Biology and new therapies in colorectal cancer

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15th Belgian Symposium on the Integration of
Molecular Biology Advances into Oncology
Clinical Practice
and
Post-MASCC

ΟΓΚΟΛΟΓΙΚΟ ΚΕΝΤΡΟ
Τράπεζας Κύπρου

Disclosures

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Outline

- Introduction/molecular biology
- MSI
- MSS
- B-RAF
- K-ras
- (Her-2)

CRC molecular classification

Chromosomic instability

CIN pathway

80-85 %

Epigenetic instability

CIMP pathway

≈20 %

Microsatellite instability

MSI pathway

15- 20 %

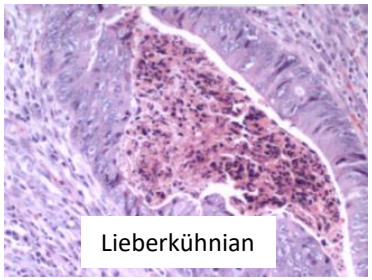
Conventionnal carcinoma

Serrated tumours

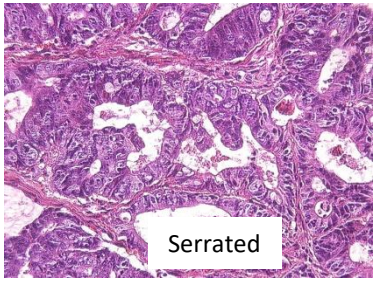
Cancer in the elderly

Lynch syndrome

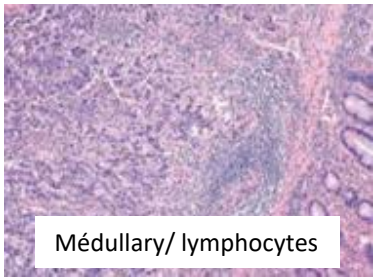
2-4%



Lieberkühnian

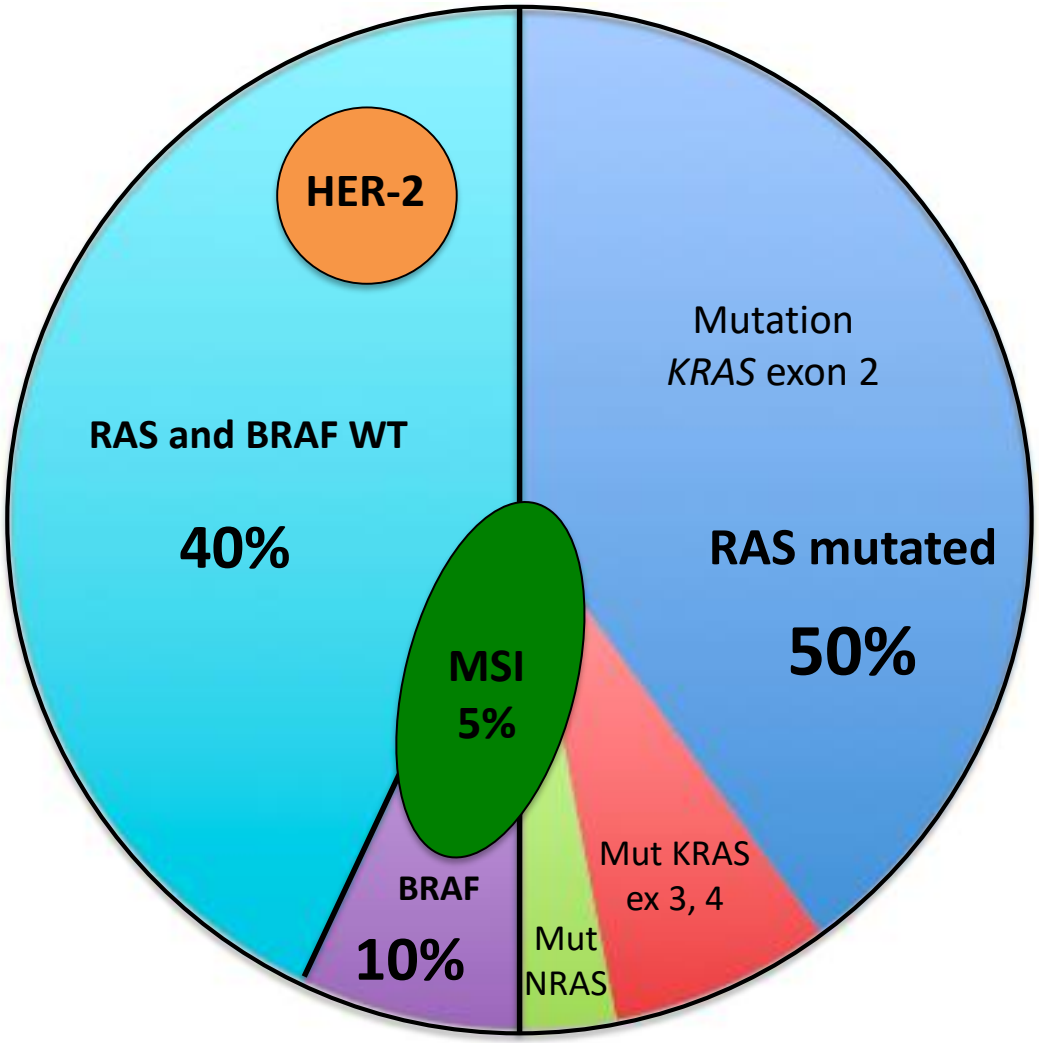


Serrated



Médullary/ lymphocytes

CRC molecular biomarkers and targets



Pembrolizumab in Tumors with Mismatch-Repair Deficiency- Le et al, NEJM, June, 2015

Table 1. Demographic and Baseline Characteristics of the Patients.*

Characteristic	Mismatch Repair–Deficient Colorectal Cancer (N=11)	Mismatch Repair–Proficient Colorectal Cancer (N=21)	Mismatch Repair–Deficient Noncolorectal Cancer (N=9)	P Value†
Median age (range) — yr	46 (24–65)	61 (32–79)	57 (34–92)	0.02
Sex — no. (%)				0.72
Female	5 (45)	8 (38)	4 (44)	
Male	6 (55)	13 (62)	5 (56)	
Race — no. (%)‡				0.66
White	8 (73)	17 (81)	8 (89)	
Black	1 (9)	3 (14)	0	
Other	2 (18)	1 (5)	1 (11)	
ECOG performance status — no. (%)§				0.07
0	0	6 (29)	2 (22)	
1	11 (100)	15 (71)	7 (78)	
Cancer type — no. (%)				>0.99
Colon	9 (82)	18 (86)	0	
Rectal	2 (18)	3 (14)	0	
Ampullary or cholangiocarcinoma	0	NA	4 (44)	
Endometrial	0	NA	2 (22)	
Small bowel	0	NA	2 (22)	
Gastric	0	NA	1 (11)	
Histologic grade — no. (%)				0.20
Well or moderately differentiated	7 (64)	18 (86)	4 (44)	
Poorly differentiated	4 (36)	3 (14)	3 (33)	
Other	0	0	2 (22)	
Stage IV cancer — no. (%)	11(100)	21 (100)	9 (100)	>0.99
Liver metastases — no. (%)	6 (55)	11 (52)	6 (67)	>0.99
Median time since initial diagnosis (range) — mo	31 (6–95)	58 (27–192)	23 (2–105)	0.07
Previous therapies — no. (%)				0.89
1	0	0	1 (11)	
2	3 (27)	4 (19)	5 (56)	
3	3 (27)	5 (24)	1 (11)	
>4	5 (45)	12 (57)	2 (22)	

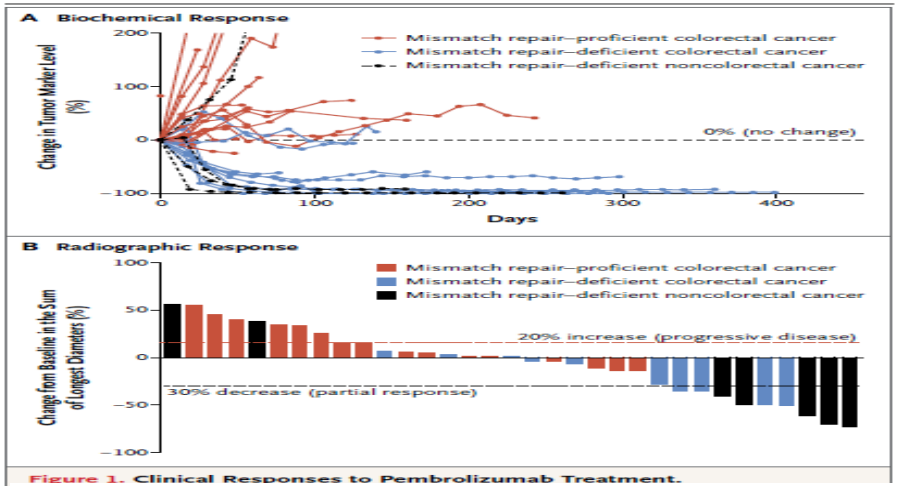
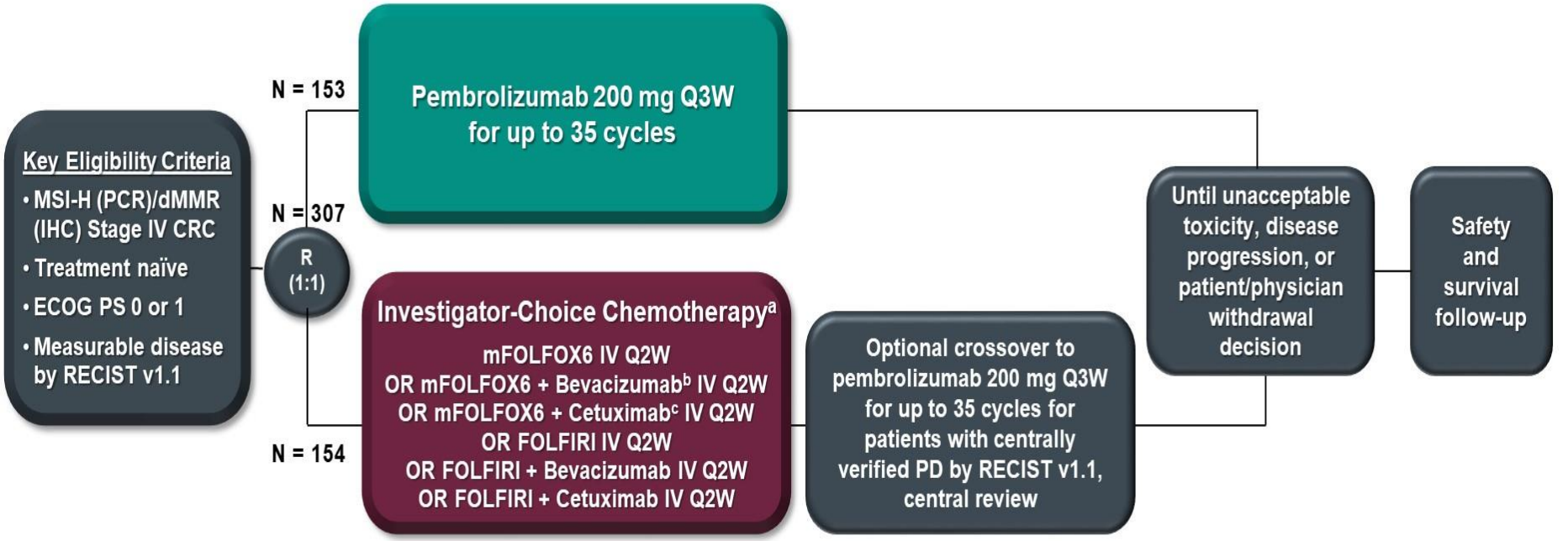


Figure 1. Clinical Responses to Pembrolizumab Treatment.

Table 2. Objective Responses According to RECIST Criteria.

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

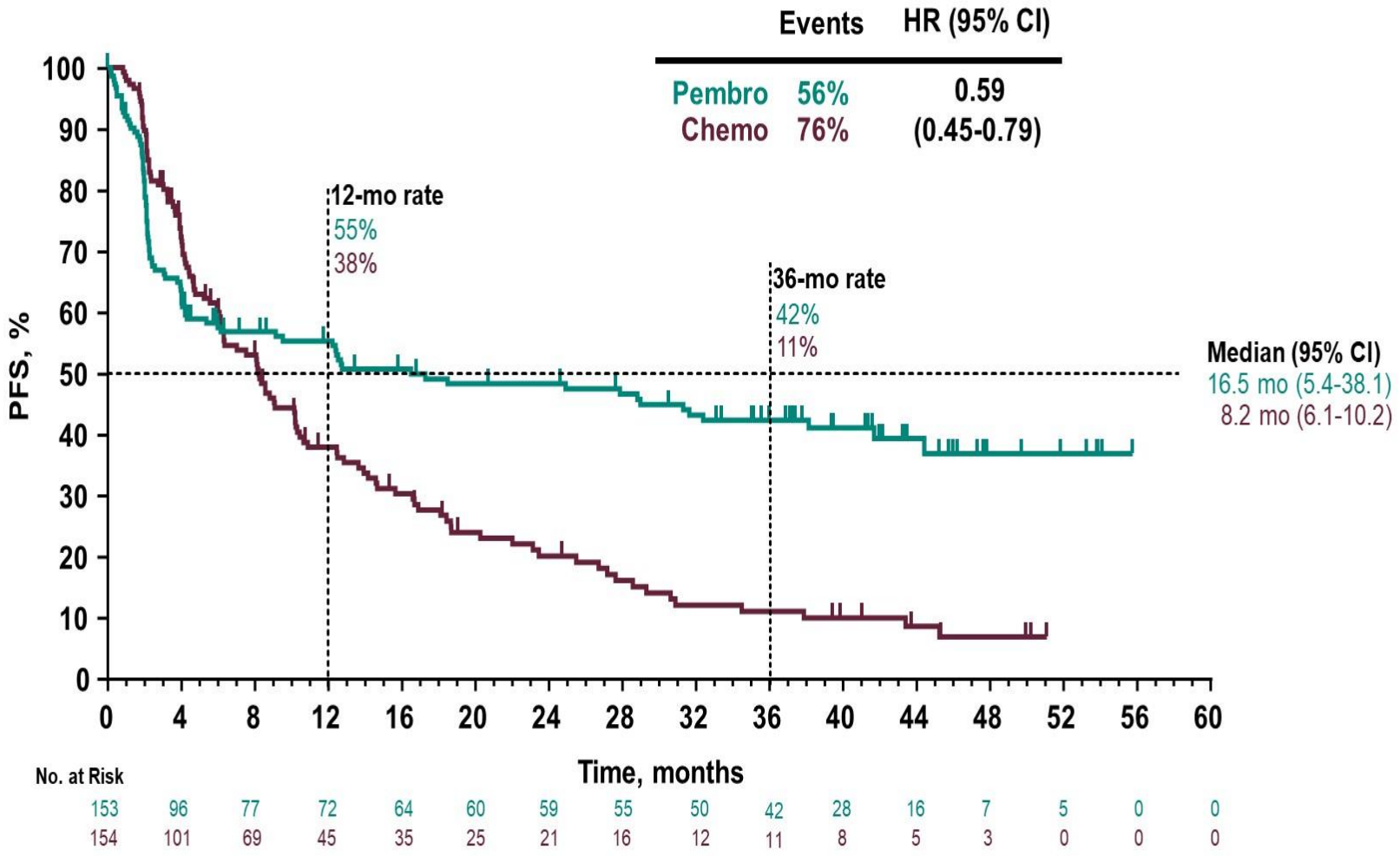
KEYNOTE-177 Study Design
(NCT02563002)



- Dual-Primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

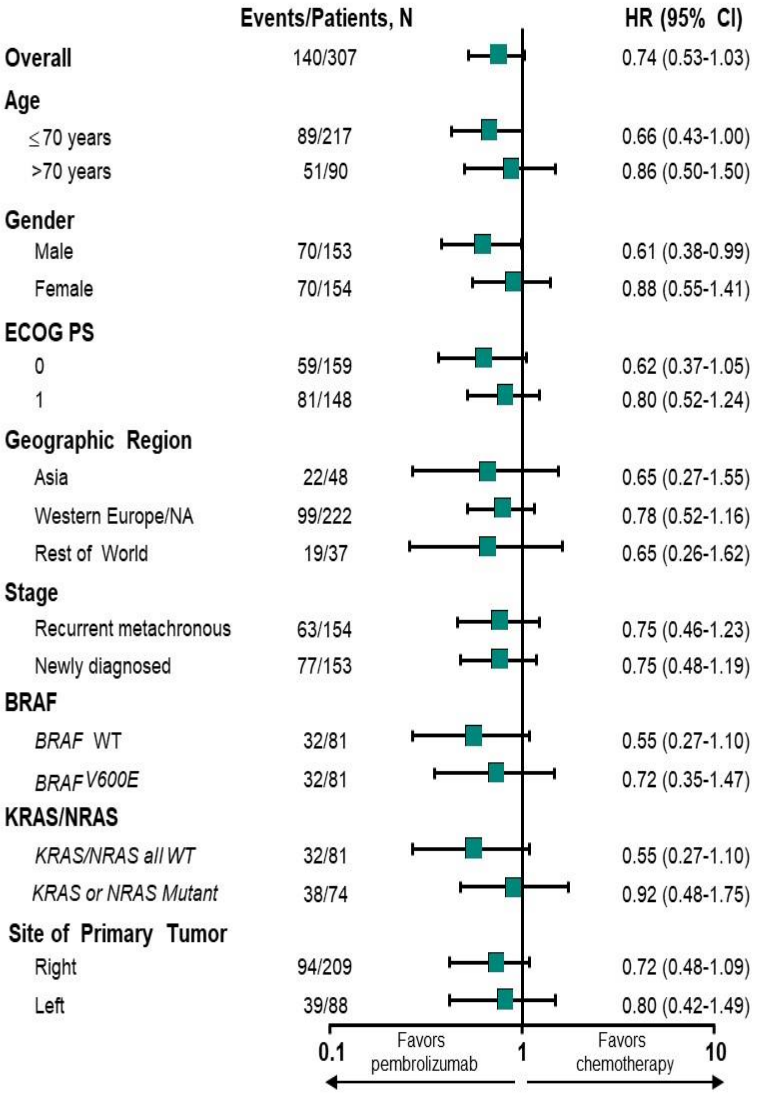
[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
BICR, blinded independent central review; IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Progression-Free Survival



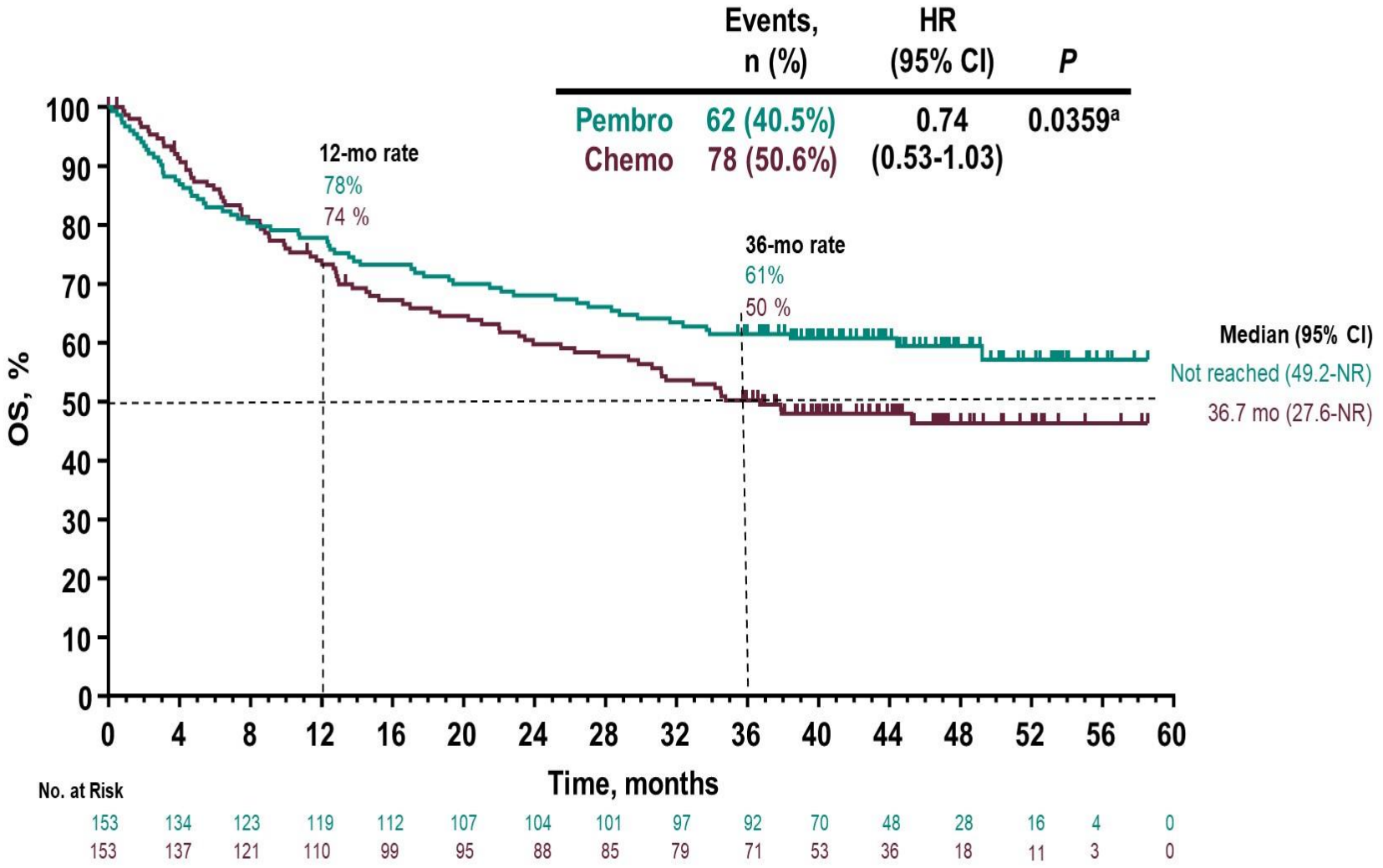
Data cut-off: 19Feb2021.

OS in Key Subgroups



Data cut-off: 19Feb2021.

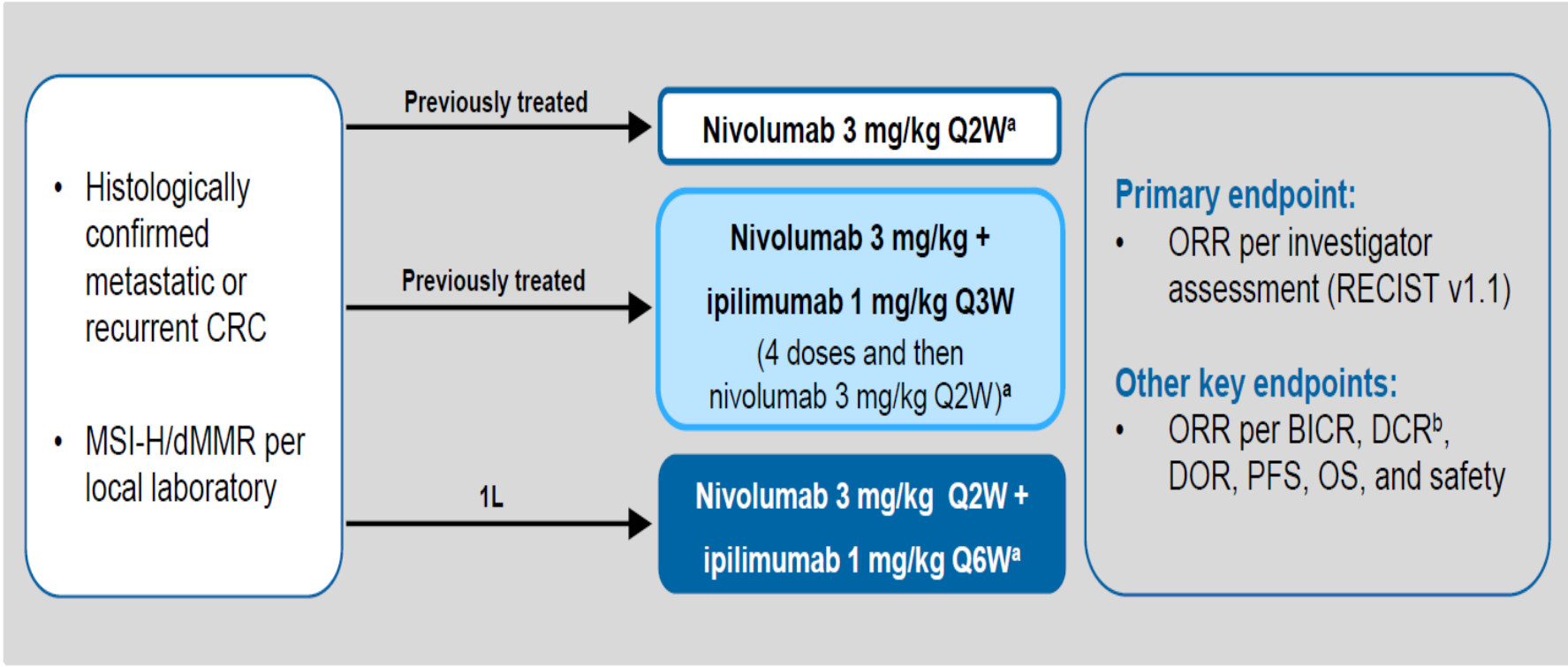
Overall Survival



[a]Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38). Data cut-off: 19Feb2021.

CheckMate-142 Study Design

- CheckMate-142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188)



- Median follow-up for the 1L nivolumab plus low-dose ipilimumab cohort was 13.8 months (range, 9–19)[c]

[a]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; [b]Patients with a CR, PR, or SD for ≥12 weeks divided by the number of treated patients; [c]Time from first dose to data cutoff

BICR = blinded independent central review; CR = complete response; CRC = colorectal cancer; DCR = disease control rate; DOR = duration of response; PFS = progression-free survival; PR = partial response; Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q6W = once every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

original reports

First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/ Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study

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abstract

PURPOSE Nivolumab received US Food and Drug Administration approval as a single agent or in combination with ipilimumab in patients with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) that progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan based on CheckMate 142. Presented are results of nivolumab plus low-dose ipilimumab in the first-line therapy cohort from the phase II CheckMate 142 study.

PATIENTS AND METHODS Patients with no prior treatment in the metastatic setting for MSI-H/dMMR CRC were treated with nivolumab every 2 weeks plus low-dose ipilimumab every 6 weeks until disease progression. The primary end point was objective response rate (investigator assessment; RECIST v1.1).

RESULTS Median age of treated patients was 66 years (N = 45). Median follow-up was 29.0 months. Objective response rate and disease control rate were 69% (95% CI, 53 to 82) and 84% (95% CI, 70.5 to 93.5), respectively, with 13% complete response rate. Median duration of response was not reached; 74% of responders had ongoing responses at data cutoff. Median progression-free survival and median overall survival were not reached with minimum follow-up of 24.2 months (24-month rates, 74% and 79%, respectively). Clinical benefit was observed regardless of baseline demographic and tumor characteristics, including *BRAF* or *KRAS* mutation status. In a post hoc analysis, of 14 patients who discontinued treatment and did not receive subsequent therapy, 10 remained progression-free. Patient-reported outcomes were stable over the treatment period. Grade 3-4 treatment-related adverse events occurred in 22% of patients; 13% discontinued because of any-grade treatment-related adverse events.

CONCLUSION Nivolumab plus low-dose ipilimumab demonstrated robust and durable clinical benefit and was well tolerated as a first-line treatment for MSI-H/dMMR mCRC. Based on these promising data, randomized studies are warranted.

J Clin Oncol 00. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT
Data Supplement
Protocol
Author affiliations and support information (if applicable) appear at the end of this article.
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INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide,[1] with poor 5-year survival rate (14%) in patients with metastatic colorectal cancer (mCRC).[2,3] Patients with microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) mCRC treated with first-line (1L), standard-of-care chemotherapy have poor outcomes (median overall survival [OS] range, 13.6-21.5 months)[4-8] and may benefit from programmed death-1 (PD-1) checkpoint blockade.[9-12] In a randomized phase III study, median progression-free survival (PFS) following 1L pembrolizumab monotherapy was 16.5 months.[7,9-12] A combination of PD-1 and cytotoxic T-lymphocyte antigen-4 immune checkpoint inhibitors, which promote antitumor immune response by distinct but complementary mechanisms, may enhance efficacy relative to monotherapy.[13]

CheckMate 142 is a phase II, multicohort, nonrandomized study of nivolumab-based therapies in patients with MSI-H (previously treated and untreated) and non–MSI-H mCRC.[12,14] In patients with MSI-H/dMMR mCRC who had one or more prior treatments (second line or greater [2L+]), nivolumab monotherapy and nivolumab plus low-dose ipilimumab followed by nivolumab monotherapy demonstrated promising clinical activity as reflected by high and durable responses after a median follow-up of 12.0 and 13.4 months, respectively.[12,14] Nivolumab monotherapy was well tolerated, and nivolumab plus low-

TABLE 2. ORR, Best Overall Response, DCR, and Median DOR (N = 45)

Response	Investigator Assessed	BICR Assessed
ORR,[a] No. (%)	31 (69)	28 (62)
95% CI	53 to 82	46.5 to 76.2
ORR by *BRAF* and/or *KRAS* mutation status,[b] No. (%)		
BRAF and *KRAS* wild-type (n = 13)	8 (62)	7 (54)
BRAF mutation (n = 17)	13 (76)	14 (82)
KRAS mutation (n = 10)	8 (80)	7 (70)
Best overall response,[c] No. (%)		
CR	6 (13)	11 (24)
PR	25 (56)	17 (38)
SD	7 (16)	8 (18)
PD	6 (13)	7 (16)
Not determined	1 (2)	2 (4)
DCR,[d] No. (%)	38 (84)	35 (78)
95% CI	70.5 to 93.5	63 to 89
Median DOR, months (range)[e]	NR (1.4+ to 29.0+)	NR (3.3+ to 29.0+)

Abbreviations: BICR, blinded independent central review; *BRAF*, V-Raf murine sarcoma viral oncogene homolog B1; CR, complete response; DCR, disease control rate; DOR, duration of response; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Patients with CR or PR divided by the number of treated patients.

[b]Excludes five patients with unknown mutation status.

[c]Per Response Evaluation Criteria in Solid Tumors version 1.1.

[d]Patients with CR, PR, and SD for ≥ 12 weeks divided by the number of treated patients.

[e]Based on 31 responders per investigator and 28 responders per BICR. + indicates a censored value.

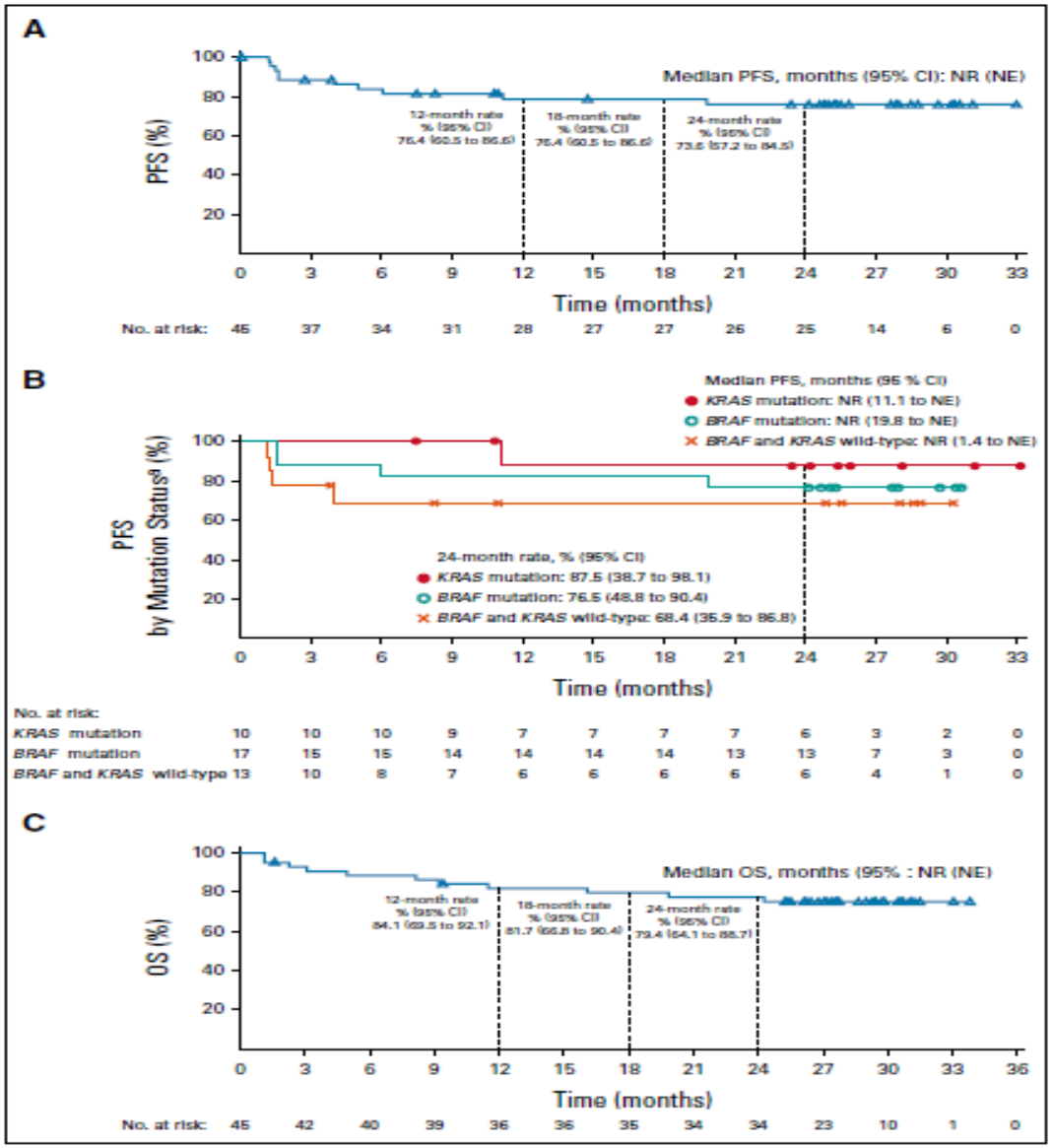


FIG 2. Kaplan-Meier estimate of (A) PFS per investigator assessment, (B) PFS per investigator assessment by mutation status, and (C) OS in all patients with a minimum follow-up of 24.2 months. [a]Excluded five patients with unknown mutation status. *BRAF*, V-Raf murine sarcoma viral oncogene homolog B1; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Summary - CheckMate 142

- Impressive results (high response rates) of Nivolumab(Q2W) plus low-dose ipilimumab (Q6W) as a 1L Tx for MSI-H/dMMRmCRC
- Nivolumab plus low-dose ipilimumab: acceptable tolerability profile with grade 3–4 TRAEs, 16% with a low rate of discontinuation due to TRAEs of 7%

BUT

- non-randomised study
- small number of patients
- no effect in about 15% of patients up front (about 30% in keynote 177)
- combination therapy results in increased costs

- Now EMA approved

IO for MSI-H mCRC

- Patient subgroups that might benefit more ?

  (all RAS/TMB, CMS, immunoscore, microbiome ?)

- Role of combination chemotherapy plus IO?

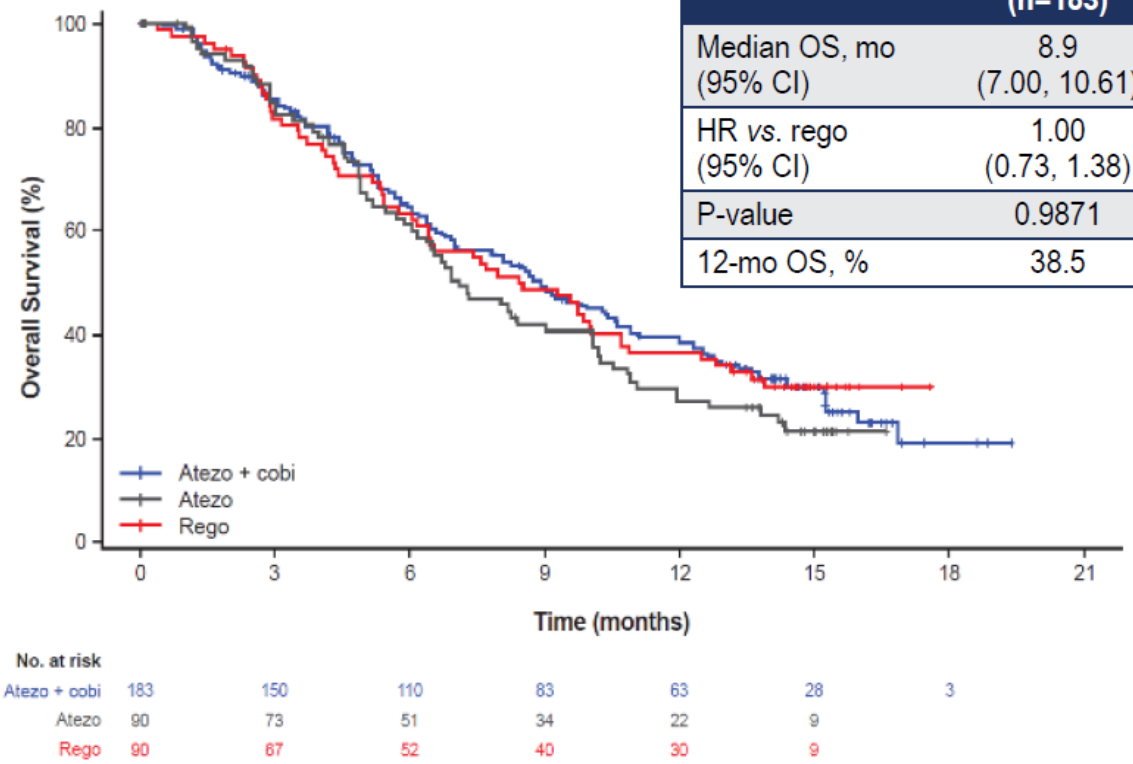
  Colorectal Cancer Metastatic dMMR Immuno-Therapy (COMMIT) study (NRG- GI004/SWOG-S1610)
  A randomized phase III study of mFOLFOX6/bevacizumab combination chemotherapy with or without atezolizumab or atezolizumab monotherapy in the first-line treatment of patients with deficient DNA mismatch repair (dMMR) metastatic colorectal cancer.

  BMS 8 HW
  A randomized phase III study of mFOLFOX6/bevacizumab combination chemotherapy with or without atezolizumab or atezolizumab monotherapy in the first-line treatment of patients with deficient DNA mismatch repair (dMMR) metastatic colorectal cancer.

- Combination IO (CheckMate 142)

- Can efficacy be increased with combination tx in MSI-H/BRAF-mut pts (IO+encorafenib /cetuximab) ?

COTEZO TRIAL
OVERALL SURVIVAL



	Atezo + cobi (n=183)	Atezo (n=90)	Rego (n=90)
Median OS, mo (95% CI)	8.9 (7.00, 10.61)	7.1 (6.05, 10.05)	8.5 (6.41, 10.71)
HR *vs.* rego (95% CI)	1.00 (0.73, 1.38)	1.19 (0.83, 1.71)	N/A
P-value	0.9871	0.3360[a]	N/A
12-mo OS, %	38.5	27.2	36.6

The COTEZO trial was negative for the overall population.
Outcomes of the CMS3 population need to be determined to validate the hypothesis

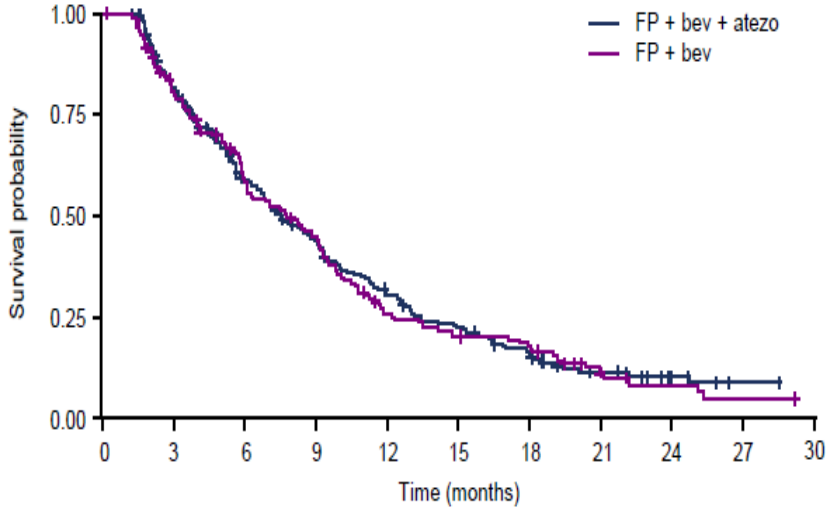
The MEK inh./ PD-L1 inh-combination did not achieve a better outcome

Bendell J, *et al*. Ann Oncol 2018;29 Suppl 5:v123, abstract LBA-004. Presented at ESMO WGI 2018. Courtesy of Dr Bendell.

Modul

Updated analysis: 1L BRAF^{wt}
Median follow-up 18.7 months

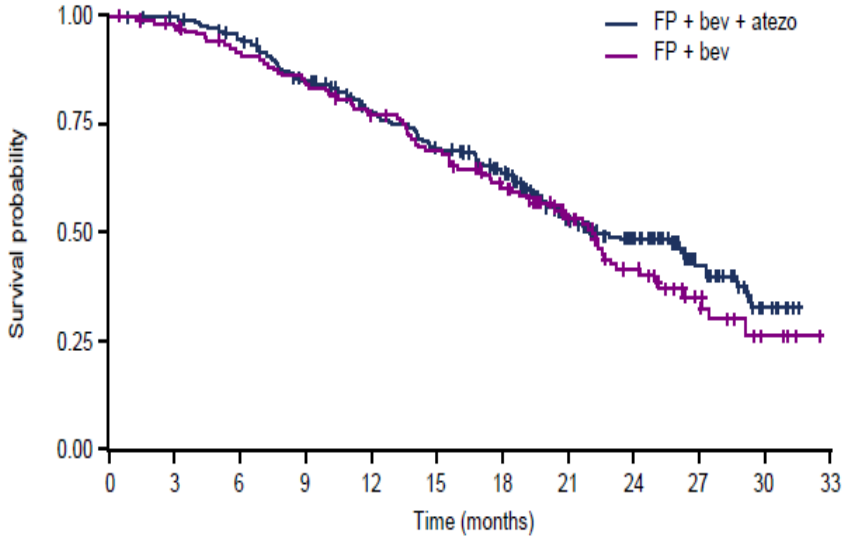
PFS



No. at risk

FP+bev+atezo	297	224	147	103	70	49	29	15	6	1	0
FP+bev	148	109	74	55	29	21	17	6	3	1	0

OS



No. at risk

FP+bev+atezo	297	293	275	244	214	189	164	104	70	28	8	0
FP+bev	148	142	130	120	108	94	79	49	30	14	5	0

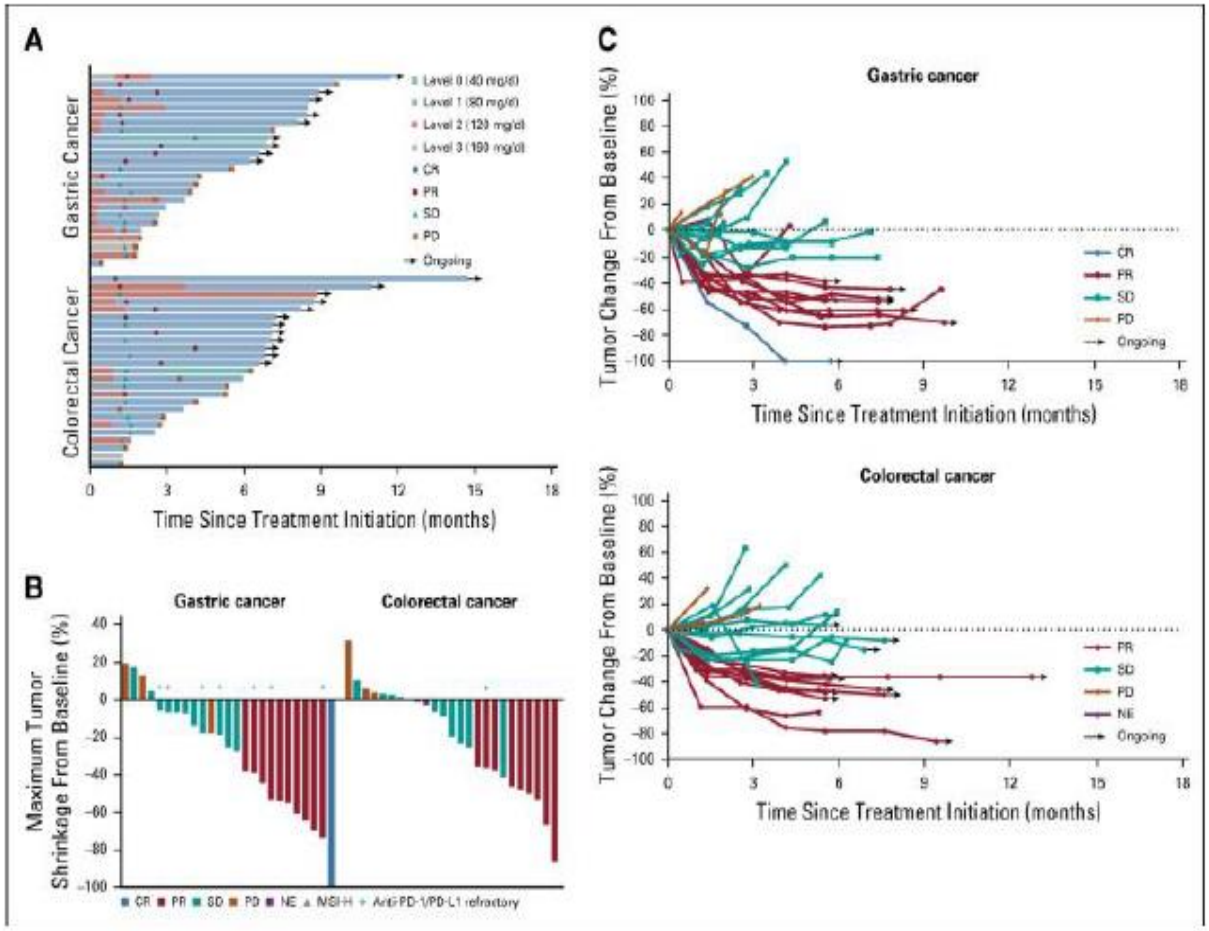
	FP + bev + atezo	FP + bev
Median PFS, months	7.20	7.39
Stratified HR (95% CI)	0.96 (0.77–1.20) p=0.727	

	FP + bev + atezo	FP + bev
Median OS, months	22.05	21.91
Stratified HR (95% CI)	0.86 (0.66–1.13) p=0.283	

Median duration of induction treatment phase: 4.1 months; for OS, 51% of patients had an event
One MSI patient in the FP + bev + atezo arm had a complete response during the maintenance treatment phase

Microsatellite Stable Colon Cancer

Rego plus Nivo



Fukuoka et al. JCO 2020

	Response Rate	Median PFS (mo)	1-year PFS (%)	Median OS (mo)	1-year OS (%)
CRC	9/25 (36)*	7.9	42	NR	68
GC	11/25 (44)**	5.6	22	12.3	55

*1 MSI-H CRC; RR RECIST liver mets (n=1 (8%)); RR RECIST lung mets (n=7 (64%))
** RR RECIST liver mets (n=5 (42%)); RR RECIST lung mets (n=4 (80%))

Fukuoka et al. JCO 2020

Regorafenib Plus Nivolumab Combo for CRC Found Not as Effective in North American Population as in Japanese Patients June 9, 2021

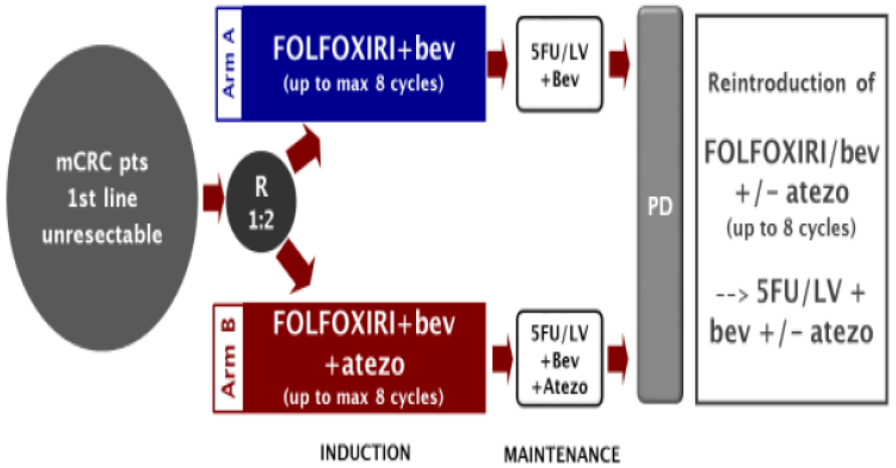
Sara Karlovitch – **ASCO Annual Meeting**

- Results of a single-arm phase 2 study of regorafenib (Stivarga) plus nivolumab (Opdivo) in patients with mismatch repair–proficient (pMMR)/microsatellite stable (MSS) colorectal cancer (CRC) found a discrepancy in efficacy between the Japanese and North American Population, according to a presentation at the 2021 American Society of Clinical Oncology Annual Meeting.[1]

- The objective response rate was 7%. For the subgroup of patients without liver metastases, the overall response rate was 22%.

Design and primary outcome- AtezoTribe

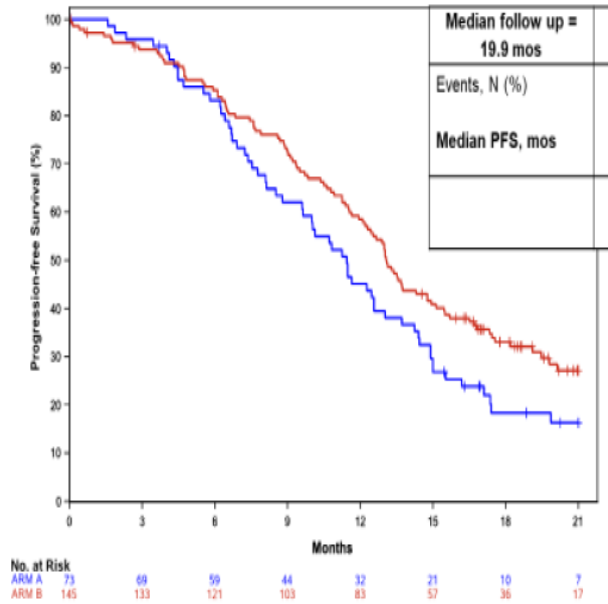
AtezoTRIBE trial



Stratification factors:

- Center
- PS 0 vs 1-2;
- primary tumor location (right vs left or rectum);
- Previous adjuvant CT

Primary endpoint: Progression Free Survival

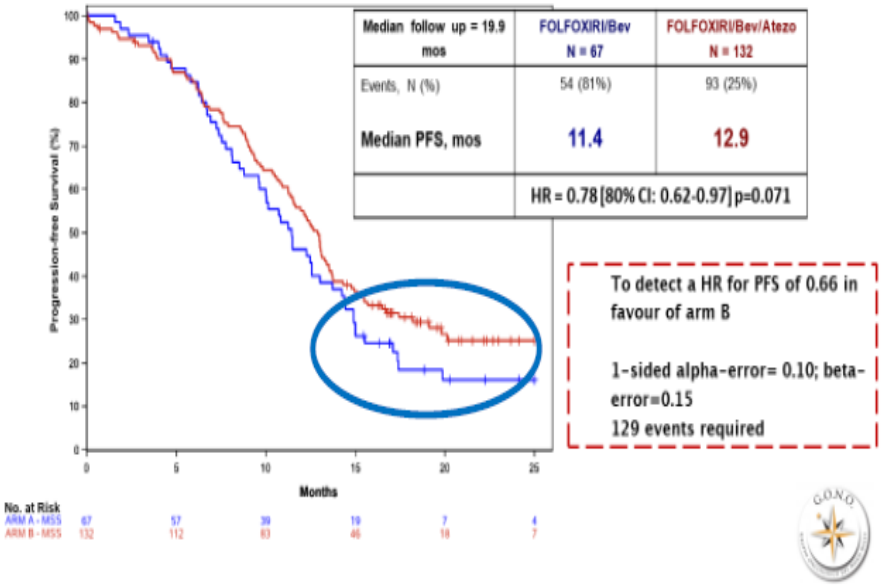


Median follow up = 19.9 mos	FOLFOXIRI/Bev N = 73	FOLFOXIRI/Bev/Atezo N = 145
Events, N (%)	60 (82%)	99 (68%)
Median PFS, mos	11.5	13.1
	HR = 0.69 [80% CI: 0.56-0.85] p=0.012	

- 201 patients arm A/B (67/134), randomized phase II, pMMR/dMMR allowed into trial
- Positive trial, PFS improved
- Without OS data yet…
- PFS gain with atezolizumab clinically relevant (HR 0.69)

Secondary efficacy data- AtezoTribe

Focus on the pMMR subgroup



Median follow up = 19.9 mos	FOLFOXIRI/Bev N = 67	FOLFOXIRI/Bev/Atezo N = 132
Events, N (%)	54 (81%)	93 (25%)
Median PFS, mos	11.4	12.9
	HR = 0.78 [80% CI: 0.62-0.97] p=0.071	

To detect a HR for PFS of 0.66 in favour of arm B

1-sided alpha-error= 0.10; beta-error=0.15
129 events required

Response and Resection Rate

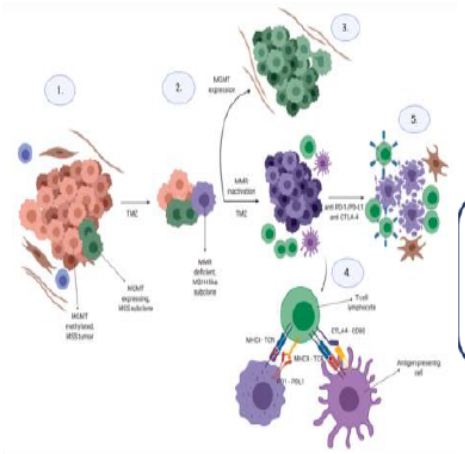
	FOLFOXIRI/Bev N = 73	FOLFOXIRI/Bev/Atezo N = 145	OR [80%CI], p
Complete Response	6%	6%	
Partial Response	58%	53%	
Response Rate	64%	59%	0.78 [0.54-1.15], p=0.412
Stable disease	29%	33%	
Progressive Disease	4%	3%	
Not Assessed	3%	6%	
R0 Resection Rate	37%	26%	p=0.175

- pMMR-PFS: the benefit with atezolizumab shrinks, but might be still relevant (HR 0.78)
- Other clinical subgroups without interaction for PFS
- Translational work-up ongoing
- ORR: no benefit with atezolizumab
- Secondary resection more frequent in control arm

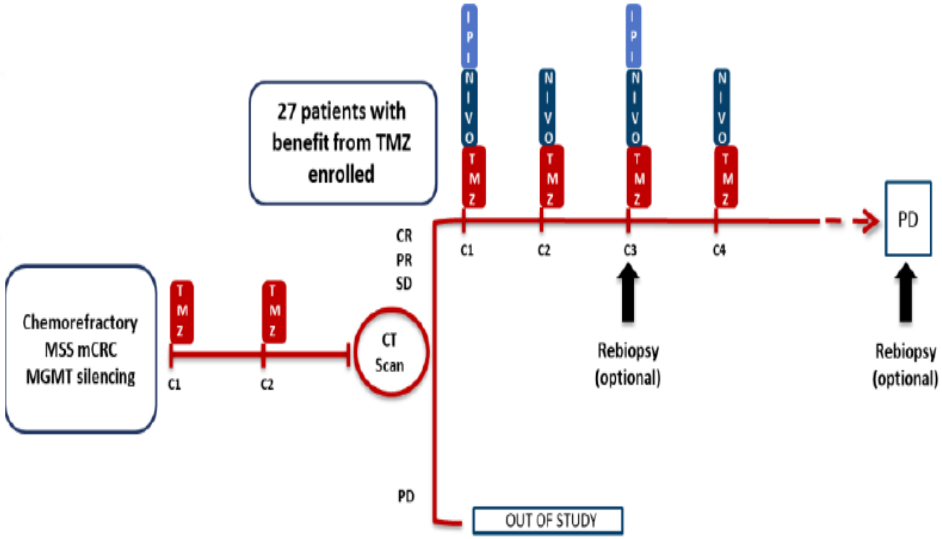
Design and rationale- MAYA

Rationale

Secondary resistance to TMZ may induce a **hypermutated status** (TMZ mutational signature #11 characterized by T>C transitions), frequently coupled with **acquired mutations in MMR genes** in diverse tumor types, including GBM, CRC and NECs [8-11]



Pietrantonio F et al, Cancer Treat Rev 2020



TMZ (temozolomide) 150 mg/sqm daily on days 1-5, every 4 weeks.
NIVO (nivolumab) 480 mg i.v. every 4 weeks.
IPI (ipilimumab)1 mg/Kg i.v. every 8 weeks

The induction of hypermutation (TMB-high) by a TMZ priming phase provides the rationale for immune-sensitization of MSS mCRCs

[8] Alexandrov et al, Nature 2013; [9] Germano G et al, Nature 2017; [10] Campbell et al, Cell 2017; [11] Klempner et al, JCO PO 2020

Filippo Pietrantonio, *MD*

- 33 pts, phase II, proof of principle trial
- Pretreated patients, selected for MSS and MGMT silencing
- EP: PFS @ 8 months (4/27 need to reach 8 months progression-free)

To be continued …

- The role of IDO inhibitors (IDO expression in about 40% of CRC – assoc. with poor prognosis and liver mets) inhibition leads to modification of tumour microenvironment)
- The role of QX40 agonists (high levels of QX40 in TILs correlated with increased OS)
- The role of MCSF receptor inhibition
- The role of CD73 inhibition (inhibition of CD73 may improve anti-cancer immune response)
- Monalizumab plus anti-PDL1: Monalizumab is an antibody that prevents the inhibition of CD8+ T cells and NK cell by tumor cells expressing HLA-E
- CEA-TCB (T cell bispecific antibody for treatment of CEA-positive solid tumors) + anti-PDL1

ORIGINAL ARTICLE

Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E–Mutated Colorectal Cancer

S. Kopetz, A. Grothey, R. Yaeger, E. Van Cutsem, J. Desai, T. Yoshino, H. Wasan, F. Ciardiello, F. Loupakis, Y.S. Hong, N. Steeghs, T.K. Guren, H.-T. Arkenau, P. Garcia-Alfonso, P. Pfeiffer, S. Orlov, S. Lonardi, E. Elez, T.-W. Kim, J.H.M. Schellens, C. Guo, A. Krishnan, J. Dekervel, V. Morris, A. Calvo Ferrandiz, L.S. Tarpgaard, M. Braun, A. Gollerkeri, C. Keir, K. Maharry, M. Pickard, J. Christy-Bittel, L. Anderson, V. Sandor, and J. Tabernero

ABSTRACT

BACKGROUND

Patients with metastatic colorectal cancer with the *BRAF* V600E mutation have a poor prognosis, with a median overall survival of 4 to 6 months after failure of initial therapy. Inhibition of BRAF alone has limited activity because of pathway reactivation through epidermal growth factor receptor signaling.

METHODS

In this open-label, phase 3 trial, we enrolled 665 patients with *BRAF* V600E–mutated metastatic colorectal cancer who had had disease progression after one or two previous regimens. Patients were randomly assigned in a 1:1:1 ratio to receive encorafenib, binimetinib, and cetuximab (triplet-therapy group); encorafenib and cetuximab (doublet-therapy group); or the investigators' choice of either cetuximab and irinotecan or cetuximab and FOLFIRI (folinic acid, fluorouracil, and irinotecan) (control group). The primary end points were overall survival and objective response rate in the triplet-therapy group as compared with the control group. A secondary end point was overall survival in the doublet-therapy group as compared with the control group. We report here the results of a prespecified interim analysis.

RESULTS

The median overall survival was 9.0 months in the triplet-therapy group and 5.4 months in the control group (hazard ratio for death, 0.52; 95% confidence interval [CI], 0.39 to 0.70; P<0.001). The confirmed response rate was 26% (95% CI, 18 to 35) in the triplet-therapy group and 2% (95% CI, 0 to 7) in the control group (P<0.001). The median overall survival in the doublet-therapy group was 8.4 months (hazard ratio for death vs. control, 0.60; 95% CI, 0.45 to 0.79; P<0.001). Adverse events of grade 3 or higher occurred in 58% of patients in the triplet-therapy group, in 50% in the doublet-therapy group, and in 61% in the control group.

CONCLUSIONS

A combination of encorafenib, cetuximab, and binimetinib resulted in significantly longer overall survival and a higher response rate than standard therapy in patients with metastatic colorectal cancer with the *BRAF* V600E mutation. (Funded by Array BioPharma and others; BEACON CRC ClinicalTrials.gov number, NCT02928224; EudraCT number, 2015-005805-35.)

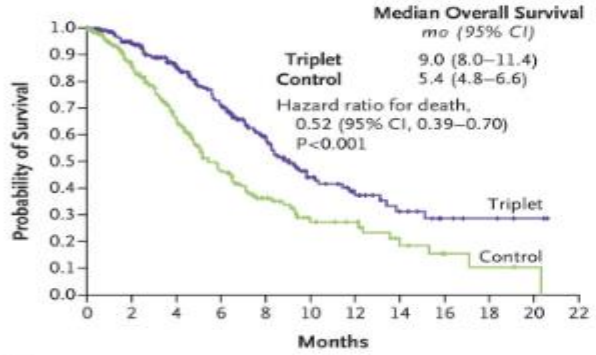
The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Tabernero at Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Passeig de la Vall d'Hebron 119-129, 08035 Barcelona Spain, or at jtabernero@vhio.net.

A list of committee members and principal investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 30, 2019, at NEJM.org.

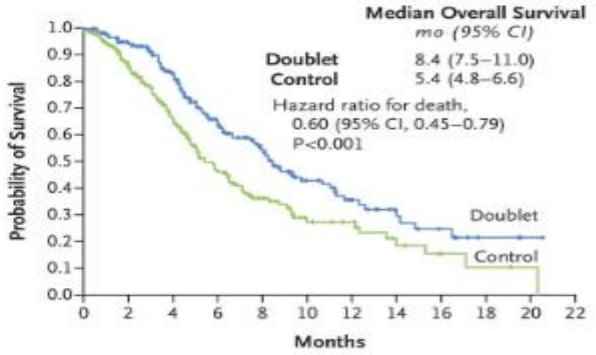
N Engl J Med 2019;381:1632-43.
DOI: 10.1056/NEJMoa1908075

A Overall Survival, Triplet Regimen vs. Control



No. at Risk												
Triplet	224	186	141	103	69	37	24	14	6	4	2	0
Control	221	158	102	60	34	18	15	7	4	2	1	0

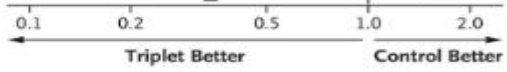
B Overall Survival, Doublet Regimen vs. Control



No. at Risk												
Doublet	220	184	133	87	57	33	21	12	8	3	1	0
Control	221	158	102	60	34	18	15	7	4	2	1	0

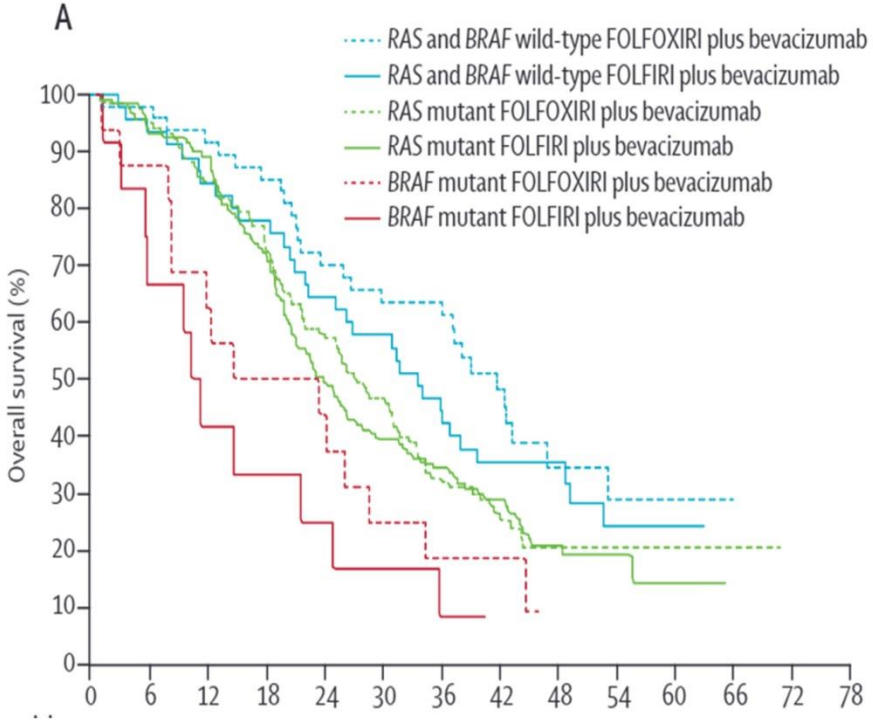
C Overall Survival According to Subgroup, Triplet Regimen vs. Control

Subgroup	No. of Deaths/No. of Patients	Hazard Ratio for Death vs. Control (95% CI)
All patients	204/445	0.52 (0.39–0.70)
ECOG performance-status score		
0	85/227	0.63 (0.41–0.96)
1	119/218	0.48 (0.33–0.70)
Previous irinotecan use		
No	99/219	0.53 (0.35–0.79)
Yes	105/226	0.55 (0.37–0.80)
Region		
North America	32/59	0.91 (0.45–1.86)
Europe	124/275	0.39 (0.27–0.56)
Rest of the world	48/111	0.74 (0.41–1.33)
No. of previous regimens for metastatic disease		
1	123/291	0.54 (0.38–0.77)
≥2	81/154	0.53 (0.34–0.82)
Age		
<65 yr	130/290	0.58 (0.41–0.82)
≥65 yr	74/155	0.48 (0.30–0.76)
Sex		
Male	100/199	0.53 (0.36–0.79)
Female	104/246	0.54 (0.36–0.80)
No. of organs involved		
≤2	104/237	0.54 (0.37–0.80)
≥3	100/208	0.50 (0.34–0.75)
Microsatellite instability status		
Abnormal, high	18/34	0.67 (0.26–1.76)
Normal	140/200	0.44 (0.31–0.62)
Unknown	46/111	0.78 (0.44–1.41)
Baseline carcinoembryonic antigen level		
Higher than the upper limit of the normal range	180/257	0.54 (0.40–0.72)
At or below the upper limit of the normal range	23/87	0.42 (0.18–0.99)
Baseline C-reactive protein level		
Higher than the upper limit of the normal range	115/185	0.61 (0.42–0.88)
At or below the upper limit of the normal range	83/247	0.46 (0.29–0.71)
Location of tumor		
Left side of the colon	53/147	0.43 (0.26–0.72)
Right side of the colon	117/245	0.63 (0.44–0.90)
Both sides of the colon	14/30	0.74 (0.22–2.42)
Unknown	10/23	0.35 (0.09–1.38)



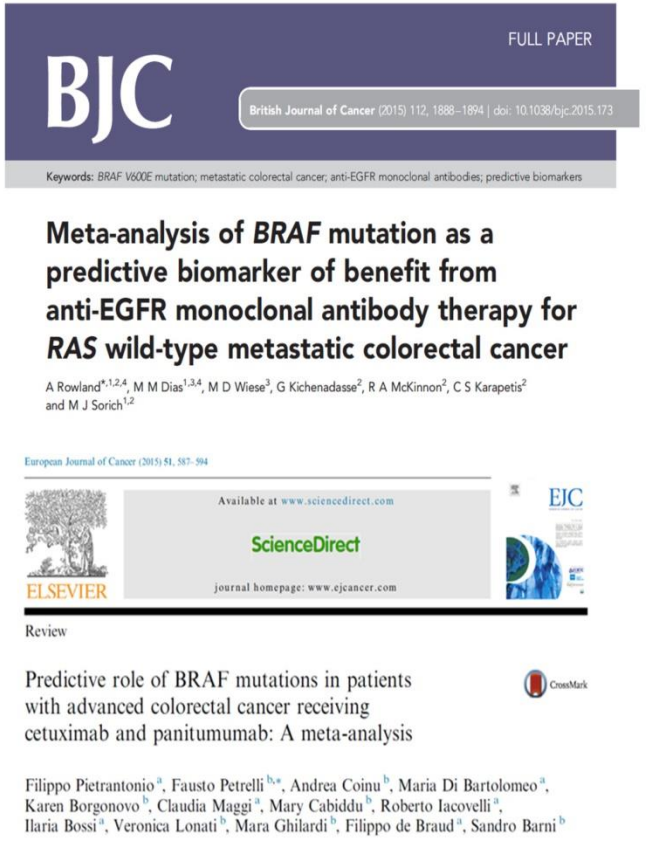
Rationale of the study design

➔ **Prospective** randomized **data** on BRAF V600E mutant in first-line mCRC **are missing**.



Cremolini C, et al. Lancet Oncol 2015;16:1306–1315.

➔ The use of **EGFR antibodies** in BRAF V600E mutant mCRC **is controversial**.



FULL PAPER

BJC

British Journal of Cancer (2015) 112, 1888–1894 | doi: 10.1038/bjc.2015.173

Keywords: *BRAF V600E* mutation; metastatic colorectal cancer; anti-EGFR monoclonal antibodies; predictive biomarkers

Meta-analysis of *BRAF* mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for *RAS* wild-type metastatic colorectal cancer

A Rowland[*,1,2,4], M M Dias[1,3,4], M D Wiese[3], G Kichenadasse[2], R A McKinnon[2], C S Karapetis[2] and M J Sorich[1,2]

European Journal of Cancer (2015) 51, 587–594

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

EJC

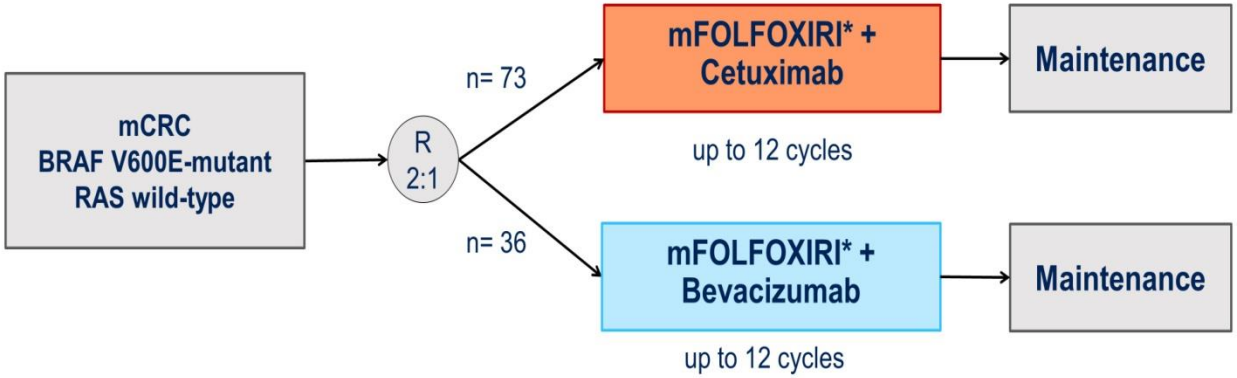
ELSEVIER

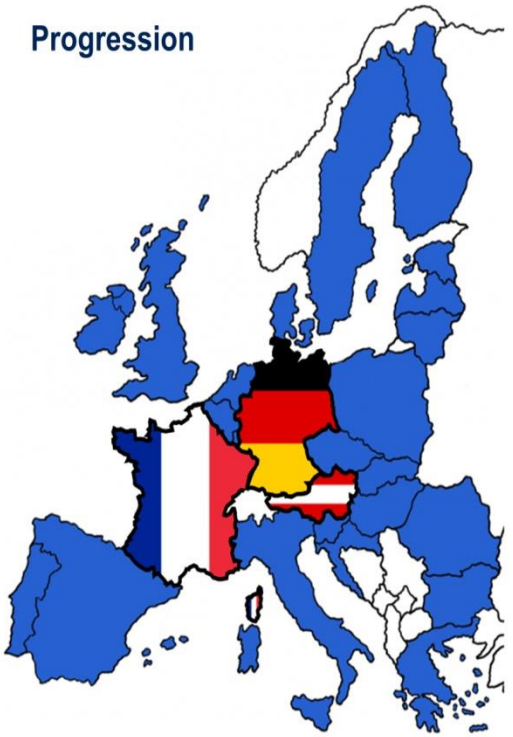
Review

Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: A meta-analysis

Filippo Pietrantonio[a], Fausto Petrelli[b,*], Andrea Coinu[b], Maria Di Bartolomeo[a], Karen Borgonovo[b], Claudia Maggi[a], Mary Cabiddu[b], Roberto Iacovelli[a], Ilaria Bossi[a], Veronica Lonati[b], Mara Ghilardi[b], Filippo de Braud[a], Sandro Barni[b]

FIRE-4.5 Study Design
AIO KRK-0116





Primary endpoint:
Objective response rate (ORR) according to RECIST 1.1

Secondary endpoints: PFS, OS, toxicity

***mFOLFOXIRI:** irinotecan 150 mg/m², oxaliplatin 85 mg/m², folinic acid 400 mg/m² 5-FU 3,000 mg/m² within 48hrs
Cetuximab: cetuximab 400mg/m² loading dose followed by 250mg/m² weekly
Bevacizumab: bevacizumab 7.5mg/kg body weight biweekly

Stratification factors: - ECOG PS: 0 vs. 1
- location of the primary: right vs. left

Presented By: Prof. Sebastian Stintzing. MD
Charité – Universitaetsmedizin Berlin

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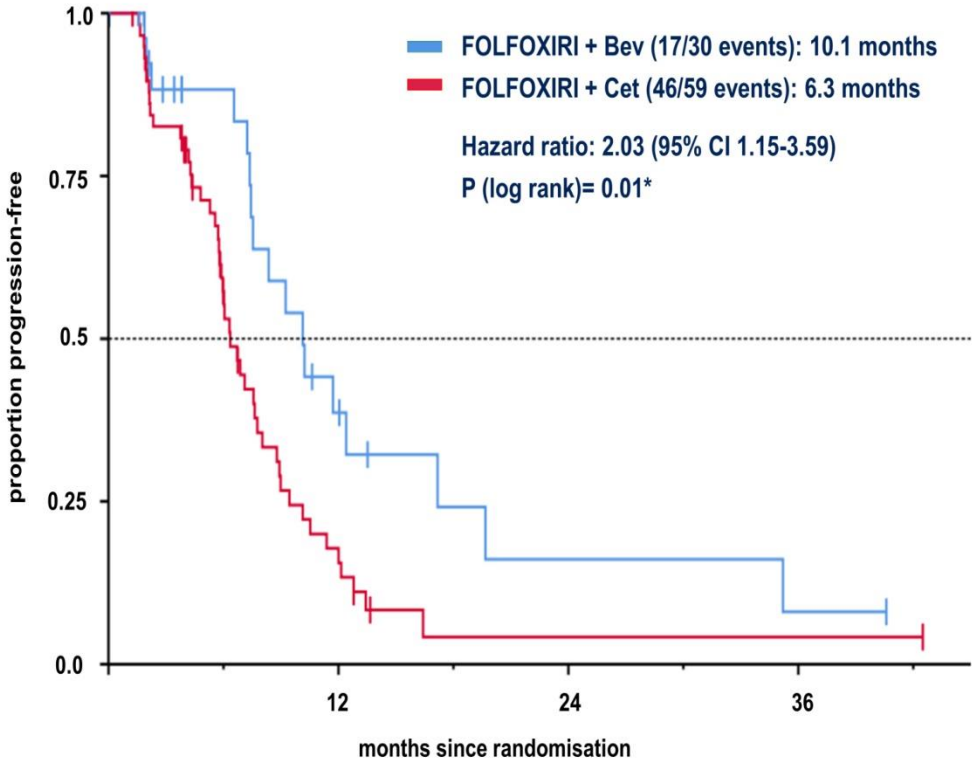
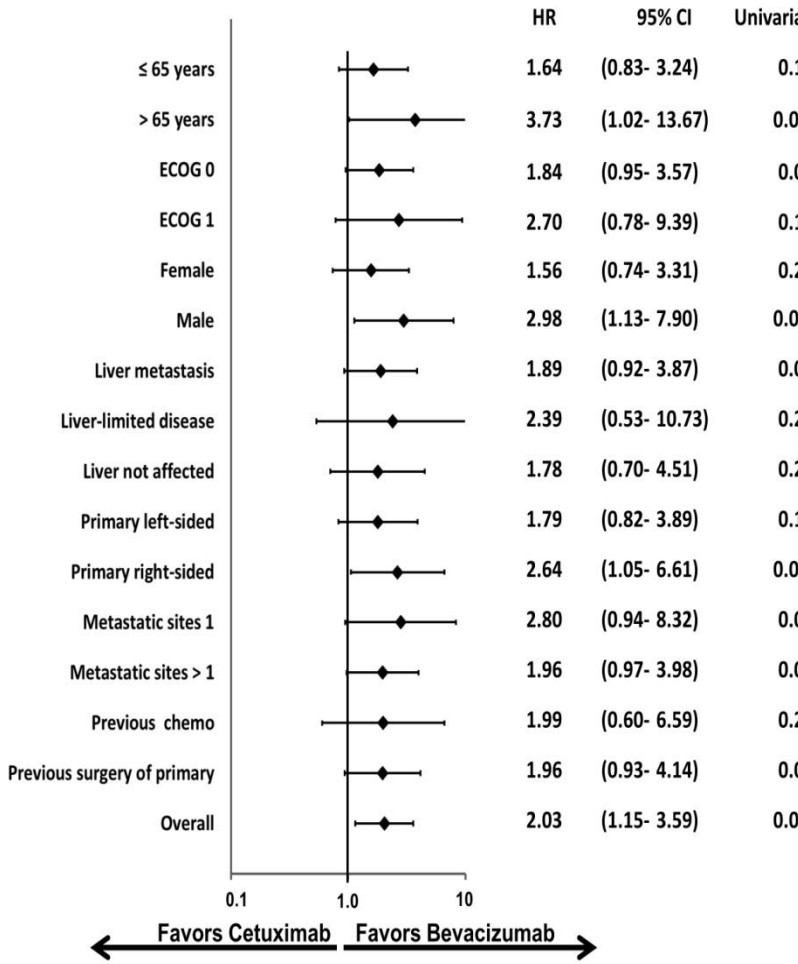
Progression-Free-Survival (PFS)

ATP (n=89)





*significant univariate value

ANCHOR -1st line Encorafenib, Binimetinib, cetuximab - NCT03693170.

In the first 40 assessable patients from ANCHOR CRC:

- ORR was 50% (95% CI 33.8% to 66.2%)
- median PFS was 4.9 months (95% CI4.4-8.1 months)
- Decrease in tumor size was observed in 85% of patients.
- Adverse events have been consistent with those observed in prior studies of the triplet combination

Van Cutsem E, *et al.* ESMO WCGC 2021 Proceedings.

BREAKWATER: Randomized phase 3 study of encorafenib (enco) + cetuximab (cetux) ± chemotherapy for first-line (1L) treatment (tx) of *BRAF* V600E-mutant (*BRAF*^{V600E}) metastatic colorectal cancer (mCRC).

	SLI (safety lead-in)	Arm A Enco 300 mg QD + cetux 500 mg/m^{2†} Arm B Enco 300 mg QD + cetux 500 mg/m^{2†} + mFOLFOX6† or FOLFIRI† (depending on SLI)
Tx*	**Enco 300 mg QD + cetux 500 mg/m^{2†} + mFOLFOX6†** **or** **Enco 300 mg QD + cetux 500 mg/m^{2†} + FOLFIRI†**	**Control (± bevacizumab) mFOLFOX6†** **or** **FOLFOXIRI†** **or** **FOLFIRI†** **or** **CAPOX (21-day cycle; oxaliplatin, Q3W; capecitabine, BID Days 1–14)**
Endpoints		
Primary	**Incidence of dose-limiting toxicities**	**Progression-free survival (PFS; by blinded independent central review [BICR]) (arm A vs control; arm B vs control)**

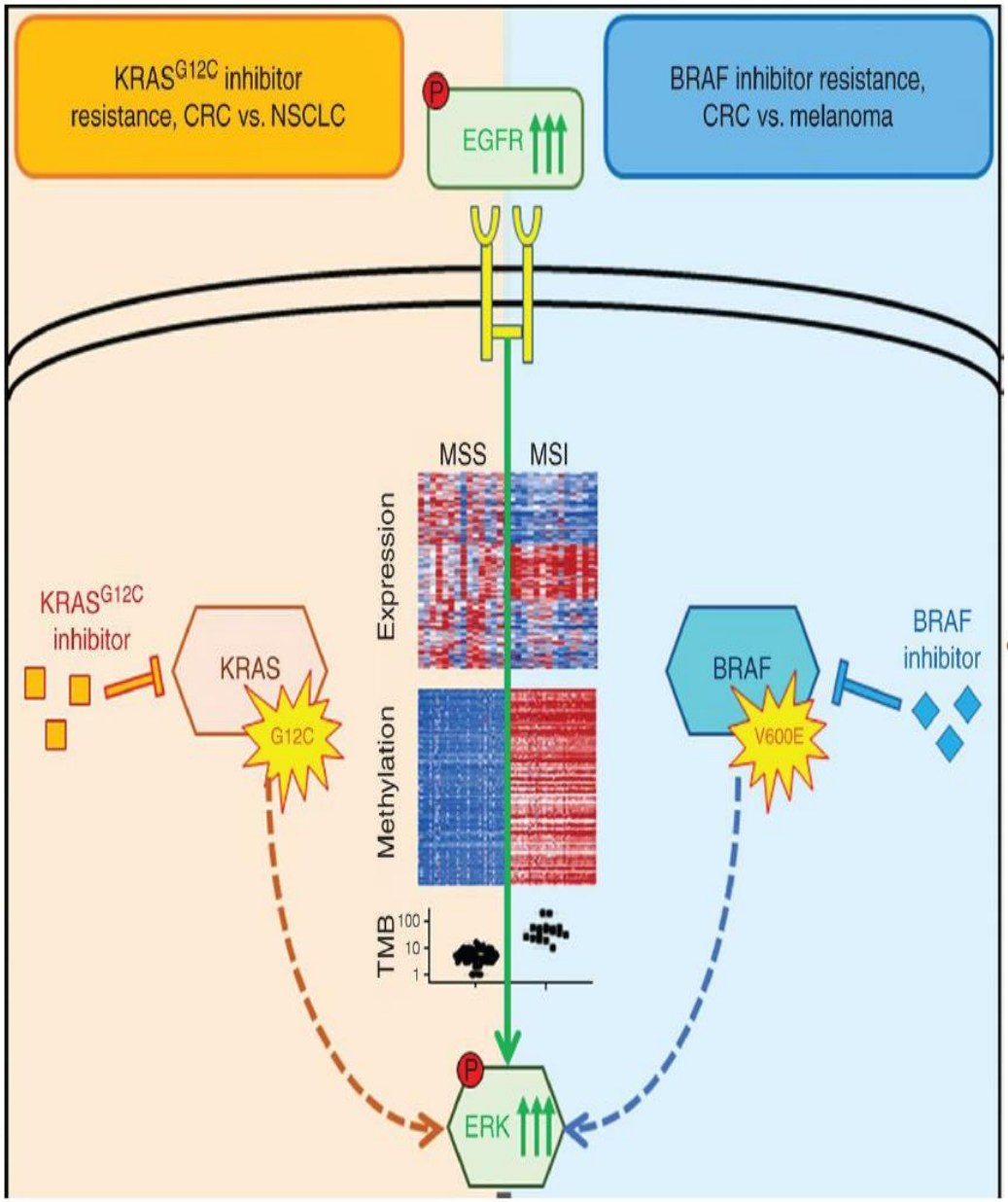
KRAS G12C inhib.
response rate

NSCLC
Sotorasib: 37%
Adagrasib : 45%

- Skoulidis F. et al., N Engl J Med 2021; 384:2371-2381
- Riely et al., ELCC 2021

mCRC
Sotorasib: 7%
(12% at full dose)
Adagrasib: 17% (3/18)

- Hong D.S., et al., N Engl J Med 2020; 383:1207-121
- Johnson ML et al., EORTC-NCI-AACR 2020



Mutant BRAF
Vemurafenib
response rate

Melanoma : >50%
mCRC : 5%

- Sosman JA et al., N Engl J Med. 2012; 366: 707–714
- Kopetz S et al., J Clin Oncol. 2015;33(34):4032-8

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Figure from Kalaitzi and Kwong, Cancer Discov 2020;10:1004–6

Duration of response to adagrasib + cetuximab in mCRC?

KRAS G12C mCRC
Adagrasib+Cetuximab

ORR 43% (12/28)

Weiss J et al., ESMO 2021

PFS =???

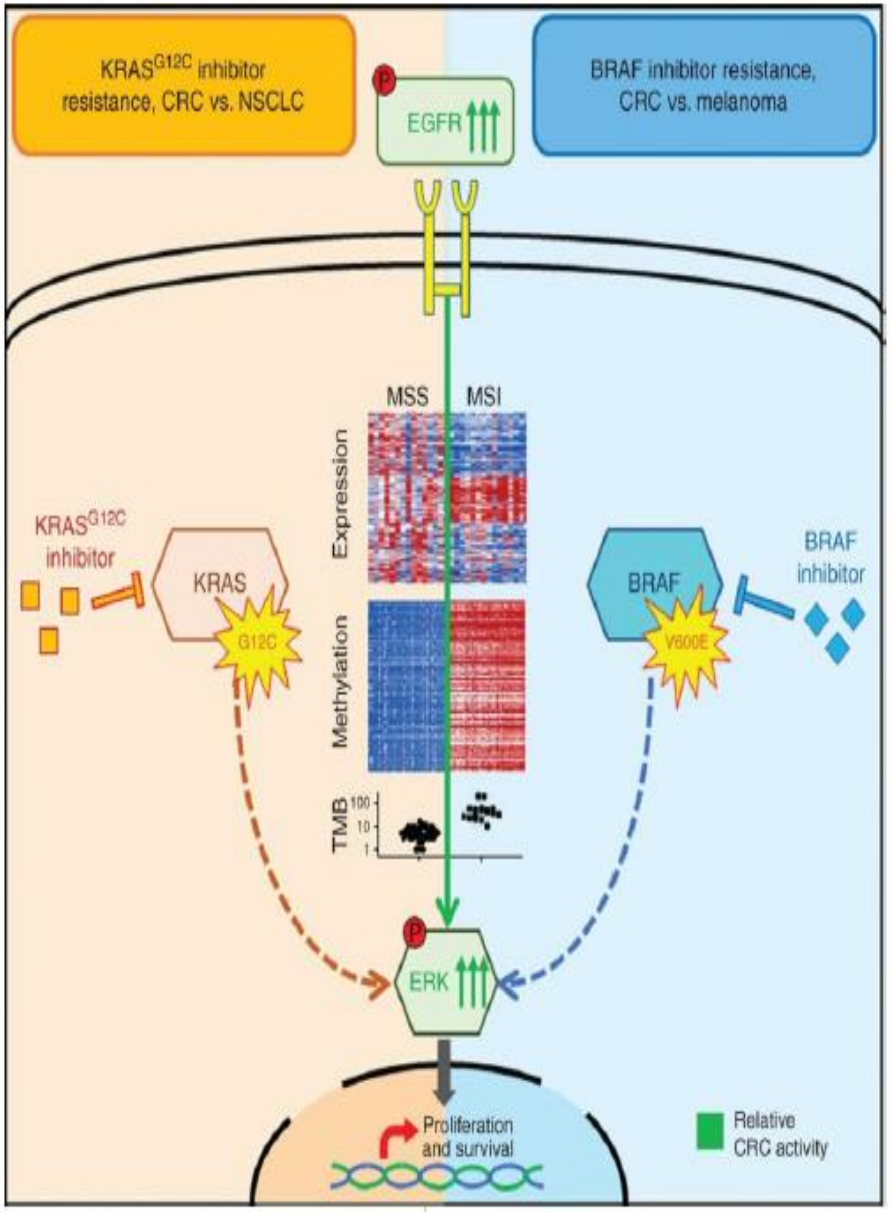

Figure from Koleilat and Kwong. Cancer Discov 2020;10:1094–6

Mutant BRAF mCRC
Encorafenib+Cetuximab
(± Binimetinib)

ORR 19.8% (doublet)
26.8% (triplet)

PFS 4.2 months doublet
(95% CI, 3.7 to 5.4)
4.3 months triplet
(95% CI, 4.1 to 5.2)

OS 9.3 mos (doublet)
9.3 mos (triplet)

- Kopetz S et al., N Engl J Med. 2019;381:1632-1643
- Tabernero J et al., J Clin Oncol. 2021;39(4):273-284

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Response rate to sotorasib + panitumumab in mCRC patients

CodeBreaK101 Subprotocol H
Part 2 Cohort A (**n = 18**)

Sotorasib 960 mg /
PMab 6 mg/kg

DCR: n = 15 (83.3%)

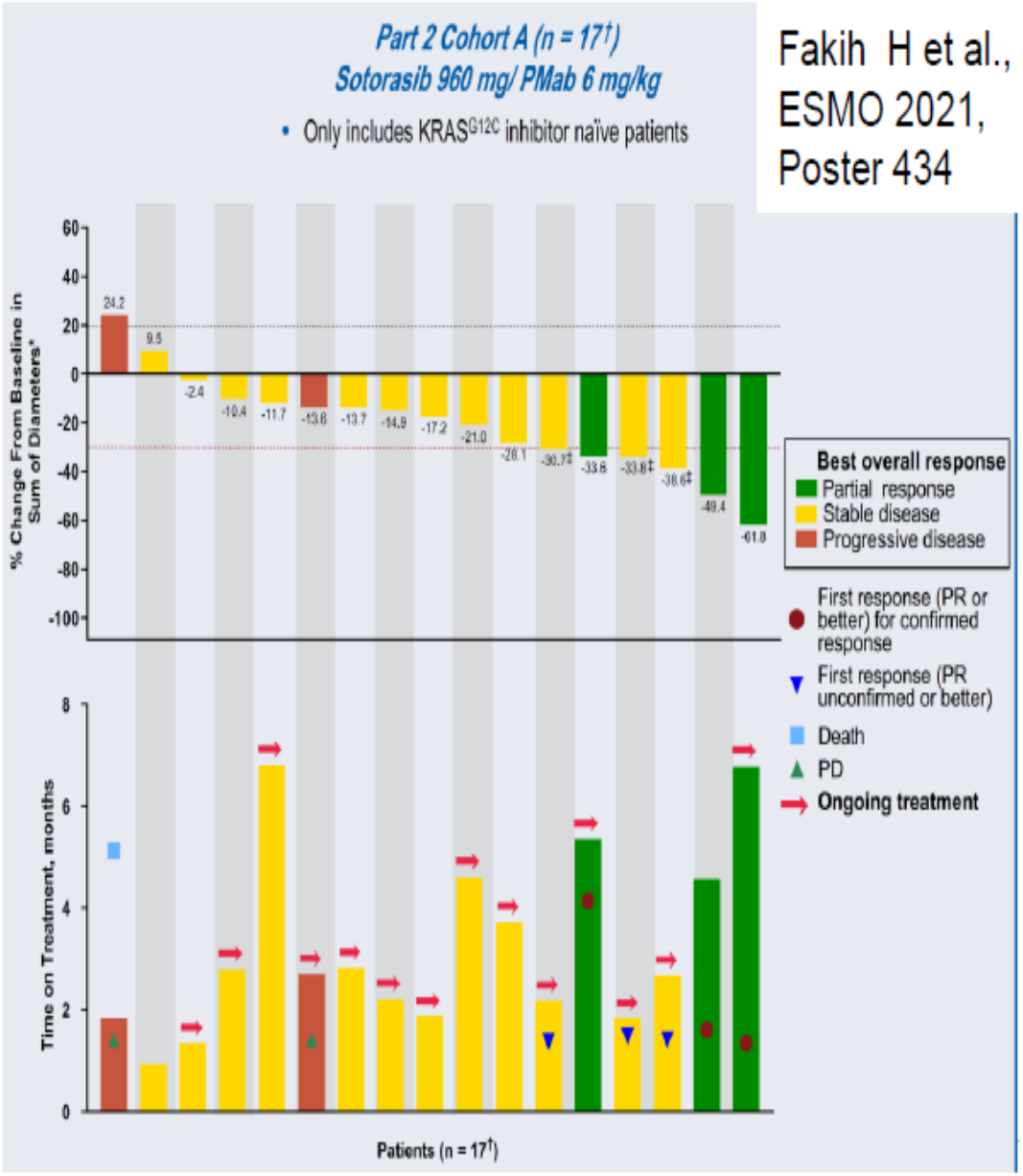
PR: n=3 (16.7%)

Unconfirmed PR n=6 (33.3%)

SD: n = 12 (66.7%)

PD: n = 2 (11.1%)

Not done: n = 1 (5.6%)



Fakih H et al.,
ESMO 2021,
Poster 434

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Thank you