Targeted Therapy for Colon Cancer: What is New?

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Tumor Sidedness

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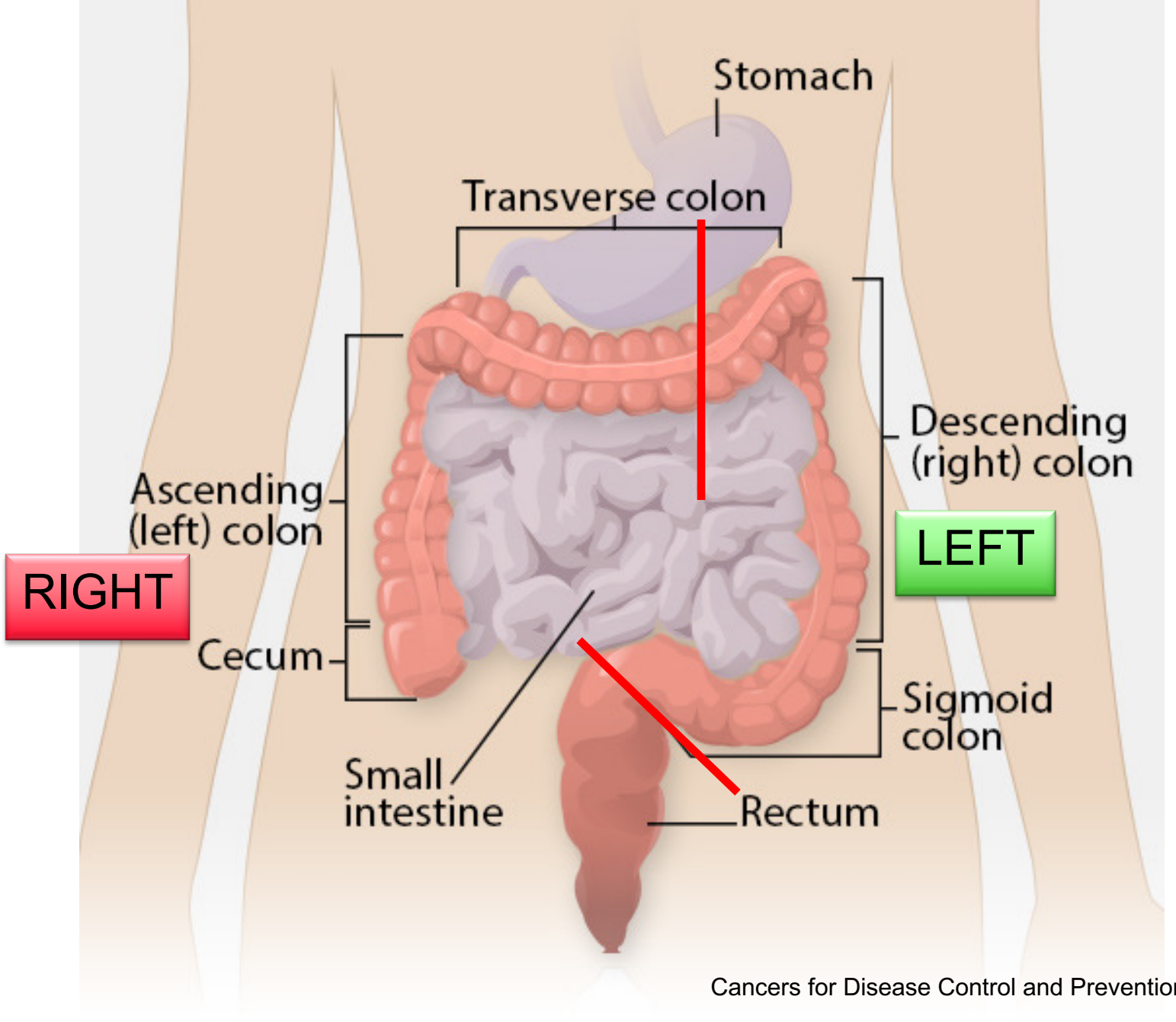


Cancers for Disease Control and Prevention

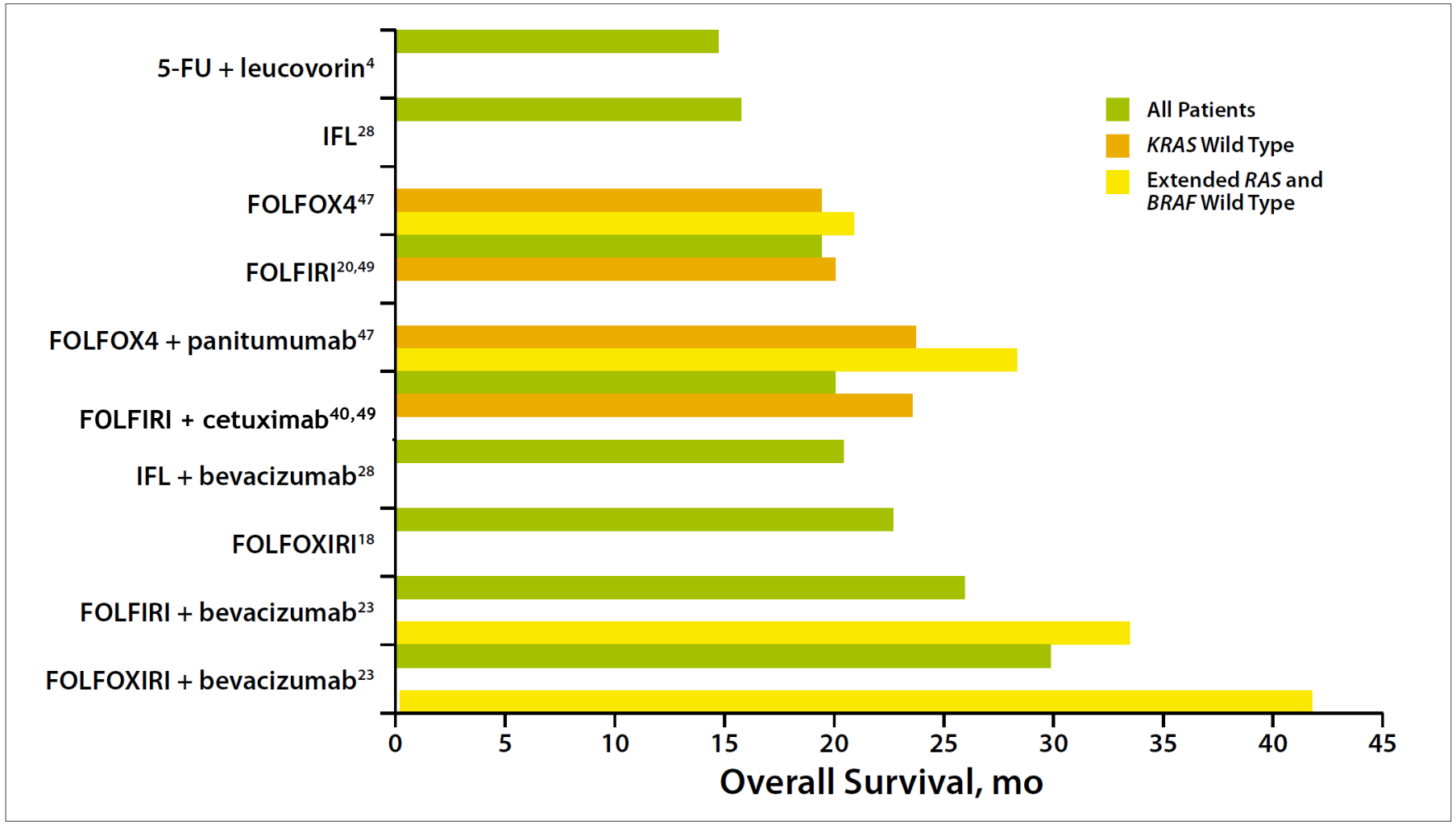


Figure 2. Overall survival of patients with metastatic colorectal cancer according to genetic predetermination and treatment choice. 5-FU, 5-fluorouracil; FOLFIRI, 5-FU/leucovorin/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; FOLFOXIRI, 5-FU/leucovorin/oxaliplatin/irinotecan; IFL, irinotecan/5-FU/leucovorin.

Weinberg BA et al. *Clin Adv Hematol Oncol* 2016.

de Gramont A et al. *J Clin Oncol* 2000. Hurwitz H et al. *N Engl J Med* 2004. Douillard JY et al. *J Clin Oncol* 2010. Souglakos J et al. *Br J Cancer* 2006. Van Cutsem E et al. *J Clin Oncol* 2011. Falcone A et al. *J Clin Oncol* 2007. Cremolini C et al. *Lancet Oncol* 2015.

GERCOR: FOLFIRI → FOLFOX vs. FOLFOX → FOLFIRI

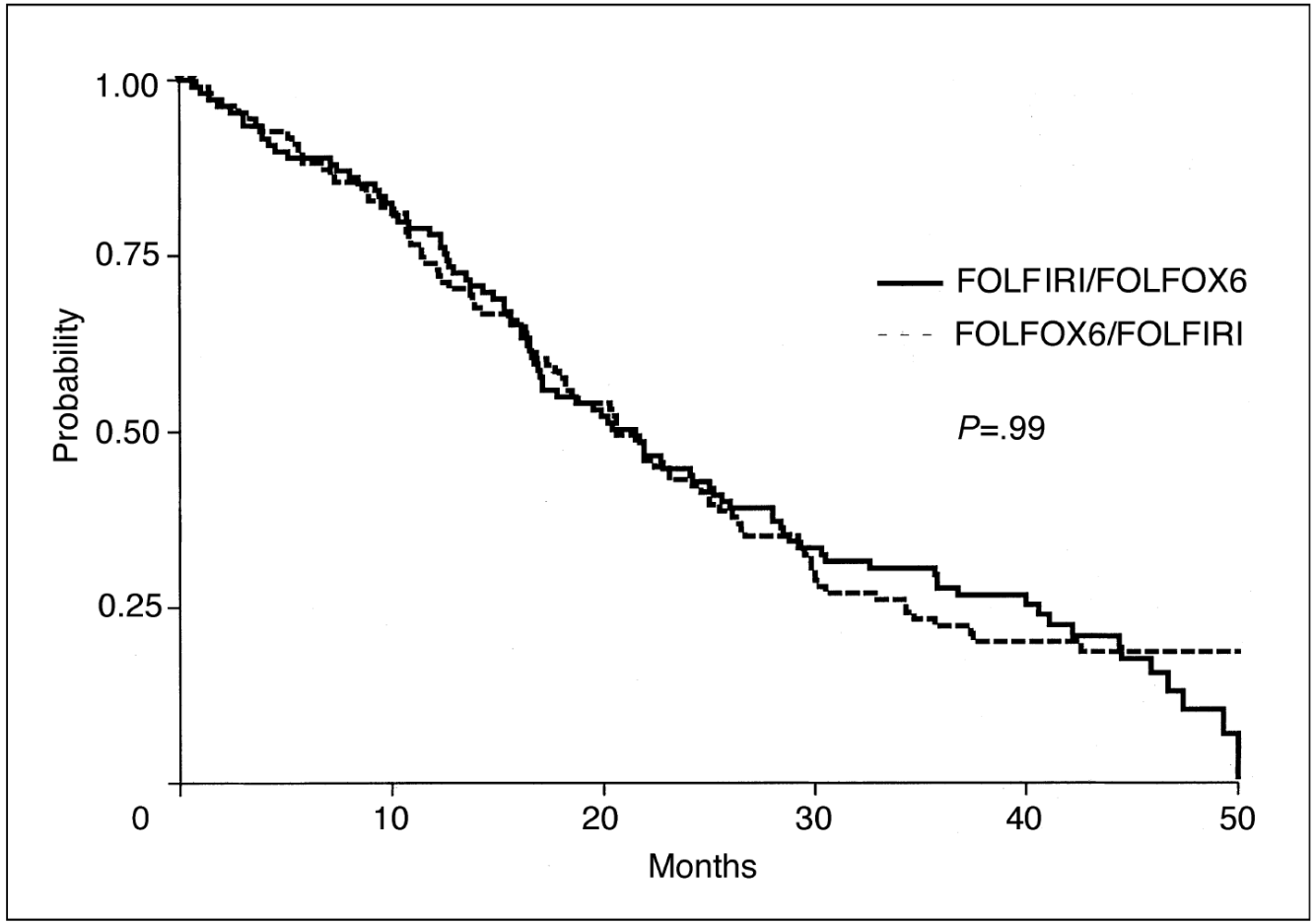
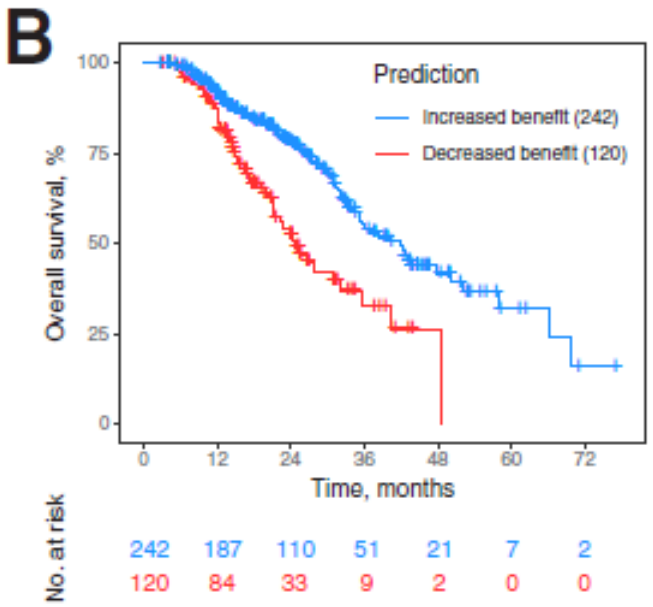


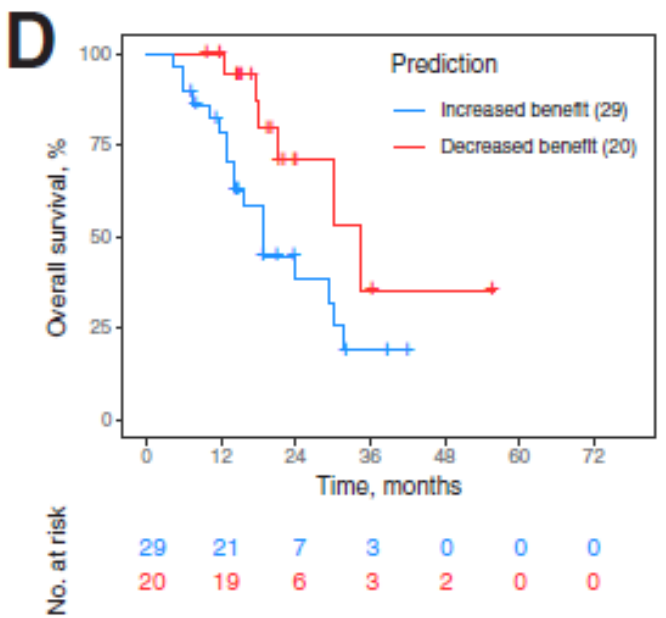
Fig 4. Overall survival curves. FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin.

Tournigand et al. *J Clin Oncol* 2004.

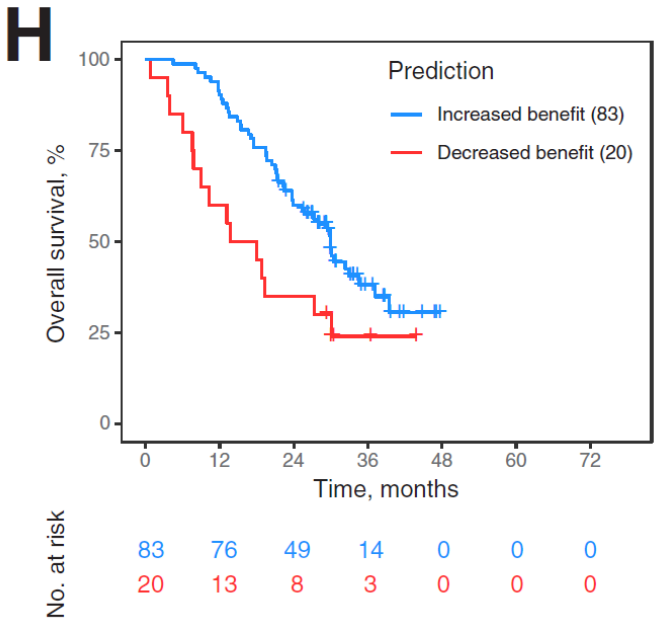
FOLFOX*ai* Algorithm – Oxaliplatin Benefit Prediction



1st Line FOLFOX



1st Line FOLFIRI



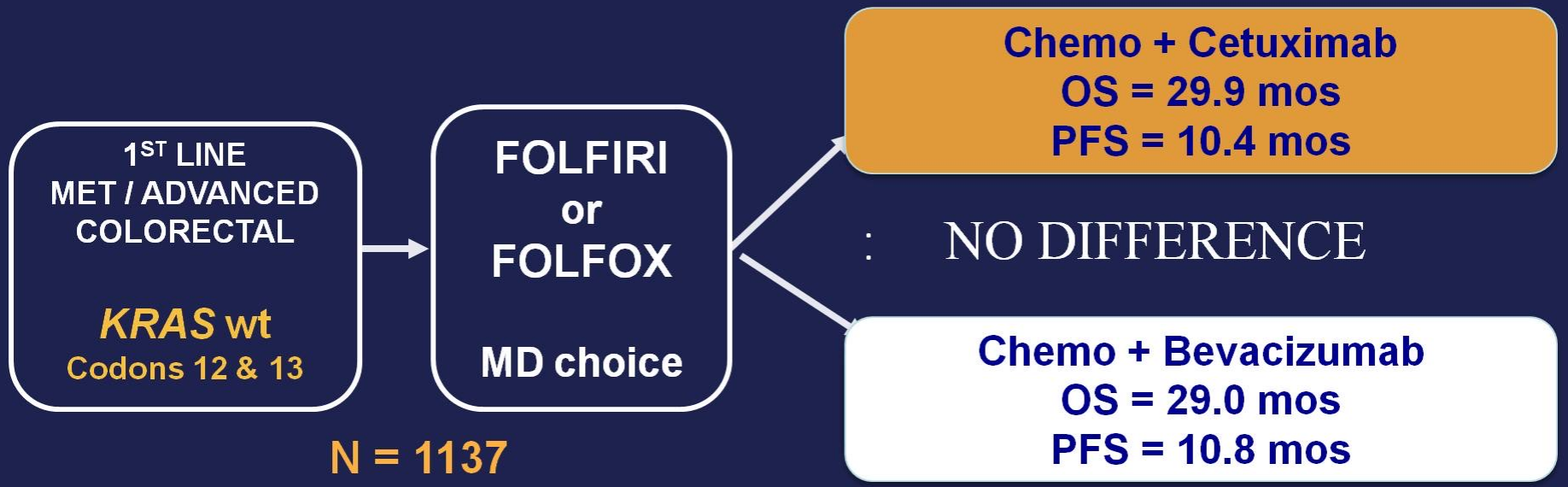
1st Line FOLFOXIRI

Table 2. List of genomic features used in the algorithm.

ACKR3	BRIP1	EWSR1	IL2	MSI2	PRRX1	TOP1
AKT2	CASP8	EZR	INHBA	MYC	RUNX1T1	TRRAP
AKT3	CCNE1	FAS	KEAP1	NFIB	SBDS	U2AF1
ARFRP1	CDX2	FCRL4	LHFPL6	NFKBIA	SDC4	WRN
ARID1A	CNTRL	FH	LMO1	NSD3	SEPT5	WWTR1
ASXL1	COX6C	FLT1	MAML2	PAX7	SMARCA4	YWHAE
AURKA	CREB1	FLT3	MAP2K4	PBX1	SOX10	ZNF217
BCL9	CRKL	GAS7	MLF1	PCM1	TCL1A	
BIRC3	EP300	GNAS	MN1	PDGFB	TERT	
BRD3	ETV6	HOXA11	MNX1	PER1	TLX3	

Abraham et al. *Clin Cancer Res* 2021.

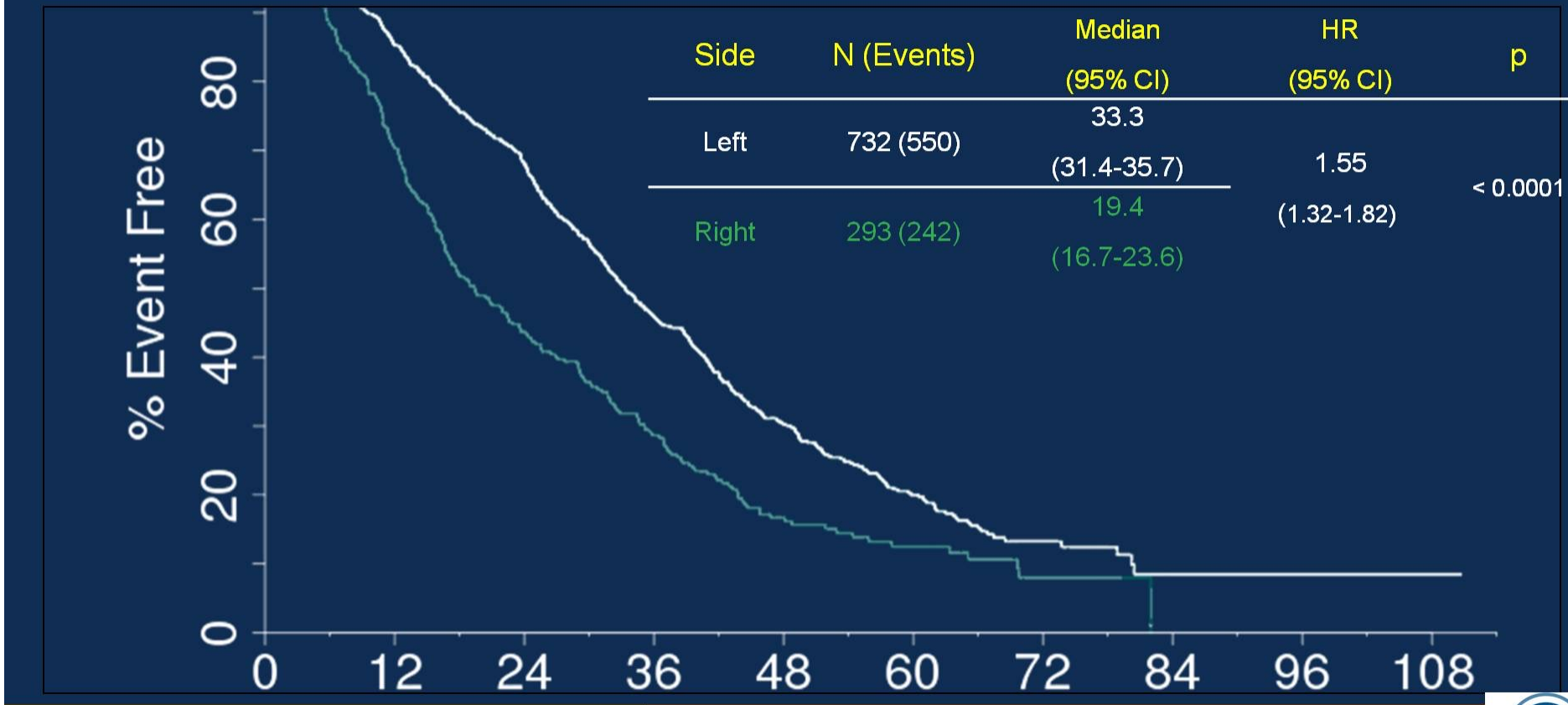
CALGB/SWOG 80405: *KRAS* wt



PRESENTED AT THE 2014 ASCO ANNUAL MEETING

Presented By Alan Venook at 2017 ASCO Annual Meeting

80405: (*KRAS* WT) Overall Survival by Sidedness

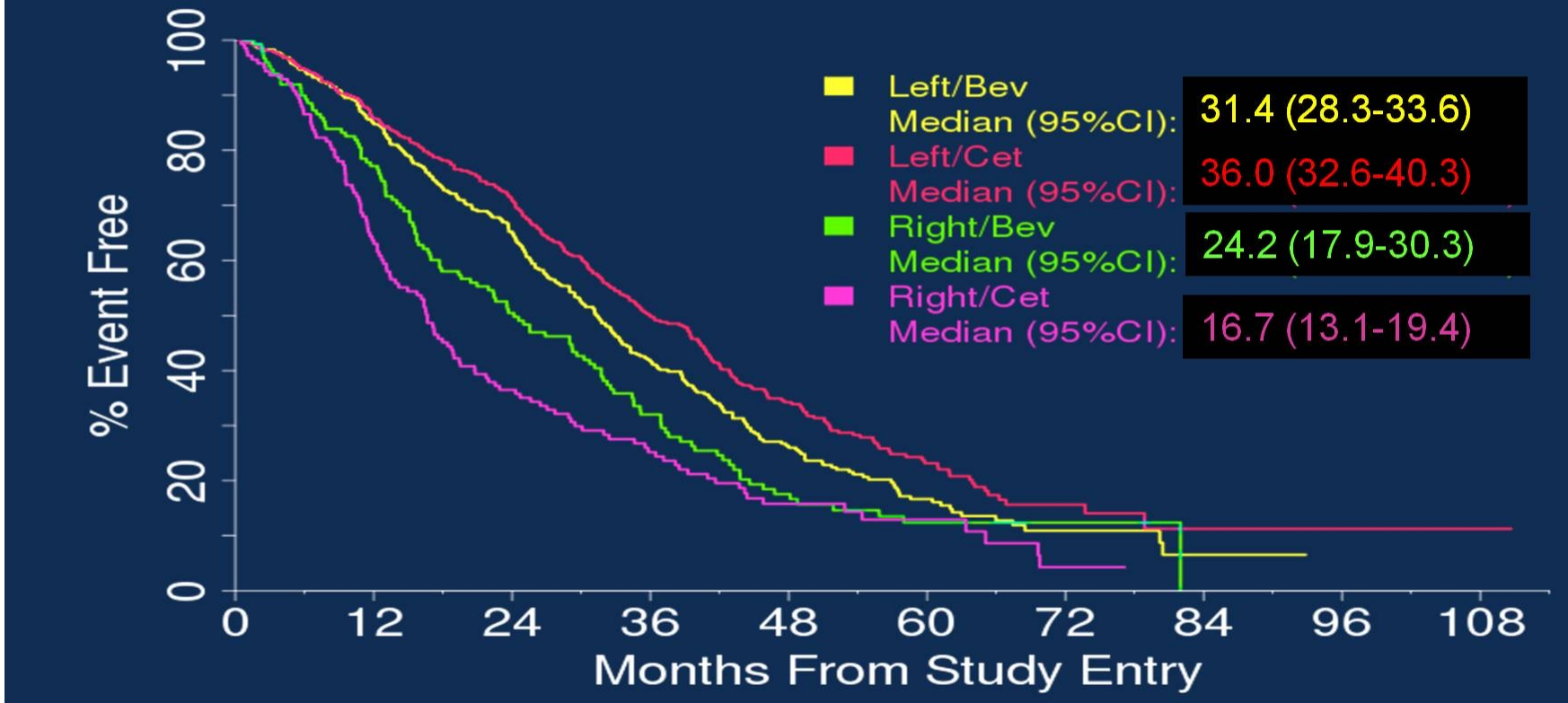


Side	N (Events)	Median (95% CI)	HR (95% CI)	p
Left	732 (550)	33.3 (31.4-35.7)	1.55 (1.32-1.82)	< 0.0001
Right	293 (242)	19.4 (16.7-23.6)		

ASCO ANNUAL MEETING '16

Presented By Alan Venook at 2017 ASCO Annual Meeting

80405 (*KRAS* WT): Overall Survival by Sidedness and Biologic



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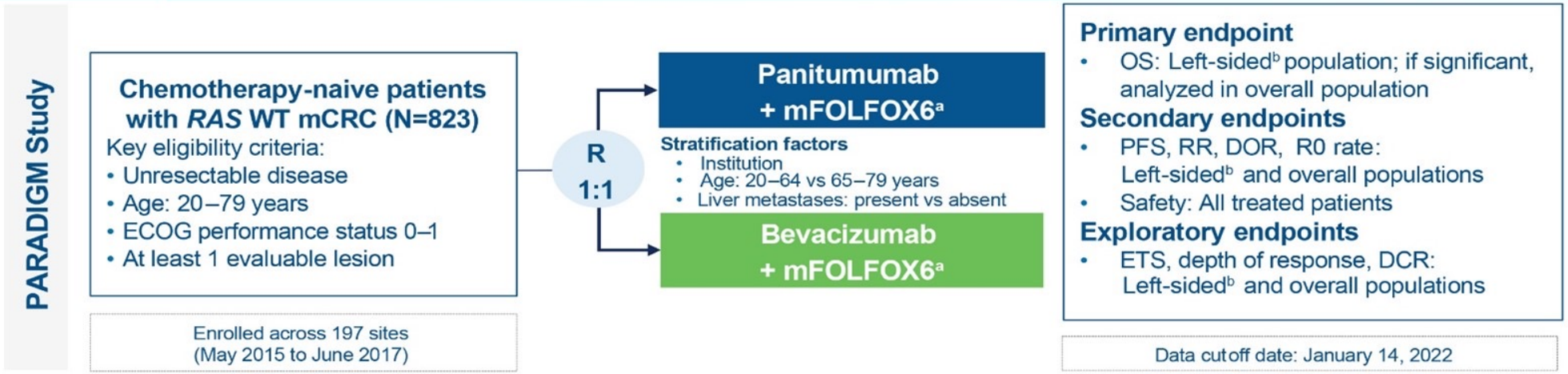
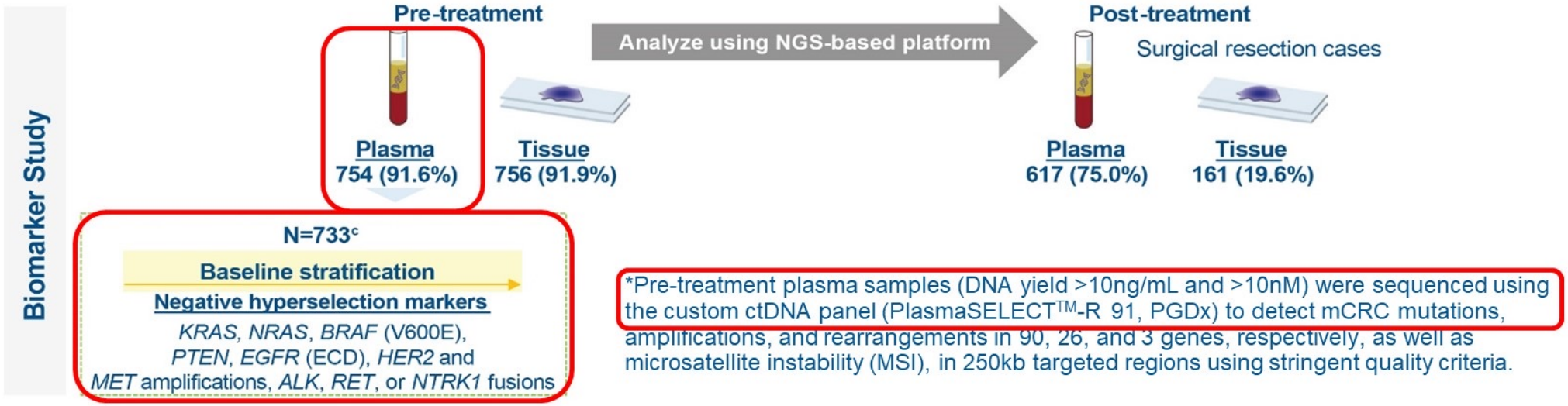
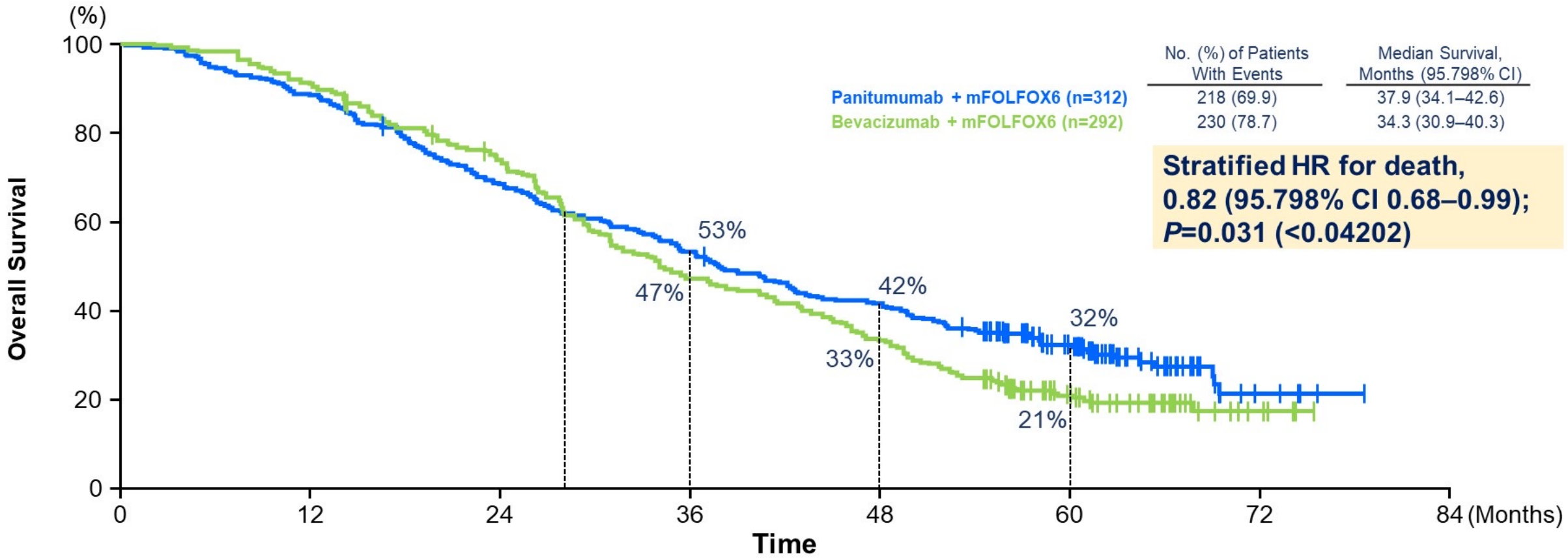
Study design





EGFR (ECD), *EGFR* extracellular domain mutations.
[a]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection; [b]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum; [c]Patients with available ctDNA among those included in efficacy analysis set in the PARADIGM study

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



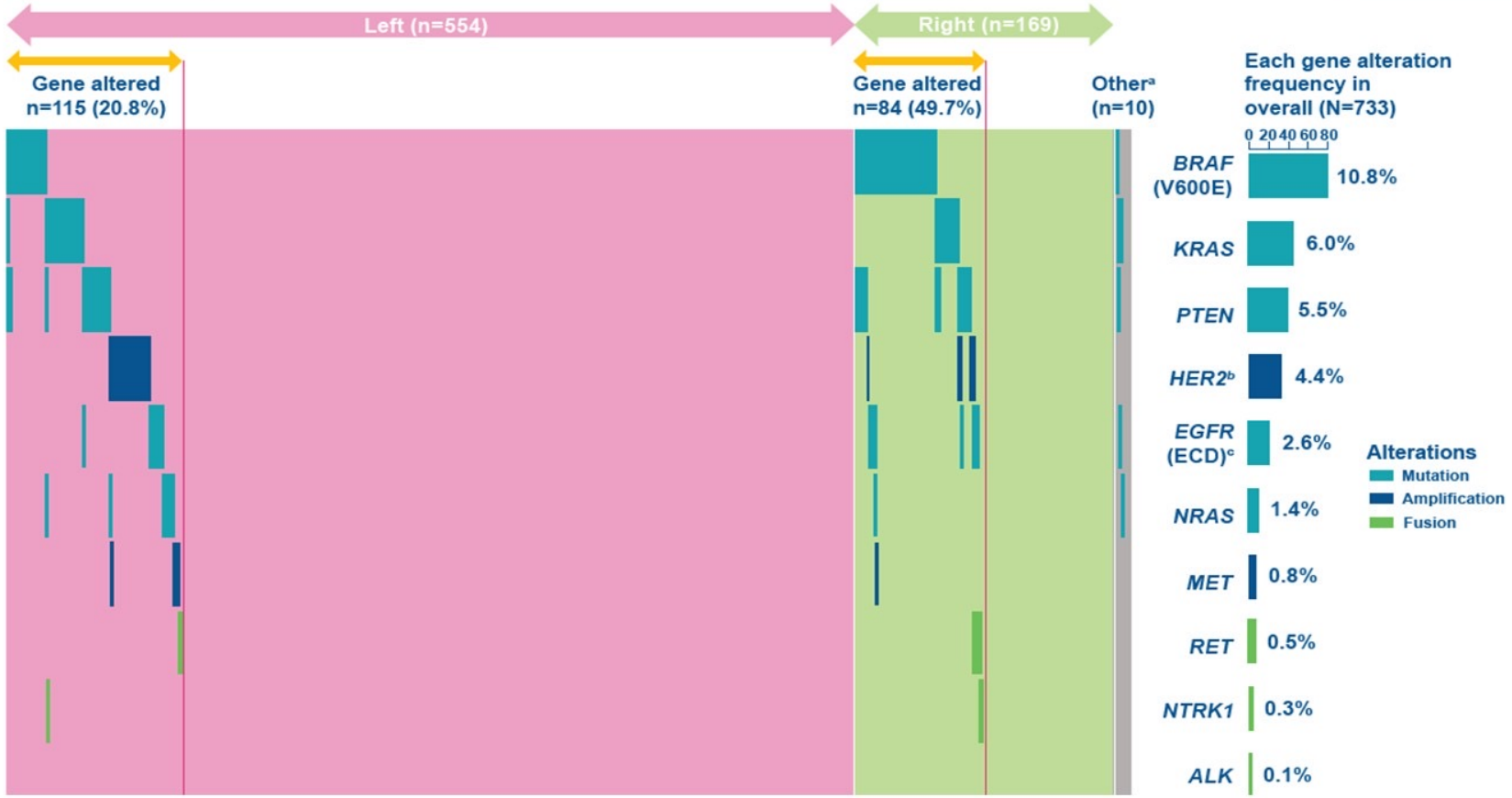
	No. (%) of Patients With Events	Median Survival, Months (95.798% CI)
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	37.9 (34.1–42.6)
Bevacizumab + mFOLFOX6 (n=292)	230 (78.7)	34.3 (30.9–40.3)

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

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

	Left-sided (n=554)	Right-sided (n=169)	Other (n=10)	Overall (N=733)
Gene altered n (%)	115 (20.8)	84 (49.7)	5 (50)	204 (27.8)
Hyperselected n (%)	439 (79.2)	85 (50.3)	5 (50)	529 (72.2)



[a]Patients who had multiple primary lesions in both the left and right sides; [b]The custom panel (Tak_Seq3) has a 1.25 threshold for *HER2* (thresholds were set based on noise in normal samples); [c]*EGFR* (ECD): Exon 1–16 (1–620)

Number of genetic alterations ctDNA

Gene alteration, n (%)	Overall population (N=733)		Left-sided mCRC (n=554)		Right-sided mCRC (n=169)	
	Panitumumab (n=368)	Bevacizumab (n=365)	Panitumumab (n=287)	Bevacizumab (n=267)	Panitumumab (n=78)	Bevacizumab (n=91)
BRAF (V600E)	43 (11.7)	36 (9.9)	17 (5.9)	8 (3.0)	26 (33.3)	27 (29.7)
KRAS	22 (6.0)	23 (6.3)	11 (3.8)	15 (5.6)	9 (11.5)	6 (6.6)
PTEN	23 (6.3)	17 (4.7)	12 (4.2)	8 (3.0)	10 (12.8)	9 (9.9)
HER2 amplification	19 (5.2)	14 (3.8)	16 (5.6)	11 (4.1)	3 (3.8)	2 (2.2)
EGFR (ECD)	12 (3.3)	7 (1.9)	7 (2.4)	3 (1.1)	5 (6.4)	3 (3.3)
NRAS	10 (2.7)	3 (0.8)	6 (2.1)	2 (0.7)	1 (1.3)	0
MET amplification	3 (0.8)	2 (0.5)	3 (1.0)	2 (0.7)	0	0
RET fusion	2 (0.5)	2 (0.5)	0	2 (0.7)	2 (2.6)	0
NTRK1 fusion	1 (0.3)	1 (0.3)	0	1 (0.4)	1 (1.3)	0
ALK fusion	0	1 (0.3)	0	0	0	1 (1.1)

Survival outcomes in the overall population analyzed for ctDNA

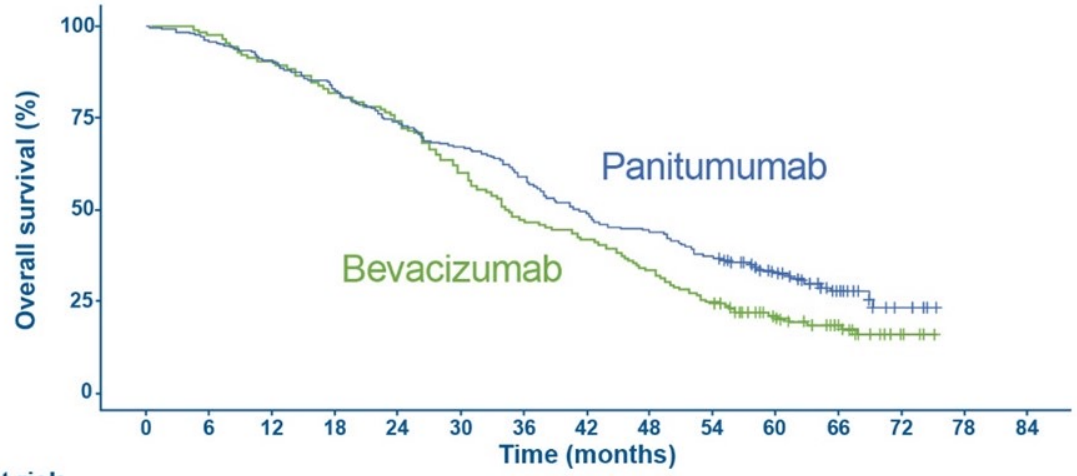
Hyperselected

mOS, months (95% CI)

Panitumumab 41.3 (37.1–48.1)

Bevacizumab 34.4 (31.3–40.3)

HR 0.75 (95% CI, 0.62–0.92)



No. at risk

Panitumumab	258	247	232	211	188	172	151	127	113	96	62	23	4	0	0
Bevacizumab	271	263	242	217	196	158	123	109	88	65	36	18	5	0	0

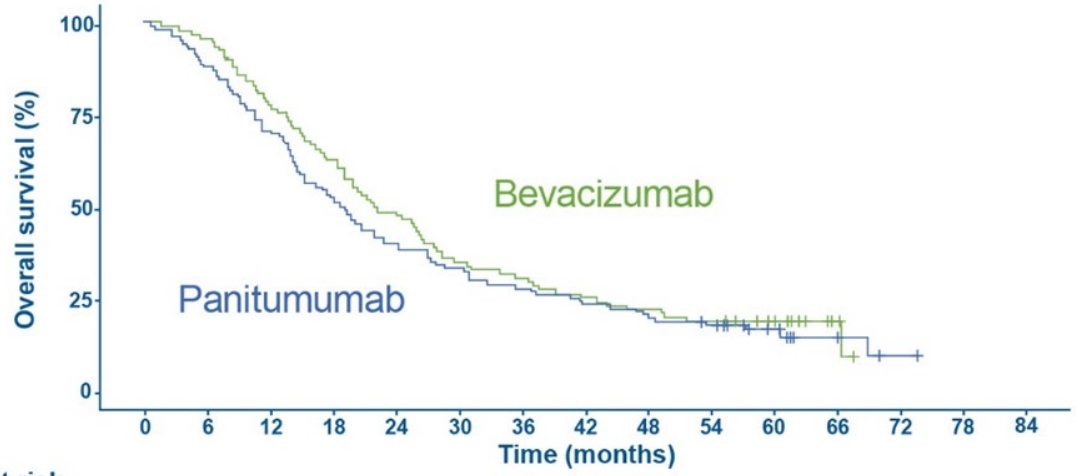
Gene Altered

mOS, months (95% CI)

Panitumumab 19.0 (14.8–23.0)

Bevacizumab 22.2 (19.1–27.7)

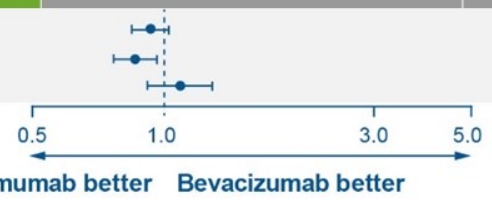
HR 1.14 (95% CI, 0.84–1.54)



No. at risk

Panitumumab	110	97	78	58	44	37	31	26	23	19	11	4	1	0	0
Bevacizumab	94	90	73	59	46	33	29	24	21	18	12	3	0	0	0

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



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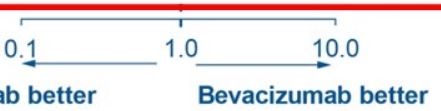
Subgroup analysis of overall survival by gene alteration in the overall population analyzed for ctDNA

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



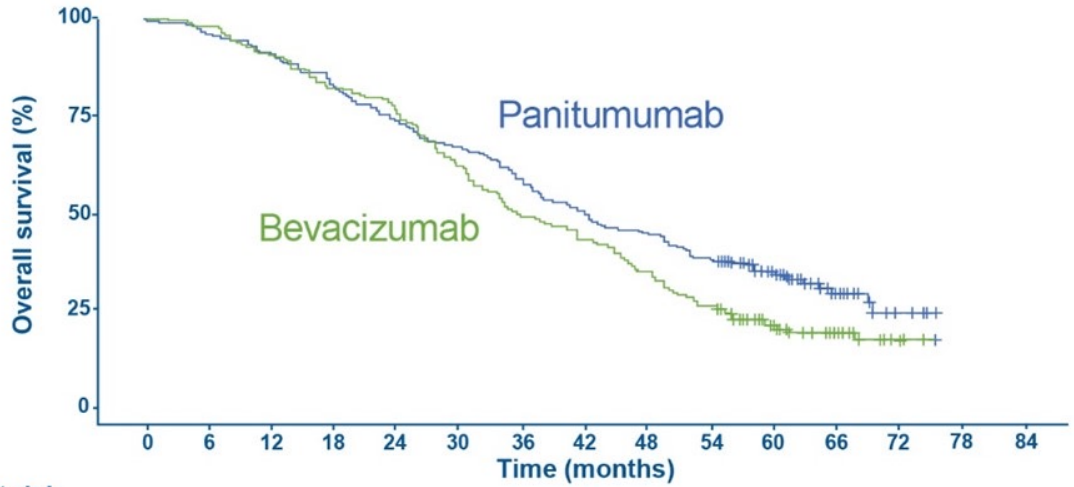
Shitara et al. ASCO GI 2023.

Survival outcomes in the left-sided population analyzed for ctDNA

Hyperselected

	mOS, months (95% CI)
Panitumumab	42.1 (36.9–49.6)
Bevacizumab	35.5 (31.6–41.4)

HR 0.76 (95% CI, 0.61–0.94)



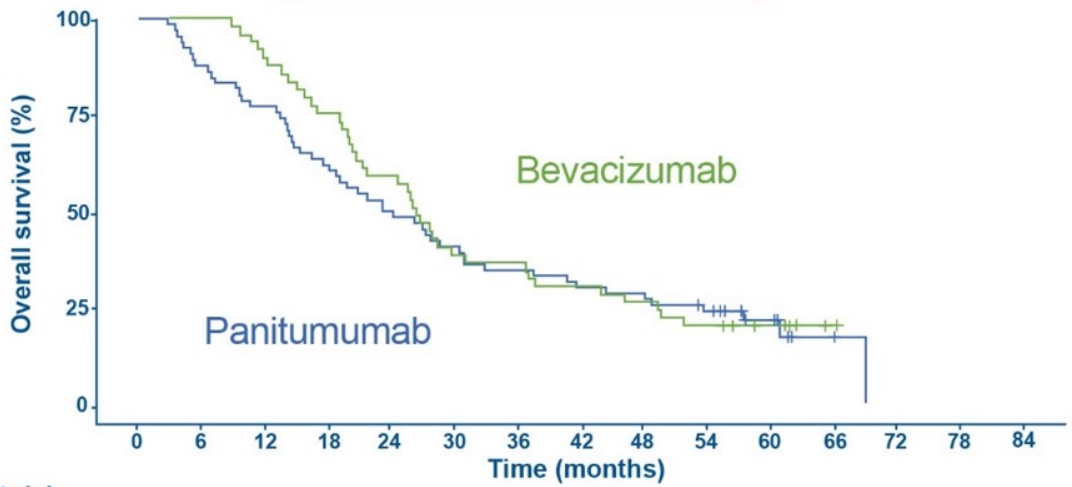
No. at risk

Panitumumab	221	213	201	182	162	147	129	111	98	84	54	20	4	0	0
Bevacizumab	218	214	198	177	163	132	104	92	73	54	28	14	5	0	0

Gene Altered

	mOS, months (95% CI)
Panitumumab	23.6 (17.5–30.9)
Bevacizumab	26.4 (20.8–30.9)

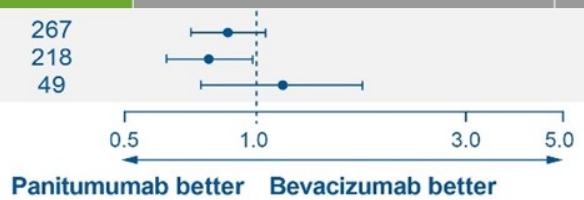
HR 1.10 (95% CI, 0.72–1.66)



No. at risk

Panitumumab	66	58	51	41	33	27	23	20	19	15	8	2	0	0	0
Bevacizumab	49	49	44	37	29	19	18	15	13	10	6	1	0	0	0

Subgroup		N	Panitumumab + mFOLFOX6	Bevacizumab + mFOFLFOX6	Hazard ratio (95% CI)	Log-rank *P*-value	*P*-value for interaction
Left-sided	Overall	554	287	267	0.83 (0.69–1.01)	0.062	
	Hyperselected	439	221	218	0.76 (0.61–0.94)	0.012	0.139
	Gene altered	115	66	49	1.10 (0.72–1.66)	0.661	



Shitara et al. ASCO GI 2023.

Survival outcomes in the right-sided population analyzed for ctDNA

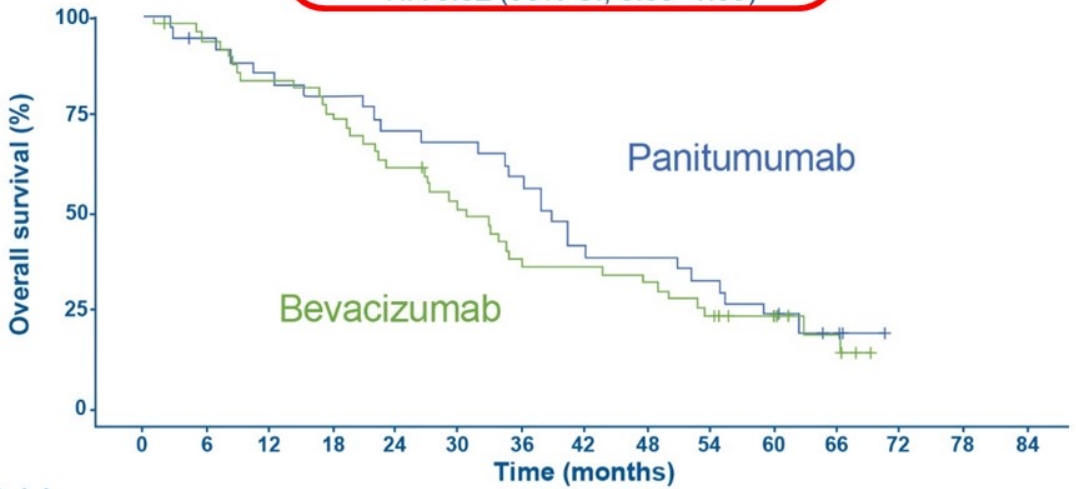
Hyperselected

mOS, months (95% CI)

Panitumumab 38.9 (26.5–52.2)

Bevacizumab 30.9 (22.4–36.1)

HR 0.82 (95% CI, 0.50–1.35)



No. at risk

Panitumumab	35	32	29	27	24	23	20	14	13	11	8	3	0	0	0
Bevacizumab	50	46	41	37	30	24	18	17	15	11	8	4	0	0	0

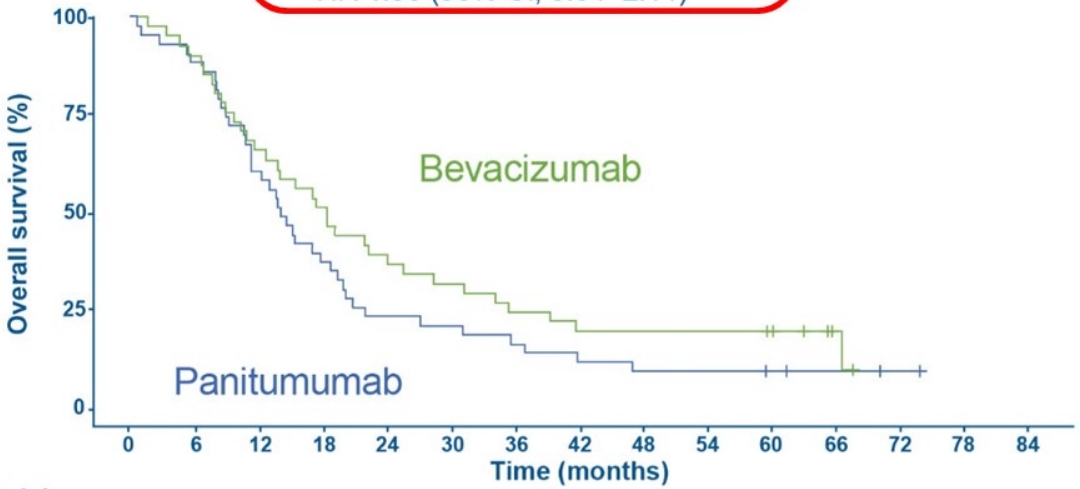
Gene Altered

mOS, months (95% CI)

Panitumumab 14.1 (11.3–18.7)

Bevacizumab 18.5 (11.6–25.5)

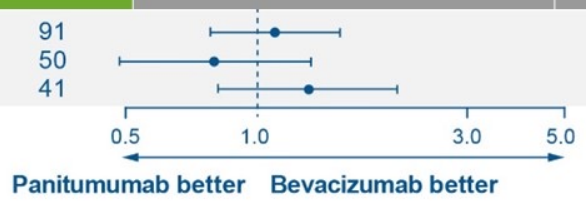
HR 1.33 (95% CI, 0.84–2.11)



No. at risk

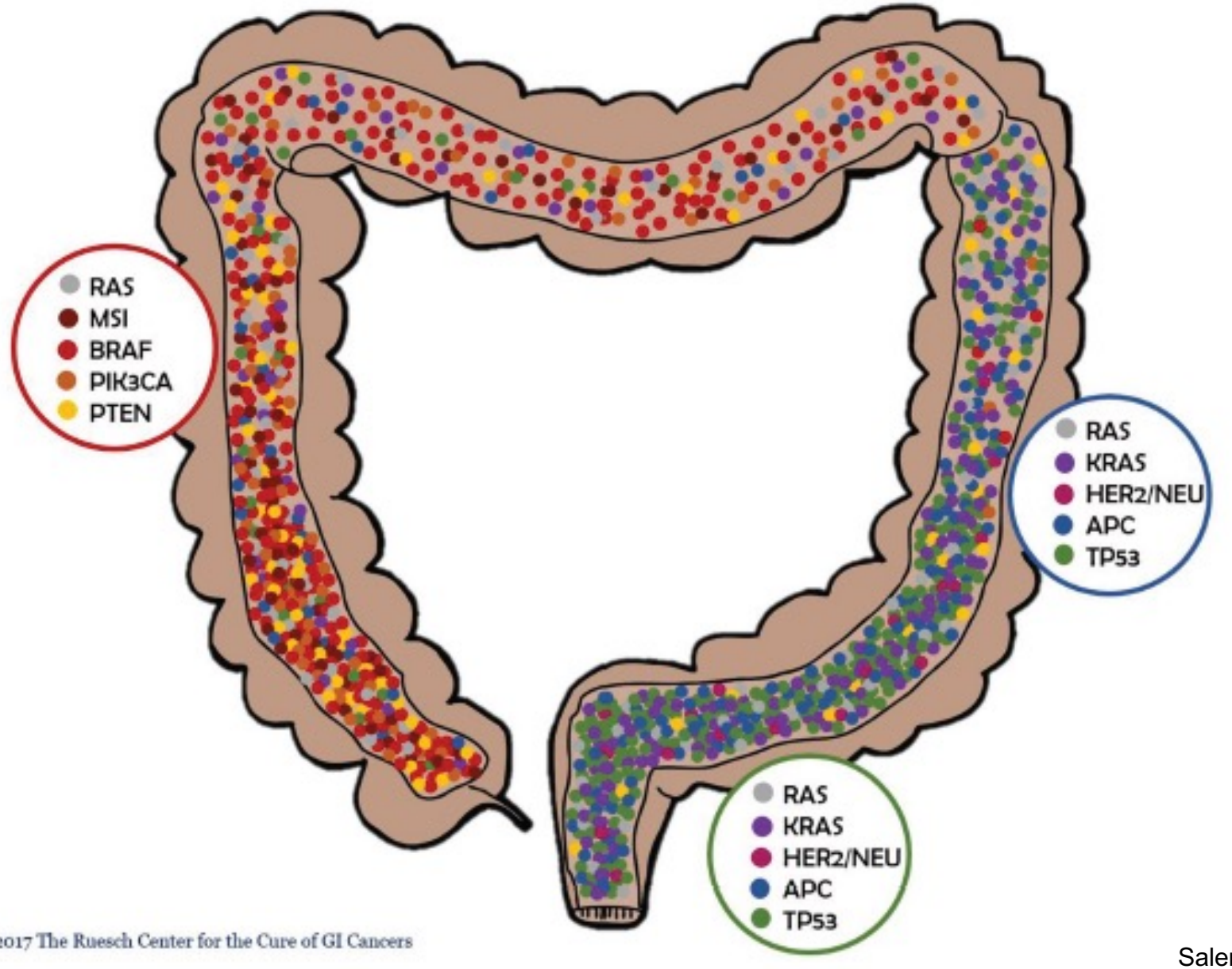
Panitumumab	43	38	26	16	10	9	7	5	4	4	3	2	1	0	0
Bevacizumab	41	37	27	21	16	13	10	8	8	8	6	2	0	0	0

Subgroup		N	Panitumumab + mFOLFOX6	Bevacizumab + mFOFLFOX6	Hazard ratio (95% CI)	Log-rank *P*-value	*P*-value for interaction
Right-sided	Overall	169	78	91	1.12 (0.80–1.56)	0.504	0.145
	Hyperselected	85	35	50	0.82 (0.50–1.35)	0.431	
	Gene altered	84	43	41	1.33 (0.84–2.11)	0.228	



Shitara et al. ASCO GI 2023.

Right vs. Left Colon vs. Rectum



Salem et al. *Oncotarget* 2017.

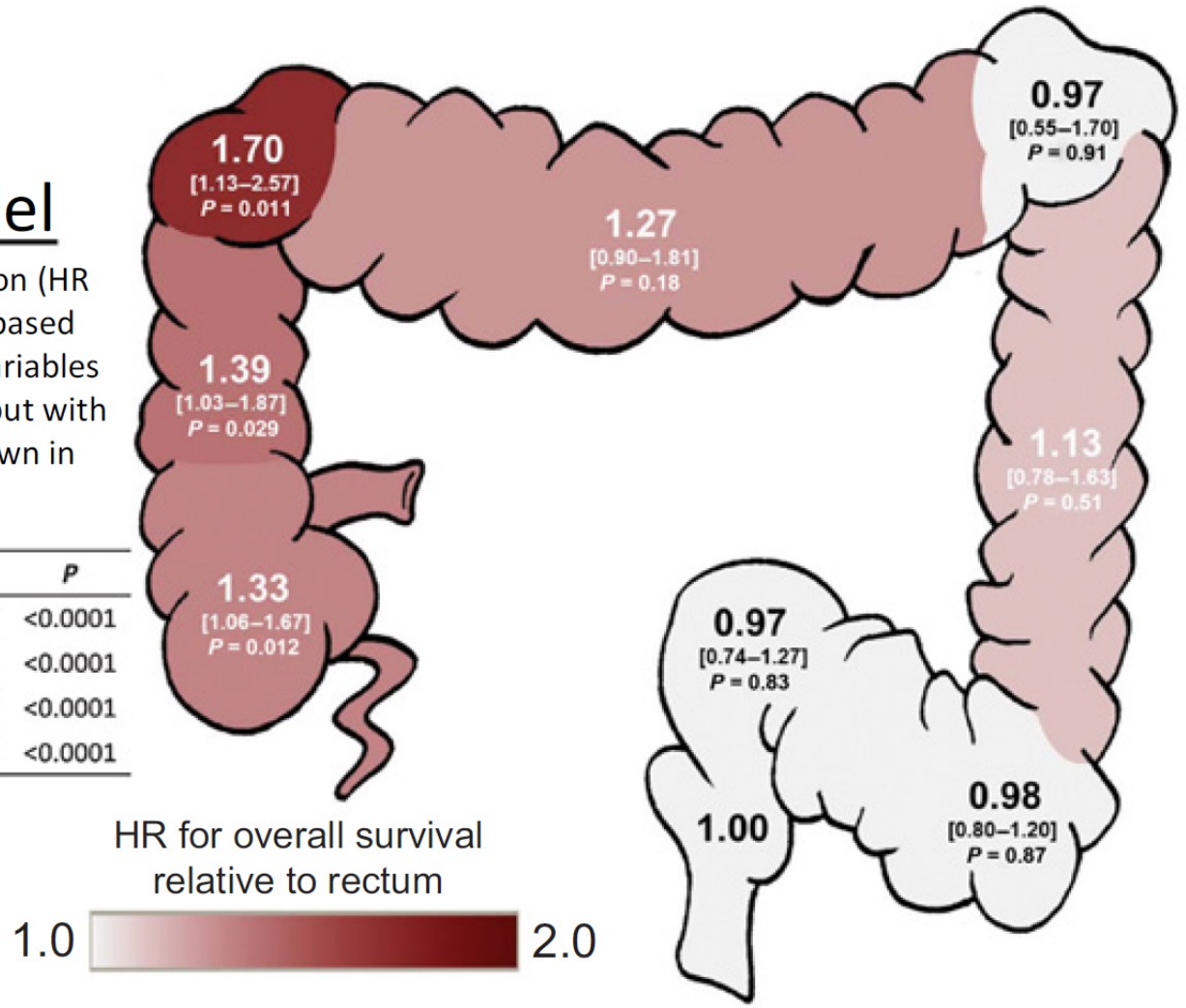
Right vs. Left Colon vs. Rectum

B

Multivariate model

Model included primary tumor location (HR shown in graphic) and non-location based variables (HR in table below). Other variables considered for inclusion in the model but with P>0.1 during model creation are shown in Supplementary Table 3.

Non-Location Based Variables	HR (95% CI)	*P*
Metastatic at Diagnosis	1.52 (1.30–1.77)	<0.0001
Mucinous/Signet Histology	1.49 (1.24–1.80)	<0.0001
BRAFV600 Mutation	1.83 (1.36–2.46)	<0.0001
KRAS	1.32 (1.13–1.54)	<0.0001



Loree et al. *Clin Cancer Res* 2018.

BRAF-Targeted Therapy

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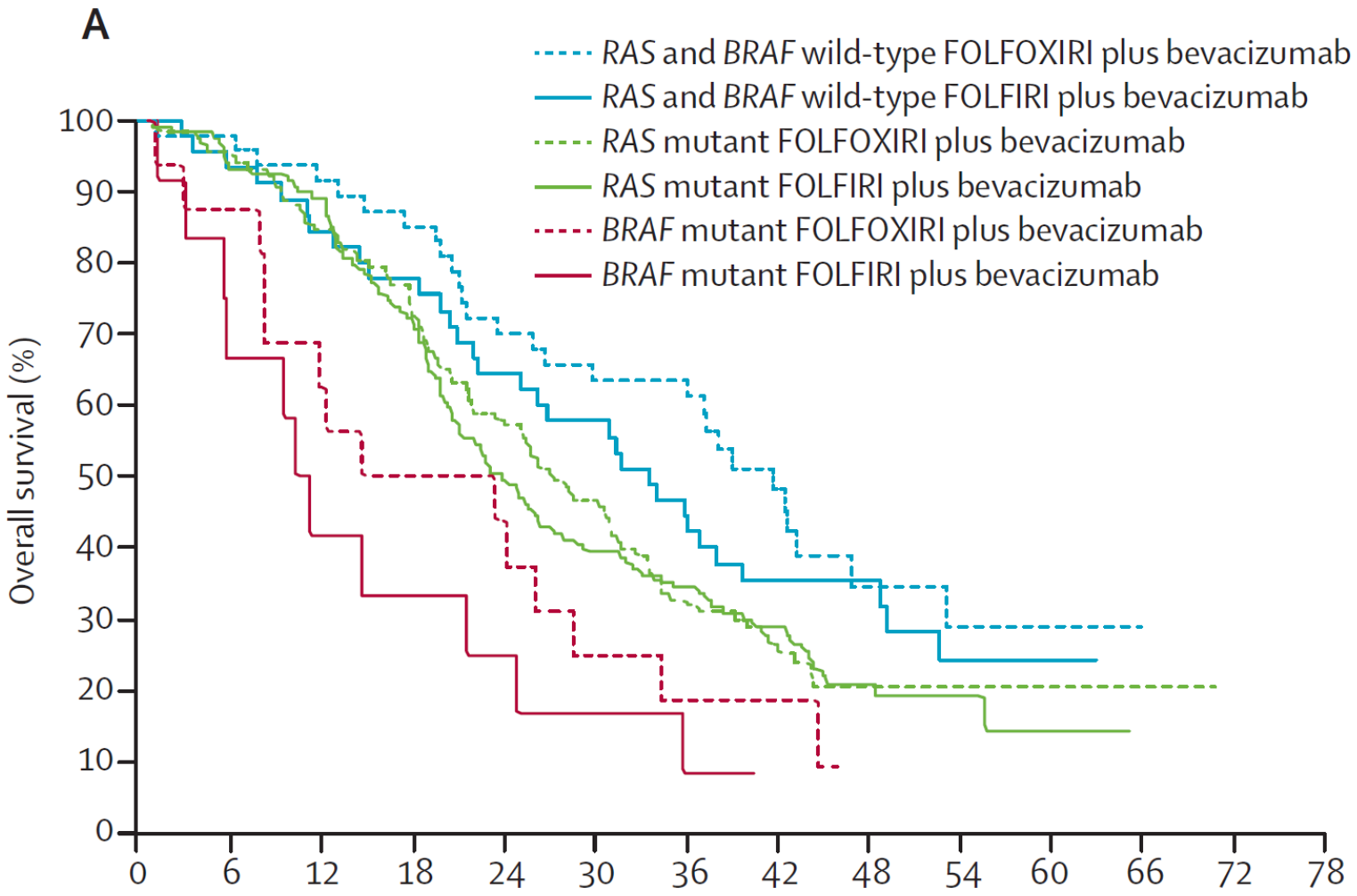
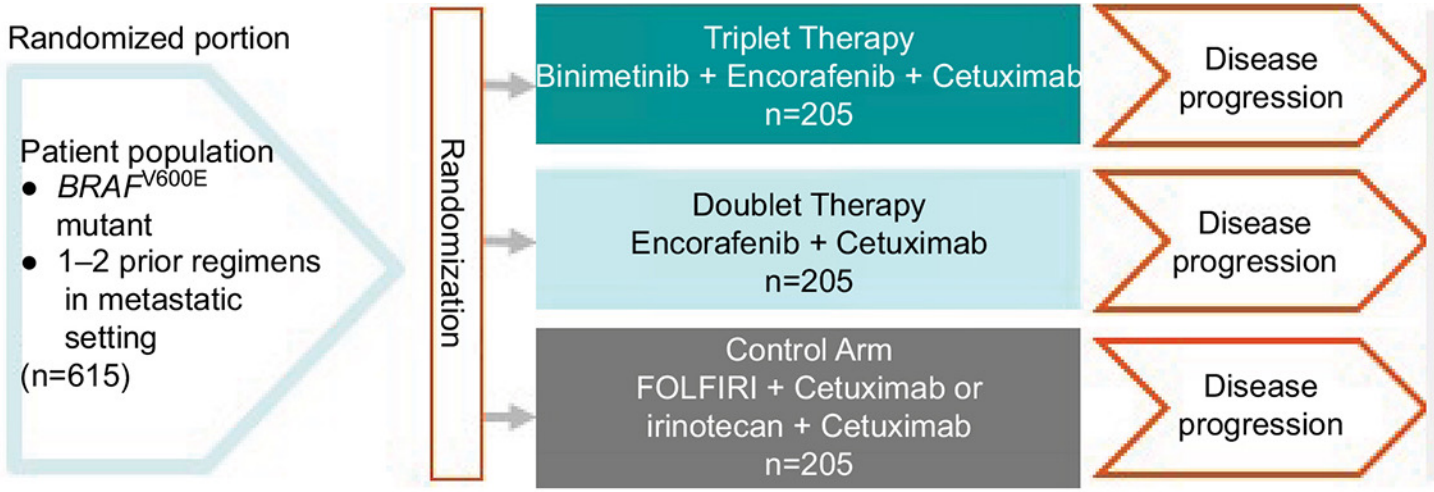
BRAF (V600E) Mutations Carry a Poor Prognosis



Cremolini et al. *Lancet Oncol* 2015.

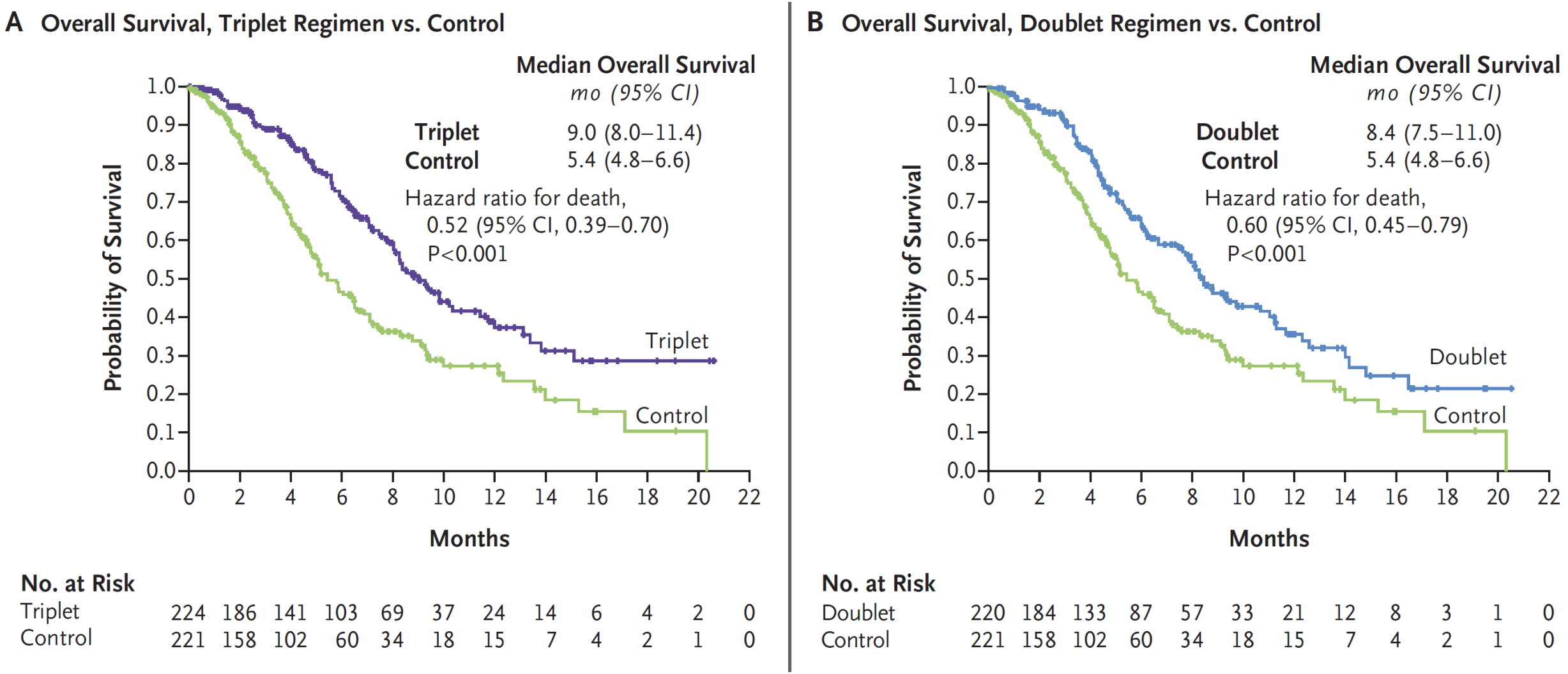
BEACON CRC



N	mOS (HR)	ORR
224	9.0 (0.52)	26%
220	8.4 (0.60)	20%
221	5.4	2%

Kopetz et al. *ESMO GI* 2019.

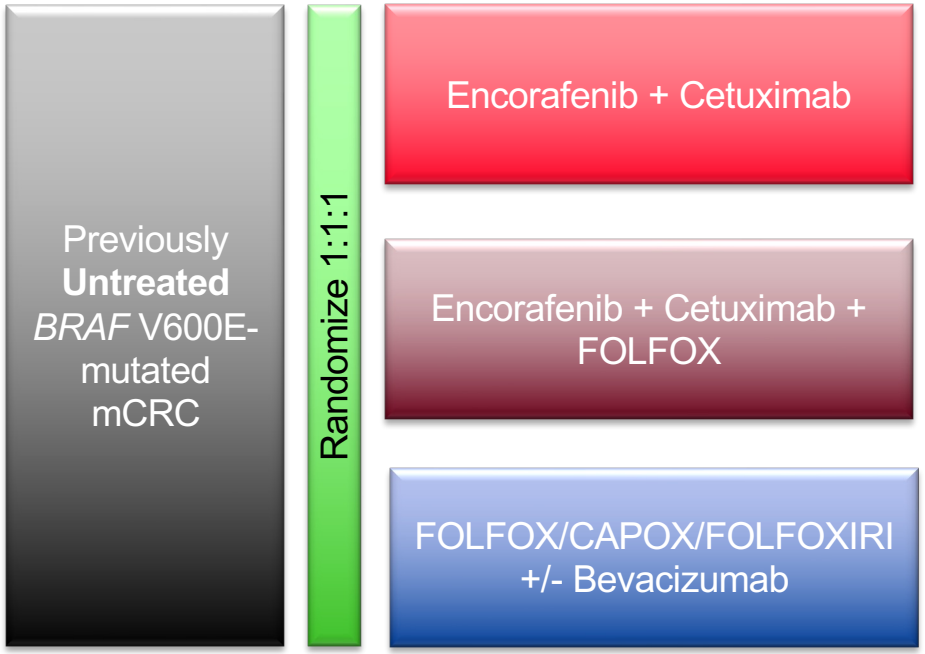
BEACON CRC



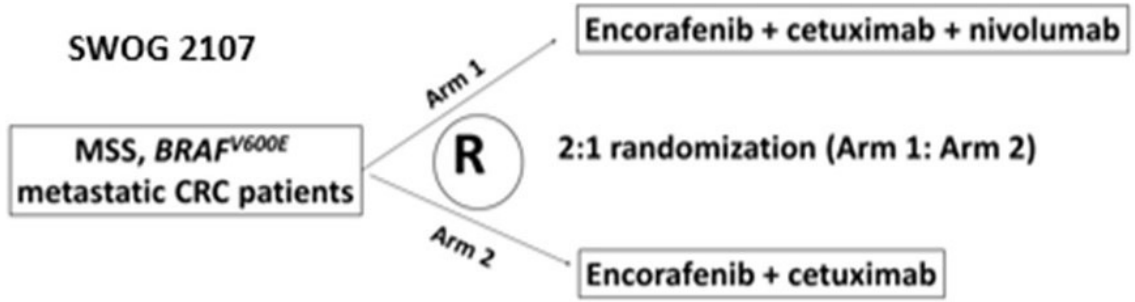
Kopetz et al. *N Engl J Med* 2019.

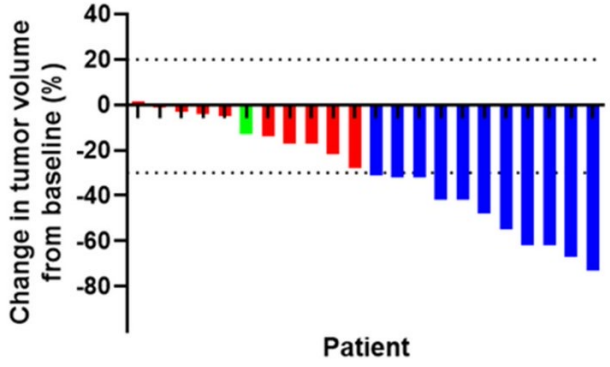
BRAF Beyond BEACON:

BREAKWATER



SWOG 2107





Partial Response
Stable Disease
Progressive Disease

22 evaluable patients:

ORR 50%(95%CI, 28-72)
DCR 96% (95% CI, 77-100)

Van Morris et al. *ASCO GI* 2022.

Third-line Options

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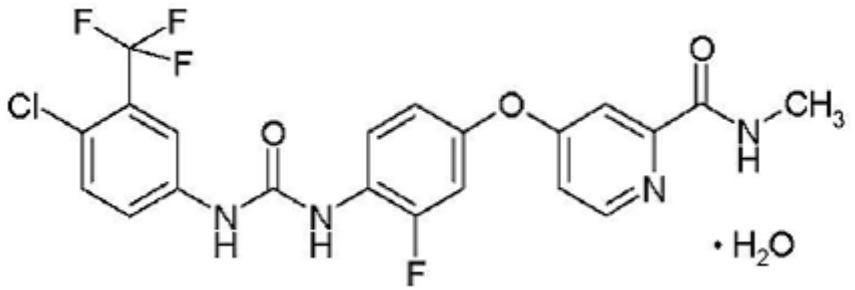
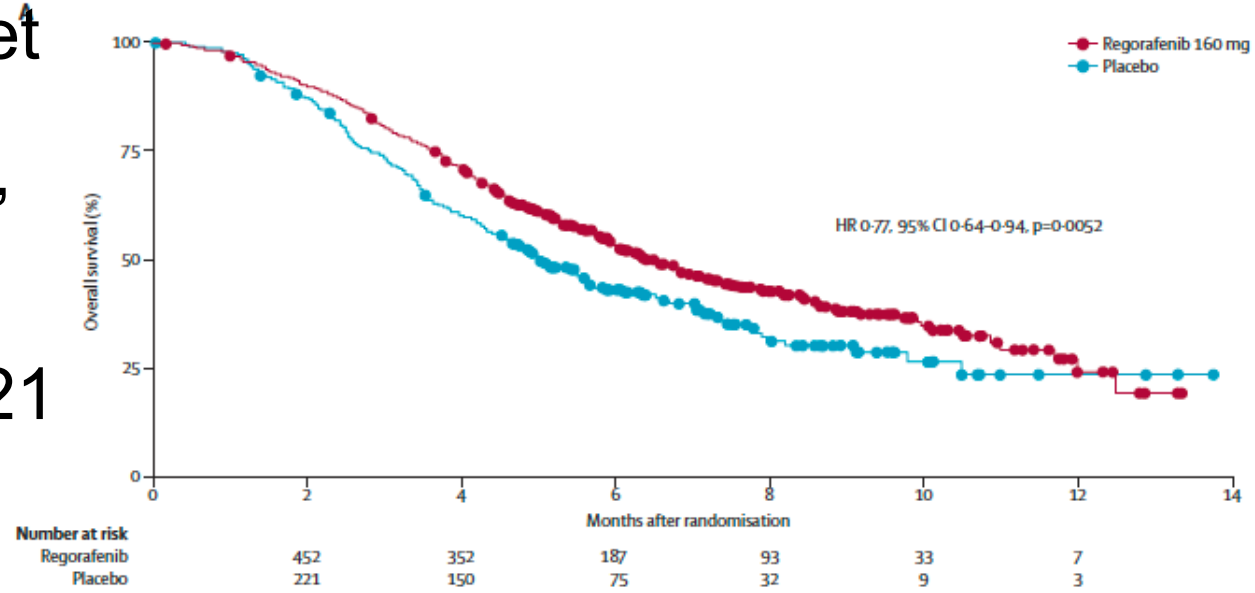
Regorafenib

- Oral poly-TKI



- Active metabolites M-2 and M-5 target KIT, RET, RAF1, BRAF, VEGFR1-3, TIE2, DDR2, Trk2A, Eph2A, PDGFR, FGFR, CSF1R

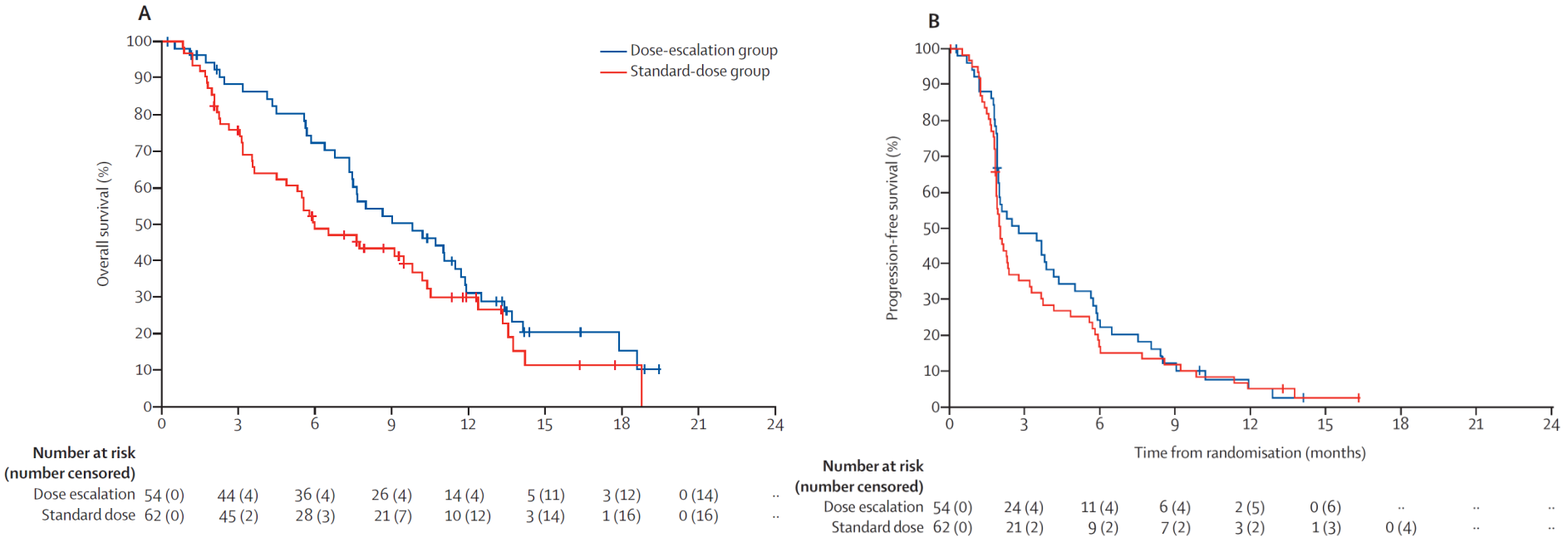
- CORRECT trial (2:1 160 mg days 1-21 vs. placebo)
  - mOS 6.4 vs. 5.0 months (HR 0.77)
  - mPFS 1.9 vs. 1.7 months (HR 0.49)
  - ORR 1% vs. 0.4%



Grothey et al. *Lancet* 2013.

Regorafenib - ReDOS

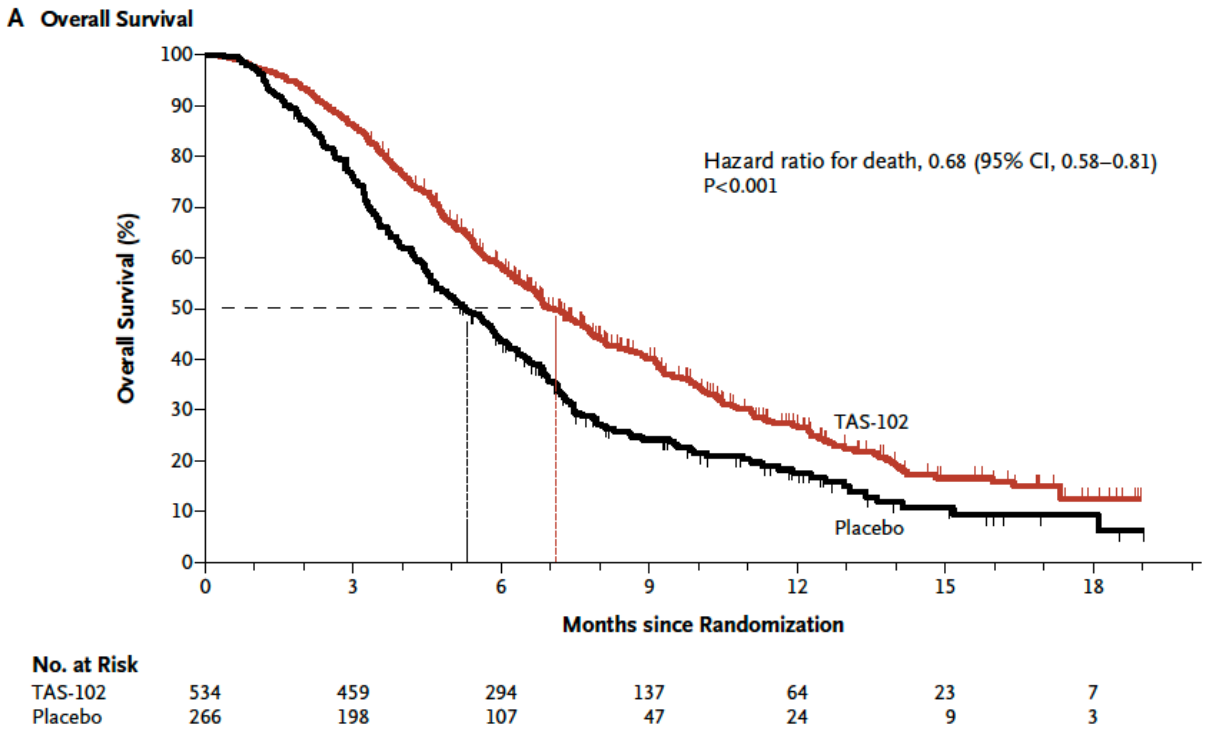
	Cycle 1				Cycle 2
Week	**1**	**2**	**3**	**4**	**1**
Once-daily dose	40 mg 40 mg 80 mg	40 mg 40 mg 40 mg 120 mg	40 mg 40 mg 40 mg 40 mg 160 mg	Dosing-free interval	Last dose from Cycle 1



Bekaii-Saab et al. *Lancet Oncol* 2019.

Trifluridine/Tipiracil

- Oral chemotherapeutic agent
- RECOURSE trial (2:1 35 mg/m2 BID days 1-5 and 8-12 every 28 days vs. placebo)
  - mOS 7.1 vs. 5.3 months (HR 0.68)
  - mPFS 2.0 vs. 1.7 months (HR 0.48)
  - ORR 1.6% vs. 0.4%



Mayer et al. *N Engl J Med* 2015.

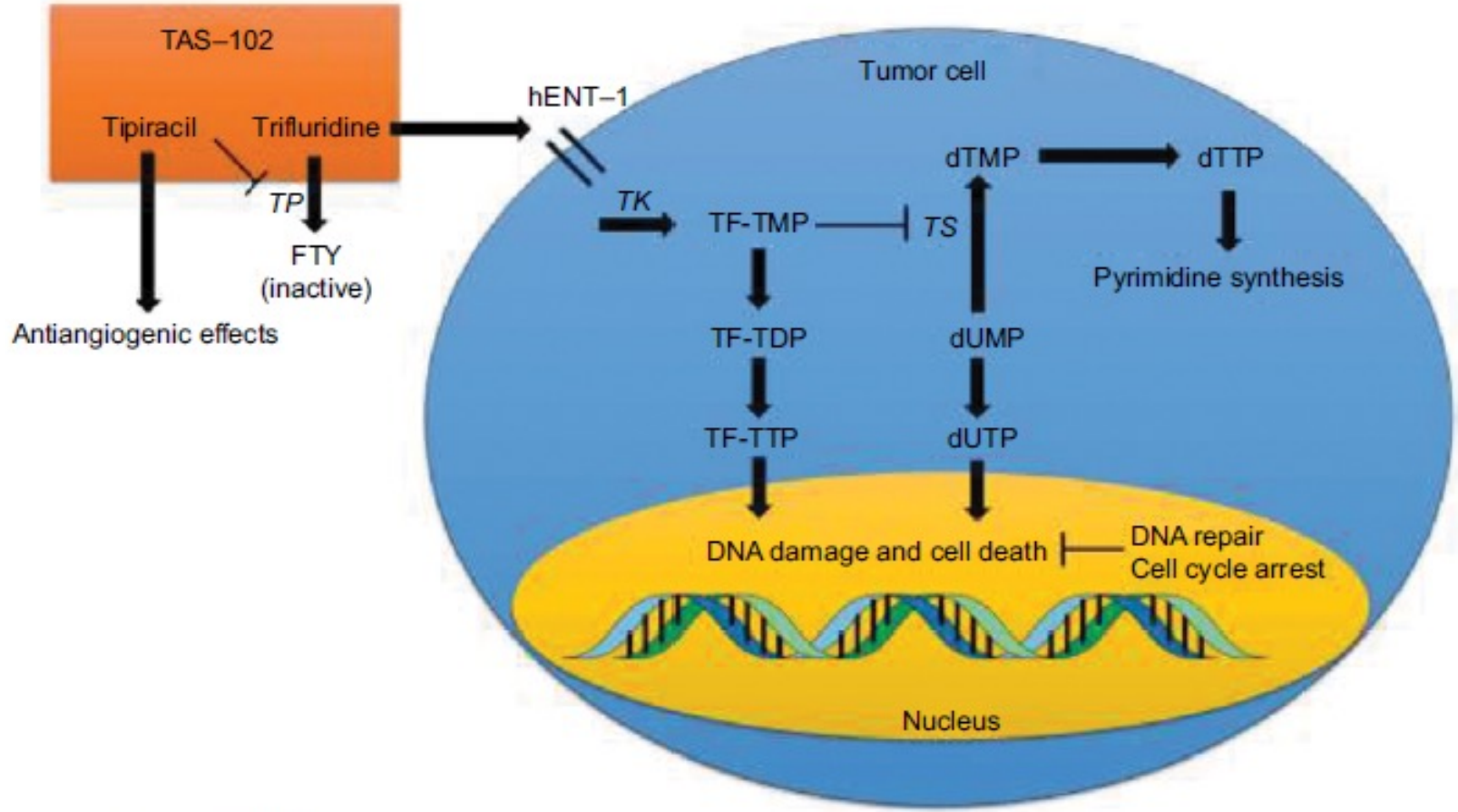


Figure 1 Mechanism of action of TAS-102.
Note: Enzymes are italicized.
Abbreviations: TP, thymidine phosphorylase; FTY, 5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione; hENT, human equilibrative nucleoside transporter; TK, thymidine kinase; TF-TMP, trifluorothymidine monophosphate; TF-TDP, trifluorothymidine diphosphate; TF-TTP, trifluorothymidine triphosphate; TS, thymidylate synthase; dTMP, 2′-deoxythymidine-5′-monophosphate; dTTP, 2′-deoxythymidine-5′-triphosphate; dUMP, 2′-deoxyuridine-5′-monophosphate; dUTP, 2′-deoxyuridine-5′-triphosphate.

Puthiamadathil et al. *Cancer Manag Res* 2016.

Regorafenib vs. Trifluridine/Tipiracil

Table 2. Efficacy of Regorafenib and Trifluridine/Tipiracil

	Regorafenib	Placebo	*P* Value	Trifluridine/Tipiracil	Placebo	*P* Value
mOS	6.4 mo	5.0 mo	.0052	7.1 mo	5.3 mo	<.001
mPFS	1.9 mo	1.7 mo	<.0001	2.0 mo	1.7 mo	<.001
DCR	41%	15%	<.0001	44%	16%	<.001

DCR, disease control rate; mo, months; mOS, median overall survival; mPFS, median progression-free survival.

Data from Mayer RJ et al. *N Engl J Med.* 2015;372(20):1909-1919[41] and Grothey A et al. *Lancet.* 2013;381(9863):303-312.[54]

Weinberg et al. *Clin Adv Hematol Oncol* 2016.

Regorafenib vs. Trifluridine/Tipiracil

Table 1. Adverse Events Reported in the RECOURSE and CORRECT Trials

Adverse Events[a]	All Grades, Regorafenib, %	Grade 3/4, Regorafenib, %	All Grades, Trifluridine/ Tipiracil, %	Grade 3/4, Trifluridine/ Tipiracil, %
Any event	100	78	98	69
Hand-foot skin reaction	47	17	2	0
Rash	29	6	NR	NR
Fatigue	63	15	35	4
Hypertension	30	8	NR	NR
Diarrhea	43	8	32	3
Nausea	22	<1	48	2
Vomiting	8	1	28	2
Anorexia	47	5	NR	NR
Abdominal pain	24	5	21	2
Stomatitis	29	3	8	<1
Voice changes	32	0	NR	NR
Fever	28	2	19	1
Febrile neutropenia	NR	NR	4	4
Neutropenia	NR	NR	67	38
Leukopenia	NR	NR	77	21
Anemia	14	6	77	18
Thrombocytopenia	16	4	42	5
ALT increase	45	5	24	2
AST increase	65	6	30	4
TB increase	45	12	36	9
ALP increase	NR	NR	39	8

[a]Adverse events occurring in at least 5% of patients treated with regorafenib and at least 10% of patients treated with trifluridine/tipiracil.

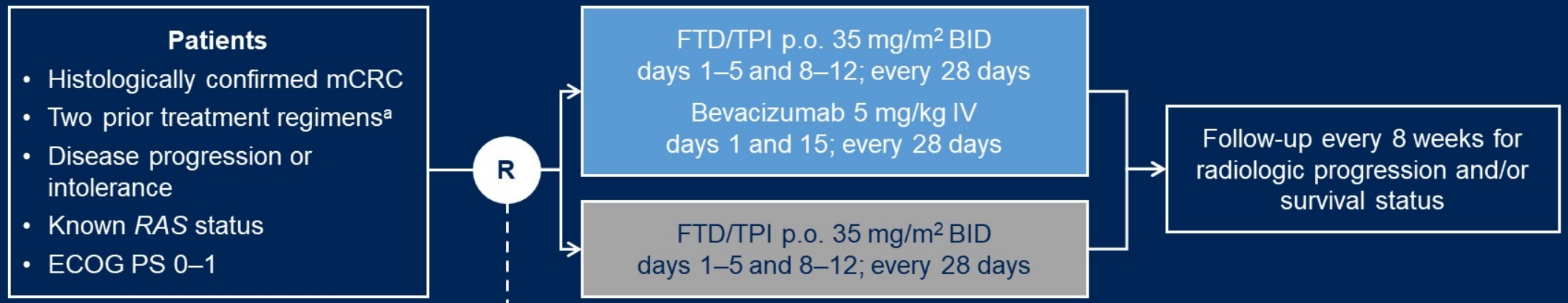
ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CORRECT, Regorafenib Monotherapy for Previously Treated Metastatic Colorectal Cancer; NR, not recorded; RECOURSE, Study of TAS-102 in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies; TB, total bilirubin.

Data from Mayer RJ et al. *N Engl J Med.* 2015;372(20):1909-1919[41,54] and Grothey A et al. *Lancet.* 2013;381(9863):303-312.[41,54]

Weinberg et al. *Clin Adv Hematol Oncol* 2016.

SUNLIGHT study design

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



Primary endpoint: OS in full analysis set

Secondary endpoints:
- PFS
- DCR
- ORR
- Safety profile
- QoL

Statistical considerations:
- Sample size: 490 (245 per arm)
- Expected OS HR: 0.70 (30% reduction in risk of death) with 90% power
- Required OS events: 331
- No planned interim analysis

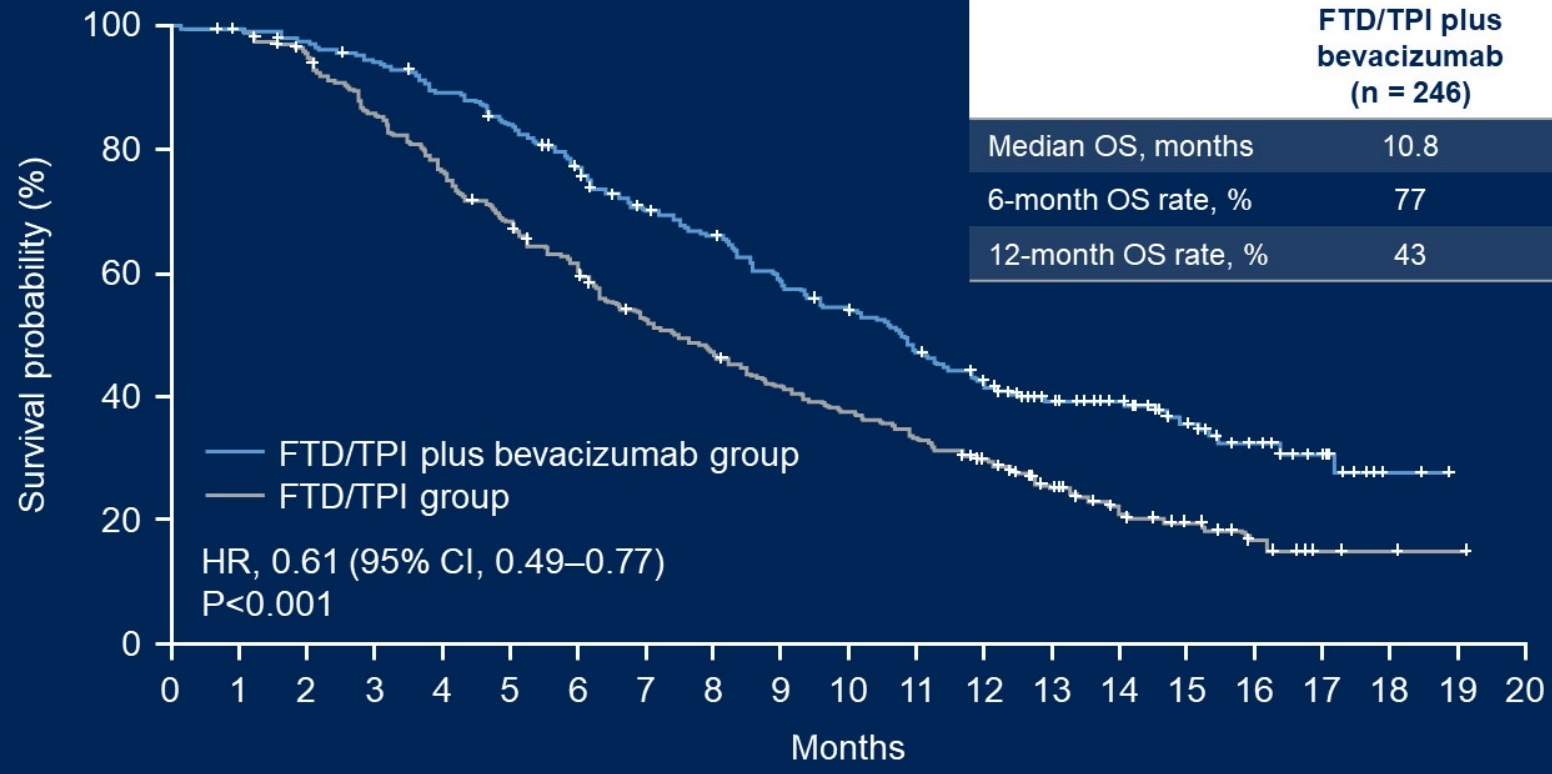
[a] Prior treatment must have included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (not necessarily bevacizumab), and/or an anti-EGFR monoclonal antibody for patients with *RAS* wild-type and could have included (neo)adjuvant chemotherapy if disease had recurred during treatment or within 6 months of the last administration of (neo)adjuvant therapy. BID, twice daily; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EFGR, epidermal growth factor receptor; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; IV, intravenous; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; p.o., orally; QoL, quality of life; R, randomization; VEGF, vascular endothelial growth factor.

Key baseline characteristics

Characteristic		FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Age	Median (range), years	62 (20–84)	64 (24–90)
	<65 years, n (%)	146 (59)	129 (52)
	≥65 years, n (%)	100 (41)	117 (48)
Sex, n (%)	Male	122 (50)	134 (55)
Region	European Union	158 (64)	157 (64)
	North America	8 (3)	8 (3)
	Rest of the world	80 (33)	81 (33)
Primary tumor localization, n (%)	Right	62 (25)	77 (31)
	Left	184 (75)	169 (69)
Time from diagnosis of first metastasis to randomization,[a] n (%)	<18 months	104 (42)	105 (43)
	≥18 months	142 (58)	141 (57)
***RAS* status,[a] n (%)**	Mutant	171 (70)	170 (69)
	Wild-type	75 (31)	76 (31)
Prior treatment with anti-VEGF, n (%)	Yes	188 (76)	188 (76)
Prior treatment with bevacizumab, n (%)	No	68 (28)	69 (28)
	Yes	178 (72)	177 (72)
ECOG PS, n (%)	0	119 (48)	106 (43)
	1	127 (52)	139 (57)
	2	0	1 (0.4)[b]

[a] As documented in the Interactive Web Response System set for randomization. [b] Patient had an ECOG PS of 1 at randomization but was assessed as having an ECOG PS of 2 on day 1, cycle 1.
ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; VEGF, vascular endothelial growth factor.

OS in full analysis set (primary endpoint)



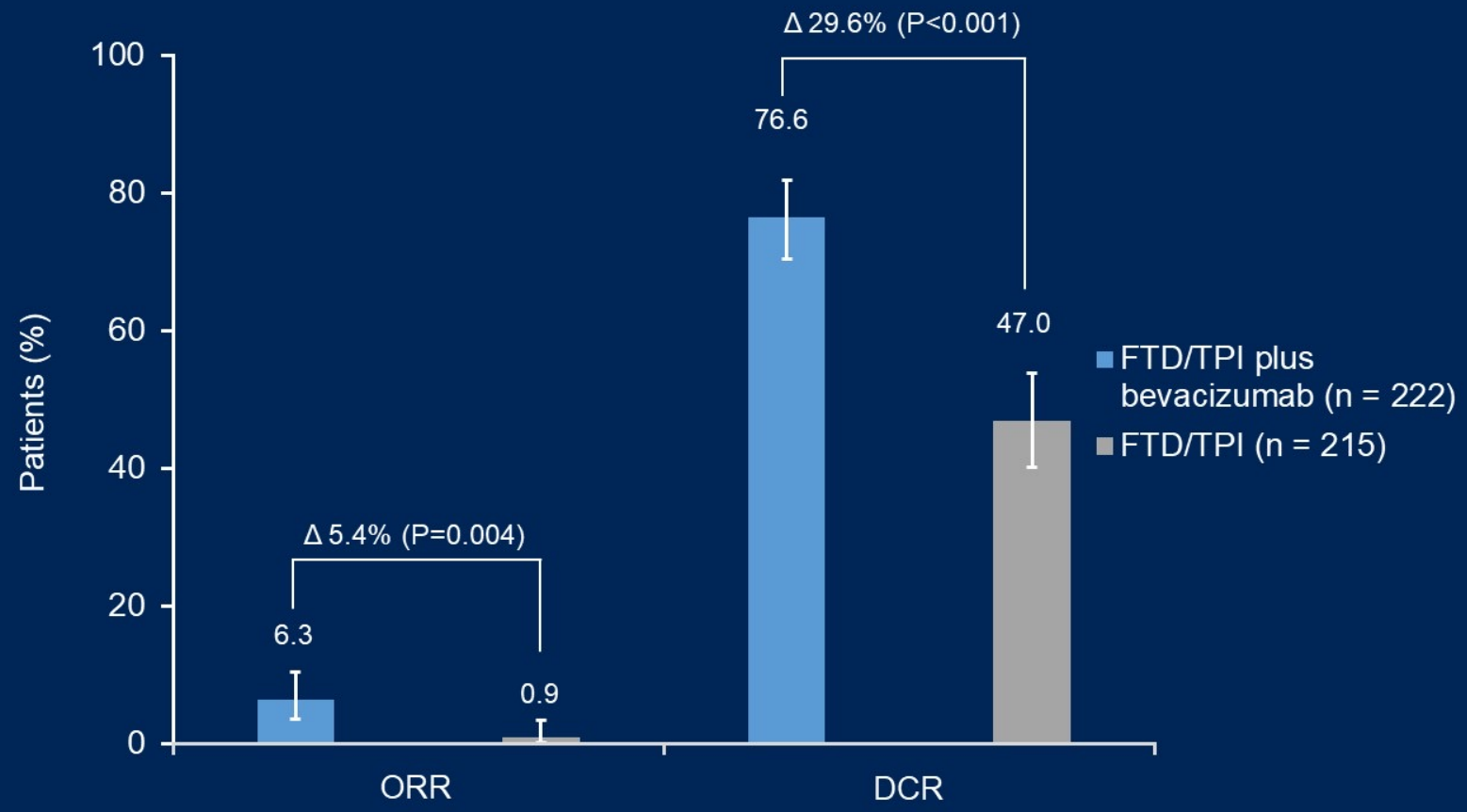
	FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Median OS, months	10.8	7.5
6-month OS rate, %	77	61
12-month OS rate, %	43	30

No. at risk

FTD/TPI plus bevacizumab group	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
FTD/TPI group	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; OS, overall survival.

ORR and DCR in patients evaluable for tumor response



DCR, disease control rate; FTD/TPI, trifluridine/tipiracil; ORR, objective response rate.

TEAEs in ≥20% of patients

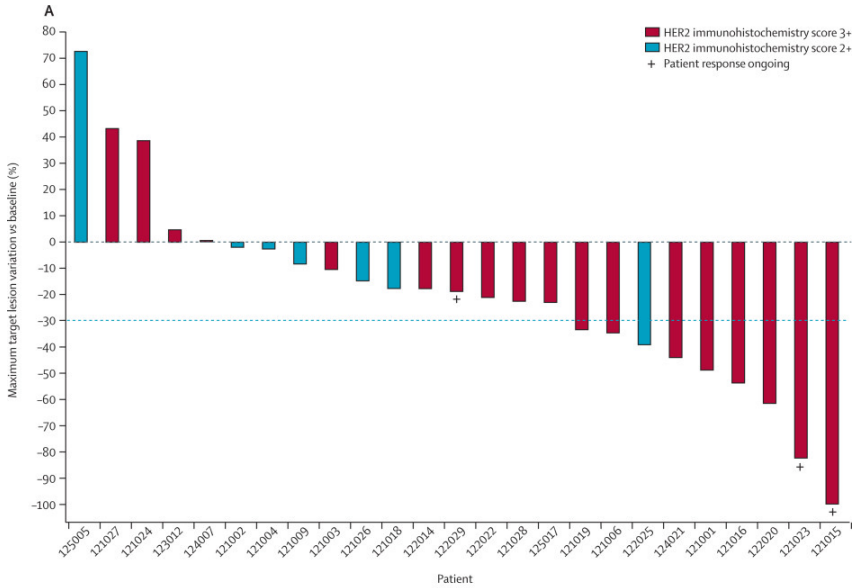
	FTD/TPI plus bevacizumab (n = 246)		FTD/TPI (n = 246)	
TEAE, n (%)	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	153 (62)	106 (43)	126 (51)	79 (32)
Nausea	91 (37)	4 (2)	67 (27)	4 (2)
Anemia	71 (29)	15 (6)	78 (32)	27 (11)
Asthenia	60 (24)	10 (4)	55 (22)	10 (4)
Fatigue	53 (22)	3 (1)	40 (16)	9 (4)
Diarrhea	51 (21)	2 (1)	46 (19)	6 (2)
Decreased appetite	50 (20)	2 (1)	38 (15)	3 (1)

Hypertension (10% vs 2%), nausea, and neutropenia were more common in the combination group; there was one case of febrile neutropenia with FTD/TPI plus bevacizumab versus six with FTD/TPI

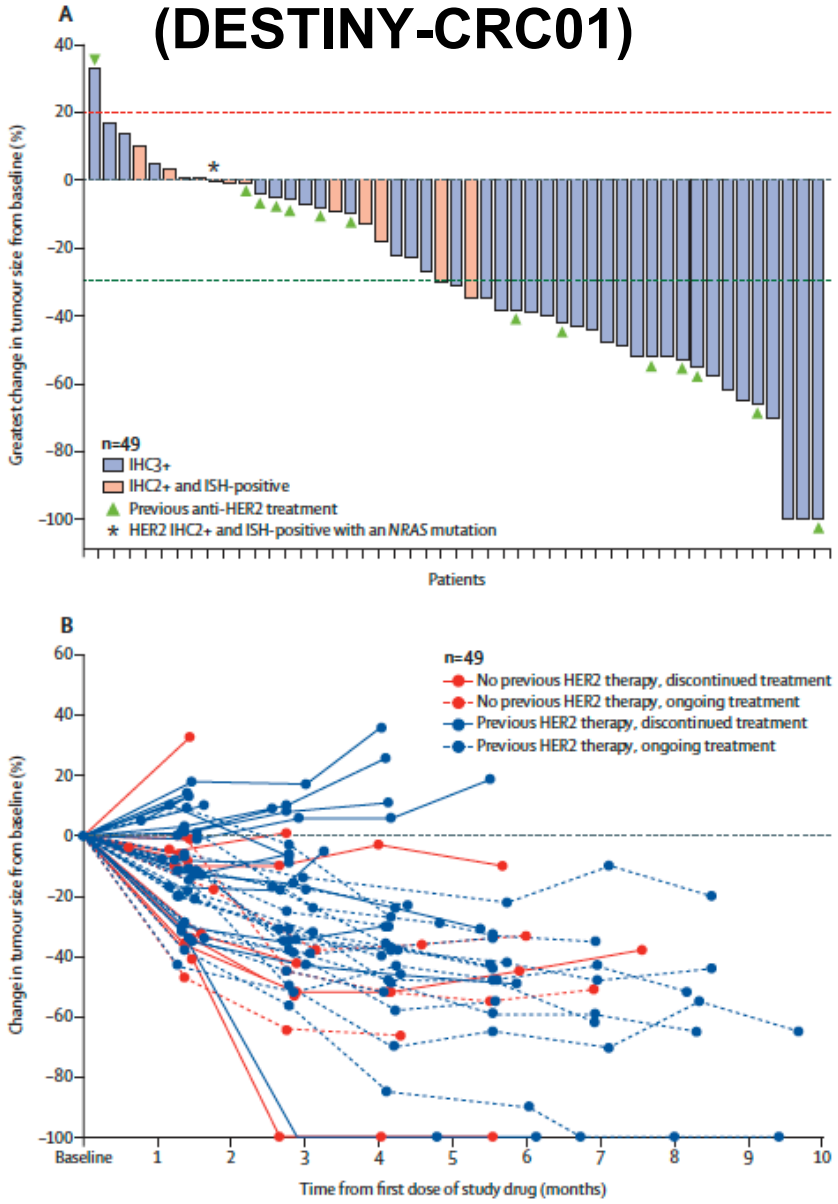
FTD/TPI, trifluridine/tipiracil; TEAE, treatment-emergent adverse event.

HER2

Trastuzumab + Lapatinib (HERACLES)



Trastuzumab Deruxtecan (DESTINY-CRC01)



Sartore-Bianchi et al. *Lancet Oncol* 2016.
Siena et al. *Lancet Oncol* 2021.

Immunotherapy

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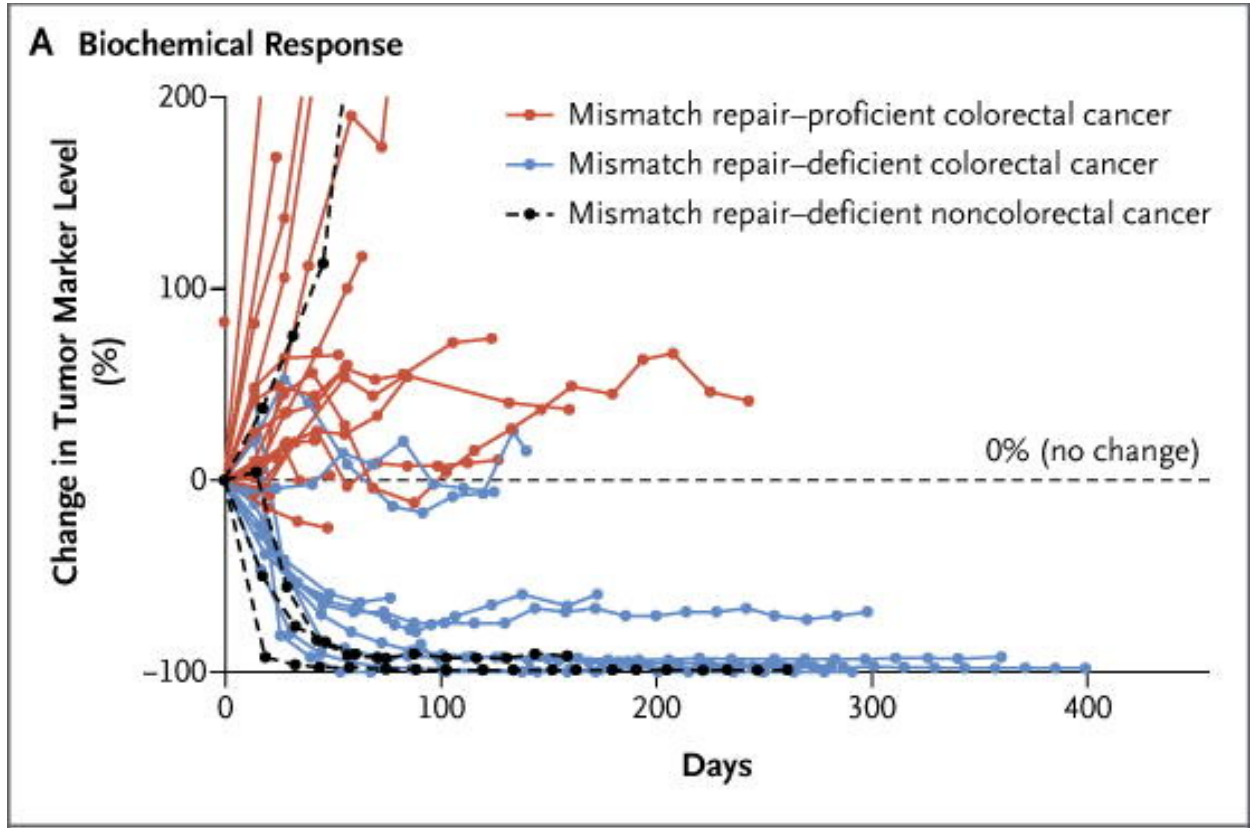
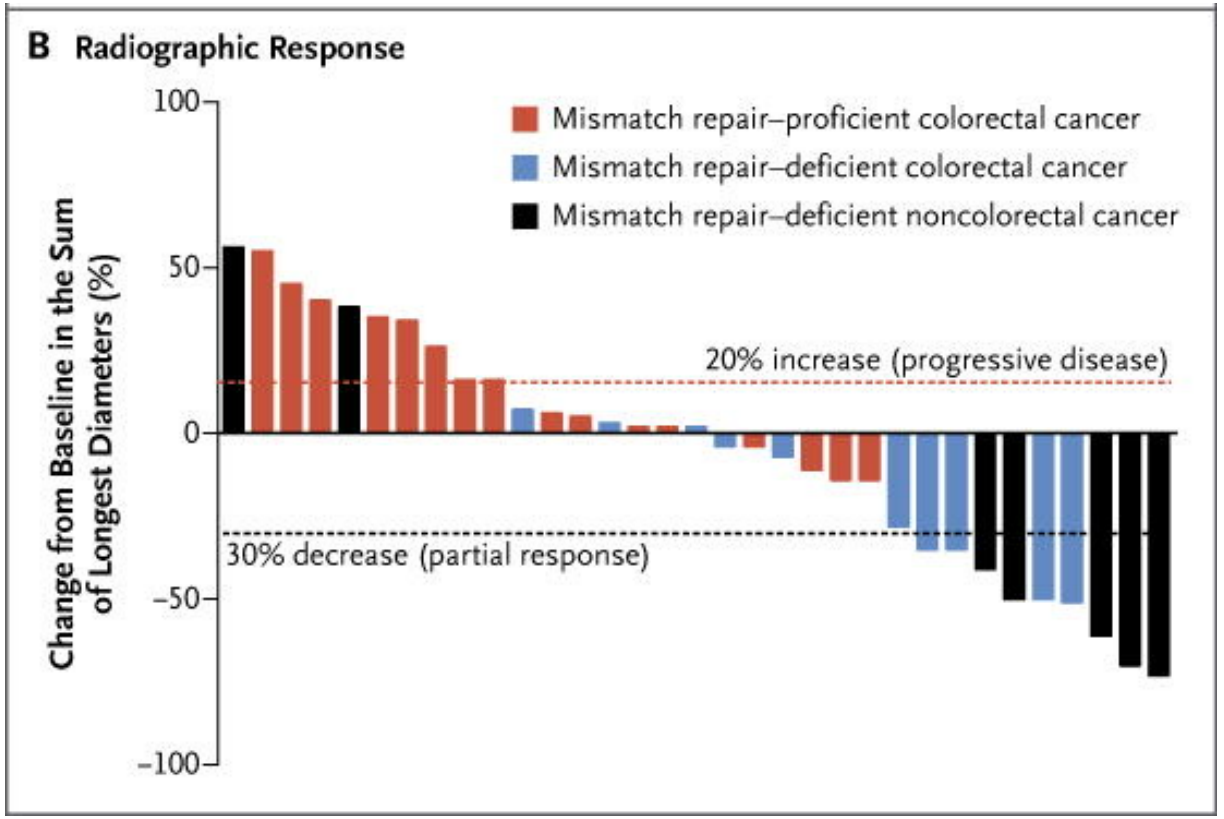
Response to Pembrolizumab Limited to MSI-H Tumors

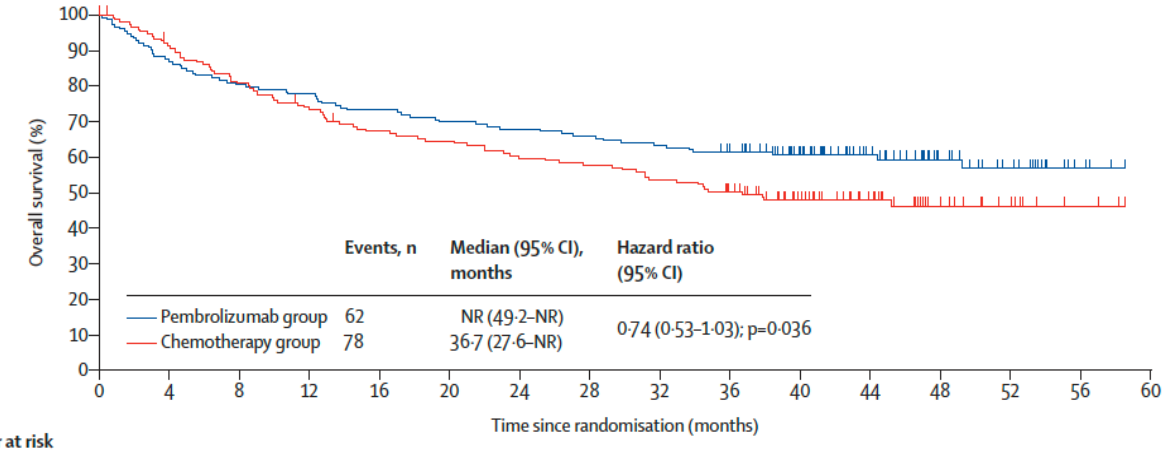




Le et al. *N Engl J Med* 2015.

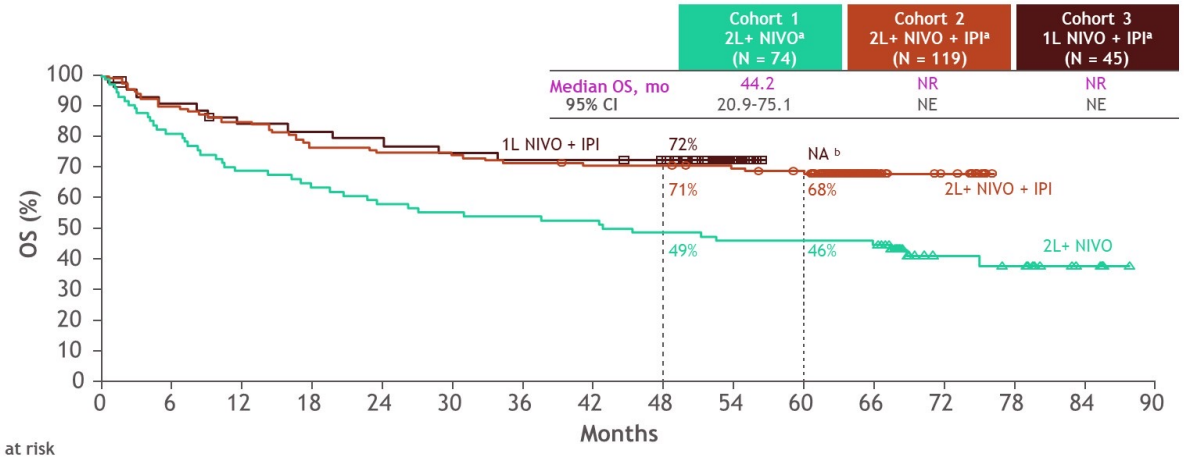
Microsatellite Instability (MSI-H) in mCRC

KEYNOTE-177: Pembrolizumab vs. FOLFOX/FOLFIRI



Number at risk (number censored)																
Pembrolizumab group	153 (0)	134 (0)	123 (0)	119 (0)	112 (0)	107 (0)	104 (0)	101 (0)	97 (2)	92 (23)	70 (45)	48 (64)	28 (75)	16 (78)	4 (91)	0 (91)
Chemotherapy group	154 (4)	137 (4)	121 (5)	110 (6)	99 (6)	95 (6)	88 (6)	85 (6)	79 (9)	71 (24)	53 (41)	36 (58)	18 (65)	11 (73)	3 (76)	0 (76)

CheckMate 142: Nivolumab 3 + Ipilimumab 1



No. at risk																
Cohort 1	74	60	51	48	43	41	40	39	36	34	34	34	13	11	4	0
Cohort 2	119	107	101	92	89	89	85	83	83	80	76	23	14	0	0	0
Cohort 3	45	40	36	35	34	32	31	31	29	11	0	0	0	0	0	0

Diaz Jr. et al. *Lancet Oncol* 2022.
Overman et al. ASCO Annual Meeting 2022.

A Phase Ib Study of Safety and Clinical Activity of Atezolizumab and Cobimetinib in Patients With Metastatic Colorectal Cancer

Johanna Bendell,[1] Yung-Jue Bang,[2] Cheng Ean Chee,[3] David P. Ryan,[4] Autumn J. McRee,[5] Laura Q. Chow,[6] Jayesh Desai,[7] Matthew Wongchenko,[8] Yibing Yan,[8] Bethany Pitcher,[8] Paul Foster,[8] Edward Cha,[8] William Grossman,[8] Tae Won Kim[9]

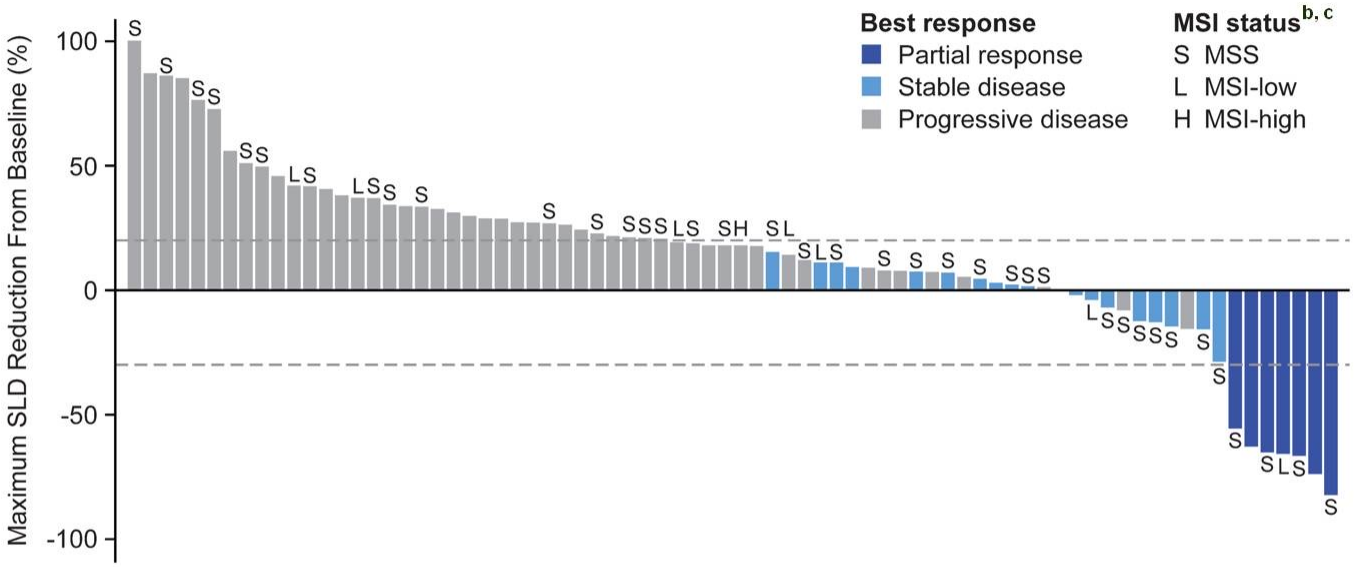
[1]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [2]Seoul National University Hospital, Seoul, South Korea; [3]National University Cancer Institute, National University Health System, Singapore; [4]Massachusetts General Hospital, Boston, MA; [5]UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; [6]University of Washington, Seattle, WA; [7]Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia; [8]Genentech, Inc., South San Francisco, CA; [9]Asan Medical Center, University of Ulsan, Seoul, South Korea

PRESENTED AT: 2018 Gastrointestinal Cancers Symposium | #GI18

Presented By Johanna Bendell at 2018 Gastrointestinal Cancers Symposium

Best Overall Response

BOR (n = 84)[a]	n (%)
ORR	7 (8%)
CR	0
PR	7 (8%)
SD	19 (23%)
DCR	26 (31%)
PD	51 (61%)



- 7 patients (8% [95% CI: 3, 16]) experienced PR (confirmed per RECIST v1.1)
  - 4 patients had MSS and 1 patient had MSI-low mCRC; the remaining 2 had unknown MSI status[b]
- The DCR was 31% (DCR defined as PR + SD ≥ 6 weeks)

BOR, best overall response; DCR, disease control rate; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SLD, sum of longest diameters.
Data cutoff: September 4, 2017. Cobimetinib dose and schedule varied based on cohort and phase of the study.
[a] 7 patients (8%) had missing or unevaluable BOR. [b] Based on combined local or centralized testing results. [c] Unlabeled bars represent patients with unknown MSI status.

Presented By Johanna Bendell at 2018 Gastrointestinal Cancers Symposium

Best Overall Response

BOR (n = 84)[a]	n (%)
ORR	
CR	
PR	
SD	
DCR	26 (31%)
PD	51 (61%)

Negative Phase III Trial

- 7 patients (8% [95% CI: 3, 16]) experienced PR (confirmed per RECIST v1.1)
  - 4 patients had MSS and 1 patient had MSI-low mCRC; the remaining 2 had unknown MSI status[b]
- The DCR was 31% (DCR defined as PR + SD ≥ 6 weeks)

BOR, best overall response; DCR, disease control rate; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SLD, sum of longest diameters.
Data cutoff: September 4, 2017. Cobimetinib dose and schedule varied based on cohort and phase of the study.
[a] 7 patients (8%) had missing or unevaluable BOR. [b] Based on combined local or centralized testing results. [c] Unlabeled bars represent patients with unknown MSI status.

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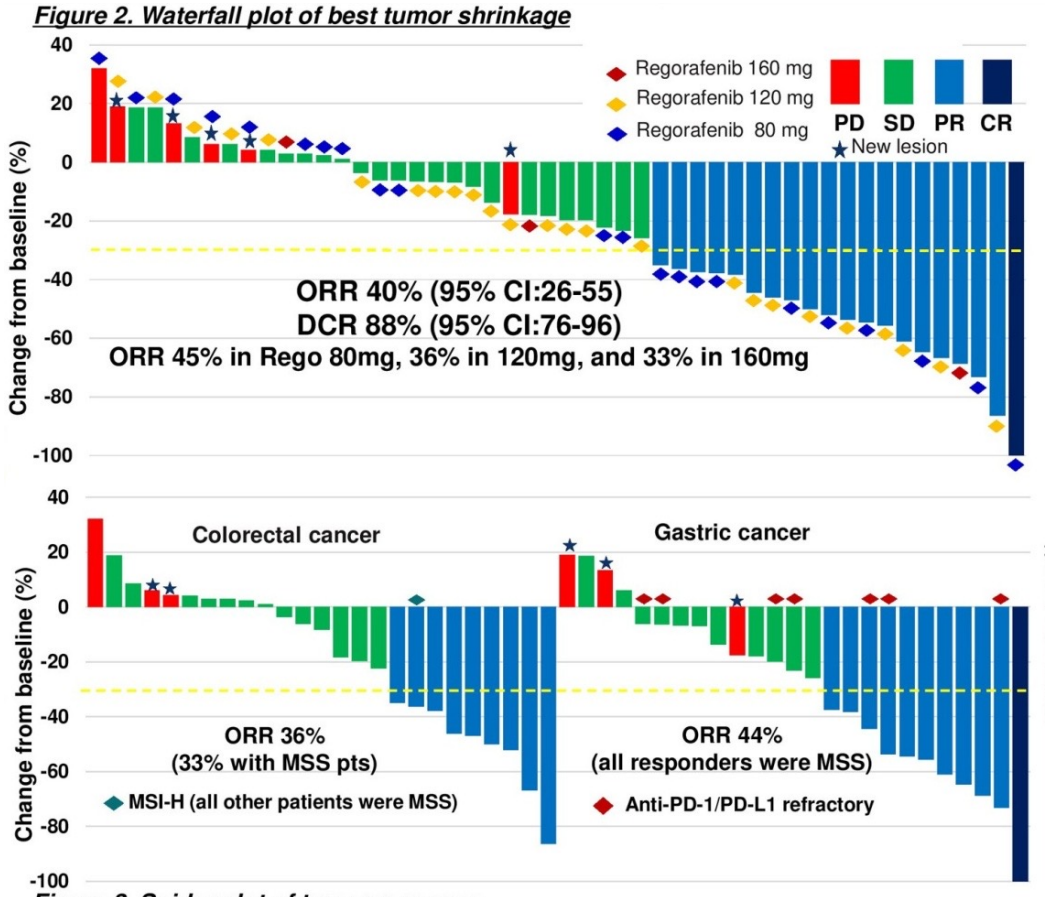
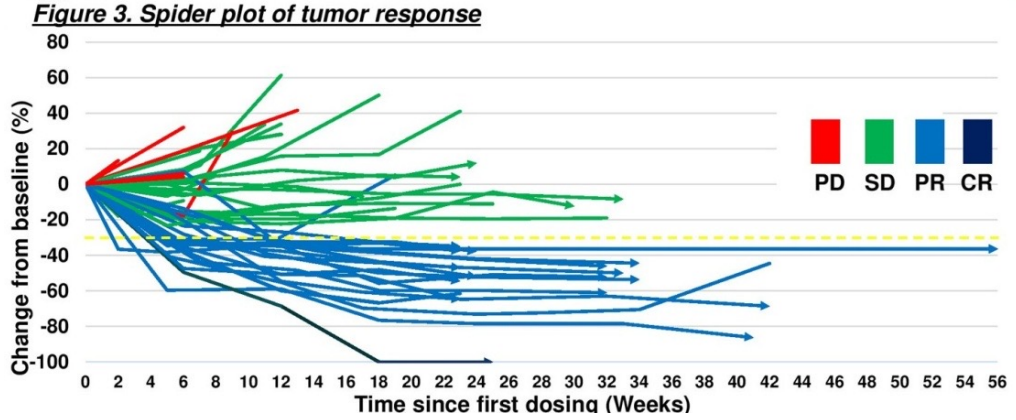
Regorafenib + Nivolumab?





Fukuoka et al. ASCO Annual Meeting 2019.

C-800 Study Design: MSS CRC Cohort

NCT03860272: First-in-human trial of botensilimab ± balstilimab in patients with advanced cancer[1]

Key Eligibility for CRC

- Refractory Metastatic CRC
- MSS by local assessment
- Prior IO allowed
- Tbili ≤ 1.5 x IULN
- AST/ALT ≤ 2.5 x IULN

Evaluable Population

Treated with 1 or 2 mg/kg bot + bal as of 29 August 2022 with ≥1 Q6W imaging assessment

BOT + **BAL**

Fc-enhanced CTLA-4
1 or 2 mg/kg Q6W

PD-1
3 mg/kg Q2W

Combination therapy

1. https://clinicaltrials.gov/ct2/show/NCT03860272.

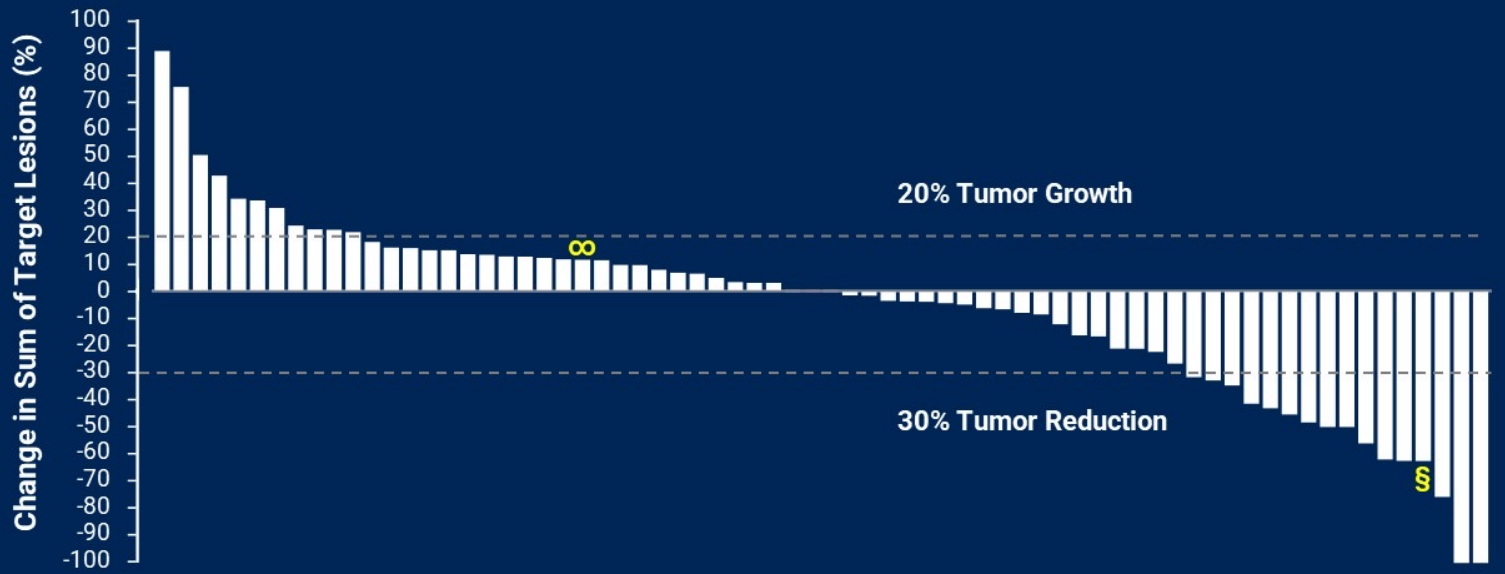
Patient Characteristics

Characteristic	Overall (N=70)*
Age, median (range)	57 (25-83)
Sex, n (%)	
Female	40 (57)
Male	30 (43)
ECOG PS at baseline, n (%)	
0	28 (40)
1	42 (60)
Prior lines of therapy, n (%)	
Median (range)	4 (1-10)

Characteristic	Overall (N=70)
Prior immunotherapy, n (%)	22 (31)
Botensilimab dose, n (%)	
1 mg/kg Q6W + bal (PD-1) Q2W	17 (24)
2 mg/kg Q6W + bal (PD-1) Q2W	53 (76)
TMB>10, n/N (%)	1/57 (2)
RAS mutation, n/N (%)	41/70 (59)
BRAF mutation, n/N (%)	2/65 (3)

* 12 patients treated as of 29 AUG 2022 who did not have a post-baseline scan at least 39 days after the first dose were excluded, 3 of these withdrew consent. Data cutoff date 15 Dec 2022.

Deep Objective Responses



Efficacy	N=70
ORR*, % (95% CI)	23 (14-34)
BOR, n (%)	
CR	1 (1)
PR	15 (21)
SD	37 (53)
DCR (CR + PR + SD), % (95% CI)	76 (64-85)
Median, OS (95% CI)	NR (10.3-NR)
Median PFS, months (95% CI)	4.1 (2.8-5.5)
Median F/U, months (Min, Max)	7 (2, 31)

*Includes unconfirmed responses. ∞ Resected target lesions showed complete pathologic response. § Response by iRECIST.

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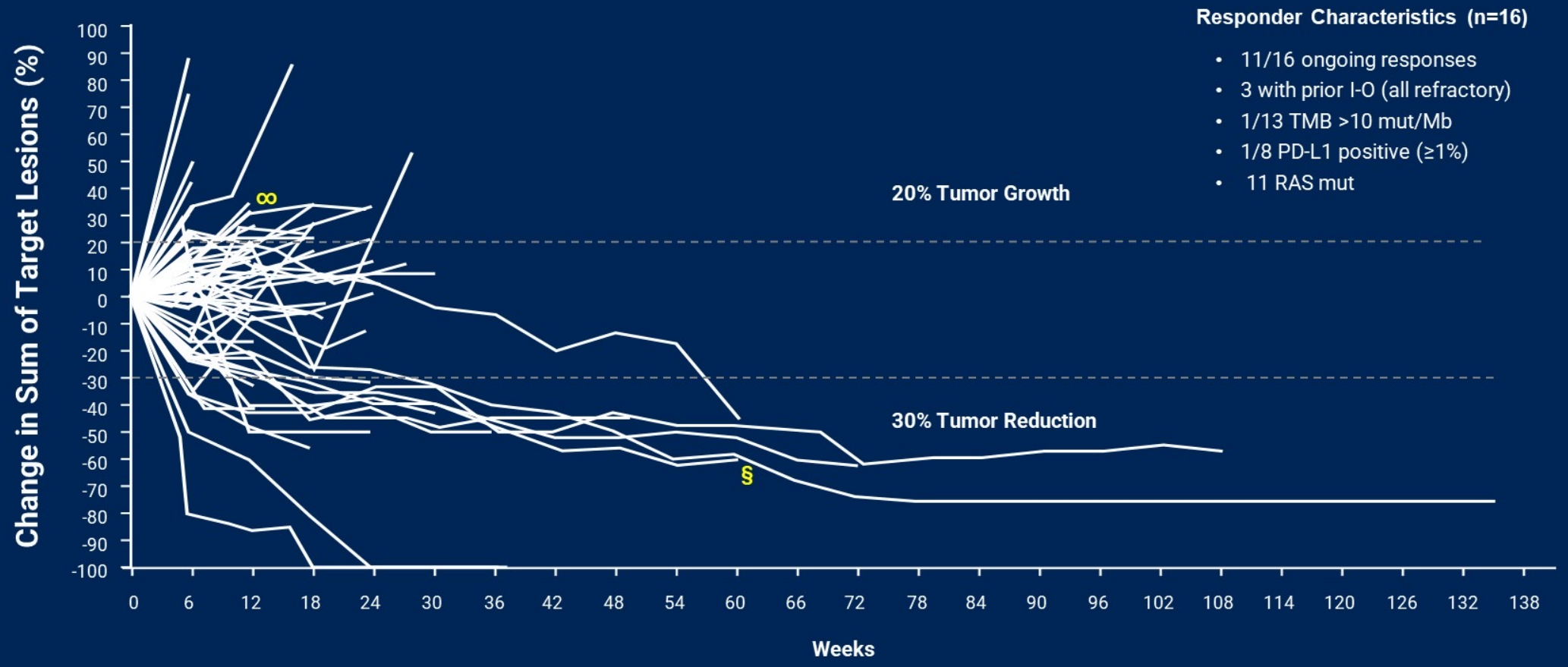
Durable Objective Responses



Responder Characteristics (n=16)

- 11/16 ongoing responses
- 3 with prior I-O (all refractory)
- 1/13 TMB >10 mut/Mb
- 1/8 PD-L1 positive (≥1%)
- 11 RAS mut

*Includes unconfirmed responses. ∞ Resected target lesions showed complete pathologic response. § Response by iRECIST.

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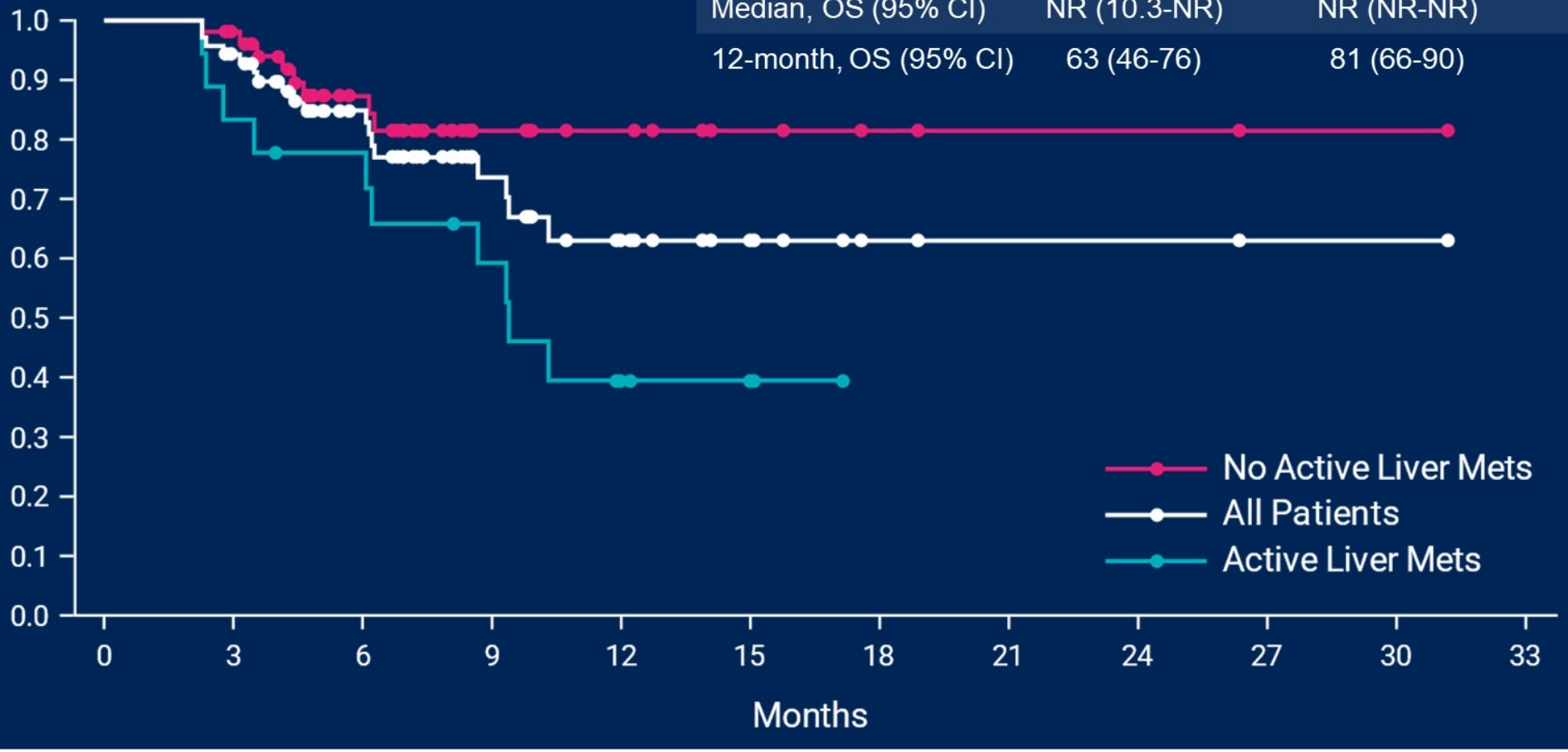
Overall Survival

Efficacy evaluable population, N=70

	Overall	No Active Liver Mets	Active Liver Mets
Median, OS (95% CI)	NR (10.3-NR)	NR (NR-NR)	9.4 (6.1-NR)
12-month, OS (95% CI)	63 (46-76)	81 (66-90)	40 (17-62)



Safety Profile

All TRAEs of Any Grade in ≥15% of All Patients

n (%)	ALL GRADE	GRADE 3	GRADE 4
ANY TRAE	64 (91)	28 (40)	2 (3)
GASTROINTESTINAL			
IM diarrhea/colitis*	30 (43)	14 (20)	1 (1)
Nausea	16 (23)	1 (1)	0
CONSTITUTIONAL			
Fatigue	24 (34)	3 (4)	0
Decreased appetite	19 (27)	0	0
Chills	15 (21)	0	0
Pyrexia	16 (23)	3 (4)	0

n (%)	ALL GRADE	GRADE 3	GRADE 4
SKIN			
Rash	19 (27)	0	0
Pruritus	12 (17)	0	0
ENDOCRINE			
Hypo/hyperthyroidism	11 (16)	0	0

* Immune-mediated (IM) diarrhea/colitis is defined as patients who received steroids or infliximab.

The Current Treatment Paradigm (mCRC)

1st line

FOLFOX/CAPOX

FOLFIRI/*CAPIRI*

FOLFIRINOX

+

Bevacizumab

<u>Cetuximab/panitumumab (if *RAS*/*BRAF* WT, left-sided)</u>

OR pembrolizumab or nivolumab ± ipilimumab (if MSI-H)

2nd line

FOLFOX/CAPOX

FOLFIRI/IRI/*CAPIRI*

Bevacizumab/ramucirumab/ziv-aflibercept

+

Cetuximab/panitumumab
(if *RAS*/*BRAF* WT)

OR encorafenib + cetuximab/panitumumab (if *BRAF* V600E mutated)

3rd line

Regorafenib
Trifluridine/tipiracil ± bevacizumab

Larotrectinib/entrectinib (if *NTRK* fusion)

If HER2+ and *RAS*/*BRAF* WT:
Trastuzumab/pertuzumab
Trastuzumab/lapatinib
Trastuzumab deruxtecan