JBUON 2019; 24(1): 68-76
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

First-line treatment choices of Turkish medical oncologists in metastatic colorectal cancer: A survey study

Ismail Beypinar[1], Murat Araz[1], Mukremin Uysal[1], Suayib Yalcin[2]

[1]Afyon Kocatepe University, Department of Medical Oncology, Afyonkarahisar, Turkey; [2]Hacettepe University, Institute of Cancer, Department of Medical Oncology, Ankara, Turkey.

Summary

Purpose: *Colorectal cancer is one of the most common malignancies in the World. RAS-BRAF mutational status and primary tumor location are also important factors for the selection of optimal combinations therapies. In this study, we aimed to evaluate the Turkish oncologists' treatment decisions depending on tumor location and mutational status in metastatic colorectal cancer.*

Methods: *An online survey link was sent to the medical oncologists who are registered to Turkish Society of Medical Oncology via e-mail and mobile applications.*

Results: *Ninety-four oncologists (85.5%) reported that tumor localization affects their treatment modality. In RAS-BRAF wild type left colon tumors, Turkish oncologists mostly use chemotherapy and anti-EGFR therapy (90.1%) for the first-line treatment, while on the right side, oncologists favored anti-VEGF therapy in combination with chemotherapy (65.5%). BRAF-mutant tumors in left colon had nearly the same rates of treatment tendency with both anti-VEGF and anti-EGFR antibodies in combination with chemotherapy, while in right-sided tumors the main treatment selection of the participants was anti-VEGF-based treatment (83.6%). In RAS-mutant patients, a great number of oncologists selected anti-VEGF-based treatment. On the right and left colon tumors, anti-VEGF treatment options ratios were 91.7 and 92.7%, respectively. Maintenance treatment is usually preferred by oncologists in both anti-VEGF and anti-EGFR-based treatment.*

Conclusion: *Turkish oncologists are considering tumor sidedness as an indicator for treatment individualization of patients. The selection of monoclonal antibodies is being affected by tumor localization and mutation status.*

Key words: *colorectal cancer, oncologists preferences, tumor sidedness, RAS mutation, BRAF mutation*

Introduction

Colorectal cancer is one of the most common malignancies in the World. Nearly half of the patients either have metastasis at the time of diagnosis or later develop metastatic disease during follow up [1]. Addition of irinotecan or oxaliplatin to fluoropyrimidine-based chemotherapy is the backbone of treatment [2,3]. The new targeted agents like vascular endothelial growth factor antagonist (anti-VEGF) and epidermal growth factor receptor antagonist (anti-EGFR) monoclonal antibodies have opened a new era in the treatment of metastatic colorectal cancer. The combination of targeted agents and chemotherapy have extended life expectancy of metastatic colorectal cancer patients over 30 months [4,5]. But, optimal combination regimens as first-line treatment are still controversial. Extended RAS mutation evaluation is a key factor for the selection of the anti-EGFR agents because these drugs are effective only in RAS-wild type patient population. BRAF mutational status and primary tumor location are also important factors for the selection of optimal combinations

Correspondence to: Ismail Beypinar, MD. Afyon Kocatepe University Hospital, Department of Medical Oncology, Dortyol Mah.2078 Sok no.3, Afyonkarahisar, Turkey.
Tel: +90 5319951906, E-mail: ibeypinar@yahoo.com
Received: 18/06/2018; Accepted: 24/07/2018

therapies [6–9]. Retrospective analyses of studies showed that left-sided colon cancer patients achieve long-term survival benefit with anti-EGFR combination therapies [10]. Still, treatment suggestions for metastatic colorectal cancer differ from guidelines to guideline due to tumor location. While National Comprehensive Cancer Network (NCCN) guidelines restrict anti-EGFR agents in right-sided tumors in the first-line setting, however, there are no suggestions for the treatment of colon cancer depended on tumor sidedness by European Society of Medical Oncology (ESMO) guidelines yet. There are also some studies which investigate the treatment choices and guideline adherence of oncologists in the adjuvant setting of colorectal cancer, but there is no study for advanced disease [11,12]. In this study, we aimed to evaluate the Turkish oncologists' treatment decisions depending on tumor location and mutational status in metastatic colorectal cancer.

Methods

Participants

An online survey link was sent to the medical oncologists who are registered to Turkish Society of Medical Oncology via e-mail and mobile applications. A total number of 599 oncologists were invited to fill in a questionnaire. The e-mail invitation and mobile application messages were sent two times in a week for increasing the response rates. The survey started on 22nd December 2017 and ended on 8th January 2018.

Survey

The online survey form was established via Google Surveys. The survey was taken voluntarily by oncologists. There were no promotions or gifts to increase participation. The questionnaire was containing 16 questions which were designed to understand the participants' experience, working conditions, and colorectal cancer treatment decisions. Information about the experience in oncology practice, academic status and the type of hospital was obtained from the participants. The accessibility of genetic tests for RAS and BRAF and the duration of having test results were asked to the oncologists via the questionnaire. The participants were told to ignore reimbursement conditions and make decisions for a patient whose ECOG performance status was equal to 0 or 1. The patient scenarios were based on RAS-BRAF mutation and tumor sidedness. Tumor sidedness was divided in three categories as right (from the caecum to hepatic flexure), transverse and left (from splenic flexure to anus) colon. Although three categories were defined in tumor location, the transverse colon was only included in RAS-BRAF wild tumor type question. In most studies that tried to elucidate the utility of anti-EGFR agents due to sidedness had excluded the transverse colon, so we investigated the treatment tendency of oncologists in this tumor localization. The answers to questions were including different treatment options which contained a combination of different chemotherapy regimens and monoclonal antibodies. The monoclonal antibodies were grouped as anti-EGFR and anti-VEGF drugs. The type of the monoclonal antibody was censored due to ethical issues. The oncologists were free to choose one or more answers and the answers were evaluated separately as only chemotherapy, chemotherapy plus anti-VEGF, chemotherapy plus anti-EGFR and more than 1 treatment option. All questions were mandatory to answer. The complete questionnaire form is shown in Appendix A.1

Statistics

The survey results were analyzed using descriptive statistics, and x^2 test was used to calculate the p values with SPSS version 21.0. Also, e-PICOS was used to analyze the difference between percentages by Z-test. The level of significance was set at $p<0.05$.

Guidelines

The 1.2018 version of NCCN and 2016 dated ESMO guidelines were used to compare the data derived from the survey.

Results

One hundred and 10 oncologists (18% of all members) responded the survey invitation. Most of the oncologists (44.5%) who responded the questionnaire had 6- to 10-year experience in oncology. Associate professors were the largest population (35.5%) answering the survey. Oncology specialists were the second group with 31 participants (28.2%). Most of the participants were working in university hospitals and educational state hospitals (39.1 and 29.1%, respectively). Other features of the study population are shown in the Table 1.

Most of the participants (72.7%) had genetic laboratories at their hospitals to make RAS and BRAF tests. The rest of the oncologists needed assistance of other facilities. A great number of oncologists (77.3%) had the results in 2-week time.

The results for treatment choices were evaluated individually in all questions. In second evaluation the results were grouped into 4 categories as only chemotherapy, chemotherapy plus anti-EGFR, chemotherapy plus anti-VEGF and multiple choices.

Ninety-four oncologists (85.5%) reported that tumor localization affects their treatment option.

In RAS-BRAF wild left colon tumors, Turkish oncologists mostly used chemotherapy and anti-EGFR therapy (90.1%) for the first-line treatment. Chemotherapy backbone was (fluorouracil/capecitabine, leucovorin, oxaliplatin) FOLFOX/XELOX and FOLFIRI (fluorouracil, leucovorin, irinotecan) (64.5 and 47.3%, respectively). Only 4.5% of oncologists tended to use anti-VEGF combined with doublet

Table 1. Oncologists' experience, working conditions and academic status

Status	%
Experience in oncology (years)	
0-5	23.6
6-10	44.5
11-15	18.2
16-20	7.3
21-30	6.4
Academic status	
Professor	17.3
Associated Professor	35.5
Assistant Professor	9.1
Specialist	28.2
Fellow	10
Working facility	
Public University Hospital	39.1
Educational Hospital	29.1
State Hospital	3.6
Private Hospital	19.1
Private Foundation University Hospital	9.1
Receiving mutational tests (week)	
1	12.7
2	58.2
3	19.1
4	7.3
>4	2.7

chemotherapy. Four oncologists had chosen more than 1 treatment option and one answered to use only chemotherapy in RAS-BRAF wild-type left colon cancers. On the right side colon cancers with RAS-BRAF wild-type, oncologists favored anti-VEGF therapy in combination with chemotherapy (65.5%). Nine oncologists chose more than one treatment modality while four reported only use of chemotherapy without monoclonal antibodies. The chemotherapy regimens most used were FOLFOX/XELOX, FOLFIRI, and FOLFOXIRI in combination with anti-VEGF antibodies (57.3, 26.4 and 11.8%, respectively) (Figure 1). A small subset of oncologists (6.4%) reported that they will use FOLFOXIRI plus anti-EGFR therapy. The medical oncologists working at an academical setting significantly preferred to use anti-EGFR antibodies in this group of patients (p=0.02). In the RAS-BRAF wild-type tumors localized to the transverse colon, the participants chose anti-EGFR treatment in combination with chemotherapy (59.1%). FOLFOX/XELOX backbone regimen was the most preferred option in this setting (52.7%). Chemotherapy plus anti-VEGF treatment was selected by 30 oncologists (27.3%). Anti-EGFR treatment choice decreased significantly from left to right colon (left: 90.9%, transverse: 59.1%, right: 22.7%, p<0.001). Thirteen participants had chosen more than one treatment option (11.8%). The oncologists who were working in university hospitals tended to use less anti-EGFR-based treatment in transverse colon tumors (University hospitals 47%, non-university hospitals 68%, p=0.03).

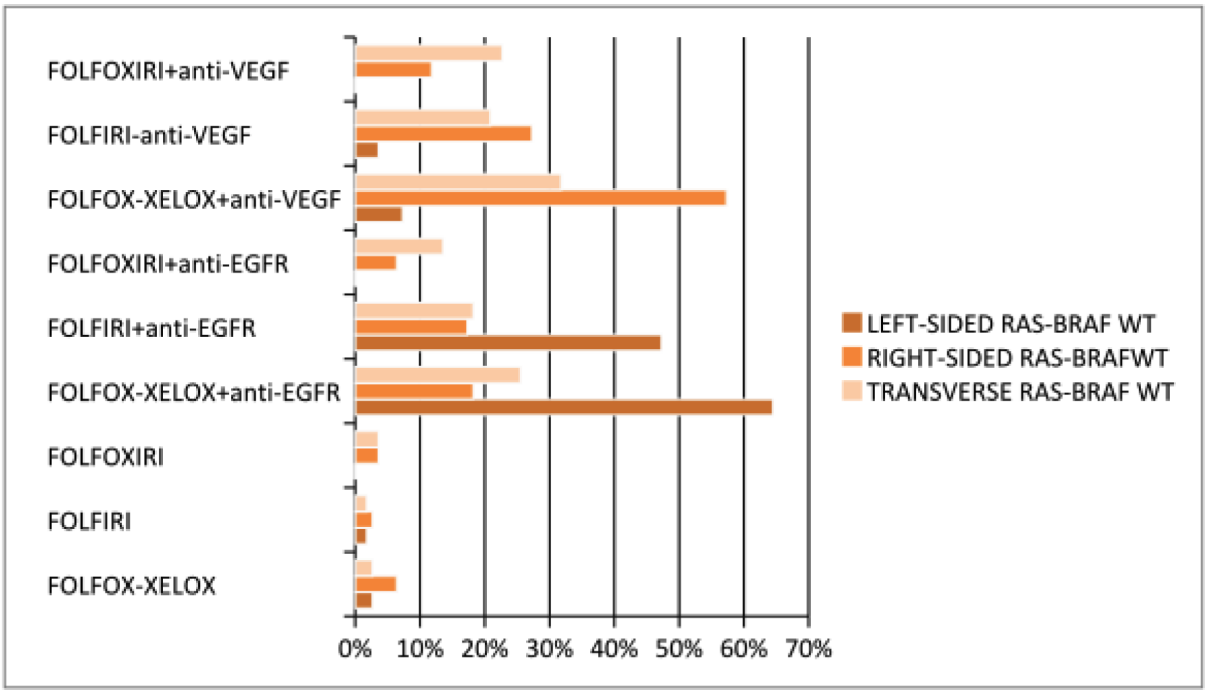

Figure 1. The chemotherapy backbone and targeted agent selection of oncologists in RAS-BRAF wild type tumors.

RAS wild and BRAF mutant tumors in the left colon had nearly the same rates of treatment tendency with both anti-VEGF and anti-EGFR antibodies in combination with chemotherapy (46.4 and 43.6%, respectively, p=0.68). In both arms, FOLFOX/XELOX backbone chemotherapy was the first option (anti-EGFR: 25.5%, anti-VEGF: 31.8%) (Figure 2). FOLFOXIRI was the second most selected option in front of FOLFIRI (22.7 and 20.9%, respectively) among medical oncologists who preferred to use an anti-VEGF agent plus chemotherapy. In right-sided tumors with RAS-wild type and BRAF mutant genetic profile, the use of anti-EGFR treatment was very low (6.4%). The main treatment selection of the participants was anti-VEGF-based treatment (83.6%). In this group, the choices of backbone chemotherapies were FOLFOX/XELOX, FOLFOXIRI, and FOLFIRI (55.5, 34.5 and 23.6%, respectively).

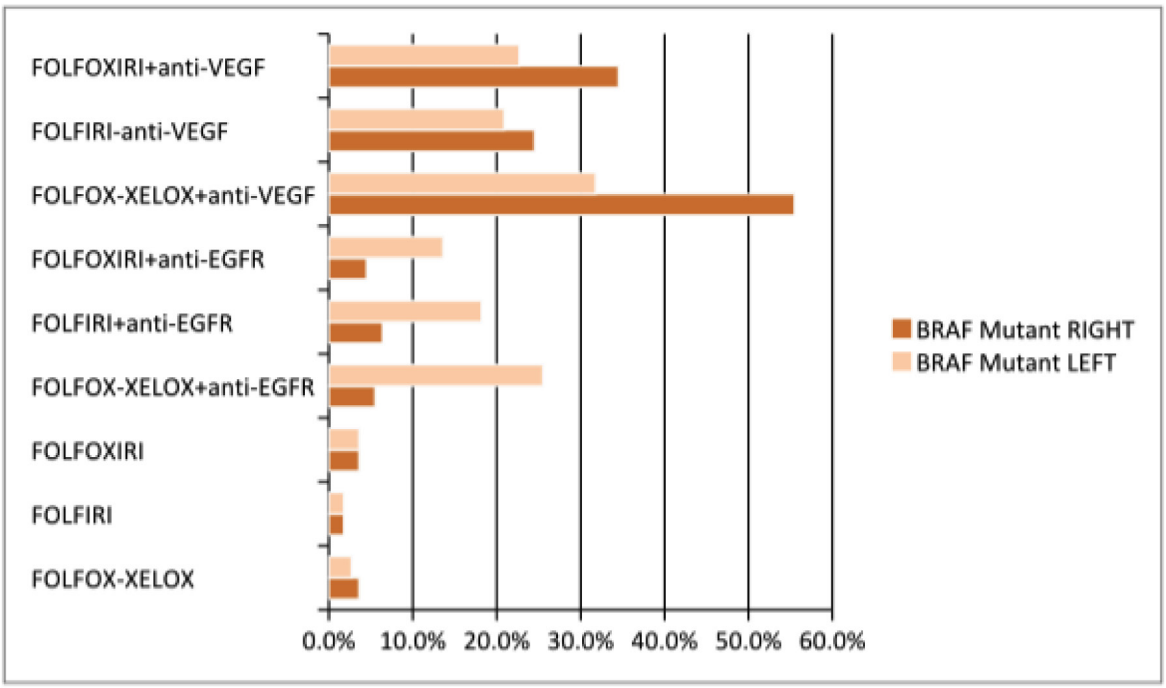

Figure 2. The chemotherapy backbone and targeted agent selection of oncologists in BRAF mutant tumors.

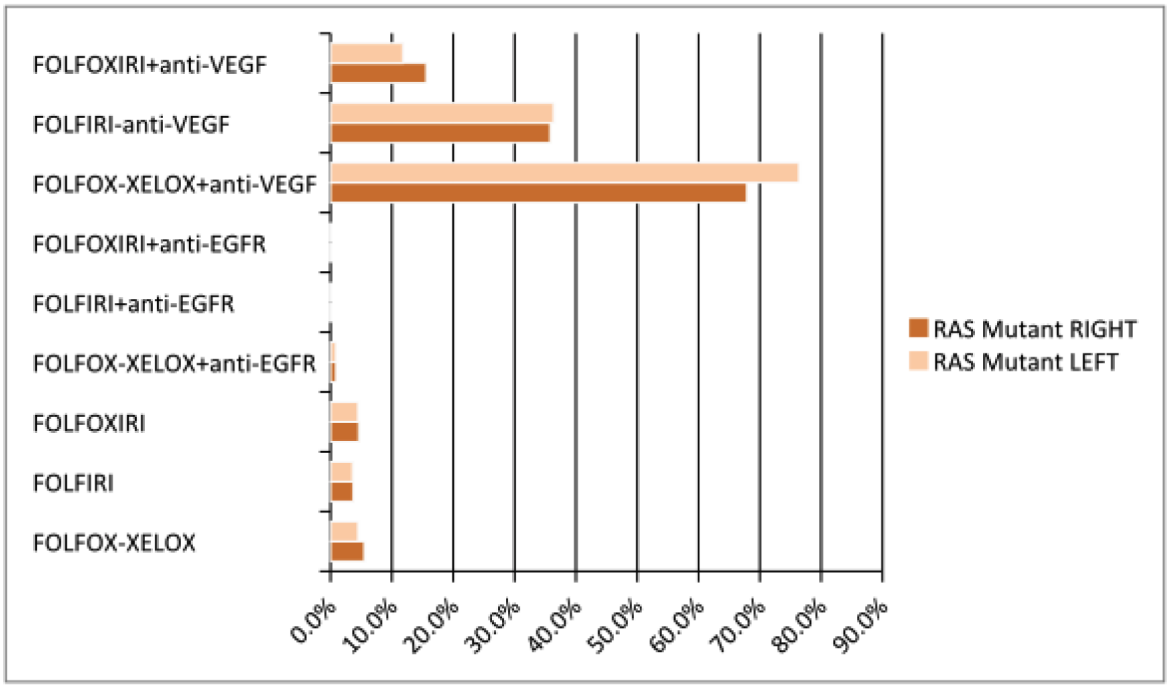

Figure 3. The chemotherapy backbone and targeted agent selection of oncologists in RAS mutant tumors.

Table 2. Treatment choices of oncologists' due to RAS-BRAF mutation and tumor location

Choices	*Left colon % (n)*			*Right colon % (n)*		
	RAS-BRAF wt	*BRAF mt*	*RAS mt*	*RAS-BRAF wt*	*BRAF mt*	*RAS mt*
Chemotherapy[1]	1 (1)	1.8 (2)	1 (1)	3.6 (4)	4.3 (5)	2.8 (3)
Chemotherapy[1]+anti-EGFR	90.9 (100)	43.6 (48)	1 (1)	22.7 (25)	6.4 (7)	1 (1)
Chemotherapy[1]+Anti-VEGF	4.5 (5)	46.4 (51)	92.7 (102)	65.5 (72)	83.6 (92)	91.7 (100)
Multiple choices[2]	3.6 (4)	8.2 (9)	5.5 (6)	8.2 (9)	5.5 (6)	4.6 (5)

[1]Including Doublet &Triplet regimens. [2]Including more than one treatment regimen.

In BRAF mutant patients with right-sided tumors oncologists preferred in significantly higher rates anti-VEGF than anti-EGFR-based treatment (83.6% and 46.4%, p<0.001).

In RAS mutant patients, a great number of oncologists selected anti-VEGF based-treatment. On the right and left colon tumors, anti-VEGF treatment options ratios were 91.7 and 92.7%, respectively. There was no statistical difference between these groups (p=0.63). As a second option, the oncologists preferred more than one option which was consisted of chemotherapy with or without a biologic agent (Figure 3). The selection of this option was higher in left-sided tumors (5.5%, 4.6%). Only chemotherapy and chemotherapy in combination with anti-EGFR agents were rarely selected (Table 2). The maintenance treatment was usually preferred by oncologists in both anti-VEGF and anti-EGFR-based treatment. The maintenance treatment rates were higher in the anti-VEGF group which was statistically significant (81.8 and 58.2%, p<0.001). The oncologists who had experience more than 10 years, used significantly less maintenance treatment with anti-EGFR antibodies (p=0.008). Also, anti-EGFR maintenance therapy was significantly less preferred in university hospitals (p=0.03).

Discussion

In this study, we investigated the guideline adherence and first-line treatment choices of Turkish oncologists in metastatic colorectal cancer. We reached 110 oncologists and had a sufficient representative sample of Turkish oncologist population. Most of the participants (85.5%) make their treatment choices according to tumor location. The retrospective analyses of phase 3 trials dependent on tumor location affected the treatment choices of Turkish oncologists in both chemotherapy regimens and targeted agents. In the retrospective analyses of FIRE-3 and CRYSTAL trials, while left-sided RAS wild colon tumors achieved great benefit from chemotherapy with or without anti-EGFR treatment, right-sided tumors had not benefited from the addition of anti-EGFR agents [13]. In our study participants chose mostly chemotherapy plus anti-EGFR treatment regimens in left-sided RAS wild type tumors. Turkish medical oncologists preferred FOLFOX/XELOX at a higher rate than FOLFIRI in combination with anti-EGFR agents. The FOLFOX/XELOX preference of participants can be based on the CALBG trial which showed the same response rate as FOLFIRI [14].

In our survey the selection of anti-EGFR agents decreased from left to right colon in RAS wild type colon cancer. In most studies, the transverse colon was excluded and there is no clear data about treatment effectiveness of these tumors. The participants mostly preferred chemotherapy plus anti-VEGF regimens in RAS-BRAF wild-type right-sided tumors (65.5%) which was correlated with Tejpar et al. and Venook et al. studies [13,15]. Although most participants declared that they were following the NCCN guidelines (89.1%), anti-EGFR treatment was preferred more than expected in right-sided colon cancers (22.7%).

The RAS mutation is very frequent in both right and left colon cancer and associated with anti-EGFR treatment resistance and even detrimental effects [16,17]. Both NCCN and ESMO guidelines do not recommend anti-EGFR-based treatment in this group of patients. Also in our survey, most of the oncologists preferred anti-VEGF-based treatments in both right and left-sided tumors (91.7 and 92.7%, respectively) with RAS mutant tumors. The other options were mostly composed of chemotherapy alone or both chemotherapy and anti-VEGF combinations. In RAS-mutated patients anti-EGFR-based treatment was very low in our survey on both sides of colon cancers by Turkish oncologists (1%, 1%).

The BRAF V600E mutation is the second most frequent mutation in colorectal cancer and rarely overlapping RAS mutations. BRAF mutation is seen in most right-sided tumors in association with tu-

mor biology and microsatellite instability. Overall, the frequency of BRAF mutation in colon cancer was determined as 8.8% [18]. De Roock et al. [19] had found BRAF mutation frequency of 4.7%. Although the BRAF-mutant tumors are composing a small proportion of all colorectal cancers, treatments of these tumors are extremely difficult [20]. BRAF mutations are also closely related to anti-EGFR treatment resistance and worse prognosis [21-23]. In the pre-planned retrospective analysis of the PRIME trial, BRAF mutation was determined to be prognostic but not predictive [16]. In contrast, the results from the COIN trial showed even detrimental effects of anti-EGFR treatment in BRAF-mutant patients [22]. The use of anti-EGFR agents is still controversial for BRAF mutant colorectal cancers. In our study, oncologists preferred nearly at the same ratio anti-VEGF and anti-EGFR-based treatments in the left colon. In the right colon, anti-VEGF-based treatment was highly chosen than the anti-EGFR agents (83.6 and 6.4%, respectively).

In both anti-VEGF and anti-EGFR-based treatment groups, the trend for maintenance therapy was more than 50%, which was higher in the anti-VEGF group (81.8 and 58.2%, respectively). Even though some trials show benefit of maintenance treatment, NCCN guideline does not strongly suggest maintenance treatment, but ESMO guideline insists for maintenance treatment with bevacizumab in colorectal cancer. Despite the non-significantly better overall survival trend in the CAIRO3 trial, maintenance with bevacizumab and capecitabine had a better progression-free survival than the observation group [24]. Also, in the Stop-and-Go trial, maintenance with bevacizumab and capecitabine had a significantly better progression-free survival than maintenance with bevacizumab and XELOX [25]. The continuation of anti-EGFR treatment as maintenance therapy is lacking evidence and isn't being suggested by the guidelines.

As a survey study, our article has some limitations which can be seen in all survey studies. As a second limitation, the low participation rates in the questionnaire made it difficult to project the results to all oncologists in Turkey.

In conclusion, we observed that Turkish oncologists are considering tumor sidedness as an indicator for patient treatment individualization. The selection of monoclonal antibodies is being affected by tumor localization and mutation status. Oncologists are in need of prospective sidedness and molecular characterization based studies to have more accurate treatment choices for their patients.

Conflict of interests

The authors declare no conflict of interests.

References

1. IARC. IA for R on CWHO (2012) GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Globocan 1-6 . doi: 10.1002/ijc.27711
2. de Gramont A, Figer A, Seymour M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938-47 .
3. Douillard JY, Cunningham D, Roth AD et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000;355:1041-7.
4. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42 .
5. Van Cutsem E, Oliveira J. Advanced colorectal cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Ann Oncol 2000;20:61-3.
6. Missiaglia E, Jacobs B, D'Ario G et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol 2014;25:1995-2001.
7. LaPointe LC, Dunne R, Brown GS et al. Map of differential transcript expression in the normal human large intestine. Physiol Genomics 2008;33:50-64.
8. Dienstmann R. Colorectal Cancer Subtyping Consortium (CRCSC) identification of a consensus of molecular subtypes. ASCO Abstract 2014 #3511.
9. Guinney J, Dienstmann R, Wang X et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350-6.
10. Heinemann V, Weikersthal LF Von, Decker T et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): A randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1065-75.
11. Loh KWJ, Michael M, Zalcberg JR, Jefford M. Views of Australian Medical Oncologists Regarding the Use of Mismatch Repair Status to Assist Adjuvant Chemotherapy Recommendations for Patients With Early-Stage Colon Cancer. Clin Colorectal Cancer 2015;14:192 -7.

12. Keikes L, van Oijen MGH, Lemmens VEPP et al. Evaluation of Guideline Adherence in Colorectal Cancer Treatment in The Netherlands: A Survey Among Medical Oncologists by the Dutch Colorectal Cancer Group. Clin Colorectal Cancer 2017;17:58-64.
13. Tejpar S, Stintzing S, Ciardiello F et al. Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer. JAMA Oncol 2017;3:194.
14. Venook AP, Niedzwiecki D, Lenz H et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer a randomized clinical trial. JAMA 2017;317:2392-2401.
15. Venook AP. Impact of primary (1o) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol 2016;34 (Suppl): abstract 3504.
16. Douillard JY, Oliner KS, Siena S et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-34.
17. Bokemeyer C, Köhne CH, Ciardiello F et al. FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer. Eur J Cancer 2018;51:1243-52.
18. Vaughn CP, Zobell SD, Furtado L V et al. Frequency of KRAS, BRAF, and NRAS mutations in colorectal cancer. Genes Chromosomes Cancer 2011;50:307-12.
19. De Roock W, Claes B, Bernasconi D et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: A retrospective consortium analysis. Lancet Oncol 2010;11:753-62.
20. Stintzing S, Miller-Phillips L, Modest DP et al. Impact of BRAF and RAS mutations on first-line efficacy of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab: analysis of the FIRE-3 (AIO KRK-0306) study. Eur J Cancer 2017;79:50-60.
21. Tveit KM, Guren T, Glimelius B et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: The NORDIC-VII study. J Clin Oncol 2012;30:1755-62.
22. Maughan TS, Adams RA, Smith CG et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011;377:2103-14.
23. Tran B, Kopetz S, Tie J et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer 2011;117:4623-32.
24. Simkens LHJ, van Tinteren H, May A et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. Lancet 2015;385:1843-52.
25. Yalcin S, Uslu R, Dane F et al. Bevacizumab + capecitabine as maintenance therapy after initial bevacizumab + XELOX treatment in previously untreated patients with metastatic colorectal cancer: Phase iii "stop and go" study results - A turkish oncology group trial. Oncology 2013;85:32835.

Appendix. The questionnaire

Please do not consider reimbursement conditions while answering questions.
Please consider the patients' ECOG performance status 0-1 while answering questions.
Anti-VEGF: Bevacizumab, Anti-EGFR: Cetuximab, Panitimumab

1. How long have you been working in Medical Oncology? (years)
   - 0-5
   - 6-10
   - 11-15
   - 16-20
   - 21-30
   - 31-40
2. What is your academic status in Medical Oncology?
   - Professor
   - Associate Professor
   - Assistant Professor
   - Specialist
   - Fellow

Continued on the next page

Please do not consider reimbursement conditions while answering questions.
Please consider the patients' ECOG performance status 0-1 while answering questions.
Anti-VEGF: Bevacizumab, Anti-EGFR: Cetuximab, Panitimumab

3. What kind of hospital are you working for?
   - Government University Hospital
   - Education and Research Hospital
   - State Hospital
   - Private Hospital
   - Foundation University Hospital
4. Are your treatment decision influenced by the tumor sidedness in first-line treatment of metastatic colorectal cancer?
   - Yes
   - No
5. Do you have an opportunity of analyzing theKRAS-BRAF status of colorectal cancer in your hospital?
   - Yes
   - No
6. What is your estimated time of receiving results of KRAS-BRAF mutation analyze?
   - 1 week
   - 2 weeks
   - 3 weeks
   - 4 weeks
   - More Than 4 weeks
7. What are your first line palliative treatment choices in a patient who has LEFT-SIDED TUMOR and RAS-BRAF WILD type? (More than one can be chosen)
   - FOLFOX/XELOX
   - FOLFIRI
   - FOLFOX/XELOX+anti-EGFR
   - FOLFIRI+anti-EGFR
   - FOLFOX/XELOX+anti-VEGF
   - FOLFIRI+anti-VEGF
8. What are your first line palliative treatment choices in a patient who has RIGHT-SIDED TUMOR and RAS-BRAF WILD type? (More than one can be chosen)
   - FOLFOX/XELOX
   - FOLFIRI
   - FOLFOXIRI
   - FOLFOX/XELOX+anti-EGFR
   - FOLFIRI+anti-EGFR
   - FOLFOXIRI+anti-EGFR
   - FOLFOX/XELOX+anti-VEGF
   - FOLFIRI+anti-VEGF
   - FOLFOXIRI+anti-VEGF
9. What are your first line palliative treatment choices in a patient who hasTRANSVERSE COLON LOCATED TUMOR and RAS-BRAF WILD type? (More than one can be chosen)
   - FOLFOX/XELOX
   - FOLFIRI
   - FOLFOXIRI
   - FOLFOX/XELOX+anti-EGFR
   - FOLFIRI+anti-EGFR
   - FOLFOXIRI+anti-EGFR
   - FOLFOX/XELOX+anti-VEGF
   - FOLFIRI+anti-VEGF
   - FOLFOXIRI+anti-VEGF

Continued on the next page

Please do not consider reimbursement conditions while answering questions.
Please consider the patients' ECOG performance status 0-1 while answering questions.
Anti-VEGF: Bevacizumab, Anti-EGFR: Cetuximab, Panitimumab

10. What are your first line palliative treatment choices in a patient who has LEFT-SIDED TUMOR and RAS WILD-BRAF MUTANT type? (More than one can be chosen)
    - FOLFOX/XELOX
    - FOLFIRI
    - FOLFOXIRI
    - FOLFOX/XELOX+anti-EGFR
    - FOLFIRI+anti-EGFR
    - FOLFOXIRI+anti-EGFR
    - FOLFOX/XELOX+anti-VEGF
    - FOLFIRI+anti-VEGF
    - FOLFOXIRI+anti-VEGF
11. What are your first line palliative treatment choices in a patient who has RIGHT-SIDED TUMOR and RAS WILD-BRAF MUTANT type? (More than one can be chosen)
    - FOLFOX/XELOX
    - FOLFIRI
    - FOLFOXIRI
    - FOLFOX/XELOX+anti-EGFR
    - FOLFIRI+anti-EGFR
    - FOLFOXIRI+anti-EGFR
    - FOLFOX/XELOX+anti-VEGF
    - FOLFIRI+anti-VEGF
    - FOLFOXIRI+anti-VEGF
12. What are your first line palliative treatment choices in a patient who has LEFT-SIDED TUMOR and RAS MUTANT type? (More than one can be chosen)
    - FOLFOX/XELOX
    - FOLFIRI
    - FOLFOXIRI
    - FOLFOX/XELOX+anti-EGFR
    - FOLFIRI+anti-EGFR
    - FOLFOXIRI+anti-EGFR
    - FOLFOX/XELOX+anti-VEGF
    - FOLFIRI+anti-VEGF
    - FOLFOXIRI+anti-VEGF
13. What are your first line palliative treatment choices in a patient who has RIGHT-SIDED TUMOR and RAS MUTANT type? (More than one can be chosen)
    - FOLFOX/XELOX
    - FOLFIRI
    - FOLFOXIRI
    - FOLFOX/XELOX+anti-EGFR
    - FOLFIRI+anti-EGFR
    - FOLFOXIRI+anti-EGFR
    - FOLFOX/XELOX+anti-VEGF
    - FOLFIRI+anti-VEGF
    - FOLFOXIRI+anti-VEGF
14. Do you use maintenance treatment with anti-VEGF agents?
    - Yes
    - No
15. Do you use maintenance treatment with anti-EGFR agents?
    - Yes
    - No
16. What is your guideline preference in colorectal cancer treatment?
    - NCCN
    - ESMO
    - Other