Real-world practices in RAS wild-type metastatic colorectal cancer patients treated with targeted agents in the first-line a nationwide onco-colon Turkey registry

Birinci basamakta hedefe yönelik ajanlarla tedavi edilen RAS mutasyonu taşımayan metastatik kolorektal kanser hastalarında gerçek yaşam verileri: Ulusal onco-colon Türkiye kayıt sistemi

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Abstract

Aim: Efficacy of antiepidermal growth factor receptor (anti-EGFR) agents has been demonstrated in metastatic colorectal cancer (mCRC). Real-world evidence is especially important to detect patient findings outside of clinical trials. Therefore, we aimed to investigate the real-world data in patients with RAS wild-type mCRC.

Methods: Medical records from 28 centers were collected for patients diagnosed with mCRC between January 2016 and April 2019. Patients were compared according to the first-line biological treatments as anti-EGFR group (Group A (panitumumab) and B (cetuximab)) and anti-VEGF group (Group C).

Results: A total of 1064 patients with documented RAS wild-type mCRC were evaluated. Of these, 33%, 37% and 30% were treated with regimens including panitumumab, cetuximab, and anti-VEGF in the first-line, respectively. Overall response rate was 46.4%, 41.9% and 41.5% in A, B, and C groups, respectively (p = 0,170). The median OS was 26, 27, and 23 months in A, B and C group respectively (p = 0.044). The median PFS of the patients that treated with panitumumab, cetuximab and bevacizumab was 11,6, 11,0 and 9,6 months respectively (p = 0.012). ECOG performance status (PS) 0-1 and Braf wild-type status were found as independent prognostic factors in multivariate analysis for OS and only BRAF wild-type status for PFS (p<0.05).

Conclusion: This analysis of real-world data confirms the comparable efficacy of anti-EGFR agents in RAS wild-type mCRC. However, anti-EGFR treatment provides PFS and OS advantage when compared with anti-VEGF treatment in these patients. Also, Braf wild-type tumors had improved PFS and OS in RAS wild-type mCRC.

Keywords: Cetuximab; colorectal neoplasms; epidermal growth factor receptor; panitumumab; vascular endothelial growth factor B

Öz

Amaç: Anti-EGFR ajanlarının etkinliği metastatik kolorektal kanserde (mKRK) gösterilmiştir. Gerçek yaşam verileri, klinik çalışmaların dışında kalan hastalara ait bulguları ortaya koymak açısından özellikle önemlidir. Bu nedenle, RAS vahşi tip mKRK'li hastalarda gerçek yaşam verilerini araştırmayı amaçladık.

Yöntemler: Ocak 2016 ile Nisan 2019 tarihleri arasında mKRK tanısı alan hastalara ait tıbbi kayıtlar 28 merkezden toplandı. Hastalar, birinci basamak biyolojik tedavilere göre anti-EGFR grubu (Grup A (panitumumab) ve B (setuksimab)) ve anti-VEGF grubu (Grup C) olarak karşılaştırıldı.

Bulgular: Belgelenmiş RAS vahşi tip mKRK'li toplam 1064 hasta değerlendirildi. Bu hastaların sırasıyla %33'ü panitumumab, %37'si setuksimab ve %30'u birinci basamakta anti-VEGF içeren rejimlerle tedavi edildi. Genel yanıt oranı Grup A, B ve C'de sırasıyla %46,4, %41,9 ve %41,5 idi (p = 0,170). Medyan genel sağkalım (OS) Grup A, B ve C'de sırasıyla 26, 27 ve 23 ay olarak bulundu (p = 0,044). Panitumumab, setuksimab ve bevacizumab alan hastaların medyan progresyonsuz sağkalımı (PFS) sırasıyla 11,6, 11,0 ve 9,6 ay idi (p = 0,012). Çok değişkenli analizde, performans durumu (PS) 0-1 ve BRAF vahşi tip durumu OS için bağımsız prognostik faktörler olarak; yalnızca BRAF vahşi tip durumu ise PFS için bağımsız prognostik faktör olarak bulundu (p<0,05).

Sonuç: Bu gerçek yaşam verilerinin analizi, RAS vahşi tip mKRK'de anti-EGFR ajanlarının karşılaştırılabilir etkinliğini doğrulamaktadır. Ancak, bu hastalarda anti-EGFR tedavisi, anti-VEGF tedavisine kıyasla PFS ve OS avantajı sağlamaktadır. Ayrıca, BRAF vahşi tip tümörlere sahip hastalarda PFS ve OS daha iyi bulunmuştur.

Anahtar Sözcükler: Epidermal büyüme faktörü reseptörü; kolorektal neoplaziler; setuksimab; panitumumab; vasküler endotelyal büyüme faktörü B

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INTRODUCTION

Colorectal cancer (CRC) is a common disease with a high mortality rate. In 2021, it was estimated that approximately 149,500 new cases of CRC and 52,980 CRC deaths would occur in the United States (1). Approximately 20% of patients with CRC already have metastases at diagnosis, and this figure has remained stable over the last two decades (2). Since 2000, the treatment of metastatic CRC (mCRC) has rapidly changed with the approval of new combinations of cytotoxic and biologic agents. Although the best way to combine and sequence these agents in previously untreated patients is still not established, it has been shown that agents targeting vascular endothelial growth factors (VEGFs) and their receptors (bevacizumab) and the epidermal growth factor receptor (EGFR) (panitumumab and cetuximab) are active in the first-line treatment of mCRC (3,4). In these studies, similar efficacies and different toxicity profiles for these combination regimens have been reported. The choice between bevacizumab and anti-EGFRs is primarily based on the RAS and BRAF mutation status and location of the primary tumor side (3-6). The choice between cetuximab and panitumumab is largely empiric, and they both have comparable efficacy (7).

The real-world patterns and outcomes are important for determining the data of the patients outside of clinical trials, and real-world evidence complements the data obtained in randomized clinical trials (RCTs). In addition, it may allow optimization of the selection and sequencing of these agents for treatment. Therefore, in this study, we decided to evaluate the real-world outcomes of anti-EGFR treatments in the first-line treatment of RAS wild-type mCRC.

MATERIAL AND METHODS

Medical records from 28 centers were collected for patients diagnosed with RAS wild-type mCRC between January 2016 and April 2019 and were included in the study. Histopathological, molecular, and clinical characteristics of the patients were recorded. The treatment duration, response rate, progression-free survival, and safety results were determined. Also, changes over the years were compared. Patients were compared according to the first-line biological treatments as anti-EGFR group (Group A and B) (panitumumab and cetuximab) and anti-VEGF group (group C). Performance status was recorded according to the Eastern Cooperative Oncology Group (ECOG) performance score (8). Toxicity was classified according to the World Health Organization criteria at each cycle of the chemotherapy (9). Ethical approval for this study was obtained from the Clinical Research Ethics Committee of İstanbul Medeniyet University Göztepe Education and Research Hospital (date: 09.03.2020, decision no: 2020/0172).

Statistical analyses

Statistical Package for the Social Sciences software for Windows, version 21.0, was used for the statistical analysis (SPSS, Chicago, IL, USA). A p-value less than 0.05 was considered to be significant. Most values were expressed as medians. The Kaplan–Meier method was used for survival analysis. The univariate analysis of potential prognostic factors was assessed by using the log-rank test. The Cox regression model was used for multivariate analysis. Overall survival (OS) was calculated from the diagnosis of patient to the date of death from any cause or of the last follow-up. Progression-free survival (PFS) was calculated from the diagnosis to the date. of disease progression, recurrence, or death from any cause. The patients were followed until their death or last follow-up.

RESULTS

A total of 1,065 patients were included in the study. The median age of the patients was 61 (range: 17-88) years. Thirty-four percent of the patients were female. Patients with high body mass index (BMI) were 62.2%. The percentage of patients with an ECOG PS of 0-1 was 92.0%. Only 6% of the patients were screened for colorectal cancer. Seventy-three percent of the patients had de novo metastatic disease, and 15.9% underwent metastasectomy. All patients were evaluated for RAS status: 97.8% had KRAS wild-type and 85.4% had NRAS wild-type status. BRAF wild-type tumors accounted for 59.1%. The majority (79.1%) of the patients had left-sided tumors. The primary tumor was resected in 85% of the patients. The clinical characteristics of the patients are shown in Table 1.

In the first-line treatment, 29.7%, 33.0% and 27.1% of patients were treated with regimens including panitumumab, cetuximab (Group A and B), and bevacizumab (Group C), respectively. Oxaliplatin-based doublet backbone therapy was administered to the 62.1% of the patients, and oxaliplatin-based regimens (62.1%) were more commonly used than irinotecan-based doublets (32.6%). Triplet chemotherapy regimens were used in only 1.7% of the patients. Cetuximab and panitumab were given to 52.6% and 47.4% of the patients who received anti-EGFR therapy, respectively. Patients received a median of six cycles of treatment. In addition, those who responded to treatment received a median of six cycles of maintenance therapy with biologics plus fluoropyrimidines. The treatment data of the patients are shown in Table 2.

Overall response rate (ORR) was 46.4%, 41.9% and 41.5% in Groups A, B and C, respectively (p = 0.170). The median OS was 26, 27, and 23 months in Groups A, B, and C, respectively (p = 0.044). The median PFS of the patients in the first-line setting who received panitumumab, cetuximab and bevacizumab was 11.6 months (SE:0.6; 95% CI: 10.4-12.7), 11.0 months (SE:0.5; 95% CI: 9.9-12.0), and 9.6 months (SE:0,4; 95% CI: 8.8-10.4), respectively (p = 0.012). In univariate analysis, metastasectomy, BRAF wild-type tumors, ECOG performance status (PS) 0-1, normal CEA levels at diagnosis, history of screening, primary tumor resection, first-line anti-EGFR treatment, and oxaliplatin-based backbone regimen were significantly associated with PFS (p<0.05). In multivariate analysis, BRAF wild-type status (p=0.012; 10,7 vs 7,2 months) and good PS (p=0.010; 10,2 vs 8,3 months) remained significant predictors of PFS. In univariate analysis for OS, female sex, left-sided tumors, ECOG PS 0-1, metastasectomy, higher body mass index (BMI), normal CA 19-9 level at diagnosis, treatment with anti-EGFR agents, and oxaliplatin-based backbone regimen were identified as favorable factors (p<0.05). In multivariate analysis, only BRAF wild-type status was found to be an independent prognostic factor for OS (p = 0.047; 26,8 vs 12,4 months) (Table 3).

Acneiform rash was observed more frequently with anti-EGFR therapy than with bevacizumab (p=0.000). Hypertension, proteinuria, mucositis, fatigue, infections excluding febrile neutropenia, and constipation side-effects were observed more frequently with bevacizumab than anti-EGFR agents (p<0.05). Acneiform rash and thrombocytopenia were more common with panitumumab than with cetuximab (p=0.011). Nausea and vomiting were more common with cetuximab than with panitumumab.

DISCUSSION AND CONCLUSION

Patient-related prognostic factors of mCRC include age and performance status (10,11). It has been shown that patients with good performance status tolerate combination chemotherapies well and have a more favorable survival outcomes. Regardless of age, individuals with poor PS usually tolerate chemotherapy poorly and have a worse short-term prognosis (11,12). Consistent with these observations, our real-world data showed that patients with ECOG PS 0–1 experienced significantly longer progression-free survival (PFS) and overall survival (OS) compared with those with poorer PS. These findings underscore the critical role of baseline performance status in guiding treatment selection and predicting clinical outcomes in RAS wild-type mCRC patients.

However, patients with mCRC who have a PS of 2 should be considered for chemotherapy, particularly if their PS decline is cancer-related. Although such patients have a median survival that is approximately half that of patients with a good PS, they benefit to a similar extent from combination chemotherapy (12,13). In our study, we did not find any relationship between age and survival outcomes. A PS score of 0-1 had a statistically significant effect on PFS but was not associated with OS. Patients with a PS score of 0-1 comprised 92% of the study population, which may have influenced the survival results. This particularly highlights the fact that, in real-world practice, similar to clinical trials, patients with poor performance status are rarely included in treatment decisions.

For decades, 5-Fluorouracil (5-FU) and leucovorin (LV) remained as the standard first-line therapy in mCRC (14). In the early 2000s, several trials established the superiority of oxaliplatin- and irinotecan-containing doublet combination regimens over 5-FU/LV regimens, as well as the equivalency of these doublet regimens in the frontline metastatic setting (15-

Table 1. Clinical characteristics of the patients

Patient characteristics	Number of patients (%)
Age	
<=60	515 (48.6)
>60	545 (51.4)
Sex	
Female	366 (34.4)
Male	699 (65.6)
Metastatis at initial diagnosis	
De Novo metastasis	776 (72.9)
Metastasis after early stage	289 (27.1)
Metastasectomy	
Present	169 (15.9)
Absent	896 (84.1)
Localization (right/left)	
Left colon	842 (79.1)
Right colon	210 (19.7)
KRAS mutation	
Wild type	1042 (97.8)
Not assessed	23 (2.2)
NRAS mutation	
Wild type	910 (85.4)
Not assessed	155 (14.6)
BRAF mutation	
Wild Type	630 (59.1)
Mutant Type	20 (1.9)
Not assesed	415 (39.0)
BMI (kg/m²)	
<25	300 (37.8)
≥25	493 (62.2)
ECOG PS	
PS 0-1	575 (92.0)
PS 2-4	50 (8.0)
CEA level	
Normal	49 (8.8)
Increased	511 (91.3)
MSI status	
Stable	272 (81.9)
High	60 (18.1)
Screening history	
Present	51 (5.9)
Absent	815 (94.1)
Surgery of primary tumor site	
No	129 (15.0)
Yes	729 (85.0)

*KRAS: 2 Kirsten rat sarcoma viral oncogene homolog, NRAS: neuroblastoma RAS viral oncogene homolog, BRAF: B-Raf proto-oncogene serine/threonine-protein kinase, BMI: body mass index, ECOG PS: eastern cooperative oncology group performance status, CEA: carcino-embriogenic antigen, MSI: micro-satellite instability, %: Percent

19). In addition, the triplet chemotherapy regimen FOLFOXIRI (irinotecan and oxaliplatin with 5-FU/LV), has higher activity but increased toxicity, with or without a biologic agent (20,21). Therefore, FOLFOXIRI regimens are particularly suggested for patients with good PS, BRAF V600E mutations, and right-sided tumors (22,23). In this real-world study, we found that oxaliplatin-based doublet regimens were chosen more frequently than irinotecan-based doublets by oncologists. Although patients with a PS score of 0-1 who had right-sided and BRAF-mutant tumors con-

stituted nearly 20% of the total population, triplet regimens were preferred in only 1.7% of the patients. This likely reflects the toxicities associated with triplet regimens in real-world practice.

The choice between bevacizumab and anti-EGFR agents in the first-line metastatic CRC setting for patients with extended RAS wild-type tumors has been extensively studied in two phase III trials. In the FIRE-3 trial, FOLFIRI plus cetuximab or bevacizumab was compared. An updated analysis showed a significant difference in median OS (33.1 vs 25.0 months, HR:

Table 2. The treatment characteristics of the patients

Treatment characteristics	n (%)
First-line treatment	
Panitumumab	316 (29.7)
Cetuximab	351 (33.0)
Bevacizumab	289 (27.1)
No biologics	109 (10.2)
First-line treatment	
Anti-EGFRs	667 (69.8)
Anti-VEGF	289 (30.2)
First-line treatment	
Panitumumab	316 (47.4)
Cetuximab	351 (52.6)
First-line treatment	
Anti-EGFR+Oxaliplatin	406 (44.2)
Anti-EGFR+İrinotecan	248 (27.0)
Anti-VEGF+Oxaliplatin	181 (19.7)
Anti-VEGF+İrinotecan	84 (9.1)
First-line treatment	
Panitumumab+ Oxaliplatin	233 (35.6)
Panitumumab+İrinotecan	78 (11.9)
Cetuximab+Oxaliplatin	173 (26.5)
Cetuximab+İrinotecan	170 (26.0)
First-line treatment	
Panitumumab+ Oxaliplatin	233 (25.4)
Panitumumab+İrinotecan	78 (8.5)
Cetuximab+Oxaliplatin	173 (18.8)
Cetuximab+İrinotecan	170 (18.5)
Bevacizumab+Oxaliplatin	181 (19.7)
Bevacizumab+İrinotecan	84 (9.1)
First-line treatment	
Oxaliplatin-based	661 (62.1)
Irinotecan-based	348 (32.6)
IRINOX-based	18 (1.7)
Single-agent Fluoropyrimidine	38 (3.6)
Patients received first-line maintenance treatment (%)	
All patient groups	220 (20.7)
In patients with treatment responder	220/715 (30.7)
Patients received second-line maintenance treatment (%)	
All patient groups	62/617 (10.0)
In patients with treatment responder	62/296 (20.9)
Subsequent treatments	
Third-line treatment (%)	24.6
Fourth-line treatment (%)	8.3
≥ 5th-line treatment (%)	2.1

*EGFR: epidermal growth factor receptor, VEGF: vascular epithelial growth factor, IRINOX: irinotecan plus oxaliplatin, n: Number of patients, %: Percent, p<0.05

0.70, p=0.0059) without a statistically significant difference in PFS (3). In contrast, in the CALBG/SWOG 80405 study, in which FOLFOX or FOLFIRI with cetuximab or bevacizumab were compared, no difference in OS was found, even after excluding all RAS-mutant cancers were excluded (4). In our registry study, we recorded the patients with RAS wild-type tumors, and frontline anti-EGFR therapy provided better outcomes than bevacizumab. There was no statistically significant difference between panitumumab and cetuximab.

Differences among these studies indicate the presence of underlying clinical and biological factors that remain poorly understood (20). Classifying colorectal tumors according to tumor location may help explain these differences. Approximately 5% to 8% of patients with RAS wild-type tumors have a BRAF V600E mutation and exhibit poor response to anti-EGFR treatments (24). Left-sided tumors often present with BRAF wild-type status, KRAS point mutations, extensive copy number alterations, and other structural

Table 3. Univariate analysis of progression-free survival according to the patient characteristics

Patient characteristics	n (%)	mPFS (months)	p
Age			0.955
≤60	515 (48.6)	10.8	
>60	545 (51.4)	10.0	
Sex			0.724
Female	366 (34.4)	10.5	
Male	699 (65.6)	10.4	
Metastatis at initial diagnosis			0.733
De Novo Metastasis	776 (72.9)	10.4	
Metastasis after early stage	289 (27.1)	10.4	
Metastasectomy			0.000*
Present	169 (15.9)	13.1	
Absent	896 (84.1)	10.0	
Localisation (right/left)			0.244
Left colon	842 (79.1)	9.8	
Right colon	210 (19.7)	10.7	
BRAF			0.026*
Wild-type	630 (59.1)	10.7	
Mutant	20 (1.9)	7.2	
Not assessed	415 (39.0)	10.4	
BMI(kg/m²)			0.305
<25	300 (37.8)	9.9	
≥25	493 (62.2)	10.4	
ECOG PS			0.003*
PS 0-1	575 (92.0)	10.2	
PS 2-4	50 (8.0)	8.3	
CEA levels			0.038*
Normal	49 (8.8)	14.4	
İncreased	511 (91.3)	10.3	
MSI status			0.603
Stable	272 (81.9)	11.0	
High	60 (18.1)	11.1	
Screening history			0.003*
Present	51 (5.9)	7.9	
Absent	815 (94.1)	10.5	
Surgery of primary tumor site			0.000
No	129 (15.0)	10.0	
Yes	729 (85.0)	11.3	
First-line treatment			0.012*
Panitumumab	316 (29.7)	11.6	
Cetuximab	351 (33.0)	11.0	
Bevacizumab	289 (27.1)	9.6	
No biologics	109 (10.2)	-**	
First-line treatment			0.005*
Anti-EGFRs	667 (69.8)	11.2	
Anti-VEGF	289 (30.2)	9.6	
First-line anti-EGFR treatment			0.270
Panitumumab	316 (47.4)	11.6	
Cetuximab	351 (52.6)	11.0	
First-line treatment			0.007*
Anti-EGFR+Oxaliplatin	406 (44.2)	12.1	
Anti-EGFR+İrinotecan	248 (27.0)	10.3	
Anti-VEGF+Oxaliplatin	181 (19.7)	9.9	
Anti-VEGF+İrinotecan	84 (9.1)	8.7	
First-line treatment			0.307
Panitumumab+ Oxaliplatin	233 (35.6)	11.7	
Panitumumab+İrinotecan	78 (11.9)	11.1	
Cetuximab+Oxaliplatin	173 (26.5)	12.6	
Cetuximab+İrinotecan	170 (26.0)	10.3	
First-line treatment			0.103
Oxaliplatin-based	661 (62.1)	10.8	
Irinotecan-based	348 (32.6)	9.5	
IRINOX-based	18 (1.7)	-**	
Single-agent Fluoropyrimidine	38 (3.6)	-**	

*KRAS: 2 Kirsten rat sarcoma viral oncogene homolog, NRAS: neuroblastoma RAS viral oncogene homolog, BRAF: B-Raf proto-oncogene serine/threonine-protein kinase, BMI: body mass index, ECOG PS: eastern cooperative oncology group performance status, CEA: carcino-embriogenic antigen, MSI: micro-satellite instability, EGFR: epidermal growth factor receptor, VEGF: vascular epithelial growth factor, IRINOX: irinotecan plus oxaliplatin, n: Number of patients, %: Percent, p<0.05

Table 4. Univariate analysis of overall survival according to the patient characteristics

Patient characteristics	n (%)	mOS (months)	p
Age			0.410
≤60	515 (48.6)	27.8	
>60	545 (51.4)	25.1	
Sex			0.030*
Female	366 (34.4)	28.7	
Male	699 (65.6)	25.6	
Metastatis at initial diagnosis			0.907
De Novo Metastasis	776 (72.9)	26.1	
Metastasis after early stage	289 (27.1)	27.5	
Metastasectomy			0.000*
Present	169 (15.9)	47.3	
Absent	896 (84.1)	24.5	
Localisation (right/left)			0.001*
Left colon	842 (79.1)	27.4	
Right colon	210 (19.7)	24.6	
BRAF			0.028*
Wild-type	630 (59.1)	26.8	
Mutant	20 (1.9)	12.4	
Not assessed	415 (39.0)	25.4	
BMI(kg/m²)			0.004*
<25	300 (37.8)	23.1	
≥25	493 (62.2)	28.5	
ECOG PS			0.001*
PS 0-1	575 (92.0)	25.9	
PS 2-4	50 (8.0)	17.7	
CEA levels			0.079
Normal	49 (8.8)	36.4	
İncreased	511 (91.3)	26.2	
MSI status			0.595
Stable	272 (81.9)	31.4	
High	60 (18.1)	34.6	
Screening history			0.308
Present	51 (5.9)	23.9	
Absent	815 (94.1)	27.6	
Surgery of primary tumor site			0.000*
No	129 (15.0)	20.5	
Yes	729 (85.0)	31.2	
First-line treatment			0.051
Panitumumab	316 (29.7)	26.5	
Cetuximab	351 (33.0)	27.6	
Bevacizumab	289 (27.1)	23.4	
No biologics	109 (10.2)	-**	
First-line treatment			0.016*
Anti-EGFRs	667 (69.8)	27.4	
Anti-VEGF	289 (30.2)	23.4	
First-line anti-EGFR treatment			0.726
Panitumumab	316 (47.4)	26.5	
Cetuximab	351 (52.6)	27.6	
First-line treatment			0.002*
Anti-EGFR+Oxaliplatin	406 (44.2)	30.2	
Anti-EGFR+İrinotecan	248 (27.0)	23.9	
Anti-VEGF+Oxaliplatin	181 (19.7)	23.9	
Anti-VEGF+İrinotecan	84 (9.1)	22.0	
First-line treatment			0.005*
Panitumumab+ Oxaliplatin	233 (35.6)	30.0	
Panitumumab+İrinotecan	78 (11.9)	18.7	
Cetuximab+Oxaliplatin	173 (26.5)	30.5	
Cetuximab+İrinotecan	170 (26.0)	26.8	
First-line treatment			0.001*
Oxaliplatin-based	661 (62.1)	27.5	
Irinotecan-based	348 (32.6)	23.1	
IRINOX-based	18 (1.7)	-**	
Single-agent fluoropyrimidine	38 (3.6)	-**	

*KRAS: 2 Kirsten rat sarcoma viral oncogene homolog, NRAS: neuroblastoma RAS viral oncogene homolog, BRAF: B-Raf proto-oncogene serine/threonine-protein kinase, BMI: body mass index, ECOG PS: eastern cooperative oncology group performance status, CEA: carcino-embriogenic antigen, MSI: micro-satellite instability, EGFR: epidermal growth factor receptor, VEGF: vascular epithelial growth factor, IRI-NOX: irinotecan plus oxaliplatin, n: Number of patients, p<0.05

genomic aberrations. Right-sided tumors are enriched for KRAS wild-type status, BRAF V600E point mutations, microsatellite instability, DNA hypermethylation, and hypermutations (25,26). Multiple trials have shown that there is a differential response to anti-EGFR therapy based on tumor sidedness (27,28). A post hoc analysis of CALBG/SWOG 80405 trial found that tumor sidedness is prognostic: left-sided tumors had increased survival and also, was predictive of response to cetuximab for left-sided tumors were associated with increased survival and also predictive of response to cetuximab for left-sided tumors and bevacizumab for right-sided tumors (29). A combined analysis of two trials similarly showed a survival advantage of cetuximab over bevacizumab for left-sided tumors (30). In our study, we found no association between tumor sidedness and survival, probably due to the selection of RAS wild-type tumors. However, we observed a statistically significant relationship between BRAF wild-type tumors and both PFS and OS. Overall survival was approximately two-fold higher in patients with BRAF wild-type tumors compared to those with BRAF-mutant tumors. This again highlights the importance of BRAF status in RAS wild-type tumors.

In CRYSTAL trial, the addition of cetuximab to FOLFIRI resulted in improvement in PFS and OS in RAS wild-type tumors (31). Similarly, another trial of FOLFOX with or without panitumumab yielded comparable results (32). Based on these findings, the use of either agent with FOLFOX or FOLFIRI is considered standard of care for the frontline treatment of RAS wild-type tumors. The main toxicities of anti-EGFR agents include acneiform rash (mostly panitumumab), diarrhea, and hypersensitivity reactions (mostly with cetuximab) (22,23). Thus, the choice between panitumumab and cetuximab is largely empiric and usually depends on the experience of the oncologist. In our study, acneiform rash more commonly with panitumumab. However, as a real-world study, there was no statistically significant difference between anti-EGFR agents. Additionally, nausea and vomiting were more common with cetuximab, while thrombocytopenia was observed mostly with panitumumab.

In conclusion, data from this registry study confirm the efficacy and safety of the anti-EGFR agents in the first-line treatment of mCRC in the real-world prac-

tices. There is no significant difference between the addition of panitumumab or cetuximab to the backbone chemotherapy regimen. Oxaliplatin-based doublet regimens are most commonly chosen as the backbone therapy in the first-line treatment of mCRC patients in real-world setting, while triplet regimens such as FOLFOXIRI are rarely used, likely due to toxicity concerns despite their activity in patients with good performance status (PS), BRAF V600E mutations, or right-sided tumors. Panitumumab and cetuximab provide better survival outcomes than bevacizumab in the first-line treatment of patients with RAS wild-type mCRC. Additionally, patients with BRAF wild-type tumors exhibit improved outcomes among RAS wild-type patients. Tumor sidedness did not show a statistically significant association with survival, possibly due to the selective inclusion of RAS wild-type tumors, whereas BRAF wild-type status was independently associated with improved progression-free survival (PFS) and overall survival (OS), highlighting its prognostic significance. Furthermore, patients with good baseline PS (ECOG 0–1) demonstrated longer PFS, emphasizing the critical role of performance status in guiding treatment selection and predicting clinical outcomes. Overall, these findings underscore the importance of integrating molecular markers, tumor characteristics, and patient-related prognostic factors when selecting first-line therapies and demonstrate the clinical value of real-world evidence in optimizing treatment strategies for patients with metastatic colorectal cancer.

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