Phase 1b/2 Study of the Selective BRAF V600 Inhibitor Encorafenib (LGX818) Combined With Cetuximab With or Without the α-Specific PI3K Inhibitor Alpelisib (BYL719) in Patients With Advanced *BRAF*-Mutant Colorectal Cancer

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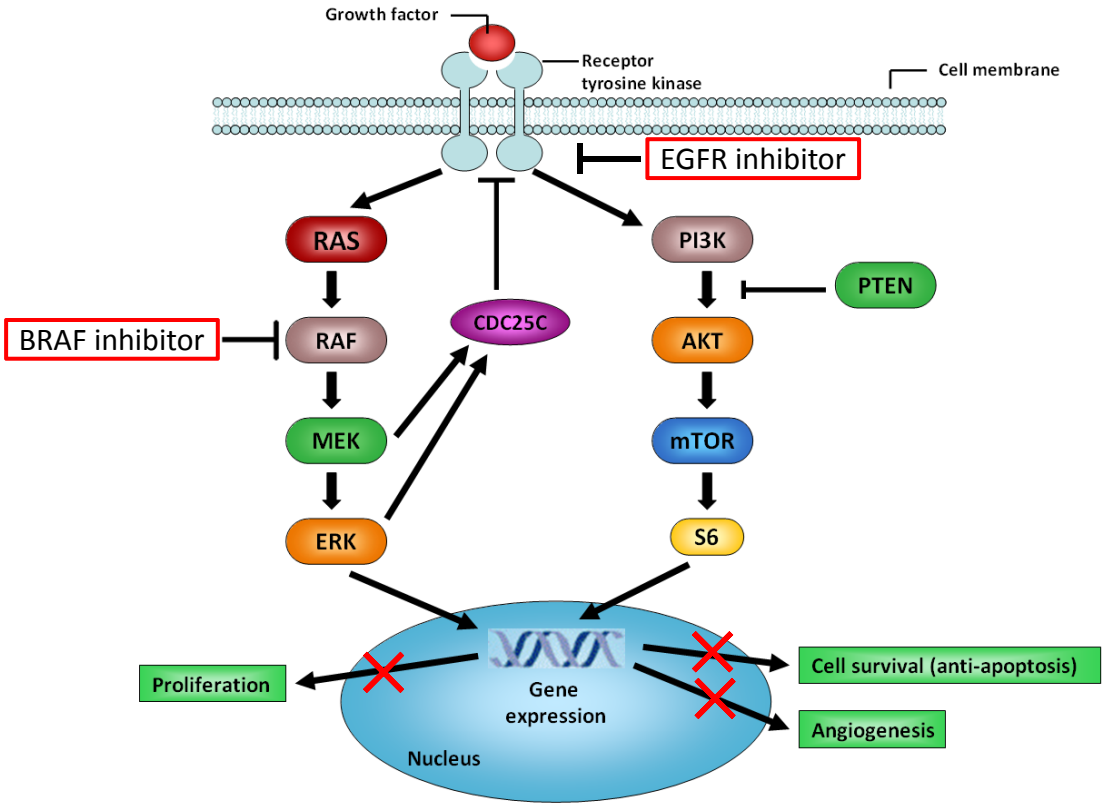
Disclosures

- I have nothing to disclose

Introduction

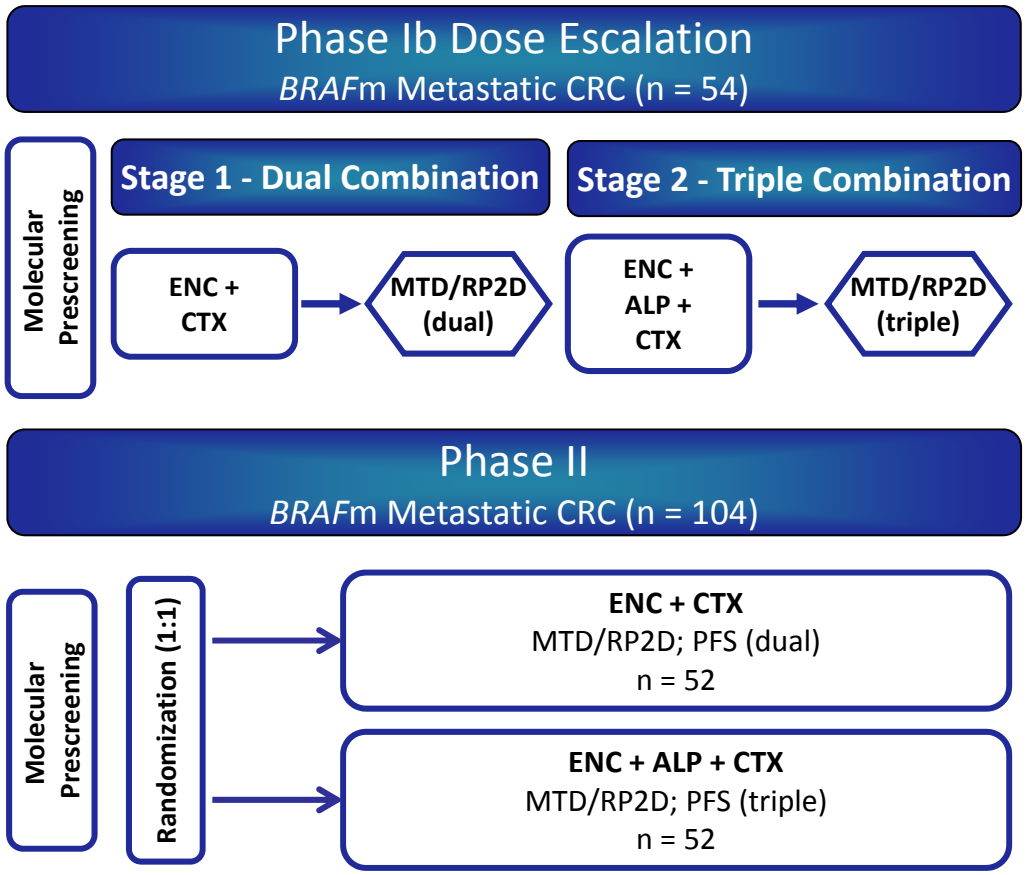
- *BRAF* V600E–mutant colorectal cancers (CRCs) have poorer clinical outcomes compared with wild-type tumors[1]
- Unlike in melanoma, BRAF inhibition alone shows limited activity in CRC[2-4]
- *BRAF*m CRC has shown synergistic response to EGFR and BRAF inhibition in vitro and in vivo[5, 6]



*BRAF*m, *BRAF* mutant.

1. Popovici V, et al. *J Clin Oncol.* 2012;30:1288-1295; 2. Flaherty KT, et al. *N Engl J Med.* 2010;363:809-819; 3. Chapman PB, et al. *N Engl J Med.* 2011;364:2507-2516; 4. Kopetz S, et al. ASCO 2010 [abstract 3534]; 5. Prahallad A, et al. *Nature.* 2012;483;100-103; 6. Corcoran RB, et al. *Cancer Discov*. 2012:227-235.

Study Design and Objectives



Objectives

Primary

- Phase Ib: determine the MTD/RP2D
- Phase II: compare the efficacy of the dual and triple combinations (PFS)

Secondary

- Characterize safety and tolerability
- Assess antitumor activity
- Determine the pharmacokinetic profile of ENC with or without ALP + CTX
- Phase II: assess gene alteration/expression of RAF and EGFR pathways

Exploratory

- Explore genetic determinants of response
- Explore potential mechanisms of resistance

ALP, alpelisib; CTX, cetuximab; ENC, encorafenib; MTD, maximum tolerated dose; PFS, progression-free survival; RP2D, recommended Phase II dose.

Key Eligibility Criteria

- *KRAS* wild type, *BRAF*m metastatic CRC[a]
- ECOG PS 0-2
- Disease progression after ≥ 1 prior standard-of-care regimen or intolerance of irinotecan-based regimens
- Evidence of measurable disease, as determined by RECIST v1.1
- No symptomatic brain metastases
- Phase II: fresh tumor biopsy at baseline
- Phase II: no prior treatment with EGFR, RAF, PI3K or MEK inhibitors

ECOG, Eastern Cooperative Oncology Group; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors.

[a] The majority of patients had *BRAF* V600–mutant disease; however, 2 patients harbored non-V600 *BRAF* mutations.

Dose Escalation and DLTs

Dual Combination (ENC + CTX[a])		Triple Combination (ENC + ALP + CTX[a])	
Dose	**DLTs**	**Dose**	**DLTs**
ENC 100 mg QD (n = 2)	None	ENC 200 mg QD + ALP 100 mg QD (n = 3)	None
ENC 200 mg QD (n = 7)	Grade 3 arthralgia (n = 1)	ENC 200 mg QD + ALP 200 mg QD (n = 8)	None
ENC 400 mg QD (n = 9)	Grade 3 vomiting (n = 1)	ENC 300 mg QD + ALP 200 mg QD (n =7)	Grade 4 increased creatinine (n = 1)
ENC 450 mg QD (n = 8)	Grade 3 corrected QT interval prolongation (n = 1)	ENC 200 mg QD + ALP 300 mg QD (n =10)	Grade 3 bilateral interstitial pneumonitis (n = 1)

- MTD[b] was not reached for either treatment combination
- The established RP2Ds were:
  - Dual combination: 200 mg QD ENC + CTX QW
  - Triple combination: 200 mg QD ENC QD + 300 mg QD ALP + CTX QW

DLT, dose-limiting toxicity; QD, once daily; QW, once weekly.

[a] CTX fixed dose across all dose levels: loading dose 400 mg/m^2; weekly dose 250 mg/m^2.

[b] Defined as the highest dose at which probabilities of DLTs are not expected to exceed 35% in the first treatment cycle.

Phase Ib: Patient Demographics

	ENC + CTX (n = 26)	ENC + ALP + CTX (n = 28)
Sex, %		
Female	57.7	64.3
Male	42.3	35.7
Age, median (range), years	63 (43-80)	59 (40-76)
Primary site of cancer derived, %		
Colon	92.3	89.3
Rectum	7.7	10.7
ECOG PS, %		
0	**30.8**	**64.3**
1	**61.5**	**35.7**
2	**7.7**	**0**
Visceral involvement at baseline, %		
Liver	57.7	57.1
Peritoneum	19.2	28.6

Data cutoff date: February 1, 2015.
ORR, objective response rate.

Phase Ib: AEs Suspected to be Drug Related

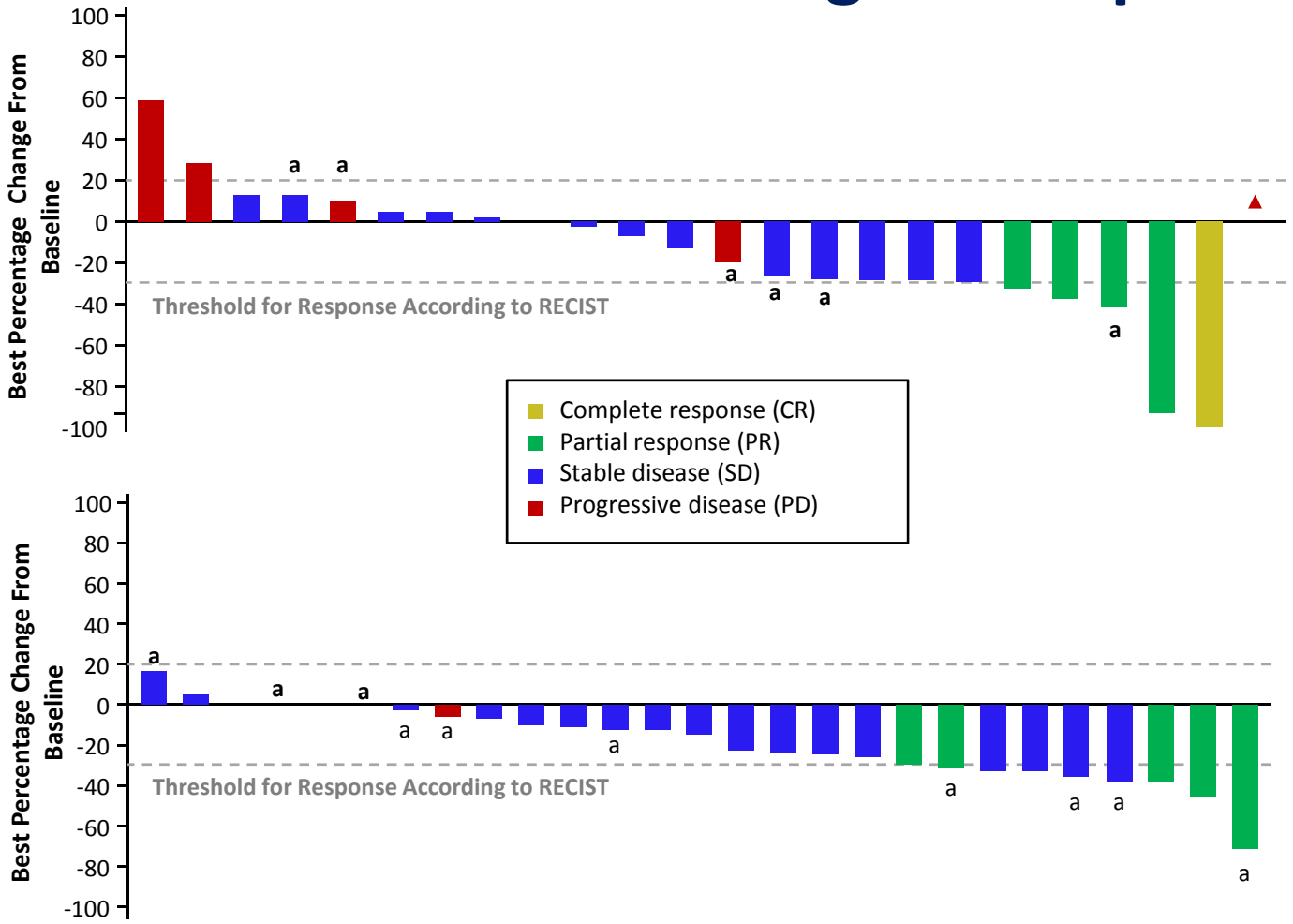
	ENC + CTX (n = 26)		ENC + ALP + CTX (n = 28)	
AE, n (%)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Total	21 (80.8)	6 (23.1)	28 (100)	15 (53.6)
Nausea	7 (26.9)	0	15 (53.6)	1 (3.6)
Diarrhea	2 (7.7)	0	10 (35.7)	1 (3.6)
Rash	4 (15.4)	0	9 (32.1)	0
Hyperglycemia	1 (3.8)	0	9 (32.1)	3 (10.7)
Vomiting	6 (23.1)	1 (3.8)	9 (32.1)	0
Dermatitis acneiform	2 (7.7)	0	8 (28.6)	1 (3.6)
Dry skin	4 (15.4)	0	7 (25.0)	0
Fatigue	11 (42.3)	2 (7.7)	7 (25.0)	0
Hypomagnesemia	3 (11.5)	0	7 (25.0)	0
Decreased appetite	5 (19.2)	0	6 (21.4)	1 (3.6)
Dysgeusia	1 (3.8)	0	6 (21.4)	0
Melanocytic nevus	1 (3.8)	0	6 (21.4)	0
Infusion-related reaction	6 (23.1)	0	1 (3.6)	0

- Discontinuations due to AEs: 3 of 26 patients (11.5%) and 2 of 28 patients (7.1%) in the dual and triple arms, respectively

Data cutoff date: February 1, 2015.
AE, adverse event.

Phase Ib: Antitumor Activity

Best Radiological Response



Dual Combination

PD: 4 (15%)
SD: 14 (54%)
PR: 5 (19%)[b]
CR: 1 (4%)
ORR: 6 (23.1%)[b]
DCR: 20 (76.9%)

Triple Combination

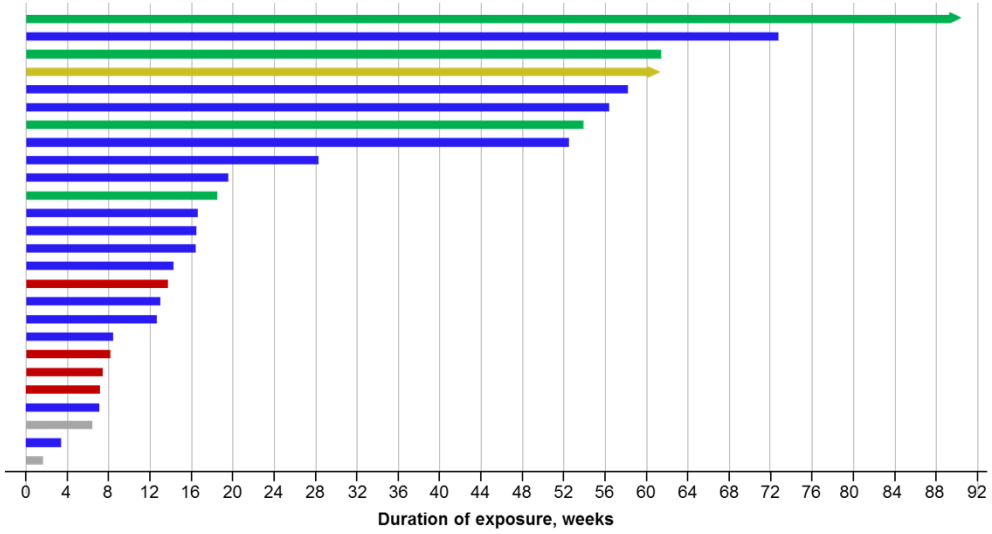
PD: 1 (4%)
SD: 17 (61%)
PR: 9 (32%)[c]
ORR: 9 (32.1%)[c]
DCR: 26 (92.8%)

Data cutoff date: February 1, 2015.
a Patients treated at the RP2D; [b] Includes 1 unconfirmed PR; [c] Includes 4 unconfirmed PRs.
DCR, disease control rate.

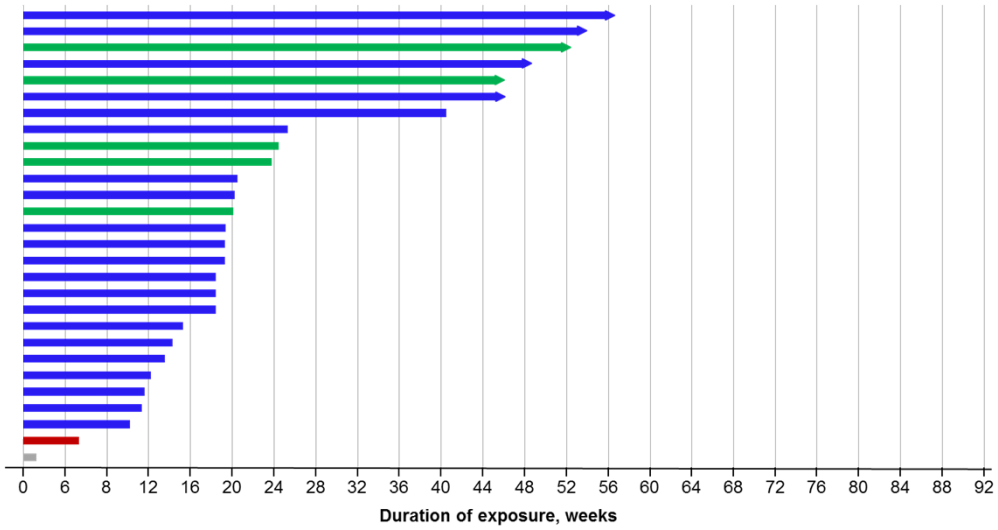
Phase Ib: Antitumor Activity

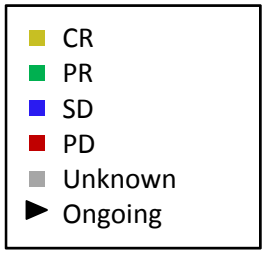
Time on Study, by Response

Dual Combination



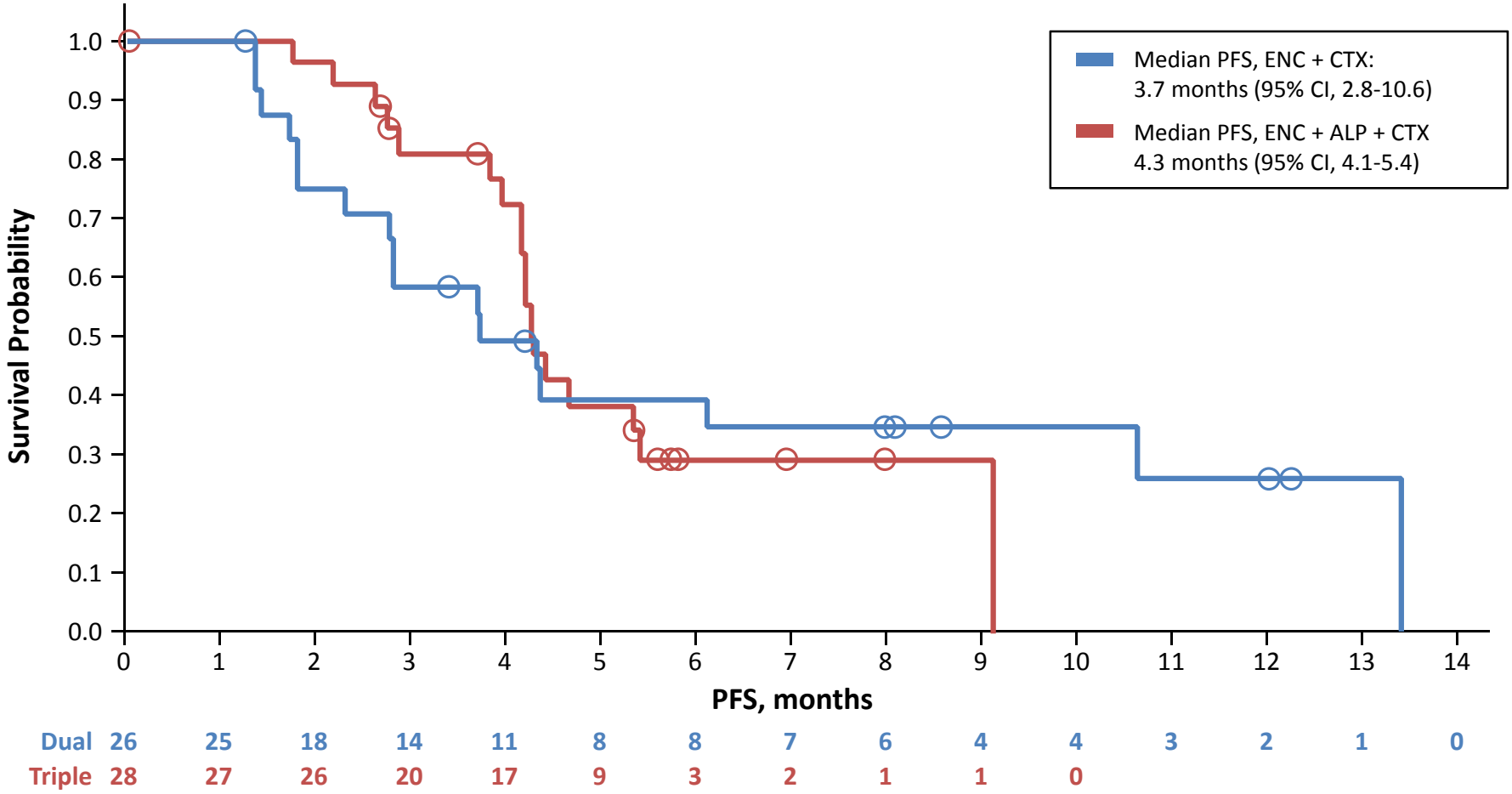
Triple Combination





Data cutoff date: February 1, 2015.

Phase Ib: PFS

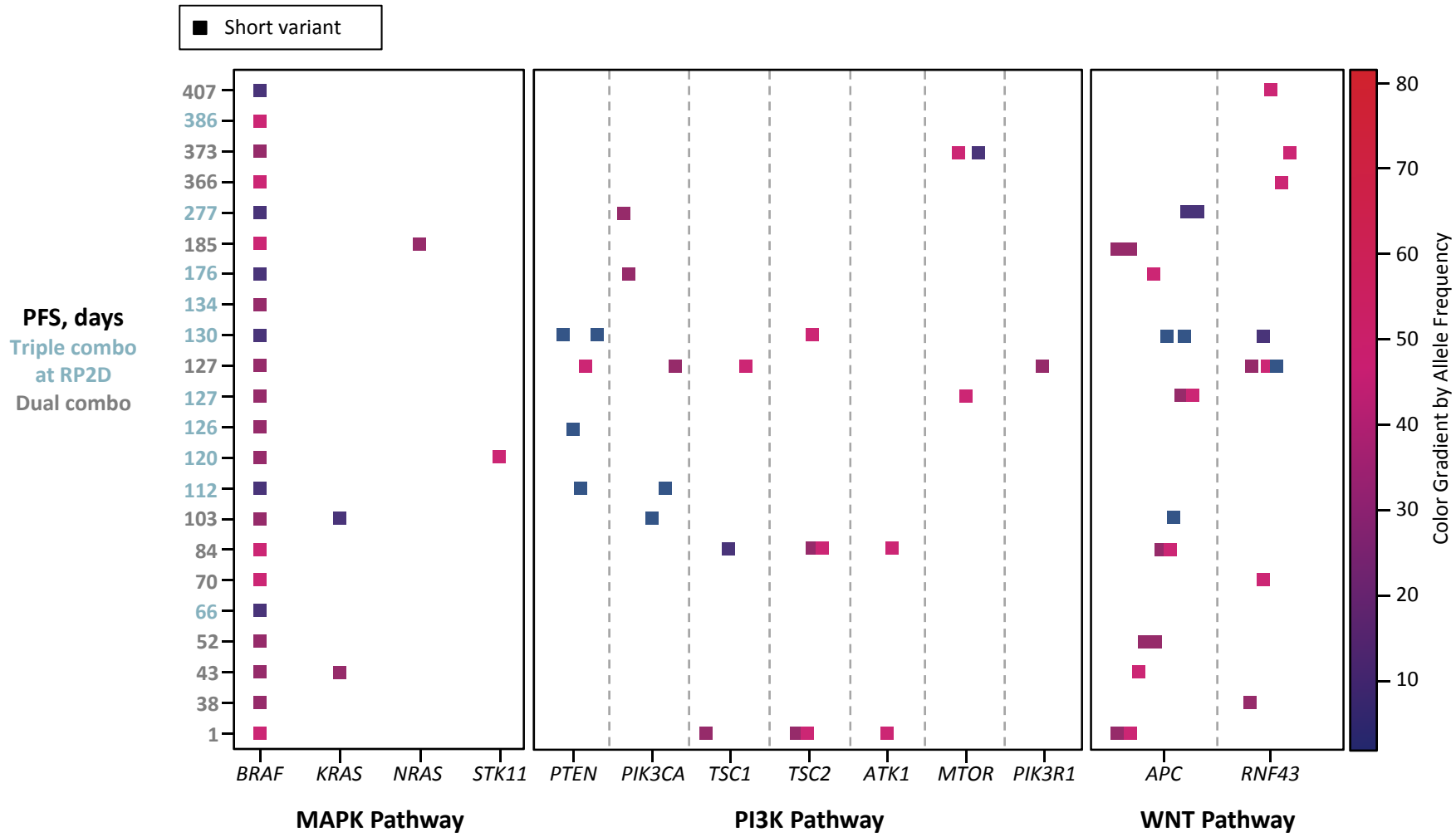


Data cutoff date: February 1, 2015.

Biomarker Analysis

- Exploratory biomarker analysis was conducted to evaluate genetic alterations in context of clinical outcomes
- Somatic mutations, loss of heterozygosity, and copy number aberrations for 22 samples were assessed by Foundation Medicine assay analytics
  - Tumor purity and ploidy were reflected in confidence for mutation and copy number calls
  - Additional annotations from the Catalogue of Somatic Mutations in Cancer were used to filter functional mutations
- Several key pathways (MAPK, PI3K, WNT/β-catenin, and EGFR), along with MSI status, were investigated in both treatment combinations

PFS vs Genetic Alterations and Allele Frequency by Gene Pathways



Data cutoff date: February 1, 2015.

Interim Phase II Analysis
Best Overall Response

	ENC + CTX (n = 42)	ENC + ALP + CTX (n = 49)
Evaluable patients[a]	38	43
CR, n (%)	0	0
PR, n (%)	11 (28.9)[b]	15 (34.9)[c]
SD, n (%)	20 (52.6)	19 (44.2)
PD, n (%)	1 (2.6)	3 (7.0)
Unknown, n (%)	6 (15.8)	6 (14.0)
Overall response rate, n (%)	**11 (28.9)[b]**	**15 (34.9)[c]**
DCR, n (%)	**31 (81.6)**	**34 (79.1)**

Data cutoff date: May 22, 2015.

[a] Evaluable patients had a tumor assessment at the 12 week visit or later and/or started treatment ≥ 13 weeks prior to data cutoff.

[b] Includes 4 unconfirmed PRs.

[c] Includes 5 unconfirmed PRs.

CR and PR were confirmed by repeat assessments performed ≥ 4 weeks after initial response.

Interim Phase II Analysis
AEs Suspected to be Drug Related

	ENC + CTX (n = 42)		ENC + ALP + CTX (n = 49)	
AE, n (%)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Total	37 (88.1)	12 (28.6)	46 (93.9)	24 (49.0)
Diarrhea	9 (21.4)	1 (2.4)	19 (38.8)	4 (8.2)
Nausea	13 (31.0)	0	18 (36.7)	3 (6.1)
Fatigue	15 (35.7)	0	16 (32.7)	3 (6.1)
Hyperglycemia	1 (2.4)	0	15 (30.6)	7 (14.3)
Rash	7 (16.7)	0	13 (26.5)	0
Stomatitis	4 (9.5)	0	13 (26.5)	2 (4.1)
Decreased appetite	9 (21.4)	0	11 (22.4)	1 (2.0)
Pruritus	7 (16.7)	0	11 (22.4)	0
Dry skin	5 (11.9)	0	10 (20.4)	0
Maculopapular rash	1 (2.4)	0	10 (20.4)	2 (4.1)
Lipase increased	10 (23.8)	7 (16.7)	4 (8.2)	2 (4.1)

Data cutoff date: May 22, 2015.

Conclusions

- Both the dual and triple combinations were well tolerated
- MTD was not reached for either combination; established RP2Ds were:
  - Dual combination: 200 mg QD ENC + CTX QW
  - Triple combination: 200 mg QD ENC QD + 300 mg QD ALP + CTX QW
- Similar ORRs were observed between dual and triple combination arms in both the Phase Ib and Phase II parts
  - Phase Ib: 23.1% and 32.1% for the dual and triple combination, respectively
  - Phase II: 28.9% and 34.9% for the dual and triple combination, respectively
- Significant correlations between exploratory genetic analyses and clinical outcomes were not observed in Phase Ib
- Updated preliminary data for this ongoing study continue to show promising clinical activity and tolerability warranting further evaluation
- Phase II enrollment is completed and follow-up for analysis of study objectives is ongoing

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