

**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**

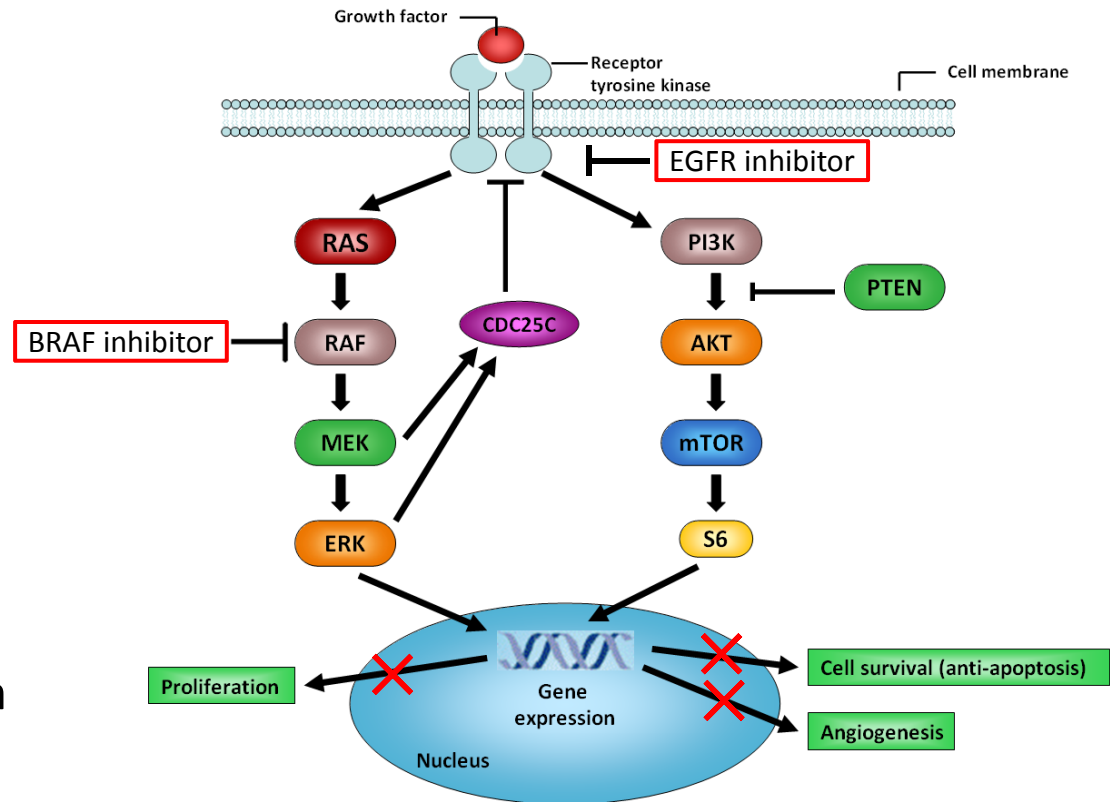
Elena Elez, Jan H.M. Schellens, Robin Van Geel, Johanna C. Bendell, Anna Spreafico,
Martin Schuler, Takayuki Yoshino, Jean-Pierre Delord, Yasuhide Yamada,
Martijn P. Lolkema, Jason E. Faris, Ferry A.L.M. Eskens, Sunil Sharma,
Rona Yaeger, Heinz-Josef Lenz, Zev A. Wainberg, Emin Avsar, Arkendu Chatterjee,
Savina Jaeger, Tim Demuth, Josep Tabernero

Disclosures

- I have nothing to disclose

Introduction

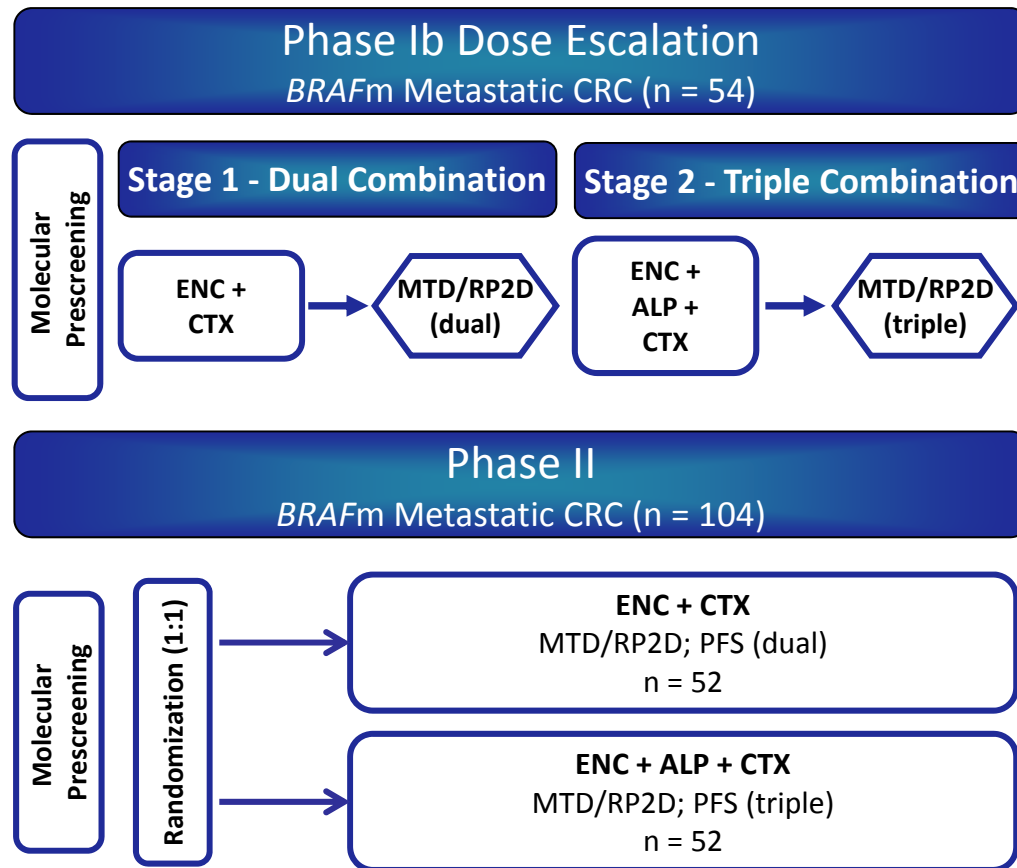
- *BRAF* V600E–mutant colorectal cancers (CRCs) have poorer clinical outcomes compared with wild-type tumors¹
- Unlike in melanoma, *BRAF* inhibition alone shows limited activity in CRC²⁻⁴
- *BRAF*_m CRC has shown synergistic response to EGFR and *BRAF* inhibition in vitro and in vivo^{5, 6}



*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

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.

^aThe 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/m²; weekly dose 250 mg/m².

^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

| AE, n (%) | ENC + CTX (n = 26) | | ENC + ALP + CTX (n = 28) | |
|---------------------------|-----------------------|-----------|-----------------------------|-----------|
| | 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 |

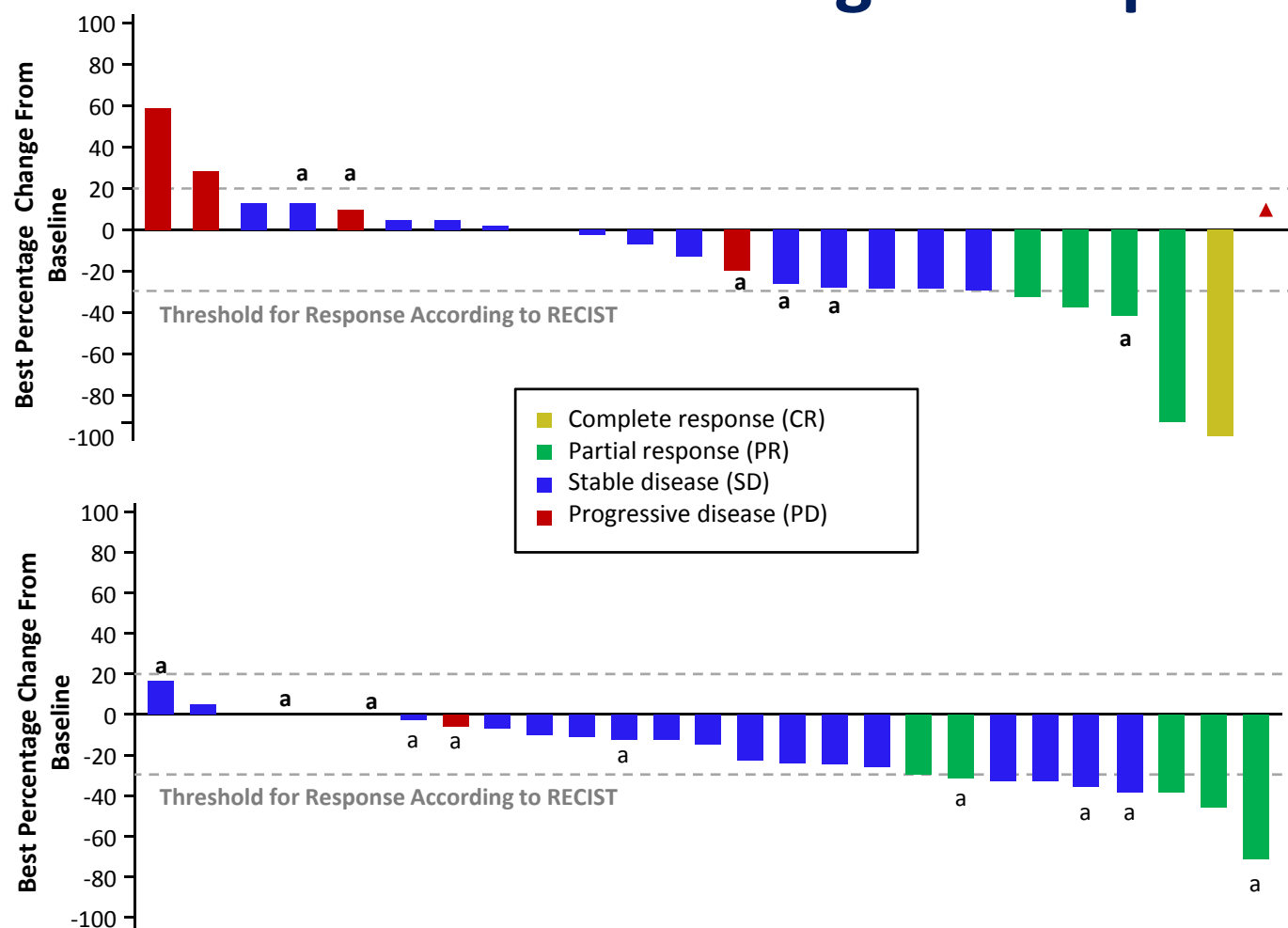
- Discontinuations due to AEs: 3 of 26 patients (11.5%) and 2 of 28 patients (7.1%) in the dual and triple arms, respectively

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%)

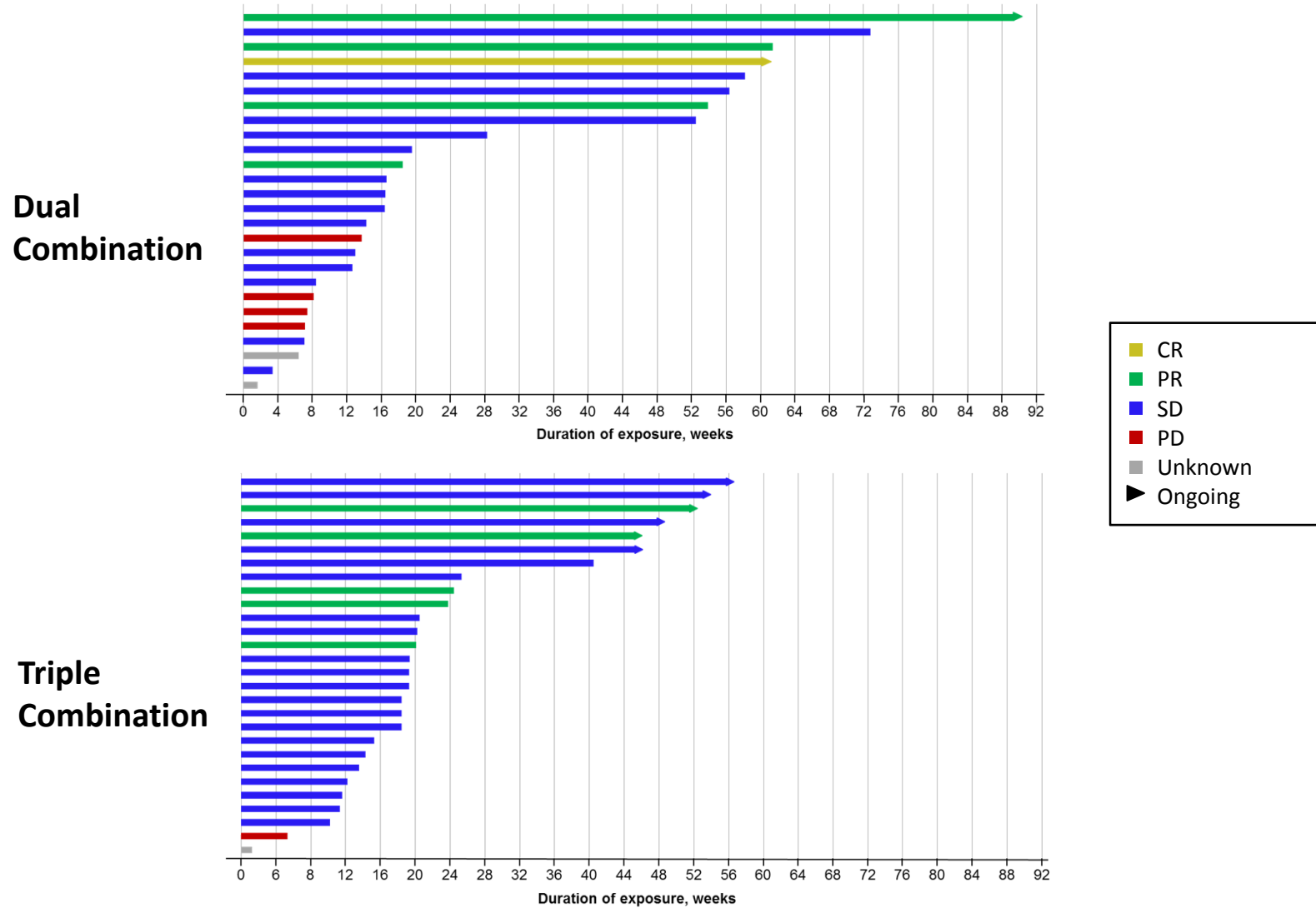
Data cutoff date: February 1, 2015.

a Patients treated at the RP2D; ^b Includes 1 unconfirmed PR; ^c Includes 4 unconfirmed PRs.

DCR, disease control rate.

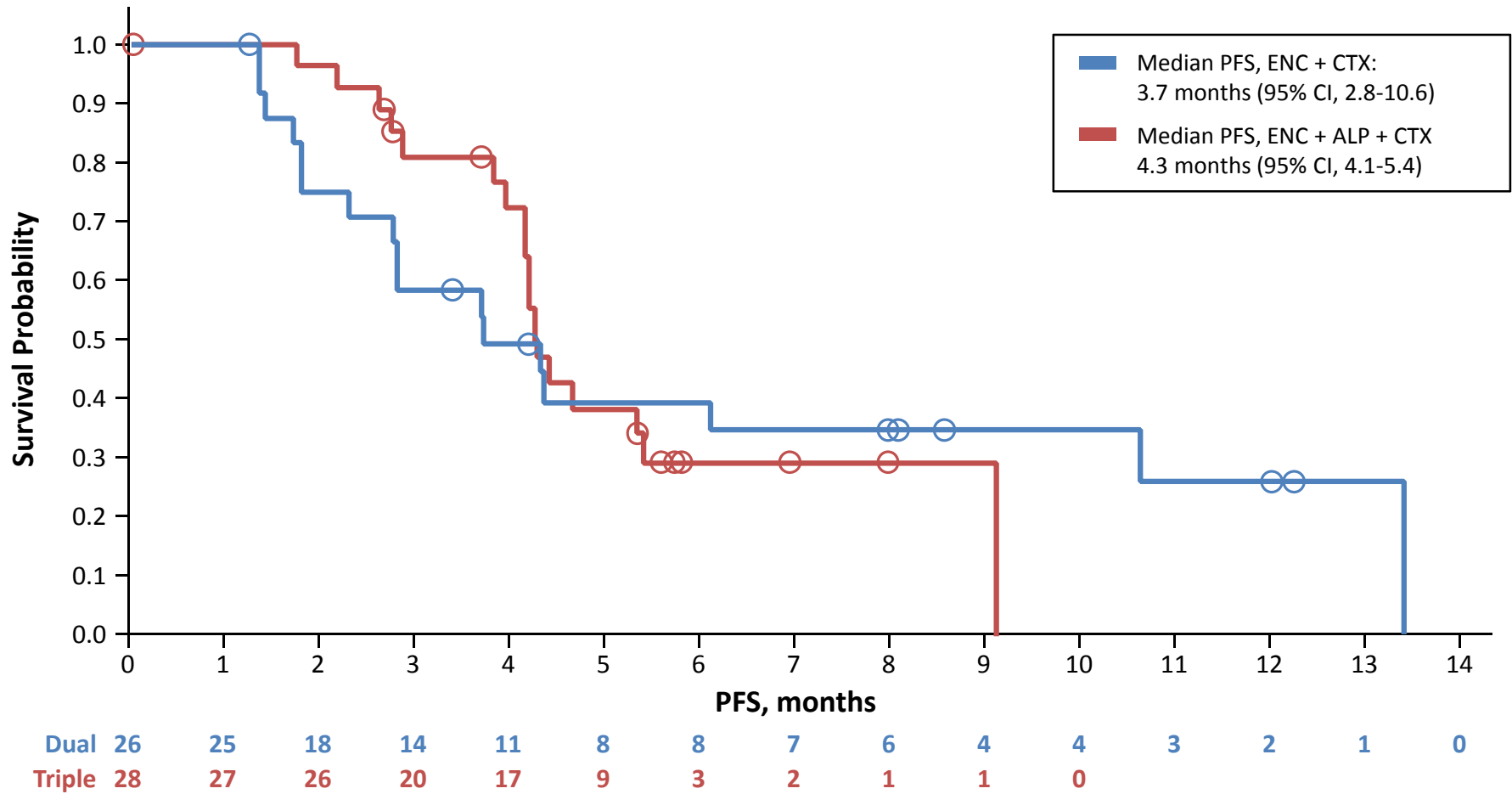
Phase Ib: Antitumor Activity

Time on Study, by Response



Data cutoff date: February 1, 2015.

Phase Ib: PFS

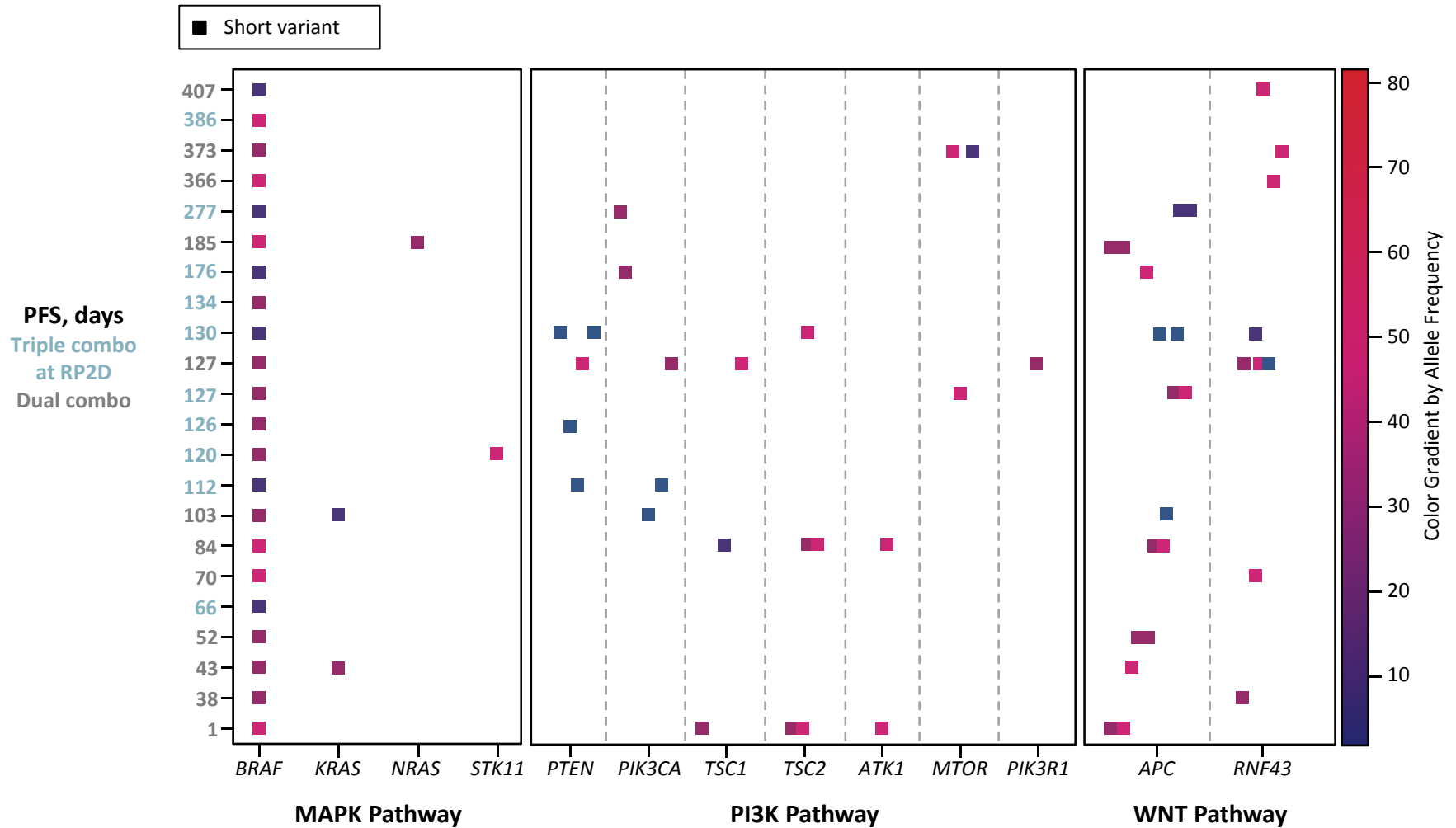


Data cutoff date: February 1, 2015.

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

| AE, n (%) | ENC + CTX (n = 42) | | ENC + ALP + CTX (n = 49) | |
|--------------------|-----------------------|-----------|-----------------------------|-----------|
| | 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

Acknowledgments

- The authors thank the patients and their families and the sites participating in this study

| | |
|---|--|
| Dr. Rocio Garcia Carbonero Hospital Universitario Virgen del Rocio, Spain | Dr. Stefano Cascinu Marche Polytechnic University, Italy |
| Dr. Eric van Cutsem University Hospitals and KU Leuven, Belgium | Dr. Jayesh Desai Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Australia |
| Dr. Ignacio Garrida-Laguna Huntsman Cancer Institute, Utah, USA | Dr. Tornod Kyre Guren Oslo University Hospital, Norway |
| Dr. Martiz Gutierrez Hackensack UMC, USA | Dr. Howard Hochster Yale Cancer Center, USA |
| Dr. Petr Kavan McGill University, Canada | Dr. Taewon Kim Asan Medical Center, South Korea |
| Dr. Jose Lopez Hospital 12 De Octubre, Spain | Dr. Michaela Maur Policlinico di Modena, Italy |
| Dr. Jeffrey Meyerhardt Dana-Farber Cancer Institute, USA | Dr. Joonoh Park Samsung Medical Center, Korea |
| Dr. Ramon Salazar Catalan Institute of Oncology, Spain | Dr. Lillian Siu Princess Margaret Cancer Centre, Canada |
| Dr. Marc Ychou Centre Val d'Aurelle Paul Lamarque, France | Dr. Thomas Zander University Hospital of Cologne, Germany |