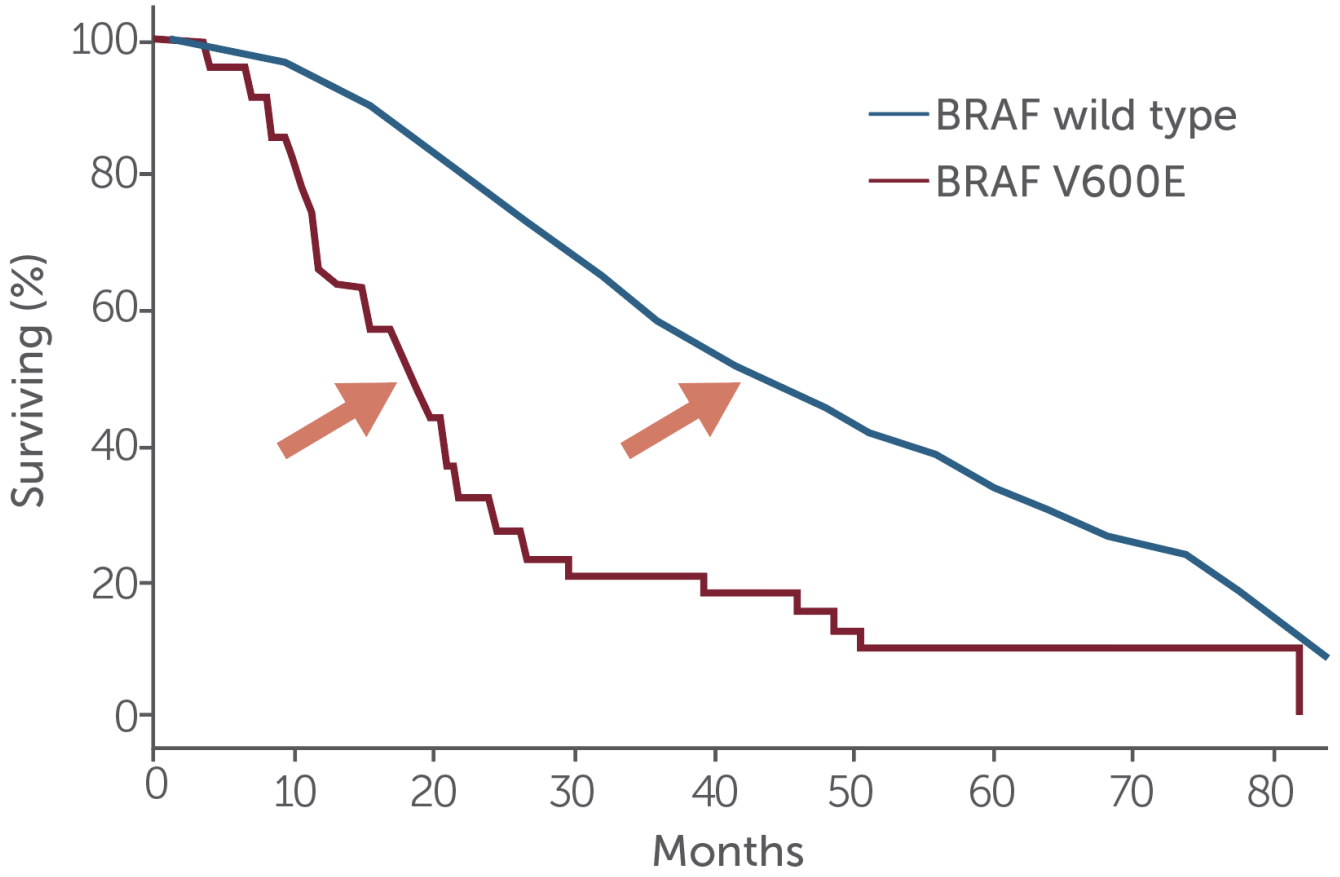
Kaplan-Meier Survival Curve of BRAF V600E–Mutated mCRC Patients vs BRAF Wild-Type mCRC Patients

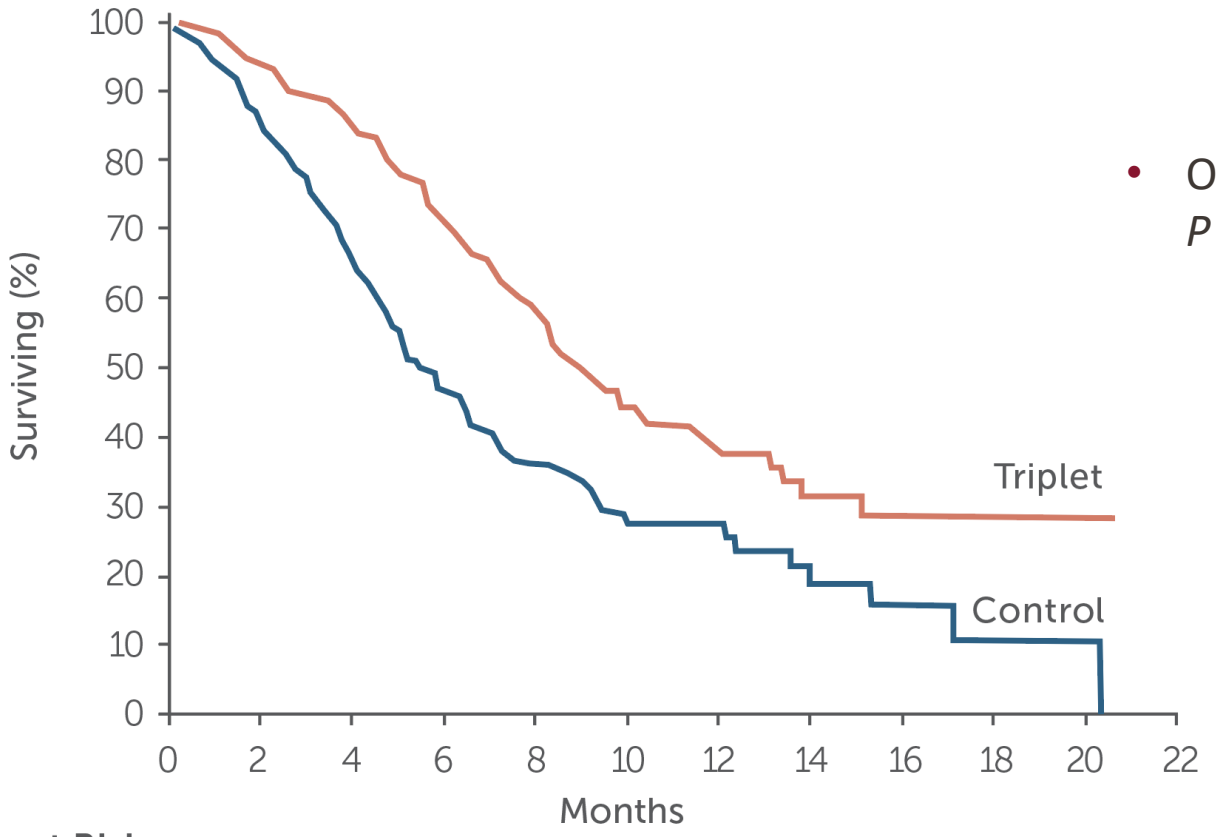


Lee HM, et al. *Oncology (Williston Park).* 2019;33(6):206-211.

BEACON: Overall Survival, Triplet Regimen vs. Control

Median Overall Survival *mo (95% CI)*	
Triplet	9.0 (8.0-11.4)
Control	5.4 (4.8-6.6)

Hazard ratio for death,
0.52 (95% CI, 0.39-0.70)
P < 0.001



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

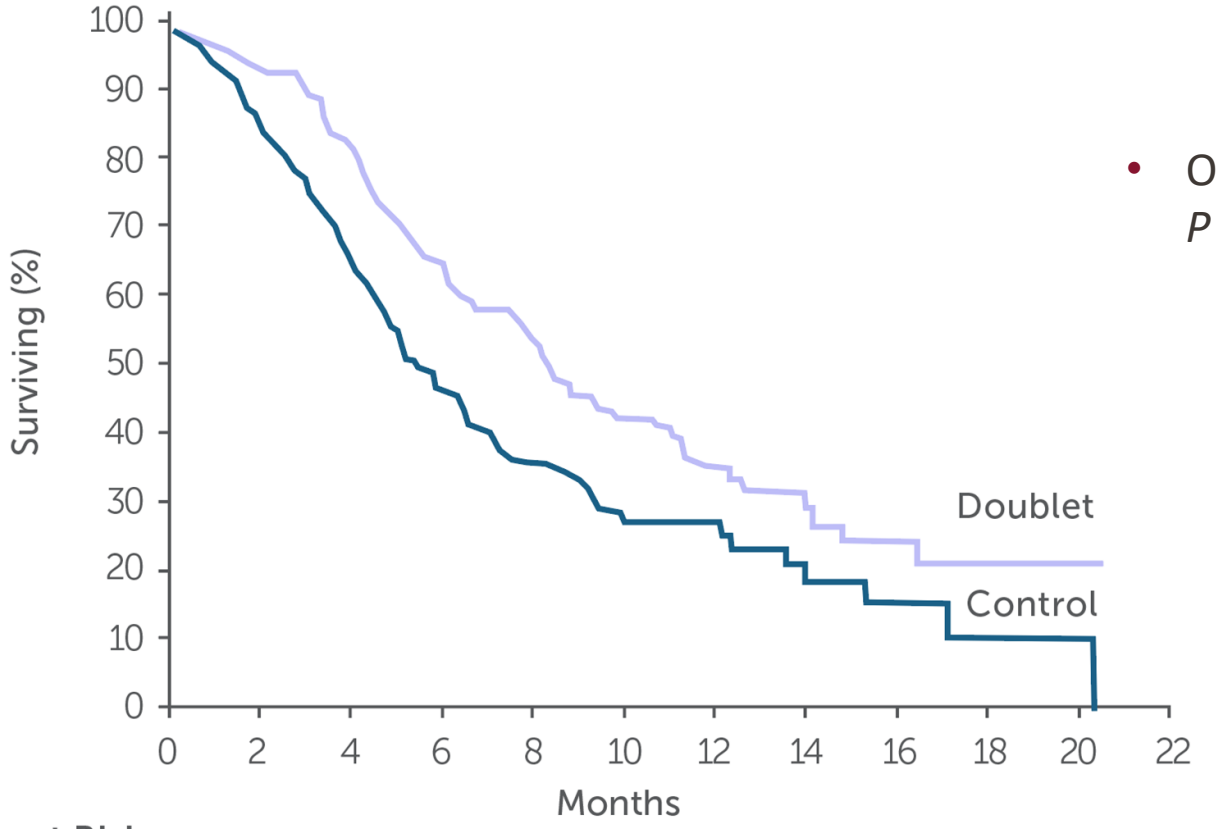
- ORR = 26% (95% CI, 18-35; *P* < 0.001 vs. control)

Kopetz S, et al. *N Engl J Med*. 2019;381(17):1632-1643.

BEACON: Overall Survival, Doublet Regimen vs. Control

Median Overall Survival *mo (95% CI)*	
Doublet	8.4 (7.5-11.0)
Control	5.4 (4.8-6.6)

Hazard ratio for death,
0.60 (95% CI, 0.45-0.79)
P < 0.001



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

- ORR = 20% (95% CI, 13-29; *P* < 0.001 vs. control)

Kopetz S, et al. *N Engl J Med*. 2019;381(17):1632-1643.

Comparison between the initial findings from BEACON and the subsequent updated, mature analysis

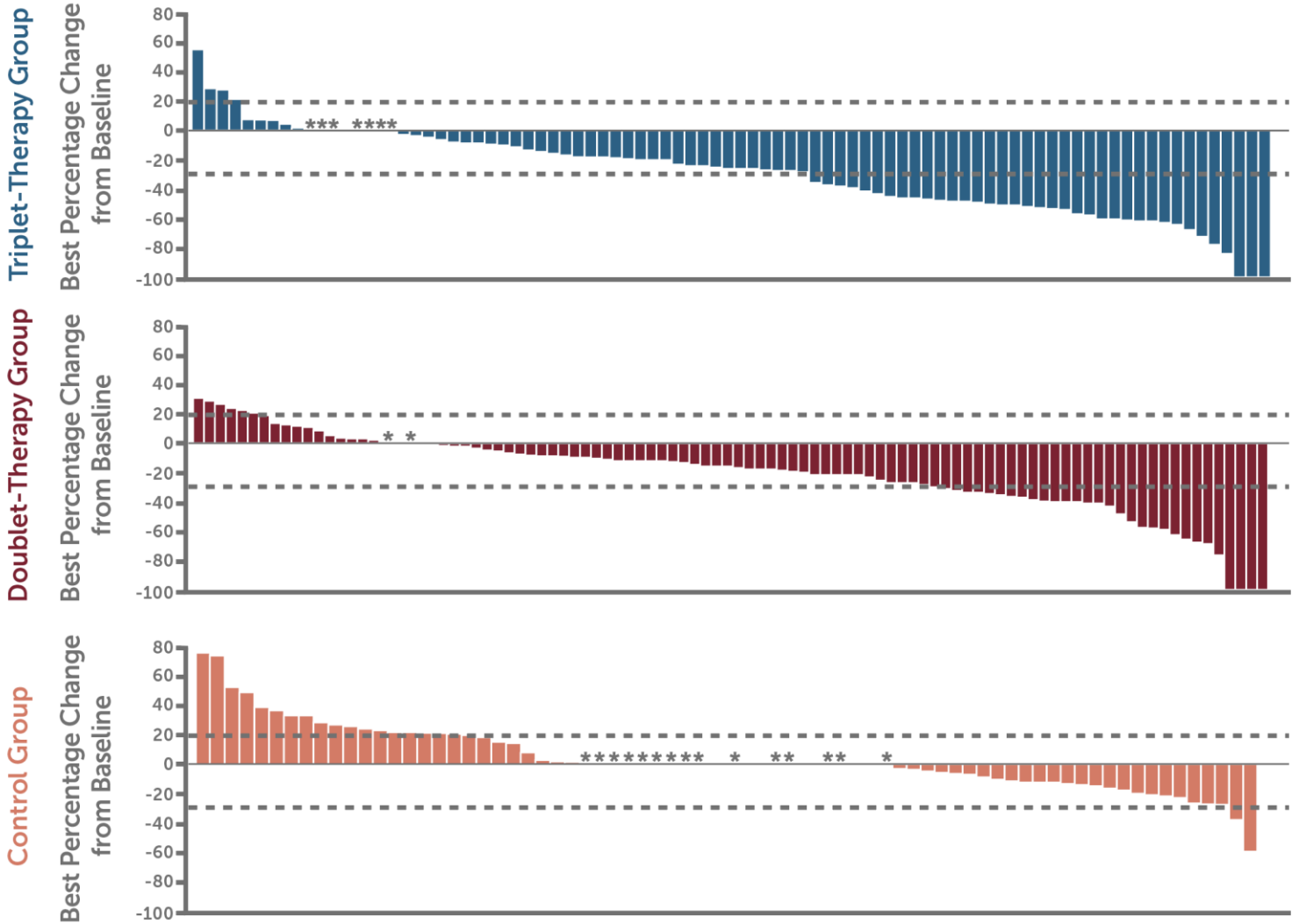
BEACON TRIAL

Table: Findings demonstrate that the triplet and doublet are equally effective with regard to median overall survival as well as hazard ratio for death.

Parameter	Prespecified Interim Analysis			Updated/Mature Analysis		
	Triplet	Doublet	Control	Triplet	Doublet	Control
Median Overall Survival (months)	9.0	8.4	5.4	9.3	9.3	5.9
Hazard Ratio (HR)	0.52	0.60	–	0.60	0.61	–
Objective Response Rate (%)	26	20	2.0	27	20	2.0

Kopetz S, et al. *N Engl J Med*. 2019;381(17):1632-1643. Kopetz S, et al. Presented at: 2020 ASCO Virtual Scientific Program; May 29-31, 2020. Abstract 4001

BEACON TRIAL: Best Percentage Change in Size of Target Lesions



Shown are the best percentage changes from baseline in the sum of the diameters of the target lesions in each patient in the three groups, as determined by central review. The dashed lines at 20% and −30% indicate progressive disease and partial response, respectively, according to Response Evaluation Criteria in Solid Tumors, version 1.1. The asterisks indicate patients who had a complete response, partial response, or stable disease with respect to target lesions but who had a new lesion, a progressing nontarget lesion, or both.

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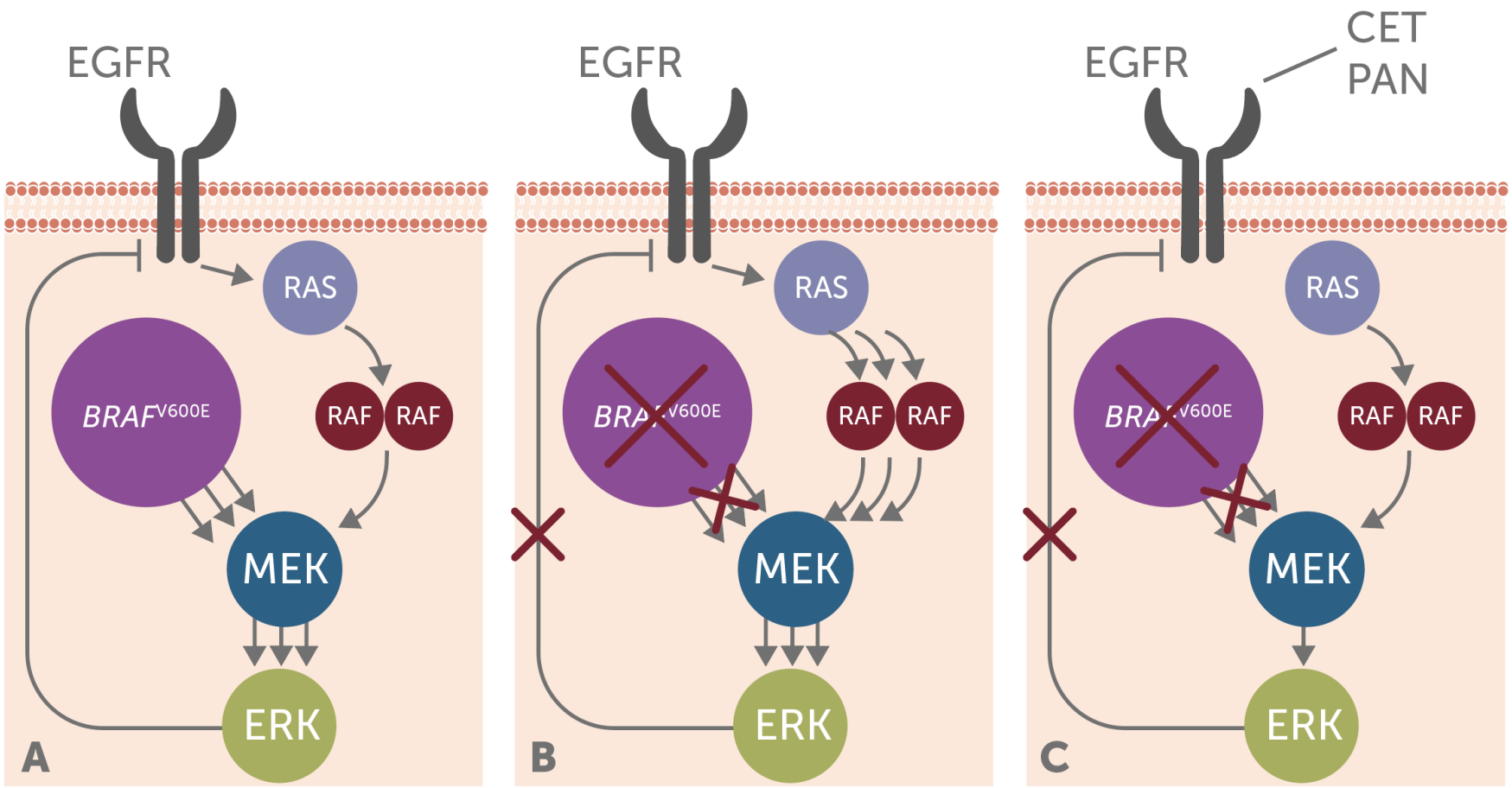
Kopetz S, et al. *N Engl J Med*. 2019;381(17):1632-1643.

Activation Pathways in BRAF V600E-Mutated Colorectal Cancer



A, Under normal circumstances in colorectal cancer with $BRAF^{V600E}$ mutation, activated monomer $BRAF^{V600E}$ activates MEK and ERK, downstream signals in the MAPK pathway, which leads to cell growth. Activated ERK suppresses the upstream activation of the MAPK pathway through negative feedback on a receptor tyrosine kinase such as EGFR.

B, Monotherapy with BRAF inhibitors blocks the monomeric activity of $BRAF^{V600E}$, which relieves the negative feedback suppression of EGFR and results in paradoxical activation of the MAPK pathway through RAS and RAF dimers.

C, Combination of BRAF inhibitors with an anti-EGFR such as cetuximab (CET) or panitumumab (PAN) can abrogate a negative feedback loop activation of the MAPK pathway. In addition, inhibition of MEK or ERK can further reduce MAPK signaling and limit adaptive therapeutic resistance.

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Janku F. *Cancer Discov.* 2018;8(4):389-391.