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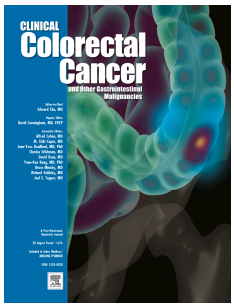

Prior bevacizumab and efficacy of later anti-epidermal growth factor receptor antibodies in metastatic colorectal cancer. Results from a large international registry

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Prior bevacizumab and efficacy of later anti-epidermal growth factor receptor antibodies in metastatic colorectal cancer. Results from a large international registry

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MicroAbstract

The sequencing of biologics used in metastatic colorectal cancer may impact outcomes. We analysed a multicentre registry to address a question that cannot be answered using current clinical trial data.

Specifically, we found that whether or not patients had received prior bevacizumab the impact of epidermal growth factor receptor antibodies in later lines of therapy was maintained.

Clinical Practice Points

- Bevacizumab and the epidermal growth factor receptor antibodies are biological therapies that improve survival in metastatic colorectal cancer.
- Patients with left sided primary tumours that are RAS wild type are most likely to benefit from treatment with an epidermal growth factor receptor inhibitor (EGFRI), whereas there are no predictive biomarkers for bevacizumab.
- Biologics are routinely combined with chemotherapy, but should not be used concurrently.
- The optimal sequencing and timing of biologic use in metastatic colorectal cancer is unknown and a subject of ongoing debate.
- In an analysis of a comprehensive clinical registry we have found no evidence that prior bevacizumab use impacts the activity of EGFRIs in later lines of therapy.
- Whilst a shorter time gap (< 6 months) between bevacizumab and epidermal growth factor receptor antibodies did not affect EGFRI activity in left sided primary tumours, it was associated with a shorter progression free survival in right sided primary tumours.
- When treating metastatic colorectal cancer, EGFRIs can be used after bevacizumab, in RAS wild type tumours, without their efficacy being compromised.
- When treating RAS wild type right sided primary tumours in later lines our data support a better outcome if the EGFRI is commenced more than 6 months after ceasing bevacizumab, although this finding may be a result of confounding rather than reflecting any true biologic interaction.

Abstract

Background. The FIRE-3 study reported that first line FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab, resulted in similar progression free survival (PFS) but improved overall survival (OS). A potential explanation is that the initial biologic administered in metastatic colorectal cancer (mCRC) impacts later line efficacy of the other. We sought to test this hypothesis.

Methods. We interrogated our mCRC registry (TRACC) regarding treatment and outcome data for RAS wild type patients receiving epidermal growth factor receptor antibodies (EGFRI) in second and subsequent lines. Survival outcomes from commencement of EGFRI were determined as a function of prior bevacizumab use and the period of time between ceasing bevacizumab and commencing EGFRI.

Results. Of 2061 patients, 222 eligible patients were identified, of whom 170 (77%) had received prior bevacizumab and 52 (23%) had not. PFS and OS from EGFRI commencement did not differ by prior bevacizumab use (median 3.8 V 4.2 months, HR 1.12. P=0.81 and 9.0 V 9.2 months HR 1.19. P=0.48 respectively) for the whole cohort or when analysed by side of primary tumour (left HR 1.07; p= 0.57; right HR 1.2; p= 0.52). PFS was significantly shorter in right sided primary tumours when the time between bevacizumab and EGFRI was < 6 versus > 6 months (median 2.2 V 6 months HR 2.23; p=0.01) but not in left sided (median 4.2 V 5.5 months; HR 1.12; P= 0.26)

Conclusions. Prior bevacizumab had no impact on the activity of subsequent EGFRI. The apparent impact of time between biologics in right sided tumours may reflect patient selection.

Keywords: biologics; sequencing; timing; interaction; survival;

Introduction:

Colorectal cancer (CRC) is a major health burden in Australia and worldwide, being the second leading cause of cancer related deaths.[1] In the treatment of metastatic colorectal cancer (mCRC), questions regarding optimal use of the available biologic options in the RAS wild type population have driven recent randomised studies comparing the sequence of epidermal growth factor receptor inhibiting antibodies; either cetuximab or panitumumab (EGFRI) and the anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab.[2,3] Such trials were conducted in the USA by the Cancer and Leukaemia Research Group (CALGB) and in Germany and Austria (FIRE-3). Patients were randomised to either biologic in the first line and thereafter, whilst not mandated or planned in the study protocols, could at the investigators discretion cross over to the alternate biologic in second line..[2,3] Whilst overall survival comparisons differed between these studies for the enrolled population, post hoc analyses defined a major impact of primary tumour side on survival outcomes.[4,5] Specifically, adding an EGFRI to first line chemotherapy improves survival in patients with left sided RAS wild type tumours. In contrast, across all first line studies, patients with right sided tumours do not benefit from EGFRI therapy.[6]

In the FIRE-3 study, the first to study biologic sequencing in RAS wild type metastatic colorectal cancer, the initial choice of biologic did not impact first line progression free survival (PFS), however improved overall survival (OS) was seen in patients randomised to initial cetuximab therapy.[3] Subsequently it was shown that the PFS for second line treatment with an EGFRI was lower than PFS for second line bevacizumab, suggesting the initial biologic use may impact response to later use of the alternate biologic.[7] Whilst EGFRI have proven activity in second and later treatment lines, these studies were conducted in an era with no or limited prior use of bevacizumab.[8,9] A recent study randomised patients to continue bevacizumab or to receive an EGFRI, after failure of first line chemotherapy plus bevacizumab. PFS and OS both favoured the continuation of bevacizumab.[10] In sum these data suggest the possibility that initial bevacizumab may alter the biology of tumour cells, reducing their sensitivity to subsequent EGFRI.[11]

Treatment and outcome data from large clinical registries may further inform our understanding of treatment sequencing, including whether prior bevacizumab impacts on the efficacy of later EGFRI. These analyses are of most value where treatment sequences or scenarios are not covered by

clinical trials, including analysis of patients who did and did not receive bevacizumab with first line chemotherapy and how this impacted the benefit of EGFRI therapy in later lines of treatment. Here we conduct this analysis of patients entered into the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry.[12] In addition, where prior bevacizumab had been used, we analysed whether there was any impact of the time elapsed since ceasing bevacizumab. As there are multiple potential confounders in this analysis due to selection biases inherent to any registry, we further examined the known impact by tumour side given the differential impact of EGFRI based on primary tumour location.

Methods

Databases and Dataset

The TRACC registry captures data at the point of care including careful annotation of baseline patient and tumour characteristics, treatment(s) received and patient outcome[12]. Data from this multicentre registry, including institutions across Australia and Hong Kong, is de-identified and linked using the BIOGRID Australia software platform, prior to analysis.

Chemotherapy drugs and biologics once reimbursed by the Australian Government under the Pharmaceutical Benefits Scheme (PBS) are freely available to patients. Prior to PBS approval treatment can only be accessed via clinical trials or patient access programs. We examined data from RAS wild-type patients diagnosed from July 2009 (when bevacizumab became PBS reimbursed as a first line therapy). EGFRI use in second and later lines, as monotherapy or in combination with chemotherapy, became PBS reimbursed from September 2011. From September 2015 first line use of EGFRI and second line use of bevacizumab became PBS reimbursed. We examined all patients diagnosed up until December 2016.

We analysed data related to clinical and pathologic factors known to impact survival outcomes, including patient demographics, sites of metastatic disease, number of metastatic sites, side of primary tumour, Eastern Co-operative Oncology Group (ECOG) performance status, whether metastases were synchronous or metachronous, whether the primary was intact, and time to progression during first line treatment. Metachronous metastases were those defined as appearing at least 6 months after diagnosis of the primary tumour. A right sided primary was defined as any tumour proximal to the splenic flexure, whereas a left sided primary was a tumour of the splenic flexure or more distal colon or rectum.

Patients who received an EGFRI in combination with chemotherapy or as a monotherapy in second or subsequent lines of treatment were included in the analysis. The specific antibody used (cetuximab or panitumumab) was recorded but data for both agents was combined given they are considered to have equivalent efficacy. Time to progression and overall survival data were calculated from the date of commencing the EGFRI.

Initially we analysed outcomes based on whether or not patients had received any prior bevacizumab. The group that did receive prior bevacizumab was then further split by the time period between last bevacizumab dose and first dose of EGFRI (<6 months versus > 6 months). Analyses were then performed separately for patients with left and right sided primary tumours.

Statistical Analyses

Progression free (PFS) and overall survival (OS), from the date the EGFRI was commenced, were calculated using the Kaplan Meier method. These were compared using the log rank test.

Progression was judged by local clinicians and imaging was not centrally reviewed.

All statistics were calculated using SAS Enterprise guide version 6.0 statistical software. Clinicopathologic differences between groups were assessed by the Chi-square and Wilcoxon rank sum tests for categorical and numerical variables, respectively.

P values < 0.05 were considered significant.

Ethical Approval

The TRACC registry received ethics approval at each participating institution to conduct combined analyses of de-identified patient data. Patients were not required to sign informed consent. This specific project also received ethics approval (Number 2009.113 from the Melbourne Health Human Research Ethics Committee)

Results

Patients

We identified 222 patients who had received an EGFRI in second or later lines of therapy, of whom 170 (77%) had received prior bevacizumab (Figure 1). Of the 170 bevacizumab treated patients 159 (92%) had received bevacizumab as part of first line therapy. Demographics, performance status, disease and treatment characteristics are summarized in Table 1. Generally, these were similar between the two groups, with the only significant difference being a longer time to progression on first line treatment in the group receiving bevacizumab. Approximately 50% of patients in each group received chemotherapy, nearly always irinotecan based, in combination with the EGFRI.

EGFRI efficacy

Whether or not prior bevacizumab had been used did not impact PFS on EGFRI (Figure 2), median being 3.8 versus 4.2 months respectively, with a hazard ratio (HR) of 1.12; P=0.81. Furthermore, no PFS difference on EGFRI was seen when patients with left and right sided primary tumours were analysed separately (Figure 2 B and C).

As the median time between ceasing bevacizumab and commencing the EGFRI was 6 months, this cut off was used to investigate any impact of the time period since last bevacizumab use on EGFRI efficacy. There were 87 and 83 patients in the < 6 month and > 6 month groups respectively. The characteristics of the patients in these 2 groups are shown in Table 2. Patients in the >6 month group had a longer time to first progression and fewer metastatic sites. Otherwise, the groups appear similar. PFS on EGFRI therapy is displayed in Figure 3. A significantly shorter PFS was seen for patients in whom the EGFRI was commenced 6 months or less after ceasing bevacizumab (median

PFS 3.2 versus 5.5 months; HR 1.37; P= 0.007). When analysed by primary tumour side, no difference was noted for left sided tumours (median PFS 4.2 V 5.5 months; HR 1.12. P=0.26), however in right sided tumours, PFS was significantly shorter with a time gap of less than 6 months (median PFS 2.2 V 6 months; HR: 2.23. p= 0.01). When analysed by primary tumour side using a 12 month cut off, a similar, but non-significant, trend was seen. For left sided primaries, median PFS was 4.6 and 5.5 months for ≤ 12 and > 12 months respectively (p=0.32) and for right sided median PFS was 2.4 and 6.2 months respectively (p=0.17). However, patient numbers were very small, with only 13 patients with a right sided primary having a greater than 12 month gap between bevacizumab and the EGFRI.

OS data, calculated from the date of commencing the EGFRI, by prior bevacizumab, use is displayed in figure 4. No difference was seen. Median OS was 9.0 versus 9.2 months in the prior and no prior bevacizumab groups respectively, HR 1.12, P=0.48.

Discussion

A number of studies exploring the optimal use and sequencing of first line biologic therapy in RAS wild type metastatic colorectal cancer have produced unexpected results. The initial studies where first line bevacizumab and an EGFRI were combined, and given with chemotherapy, showed this combination to be detrimental.[13,14] Therefore subsequent studies have explored optimal biologic sequencing. The FIRE-3 study compared first line FOLFIRI with either cetuximab or bevacizumab, with many patients, at investigator discretion, crossing to the alternate biologic in the second line. No difference in PFS was seen but there was a significant OS benefit in favour of first line cetuximab use.[3] One possible explanation is that the initial biologic choice impacts later activity of the other biologic. Consistent with this hypothesis are the observed differences in 2nd line PFS after patients crossed over to the alternate antibody in the FIRE3 study. Specifically, 2nd line PFS favoured bevacizumab treated patients, suggesting the possibility that initial cetuximab either improved the efficacy of subsequent bevacizumab or initial bevacizumab reduced the subsequent efficacy of cetuximab.[7] Here, using registry data, we have further explored the latter possibility, finding that the initial use of bevacizumab did not impact on later activity of an EGFRI therapy, suggesting clinicians can use EGFRI therapy after bevacizumab without concern that treatment efficacy will be compromised. However, a longer time gap (> 6 months) between bevacizumab and an EGFRI was associated with a longer PFS, a finding which was driven by patients with a right sided primary tumour.

Our findings are consistent with those of other registry analyses which have shown no impact of prior bevacizumab on later EGFRI efficacy.[15,16] In contrast, prospective trials investigating the optimal second line biologic, after first line bevacizumab, have produced conflicting results. The PRODIGE-18 study randomised 133 KRAS exon 2 wild type patients who had progressed after first line chemotherapy plus bevacizumab to the alternate chemotherapy backbone plus either cetuximab or bevacizumab. There was a trend for both PFS and OS in favour of continuing bevacizumab that was maintained even when analysing the subset of extended RAS and BRAF wild type patients.[10] In this subgroup, median PFS and OS was 8.2 and 21.1 months versus 5.7 and 12.6 months respectively (P value for PFS 0.1). An analysis of outcome by primary tumour side has not been presented to date. However the suggestion of superiority for continuation of bevacizumab into second line versus switching to an EGFRI was not supported by 2 further studies from Japan (WJOG 6210G) and the US (SPIRRIT), both of which found no suggestion of a difference in outcome.

Again, to our knowledge, no analysis by primary tumour side is available from these studies[17,18]Another prospective, randomised phase 2 study conducted by the GISCAD group, in concordance with our findings, noted a significant interaction between side of primary tumour and the impact of time elapsed between bevacizumab and cetuximab on outcomes. Patients were randomised to FOLFOX then irinotecan/cetuximab, or the reverse sequence, after failure of first line FOLFIRI/bevacizumab. A trend to superior PFS and OS was noted in the FOLFOX then cetuximab/irinotecan sequence, i.e. when a longer time gap between bevacizumab and cetuximab use had elapsed. This improvement was driven by patients with a right sided primary tumour.[19]

When analysing these second line studies of EGFRI efficacy, it should be remembered that benefit as measured by PFS and OS may not correlate, as has been seen in first line treatment.[20] In that setting greater depth of response influences post progression survival time. This phenomenon has not been adequately addressed in later line studies.

International guidelines now recommend first line EGFRI use in combination with chemotherapy for left sided RAS wild type mCRC. Therefore any interaction between first line bevacizumab use and subsequent EGFRI efficacy will be most relevant for right sided primary tumours, perhaps raising the importance of the findings from our analysis.[21]

The specific sequence in which bevacizumab and EGFRI are used may impact treatment benefit due to a biologic impact on malignant cells and/or the microenvironment in response to treatment with one biologic, which then impacts the activity of the other. For example, in pre-clinical experiments, exposure to the anti-VEGF antibody bevacizumab results in increased serum free VEGF levels which in turn activates VEGFR receptor 2 and Stat-3 leading to cellular resistance to the EGFRI cetuximab.[11] This might suggest a longer time gap between bevacizumab and cetuximab is preferable, which is supported by our findings and those of the GISCAD study in patients with metastases from right sided primary tumours..

The potential for a detrimental interaction between EGFRI and bevacizumab was first suggested by the findings of the CAIRO-2 and PACCE studies, which tested a combination of the two as part of first line treatment for mCRC.[13,14] As well as an excess of adverse events with the biologic combination there was also an evident negative impact on survival outcomes. This observation suggests that a separation in time between biologic use may be important, prompting us to explore the impact of the time between bevacizumab and an EGFRI. To our knowledge, this is the first study to report such data. We found no impact of timing on the efficacy of the EGFRI in left side tumours, a subset in which EGFRI are expected to be active. However, patients with a right sided primary receiving the EGFRI more than 6 months after bevacizumab had an increased PFS on EGFRI therapy. Given we are not expecting much activity of EGFRI therapy in patients with a right side primary,[22] we would suggest this difference is mostly explained by confounding factors. For example, patients that received treatment after more than 6 months likely had more indolent biology and were destined to do better regardless of therapy. This is supported by the longer first line PFS and fewer metastatic sites noted in the > 6month group. In other words, the right sided patients living long enough to have treatment beyond 6 months represent a distinct subset with a superior survival outcome even when receiving an inactive therapy. Regardless of the explanation, this finding does highlight the challenges of defining the impact of the number of lines of treatment received. For example, an

analysis of a large number of mCRC clinical trials found patients who had received all active chemotherapy drugs had the best outcome, [23] the authors interpreting this data to mean it was important to expose patients to as many drugs as possible. Our data suggest an alternative explanation for at least part of the observed survival impact: it is the patients who live long enough (due to indolent disease biology) to receive all the drugs that have the best outcome, even where they are treated with an inactive therapy such as an EGFRI in right colon cancers.

A similar confounder might be expected in the left side tumours, but we did not observe a time based difference in this group. This may reflect the known prognostic differences between left and right tumours, with left cancer patients having a more indolent biology, hence a more mixed population of left sided cancers may be included if a 6 month cut off is used. To further explore this we looked at a cut off of 12 months, but again found no efficacy difference in left patients.

We acknowledge the limitations of our study, which was not prospective or randomised. Patients were treated at clinician discretion, with no pre-planned sequence of therapy. Some patients received EGFRI monotherapy, others combined with chemotherapy and we had insufficient numbers to further explore by these subsets. As such, biases may exist with undetected differences between the groups examined. Nonetheless, the registry data we analysed is very detailed and meticulously completed for each patient. The electronic database possesses an automated checking system to ensure validity of data as it is entered. A major strength of our registry is that it captures consecutive patients as they present to each institution, thus containing a true representation of the population with mCRC treated in daily practice, as opposed to randomised trials where eligibility criteria lead to considerable patient selection.

In conclusion, whilst there remains considerable ongoing debate as to the optimal sequence of biologic therapy in metastatic colorectal cancer, our registry data does not support the hypothesis that first line bevacizumab use negatively impacts the subsequent efficacy of EGFRI therapy. There is an apparent relationship between the time between bevacizumab and EGFRI therapy and outcome in patients with right sided primary tumours, the reasons for which are unclear, but potentially due to confounding factors.

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Figure 1. Consort diagram of patients.

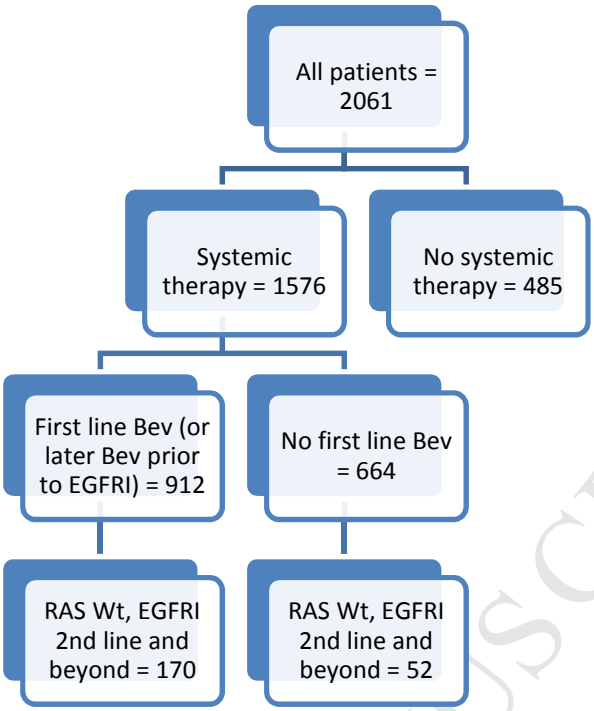


Table 1. Patient and tumour characteristics

	Prior Bevacizumab	No Prior Bevacizumab	P value
N (%)	170	52	
Age			
< 70	126 (74%)	39 (75%)	0.90
> 70	44 (26%)	13 (25%)	
Sex			
- Male	109 (64%)	33 (63%)	0.93
- Female	61 (36%)	19 (37%)	
ECOG PS			
-0	87 (51%)	26 (50%)	
-1	73 (43%)	20 (38%)	0.37
- ≥ 2	10 (6%)	6 (12%)	
Chemotherapy with EGFR antibody		23 (44%)	

- None - Oxaliplatin based - Irinotecan based - Other	85(50%) 2 (1%) 81 (48%) 2 (1%)	0 28 (54%) 1 (2%)	0.71
Primary tumour side - Right - Left - Unknown	 54 (32%) 115 (68%) 1 (1%)	 10 (19%) 41 (79%) 2 (2%)	 0.11
Primary tumour resected - Yes - No	 124 (73%) 46 (27%)	 37 (71%) 15 (29%)	 0.80
Synchronous Metachronous	109 (64%) 61 (36%)	33 (63%) 19 (37%)	 0.93
Number of metastatic sites 1 2-3 > 4	 83 (49%) 76 (45%) 11 (6%)	 26 (50%) 24 (46%) 2 (4%)	 0.78
Metastatic sites - Peritoneum/Omentum - Liver - Lung	 43 (25%) 115 (68%) 42 (25%)	 11 (21%) 39 (75%) 15 (29%)	 0.59 0.39 0.59
BRAF mutated Yes No unknown	 16 (9%) 79 (47%) 75 (44%)	 7 (14%) 23 (44%) 22 (42%)	 0.43
Months to first line progression (median and	9.1 (8.2 – 10.6)	6.9 (4.8 – 9.6)	0.02

95% CI)			

Table 2: Patient and tumour characteristics by time between ceasing bevacizumab and commencing EGFRI

	<=6 months	>6 months	P value
N (%)	87	83	
Age			
< 70	62 (71%)	64 (77%)	0.38
> 70	25 (29%)	19 (23%)	
Sex			
Male	49 (56%)	60 (72%)	0.03
Female	38 (44%)	23 (28%)	
ECOG PS			
0	42 (48%)	45 (54%)	
1	40 (46%)	33 (40%)	0.71
≥ 2	5 (6%)	5 (6%)	
Chemotherapy with EGFR antibody			
- None	40(46%)	45 (54%)	
- Oxaliplatin based	2 (2%)	0	0.42
- Irinotecan based	44 (51%)	37 (45%)	
- Other	1 (1%)	1 (1%)	
Primary tumour side			
- Right	32 (37%)	22 (27%)	
- Left	54 (62%)	61 (73%)	0.20

- Unknown	1 (1%)	0	
Primary tumour resected			
Yes	62 (71%)	62 (75%)	0.61
No	25 (29%)	21 (25%)	
Synchronous	53 (61%)	56 (67%)	0.37
Metachronous	34 (39%)	27 (33%)	
Number of metastatic sites			
1	33 (38%)	50 (60%)	
2-3	47 (54%)	29 (35%)	0.01
> 4	7 (8%)	4 (5%)	
Metastatic sites			
- Peritoneum/Omentum	24 (28%)	19 (23%)	0.48
- Liver	63 (37%)	52 (31%)	0.17
- Lung	24 (14%)	18 (11%)	0.37
BRAF mutated			
Yes	10 (12%)	6 (7%)	
No	41 (47%)	38 (46%)	0.58
unknown	36 (41%)	39 (47%)	
Months to first line progression (median and 95% CI)	6.9 (5.7 – 8.1)	11.8 (10.8 – 13.1)	0.001

Figure 2. PFS from commencing EGFRI by first line bevacizumab use. 2A = All patients 2B = Left primary 2C = Right primary.

Figure 2A

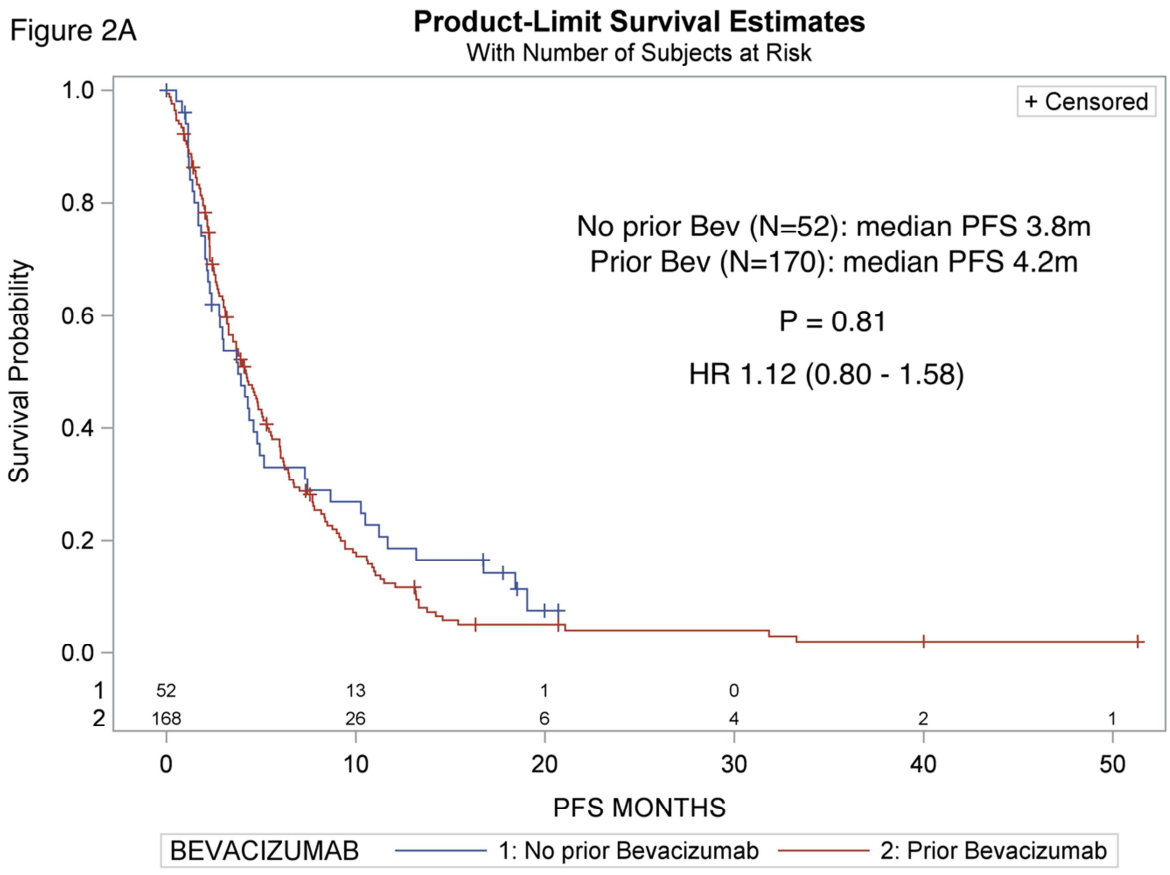
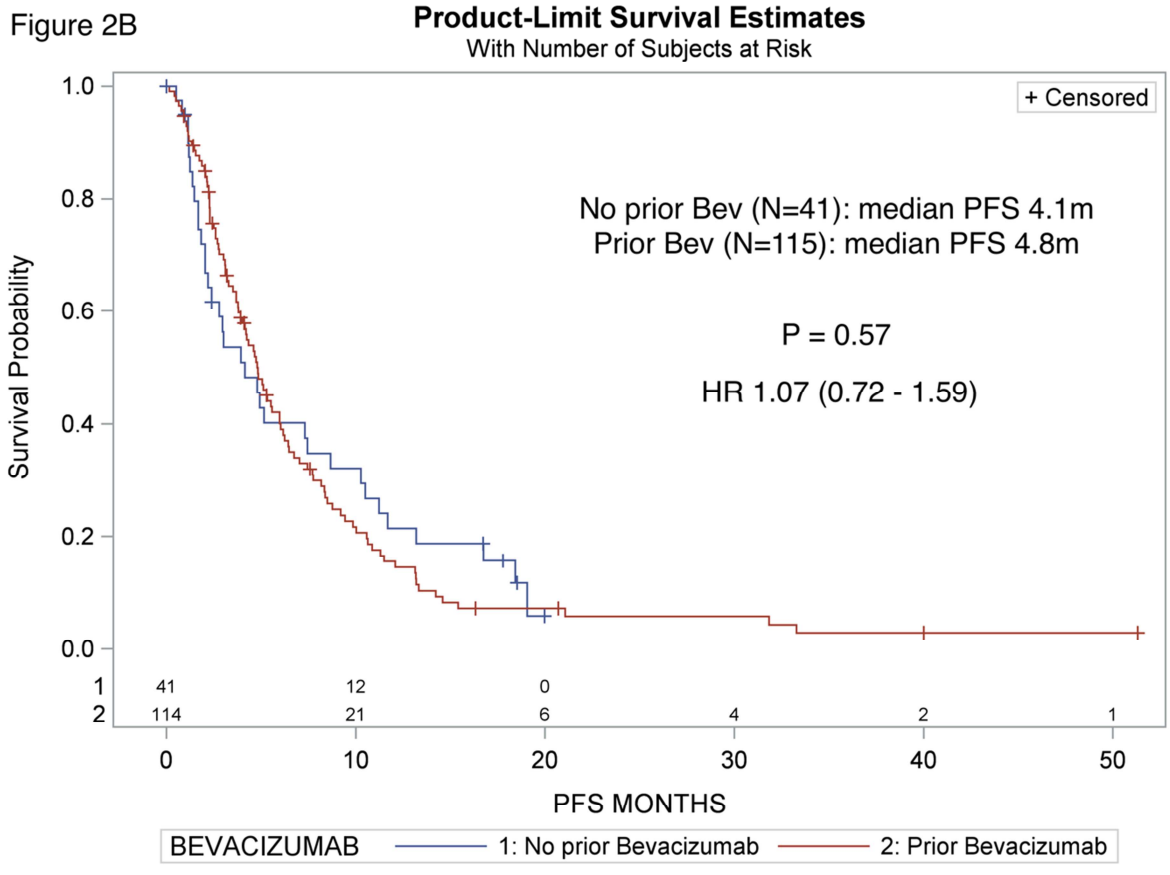


Figure 2B



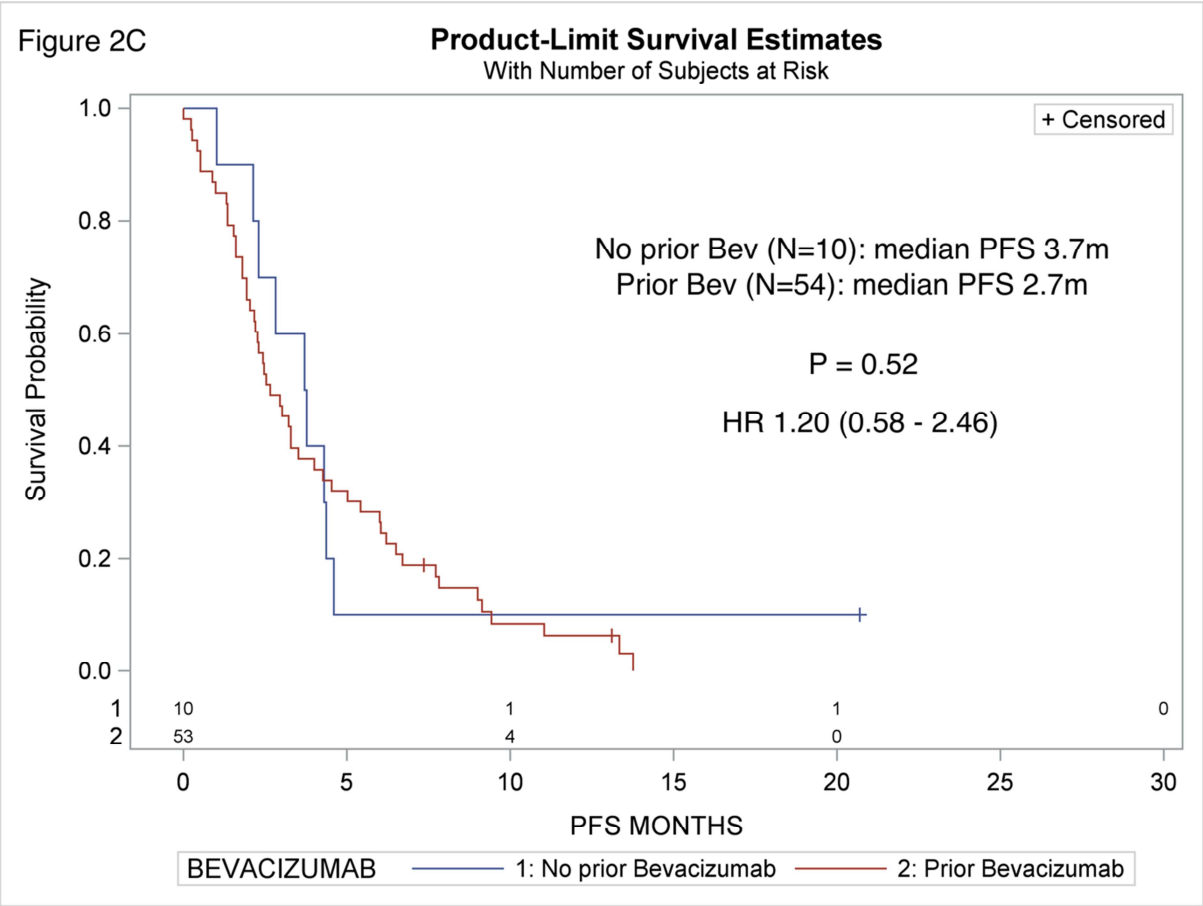


Figure 3. PFS from commencing EGFRI by time since last bevacizumab administration. 3A = All patients 3B = Left primary 3C = Right primary.

Figure 3A

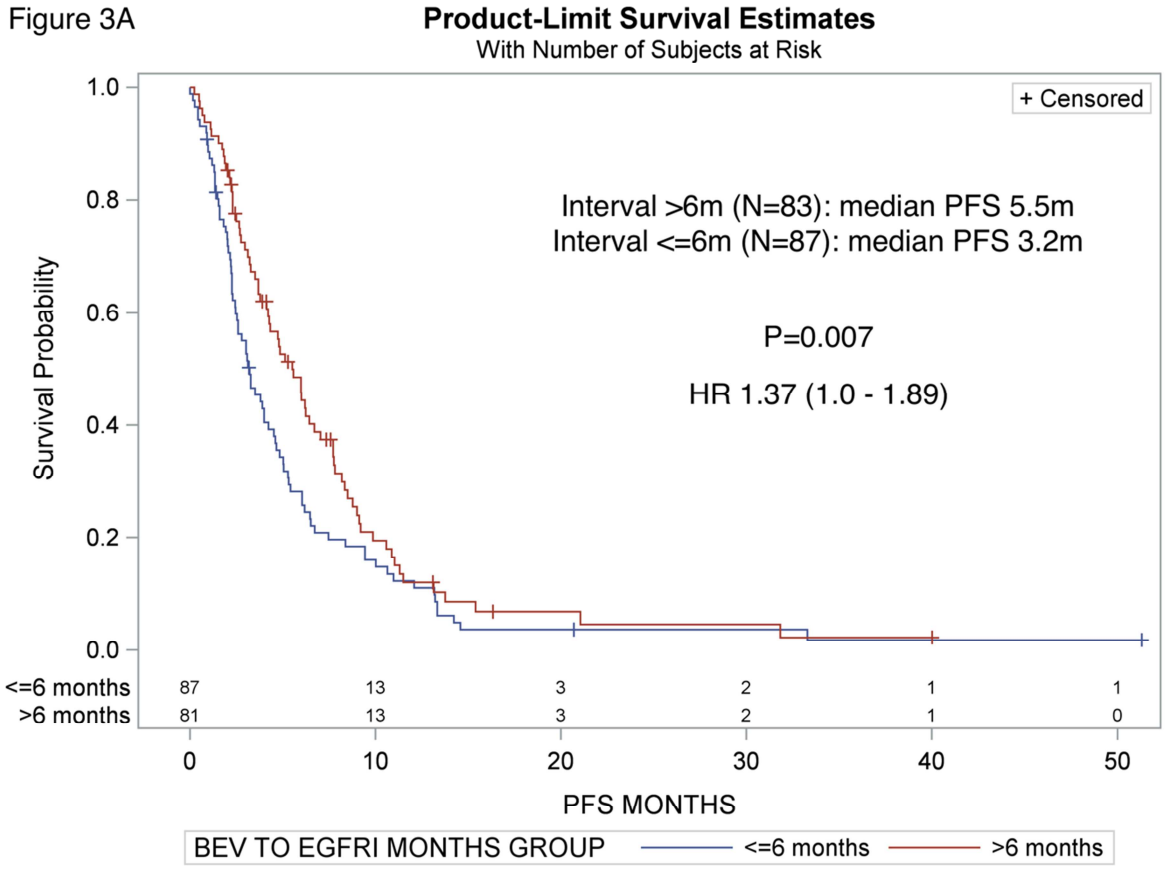
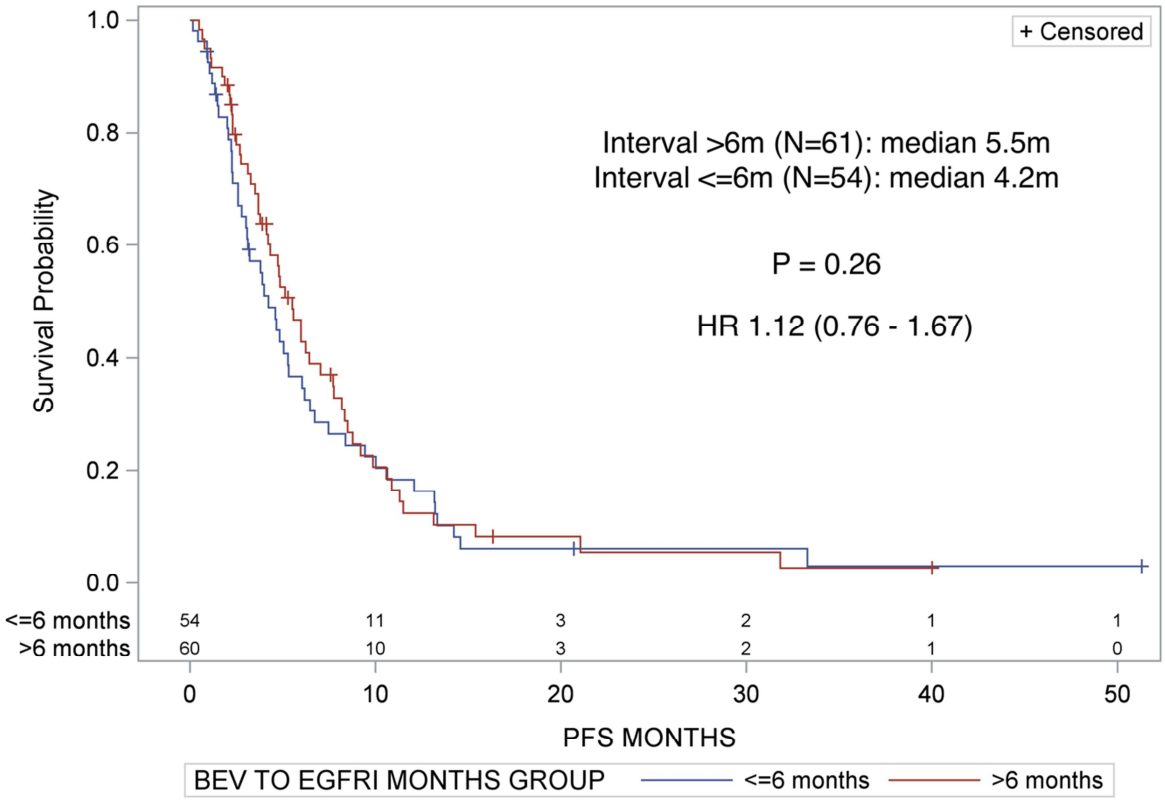


Figure 3B



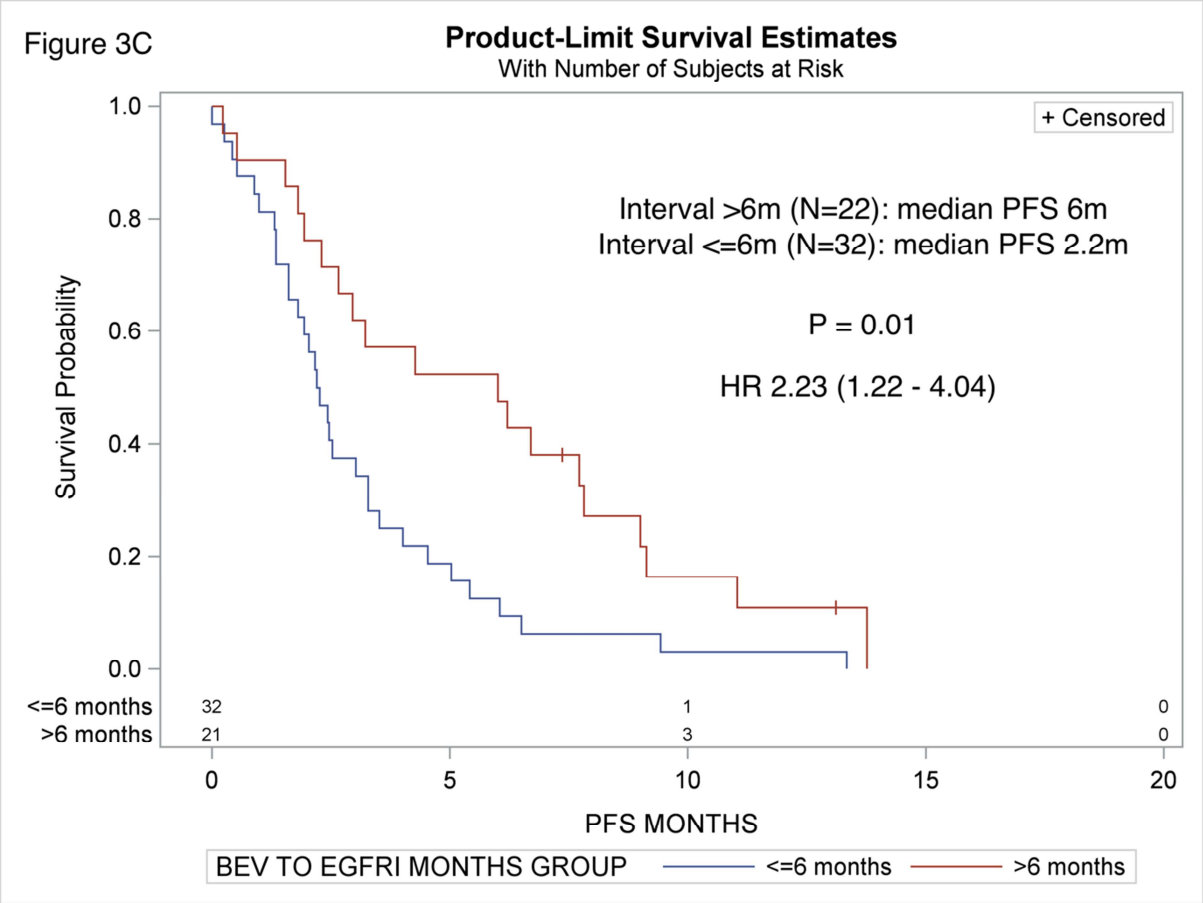


Figure 4: Overall survival from starting anti EGFR antibody, by first line bevacizumab use.

Figure 4