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RETROSPECTIVE ANALYSIS OF FOLFOX VERSUS FOLFOX AND CETUXIMAB FOR PATIENTS WITH METASTATIC CANCER COLON

Eman El-sheikh, Amr Lotfy, Nesreen Ahmed Mosalam and Kyrillous Mounir Beniamin*

Department of Clinical Oncology, Faculty of Medicine – Ain Shams University.

***Corresponding Author: Kyrillous Mounir Beniamin**
Department of Clinical Oncology, Faculty of Medicine – Ain Shams University.
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ABSTRACT

Background: Cetuximab which is a monoclonal antibody can be added to folfox regimen in treatment of patients with RAS wild metastatic cancer colon and this may improve the progression free survival and overall survival of these patients. We investigated the efficacy of cetuximab plus oxaliplatin, fluorouracil, and leucovorin (FOLFOX) as first-line treatment for metastatic colorectal cancer. **Objective:** To retrospective analyses of progression-free survival, overall survival, overall response rate, resectability and safety within the different patient populations with metastatic cancer colon treated by cetuximab plus FOLFOX versus FOLFOX alone. **Patients and Methods:** A Retrospective controlled trial study, 100 patients were selected to participate in our study based on our inclusion criteria. They were recruited from Ain shams University Teaching Hospital and Alexandria Military Hospital, from January 2012 to December 2016. **Results:** The initial treatment of metastatic colorectal cancer with a combination of Cetuximab plus FOLFOX, as compared with FOLFOX alone, reduced the risk of disease progression by 33.4% and also increased the response rate by nearly 13%. There was significant difference between the treatment groups in overall survival by 39%. **Conclusion:** First-line treatment with cetuximab plus FOLFOX, as compared with FOLFOX alone, reduced the risk of progression of metastatic colorectal cancer.

KEYWORDS: Epidermal growth factor receptor, intention-to-treat.

INTRODUCTION

The epidermal growth factor receptor (EGFR) targeting monoclonal antibody cetuximab improves overall survival when added to standard chemotherapy used in the treatment of metastatic colorectal cancer (mCRC). (Oxaliplatin and Cetuximab in First-Line Treatment of mCRC) study demonstrated that the tumor mutation status of codons 12 and 13 of the *KRAS* gene was predictive for the activity of cetuximab combined with oxaliplatin plus infusional (5-FU) and folinic acid (FOLFOX-4) in the first-line treatment of mCRC ***(Bokemeyer et al., 2009).***

Cetuximab activity is limited to patients whose tumors were *RAS* wild type. It was also consistent with retrospective analysis in mCRC involving cetuximab administered as monotherapy in patients who had failed prior chemotherapy and as first-line treatment in combination with irinotecan and infusional 5-FU/folinic acid (FOLFIRI). These analyses demonstrated improved outcome for patients with *RAS* wild-type mCRC who received treatment including cetuximab, with overall survival improved in both studies ***(Van Cutsem et al., 2010).***

At the time of initial reporting, overall survival data were not available for the study. In addition, *RAS* tumor mutation data were not completely available for all of patients in the intention-to-treat (ITT) population. Although comparison of the baseline characteristics and efficacy data suggested that the *RAS* population was essentially representative of the ITT population, it was believed that the accuracy and strength of the conclusions would be increased if tumor *KRAS* mutation status could be determined for a higher proportion of patient samples. This study therefore reports an updated analysis based on the consideration of overall survival and other end points in an increased population of patients for which tumor *RAS* mutation status has been determined ***(Lievre et al., 2008).***

Patients were randomly assigned to receive FOLFOX-4 (oxaliplatin 85 mg/m^2; folinic acid 200 mg/m^2, followed by 5-FU, as a 400 mg/m^2 intravenous bolus then a 600 mg/m^2 infusion over 22 h, days 1 and 2 of a 14-day

cycle) with or without cetuximab (initial dose 400 mg/m^2 and 250 mg/m^2/week thereafter), until disease progression or unacceptable toxicity, as first-line treatment for mCRC. Response was assessed radiologically, every 12 weeks ***(De Roock et al., 2008).***

The addition of cetuximab to first-line FOLFOX chemotherapy statistically significantly improved PFS, OS, and ORR in pts with RAS wt mCRC. The TAILOR study met its primary objective and confirms cetuximab in combination with chemotherapy as a standard-of-care first-line treatment regimen for patients with RAS wt mCRC ***(Qin et al., 2016).***

AIM OF THE WORK

Retrospective analyses of progression-free survival, overall survival, overall response rate, resectability and safety within the different patient populations with metastatic cancer colon treated by cetuximab plus FOLFOX versus FOLFOX alone.

PATIENTS AND METHODS

Type of study: A Retrospective controlled trial study.

Study setting: Ain shams University Teaching Hospital and Alexandria Military Hospital. All data was collected from patients files regarding: Personal data. Pathology reports. Radiological reports. Progression free survival. Overall survival. Overall response rate. Resectability. Safety.

Study period: 5 years (from January 2012 to December 2016)

Study population: The study was committed on 100 patients with metastatic cancer colon

Patients were randomized into 2 equal groups: *Group (A):* 50 patients treated by FOLFOX-4 (oxaliplatin 85 mg/m^2; folinic acid 200 mg/m^2, followed by 5-FU, as a 400 mg/m^2 intravenous bolus then a 600 mg/m^2 infusion over 22 h, days 1 and 2 of a 14-day cycle) with cetuximab (initial dose 400 mg/m^2 and 250 mg/m^2/week thereafter). These 50 patients received treatment in Alexandria military hospital. ***Group (B):*** 50 patients treated by FOLFOX-4 (oxaliplatin 85 mg/m^2; folinic acid 200 mg/m^2, followed by 5-FU, as a 400 mg/m^2 intravenous bolus then a 600 mg/m^2 infusion over 22 h, days 1 and 2 of a 14-day cycle) alone**.** these 50 patients received treatment in Ain shams university teaching hospital.

Inclusion criteria: Adults > 18 years old giving informed consent. Patients with metastatic cancer colon. *RAS* mutation status wild type. Patients treated by folfox.

Exclusion criteria: Non metastatic cancer colon. *RAS* mutation status mutant. Patients with mtastatic cancer colon to the brain. Patients with double primary tumors.

Sampling Method: Retrospective study.

Sampling Size: 100 patients.

Study interventions: Treatment by cetuximab plus FOLFOX-4 versus FOLFOX-4 alone.

Ethical considerations: This study was carried out after obtaining approval of ethical committee of faculty of medicine-Ain Shams university hospital.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also qualitative variables were presented as number and percentages. The Comparison between groups with qualitative data were done by using ***Chi-square test***. The comparison between two groups with quantitative data and parametric distribution were done by using ***Independent t-test***.; While data with non parametric distribution were done by using ***Mann-Whitney test.*** The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P > 0.05: Non significant. P < 0.05: Significant. P < 0.01: Highly significant.

RESULTS

Table (1): Descriptive data regarding Demographic and anthropometric measures of the studied cases.

		No. = 100
Age	Mean ± SD	55.69 ± 9.82
	Range	33 – 76
Gender	Female	42 (42.0%)
	Male	58 (58.0%)
PS	1	63 (63.0%)
	2	35 (35.0%)
	3	2 (2.0%)

Special h	Non-smoker	54 (54.0%)
	Smoker	46 (46.0%)
Medical history	Negative	46 (46.5%)
	DM	19 (19.2%)
	HTN	32 (32.3%)
	DM+HTN	2 (2.0%)
Family History	No	59 (59.0%)
	Yes	41 (41.0%)
Surgical History	No	88 (88.0%)
	Yes	12 (12.0%)
Risk Factor	Negative	46 (46.0%)
	DM	20 (20.0%)
	HTN	32 (32.0%)
	DM+HTN	2 (2.0%)
Side	Right	39 (39.0%)
	Left	61 (61.0%)

Table (2): Descriptive data regarding pathology, grade and metastatic sites.

		No.	%
Pathology	Adenocarcinoma	100	100.0%
Grade	I	25	25.0%
	II	55	55.0%
	III	20	20.0%
Metastatic site	Liver	80	80.0%
	2 organs except perit	7	7.0%
	Peritonium	13	13.0%

Table (3): Descriptive data regarding T, N and stage.

		No.	%
T	T4a	35	35.0%
	T4b	25	25.0%
	T4c	40	40.0%
N	N0	2	2.0%
	N1	33	33.0%
	N2	65	65.0%
Stage	Iva	35	35.0%
	IVb	25	25.0%
	IVc	40	40.0%

Table (4): Descriptive data regarding Time of metastasis, Site of biopsy, Site of biopsy, Imaging, CEA, Type of previous treatment and Aim of the treatment.

		No. = 100
Time of metastasis	From the start	100 (100.0%)
Site of biopsy	Liver	40 (40.0%)
	Colon	60 (60.0%)
	Other	0 (0.0%)
Imaging	Ct	43 (43.0%)
	CT+Colon	7 (7.0%)
	PET/CT	36 (36.0%)
	PET/CT + Colon	14 (14.0%)
CEA	Median (IQR)	18.5 (7 - 123)
	Range	0 – 910
Type of previous treatment	No	100 (100.0%)
Aim	Curative	31 (31.0%)
	Palliative	69 (69.0%)

Table (5): Descriptive data regarding response after three and six months.

		No.	%
Response after 3 months	Regression	93	93.0%
	Stationary	2	2.0%
	Progression	5	5.0%
	Can't be assessed	0	0.0%
Response after 6 months	Regression	62	62.0%
	Stationary	16	16.0%
	Progression	18	18.0%
	Can't be assessed	4	4.0%

Table (6): Descriptive data regarding side effects, treatment received and resectability.

		No.	%
Side effect	Nausea + vomiting + gastritis	28	28.0%
	Anemia + Neutropenia + thrombocytopenia	31	31.0%
	Neuropathy	22	22.0%
	Embolism, DVT	13	13.0%
	Renal insult	6	6.0%
Treatment	Folfox	50	50.0%
	Folfox + Erbitux	50	50.0%
Resectablity	Resectable	33	33.0%
	Irresectable	67	67.0%

Table (7): Descriptive data regarding PFS, relapse,OAS and death.

		No. = 100
PFS	Median (IQR)	10 (8 - 18)
	Range	3 – 42
Relapse	No	0 (0.0%)
	Progress	100 (100.0%)
OAS	Median (IQR)	17.5 (12 - 27)
	Range	4 – 60
Death	Alive	4 (4.0%)
	Died	96 (96.0%)

Table (8): Comparison between Folfox only and folfox-Erbitux regarding Demographic and anthropometric data.

		Folfox only	Folfox + Erbitux	Test value	P-value	Sig.
		No. = 50	No. = 50			
Age	Mean ± SD	53.70 ± 9.34	57.68 ± 9.98	2.059•	0.042	S
	Range	33 – 72	36 – 76			
Gender	Female	27 (54.0%)	15 (30.0%)	5.911*	0.015	S
	Male	23 (46.0%)	35 (70.0%)			
PS	1	31 (62.0%)	32 (64.0%)	0.044*	0.978	NS
	2	18 (36.0%)	17 (34.0%)			
	3	1 (2.0%)	1 (2.0%)			
Special habits	Non-smoker	30 (60.0%)	24 (48.0%)	1.449*	0.229	NS
	Smoker	20 (40.0%)	26 (52.0%)			
Medical history	Negative	26 (53.1%)	20 (40.0%)	5.477*	0.140	NS
	DM	6 (12.2%)	13 (26.0%)			
	HTN	15 (30.6%)	17 (34.0%)			
	DM+HTN	2 (4.1%)	0 (0.0%)			
Family History	No	26 (52.0%)	33 (66.0%)	2.026*	0.155	NS
	Yes	24 (48.0%)	17 (34.0%)			
Surgical History	No	45 (90.0%)	43 (86.0%)	0.379*	0.538	NS
	Yes	5 (10.0%)	7 (14.0%)			

Risk Factor	Negative	27 (54.0%)	20 (40.0%)	4.708*	0.195	NS
	DM	6 (12.0%)	13 (26.0%)			
	HTN	15 (30.0%)	17 (34.0%)			
	DM+HTN	2 (4.0%)	0 (0.0%)			
Side	Right	21 (42.0%)	18 (36.0%)	0.378*	0.539	NS
	Left	29 (58.0%)	32 (64.0%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test; •: Independent t-test

Table (9): Comparison between Folfox only and folfox-Erbitux regarding pathology, grade and metastatic sites.

		Folfox only		Folfox + Erbitux		Test value*	P-value	Sig.
		No.	%	No.	%			
Pathology	Adenocarcinoma	50	100.0%	50	100.0%	NA	NA	NA
Grade	I	13	26.0%	12	24.0%	0.058	0.971	NS
	II	27	54.0%	28	56.0%			
	III	10	20.0%	10	20.0%			
Metastatic site	Liver	44	88.0%	36	72.0%	4.009	0.135	NS
	2 organs except perit	2	4.0%	5	10.0%			
	Periton	4	8.0%	9	18.0%			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test

Table (10): Comparison between Folfox only and folfox-Erbitux regarding T,N and stage.

		Folfox only		Folfox + Erbitux		Test value*	P-value	Sig.
		No.	%	No.	%			
T	T4a	16	32.0%	19	38.0%	0.397	0.820	NS
	T4b	13	26.0%	12	24.0%			
	T4c	21	42.0%	19	38.0%			
N	N0N	0	0.0%	2	4.0%	2.061	0.357	NS
	N1	16	32.0%	16	32.0%			
	N2	34	68.0%	32	64.0%			
Stage	Iva	16	32.0%	19	38.0%	0.397	0.820	NS
	IVb	13	26.0%	12	24.0%			
	IVc	21	42.0%	19	38.0%			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test

Table (11): Comparison between Folfox only and folfox-Erbitux regarding time of metastasis, site of biopsy, imaging, CEA, type of previous treatment and aim of treatment.

		Folfox only	Folfox + Erbitux	Test value	P-value	Sig.
		No. = 50	No. = 50			
Time of metastasis	From the start	50 (100.0%)	50 (100.0%)	NA	NA	NA
Site of biopsy	Liver	19 (38.0%)	21 (42.0%)	0.167*	0.683	NS
	Colon	31 (62.0%)	29 (58.0%)			
	Other	0 (0.0%)	0 (0.0%)			
Imaging	Ct	30 (60.0%)	13 (26.0%)	11.927*	0.008	HS
	CT+Colon	2 (4.0%)	5 (10.0%)			
	PET/CT	13 (26.0%)	23 (46.0%)			
	PET/CT + Colon	5 (10.0%)	9 (18.0%)			
CEA	Median (IQR)	12 (6 - 62)	37 (10 - 144)	-1.962‡	0.050	NS
	Range	0 – 910	0 – 910			
Type of previous treatment	No	50 (100.0%)	50 (100.0%)	NA	NA	NA
Aim	Curative	11 (22.0%)	20 (40.0%)	3.787*	0.052	NS
	Palliative	39 (78.0%)	30 (60.0%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test; ‡: Mann Whitney test

Table (12): Comparison between Folfox only and folfox-Erbitux regarding response after 3 and 6 months.

		Folfox only		Folfox + Erbitux		Test value*	P-value	Sig.
		No.	%	No.	%			
Response rate after 3 months	Regression	46	92.0%	47	94.0%	0.211	0.900	NS
	Stationary	1	2.0%	1	2.0%			
	Progression	3	6.0%	2	4.0%			
	Can't be assessed	0	0.0%	0	0.0%			
Response rate after 6 months	Regression	28	56.0%	34	68.0%	2.053	0.562	NS
	Stationary	9	18.0%	7	14.0%			
	Progression	10	20.0%	8	16.0%			
	Can't be assessed	3	6.0%	1	2.0%			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test

Table (13): Showing comparison between Folfox only and folfox-Erbitux regarding side effects and resectability.

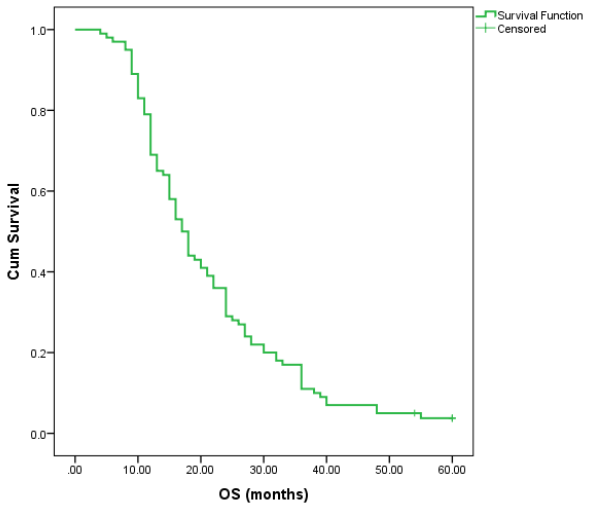
		Folfox only		Folfox + Erbitux		Test value*	P-value	Sig.
		No.	%	No.	%			
Side effect	Nausea + vomiting + gastritis	17	34.0%	11	22.0%	4.226	0.376	NS
	Anemia + Neutropenia + thrombocytopenia	17	34.0%	14	28.0%			
	Neuropathy	9	18.0%	13	26.0%			
	Embolism,DVT	4	8.0%	9	18.0%			
	Renal insult	3	6.0%	3	6.0%			
Resectablity	Resectable	14	28.0%	19	38.0%	1.131	0.288	NS
	Irresectable	36	72.0%	31	62.0%			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test

Table (14): Showing comparison between Folfox only and folfox-Erbitux regarding PFS, relapse, OS and death.

		Folfox only	Folfox + Erbitux	Test value	P-value	Sig.
		No. = 50	No. = 50			
PFS	Median (IQR)	9 (6 - 12)	12 (9 - 21)	-1.737	0.082	NS
	Range	3 – 30	3 – 42			
Relapse	No	0 (0.0%)	0 (0.0%)	NA	NA	NA
	Progress	50 (100.0%)	50 (100.0%)			
OS	Median (IQR)	16 (12 - 24)	22 (13 – 33)	-2.178	0.029	S
	Range	5 – 54	4 – 60			
Death	Alive	1 (2.0%)	3 (6.0%)	1.042	0.307	NS
	Died	49 (98.0%)	47 (94.0%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test; ‡: Mann Whitney test



No.	OS (months)		95% CI		OS at (%)		
	Median	SE	Lower	Upper	1 year	2 years	3 years
100	17	1.071	14.9	19.1	79.00%	29.00%	11.00%

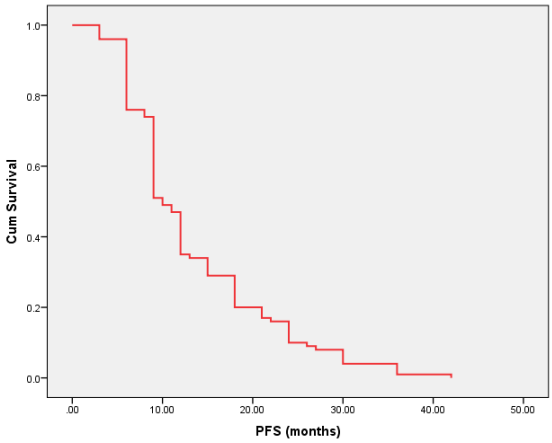


Figure (1): Kaplan Mayer analysis for OS for all the studied cases.

Figure (2): Kaplan Mayer analysis for PFS for all the studied cases.

No.	PFS (months)		95% CI		PFS at (%)		
	Median	SE	Lower	Upper	1 year	2 years	3 years
100	10	0.513	8.995	11.005	47.00%	10.00%	4.00%

Table (15): Kaplan Mayer Survival Analysis for the comparison between the two studied groups regarding overall survival (OS) (months).

Treatment	Total N	N of Events	OS (months)		95% CI		Test value	P-value	Sig.
			Median	SE	Lower	Upper			
Folfox	50	49	16	2.019	12.043	19.957	6.180	0.013	S
Folfox + Erbitux	50	47	21	2.828	15.456	26.544			

Table (16): Kaplan Mayer Survival Analysis for the comparison between the two studied groups regarding progression free survival (PFS) (months).

Treatment	Total N	N of Events	PFS (months)		95% CI		Test value	P-value	Sig.
			Median	SE	Lower	Upper			
Folfox	50	50	9	0.251	8.509	9.491	4.940	0.026	S
Folfox + Erbitux	50	50	12	1.762	8.546	15.454			

Table (17): Relation of overall survival with the other studied parameters in all patients.

		Total N	N of Events	Median	SE	95% CI		Test value	P-value	Sig.
						Lower	Upper			
Age >55	< 55 yrs	46	42	22	2.422	17.252	26.748	18.316	<0.001	HS
	> 55 yrs	54	54	13	1.13	10.786	15.214			
Gender	Female	42	40	17	1.21	14.629	19.371	0.846	0.358	NS
	Male	58	56	18	2.96	12.199	23.801			
PS	1	63	59	22	1.587	18.889	25.111	20.169	<0.001	HS
	2	35	35	12	0.715	10.599	13.401			
	3	2	2	10	.	.	.			
Special h	Non-smoker	54	52	18	1.836	14.402	21.598	0.093	0.760	NS
	Smoker	46	44	15	2.261	10.569	19.431			
Medical history	Negative	46	43	20	2.119	15.846	24.154	5.186	0.159	NS
	DM	19	18	17	1.306	14.441	19.559			
	HTN	32	32	12	2.263	7.565	16.435			
	DM+HTN	2	2	8	.	.	.			
Family	No	59	58	18	1.144	15.758	20.242	1.285	0.257	NS

History	Yes	41	38	17	2.134	12.818	21.182			
Surgical History	No	88	84	16	1.103	13.837	18.163	0.372	0.542	NS
	Yes	12	12	20	3.464	13.21	26.79			
Risk Factor	Negative	46	43	20	2.119	15.846	24.154	4.949	0.176	NS
	DM	20	19	16	1.491	13.078	18.922			
	HTN	32	32	12	2.263	7.565	16.435			
	DM+HTN	2	2	8	.	.	.			
Side	Right	39	38	14	1.135	11.775	16.225	4.574	0.032	S
	Left	61	58	21	1.95	17.178	24.822			
Grade	I	25	24	24	2.498	19.104	28.896	14.537	0.001	HS
	II	55	52	16	1.058	13.927	18.073			
	III	20	20	11	0.894	9.247	12.753			
Metastatic site	Liver	80	77	17	1.22	14.609	19.391	4.105	0.128	NS
	2 organs except perit	7	6	22	2.619	16.868	27.132			
	Periton	13	13	15	3.595	7.954	22.046			
N	N0	2	2	9	.	.	.	1.382	0.501	NS
	N1	32	30	17	1.414	14.228	19.772			
	N2	66	64	17	1.523	14.014	19.986			
Stage	Iva	35	31	30	2.464	25.171	34.829	54.826	<0.001	HS
	IVb	25	25	17	1.225	14.6	19.4			
	IVc	40	40	12	0.632	10.76	13.24			
Site of biopsy	Liver	40	38	16	1.581	12.901	19.099	0.201	0.654	NS
	Colon	60	58	18	1.932	14.213	21.787			
Imaging	Ct	43	42	16	1.227	13.596	18.404	2.023	0.568	NS
	CT+Colon	7	7	18	3.928	10.301	25.699			
	PET/CT	36	34	16	2.25	11.59	20.41			
	PET/CT + Colon	14	13	24	2.777	18.556	29.444			
Aim	Curative	31	27	28	5.217	17.775	38.225	22.280	<0.001	HS
	Palliative	69	69	15	0.828	13.376	16.624			
Resectablity	Resectable	33	29	36	1.805	32.462	39.538	63.070	<0.001	HS
	Irresectable	67	67	14	1.116	11.813	16.187			

Table (18): Relation of PFS with the other studied parameters in all patients.

		Total N	N of Events	Median	SE	95% CI		Test value	P-value	Sig.
						Lower	Upper			
Age >55	< 55 yrs	46	46	15	2.033	11.016	18.984	15.416	<0.001	HS
	> 55 yrs	54	54	9	0.217	8.576	9.424			
Gender	Female	42	42	9	0.747	7.536	10.464	2.288	0.130	NS
	Male	58	58	12	0.75	10.53	13.47			
PS	1	63	63	12	1.134	9.778	14.222	22.536	<0.001	HS
	2	35	35	6	0.771	4.488	7.512			
	3	2	2	8	.	.	.			
Special h	Non-smoker	54	54	12	0.638	10.749	13.251	0.068	0.794	NS
	Smoker	46	46	9	0.306	8.401	9.599			
Medical history	Negative	46	46	12	1.448	9.162	14.838	4.381	0.223	NS
	DM	19	19	9	0.307	8.397	9.603			
	HTN	32	32	9	0.556	7.911	10.089			
	DM+HTN	2	2	6	.	.	.			
Family History	No	59	59	10	0.64	8.746	11.254	1.630	0.202	NS
	Yes	41	41	10	1.28	7.491	12.509			
Surgical History	No	88	88	9	0.374	8.266	9.734	0.452	0.501	NS
	Yes	12	12	12	2.049	7.983	16.017			
Risk Factor	Negative	46	46	12	1.448	9.162	14.838	4.091	0.252	NS
	DM	20	20	9	0.313	8.387	9.613			
	HTN	32	32	9	0.556	7.911	10.089			
	DM+HTN	2	2	6	.	.	.			

Side	Right	39	39	9	0.268	8.475	9.525	3.605	0.058	NS
	Left	61	61	12	0.386	11.243	12.757			
Grade	I	25	25	15	1.837	11.399	18.601	13.574	0.001	HS
	II	55	55	9	1.03	6.981	11.019			
	III	20	20	8	0.839	6.356	9.644			
Metastatic site	Liver	80	80	9	0.516	7.989	10.011	6.209	0.045	S
	2 organs except perit	7	7	15	3.928	7.301	22.699			
	Periton	13	13	6	1.797	2.477	9.523			
N	N0	2	2	6	.	.	.	0.037	0.982	NS
	N1	32	32	9	0.627	7.77	10.23			
	N2	66	66	11	0.602	9.821	12.179			
Stage	Iva	35	35	21	2.342	16.409	25.591	48.118	<0.001	HS
	IVb	25	25	9	0.414	8.189	9.811			
	IVc	40	40	9	0.632	7.761	10.239			
Site of biopsy	Liver	40	40	9	1.18	6.687	11.313	0.016	0.901	NS
	Colon	60	60	11	0.968	9.102	12.898			
Imaging	Ct	43	43	9	0.503	8.014	9.986	3.493	0.322	NS
	CT+Colon	7	7	9	3.928	1.301	16.699			
	PET/CT	36	36	9	1.385	6.286	11.714			
	PET/CT + Colon	14	14	15	2.777	9.556	20.444			
Aim	Curative	31	31	18	1.356	15.342	20.658	22.154	<0.001	HS
	Palliative	69	69	9	0.213	8.582	9.418			
Resectability	Resectable	33	33	22	1.723	18.624	25.376	65.462	<0.001	HS
	Irresectable	67	67	9	0.181	8.646	9.354			

DISCUSSION

We found that the initial treatment of metastatic colorectal cancer with a combination of Cetuximab plus FOLFOX, as compared with FOLFOX alone, reduced the risk of disease progression by 33.4% {hazard ratio, (95% CI)} {0.666(0.443 – 1.001, P = 0.051). The addition of cetuximab to FOLFOX also increased the response rate by nearly 13%. There was significant difference between the treatment groups in overall survival by 39% {hazard ratio (95% CI)}{0.610(0.404-0.920), P = 0.018}.

Treatment added after the conclusion of a study can confound the analysis of overall survival and in this study,. Adding cetuximab to FOLFOX increased the rate of resection of metastases by 10%, and this increase improves the potential for cure or long-tem survival**.**

Tumor tissue for the analysis of KRAS mutation status was available from all the patients. The hazard ratio for progression-free survival among patients in the cetuximab–FOLFOX group, as compared with the FOLFOX group, was 0.68 (95% CI, 0.50 to 0.94), which suggests that the cetuximab–FOLFOX combination reduces the risk of progression in such patients. The hazard ratio of 0.68 for progression- free survival in this group is consistent with the hazard ratio of 0.57 reported in the randomized,

RAS mutation status was available from all the patients then our patients were selected by eliminating patients with RAS mutations ,one group received FOLFOX plus Erbitux and the other group received FOLFOX alone due to financial reasons.

The safety profile of the cetuximab–FOLFOX treatment was in line with that expected. The incidence rates of neuropathy, DVT and infusion-related reactions were higher with cetuximab plus FOLFOX than with FOLFOX alone, and there was no significant difference regarding the overall incidence of grade 3 or 4 adverse events in both groups. However, these adverse events were generally manageable.

This study provides confirmation that, as compared with FOLFOX alone, cetuximab plus FOLFOX reduces the risk of progression of metastatic colorectal cancer when used as the first-line treatment and that this benefit is seen in patients with wild-type–RAS tumors.

Confirmed tumour response was evaluated by an Independent Review Committee using modified World Health Organisation (WHO) criteria. PFS time was defined as the time in months from randomisation until radiological confirmed PD was first observed, or death occurred due to any cause within 90 days after the last tumour assessment or randomisation. In patients without a progression date or death date more than 90 days after the last tumour assessment or randomisation, the PFS time was censored on the date of last tumour assessment before the end of the study or randomisation, whatever came later. Overall survival time was defined as the time

from the day of randomisation to death. For patients who were still alive at the time of study analysis or who were lost to follow up, survival time was censored at the last recorded date that the patient was known to be alive or at the date of data cutoff, whatever occurred earlier.

When planning this study, a 19-months' median survival was expected for the combination of Erbitux and the chemotherapeutic regimen, yet survival was at least 22 months in this group. Better chemotherapeutic regimens, patient selection, and changing multidisciplinary management likely contributed to these outcomes as did the exclusion of patients with KRAS mutations.

This eligibility change increased the proportion of study patients who might benefit from cetuximab but also improved the prognosis for the entire group by eliminating patients with RAS mutations. Also, patients in this study likely had lower tumor burden compared with patients who participated in earlier studies as a result of better imaging at diagnosis as well as the coincidental detection of small cancers when patients undergo diagnostic imaging for other indications. The majority of patients also had access to cetuximab because each biologic therapy was commercially available. 38 percent of patients who received the combination of Erbitux and the chemotherapeutic regimen were rendered temporarily disease free with surgery of all sites of disease. This also contributed to the survival results.

the study achieved the primary objective by demonstrating a significant improvement in the probability of being alive without disease progression when Erbitux is added to chemotherapy for patients with Wild type RAS tumors. The difference in median OS for patients withWild type RAS status, although not statistically significant, was also favorable, with a 6 month improvement in the Erbitux-FOLFOX arm compared with the FOLFOX arm. There was a statistically significant interaction between the treatment effect and RAS tumor status for The goal of the primary OS analysis was to obtain median estimates. Responses were more frequent in the Erbitux-FOLFOX group versus the FOLFOX group and resection rates were higher.

All planned subsets consistently demonstrated favorable effects of Erbitux on PFS, with the exception of patients aged more than 55, and the small subset of patients with ECOG PS of 2. Importantly, however, a favorable OS effect was observed in men. In addition, absolute differences in RR were similar between men and women.

Furthermore, our observations regarding beneficial treatment effects upon the addition of cetuximab to FOLFOX in patients with RAS wild-type tumours is consistent with prior data from CRYSTAL and PRIME trials.

Additionally, in the phase III CALGB/SWOG 80405 trial, patients in the RAS wild-type subgroup who received FOLFOX plus cetuximab had a long overall survival time. Taken together with the survival data from the phase III FIRE-3 trial and the phase II PEAK trial, the above observations indicate that in patients with RAS wild type tumors, EGFR antibody therapy in combination with first-line chemotherapy can now achieve median overall survival times in excess of 20 months.

Nevertheless, and consistent with the current revised European regulatory label, restricting cetuximab administration to patients with RAS wild-type tumours seems to enable the further tailoring of therapy to maximise patient benefit.

CONCLUSION

We concluded that first-line treatment with cetuximab plus FOLFOX, as compared with FOLFOX alone, reduced the risk of progression of metastatic colorectal cancer.

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