

# Epidermal Growth Factor Receptor Inhibitor Treatment Timing does not Impact Survival in Stage 4 Colon Cancer Treatment: A Retrospective Study

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## ABSTRACT

**Introduction.** Colon cancer impacts the lives of Kansans and those across the United States. Epidermal growth factor receptor (EGFR) inhibitors, such as panitumumab and cetuximab, have gained popularity as first-line treatment for stage 4 colon cancer despite their toxicities and have been used by clinicians in later lines of therapy. EGFR inhibitors have been proven to be an efficacious first-line treatment for stage 4 colon cancer, but no study has investigated outcomes comparing EGFR inhibitors as first-line treatment to its use as second- or third-line treatment. This study investigated EGFR inhibitor therapy estimated overall survival when used as first-, second-, and third-line treatment for stage 4 colon cancer.

**Methods.** A retrospective review was done for patients with stage 4 colon cancer who underwent EGFR inhibitor treatment at a large academic center from November 2007 to August 2021. The patients were stratified into five groups by the line in which they received the EGFR inhibitor treatment. A log-rank test was used to analyze the groups, and the median survival for each group was determined.

**Results.** A total of 68 patients were reviewed; 18 received first-line, 23 received second-line, 18 received third-line, 6 received fourth-line, and 3 received sixth-line treatment with an EGFR inhibitor. Fourth- and sixth-line therapies were excluded due to small patient size. There was no significant difference in estimated survival time between any of the lines. Median survival of the therapies was found.

**Conclusions.** There was no statistical difference in survival between the first-, second-, or third-line groups, which may provide justification for its use as a second- or third-line therapy.

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## INTRODUCTION

Colon cancer is the third leading diagnosis and cause of cancer death in Kansas and is expected to take 608,570 lives in the United States by the end of 2021.<sup>1,2</sup> Of the 1,300 new diagnoses each year in Kansas, half are diagnosed as late-stage. The Kansas Cancer Registry reported that colon cancer takes the lives of 500 Kansans annually and disproportionately impacts rural Kansans compared to those living in urban areas.<sup>2</sup> Rural Kansas has an increased total incidence, late-stage incidences, and mortality of colon cancer, and rural counties make up the highest incidences and mortality of colorectal cancer compared to their urban counterparts. Knowing the treatment efficacies for new chemotherapies for late-stage colon cancer and their justification for use in later lines of treatment is important for Kansas providers to understand.

Epidermal growth factor receptor (EGFR) inhibitors, such as panitumumab and cetuximab, have gained popularity as first-line treatment for KRAS wild type stage 4 colon cancer since the findings in several randomized control trials.<sup>3-6</sup> Other papers have found that EGFR inhibitors improve patient outcomes, such as progression free survival, overall survival, and tumor response rate, and recommend its use in stage 4 KRAS wild type colon cancer.<sup>7-11</sup> EGFR inhibitors commonly are combined with other chemotherapies and these regimens have shown positive patient outcomes.<sup>8,12-22</sup> EGFR inhibitors and KRAS screening have shown a cost benefit due to its effectiveness as a therapy by limiting chemotherapy changes.<sup>23-27</sup> This treatment was associated with many side effects, especially skin toxicity, that both the patient and all physicians on the care team must be aware of and its impact on patient's quality of life before starting and during treatment.<sup>7,8,28-36</sup> If these toxicities are not handled appropriately it can delay treatment.<sup>35,37</sup> There was no previous research that compared the patient outcomes of EGFR inhibitors in first-line to its use in later lines. Due to the large number of late colon cancer diagnoses in Kansas and EGFR inhibitors side effect profile and impact on the patient's quality of life, it is beneficial to understand if patient outcomes differ when prescribed as a first-line compared to a later line therapy.

This study compared the estimated overall survival from time of diagnosis of patients who received EGFR inhibitors as first-, second-, and third-line treatment for stage 4 colon cancer. This study investigated the justifications for the use EGFR inhibitor therapy in later lines. Due to its risk of toxicity and possibility of delayed treatment, its use in later lines may not outweigh the benefit of EGFR inhibitor therapy. One potential implication of this study was guiding the decision to consider, or not consider, selecting EGFR inhibitor as later line therapy and developing a better understanding of its efficacy in later lines.

## METHODS

The Institutional Review Board approved a retrospective chart review on stage 4 colon cancer patients at our academic medical center. The initial lists of patients for screening were collected using a list of all patients who received EGFR inhibitor treatments cetuximab or panitumumab over the study's time period. Patients were divided into groups 1, 2, 3, 4, and 6 depending on which line they received cetuximab or panitumumab for their stage 4 colon cancer treatment. The study size was determined by the maximum number of patients who qualified for the study on this list. Patients who underwent treatment with cetuximab or panitumumab for stage 4 colon cancer and were at least 18 years of age were included. Patients with KRAS, NRAS, or BRAF mutations or those who did not undergo APC and TP53 testing were excluded. Chart reviewing was used to gather clinical information about the patients and reports from Next-Generation Sequencing (Illumina Inc., San Diego, CA, USA, 2021) and Caris Molecular Intelligence® (Caris Life Sciences, Irving, TX, USA, 2021) were used to determine KRAS, NRAS, BRAF, APC, and TP53 status.

Demographics collected included age, ethnicity, weight, height, medical comorbidities, and residence. The Eastern Cooperative Oncology Group (ECOG) Performance Status Scale at the time of starting EGFR inhibitor treatment was recorded. Dates of initial colon cancer diagnosis and stage 4 diagnosis, right or left tumor location, surgery dates, metastases, cancer's response to chemotherapy, date of recurrence or progression, date of last follow-up, and date of expiry were collected. First-, second-, and third-line chemotherapy regimens, start and end dates, and the number of cycles for each chemotherapy used were recorded. Fourth- and sixth-line chemotherapy were recorded when the therapy consisted of EGFR inhibitor use. "First-line" chemotherapy in this study was described as the first chemotherapy regimen the patient underwent after their stage 4 chemotherapy diagnosis. Overall survival was collected for patients and is defined as the length of time the patient is alive from the start of their initial treatment for metastatic colorectal cancer until date of last follow-up, and/or date of expiry. Overall survival is referred to as "survival" throughout the paper. The term "later-lines" in this paper referred to therapies after the "first-line" regimen. Research Electronic Data Capture (REDCap®) tools were used to collect the data.<sup>38</sup>

There was no protocol in the decision to start or discontinue the chemotherapy lines. The oncologist determined the chemotherapy regimens and number of cycles for each line. Some patients underwent EGFR inhibitor therapy concurrently with other chemotherapy drugs. Multiple oncologists treated the patients in this study.

Descriptive statistics were provided using the start date of EGFR inhibitor regimen, date of last follow-up, and/or date of expiry. Patients were divided into groups depending on which line they received the EGFR inhibitor. Appropriate data determined by a statistician was censored for analysis. Survival estimates for each EGFR inhibitor line was determined. Each EGFR inhibitor line was stratified and compared to one another using a log-rank test. The Chi-square test was used to find associations between the EGFR inhibitor treatment lines. Median survival for each EGFR inhibitor line was calculated for completeness. A p value greater than 0.05 was considered statistically significant. SAS v9.4 (Copyright 2002-2012 by SAS Institute Inc., Cary, NC, USA) was used to analyze data.

## RESULTS

A total of 239 patients received cetuximab or panitumumab and these patients were reviewed. Of these 239 patients, 68 patients met the qualification for the study; 38 patients were observed and 30 were censored for statistical analysis. No significant difference of demographics, ECOG Performance Status Scale, and tumor location was found between each line of the patients reviewed. Demographics, ECOG Performance Status Scale, and tumor location are summarized in Table 1. There was a total of 18 patients who received EGFR inhibitor as a first-line therapy. Of these patients, 9 were observed and 9 were censored. The second-line group had a total of 23 patients; 13 patients were observed and 10 were censored. The third-line group had 18 total

patients; 10 patients were observed and 8 were censored. The fourth-line group had a total of 6 patients (4 observed and 2 censored) and the sixth-line group had a total of 3 patients (2 observed and 1 censored). Total patients per EGFR inhibitor line and censor status is summarized in Table 2. The survival estimates for each EGFR inhibitor line is shown in Figure 1. The median survival of the groups was 1,444 days for the first-line group, 1,196 days for the second-line group, 1,402 days for the third-line group, 1,395 days for the fourth-line group, and 2,235 days for the sixth-line group. Median survival for each line is summarized in Table 3.

No patients were lost to follow-up during their EGFR inhibitor treatment. All lines of stage 4 therapy received at outside institutes were recorded. All start and stop dates and chemotherapy line number for EGFR inhibitor therapy were recorded. No patients were still receiving EGFR inhibitor treatment at the conclusion of the study. There were 27 patients still living at the conclusion of this study.

There was no significant difference in survival time between first- and second-lines ( $p = 0.8639$ ), first- and third-lines ( $p = 0.5239$ ), first- and fourth-lines ( $p = 0.6380$ ), first- and sixth-lines ( $p = 0.8223$ ), second- and third-lines ( $p = 0.6755$ ), second- and fourth-lines ( $p = 0.8239$ ), second- and sixth-lines ( $p = 0.6649$ ), third- and fourth-lines ( $p = 0.7462$ ), third- and sixth-lines ( $p = 0.2870$ ), and fourth- and sixth-lines ( $p = 0.3462$ ). The fourth- and sixth-lines sample sizes were very small and were considered unreliable for this study. Additional statistical information is shown in Table 4.

## DISCUSSION

Stage 4 colon cancer is devastating and greatly impacts the lives of many in Kansas and in the U.S.<sup>1,2</sup> Fortunately, new chemotherapies, such as cetuximab and panitumumab, have shown positive patient outcomes.<sup>3-22</sup> EGFR inhibitors have shown to have severe toxicities which can influence the patient's quality of life and may affect the decision to begin treatment with these medications.<sup>7,8,28-37</sup> Inferior patient outcomes of EGFR inhibitor treatment in later lines might be an important determinant for the decision to choose a different chemotherapy to avoid the risk of these toxicities and potential treatment delays. It is also important for clinicians to have justifications for the use of EGFR inhibitors in later lines. This study demonstrated that there was no statistically significant change in estimate survival for patients receiving EGFR inhibitor therapy first-line compared to second- or third-line and clinicians may have justification for using these therapies as a third-line treatment.

This study showed that EGFR inhibitors may provide similar patient survival when used as second- or third-line therapy as it would first-line, and provided additional support for its clinical use as a third-line treatment option. The PRIME and PEAK randomized control trials have shown the effectiveness of first-line EGFR inhibitor use in metastatic colon cancer.<sup>3,5</sup> EGFR inhibitor use for metastatic colon cancer also has been shown to be effective in the treatment for metastatic colon cancer and is used as a third-line option by clinicians.<sup>39-42</sup> With findings similar to the first-line line patients, this study provided further justification for its use as a third-line treatment option.

The toxicities of EGFR inhibitors are well documented.<sup>7,8,28-37</sup> The toxicity profile EGFR inhibitors can evolve depending on the time and duration of its use, and can impact multiple organ systems.<sup>43-45</sup> Although

this study showed patients may have similar survival in later line treatments compared to first-line, accumulation toxicity of the therapy may impact the justifications for its use in later lines. Clinicians using EGFR inhibitors as a third-line treatment strongly should consider the accumulation toxicity.

Healthcare value should be considered when deciding on therapy. EGFR inhibitors reduced health care costs due to the decreased need to change therapy.<sup>23-27</sup> This study suggested that the healthcare value might be similar for first-, second, and third-line EGFR inhibitor use. Later line treatment may be beneficial to smaller treatment centers. Patients and physicians should consider this when they are deciding on using EGFR inhibitors as second- or third-line therapy.

This study had limitations. A larger patient population with less censored data would provide stronger evidence for this study. Although this study had only 68 total patients, the total number of patients and number of patients censored were distributed evenly throughout the groups. Performing a study with a controlled number of EGFR inhibitor cycles per patient along with controlling for any additional concurrent chemotherapy medications used in the patients' treatment would

provide additional evidence that the EGFR inhibitor was impacting the patients' survival. This follow-up study would be difficult to conduct due to the unique treatment regimen every patient receives due to cancer response and change of medication due to patients' toxicities. This study was unable to adjust for prior lines of treatment for second- and third-lines, and we acknowledge that this impact places limitations on the results. Follow-up studies with larger studies with a more structured chemotherapy regimen at different institutions would increase external validity for our findings. Additional studies should continue to investigate how the side effect profile or toxicity frequency changes in later lines of EGFR inhibitor therapy, as this will impact its justification for its use in later lines. Despite its limitations, this study may provide justification for the use of cetuximab and panitumumab as a second- or third-line treatment for stage 4 KRAS, NRAS, and BRAF wild type colon cancer.

**Table 1. Patient demographics, ECOG Performance Status Scale, and tumor location.**

Characteristic	Statistic/Category	First Line	Second Line	Third Line	Overall	p Value
Number of Subjects	N	18	23	18	59	
Age	Mean	53.2	52.3	51.7	52.4	0.9351
	Std. Dev.	11.60	12.59	14.34	12.66	
	Median	53.5	52.0	49.5	52.0	
	Min, Max	32, 72	26, 69	27, 77	26, 77	
Sex [N (% of Column)]	Male	11 (61.11)	16 (69.57)	13 (72.22)	40 (67.80)	0.7547
	Female	7 (38.89)	7 (30.43)	5 (27.78)	19 (32.20)	
Ethnicity [N (% of Column)]	Hispanic	0	1 (4.35)	2 (11.11)	3 (5.08)	0.3096
	Non-Hispanic	18 (100.0)	22 (95.65)	16 (88.89)	56 (94.92)	
Race [N (% of Column)]	White	17 (94.44)	20 (86.96)	15 (83.33)	52 (88.14)	0.5683
	Asian	1 (5.56)	2 (8.70)	0	3 (5.08)	
	Other	0	0	1 (5.56)	1 (1.69)	
	Unknown	0	1 (4.35)	2 (11.11)	3 (5.08)	
Smoker [N (% of Column)]	Yes	6 (33.33)	8 (34.78)	7 (38.89)	21 (35.59)	0.9299
	No	11 (61.11)	14 (60.87)	10 (55.56)	35 (59.32)	
	Unknown	1 (5.56)	1 (4.35)	1 (5.56)	3 (5.08)	
ECOG Status [N (% of Column)]	0	8 (44.44)	12 (52.17)	9 (50.00)	29 (49.15)	0.8003
	1	10 (55.56)	10 (43.48)	8 (44.44)	28 (47.46)	
	Unknown	0	1 (4.35)	1 (5.56)	2 (3.39)	
Tumor Location [N (% of Column)]	Right	15 (83.33)	19 (82.61)	15 (83.33)	49 (83.05)	1.0000
	Left	3 (16.67)	4 (17.39)	3 (16.67)	10 (16.95)	

**Table 2. Total patients per line.**

Line	Total Patients	Observed Patients	Censored Patients	Percent Censored
First-Line	18	9	9	50.00
Second-Line	23	13	10	43.48
Third-Line	18	10	8	44.44
Fourth-Line	6	4	2	33.33
Sixth-Line	3	2	1	33.33
	68	38	30	44.12

**Table 3. Median estimate survival.**

Line	Estimate Survival (Days)
First-Line	1444.00
Second-Line	1196.00
Third-Line	1402.00
Fourth-Line	1395.50
Sixth-Line	2235.00

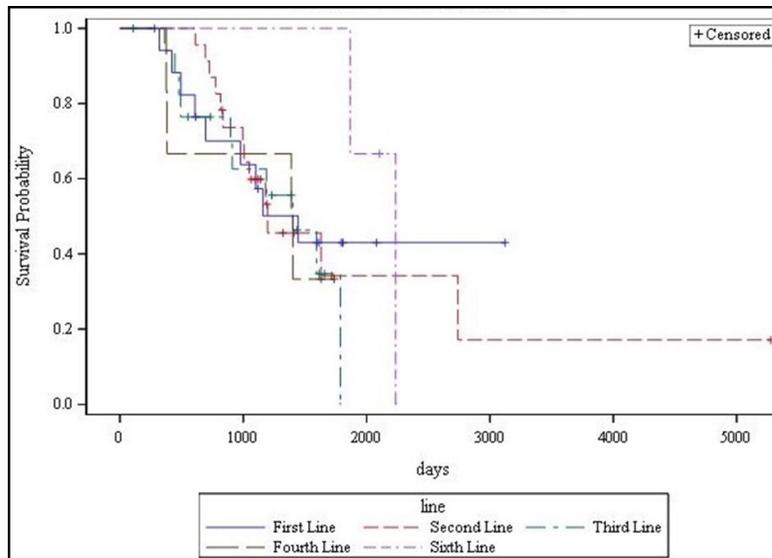


Figure 1. Product-limit survival estimates.

**Table 4. Line survival comparison.**

Strata Comparison		Chi-Square	p Values	
Line	Line		Raw	Tukey-Kramer
First-Line	Second-Line	0.0294	0.8639	0.9998
First-Line	Third-Line	0.4062	0.5239	0.9690
First-Line	Fourth-Line	0.2214	0.6380	0.9900
First-Line	Sixth-Line	0.0505	0.8223	0.9994
Second-Line	Third-Line	0.1752	0.6755	0.9936
Second-Line	Fourth-Line	0.0495	0.8239	0.9995
Second-Line	Sixth-Line	0.1876	0.6649	0.9927
Third-Line	Fourth-Line	0.1048	0.7462	0.9976
Third-Line	Sixth-Line	1.1337	0.2870	0.8246
Fourth-Line	Sixth-Line	0.8872	0.3462	0.8805

### CONCLUSIONS

The EGFR inhibitors cetuximab and panitumumab used as a second- or third-line treatment may provide similar patient survival compared to its use as first-line therapy. No statistically significant difference in estimated survival was found when they were used as a first-, second-, or third-line therapy. This information may provide justification for EGFR inhibitors use as a second- or third-line treatment options for stage 4 KRAS, BRAF, and NRAS wild type colon cancer, although clinicians should continue to account for the changes in toxicity profile of the treatment.

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