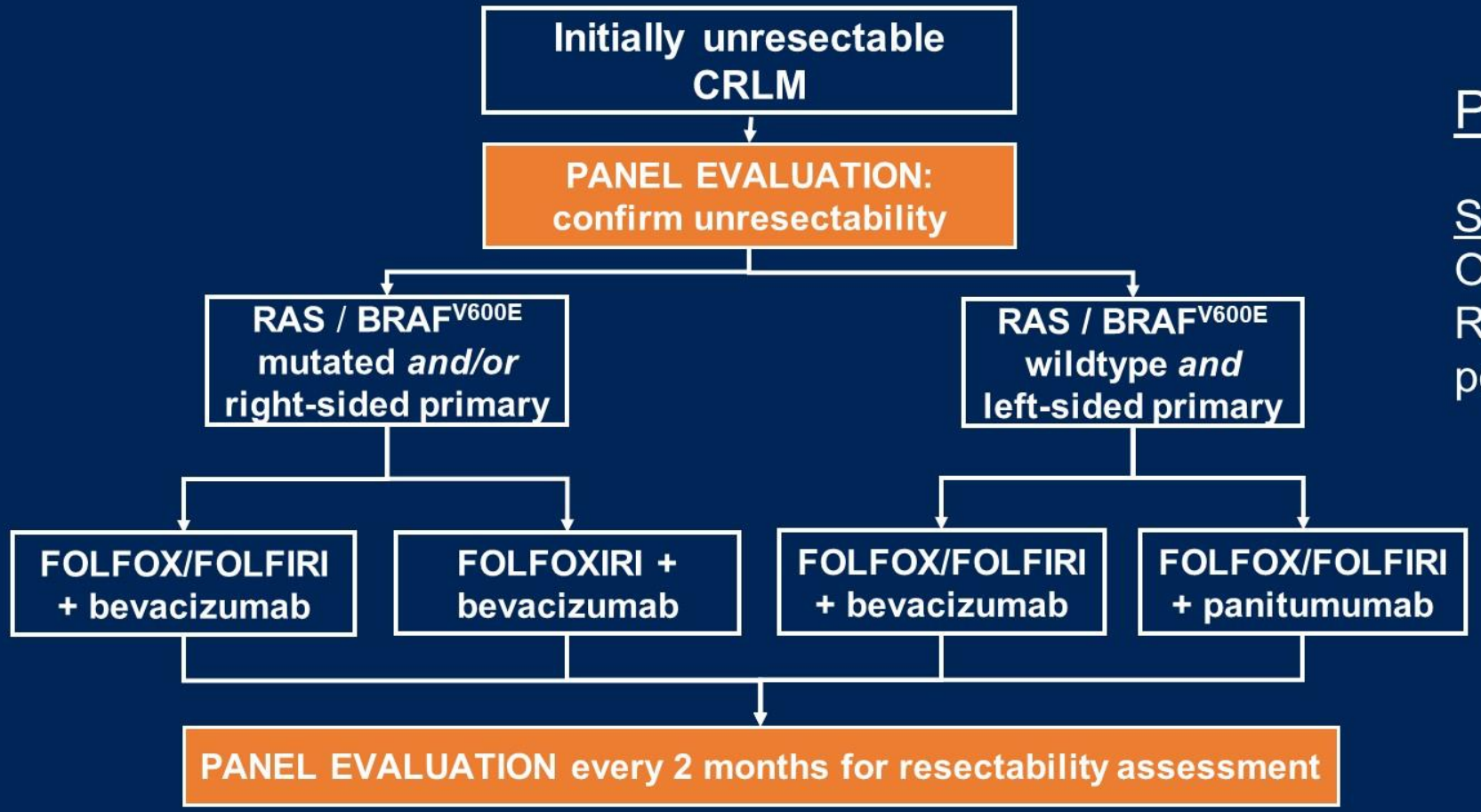
Are there other biomarkers besides sidedness that might explain this mild increase in survival? Awaiting pre- and post-treatment tissue and plasma DNA sequencing analysis, including MSI, TMB, CMS, IFN

What about FOLFOXIRI + bevacizumab in L mCRC?

How to optimally debulk R and L sided metastatic colon cancer: the **CAIRO5** and **TRIPLETE** story.



CAIRO5: prospective randomized comparison of currently most active systemic regimens in defined subgroups of patients with initially unresectable CRLM



Primary endpoint: PFS

Secondary endpoints:
OS, ORR, toxicity
R0/1 resection rates
postoperative morbidity

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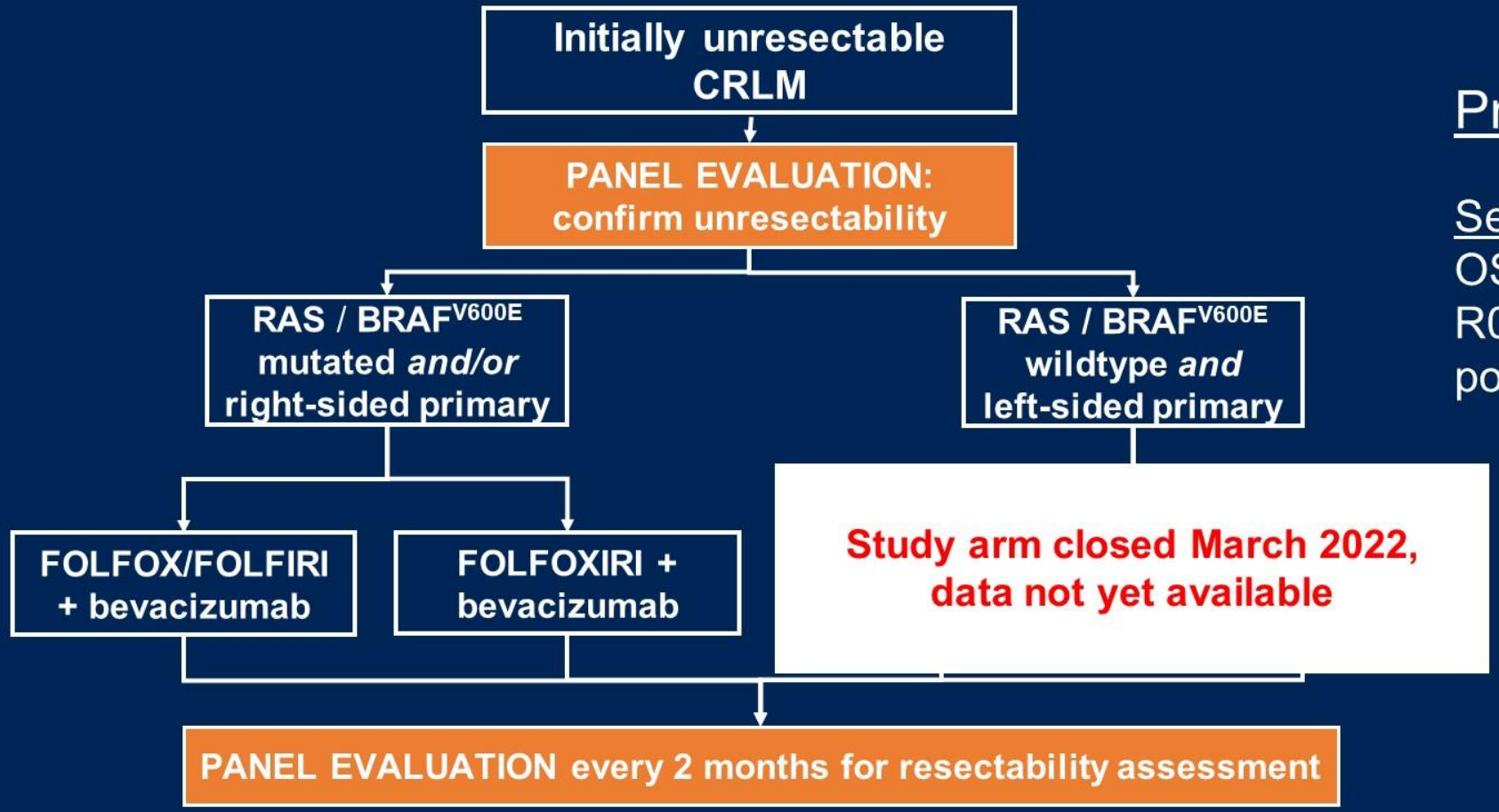
Prof. Cornelis J.A. Punt, MD, PhD

CAIRO5: prospective randomized comparison of currently most active systemic regimens in defined subgroups of patients with initially unresectable CRLM



Primary endpoint: PFS

Secondary endpoints:
OS, ORR, toxicity
R0/1 resection rates
postoperative morbidity

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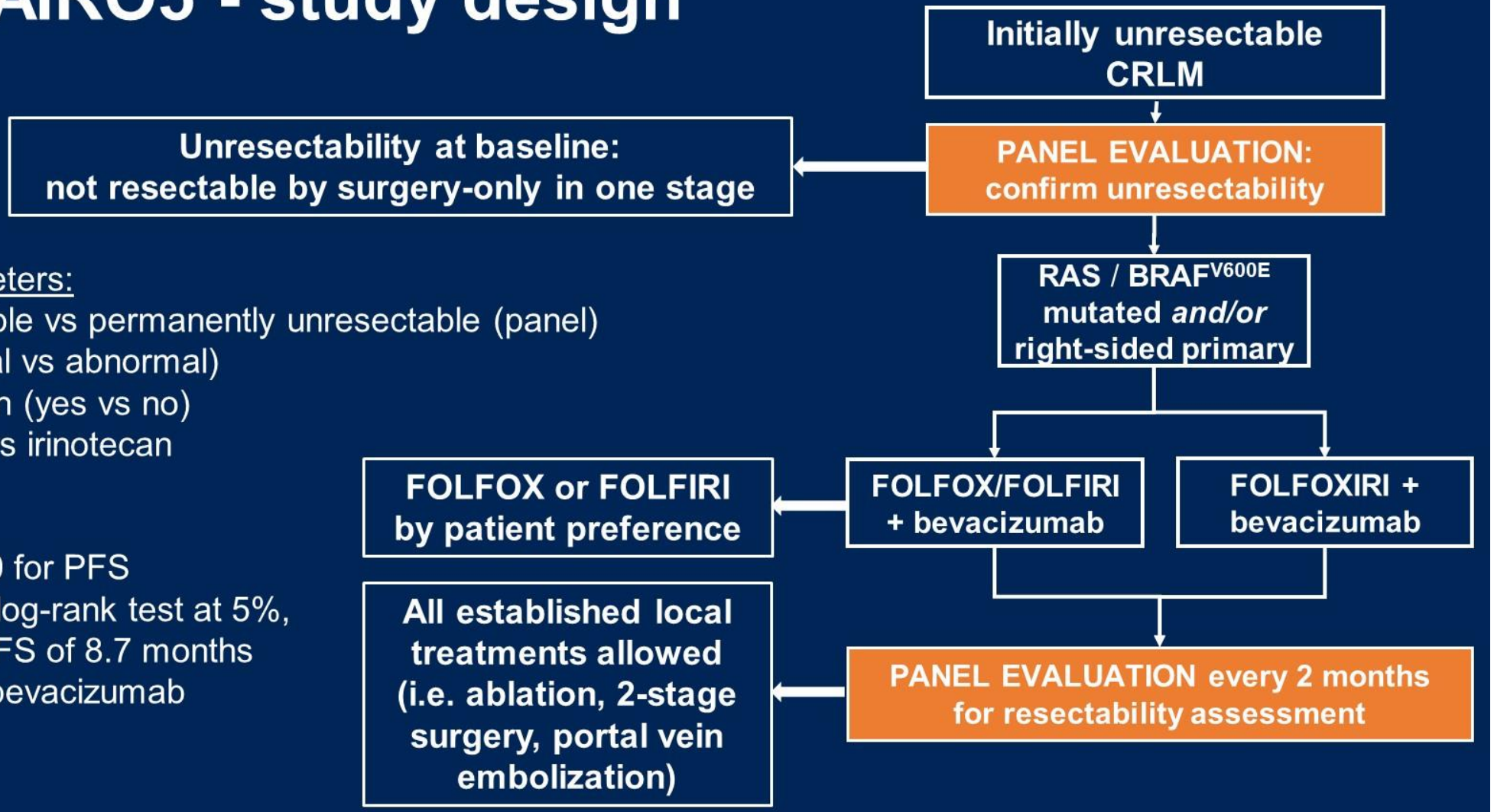
CAIRO5 - study design



Stratification parameters:
- potentially resectable vs permanently unresectable (panel)
- serum LDH (normal vs abnormal)
- *BRAF*^{V600E} mutation (yes vs no)
- choice oxaliplatin vs irinotecan

Statistics:
257 events, HR 0.70 for PFS
80% power 2-sided log-rank test at 5%, assuming median PFS of 8.7 months for doublet chemo+bevacizumab

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CAIRO5 – eligibility criteria

- Metastatic colorectal cancer with previously untreated liver-only metastases
- Metastases not resectable with surgery in one stage as defined by expert panel
- Patients with small (≤ 1 cm) extrahepatic lesions that are not clearly suspicious of metastases are eligible
- Right-sided primary tumor and/or *RAS* or $BRAF^{V600E}$ mutated tumor
- WHO performance status 0-1, age ≥ 18 years
- Eligible for study procedures (systemic regimens, local treatments)
- Primary tumor, if in situ, should be resectable
- Written informed consent

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CAIRO5 – patient characteristics

	FOLFOX/FOLFIRI + beva	FOLFOXIRI + beva
n	147	144
Male gender	64%	60%
Age (median, range)	61 (39-79) yrs	65 (35-81) yrs
WHO PS 0	64%	69%
Right-sided primary	41%	42%
RAS mutation	86%	86%
$BRAF^{V600E}$ mutation	7%	8%
Synchronous metastases	86%	90%
Prior adjuvant chemotherapy	5%	5%
Median number of CRLM	12 (7-24)	12 (7-22)
Normal serum LDH	52%	52%
Preference for oxaliplatin	93%	94%
Potentially resectable CRLM (panel)	88%	86%

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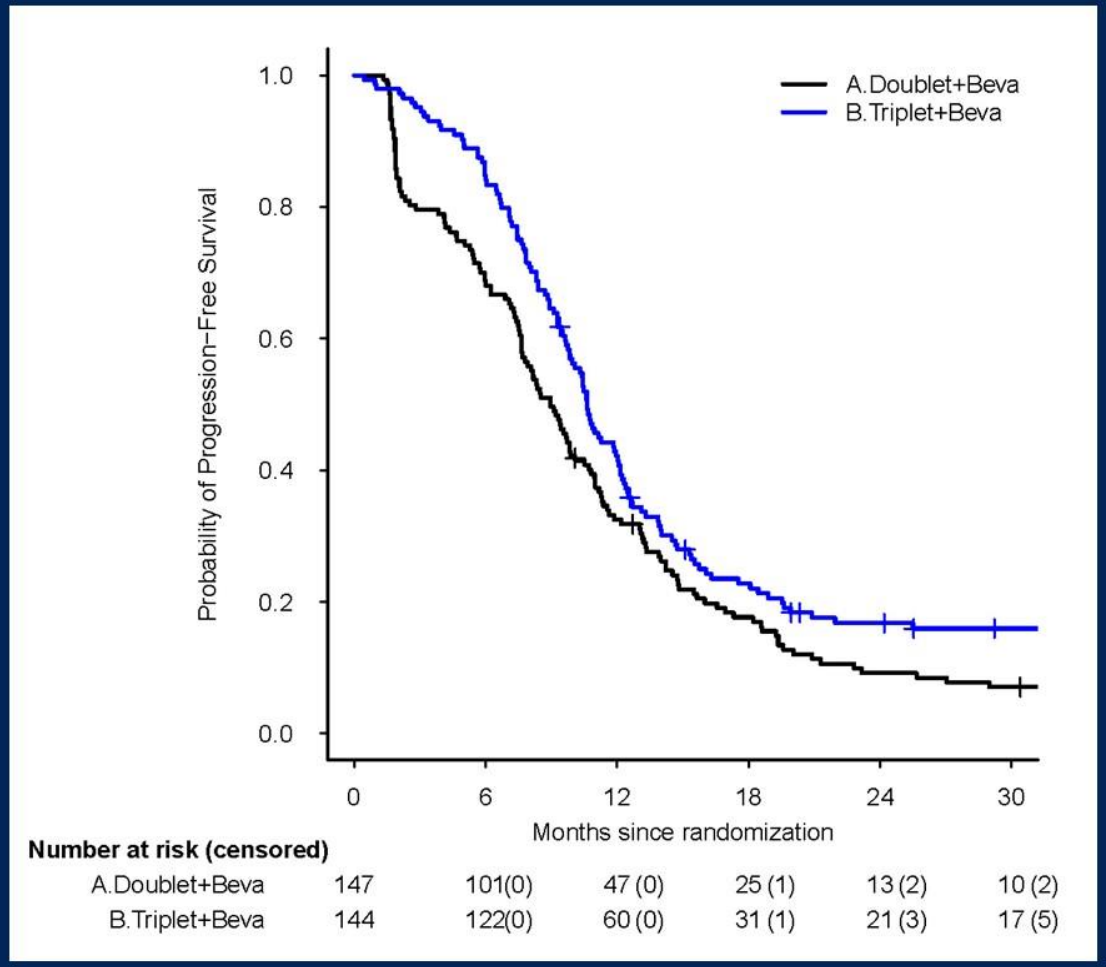
CAIRO5 – progression-free survival



Median follow up 41 months

FOLFOX/FOLFIRI + bevacizumab 9.0 months
FOLFOXIRI + bevacizumab 10.6 months

HR 0.77, 95% CI 0.60-0.99, p=0.038

Data on overall survival not yet mature

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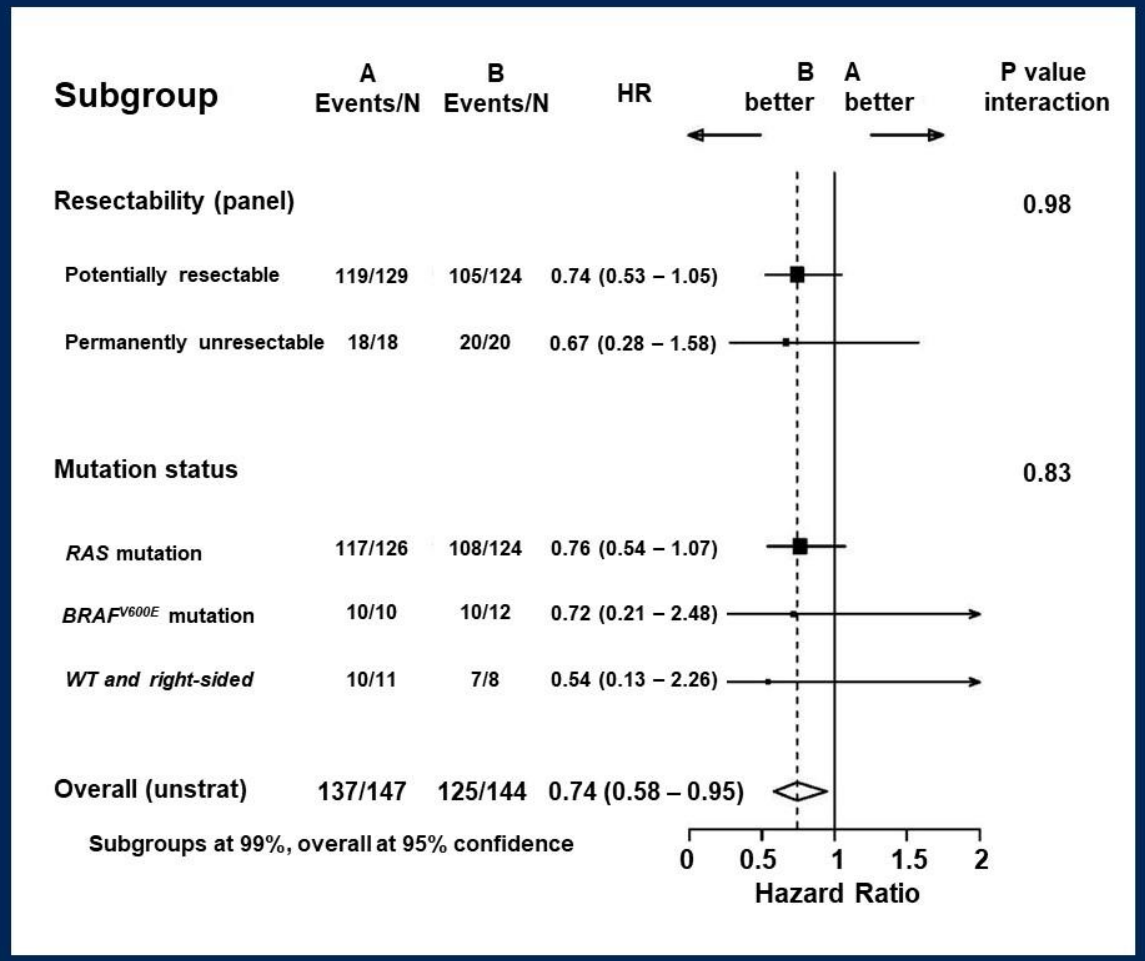
CAIRO5 – subgroup analysis PFS



No significant interaction between baseline unresectability status or mutation status and PFS

B: FOLFOXIRI + bevacizumab
A: FOLFOX/FOLFIRI + bevacizumab

CAIRO5 – systemic treatment

	FOLFOX/FOLFIRI + beva	FOLFOXIRI + beva	
n	147	144	
Number of cycles (median)*	8 (1-16)	8 (1-15)	
Overall response rate	33.3%	53.5%	p<0.001
Grade ≥ 3 adverse events	59.2%	75.7%	p=0.003
neutropenia	12.9%	38.2%	p<0.001
diarrhea	3.4%	19.4%	p<0.001
death	0%	1.4% (n=2)	

* excluding maintenance cycles and any adjuvant chemotherapy

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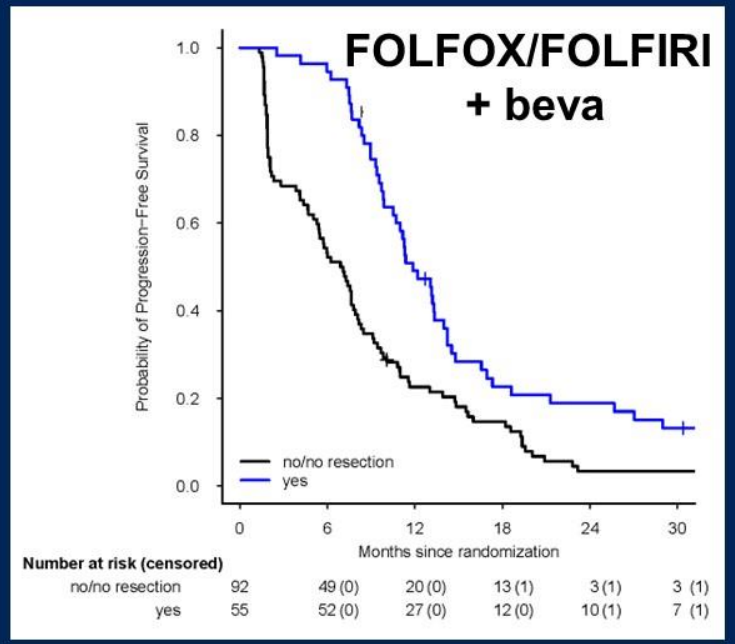
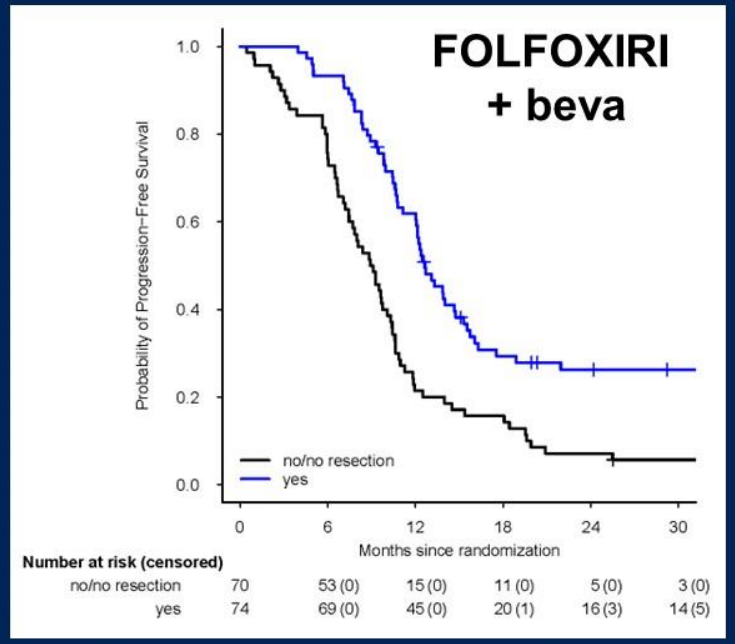
CAIRO5 – local treatment

	FOLFOX/FOLFIRI + beva	FOLFOXIRI + beva	
n	147	144	
Resection +/- ablation rate postoperative complications Clavien Dindo grade ≥3 grade 5 (death)	46% 40% 15% 0%	57% 51% 27% 2% (n=3)	p=0.08 p=0.19 p=0.08
Number of induction cycles (median, range)	7 (4-12)	6 (2-12)	
Adjuvant chemotherapy	38%	45%	
Number of adjuvant cycles (median, range)	6 (1-8)	4 (1-8)	
R0/1 resection +/- ablation rate 2-stage surgery +/- PVE	37% 16%	51% 32%	p=0.02 p=0.04

CAIRO5 – outcome of R0/1 resections +/- ablation





	median PFS <u>without</u> successful local treatment	median PFS <u>with</u> succesful local treatment	
FOLFOX/FOLFIRI + bevacizumab	7.0 months	11.9 months	HR 0.49, p<0.0001
FOLFOXIRI + bevacizumab	9.0 months	12.7 months	HR 0.43, p<0.0001

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How to optimally debulk R and L sided metastatic colon cancer: the **CAIRO5** and **TRIPLETE** story.

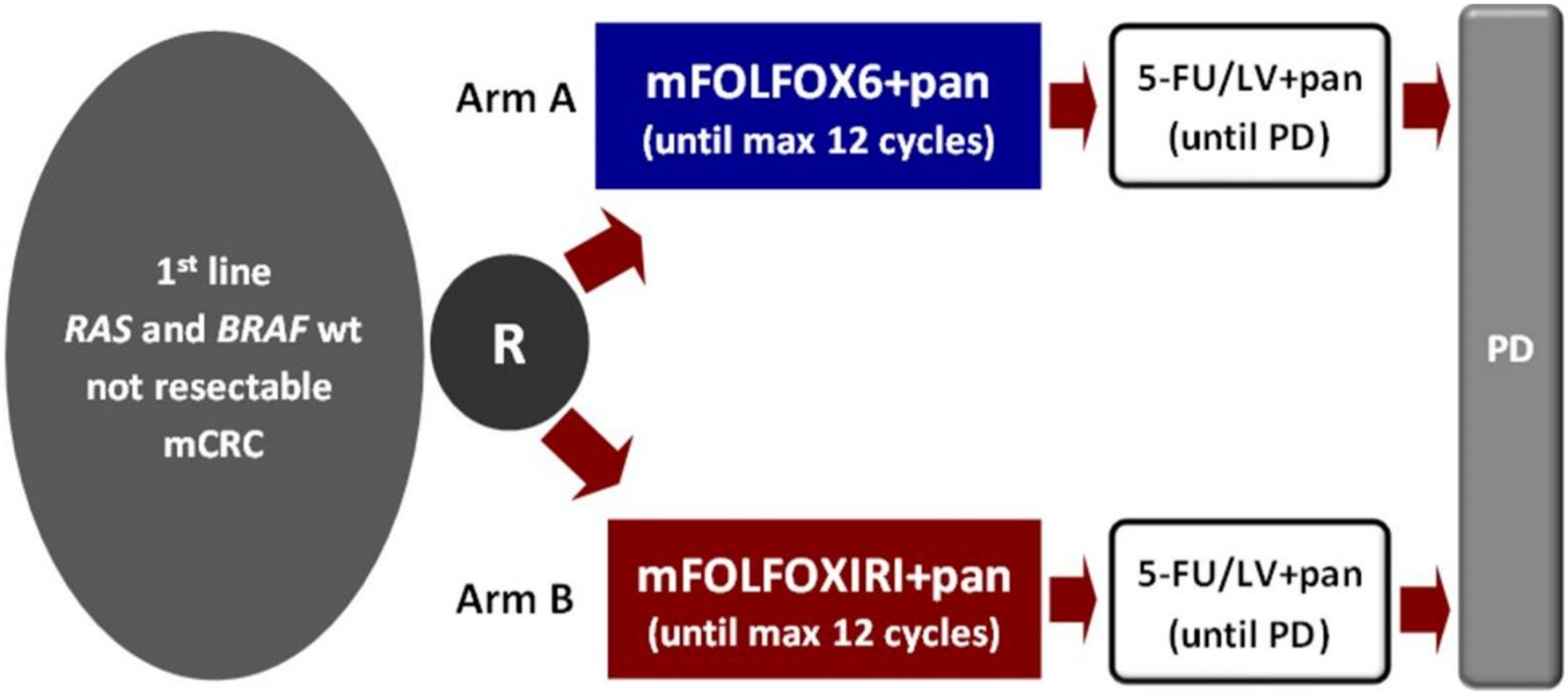
2022 ASCO Annual Meeting

Chicago, 6th June 2022

Modified FOLFOXIRI plus panitumumab (mFOLFOXIRI/PAN) versus mFOLFOX6/PAN as initial treatment of patients with unresectable *RAS* and *BRAF* wild-type metastatic colorectal cancer (mCRC): Results of the phase III randomized TRIPLETE study by GONO.

Cremolini C, Rossini D, Lonardi S, Antoniotti C, Pietrantonio F, Marmorino F, Antonuzzo L, Boccaccino A, Randon G, Giommoni E, Pozzo C, Moretto R, De Grandis MC, Viola MG, Passardi A, Buonadonna A, Formica V, Aprile G, Boni L, Masi G
on behalf of the GONO Investigators

TRIPLETE trial



Stratification factors:

- ECOG Performance Status (0-1 vs 2)
- Primary tumor location (right vs left)
- Metastatic spread (liver-only vs not liver-only)

57 participating centers
From September 2017 to September 2021

Patients' characteristics – ITT population

Characteristic, % patients	N=435 FOLFOX/Pan N = 217	 mFOLFOXIRI/Pan N = 218
Gender (M / F)	64 / 36	62 / 38
Median Age (IQ range)	59 (51 – 65)	59 (51 – 64)
ECOG PS (0 / 1-2)	**80** / 20	**84** / 16
Synchronous Metastases (Y / N)	**88** / 12	**87** / 13
Prior Adjuvant CT (Y / N)	2 / 98	6 / 94
Resected primary tumor (Y / N)	43/57	51/49
Number Metastatic Sites (1 / >1)	48 / 52	47 / 53
Liver Only Disease (Y / N)	**37** / 63	**39** / 61
Primary Tumor Side (right / left)	12 / **88**	12 / **88**
MMR status (pMMR / dMMR*/ NE)	67 / **1** / 32	74 / **3** / 23

* Local evaluation by IHC

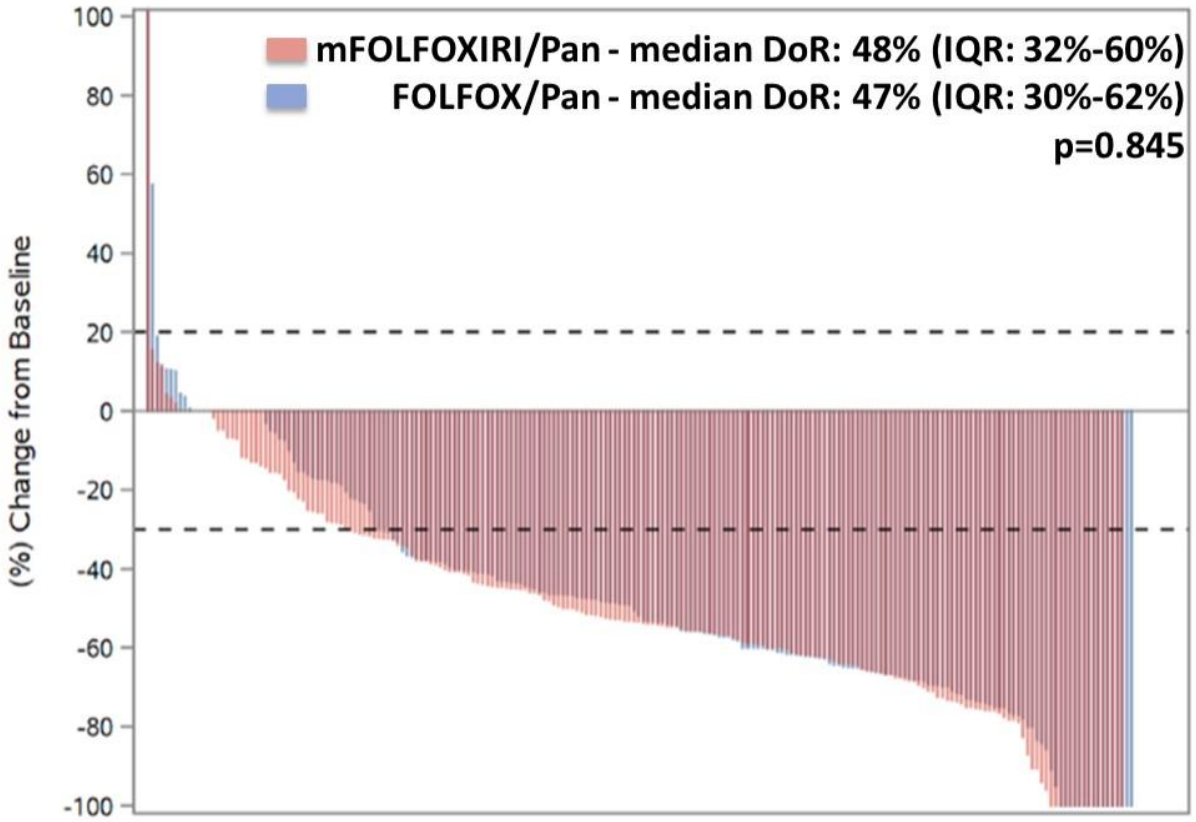
Response and Resection Rate

	FOLFOX/Pan N = 213	mFOLFOXIRI/Pan N = 218	OR [95%CI], p
Complete Response	7%	7%	
Partial Response	69%	66%	
Response Rate	**76%**	**73%**	**0.87 [0.56-1.34], p=0.526**
Stable disease	17%	18%	
Progressive Disease	5%	5%	
Not Assessed	2%	4%	
R0 Resection Rate	**29%**	**25%**	**0.81 [0.53-1.23], p=0.317**

Deepness of Response and Early Tumor Shrinkage

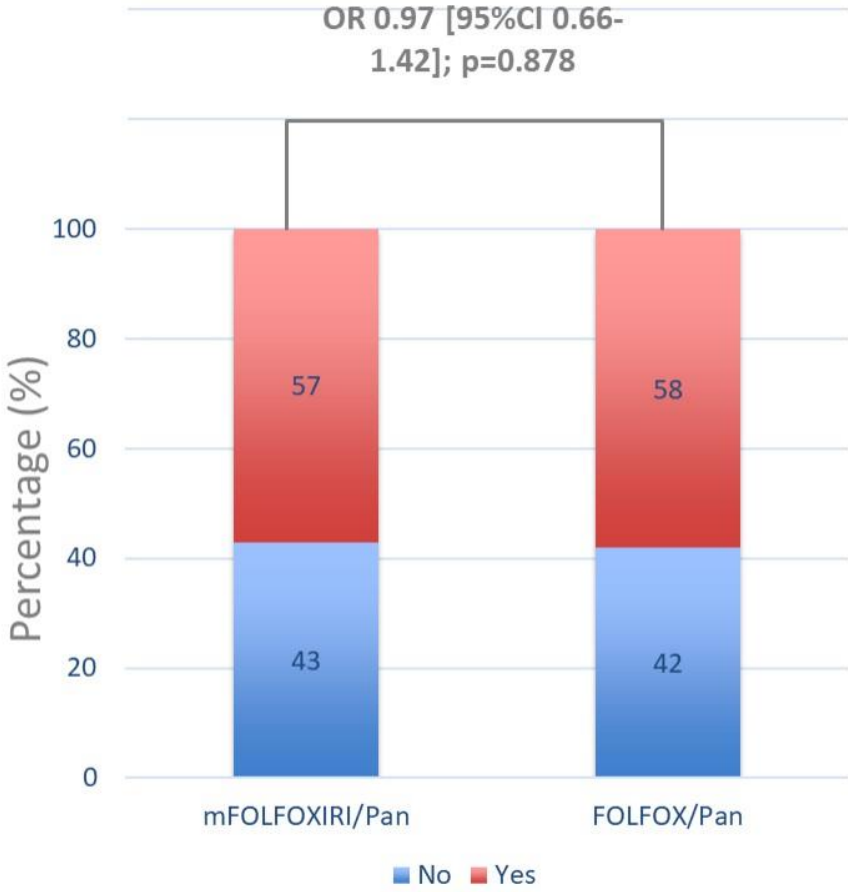
Deepness of Response

(relative change in the sum of the longest diameters of the target lesions at the nadir, in the absence of new lesions or progression of non-target lesions)

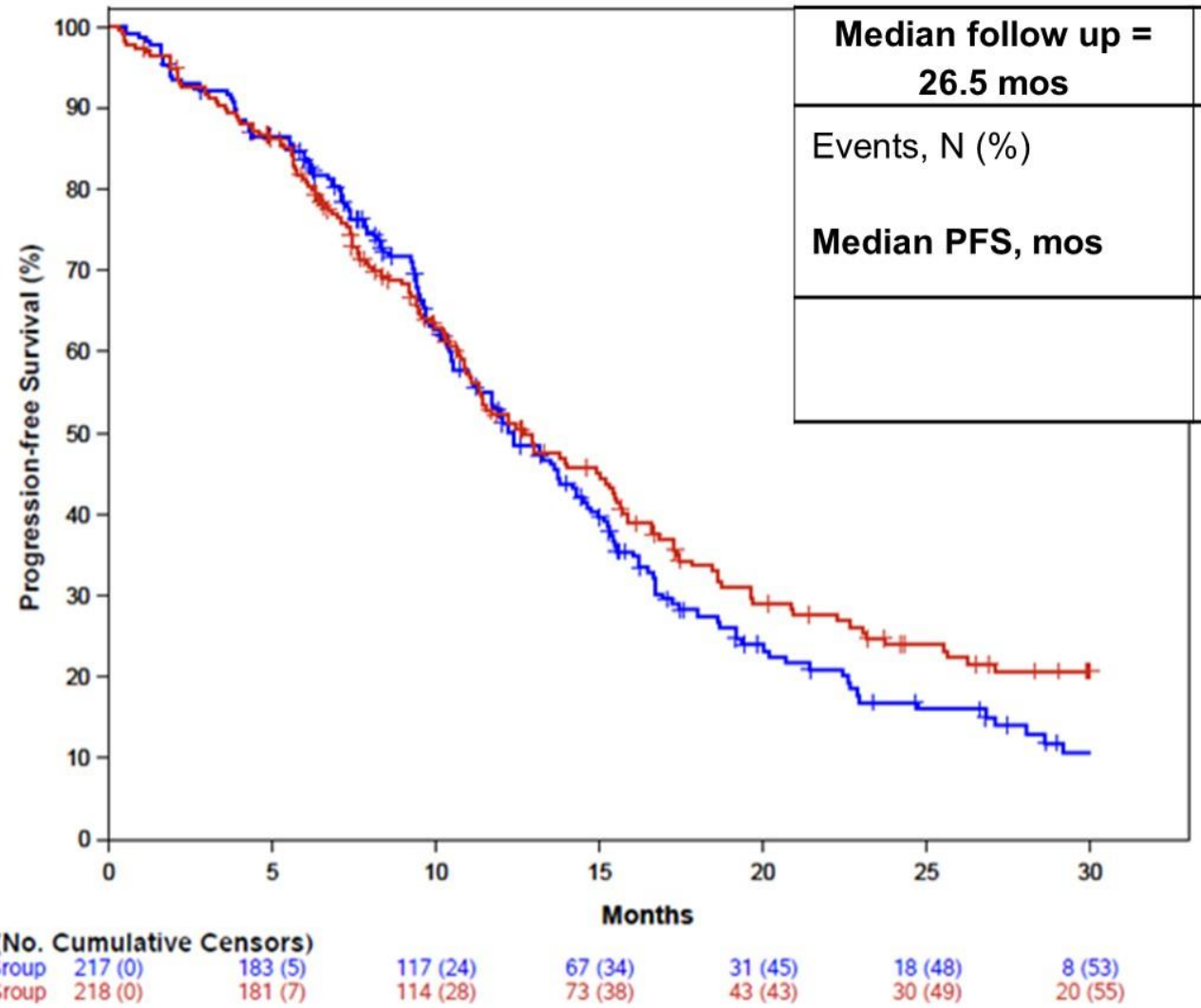


Early tumor shrinkage

(≥20% decrease in the sum of the diameters of the RECIST target lesions after 8 weeks)



Progression Free Survival



Median follow up = 26.5 mos	FOLFOX/Pan N = 217	mFOLFOXIRI/Pan N = 218
Events, N (%)	157 (72%)	148 (68%)
Median PFS, mos	**12.3**	**12.7**
	HR = 0.88 [95% CI: 0.70-1.11] p=0.277	

Summary

- ✓ The primary endpoint is NOT met: the intensification of the upfront chemotherapy backbone with mFOLFOXIRI is not associated with improved ORR as compared with mFOLFOX6 when both regimens are combined with panitumumab (73% vs 76%, p=0.526) in *RAS* and *BRAF* wt mCRC patients.
- ✓ The ORR achieved in the control arm is higher than expected in the null hypothesis (76% vs 60%) probably as a consequence of patients' selection according to primary tumor site (88% of patients had left-sided tumors).
- ✓ No difference is shown either in terms of ETS, DoR, R0 resection rate and PFS (12.7 vs 12.3 months, log-rank test p=0.277). OS results are not mature, yet.
- ✓ No subgroups of special interest for the efficacy of the experimental treatment are identified.
- ✓ Higher rates of G3/4 AEs, in particular diarrhea (23%) are shown in the experimental arm, though with reduced doses of irinotecan (150 mg/sqm) and 5-fluorouracil (2400 mg/sqm) compared with the FOLFOXIRI schedule

How to optimally debulk R and L sided metastatic colon cancer: the **CAIRO5** and **TRIPLETE** story.

In **right-sided** colon cancer, FOLFOXIRI + bev significantly increased PFS, ORR, and rate of R0/R1 resections with AND without ablation in initially unresectable liver mets, even including RAS- and BRAF-mutated V600E mutations – BUT:

PFS benefit is small, data is still immature for overall survival and G3/4 AEs much higher. Probably still best served as a bridging therapy to resection where PFS benefit is maximal.

In **left-sided** RAS/RAF wildtype colon cancer, response outcomes are so good with doublet chemotherapy + anti-EGFR regimens that it doesn't benefit patients in any appreciable way to add irinotecan to first-line anti-EGFR therapy, even with bridging intent.

2022 ASCO® ANNUAL MEETING

SYNCHRONOUS & CCRe-IV

Randomized clinical trial on resection of the primary tumor versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases

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on behalf of the SYNCHRONOUS and CCRe-IV Trial Groups

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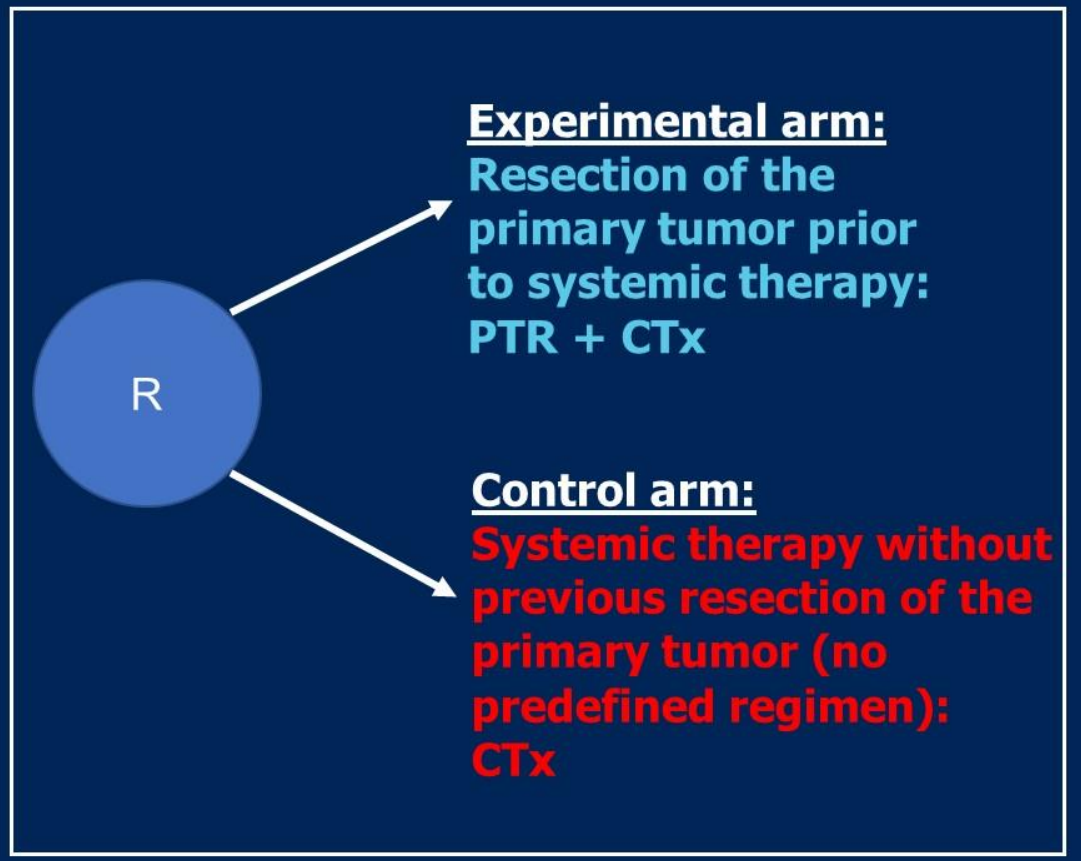
Eligibility Criteria/Study Design

- Newly diagnosed, histologically confirmed colon or high rectal cancer (>12 cm from anal verge) with synchronous metastases not amenable to curative therapy
- Resectable primary tumor, without tumor-related symptoms or diagnostic findings requiring urgent surgery
- No extensive peritoneal metastases
- ECOG performance status of 0, 1 or 2
- Patient considered to tolerate surgery and chemotherapy
- ≥ 18 years of age
- Written informed consent



Endpoints

- **Primary Endpoint:** **Overall Survival**
- **Secondary Endpoints:**

CTx	PTR + CTx
• Time-to-local tumor symptoms	• Peri-operative morbidity & mortality
• Intervention due to primary tumor complications	
• Interventions with curative intent	• Interventions with curative intent
• Administration of chemotherapy	• Administration of chemotherapy
• Quality of Life	• Quality of Life

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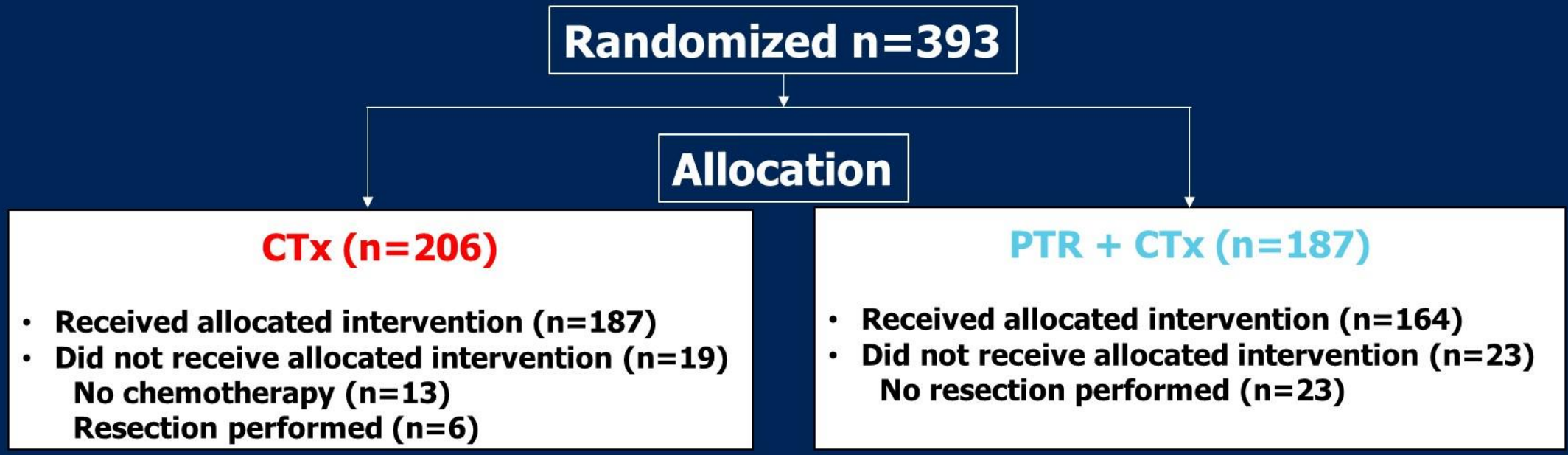
Study Flow (CONSORT)



Demographics

	CTx (N=206)	PTR + CTx (N=187)
Age (median, IQR)	69 (62-75)	69 (61-75)
Male (n,%)	136 (66.0%)	126 (67.4%)
Female (n,%)	70 (34.0%)	61 (32.6%)
ECOG (n,%)		
0	96 (46.6%)	87 (46.5%)
1	88 (42.7%)	70 (37.4%)
2	22 (10.7%)	30 (16.0%)

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Disease Characteristics

	CTx (N=206)	PTR + CTx (N=187)
Right-sided cancer	96 (46.6%)	84 (44.9%)
Metastatic sites		
Liver	196 (95.1%)	178 (95.2%)
Lung	61 (29.6%)	52 (27.8%)
Non-regional lymph nodes	31 (15.0%)	40 (21.4%)
Peritoneum	11 (5.3%)	13 (7.0%)
Bone	5 (2.4%)	1 (0.5%)
Other	5 (2.4%)	13 (7.0%)
Number of metastatic sites		
Missing	1 (0.5%)	1 (0.5%)
1	126 (61.2%)	110 (58.8%)
2-5	79 (38.3%)	76 (40.6%)

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Surgical Approach

	CTx (N=206)	PTR + CTx (N=187)
Resection of primary tumor	6 (2.9%)	164 (87.7%)
Laparotomy (open)	4 (80%)	89 (54.3%)
Surgical procedure		
(Extended) right hemicolectomy	1 (16.6%)	65 (39.6%)
(Extended) left hemicolectomy	1 (16.6%)	28 (17.1%)
Sigmoid colectomy	1 (16.6%)	53 (32.3%)
Segmental resection	1 (16.6%)	9 (5.5%)
Other	2 (33.3%)	9 (5.5%)
Anastomosis	4 (80%)	38 (23.2%)

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Administered Chemotherapy

	CTx (N=206)	PTR + CTx (N=187)
No chemotherapy administered	13 (6.4%)*	45 (24.1%)
1st line chemotherapy#		
Fluoropyrimidine mono	15 (7.9%)	18 (12.7%)
Irinotecan doublet	64 (33.7%)	41 (28.9%)
Oxaliplatin doublet	105 (55.3 %)	73 (51.4%)
Chemotherapy triplet	3 (1.6%)	5 (3.5%)
Other	2 (1.1%)	3 (2.1%)
Chemo + Bevacizumab	82 (43.2%)	55 (38.0%)
Chemo + EGFR-Antibody	33 (17.4%)	38 (26.8%)
Chemo + Bev + EGFR-Antibody	1 (0.5%)	0
No antibody	74 (38.9%)	49 (34.5%)
Number of cycles of 1st line CTx regimen given§	7.8 (± 6.3)	7.4 (± 5.7)

*Missing information for 3 pts.
#Missing information for CTx: 1 pt., for PTR+CTx: 2 pts.
§ Mean, SD

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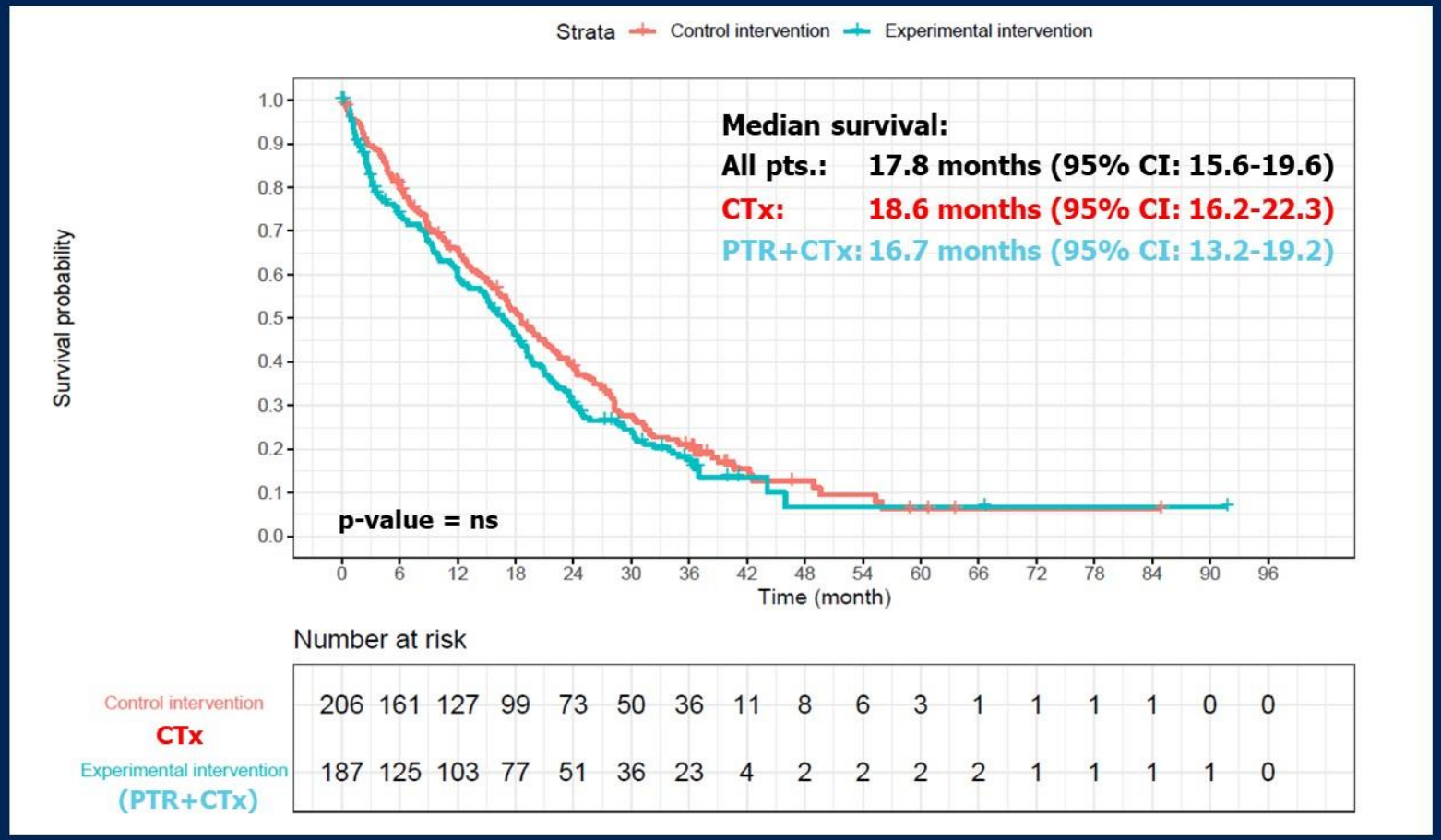
Primary Endpoint: Overall Survival (ITT)



Primary Endpoint: Overall Survival (ITT)

Primary Endpoint Model
Cox Regression Model (shared frailty)

	HR	95% CI	P value
Random Group	0.946	0.740-1.209	0.658
No chemotherapy administered	5.32	3.55-8.00	<0.001
Patient age (years)	1.013	1.001-1.026	0.033

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Serious Adverse Events (SAE)

	CTx (N=206)	PTR + CTx (N=187)
Number of patients with at least one SAE	37 (18.0%)	19 (10.2%)
Number of patients with „GI-tract related" SAEs	22 (10.7%)	8 (4.8%)*
Number of SAEs	43	22
„GI-tract related" SAEs	24 (55.8%)	8 (36.4%)
Diarrhea	1 (2.3%)	0
Vomiting	2 (4.7%)	1 (4.5%)
Ileus/Bowel obstruction	18 (41.9%)	2 (9.1%)
Bowel perforation	3 (7.0%)	3 (13.6%)
Colonic fistula	0	2 (9.1%)
Other	19 (44.2%)	14 (4.8%)

(excluding perioperative complications)

*p=0.031 (chi-square test)

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There is no improvement in OS in metastatic colorectal cancer management with resection of the primary unless the primary is symptomatic: the **SYNCHRONOUS and CCRe-IV** trial.

Overall survival was only impacted by whether the patient received chemotherapy

- Resection of the primary might have *worsened* survival!
- Nearly 25% of patients randomized to upfront surgery arm never received chemotherapy
- No significant subgroup benefit identified

Other Metastatic Colon Cancer Studies

Nivolumab in combination with FOLFOXIRI+bevacizumab in 1st line RAS/RAF mutated mCRC is feasible: The **NIVACOR** trial.

Nivolumab and ipilimumab are found in 5-year follow-up to have a high overall response rate and 48-mo PFS rate compared to nivolumab alone in dMMR/MSI-H mCRC: the **CheckMate 142(a)** trial**, cohorts 1-3**.

Intermittent vs continuous FOLFIRI + panitumumab for first line mCRC seems to improve progression on treatment survival as well as patient exposure to toxicities: the **IMPROVE** study.

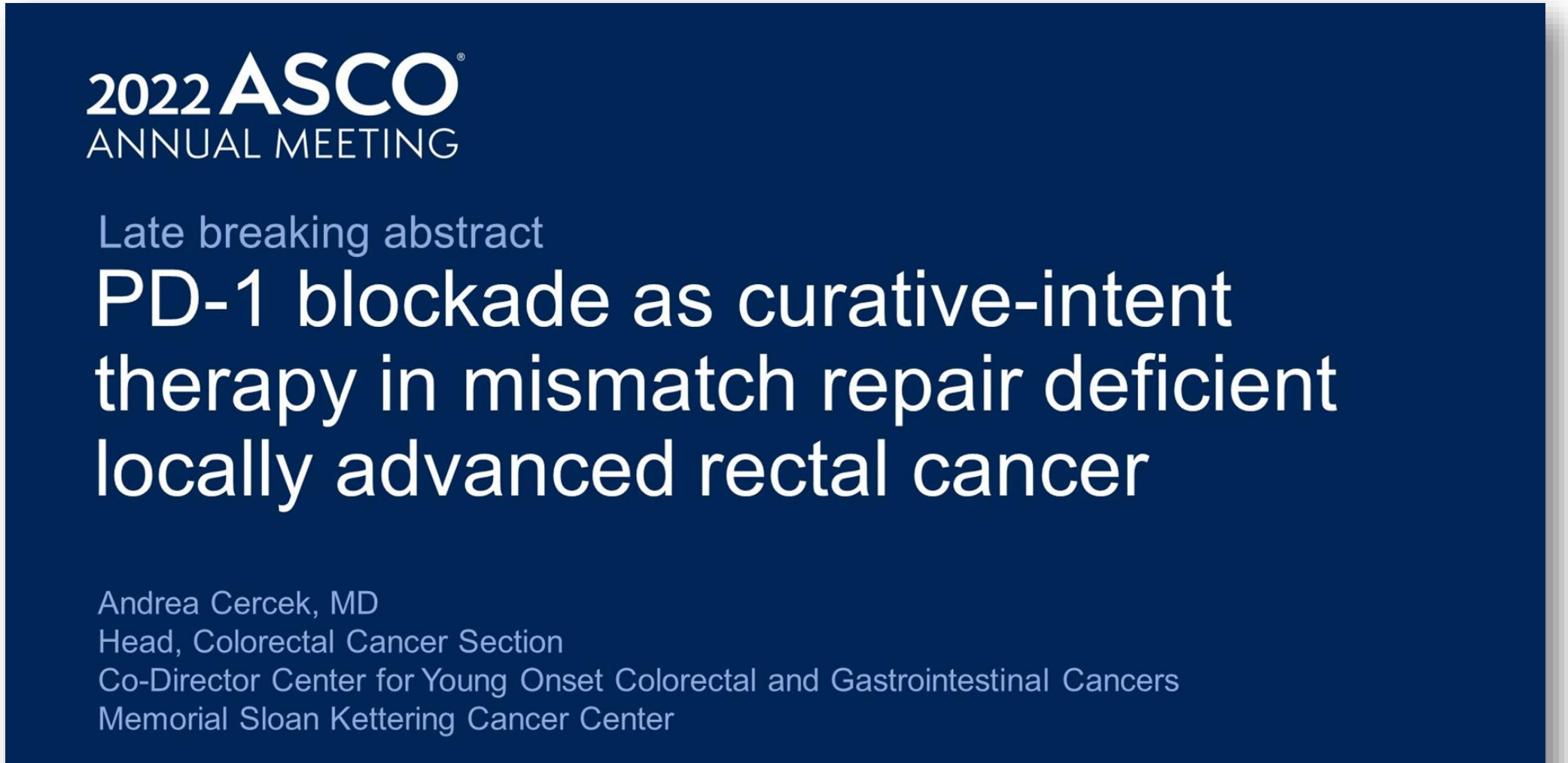
Optimal treatment sequencing for RAS/RAF wildtype mCRC still remains muddled: the complex **STRATEGIC-1** trial.

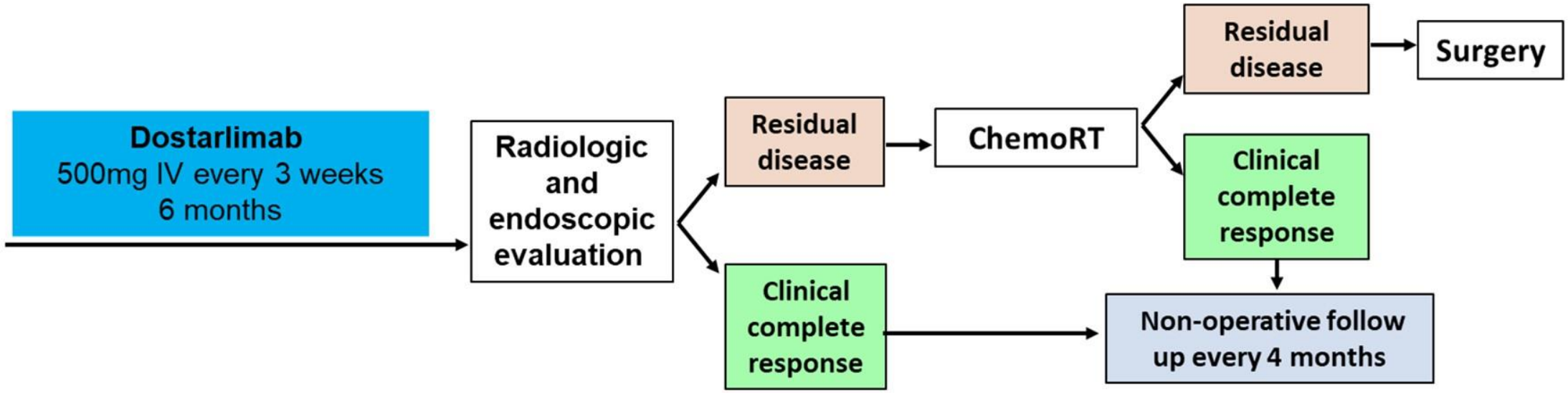
Rectal Cancer Updates

Late Breaking Abstract 5:

Neoadjuvant dostarlimab in mismatch repair deficient (dMMR) or microsatellite-unstable (MSI-H) rectal cancer (**Cercek et al**)

Neoadjuvant immunotherapy may become standard of care for mismatch repair deficient / microsatellite unstable locally advanced rectal cancer.





Patient population: Stage II and III mismatch repair deficient rectal cancer

Target Enrollment: 30 subjects

Study Design: Simon's two stage minimax design

NCT04165772

Response Criteria

Overall response

Rectal MRI and endoscopic exam graded as stable disease (SD), partial response (PR), near complete response (nCR) and complete response (CR)

Clinical complete response (cCR)

Endoscopic exam:

- Visual disappearance of the rectal primary
- Normal digital rectal exam

Rectal MRI

- Lack of signal at DWI with scar on T2WI (DWI volume = 0)
- Each target lymph node must have decreased short axis to <0.5cm

Maas M, et al., Ann Surg Oncol 2015;22:3873-80

Demographic and disease characteristics of the patients at baseline

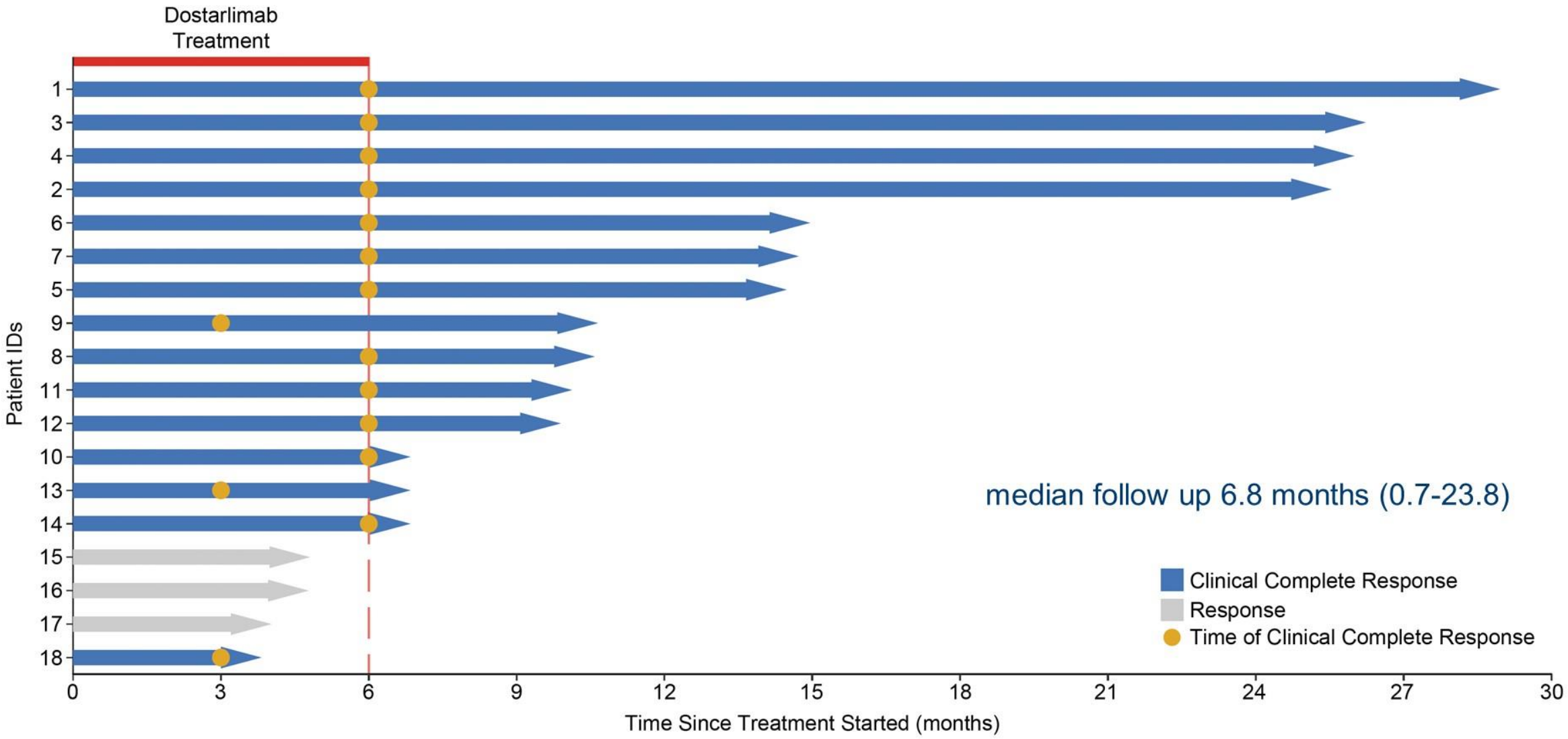
	Value (%)
Sex	
Male	6 (33)
Female	12 (67)
Age, median (range)	54 (26-78)
Race/Ethnicity	
White non-Hispanic	11 (61)
Hispanic	1 (6)
Black or African American	3 (17)
Asian-Far East/Indian Subcontinent	3 (17)
Tumor Staging	
T1/2	4 (22)
T3, T4	14 (78)
Nodal Staging	
Node-positive	17 (94)
Node-negative	1 (6)
Germline Mutation Status n=17	
MSH2, MLH1, MSH6, or PMS2	10 (59)
Negative	7 (41)
BRAF V600E wild type	18 (100)
Tumor Mutational Burden (mut/Mb), mean (range)	67 (36 -106)

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

Duration of response



Key Observations

- **100% clinical COMPLETE response** in the first 14 consecutive patients
- No grade 3 or 4 adverse events were observed
- No patients have required chemotherapy, radiation or surgery
- No disease recurrence observed during the follow-up period
- Longer follow up required

Other Rectal Cancer Studies

Neoadjuvant chemoradiation and local excision (TEM) might be as effective at achieving high pathologic complete response rates, lower complication/hospitalization rates compared to upfront total mesorectal excision in early stage rectal cancer; long-term follow-up pending: the **TAUTEM-**study.

Organ preservation and other risk-adapted deescalation of preoperative chemoradiation based on radiotherapy response assessment: The **STAR-TREC** phase II study.

Upfront surgery for locally advanced rectal cancer worsens 3-year disease free survival compared to conventional preoperative chemoradiation, even if the CRM isn't threatened: The **PSSR** Trial.

Intensified multimodality approaches to the treatment of rectal cancer: **PANDORA** and **OPERA** trials.

- PANDORA: Adding durvalumab to LC-CRT
- OPERA: X-ray brachytherapy in addition to CRT to improve organ preservation in cT2-T3 disease

Main mCRC/Rectal Cancer Takeaways from ASCO 2022

L mCRC, RAS wildtype tumors is preferentially treated with 1L FOLFOX + anti-EGFR therapy, but downstaging for resectable oligometastatic disease might still benefit from triplet chemo + bevacizumab in certain circumstances

Triplet chemo + bevacizumab is still likely the best 1L option for R mCRC, RAS/RAF mutated cancers

Immunotherapy will likely become the next standard of care for locally advanced rectal cancer, but patients need to be enrolled in appropriate trials with long-term follow-up