Supplementary Online Content

Boige V, Blons H, François E, et al. Maintenance therapy with cetuximab after FOLFIRI plus cetuximab for *RAS* wild-type metastatic colorectal cancer: a phase 2 randomized clinical trial. *JAMA Netw Open.* 2023;6(9):e2333533. doi:10.1001/jamanetworkopen.2023.33533

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. List of Recruiting Study Centers

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CHI COTE BASQUE BAYONNE	Dr Franck AUDEMAR
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CHD VENDEE LA ROCHE SUR YON	Dr Margot LALY
CHU SAINT ETIENNE SAINT PRIEST EN JAREZ	Pr Jean-Marc PHELIP
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CENTRE LEON BERARD LYON	Dr Christelle DE LA FOUCHARDIERE
CENTRE HOSPITALIER DE BEAUVAIS	Dr Fayçal HOCINE
CENTRE HOSPITALIER VICTOR PROVO ROUBAIX	Dr Sylvie BLOCK
CENTRE HOSPITALIER JEAN ROUGIER CAHORS	Dr Nadia LEVASSEUR
CENTRE HOSPITALIER DE BLOIS	Dr Dany GARGOT
CENTRE HOSPITALIER D'AUXERRE	Dr Anne-Laure VILLING
CHU AMIENS	Dr Vincent HAUTEFEUILLE
CENTRE HOSPITALIER INTERCOMMUNAL FREJUS	Dr Bruno VALENZA
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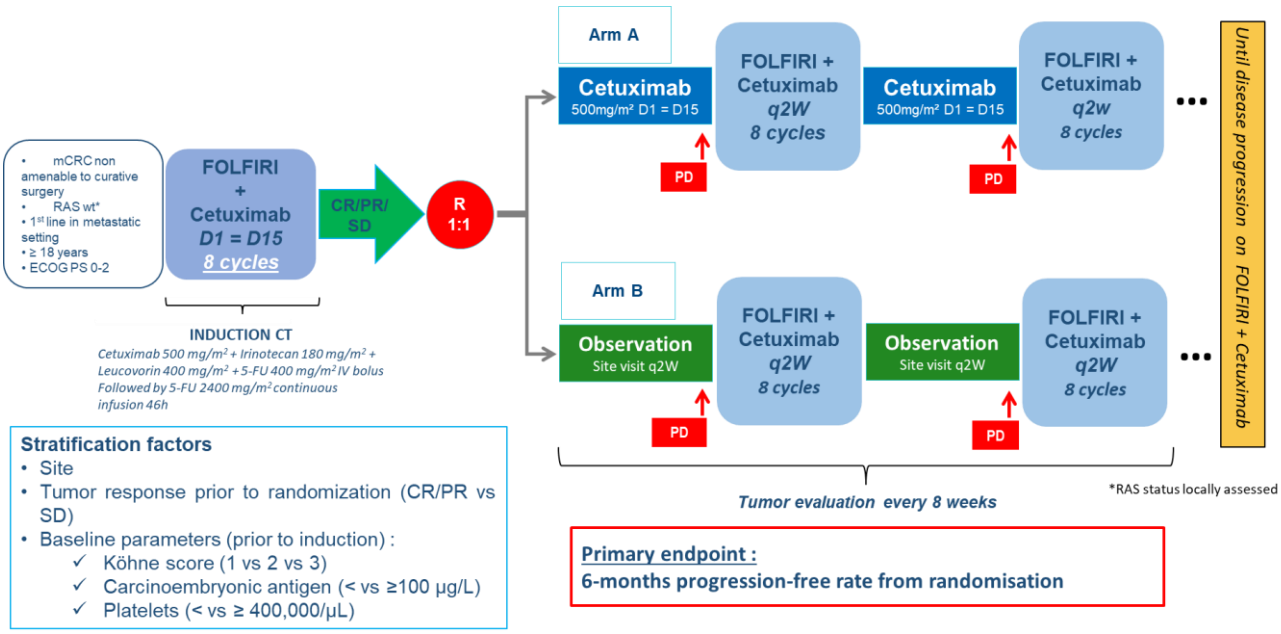
CENTRE HOPSITALIER ESTAING CLERMONT FERRAND	Dr Caroline PETORIN
POLYCLINIQUE DE L'ORMEAU TARBES	Dr Philippe AYELA
ICM VAL D'AURELLE MONTPELLIER	Dr Emmanuelle SAMALIN

eFigure 1. Study Design



CR, complete response; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, fluorouracil, folinic acid, and irinotecan; mCRC, metastatic colorectal cancer; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; q2w, beweekly; R, random assignment; SD, stable disease; wt, wild type.

eTable 1. Stratification Factors in Patients Randomized (ITT2 Population)

	Arm A Cetuximab n=67	Arm B Observation, n=72
Baseline CEA (µg/l)		
< 100, %	59.7	59.7
≥ 100, %	40.3	40.3
Baseline platelets (/µl),%		
< 400,000, %	77.6	77.8
≥ 400,000, %	22.4	22.2
Köhne score		
Low, %	35.8	34.7
Intermediate, %	46.3	50.0
High, %	17.9	15.3

CEA, carcinoembryonic antigen

eTable 2. Number of FOLFIRI Plus Cetuximab Sequence Reintroductions in Patients Randomized (ITT2 Population)

	Arm A **Cetuximab maintenance (n = 67)**	**Arm B** **Observation (n = 72)**
Number of FOLFIRI-cetuximab sequence reintroductions Median [Range]	1 [0-3]	1 [0-6]
0, No. (%)	19 (28.4)	17 (23.6)
1, No. (%)	34 (50.7)	29 (40.3)
2, No. (%)	9 (13.4)	17 (23.6)
≥ 3, No. (%)	5 (7.5)	9 (12.5)

FOLFIRI, fluorouracil, folinic acid, and irinotecan

eTable 3. Summary of Outcomes in *RAS* and *BRAF* ^{V600} Wild-Type Randomized Patients (ITT3 Population)

	Patients randomized			
	Arm A (Cetuximab)		Arm B (observation)	
	ITT2 n = 67	**ITT3** *BRAF* ^{V600} + *RAS* WT n = 60 (90%)	ITT2 n=72	**ITT3** *BRAF* ^{V600} + *RAS* WT n = 66 (92 %)
ORR during induction CT, (% evaluable patients)	75	78	69	68
6-month PFR, % (95%CI)	39 (27; 52)	42 (29; 55)	6 (2; 14)	6 (2; 15)
Median PFS from randomization, months (95%CI)	5.3 (3.7; 7.4)	5.7 (3.7; 7.7)	2.0 (1.8; 2.7)	2.0 (1.8; 2.8)
Median OS from randomization, months (95%CI)	24.8 (18.7; 30.4)	25.6 (19.4; 31.1)	19.7 (13.3; 24.4)	19.7 (13.4; 24.4)
Median OS from inclusion, months (95%CI)	28.6 (22.8; 35.0)	29.6 (24.1; 35.1)	24.4 (17.2; 28.6)	24.4 (17.2; 28.6)
Median TSF, months (95%CI)	8.7 (7.5; 15)	9.4 (7.7; 15.9)	10.1 (7.3; 10.9)	10.3 (7.4; 11)

ORR, objective response rate; PFR, progression-free rate; CT, chemotherapy; PFS, progression-free survival; PR, partial response; TSF, time to strategy failure

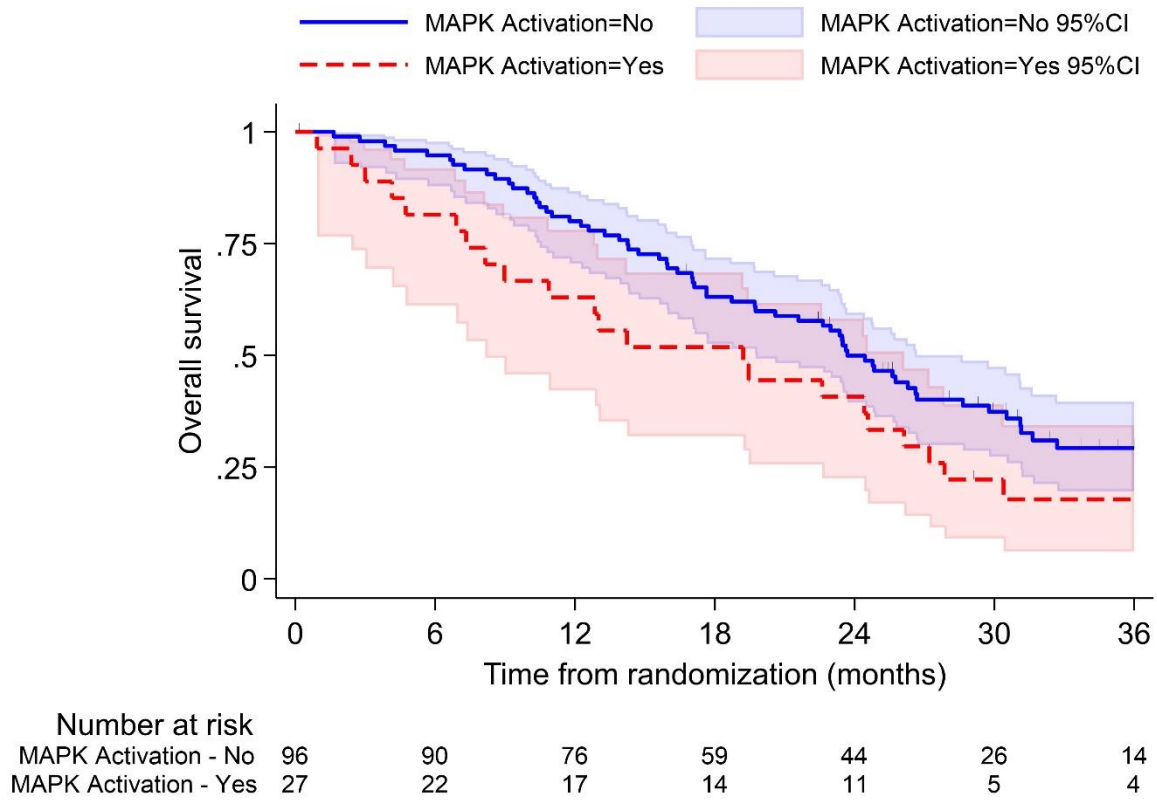
eTable 4. Detailed Tumor NGS Data Available in the ITT1 Population (n=189)
See Supplement 3

eTable 5. Summary of *TP53*, MAPK or *PIK3CA* Pathway Activating Mutations (ITT1 Population)

		Patients not randomized n=75	Patients randomized			Overall population n=214
			Cetuximab N=67	Observation N=72	Total, n=139	
TP53	wt, No. (%)	27 (40.9)	22 (36.1)	24 (38.7)	46 (37.4)	73 (38.6)
	Mutated, No. (%)	39 (59.1)	39 (63.9)	38 (61.3)	77 (62.6)	116 (61.4)
	Missing, No.	*9*	*6*	*10*	*16*	*25*
MAPK	wt, No. (%)	39 (59.1)	47 (77.0)	49 (79.0)	96 (78.0)	135 (71.4)
	Mutated, No. (%)	27 (40.9)	14 (23.0)	13 (21.0)	27 (22.0)	54 (28.6)
	Missing, No.	*9*	*6*	*10*	*16*	*25*
PIK3CA	wt, No. (%)	54 (81.8%)	49 (80.3%)	50 (80.6%)	99 (80.5%)	153 (80.9%)
	Mutated, No. (%)	12 (18.2%)	12 (19.7%)	12 (19.4%)	24 (19.5%)	36 (19.1%)
	Missing, No.	*9*	*6*	*10*	*16*	*25*

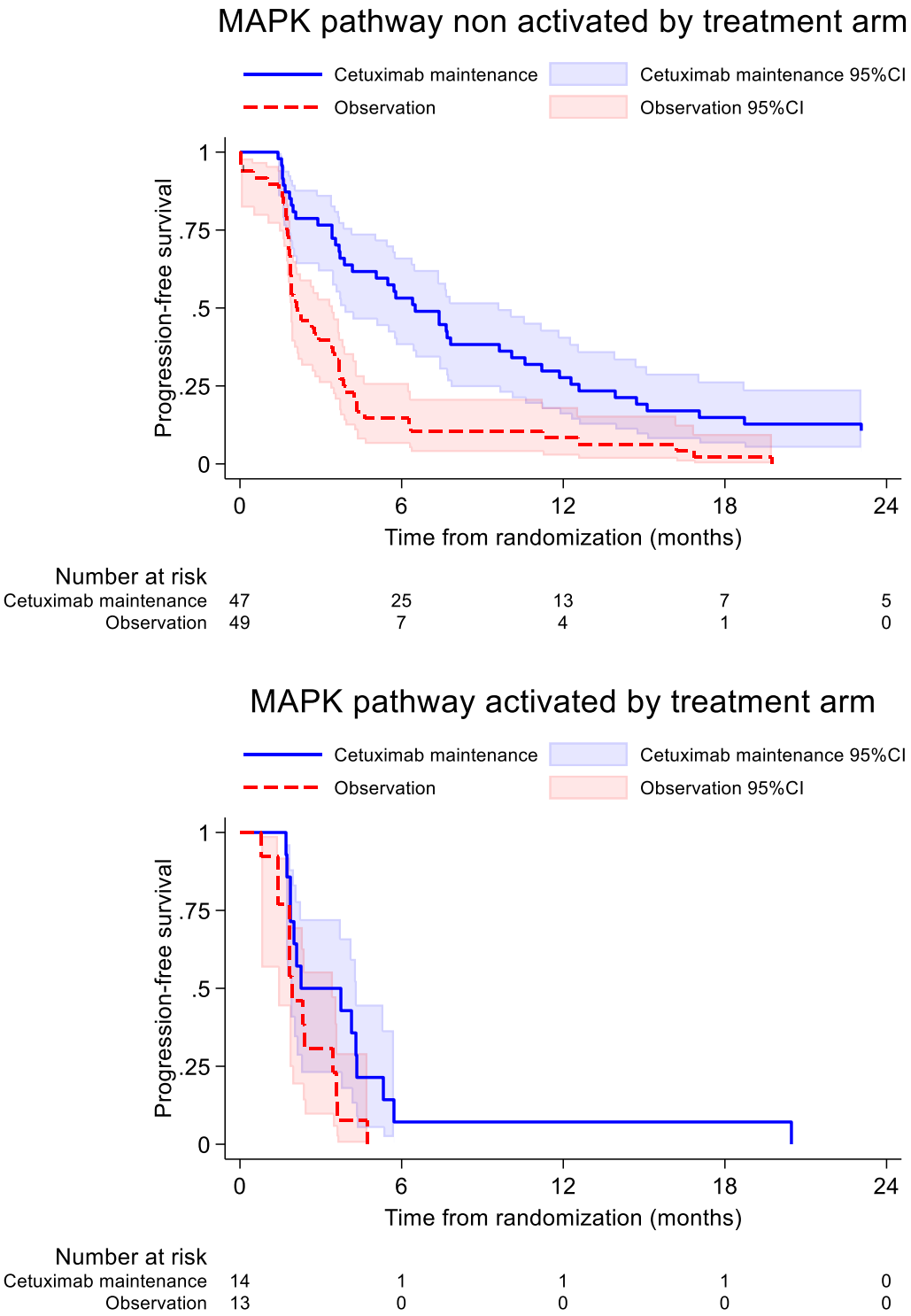
MAPK, Mitogen-activated protein kinase; wt, wild-type

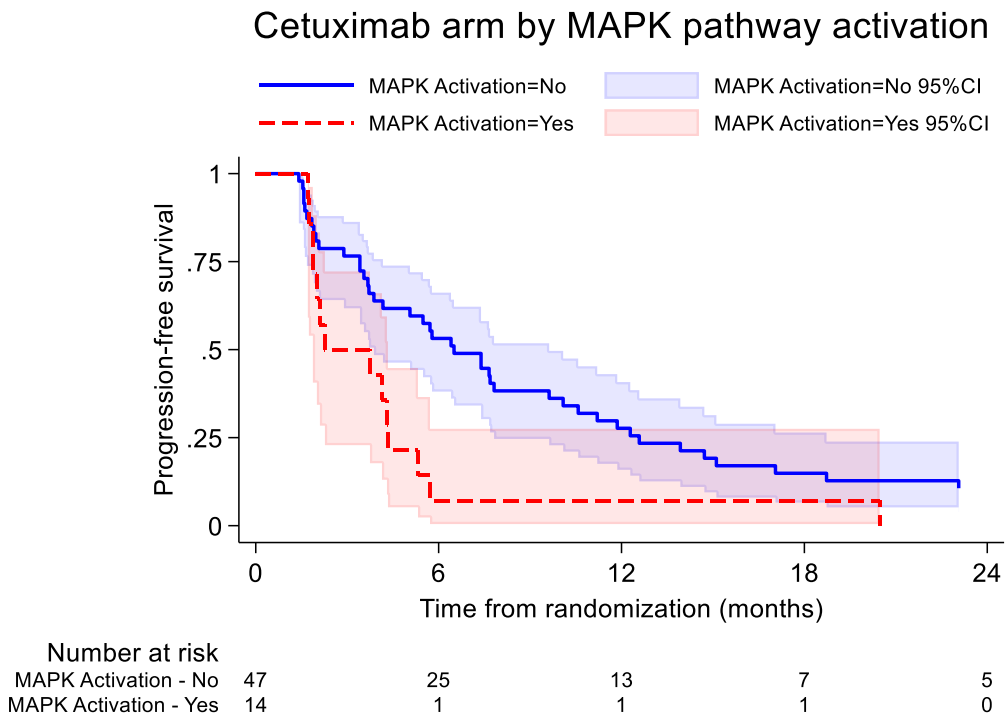
eFigure 2. Kaplan-Meier Estimates of Overall Survival From Randomization According to MAPK Pathway Activation (ITT2 Population)

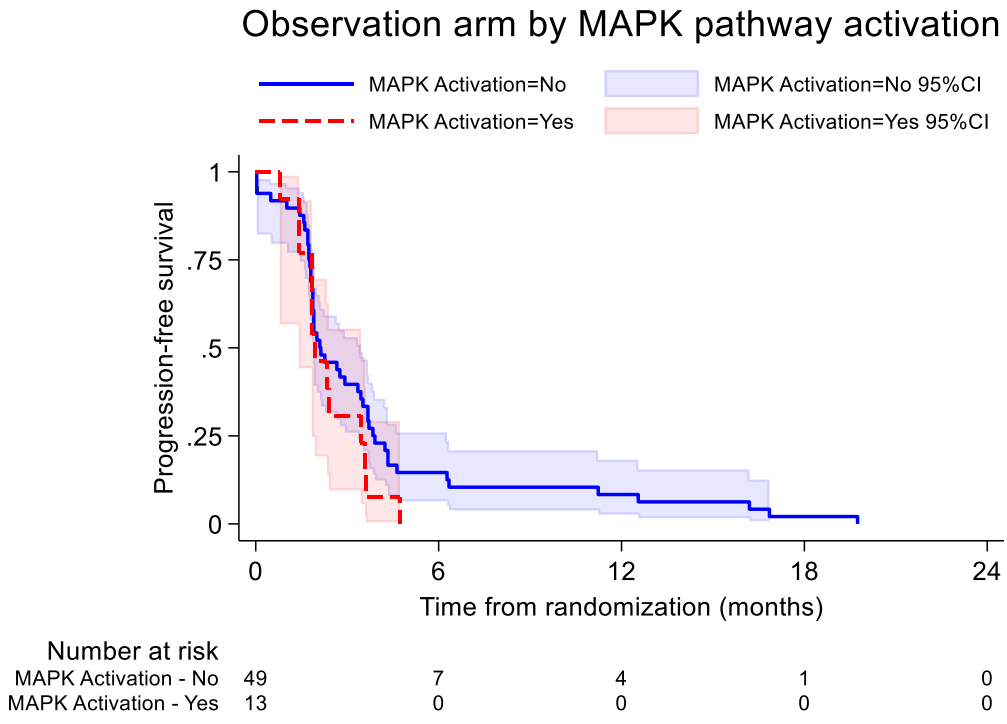


MAPK, Mitogen-activated protein kinase

eFigure 3. Kaplan-Meier Estimates of Progression-Free Survival From Randomization According to MAPK Pathway Activation and to Treatment Arm (ITT2 Population)







MAPK, Mitogen-activated protein kinase

eTable 6. Exploratory Multivariate Analysis: Factors Significantly Associated With Progression-Free (A) and Overall Survival (B) in Patients Randomized (ITT2 Population)

A)

Progression-free survival N = 122, Events = 119	Hazard Ratio (95% CI)[Cox]	*p*-value
Arm		**<.0001**
Cetuximab	0.36 (0.24-0.53)	
Observation	Reference	
Baseline platelet count		**0.0397**
< 400 x 10^9/L	Reference	
≥ 400 x 10^9/L	1.64 (1.03-2.63)	
Köhne Score		**0.0368**
1	Reference	
2	1.52 (1.00-2.29)	
3	0.81 (0.46-1.45)	
Site of primary tumor		**0.0014**
Right	2.33 (1.39-3.92)	
Left	Reference	
MAPK pathway activation		**0.0437**
No	Reference	
Yes	1.63 (1.01-2.62)	

B)

Overall survival N=138, Events = 104	Hazard Ratio (95% CI)[Cox]	*p*-value
Baseline platelet count		**0.0289**
< 400 x 10^9/L	Reference	
≥ 400 x 10^9/L	1.66 (1.05-2.61)	
Site of primary tumor		**0.0011**
Right	2.13 (1.35-3.36)	
Left	Reference	

MAPK, Mitogen-activated protein kinase

eTable 7. Adverse Events of Interest During Induction FOLFIRI Plus Cetuximab and During First Chemotherapy-Free Interval

	Induction FOLFIRI plus cetuximab		First chemotherapy free interval			
	Safety set N = 208		Arm A (Cetuximab) N = 67		Arm B (Observation) N = 72	
	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3
Anemia	123 (59.1%)	4 (1.9%)	25 (37.3%)	0 (0.0%)	22 (30.6%)	0 (0.0%)
Leucopenia	86 (41.3%)	6 (2.9%)	5 (7.5%)	0 (0.0%)	3 (4.2%)	0 (0.0%)
Neutropenia	85 (40.9%)	33 (15.9%)	7 (10.4%)	1 (1.5%)	4 (5.6%)	0 (0.0%)
Febrile neutropenia	9 (4.3%)	9 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphopenia	73 (35.1%)	7 (3.4%)	15 (22.4%)	0 (0.0%)	18 (25.0%)	2 (2.8%)
Pancytopenia	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thrombocytopenia	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Conjunctivitis	16 (7.7%)	1 (0.5%)	10 (14.9%)	0 (0.0%)	2 (2.8%)	0 (0.0%)
Constipation	44 (21.2%)	1 (0.5%)	8 (11.9%)	0 (0.0%)	5 (6.9%)	2 (2.8%)
Diarrhea	119 (57.2%)	19 (9.1%)	22 (32.8%)	4 (6.0%)	6 (8.3%)	1 (1.4%)
Abdominal pain	37 (17.8%)	8 (3.8%)	14 (20.9%)	3 (4.5%)	12 (16.7%)	5 (6.9%)
Gastroenteritis	1 (0.5%)	1 (0.5%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucositis	63 (30.3%)	6 (2.9%)	2 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	92 (44.2%)	7 (3.4%)	13 (19.4%)	1 (1.5%)	5 (6.9%)	1 (1.4%)
Pancreatitis	1 (0.5%)	1 (0.5%)	1 (1.5%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
Gastrointestinal obstruction	12 (5.8%)	10 (4.8%)	2 (3.0%)	1 (1.5%)	3 (4.2%)	3 (4.2%)
Vomiting	41 (19.7%)	8 (3.8%)	7 (10.4%)	1 (1.5%)	2 (2.8%)	0 (0.0%)
General physical healthdeterioration	10 (4.8%)	8 (3.8%)	1 (1.5%)	1 (1.5%)	4 (5.6%)	4 (5.6%)
Fatigue	115 (55.3%)	10 (4.8%)	28 (41.8%)	2 (3.0%)	18 (25.0%)	2 (2.8%)
Fever	20 (9.6%)	2 (1.0%)	3 (4.5%)	0 (0.0%)	3 (4.2%)	1 (1.4%)
Malaise	5 (2.4%)	2 (1.0%)	2 (3.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
Edema	13 (6.3%)	1 (0.5%)	6 (9.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Allergic reaction	20 (9.6%)	9 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infection	37 (17.8%)	13 (6.3%)	11 (16.4%)	3 (4.5%)	4 (5.6%)	2 (2.8%)
ALT/AST increased	88 (42.3%)	2 (1.0%)	21 (31.3%)	0 (0.0%)	20 (27.8%)	2 (2.8%)
Gama GT increased	110 (52.9%)	42 (20.2%)	36 (53.7%)	12 (17.9%)	28 (38.9%)	14 (19.4%)
Alkaline phosphatase increased	104 (50.0%)	8 (3.8%)	27 (40.3%)	2 (3.0%)	23 (31.9%)	4 (5.6%)
Hypophosphatemia	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (1.4%)	1 (1.4%)
Anorexia	40 (19.2%)	8 (3.8%)	5 (7.5%)	2 (3.0%)	6 (8.3%)	1 (1.4%)
LDH increased	27 (13.0%)	0 (0.0%)	16 (23.9%)	1 (1.5%)	9 (12.5%)	0 (0.0%)
Dehydration	3 (1.4%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperglycemia	20 (9.6%)	1 (0.5%)	8 (11.9%)	2 (3.0%)	4 (5.6%)	0 (0.0%)
Hyperkalemia	6 (2.9%)	0 (0.0%)	10 (14.9%)	0 (0.0%)	6 (8.3%)	1 (1.4%)
Hypoalbuminemia	25 (12.0%)	3 (1.4%)	5 (7.5%)	0 (0.0%)	3 (4.2%)	0 (0.0%)
Hypocalcemia	52 (25.0%)	1 (0.5%)	9 (13.4%)	0 (0.0%)	4 (5.6%)	0 (0.0%)
Hypokalemia	28 (13.5%)	5 (2.4%)	5 (7.5%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Hypomagnesemia	70 (33.7%)	1 (0.5%)	31 (46.3%)	3 (4.5%)	7 (9.7%)	0 (0.0%)
Hypophosphoremia	4 (1.9%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)

	Induction FOLFIRI plus cetuximab		First chemotherapy free interval			
	Safety set N = 208		Arm A (Cetuximab) N = 67		Arm B (Observation) N = 72	
	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3
Malnutrition	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)
Intercranial hypertension	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	16 (7.7%)	2 (1.0%)	5 (7.5%)	0 (0.0%)	3 (4.2%)	1 (1.4%)
Dyspnea	8 (3.8%)	3 (1.4%)	8 (11.9%)	0 (0.0%)	2 (2.8%)	1 (1.4%)
Rash/Erythema	123 (59.1%)	9 (4.3%)	50 (74.6%)	8 (11.9%)	3 (4.2%)	0 (0.0%)
Alopecia	38 (18.3%)	0 (0.0%)	7 (10.4%)	0 (0.0%)	3 (4.2%)	0 (0.0%)
Nail damage	27 (13.0%)	1 (0.5%)	18 (26.9%)	0 (0.0%)	3 (4.2%)	0 (0.0%)
Erythroderma	17 (8.2%)	2 (1.0%)	10 (14.9%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Palmoplantar erythrodysesthesia	31 (14.9%)	1 (0.5%)	13 (19.4%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
Skin crack	39 (18.8%)	0 (0.0%)	21 (31.3%)	0 (0.0%)	3 (4.2%)	0 (0.0%)
Mycosis	5 (2.4%)	1 (0.5%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pruritus	25 (12.0%)	1 (0.5%)	8 (11.9%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Dry skin	75 (36.1%)	0 (0.0%)	21 (31.3%)	0 (0.0%)	5 (6.9%)	0 (0.0%)
Thromboembolic event	24 (11.5%)	11 (5.3%)	2 (3.0%)	1 (1.5%)	1 (1.4%)	1 (1.4%)
Hypertension	11 (5.3%)	1 (0.5%)	2 (3.0%)	0 (0.0%)	2 (2.8%)	0 (0.0%)
Cardiac disorder	8 (3.8%)	3 (1.4%)	3 (4.5%)	0 (0.0%)	2 (2.8%)	0 (0.0%)

eMethods. Sequencing

Samples were characterized for molecular alterations by targeted NGS (Ion AmpliSeq™ Colon-Lung Cancer Research Panel v2, Life Technologies™). Briefly the multiplex barcoded libraries are generated from 30-10ng of DNA following manufacturer's recommendations (Ion ampliseq library kit V2) and are normalized using the Ion Library Equalizer™ Kit. The pooled libraries (max 96) are processed on Ion Chef™ System for template preparation and chip loading (Ion PI HI-Q Chef Kit, Ion PI Chip V3), and sequenced on the Ion Proton™ System (Life Technologies™). The FASTQs sequencing data are aligned to the human genome (hg19) and processed using IonTorrent Suite. This package included the Torrent Variant Caller using the built-in "Somatic - low stringency" with optimized parameters to automatically call variants with allelic ratio >2%. Minimal depth used was 300X.