Colorectal Cancer: Chemotherapy Combinations Targeted Therapy and Immunotherapy

Axel Grothey, MD

Director, GI Cancer Research

West Cancer Center and Research Institute
University of Memphis

Memphis, TN, USA

Chemotherapy Combinations

PARADIGM

SUNLIGHT

2022 ASCO® ANNUAL MEETING

Panitumumab plus mFOLFOX6 versus Bevacizumab plus mFOLFOX6 as first-line treatment in patients with *RAS* wild-type metastatic colorectal cancer: results from the phase 3 PARADIGM trial

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

[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [2]Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan; [3]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [4]Division of Medical Oncology, Japanese Red Cross Ishinomaki Hospital, Miyagi, Japan; [5]Division of Gastrointestinal Surgery, Kanagawa Cancer Center, Kanagawa, Japan; [6]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [7]Research and Development Center for Medical Education, Department of Clinical Skills Education, Kitasato University School of Medicine, Sagamihara, Japan; [8]Department of Lower Gastrointestinal Surgery, Kitasato University School of Medicine, Sagamihara, Japan; [9]Division of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Japan; [10]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan; [11]Japan Medical Affairs, Japan Oncology Business Unit, Takeda Pharmaceutical Company Ltd., Tokyo, Japan; [12]Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan; [13]Division of Molecular Diagnosis and Cancer Prevention, Saitama Cancer Center, Saitama, Japan; [14]Pathology Division, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan; [15]National Hospital Organization, Disaster Medical Center, Tokyo, Japan; [16]Division of Translational Informatics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan; [17]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

PARADIGM Trial Design

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

Patients with *RAS* WT mCRC

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

N=823

R
1:1

Panitumumab +mFOLFOX6[b]

Bevacizumab +mFOLFOX6[b]

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

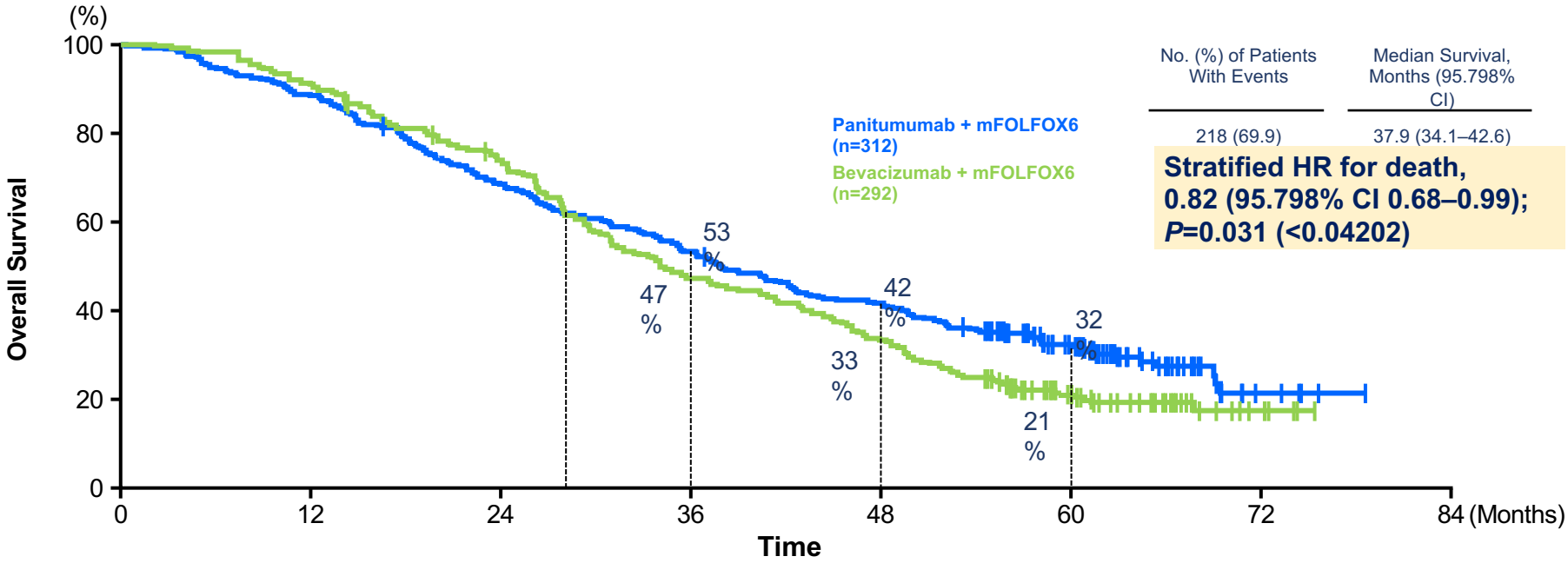
Secondary endpoints
- PFS, RR, DOR, R0 resection: left-sided[c] and overall populations
- Safety: all treated patients

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

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

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

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

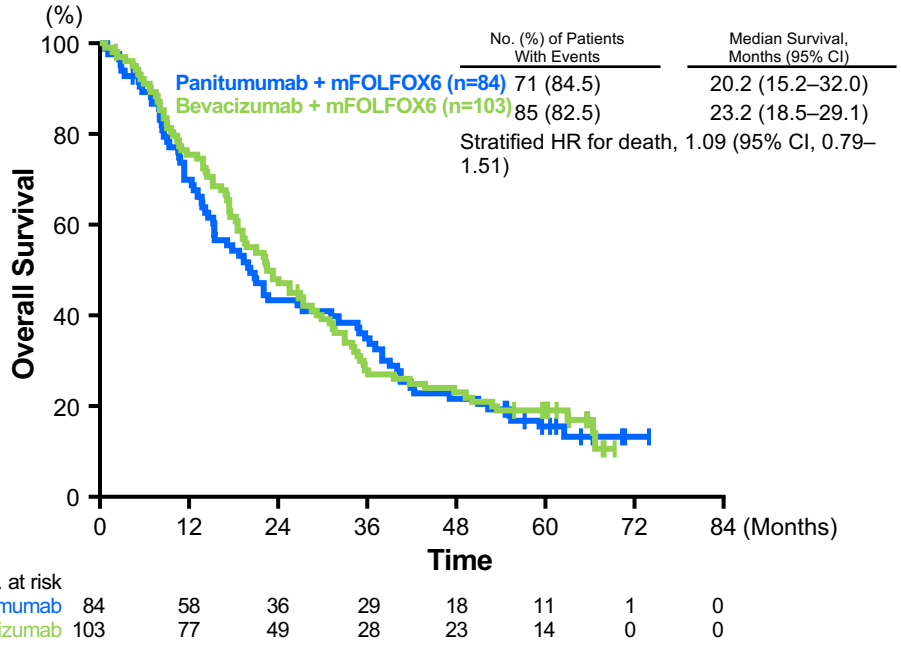


	No. (%) of Patients With Events	Median Survival, Months (95.798% CI)
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	37.9 (34.1–42.6)

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

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.

Negative hyperselection of patients with *RAS* wild-type metastatic colorectal cancer for panitumumab: A biomarker study of the phase III PARADIGM trial

Kohei Shitara[1], Kei Muro[2], Jun Watanabe[3], Kentaro Yamazaki[4], Hisatsugu Ohori[5], Manabu Shiozawa[6], Hirofumi Yasui[4], Eiji Oki[7], Takeo Sato[8], Takeshi Naito[9], Yoshito Komatsu[10], Takeshi Kato[11], Kazunori Yamanaka[12], Junpei Soeda[13], Ikuo Mori[13], Masamitsu Hihara[13], Kouji Yamamoto[14], Riu Yamashita[15], Kiwamu Akagi[16], Atsushi Ochiai[17], Hiroyuki Uetake[18], Katsuya Tsuchihara[15], Takayuki Yoshino[1]

[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [2]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [3]Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan; [4]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [5]Division of Medical Oncology, Japanese Red Cross Ishinomaki Hospital, Miyagi, Japan; [6]Division of Gastrointestinal Surgery, Kanagawa Cancer Center, Kanagawa, Japan; [7]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [8]Research and Development Center for Medical Education, Department of Clinical Skills Education, Kitasato University School of Medicine, Sagamihara, Japan; [9]Department of Lower Gastrointestinal Surgery, Kitasato University School of Medicine, Sagamihara, Japan; [10]Division of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Japan; [11]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan; [12]Pharmaceutical Research Division, Takeda Pharmaceutical Company Ltd, Tokyo, Japan; [13]Japan Medical Affairs, Japan Oncology Business Unit, Takeda Pharmaceutical Company Ltd, Tokyo, Japan; [14]Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan; [15]Division of Translational Informatics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan; [16]Division of Molecular Diagnosis and Cancer Prevention, Saitama Cancer Center, Saitama, Japan; [17]Research Institute for Biomedical Sciences, Tokyo University of Science, Tokyo, Japan; [18]National Hospital Organization, Disaster Medical Center, Tokyo, Japan

Shitara et al., ASCO GI 2023

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)

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Survival outcomes in the right-sided population analyzed for ctDNA

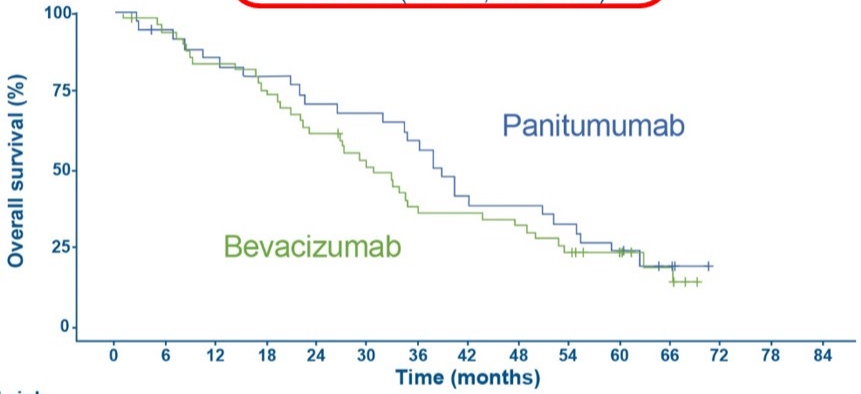
Hyperselected

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

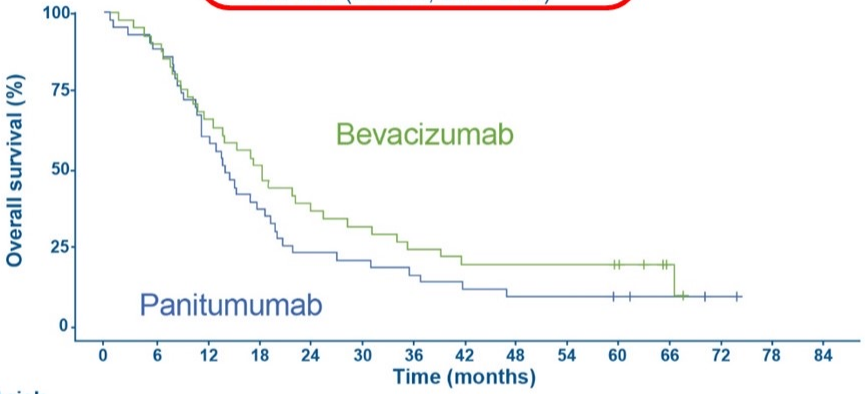
Gene Altered

mOS, months (95% CI)

Panitumumab 14.1 (11.3–18.7)

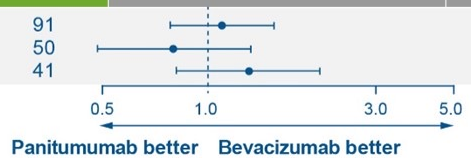
Bevacizumab 18.5 (11.6–25.5)

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	
	Hyperselected	85	35	50	0.82 (0.50–1.35)	0.431	0.145
	Gene altered	84	43	41	1.33 (0.84–2.11)	0.228	



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ASCO Gastrointestinal Cancers Symposium

Trifluridine/tipiracil plus bevacizumab for third-line treatment of refractory metastatic colorectal cancer

The phase 3 randomized SUNLIGHT study

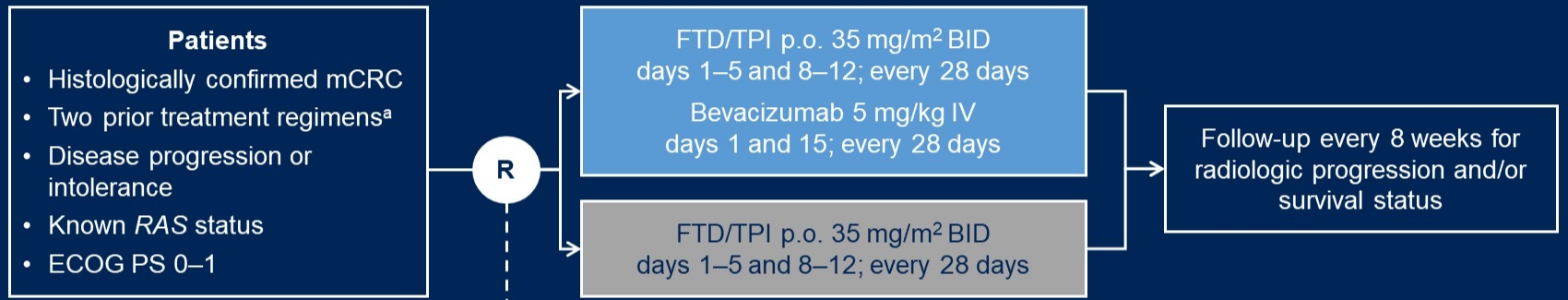
Josep Tabernero[1], Gerald W. Prager[2], Marwan Fakih[3], Fortunato Ciardiello[4], Eric Van Cutsem[5], Elena Elez[1], Felipe Melo Cruz[6], Lucjan Wyrwicz[7], Daniil Stroyakovskiy[8], Zsuzsanna Pápai[9], Pierre-Guillaume Poureau[10], Gabor Liposits[11], Chiara Cremolini[12], Igor Bondarenko[13], Dominik Paul Modest[14], Karim A. Benhadji[15], Ronan Fougeray[16], Catherine Leger[16], Nadia Amellal[16], and Julien Taieb[17]

[1]Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; [2]Medical University Vienna, Vienna, Austria; [3]City of Hope Comprehensive Cancer Center, Duarte, USA; [4]Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy; [5]University Hospitals Leuven and KU Leuven, Herent, Belgium; [6]Núcleo de Pesquisa e Ensino da Rede São Camilo, Sao Paulo, Brazil; [7]Maria Sklodowska-Curie National Cancer Research Institute, Warsaw, Poland; [8]Moscow City Oncological Hospital #62, Moscow, Russian Federation; [9]Duna Medical Centre, Budapest, Hungary; [10]Institut de Cancérologie, Brest, France; [11]University of Southern Denmark, Odense, Denmark; [12]University of Pisa, Pisa, Italy; [13]Dnipropetrovsk Medical Academy, Dnipro, Ukraine; [14]Charité Universitätsmedizin, Berlin, Germany; [15]Taiho Oncology, Inc., Princeton, USA; [16]Servier International Research Institute, Suresnes, France; [17]Université Paris-Cité, (Paris Descartes), Georges Pompidou European Hospital, SIRIC CARPEM, Paris, France.

PRESENTED BY: Prof. Josep Tabernero

SUNLIGHT study design

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

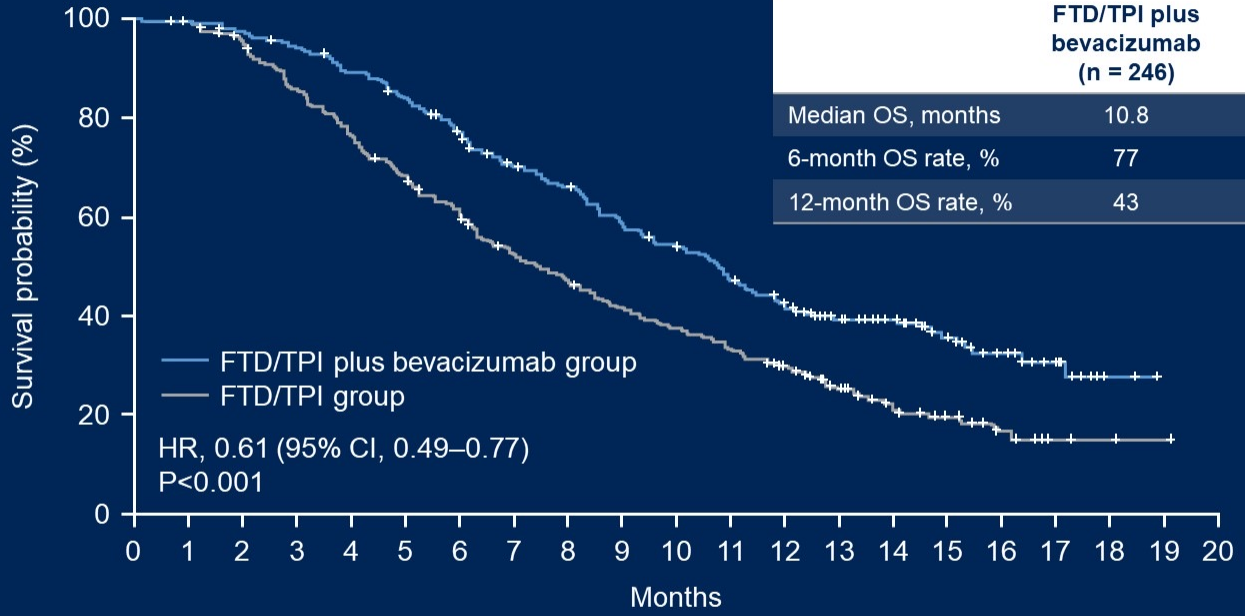


[a] Prior treatment must have included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (not necessarily bevacizumab), and/or an anti-EGFR monoclonal antibody for patients with *RAS* wild-type and could have included (neo)adjuvant chemotherapy if disease had recurred during 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.

OS in full analysis set (primary endpoint)

PFS 5.6 vs 2.4 mos
HR 0.44, P<0.0001

RR 6.3 vs 0.9%
DCR 77 vs 47%



	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

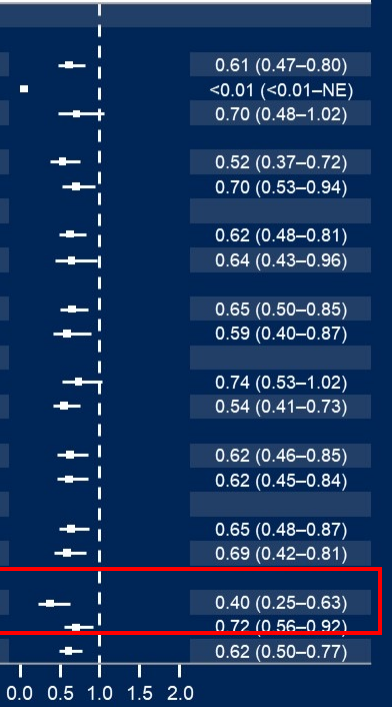
No. at risk

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.

OS by prespecified subgroup

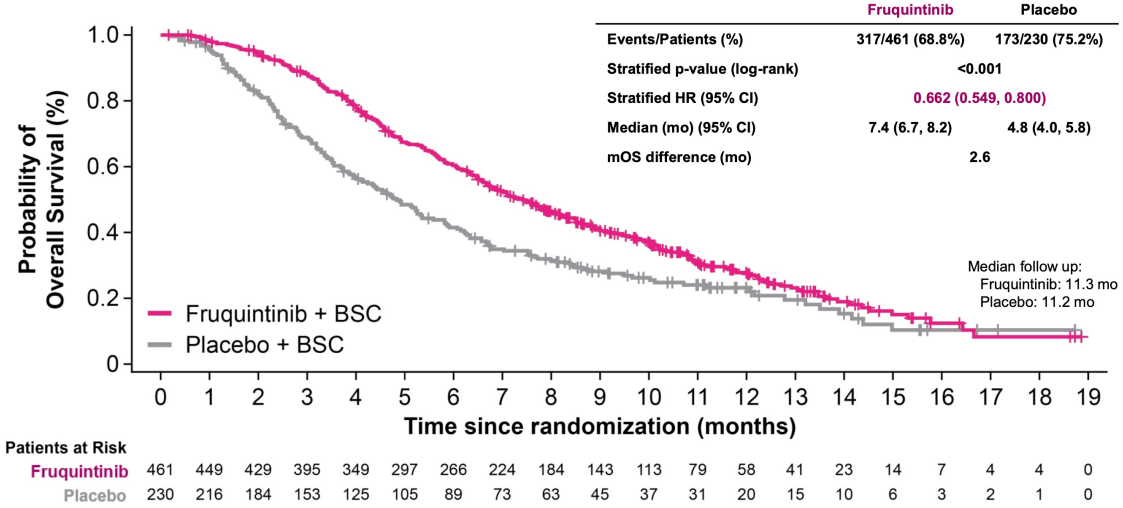
Subgroup	FTD/TPI plus bevacizumab group	FTD/TPI group	FTD/TPI plus bevacizumab group	FTD/TPI group	HR
	No. of events/total no.		*Median OS (95% CI)*		
Region					
European Union	97/158	121/157	10.6 (9.0–11.8)	7.0 (6.0–8.5)	0.61 (0.47–0.80)
North America	0/8	4/8	NE	6.0 (4.2–NE)	<0.01 (<0.01–NE)
Rest of the world	51/80	58/81	10.7 (8.5–14.2)	8.5 (6.3–10.7)	0.70 (0.48–1.02)
Time from diagnosis of first metastasis, months					
<18	65/104	82/105	10.8 (8.8–12.5)	6.1 (5.1–7.4)	0.52 (0.37–0.72)
≥18	83/142	101/141	10.8 (9.0–12.1)	8.6 (7.2–10.6)	0.70 (0.53–0.94)
RAS status					
Mutant	103/171	128/170	10.6 (9.0–11.3)	7.5 (6.3–8.6)	0.62 (0.48–0.81)
Wild-type	45/75	55/76	11.9 (9.0–14.9)	7.1 (5.9–10.9)	0.64 (0.43–0.96)
Location of primary disease					
Left	108/184	120/169	10.7 (9.3–12.2)	8.2 (6.7–9.3)	0.65 (0.50–0.85)
Right	40/62	63/77	10.8 (8.5–11.9)	6.2 (5.2–8.0)	0.59 (0.40–0.87)
ECOG PS					
0	70/119	74/106	10.8 (8.8–14.5)	9.3 (7.7–11.6)	0.74 (0.53–1.02)
≥1	78/127	109/140	10.8 (9.0–11.9)	6.3 (5.4–7.5)	0.54 (0.41–0.73)
Sex					
Female	79/124	85/112	10.7 (9.0–11.4)	6.9 (6.0–9.0)	0.62 (0.46–0.85)
Male	69/122	98/134	10.8 (9.0–14.6)	7.8 (6.5–9.4)	0.62 (0.45–0.84)
Age, years					
<65	89/146	94/129	10.7 (8.5–12.1)	7.5 (6.3–9.3)	0.65 (0.48–0.87)
≥65	59/100	89/117	11.0 (9.4–12.9)	7.2 (6.0–8.8)	0.69 (0.42–0.81)
Prior bevacizumab					
No	30/68	48/69	15.1 (12.1–NE)	8.1 (6.3–9.7)	0.40 (0.25–0.63)
Yes	118/178	135/177	9.0 (8.3–10.8)	7.1 (6.0–8.5)	0.72 (0.56–0.92)
Overall	148/246	183/246	10.8 (9.4–11.8)	7.5 (6.3–8.6)	0.62 (0.50–0.77)



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; NE, not evaluable; OS, overall survival.

My Conclusions from SUNLIGHT

- **TAS-102 plus BEV is the new SOC for patients with mCRC when TAS-102 is considered**
  - Study confirms data from prior phase 2 studies
  - TAS-102 plus BEV is already listed in NCCN guidelines as CAT 2A
- **Combination should be used before regorafenib**
- **Confirms the concept of VEGF inhibition beyond progression, as does fruquintinib FRESCO-2 trial, ESMO 2022)**



Targeted Therapies

BRAF

KRAS G12C

HER-2

Overview of Precision Medicine Approaches in GI Cancers

GI Cancer	Negative predictive markers	Positive predictive markers	Cancer-agnostic markers
Gastroesophageal		HER-2 PD-L1 FGFR2b CLDN-18.2	MSI-H/ MMR-D POLe/d TMB? NTRK fusions RET fusions BRAF V600E KRAS G12C? NRG1 fusions?
CRC	RAS mutations BRAF V600E Sidedness (HER-2)?	**HER-2** **BRAF V600E** **MSI-H/ MMR-D** **KRAS G12C**	
Biliary cancers (IHCC!)		IDH-1 FGFR fusions HER-2 BRAF V600E	
Pancreas cancer		BRCA (-like)	
HCC		(AFP high)	

BEACON: Phase 3 in 2nd/ 3rd Line BRAF V600E mut mCRC

Patients with *BRAF*^{V600E} mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

ENCORAFENIB + BINIMETINIB + CETUXIMAB
N = 30

Encorafenib 300 mg PO daily
Binimetinib 45 mg PO bid
Cetuximab standard weekly dosing

R 1:1:1

Triplet therapy
ENCORAFENIB + BINIMETINIB + CETUXIMAB
n = 205

Doublet therapy
ENCORAFENIB + CETUXIMAB
n = 205

Control arm
FOLFIRI + CETUXIMAB, or irinotecan + CETUXIMAB
n = 205

Primary Endpoints:

Triplet vs Control

OS
(All randomized Pts)

ORR – Blinded Central Review
(1st 331 randomized Pts)

Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

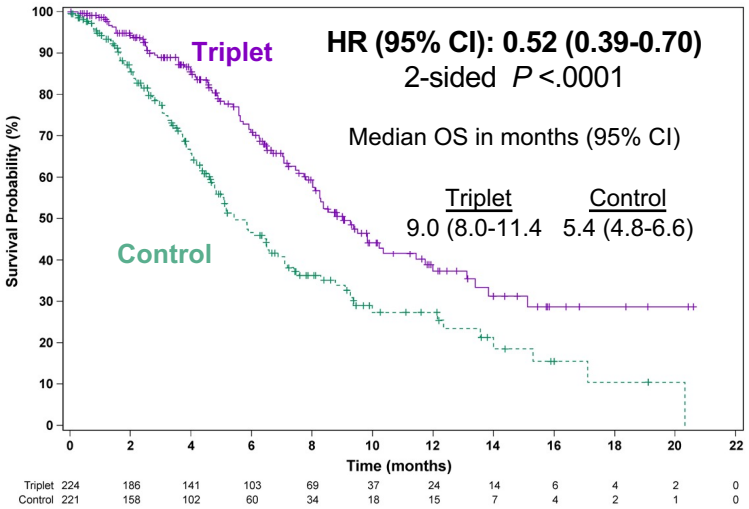
Secondary Endpoints: Doublet vs Control and Triplet vs Doublet - OS & ORR, PFS, Safety

QOL Assessments: EORTC QOL Questionnaire (QLQ C30), Functional Assessment of Cancer Therapy Colon Cancer, EuroQol 5D5L, and Patient Global Impression of Change).

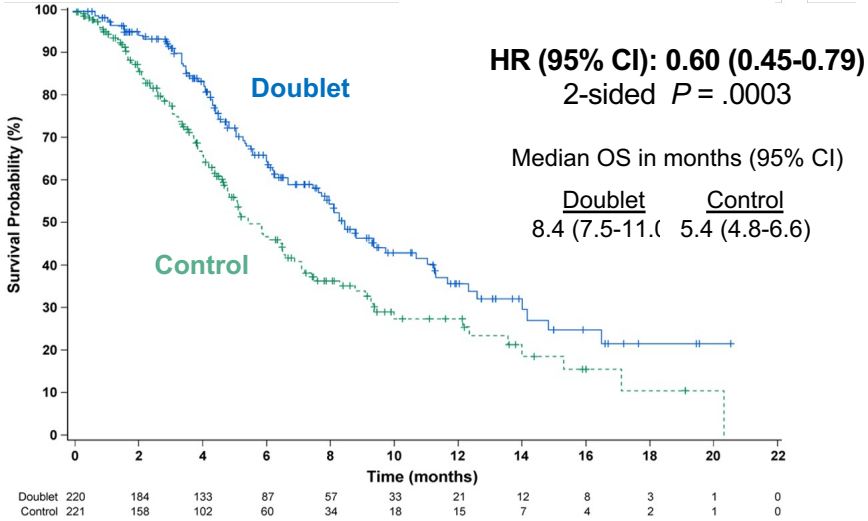
Kopetz et al., NEJM 2019

BEACON: Overall Survival and Objective Response Rate

Triplet vs Control



Doublet vs Control



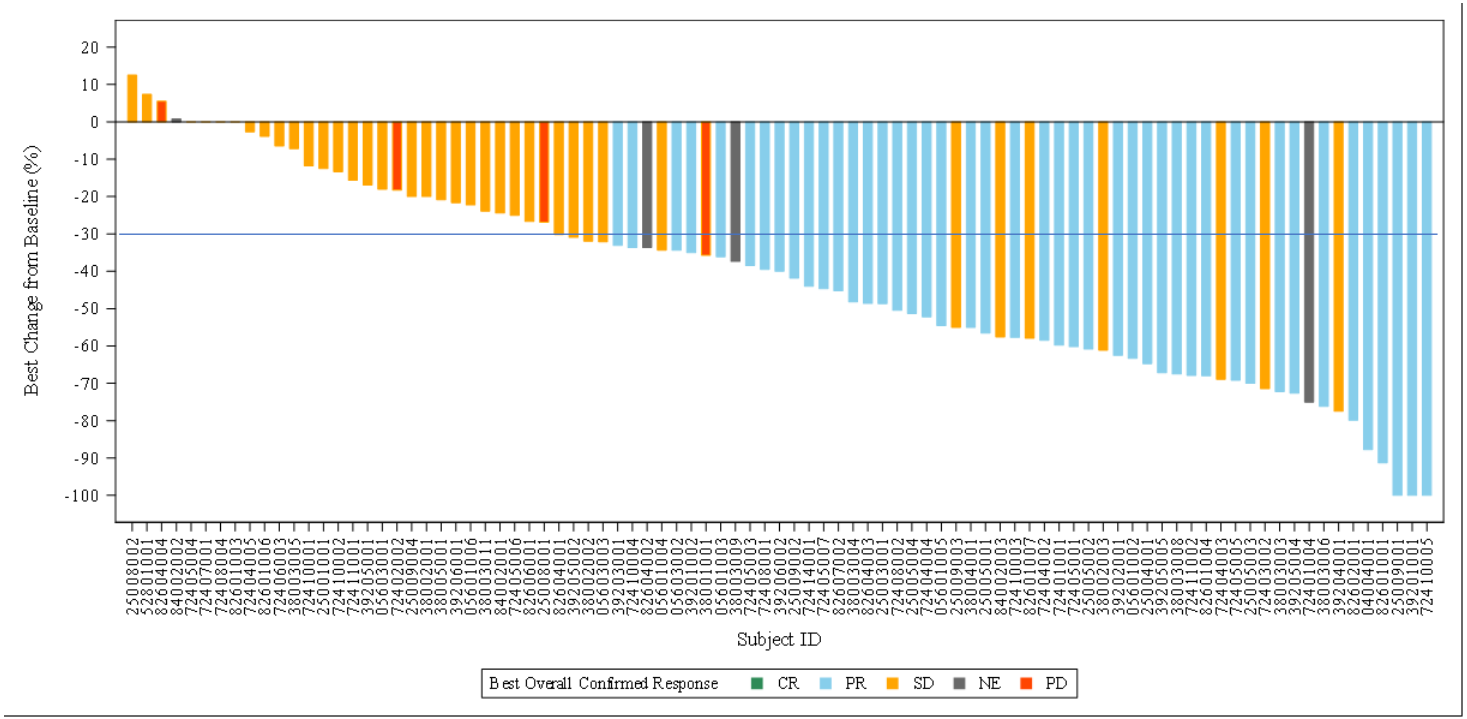
Objective Response Rate (first 331 randomized patients)

Confirmed Response by BICR	Triplet N = 111	Doublet N = 113	Control N = 107
Objective response rate	**26%**	**20%**	**2%**
(95% CI)	(18–35)	(13–29)	(<1–7)
P value vs control	<.0001	<.0001	

Kopetz S, Grothey A, et al. ESMO 2019. Abstract LBA-006; Kopetz S, Grothey A, et al. *N Engl J Med*. 2019;381:1632-1643.

ANCHOR CRC, Phase 2 study in FIRST LINE BRAF^{V600E} mCRC

Investigator's assessment, patients evaluable for efficacy (N=92)



RR 48%
DCR 88%
PFS 5.8 mos
OS 18.3 mos

3 patients have been excluded from the efficacy analysis as the BRAF mutation was not confirmed/indeterminate by central lab
The 4 subjects with the best percentage change from baseline equal to 0% have their Best Overall Confirmed Response equal to Stable Disease (SD).
Two subjects (38003012 and 72406001) with BOCR equal to NE are not presented in the plot because they don't have post-baseline tumor diameters.
One subject (72402001) with BOCR equal to PD is not presented in the plot because 1 target lesion was not evaluable and sum of longest diameters cannot be calculated at the unique post-baseline evaluation.

Van Cutsem et al., ASCO 2021; JCO 2023

Frontline BRAF V600E Phase III RCT

BREAKWATER Study Schema

Safety Lead-in (completed)

Patients with *BRAF* V600E mutant, MSS/pMMR mCRC with 0 -1 prior regimens in the metastatic setting

Encorafenib + Cetuximab + mFOLFOX6
N=30
Encorafenib + Cetuximab + FOLFIRI
N=30

Doses:
Encorafenib- 300 mg PO QD
Cetuximab- 500 mg/m^2 IV Q2W
FOLFOX- full doses IV Q2W
FOLFIRI- full doses IV Q2W

ENDPOINTS

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

Phase 3

Patients with *BRAF* V600E mutant, MSS/pMMR mCRC and no prior systemic therapy in the metastatic setting

Randomize 1:1:1*

- Arm A**
  Encorafenib + Cetuximab
  N=290
- Arm B**
  Encorafenib + Cetuximab + FOLFOX or FOLFIRI[β]
  N=290
- Control Arm [§]
  Physicians Choice: FOLFOX, FOLFIRI, FOLFOXIRI, CAPOX, all +/- anti-VEGF antibody
  N=290

1° ENDPOINTS

- PFS (BICR) Arm A v. Control
  AND
- PFS (BICR) Arm B v. Control

(BICR-blinded independent central review)

KEY 2° ENDPOINTS

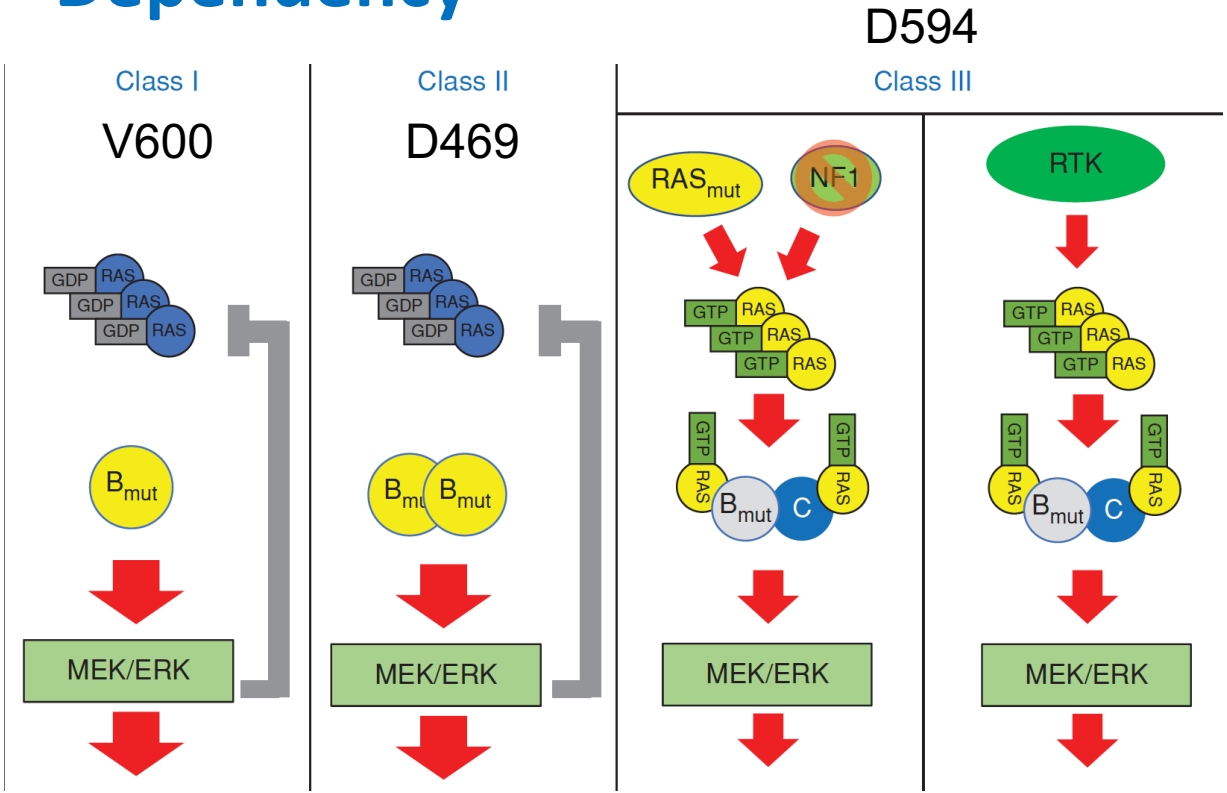
- OS Arm A v. Control
  AND
- OS Arm B v. Control

*Stratified by: ECOG PS 0 v. 1, Region US/Canada v. Europe v. ROW

**Same dosing as SLI; [β]FOLFOX or FOLFIRI based on SLI results; [§] No crossover

ClinicalTrials.gov Identifier: NCT04607421

BRAF Mutations: Kinase Activity and RTK Signaling Dependency



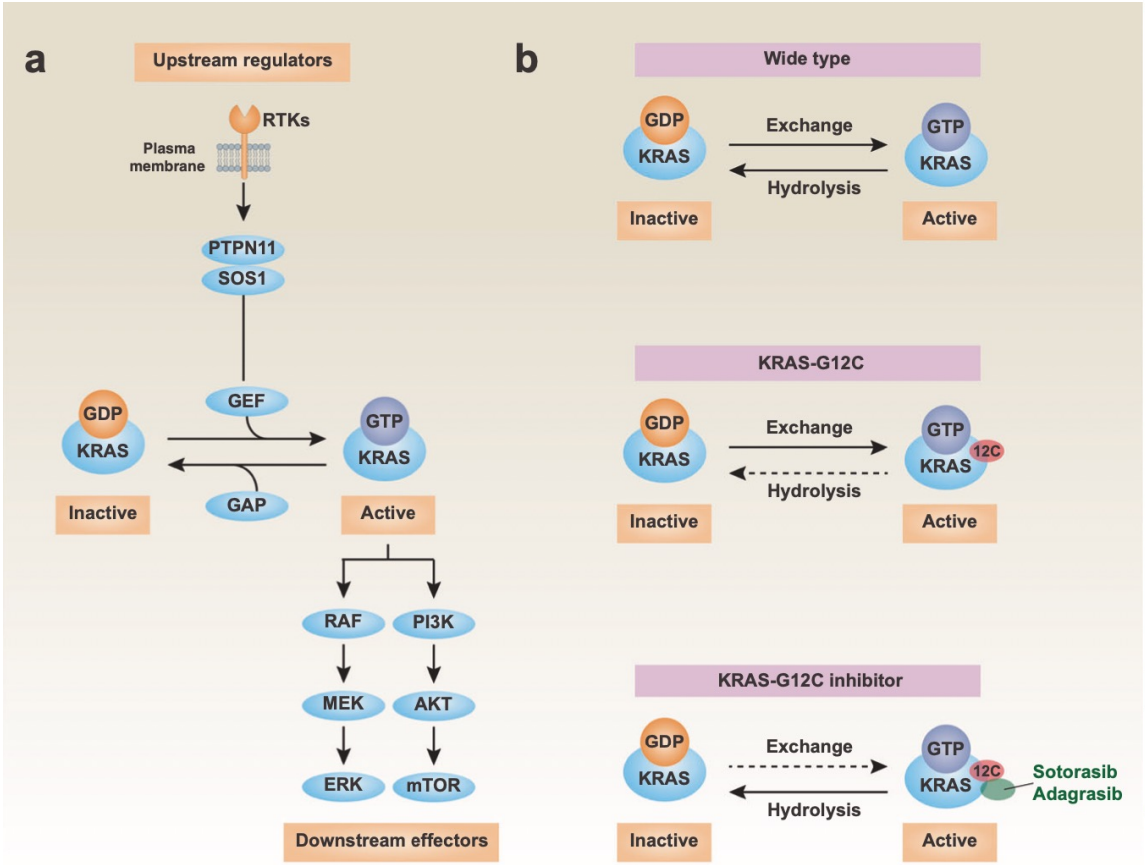
Yaeger. Cancer Discov. 2019;9:329.

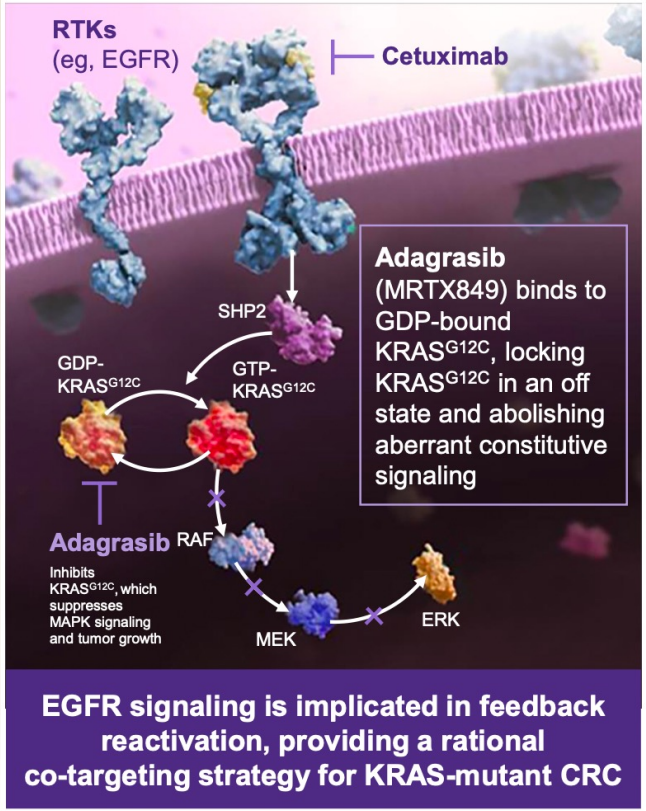
Class I mutations:
V600E/K/D/R/M

Class II mutations:
P367L/S, G464V/E, **G469A/V/R**, L485W, N486_A489delinsK, N486_P490del, E586K, L597Q/R/S/V, T599TT/TS, T599I/K, K601E/N/T, K601_S602delinsNT, BRAF kinase duplication, BRAF kinase domain fusions

Class III mutations:
D287H, V459L, G466A/E/V, S467L, G469E, N581I/S/T, **D594A/G/H/N**, F595L, G596D/R

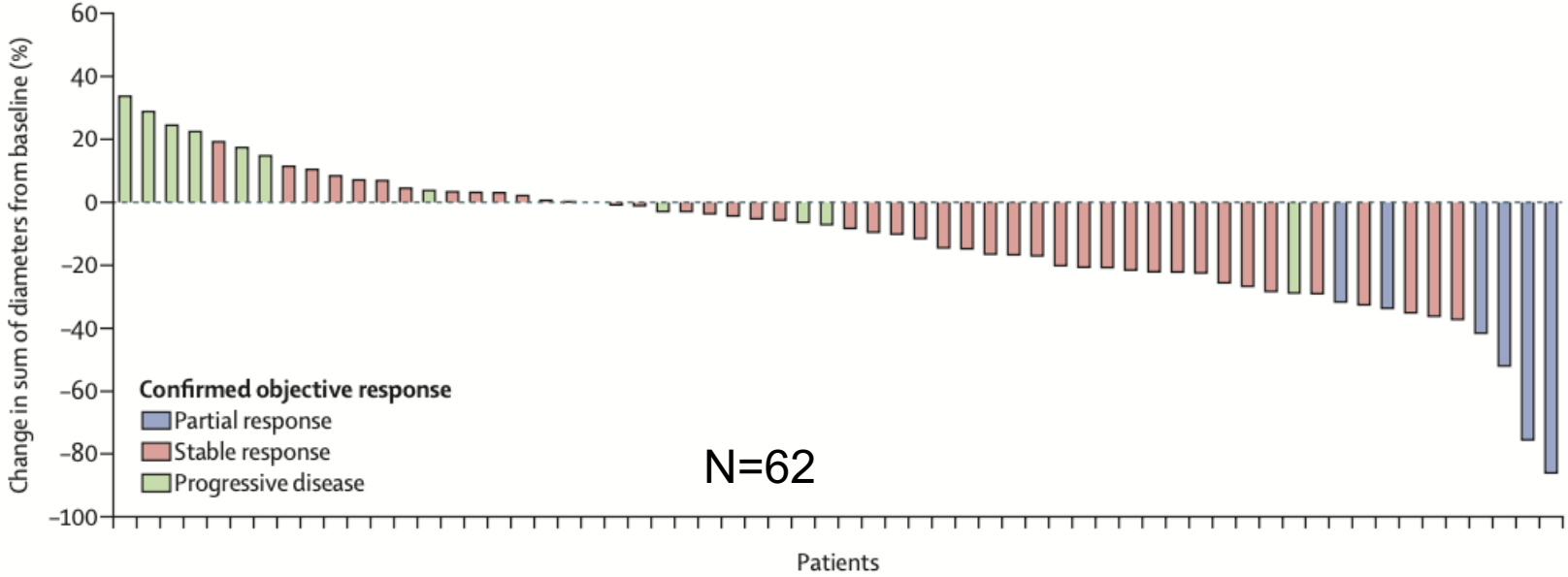
KRAS G12C Inhibitors (3-4% of mCRC)





Liu et al, Cancer Gene Therapy 2021

Sotorasib Single agent – CodeBreak 100

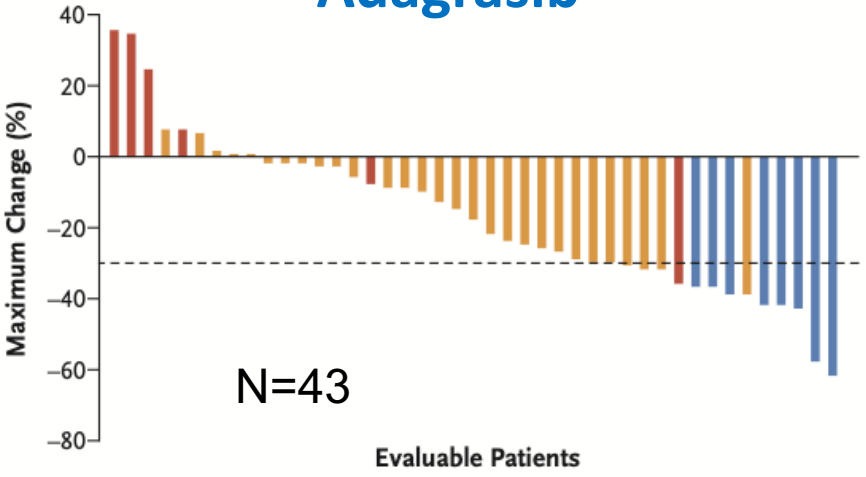


RR: 9.7% (6 pts)
PFS: 4.0 mos
OS: 10.6 mos

Fakih et al. Lancet Oncol 2021

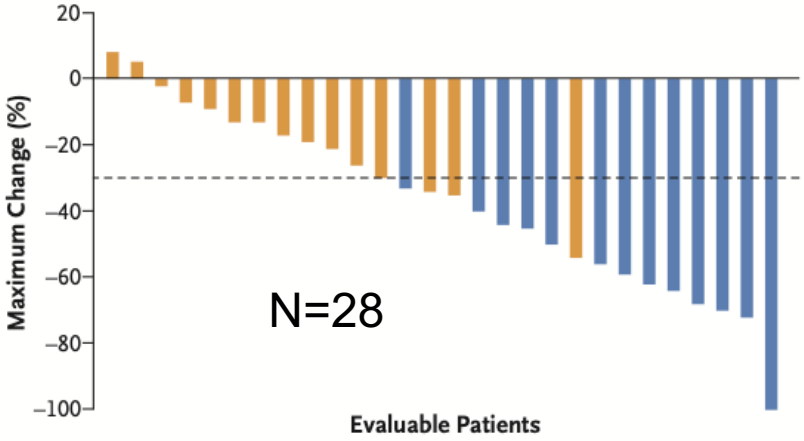
KRYSTAL-1:

Adagrasib



RR: 23%
DOR: 4.3 mos
PFS: 5.6 mos
OS: 19.8 mos

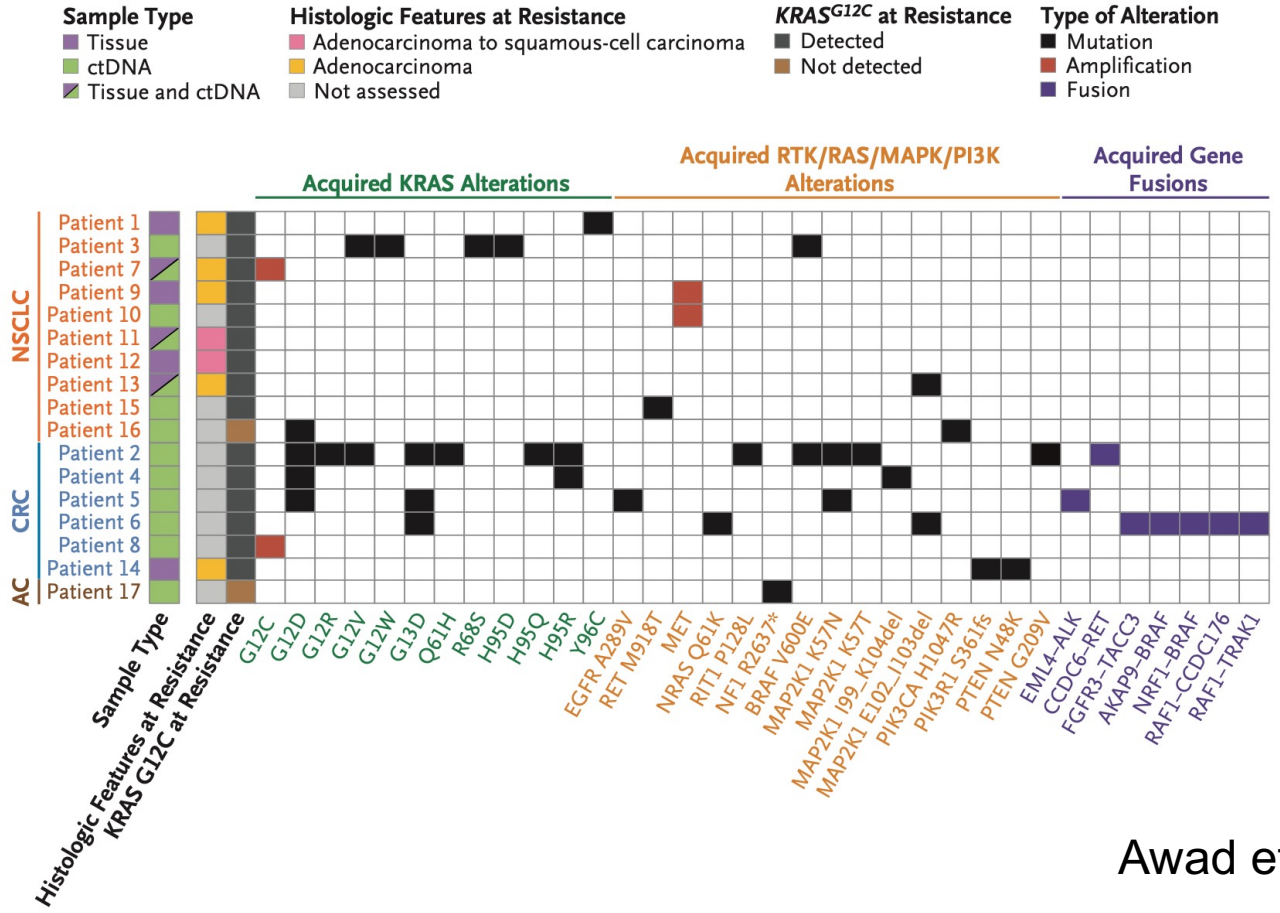
Adagrasib + Cetuximab



RR: 46%
DOR: 7.6 mos
PFS: 6.9 mos
OS: 13.4 mos

Yaeger et al. NEJM 2022

Acquired Resistance Mechanisms on Adegrasib



Awad et al., NEJM 2021

Key Clinical Trials in *HER2*+ mCRC

Trial	Regimen	N	ORR, %	Median PFS, mo	Median OS, mo
HERACLES-A[1]	Trastuzumab + lapatinib[a]	27	30 (14-50)	4.8 (3.7-7.4)	10.6 (7.6-15.6)
MyPathway (*KRAS*wt subgroup)[2]	Trastuzumab + pertuzumab[a]	43	40 (25-56)	5.3 (2.7-6.1)	14 (8-NE)
TRIUMPH[3]	Trastuzumab + pertuzumab[a]	17 (tissue)	35 (14-62)	4 (1.4-5.6)	—
TAPUR[4] **(no *RAS* data)**	Trastuzumab + pertuzumab[a]	28	25 (11-45)	4 (2.6-6.3)	25 (6-NE)
MOUNTAINEER[5] **(Cohorts A + B)**	**Trastuzumab + tucatinib**	**86**	**38 (28-39)**	**8.2 (4.2-10.3)**	**24.1 (20.3-36.7)**
DESTINY-CRC01[6,b] **(Cohort A)**	**T-DXd**	**54**	**45 (32-60)**	**6.9 (4.1-8.7)**	**15.5 (8.8-20.8)**
HERACLES-B[7,c]	T-DM1 + pertuzumab	30	10 (0-28)	4.8 (3.6-5.8)	—

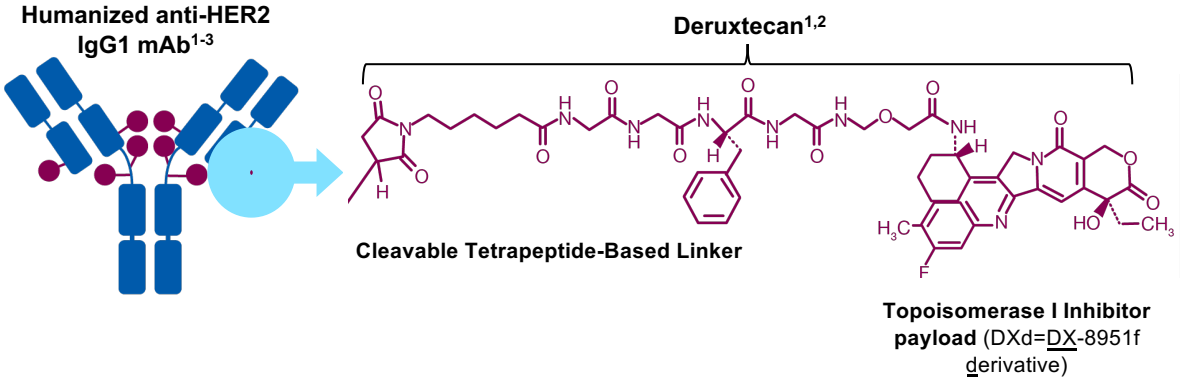
[a] In NCCN guidelines. [b] ORR in subgroup with prior HER2 rx 43.8% (19.8-70.1); without prior HER2 rx 45.9% (29.5-63.1). [c] Did not meet primary endpoint. T-DM1 had 0% response rate in MATCH Arm Q[8] and MSKCC Basket Trial.[9]

1. Sartore-Bianchi A et al. *Lancet Oncol*. 2016;17:738-746. 2. Meric-Bernstam F et al. *Lancet Oncol*. 2019;20:518-530. 3. Nakamura Y et al. ESMO 2019. Abstract 1057. 4. Gupta R et al. ASCO GI 2020. Abstract 132. 5. Strickler J et al. ESMO GI 2022. Abstract LBA 2. 6. Yoshino T et al. Nat Com 2023 in press
7. Sartore-Bianchi A. ESMO 2019. Abstract 3857. 8. Jhaveri KL et al. *Ann Oncol*. 2019;30:1821-1830. 9. Li BT et al. *J Clin Oncol*. 2018;36:2532-2537.

T-DXd is an ADC Designed to Deliver an Antitumor Effect

T-DXd is an ADC with 3 components:

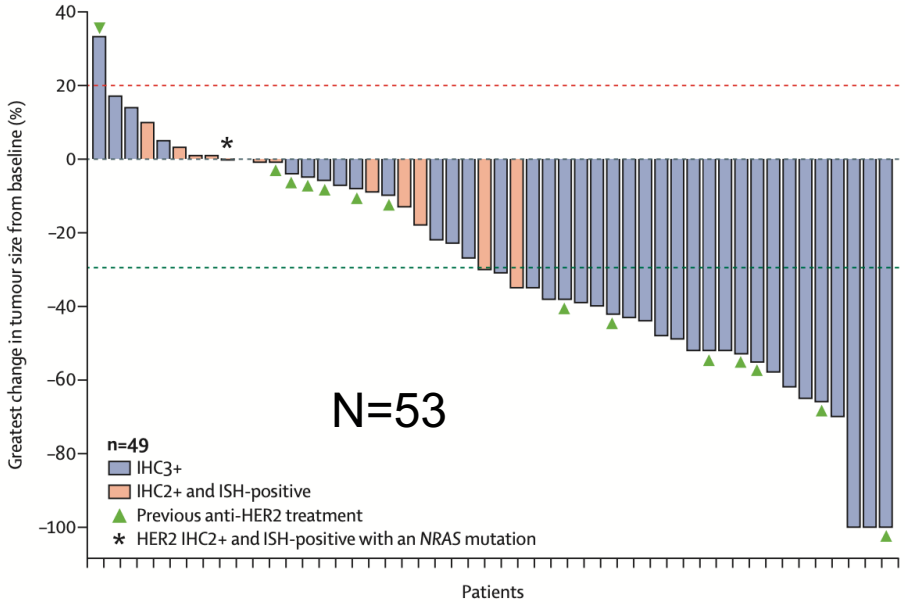
- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

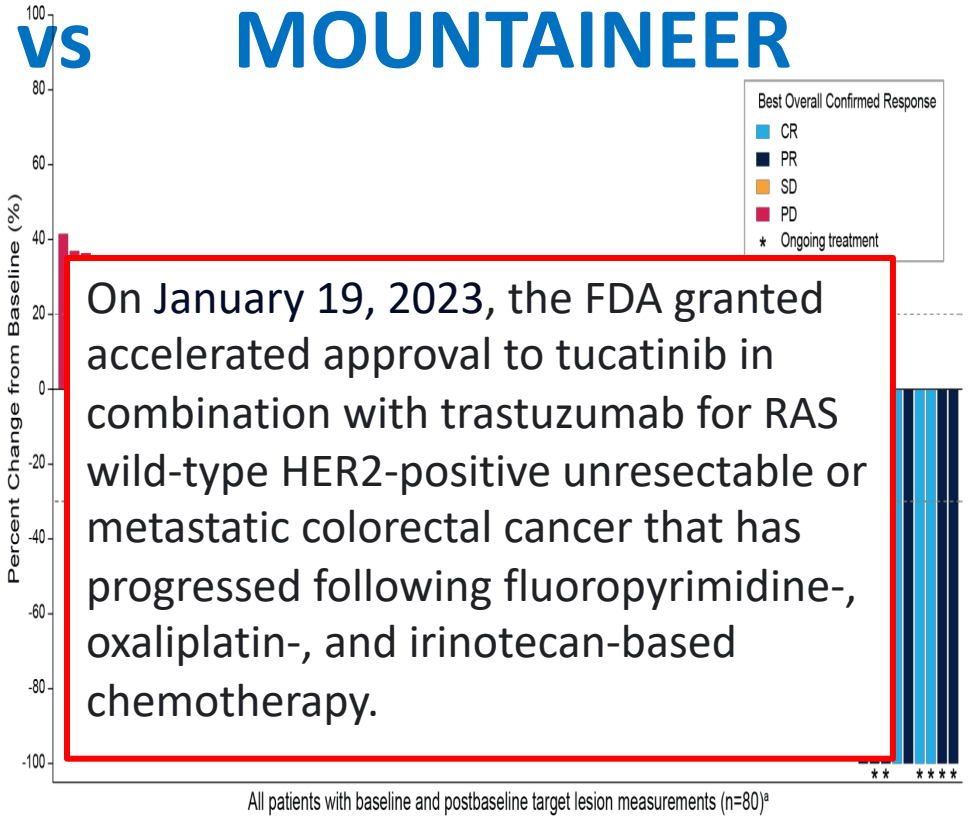


Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody.
1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142.

Destiny-CRC01 vs MOUNTAINEER





On January 19, 2023, the FDA granted accelerated approval to tucatinib in combination with trastuzumab for RAS wild-type HER2-positive unresectable or metastatic colorectal cancer that has progressed following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

Median # of prior lines: Destiny: 4, MOUNTAINEER: 2
Prior anti-HER-2 therapy: Destiny: 30%, MOUNTAINEER: 0%

Siena et al., Lancet Oncol 2021
Strickler et al., ESMO GI 2022

Immunotherapy

Neoadjuvant IO

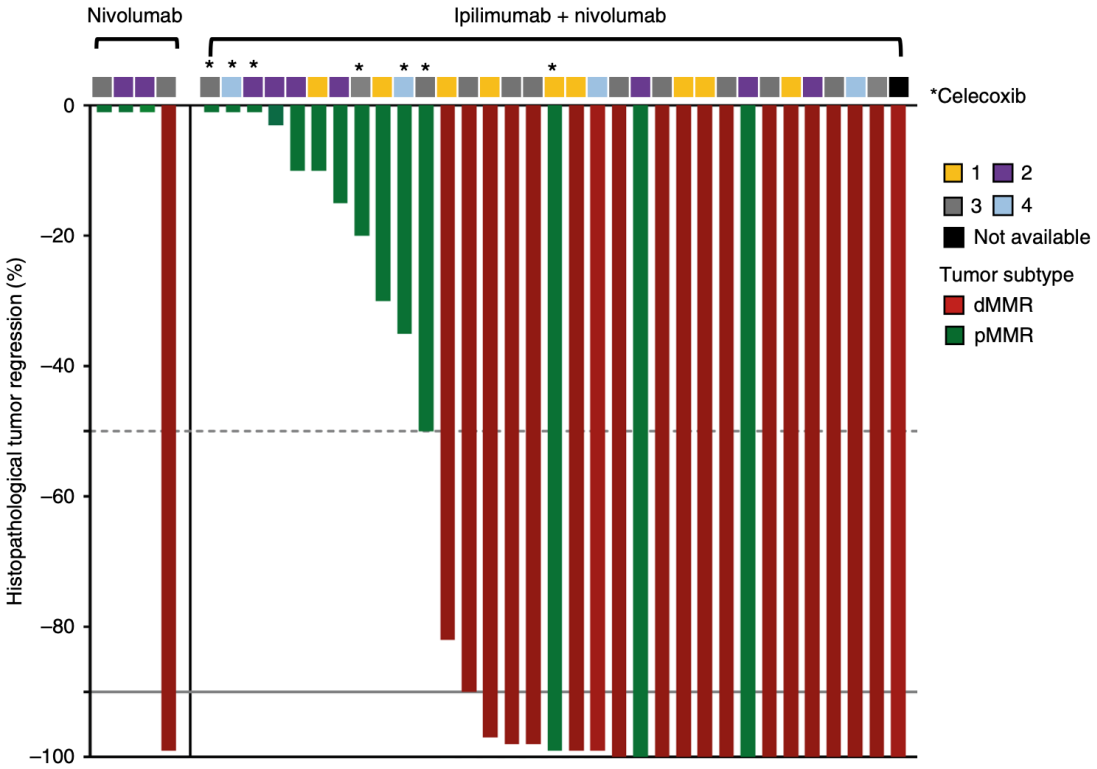
Novel IO combinations in MSS CRC

Neoadjuvant therapy in rectal cancer by MMR status

Outcome	No. of patients (%)	
	dMMR	pMMR
FOLFOX as initial treatment	*n = 21*	*n = 63*
Progression of disease	6 (29)	0
Response or stable disease	15 (71)	63 (100)
Chemoradiation as initial treatment	*n = 16*	*n = 48*
Progression of disease	0	0
Complete pathologic response	2 (13)	8 (17)

Cercek et al, Clin Cancer Res 2020

Rectal Ca: Neoadjuvant IO Therapy



41 pts with rectal cancer treated with Nivo and Nivo/Ipi (35 assessable for response)

Path response in:

20/20 dMMR (12 pCR)

4/15 pMMR

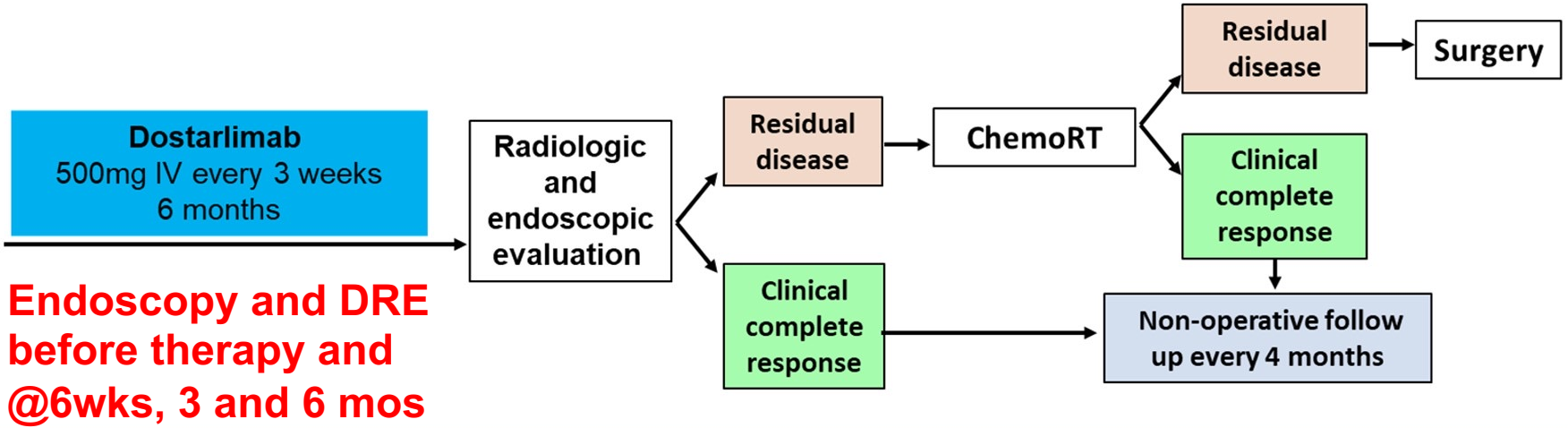
Chalabi et al., Nat Med 2020

2022 ASCO® ANNUAL MEETING

Late breaking abstract

PD-1 blockade as curative-intent therapy in mismatch repair deficient locally advanced rectal cancer

Andrea Cercek, MD
Head, Colorectal Cancer Section
Co-Director Center for Young Onset Colorectal and Gastrointestinal Cancers
Memorial Sloan Kettering Cancer Center



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

Target Enrollment: 30 subjects

Target RR: 25%

Study Design: Simon's two stage minimax design

NCT04165772

Demographic and disease characteristics of the patients at baseline

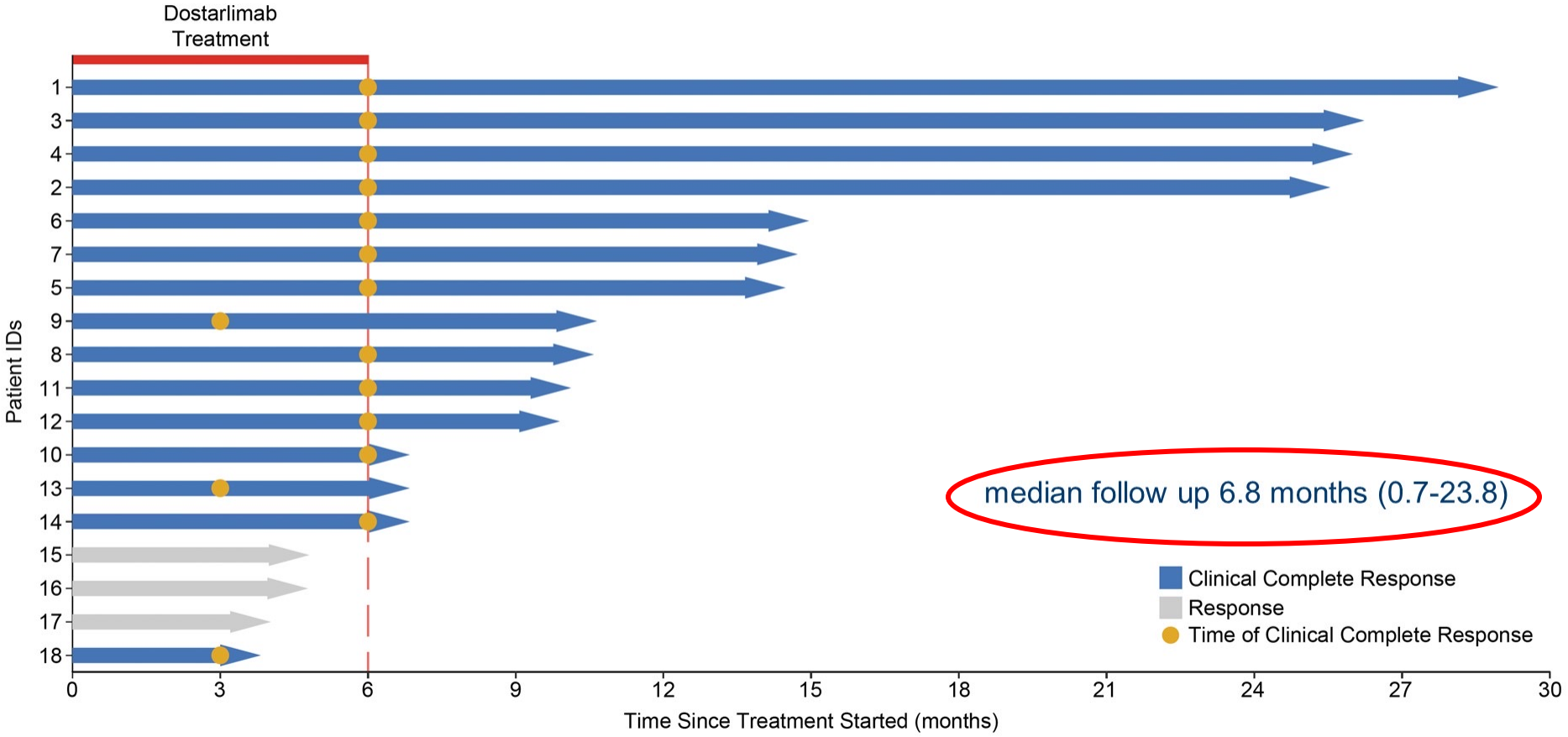
	Value (%)
Sex	
Male	6 (33)
Female	12 (67)
Age, median (range)	54 (26-78)
Race/Ethnicity	
White non-Hispanic	11 (61)
Hispanic	1 (6)
Black or African American	3 (17)
Asian-Far East/Indian Subcontinent	3 (17)
Tumor Staging	
T1/2	4 (22)
T3, T4	14 (78)
Nodal Staging	
Node-positive	17 (94)
Node-negative	1 (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
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

Duration of response



PARIS 2022 ESMO congress

Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: the NICHE-2 study

M. Chalabi[1], **Y. Verschoor, J. Van den Berg, K. Sikorska, G. Beets, A. Van Lent, C. Grootscholten, A. Aalbers, N. Buller, H. Marsman, E. Hendriks, P. Burger, T. Aukema, S. Oosterling, R. Beets-Tan, T.N. Schumacher, M.E. Van Leerdam, E.E. Voest, J.B. Haanen**

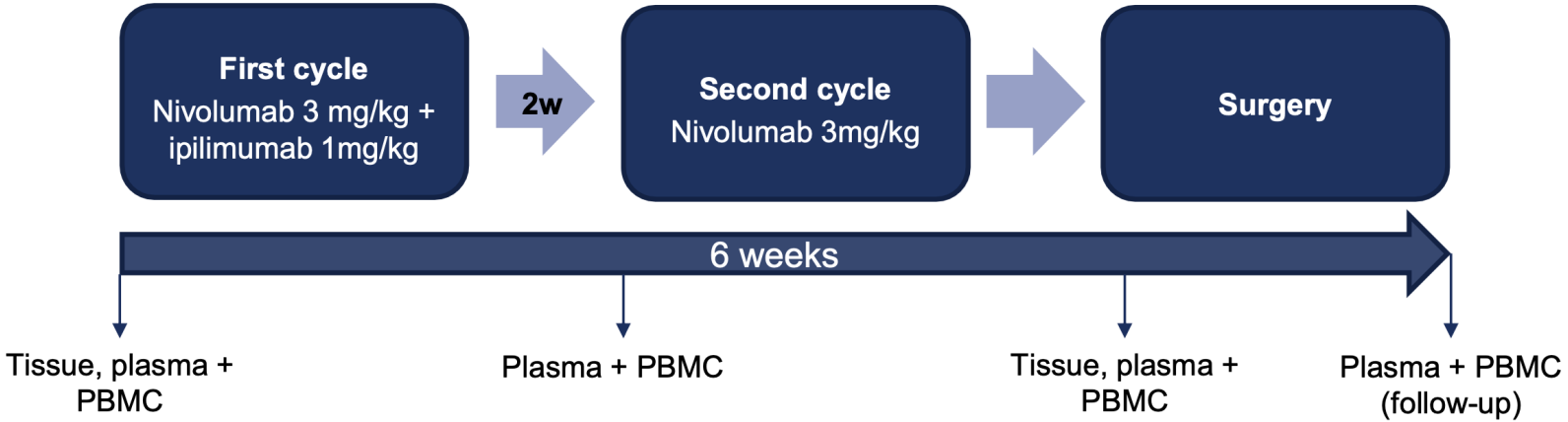
[1]Dept. of Gastrointestinal Oncology, Netherlands Cancer Institute
Amsterdam, the Netherlands

September 11th 2022

NICHE-2 study design

MSI-H/ dMMR colon cancers
cT3 and/or N+ per radiology
No obstruction, no perforation

- Investigator-initiated, non-randomized multicenter* study

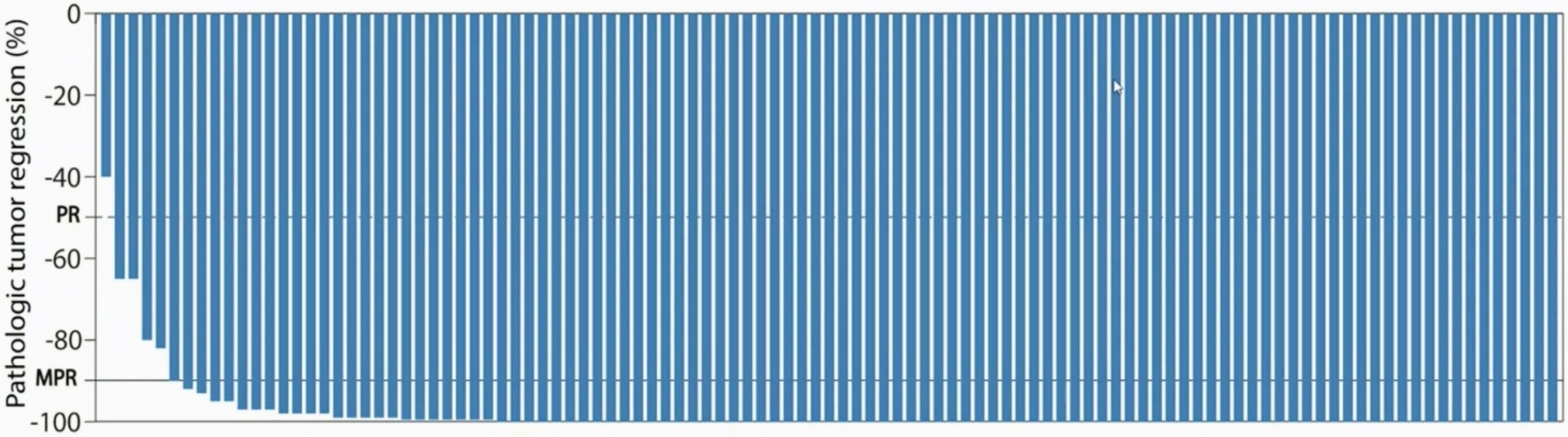


*6 participating hospitals in the Netherlands
PBMC = peripheral blood mononuclear cells

Neoadjuvant Nivo/Ipi in dMMR early stage colon cancer
68% right-sided, 63% cT4a/b; 31% Lynch

Major pathologic response in 95% of patients; 67% pCR

N=107



1 dose of Nivo/Ipi -> 1 dose of Nivo -> surgery

Chalabi et al., ESMO 2022

My Conclusions for Neoadjuvant/ Definitive IO Therapy in MSI-H/ dMMR CRC

- **Upfront, definitive IO therapy has emerged as SOC in MSI-H/ dMMR rectal cancer**
  - Hard to beat 14/14 cCR…
  - FOLFOX does not work well, if at all
  - Matches results in advanced disease and consistent with prior studies
- **But:**
  - Follow up still short (median: 6.8 mos)
  - What is the best IO therapy? PD-1 single agent? Combo? Duration?
  - Will it always lead to NOM? Role of radiation?
- **In locally advanced MSI-H/ dMMR colon cancer, I would also favor IO therapy as neoadjuvant treatment, but cancer should still be resected**

ASCO® Gastrointestinal Cancers Symposium

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Results from a phase 1a/1b study of botensilimab (BOT), a novel innate/adaptive immune activator, plus balstilimab (BAL; anti-PD-1 antibody) in metastatic heavily pretreated microsatellite stable colorectal cancer (MSS CRC)

Authors: Anthony B. El-Khoueiry, MD[1], Marwan G. Fakih, MD[2], Michael S. Gordon, MD[3], Apostolia M. Tsimberidou, MD, PhD[4], Andrea J. Bullock, MD, MPH[5], Breelyn A. Wilky, MD[6], Jonathan C. Trent, MD, PhD[7], Kim A. Margolin, MD, FACP, FASCO[8], Daruka Mahadevan, MD, PhD[9], Ani S. Balmanoukian, MD[10], Rachel E. Sanborn, MD[11], Gary K. Schwartz, MD[12], Bruno Bockorny, MD[5], Justin C. Moser, MD[3], Joseph E. Grossman, MD[13], Waldo Ortuzar Feliu, MD[13], Katherine Rosenthal, RN, MSN, OCN, CCRP[13], Steven J. O'Day, MD[13], Heinz-Josef Lenz, MD, FACP[1], Benjamin L. Schlechter, MD[14]

[1]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [2]City of Hope Comprehensive Cancer Center, Duarte, CA, USA, [3]Honor Health Research and Innovation Institute, Scottsdale, AZ, USA, [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [5]Beth Israel Deaconess Medical Center, Boston, MA, USA, [6]University of Colorado Cancer Center, Aurora, CO, USA, [7]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA, [8]Providence Saint John's Cancer Institute, Santa Monica, CA, USA, [9]The University of Texas Health Sciences Center at San Antonio, San Antonio, TX, USA, [10]The Angeles Clinic and Research Institute, Los Angeles, CA, USA, [11]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA, [12]Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY, USA, [13]Agenus Inc., Lexington, MA, USA, [14]Dana-Farber Cancer Institute, Boston, MA, USA

Presented by: Anthony B. El-Khoueiry, MD

University of Southern California
Norris Comprehensive Cancer Center
Los Angeles, California, United States

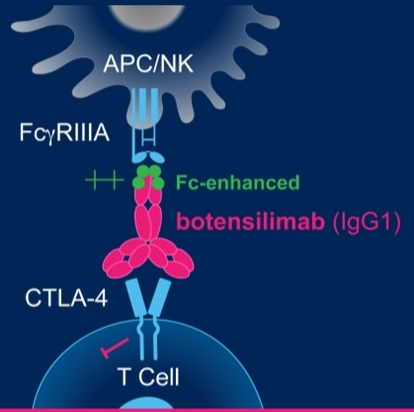
January 21, 2023
Abstract Number: LBA8

Active in 'Cold' and IO Refractory Tumors

agenus

botensilimab

Fc-enhanced CTLA-4 Inhibitor

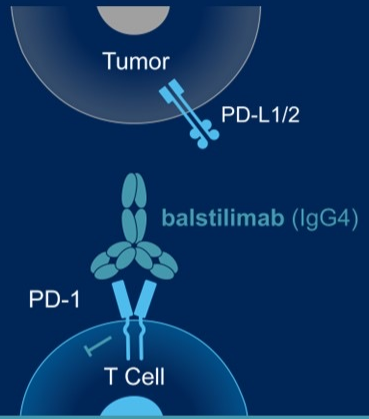


Active in 'cold' and IO refractory tumors[1,2]

- >300 patients treated across 4 trials
- ↑ T cell priming, expansion, memory[3,4]
- ↑ Frequency of activated APCs
- ↑ Treg depletion
- ↓ Complement mediated toxicity

balstilimab

PD-1 Inhibitor



Safety and efficacy analogous to approved anti-PD-1 mAbs[5,6]

- >750 patients treated; 10 ongoing trials / 2 completed
- Complete blocker of PD-1-PD-L1/2 interactions
- Enhanced T cell activation and effector function

1. El-Khoueiry AB. SITC 2021 Annual Meeting. Poster #479. 2. Wilky B. SITC 2022 Annual Meeting. Oral #778. 3. Waight et al. Cancer Cell. 2018;33(6): 1033-1047. 4. Levey D. SITC 2022. Annual Meeting. Oral #470. 5. O'Malley, et al. Gynecol Oncol. 2021; 163: 274-280. 6. O'Malley et al, J Clin Oncol. 2022; 40(7): 762-771.

Deep Objective Responses

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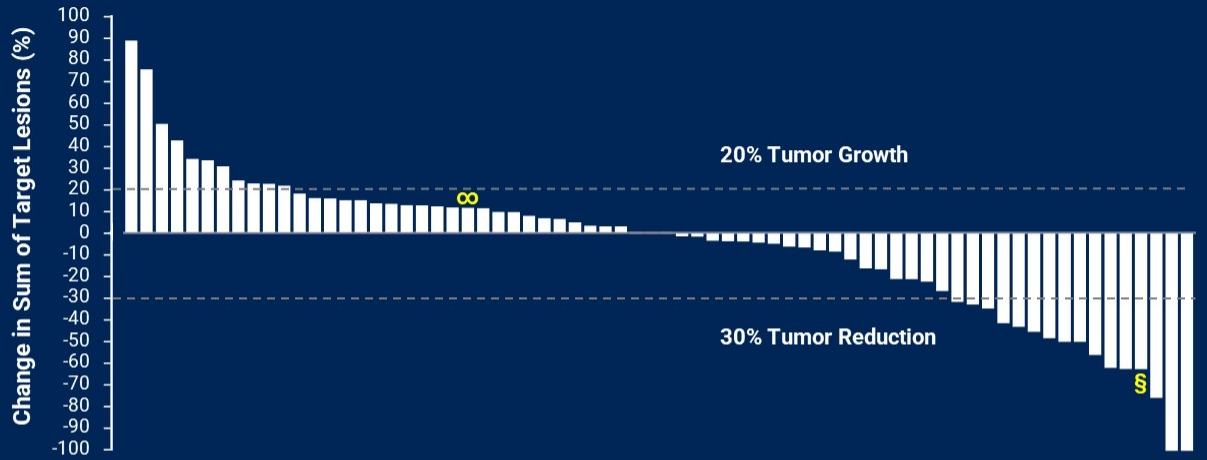


Median prior lines: 4
Prior IO: 31%
RAS mut: 59%
BRAF mut: 3%

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)

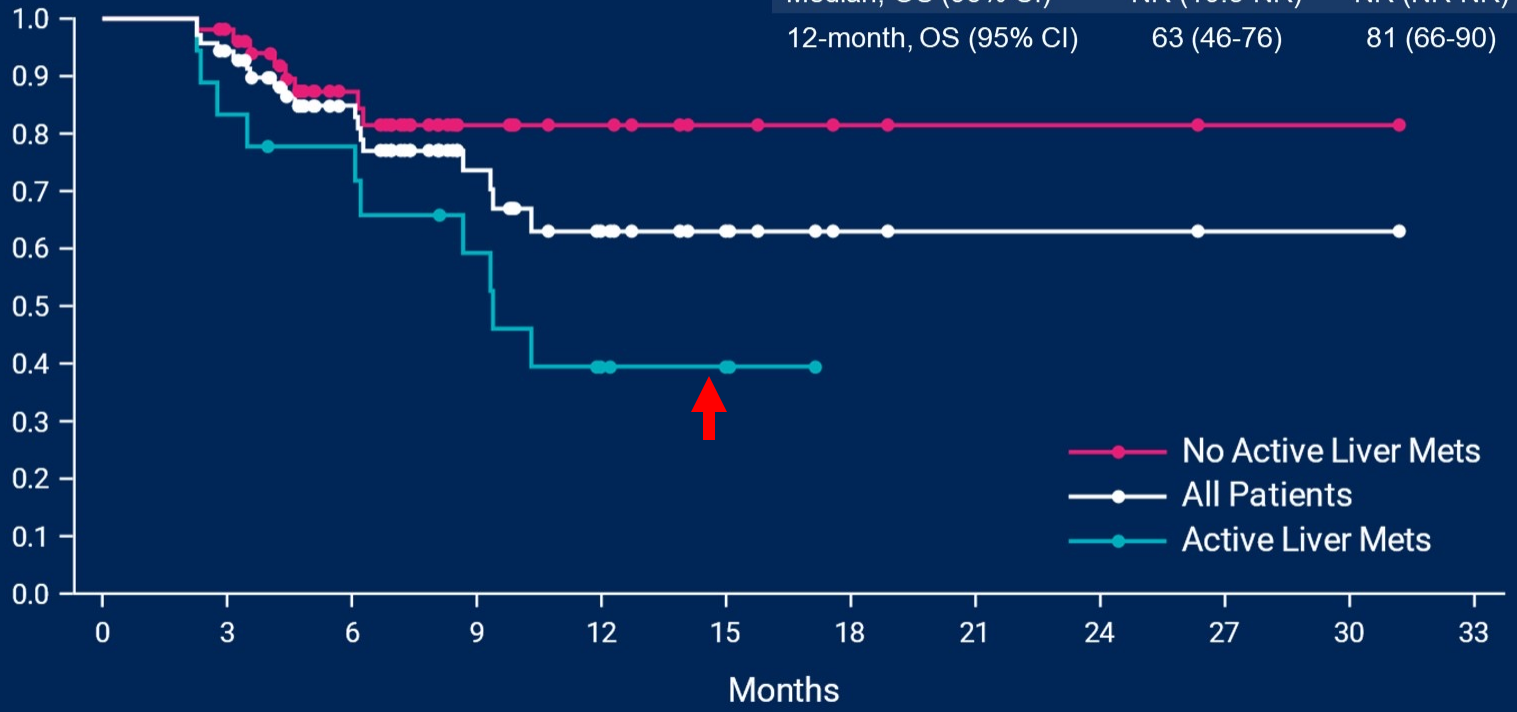
*Includes unconfirmed responses. ∞ Resected target lesions showed complete pathologic response. § Response by iRECIST.

Overall Survival

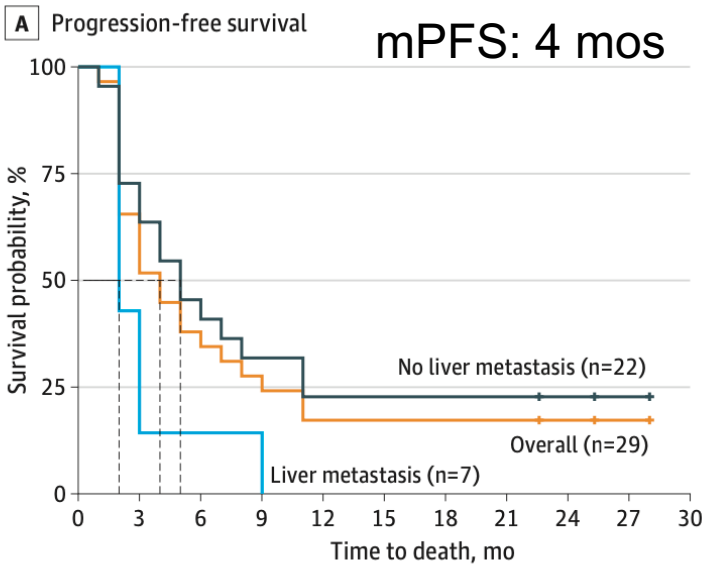
agenus

Efficacy evaluable population, N=70

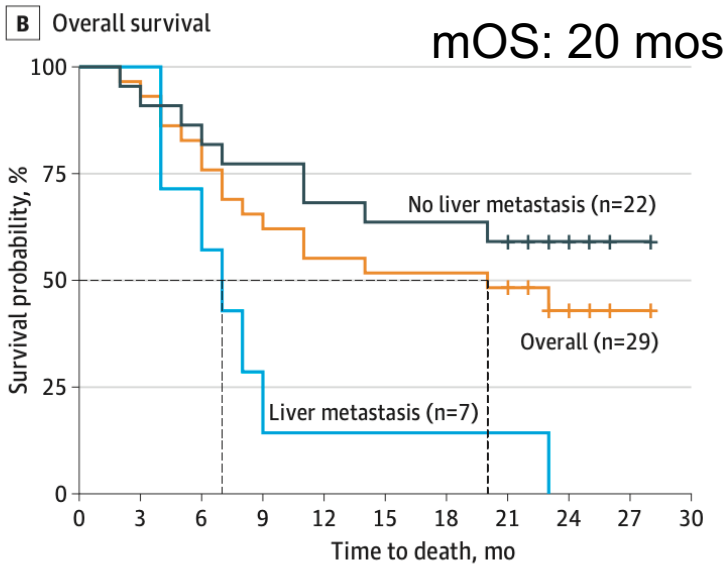
	Overall	No Liver Mets	Liver Mets
Median, OS (95% CI)	NR (10.3-NR)	NR (NR-NR)	9.4 (6.1-NR)
12-month, OS (95% CI)	63 (46-76)	81 (66-90)	40 (17-62)



Phase 1 study Rego/Nivo/Ipi in MSS mCRC



No. at risk											
Overall	29	19	11	8	5	5	5	5	2	1	0
Liver metastasis	7	3	1	1	0	0	0	0	0	0	0
No liver metastasis	22	16	10	7	5	5	5	5	2	1	0



No. at risk											
Overall	29	28	24	19	16	15	15	14	7	1	0
Liver metastasis	7	7	5	2	1	1	1	1	0	0	0
No liver metastasis	22	21	19	17	15	14	14	13	7	1	0

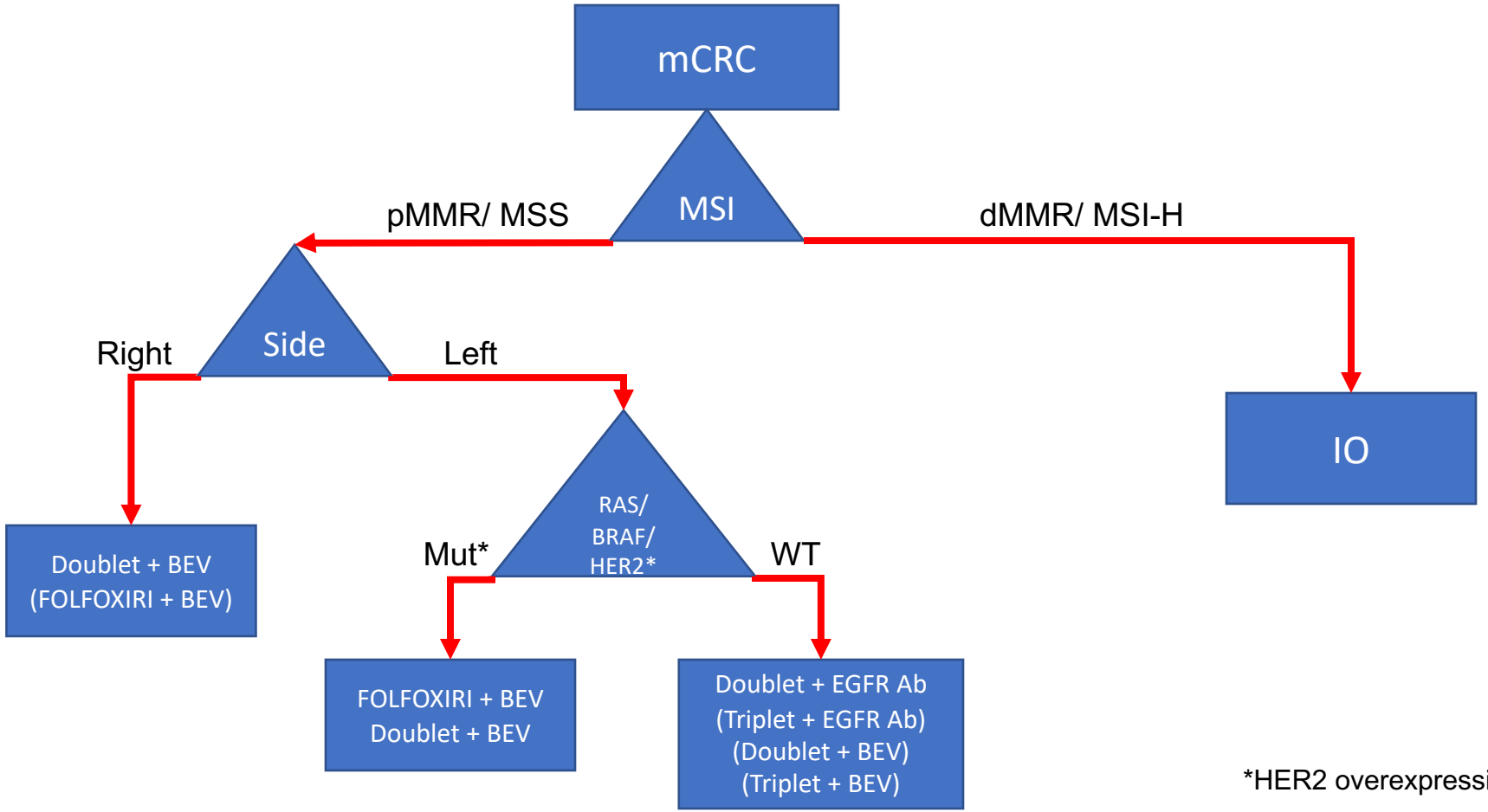
RR: No liver mets (22): 36%, Liver mets (7): 0%

Fakih et al., JAMA Oncol 2023

My Conclusions from B&B study

- **BAL-BOT shows interesting activity in metastatic MSS/pMMR CRC without liver metastases**
  - Reminiscent of data generated with Rego/Nivo (+/- Ipi) and Pembro/Lenvatinib (Note: Phase 3 LEAP-17 negative! – press release April 7, 2023)
- **Observed activity passed my personal benchmark for IO in later line mCRC: >20% RR with durability of response >9 months**
- **More data and randomized comparison needed to see if time-related endpoints can be met**
- **We need to find a way to make CRC liver metastases respond to IO therapy -> high unmet need!**

Optimized first-line therapy for mCRC



*HER2 overexpression

The Present and the Future

Where we are now		Where we will go
Early stage colon cancer		
Adjuvant therapy	Duration and intensity based on traditional TNM staging	**ctDNA as MRD marker** • to select patients for adjuvant therapy • to identify high-risk patients with distinct molecular profile for targeted intervention • to serve as endpoint in adjuvant trials **Neoadjuvant IO therapy for locally advanced cancers**
	No targeted agents or immunotherapy	
Advanced CRC		
Palliative therapy	Chemotherapy as backbone	**Identify more patients suitable for targeted therapies** • Characterize markers of secondary resistance • Immunotherapy for MSS/ pMMR cancers **Define the role of tumor microbiota** • in oncogenesis • as prognostic and predictive marker • as target for therapeutic intervention
	Targeted agents based on molecular profile and sidedness	
	Immunotherapy only for MSI-H/ dMMR cancers	

The Present and the Future

Where we are now		Where we will go
Early stage rectal cancer		
Neo-Adjuvant therapy	Ongoing shift from radio-chemotherapy followed by surgery and post-op adj Tx to TNT	**Firm establishment of TNT as SOC** • Best sequencing strategy TBD • ? SCRT vs LC-chemo-rads
	Increased use of short-course radiation therapy	
	Even in cCR surgery considered SOC	**Non-operative management as SOC in suitable cases** • Role of imaging, endoscopy and serial ctDNA testing to monitor response and in follow-up TBD
	Molecular markers largely ignored for treatment decisions	**Neoadjuvant or definitive IO therapy is SOC in dMMR/MSI-H rectal cancers**

MOC Question:

The SUNLIGHT trial investigated the addition of bevacizumab to TAS-102 (trifluridine/ tipiracil) in refractory mCRC.

Which of the following statements is not true?

A. **The addition of bevacizumab improved OS**
B. **The addition of bevacizumab improved PFS**
C. **The addition of bevacizumab improved OS only in bevacizumab-naïve patients**
D. **The response rate of TAS-102 plus bevacizumab was less than 10%**
E. **The addition of bevacizumab to TAS-102 led to an almost 40% reduction in death events on the study**