

Anti-EGFR–Based Treatment of Patients with Metastatic Colorectal Cancer: Data from the National Oncology Institute of Panama

Kayra Sánchez-Muñoz¹, José Pinto-Llerena^{2,*}

¹Medical Oncology Service, National Oncology Institute of Panama, Panama City, Panama

²Gastrointestinal Tumors Unit, Medical Oncology Service, National Oncology Institute of Panama, Panama City, Panama

Email address:

josepintollerena@gmail.com (J. Pinto-Llerena)

*Corresponding author

To cite this article:

Kayra Sánchez-Muñoz, José Pinto-Llerena. Anti-EGFR–Based Treatment of Patients with Metastatic Colorectal Cancer: Data from the National Oncology Institute of Panama. *International Journal of Clinical Oncology and Cancer Research*. Vol. 7, No. 2, 2022, pp. 35-40. doi: 10.11648/j.ijcoocr.20220702.14

Received: March 31, 2022; **Accepted:** April 25, 2022; **Published:** May 12, 2022

Abstract: Treatments directed against EGFR, such as anti-VEGF monoclonal antibodies (bevacizumab) and anti-EGFR cetuximab or panitumumab, improve clinical outcomes in terms of overall survival and disease-free survival when combined with first-line chemotherapy treatments for metastatic colon cancer. *Aims.* To determine the epidemiological, clinical, and survival-related variables associated with the treatment of KRAS wild-type metastatic colon cancer with anti-EGFR agents in our institution. *Patients & methods.* We performed a retrospective review of the electronic files of patients with KRAS wild-type metastatic colon cancer treated with cetuximab between 2014 and 2019. *Results.* 169 patients diagnosed with metastatic Colorectal Cancer RAS WT receiving anti-EGFR treatment. The median age was 65 years, with 54% male. 91% with ECOG 0 – 1. KRAS test was performed to 100% of patients. 70% had a tumor on the left side of the colon. Objective response was 4.8%. The median PFS was 3 months and median OS was 5 months. Only the use of combined schemes such as FOLFIRI with cetuximab and exposure to cetuximab in some lines of treatment were shown to be significant prognostic factors for PFS, compared with those who did not receive it. Rash G1-2 was the most common adverse event. *Conclusions.* the epidemiological and clinical characteristics of our patients are like the world literature, however, the PFS and OS reached are lower than expected as well as adverse events registered. Most of the patients received anti-EGFR treatment in second line. These results allowed us to propose anti-EGFR treatment in colorectal cancer from the front line at the National Oncology Institute.

Keywords: Colorectal Cancer, Metastatic, KRAS Wild-Type, Anti-EGFR, Progression-Free Survival, Overall Survival

1. Introduction

Of all cancers diagnosed colon cancer represents 10% and is the third most common cancer in men and the second most common in women. [1]. In Panama, it is the fourth most frequent cancer in both sexes, according to the Cancer Registry of the National Oncology Institute [2]. The incidence rate is 15.7 cases per 100,000 inhabitants, and the mortality rate is 5.2 deaths per 100,000 inhabitants [3]. The incidence is higher in individuals under 50 years of age, among whom the disease is in the localized stage 39%, the regional stage in 35%, and the advanced stage in 22% of the cases [4].

In colorectal cancer, the epidermal growth factor receptor

(EGFR) is overexpressed in 25-77% of cases [5]. The biology of colorectal cancer has led to the development of targeted agents, such as monoclonal antibodies. Monoclonal antibody IgG1 such as cetuximab that competitively binds to EGFR for inhibiting phosphorylation of tyrosine kinase, thus blocking a series of reactions, such as gene transcription and cell proliferation [6]. The Panitumumab is other monoclonal antibody, recombinant humanized IgG-2, whose pharmacological mechanism of action is like that of cetuximab [6].

In the BOND trial, the treatment with cetuximab in patients

with metastatic colorectal cancer, revealed extended progression-free survival (PFS) in comparison with irinotecan alone [7]. After the approval of cetuximab in 2004, the CRYSTAL phase III trial, which analyzed cetuximab plus FOLFIRI in the first line of treatment, revealed that in the subgroup of patients with KRAS wild-type disease, mean survival was 9.9 months vs 8.7 months (HR = 0.68 [95% CI: 0.50–0.94]; $p = 0.02$). However, no statistically significant differences were observed in overall survival (OS) [8].

The PRIME phase III study showed an extension of PFS with the combination of FOLFOX plus panitumumab, 9.6 months vs 8 months (HR=0.80 [95% CI: 0.66–0.97]; $p = 0.02$), with no differences in overall survival in patients KRAS wild type [9].

Several studies have evaluated monoclonal antibody in second-line treatment, for example in the EPIC trial, the combination of cetuximab plus irinotecan was compared with irinotecan alone in patients expressing EGFR who had progressed to a first-line treatment with oxaliplatin. The combination improved PFS (4.0 vs. 2.6 months; HR, 0.692 [95% CI, 0.617-0.776]; $p = 0.0001$), with a response rate of 16.4% vs. 4.2% ($p < 0.0001$). The authors reported no statistically significant differences in OS [10]. Other study with interesting data were ITACa trial, a prospective study of the impact of cetuximab in second-line treatment in patients with metastatic colon cancer who had received first-line chemotherapy (FOLFOX or FOLFIRI). PFS was 6.2 months vs 3.4 months (HR = 0.64 [95% CI: 0.35–1.16], $p = 0.144$), and OS was 11.1 months vs 9.3 months (HR = 1.30 [95% CI: 0.70–2.44], $p = 0.402$) [11].

The adverse effects of anti-EGFR monoclonal antibodies differ from those of conventional therapy in that they are not so much associated with hematologic toxicity, but rather are limited mainly to acneiform (papulopustular) skin eruptions in 80-95% of cases, mainly affecting the face, scalp, and upper torso. This adverse effect is dose-limiting and occurs at grade 3 in 5–18% of patients [12–14].

The main objective of our study was to determine the epidemiological, clinical, and survival-related variables associated with the treatment of metastatic KRAS wild-type metastatic colon cancer with the anti-EGFR medication available at our institution.

2. Patients & Methods

2.1. Data Selection

Our data were retrospectively collected from patients with KRAS wild-type metastatic colon cancer treated with cetuximab between 2014 and 2019. The data were obtained from the electronic records and the Oncofarmis database of the National Oncology Institute, with the prior consent of the institutional authorities.

2.2. Patient Selection

The inclusion criteria were a histopathological confirmed diagnosis of KRAS wild-type metastatic colon cancer and age

≥ 18 years.

We excluded those who died within the first 30 days of initiation of care at our institution.

We defined PFS as the time in months from the start of treatment to disease progression and OS as the time in months from the start of treatment to death or completion of the study.

2.2.1. Patients Follow up

The following of the patients were realized every 2 to 3 weeks through appointments with their treating oncologist depending on the chemotherapy schedule used. Cetuximab was administered weekly in most cases. Computed tomography was performed after every 3 to 4 treatment cycles. Treatment was continued until progression or poor tolerance. In Our Institute, cetuximab is approved for second line of treatment of patients with extended KRAS wild-type disease.

2.2.2. Statistical Analysis

Data were collected utilized the electronics clinical records and analyzed using IBM SPSS Statistics (version 24). Patient characteristics were reported using frequencies and a descriptive analysis. The Kaplan-Meier method was used to analyze PFS and OS. Nonparametric studies were used to compare associations between variables.

3. Results

The original sample comprised patients with a diagnosis of KRAS wild-type metastatic colon cancer treated with anti-EGFR agents from 2014 to 2019 at the National Oncology Institute. An initial population of 171 patients was included. Our sample consisted of 169 patients, because 2 patients did not meet the inclusion criteria.

The mean age was 65 years (range 28–96). Most of the patients were male (54%), and 91% had an ECOG of 0-1.

Table 1. Demographic and pathological characteristics (n = 169).

Characteristic	No. of patients	%
Sex		
Male	92	54
Female	77	46
Age, years		
19 – 34	3	2
35 – 49	24	14
50 – 65	56	33
66 – 80	79	47
81+	7	4
ECOG Scale		
ECOG 0	52	31
ECOG 1	102	60
ECOG 2	12	7
ECOG 3	3	2
Clinical Stage		
EC I	2	1
EC II	12	7
EC III	42	25
EC IV	113	67

Characteristic	No. of patients	%
Anatomic site		
Cecum	9	5
Ascending colon	31	18
Transverse colon	9	5
Descending colon	13	8
Sigmoid colon	33	20
Sigmoid rectum	17	10
Rectum	56	33
Undetermined	1	1
Tumor location (laterality)		
Right	49	29
Left	119	70
Undetermined	1	1
Histology		
Adenocarcinoma	169	100
Level of differentiation		
Well differentiated	10	6
Moderately differentiated	147	87
Poorly differentiated	9	5
Not specified	3	2
RAS determination		
KRAS wild type	169	100
NRAS wild type	146	86.4
Undetermined	23	13.6
Metastasis site		
One site	139	82
More than 2 sites	30	18

At diagnosis, 67% of patients had advanced disease, with a single site of metastasis in 82% of cases, mostly in the liver (Table 1). The primary tumor was in the rectum in 33% of cases, and 70% were left-sided. Histology revealed

adenocarcinoma (100%) and KRAS wild type (100%). Recurrence after anti-EGFR treatment was recorded in 50.29%. The most frequent site of recurrence was the liver (34.1%) (Table 1).

The first line of treatment was administered to 100% of patients and consisted of platinum-based chemotherapy plus 5-fluorouracil in 74%, with XELOX plus bevacizumab being the most frequent schedule (40%). Second-line treatment was administered in 97% of cases, of these, 73% received second line cetuximab; the most common schedule (32%) was irinotecan plus cetuximab (Table 2). Only 31% of patients received a third line of palliative chemotherapy, of which 83% involved schedules containing cetuximab. And Cetuximab was administered in monotherapy in 30%.

Table 2. Second line treatment in patients with metastatic colon cancer.

Treatment	Patients, %
Irinotecan + cetuximab	32
FOLFIRI + cetuximab	26
Cetuximab	12
FOLFOX + cetuximab	2
Xelox + cetuximab	1
Other	27

Other: xelox; xelox cetuximab; xelox + bevacizumab.

Mean PFS was 3 months (95% CI, 2.22-3.77), and mean OS was 5 months (95% CI, 3.99-6.01) in patients treated with anti-EGFR agents (Figures 1 and 2).

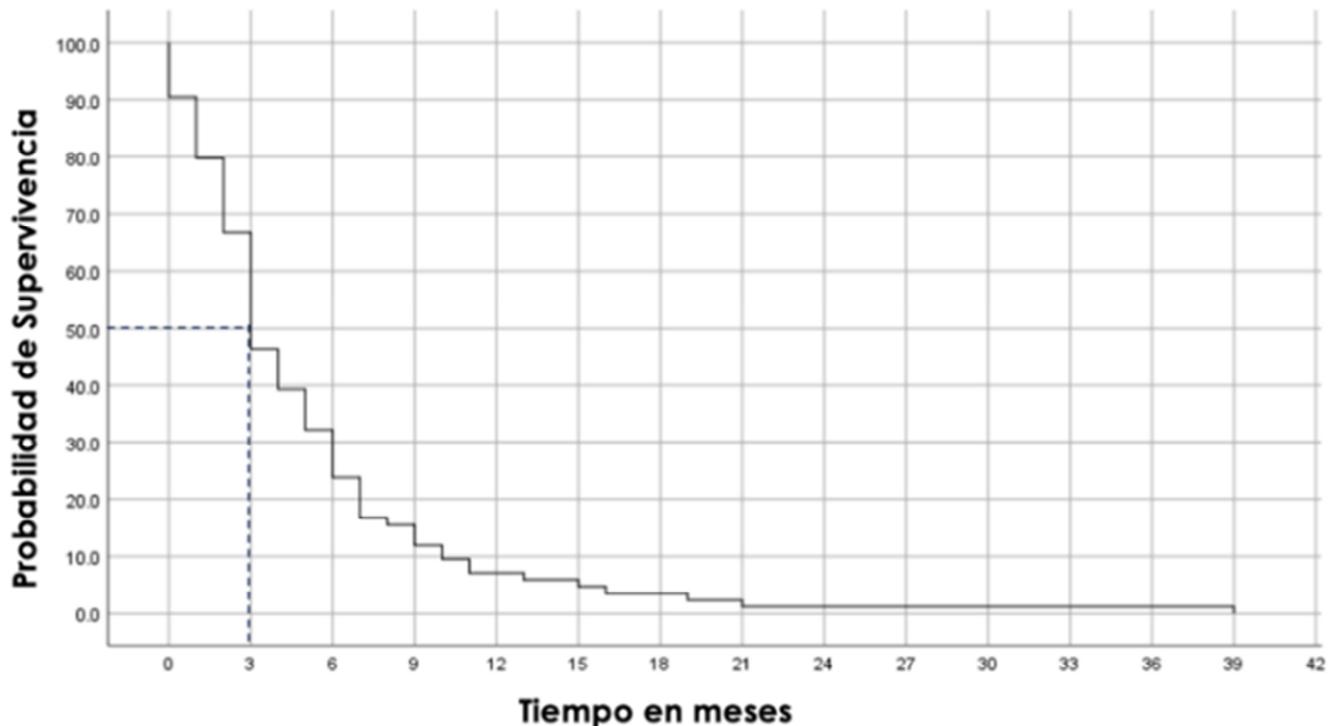


Figure 1. Progression-free survival in patients with KRAS wild-type metastatic colon cancer.

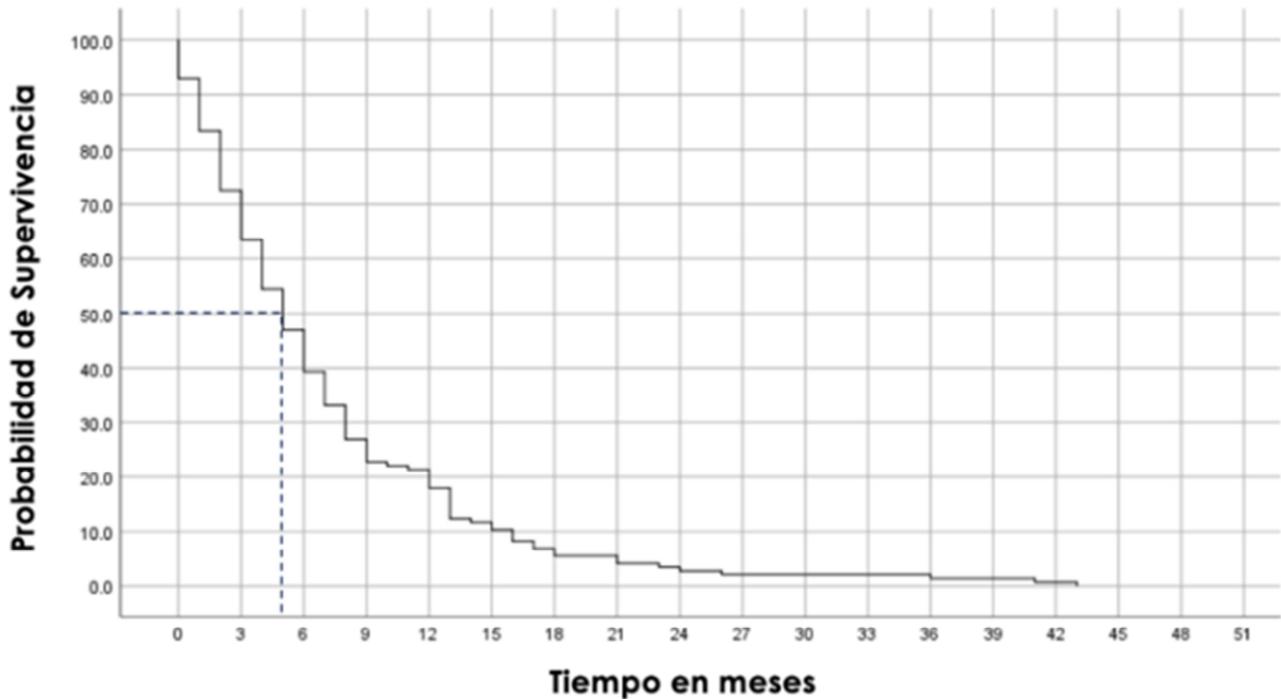


Figure 2. Overall survival in patients with KRAS wild-type metastatic colon cancer.

3.1. Multivariate Analysis

The multivariate analysis revealed that OS with cetuximab in second line was not associated with any variable studied because were not statistically significant, more than 1 site of metastasis at diagnosis (HR = 1.216 [95% CI: 0.75–1.96] p = 0.42), left-sided tumor (HR = 0.811, [95% CI: 0.56–1.15]; p = 0.246), and response to treatment (HR = 0.869 [95% CI: 0.521–1.449]; p = 0.59).

The prognostic factors associated with PFS in second-line treatment with cetuximab were exposure to cetuximab (median PFS, 4 months, p=0.033) and receiving a combined regimen such as FOLFIRI plus cetuximab (median PFS, 6 months, p<0.0001). The results for tumor location and more than 1 site of metastasis at diagnosis were not statistically significant (p=0.131 and p=0.972, respectively).

3.2. Response to Treatment

Response was evaluated in the clinical records of 73% of patients. The objective response rate (partial response + complete response) was 4.8%, with a clinical benefit (partial response + complete response + stable disease) of 24.3% (Table 3).

Table 3. Response to anti-EGFR therapy in patients with KRAS wild-type metastatic colon cancer.

Evaluation of the response	Frequency (%)
Partial	6 (4.8%)
Stable	24 (19.5%)
Progression	93 (75.6%)
Objective response rate	6 (4.8%)
Clinical benefit	30 (24.3%)

* According to clinical records, response not evaluated in 46 patients.

3.3. Adverse Events

Adverse events were recorded in the clinical records of 18% of patients, with rash (G1-2) being the most common (13%) and gastrointestinal effects (vomiting and nausea) in 2% of all cases (Figure 3).

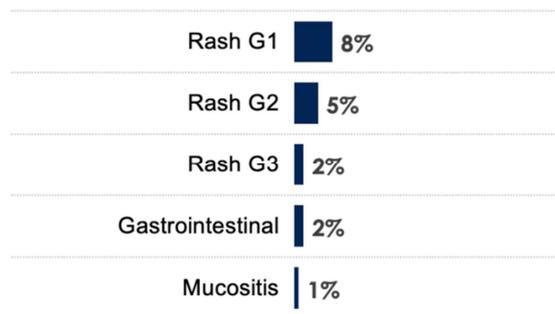


Figure 3. Adverse events.

4. Discussion

This is the first report of experience with cetuximab at the National Oncology Institute. The drug is approved as a second-line treatment for patients with extended KRAS wild-type metastatic colon cancer. Most of the epidemiological and histopathological features are similar to those reported in the literature [15, 16].

The most common second-line chemotherapy regimen was irinotecan plus cetuximab, as reported in the EPIC trial [10].

The PFS of 3 months and OS of 5 months were lower than the results obtained in second-line studies such as EPIC [10] and ITACa [11] possibly to use of chemotherapy without cetuximab in 27% of patients. The most used regimen was

irinotecan with cetuximab, although not based on multidrug regimens, such as FOLFIRI plus cetuximab, for which PFS and OS are longer [17]. The greatest benefit of anti-EGFR therapy is achieved in the first line of treatment but not in the second line [8, 9, 18, 19].

In the multivariate analysis, the prognostic factors significantly associated with PFS were exposure to cetuximab as a second-line agent and the use of combined regimens such as FOLFIRI plus cetuximab. However, other prognostic factors such as tumor laterality, number of metastases, and response to treatment were not associated with significant differences in OS or PFS in our study, although the location of the primary tumor (right) has been associated with higher mortality (HR=1.43 [95% CI, 1.26-1.61; p<0.001] [20]. Functional status is also a prognostic factor for both PFS and OS (patients with ECOG 0 vs ECOG 1; PFS 8.7 vs 4.6 months; OS 21.2 vs 12.3 months) [21].

Adverse effects with cetuximab, such as acne-like rash, have been reported in up to 85.3% of cases (G3-4 in 16.2%) [14]. We found a low number of adverse effects (18%), probably because the data depended on patient records. This percentage was much lower than expected.

Our study was limited because its retrospective design. In addition, it was based on data from the clinical records. Finally, the second line of treatment did not always involve anti-EGFR drugs as stipulated in the indications approved by our institution.

5. Conclusion

The epidemiological and clinical characteristics of patients studied here are like those reported in the literature. However, PFS and OS were lower than expected, as was the frequency of adverse effects. Most of the patients received anti EGFR therapy in second line. These results enable us to propose anti-EGFR therapy as the first line of treatment of colorectal cancer at the National Oncology Institute of Panama.

Disclosures

The authors declare that they have no conflicts of interest with respect to this study.

Ethical Conduct of Research Statement

This study was approved by the National Oncology Institute of Panama.

Financial &-Competing Interests' Disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Acknowledgements

To our patients, whose well-being is the driving force behind our study and research. We thank the Medical Oncology Service of the National Oncology Institute of Panama for their valuable contributions to the completion of this research.

References

- [1] Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet*. 394 (10207), 1467–1480 (2019).
- [2] REGISTRO HOSPITALARIO DE CÁNCER RHC-ION. Boletín 2019.
- [3] Del RN, Panam NDE. República de Panamá Ministerio de Salud Dirección de Planificación de Salud Departamento de Registros y Estadísticas de Salud REGISTRO NACIONAL DEL CÁNCER BOLETÍN ESTADÍSTICO. 2014-6, (2012).
- [4] Porru M, Pompili L, Caruso C, Biroccio A, Leonetti C. Targeting KRAS in metastatic colorectal cancer: current strategies and emerging opportunities. *J. Exp. Clin. Cancer Res.* 37 (1), 57 (2018). This review highlights the emerging experimental strategies for blocking KRAS function and signaling its direct targeting.
- [5] Xie Y-H, Chen Y-X, Fang J-Y. Comprehensive review of targeted therapy for colorectal cancer. *Signal Transduct. Target. Ther.* 5 (1), 22 (2020). The authors provide an overview of existing CRC-targeted agents and their underlying mechanisms, as well as a discussion of their limitations and future trends.
- [6] Li QH, Wang YZ, Tu J *et al.* Anti-EGFR therapy in metastatic colorectal cancer: mechanisms and potential regimens of drug resistance. *Gastroenterol. Rep. (Oxf)*. 8 (3), 179–191 (2020).
- [7] Cunningham D, Humblet Y, Siena S *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N. Engl. J. Med.* 351 (4), 337–345 (2004).
- [8] Van Cutsem E, Köhne C-H, Hitre E *et al.* Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N. Engl. J. Med.* 360 (14), 1408–1417 (2009).
- [9] Douillard JY, Siena S, Cassidy J *et al.* Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann. Oncol.* 25 (7), 1346–1355 (2014).
- [10] Sobrero AF, Maurel J, Fehrenbacher L *et al.* EPIC: Phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J. Clin. Oncol.* 26 (14), 2311–2319 (2008). Cetuximab and irinotecan improved progression-free survival and response rate and led to better quality of life than irinotecan alone.
- [11] Passardi A, Scarpi E, Gelsomino F *et al.* Impact of second line cetuximab-containing therapy in patients with KRAS wild-type metastatic colorectal cancer: Results from the ITACa randomized clinical trial. *Sci. Rep.* 7 (1), 10246 (2017). Results from the ITACa trial showed that, in patients with wild-type KRAS metastatic colorectal cancer, addition of cetuximab to second-line chemotherapy increased PFS.

- [12] Scope A, Agero ALC, Dusza SW *et al.* Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J. Clin. Oncol.* 25 (34), 5390–5396 (2007).
- [13] Bouché O, Ben Abdelghani M, Labourey J-L *et al.* Management of skin toxicities during panitumumab treatment in metastatic colorectal cancer. *World J. Gastroenterol.* 25 (29), 4007–4018 (2019).
- [14] Petrelli F, Ardito R, Ghidini A *et al.* Different toxicity of cetuximab and panitumumab in metastatic colorectal cancer treatment: a systematic review and meta-analysis. *Oncology.* 94 (4), 191–199 (2018).
- [15] Chen K-H, Shao Y-Y, Chen H-M *et al.* Primary tumor site is a useful predictor of cetuximab efficacy in the third-line or salvage treatment of KRAS wild-type (exon 2 non-mutant) metastatic colorectal cancer: A nationwide cohort study. *BMC Cancer.* 16, 327 (2016). Left-sided primary tumor site is a useful predictor of improved efficacy of cetuximab in third-line or salvage treatment of KRAS wild-type metastatic colorectal cancer.
- [16] Siegel RL, Miller KD, Goding Sauer A *et al.* Colorectal cancer statistics, 2020 CA. *Cancer J. Clin.* 70 (3), 145–164 (2020).
- [17] Iwamoto S, Hazama S, Kato T *et al.* Multicenter phase II study of second-line cetuximab plus folinic acid/5-fluorouracil/irinotecan (FOLFIRI) in KRAS wild-type metastatic colorectal cancer: the FLIER study. *Anticancer Res.* 34 (4), 1967–1973 (2014).
- [18] Yang YF, Wang GY, He JL, Wu FP, Zhang YN. Overall survival of patients with KRAS wild-type tumor treated with FOLFOX/FOLFIRI±cetuximab as the first-line treatment for metastatic colorectal cancer: A meta-analysis. *Medicine (Baltimore).* 96 (12), e6335 (2017).
- [19] Sotelo MJ, García-Paredes B, Aguado C, Sastre J, Díaz-Rubio E. Role of cetuximab in first-line treatment of metastatic colorectal cancer. *World J Gastroenterol.* 20 (15), 4208–4219 (2014). Adding cetuximab to standard chemotherapy increases the response rate in patients with wild-type KRAS and can thus increase the resectability rate for liver metastases.
- [20] Aljehani MA, Morgan JW, Guthrie LA *et al.* Association of primary tumor site with mortality in patients receiving bevacizumab and cetuximab for metastatic colorectal cancer. *JAMA Surg.* 153 (1), 60–67 (2018).
- [21] Liu Y, Wang F, Ma N *et al.* Continued cetuximab in second-line treatment for patients with unresectable metastatic wild-type KRAS, NRAS, and BRAF colorectal cancer after disease progression during first-line cetuximab-based therapy. *J. Clin. Oncol.* Abstract 127 (2020).