Immunotherapy and Targeted therapy in Colon Cancer

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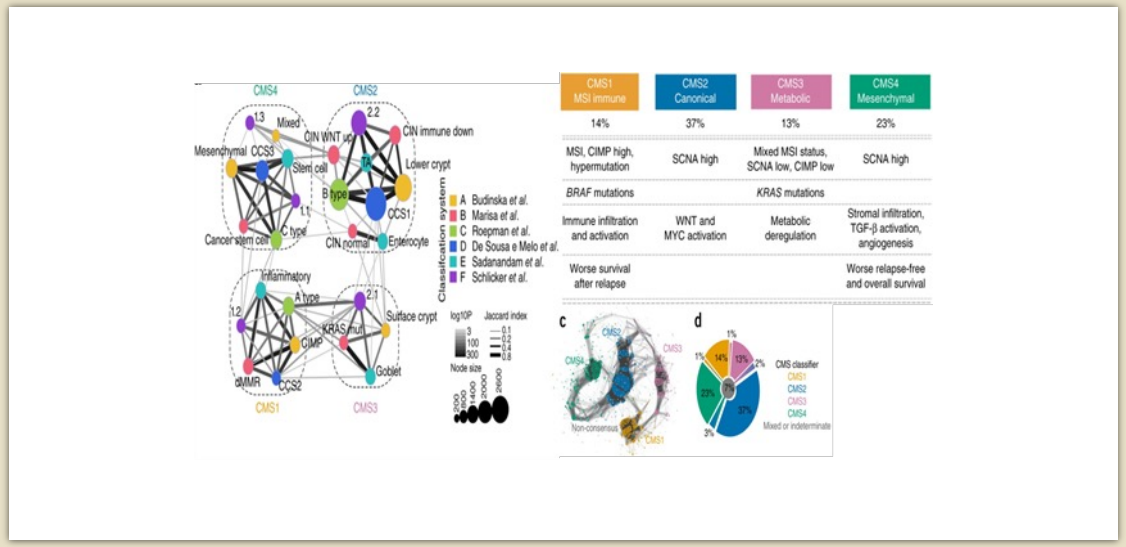
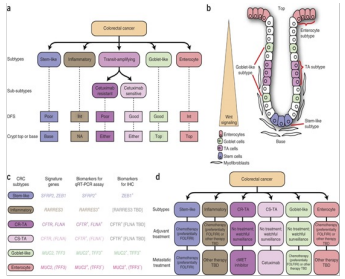
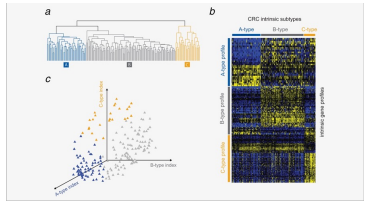
CRC classifications

- Guinney J. et al : **The consensus molecular subtypes of colorectal cancer**





Sadanandam, A. et al.



Roepman, P. et al: Single sample predictor for molecular subtype classification

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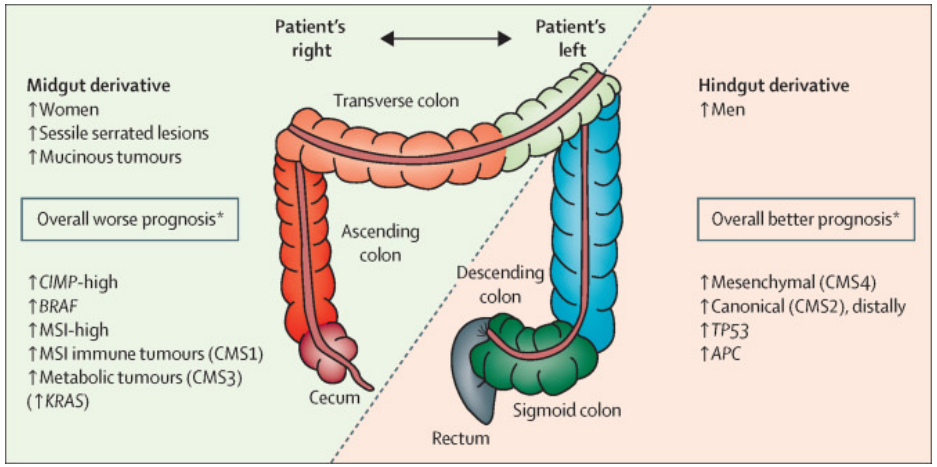
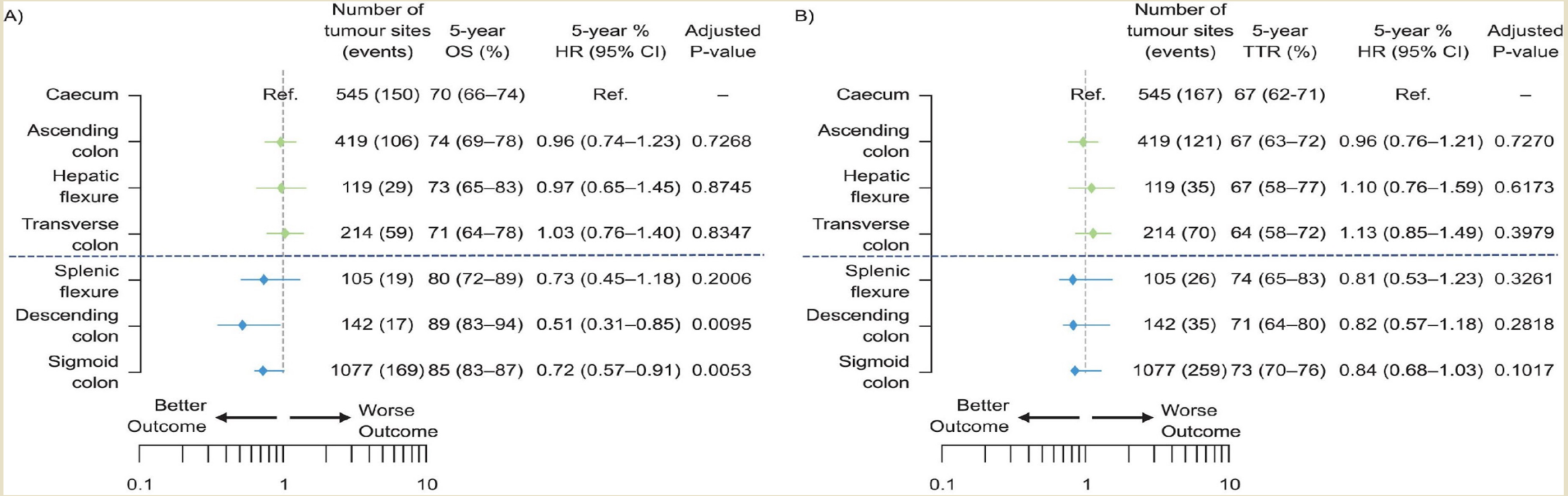


Sidedness in Colon Cancer

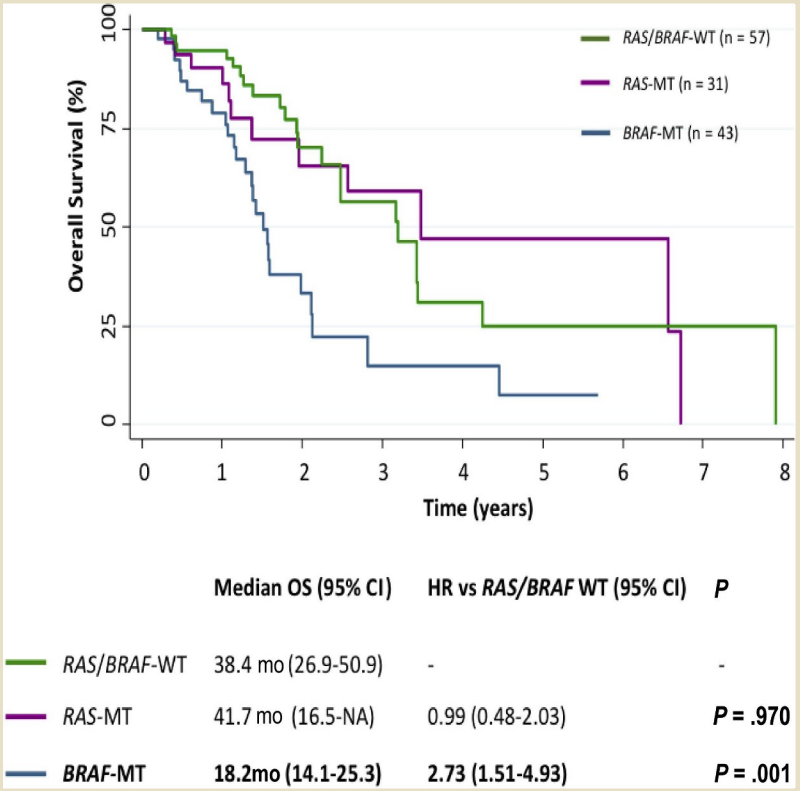
- Dekker et al, *Lancet* 2019

Clinical outcomes of patients with stage III CRC according to tumor localization

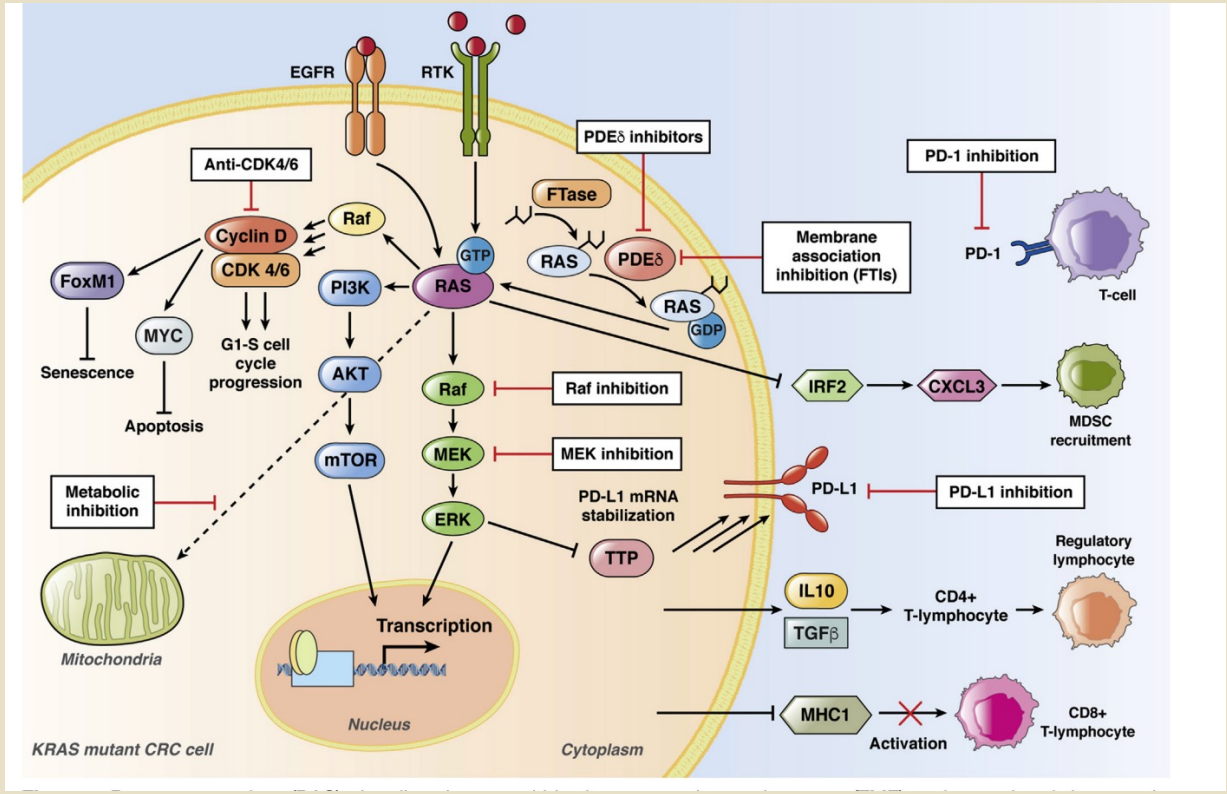


European Journal of Cancer 2017 84, 69-80 doi: (10.1016/j.ejca.2017.07.016)

Survival Based on RAS-RAF Mutations in advanced stage CRC



	Median OS (95% CI)	HR vs *RAS/BRAF* WT (95% CI)	*P*
RAS/BRAF-WT	38.4 mo (26.9-50.9)	-	-
RAS-MT	41.7 mo (16.5-NA)	0.99 (0.48-2.03)	*P* = .970
BRAF-MT	18.2mo (14.1-25.3)	2.73 (1.51-4.93)	*P* = .001



Her2/neu ~4-6%

Clinical Colorectal Cancer 2018 17, e69-e76DOI: (10.1016/j.clcc.2017.10.006
Dienstman et al. Precision Therapy in RAS Mutant Colorectal Cancer.
Gastroenterology 2020 Mar;158(4):806-811

Table 1. Efficacy Results for *RAS* Wild-Type CRYSTAL and FIRE-3 Study Patients, Stratified Based on Treatment Arm

	CRYSTAL				FIRE-3			
	FOLFIRI + Cetuximab		FOLFIRI		FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab	
Parameter	Right-Sided Tumors (n = 33)	Left-Sided Tumors (n = 142)	Right-Sided Tumors (n = 51)	Left-Sided Tumors (n = 138)	Right-Sided Tumors (n = 38)	Left-Sided Tumors (n = 157)	Right-Sided Tumors (n = 50)	Left-Sided Tumors (n = 149)
ORR								
Rate, %	42.4	72.5	33.3	40.6	52.6	68.8	50.0	61.7
Odds ratio (95% CI)	3.55 (1.63-7.75)		1.39 (0.70-2.76)		1.98 (0.97-4.08)		1.61 (0.85-3.08)	
P value	<.001		.34		.09		.18	
PFS								
Median, mo	8.1	12.0	7.1	8.9	7.6	10.7	9.0	10.7
HR (95% CI)	1.77 (1.08-2.91)		1.54 (0.96-2.46)		2.00 (1.36-2.93)		1.38 (0.99-1.94)	
P value	.02		.07		<.001		.06	
OS								

Tejpar. JAMA Oncol. 2017;3(2):194-201. doi:10.1001/jamaoncol.2016.3797

Anti-EGFR Therapy in wild type Colorectal cancer

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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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Takayuki YOSHINO, MD, PhD

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.

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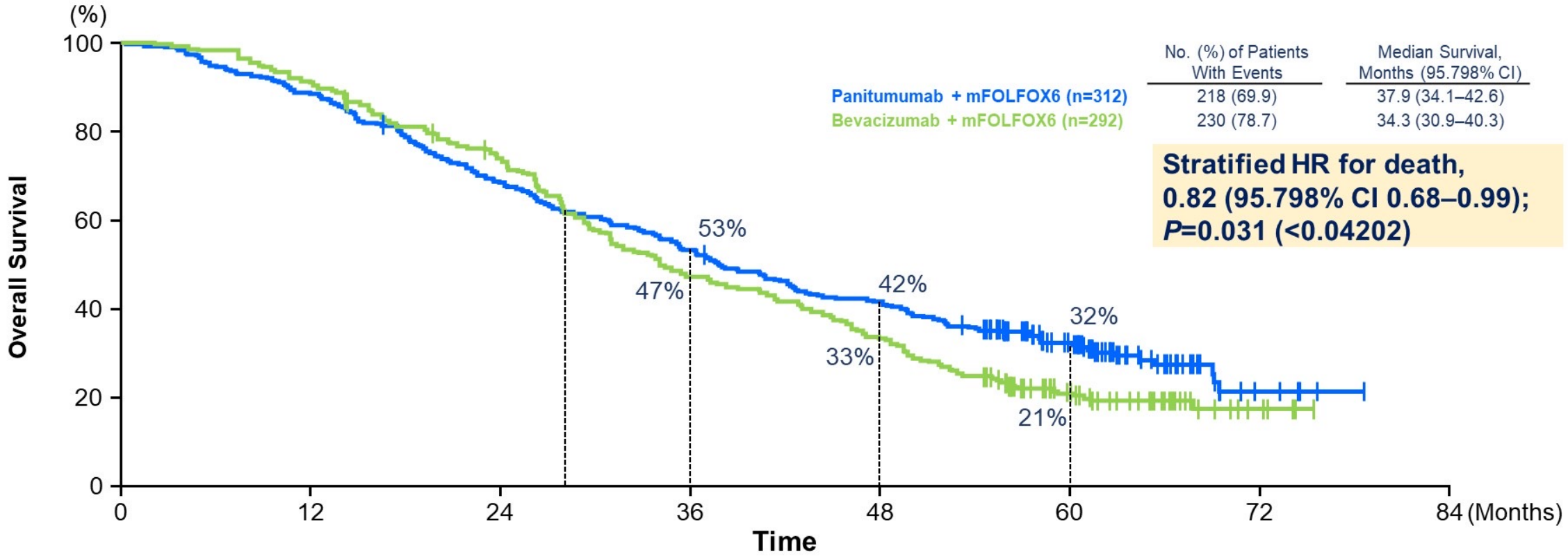
Primary Endpoint-1; Overall Survival in Left-sided Population



	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

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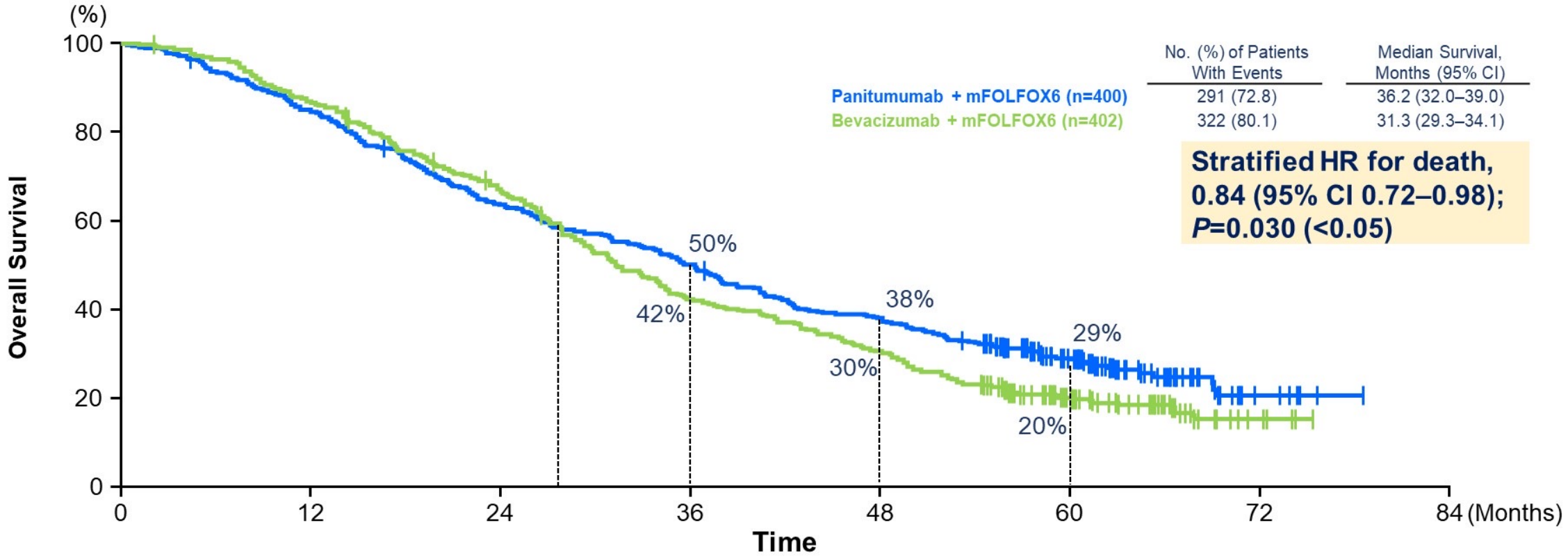
Primary Endpoint-2; Overall Survival in Overall Population



	No. (%) of Patients With Events	Median Survival, Months (95% CI)
Panitumumab + mFOLFOX6 (n=400)	291 (72.8)	36.2 (32.0–39.0)
Bevacizumab + mFOLFOX6 (n=402)	322 (80.1)	31.3 (29.3–34.1)

Stratified HR for death, 0.84 (95% CI 0.72–0.98); *P*=0.030 (<0.05)

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

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).

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Summary of Adverse Events

Adverse Event, n (%)	Panitumumab + mFOLFOX6 (n=404)	Bevacizumab + mFOLFOX6 (n=407)
Any adverse event	402 (99.5)	399 (98.0)
Grade ≥3 adverse events	290 (71.8)	264 (64.9)
Serious adverse events related to study treatment	72 (17.8)	44 (10.8)
Adverse events leading to discontinuation of study treatment	96 (23.8)	75 (18.4)

No new safety signals were observed.
Treatment-related deaths:
Panitumumab (n=10), 4 with interstitial lung disease and 1 patient each with lung disorder, pneumonia, pneumonitis, pneumonia and pancytopenia, sepsis and peritonitis, and cerebral hemorrhage
Bevacizumab (n=2), 1 with respiratory failure and 1 was not specified

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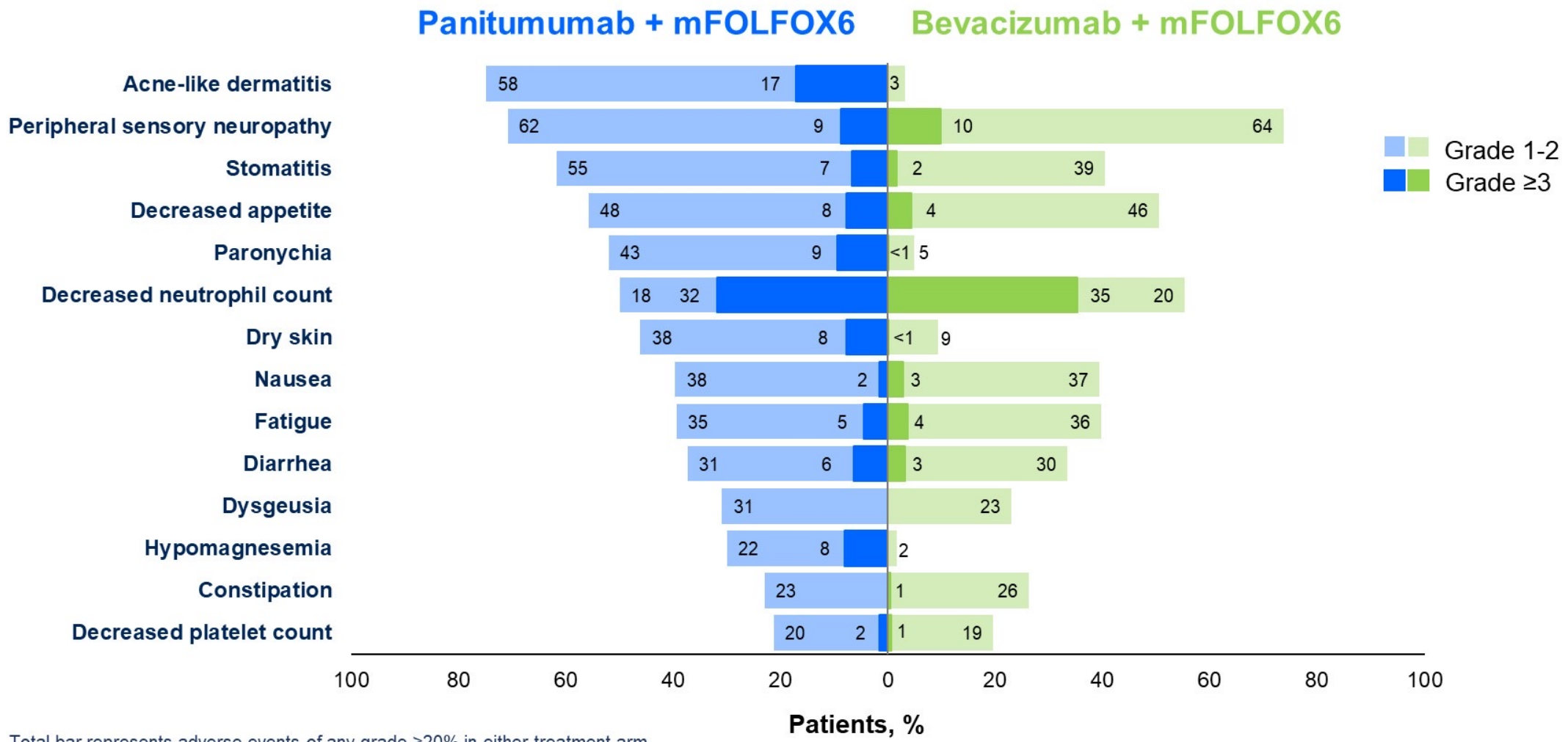
Adverse Events Reported in ≥ 20% of Patients



Total bar represents adverse events of any grade ≥20% in either treatment arm.

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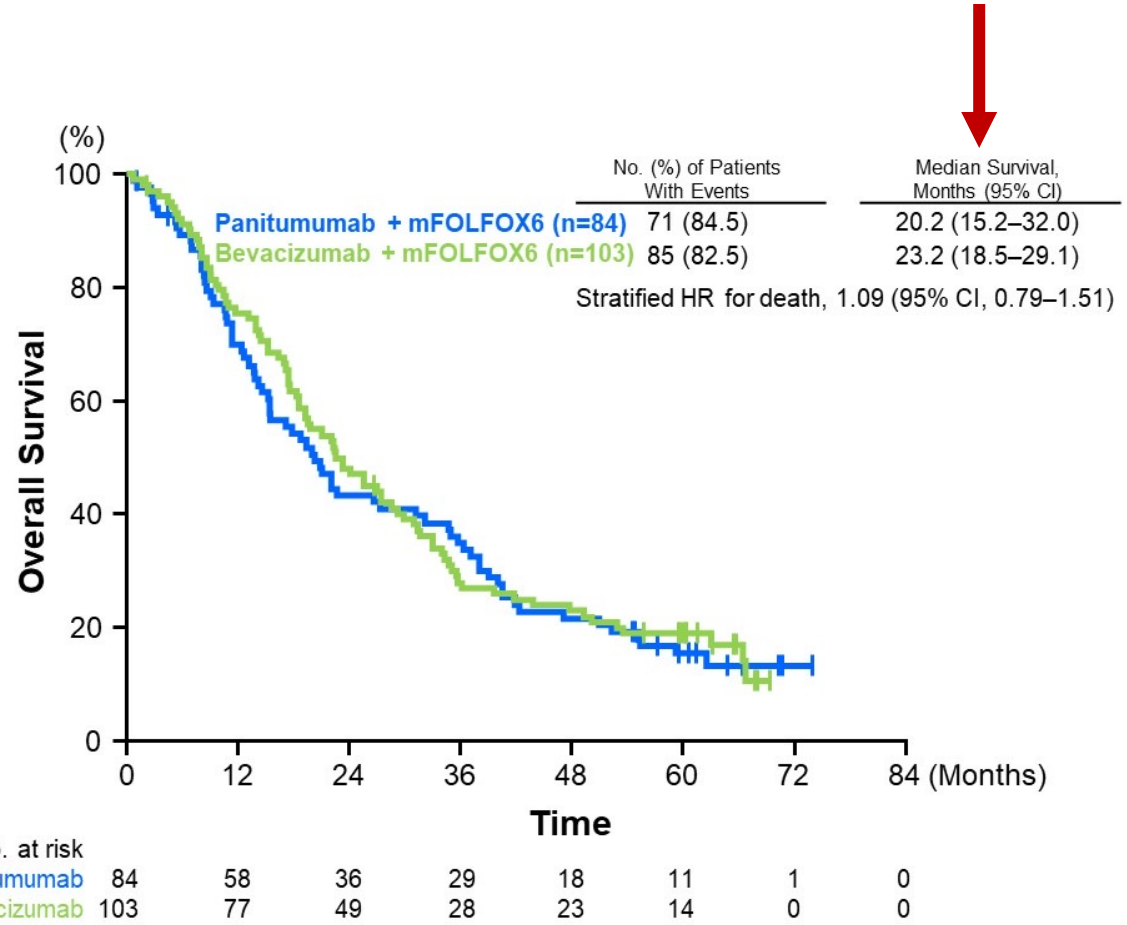
Subsequent Systemic Treatment

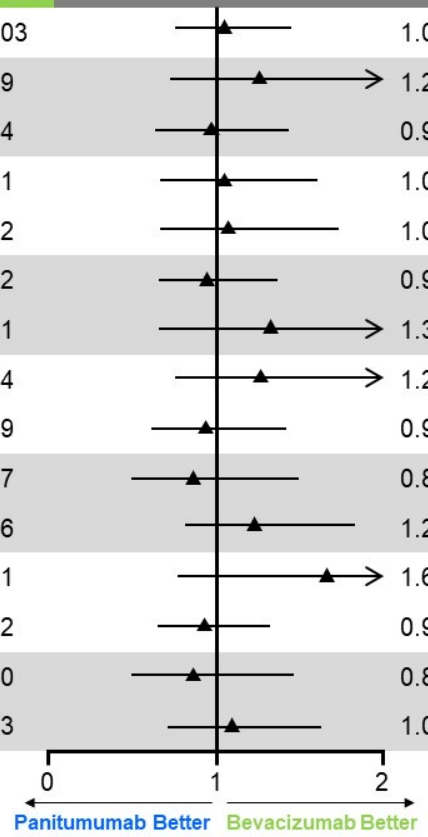
	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=312)	Bevacizumab + mFOLFOX6 (n=292)	Panitumumab + mFOLFOX6 (n=400)	Bevacizumab + mFOLFOX6 (n=402)
Patients receiving subsequent line of therapy, n (%)				
Second-line therapy	**253 (81.1)**	**241 (82.5)**	**321 (80.3)**	**329 (81.8)**
Third-line therapy	**195 (62.5)**	**190 (65.1)**	**242 (60.5)**	**261 (64.9)**
Fourth-line therapy	**130 (41.7)**	**139 (47.6)**	**160 (40.0)**	**185 (46.0)**
Post-study treatment during any lines of therapy				
Cytotoxic Agents				
Fluoropyrimidine	232 (74.4)	222 (76.0)	293 (73.3)	300 (74.6)
Irinotecan	191 (61.2)	190 (65.1)	245 (61.3)	258 (64.2)
Oxaliplatin	81 (26.0)	60 (20.5)	99 (24.8)	77 (19.2)
VEGF inhibitor	**168 (53.8)**	**166 (56.8)**	**224 (56.0)**	**227 (56.5)**
Bevacizumab	139 (44.6)	148 (50.7)	185 (46.3)	192 (47.8)
Ramucirumab	32 (10.3)	26 (8.9)	44 (11.0)	46 (11.4)
Aflibercept	20 (6.4)	13 (4.5)	25 (6.3)	26 (6.5)
EGFR inhibitor	**97 (31.1)**	**160 (54.8)**	**123 (30.8)**	**222 (55.2)**
Panitumumab	82 (26.3)	134 (45.9)	101 (25.3)	183 (45.5)
Cetuximab	17 (5.4)	36 (12.3)	24 (6.0)	49 (12.2)
Trifluridine/tipiracil hydrochloride	69 (22.1)	77 (26.4)	90 (22.5)	95 (23.6)
Regorafenib	25 (8.0)	33 (11.3)	37 (9.3)	44 (10.9)

Anti-PD-1/PD-L1 therapies, ipilimumab, and BRAF/MEK inhibitors were used in a few patients.

OS and Subgroup Analysis in Right-sided Population



Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Bevacizumab + mFOLFOX6	Hazard Ratio (95% CI)
	Overall*	71/84	85/103	1.09 (0.79-1.51)
Age	20-64 yr	22/26	32/39	1.26 (0.73-2.17)
	65-79 yr	49/58	53/64	0.97 (0.66-1.44)
Sex	Male	37/41	51/61	1.04 (0.68-1.60)
	Female	34/43	34/42	1.08 (0.67-1.74)
ECOG PS	0	54/65	68/82	0.96 (0.67-1.37)
	1	16/18	17/21	1.33 (0.66-2.67)
No. of organs with metastasis	0-1	31/40	30/44	1.27 (0.77-2.10)
	≥2	40/44	55/59	0.94 (0.63-1.42)
Liver metastasis	No	26/35	29/37	0.87 (0.51-1.49)
	Yes	45/49	56/66	1.23 (0.83-1.83)
Organs with metastasis	Liver only	13/14	15/21	1.66 (0.79-3.50)
	Other	58/70	70/82	0.93 (0.66-1.32)
Primary tumor resection	No	30/33	28/30	0.87 (0.51-1.45)
	Yes	41/51	57/73	1.09 (0.73-1.63)



*Stratified Hazard Ratio is shown with 95% CI.

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Istituto Nazionale Tumori Fondazione G. Pascale

Randomized intermittent or continuous panitumumab plus FOLFIRI (FOLFIRI/PANI) for first-line treatment of patients (pts) with RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC): the IMPROVE study.

Antonio Avallone[1], Francesco Giuliani[2], Guglielmo Nasti[1], Vincenzo Montesarchio[3], Giuseppe Santabarbara[4], Silvana Leo[5], Alfonso De Stefano[1], Gerardo Rosati[6], Ivan Lolli[7], Emiliano Tamburini[8], Alfredo Colombo[9], Daniele Santini[10], Lucrezia Silvestro[1], Gaetano Facchini[11], Francesco Mannavola[12], Antonio Febbraro[13], Giancarlo Troncone[14], Alberto F. Sobrero[15], Diana Giannarelli[16], Alfredo Budillon[1]

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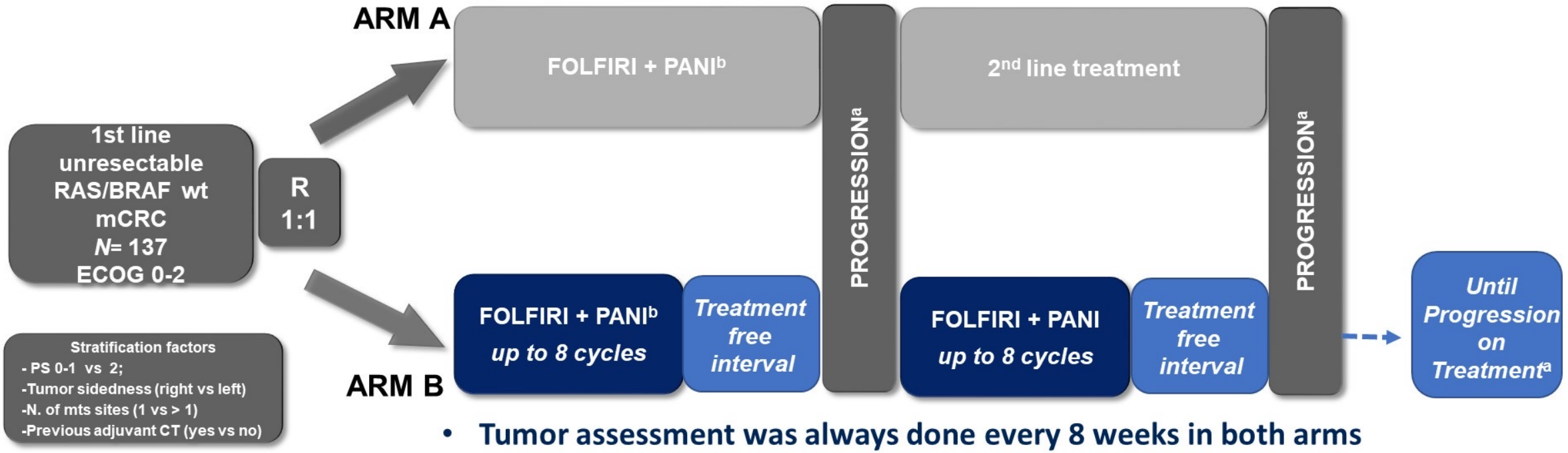
IMPROVE study design

- IMPROVE is a randomized, non-comparative, open-label, multicenter phase 2 study



- Tumor assessment was always done every 8 weeks in both arms

- At data cutoff (April 22, 2022), the minimum follow-up was 10 months[c]

ClinicalTrials.gov.NCT04425239; [a]or until unacceptable toxicity or withdrawal consent; [b]Irinotecan 180 mg/m^2, folinic acid 200 mg/m^2, fluorouracil bolus 400 mg/m^2 followed by 2400 mg/m^2 continuous infusion over 46 hours plus panitumumab 6 mg/kg on day 1 every 2 weeks; [c]Time from randomization of the last patietn to clinical data cutoff.

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Treatment exposure and disposition

	ARM A FOLFIRI-PANI continuous N= 69	ARM B FOLFIRI-PANI intermittent N= 68
Number of cycles per patient, median (IQR)	**13 (9-22)**	**13 (8-23)**
Patients with treatment delay, n (%)	**24 (35)**	**21 (31)**
Patients with dose reduction, n (%)	**43 (62)**	**41 (60)**
Planned dose of treatment with Pani, %		
Full dose	**65**	**68**
Reduced dose	**35**	**32**
Planned dose of treatment with FOLFIRI, %		
Full dose	**55**	**54**
Reduced dose	**45**	**46**
Ongoing treatment, n (%)	**7 (10)**	**25 (37)**
Discontinued treatment, n (%)	**62 (90)**	**43 (63)**
Reason for treatment discontinuation, n (%)		
Disease Progression	**44 (64)**	**37 (54)**
AE related to treatment	**12 (17)**	**3 (4)**
Patient request	**4 (6)**	**3 (4)**
Other	**2 (7)**	**0**

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Response and Resection Rate

ITT Population Best Response (RECIST v1.1 criteria)	ARM A FOLFIRI-PANI continuous N= 69	ARM B FOLFIRI-PANI intermittent N= 68
Complete Response	7%	3%
Partial Response	59%	54%
Stable Disease	27%	32%
Progressive Disease	6%	7%
Not Assessed	0%	3%
Disease Control Rate (CR+PR+SD)	94%	90%
Progressive Disease within 4 months	16%	15%
R0 Resection Rate	19%	15%

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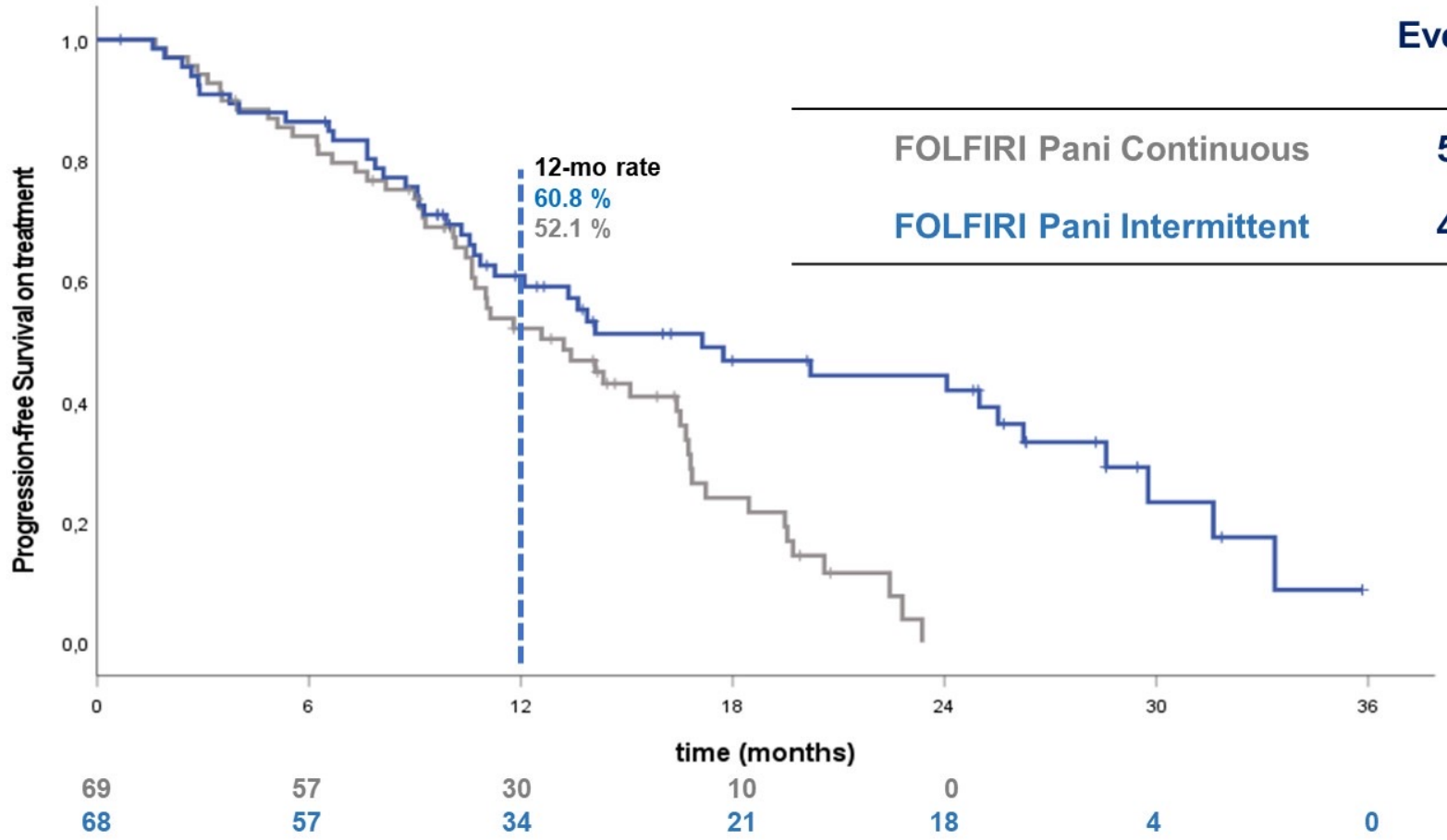
PFS_{OT} curve



	Events	Median PFS_{OT} mos	95% CI
FOLFIRI Pani Continuous	52	13.2	9.6-16.8
FOLFIRI Pani Intermittent	41	17.1	9.3-24.9

In intermittent arm 34 patients alive and without PD at 1 year

PRESENTED BY:
Antonio Avallone, MD; @AvalloneAnt

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Safety analysis

Main Grade 3/4 adverse eventsof	ARM A FOLFIRI-PANI continuous N= 69	ARM B FOLFIRI-PANI intermittent N= 67
Neutropenia	23 %	24 %
Anemia	3 %	3 %
Diarrhea	13 %	15 %
Stomatitis	3 %	3 %
Nausea/Vomiting	5 %	4 %
Fatigue	3 %	7 %
Liver toxicicty	3 %	3 %
Skin related	25 %	13 %
Hypomagnesemia	3 %	0 %

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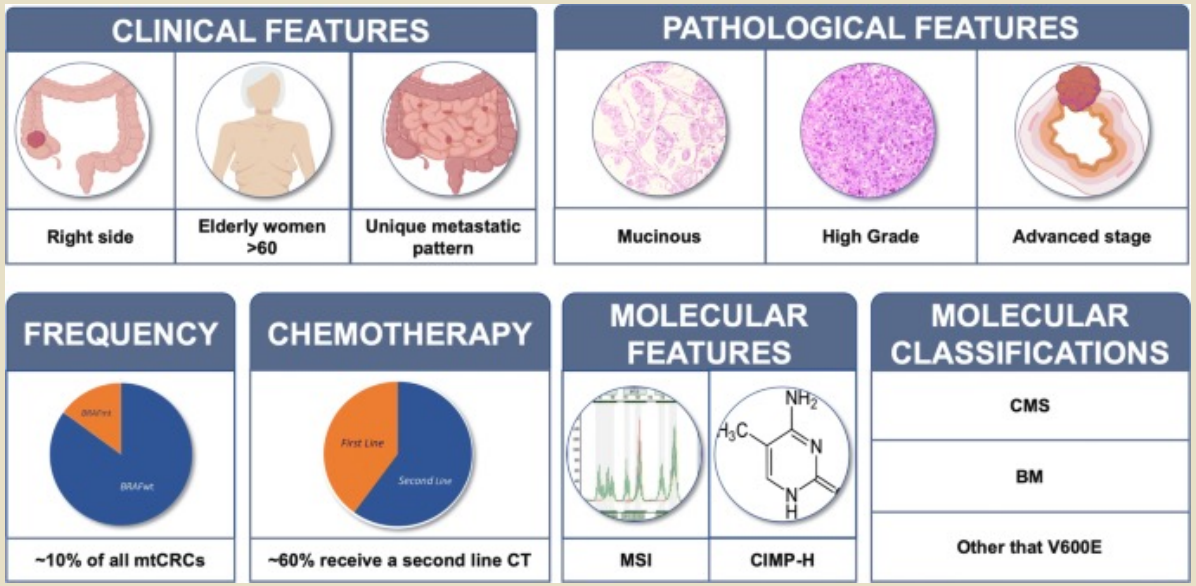
Anti-EGFR Review

Trial	Median OS in Months	
Primary Tumor	RIGHT side	LEFT side
PEAK		
Pmab FOLFOX	18	43
Bev FOLFOX	21	32
FIRE-3		
Cmab FOLFIRI	18	38
Bev FOLFIRI	23	28
CALGB 80405		
Cmab chemotherapy	17	36
Bev chemotherapy	24	31
PARADIGM		
Pmab FOLFOX	20	38
Bev FOLFOX	23	34

Anti-EGFR Strategies

- Benefit in the first line setting only for *RAS/RAF* WT, *HER2* non-amplified left sided CRC
  - Risk/benefit discussion with patient due to skin toxicity
- Intermittent anti-EGFR strategy spares skin toxicity
- Would NOT use anti-EGFR in 1L if goal is resection
  - NEW EPOC (peri-operative anti-EGFR): mOS 81.0m vs 55.4m

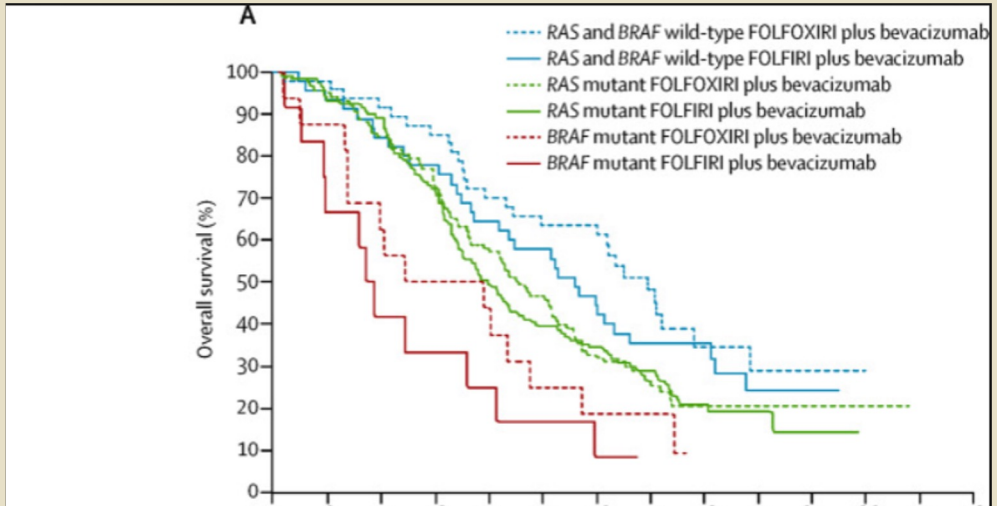
BRAF V600E mutant mCRC



Fanelli et al: https://cancerci.biomedcentral.com/articles/10.1186/s12935-020-1117-2

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

FOLFOXIRI + Bev was superior in TRIBE study



Number at risk														
RAS and *BRAF* wild-type FOLFOXIRI plus bevacizumab	48	46	43	40	32	29	26	17	8	5	3	0	0	0
RAS and *BRAF* wild-type FOLFIRI plus bevacizumab	45	42	38	35	29	26	20	14	10	5	1	0	0	0
RAS mutant FOLFOXIRI plus bevacizumab	117	111	99	85	67	54	36	20	13	8	3	2	0	0
RAS mutant FOLFIRI plus bevacizumab	119	111	106	85	58	47	40	27	13	7	1	0	0	0
BRAF mutant FOLFOXIRI plus bevacizumab	16	14	10	8	7	4	3	3	0	0	0	0	0	0
BRAF mutant FOLFIRI plus bevacizumab	12	8	5	4	3	2	1	0	0	0	0	0	0	0

Targeting BRAF V600E mutated mCRC

Table 6 Targeting the RAS/RAF/MAPK pathway in BRAF-mutant metastatic colorectal cancer

Study	n= size	Arm (s)	ORR	PFS	OS
Kopetz *et al*. (62)	21	Vemurafenib	5%	Median 2.1 months	Median 7.7 months
Falchook *et al*. (63)	9	Dabrafenib	11.1%	NR	NR
Infante *et al*. (64)	28 (KRAS- or BRAF-mutant)	Trametinib	0%	NR	NR
Hong *et al*. (65)	17	Vemurafenib + cetuximab + irinotecan	35%	Median 7.7 months	NR
Hyman *et al*. (66)	27	Vemurafenib + cetuximab	4% (95% CI, <1–20)	Median 3.7 months (95% CI, 1.8–5.1)	Median 7.1 months (95% CI, 4.4–not reached)
Tabernero *et al*. (67)	14	Vemurafenib + cetuximab	SD 60% at week 8, SD 66.6% at week 16	NR	NR
Yaeger *et al*. (68)	15	Vemurafenib + panitumumab	16.7%	Median 3.2 months (95% CI, 1.6–5.3)	Median OS 7.6 months (95% CI, 2.1–not reached)
Corcoran *et al*. (69)	43	Dabrafenib + trametinib	12%	Median 3.5 months (95% CI, 3.4–4.0)	NR
Schellens *et al*. (70)	54	Encorafenib + cetuximab (A); encorafenib + cetuximab + alpelisib (B)	A: 23%; B: 32%	A: median 3.7 months; B: median 4.3 months	NR
Van Cutsem *et al*. (71)	55	Dabrafenib + panitumumab (D + P); dabrafenib + trametinib + panitumumab (D + T + P)	D + P: 10% (95% CI, 1.2–31.7); D + T + P: 26% (95% CI, 12.5–43.3)	D + P: median 3.5 months (95% CI, 2.8–5.8); D + T + P: median 4.1 months (95% CI, 2.6–5.5)	NR

ORR, overall response rate; PFS, progression-free survival; OS, overall survival; NR, not reported; CI, confidence interval; SD, stable disease.

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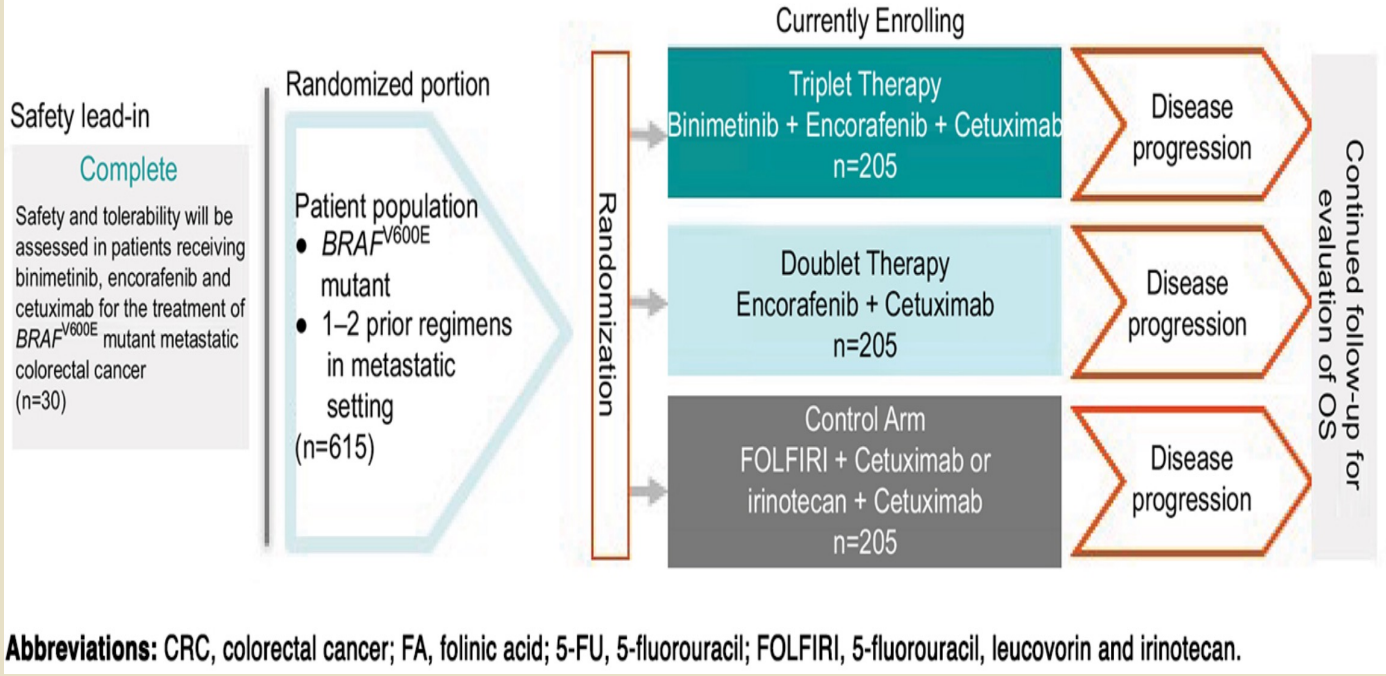
Gong. J. J Gastrointest Oncol. 2016 Oct;7(5):687-704

Figure 2. Schematic representation of the Phase III study of encorafenib + cetuximab plus or minus binimetinib vs irinotecan/cetuximab or infusional 5-FU/FA/irinotecan (FOLFIRI)/cetuximab with a safety lead-in of encorafenib + binimetinib + cetuximab in patients with BRAFV600E-mutant metastatic CRC (BEACON CRC).



Abbreviations: CRC, colorectal cancer; FA, folinic acid; 5-FU, 5-fluorouracil; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan.

- Emerging Treatment Options for BRAF-mutant Colorectal Cancer. https://www.oncologynurseadvisor.com/home/cancer-types/colorectal-cancer/emerging-treatment-options-for-braf-mutant-colorectal-cancer/4/

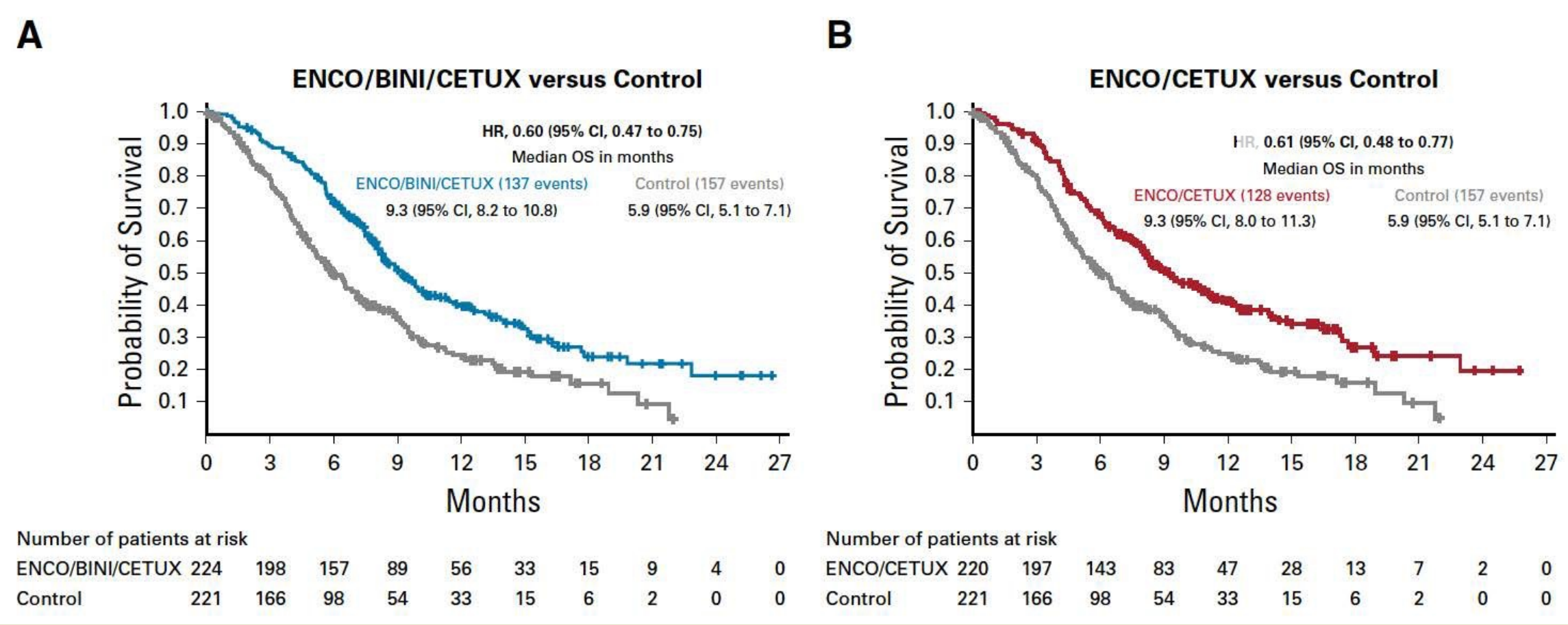
rapid communications

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

Josep Tabernero, MD, PhD[1]; Axel Grothey, MD[2]; Eric Van Cutsem, MD, PhD[3]; Rona Yaeger, MD[4]; Harpreet Wasan, MD[5]; Takayuki Yoshino, MD, PhD[6]; Jayesh Desai, MBBS[7]; Fortunato Ciardiello, MD, PhD[8]; Fotios Loupakis, MD, PhD[9]; Yong Sang Hong, MD, PhD[10]; Neeltje Steeghs, MD, PhD[11]; Tormod Kyrre Guren, MD, PhD[12]; Hendrik-Tobias Arkenau, MD, PhD[13]; Pilar Garcia-Alfonso, MD[14]; Elena Elez, MD, PhD[1]; Ashwin Gollerkeri, MD[15]; Kati Maharry, PhD[15]; Janna Christy-Bittel, MSN[15]; and Scott Kopetz, MD, PhD[16]

• *J Clin Oncol* 2021;39(4):273-84.

BEACON: Overall Survival Results

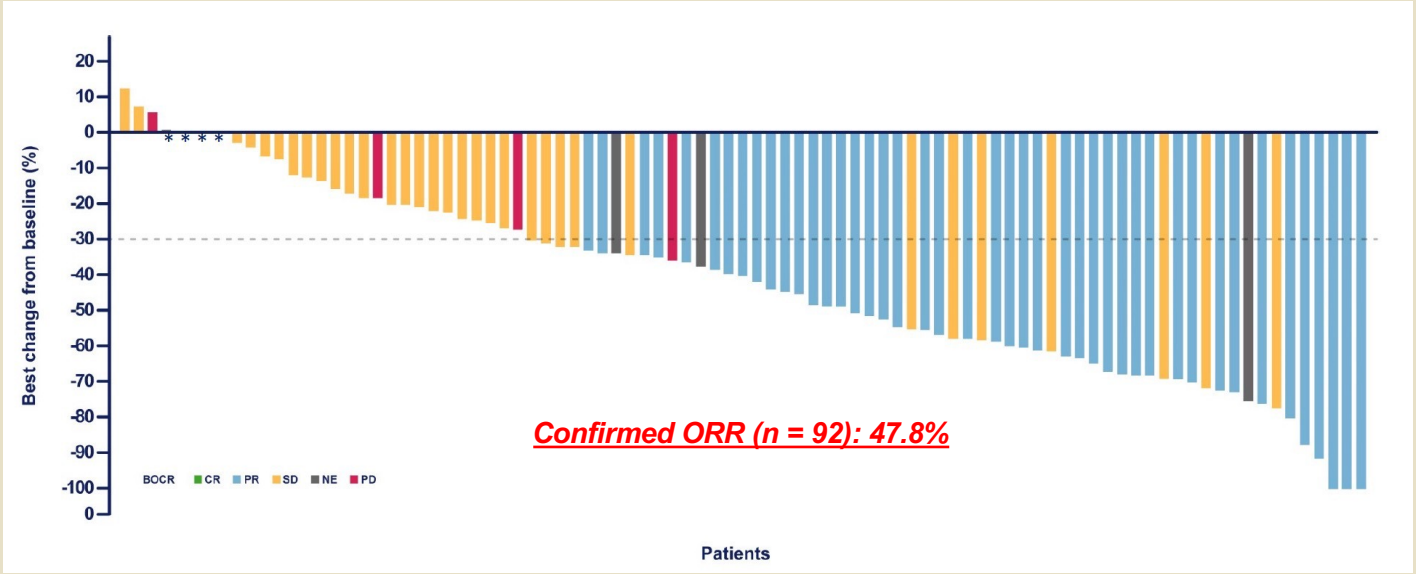


Targeting BRAF V600E in First Line setting

original reports

ANCHOR CRC: Results From a Single-Arm, Phase II Study of Encorafenib Plus Binimetinib and Cetuximab in Previously Untreated *BRAF*^{V600E}-Mutant Metastatic Colorectal Cancer

Eric Van Cutsem, MD, PhD[1]; Julien Taieb, MD, PhD[2]; Rona Yaeger, MD[3]; Takayuki Yoshino, MD[4]; Axel Grothey, MD[5]; Evaristo Maiello, MD[6]; Elena Elez, MD, PhD[7]; Jeroen Dekervel, MD[1]; Paul Ross, MD[8]; Ana Ruiz-Casado, MD, PhD[9]; Janet Graham, MD, PhD[10]; Takeshi Kato, MD[11]; Jose C. Ruffinelli, MD[12]; Thierry André, MD[13]; Edith Carrière Roussel, PhD[14]; Isabelle Klauck, MD[15]; Mélanie Groc, MSc[14]; Jean-Claude Vedovato, MD[14]; and Josep Tabernero, MD, PhD[16]



ORR = objective response rate.

- ***Overall survival (OS) = 18.2 mo (with a median follow-up of 14.4 mo)***
- ***PFS = 5.8 mo (median)***

Van Cutsem E et al. ESMO World Congress on Gastrointestinal Cancer 2021;Abstract O-10.

An open-label, multicenter, randomized phase 3 study of 1st line encorafenib plus cetuximab with or without chemotherapy versus standard of care therapy in patients with metastatic *BRAF* V600E-mutant mCRC

Safety lead-in

Patients with *BRAF*^{V600E} mutant mCRC with 0 to 1 prior regimens in the metastatic setting

Phase 3

Patients with *BRAF*^{V600E} mutant mCRC and no prior systemic therapy in the metastatic setting

Encorafenib + cetuximab + mFOLFOX6
N=30
Encorafenib + cetuximab + FOLFIRI
N=30

Dosages
- Encorafenib, 300 mg PO QD
- Cetuximab, 500 mg/m² IV Q2W
- **FOLFOX, full dose IV Q2W**
- FOLFIRI, full dose IV Q2W

Randomize 1:1:1*

Arm A**
Encorafenib + cetuximab, N=290

Arm B**
Encorafenib + cetuximab + FOLFOX or FOLFIRI$^{\beta}$, N=290

Control arm§
Physician's choice: FOLFOX, FOLFIRI, FOLFOXIRI, CAPOX, all ± anti-VEGF antibody, N=290

PRIMARY ENDPOINTS
PFS (BICR) Arm A vs Control
AND
PFS (BICR) Arm B vs Control
(BICR, blinded independent central review)

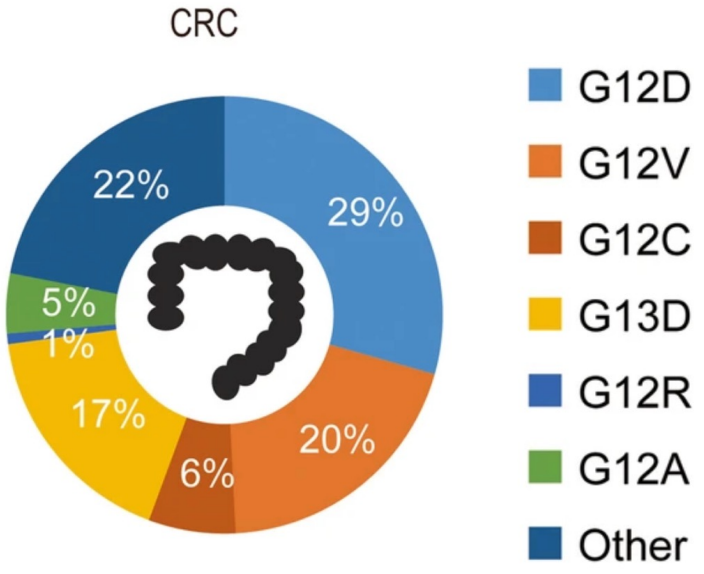
KEY SECONDARY ENDPOINTS
OS Arm A vs Control
AND
OS Arm B vs Control

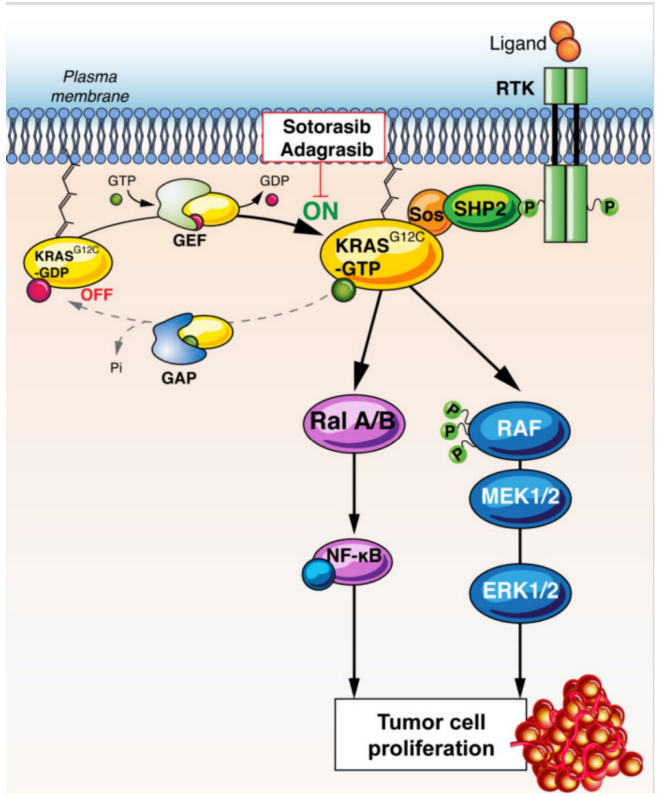
OTHER ENDPOINTS
- Incidence of DLTs, adverse events, dose modifications/discontinuations due to AEs
- PK including drug-drug interactions

BREAKWATER STUDY

*Stratified by: ECOG PS 0 v. 1, Region US/Canada v. Western Europe v. ROW
**Same dosing as SLI; $^{\beta}$FOLFOX or FOLFIRI based on SLI results; § No crossover.
ClinicalTrials.gov Identifier: NCT04607421

Van Cutsem E et al. ESMO World Congress on Gastrointestinal Cancer 2021 (Abstract O-10)





KRAS G12C TARGETING IN CRC

Dienstman et al. Precision Therapy in RAS Mutant Colorectal Cancer. Gastroenterology 2020 Mar;158(4):806-811
Zhu et al. Targeting KRAS mutant cancer: from druggable to drug resistance.
Addeo et al. Kras g12c mutations in nsclc: From target to resistance. Cancers 13(11):2541

PARIS 2022 ESMO congress

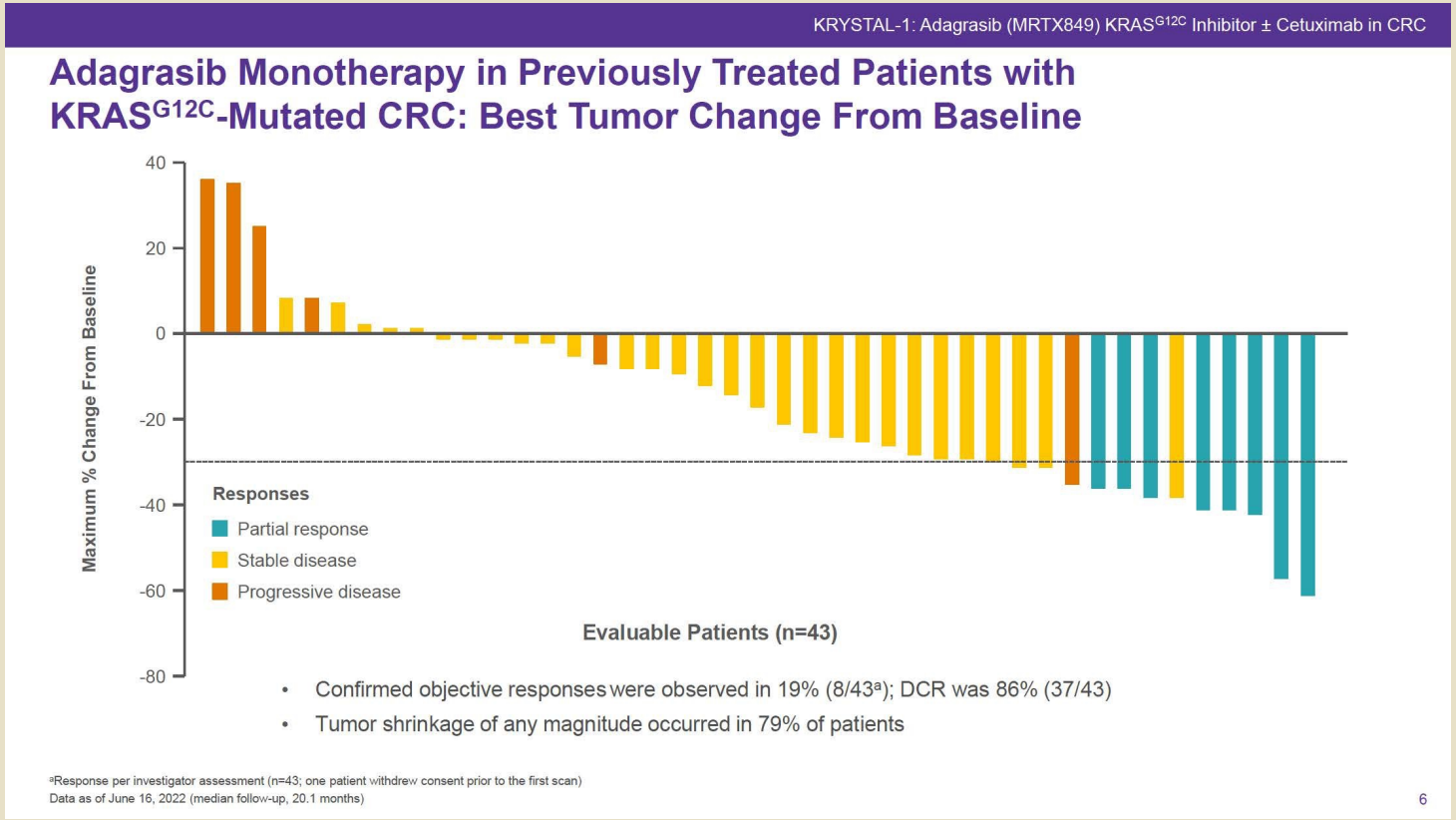
KRYSTAL-1: Updated Efficacy and Safety of Adagrasib (MRTX849) With or Without Cetuximab in Patients With Advanced Colorectal Cancer (CRC) Harboring a KRAS^{G12C} Mutation

Samuel J. Klempner[1], Jared Weiss[2], Meredith S. Pelster[3], Alexander I. Spira[4], Minal Barve[5], Sai-Hong Ignatius Ou[6], Ticiana A. Leal[7], Tanios S. Bekaii-Saab[8], James G. Christensen[9], Thian Kheoh[9], Karen Velastegui[9], Hirak Der-Torossian[9], Rona Yaeger[10]

[1]Massachusetts General Cancer Center, Boston, Massachusetts, USA; [2]University of North Carolina-Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, USA; [3]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, USA; [4]Virginia Cancer Specialists, US Oncology Research, Fairfax, Virginia, USA; [5]Mary Crowley Cancer Research, Dallas, TX, USA; [6]University of California Irvine, Chao Family Comprehensive Cancer Center, Orange, CA, USA; [7]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [8]Department of Medical Oncology and Hematology, Mayo Clinic, Scottsdale, Arizona, USA; [9]Mirati Therapeutics, Inc., San Diego, CA, USA; [10]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

- ESMO Abstract LBA24

Adagrasib showed single agent activity in CRC in Phase1/2 study

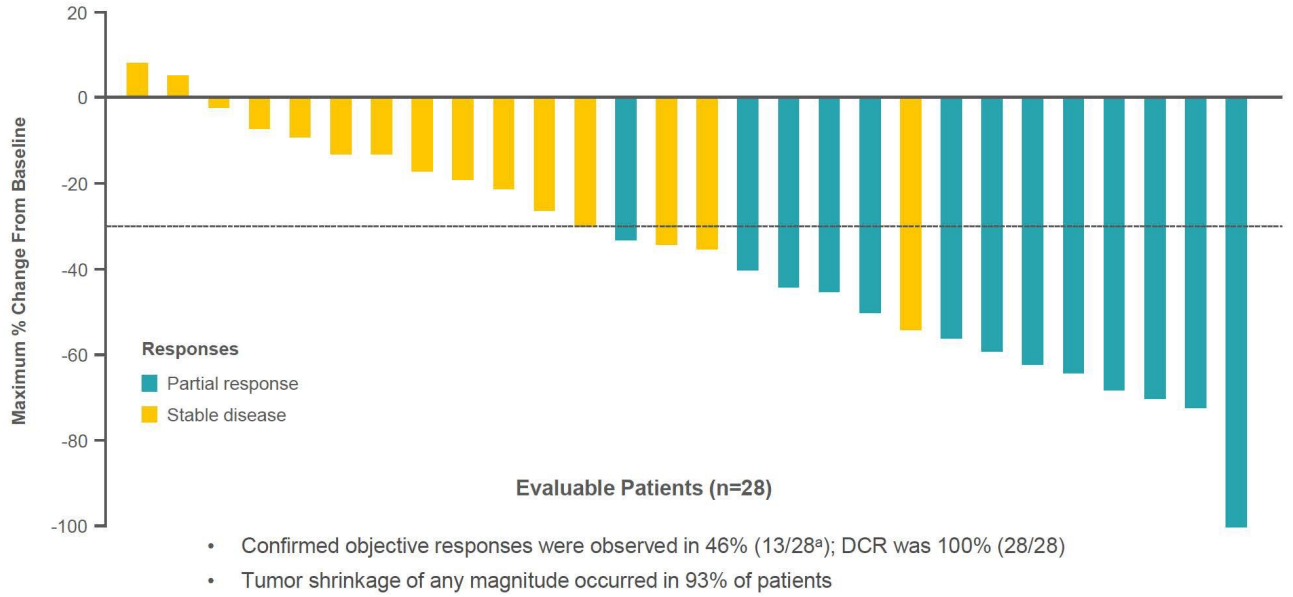


Klemper S et al. ESMO 2022; Abstract LBA24.

Improved objective response in combination with Anti-EGFR inhibitor

Klempner et al. ESMO 2022, Abstract LBA24

Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Best Tumor Change From Baseline



- Confirmed objective responses were observed in 46% (13/28[a]); DCR was 100% (28/28)
- Tumor shrinkage of any magnitude occurred in 93% of patients

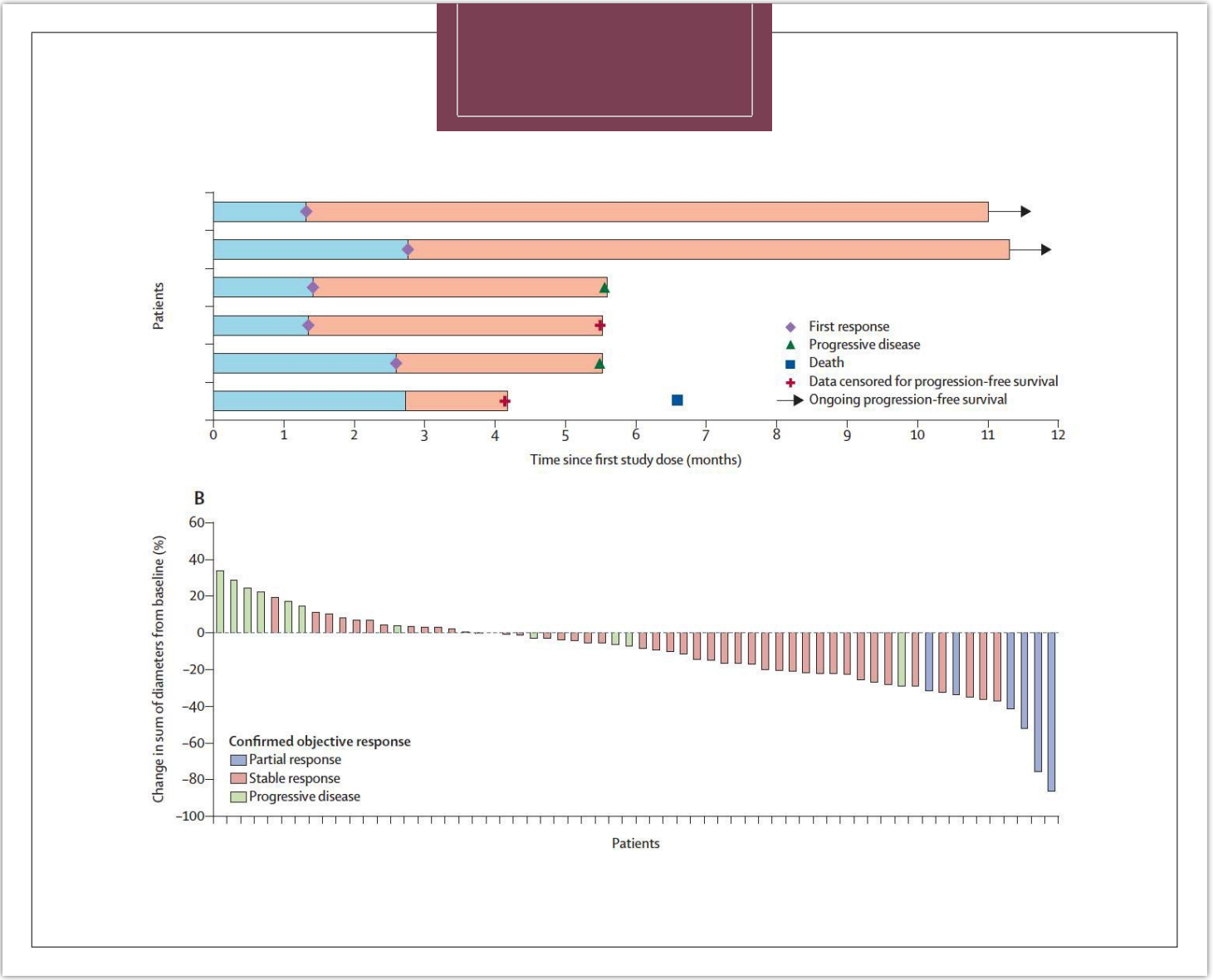
[a]Response per investigator assessment (n=28; four patients are not included due to no post-baseline assessment of target lesions)
Data as of June 16, 2022 (median follow-up, 17.5 months)

Lancet Oncol 2022;23(1):115-24.

Articles

Sotorasib for previously treated colorectal cancers with *KRAS*^{G12C} mutation (CodeBreaK100): a prespecified analysis of a single-arm, phase 2 trial

Marwan G Fakih, Scott Kopetz*, Yasutoshi Kuboki, Tae Won Kim, Pamela N Munster, John C Krauss, Gerald S Falchook, Sae-Won Han, Volker Heinemann, Kei Muro, John H Strickler, David S Hong, Crystal S Denlinger, Gustavo Girotto, Myung-Ah Lee, Haby Henary, Qui Tran, Joseph K Park, Gataree Ngarmchamnanrith, Hans Prenen, Timothy J Price*



Fakih MG et al. *Lancet Oncol* 2022;23(1):115-24.

CODE BREAK 100 RESULTS

PARIS 2022 ESMO congress

Additional analyses of MOUNTAINEER: A phase 2 study of tucatinib and trastuzumab for HER2-positive mCRC

John H. Strickler, MD
Duke University Medical Center, Durham, NC, USA

Andrea Cercek, Salvatore Siena, Thierry Andre, Kimmie Ng, Eric Van Cutsem, Christina Wu, Andrew Scott Paulson, Joleen M. Hubbard, Andrew L. Coveler, Christos Fountzilas, Adel Kardosh, Pashtoon Murtaza Kasi, Heinz-Josef Lenz, Kristen Ciombor, Elena Elez, David L. Bajor, Michael Stecher, Wentao Feng, Tanios S. Bekaii-Saab

Abstract LBA27

Mounteer Results

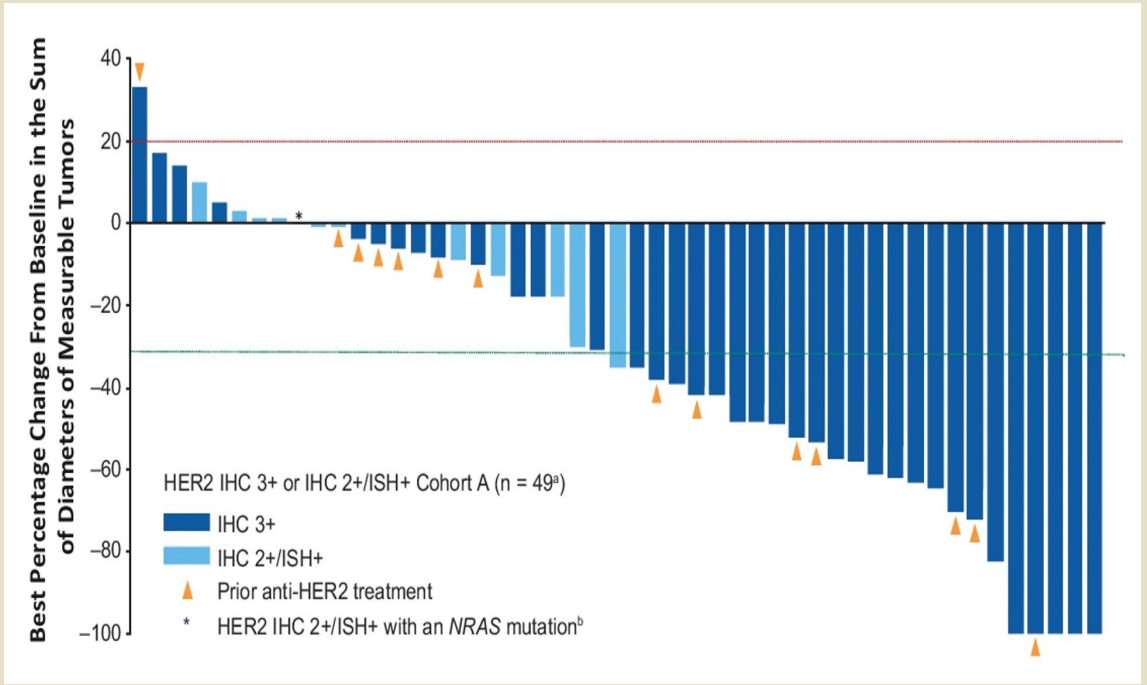
Responses		Tucatinib + Trastuzumab Cohorts A+B n=84[1]	Tucatinib Monotherapy Cohort C n=30	Tucatinib + Trastuzumab Post-Crossover n=28
Best overall response per BICR[a], n (%)	CR	3 (3.6)	0	0
	PR	29 (34.5)	1 (3.3)	5 (17.9)
	SD[b]	28 (33.3)	23 (76.7)	18 (64.3)
	PD	22 (26.2)	4 (13.3)	5 (17.9)
	Not available[c]	2 (2.4)	2 (6.7)	0
ORR per BICR, % (95% CI)[d]		**38.1 (27.7-49.3)[f]**	**3.3 (0.1-17.2)[g]**	**17.9 (6.1-36.9)[f]**
DCR[e] per BICR, n (%)		**60 (71.4)**	**24 (80.0)**	**23 (82.1)**

R = objective response rate; DCR = disease control rate;
BICR = blinded independent central review

Srickler JH et al. ESMO 2022;Abstract LBA27

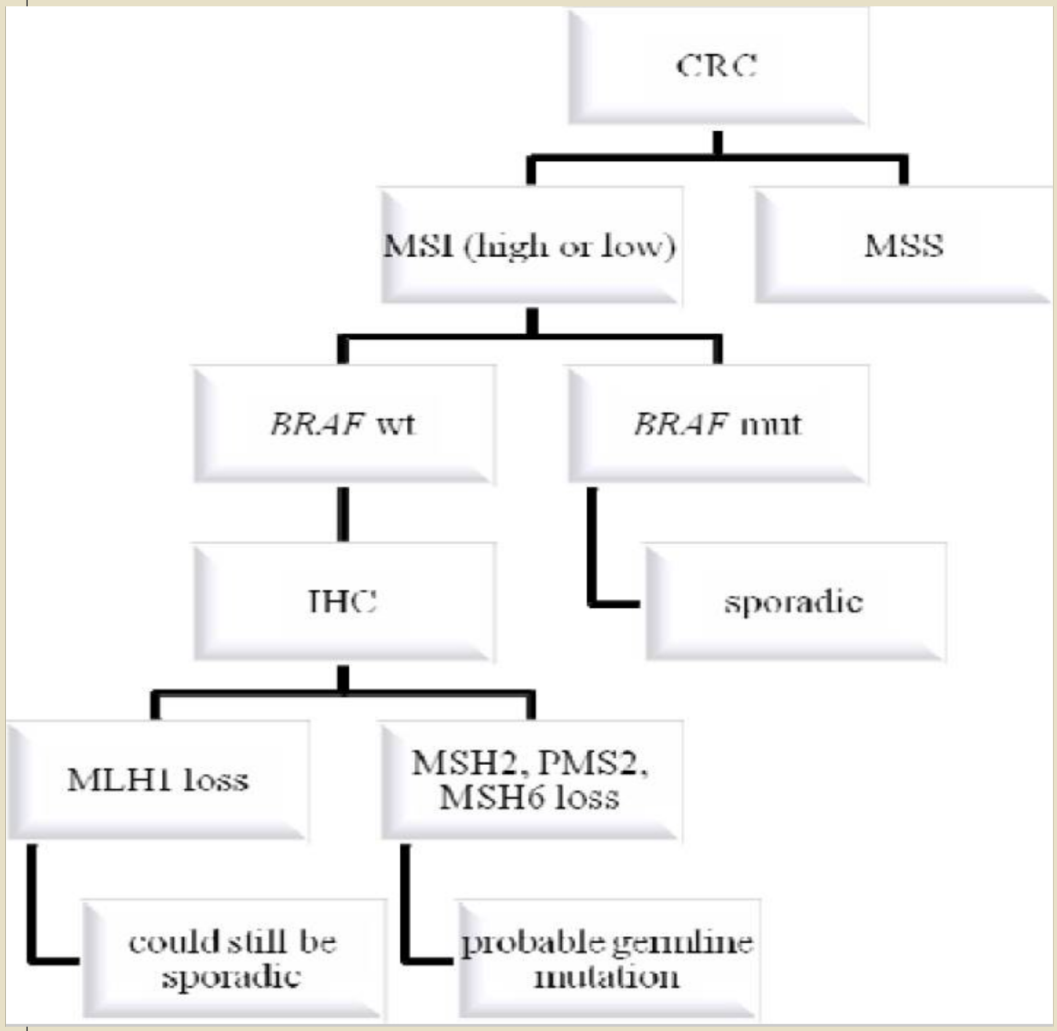
Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-expressing Metastatic Colorectal Cancer (mCRC): Final Results From a Phase 2, Multicenter, Open-label Study (DESTINY-CRC01)

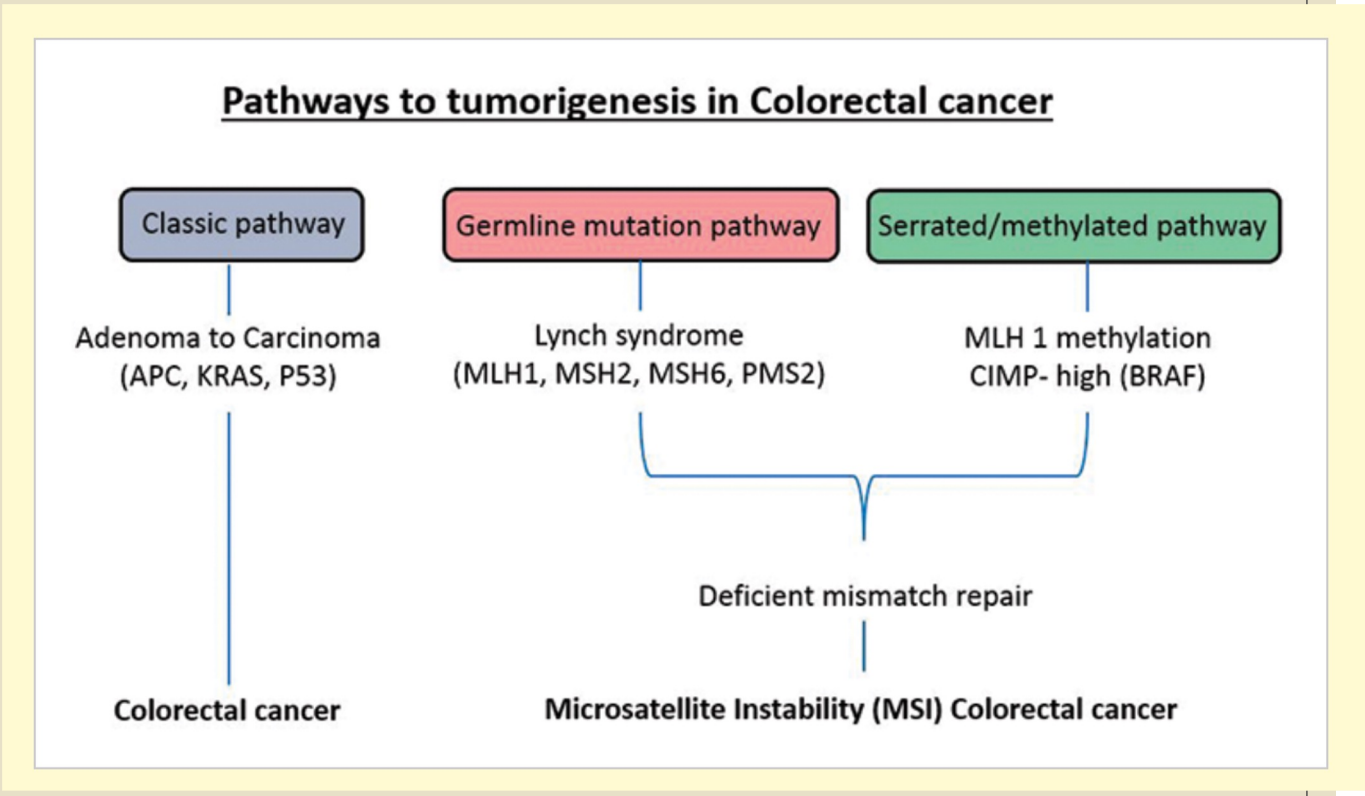
Takayuki Yoshino,[1] Maria Di Bartolomeo,[2] Kanwal Raghav,[3] Toshiki Masuishi,[4] Hisato Kawakami,[5] Kensei Yamaguchi,[6] Tomohiro Nishina,[7] Zev Wainberg,[8] Elena Elez,[9] Javier Rodriguez,[10] Marwan Fakih,[11] Fortunato Ciardiello,[12] Kapil Saxena,[13] Kojiro Kobayashi,[13] Emarjola Bako,[13] Yasuyuki Okuda,[14] Gerold Meinhardt,[13] Axel Grothey,[15] Salvatore Siena[16,17]



ASCO Gastrointestinal Cancers Symposium 2022;Abstract 119.

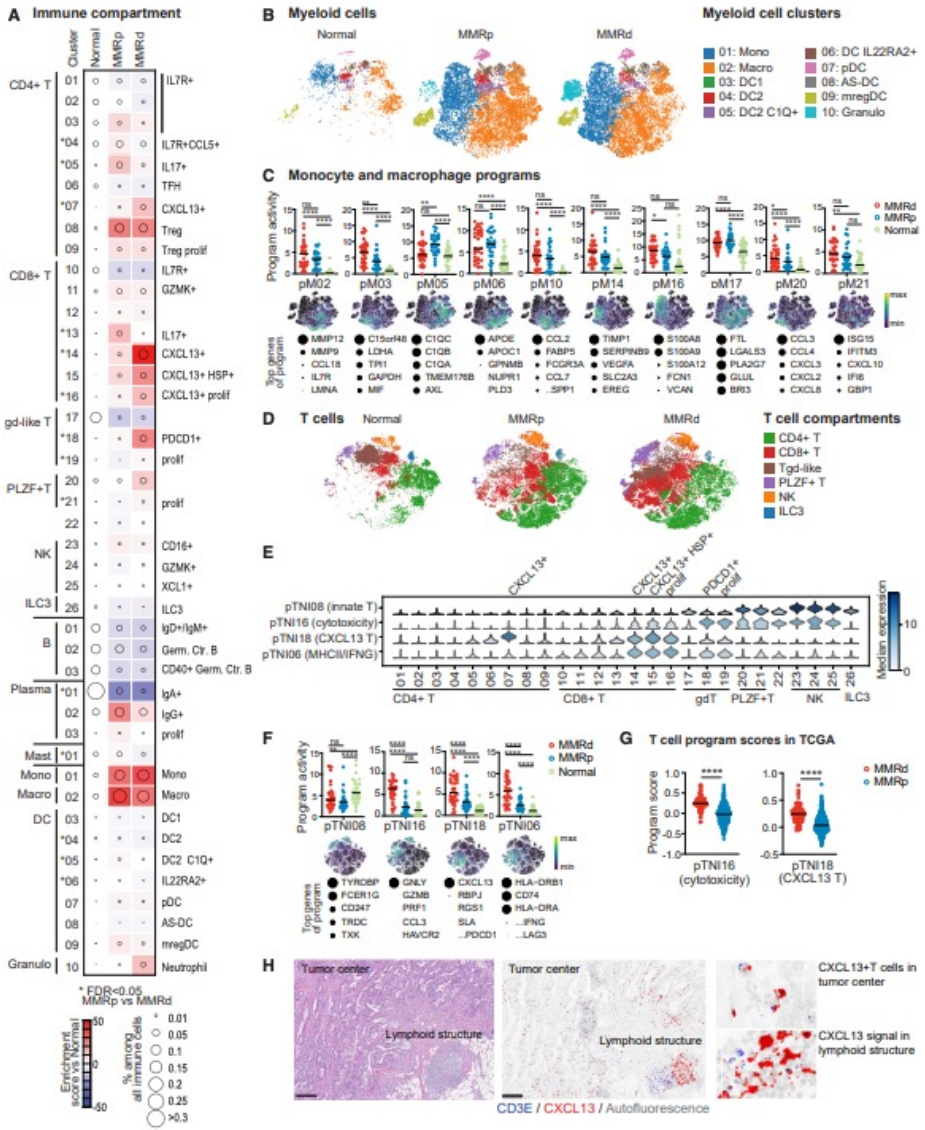
Immunotherapy in Colorectal Cancer





Mojarad. Gastroenterol Hepatol Bed Bench. 2013 Winter; 6(1): 6–13.

https://www.intechopen.com/books/colorectal-cancer-from-pathogenesis-to-treatment/braf-mutation-in-colorectal-cancer



- Single cell analysis of CRC finds differences between microsatellite stable and Microsatellite unstable tumors.

- MMRd tumors were CXCL13+ T cells (marker of human tumor-reactive CD8+ T cells and response to immunotherapy) and PDCD1+ gd-like T cells.

- IL17+ T cells were enriched in MMRp tumors.

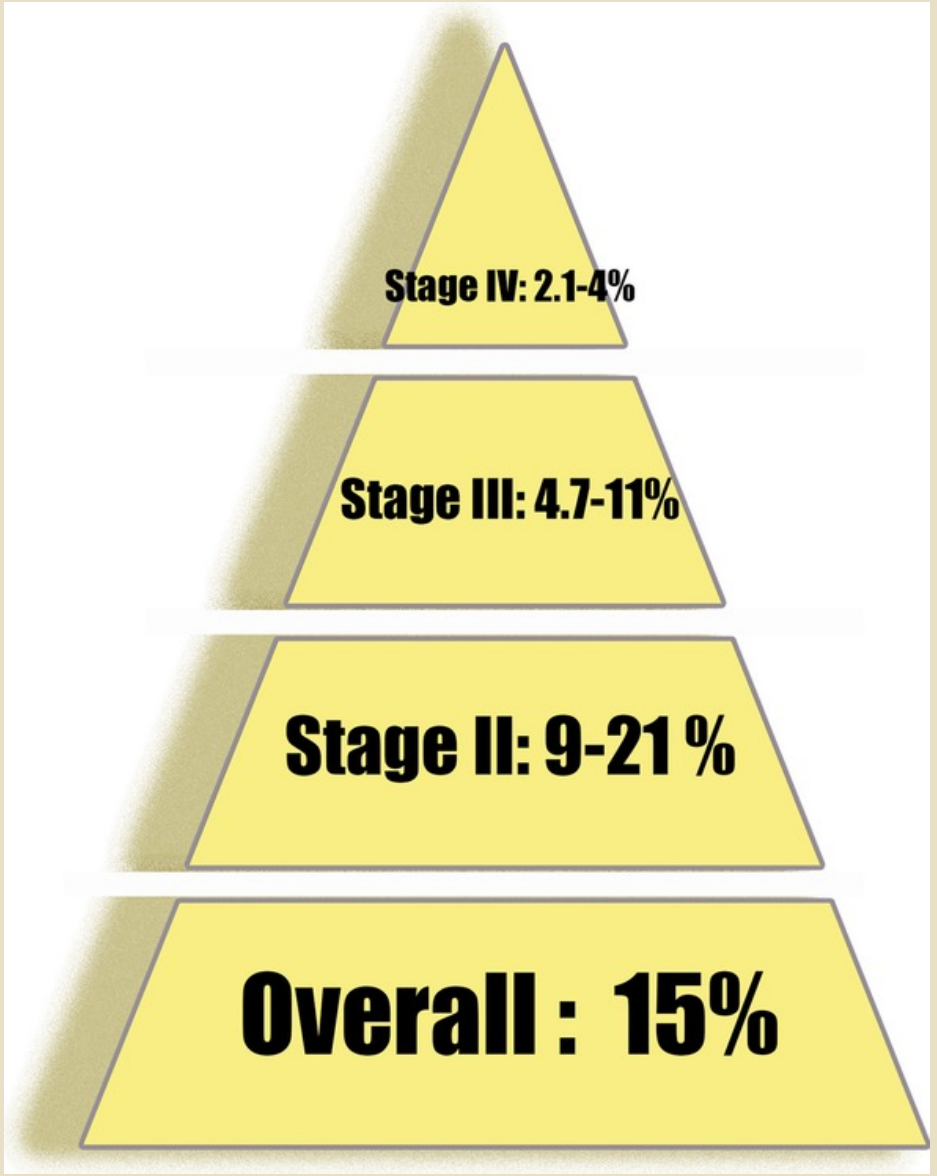
- Monocytes and macrophages upregulated tumor-specific NMF-derived transcriptional programs stimulate growth (growth factors VEGFA and EREG in pM14), and resolve inflammation (APOE in pM06). Myeloid cells from MMRd tumors showed higher activities of programs with genes in glycolysis (pM03), immuneactivating alarmins such as S100A8/9/12 (pM16), and chemokines that attract monocytes and neutrophils (pM20).

- CXCL13+ T cells throughout MMRd tumors, outside of tertiary lymphoid structures , which are usually found at the invasive border.

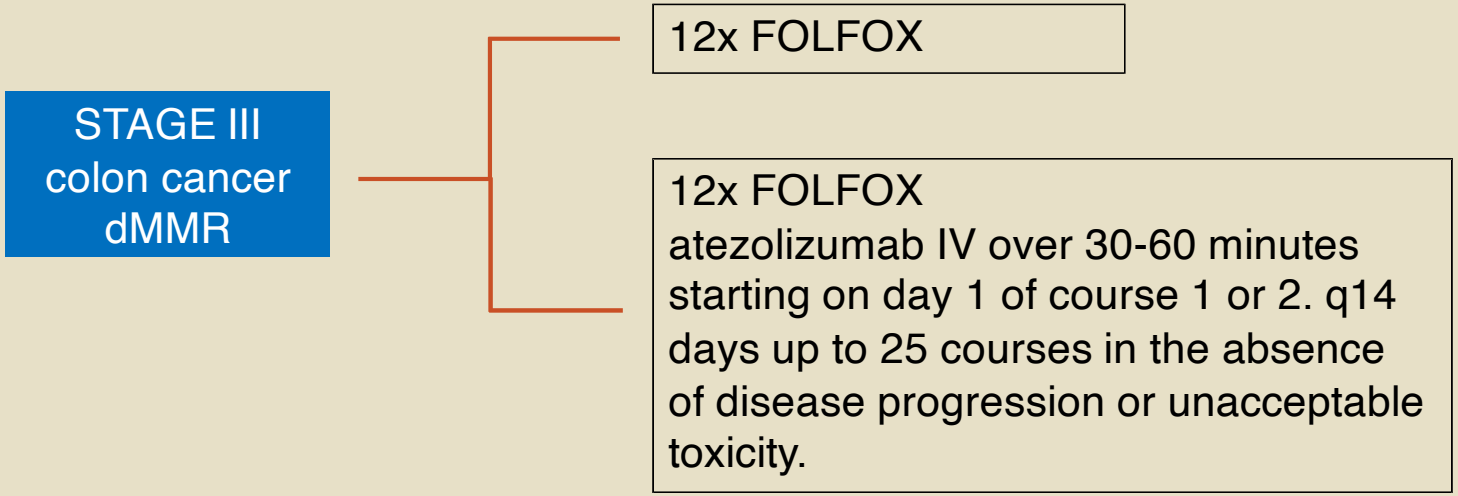
- Pelka et.al., (2021), Cell.

-

- Proportion of dMMR/MSI-H in different tumor stages



Randomized Trial of Standard Chemotherapy Alone or Combined With Atezolizumab as Adjuvant Therapy for Patients With Stage III Colon Cancer and Deficient DNA Mismatch Repair

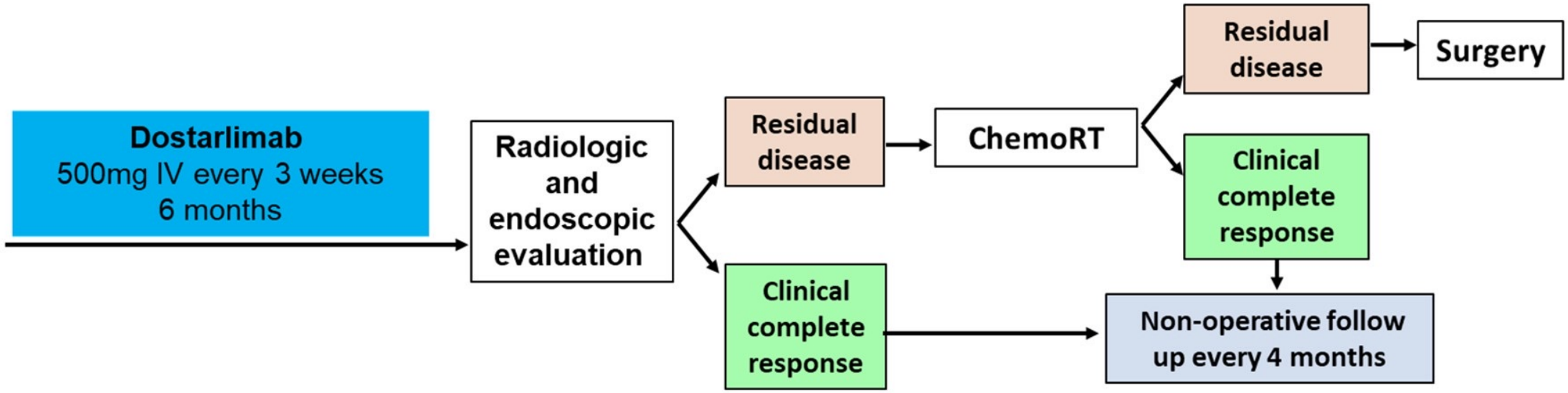


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 23, 2022 VOL. 386 NO. 25

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.



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

Target Enrollment: 30 subjects

Study Design: Simon's two stage minimax design

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**

2022 ASCO® ANNUAL MEETING

Neoadjuvant nivolumab, ipilimumab, and celecoxib in MMR-proficient and MMR-deficient colon cancers: Final clinical analysis of the NICHE study.

Y.L. Verschoor, J. van den Berg, G. Beets, K. Sikorska, A. Aalbers, A. van Lent, C. Grootscholten, I. Huibregtse, H. Marsman, S. Oosterling, M. van de Belt, M. Kok, T. Schumacher, M.E. van Leerdam, J.B.A.G. Haanen, E.E. Voest, M. Chalabi

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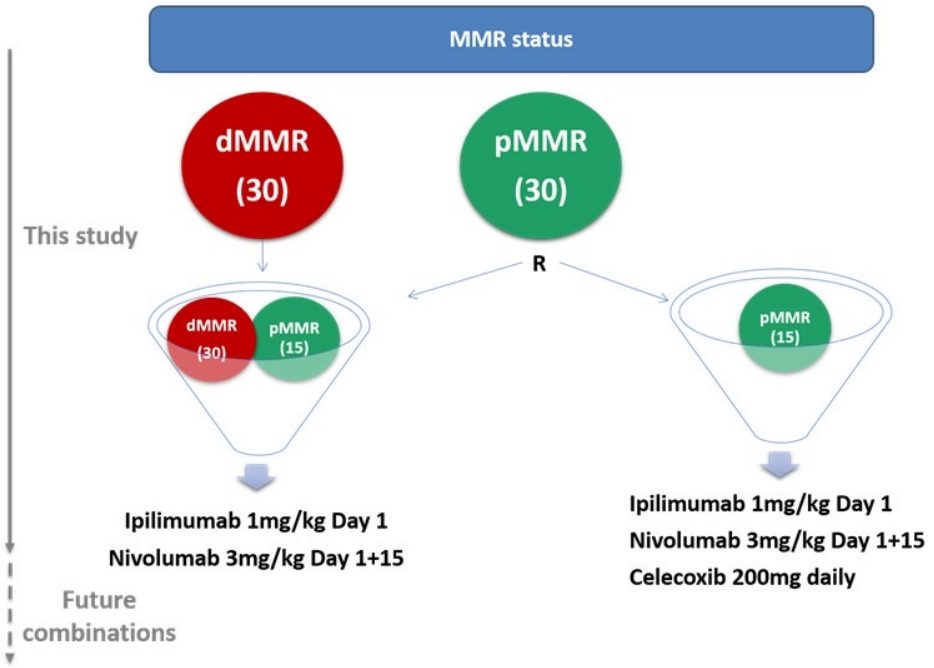
NICHE study design

- Open-label, exploratory study with an adaptive design
- **Study population:** non-metastatic, resectable and previously untreated adenocarcinoma of the colon
- **Original cohorts:** 30 patients with dMMR and 30 with pMMR tumors
- **Treatment** in all patients: nivolumab 3 mg/kg on D1+15 *plus* ipilimumab 1 mg/kg on D1
  - **pMMR cohort:** randomized to additionally receive celecoxib
  - **Surgery within 6 weeks** of registration
- Tumor and normal tissue at baseline and resection, plasma + PBMCs baseline during treatment and follow-up



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Baseline characteristics

	dMMR (*n*= 32)	pMMR (*n*= 33) *
Age, median (range)	54 (22-82)	62 (44-77)
Sex		
Male	14 (44%)	18 (55%)
Female	18 (56%)	15 (45%)
Clinical T stage		
T2	6 (19%)	11 (33%)
T3	10 (31%)	19 (58%)
T4	15 (47%)	1 (3%)
Tx	1 (3%)	2 (6%)
Clinical N stage		
N-	7 (22%)	20 (61%)
N+	25 (78%)	13 (39%)
Primary tumor location		
Right colon	20 (62%)	8 (24%)
Left colon	8 (25%)	23 (70%)
Transverse colon	4 (13%)	2 (6%)
Lynch syndrome	13 (41%)	0 (0%)

* Two pMMR patients excluded from efficacy analysis due to not matching inclusion criteria

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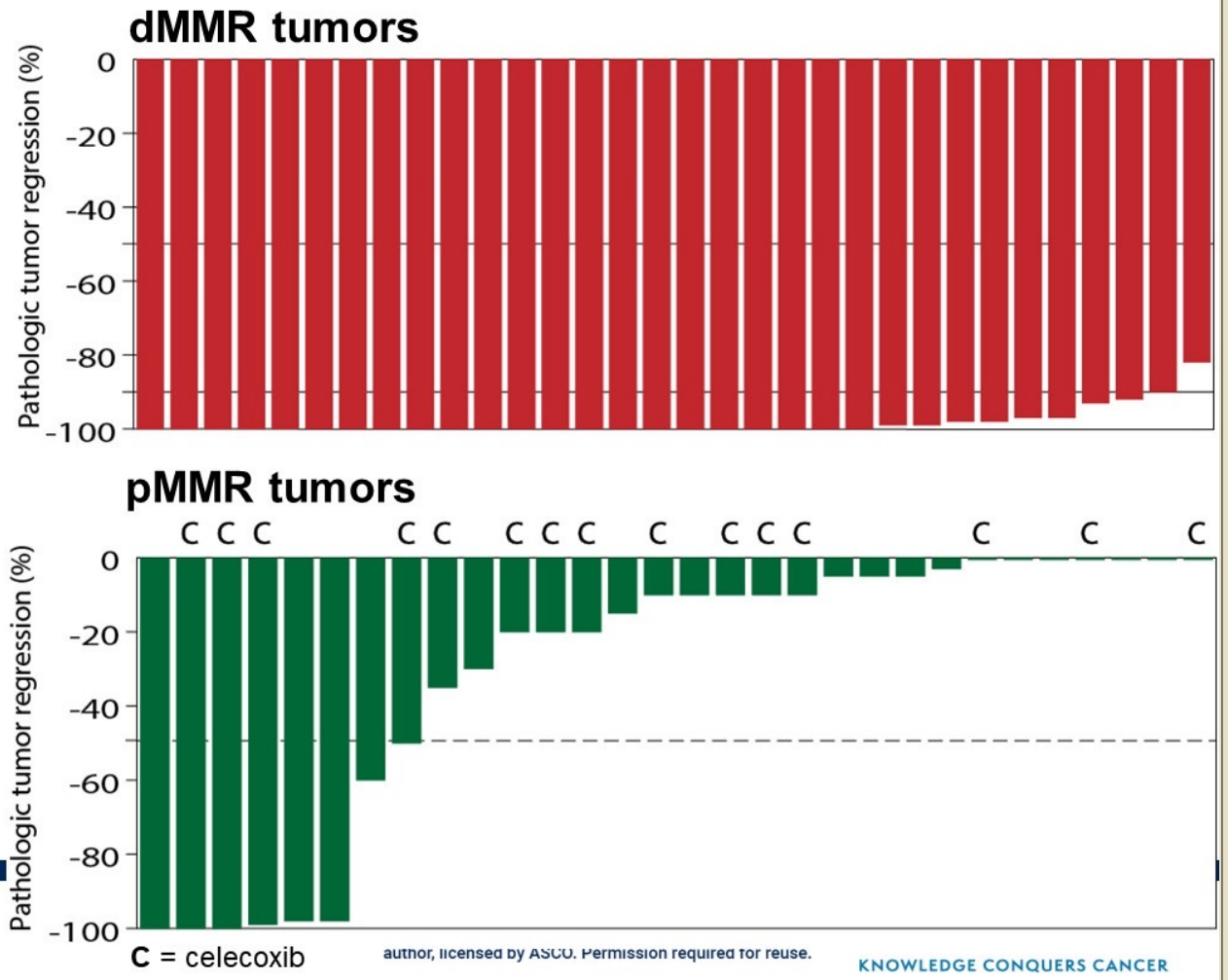
Responses in 29% of pMMR and 100% of dMMR tumors

Pathologic response	dMMR *n*= 32	pMMR *n*= 31
Major (≤10% VTR)	31 (97%)	7 (23%) *
Complete	22 (69%)	4 (13%) *
Partial (≤50% VTR)	1 (3%)	2 (6%)
Nonresponse (>50% VTR)	0 (0%)	22 (71%)

- **dMMR: 32/32 (100%) responders**
  - Lynch: 13/13 MPR, 12 pCR
  - Non-Lynch: 18/19 MPR, 10 pCR; 1 PR
- **pMMR: 9/31 (29%) responders**

*1 patient has not undergone surgery, now 1 year after treatment completion and no longer evidence of intraluminal or radiological disease, incl neg biopsies

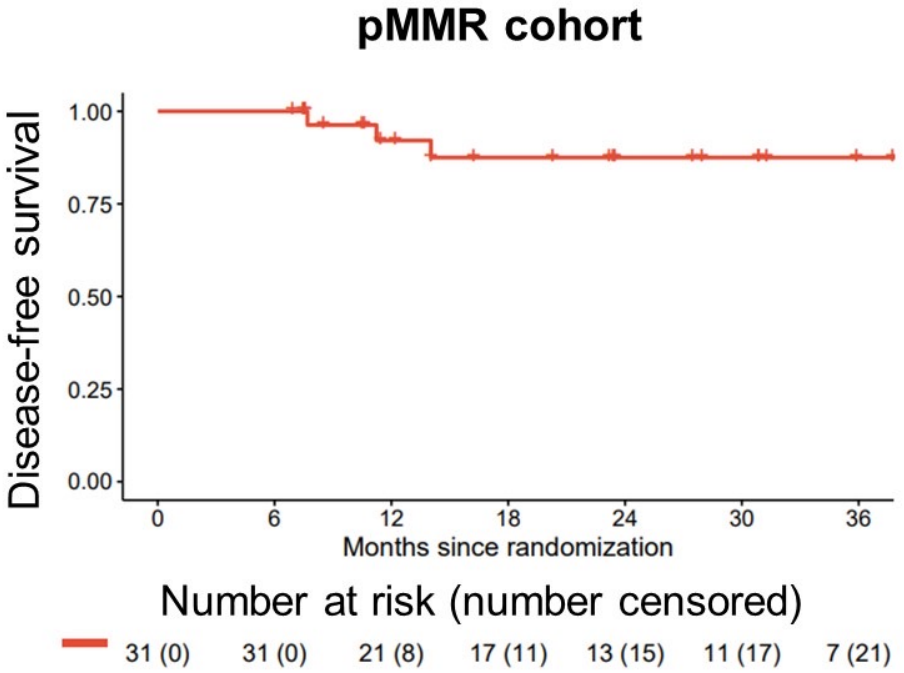
VTR= viable tumor rest; MPR = major pathologic response; pCR = pathologic complete response; PR= partial response



Adjuvant chemotherapy and disease recurrences

- **Adjuvant chemotherapy**
  - 2 dMMR patients with post-treatment positive lymph nodes (1 MPR, 1 PR)
  - 8 pMMR patients (all NR)

- Median follow-up time **pMMR** cohort **28 months**; disease recurrence in 2/31 (6%) patients, both nonresponders*
- Median follow-up time **dMMR** cohort **32 months**: no recurrences to date



* 1 patient had received adjuvant chemotherapy

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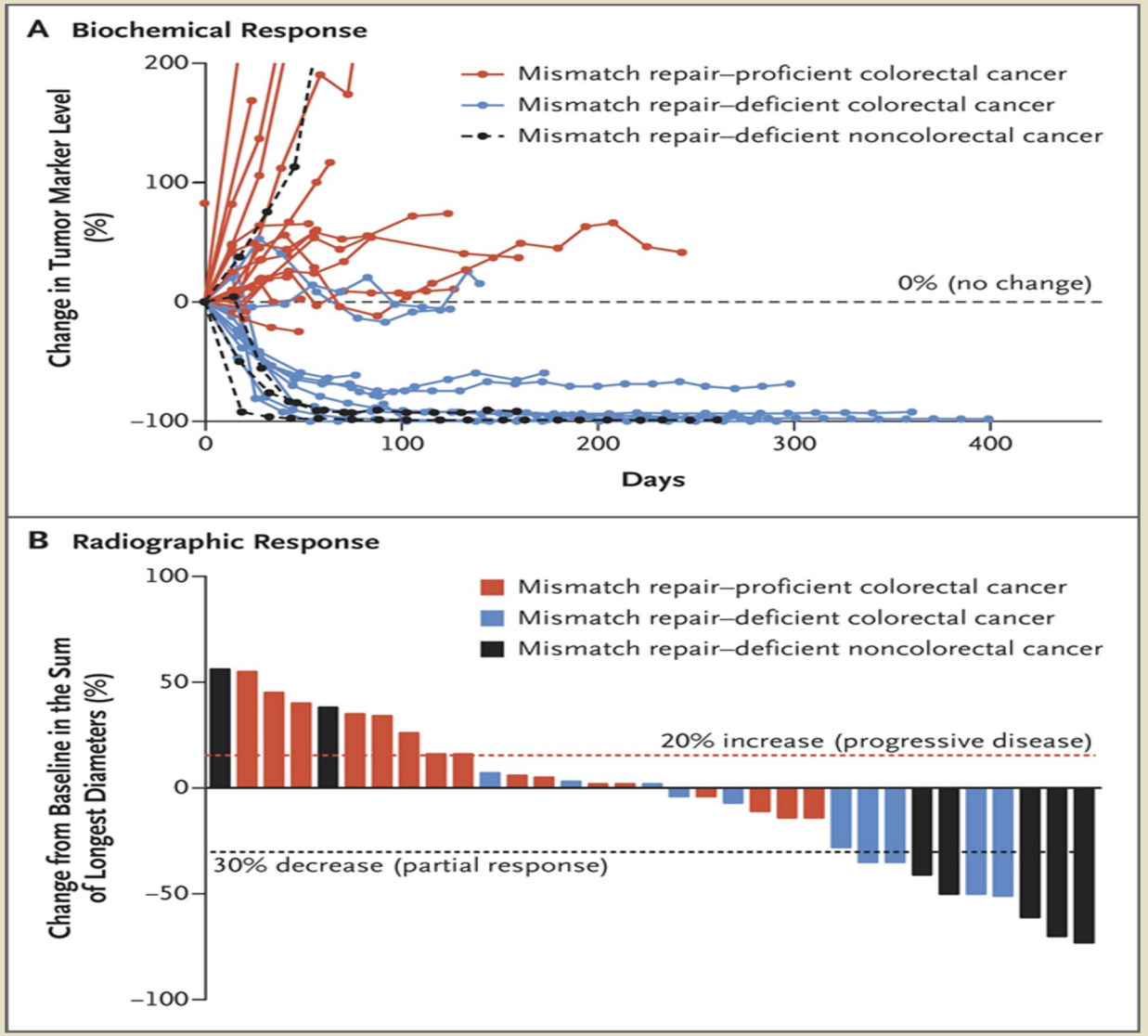
MSI-H Colorectal tumors respond to PD1 Blockade Treatment



Le DT et al. N Engl J Med 2015;372:2509-2520

The NEW ENGLAND JOURNAL of MEDICINE

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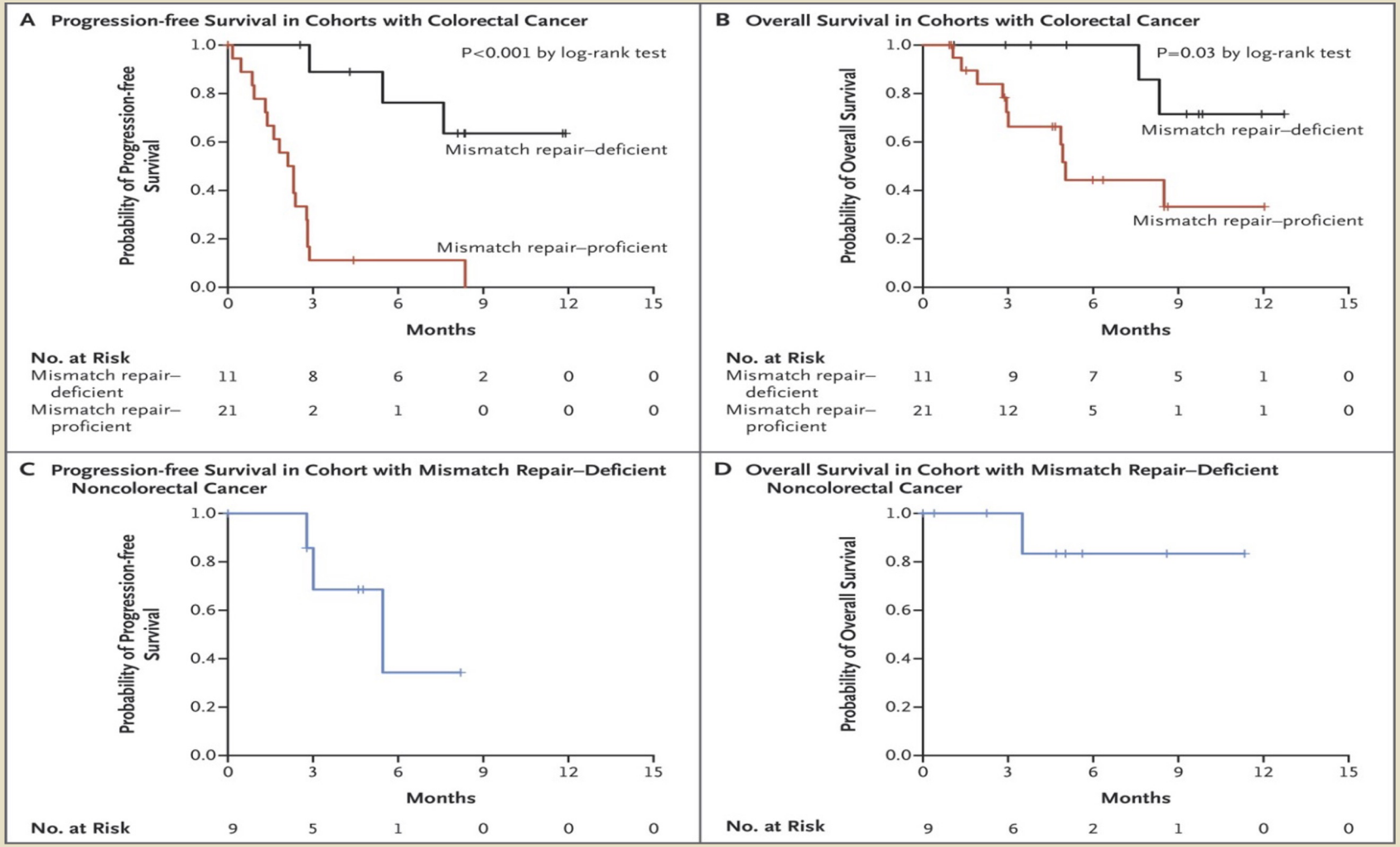

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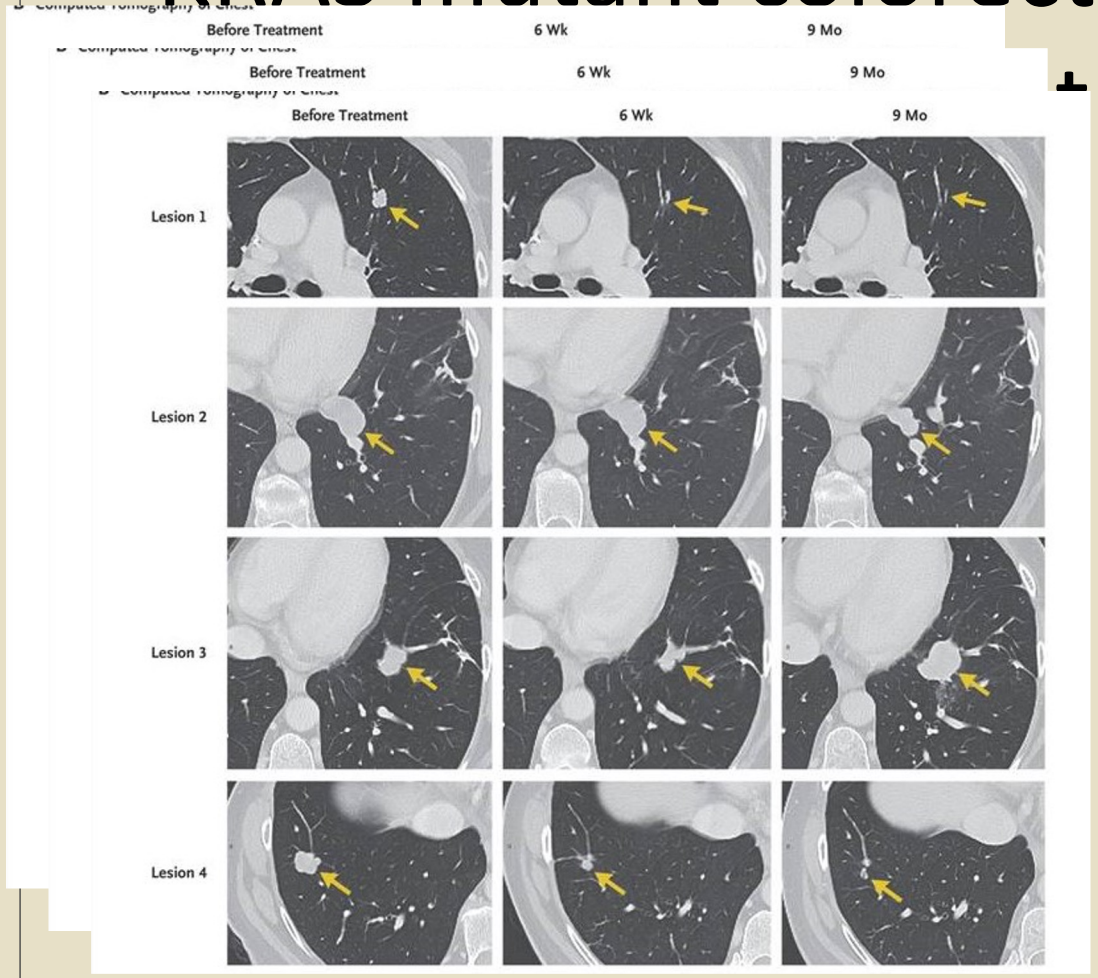
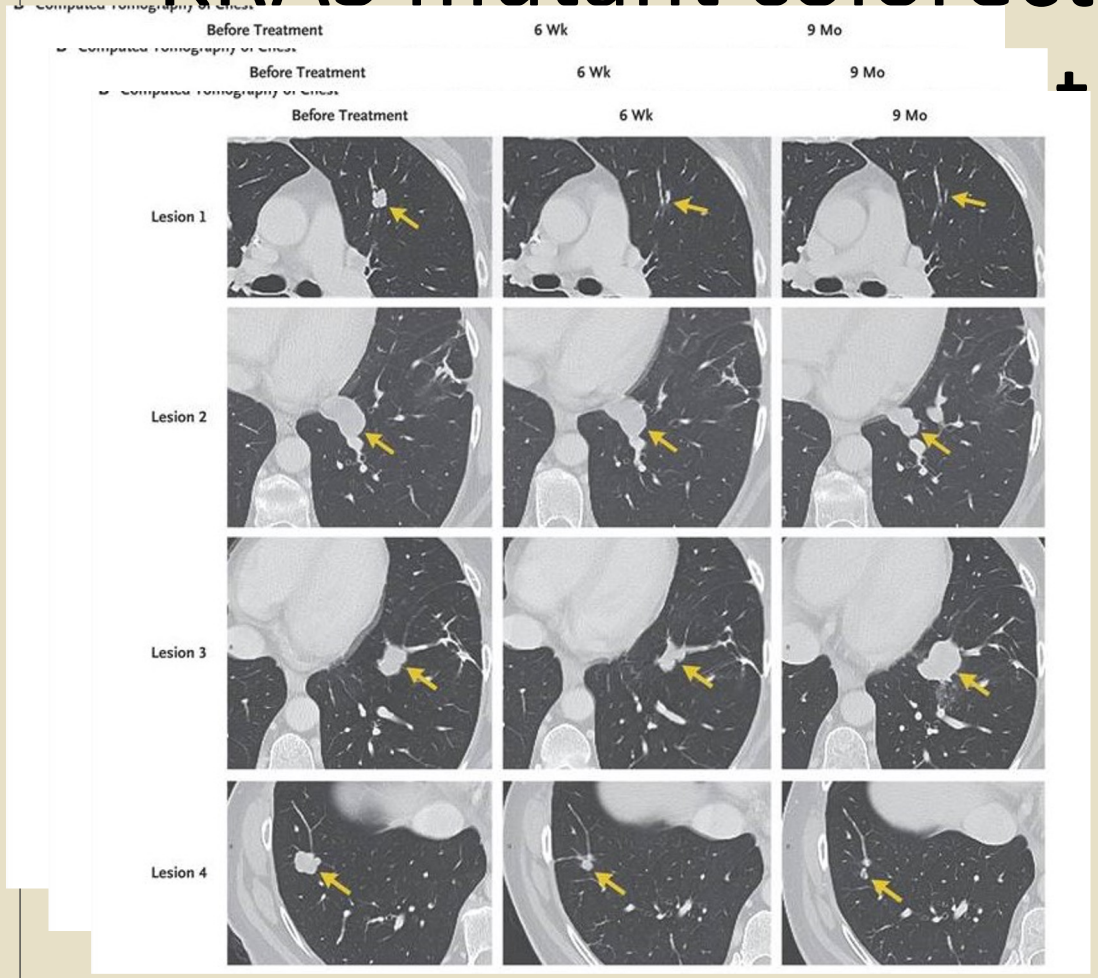
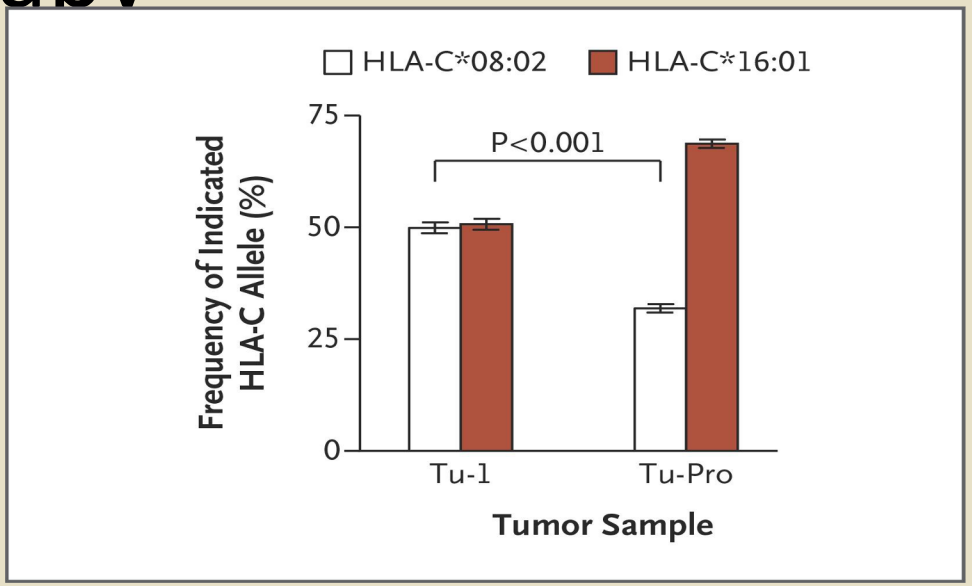
KRAS mutant colorectal cancer and T-cell Transfer therapy



Tran. et.al. T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer
N Engl J Med 2016; 375:2255-2262

KRAS mutant colorectal cancer and T-cell Transfer therapy





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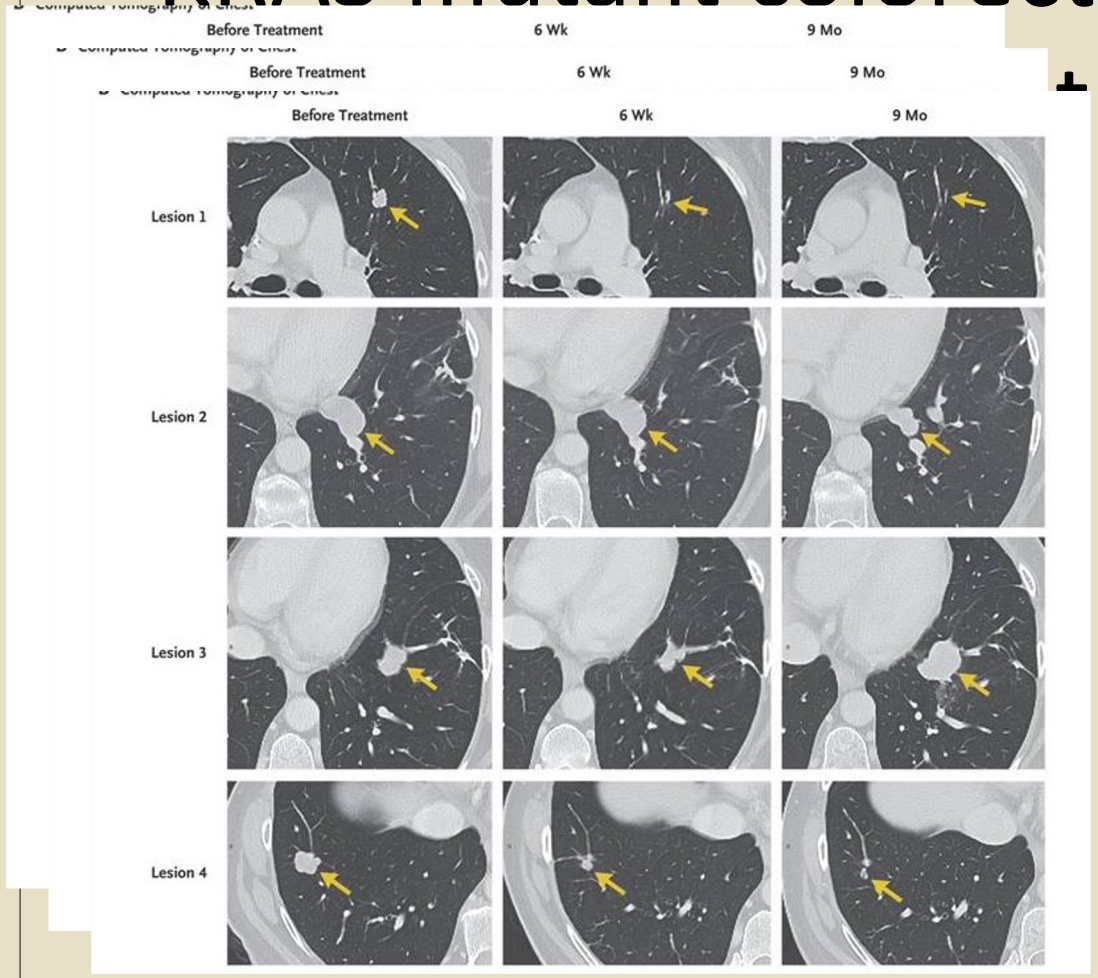
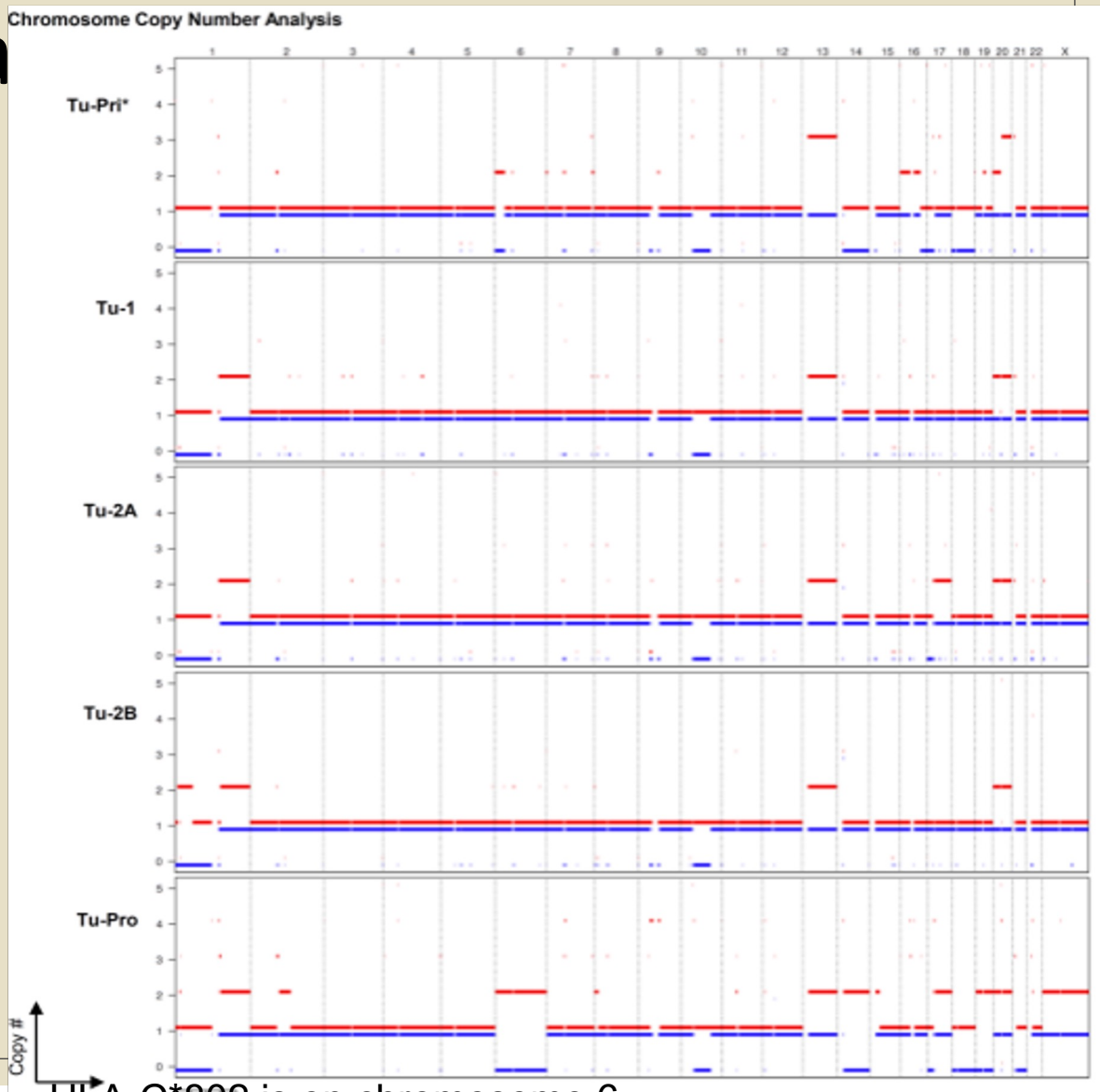
KRAS mutant colorectal cancer and T-cell Transfer +hera





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HLA-C*802 is on chromosome 6

Thank you!

- Any questions? Email me: asmasood@iu.edu