Evolving Treatments for the Oncology Practice
How the Masters Treat Cancer: Updates in Colorectal Cancer and Anal Cancer

VANDERBILT-INGRAM CANCER CENTER

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August 27, 2022

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GLOBOCAN 2020

Expected global incidence of CRC and anal cancer by 2040

Estimated number of new cases from 2020 to 2040.

Cancer sites	2020		2040
Colon	1,148,515	↑ 67%	1,916,781
Rectum	732,210	↑ 58%	1,160,296
Anus	50,865	↑ 53%	77,597
Total	1,931,590		3,154,674

Sung et al: GLOBOCAN Cancer J. Clin. 2021

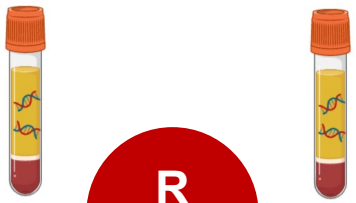
DYNAMIC Study Design

ACTRN12615000381583

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections
Week 4 + 7 post-op



R
2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo**
  (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

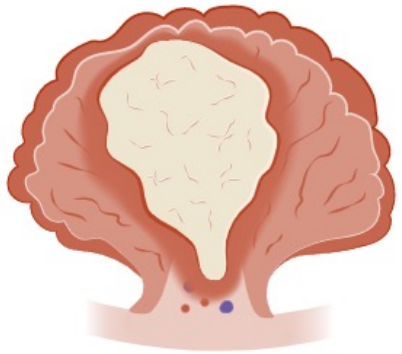
Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

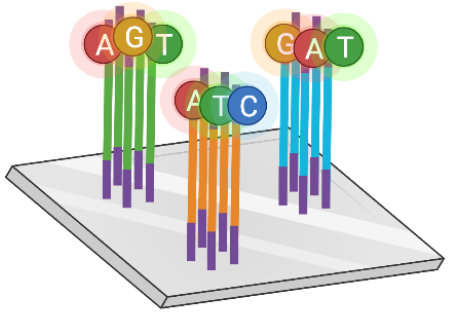
ctDNA Analysis: Tumor-Informed Personalized Approach

Resected tumor tissue



FFPE tissue from primary tumor

Targeted sequencing identifies mutation(s) unique to that cancer

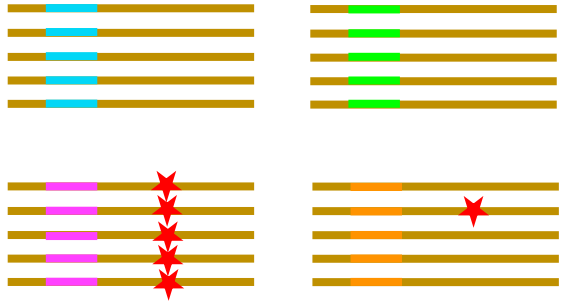


15 recurrently mutated genes in colorectal cancer

(APC, TP53, KRAS, PIK3CA, FBXW7, BRAF, SMAD4, RNF43, POLE, CTNNB1, ERBB3, NRAS, PPP2R1A, AKT1, HRAS)

Week 4 + 7 plasma

At least one patient-specific mutation assessed in plasma



ctDNA detection by Safe-Sequencing System*

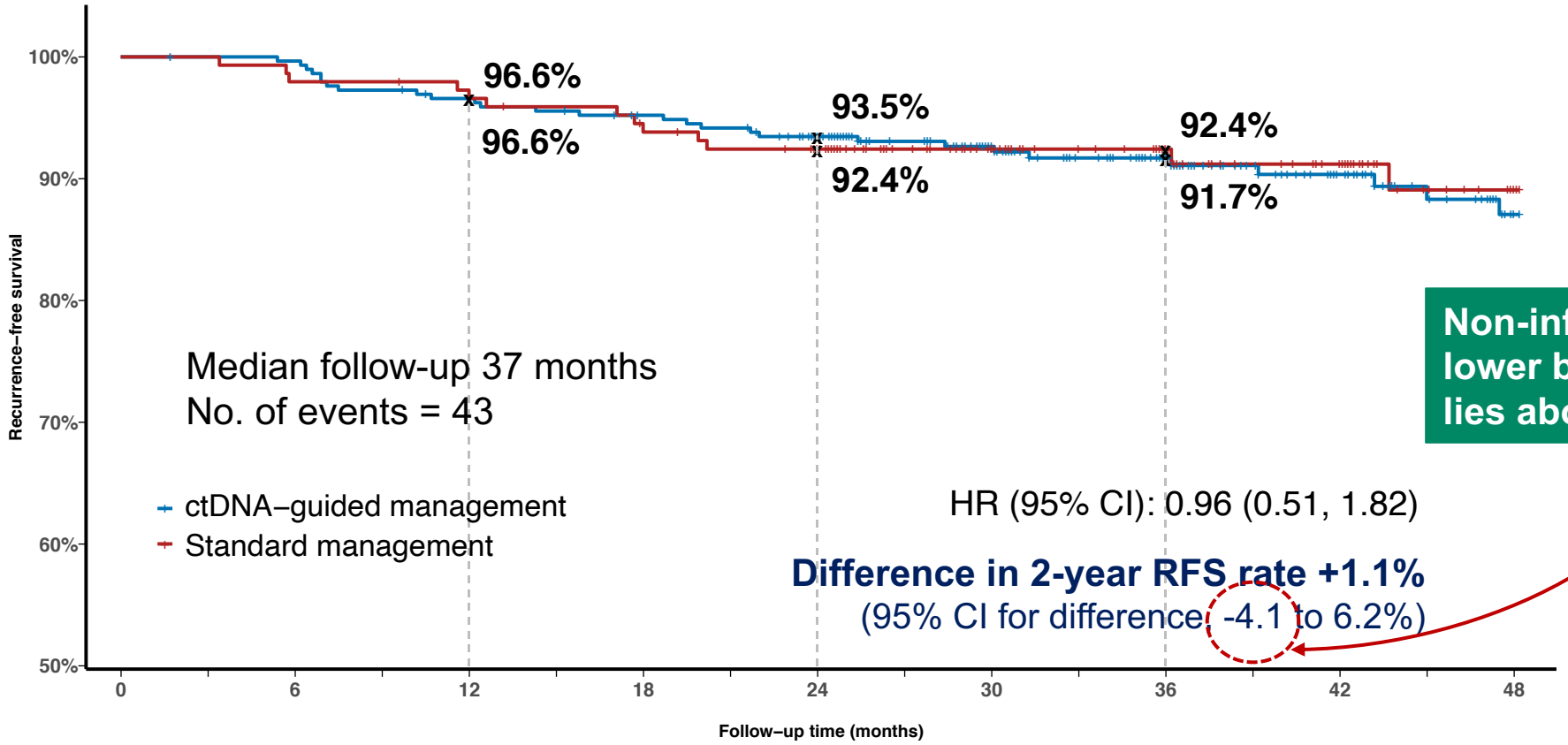
(error reduction technology designed to detect low frequency mutations using unique molecular identifier)

*Kinde *et al*. Proc Natl Acad Sci U S A. 2011;108(23):9530-5

Adjuvant Treatment Delivery

Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen received, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent fluoropyrimidine	17/45 **(38%)**	37/41 **(90%)**	<.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318
Completed planned treatment, n	38 (85%)	32 (78%)	0.7036
Percentage of full dose delivered, median (IQR)	78 (56, 100)	84 (64, 100)	0.6194

Recurrence-Free Survival (RFS)

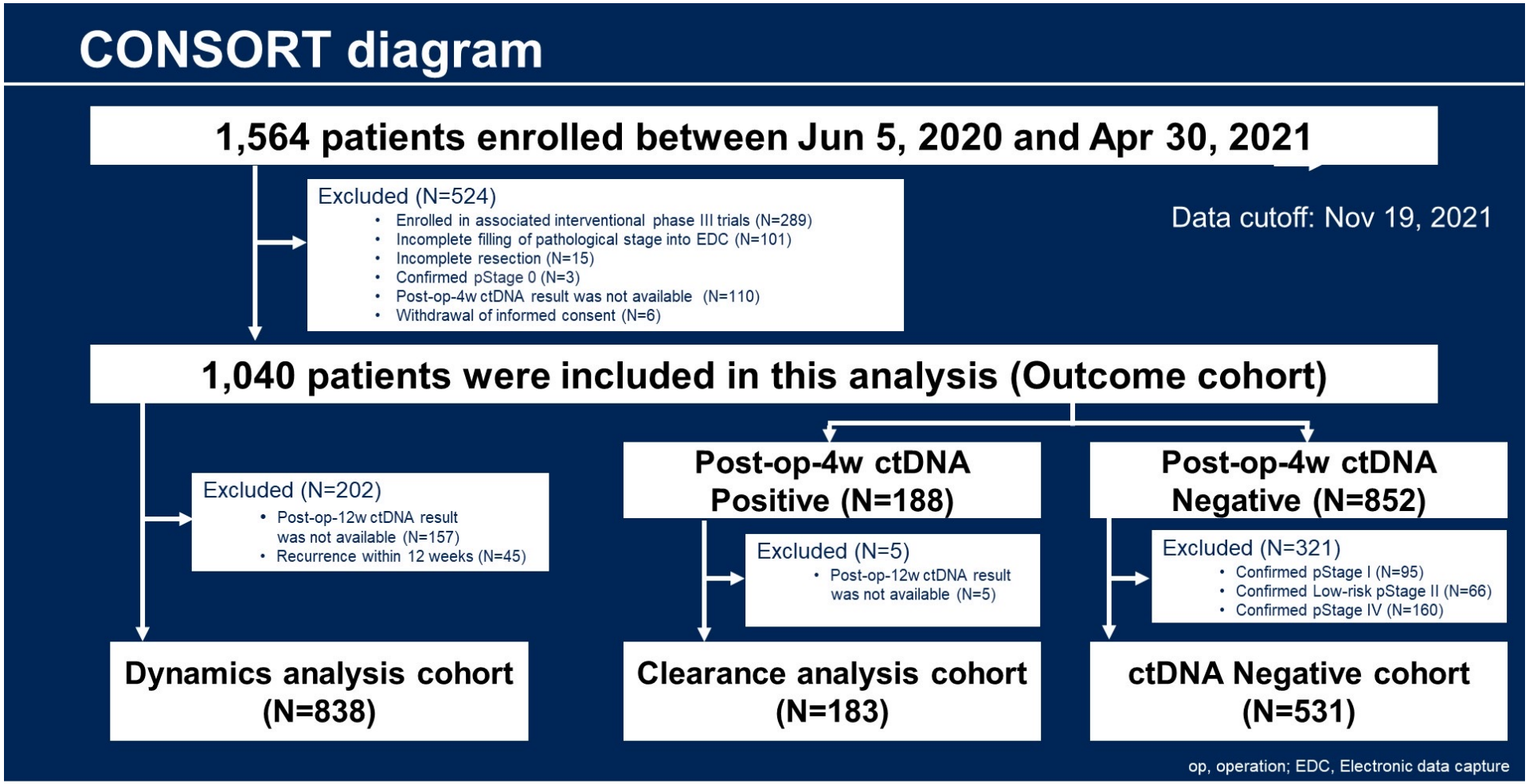


Non-inferiority confirmed: lower bound of 95% CI lies above -8.5%

Numbers at risk

ctDNA-guided	294	292	281	273	259	207	155	109	64
Standard	147	144	142	136	128	97	78	57	33

CIRCULATE-JAPAN (GALAXY Study) Results

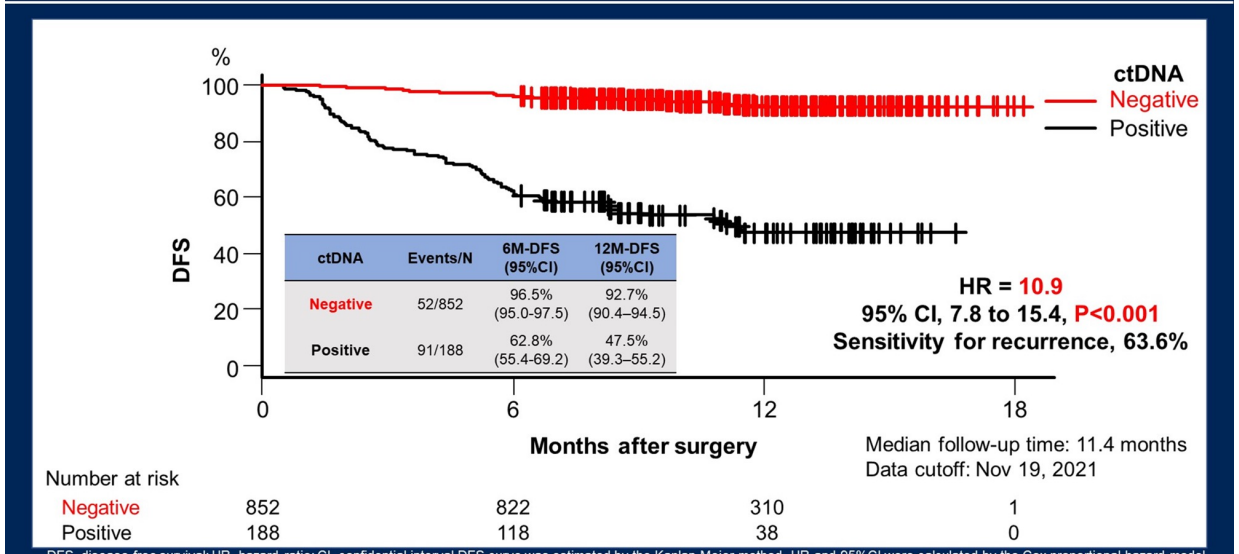


PRESENTED BY: Masahito Kotaka

JCO.2022.40.4_suppl.009

ctDNA May Guide Adjuvant Treatment for CRC

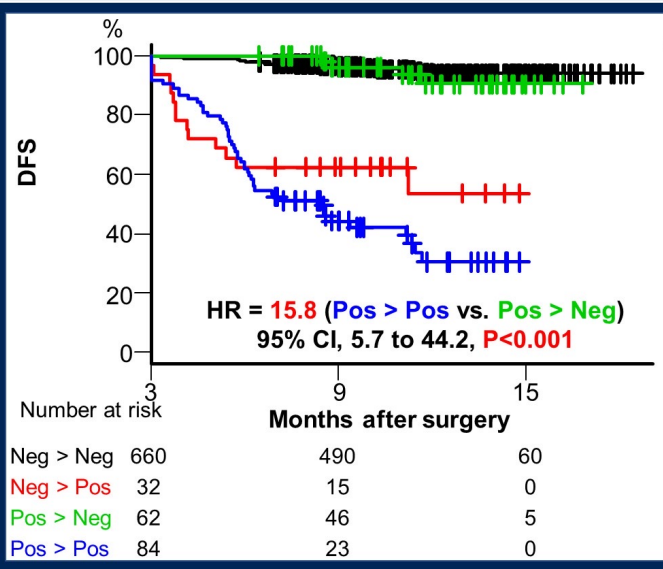
DFS by post-op-4w ctDNA status in overall population (pStage I-IV)



ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
Negative	52/852	96.5% (95.0-97.5)	92.7% (90.4–94.5)
Positive	91/188	62.8% (55.4-69.2)	47.5% (39.3–55.2)

DFS, disease-free survival; HR, hazard ratio; CI, confidential interval DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

DFS by ctDNA dynamics from post-op-4w to 12w



dynamics	Neg > Neg	Neg > Pos	Pos > Neg	Pos > Pos
Events/N	31/660	13/32	4/62	50/84
6M-DFS	98.0%	62.5%	100%	58.3%
HR	0.8	9.2	Reference	15.8
95%CI	0.27–2.15	3.0–28.4	-	5.7-44.2
P	0.60	<0.001	-	<0.001

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

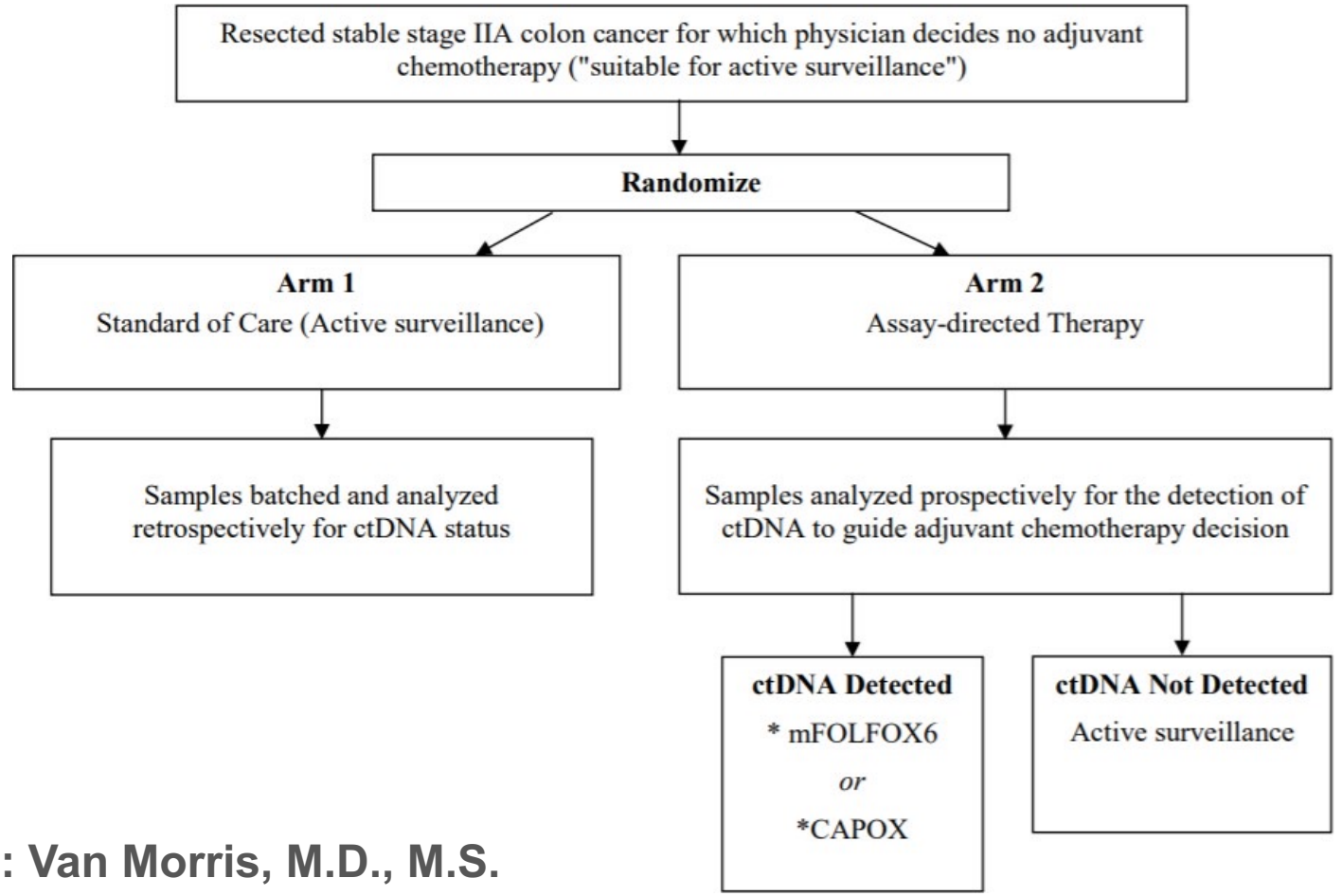
Landmark analysis at the post-op-12w was performed.
DFS, disease-free survival; HR, hazard ratio; CI, confidential interval DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

JCO.2022.40.4_suppl.009

NRG GI-005 (COBRA)

- **Phase II - To compare the rate of ctDNA clearance in "ctDNA detected" patients treated with or without adjuvant chemotherapy following resection of stage IIA colon cancer.**

- **Phase III - To compare recurrence-free survival (RFS) in "ctDNA detected" patients treated with or without adjuvant chemotherapy following resection of state IIA colon cancer**

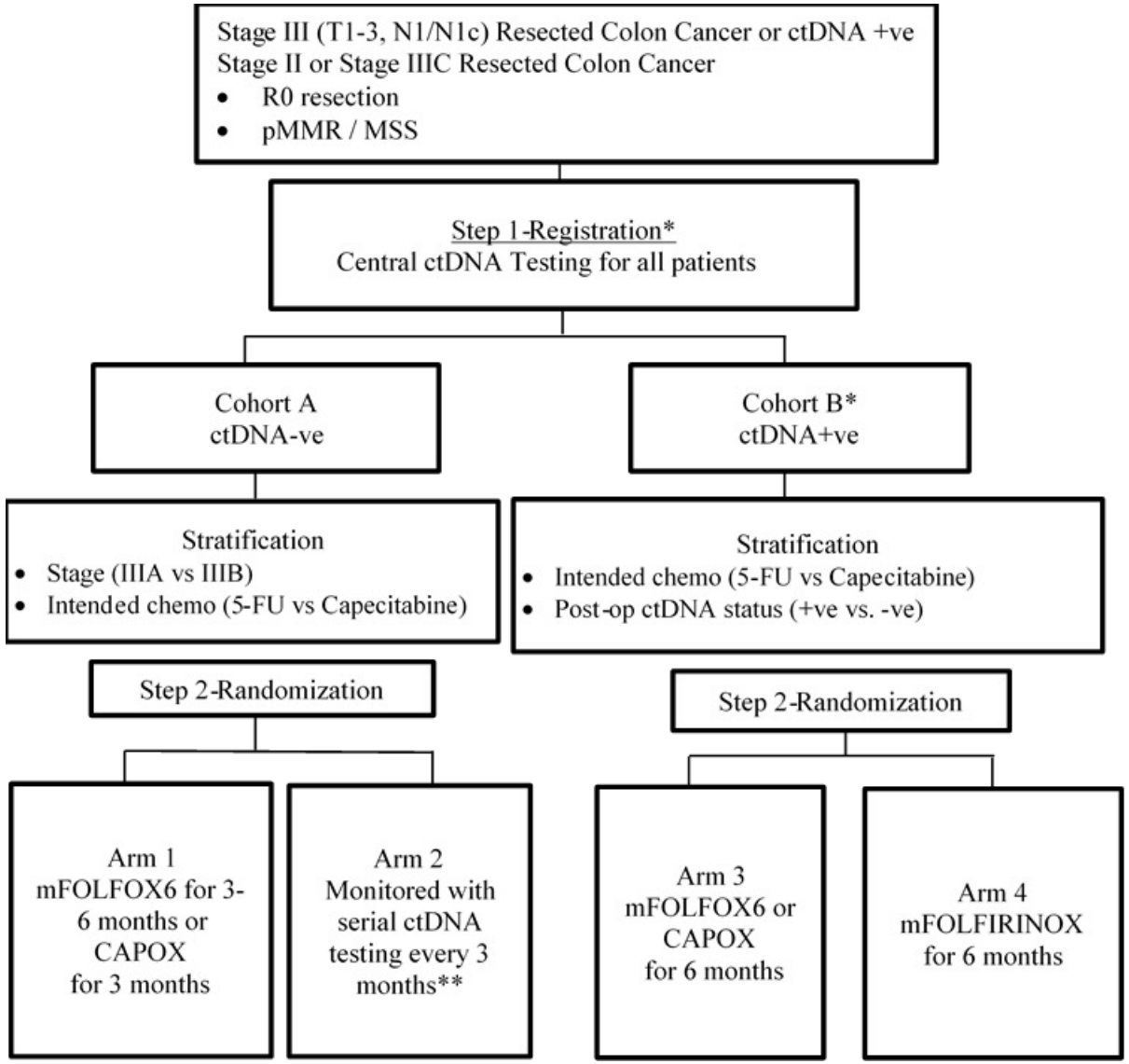


**PI's: Van Morris, M.D., M.S.
Greg Yothers, Ph.D.,
Scott Kopetz, M.D., Ph.D,
Thom George, M.D.**

NRG ONCOLOGY™

NCT04068103

Study Schema

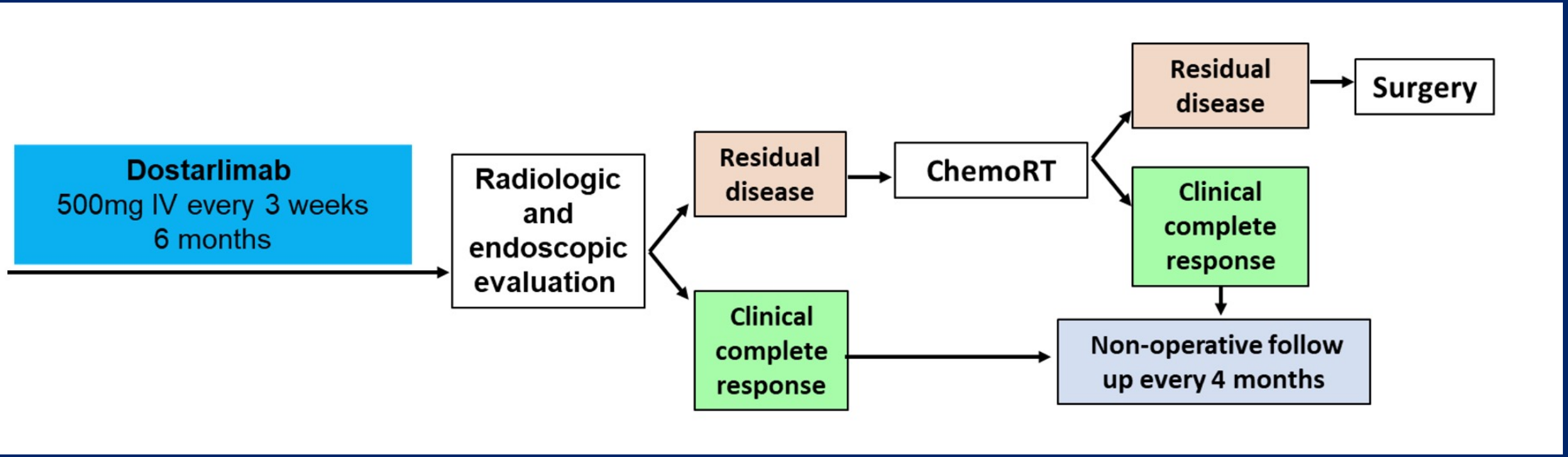


*Patients with completely resected stages II or IIIC colon cancer who are ctDNA +ve as determined by an informed tumor ctDNA test performed outside of the trial through routine clinical care and who otherwise meet all eligibility criteria for Step 1-Registration are eligible for enrollment into Cohort B.

**Patients in Cohort A (Arm 2) who develop a ctDNA +ve assay during serial monitoring may transition to the ctDNA+ve cohort (Cohort B) and undergo a second randomization.

NCT04089631

PD-1 Blockade as Curative-Intent Therapy in dMMR (MSI-H) 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 for primary endpoint of RR

Cercek et al: NEJM, 2022

NCT04165772

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)

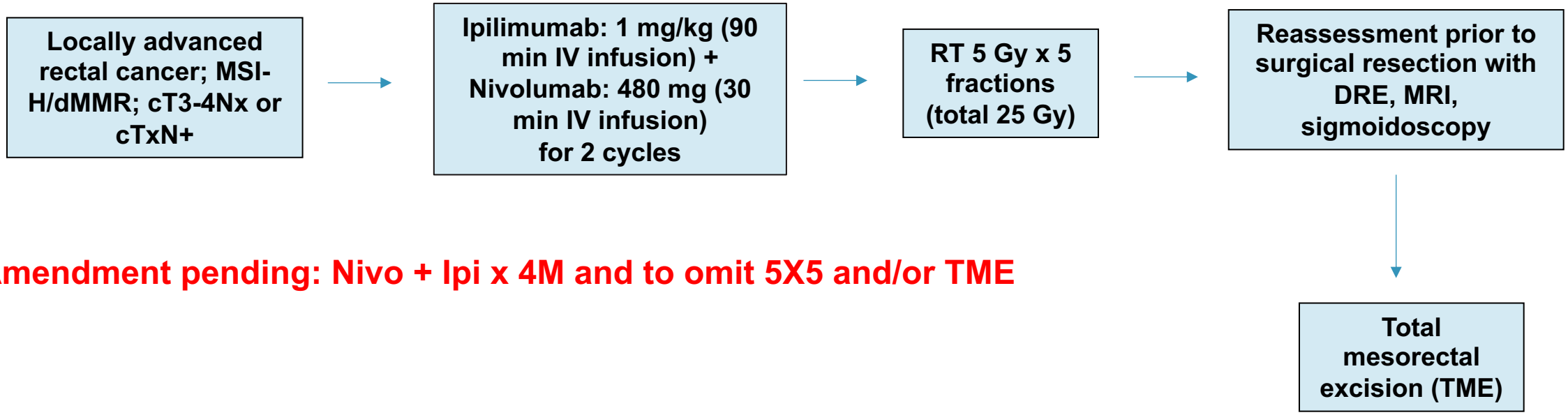
Individual responses to PD-1 blockade with dostarlimab

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**

EA2201: Phase II Study of Neoadjuvant Nivolumab plus Ipilimumab +/- Short Course Radiation in MSI-H Rectal Tumors

- Rectal adenocarcinoma
- T3-4Nx or TxN+ disease based on imaging
- MSI-H/dMMR based on IHC or PCR
- Integral biomarker
- ECOG PS 0-2

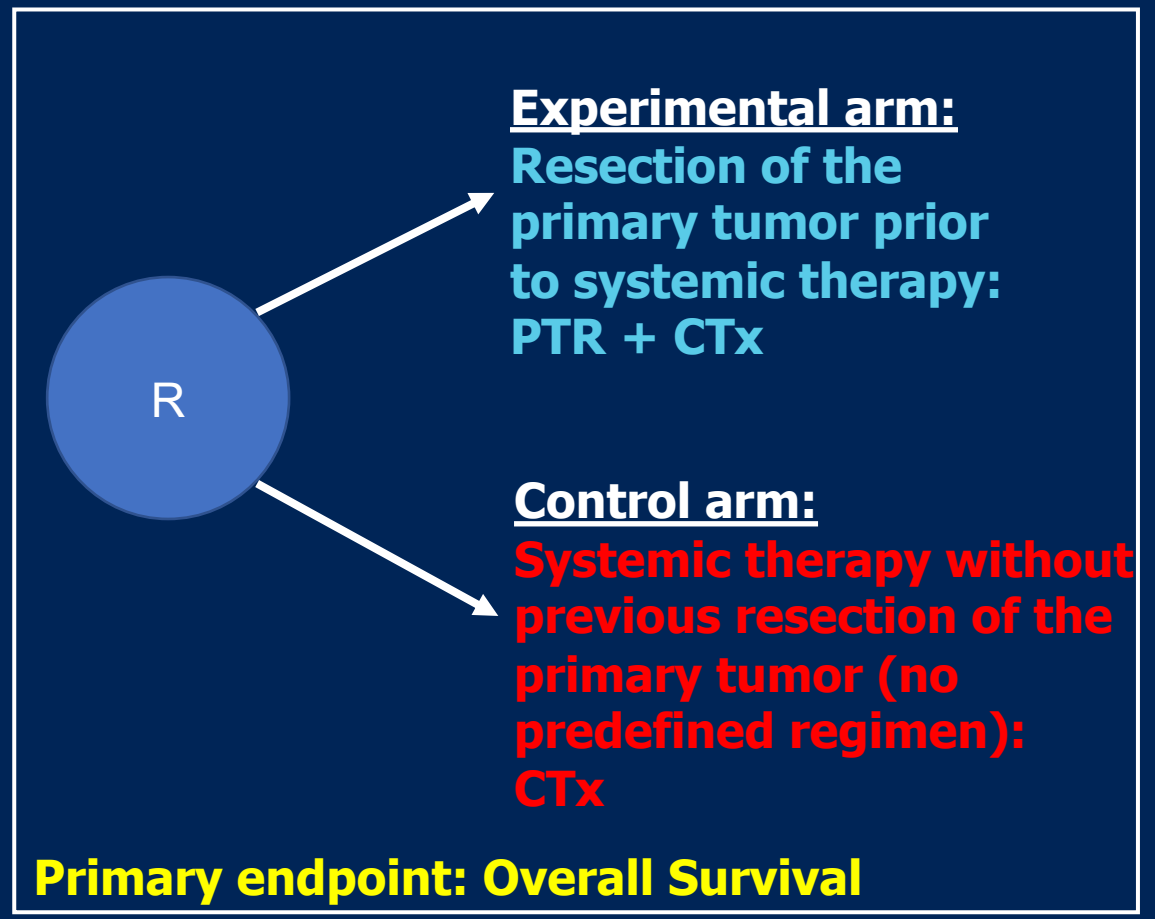


Amendment pending: Nivo + Ipi x 4M and to omit 5X5 and/or TME

NCT04751370: PI: Kristen Ciombor and co-PI: Cathy Eng

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

- Tx naïve colorectal CA 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- 2
- ≥ 18 years of age



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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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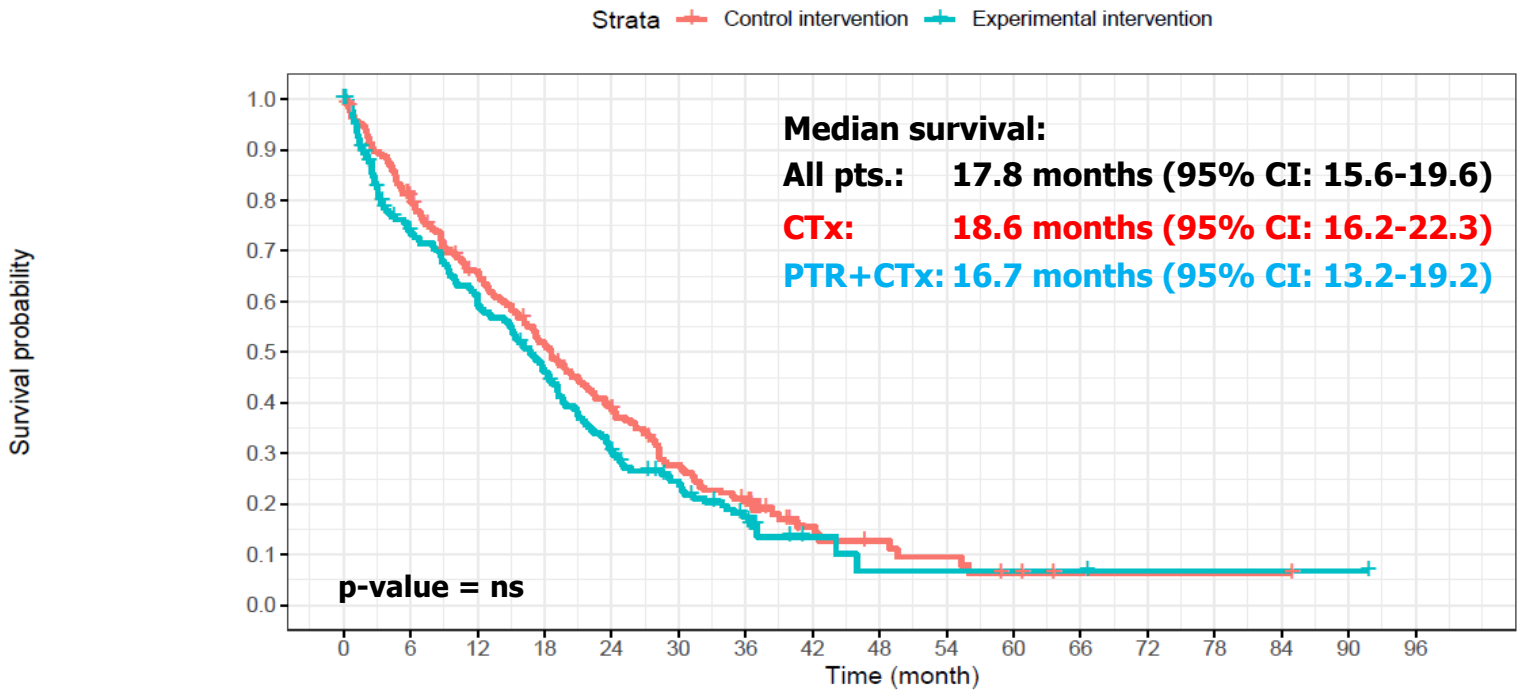
Primary Endpoint: Overall Survival (ITT)



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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]

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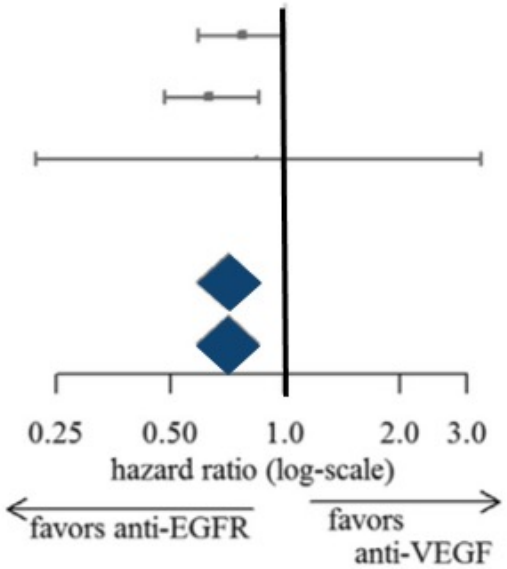
Meta-Analysis of PEAK, FIRE-3 and CALGB 80405: OS

Left-sided mCRC

A

study	n	Weight (%)	OS HR	95% CI	P-value
CALGB/SWOG 80405	325	53.8	0.77	(0.59 , 0.99)	
FIRE-3	306	44.2	0.63	(0.48 , 0.85)	
PEAK	107	2	0.84	(0.22 , 3.27)	
Summary (FE)			**0.71**	**(0.58 , 0.85)**	**0.0003**
Summary (RE)			**0.71**	**(0.58 , 0.85)**	**0.0003**

Heterogeneity: I^2 = 0%, 95% CI = (0% , 95.1%)
P-value = 0.575 (χ^2 test)



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

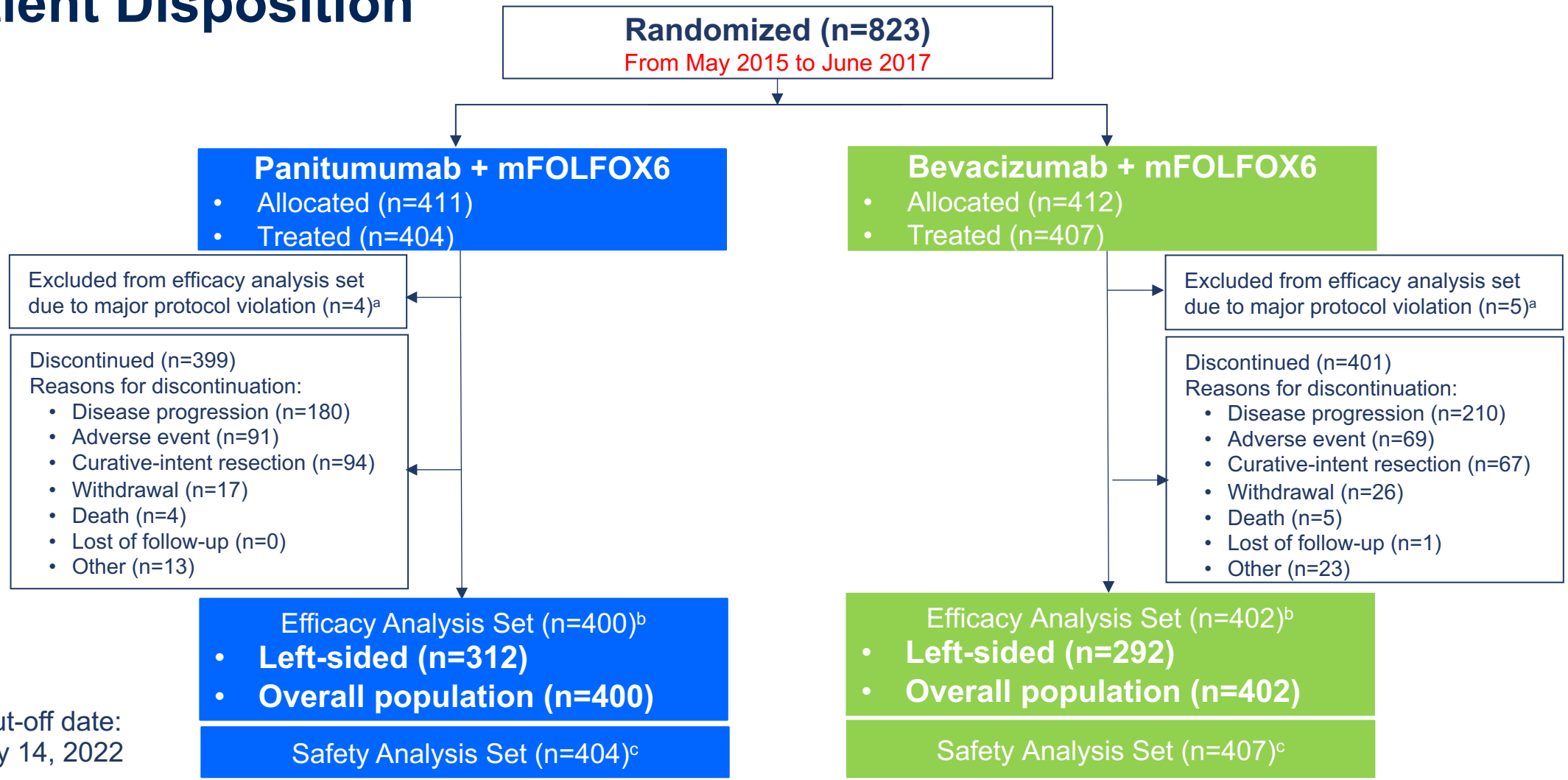
- ETS, depth of response, DCR: left-sided[c] and overall populations

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.

Patient Disposition



Data cut-off date:
January 14, 2022

Median follow-up time: 61 months

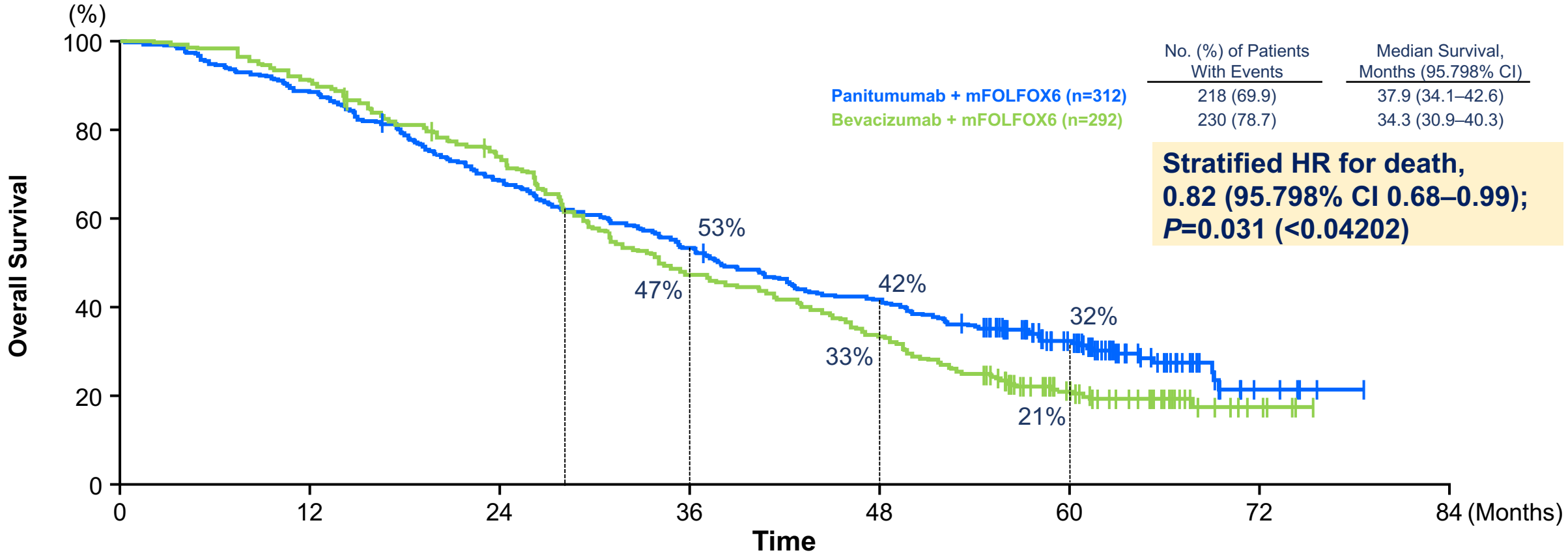
[a]Panitumumab arm (2 patients [pts] with Stage 3 and 2 pts with previous chemotherapy), Bevacizumab arm (3 pts with Stage 3, one pt with previous chemotherapy and one pt with prostate cancer with rectal invasion). [b]Randomized pts who received at least one dose of study treatment and satisfied the eligibility criteria. [C]Randomized pts who received at least one dose of study treatment.

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



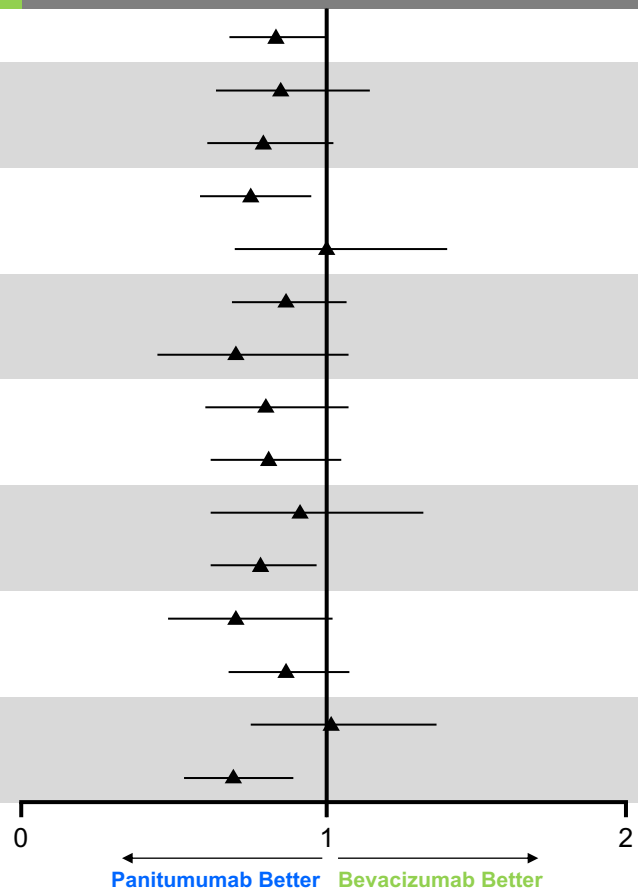
	No. (%) of Patients With Events	Median Survival, Months (95.798% CI)
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	37.9 (34.1–42.6)
Bevacizumab + mFOLFOX6 (n=292)	230 (78.7)	34.3 (30.9–40.3)

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

Subgroup Analyses of Overall Survival in Left-sided Population

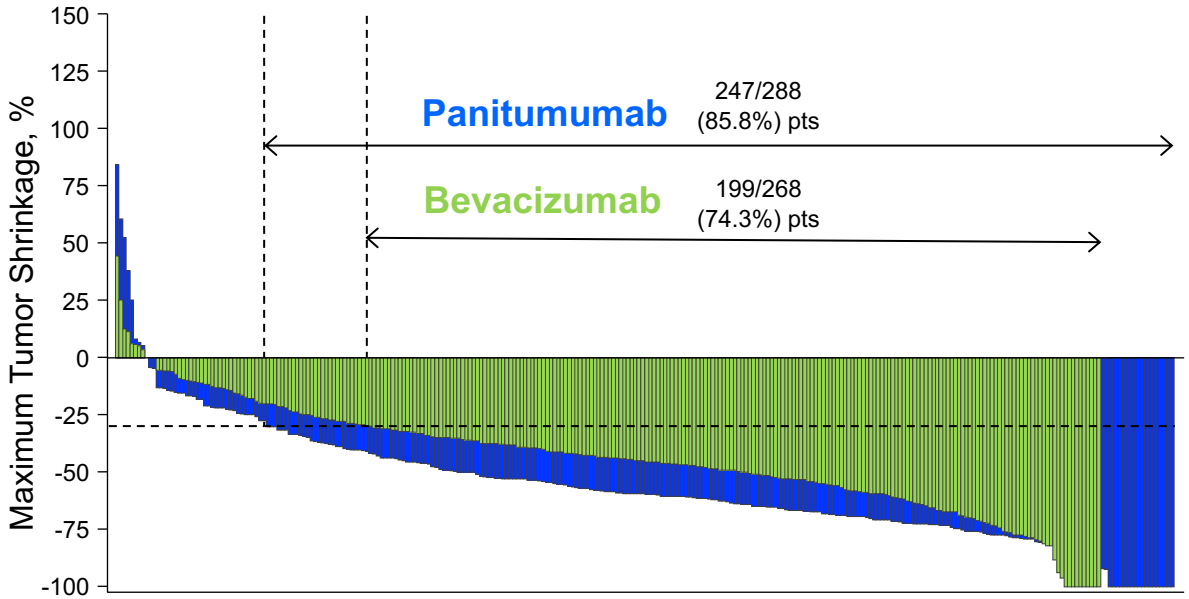
Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Bevacizumab + mFOFLFOX6	Hazard Ratio (95% CI)
	Overall*	218/312	230/292	0.82 (0.68–0.99)
Age	20-64 yr	95/138	95/127	0.86 (0.65–1.15)
	65-79 yr	123/174	135/165	0.80 (0.63–1.02)
Sex	Male	147/208	164/201	0.76 (0.61–0.95)
	Female	71/104	66/91	1.00 (0.71–1.40)
ECOG PS	0	182/261	179/231	0.87 (0.70–1.07)
	1	36/51	51/61	0.70 (0.46–1.08)
No. of organs with metastasis	0-1	91/155	100/147	0.81 (0.61–1.08)
	≥2	127/157	130/145	0.81 (0.64–1.04)
Liver metastasis	No	56/87	59/86	0.91 (0.63–1.32)
	Yes	162/225	171/206	0.79 (0.63–0.97)
Organs with metastasis	Liver only	52/90	65/89	0.71 (0.49–1.02)
	Other	166/222	165/203	0.87 (0.70–1.07)
Primary tumor resection	No	101/127	81/99	1.02 (0.76–1.37)
	Yes	117/185	149/193	0.69 (0.54–0.89)



*Stratified Hazard Ratio is shown with 95.798% CI.

Other Efficacy Outcome: Depth of Response and RR

Left-Sided Population



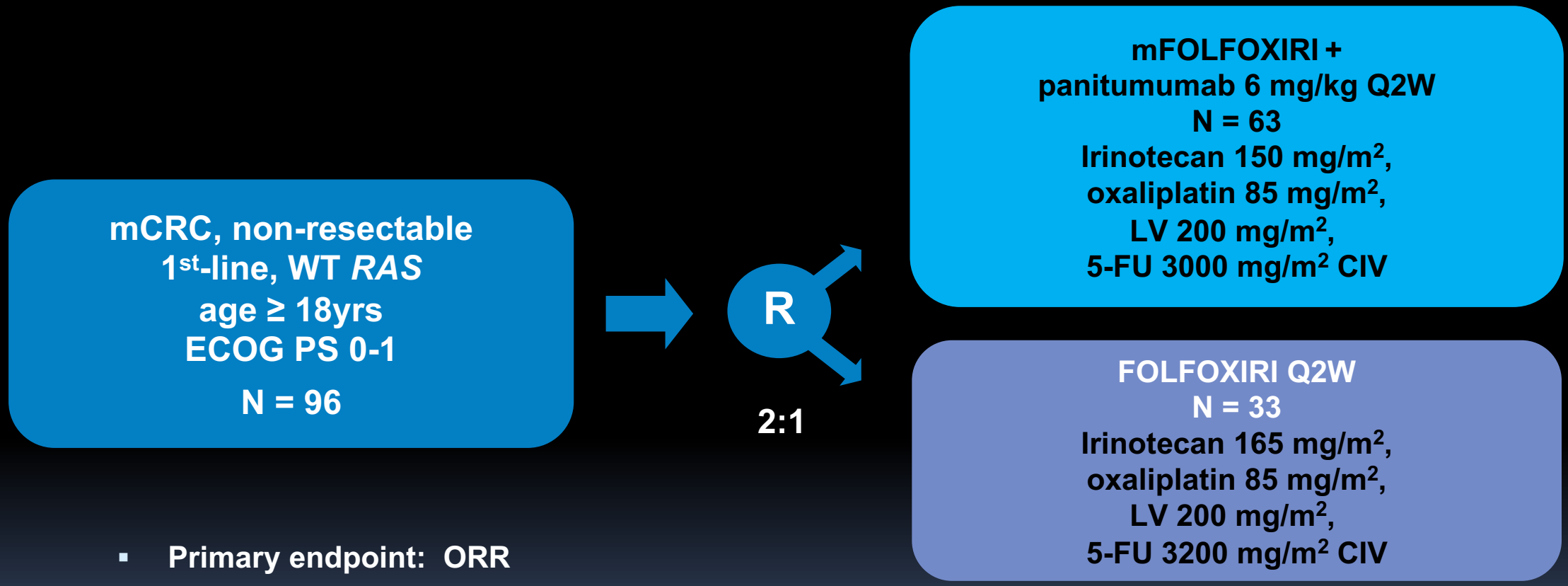
Horizontal dotted line at 30% indicates response per RECIST v1.1.

Parameter	Left-sided Population	
	Panitumumab + mFOLFOX6 (n=308)	Bevacizumab + mFOLFOX6 (n=287)
Response rate, % (95% CI)	80.2 (75.3–84.5)	68.6 (62.9–74.0)
Difference, % (95% CI)	11.2 (4.4–17.9)	
DCR, % (95% CI)	97.4 (94.9–98.9)	96.5 (93.7–98.3)
Median DOR,[a] months (95% CI)	13.1 (11.1–14.8)	11.2 (9.6–13.1)
R0 rate,[b] % (95% CI)	18.3 (14.1–23.0)	11.6 (8.2–15.9]

	Left-sided Population	
	Panitumumab + mFOLFOX6 (n=288)	Bevacizumab + mFOLFOX6 (n=268)
Median, %	-59.4	-43.6

Depth of response was assessed in patients with measurable lesions at baseline.

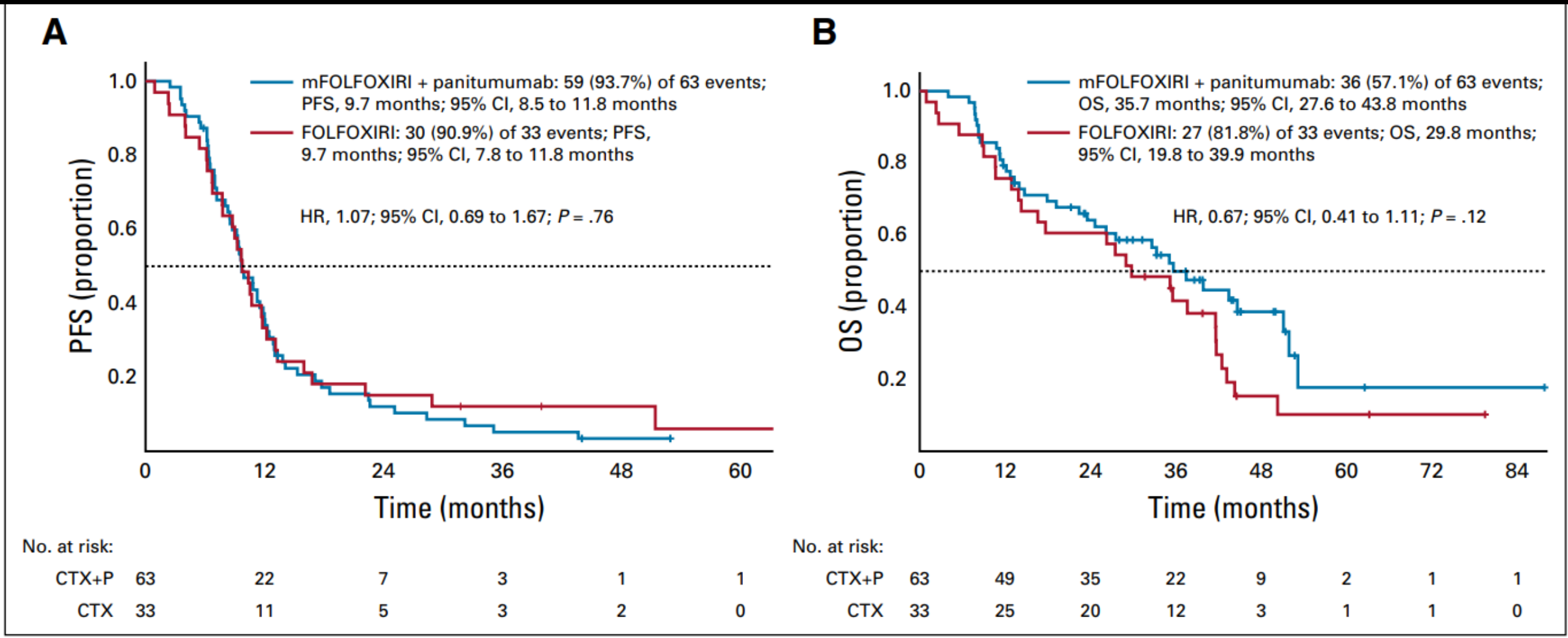
VOLFI: Randomized Phase II study of mFOLFOXIRI + panitumumab vs. FOLFOXIRI in treatment-naïve with *RAS* wild-type mCRC: AIO (AIO-KRK-0109)



- Primary endpoint: ORR
- Open-label, 2:1 randomized phase II study
- Study population: Adults with previously untreated non-resectable mCRC (randomization period 6/2011-1/2017)

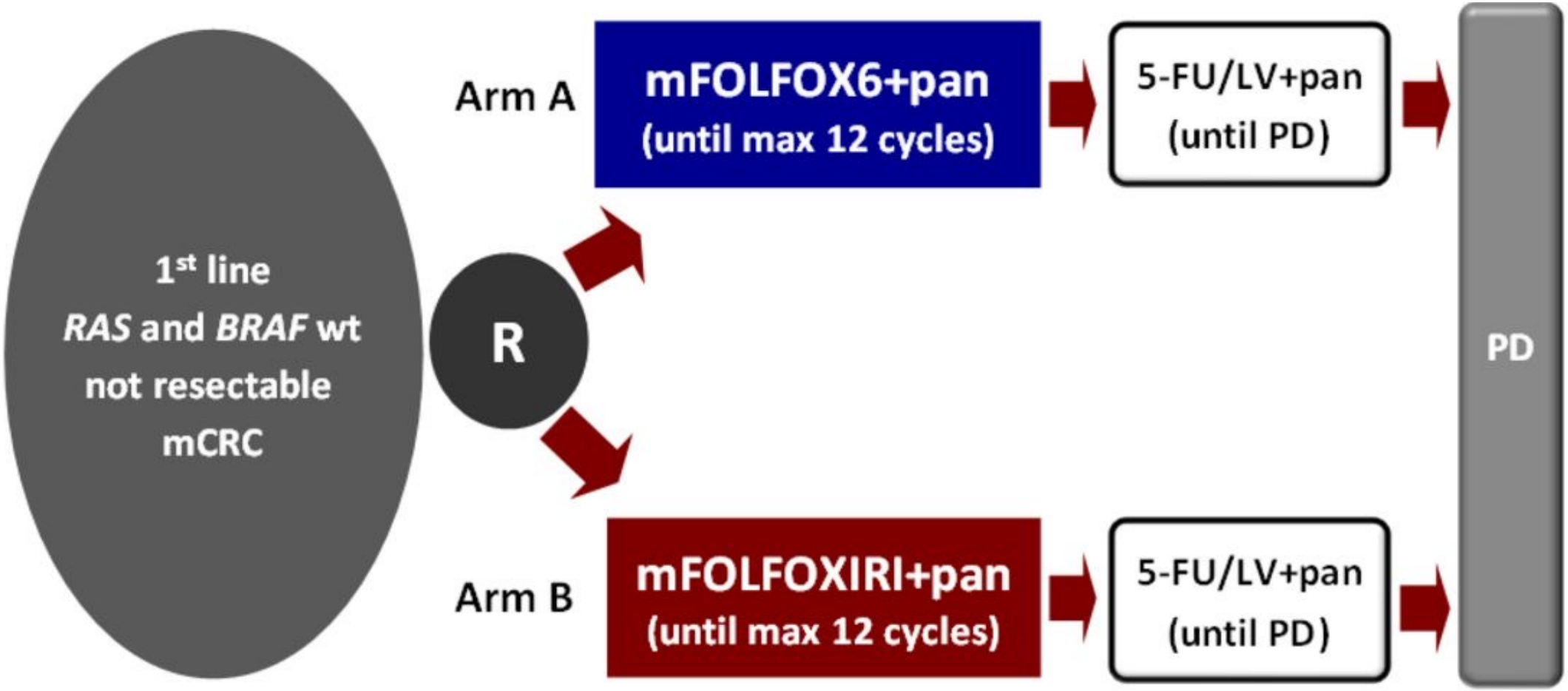
Modest et al: JCO 2019

VOLFI: Randomized Phase II study of mFOLFOXIRI + panitumumab vs. FOLFOXIRI in treatment-naïve with *RAS* wild-type mCRC: AIO (AIO-KRK-0109)



Modest et al: JCO 2019

TRIPLETE trial



Stratification factors:

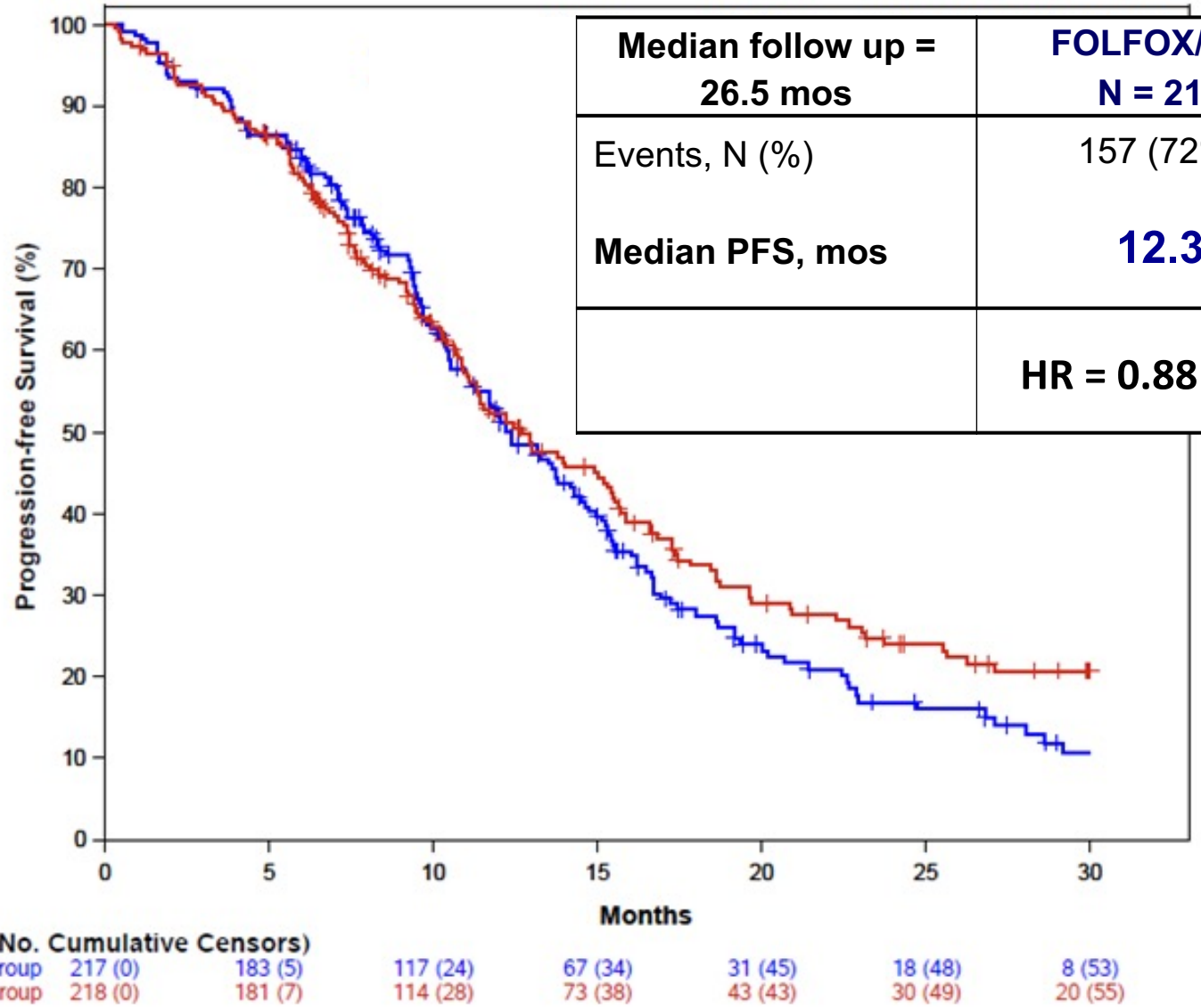
- ECOG Performance Status (0-1 vs 2)
- Primary tumor location (right vs left)
- Metastatic spread (liver-only vs not liver-only)

57 participating centers
From September 2017 to September 2021

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**

Progression Free Survival



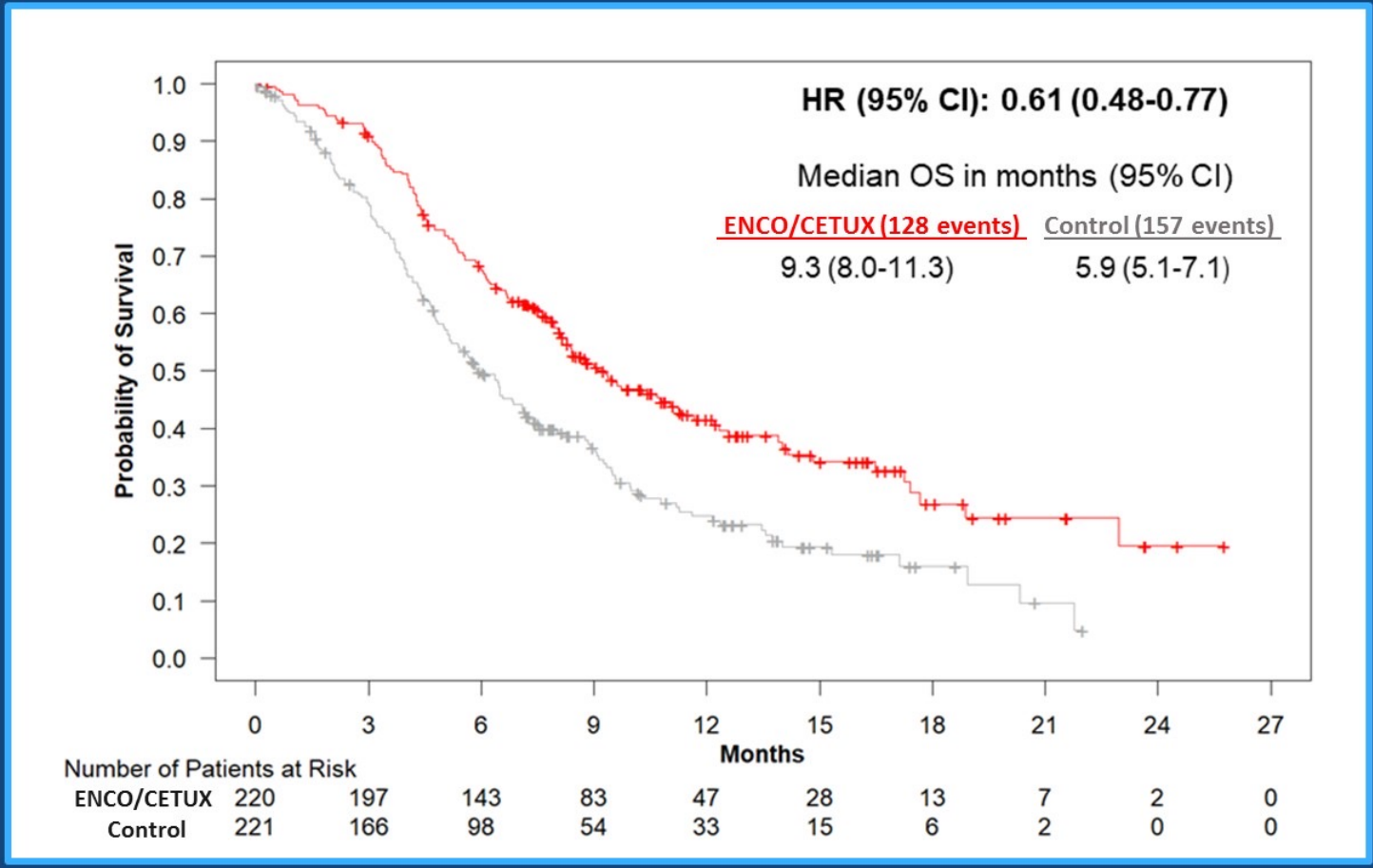
Median follow up = 26.5 mos	FOLFOX/Pan N = 217	mFOLFOXIRI/Pan N = 218
Events, N (%)	157 (72%)	148 (68%)
Median PFS, mos	**12.3**	**12.7**
	HR = 0.88 [95% CI: 0.70-1.11] p=0.277	

Conclusions

- ✓ **mFOLFOXIRI plus panitumumab should NOT be recommended as upfront therapy for *RAS* and *BRAF* wt mCRC patients**
- ✓ **Our results indirectly support patients' selection according to primary tumor site beside *RAS* and *BRAF* mutational status to improve the efficacy of anti-EGFR-based regimens.**
- ✓ **When the use of targeted agents is optimized in a clinically and molecularly selected population, there is no added value from the intensification of the associated chemotherapy backbone.**

MSI-S Colorectal Cancer: BRAF MT

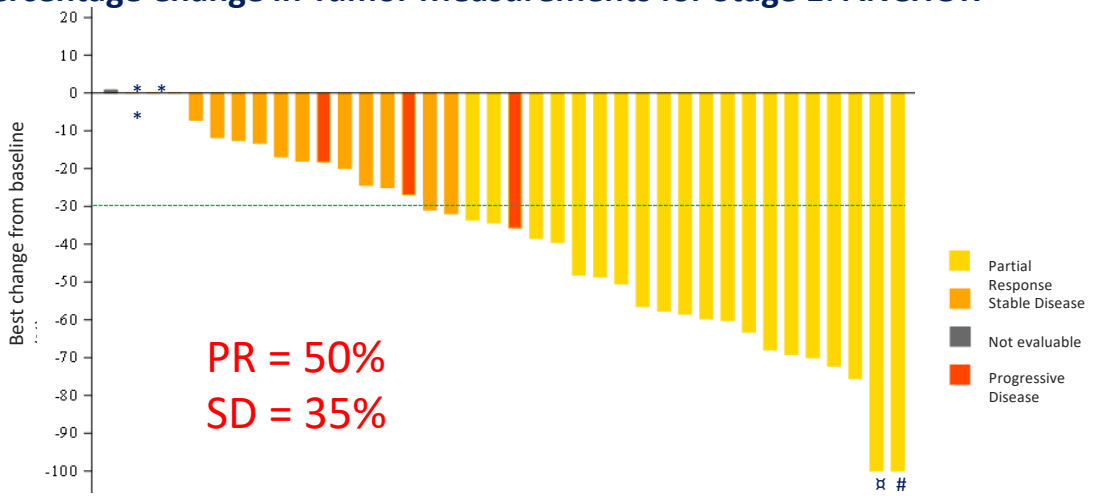
Updated Overall Survival: ENCO/CETUX vs Control



J Tabenero et al: JCO 2021

ANCHOR CRC: a single-arm, phase 2 study of encorafenib, binimetinib plus cetuximab in treatment-naïve BRAF^{V600E}–mutant mCRC

Best Percentage Change in Tumor Measurements for Stage 1: ANCHOR

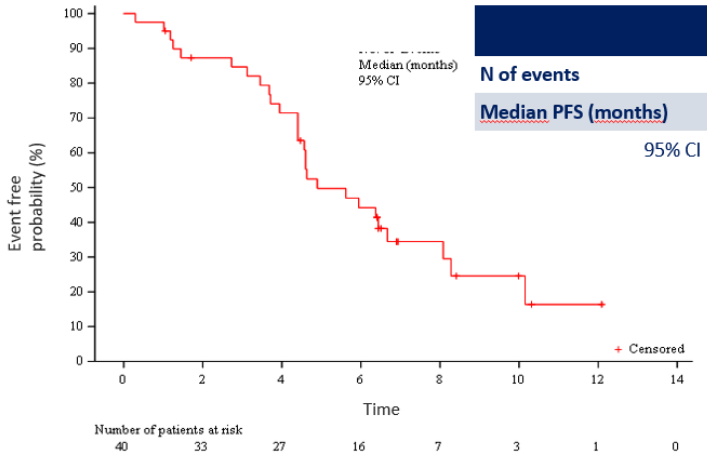


*3 patients with best percent change from baseline=0% and have Confirmed Best Overall Response=stable disease
¤ Complete Response on target lesion but non target lesion still present
Complete Response was not confirmed at the subsequent tumor evaluation

Investigator's assessment, patients evaluable for efficacy

Progression Free Survival for Stage 1: ANCHOR

Investigator's assessment, median follow-up: 4.6 months



	Patients (N=40#)
N of events	27 (68%)
Median PFS (months)	4.9
95% CI	[4.4 ; 8.1]

1 patient has been excluded from the efficacy analysis as the BRAF mutation was not confirmed by central lab

Note: the data have not been fully cleaned due to Covid-19 pandemic.

World GI Congress ESMO 2021: Stage 2 update

- N=92
- The investigator-assessed **cORR was 47.8%** (95% confidence interval [CI] 37.3-58.5). There were no meaningful differences in cORR in subgroup analysis. The DCR was 88%.
- Regarding survival, **median PFS was 5.8 months** (95% CI 4.6-6.4) and **median OS was 17.2 months** (95% CI 14.1-NE

ASCO Gastrointestinal Cancers Symposium

Phase I/II trial of encorafenib, cetuximab, and nivolumab in patients with microsatellite stable, *BRAF*^{V600E} metastatic colorectal cancer

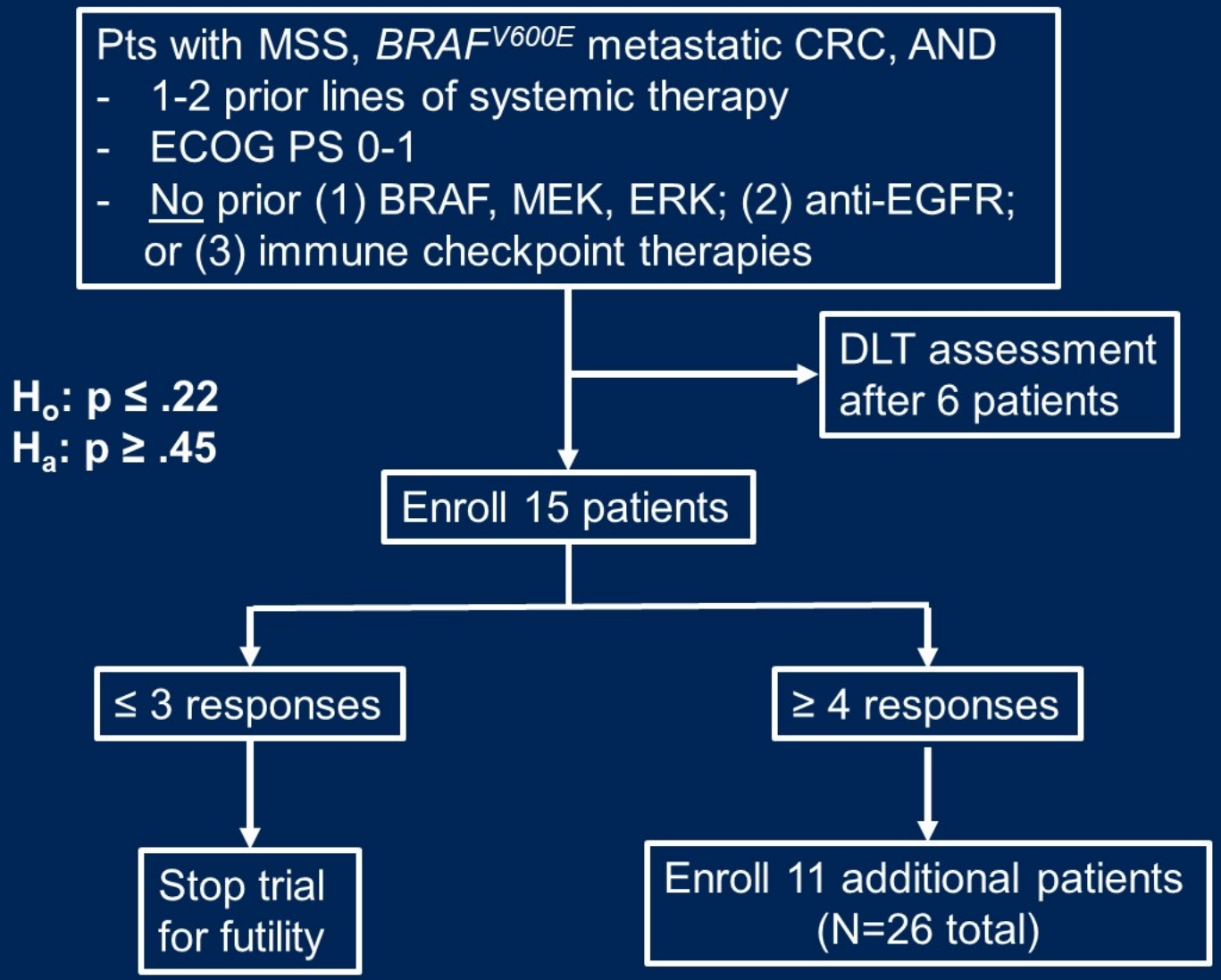
Abstract #351993

Van K. Morris[1], Christine M. Parseghian[1], Michelle Escano[1], Benny Johnson[1], Kanwal Pratap Singh Raghav[1], Arvind Dasari[1], Ryan Huey[1], Michael J. Overman[1], Jason Willis[1], Michael S. Lee[1], Robert A. Wolff[1], Bryan K. Kee[1], John Paul Y.C. Shen[1], M. Pia Morelli[1], Alda Tam[2], Wai Chin Foo[3], Lianchun Xiao[4], Scott Kopetz[1]

Departments of [1]Gastrointestinal Medical Oncology, [2]Interventional Radiology, [3]Pathology, & [4]Biostatistics

University of Texas – MD Anderson Cancer Center, Houston TX

Study Design



Study Treatment:

Encorafenib 300 mg PO daily

Cetuximab 500 mg/m^2 IV every 14 days

Nivolumab 480 mg IV every 28 days

Primary endpoints:

- Radiographic response (RECIST 1.1)
- Safety/tolerability (CTCAE v5)

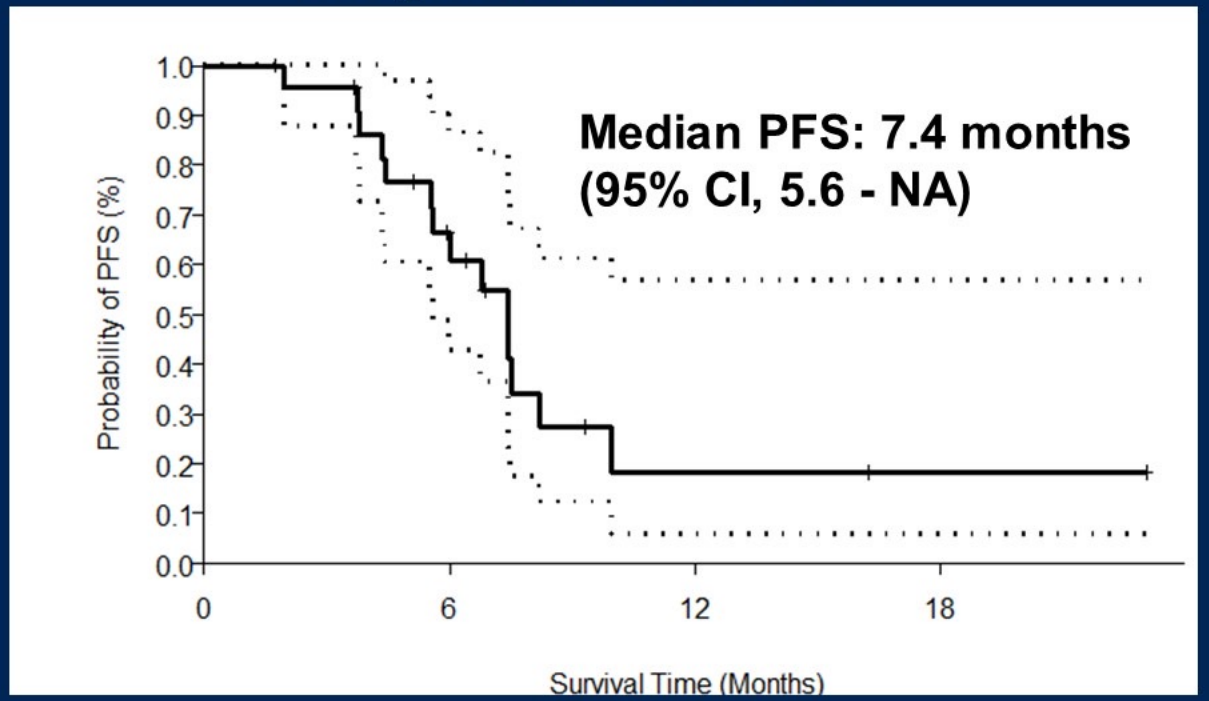
Secondary endpoints:

- Progression-free survival
- Overall survival
- Duration of response
- Disease control rate
- Time to response

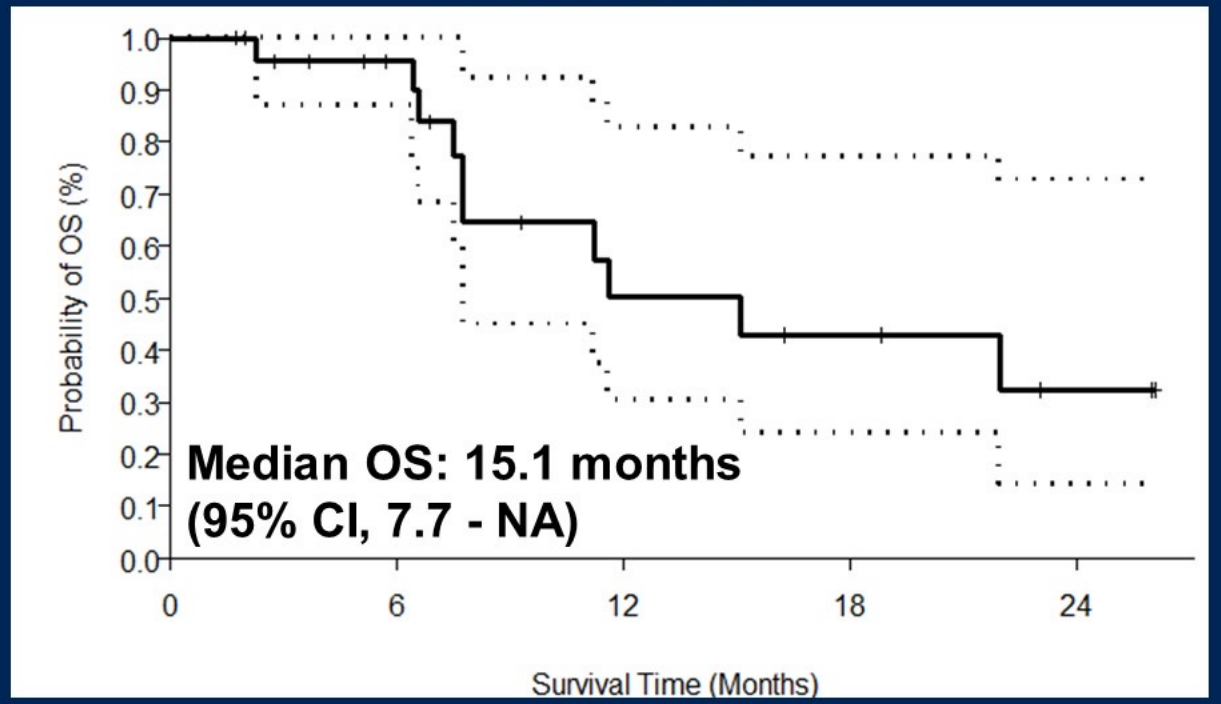
PRESENTED BY: Van Morris, MD

Survival outcomes: encorafenib + cetuximab + nivolumab

Progression-free survival



Overall survival



- ORR = 50%

Median follow-up time: 16.3 months (95% CI, 6.9 –NA)
Median duration of response: 7.7 months (95% CI, 3.8 – NA)

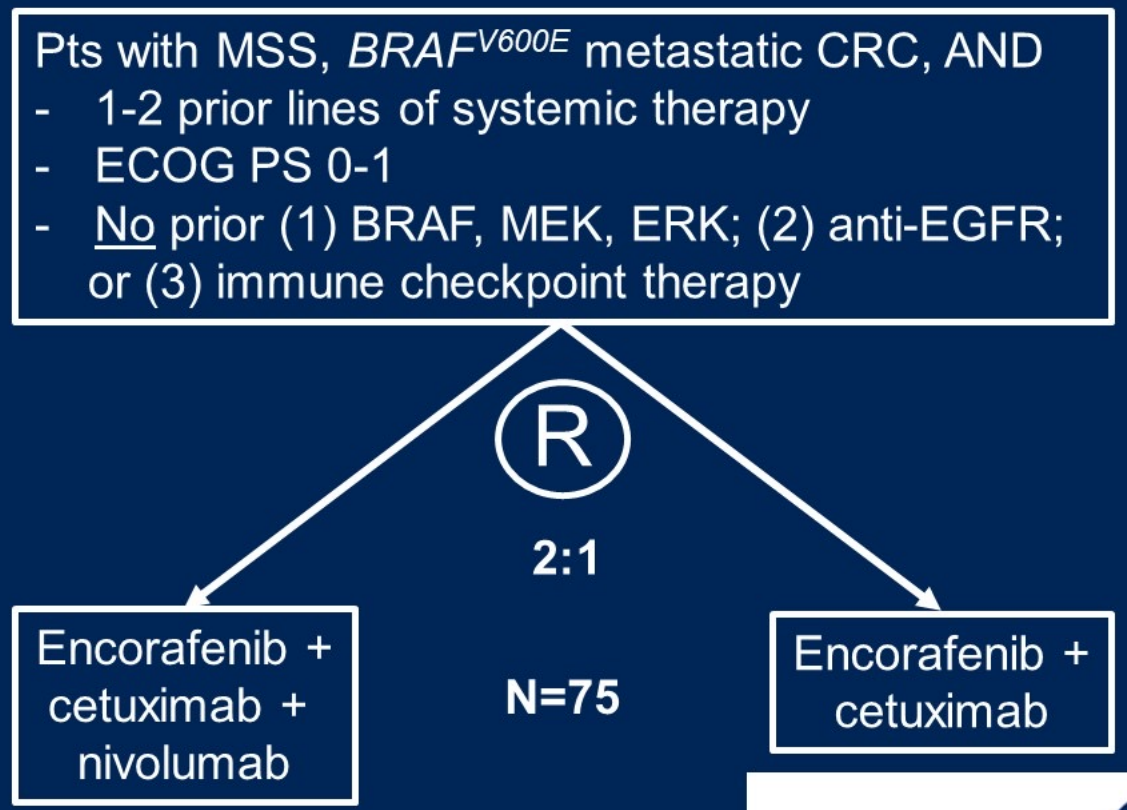
Encorafenib + cetuximab: median PFS 4.2 months (95% CI, 3.7-5.4), median OS 8.4 months (95% CI, 7.5-11.0) [1]

[1]Kopetz S et al, NEJM 2019

Conclusions

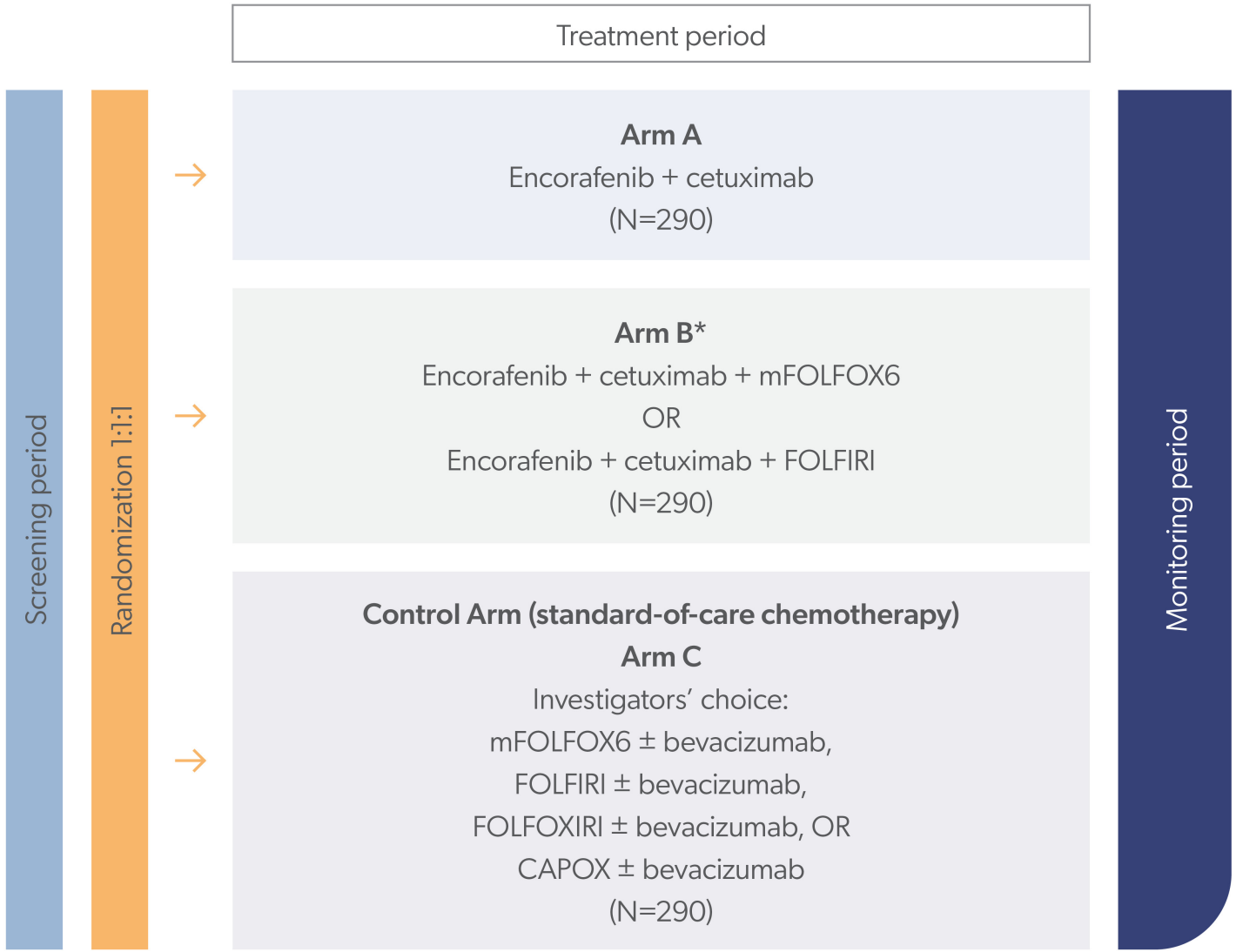
- Encorafenib + cetuximab + nivolumab is safe and well tolerated for participants with MSS, *BRAF*^{V600E} metastatic CRC.
- The predefined efficacy endpoint for encorafenib + cetuximab + nivolumab has been met for participants with MSS, *BRAF*^{V600E} metastatic CRC: ORR is 50%, and median PFS is 7.4 months.
- These results compare favorably relative to encorafenib + cetuximab (without immunotherapy) as reported in the BEACON study.
- SWOG 2107 is a randomized phase II study that will activate across the United States in 2022 to evaluate encorafenib + cetuximab with or without nivolumab in this population.

SWOG 2107



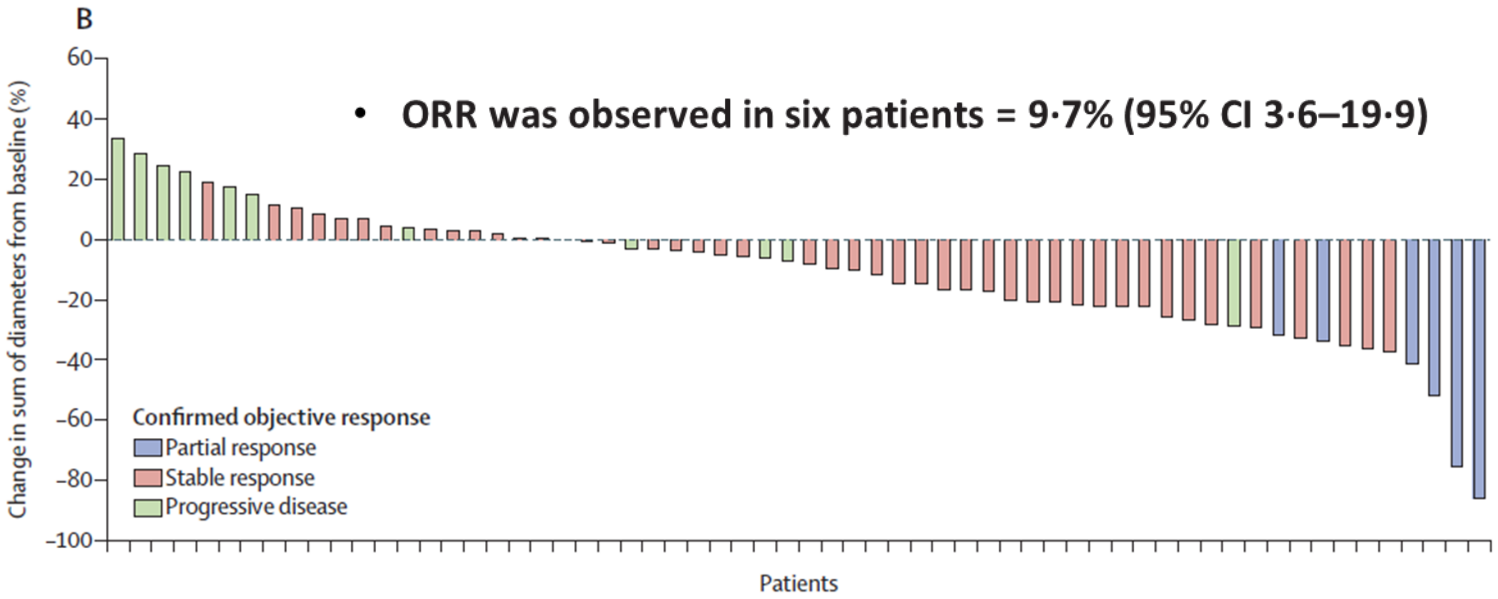
SWOG
Leading cancer research. Together.

Phase III Breakwater Trial

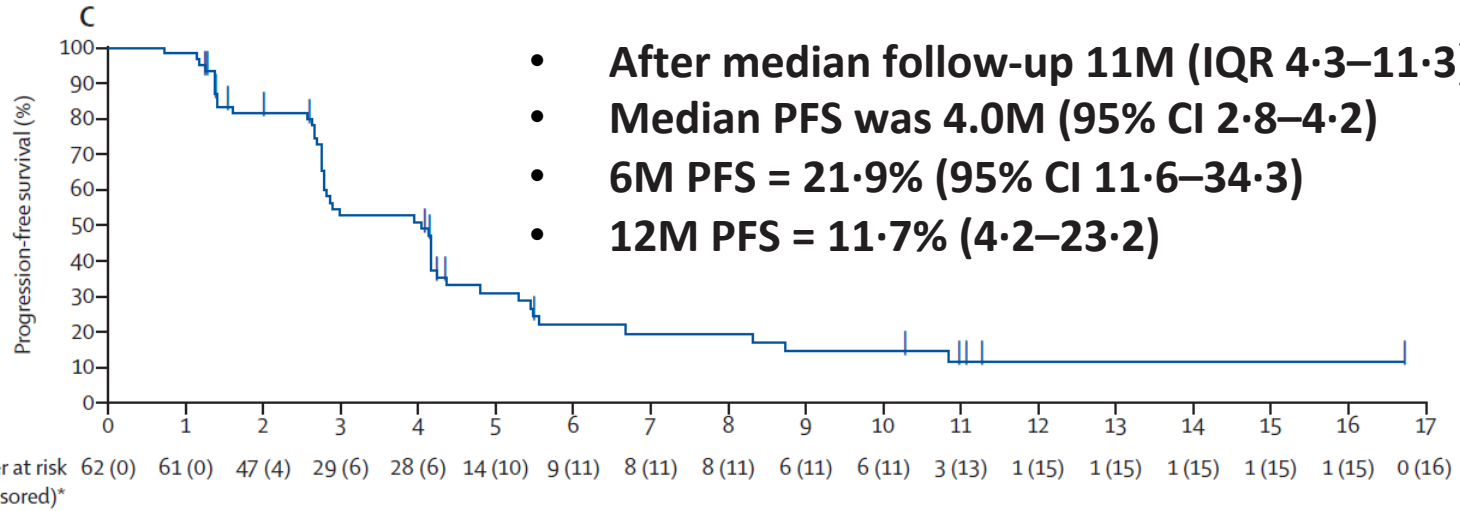


KRAS G12C Mutation Inhibitors

Sotarasib: KRAS G12C Previously Treated mCRC



- ORR was observed in six patients = 9·7% (95% CI 3·6–19·9)



- After median follow-up 11M (IQR 4·3–11·3)
- Median PFS was 4.0M (95% CI 2·8–4·2)
- 6M PFS = 21·9% (95% CI 11·6–34·3)
- 12M PFS = 11·7% (4·2–23·2)

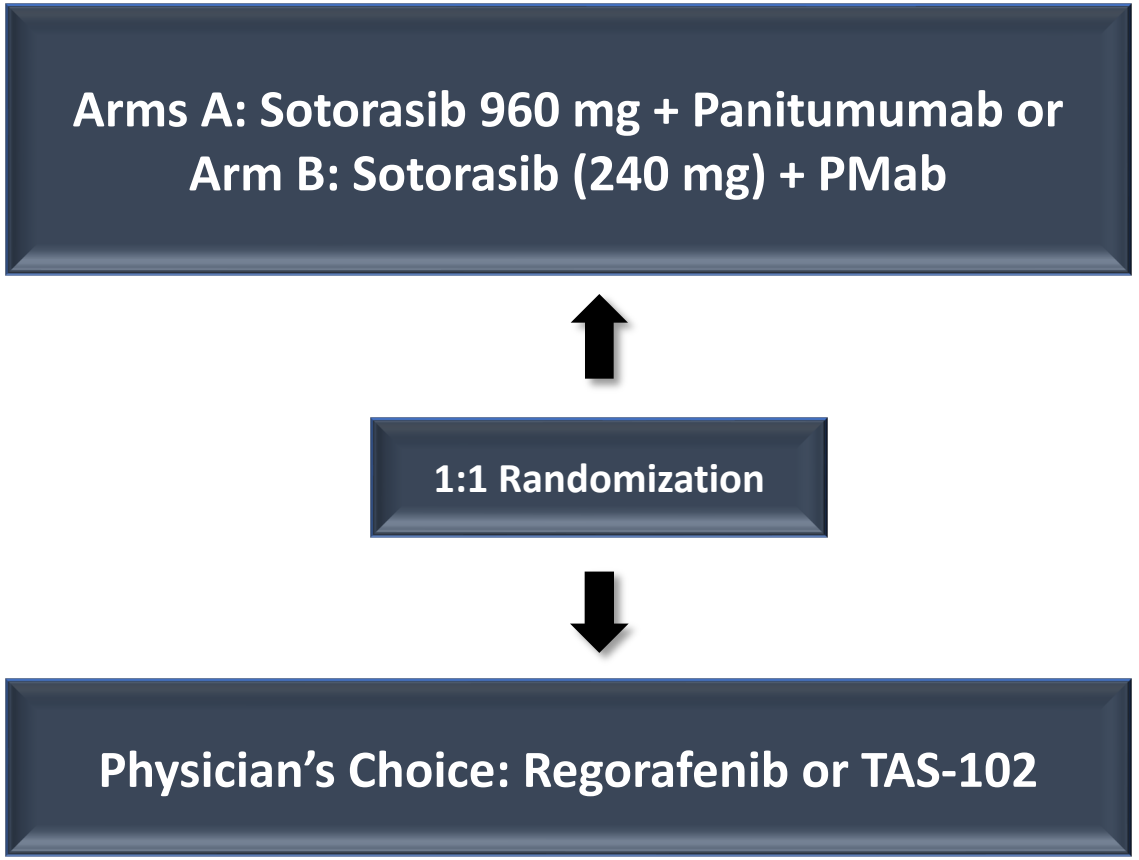
Fakih et al, Lanc Onc 2021

Phase 3: Sotorasib + Panitumumab

Patients

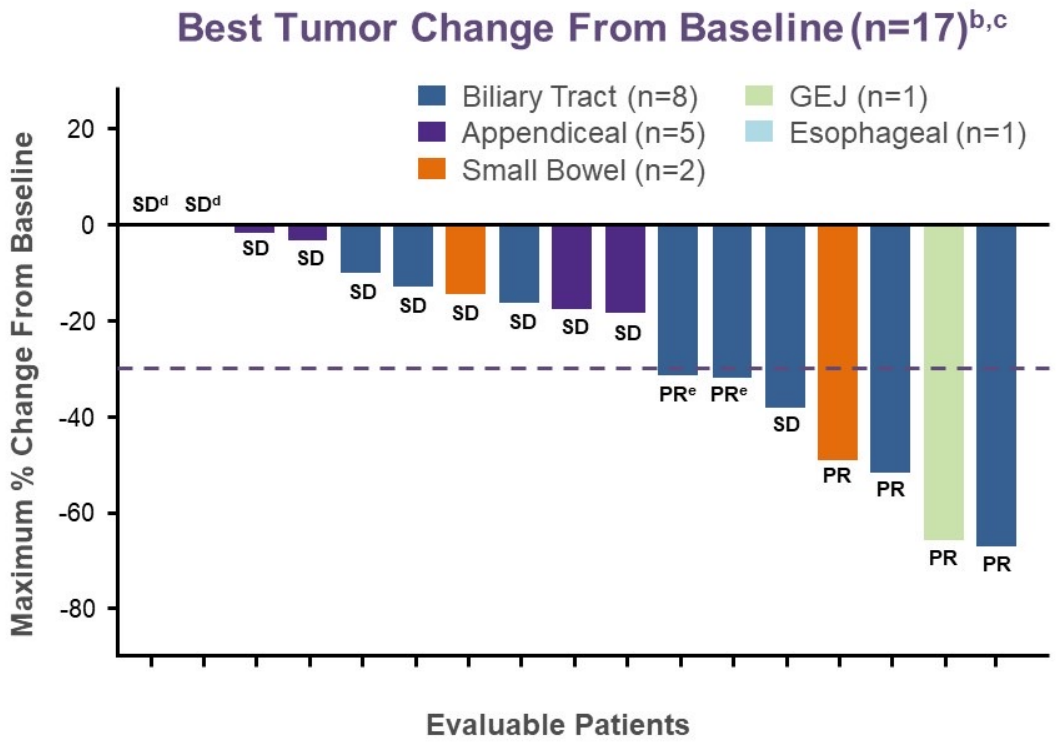
- > 1 prior line of treatment for mCRC
- KRAS G12C MT
- ECOG PS 0-2
- **N=193**
- ***Not yet recruiting**

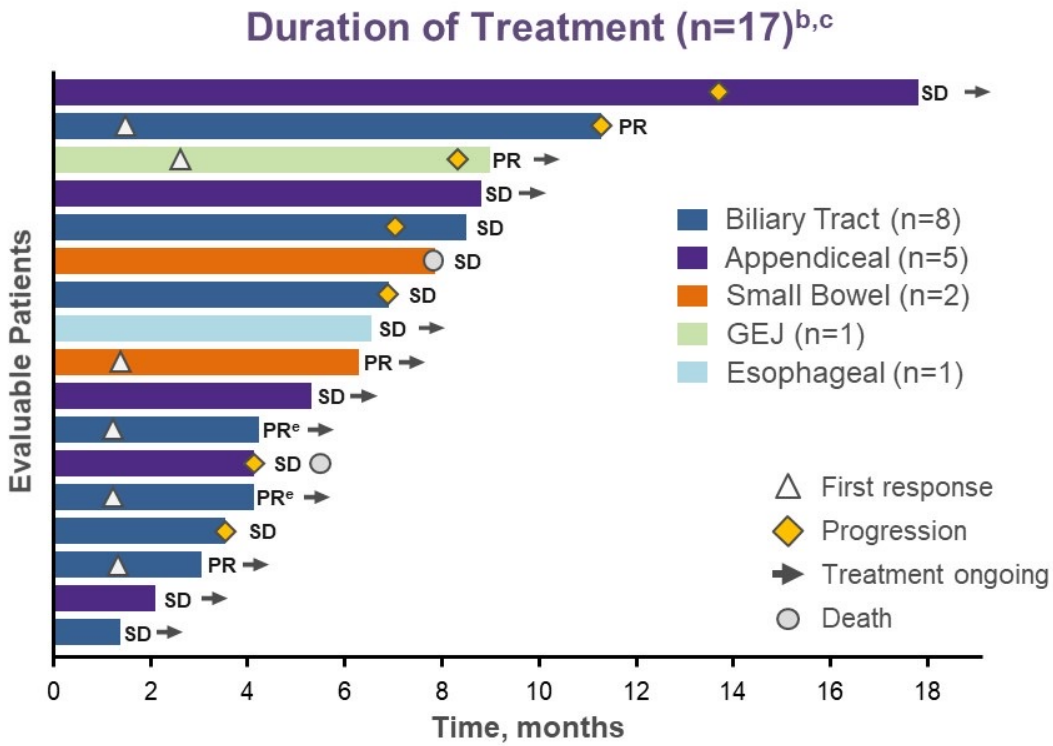
NCT05198934



Primary Endpoint: PFS

Adagrasib in Patients With Other GI Tumors:[a] Best Tumor Change From Baseline and Duration of Treatment





- Response rate:
  - Biliary tract cancer: 50% (4/8), including 2 unconfirmed PRs
  - GEJ and small bowel cancer: 1 PR each
- DCR: 100% (17/17 patients)

- Median TTR: 1.3 months
- Median DOR: 7.85 months
- Median PFS: 7.85 months (95% CI 6.90–11.30)
- Treatment ongoing in 65% (11/17) of patients

DCR, disease control rate; DOR, duration of response; GEJ, gastro-esophageal junction; PR, partial response; SD, stable disease; TTR, time to response.
[a]Excluding CRC and PDAC; [b]Evaluable population (n=17) excludes 1 patient who withdrew consent prior to the first scan; [c]All results are based on investigator assessments; [d]1 patient with appendiceal cancer and 1 patient with esophageal cancer had maximum % change from baseline of 0; [e]At data cut-off, 2 patients had unconfirmed PR.
Data as of 10 Sept 2021 (median follow-up: 6.3 months).

Ongoing Phase I and III Trials: Mirati and Eli-Lilly

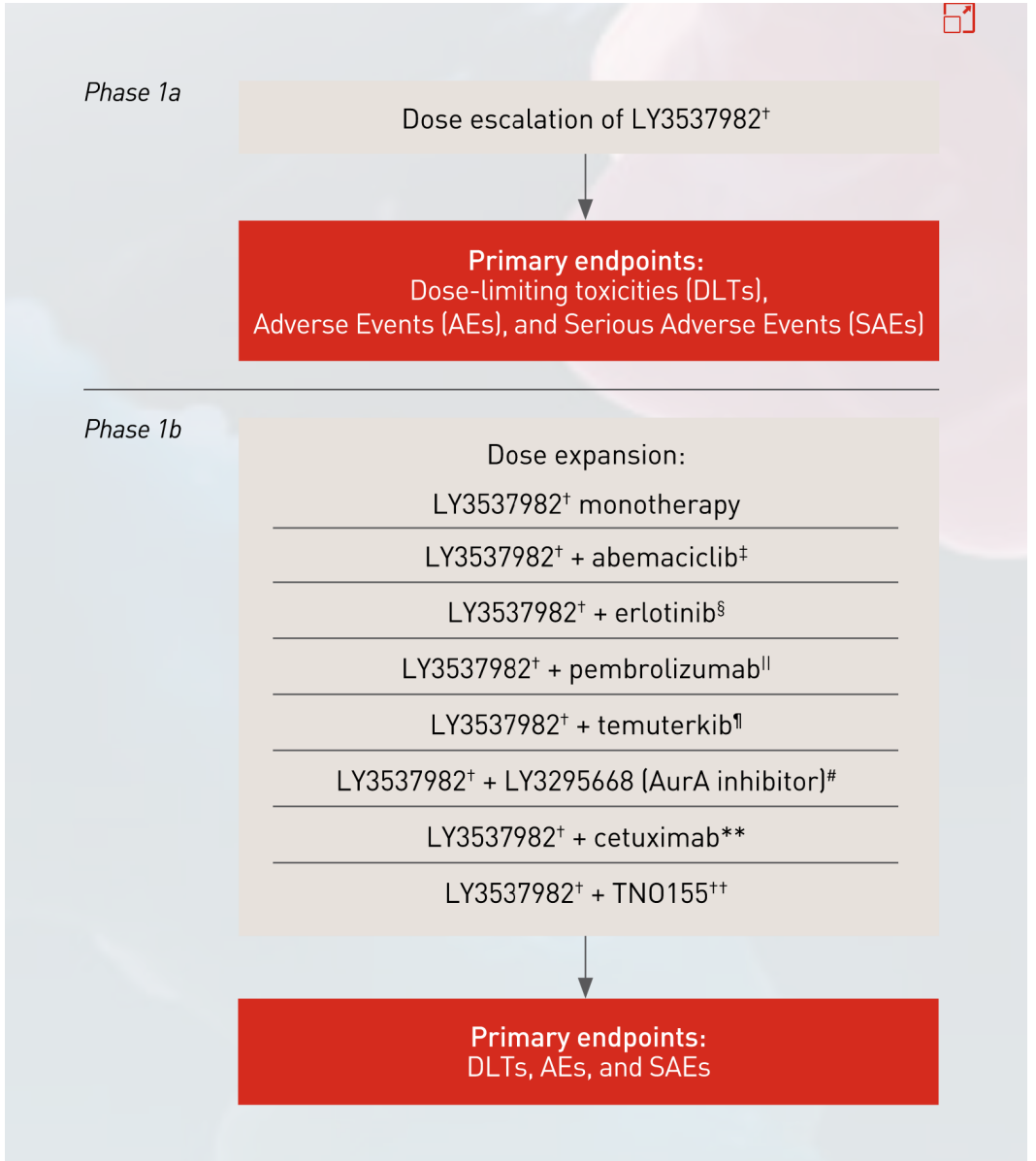
- **Metastatic CRC**
- ***KRAS* G12C in tumor**
  - Local test acceptable for enrollment; central confirmation req'd w/in 30d
- **PD on 1L fluoropyrimidine + oxaliplatin or irinotecan**
- **No prior anti-EGFR or direct KRAS G12Ci**

1:1
N~420

Adagrasib 600 mg BID + Cetuximab 500 mg/m^2 Q2W

FOLFIRI or mFOLFOX6§

§Anti-VEGF/VEGFR allowed per Investigator discretion



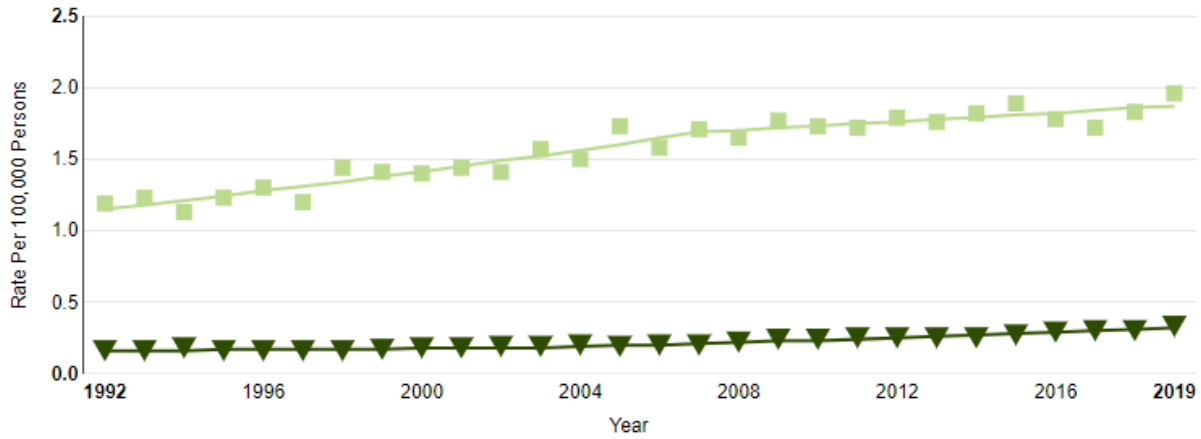
Incidence of Anal Cancer

Rising in annual incidence by 2.7%

Estimated New Cases in 2022	9,440
% of All New Cancer Cases	0.5%

Estimated Deaths in 2022	1,670
% of All Cancer Deaths	0.3%

5-Year Relative Survival
70.1%
2012–2018



https://seer.cancer.gov/statfacts/html/anus.html; Eng et al: JCO, 2022

Ongoing Pending Trials: Locally Advanced Disease

EA2182 (NCT04166318) A Randomized Phase II Study of De-Intensified ChemoRadiation for Early-Stage Anal Squamous Cell Carcinoma (DECREASE)

Eligibility:
T1-2N0M0 anal canal or anal margin squamous cell carcinoma (SCCA) measuring ≤4 cm (HIV+ allowed)

Accrual Goal
N = 71/252

PRE-REGISTRATION

Stratification Factors:
- Tumor stage: T1 vs T2
- HIV Status: HIV-positive vs. HIV-negative

Arm S: HIV-positive patients

Central Imaging Review Required

Arm R: HIV-negative patients

Central Imaging Review NOT Required

PI: J Dorth

RANDOMIZATION

2:1

Arm A: Standard-Dose Chemoradiation

Radiation:
- Primary tumor: 50.4 Gy in 28 fractions
- Elective nodal regions: full pelvis + inguinal 42 Gy in 28 fractions
- Mitomycin C (MMC) 12 mg/m^2 X 1; 5-fluorouracil (5-FU) CI X 2 cycles OR Capecitabine

Arm B: De-Intensified Chemoradiation

Radiation:
- Primary tumor:
  - T1: 36 Gy in 20 fractions
  - T2: 41.4 Gy in 23 fractions
- Elective nodal regions: true pelvis + inguinal
  - T1: 32 Gy in 20 fractions
  - T2: 34.5 Gy in 23 fractions
- MMC 10 mg/m^2 X 1; 5-FU CI X 1 cycle OR Capecitabine

Concurrent Chemo:
- MMC on day 1
- 5-FU CI 1000 mg/m^2/d days 1-4 (c1), days 29-32 (c2) OR
- Capecitabine 825 mg/m^{2}BID M-F on days of RT

*Cycle = 4 weeks (28 days)

LONG TERM FOLLOW-UP

Primary Endpoint:
2-year Disease Control

Eng et al: JCO*, in press*, 2022

Premise for Immunotherapy in Metastatic Anal Cancer

Efficacy of Immune Checkpoint Inhibition in Previously Treated Metastatic SCCA

Drug	Phase	N	Dose	Primary endpoint	Secondary Endpoints
ETCTN NCI9673: Nivolumab (Part A)	II	34	3 mg/kg IV q2 wks	ORR: 24% (2CR's)	PFS: 4.1M OS: 11.5M
Pembrolizumab (KN-158)	I/II	112	200 mg IV q3 wks	ORR:11% (No CR's)	PFS: 2.0M OS: 11.9M
Retifanlimab (POD1UM-202)	II	94	500 mg IV q4 wks	ORR: 14% (1CR)	PFS: 2.3M OS:10.1M

Morris et al: Lanc Onc, 2017; Marabelle et al: Lancet Gastro and Hep, 2022;; Rao et al: Annals of Onc, 2020

Immunotherapy Trials in Anal Cancer

Localized Disease			Advanced Disease		Treatment	Trial Number	Phase
Neoadjuvant	Concomitant	Adjuvant	First-Line	≥Second-Line			
		NCI-EA2165			Nivolumab + IMRT	NCT03233711	III
	INTERACT-ION				Ezabenlimab + mDCF + IMRT	NCT04719988	II
		RADIANCE			Durvalumab + IMRT	NCT04230759	II
	CORINTH				Pembrolizumab + IMRT	NCT04046133	I/II
	BrUOG 276				ADXS11-001 + IMRT	NCT01671488	I/II
			POD1UM-303		Retifanlimab + CP	NCT04472429	III
			NCI-EA2176		Nivolumab + CP	NCT04444921	III
			SCARCE		Atezolizumab + mDCF	NCT03519295	II
			SPARTANA		Spartalizumab + mDCF + SBRT	NCT04894370	I/II
				VolaTIL	Atezolizumab + UCPVax	NCT03946358	II
				NCI-2015-01004	Nivolumab + ISA101	NCT02426892	II
				NCI-2018-00914	Durvalumab + INO311	NCT03439085	II
				NCI-20-C-0104	M7824 + PRGN-2009	NCT04432597	I/II
				NCI9673	Nivolumab + Ipilimumab	NCT02314169	II
				DUET-2	XmAb20717	NCT03517488	I
				HESTIA	Nivolumab + HPVST cells	NCT02379520	I
				CARACAS	Avelumab + Cetuximab	NCT03944252	II
				NCI-2017-00501	Atezolizumab + Bevacizumab	NCT03074513	II

Spehner et al: Cancers, 2021

2022 ASCO® ANNUAL MEETING

GERCOR

PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

LBA 3508: Atezolizumab plus modified DCF (docetaxel, cisplatin, and 5-fluorouracil) as first-line treatment for metastatic or locally advanced squamous cell anal carcinoma (SCCA). A SCARCE-PRODIGE 60 randomized phase II study

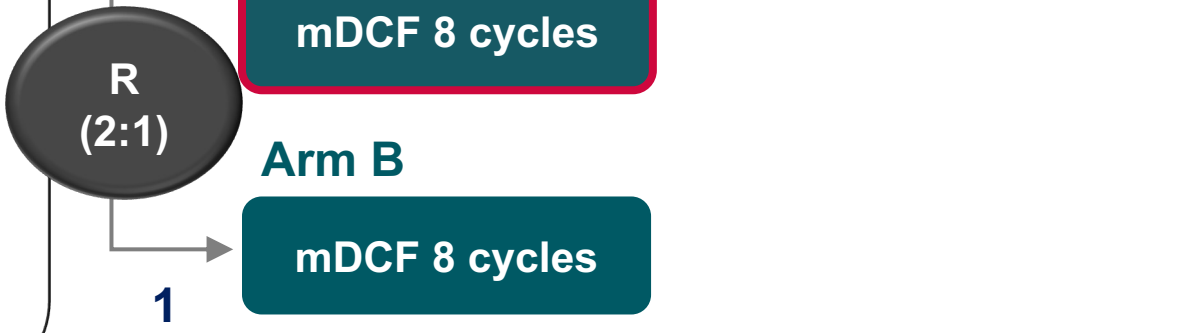
Stefano Kim,[1] François Ghiringhelli, Christelle de la Fouchardière, Eric François, Denis Smith, Emmanuelle Samalin, Daniel Lopez-Trabada Ataz, Aurélia Parzy, Jérôme Desramé, Nabil Baba Hamed, Bruno Buecher, David Tougeron, Oliver Bouché, Benoist Chibaudel, Farid El Hajbi, Marie-Line Garcia-Larnicol, Aurélia Meurisse, Dewi Vernerey, Simon Pernot, Christophe Borg

[1]Clinical Investigational Center CIC-1403, University Hospital of Besançon; University of Bourgogne-Franche Comté, Besançon, France

Atezolizumab plus modified DCF (docetaxel, cisplatin, and 5-fluorouracil) for metastatic or locally advanced squamous cell anal carcinoma (SCCA): A randomized phase II study (SCARCE-PRODIGE 60)

Key eligibility criteria

- Advanced SCCA
  - Metastatic
  - Non-resectable local recurrence
- **Treatment naïve**
- Age ≥ 18 years
- ECOG PS 0-1
- Evaluable disease



Primary endpoint
- 1-year PFS rate by mITT

Secondary endpoints
- Median PFS
- OS
- ORR
- Safety
- HRQoL
- Biomarkers

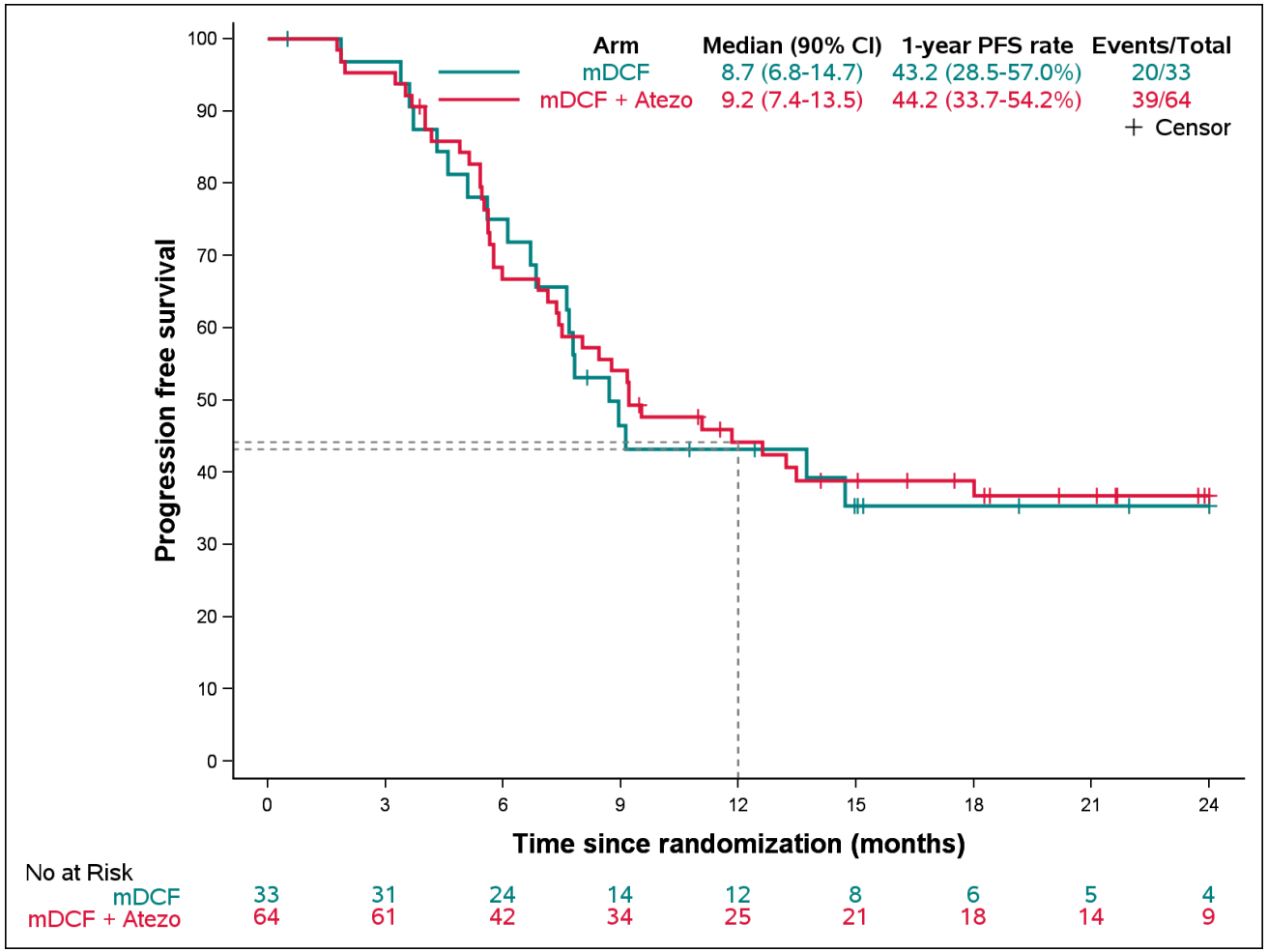
Stratification: age (<65 vs ≥65 years), stage (synchronous metastatic vs metachronous metastatic vs locally advanced unresectable disease without metastasis)

Kim et al: ASCO, 2022

Primary endpoint – 1-year PFS rate

Arm A

1-year PFS rate: 44.2%
(90% CI 31.7-56.0)



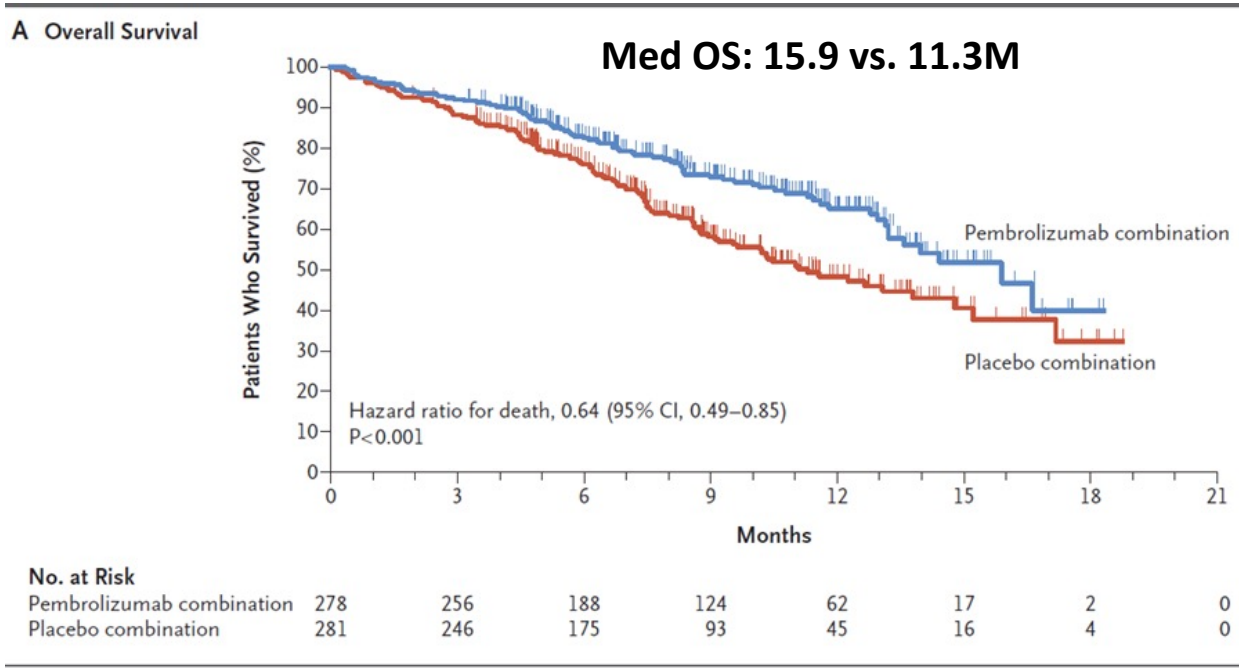
Arm B

1-year PFS rate: 43.2%
(90% CI 25.8-59.4)

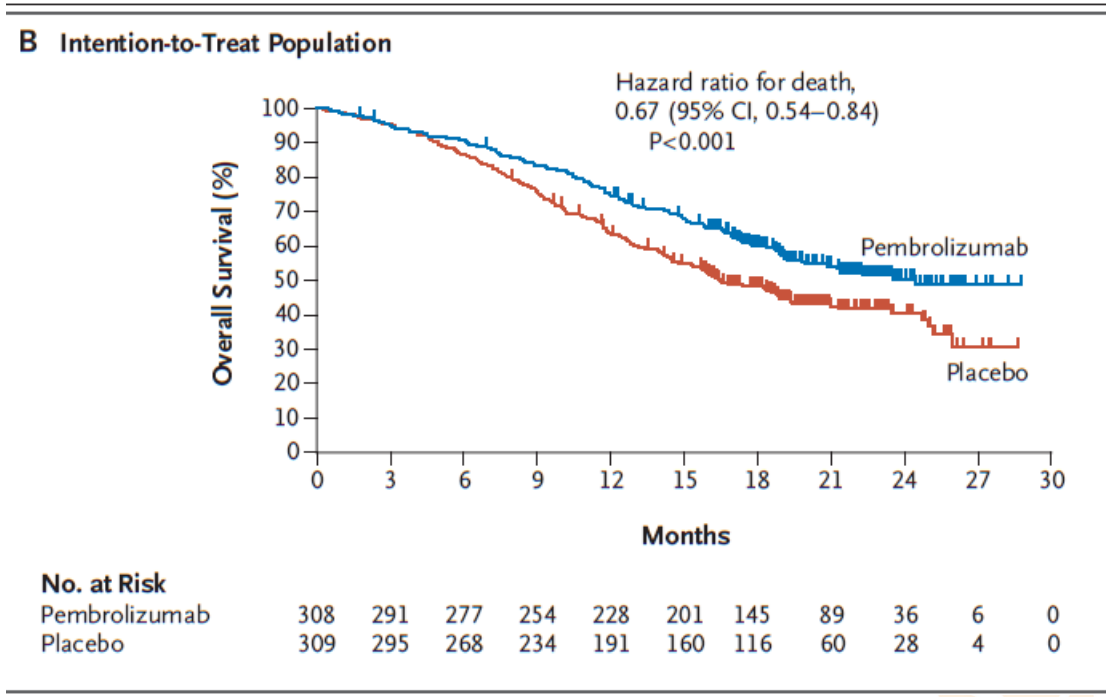
Kim et al: ASCO, 2022

Platinum +/- Immune Checkpoint Inhibitors in Other Squamous Cell Cancers

Phase III: Carboplatin + Paclitaxel (Nab) +/- Pembrolizumab in Squamous NSCLC (KN407)



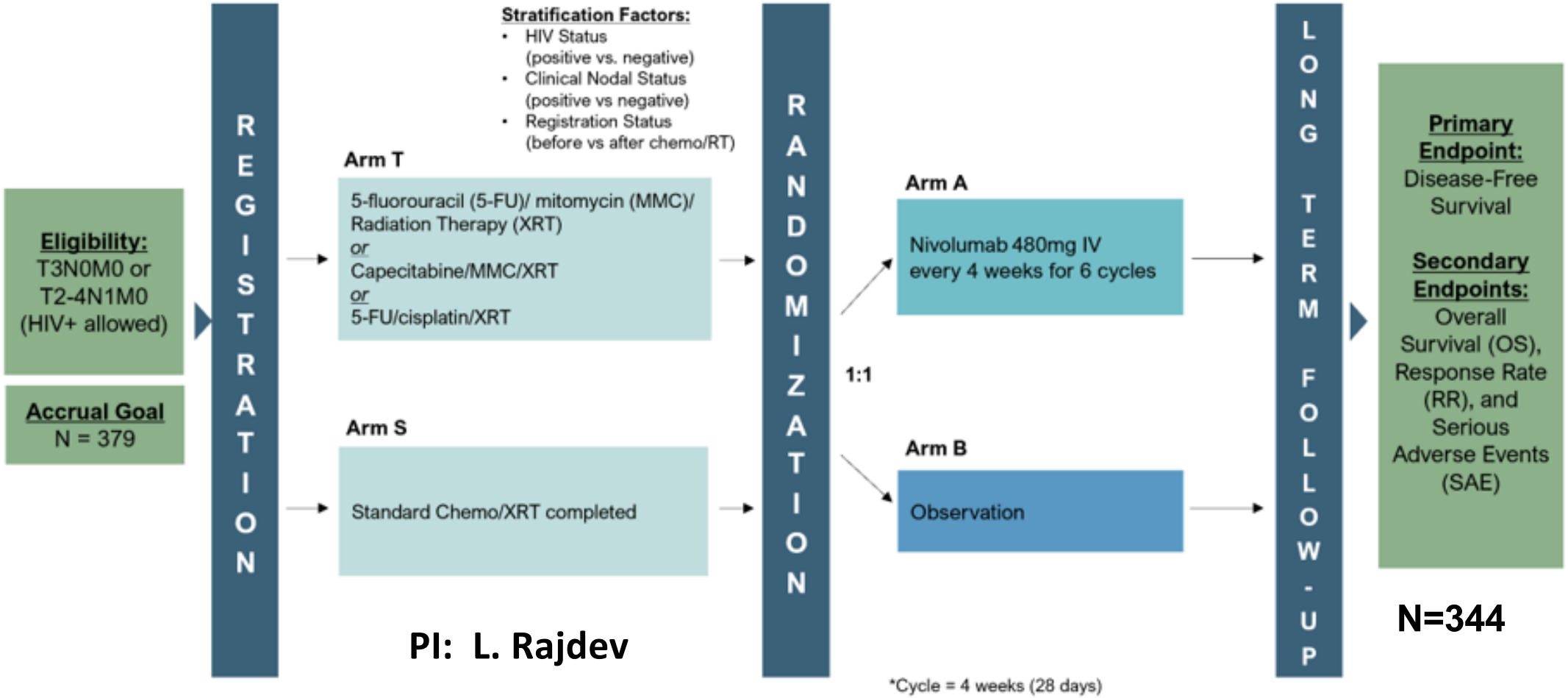
Platinum +/- Pembrolizumab in Cervical Cancer 24M OS = 50.4% and 40.4% (KN826)



Paz-Arez et al: NEJM, 2018; Colombo et al: NEJM, 2021

Ongoing Pending Trials: Metastatic Anal Cancer

EA2165 (NCT03233711): A Randomized Phase III Study of Nivolumab After Combined Modality Therapy (CMT) in High-Risk Anal Cancer

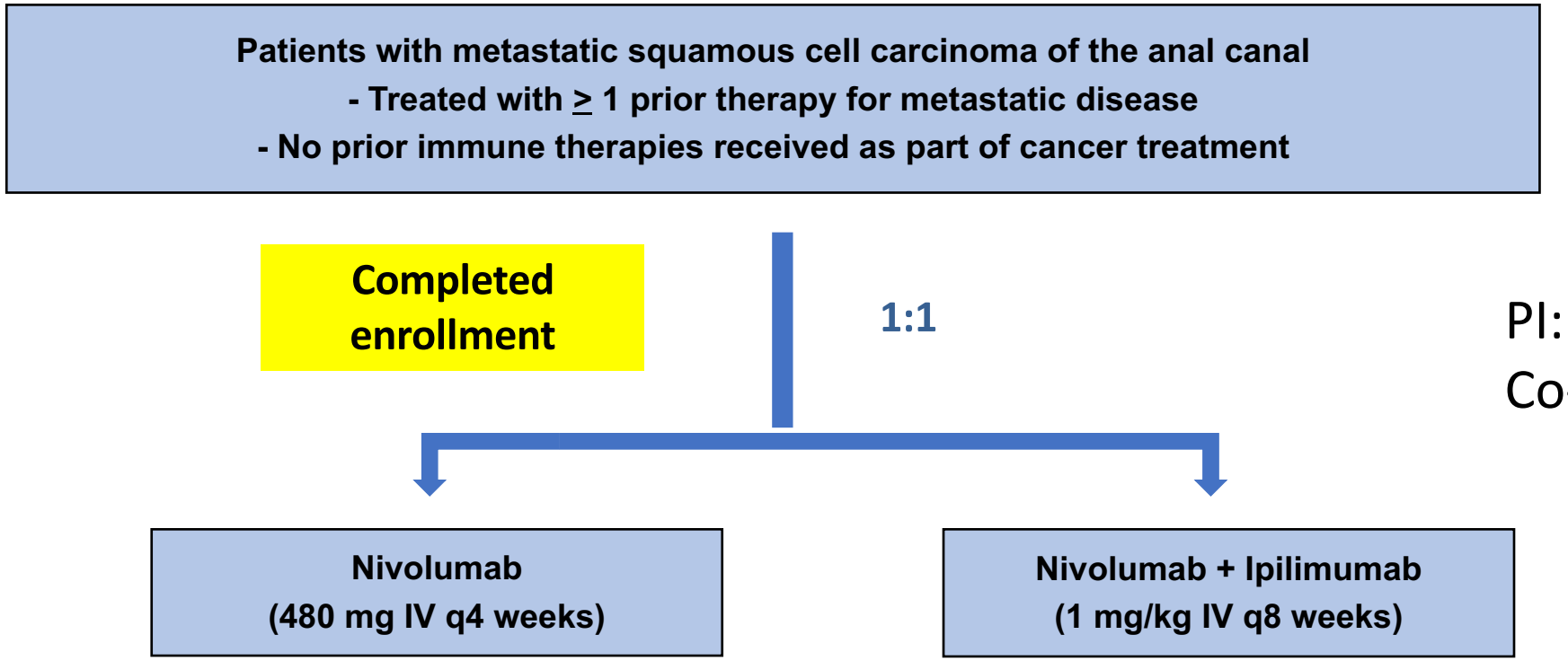


PI: L. Rajdev

Completed enrollment; final data pending

Eng et al: JCO 2022

NCI9673 (Part B): Randomized Phase II ETCTN Study of Nivolumab +/- Ipilimumab in Metastatic SCCA of the Anal Canal:



PI: C. Eng
Co-PI: V. Morris

Primary endpoint: PFS
Secondary endpoints: OS, RR, and SAE's
Exploratory correlatives to be collected

NCT02314169

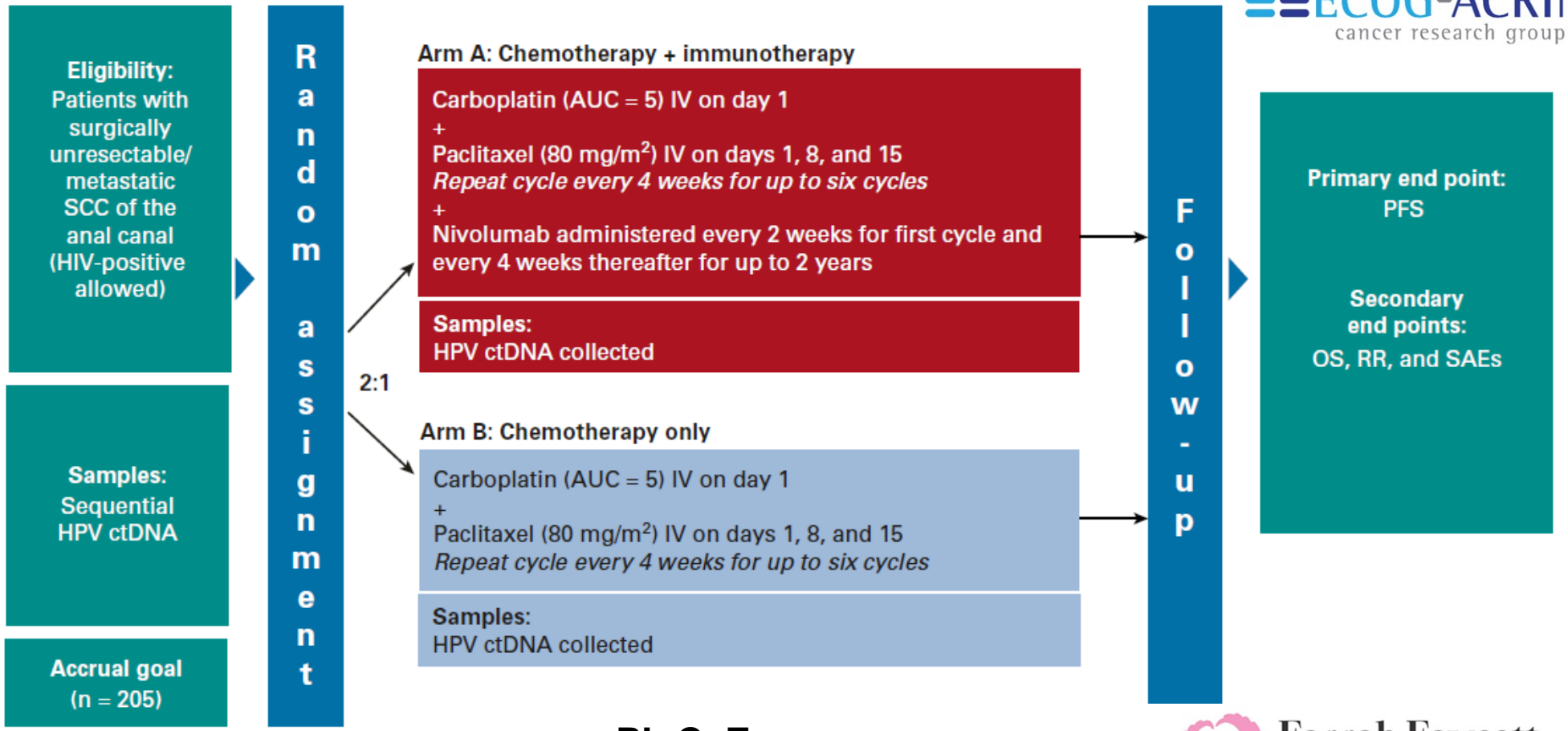
Phase II evaluation of the triple combination of PDS0101, M9241, and bintrafusp alfa in patients with HPV-16 positive malignancies NCT04287868

- HPV 16 E6/E7 vaccine + immunocytokine (IL-12) + bifunctional fusion protein of TGF-*ß*+ PD-L1
- Allowed IO-naïve and refractory patients
- N=56 (actively enrolling)
- 5 cervical, 2 vaginal/vulvar, 4 anal, 3 oropharyngeal SCCA
- Grade 3 SAE's (29%): Hematuria, elevation in transaminases
- Grade 4: Neutropenia
- RR = 71% (83% IO naïve; 63% IO refractory)
  - 1CR, 9 PR's (Anal CA = 2)
    - *Early data: Median follow-up only 5M
- Other combo trial: Bintrafusp alfa + M9241+ entinostat (NCT04708470)

Strauss et al: ASCO 2021

EA2176: Phase 3 Clinical Trial of Carboplatin and Paclitaxel +/- Nivolumab in Treatment-Naive Metastatic Anal Cancer Patients

NCT04444921



ECOG-ACRIN cancer research group

PI: C. Eng
Co-PI's: A. Benson, K. Ciombor

Farrah Fawcett Foundation

Eng et al, JCO 2022

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

DOI: 10.1200/JCO.21.02566 *Journal of Clinical Oncology*

Published online June 01, 2022.

PMID: 35649196

review articles

SPECIAL SERIES: PRECISION MEDICINE AND IMMUNOTHERAPY IN GI MALIGNANCIES

Anal Cancer: Emerging Standards in a Rare Disease

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abstract

The social stigma surrounding an anal cancer diagnosis has traditionally prevented open discussions about this disease. However, as recent treatment options and an increasing rate of diagnoses are made worldwide, awareness is growing. In the United States alone, 9,090 individuals were expected to be diagnosed with anal cancer in 2021. The US annual incidence of squamous cell carcinoma of the anus continues to increase by 2.7% yearly, whereas the mortality rate increases by 3.1%. The main risk factor for anal cancer is a human papillomavirus infection; those with chronic immunosuppression are also at risk. Patients with HIV are 19 times more likely to develop anal cancer compared with the general population. In this review, we have provided an overview of the carcinoma of the anal canal, the role of screening, advancements in radiation therapy, and current trials investigating acute and chronic treatment–related toxicities. This article is a comprehensive approach to presenting the existing data in an effort to encourage continuous international interest in anal cancer.

Eng et al: JCO, 2022

Acknowledgements:

- ECOG and NCI-CTEP:
  - Al Benson (Northwestern)
  - Van Morris, MD (MD Anderson Cancer Center)
  - Kristin Ciombor, MD (Vanderbilt-Ingram Cancer Center)
  - Peter O'Dwyer (ECOG Chair)
  - Howard Streicher (NCI)
- International Rare Cancers Initiative (IRCI)
- Thank you to our anal CA patients, caregivers, and our national patient advocates
- In memory:
  - Michelle Longabaugh, RN, author, blogger, friend, and NCI patient advocate