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Encorafenib plus cetuximab in patients with *BRAF*^{V600E}-mutated metastatic colorectal cancer — Polish multicenter experience

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ABSTRACT

Introduction. The *BRAF* mutation occurs in 8–12% of patients with colorectal cancer. This is associated with unfavorable prognosis — in metastatic disease, median survival does not exceed one year. Molecularly targeted treatment — encorafenib with cetuximab — is the standard of care in cases of chemotherapy failure.

Material and methods. Medical data of 18 patients treated with encorafenib and cetuximab in 2021–2023 in 10 oncology centers in Poland were assessed. We analyzed clinical, pathomorphological, and molecular factors, as well as the effectiveness and safety of treatment.

Results. The median age in the group was 63 years. Patients with metastases limited to one location predominated (78%). Treatment with encorafenib and cetuximab was used not only in the third (in 50% of patients) or fourth (in 28%) lines of treatment but also in the second (in 22%). The objective response rate was 29.4%, and the disease control rate was 76.4%. The median progression-free survival was 7.1 months. Four patients (22%) had a response lasting over 12 months.

Conclusions. The results of the analysis confirmed the efficacy and safety of targeted treatment with encorafenib and cetuximab in patients with metastatic colorectal cancer with the *BRAF*^{V600E} mutation, known from other studies.

Keywords: colorectal cancer, *BRAF*^{V600E} mutation, encorafenib, cetuximab

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Introduction

Colorectal cancer (CRC) is the third most common malignancy with a global incidence of 2.17 million per year [1]. In Poland, in 2019, over 18.7 thousand people were diagnosed with CRC, of whom 41% were patients aged ≥ 70 years [2]. In 15–30% of patients, synchronous metastases to distant organs are detected at diagnosis. Additionally, metachronous metastases are diagnosed in 20–50% of patients after primary treatment [3]. Treatment of metastatic disease, therefore, applies to a significant percentage of patients. Over the last quarter of a century, there has been an improvement in the treatment outcomes in this population, mainly due to introduction of multidisciplinary care and progress in systemic treatment [4]. Clinical trials have shown that median overall survival of patients treated in the last decade increased from 16 to 30 months.

The population of patients with metastatic colorectal cancer (mCRC) is very heterogeneous, with patients with the BRAF^{V600E} mutation constituting a particularly demanding subgroup. This is a group with unfavorable prognosis — in metastatic disease, median overall survival does not exceed one year [5].

Mutation of the gene encoding BRAF (type B rapidly accelerated fibrosarcoma) kinase occurs in 8–12% of patients, of whom over 95% have the BRAF^{V600E} mutation. Cancers with this genetic disorder have specific clinicopathological characteristics — they occur more often in women than in men, more often in elderly people than in younger, primary tumors are usually located on the right side, and metastases often involve the peritoneum. Additionally, mucinous carcinoma and coexisting microsatellite instability (MSI) are more common than in the general population of CRC patients [5]. The disease often has an aggressive course, and dissemination in the peritoneum makes treatment difficult.

This molecular disorder also has a predictive value — the presence of the BRAF^{V600E} mutation is associated with resistance to epidermal growth factor receptor inhibitors (EGFRi) [6]. On June 2, 2020, the European Medicines Agency (EMA) registered the first molecularly targeted therapy for mCRC patients with the BRAF^{V600E} mutation, e.g. combination of encorafenib with cetuximab (EC). The updated 2022 European Society for Medical Oncology (ESMO) guidelines introduced such therapy as the standard of care in patients after failure of first-line chemotherapy [3]. In Poland, this treatment is not reimbursed under the drug program. It is possible to use it on the basis of the Emergency Access to Drug Technologies (EADT) program, after exhausting available treatment methods. Due to the specific

clinical profile of the disease and financing method, few patients can benefit from such treatment. An attempt was made to assess the outcomes of EC use within the EADT program in Poland.

This analysis aimed to determine patient characteristics, assess the effectiveness and safety of the treatment, and compare the outcomes with other published real-world data.

Material and methods

Clinical data of 18 patients treated with EC in 2021–2023 in 10 oncology centers in Poland were assessed. We analyzed basic clinical, pathomorphological, and molecular characteristics, as well as treatment effectiveness and safety. Objective response rates (ORR) were assessed based on the RECIST 1.1 criteria, and disease control rates (DCR), defined as the sum of ORR and disease stabilization (DS) [7]. The progression-free survival (PFS) was defined as the time from initiation of treatment to disease progression or death. The Kaplan-Meier estimator was used in the PFS analysis.

Results

The median age in the analyzed group was 63 years (range 43–73; Tab. 1), with male sex predominant (60%). Almost all patients remained in good or very good performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale (PS = 1–72% and PS = 0–22%). The primary tumor was resected in 83% of patients. The tumor was located on the right side (78%), most often in the ascending colon. More than half of patients had metachronous metastases, mainly limited to one location (78%); only two patients had metastases in three different locations (11%). The most common locations of metastases were the liver (50%), peritoneum (39%) and lungs (22%). The BRAF^{V600E} mutation was found in all patients. MSI assessment was performed in 83% of patients, and its presence was confirmed in 16% (3 patients).

Encorafenib with cetuximab treatment was used not only in the third (50% of patients) or fourth (28%) but also in the second treatment line (22%). Almost all patients had previously received irinotecan (94%) and oxaliplatin (83%), while only 39% had received antiangiogenic therapy. The median follow-up was 8.2 months, and in 38% of patients was shorter than 6 months. The patients observations during and after EC treatment are presented in Figure 1. The treatment response was

Table 1. Characteristics of patients treated with encorafenib and cetuximab

Characteristics	Number of patients n = 18
Age in years	
Median	63.4
Range	(43.1–73.0)
Sex	
Women	7 (38.9%)
Men	11 (61.1%)
PS according to the ECOG scale	
0	4 (22.2%)
1	13 (72.2%)
2	1 (5.6%)
MSI	
Present	3 (16.7%)
Absent	12 (66.7%)
Not assessed	3 (16.7%)
Number of previous treatment lines	
1	4 (22.22%)
2	9 (50.00%)
3	5 (27.78%)
The type of previous treatment received	
Oxaliplatin	15 (83.3%)
Irinotecan	17 (94.4%)
VEGF inhibitors	7 (38.9%)
Location of the primary tumor	
Right-sided	14 (78.8%)
Left-sided	4 (22.2%)
Location of the primary tumor	
Caecum	4 (22.2%)
Ascending colon	5 (27.8%)
Hepatic flexure	2 (11.1%)
Transverse colon	3 (16.7%)
Splenic flexure	0 (0.00%)
Descending colon	0 (0.00%)
Sigmoid colon	2 (11.1%)
Rectosigmoid flexure	1 (5.6%)
Rectum	1 (5.6%)
Metastases	
Synchronous	7 (38.9%)
Metachronous	10 (55.6%)
No data	1 (5.6%)
Resection of the primary tumor	
Yes	15 (83.3%)
No	3 (16.7%)
Metastases	
≥ 3 locations	2 (11.1%)
Liver	9 (50.0%)
CEA*	
Median	17
Range	(1.30–896.90)

*No data on CEA for one patient; CEA — carcinoembryonic antigen; ECOG — Eastern Cooperative Oncology Group; MSI — microsatellite instability; PS — performance status; VEGF — vascular endothelial growth factor

assessed in 17 patients. The ORR was 29.4%, which corresponds to a partial response in 5 patients, and the DCR was 76.4%, which corresponds to 13 patients (Fig. 2). The median PFS was 7.1 months. The PFS curve estimated by Kaplan-Meier method is shown in Figure 3. A subgroup of 4 patients (22%) with the response longer than 12 months was identified. At the end of follow-up (June 30, 2023), 8 patients continued treatment.

The safety profile is presented in Table 2. There were no treatment discontinuations due to adverse events before the end of follow-up. Cetuximab dose reduction was required in 3 patients and encorafenib dose reduction in 2 patients (18% and 12%, respectively). The most frequently reported adverse events were asthenia (64%), skin toxicity (47%), anemia (47%), and abdominal pain (35%). Grade 3 and 4 adverse effects according to the Common Toxicity Criteria for Adverse Events (CTCAE scale) v5.0 were reported in 35% of patients. Only 1 patient experienced grade 4 toxicity (intestinal obstruction).

Discussion

Molecularly targeted treatment in CRC patients with the *BRAF*^{V600E} mutation with progression after chemotherapy is currently the treatment of choice. This standard was established based on the results of the BEACON study, which showed that EC improves progression-free survival and overall survival compared to the combination of chemotherapy with cetuximab. There was a reduction in the risk of disease progression (HR = 0.44; 95% CI 0.35–0.55) and risk of death (HR = 0.61; 95% CI 0.48–0.77) in the experimental arm [8], which resulted in an extension of median PFS from 1.5 to 4.3 months and median OS from 5.9 to 9.3 months. Subgroup analysis in this study showed that patients with metastases in fewer than 3 locations may benefit more from such treatment, as evidenced by a 52% reduction in the risk of death in this subgroup compared to a 24% reduction in patients with metastases in at least 3 locations [9].

The ORR was 20%, and in 37% of patients, the response lasted at least 6 months. The median duration of response was 5.5 months (95% CI 4.1–8.3). In the BEACON study, the most frequently reported adverse events were diarrhea (38%), nausea (38%), asthenia (33%), decreased appetite (31%), and skin toxicity (30%). Adverse events of grade 3 or higher occurred in 57% of patients, and 9% of patients discontinued EC treatment due to complications.

The effectiveness of this strategy is also confirmed by analysis of real-world data (RWD). In a population

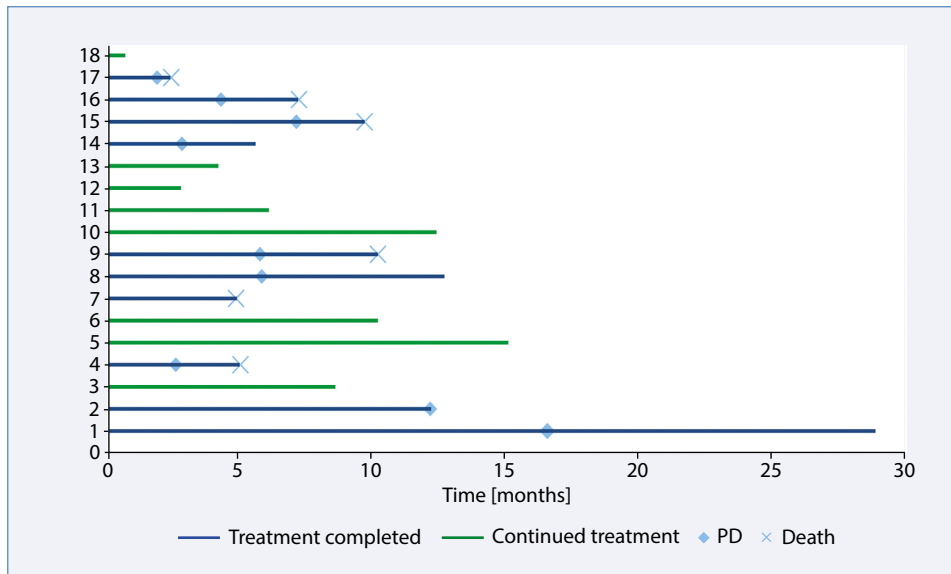


Figure 1. Patients observations during and after treatment with encorafenib and cetuximab; PD — progressive disease

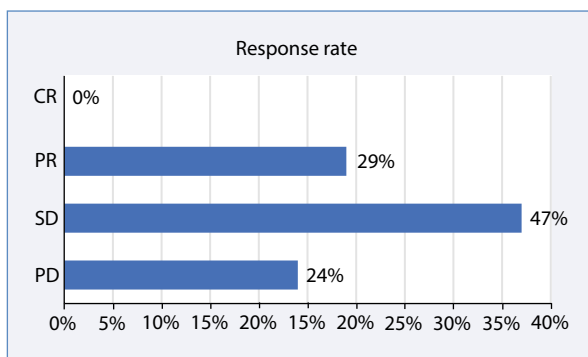


Figure 2. Response rate to treatment with encorafenib and cetuximab; CR — complete remission; PD — progressive disease; PR — partial response; SD — stable disease

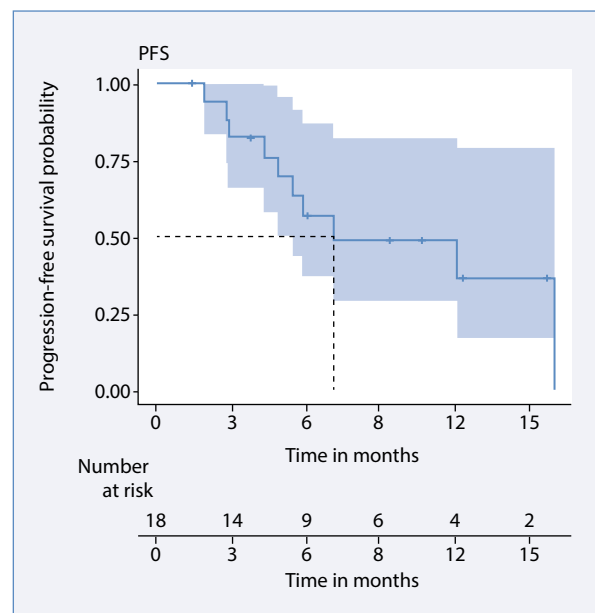


Figure 3. The progression free survival (PFS) curve estimated by Kaplan-Meier method

of 97 mCRC patients with the *BRAF*^{V600E} mutation treated with EC in Italian cancer centers as part of the early access program, the ORR was 17% and the DCR was 65% [10]. Median PFS was 4.6 months and median OS was 7.2 months. The shorter survival time in the analyzed population may result from the qualification to treatment also patients with ECOG PS = 2. In 33% of patients, metastases were found in three or more locations. Anti-BRAF treatment in the fourth or subsequent line was used in only 8% of patients. A retrospective analysis of a Spanish cohort of 81 mCRC patients showed that the use of EC in the second treatment line was associated with ORR = 33% [11]. Median PFS was 5.5 months, and median OS was 12.6 months. Longer PFS was observed in the subgroup of patients without liver metastases (HR = 2.0; 95%

CI 1.2–3.3) and with fewer than three metastatic foci (HR = 2.8; 95% CI 1.6–5.1).

A prospective study is currently underway to evaluate the effectiveness of second and third-line treatment with EC in daily clinical practice in Germany, Austria, and Switzerland. During the 2023 Gastrointestinal Cancer Symposium of American Society of Clinical Oncology (ASCO), the characteristics of the first 81 patients included in the study were presented. The median age was

Table 2. Safety of treatment with encorafenib and cetuximab

Characteristics	Number of patients n = 17*
The most common adverse events	
Asthenia	11 (64.71%)
Skin toxicity	8 (47.06%)
Anemia	8 (47.06%)
Abdominal pain	6 (35.29%)
Grade 3 adverse events	
Asthenia	3 (17.65%)
Diarrhea	1 (5.88%)
Loss of appetite	1 (5.88%)
Weight loss	1 (5.88%)
Anemia	1 (5.88%)
Grade 4 adverse events	
Intestinal obstruction	1 (5.88%)
Cetuximab treatment course**	
Dose reduction	3 (18.75%)
Dose delay	3 (18.75%)
Treatment discontinuation due to adverse events	0 (0.00%)
Encorafenib treatment course**	
Dose reduction	2 (12.50%)
Dose delay	4 (25.00%)
Treatment discontinuation due to adverse events	0 (0.00%)

*No data for one patient; **No data for two patients

67 years. The majority of patients (61%) had synchronous metastases, and 16% of patients had 3 or more locations [12].

The analyzed group of 18 patients differs from the population from both the pivotal study and the aforementioned RWD analyses. Our group was dominated by patients receiving EC treatment in the third or fourth line, while in the BEACON study — in the second line. In the majority of patients in the analyzed group, metastases were found in only one location, while in the BEACON study, almost half of patients had metastases in at least three locations, with liver metastases reported in 60% of patients.

The assessment of treatment effectiveness measured by ORR showed a numerically higher percentage in the study group compared to the BEACON study or Italian analysis. Although 8 patients are still on treatment, 4 of them have already had a response lasting more than a year. Although very rare, long-term responses to anti-BRAF treatment are reported in the literature. In a phase I study evaluating the activity of dabrafenib with trametinib, a response to treatment lasting more than 36 months was observed in one patient [13]. In a phase II trial evaluating the combination of dabrafenib and panitumumab, 2 patients showed a response to treatment lasting more than 24 months [14].

The median PFS we obtained, which is longer than in the studies mentioned above, may be the result of imaging tests performed at different time points, depending on the assessment of the treating physician.

The median PFS we obtained, which is longer than in the studies mentioned above, may be the result of imaging tests performed at different time points, depending on the assessment of the treating physician.

The profile of evaluated patients may result from the need to exhaust reimbursed treatment options before applying for EADT. Published data indicate that the chance of receiving second and third-line treatment in CRC patients receiving first-line chemotherapy was 69 and 44%, respectively [15]. Data from the CAPSTAN study, which retrospectively evaluated the treatment of 224 mCRC patients with the *BRAF*^{V600E} mutation, show that in this population respective percentages were even lower — 53% and 30% respectively [16].

An important aspect of the presented analysis is showing the characteristics of patients and the effect of EC treatment within the EADT program. The advantage of this work is its multi-center nature. A limitation is undoubtedly the small sample size, which reflects the actual limitations in the functioning of EADT in the case of an aggressive disease with unfavorable prognosis.

Conclusions

The clinical characteristics of the analyzed patient group indicate differences in comparison with cohorts presented in the literature, which most likely result from a careful selection of patients for treatment with the EADT program. Numerous publications as well as clinical practice indicate poor prognosis and poor effectiveness of chemotherapy in patients with CRC with the *BRAF*^{V600E} mutation, which emphasizes the need for and importance of using new treatment options in this special population.

The analysis of a group of patients treated with EC in Polish centers confirms the safety and effectiveness of such treatment in daily clinical practice, known from other studies. According to the ESMO guidelines, it is recommended in patients after failure of the first line of treatment.

Article Information and Declarations

Data availability statement

All analyzed data is included in this article. Further inquiries may be directed to the corresponding author.

Ethics statement

Due to the retrospective nature of the study, local Bioethics Committee approval was not necessary.

Author contributions

MG: should be considered the main author, author of the concepts, methods, research, data analysis, literature review, original manuscript; data collection, and final approval of the article.

PZ: data collection, statistical analysis, and final approval of the article.

MD, AD-W, BG, ŁG, AG-C, KH, MK, MM, JS, KW, PW: data collection, final approval of the article.

BR: should be considered the senior author, author of the concepts, methods, research, data analysis, literature review, original manuscript; data collection, and final approval of the article.

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BR: has received personal compensation from Amgen, AstraZeneca, BMS, Gilead, Lilly, Merck, MSD, Novartis, Pfizer, Pierre-Fabre, Roche, and Servier, unrelated to the article.

The other authors report no conflict of interest related to the article.

Supplementary material

None.

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