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INTRODUCTION

- Patients with relapsed BRAFM colorectal cancer (CRC) have a poor prognosis vs those with wild-type BRAF CRC.
 - Treatment nonresponse¹⁻³
 - Shorter progression-free survival (PFS; ~2 vs ~6 months)²
 - Reduced overall survival (OS; ~5 vs ~17 months)²
- Unlike in melanoma, BRAF inhibitor monotherapy has shown limited efficacy in BRAFM CRC.^{4,5}
 - Attributed to reactivation of epidermal growth factor receptor (EGFR) signaling with BRAF inhibition and uninhibited phosphatidylinositol 3-kinase (PI3K) signaling⁶⁻⁸
- Preclinical study results show synergistic antitumor activity with combination of:⁶⁻⁹
 - BRAF and EGFR inhibitors
 - BRAF, EGFR, and PI3K inhibitors

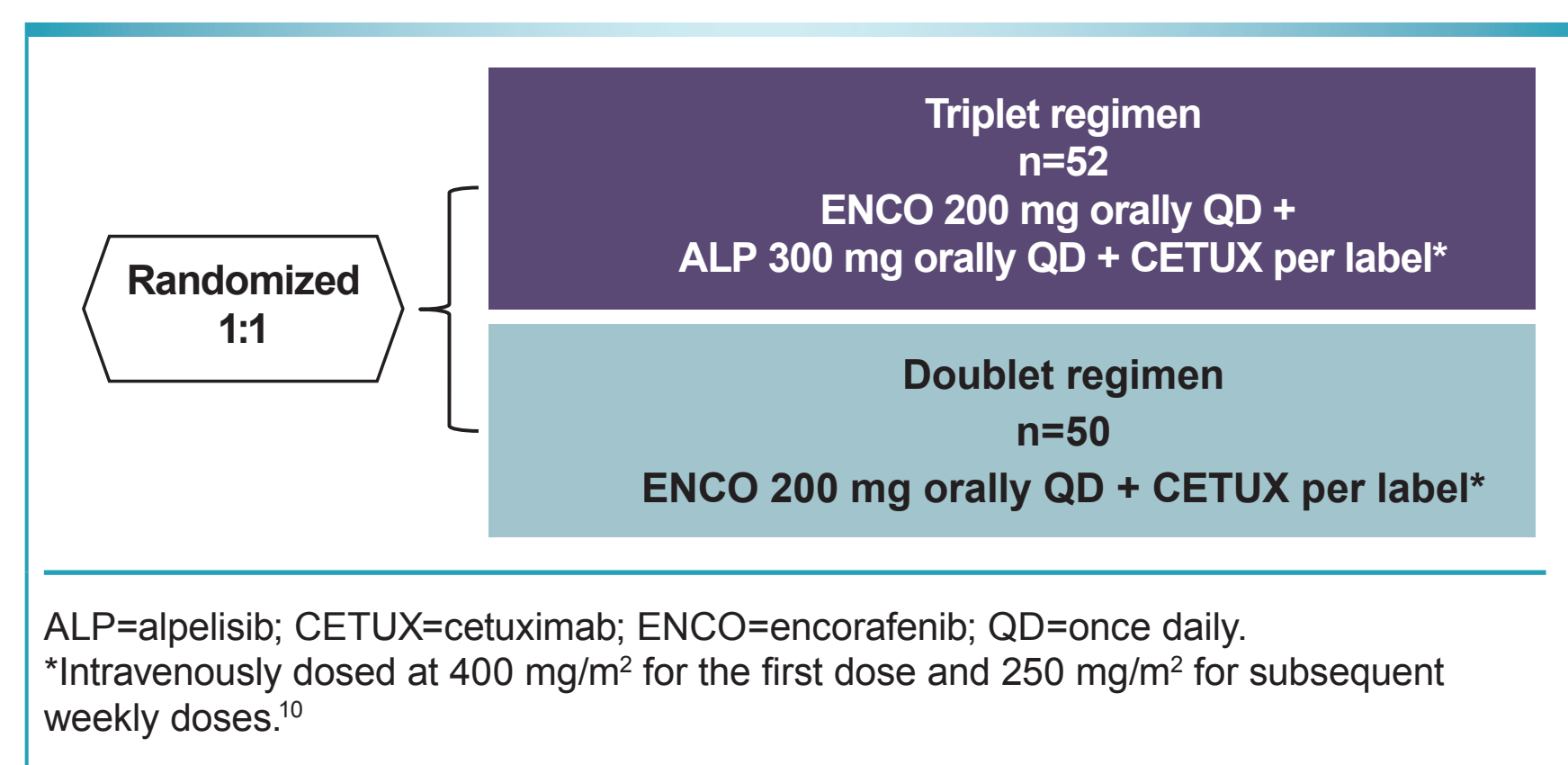
OBJECTIVE

- To describe efficacy and safety from the randomized phase 2 portion of an ongoing phase 1b/2 study evaluating the combination of the BRAF inhibitor encorafenib, the PI3K- α inhibitor alpelisib, and the EGFR antibody cetuximab (triplet regimen) and a combination of encorafenib and cetuximab (doublet regimen) in patients with advanced BRAFM CRC (ClinicalTrials.gov: NCT01719380)

METHODS

- The phase 1b portion of the study established the recommended phase 2 doses for encorafenib and alpelisib in the combination regimens.
- The phase 2 portion of the study included 102 patients with BRAFM CRC failing ≥ 1 prior therapy.
- Evaluated efficacy and safety of the triplet vs doublet regimen (Figure 1)
 - Primary endpoint: PFS
 - Secondary endpoints: confirmed overall response rate (ORR), OS, and safety and tolerability

Figure 1. Phase 2 Study Design



RESULTS

Patients

- A total of 102 patients were randomized (triplet regimen, n=52; doublet regimen, n=50; Table 1).

Table 1. Demographic and Clinical Characteristics at Baseline

Characteristic	ENCO + ALP + CETUX n=52	ENCO + CETUX n=50
Female sex, n (%)	27 (52)	36 (72)
Age, median (range), y	60 (29–76)	60 (20–79)
Colon as the primary site of cancer, n (%)	44 (85)	46 (92)
ECOG performance status, n (%)		
0	20 (38)	21 (42)
1	29 (56)	28 (56)
2	3 (6)	1 (2)
LDH >ULN,* n (%)	15 (29)	15 (30)
Prior treatment regimen		
Median number (range)	2 (1–4)	2 (1–6)
Prior regimens, n (%)		
1	23 (44)	21 (42)
2	18 (35)	20 (40)
≥ 3	11 (21)	9 (18)

ALP=alpelisib; CETUX=cetuximab; ECOG=Eastern Cooperative Oncology Group; ENCO=encorafenib; LDH=lactate dehydrogenase; ULN=upper limit of normal. *LDH information missing in 23% of patients in the triplet and 18% of patients in the doublet regimen groups.

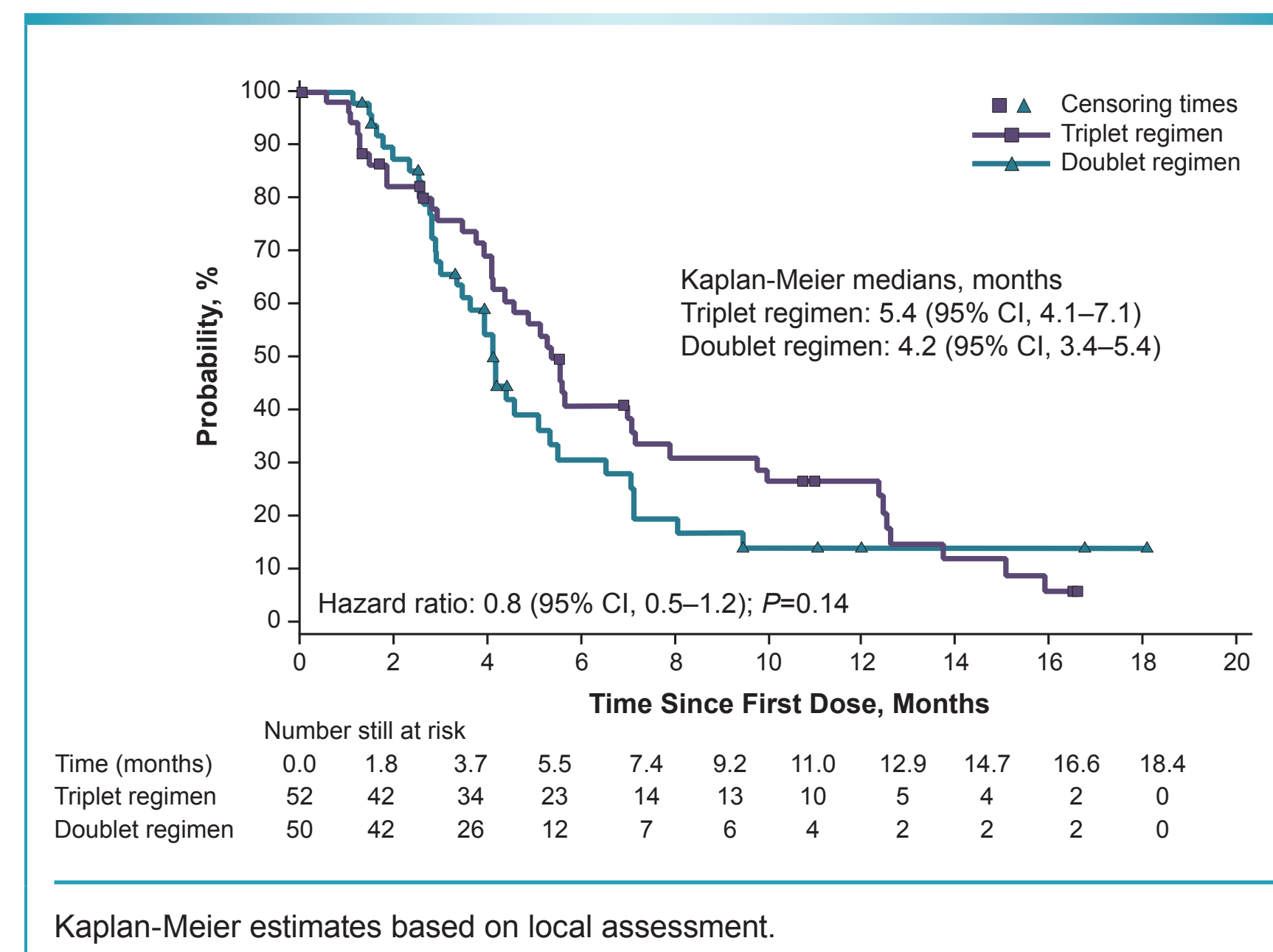
- As of February 15, 2016, treatment was ongoing in 5 patients (10%) in the triplet regimen arm and 4 patients (8%) in the doublet regimen arm.

RESULTS (CONTINUED)

Efficacy

- A PFS analysis comparing the triplet with the doublet regimen was performed after 77 events (Figure 2).

Figure 2. Progression-Free Survival



- Confirmed response rates are provided in Table 2.

Table 2. Confirmed Response Rates as per Local Assessment

Confirmed Response	ENCO + ALP + CETUX n=52	ENCO + CETUX n=50
Best overall response, n (%)		
Complete response	0	0
Partial response	14 (27)	11 (22)
Stable disease	30 (58)	31 (62)
Progressive disease	5 (10)	4 (8)
Unknown	3 (6)	4 (8)
Overall response rate,* % (95% CI)	27 (16–41)	22 (12–36)
Disease control rate, [†] % (95% CI)	85 (72–93)	84 (71–93)
Median (95% CI) duration of response, mo	9.9 (2.8–11.0)	4.6 (2.0–6.7)

ALP=alpelisib; CETUX=cetuximab; ENCO=encorafenib. *Complete response + partial response. [†]Complete response + partial response + stable disease.

- Interim OS analysis was determined with 44 events (Figure 3).
 - Median OS was improved with the triplet and doublet regimens relative to historical controls in patients with BRAFM CRC (Figure 4).

Figure 3. Overall Survival

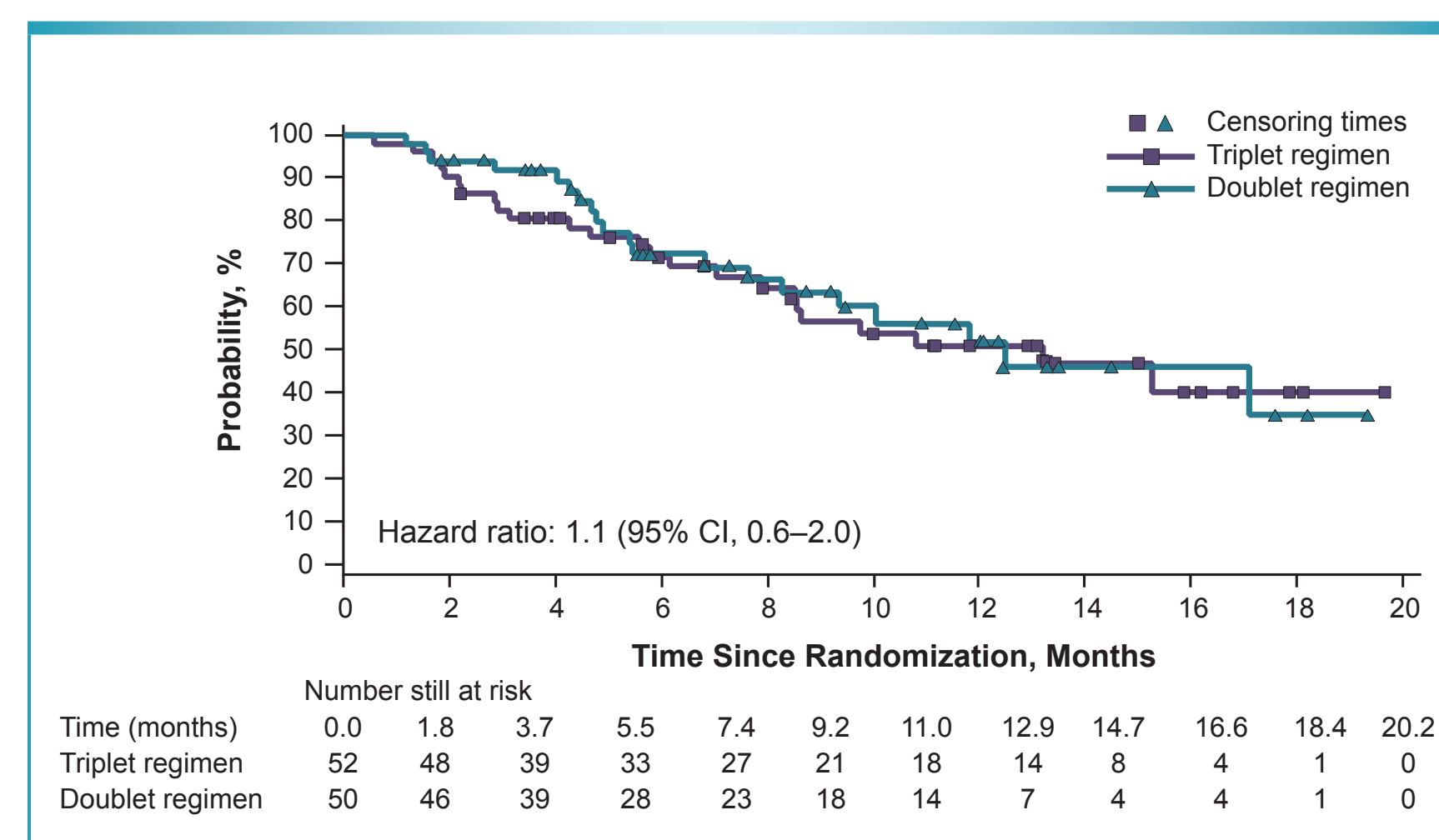
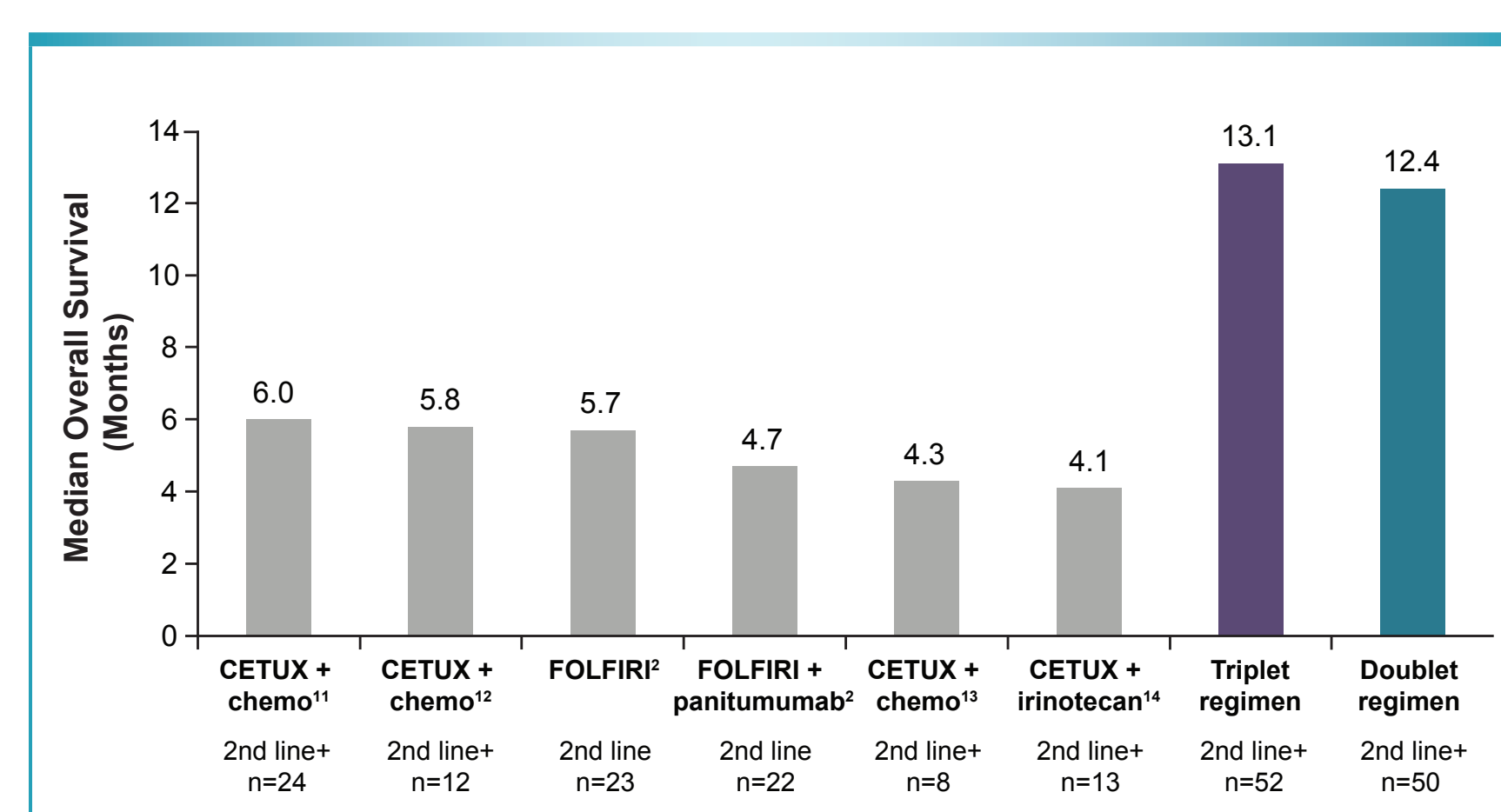


Figure 4. Median Overall Survival in BRAFM CRC With the Triplet and Doublet Regimens Compared With Historical Controls*



Safety

- The most frequent all-cause AEs and grade 3/4 AEs are listed in Table 3.

Table 3. All-Cause AEs, Any Grade* and Grade 3/4[†]

AE, n (%)	ENCO + ALP + CETUX n=52		ENCO + CETUX n=50	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Total	51 (98)	41 (79)	50 (100)	31 (62)
Nausea	29 (56)	3 (6)	23 (46)	0
Diarrhea	28 (54)	4 (8)	14 (28)	2 (4)
Vomiting	27 (52)	1 (2)	16 (32)	0
Fatigue	24 (46)	4 (8)	25 (50)	2 (4)
Abdominal pain	21 (40)	5 (10)	21 (42)	4 (8)
Decreased appetite	19 (37)	3 (6)	17 (34)	1 (2)
Decreased weight	19 (37)	3 (6)	8 (16)	0
Hyperglycemia	19 (37)	7 (13)	5 (10)	1 (2)
Rash	17 (33)	0	7 (14)	0
Stomatitis	16 (31)	2 (4)	5 (10)	0
Dry skin	15 (29)	0	9 (18)	0
Arthralgia	14 (27)	1 (2)	17 (34)	0
Headache	13 (25)	0	16 (32)	0
Pyrexia	12 (23)	0	13 (26)	0
Dermatitis acneiform	12 (23)	0	9 (18)	0
Anemia	12 (23)	9 (17)	8 (16)	3 (6)
Hypomagnesemia	11 (21)	1 (2)	4 (8)	0
Myalgia	11 (21)	0	8 (16)	1 (2)
Back pain	9 (17)	1 (2)	12 (24)	1 (2)
Asthenia	8 (15)	3 (6)	0	0
Increased lipase	7 (13)	4 (8)	15 (30)	11 (22)
Hypophosphatemia	7 (13)	4 (8)	3 (6)	1 (2)
Constipation	6 (12)	0	13 (26)	2 (4)
Malignant melanoma	3 (6)	3 (6)	0	0

AE=adverse event; ALP=alpelisib; CETUX=cetuximab; ENCO=encorafenib.

*Occurring in >20% of patients in either treatment group.

[†]Occurring in >5% of patients in either treatment group.

CONCLUSIONS

- Encorafenib and cetuximab combinations \pm alpelisib show promising clinical activity in patients with advanced BRAFM CRC.
 - PFS and OS with the triplet and doublet regimens were improved compared with historical data.^{2,11-15}
 - Compared with the encorafenib + cetuximab regimen, addition of alpelisib may increase PFS benefit for patients with advanced BRAFM CRC.
- Both regimens were generally well tolerated.
 - Additional toxicities were seen with the triplet regimen.
 - Grade 3/4 dermatologic AEs were infrequent in either treatment arm.
 - Cetuximab monotherapy studies have reported 12%–18% grade 3/4 skin-related AEs.^{16,17}
- Results of pharmacokinetic, pharmacodynamic, and biomarker analyses (not yet available) may be informative for interpretation of efficacy and safety data.

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 EA is employed by and owns stock in Novartis Pharmaceuticals.
 TD has been employed by Novartis AG and Sandoz AG and owns stock in Novartis AG.
 VS is employed by and has a leadership role at Array BioPharma, and owns stock in Array BioPharma and Inocyte Corp. VS was previously employed by and had a leadership role at Inocyte Corp.
 EE has received consulting fees from Array BioPharma. RRMJMvG, TKG, AS, YY, JCB, H-JL, and JHMS have nothing to disclose.

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