BEACON CRC Study Safety Lead-in: Assessment of the BRAF Inhibitor Encorafenib + MEK Inhibitor Binimetinib + Anti–Epidermal Growth Factor Receptor Antibody Cetuximab for *BRAF*^{V600E} Metastatic Colorectal Cancer

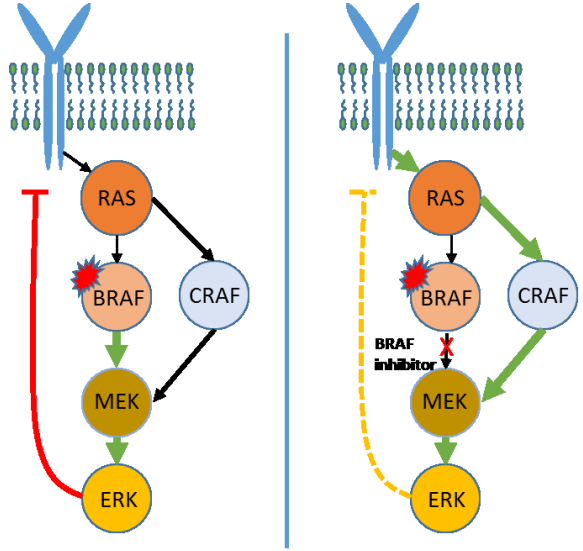
Eric Van Cutsem
University Hospitals Leuven, Belgium

Pieter-Jan Cuyle, Sanne Huijberts, Jan H.M. Schellens, Elena Elez, Rona Yaeger, Marwan Fakih, Clara Montagut, Marc Peeters, Jayesh Desai, Takayuki Yoshino, Fortunato Ciardiello, Harpreet Wasan, Kati Maharry, Janna Christy-Bittel, Ashwin Gollerkeri, Scott Kopetz, Axel Grothey, Josep Tabernero

BRAF^{V600E} mutation in mCRC

- Occurs in 10%–15% of patients and confers a poor prognosis[1,2]
- Standard therapies have limited benefits after ≥1 line of treatment:
  - Median OS 4–6 mo, median PFS ~2 mo and ORR <10%[1,3-5]
  - SWOG S1406 results with vemurafenib, irinotecan, cetuximab (VIC): Median OS of 9.6 mo, median PFS of 4.3 mo, and ORR in 16% (confirmed + unconfirmed)[6]
- BRAF inhibitors cause feedback activation of EGFR in *BRAF*-mutant CRC, leading to continued cell proliferation[7,8]
  - Feedback may be overcome by targeting multiple nodes in the pathway
- Updated mature phase 2 results with doublet of ENCO + CETUX*: Median OS of 9.3 mo, median PFS of 4.2 mo and ORR in 24%[9]

MAPK Signaling in Colorectal Cancer[10]



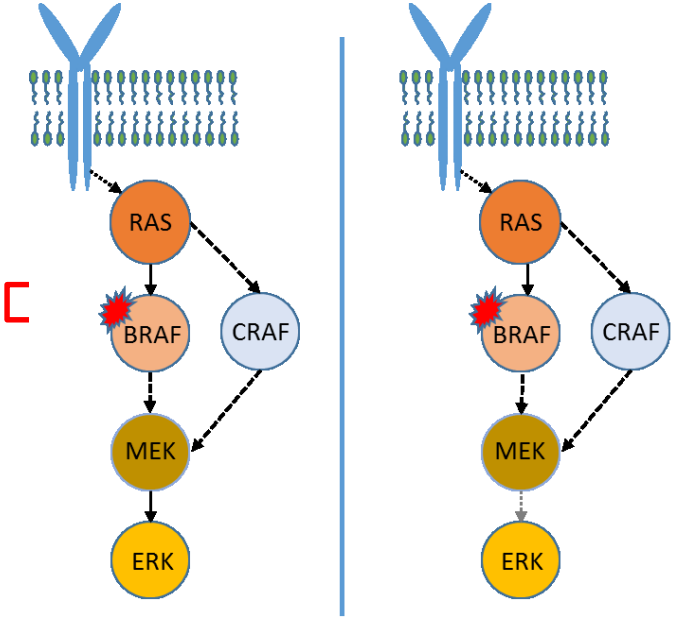
* Data cut-off January 2018; last patient enrolled 14 April 2015. Full updated data to be presented at future meeting.

1. Loupakis F, et al. *Br J Cancer*. 2009;101:715. 2. Tie J, et al. *Int J Cancer*. 2011;128:2075. 3. De Roock W, et al. *Lancet Oncol*. 2010;11(8):753. 4. Mitani S, et al. *Ann Oncol*. 2017;28(5s). 5. Ulivi P, et al. *J Transl Med*. 2012;10:87. 6. Kopetz S, et al. *J Clin Oncol*. 2017;35(15):3505. 7. Corcoran RB, et al. *Cancer Disc*. 2012;2(3):227. 8. Prahallad A, et al. *Nature* 2012;100:100. 9. Tabernero J, et al. *J Clin Oncol*. 2016;34:3544. 10. Adapted From: Strickler JH. *Cancer Treatment Reviews*. 2017; 60:109.

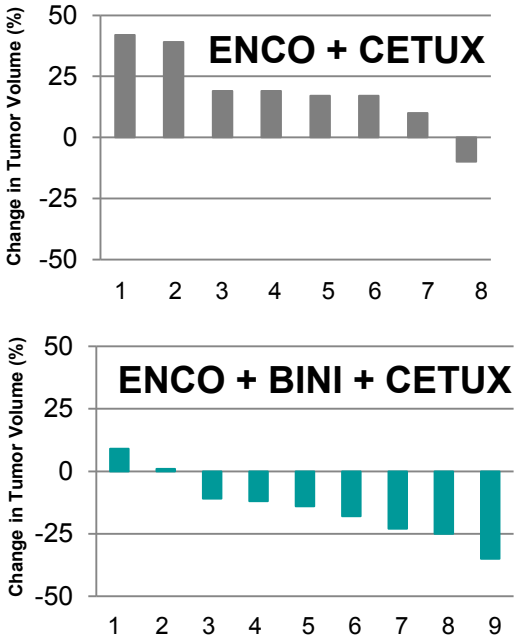
CETUX=cetuximab; EGFR=epidermal growth factor receptor; ENCO=encorafenib; MAPK=mitogen-activated protein kinase; mCRC=metastatic colorectal cancer; PFS=progression-free survival; ORR=objective response rate; OS=overall survival; VIC=vemurafenib + irinotecan + cetuximab.

Triple MAPK Pathway Inhibition in *BRAF*-mutant CRC

MAPK Signaling in Colorectal Cancer[1]



HT-29 *BRAF*^{V600E} colorectal xenografts[2]



Each bar represents change in tumor volume in one animal at day 21.
The control group showed increases in tumor size for all animals, with mean increase in tumor volume versus baseline of 285%.

1.Adapted From: Strickler JH. *Cancer Treatment Reviews*. 2017; 60:109-119

2. Data on File. Array BioPharma Inc.

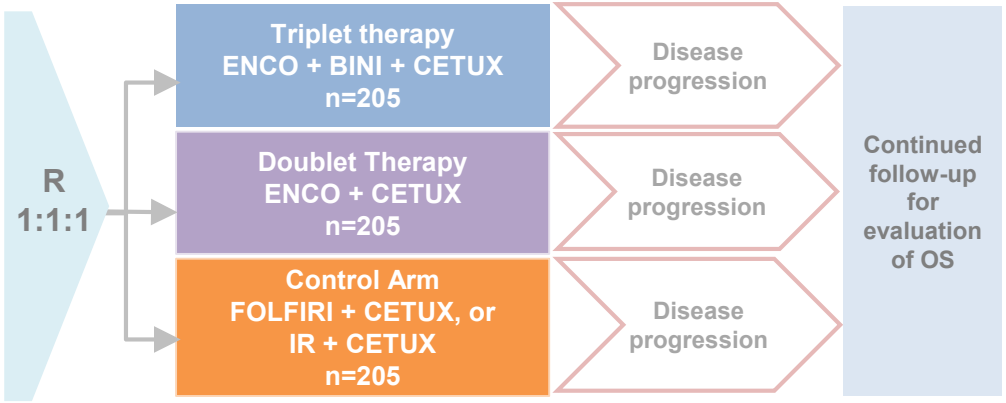
BEACON CRC Phase 3 Study Design[1]

Safety Lead-in Completed

ENCO 300 mg QD
+
BINI 45 mg BID
+
CETUX 400 mg/m^2 (initial) then
250 mg/m^2 QW

N=30

Phase 3 Currently Enrolling



1. Clinicaltrials.gov/ct2/show/NCT02928224; https://clinicaltrials.gov/ct2/show/NCT02928224 (February 2018).

FOLFIRI=folinic acid, fluorouracil, and irinotecan hydrochloride; IR=irinotecan

Safety Lead-in to the BEACON CRC Phase 3 Trial

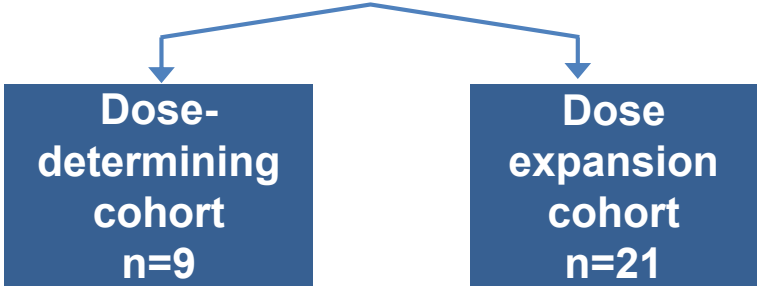
ELIGIBLE PATIENTS

- *BRAF*^{V600E}mutant mCRC
- Progressed after 1 or 2 previous regimens
- ECOG PS of 0 or 1
- No prior treatment with any RAFi, MEKi, or EGFRi
- Prior treatment with irinotecan allowed
- Eligible to receive CETUX per local label

SAFETY LEAD-IN

ENCO + BINI + CETUX

N=30



ECOG PS=Eastern Cooperative Oncology Group performance status; EGFRi=epidermal growth factor receptor inhibitor; MEKi=MEK inhibitor; RAFi=RAF inhibitor.

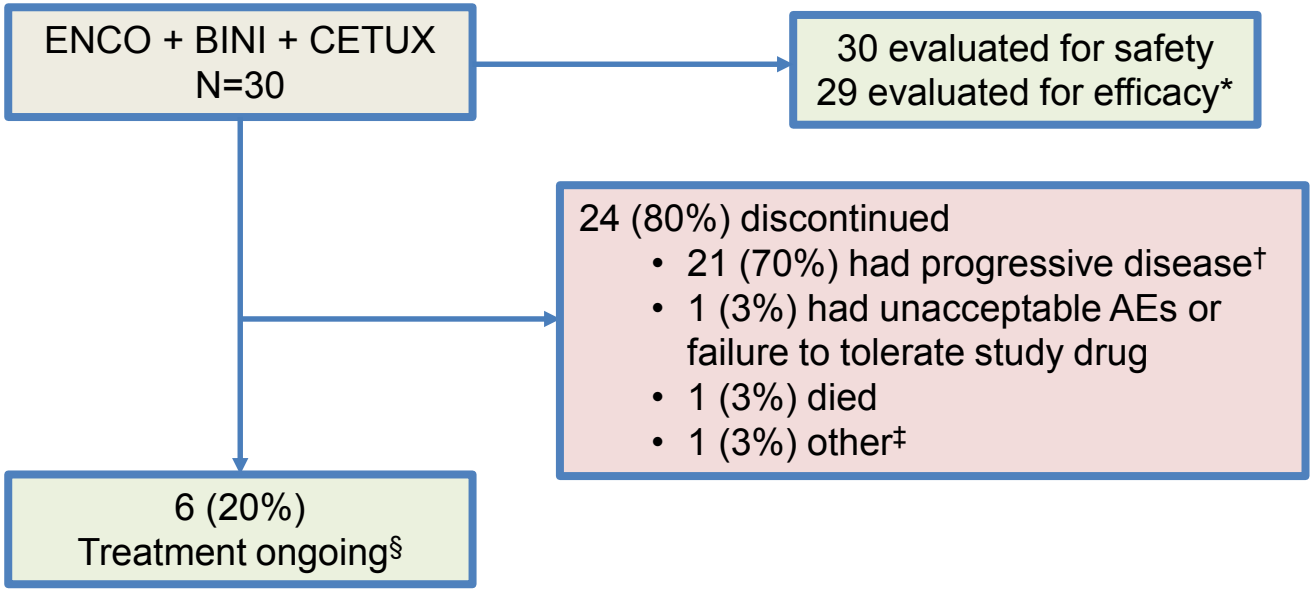
Baseline Patient and Disease Characteristics

CHARACTERISTIC	PATIENTS (N=30)
BRAF^{V600E} mutation*	29 (97%)
Male	13 (43%)
Age, median (range), year	59 (38–77)
ECOG PS 0	17 (57%)
Location of primary tumor	
Right side	18 (60%)
Left side	9 (30%)
No. of organs with metastases, >1	22 (73%)
Metastatic site locations	
Liver	20 (67%)
Lymph nodes	15 (50%)
Peritoneum	11 (37%)
Lung	9 (30%)
Colon/rectum	8 (27%)
Other	15 (50%)
No. of prior systemic therapies†	
1	17 (57%)
2	13 (43%)
Received prior irinotecan	13 (43%)
MSI-H‡	1 (3%)

*1 patient treated with a non-V600E *BRAF* mutation. †Includes prior systemic therapies in the metastatic setting only. ‡Based on immunohistochemical assessment of MLH1 and MSH6 proteins successfully analyzed in 23 patients.

MSI-H=microsatellite instability high.

Patient Disposition



*One treated patient had a non-V600 *BRAF* mutation (*BRAF*^{G466V}).
†Includes 2 patients with changes in condition or development of an intercurrent illness.
‡Dose interruption >28 consecutive days.
§As of the data cutoff date of 3 May 2018.

Confirmed Best Overall Response

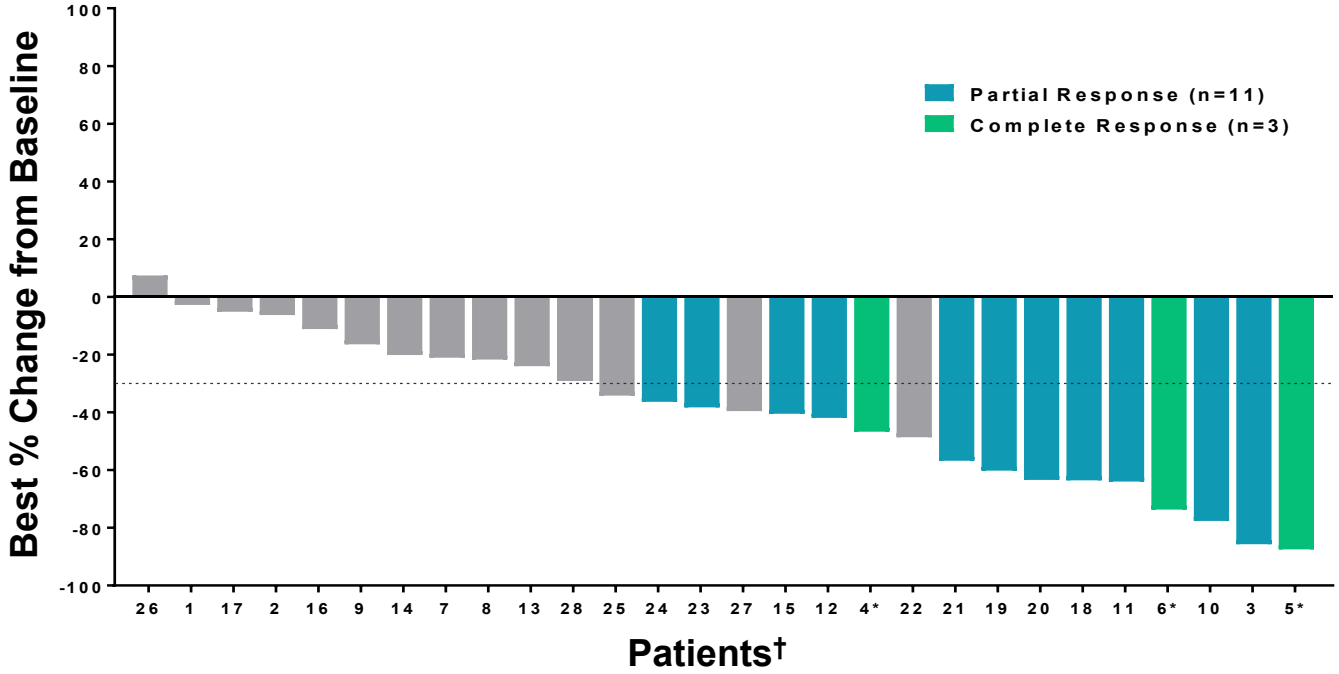
CONFIRMED BEST OVERALL RESPONSE*	PATIENTS (N=29)†
ORR (CR + PR)	**14 (48%)** **(95% CI 29%–67%)**
CR	3 (10%)
PR	11 (38%)
SD	13 (45%)
PD	0
Not evaluable for response‡	2 (7%)

- **ORR for patients with 1 and 2 prior regimens were 62% and 31% respectively**
- **43% of responders have response ≥6 months**
- **Median DOR: 5.5 mo (95% CI, 4.1–NR)**

*Local assessed confirmed responses per RECIST 1.1
†Patients with *BRAF*^{V600E} mutations.
‡Non-responders per intent-to-treat analysis.

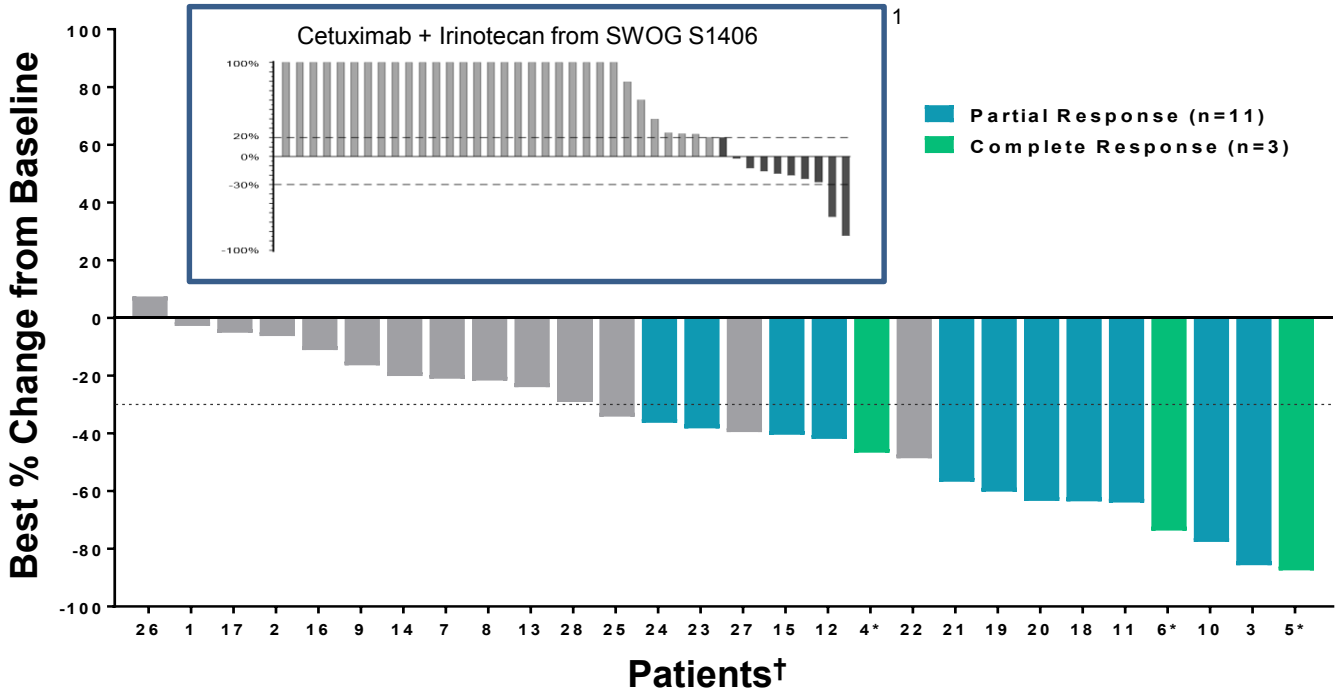
CR=complete response; DOR=duration of response; NR=not reached; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease.

Best Percentage Change in Tumor Measurements from Baseline



*Patients with lymph node disease with decreases in short axis dimensions consistent with RECIST 1.1 defined Complete Response.
†One patient had no baseline sum of longest diameters and is not presented.

Best Percentage Change in Tumor Measurements from Baseline



*Patients with lymph node disease with decreases in short axis dimensions consistent with RECIST 1.1 defined Complete Response.
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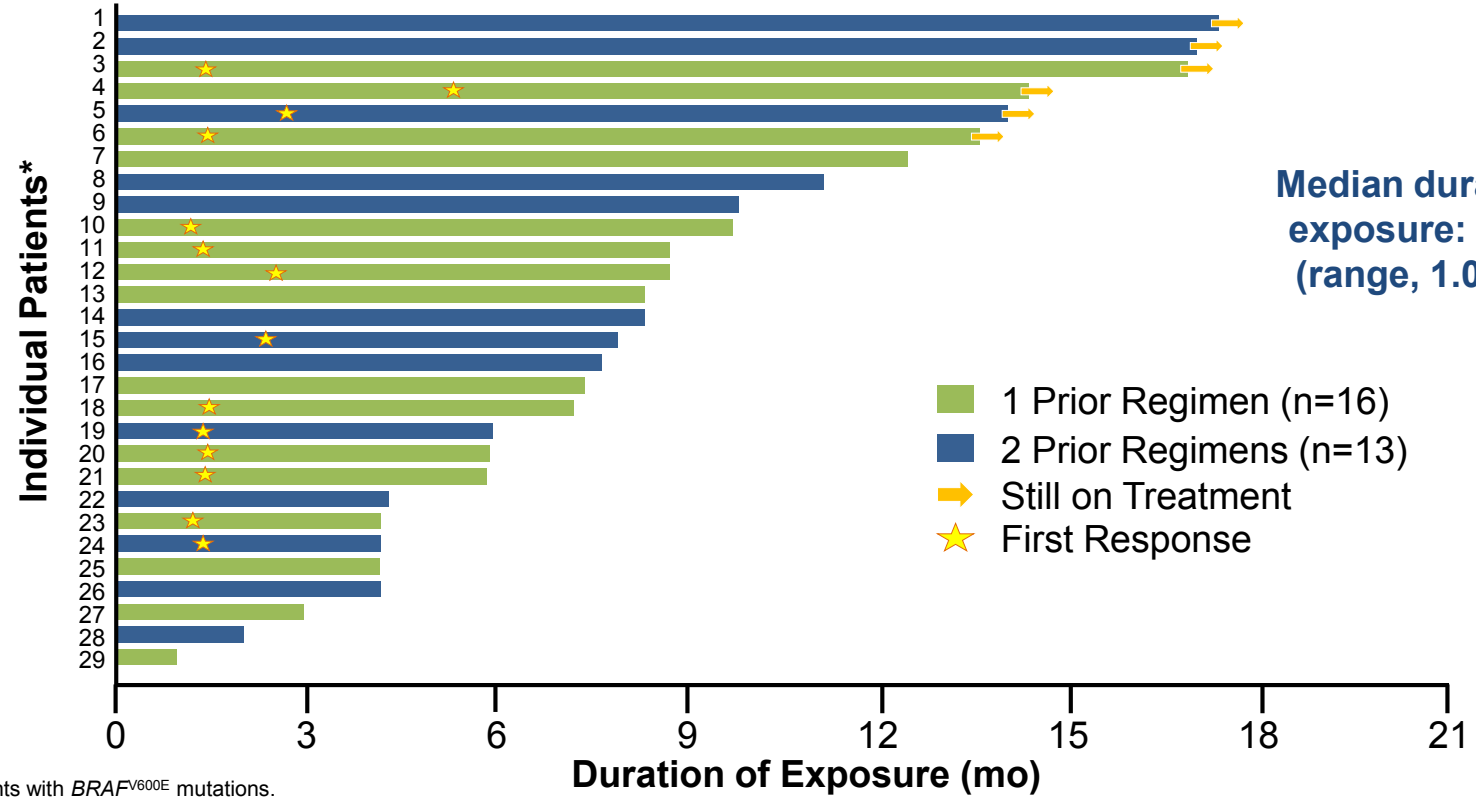
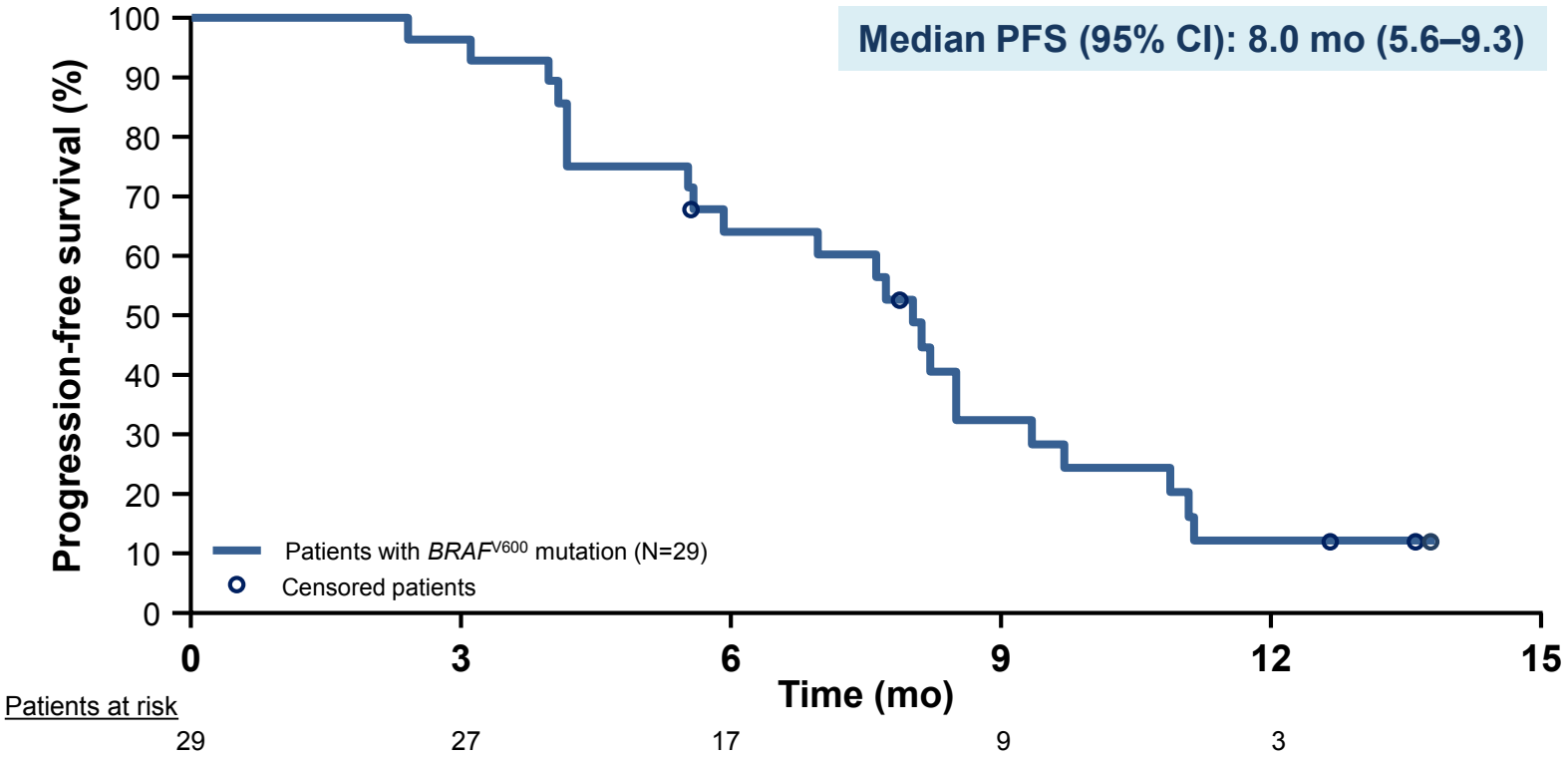
1. Kopetz S, et al. *J Clin Oncol*. 2017;35:Abstr 3505, with permission.

Duration of Exposure by Number of Prior Regimens

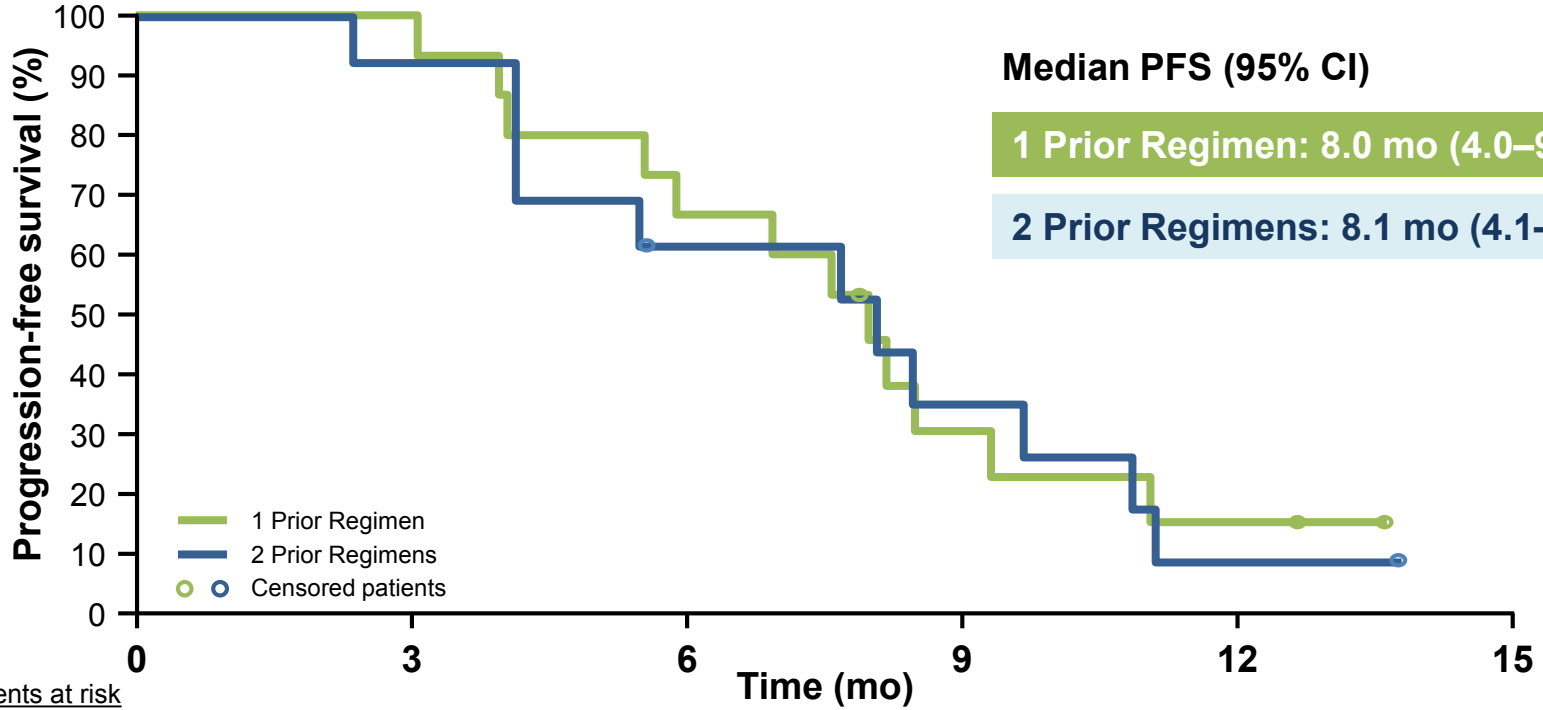


*Patients with *BRAF*^{V600E} mutations.

Progression-Free Survival



Progression-Free Survival by Number of Prior Regimens



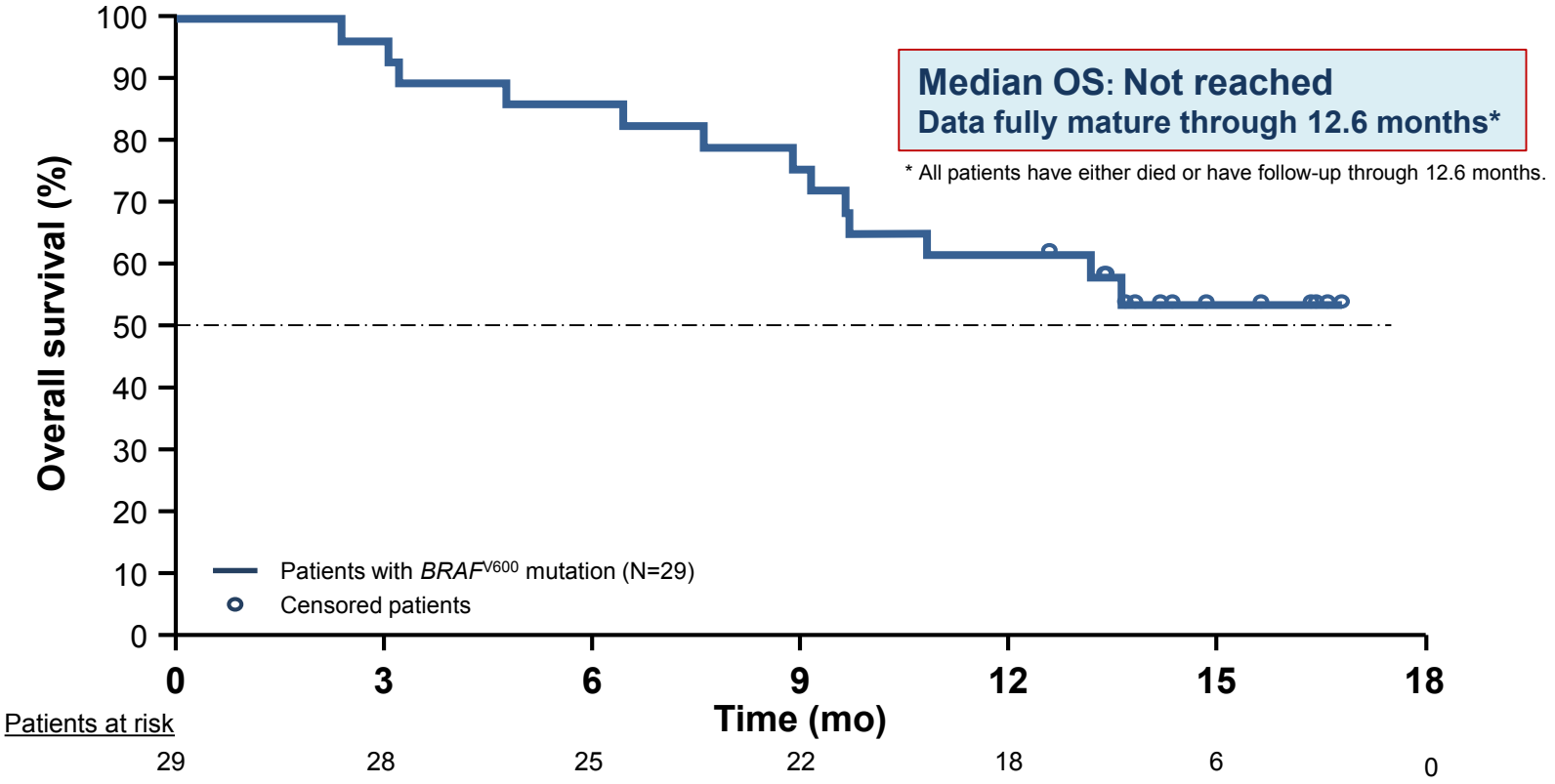
Median PFS (95% CI)

1 Prior Regimen: 8.0 mo (4.0–9.3)

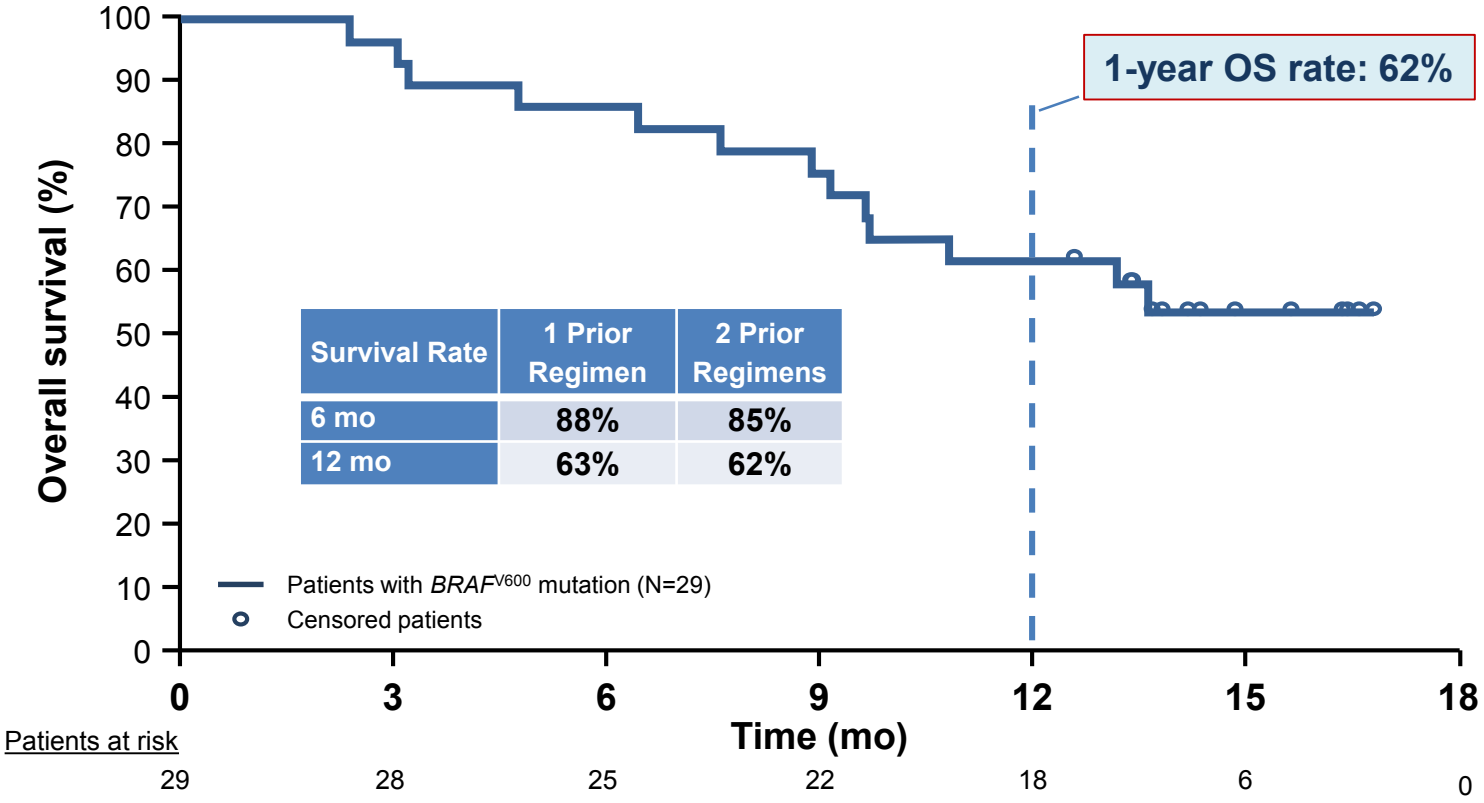
2 Prior Regimens: 8.1 mo (4.1–10.8)

Patients at risk					
1 Prior regimen	16	15	10	4	2
2 Prior regimens	13	12	7	4	1

Overall Survival



Overall Survival



Overall Summary of Safety

	PATIENTS (N=30)
AEs	30 (100%)
Grade 3/4 AEs	21 (70%)
AEs leading to discontinuation*†	6 (20%)
AEs leading to dose interruption/change†	5 (17%)
On-treatment deaths‡	5 (17%)

*Includes increased blood bilirubin (1 patient), drug hypersensitivity (1 patient), dyspnea (1 patient), fatigue (1 patient), hypersensitivity (1 patient), malaise (1 patient), retinal detachment (1 patient).
†Discontinuation or dose interruption/change of at least one study drug
‡Includes on-treatment deaths and deaths within 30 days of stopping study treatment. On-treatment deaths were due to disease progression.

Adverse Events* Regardless of Causality (N=30)

EVENT	ANY GRADE	GRADE 3/4
Diarrhea	23 (77%)	1 (3%)
Dermatitis acneiform	19 (63%)	0
Fatigue	19 (63%)	4 (13%)
Nausea	19 (63%)	2 (7%)
Vomiting	15 (50%)	2 (7%)
Dry skin	14 (47%)	0
Anemia	12 (40%)	3 (10%)
Decreased appetite	12 (40%)	2 (7%)
Abdominal pain	11 (37%)	1 (3%)
Increased CK	11 (37%)	3 (10%)
Dyspnea	10 (33%)	2 (7%)
Pyrexia	10 (33%)	0
Constipation	9 (30%)	0
Arthralgia	8 (27%)	0
Creatinine increased	8 (27%)	0
Skin fissures	8 (27%)	0
Vision blurred	8 (27%)	0
Increased AST	6 (20%)	3 (10%)
Asthenia	6 (20%)	0
Myalgia	6 (20%)	0
PPED syndrome	6 (20%)	0
Rash maculopapular	6 (20%)	0

*AEs occurring in ≥20% of patients
Aspartate aminotransferase=AST; CK=creatine phosphokinase. PPED=palmar-plantar erythrodysesthesia

Conclusions

- All efficacy outcomes (ORR, PFS and OS) for the ENCO + BINI + CETUX triplet showed substantial improvements over historical data and over updated results for the doublet of ENCO + CETUX in patients with *BRAF*^{V600E} mCRC[1-5]
  - OS data are fully mature through 12.6 mo and median OS was not reached
    - Observed 1-year OS rate was 62%
  - Median PFS was 8.0 mo and ORR was 48%; 43% of responses lasted ≥6 mo
- The triplet was well tolerated with no unexpected toxicities
- The phase 3 portion of the BEACON CRC trial has been initiated and enrollment is ongoing

In BEACON CRC SLI, ENCO + BINI + CETUX triplet combination showed promising safety and efficacy data in patients with *BRAF*^{V600E} mCRC

1. Loupakis F, et al. *Br J Cancer*. 2009;101(4):715.
2. De Roock W, et al. *Lancet Oncol*. 2010;11(8):753.
3. Kopetz S, et al. *J Clin Oncol*. 2017;35(15):Abstract 3505.
4. Mitani S, et al. *Ann Oncol*. 2017;28(5s).
5. Ulivi P, et al. *J Transl Med*. 2012;10:87.