Colon Cancer: Are We Making Progress?

Axel Grothey

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Historic debates on best first-line therapy

- **1990s:**
  - Best modulator of 5-FU? (MTX, IFN, folinic acid…)
  - Infusional vs bolus 5-FU

REVIEW ARTICLE

Fluorouracil in Colorectal Cancer—A Tale of Two Drugs: Implications for Biochemical Modulation

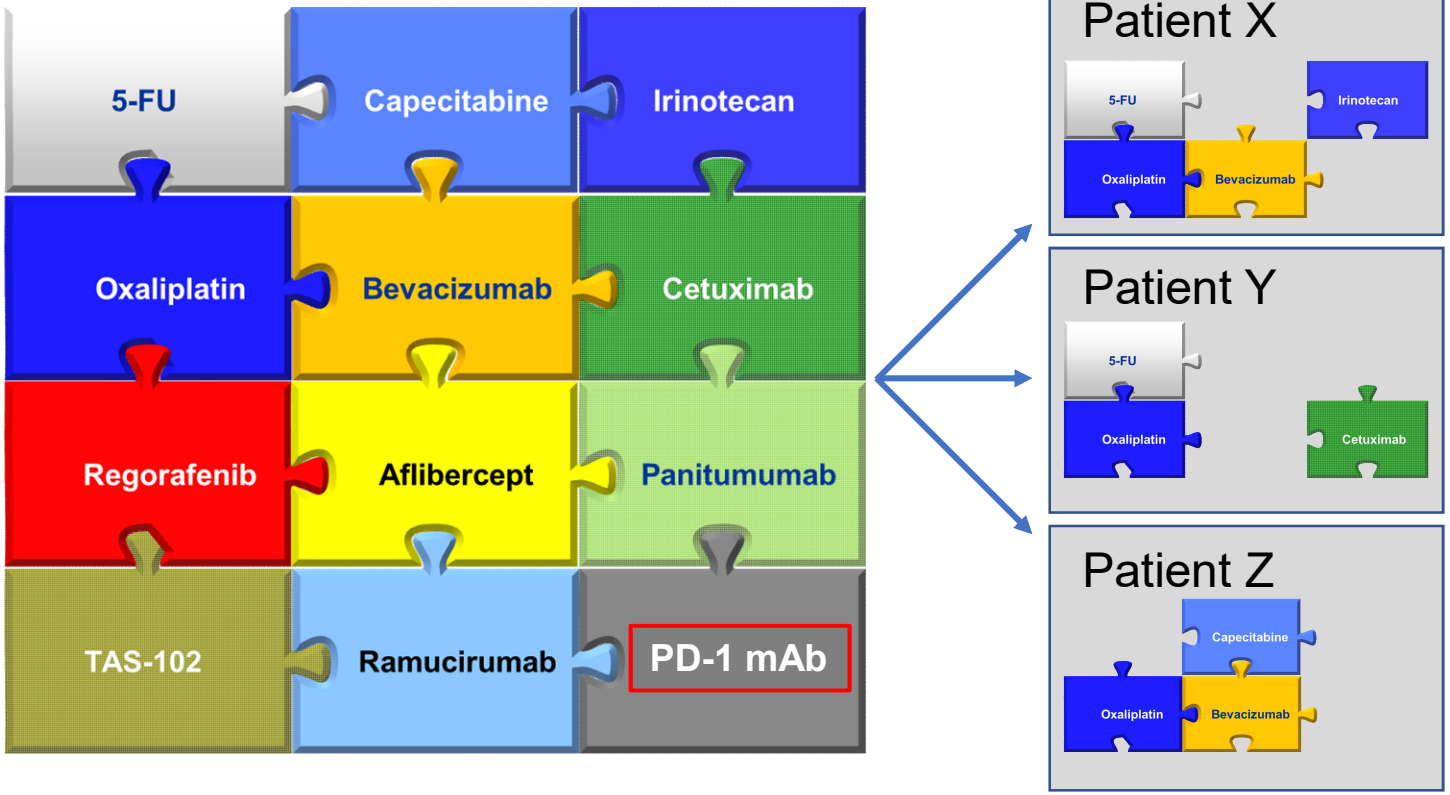
By Alberto F. Sobrero, Carlo Aschele, and Joseph R. Bertino

J Clin Oncol 1997

Historic debates on best first-line therapy

- **1990s:**
  - Best modulator of 5-FU? (MTX, IFN, folinic acid…)
  - Infusional vs bolus 5-FU
- **Early 2000s:**
  - Oxaliplatin vs Irinotecan
- **Mid-2000s-2010:**
  - Bevacizumab vs Cetuximab/ Panitumumab

The Luxury of So Many Options . . .
How Do We Personalize?

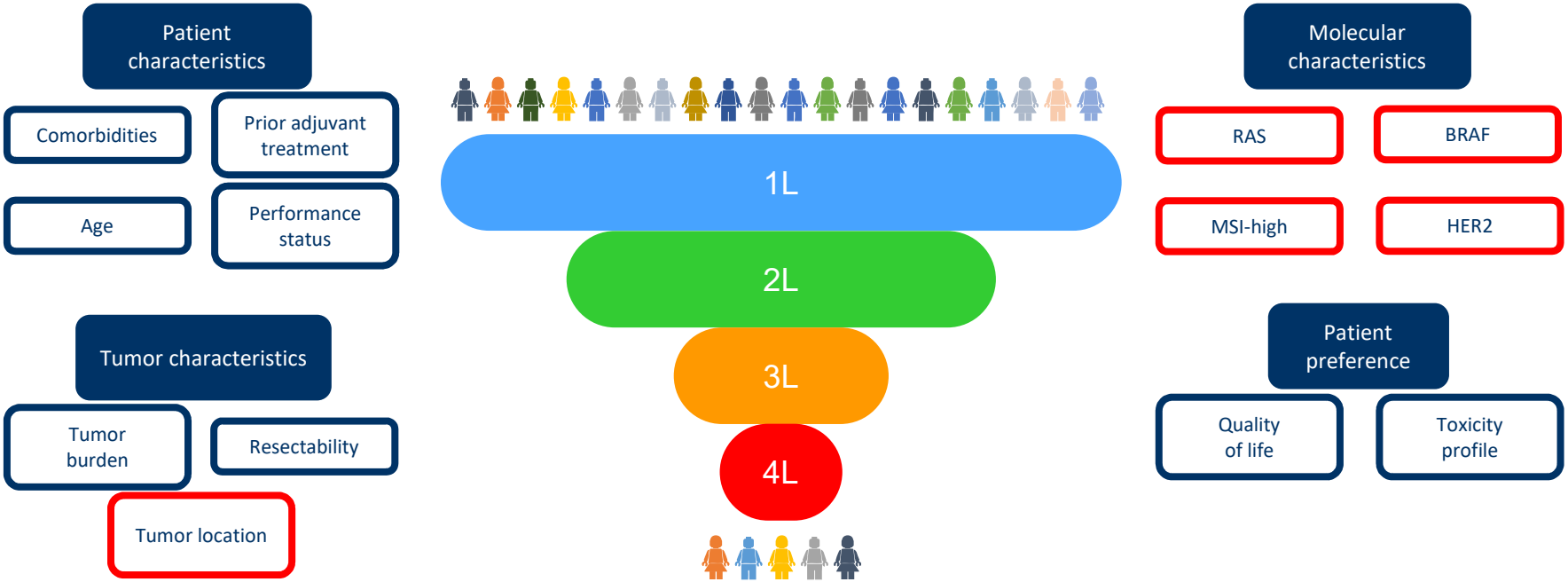


Goal of medical therapy in mCRC

Finding the right treatment
for the right patient
at the right time

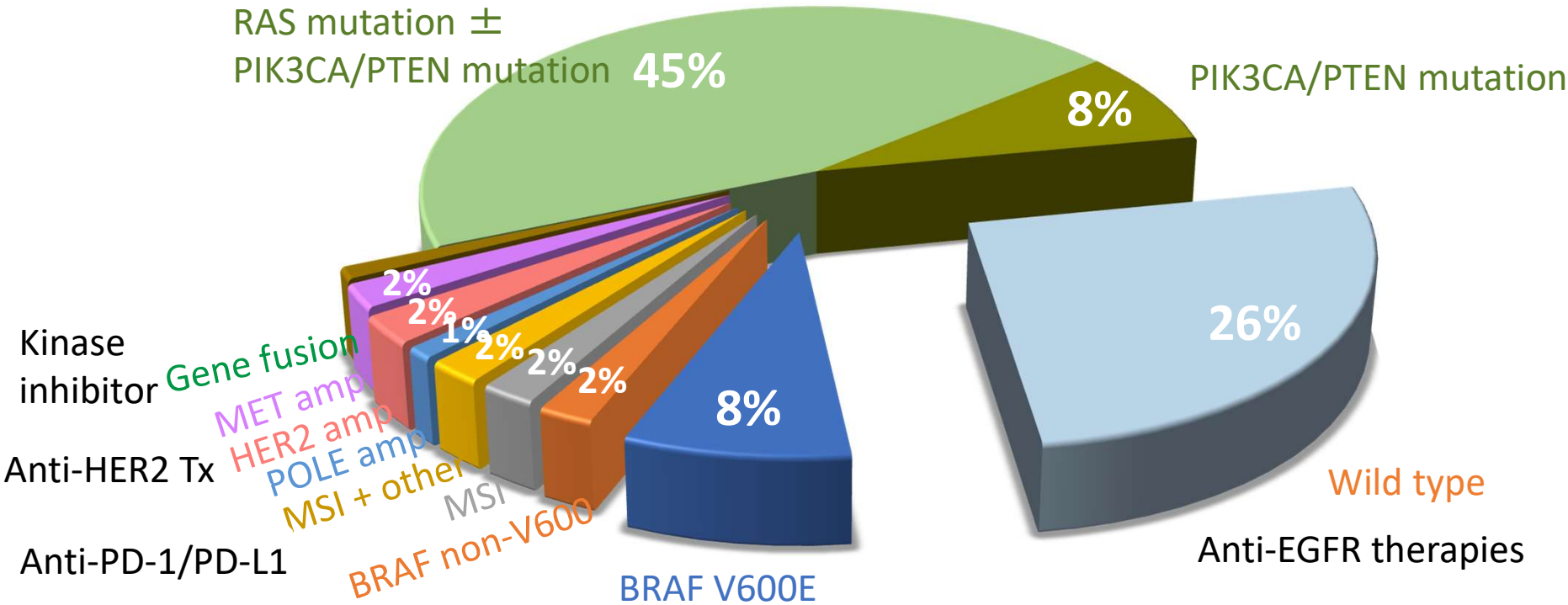
Individualized therapy in CRC did not start with KRAS

What influences treatment choices in mCRC?



Therapy tailored according to individual patient needs

Genomic Markers in CRC



Dienstmann. ASCO Ed Book. 2018.

Current Treatment Pattern in the US

- **FOLFOX + BEV undisputedly most commonly used first-line therapy in mCRC regardless of sidedness and RAS/ BRAF mutation status**
- **FOLFIRI + BEV mainly in academic centers**
- **Use of EGFR mAbs slowly increasing in left-sided RAS/ BRAF wild-type cancers**
  - SOC in Europe and elsewhere (rightfully so)
- **For BRAF V600E mutated cancers, FOLFOXIRI + BEV recognized as an option, but not commonly used**
- **In MSI-H/ MMR-D cancers, IO tested in first-line trials – but also used in front-line outside of trials**
- **No HER-2 targeting first-line approaches**

Treatment Options in First-line

Regimen	Sidedness restriction	Molecular restriction	Preferred indication
Cape + BEV	None	None	Elderly patients, low-volume disease
FOLFOX/ CAPOX/ FOLFIRI + BEV	None	None	
FOLFOXIRI + BEV	None	None	Aggressive cancers (w.g. BRAF mut, R-sided)
FOLFOX/ FOLFIRI + EGFR mAb	Left-sided*	RAS/ BRAF wt (HER-2 neg?)	SOC left-sided cancers
FOLFOXIRI + EGFR mAb	Left-sided*	RAS/ BRAF wt (HER-2 neg?)	Left-sided cancers with high tumor load
PD-1 antibody/ IO combo	None	MSI-H/ MMR-D	Pts with MSI-H cancers not considered for chemo
BEACON(-like)	None	BRAF V600E mut	Data in first-line pending

*ESMO guidelines allow EGFR mAbs in R-sided cancers

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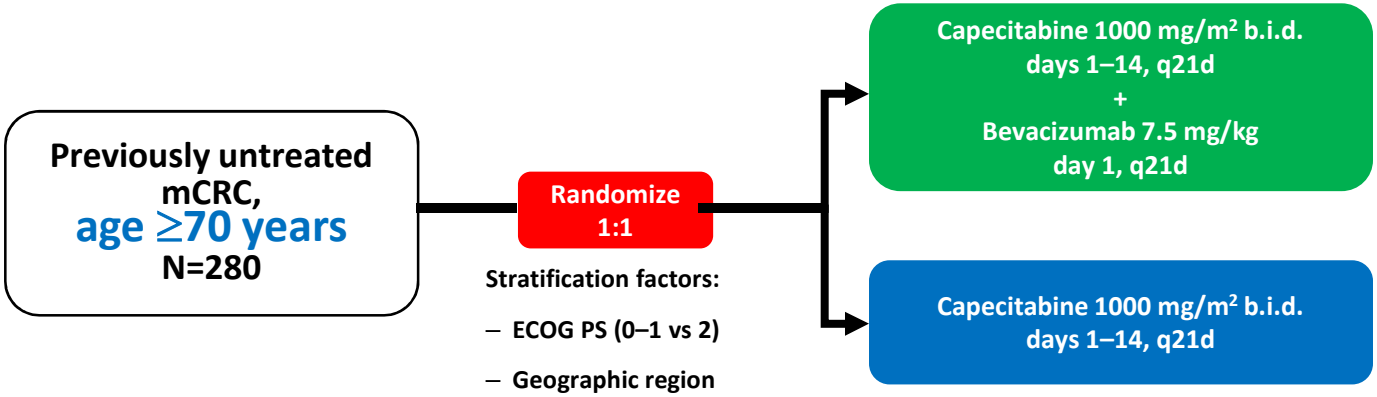
AVEX - Study design

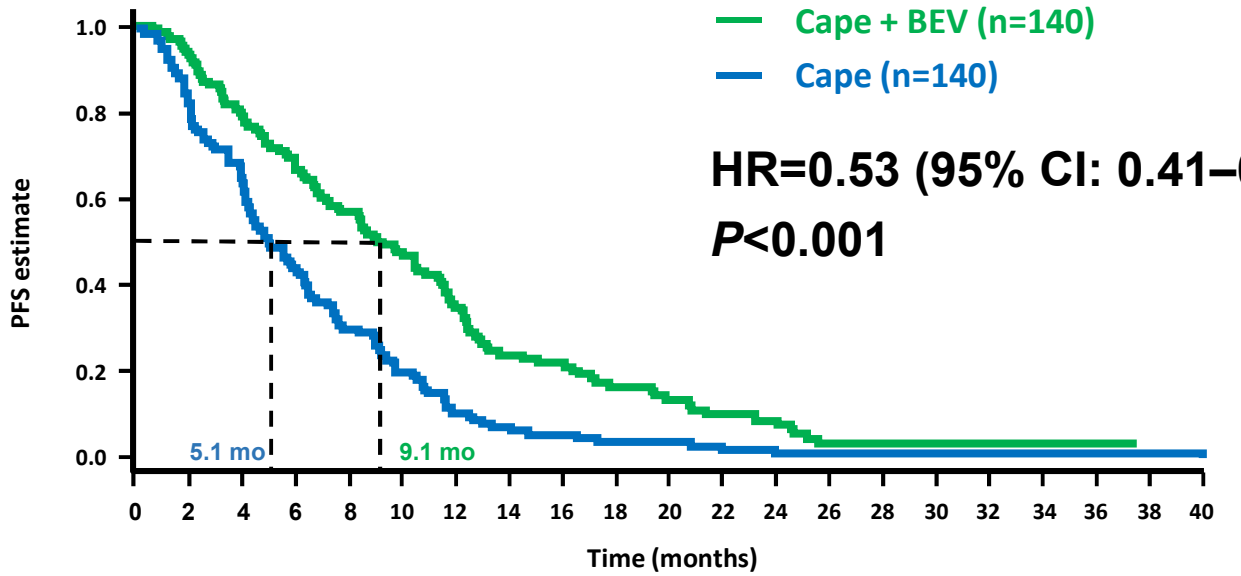


- **Key inclusion criteria**
  - ECOG PS 0–2
  - Prior adjuvant chemotherapy allowed if completed >6 month before inclusion
  - Not optimal candidates for a combination chemotherapy with irinotecan or oxaliplatin

- **Key exclusion criteria**
  - Prior chemotherapy for mCRC or prior adjuvant anti-VEGF treatment
  - Clinically significant cardiovascular disease
  - Current or recent use of aspirin (>325 mg/day) or other NSAID
  - Use of full-dose anticoagulants or thrombolytic agents

Cunningham et al, Lancet Oncol 2013

AVEX – PFS (Primary Endpoint)



Cunningham et al, Lancet Oncol 2013

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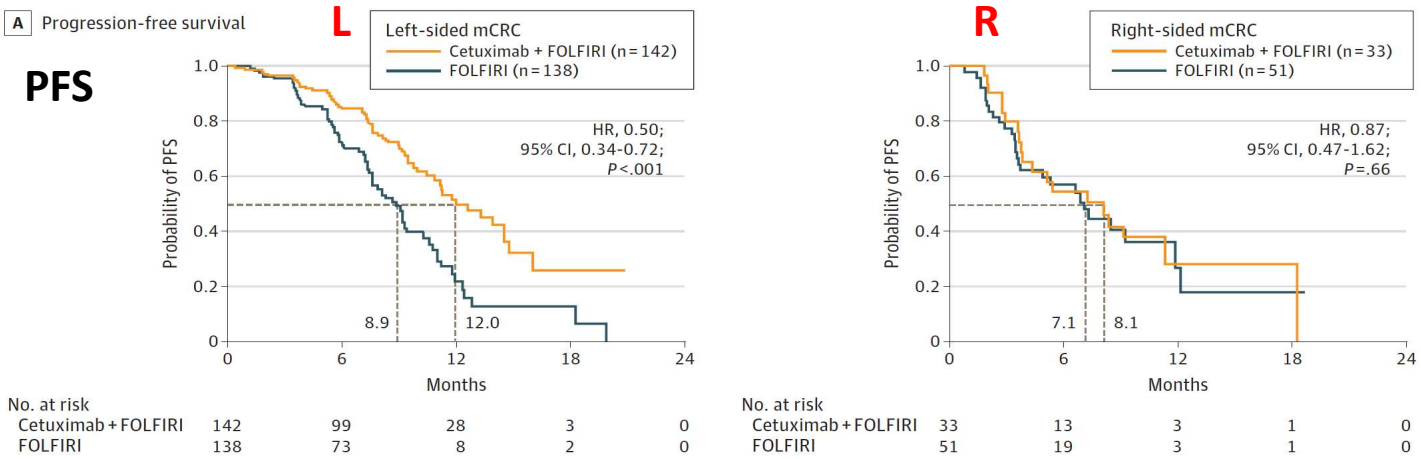
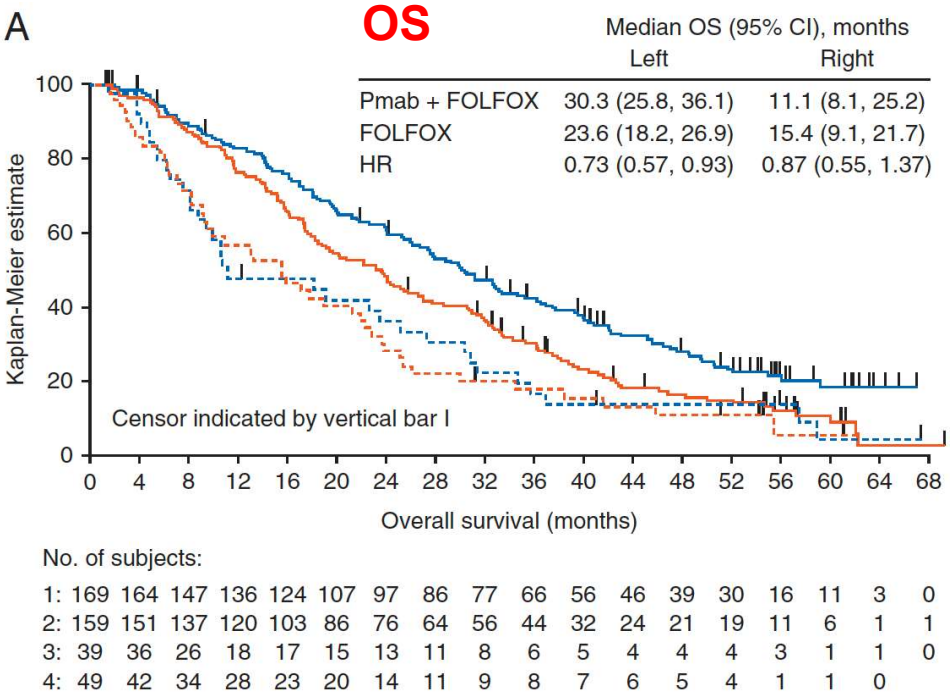
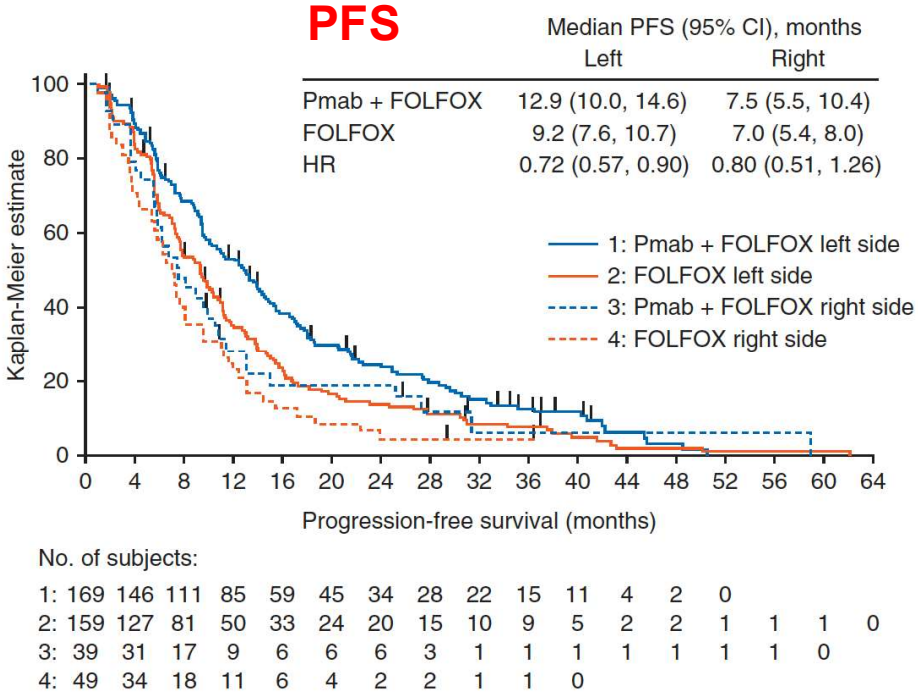
CRYSTAL: FOLFIRI +/- Cetuximab



Tejpar et al., JAMA Oncol 2016

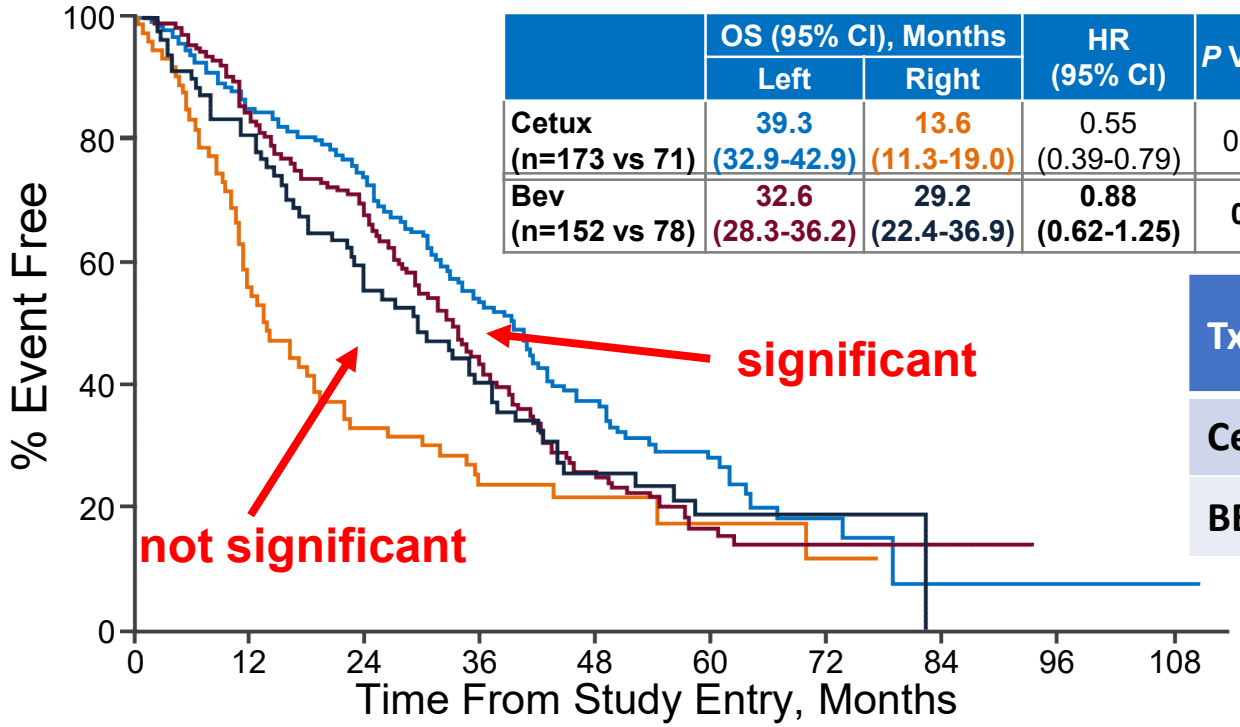
OS and PFS by Sidedness in PRIME (FOLFOX +/- Pmab)





Boeck, et al. Ann Oncol 2017

CALGB/SWOG 80405: OS by Tumor Location (*RAS* WT)



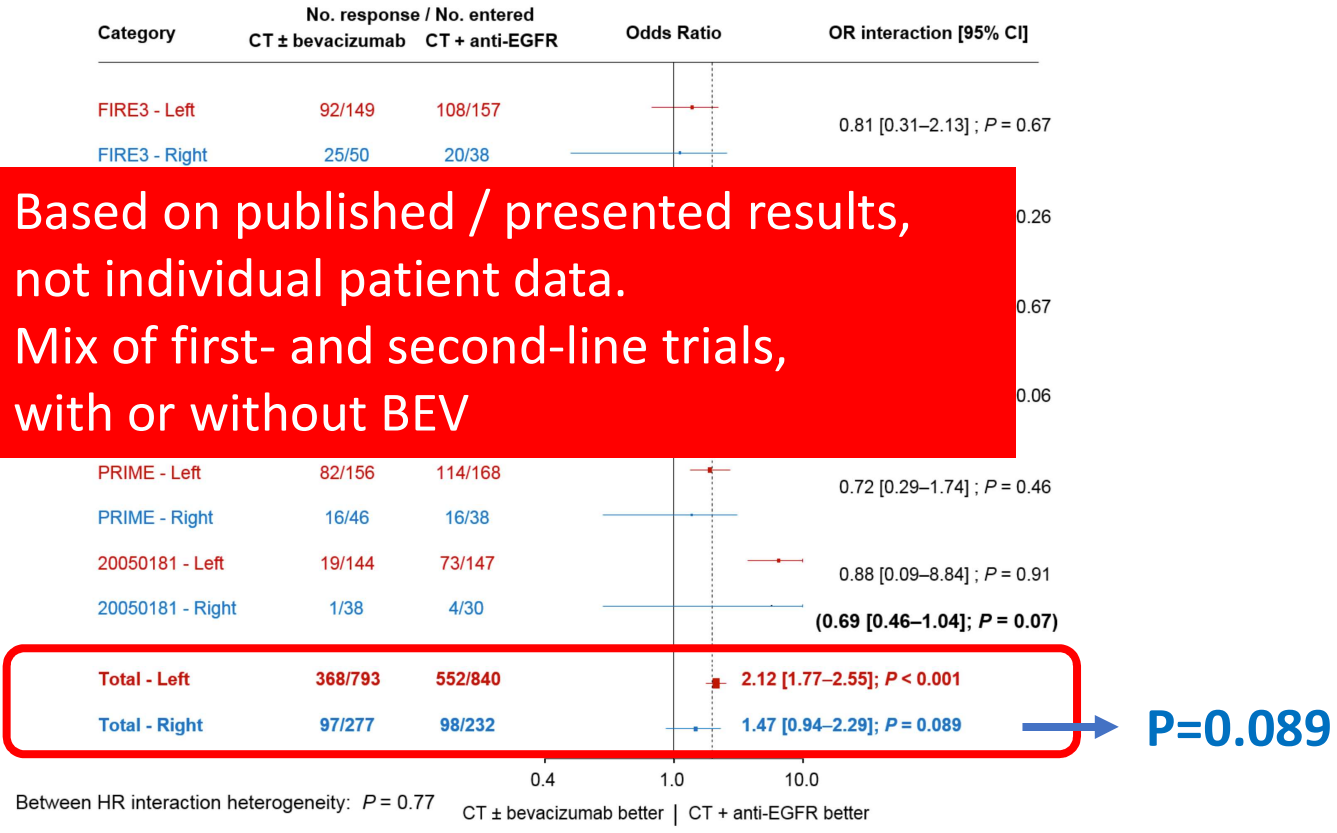
	OS (95% CI), Months		HR (95% CI)	*P* Value*
	Left	Right		
Cetux (n=173 vs 71)	39.3 (32.9-42.9)	13.6 (11.3-19.0)	0.55 (0.39-0.79)	0.001
Bev (n=152 vs 78)	32.6 (28.3-36.2)	29.2 (22.4-36.9)	0.88 (0.62-1.25)	0.50

Tx	ΔR vs L (mos)
Cetux	25.7
BEV	3.4

*Adjusted for biologic, protocol CT, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases.

Venook A, et al. Presented at: ESMO. 2016.

ESMO Guidelines: Sidedness and Tumor Response



- Based on published / presented results,
- not individual patient data.
- Mix of first- and second-line trials,
- with or without BEV

P=0.089

Arnold et al., Ann Oncol 2017

The “Perfect” Candidate for First-Line EGFR mAbs

Negative selection (mutually exclusive)

- **KRAS/ NRAS/ HRAS exon 2, 3, 4 wild-type - 55%**
- **No BRAF V600E mutation - 8%**
- **(No HER-2 amplification -2.5%)**

Further exclusion criteria (not mutually exclusive)

- **Right-sided cancers 30%**

Treatment Options in First-line

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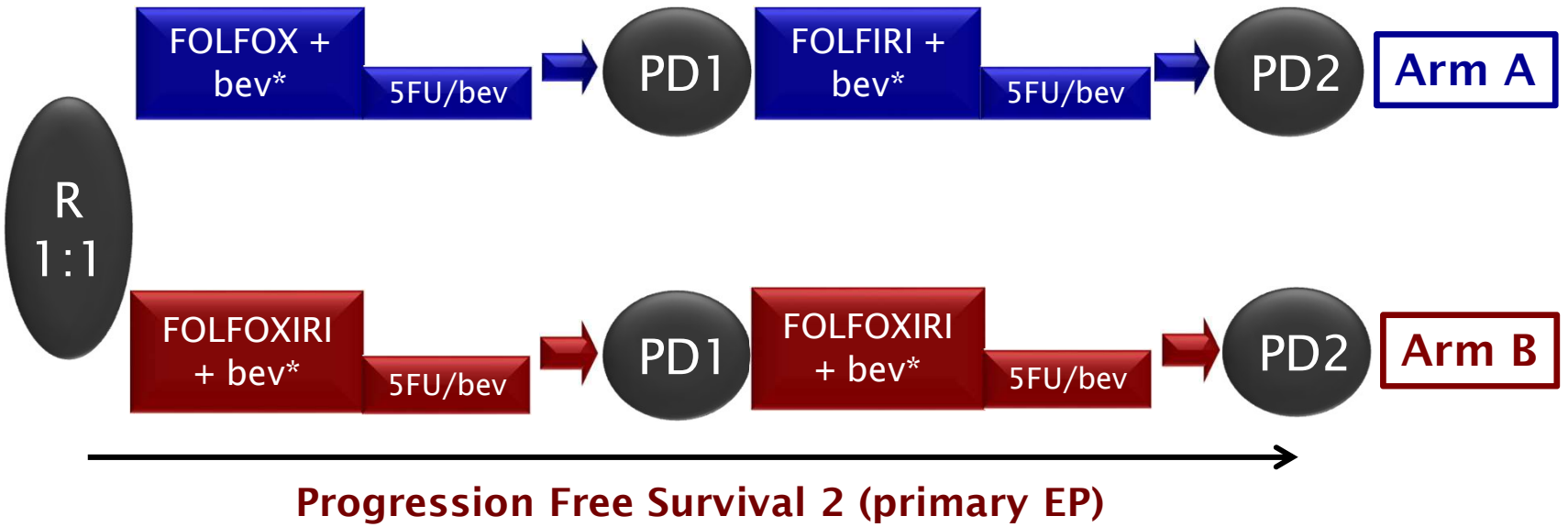
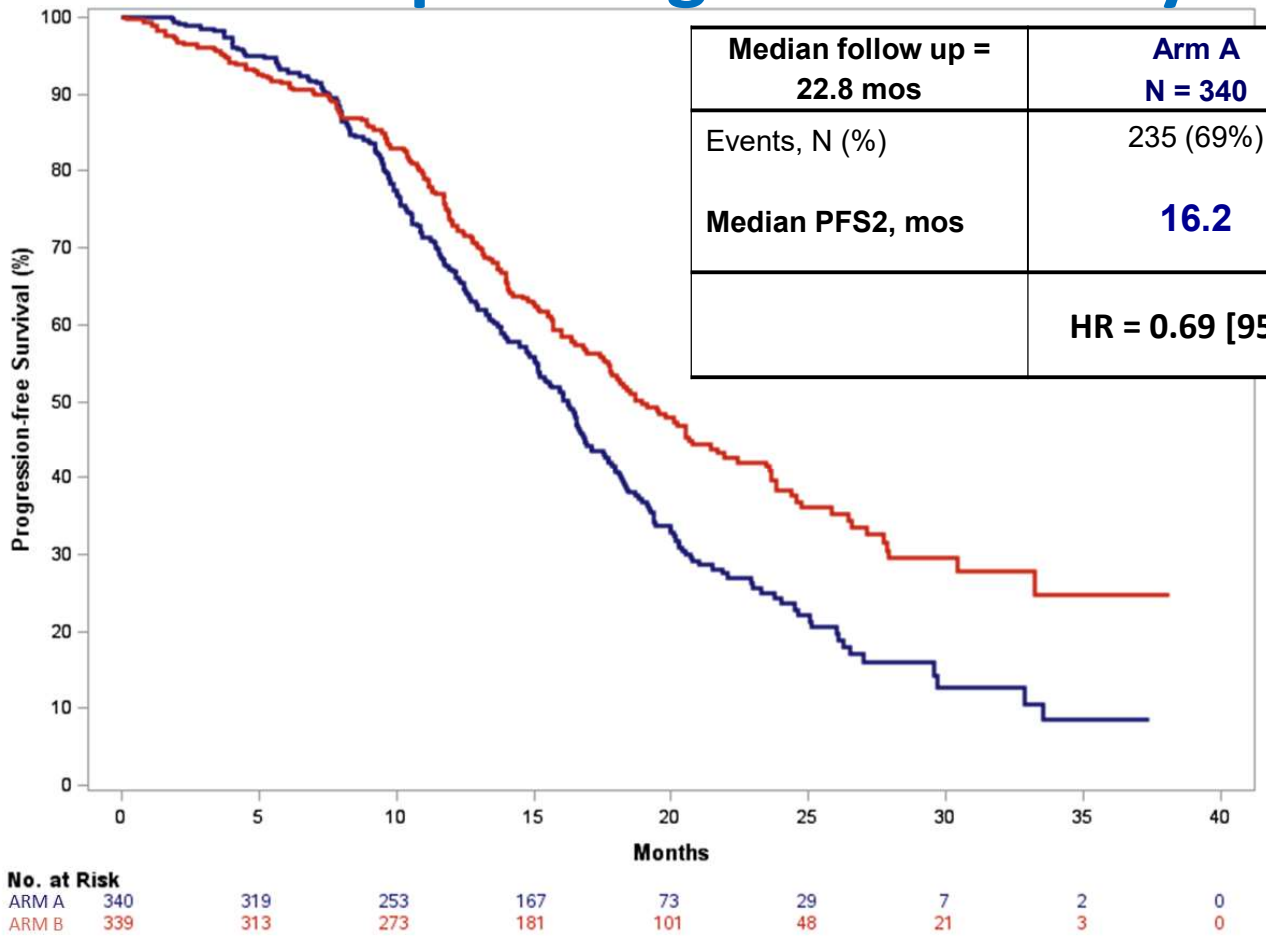
TRIBE-2 Sequencing trial



* Up to 8 cycles

Cremolini et al., ASCO 2019

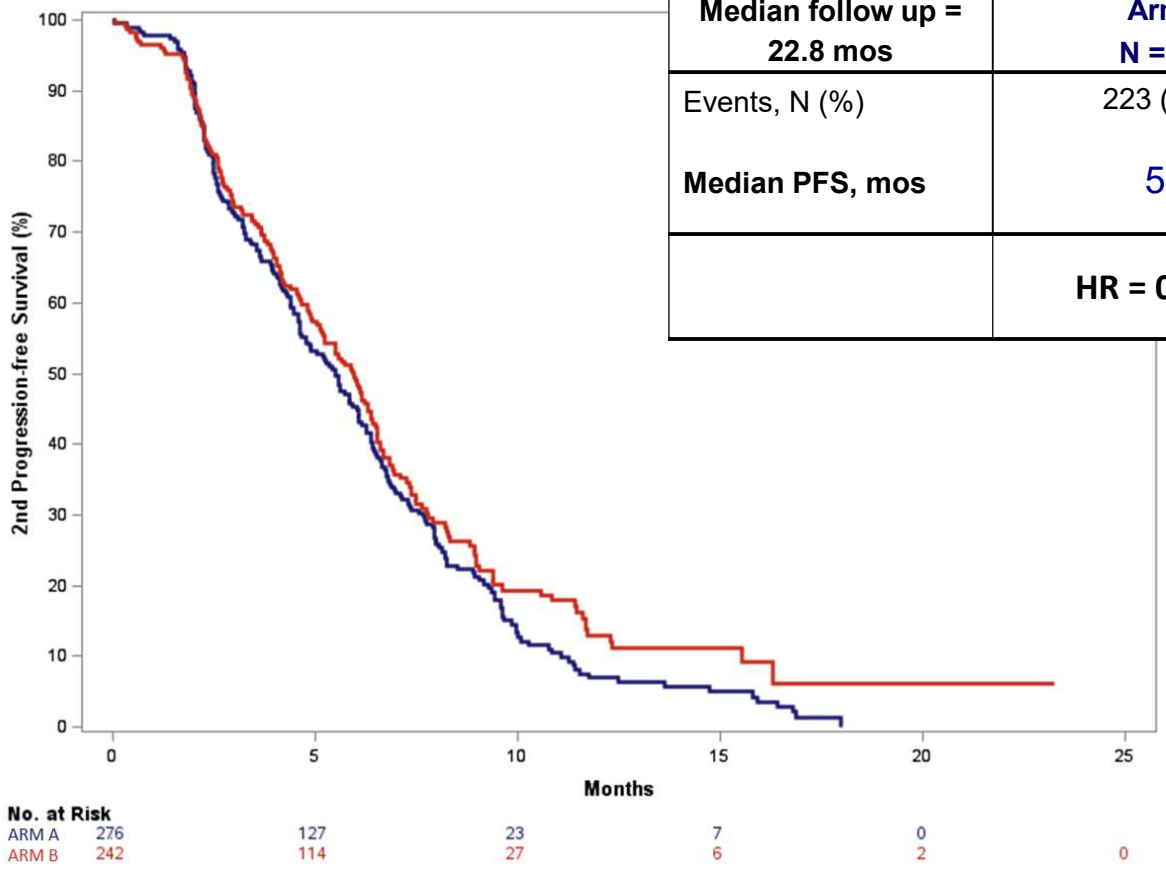
TRIBE-2 Sequencing trial: Primary EP



Median follow up = 22.8 mos	Arm A N = 340	Arm B N = 339
Events, N (%)	235 (69%)	188 (55%)
Median PFS2, mos	**16.2**	**18.9**
	HR = 0.69 [95% CI: 0.57-0.83] p<0.001	

Cremolini et al., ASCO 2019

TRIBE-2: Second PFS

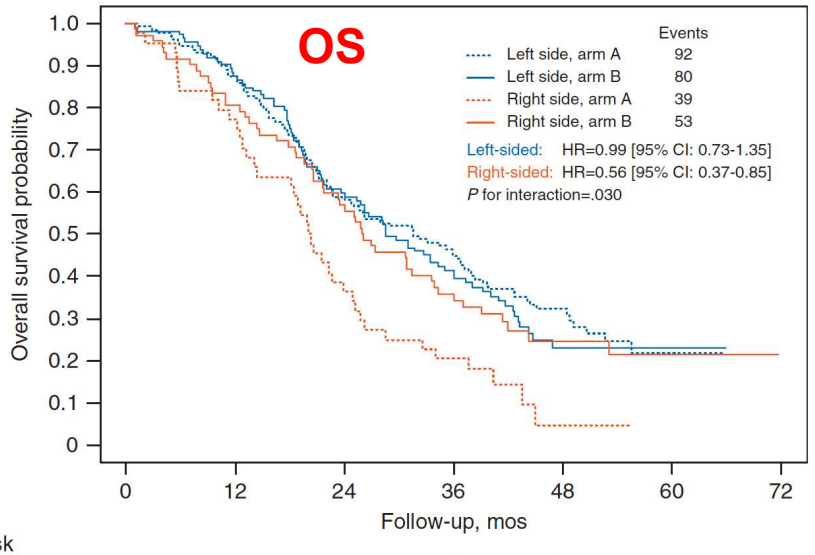


Median follow up = 22.8 mos	Arm A N = 276	Arm B N = 242
Events, N (%)	223 (81%)	169 (70%)
Median PFS, mos	5.5	6.0
	HR = 0.86 [95%CI: 0.70-1.05] p=0.120	

Cremolini et al., ASCO 2019

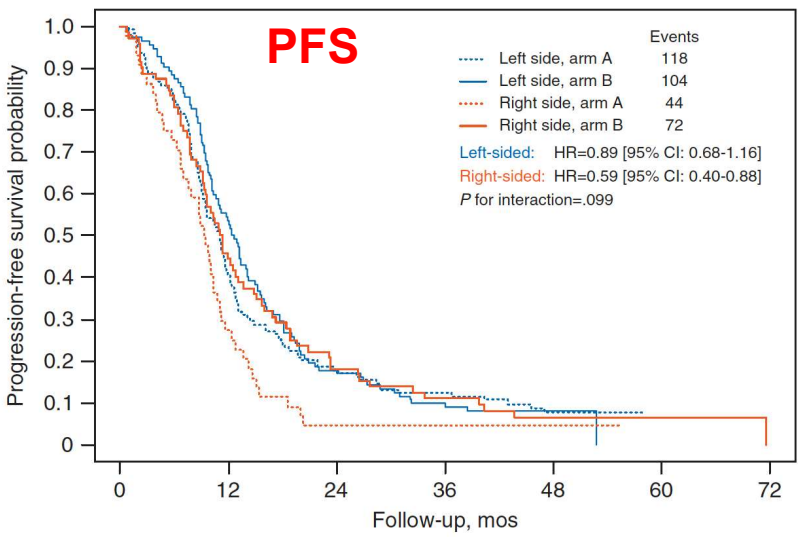
OS and PFS by Sidedness in TRIBE (FOLFIRI+ BEV vs FOLFOXIRI + BEV)

B



No. at risk							
Left side, arm A	129	113	75	57	23	2	0
Left side, arm B	113	98	65	43	13	4	0
Right side, arm A	44	34	16	9	1	0	0
Right side, arm B	72	58	41	23	9	2	0

A



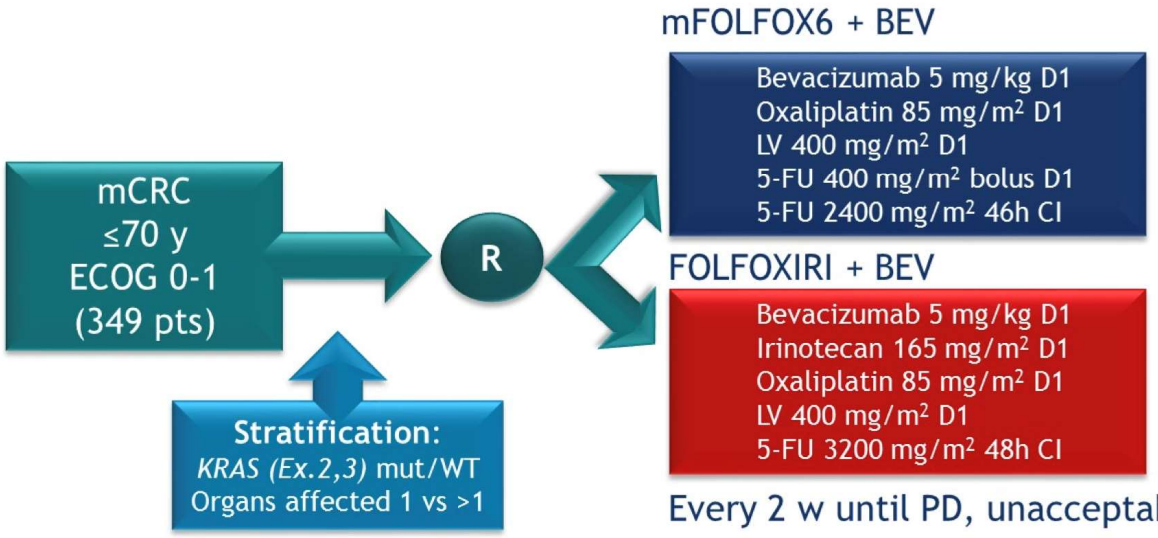
No. at risk							
Left side, arm A	129	52	23	15	7	0	0
Left side, arm B	113	60	20	11	4	0	0
Right side, arm A	44	12	2	2	1	0	0
Right side, arm B	72	32	13	8	4	2	0

Triplet improved outcome (only) in right-sided cancers! Cremolini, et al. Ann Oncol 2018

GRUPO DE TRATAMIENTO
DE LOS TUMORES DIGESTIVOS

VISNU-1: Study Design

- Open, multicenter phase III trial in mCRC patients with ≥ 3 CTCs at baseline.



- Accrual: 50 months.
  October 2012-November 2016.
- Data base cut-off: November 2018.
- Tumor evaluations every 12 weeks.
- Protocol amended to add recommended prophylactic GCS-F in the FOLFOXIRI+BEV arm (after 63 pts included).

Every 2 w until PD, unacceptable toxicity or withdrawal of IC

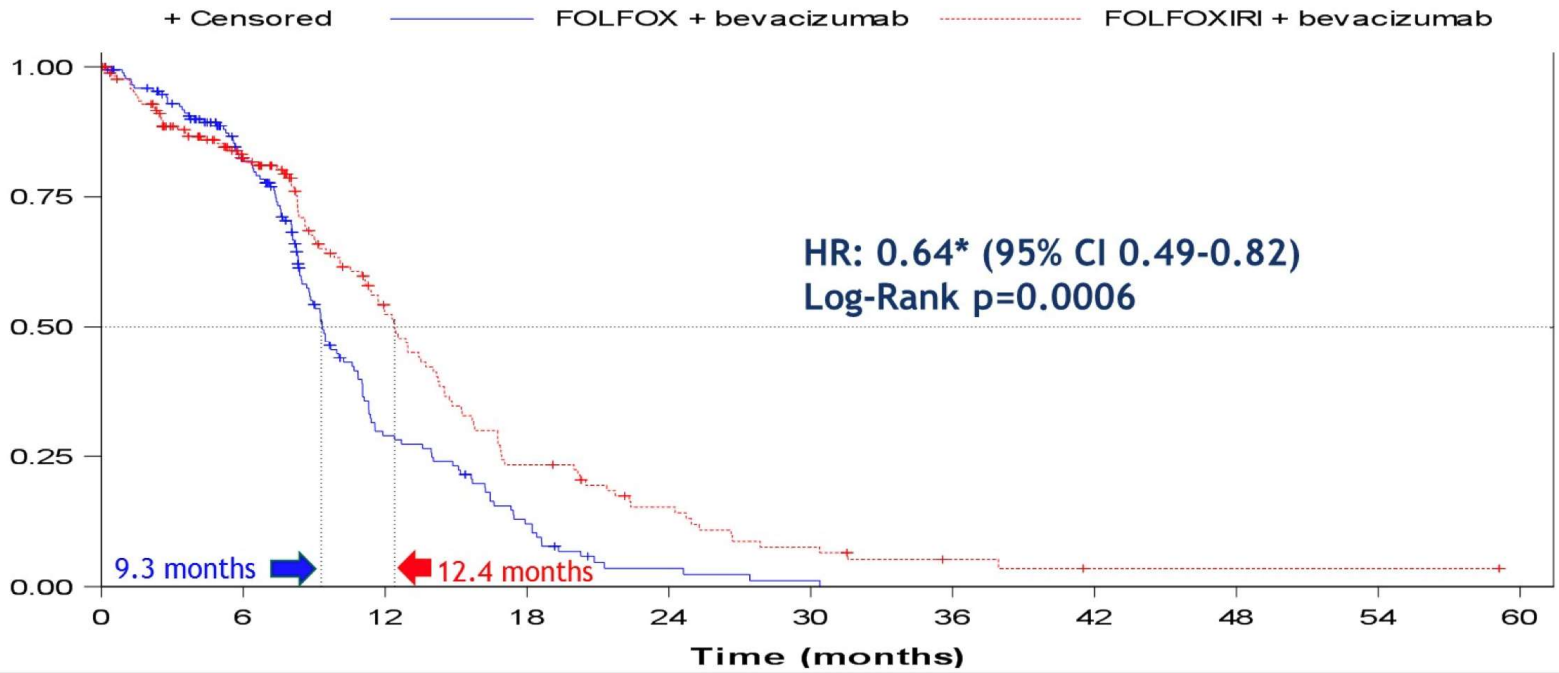
Primary endpoint: efficacy in terms of PFS.

Secondary endpoints: OS; ORR; Resection rate and safety analysis.

Sastre, et al. ASCO 2019

PFS by treatment arm

GRUPO DE TRATAMIENTO
DE LOS TUMORES DIGESTIVOS

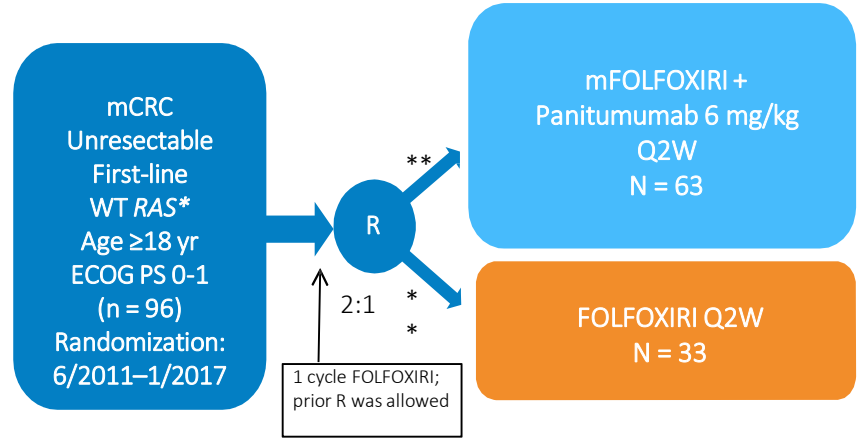


FOLFOX + bevacizumab	177	119	35	14	3	1	0	0	0	0	0
FOLFOXIRI + bevacizumab	172	113	56	25	14	7	3	1	1	1	0

* Cox model proportional hazard assumption is not met

Sastre, et al. ASCO 2019

VOLFI: Phase II trial design



Strata

Cohort 1: histologically confirmed and definitively inoperable or unresectable

Cohort 2: chance of secondary resection with curative intent (**Pretreatment liver/tumor biopsy)

Treatment until PD, resectability, or to maximum 12 cycles

If resectable:
surgery, then
protocol treatment
to maximum 12
cycles

If CR/PR/SD after 12 cycles:
reinduction
(same combination)
recommended on PD

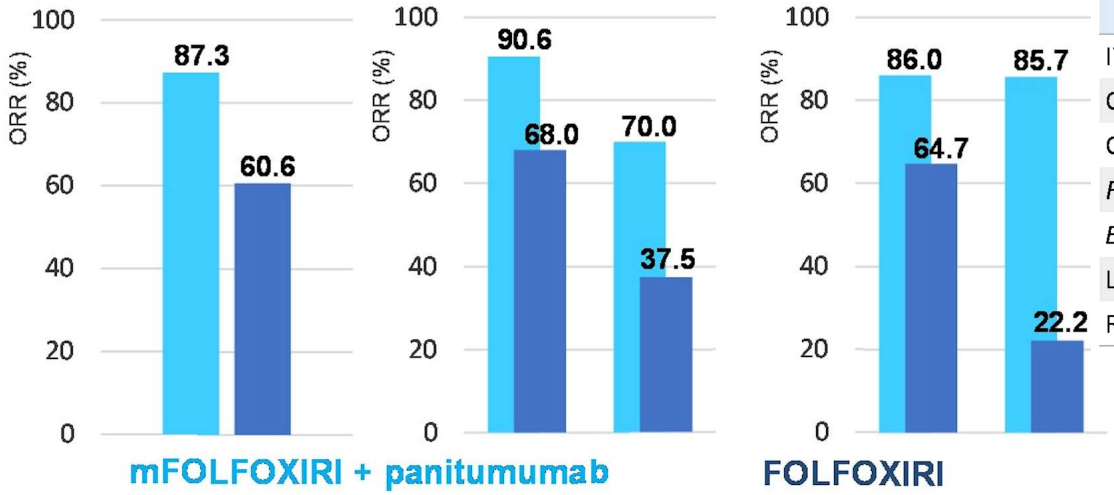
- 21 active centers in Germany

***Amendment in 11/2013 to include all *RAS* wild-type only.**
†Trial started with irinotecan 165 mg/m² (n = 2), first amendment to 130 mg/m² (n = 9), and final amendment to 150 mg/m² (n = 52).

Geissler et al., ASCO 2019

VOLFI - Primary endpoint: objective response rate

Full Analysis Set	by Tumor Sidedness		by Genotype	
	Left	Right	*RAS/BRAF* wt	*BRAF* mut
N=96	N=78	N=18	N=60	N=16
P=0.004	P=0.021	P=0.345	P=0.081	P=0.041
OR=4.47	OR=4.52	OR=3.89	OR=3.36	OR=21.0
95%CI 1.61 – 12.38	1.30 – 15.72	0.54 – 27.89	0.90 – 12.55	1.50 – 293.25



Overall Survival

Months (95% CI)	mFOLFOXIRI + P	FOLFOXIRI
ITT	**35.7** (27.6 – 43.8)	**29.8** (19.8 – 39.9)
Cohort 1	**24.7** (13.3 – 39.9)	**28.3** (13.9 – 37.7)
Cohort 2	**52.0** (35.2 –)	**41.7** (10.7 – 44.4)
RAS/BRAF WT	**43.5** (35.7 – 53.3)	**35.3** (17.7 – 41.7)
BRAF mut	**8.0** (7.7 – 22.4)	**9.0** (2.7 – 13.9)
Left sided	**39.9** (32.7 – 52.0)	**35.3** (14.3 – 41.8)
Right sided	**11.5** (7.7 –)	**22.0** (12.9 – 41.7)

Geissler et al., ASCO 2019

Best Conversion Therapy

Molecular status	Sidedness	
	Right (30%)	**Left (70%)**
RAS/BRAF wt (35-40%)	FOLFOXIRI +/- BEV (FOLFOX +/- BEV)	FOLFOX + EGFR mAb (FOLFOXIRI + EGFR mAb)
RAS mut (50-55%)	FOLFOXIRI +/- BEV (FOLFOX +/- BEV)	FOLFOXIRI +/- BEV (FOLFOX +/- BEV)
BRAF V600E mut (8-10%)	FOLFOXIRI + BEV	FOLFOXIRI + BEV
BRAF non-V600E mut (2%)	FOLFOXIRI +/- BEV (FOLFOX +/- BEV)	FOLFOX + EGFR mAb (FOLFOXIRI + EGFR mAb)

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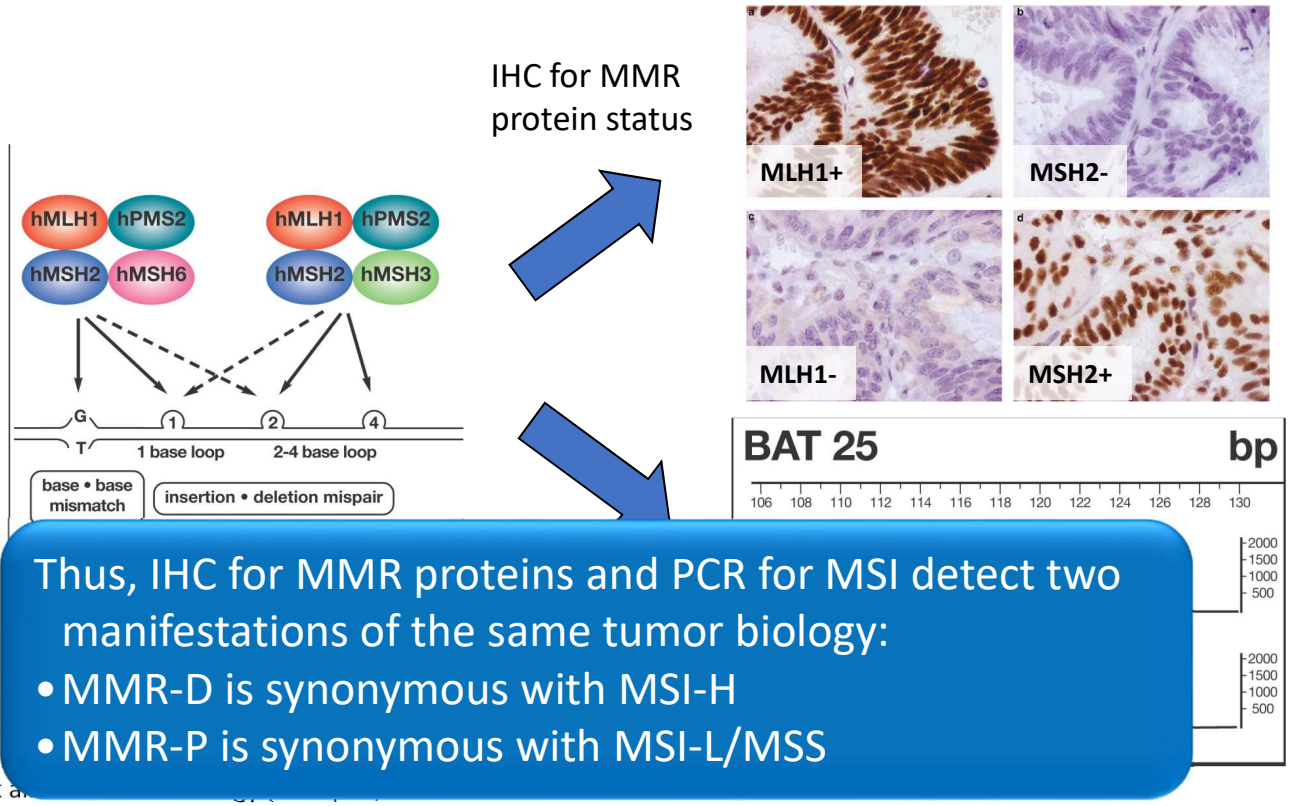
Mismatch Repair Deficiency (MMR-D): Unique Biological Subgroup of Colon Cancer



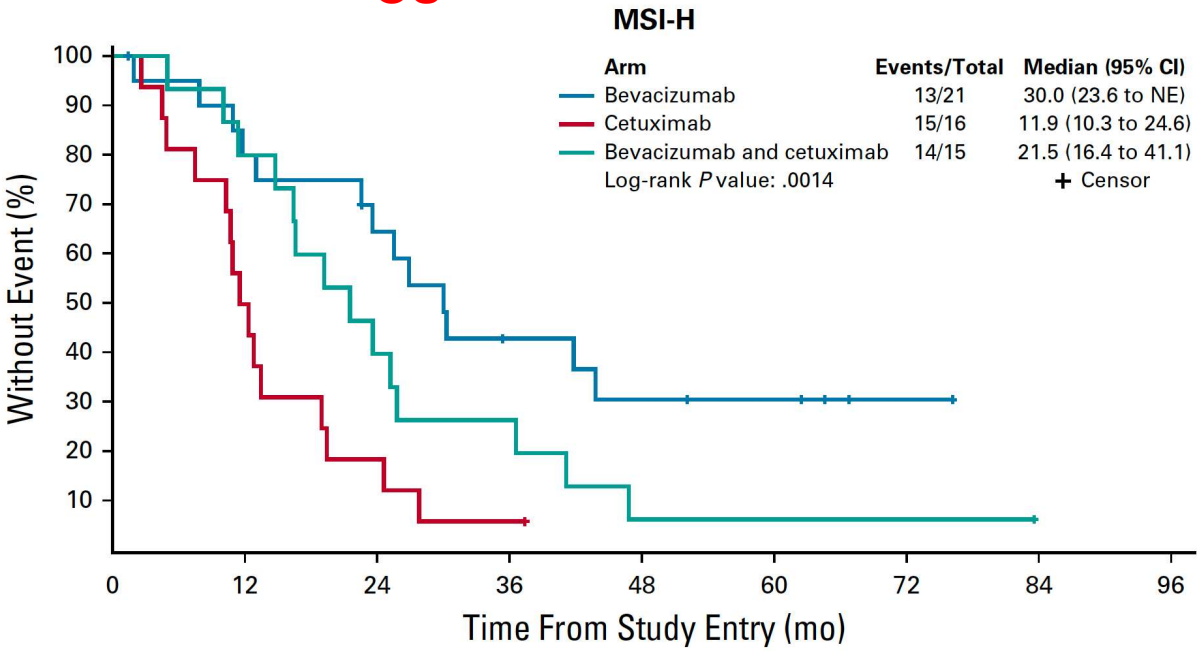
Thus, IHC for MMR proteins and PCR for MSI detect two manifestations of the same tumor biology:

- MMR-D is synonymous with MSI-H
- MMR-P is synonymous with MSI-L/MSS

Imai and
Umetani
Rosen et a

BEV-containing first-line therapy active in MSI-H mCRC
Data from CALGB/ SWOG 80405

OS



80405: mOS Chemo+BEV: 30 mos

PFS (months)

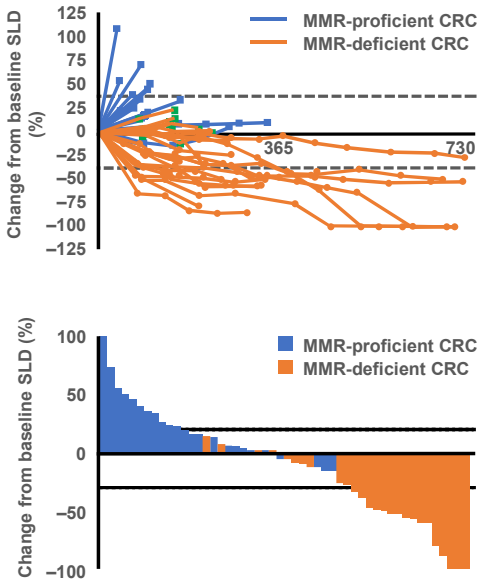
BEV + Cetux:	7.7
BEV	**9.3**
Cetux	5.4

BEV vs Cetux:
P<0.001

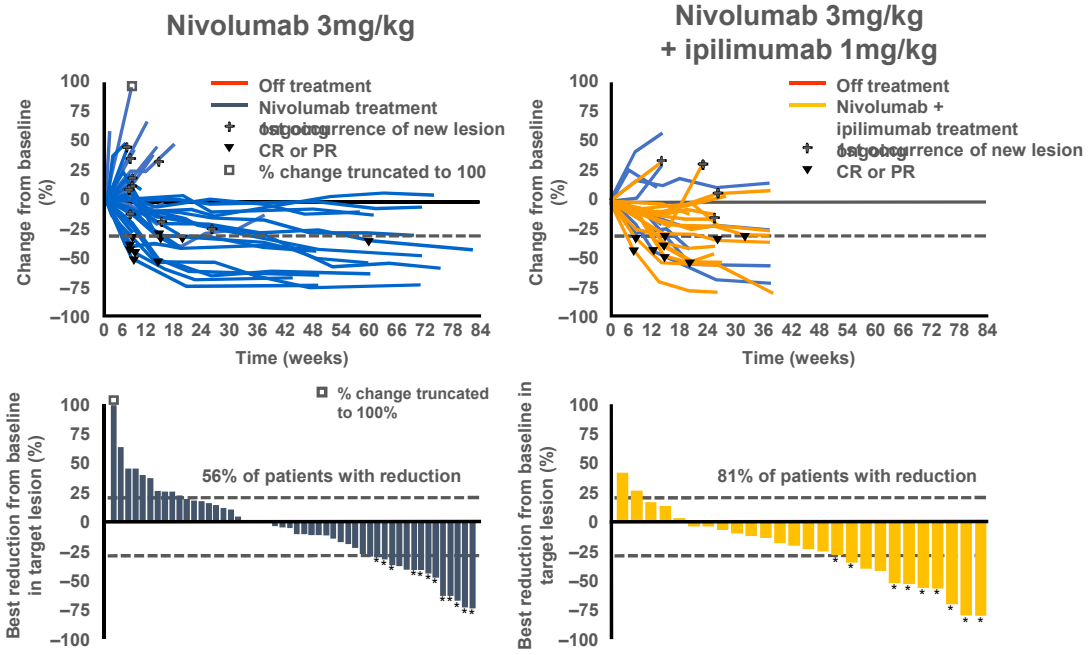
Innocenti et al., JCO 2019

MSI-high CRCs are responsive to PD-1 inhibitors

Pembrolizumab (KEYNOTE 016, phase II)[1,*]



Nivolumab ± ipilimumab (CheckMate-142, phase II)[2]

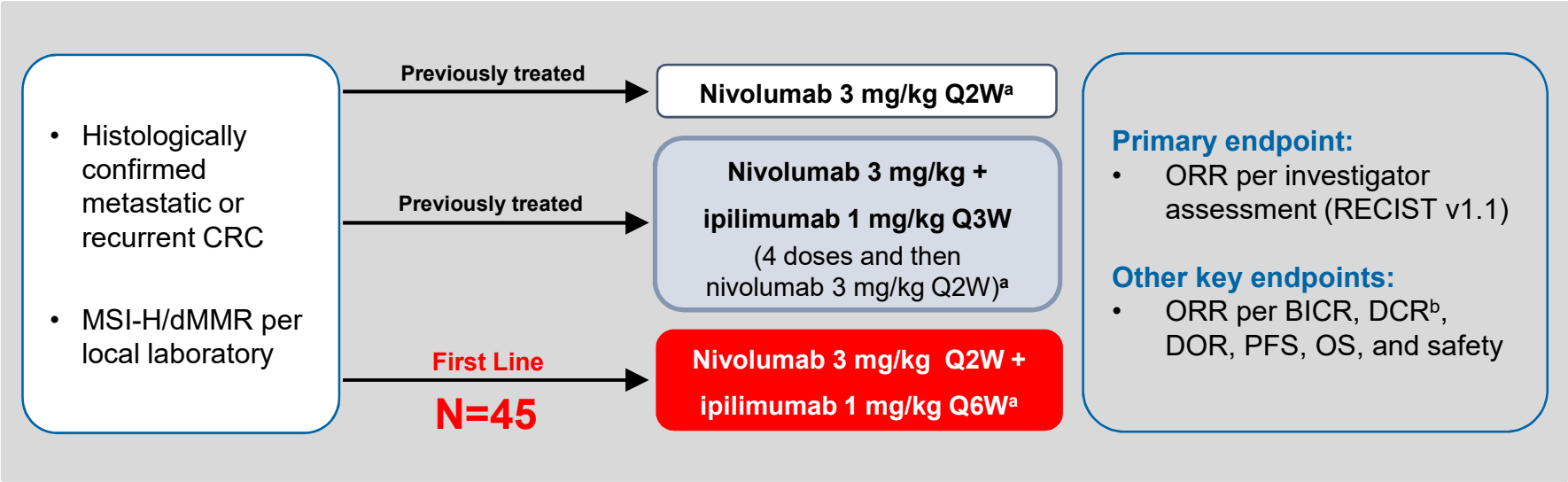


- ***Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0**

1. Le et al. ASCO 2016; 2.Overman et al. ASCO 2016

CheckMate-142 Study Design

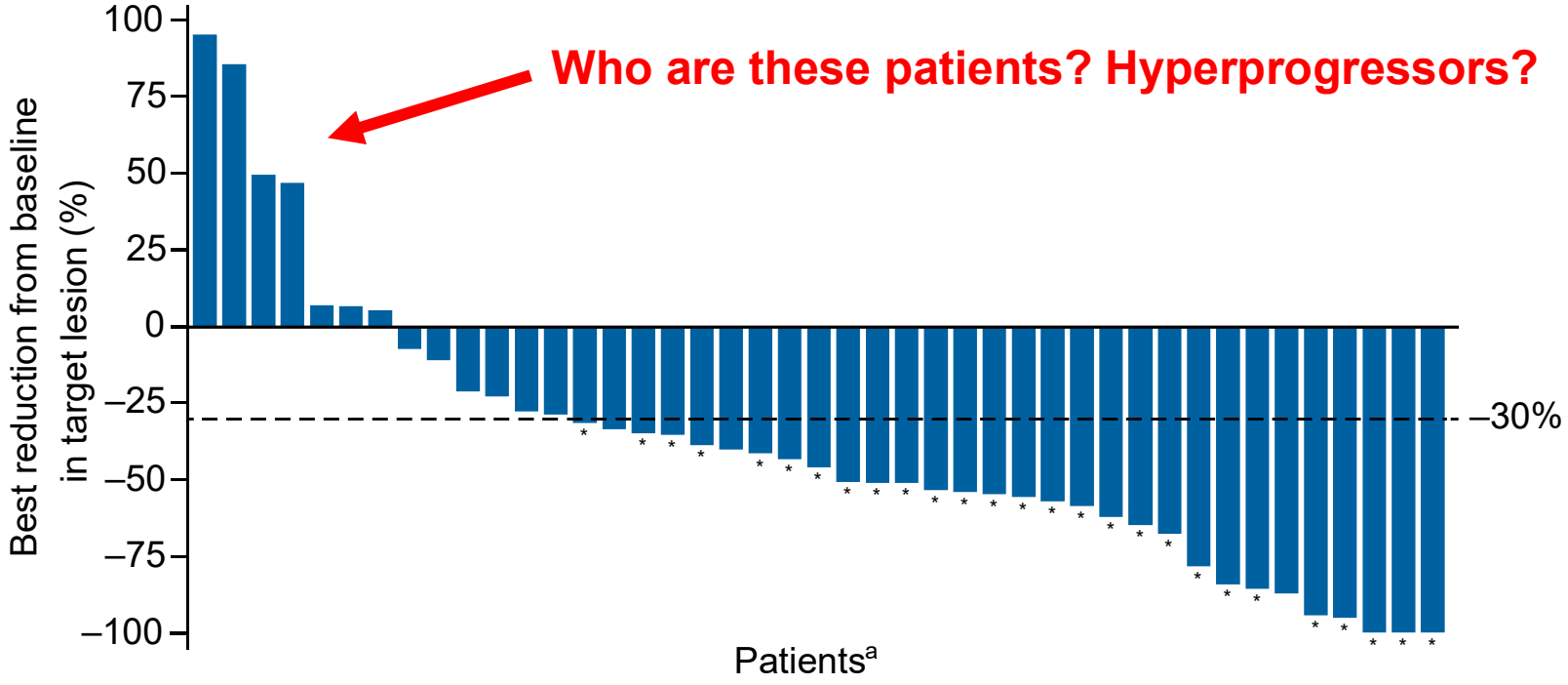
- CheckMate-142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188)



[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

Lenz et al., ESMO 2018

Best Reduction in Target Lesions

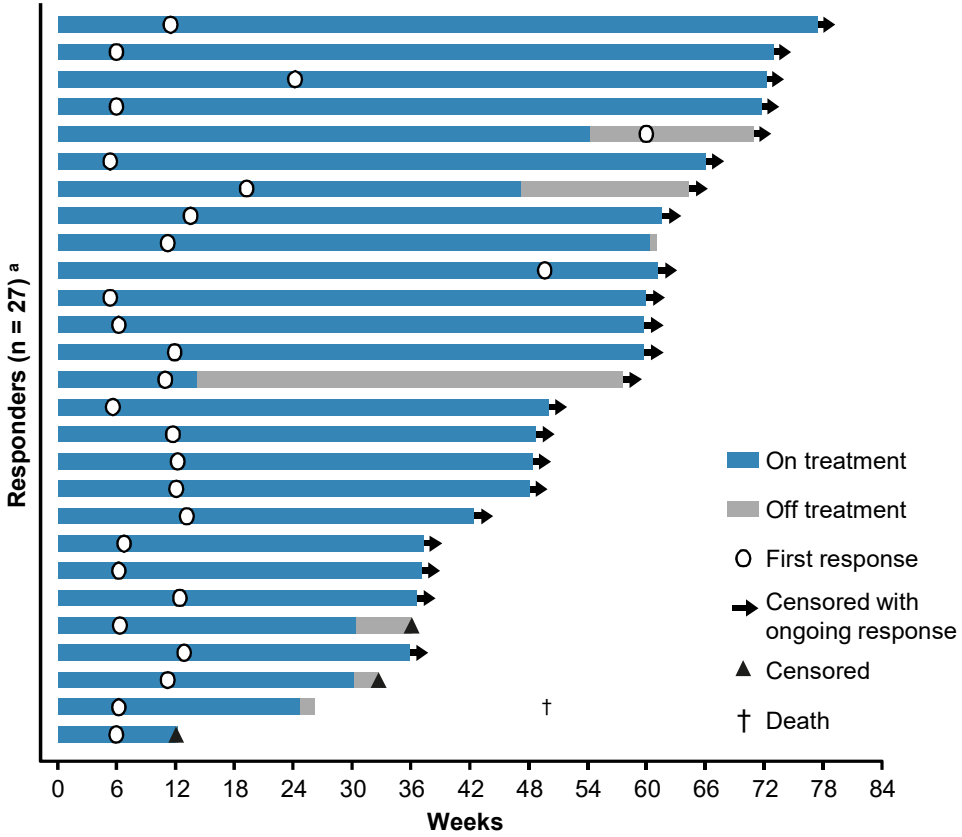


- 84% of patients had a reduction in tumor burden from baseline

*Confirmed response per investigator assessment
[a]Evaluable patients per investigator assessment

Lenz et al., ESMO 2018

Characterization of Response



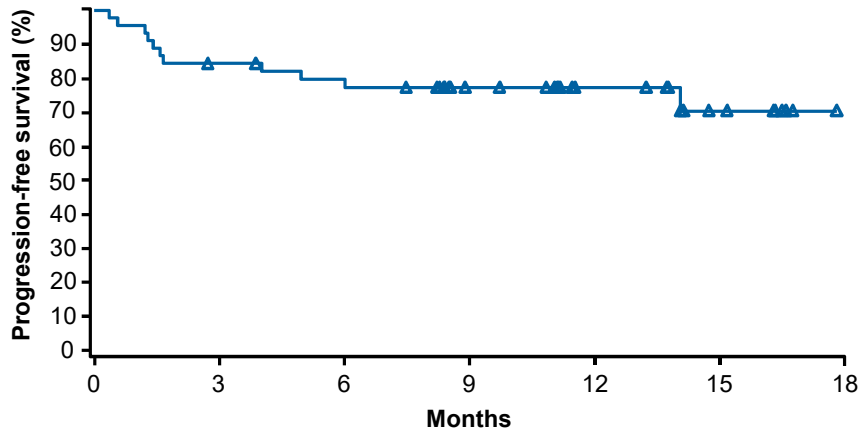
[a]Response per investigator assessment

- Median time to response was 2.6 months (range, 1.2–13.8 months)
- Responses were durable:
  - Median DOR was not reached
  - 82% of responders had ongoing responses at data cutoff
  - 74% of responders have already had responses lasting ≥6 months
  - Most responders (96%) were alive at data cutoff

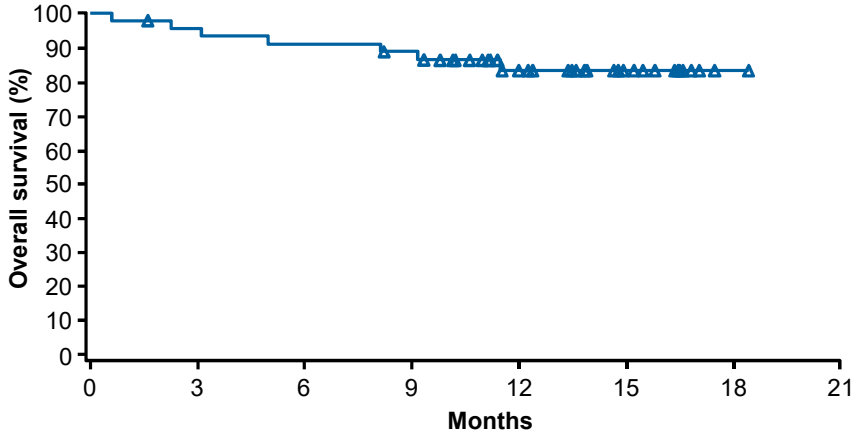
Lenz et al., ESMO 2018

Progression-Free and Overall Survival

PFS[a]	Nivolumab + ipilimumab N = 45
Median PFS, months (95% CI)	NR (14.1–NE)
9-mo rate (95% CI), %	77 (62.0–87.2)
12-mo rate (95% CI), %	77 (62.0–87.2)



OS[a]	Nivolumab + ipilimumab N = 45
Median OS, months (95% CI)	NR (NE)
9-mo rate (95% CI), %	89 (74.9–95.1)
12-mo rate (95% CI), %	83 (67.6–91.7)

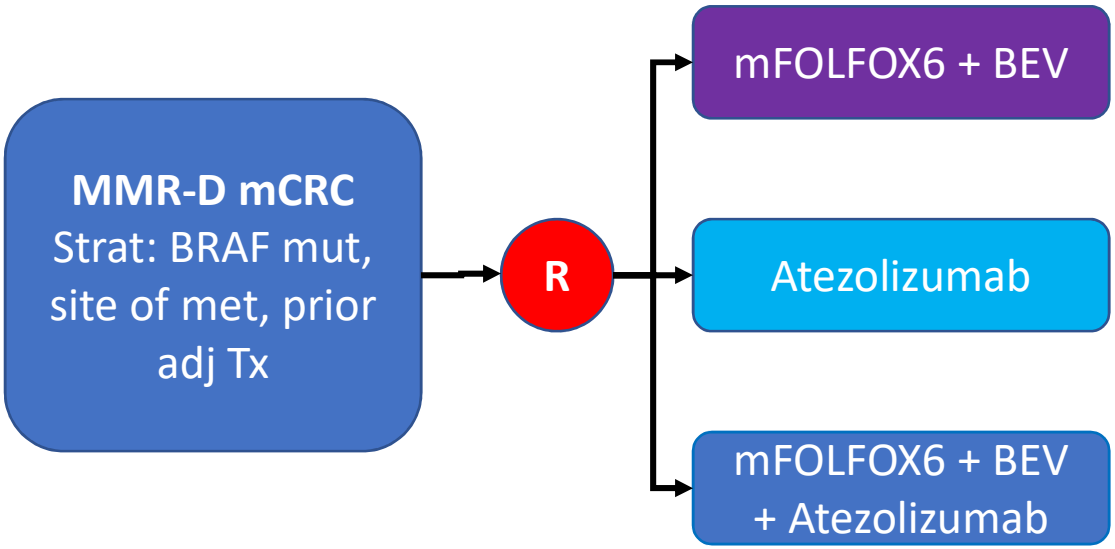


No. at risk							
	45	37	34	24	15	7	7
	45	42	40	38	24	13	1	0

[a]Per investigator assessment.
mo = month; NE = not estimable; NR = not reached

Lenz et al., ESMO 2018

Evaluation of First-Line IO in MSI-H mCRC is Ongoing



COMMIT Trial
NRG-GI004/
SWOG 1610

N=26/347

Primary EP: PFS

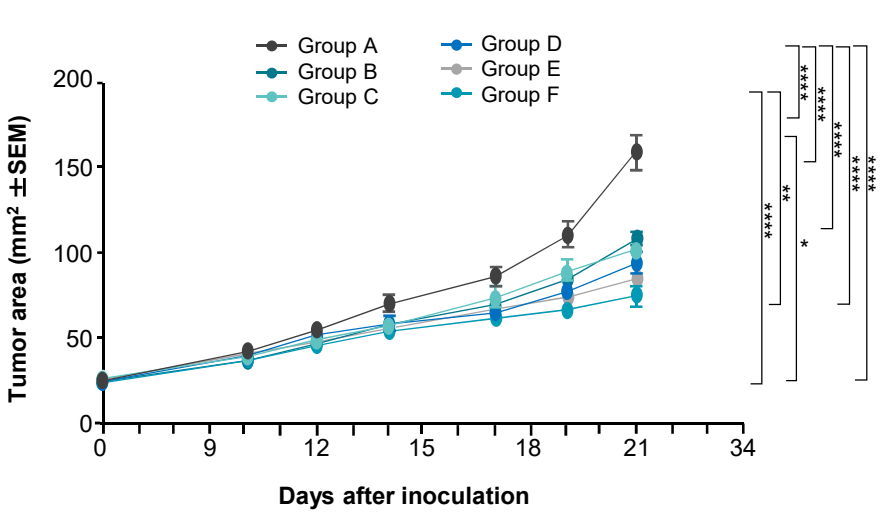
PIs: James Lee, Mike Overman

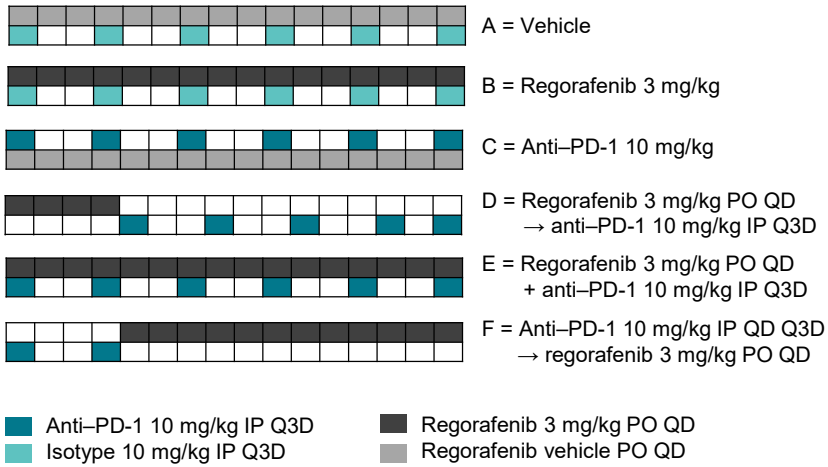
Not yet reported first-line phase III IO trial

- **KEYNOTE-177 (NCT02563002)**
  - **Pembrolizumab** (200 mg IV q3w) vs SOC choice (FOLFOX or FOLFIRI +/- BEV or cetuximab)
  - 308 patients in 21 countries
  - Co-primary EP: PFS and OS
  - Accrual completed, results expected later this year (?)

Preclinical evidence demonstrates anti-tumor activity of Regorafenib in combination with I/O

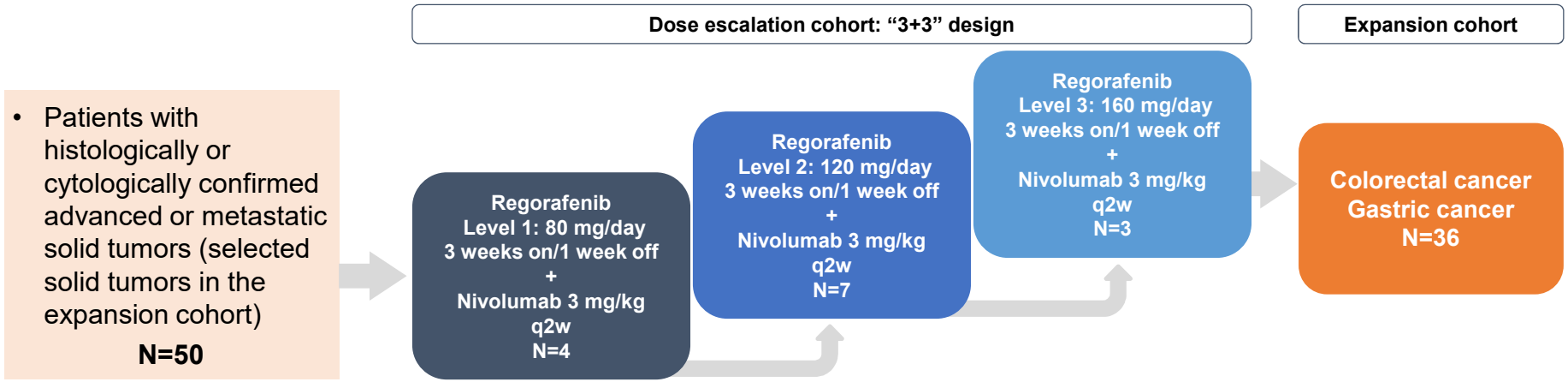
Antitumor activity of regorafenib and anti–PD-1 alone and in combination in a syngeneic murine MC38 CRC MSI model





*P <.05, **P <.01, ***P <.001, ****P <.0001.
IP, intraperitoneally; PO, orally; Q3D every third day; QD, once daily; SEM, standard error of mean.
For simplicity, the statistical analysis on Day 21 only is shown.
Hoff S, et al. ESMO 2017. Poster 1198.

REGONIVO: A phase 1/2 study of regorafenib plus nivolumab in advanced gastric cancer and CRC (EPOC1603/NCT03406871)



Key inclusion criteria:

- Patients with unresectable, recurrent solid tumors who are refractory or intolerant to standard chemotherapy
- ECOG PS 0 or 1

Key exclusion criteria:

- Prior regorafenib treatment; prior immune checkpoint blockade was permitted

Primary endpoints:

- Dose escalation: MTD/RD and safety of combination treatment
- Dose expansion: Safety and efficacy of the combination treatment at the regorafenib MTD/RD

Secondary endpoints:

- ORR (RECIST v1.1 and irRECIST)
- PFS
- OS
- DCR
- Incidence of TEAEs

Translational research:

- T-cell phenotype assays including Treg analysis using both flow cytometry and CyTOF
- *In vitro* functional assays
- HLA typing
- Immunohistochemistry (e.g., PD-L1, FoxP3, CD68, CD163)
- Mutational analyses (whole exome sequencing)
- RNA sequencing
- 16S sequencing

Clinicaltrials.gov: https://www.clinicaltrials.gov/ct2/show/NCT03406871 (Accessed April 15, 2019); Fukuoka S, et al. ASCO 2018:Poster TPS3124; Fukuoka S, et al. ASCO 2019:Poster 2522.

REGONIVO: All patients, except one with CRC, were MSS, and 56% had liver metastasis

Characteristics	Total (N=50)	Dose escalation (n=14)	Dose expansion (n=36)
Median age, years (range)	60.5 (31–80)	60.5 (31–77)	60.5 (41–80)
Male sex, n (%)	40 (80)	12 (86)	28 (78)
ECOG PS 0, n (%)	49 (98)	14 (100)	35 (97)
Cancer type, n (%) Gastric cancer Colorectal cancer	 25 (50) 25 (50)	 9 (64) 5 (36)	 16 (44) 20 (56)
Site of metastases, n (%) Lymph node Liver Lung Peritoneum	 35 (70) 28 (56) 22 (44) 10 (18)	 12 (85) 10 (71) 5 (36) 0	 23 (64) 18 (50) 17 (47) 10 (28)
Number of prior regimens, median (range) Angiogenesis inhibitors, n (%) Anti-PD-1/PD-L1, n (%)	3 (2–8) 48 (96) 7 (14)	3 (2–8) 13 (93) 4 (29)	3 (2–8) 35 (97) 3 (9)
HER2-positive in gastric cancer, n (%)	6 (24)	2 (22)	4 (25)
MSI status, n (%) MSI-H MSS	 1 (2) 49 (98)	 1 (7) 13 (93)	 0 36 (100)
PD-L1 CPS, n (%) Positive (CPS ≥1) Negative (CPS <1)	 18 (41)* 26 (59)*	 3 (25)* 9 (75)*	 15 (47)* 17 (53)*

*Percentage among evaluable patients.

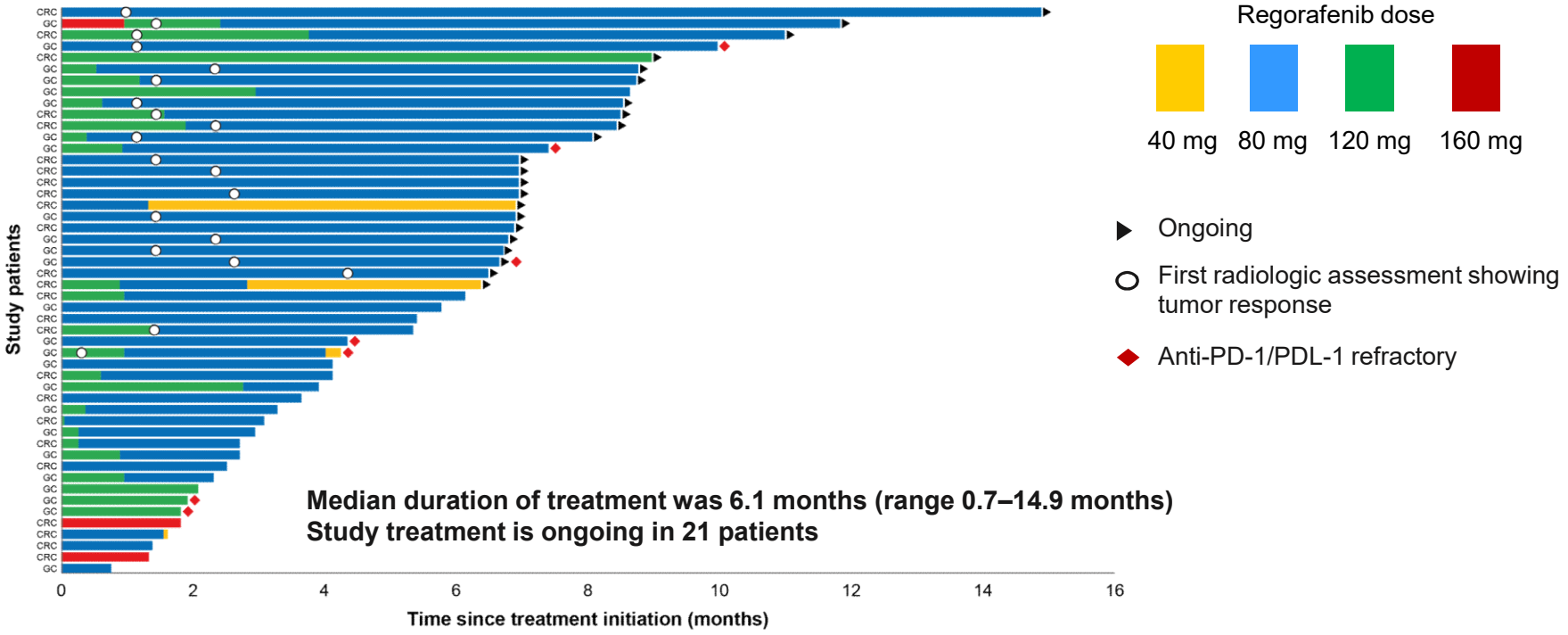
Fukuoka S, et al. ASCO 2019:Poster 2522.

REGONIVO: Grade ≥3 treatment-related adverse events occurred in 40% of patients

Treatment-related AEs (≥10%), n (%)	All (N=50)		Regorafenib 80 mg/day (n=22)		Regorafenib 120 mg/day (n=25)		Regorafenib 160 mg/day (n=3)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
All events	50 (100)	20 (40)	22 (100)	6 (27)	25 (100)	11 (44)	3 (100)	3 (100)
Palmar-plantar erythrodysesthesia	35 (70)	5 (10)	13 (59)	0 (0)	20 (80)	5 (20)	2 (67)	0
Hypertension	24 (48)	2 (4)	10 (46)	2 (9)	14 (56)	0	0	0
Fatigue	23 (46)	0	10 (46)	0	12 (48)	0	1 (33)	0
Rash	**21 (42)**	**6 (12)**	**8 (36)**	**0**	**11 (44)**	**5 (20)**	**2 (66)**	**1 (33)**
Fever	20 (40)	0	8 (36)	0	11 (44)	0	1 (33)	0
Proteinuria	15 (30)	6 (12)	5 (23)	2 (9)	8 (32)	3 (12)	2 (67)	1 (33)
Liver dysfunction	14 (28)	3 (6)	5 (23)	2 (9)	8 (32)	1 (4)	1 (33)	0
Oral mucositis	11 (22)	0	3 (14)	0	6 (24)	0	2 (67)	0
Diarrhea	11 (22)	1 (2)	5 (23)	0	4 (16)	1 (4)	2 (67)	0
Decreased appetite	11 (22)	0	6 (27)	0	5 (20)	0	0	0
Hyperthyroidism	6 (12)	0	4 (18)	0	2 (8)	0	0	0
Hypothyroidism	6 (12)	0	4 (18)	0	2 (8)	0	0	0
Hoarseness	5 (10)	0	4 (18)	0	1 (4)	0	0	0
Platelet count decreased	5 (10)	1 (2)	0	0	4 (16)	1 (4)	1 (33)	0

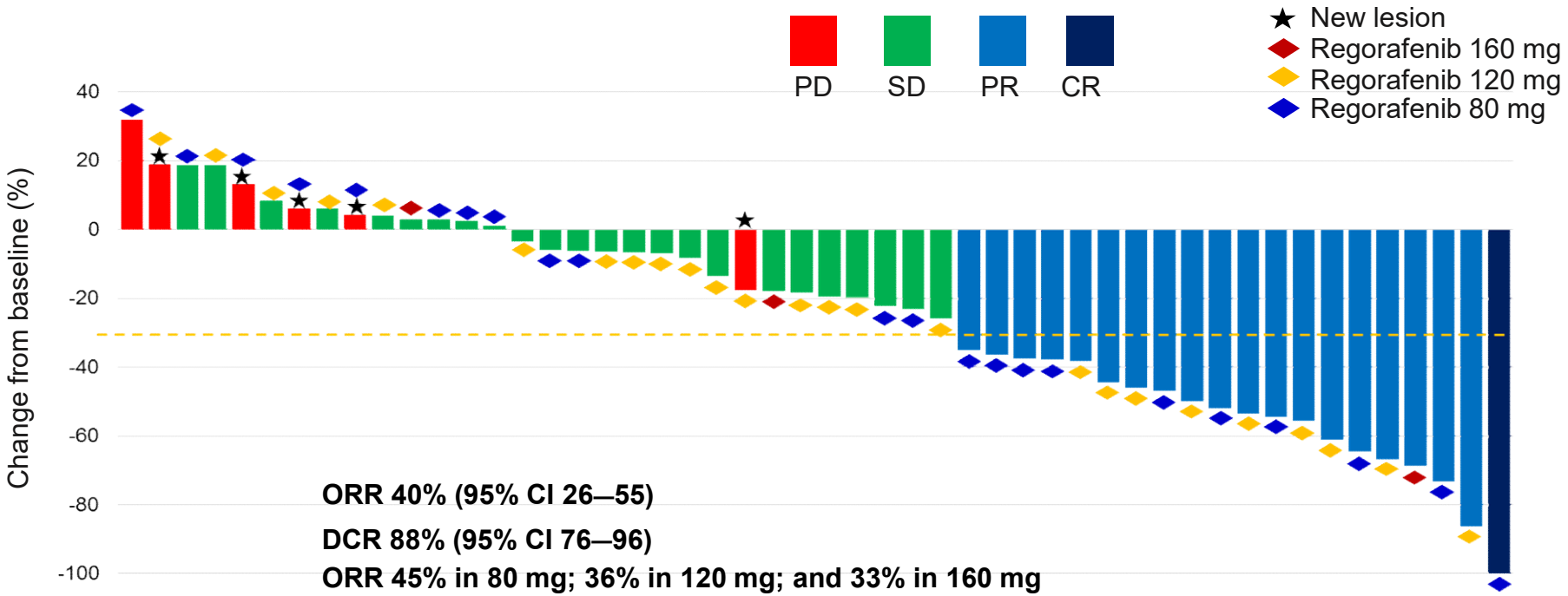
One treatment-related death was observed due to diabetic ketoacidosis.
Fukuoka S, et al. ASCO 2019:Poster 2522.

REGONIVO: Median duration of treatment was 6.1 months, with study treatment ongoing in 21 patients



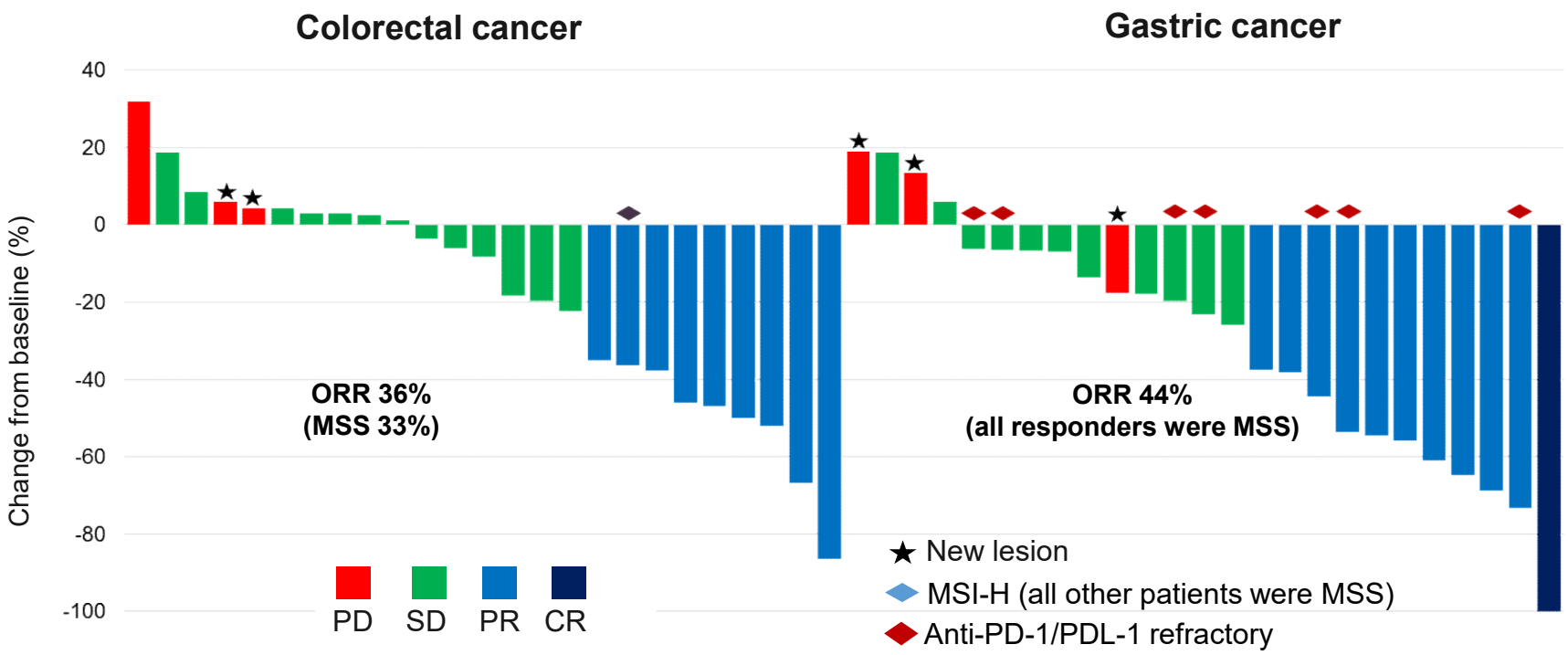
Fukuoka S, et al. ASCO 2019:Poster 2522.

REGONIVO: The overall ORR was 40% and DCR was 88%



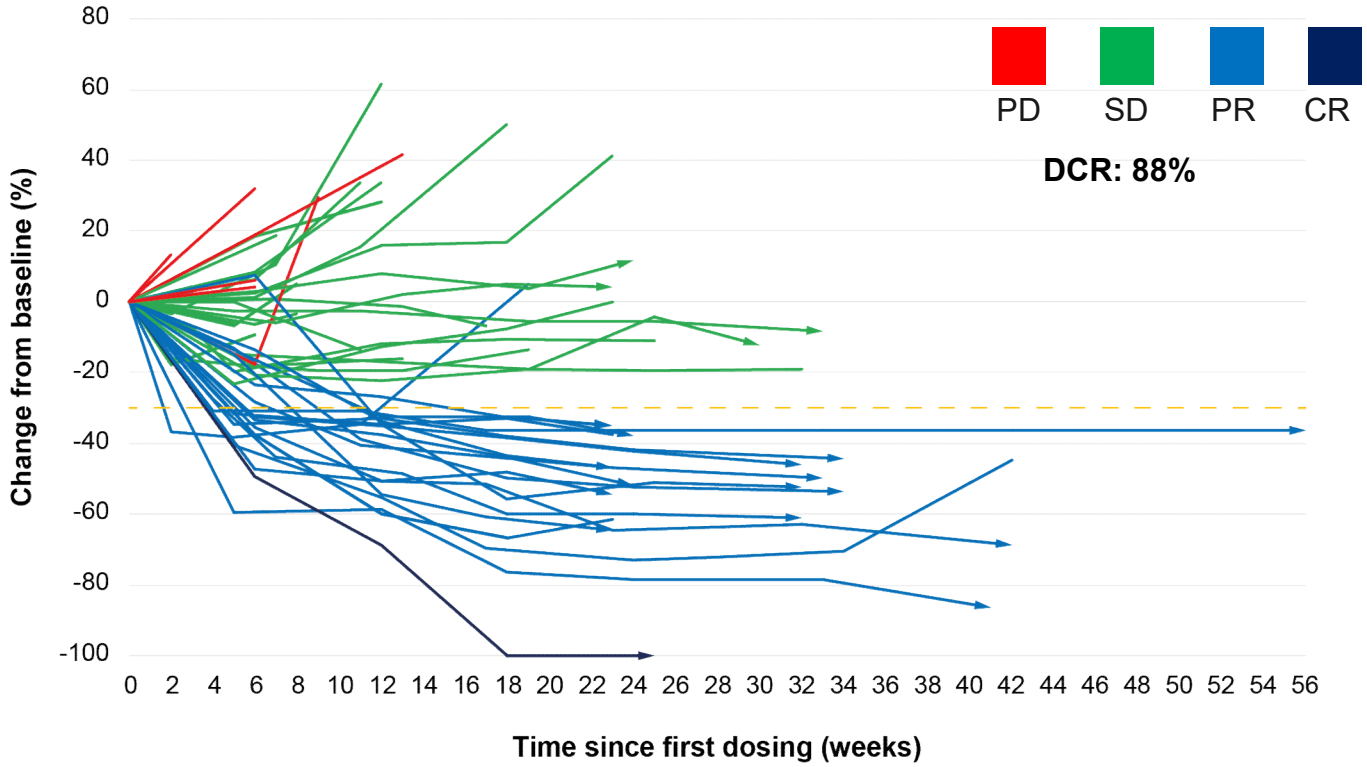
Fukuoka S, et al. ASCO 2019:Poster 2522.

REGONIVO: The ORR was 36% in CRC and 44% in gastric cancer



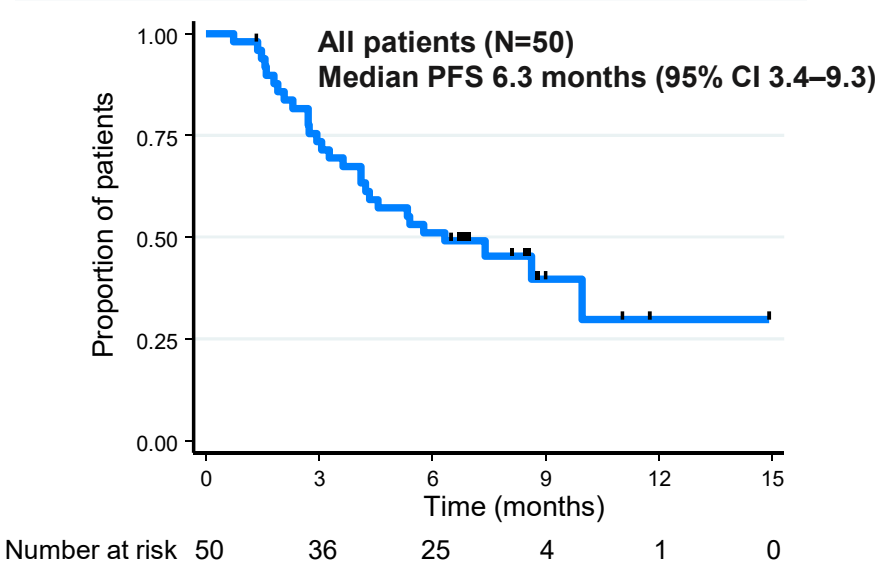
Fukuoka S, et al. ASCO 2019:Poster 2522.

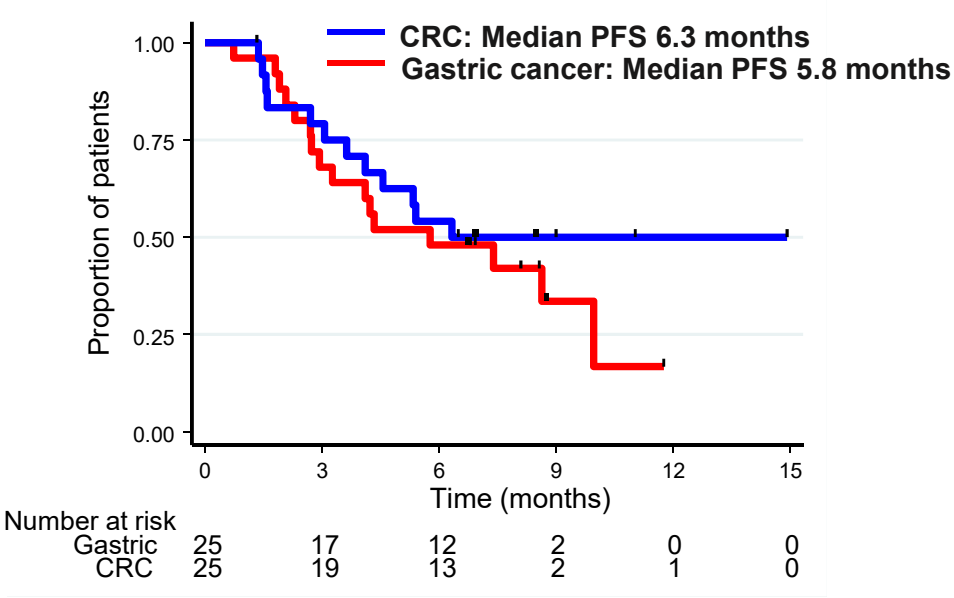
REGONIVO: The majority of patients experienced PR and SD, with a DCR of 88%



Fukuoka S, et al. ASCO 2019:Poster 2522.

REGONIVO: Median PFS was 6.3 and 5.8 months in CRC and gastric cancer, respectively





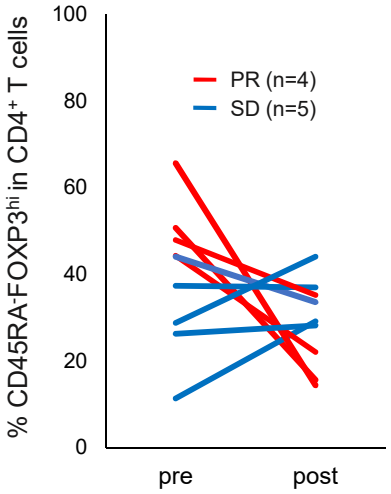
- Median follow-up: 8.0 months; date cut-off: April 23, 2019

Fukuoka S, et al. ASCO 2019:Poster 2522.

REGONIVO: Patients with objective response showed a trend of Treg decrease in TILs

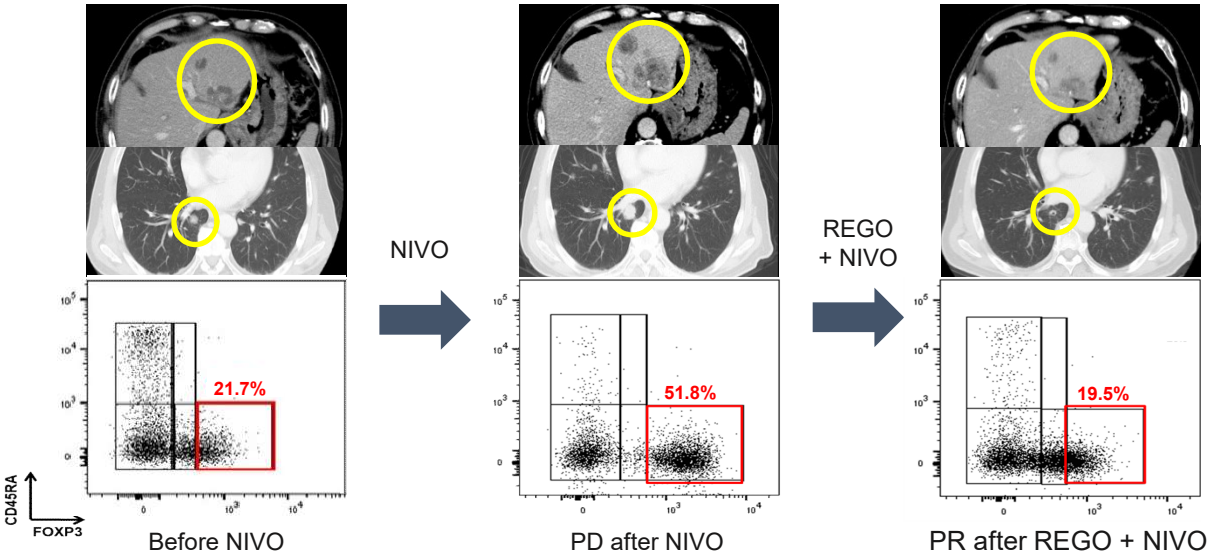
Pre-and post-treatment biopsied samples in 9 patients were analyzed using flow cytometry

Fraction of Tregs within TILs



PR cases showed decrease in CD45RA^{-}FoxP3^{hi} effector Tregs

67-year-old male with HER2-negative gastric cancer
Disease progression after nivolumab monotherapy



CD45RA^{-}FoxP3^{hi} effector Tregs increased at PD state after NIVO, then decreased after REGO + NIVO

Fukuoka S, et al. ASCO 2019:Poster 2522.

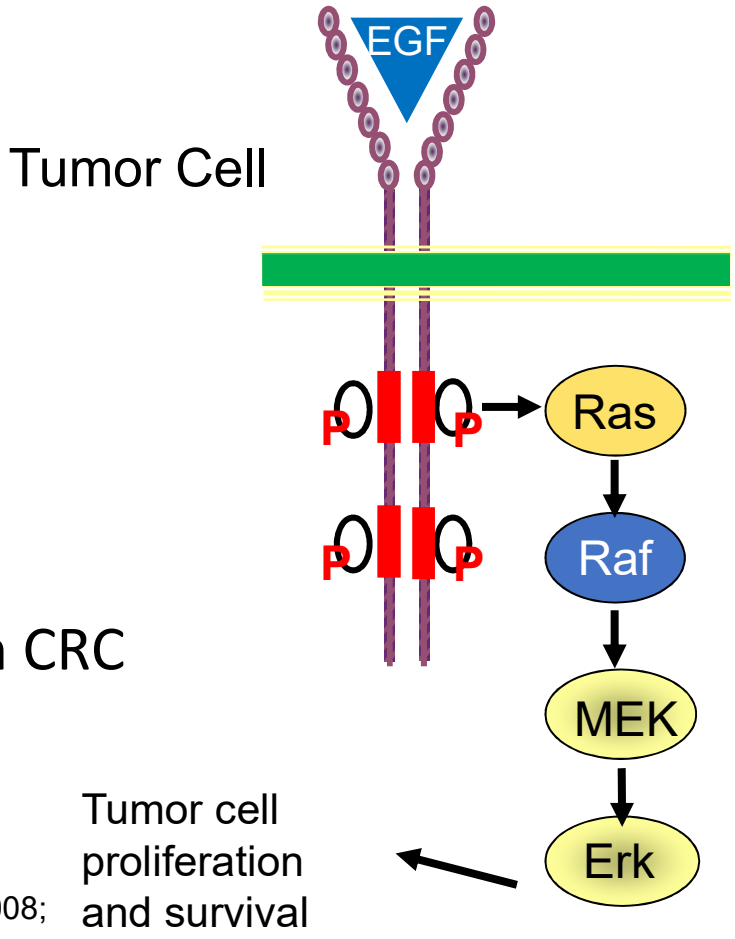
Treatment Options in First-line

Regimen	Sidedness restriction	Molecular restriction	Preferred indication
Cape + BEV	None	None	Elderly patients, low-volume disease
FOLFOX/ CAPOX/ FOLFIRI + BEV	None	None	
FOLFOXIRI + BEV	None	None	Aggressive cancers (w.g. BRAF mut, R-sided)
FOLFOX/ FOLFIRI + EGFR mAb	Left-sided*	RAS/ BRAF wt (HER-2 neg?)	SOC left-sided cancers
FOLFOXIRI + EGFR mAb	Left-sided*	RAS/ BRAF wt (HER-2 neg?)	Left-sided cancers with high tumor load
PD-1 antibody/ IO combo	None	MSI-H/ MMR-D	Pts with MSI-H cancers not considered for chemo
BEACON(-like)	None	BRAF V600E mut	Data in first-line pending

*ESMO guidelines allow EGFR mAbs in R-sided cancers

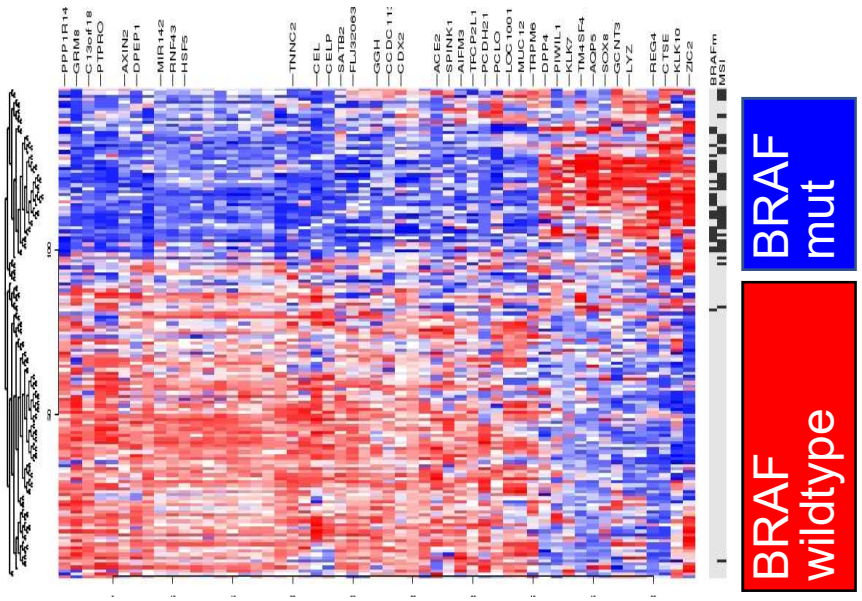
BRAF Mutations in CRC

- **BRAF is primary effector of KRAS signaling**
- **BRAF mutations:**
  - Occur most frequently in exon 15 (V600E)
  - Found in 4%-14% of patients with CRC
  - Mutually exclusive with KRAS mutations

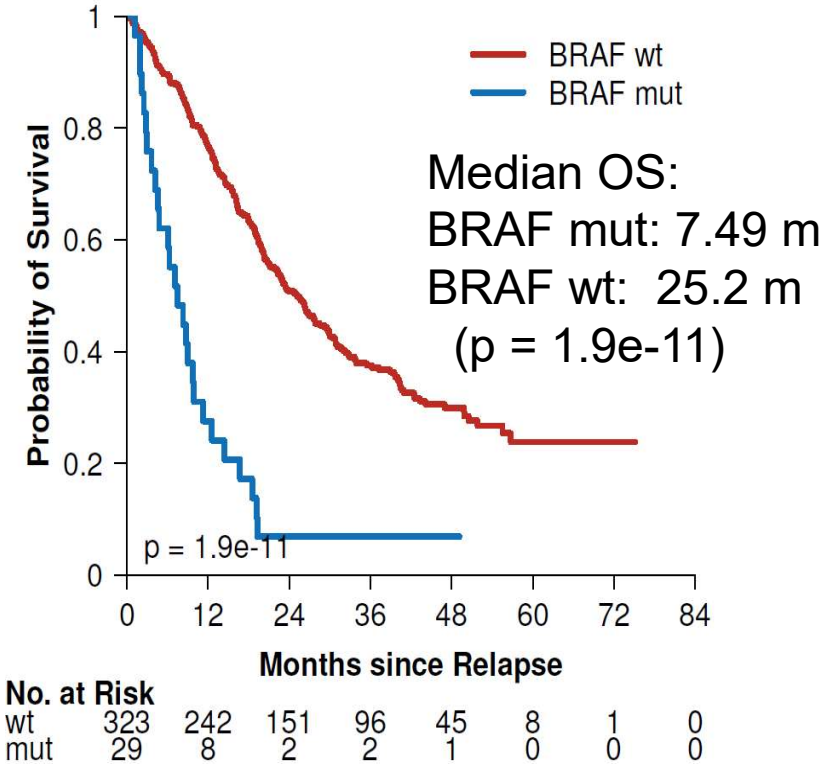


Yarden. *Nat Rev Mol Cell Biol*. 2001; Di Nicolantonio. *J Clin Oncol*. 2008; Artale. *J Clin Oncol*. 2008.

PETACC-3: Survival after relapse according to BRAF mutation status



Tejpar et al, ASCO 2010



Median OS:
BRAF mut: 7.49 m
BRAF wt: 25.2 m
(p = 1.9e-11)

Roth et al. JCO 2010

BEACON CRC:

A Randomized, 3-Arm, Phase 3 Study of Encorafenib and Cetuximab With or Without Binimetinib vs. Choice of Either Irinotecan or FOLFIRI, plus Cetuximab in *BRAF* ^{V600E} Mutant Metastatic Colorectal Cancer

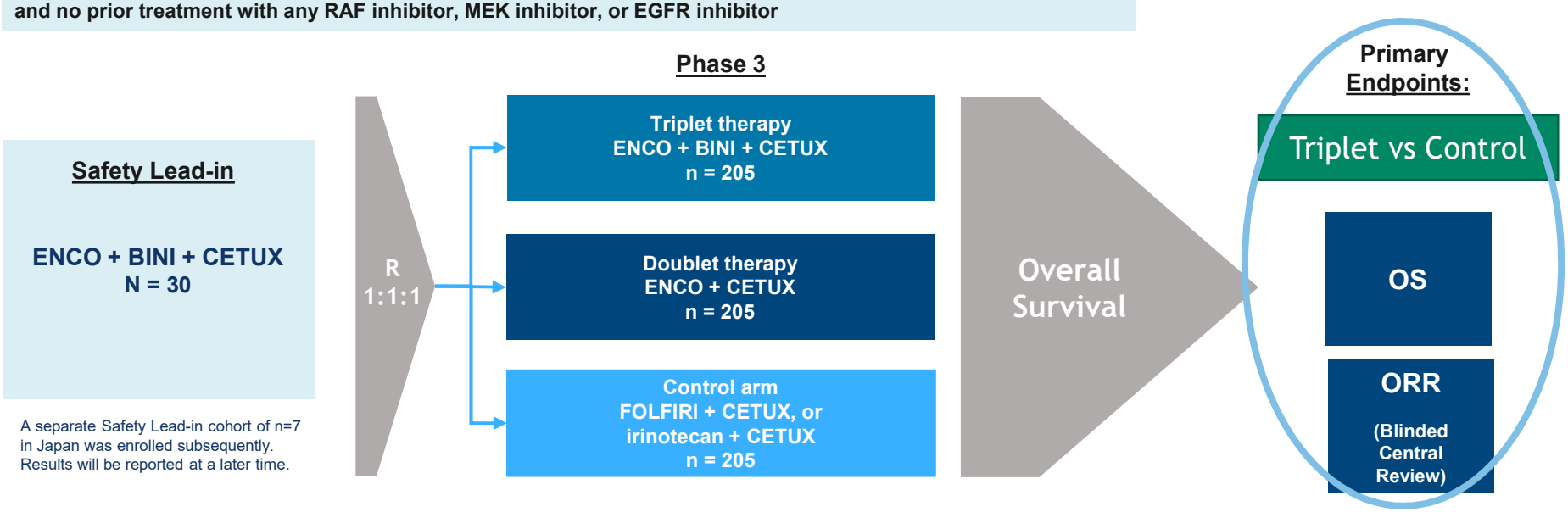
Scott Kopetz, Axel Grothey, Eric Van Cutsem, Rona Yaeger, Harpreet Wasan, Takayuki Yoshino, Jayesh Desai, Fortunato Ciardiello, Fotios Loupakis, Yong Sang Hong, Neeltje Steeghs, Tormod Kyrre Guren, Hendrik-Tobias Arkenau, Pilar Garcia-Alfonso, Ashwin Gollerkeri, Kati Maharry, Janna Christy-Bittel, Lisa Anderson, Victor Sandor and Josep Tabernero

BEACON CRC: **B**inimetinib, **E**ncorafenib, **A**nd **C**etuximab C**O**mbi**N**ed to Treat *BRAF*-mutant **C**olo**R**ectal **C**ancer

Final Study Design

Results of Safety Lead-In led to the introduction of an additional primary endpoint of ORR and an interim OS analysis to allow for early assessment

Patients with *BRAF* V600E–mutant 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



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

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

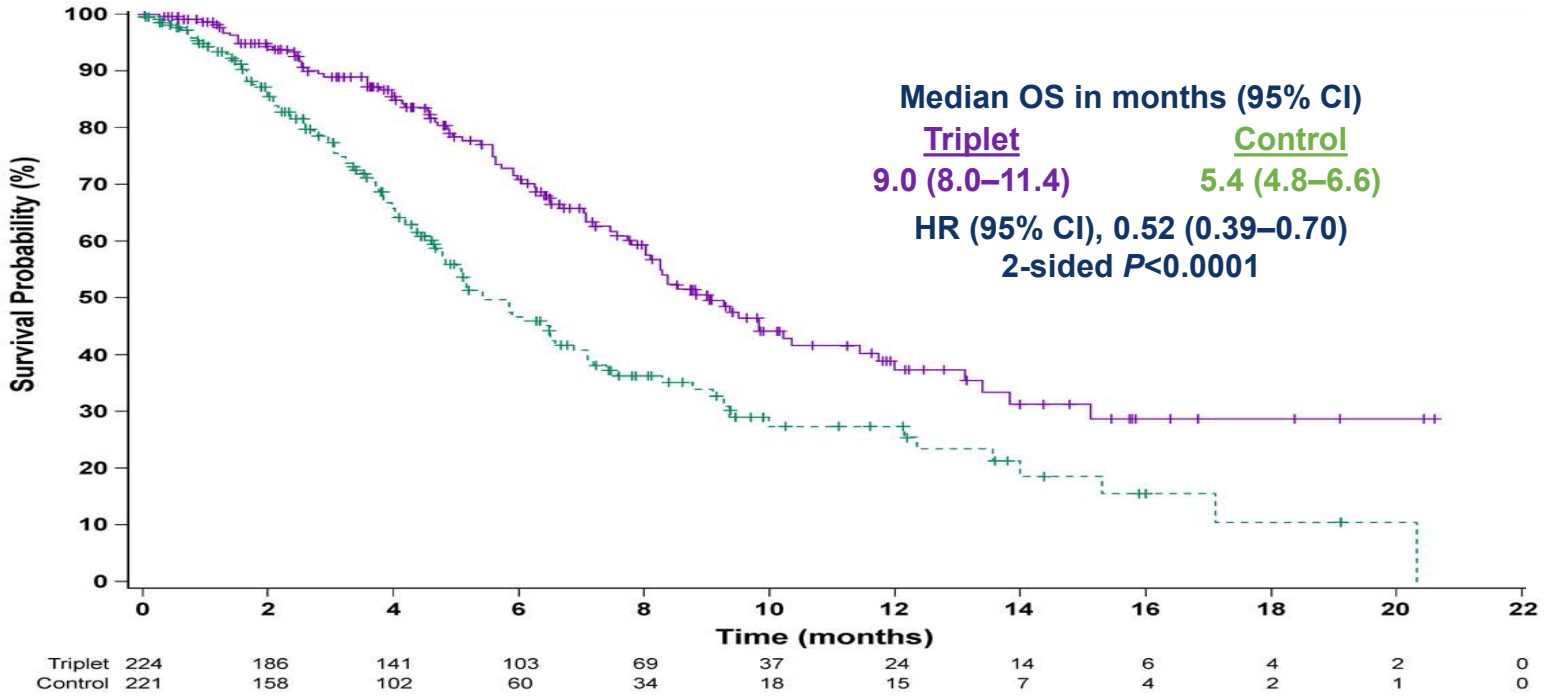
Kopetz et al, ESMO GI 2019

Baseline Patient Characteristics

CHARACTERISTIC	Triplet N=224	Doublet N=220	Control N=221
Female	53%	48%	57%
Age, median (range), years	62 (26, 85)	61 (30, 91)	60 (27, 91)
ECOG PS 0	52%	51%	49%
Location of primary tumor*			
Left colon (includes rectum)	35%	38%	31%
Right colon	56%	50%	54%
≥3 organs involved	49%	47%	44%
Presence of liver metastases	64%	61%	58%
Prior lines of therapy			
1	65%	66%	66%
>1	35%	34%	34%
MSI-H†	10%	9%	5%
CEA Baseline Value > 5 ug/L	80%	70%	81%
CRP Baseline Value > 10mg/L	42%	37%	41%

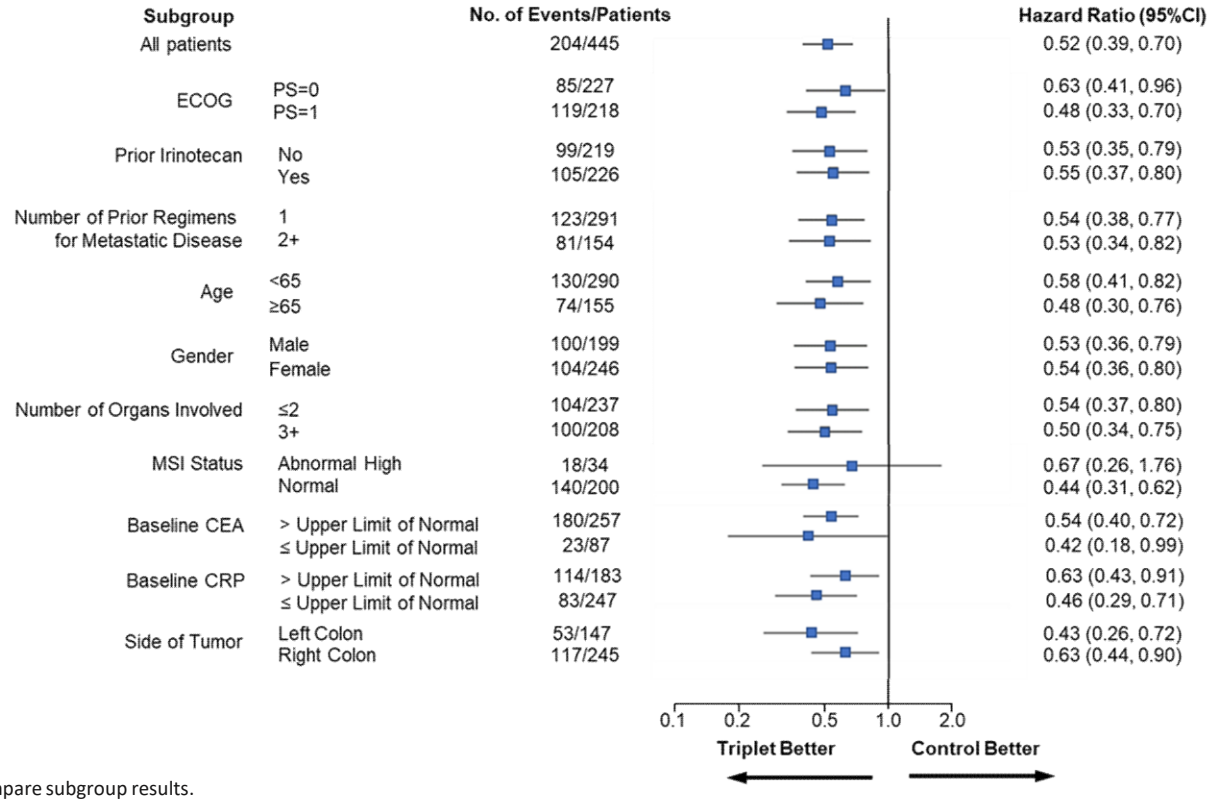
Abbreviations: CEA, carcinoembryonic antigen; CRP, c-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSI-H, microsatellite instability high (abnormal high).
Baseline characteristics are summarized for all 665 randomized patients.
†Based on assessment by polymerase chain reaction. MSI status is missing in 23% of patients.
*Remaining patients had primary tumor in both left and right sides of colon and those with unknown location of primary tumor.

1º Endpoint Overall Survival: Triplet vs Control
(all randomized patients)



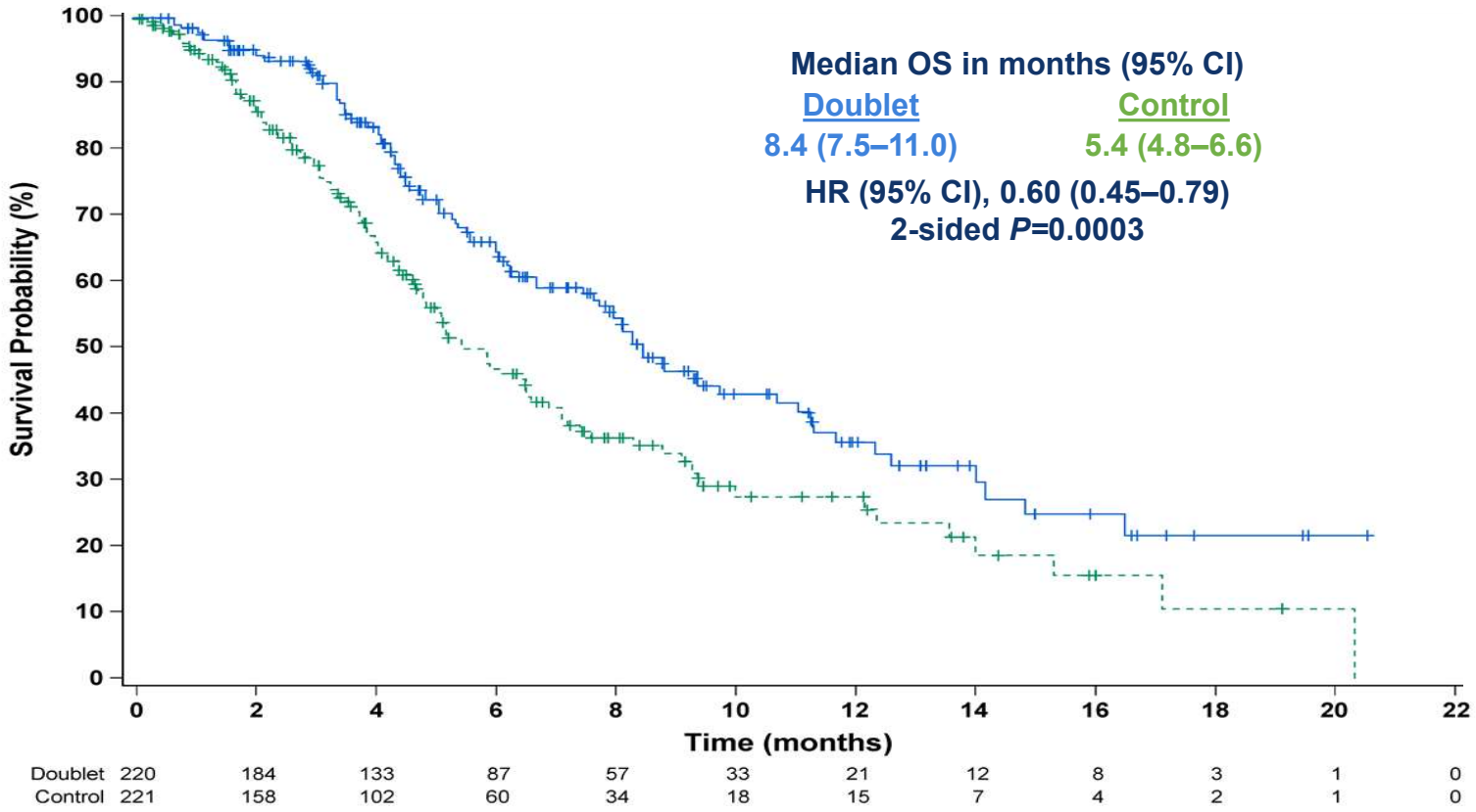
Kopetz et al, ESMO GI 2019

Overall Survival: Subgroup Analysis (all randomized patients)



Study not powered to formally compare subgroup results.

Overall Survival: Doublet vs Control (all randomized patients)

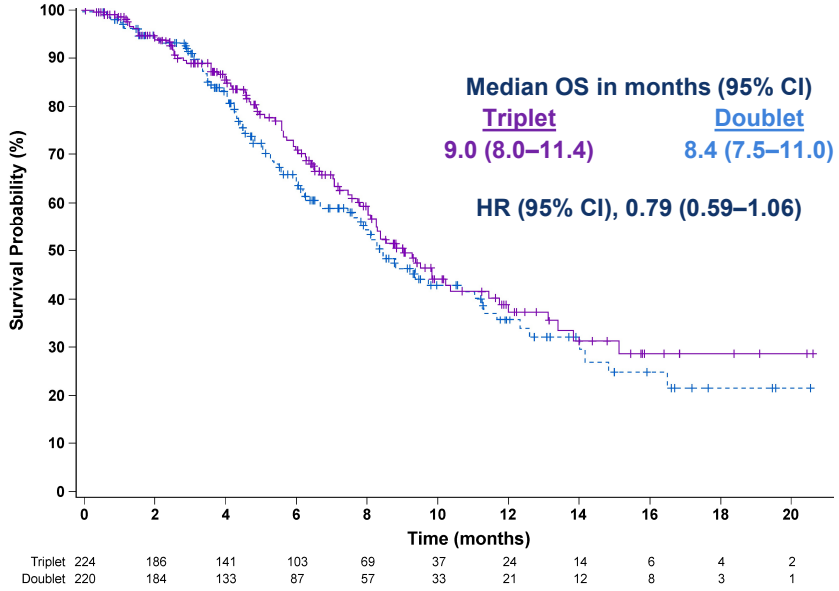


Kopetz et al, ESMO GI 2019

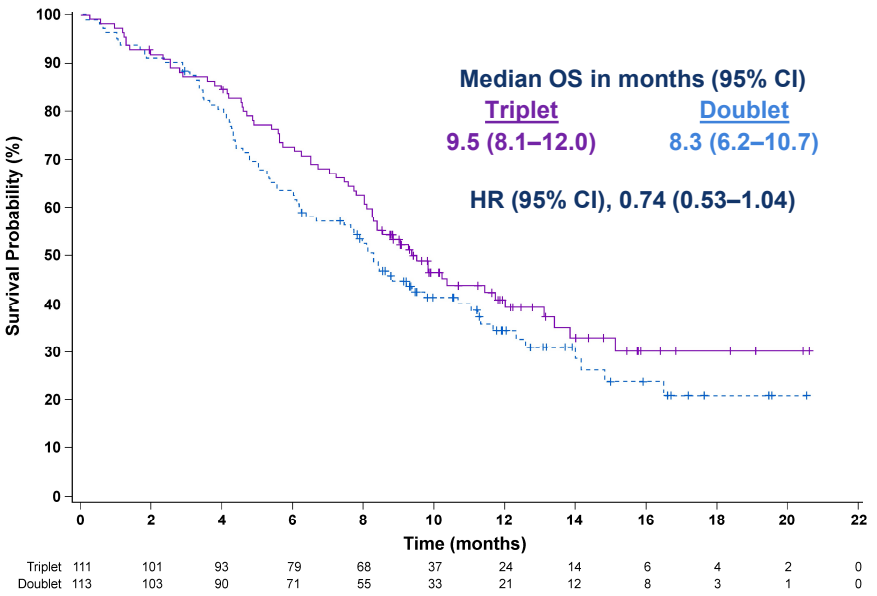
Overall Survival: Triplet vs Doublet

Study not powered to formally compare the results of the triplet combination to the doublet combination

All Randomized Patients



*First 331 Randomized Patients**



*Post-hoc descriptive analysis.

Additional OS analysis to be presented at a later date

Kopetz et al, ESMO GI 2019

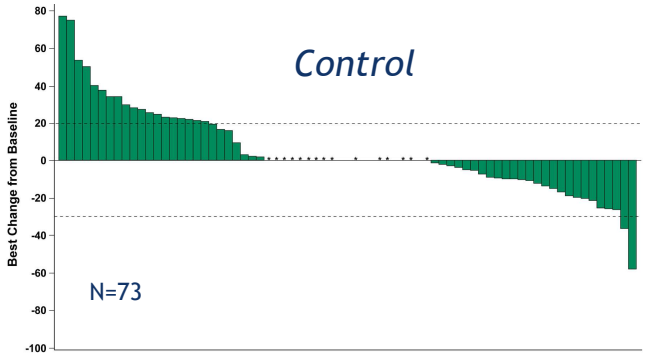
Objective Response Rate (first 331 randomized patients)

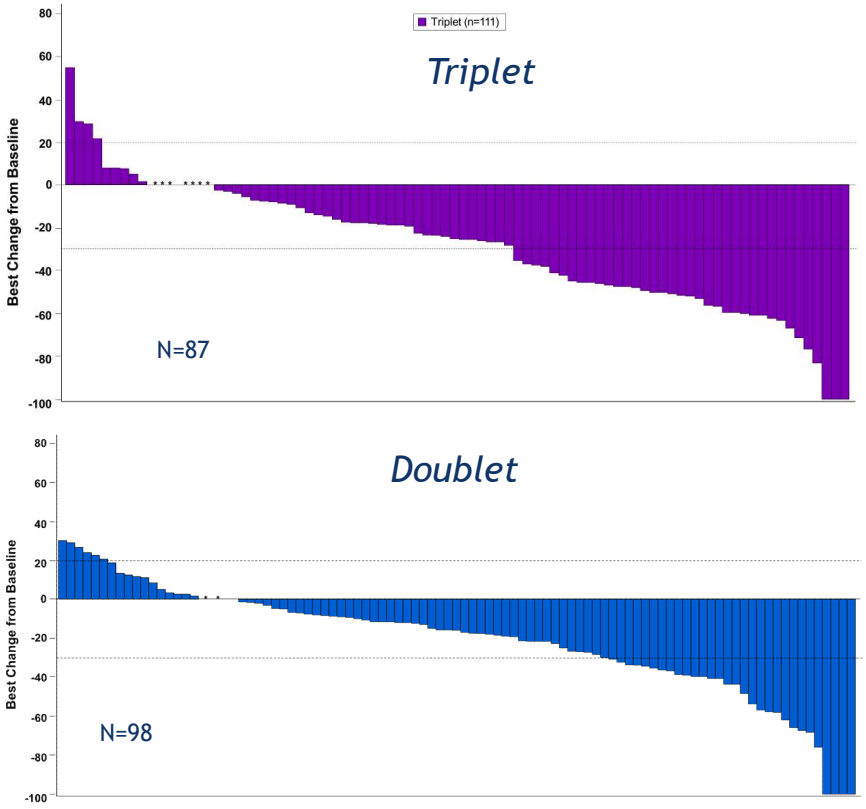
Confirmed Response by BICR	Triplet N=111	Doublet N=113	Control N=107
Objective Response Rate	**26%**	**20%**	**2%**
95% (CI)	(18, 35)	(13, 29)	(<1, 7)
p-value vs. Control	<0.0001	<0.0001	
Objective Response Rate			
1 prior line of therapy	34%	22%	2%
>1 prior line of therapy	14%	16%	2%
Best Overall Response			
Complete Response	4%	5%	0
Partial Response	23%	15%	2%
Stable Disease	42%	54%	29%
Progressive Disease	10%	7%	34%
Non Evaluable by RECIST	22%	19%	36%
Clinical progression or adverse event[a]	14%	17%	16%
Insufficient information to assess response[b]	8%	2%	20%

BICR=blinded independent central review.
a. Includes patients considered not evaluable by central assessment with clinical progression or radiological progression by local assessment or discontinuation due to adverse event.
b. Includes patients who were untreated, withdrew consent, had stable disease < 42 days, had no baseline scans, or had no post-baseline scans without evidence of clinical progression or adverse event as the reason for missing scans.

Kopetz et al, ESMO GI 2019

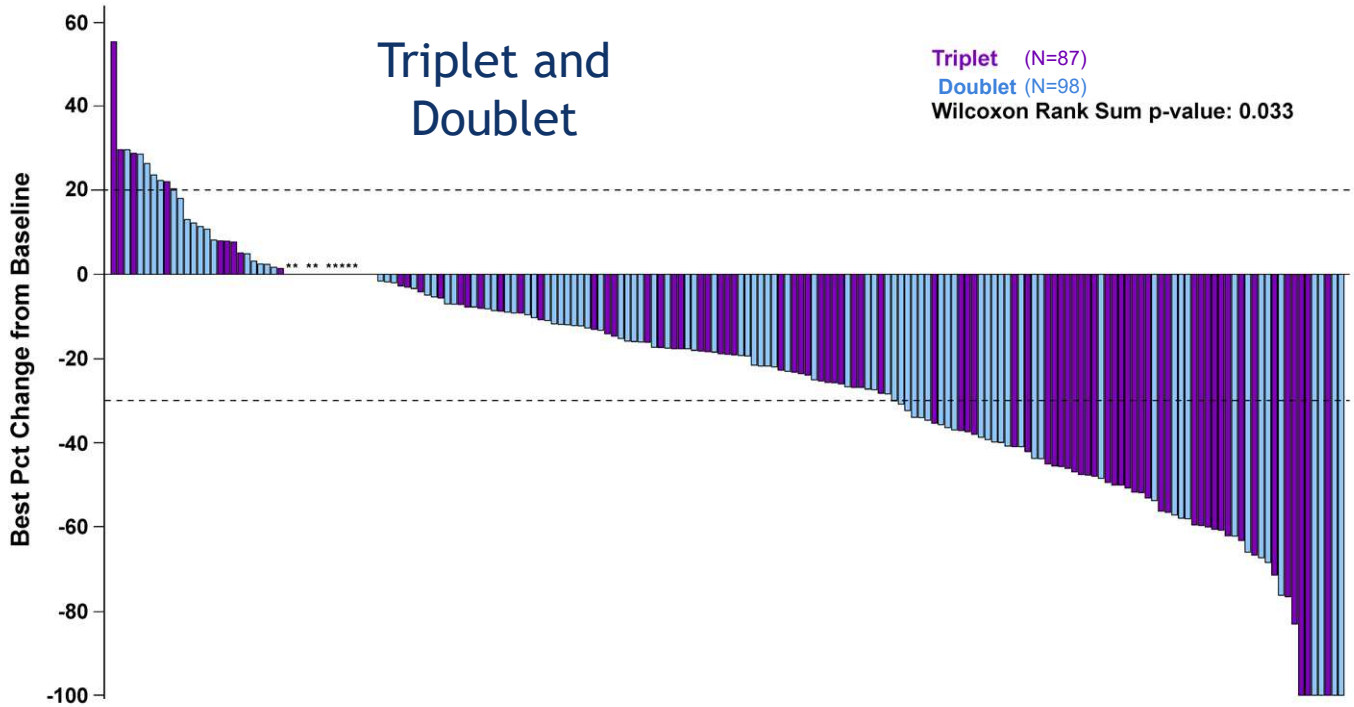
Waterfall Plots of Best Change in Sum of Diameters
(based on central review)





*Patients whose SoD was contraindicated by assessment of PD. SoD=sum of longest diameter. Includes patients with measurable disease with a baseline and at least one post-baseline scan

Waterfall Plots of Best Change in Sum of Diameters
(first 331 randomized patients)

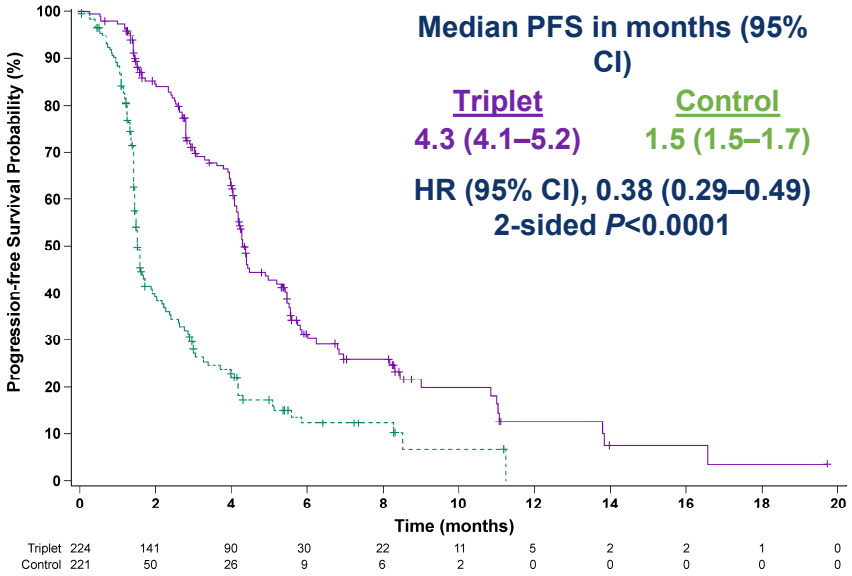


*Patients whose SoD was contraindicated by assessment of PD. SoD=sum of longest diameter. p-value is descriptive only for this analysis.
Comparison of the two waterfall plots is suggestive of a shift towards greater tumor reduction from baseline in the Triplet.

Kopetz et al, ESMO GI 2019

Progression Free Survival (all randomized patients)*

Triplet vs Control

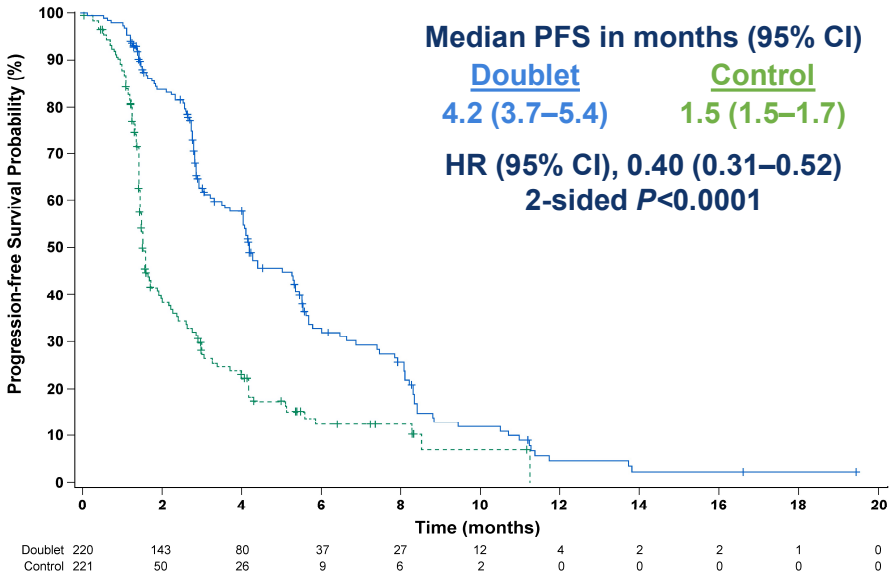


Median PFS in months (95% CI)

Triplet	Control
4.3 (4.1–5.2)	1.5 (1.5–1.7)

HR (95% CI), 0.38 (0.29–0.49)
2-sided *P*<0.0001

Doublet vs Control



Median PFS in months (95% CI)

Doublet	Control
4.2 (3.7–5.4)	1.5 (1.5–1.7)

HR (95% CI), 0.40 (0.31–0.52)
2-sided *P*<0.0001

*PFS by BICR (blinded independent central review).

Adverse Events and Laboratory Abnormalities*

Event	Triplet N=222 Grade ≥3	Doublet N=216 Grade ≥3	Control N=193 Grade ≥3
Diarrhea	10%	2%	10%
Abdominal pain	6%	2%	5%
Nausea	5%	<1%	1%
Vomiting	4%	1%	3%
Pulmonary embolism	4%	1%	4%
Intestinal obstruction	3%	4%	3%
Asthenia	3%	3%	5%
Acute kidney injury	3%	2%	<1%
Fatigue	2%	4%	4%
Dermatitis acneiform	2%	<1%	3%
Ileus	2%	1%	2%
Urinary tract infection	1%	2%	1%
Cancer pain	<1%	2%	<1%
Laboratory Abnormality	**Grade ≥3**	**Grade ≥3**	**Grade ≥3**
Hemoglobin (g/L), hypo	10%	5%	4%
Creatinine (umol/L), hyper	4%	2%	1%
Bilirubin (umol/L), hyper	2%	2%	3%
Creatine Kinase (IU/L), hyper	2%	0	0

*Occurring in at least 2% of patients in either triplet or doublet arms.

Kopetz et al, ESMO GI 2019

Conclusions

- *BRAF*^{V600E} mutant metastatic colorectal cancer has historically dismal outcomes
- Encorafenib, binimetinib and cetuximab (triplet), and encorafenib and cetuximab (doublet), significantly improved OS and ORR relative to the current standard of care (control) in patients with *BRAF*^{V600E} mutant metastatic CRC
  - The control arm results were consistent with previous reported studies
  - Results suggest increased efficacy in earlier lines of therapy
- The safety and tolerability profile of both combinations allow maintenance of high dose intensity for most patients and are consistent with the known profiles of the component agents
- Data suggest that the triplet combination offers improved efficacy relative to the doublet with the addition of some manageable toxicity

First evidence of survival benefit for a chemotherapy-free targeted treatment regimen in prospective biomarker-defined patients with metastatic CRC, defining a new standard of care

Kopetz et al, ESMO GI 2019

ANCHOR: Single Arm Phase II Study of *First-line* Encorafenib + Binimetinib + Cetuximab

CLINICAL STUDY PROTOCOL

The ANCHOR CRC Study : encor**A**fenib, bi**N**imetinib and **C**etuximab in subjects wit**H** previ**O**usly untreated B**R**AF-mutant Colo**R**ectal **C**ancer

Phase II, open-label, single arm, multicenter study of encorafenib, binimetinib plus cetuximab in subjects with previously untreated *BRAF* ^{V600E} -mutant Metastatic Colorectal Cancer

N = 90, Primary Endpoint: ORR (Goal > 41%)

NCT03693170.

Grothey et al., TIP ESMO GI 2019

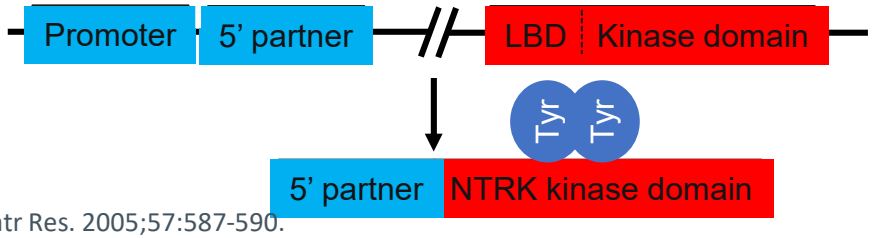
Tropomyosin Receptor Kinase (TRK): Role in Normal Biology and Cancer

- **TRK receptors[1]:**
  - In normal biology, expressed in neuronal tissue; roles in development, nervous system function via activation by neurotrophins
  - Rarely expressed in normal

Receptor[2-4]	Gene	Function
TRKA	NTRK1	Pain, thermoregulation
TRKB	NTRK2	Movement, memory, mood, appetite, weight
TRKC	NTRK3	Proprioception

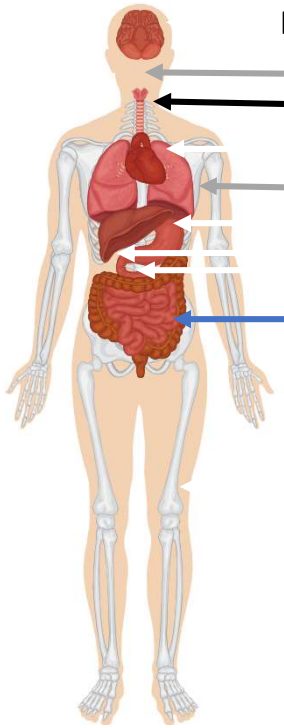
- **TRK fusions[1]:**
  - Rearrangement of *NTRK* gene couples tyrosine kinase domain with a 5’ fusion partner to generate a chimeric TRK protein lacking ligand binding domain
  - Leads to overexpression or constitutive activation of TRK receptor kinase domain

TRK Fusions[5]



1. Amatu A, et al. ESMO Open. 2016;1:e000023. 2. Loewenthal N, et al. Pediatr Res. 2005;57:587-590.
3 . Razzoli M, et al. Genes Brain Behav. 2011;10:424-433. 4. Inoue K, et al. Blood Cells Mol Dis. 2003;30:157-160.
5. Hyman DM, et al. ASCO 2017. Abstract LBA2501.

Tropomyosin Receptor Kinase (TRK) Fusions Observed Across Diverse Cancer Types in Both Adults and Children



Brain cancers (glioma, GBM, astrocytoma)

Salivary (MASC)

Lung cancer

Secretory breast cancer

Pancreatic

Cholangiocarcinoma

GIST

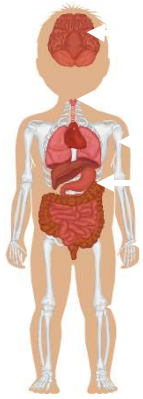
Colon

Melanoma

Sarcoma (multiple)

Common cancer with low TRK fusion frequency

Rare cancer with high TRK fusion frequency



Gliomas

Thyroid cancer

Infantile fibrosarcoma

Congenital nephroma

Spitz nevi

Sarcoma (multiple)

***NTRK* fusions are rare events: 0.21% across 11,116 patients with tumors of all types**

Multiple TRK Inhibitors in Advanced Stages of Development

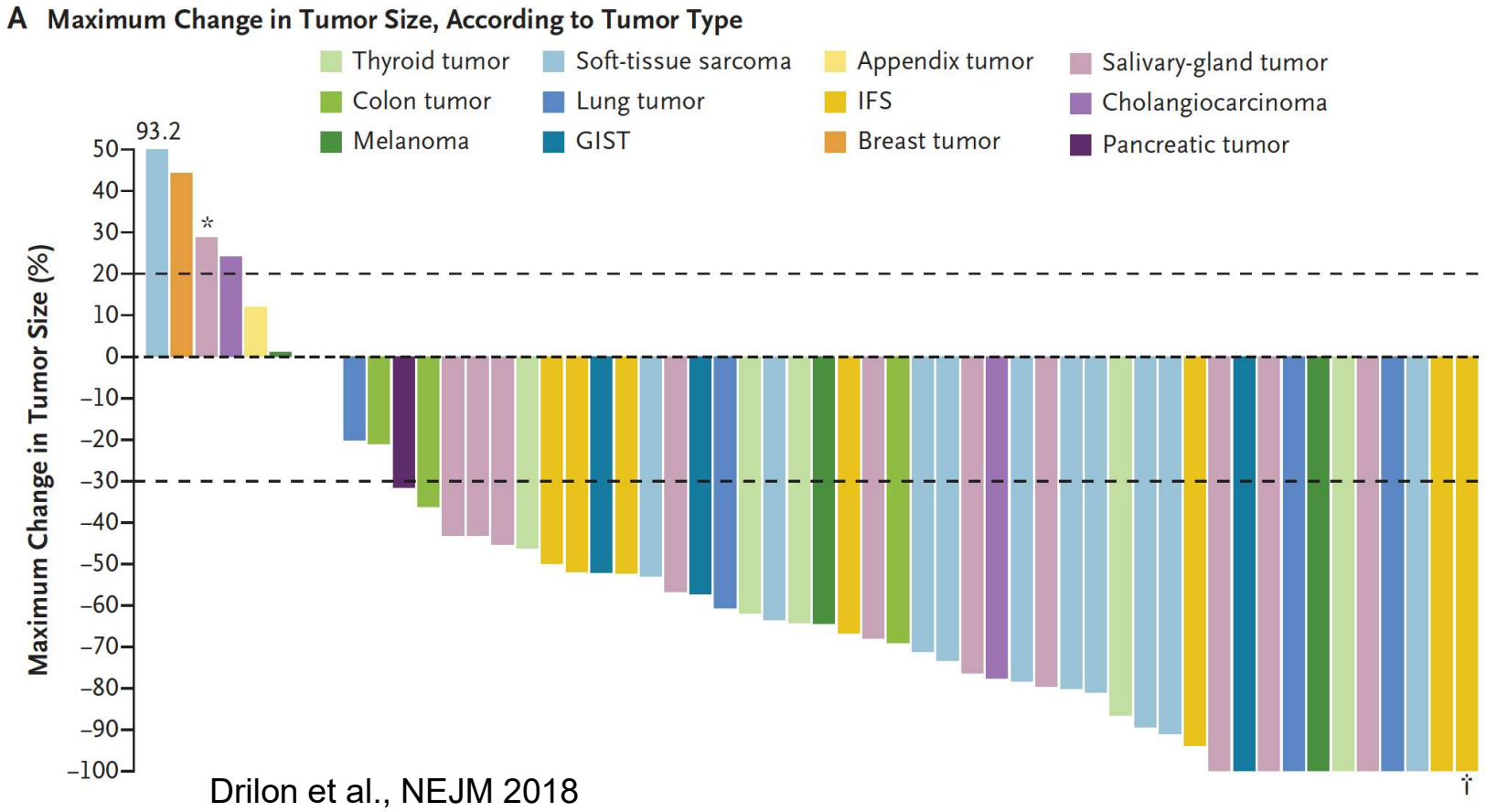
Target(s)	Agent
TRK-specific inhibitors	Larotrectinib – FDA approved Nov 2018 LOXO-195 PLX7486*
TRK/ALK/ROS1-specific inhibitors	Entrectinib – FDA Breakthrough Designation TPX-0005 DS-6051b
Nonspecific TKIs that may also cover TRK	Cabozantinib† Sitravatinib (MGCD516) Merestinib (LY2801653)

*Also selectively inhibits colony-stimulating factor-1 receptor.

†Approved by FDA for advanced RCC (in tablet form) or for progressive, metastatic medullary thyroid cancer (in capsule form).

Khotskaya YB, et al. Pharmacol Ther. 2017;173:58-66. ClinicalTrials.gov. NCT03215511. NCT01804530. NCT03093116. NCT02279433. NCT02219711.

Larotrectinib in Cancers with *NTRK* Fusion



Drilon et al., NEJM 2018

Conclusions

- **Individualization of first-line chemotherapy plus biologics is warranted based on mutational status, sidedness, treatment goals, prognosis, patient disposition**
  - Triplet chemotherapy approaches (+/- biologics) are likely underutilized
- **Targeted agents, beyond EGFRi and VEGFi, are moving into first-line therapy**
  - IO and IO combos for MSI-H/ MMR-D cancers
  - Combination of MAPK inhibitors in BRAF V600E mutated mCRC
  - NTRK inhibitors for mCRC with NTRK fusion (<0.5%)
  - Potentially HER-2 targeted agents (no trials in first-line yet)