ANCHOR CRC: A SINGLE-ARM, PHASE 2 STUDY OF ENCORAFENIB, BINIMETINIB PLUS CETUXIMAB IN PREVIOUSLY UNTREATED *BRAF*V600E–MUTANT METASTATIC COLORECTAL CANCER

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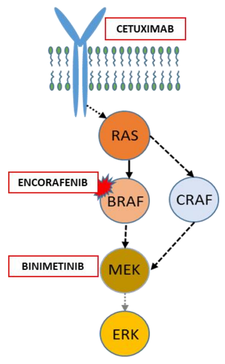
INTRODUCTION

- *BRAF*V600E mutation occurs in 10%–15% of patients and confers a poor prognosis[1,2,3].
- Recent studies with chemotherapy-based regimens have shown poor outcomes[3,4,5,6].
- Expected median OS with 1st-line irinotecan-based chemotherapy ± cetuximab is 10 to 14 months, median PFS of 6 to 8 months, and ORR of 15 to 19%[7].
- BRAF inhibitors are not effective alone due to the feedback activation of EGFR in *BRAF*-mutant CRC, leading to continued cell proliferation[8,9].
- Feedback may be overcome by targeting multiple nodes in the MAPK pathway.
- New effective therapies are urgently needed.

MAPK Signaling in Colorectal Cancer[10]

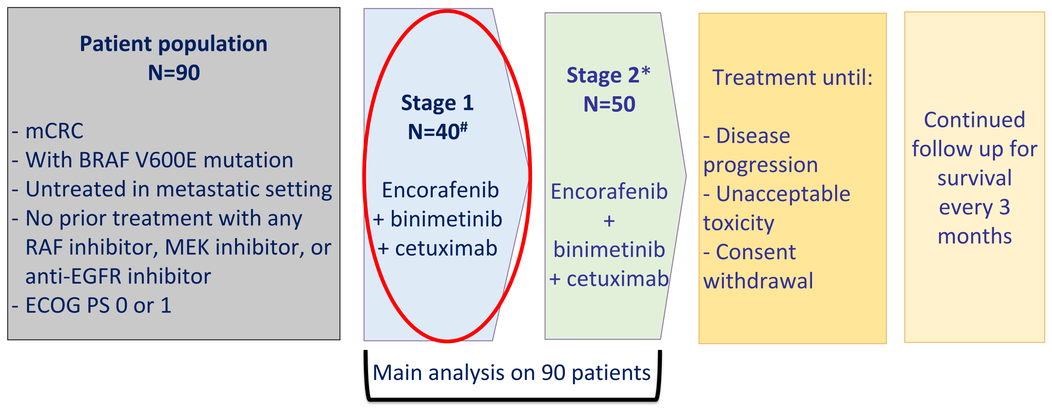


MAPK=mitogen-activated protein kinase
mCRC=metastatic colorectal cancer
PFS=progression-free survival
ORR=objective response rate
OS=overall survival

1. De Roock W, et al. *Lancet Oncol*. 2010;11(8):753. 2. Sorbye H, et al. PLoS One. 2015;10:e0131046. 3. Loupakis F, et al. *Br J Cancer*. 2009;101:715. 4. Kopetz S, et al. *J Clin Oncol*. 2017;35(15):3505. 5. Bokemeyer C et al, *EJC*. 2012;48(10):1466. 6. Oliner K, et al. *J Clin Oncol*. 2013;31(15)suppl:3511. 7. Van Cutsem E, et al. *J Clin Oncol*. 2011;29(15):2011. 8. Corcoran RB, et al. *Cancer Disc*. 2012;2(3):227. 9. Prahallad A, et al. *Nature* 2012;100:100. 10. Adapted From: Strickler JH. *Cancer Treatment Reviews*. 2017; 60:109.

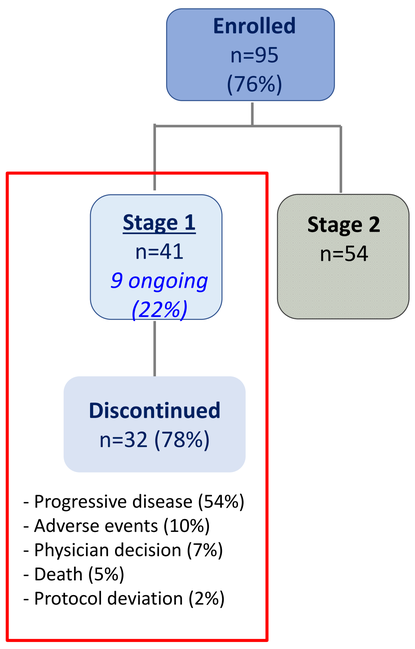
STUDY DESIGN, ENDPOINTS AND STATUS

2-stage design[1]



Primary objective & endpoint: cORR (investigator assessed)

Secondary endpoints: PFS, OS, Safety, QoL, PK



1. Grothey A, et al. *Annals Oncol*. 2019;30(suppl 4):P-400
#Futility analysis
*Stage 2 enrollement only after ≥ 12 responses observed in stage 1
cORR=confirmed objective response rate, OS=overall survival, PK=pharmacokinetics, PFS=progression free survival, QoL=quality of life

Cut-off date: 06-Feb-2020

BASELINE AND DISEASE CHARACTERISTICS (STAGE 1)

	Encorafenib + Binimetinib + Cetuximab (N=41), n (%)¤
BRAF^{V600E} mutation centrally confirmed	40 (98%)*
Female	27 (68%)
Age, median, range (years)	67 (36 – 80)
≥ 65 years	25 (61%)
ECOG PS 1	23 (56%)
Location of primary tumor	
Right side	28 (68%)
Left side (includes rectum)	13 (32%)
Time since initial diagnosis, median, range (days)	63 (21 – 3235)
Number of metastatic organs	
1	9 (22%)
≥ 2	32 (78%)
Metastatic site locations	
Peritoneum	21 (51%)
Lymph node	21 (51%)
Liver	18 (44%)
Lung	13 (32%)
Other	7 (17%)
Prior systemic therapy, adjuvant / neoadjuvant	7 (17%) / 2 (5%)

¤except when specifically mentioned
*locally positive BRAF^{V600E} mutation was not confirmed by central lab for 1 patient

SAFETY RESULTS (STAGE 1), N=41

Overall Safety Summary

	All Grades n (%)	Grade ≥3 n (%)
Any adverse event	**41 (100%)**	**28 (68%)**
Any serious adverse event	23 (56%)	20 (49%)
Any adverse event leading to dose interruption or dose reduction*	28 (68%)	18 (44%)
Any adverse event leading to discontinuation*	8 (20%)	7 (17%)
Any adverse event leading to death#	3 (7%)	3 (7%)

n: number of patients with adverse event
* At least one study drug
# AE leading to death: intestinal obstruction, acute renal failure and progressive disease, pneumonitis

Most frequent AEs (> 10%) regardless of relationship to drugs (by Preferred Term)

	All Grades n (%)	Grade ≥3 n (%)
Any adverse event	**41 (100%)**	**28 (68%)**
Diarrhoea	30 (73%)	6 (15%)
Nausea	25 (61%)	3 (7%)
Vomiting	17 (42%)	1 (2%)
Asthenia	20 (49%)	1 (2%)
Rash	16 (39%)	-
Acneiform dermatitis	14 (34%)	1 (2%)
Abdominal pain	13 (32%)	2 (5%)
Anemia	12 (29%)	5 (12%)
Constipation	11 (27%)	-
Dyspnoea	9 (22%)	-
Pyrexia	8 (20%)	-
Cough	7 (17%)	-
Decreased appetite	7 (17%)	1 (2%)
Dry skin	7 (17%)	-
Fatigue	7 (17%)	-
Acute kidney injury	6 (15%)	5 (12%)
Headache	6 (15%)	-
Abdominal discomfort	5 (12%)	-
Back pain	5 (12%)	-
Blurred vision	5 (12%)	-
Mucosal inflammation	5 (12%)	-

n: number of patients with adverse event

EFFICACY RESULTS (STAGE 1), N=40#

Confirmed Objective Response Rate (primary endpoint)

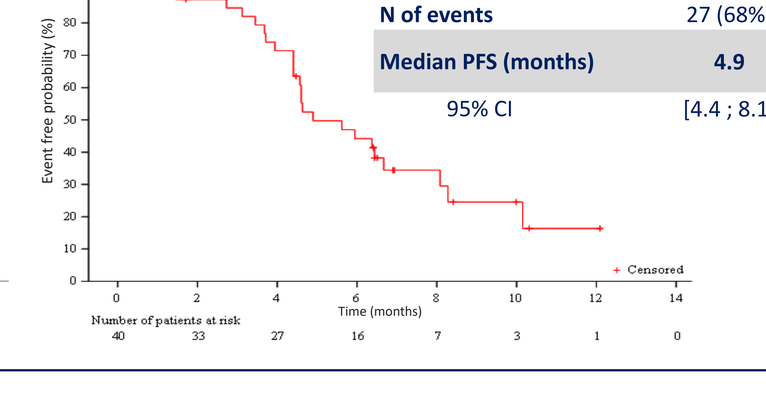
Investigator's assessment, median time on treatment: 4.9 months

	Patients (N=40#), n (%)
Confirmed Objective Response Rate	**20 (50%)**
95% CI	[34 ; 66]
Best Overall Confirmed Response	
Complete response	0
Partial response	20 (50%)
Stable disease	14 (35%)
Progressive disease	4 (10%)
Not evaluable*	2 (5%)

DCR=Disease Control Rate
* 1 patient with no adequate post-baseline assessment
1 patient with 1st CT-scan performed < 6 weeks (32 days after study drug start, stable disease) and discontinued due to AE (myocardial infraction)

Best Percentage Change in Tumor Measurements

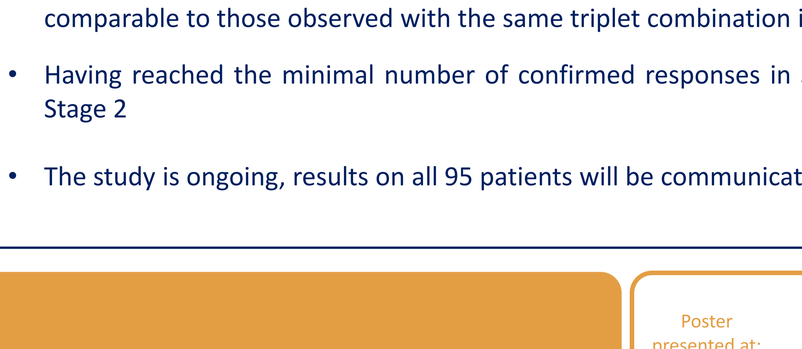
Investigator's assessment, patients evaluable for efficacy



*3 patients with best percent change from baseline=0% and Confirmed Best Overall Response=stable disease
¤ Complete Response on target lesion but non target lesion still present
Complete Response was not confirmed at the subsequent tumor evaluation

Confirmed Best Overall Response and Treatment Duration

Investigator's assessment, patients evaluable for efficacy



Progression Free Survival

Investigator's assessment, median time on treatment: 4.6 months

	Patients
N of events	27 (68%)
Median PFS (months)	**4.9**
95% CI	[4.4 ; 8.1]

1 patient has been excluded from the efficacy analysis as the BRAF mutation was not confirmed by central lab

CONCLUSIONS

- ANCHOR study is the first prospective study using a BRAF inhibitor based therapy in 1st line *BRAF*V600E-mutant mCRC
- Population with a high median age (67 years), high proportion of elderly patients (61% ≥ 65 years old), and an advanced stage at diagnosis (56% ECOG 1, 78% had metastases to at least 2 organs, 51% had peritoneal metastasis)
  This 1st line *BRAF*V600E metastatic CRC population is notably different to that observed in retrospective analyses of prior studies[1,2,3]
- High confirmed objective response rate (50%) is observed. Almost all patients had decrease in tumor size
- The median PFS of 5 months is similar to that observed with chemotherapy in 1st line *BRAF*-mutant metastatic CRC[1,2,3]
- The triplet combination was well tolerated and manageable with no unexpected toxicities. Most frequent adverse events are comparable to those observed with the same triplet combination in BEACON study[4]
- Having reached the minimal number of confirmed responses in Stage 1, the futility analysis allowed to enrol additional patients in Stage 2
- The study is ongoing, results on all 95 patients will be communicated in 2021

1. Tveit KM et al, *JCO*. 2012;30(15):1755
2. Bokemeyer C et al, *EJC*. 2012;48(10):1466
3. Cremolini C et al, *Lancet Oncol*. 2015;16(13):1306
4. Kopetz S et al, *NEJM*. 2019;381(17):1632

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