Efficacy and Safety of Bevacizumab in Combination with Chemotherapy for Colorectal Cancer – A Real World Study in China

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Abstract

Background

Large scale randomized trials have demonstrated that bevacizumab in addition to chemotherapy as first-line or second-line treatment has significant survival benefits. We aim to explore the clinical impact of bevacizumab in combination with chemotherapy in first-line or second-line in patients with colorectal cancer (CRC).

Methods

The medical records of patients with CRC who received bevacizumab at first or second-line of treatment were collected retrospectively. The primary outcome of the study was to evaluate the efficacy of bevacizumab in combination with chemotherapy by survival endpoints i.e. overall survival (OS) and progression-free survival (PFS) and the secondary outcome was to evaluate its safety by incidence of adverse events (AE).

Results

Fifty-one patients with CRC had met the selection criteria for treatment with bevacizumab to either cetuximab or FOLFOX or both. The median age was 54 years. During follow-up, ten patients had exhibited progression after treatment while 5 patients died. The median OS and PFS of the overall population were not reached. The Cox proportional regression analysis revealed no significant prognostic factors of OS and PFS for treatment with bevacizumab in various demographic subgroups. The 1-year PFS rates of all 51 patients was 76%. The 1-year and 3-year OS rates for all 51 patients were 95% and 88%, respectively. Toxicities were usually mild in nature, with nausea, vomiting, hand and foot syndrome, neutropenia, asthenia and palpitation being the commonly reported adverse events.

Conclusion

In this real-world setting, the efficacy and safety of bevacizumab in combination with chemotherapy is limited and further research is warranted as to whether bevacizumab with chemotherapy is an optimal treatment as first-line or second-line therapy in Chinese CRC patients.

Background

Colorectal cancer (CRC) represents the third most common cancer worldwide accounting for 1,849,518 (10.2%) of new cases and second most deadly cancer with 880,792 (9.2%) cases across all the age groups in 2018.(1) The 5-year survival rate of CRC is estimated to be 64.4% based on SEER data from 2009–2015.(2) This disease is more commonly observed in men than in women especially among those with African American descent.(2) The rates of CRC was observed to be higher among some regions such as North

America, Australia and Europe in contrast to Asia, Africa and South America where lower rates of patients with CRC were reported.(3) The higher rates of CRC in patients could be attributed to “westernized lifestyle” including physical inactivity, obesity, increased alcohol consumption and long term smoking habits.(4) As per World Health Organization (WHO) in 2014, China alone has reported 253,427 new cases of CRC with the mortality rate being 13.2% in the overall population.(5)

The treatment options for CRC depends on the stage of cancer at diagnosis and has a strong influence on the length of survival.(2) The earlier CRC is diagnosed, the better chances a person has of surviving the next five years. About 38.8% of CRC patients are diagnosed at localized stage.(2) Chemotherapy (CT) is the first line of treatment usually preferred when tumor lesions do not reach the metastatic stage or are fully resectable.(6) The 5-fluorouracil (FU) based chemotherapies increased the overall survival (OS) to 12 months while addition of oxaliplatin and irinotecan to 5-FU increased the OS to 18 months.(7–9) However, use of chemotherapies is associated with higher toxicity rates such as neutropenia, stomach poisoning disease, hematopoietic disorders.(10, 11) The current therapy for CRC involves chemotherapy based on 5-FU with oxaliplatin and irinotecan and combined with anti-vascular endothelial growth factor (anti- VEGF) (e.g. bevacizumab, aflibercept, ramucirumab) or anti- epidermal growth factor receptor (EGFR) (e.g. cetuximab, panitumumab) targeted therapy.(12) According to the Asian consensus for CRC, most common regimens used in China for CRC include FOLFIRI, mFOLFOX6, XELOX, FOLFOXIRI, bevacizumab or cetuximab combined with raltitrexed or regorafenib.(13)

Bevacizumab is a humanized monoclonal antibody (moAb) that can bind to VEGF and is currently the most frequently used anti-VEGF moAb.(14, 15) Bevacizumab was indicated for the first-line as well as second-line treatment option for patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-FU based CT.(16) Many studies have reported that treatment with bevacizumab as first line treatment demonstrated variable results on survival. In the AVF2107g study, bevacizumab in combination with irinotecan/fluorouracil/leucovorin (IFL) significantly improved PFS, OS and ORR in comparison with IFL regimen alone.(17) In another study, a significant effect on PFS and OS was observed only when bevacizumab was added to fluoropyrimidine monotherapy.(18) Few randomized trials have reported significant improvements in OS in patients with mCRC when treated with bevacizumab in combination with CT in first and second line settings.(19, 20) However, a study with evidence from seven randomized controlled trials showed that addition of bevacizumab to first line chemotherapy reported significant survival in PFS [HR (95% CI): 0.68 (0.59–0.78)]; P < 0.00001 but not in OS [HR (95% CI): 0.89 (0.78–1.02)]; P = 0.08.(21) Continuation of bevacizumab beyond progression as first line treatment in mCRC improved the PFS with median of 6.8 months versus 5.0 months in bevacizumab and bevacizumab plus CT group, respectively.(22) Addition of oxaliplatin based CT to bevacizumab in first line therapy improved the PFS in mCRC patients. However no statistical significance was observed for OS and response rate (RR) on addition of bevacizumab.(23) Bevacizumab in second line setting also showed improved PFS and OS in various studies.(24, 25) Although an increasing number of studies have explored the treatment of bevacizumab in addition to chemotherapy in first-line and second-line setting, the efficacy of bevacizumab as a treatment option for patients with CRC is unclear due to contrasting results on the survival benefits. Therefore, data from a real-world study will help the clinicians to gain insight on the effectiveness of this treatment regimen in daily practice across various age groups and clinico-pathophysiological outcomes in patients with CRC.

This study was carried out to assess the efficacy and safety of the use of the bevacizumab therapy when added to FOLFOX or cetuximab in CRC patients in first-line settings.

Methods

Study design

This is a retrospective, observational, longitudinal real-world study in a single centre in China. All consecutive patients with CRC treated with bevacizumab either in first-line or second-line in combination with FOLFOX or cetuximab or their combination between October 2014 and March 2018 were included for the analysis. None of the fifty-one patients displayed KRAS mutation while BRAF mutations were unknown in thirty-two patients. Patients who were not treated with bevacizumab either alone or in combination with CT in first- or second-line settings and those with missing clinical data were excluded from analysis.

The study was approved by Ethics committee of The Third Affiliated Hospital of Kunming Medical University, Kunming, China (TKMMU-ONC-45378Z) and the study was performed in accordance with the Declaration of Helsinki.

Study Population

The medical records of patients with CRC who received bevacizumab as first-line or second-line of treatment in combination with chemotherapy was retrospectively collected. The information collected include gender, age at diagnosis, site of disease, American joint committee on cancer (AJCC) staging, body mass index (BMI), site and location of primary tumor, previous therapy (if any), line of current bevacizumab treatment and Eastern cooperative oncology group performance status (ECOG-PS). Information related to outcomes of interest included date of disease progression as per RECIST 1.1 criteria, date of death and incidence of adverse events. A total of 51 patients with 1- and 3-year survival data were identified and included for the analysis.

Study outcomes and endpoints

The primary outcome of the study was to evaluate efficacy of bevacizumab treatment assessed by survival endpoints (OS and PFS) while the secondary outcome was to evaluate safety of bevacizumab assessed by incidence of adverse events (AE). The OS end point was defined as the time between the date of start of bevacizumab treatment and the date of death from any cause and patients alive or lost to follow-up were censored at the date of last follow-up visit. PFS was defined as the time between the date of start of bevacizumab treatment and the date of detection of disease progression or death, whichever occurred first.

Statistical analysis

Quantitative variables were reported as mean and standard deviation while qualitative variables were provided as frequencies and percentages. Kaplan-Meier (KM) curves were constructed for OS and PFS stratified based on gender, age, AJCC staging, ECOG performance status, line of bevacizumab treatment, treatment combination, site and location of primary tumor and BMI. KM estimator function was used to predict 1- and 3-year survival for OS in different stratified groups of patients. The survival curves were

compared by log-rank test and cox proportional hazards regression analysis was performed for the different clinicopathological factors. Both, univariate and multi variable Cox proportional hazards regression analysis was performed to evaluate the factors predicting survival outcomes. Two-tailed P-values, less than 0.05 was considered to be statistically significant. All analysis was performed using R software (Version 3.6.1).

Results

Patient Demographics Details

A total of 51 patients from a single center in China received bevacizumab in addition to FOLFOX or cetuximab or both (cetuximab with FOLFOX). Most of the patients were older in age with thirty-one patients aged >50 years and had a median age of 54 years (range: 24-80 years). The median BMI of the overall population was 22.75 kg/m^2. Most of the patients belonged to ECOG PS ≤1 (n=41) and AJCC II stage (n=34). Majority of the patients were on first line therapy of bevacizumab with cetuximab and FOLFOX (n=43, 84.31%) while remaining were on bevacizumab with FOLFOX (n=4) and bevacizumab with cetuximab (n=1). Patients on second line therapy of bevacizumab with cetuximab and FOLFOX were very few (n=3). The main site of disease was rectum for 28 patients, while colon was site of the disease in 23 patients. Forty-seven patients exhibited left sided primary tumor while 4 patients had right sided primary tumor. None of the patients had history of KRAS mutation. Out of the 51 patients, 19 patients had no history of BRAF mutation while it was unknown in 32 patients. The demographic and the clinical characteristics details of overall study population are shown in table 1.

Survival analysis of overall patient population

The 1-year PFS rates of all 51 patients was 76% while the 3-year PFS survival rate was not reached due to no CRC progression after current line of treatment. Ten patients showed progression after one year of first line of current treatment. The 1-year and 3-year OS rates for all 51 patients were 95% and 88%, respectively. The median duration of treatment was 23.5 weeks (range: 9 weeks to 51.8 weeks). The median OS and PFS for various demographic subgroup of patients were not reached. The Kaplan Meir survival analysis revealed no significant difference in demographics characteristics of patients including gender, age at diagnosis, site of disease, AJCC staging, BMI, site and side of primary tumor, line of current bevacizumab treatment and ECOG PS (Table 2).

Survival Analysis of Subgroups based on Demographics Characteristics

The univariate analysis for PFS revealed that bevacizumab with chemotherapy was more effective in males [HR (95% CI): 0.68 (0.2-2.4)], aged ≤50 years [HR 95% CI: 2 (0.52 – 7.8)], AJCC ≤ II stage, BMI ≤25 kg/m^2 and rectum as main site of disease. There was no treatment difference between patients with ECOG PS ≤1 and ECOG PS>1. Addition of bevacizumab to cetuximab and FOLFOX treatment yielded better results than its addition to either cetuximab and FOLFOX regimen [HR (95% CI): 0.44 (0.094-2.1)]. However, no statistical significance was observed in any of these subgroups. Similarly, multivariate analysis for PFS revealed that bevacizumab with chemotherapy favoured male patients, aged ≤50 years, ECOG PS ≤1, rectum as the main site of disease, BMI ≤25 kg/m^2 and combination with cetuximab and FOLFOX (Table 2).

The univariate analysis for OS revealed no significant difference across the various subgroups for patient demographics. Addition of bevacizumab therapy to chemotherapy resulted in more effective response in males [HR (95% CI): 0.65 (0.092-4.6)], aged >50 years [HR (95% CI): 0.21 (0.022-2)], AJCC ≤ II [HR (95% CI): 6.8 (0.7-65)], rectum as main site of disease [HR (95% CI): 0.23 (0.024-2.3)] and BMI ≤25 kg/m^2 [HR (95% CI): 1.4 (0.14-13)]. The multivariate analysis for OS revealed favourable response in females, aged ≤50 years, AJCC ≤ II, rectum as main site of disease and BMI >25 kg/m^2 (Table 2).

Survival Analysis based on First Line of Treatment

Log-rank tests comparing the OS and PFS for patients stratified based on demographic factors revealed no statistically significant difference in survival curves. PFS was marginally better in males [HR (95% CI): 0.64 (0.18-2.2)], aged ≤50 [HR (95% CI): 1.8(0.47-7)], ECOG PS ≤1[HR (95% CI): 0.95(0.2-4.5)], AJCC ≤ II [HR (95% CI): 0.92(0.24-3.5)], rectum as main site of disease [HR (95% CI): 0.61(0.17-2.1)], BMI ≤25 kg/m^2 [HR (95% CI): 1.3(0.27-6)] and combination with cetuximab and FOLFIRI [HR (95% CI): 0.47(0.099-2.2)]. After adjusting for multiple variables, males, patients aged <60, with ECOG PS≤1, AJCC ≤II, BMI ≤25 and combination with cetuximab and FOLFIRI had marginally better PFS (Table 3).

OS was marginally better in males [HR (95% CI): 0.64(0.09-4.5)], aged >50 [HR (95% CI): 0.17(0.018-1.7)], rectum as main site of disease [HR (95% CI): 0.22(0.023-2.2)], BMI ≤25 [HR (95% CI): 1.3(0.13-12)]. After adjusting for multiple variables, patients aged >50, BMI >25 and rectum as site of disease had marginally better OS with bevacizumab (Table 3).

Safety in Overall Population as well as in First Line of Treatment

Toxicity was evaluated according to the WHO chemotherapeutic toxicity classification criteria (WHO criteria and Common Toxicity Criteria). Toxicities were usually observed in the acute stage, while late toxicity was rare. Fifteen patients (29.4%) reported grade I nausea and 26 patients (50.98%) with grade II nausea, 30 patients (58.82%) reported grade I neutropenia. Twenty-two patients (43.13%) experienced grade I vomiting while 15 patients (29.41%) reported hand and foot syndrome. Few patients reported other adverse events such as asthenia (7.84%) and palpitation (31.37%). No grade IV toxicity was observed. Toxicities associated with treatment with bevacizumab is reported in table 4.

Discussion

This study aimed to verify the efficacy and safety of addition of bevacizumab therapy to either cetuximab or FOLFOX or both in patients with CRC in real-world setting. Most of the clinical trials on bevacizumab have been carried out in the Western countries with a large number of subjects and positive results were also obtained, however, clinical trials in Asian countries are limited and usually carried in small sample size.(26) In China, bevacizumab was first approved in October 2010 for the treatment of mCRC.(27) A meta-analysis of bevacizumab with CT in first-line treatment showed statistically significant increase in PFS (HR = 0.56, 95% CI = 0.46–0.69, P < 0.00001) and OS (HR = 0.83, 95% CI = 0.76–0.91, P < 0.0001).(28) Similar results were observed on PFS and OS after treatment with bevacizumab monotherapy in Chinese patients with mCRC.(29, 30)

First-line treatment of bevacizumab in combination with FOLFIRI in a single arm, multicentre study with 55 patients with mCRC resulted in median PFS of 6 months and median OS of 17 months.(31) A study by Yin et al. demonstrated that addition of bevacizumab to chemotherapy in patients with mCRC significantly improved the OS in both first and second line of treatment compared to control group receiving CT alone (49.9 months versus 36.1 months; $P = 0.002$) and (34.8 months versus 24.6 months; $P = 0.022$). Further, PFS was prolonged in bevacizumab treated patients in both first- and second-line therapies (10.1 months versus 6.2 months; $P < 0.001$) and (6.3 months versus 3.1 months; $P < 0.001$). However, the OS were statistically insignificant when compared between first- and second-line bevacizumab groups ($P < 0.189$). This proves that bevacizumab combined with CT will bring survival benefit irrespective of the line of treatment.(32) In general, the clinical outcomes of bevacizumab in our study is good, as the median OS and PFS was not reached for the overall population. However, the cohort is still being followed up for further observations.

Age is a major risk factor for the incidence of CRC. CRC is predominantly a disease in older individuals with 90% of cases diagnosed over 50 years.(33) The percentage of deaths due to CRC is highest among people aged 75–84 years (24.3%).(2) Results from pooled analysis of RCTs showed that treatment with bevacizumab and CT added a meaningful benefit in older patients and was comparable with that observed in younger patients.(34) First-line bevacizumab based CTs were effective in patients > 75 years of age, however shorter PFS and OS was observed when compared to younger patients.(35) In our study, the Cox proportional hazard ratios showed that patients aged ≤ 50 years were more responsive to bevacizumab treatment than patients aged > 50 years. However, the current study does not draw any solid conclusion as only 20 patients out of 51 patients were aged ≤ 50 years. However, these data are important as it provides evidence that treatment in elderly patients with CRC is underrated. Further, improvement in PFS and OS due to bevacizumab treatment were found to be independent of gender disparities in another study.(36) Our analysis revealed that males were more responsive to bevacizumab treatment than females in both univariate and multivariate regression analysis, however, results were not statistically significant..

A meta-analysis of seven RCTs reported that female gender and rectal primary site were significant predictors for PFS benefit.(37) The univariate and multivariate HRs in our study showed that rectal site of disease was associated with a more favourable response on addition of bevacizumab to first-line CT than colon site of disease. The impact of primary tumour location on bevacizumab plus adjuvant CT in CRC patients remains controversial. It is an important prognostic factor to predict the clinical response of a patient to bevacizumab treatment. Loupakis et al. reported that clinical outcomes of both two-sided mCRC patients were improved by treatment with bevacizumab and CT.(38) A study of bevacizumab in first-line treatment demonstrated that the left sided primary tumour was superior compared to right sided tumour (median PFS and OS: 9.6 months 27.1 months versus 7.3 months and 19.4 months).(39) In another prospective study, the PFS of the left-sided primary tumour patients on bevacizumab plus FOLFIRI regimen showed superior results compared to right-sided tumour patients [unadjusted HR (95% CI): 0.31 (0.11–0.87)]; $P = 0.03$.(40) Though our study did not report any HRs with respect to OS and PFS, it was observed that for most of the patients, primary side of tumour was located on left side than the right side.

Bevacizumab is generally well-tolerated however is associated with risk of thromboembolic events.(20, 41) The other AEs associated with bevacizumab treatment include higher incident rates of hypertension,

proteinuria and bleeding.(22, 24) No grade IV toxicities were observed in our study. The toxicities majorly observed included grade II nausea, grade I neutropenia, grade I vomiting, grade I hand and foot syndrome which were mild in nature.

The choice of bevacizumab treatment with chemotherapy is dependent on patient comorbidities, preferences around toxicities and practical considerations such as convenience and cost. For patients with good ECOG PS, initial therapy with bevacizumab and combination regimen with FOLFOX, FOLFIRI and XELOX is preferred, while with poor ECOG PS status, fluoropyrimidine plus bevacizumab without second cytotoxic agent is recommended.(16) In China, most patients receive bevacizumab at their own expense due to high cost of the drug. In addition, due to concerns over toxicity with chemotherapy, the durations of bevacizumab and chemotherapy exposure may not be adequate.(32) This is the first study as per our knowledge to analyse the efficacy and safety of bevacizumab in combination to chemotherapy in a real world setting. However, the limitations of the study should be taken into account before drawing a conclusion. Since this study is based on real-world data in Chinese population, the small sample size of patients may introduce bias. Though our study points out the various demographic factors associated on deciding the clinical regimen for patient with CRC, large scale prospective studies are required to establish the efficacy of bevacizumab in clinical practice with respect to various socio-demographic details of patients.

Conclusion

Our study points out the various demographic factors associated on deciding the clinical regimen for patient with CRC. However, further research is warranted as to whether bevacizumab with chemotherapy is an optimal treatment as first-line or second-line therapy in Chinese CRC patients.

Abbreviations

CRC
Colorectal Cancer
OS
Overall survival
PFS
Progression-free survival
AE
Adverse events
CT
Chemotherapy
FU
5-Fluorouracil
VEGF
Vascular endothelial growth factor
EGRF
Epidermal growth factor receptor

IFL
Irinotecan/Fluorouracil/Leucovorin
AJCC
American Joint Committee on Cancer Staging
BMI
Body mass index
KM
Kaplan-Meier
ECOG-PS
Eastern cooperative oncology group performance status

Declarations

Ethics approval and consent to participate: The study was approved by Ethics committee of The Third Affiliated Hospital of Kunming Medical University, Kunming, China (TKMMU-ONC-45378Z) and the study was performed in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Tables

Table 1: Demographic Characteristics of Colorectal Cancer patients

Characteristics	Patients n (%)	Mean (SD)
Age (years)	-	54 (15.23)
Gender		
Male	29 (56%)	
Female	22 (43%)	
BMI		22.75 (2.011)
BMI ≤ 25 kg/m^2	41 (80.40%)	
BMI >25 kg/m^2	10 (19.61%)	
ECOG PS		
ECOG =0	7 (13.73%)	
ECOG =1	34 (66.67%)	
ECOG =2	10 (19.61%)	
AJCC Staging		
Stage I	0 (0)	
Stage II	34 (66.67%)	
Stage III	9 (17.65%)	
Stage IV	8 (15.69%)	
Previous line of treatment regimen		
Erbitux	1 (1.96%)	
Erbitux with FOLFOX	46 (90.20%)	
FOLFOX	4 (7.84%)	
Main site of disease		
Colon	23 (45.10%)	
Rectum	28 (54.90%)	
Line of current treatment		

First-line	47 (92.16%)
Second-line	4 (7.84%)
Progression of disease after treatment	
Yes	10 (19.61%)
No	41 (80.40%)
Death after current line of treatment	
Yes	5 (9.80%)
No	46 (90.20%)

Abbreviations: BMI: Body Mass Index, AJCC – American joint committee on cancer, ECOG – Eastern cooperative oncology group

Table 2: Survival Analysis of overall CRC patient population

Group	Median PFS/OS (95%CI)	Univariate HR (95% CI)	*P* value	Multi variable HR (95% CI)	*P* value	1-year survival (%)	3-years survival (%)
Progression Free survival							
Gender Male	NA (NA – NA)	0.68 (0.2 – 2.4)	0.542	0.53 (0.117 – 2.4)	0.409	83%	-
Gender Female	NA (11 – NA)	Ref		Ref		68%	-
Age ≤50	NA (NA – NA)	Ref	0.31	Ref	0.485	83%	-
Age>50	NA (14.6 – NA)	2 (0.52-7.8)		1.74 (0.369-8.2)		70%	-
ECOG Performance Status ≤1	NA (NA – NA)	Ref		Ref		76%	-
ECOG Performance Status >1	NA (NA – NA)	1 (0.15-18)	0.698	1.72 (0.178-16.6)	0.64	76%	-
AJCC Category ≤II	NA (NA – NA)	Ref		Ref		72%	-
AJCC Category >II	NA (14.6 – NA)	0.92(0.24-3.6)	0.901	1(0.222-5.2)	0.996	86%	-
Main Site of Disease = C	NA (10.2 – NA)	Ref	0.416	Ref	0.917	61%	-
Main Site of Disease = R	NA (NA – NA)	0.6 (0.17-2.1)		0.93(0.222-3.9)		84%	-
BMI Category ≤25	NA (NA – NA)	Ref		Ref		76%	-
BMI Category >25	NA (6.3 – NA)	1.3 (0.28-6.3)	0.71	1.31(0.151-11.4)	0.806	71%	-

Site of Primary Tumour = L	NA (NA – NA)	-	-	-	-	73%	-
Site of Primary Tumour = R	NA (NA – NA)	-	-	-	-	100%	-
Treatment Combination = Cetuximab/FOLFOX	NA (7.6 – NA)	Ref	0.305	Ref	0.38	60%	-
Treatment Combination = Cetuximab + FOLFOX	NA (NA – NA)	0.44 (0.094-2.1)		0.45(0.073-2.7)		78%	-
Line of Treatment = First	NA (NA – NA)	-	-	-	-	75%	-
Line of Treatment = Second	NA (NA – NA)	-		-		100%	-
Overall Survival							
Gender Male	NA (NA – NA)	0.65 (0.092-4.6)	0.671	1.18(0.13-10.2)	0.88	92%	92%
Gender Female	NA (NA – NA)	Ref		Ref		100%	80%
Age ≤50	NA (NA – NA)	Ref	0.176	Ref	0.313	95%	76%
Age>50	NA (NA – NA)	0.21 (0.022-2)		0.28(0.024-3.3)		96%	96%
ECOG Performance Status ≤1	NA (NA – NA)	-	-	-		94%	85%
ECOG Performance Status >1	NA (NA – NA)	-	-	-		100%	100%
AJCC Category ≤II	NA (NA – NA)	Ref	0.098	Ref	0.23	96%	96%
AJCC Category >II	NA (18.3 – NA)	6.8 (0.7-65)		4.73 (0.373-60)		94%	70%
Main Site of Disease = C	NA (NA – NA)	Ref	0.209	Ref	0.293	94%	75%

Main Site of Disease = R	NA (NA – NA)	0.23 (0.024-2.3)		0.28(0.026-3)		96%	96%
BMI Category ≤25	NA (NA – NA)	Ref	0.77	Ref	0.747	94%	89%
BMI Category >25	NA (NA – NA)	1.4 (0.14-13)		0.66 (0.055-8.1)		100%	80%
Site of Primary Tumour = L	NA (NA – NA)	-	-	-		95%	88%
Site of Primary Tumour = R	NA (NA – NA)	-	-	-		-	-
Treatment Combination = Cetuximab /FOLFOX	NA (NA – NA)	-	-	-		100%	100%
Treatment Combination = Cetuximab + FOLFOX	NA (NA – NA)	-		-		95%	85%
Line of Treatment = First	NA (NA – NA)	-		-		95%	87%
Line of Treatment = Second	NA (NA – NA)	-		-		100%	100%

Table 3: Survival Analysis of patients on first line treatment

Group	Median PFS/OS (95%CI)	Univariate HR (95% CI)	*P* value	Multi variable HR (95% CI)	*P* value	1-year survival (%)	3-years survival (%)
Progression Free survival							
Gender Male	NA (NA – NA)	0.64 (0.18 – 2.2)	0.48	0.52 (0.112 – 2.4)	0.397	82%	-
Gender Female	NA (11 – NA)	Ref		Ref		65%	-
Age ≤50	NA (NA – NA)	Ref	0.393	Ref	0.584	81%	-
Age>50	NA (14.6 – NA)	1.8 (0.47-7)		1.54 (0.327-7.3)		70%	-
ECOG Performance Status ≤1	NA (NA – NA)	Ref		Ref		74%	-
ECOG Performance Status >1	NA (NA – NA)	0.95 (0.2-4.5)	0.95	1.69 (0.184-15.5)	0.643	76%	-
AJCC Category ≤II	NA (NA – NA)	Ref		Ref		71%	-
AJCC Category >II	NA (14.6 – NA)	0.92(0.24-3.5)	0.898	0.97(0.202-4.7)	0.973	85%	-
Main Site of Disease = C	NA (10.2 – NA)	Ref	0.429	Ref	0.925	60%	-
Main Site of Disease = R	NA (NA – NA)	0.61 (0.17-2.1)		0.93(0.22-4.0)		83%	-
BMI Category ≤25	NA (NA – NA)	Ref		Ref		75%	-
BMI Category >25	NA (6.3 – NA)	1.3 (0.27-6)	0.77	1.26(0.152-10.4)	0.832	71%	-
Site of Primary Tumour = L	NA (NA – NA)	-	-	-		72%	-

Site of Primary Tumour = R	NA (NA – NA)	-	-	-		100%	-
Treatment Combination = Cetuximab/FOLFOX	NA (7.6 – NA)	Ref	0.339	Ref	0.388	60%	-
Treatment Combination = Cetuximab + FOLFOX	NA (NA – NA)	0.47 (0.099-2.2)		0.45 (0.075-2.7)		77%	-
Overall Survival							
Gender Male	NA (NA – NA)	0.64 (0.09-4.5)	0.655	83.58 (0.310-22496)	0.121	92%	92%
Gender Female	NA (NA – NA)	Ref		Ref		100%	78%
Age ≤50	NA (18.3 – NA)	Ref	0.127	Ref	0.069	94%	71%
Age>50	NA (NA – NA)	0.17 (0.018-1.7)		0.034 (0.00088-3.3)		96%	96%
ECOG Performance Status ≤1	NA (NA – NA)	-	-	-		94%	84%
ECOG Performance Status >1	NA (NA – NA)	-	-	-		100%	100%
AJCC Category ≤II	NA (NA – NA)	Ref	0.088	Ref	0.056	96%	96%
AJCC Category >II	NA (18.3 – NA)	7.2 (0.74-69)		84.734 (0.888-8079.9)		93%	67%
Main Site of Disease = C	NA (NA – NA)	Ref	0.197	Ref	0.077	94%	73%
Main Site of Disease = R	NA (NA – NA)	0.22 (0.023-2.2)		0.021 (0.00028-1.5)		96%	96%
BMI Category ≤25	NA (NA – NA)	Ref	0.841	Ref	0.252	94%	89%

BMI Category >25	NA (NA – NA)	1.3 (0.13-12)		0.189 (0.01091-3.3)		100%	80%
Site of Primary Tumour = L	NA (NA – NA)	-	-	-	-	95%	87%
Site of Primary Tumour = R	NA (NA – NA)	-	-	-		-	-
Treatment Combination = Cetuximab /FOLFOX	NA (NA – NA)	-	-	-	-	100%	100%
Treatment Combination = Cetuximab + FOLFOX	NA (NA – NA)	-	-	-	-	94%	85%

Table 4: Treatment related Toxicities with Bevacizumab in Patients with CRC

	Number of Patients (%)				
Toxicities	Grade 0	Grade I	Grade II	Grade III	Unknown
Nausea	5 (9.8%)	15 (29.4%)	26 (50.98%)	5 (9.8%)	-
Neutropenia	6 (11.76%)	30 (58.82%)	5 (9.80%)	-	10 (19.6%)
Vomiting	2 (3.92%)	22 (43.13%)	15 (29.41%)	1 (1.96%)	11 (21.57%)
Hand and foot syndrome	20 (39.22%)	15 (29.41%)	6 (11.76%)	1 (1.96%)	9 (17.65%)
Other Adverse events			Number of Patients (%)		
Asthenia	4 (7.84%)				
Palpitation	16 (31.37%)				
Unknown	31 (60.78%)				