Int. j. adv. multidisc. res. stud. 2024; 4(2):678-684

Received: 07-02-2024
Accepted: 17-03-2024

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

First Line Chemotherapy in Metastatic Colorectal Cancers: A Review

[1] Alfredo Colombo, [2] Roberto Bordonaro, [3] Tommaso Sciacchitano, [4] Concetta Maria Porretto
[1, 3, 4] CDC Macchiarella Oncology Unit, Palermo, Viale Regina Margherita, Italy
[2] Oncology Unit ARNAS Garibaldi, Catania, Via Palermo, Italy

DOI: https://doi.org/10.62225/2583049X.2024.4.2.2556
Corresponding Author: **Alfredo Colombo**

Abstract
Colorectal cancer (CRC) is a common malignancy detected. Approximately, 22% of CRCs are metastatic at initial diagnosis, and about 70% of patients will eventually develop metastatic relapse. Metastatic colorectal cancer is a disease with poor prognosis whose treatment is always palliative chemotherapy. Today, thanks to the knowledge of molecular biology and the discoveries of new pathways, we have managed to increase survival to around 40 months which can increase thanks to the use of surgery and locoregional treatments. The choice of chemotherapy in these patients therefore depends on the characteristics of the molecular profile and includes, in fit patients, chemotherapy with the addition of targeted therapies.
In this article, we examine the most recent data from randomized clinical trials supporting the use of chemotherapy triplets or doublets as well as the addition of bevacizumab or anti-epidermal growth factor receptor (EGFR) agents.

Keywords: Colon, Cancer, Chemotherapy, Targeted Therapy, Immunotherapy

Introduction

Colorectal cancer is the third most common cancer worldwide, the second leading cause of cancer-related death and accounts for approximately 10% of all cancer cases. Adenocarcinoma is the most typical histology. Despite advancements in screening techniques, metastatic CRC (mCRC), which has a 14 % 5-year survival rate, is diagnosed in about 20 percent of patients. The site of metastasis that occurs most frequently is the liver. It is occasionally possible for patients with Stage IV disease to remove metastases surgically with the intention of curing the disease. However, palliative care is the mainstay of mCRC treatment. Since the introduction of targeted agents, modern cytotoxic chemotherapy (CT), and advances in multimodal management, the median survival for patients with unresectable mCRC, representing more than 70% of this population, has significantly increased up to 30 months. Because there are many therapeutic options, clinical decision-making is difficult, and is mandatory to treat mCRC is in a multidisciplinary team. The main objectives of treatment are to increase overall survival, reduce disease symptoms, and preserve quality of life for as long as possible [1]. Disease-related characteristics (clinical presentation, tumor burden, resectability, and tumor biology), patient-related characteristics (performance status, age, comorbidity, socioeconomic factors, and expectations), and treatment-related characteristics (toxicity profile, administration schedule), are all important considerations when choosing one therapy. The need to profile each mCRC for RAS and BRAF mutations, as well as the instability of microsatellites, has been demonstrated by molecular research results. The therapeutic landscape is changing as a result of improved knowledge of the heterogeneity of mCRC, including primary tumor location (sidedness), microsatellite instability (MSI) status, and other clinically actionable tumor mutations [2]. According to each patient's molecular status, a CT combination is currently the preferred first-line treatment. This combination is frequently used in conjunction with a biologic agent. Here, we examine the most recent data from randomized clinical trials (RCTs) supporting the use of CT doublets or triplets in combination with bevacizumab or anti-epidermal growth factor receptor (EGFR) agents as the first-line therapy for patients with mCRC. Also are discussed novel treatments, for limited patients, that have microsatellite instability.

Methods

We searched PubMed (www.ncbi.nlm.nih.gov/pubmed) for full-text articles from 2017 to May 31, 2023, using the keywords colon, cancer, chemotherapy, targeted therapy, immunotherapy.

The full-text articles found were carefully examined. In addition, all abstracts presented at international conferences between January 2020 and January 2023 were examined.

Chemotherapy choice

The pivotal component of treatment for mCRC is systemic combination CT. In comparison to supportive care, its use increases patient survival and quality of life. It has been established that early treatment initiation is preferable to delaying treatment until the onset of symptoms. The foundation of combination schemes is made up of fluoropyrimidines (FPs). There are primarily two options: Intravenous 5-fluorouracil (5-FU) and capecitabine. Because 5-FU is more efficient and less toxic when administered continuously (CI), it should be used instead of bolus administration, but it necessitates the implantation of a central venous access device. With the benefit of oral administration, capecitabine exhibits comparable clinical activity and tolerance. In either monotherapy or in combination, RCTs have demonstrated similar efficacy for both drugs. They provide response rates (RRs) of about 20% and a median overall survival (OS) of 12 months as single agents. In contrast to capecitabine use, which is linked to a higher incidence of diarrhea and hand-foot syndrome, CI 5-FU more frequently causes neutropenia and thromboembolic events. Since 2000, two new active treatments for mCRC had been developed: Irinotecan, a camptothecin-inhibiting topoisomerase I agent, and oxaliplatin, a platinum derivative. All treatment efficacies are significantly improved when they are combined with either 5-FU or capecitabine. According to four RCTs, first-line oxaliplatin- or irinotecan-based combination CT schedules offer a comparable RR of 34-55 percent, time to progression (TTP) of 7-8 months, and median OS of 14-21 months [3]. They are therefore interchangeable in this clinical setting. Irinotecan use is more frequently linked to diarrhoea and leukocytopenia, whereas oxaliplatin causes more neurotoxicity and thrombocytopenia. In published large Phase III trials, there is a significant correlation between median survival and the percentage of patients exposed to all active drugs (FPs, oxaliplatin, and irinotecan), either concurrently or sequentially. The probability of getting them is lower when using a sequential sequence of single-agent treatments than when using a sequential sequence of combination therapies [4]. The three main doublet therapies used in first-line are capecitabine plus oxaliplatin (XELOX), CI 5-FU plus oxaliplatin (FOLFOX), and FOLFIRI (CI 5-FU plus irinotecan). The toxicity profiles are different, but the efficacy parameters are similar. Less used is XELIRI (capecitabine plus irinotecan) because it causes more severe diarrhoea. Three trials compared the triple therapy with FOLFOXIRI with FOLFOX or FOLFIRI; two of them suggested that FOLFOXIRI was superior in terms of RR, PFS, and OS. However, the triplet was more likely to experience toxic effects of grades 3 to 4 [5]. As will be discussed below, adding targeted agents to CT combination schedules has further improved efficacy and survival outcomes (primarily antiangiogenic drugs and anti-EGFR agents).

Table 1: Main first line chemotherapy in mCRC

Author, Journal Year (ref)	N	Treatments	HR PFS/OS < 0.8	Adequate Control Arm	PFS Censored <20% at 2y	Any Change in Primary End-Point or Sample	Achieved Pre-Specified Objective	Quality Design	ESMO/MCBS 1.1
Bevacizumab vs. no bevacizumab									
Kabbinavar F, JCO 2003 [6]	104	bev plus FU vs. FU	0.54/0.86. 0.62	no	NA	no	NA	2 of 5	1 of 3
Kabbinavar FF, JCO 2005 [7]	209	bev plus FU vs. FU	0.5/0.79. 0.63	no	yes	no	no	3 of 5	0 of 3
Hurwitz H, NEJM 2004 [8]	813	bev plus IFL vs. IFL	0.54/0.66. 0.95	yes	yes	no	yes	4 of 5	2 of 3
Saltz LB, JCO 2008 [9]	1401	bev plus FOLFOX/CAPOX vs FOLFOX/CAPOX	0.83/0.89.0.93	yes	yes	no	no	3 of 5	0 of 3
Tebbutt NC, JCO 2010 [10]	471	bev plus cap or cap/mit vs. cap or cap/mit	0.61/0.86. 0.71	no	yes	no	yes	4 of 5	0 of 3
Stathopoulos GP, Oncology 2010 [11]	222	bev plus IFL vs. IFL	NA	no	NA	no	NA	1 of 5	0 of 3
Guan ZZ, Chin J Cancer 2011 [12]	214	bev plus IFL vs. IFL	0.44/0.62. 0.71	no	yes	NA	NA	2 of 5	2 of 3
Pasardi A, Ann Oncol 2015 [13]	376	bev plus FOLFIRI or FOLFOX vs FOLFIRI or FOLFOX	0.86/1.13. 0.76	yes	yes	yes	no	3 of 5	0 of 3
Loupakis F, NEJM 2014 [14]	508	bev plus FOLFOXIRI vs. FOLFIRI	0.75/0.79. 0.94	yes	yes	no	yes	4 of 5	0 of 3
Anti-EGFR vs. no anti-EGFR in RAS WT									
Van Cutsem E, JCO 2015 [15]	430/1198	cet plus FOLFIRI vs. FOLFIRI	0.56/0.69. 0.81	yes	no	yes	no	1 of 5	3 of 3
Maugham TS, Lancet 2011 [16]	729/1630	cet plus FOLFOX or CAPOX vs FOLFOX or CAPOX	0.96/1.04. 0.92	yes	yes	yes	no	2 of 5	0 of 3
Tveit KM, JCO 2012 [17]	274/571	cet plus FLOX vs. FLOX	1.07/1.14. 0.93	no	yes	yes	no	1 of 5	0 of 3
Douillard JY, NEJM 2013 [18]	512/1183	pani plus FOLFOX vs. FOLFOX	0.72/0.78. 0.92	yes	no	yes	no	1 of 5	2 of 3
Bokemeyer C, Eur J Cancer 2015 [19]	87/297	cet plus FOLFOX vs. FOLFOX	0.53/0.94. 0.56	yes	yes	yes	no	3 of 5	0 of 3
Qin S, JCO 2018 [20]	393	cet plus FOLFOX vs. FOLFOX	0.69/0.76. 0.91	yes	yes	yes	no	2 of 5	1 of 3

Table 1: Continued

Author, Journal Year (ref)	N	Treatments	HR PFS/OS < 0.8	Adequate Control Arm	PFS Censored <20% at 2y	Any Change in Primary End-Point or Sample	Achieved Pre-Specified Objective	Quality Design	ESMO/MCBS 1.1
Anti-EGFR vs. bevacizumab in RAS WT									
Venook AP, JAMA 2017 [21]	474/1137	bev plus FOLFOX or FOLFIRI vs cet plus FOLFOX or FOLFIRI	1.03/0.83. 1.24	yes	NA	yes	NA	1 of 5	1 of 3
Heinemann V, Lancet Onol 2014 [22]	342/592	bev plus FOLFIRI vs. cet plus FOLFIRI	0.93/0.7. 1.32	yes	NA	yes	NA	1 of 5	3 of 3
Schwartzberg LS, JCO 2014 [23]	170/283	bev plus FOLFOX vs. pani plus FOLFOX	0.65/0.62. 1.04	yes	yes	yes	NA	2 of 5	3 of 3
Triplets vs. doublets									
Souglakos J, Br J Cancer 2006 [24]	283	FOLFIRI vs. FOLFOXIRI	0.83/NA	no	yes	no	no	2 of 5	0 of 3
Falcone A, JCO 2007 [25]	244	FOLFOXIRI vs. FOLFIRI	0.63/0.7. 0.9	no	yes	no	yes	3 of 5	2 of 3
Loupakis F, NEJM 2014 [14]	508	bev plus FOLFOXIRI vs. FOLFIRI	0.75/0.79. 0.94	yes	yes	no	yes	4 of 5	0 of 3
Sastre J, JCO 2019 [26]	349	Bev plus FOLFOX vs. bev plus FOLFOXIRI	0.64/0.84. 0.76	yes	NA	no	yes	3 of 5	1 of 3
Cremolini C, Lancet Oncol 2020 [27]	679	bev plus FOLFOX the bev plus FOLFIRI vs. bev plus FOLFOXIRI then bev plus FOLFOXIRI	0.79/0.82. 0.96	yes	yes	no	yes	3 of 5	1 of 3

HR: hazard ratio, PFS: progression-free survival, OS: overall survival, NA: not available, ESMO/MCBS 1.1: European Society of Medical Oncology Magnitude of Clinical Benefit Scale version 1.1. [28].

Table 1 provides a summary of the major RCTs that compared CT doublets to first-line CT schedules for patients with unresectable mCRC. Adding bevacizumab or anti-EGFRs to triplets is being evaluated [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. Additionally, they were evaluated using the ESMO-Magnitude of Clinical Benefit Scale version 1.1 [28].

Chemotherapy and bevacizumab

In the patients with mCRC, RAS mutations account for about 50%. They have fewer treatment options and a worse prognosis than RAS wild-type patients (hazard ratio of 1:5-2 for OS). In this situation, tumor sidedness has bearing on the choice of treatment. Several clinical trials have demonstrated that anti-EGFR therapies are ineffective in treating tumor with any activating mutation of KRAS or NRAS (exons 2-4). They should not be used because they may even detrimental. Bevacizumab, a monoclonal antibody that targets the circulating vascular endothelial growth factor A (VEGF-A), has been approved since 2004 in conjunction with CT for the first-line treatment of patients with mCRC, regardless of the presence or absence of RAS mutations. It has a predictable, well-known, and manageable toxicity profile. Its primary side effects include arterial hypertension, proteinuria, arterial thrombotic incidents, bowel perforation (rare), bleeding, and issues with wound healing. With either monotherapy or multiagent CT schemes used as first-line treatments, bevacizumab consistently improves PFS, making its use standard for most patients with no formal contraindications. Bevacizumab and CT doublets together result in objective responses of approximately 45%, median PFS of 9–10 months, and median OS of almost 24 months. Bevacizumab combined with less active CT schedules or FP monotherapy, however, has a greater relative added efficacy in terms of survival increment. Nine comparative clinical trials [6, 7, 8, 9, 10, 11, 12, 13, 14] evaluating the addition of the antiangiogenic drug bevacizumab were successful in achieving their predetermined end points in three of the nine trials. Only two of them, using the outdated bolus 5-FU IFL (irinotecan, fluorouracil, and leucovorin) regimen, saw a significant improvement in survival. Bevacizumab significantly improves PFS when combined with less-active CT schedules like 5-FU/leucovorin or bolus IFL, but this improvement appears to be diminished when combined with more active CT schedules like FOLFOX, XELOX, or FOLFIRI. Bevacizumab and either FOLFOXIRI or FOLFOX were combined in two trials, and both studies discovered higher RR. Patients with either wild-type or mutant RAS may benefit from this treatment, and there is no diagnostic biomarker for bevacizumab efficacy.

Chemotherapy and Anti-EGFR

To choose the best treatment for healthy patients with unresectable mCRC, it is now mandatory to determine the RAS and BRAF mutational status. RAS mutations should always be ruled out before the use of anti-EGFR because they are poor predictors of their effectiveness. BRAF mutation V600E has a low prevalence and a dismal prognosis. The RAS and BRAF wild type is present in about 40% of patients. The selection of individuals who might benefit from EGFR-targeting strategies is made possible by RAS mutation status [29]. The anti-EGFR monoclonal antibodies cetuximab and panitumumab should only then be used for patients whose tumors are RAS wild type (KRAS exons 2, 3 and 4 and NRAS exons 2, 3 and 4). Patient OS is increased significantly from 20 to 26–28 months by the addition of cetuximab or panitumumab to either FOLFIRI or FOLFOX [15, 18]. It is, however, linked to an increase in grade 3–4 toxic events, particularly acneiform rash, infusional reactions, diarrhoea, and hypomagnesemia. Studies comparing Doublet chemotherapy with Cetuximab or Panitumumab, have shown no differences in efficacy and are now regarded as being equivalent. Contrarily, the combination of anti-EGFR antibodies with capecitabine or bolus 5-FU plus oxaliplatin is not advised [16, 17]. The use of anti-EGFR drugs in first-line therapy has been assessed in a

total of six clinical trials [15, 16, 17, 18, 19, 20] (Table 1). Most of them were originally planned for the entire mCRC population and then re-examined retrospectively for patients with RAS wild type. In terms of survival, half of them showed a significant improvement. Compared to patients with any RAS mutation, patients with RAS wild type had significantly higher RR and PFS (positive predictive value).

Anti VEGF versus Anti-EGFRs

Bevacizumab and anti-EGFR drugs shouldn't be added, together, to combination CT because they have been shown to have negative effects [30, 31]. Data from three first-line trials comparing anti-EGFR to bevacizumab in conjunction with CT doublets for patients with RAS wild-type have been reported (Table 1) [21, 22, 23]. Results were contradictory and therefore inconclusive. PFS was equal in all three, and none of them met the predetermined endpoint. But with anti-EGFR, there was a rise in RR and a positive trend toward better survival. The primary tumor site may have an impact on the choice of treatment. Results from meta- analysis of trials combining CT and anti-EGFR antibodies revealed a greater benefit in left-sided tumors, while greater benefit was seen for right-sided cancers when CT was given alone or in combination with bevacizumab [32]. Bevacizumab plus CT, regardless of the primary site, should be the first line of treatment for tumors with the RAS mutation.

Doublets and Triplets chemotherapy

With or without monoclonal antibodies, two-drug regimens, FOLFOX/XELOX and FOLFIRI/XELIRI are used to administer 5-FU, oxaliplatin, and irinotecan. The ideal sequencing has not yet been determined, but some Phase III trials have demonstrated that the FOLFOXIRI regimen, which includes 5-FU, oxaliplatin, and irinotecan, can improve outcomes for patients with metastatic colorectal cancer (mCRC) [14, 24, 25, 26, 27] (Table 1). In a recent meta-analysis of eight RCTs, FOLFOXIRI had better efficacy outcomes, most notably with a 25% increase in survival. The grade 3–4 toxicity of FOLFOXIRI was also elevated [5]. To estimate the benefit of adding bevacizumab to FOLFOXIRI, a phase III randomized study (TRIBE) was conducted comparing FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab. The median progression free survival (P.F.S) was 12.1 months in the experimental arm versus 9.7 in the control arm. The overall survival (O.S) and overall response rate (O.R.R) were 31 months respectively versus 25.8 and 65% versus 53% all in favour of the experimental arm with statistically significant differences [33]. Regarding triplet therapy and anti-EGFR, there is less research available. Recently, a randomized Phase II trial comparing FOLFOXIRI to mFOLFOXIRI plus panitumumab in 96 RAS WT patients was presented. The panitumumab-containing arm's OS demonstrated a trend in favor of increased ORR and secondary metastasis resections, similar PFS, and favorable OS [34]. In TRIBE-2, the sequence of mFOLFOX6 and FOLFIRI doublets in addition to bevacizumab was contrasted with the preplanned strategy of upfront FOLFOXIRI followed by the reintroduction of the same regimen after disease progression. This Phase III trial demonstrated that, in terms of PFS and OS, upfront FOLFOXIRI plus bevacizumab appears to be a more advantageous therapeutic approach [27]. In the majority of clinical trials, the advantages of triplets are more pronounced in healthy, younger patients without comorbidities and without a history of adjuvant oxaliplatin exposure. Multiple recommendations for FOLFOXIRI plus bevacizumab for patients with BRAF mutations were made based on small individual patient data. This suggestion has been contested by a recent meta-analysis [33].

Drivers of treatment

Recent clinical trials have shown that new targeted therapies may be beneficial for small, molecularly selected subgroups of patients with mCRC. Less than 5% of mCRC patients have tumors with high MSI scores or that lack mismatch repair (dMMR). In these situations, immunotherapy is a more effective form of treatment than conventional CT (with or without antiangiogenic or anti-EGFR agents), both in the initial [35] and subsequent lines of treatment [36]. 8–15 percent of cases of mCRC have the V600E BRAF mutation, which is associated with a worse prognosis and resistance to common chemotherapy regimens. Encorafenib and cetuximab, with or without binimetinib, have shown promising results in second and later lines of treatment [37], and their combination is currently being tested in patients receiving less pretreatment. Finally, less than 5% of patients with mCRC exhibit HER2 amplifications (more frequently linked to rectal primaries) or NTRK fusions (more frequently seen in patients with high MSI scores or dMMR). With drugs like trastuzumab [38] or larotrectinib [39], these uncommon alterations can be effectively treated. For first-line treatment of patients with mCRC and MSI-high tumors, only immunotherapy using pembrolizumab is currently approved.

Conclusion

In the Western country, CRC continues to be the main cause of cancer death. The prognosis for patients with metastatic colorectal cancer is beginning to change as a result of knowledge of the primary tumor location and specific targetable tumor mutations. Palliative CT (typically doublets or triplets) in conjunction with targeted therapy is the mainstay of treatment for unresectable, metastatic disease. New therapeutic options brought about by molecular profiling give patients hope for improved survival. It is now required to test for RAS, BRAF, and MSI status because these mutations have an immediate impact on the way that patients receive treatment. Still being actively investigated are additional treatable tumor aberrations. Predictive biomarkers for the selection of conventional and targeted therapeutic will draw on new insights in mCRC are in a state of rapid change.

Author Contributions

Concept: A.C- Design: T.S – Supervision: A.C - Writing A.C and TS.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Gómez-España MA, Gallego J, González-Flores E, Maurel J, Páez D, Sastre J, Aparicio J, *et al*. SEOM clinical guidelines for diagnosis and treatment of metastatic colorectal cancer (2018) Clin. Transl. Oncol.

2019; 21:46-54. Doi: 10.1007/s12094-018-02002-w. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, *et al*. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann. Oncol. 2016; 27:1386-1422. Doi: 10.1093/annonc/mdw235. [PubMed] [CrossRef] [Google Scholar]
3. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, *et al*. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J. Clin. Oncol. 2004; 22:229. Doi: 10.1200/JCO.2004.05.113. [PubMed] [CrossRef] [Google Scholar]
4. Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, *et al*. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): A phase III randomised controlled trial. Lancet. 2007; 370:135. Doi: 10.1016/S0140-6736(07)61086-1. [PubMed] [CrossRef] [Google Scholar]
5. Marques RP, Duarte GS, Sterrantino C, Pais HL, Quintela A, Martins AP, *et al*. Triplet (FOLFOXIRI) versus doublet (FOLFOX or FOLFIRI) backbone chemotherapy as first-line treatment of metastatic colorectal cancer: A systematic review and meta-analysis. Crit. Rev. Oncol. Hematol. 2017; 118:54-62. Doi: 10.1016/j.critrevonc.2017.08.006. [PubMed] [CrossRef] [Google Scholar]
6. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, *et al*. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J. Clin. Oncol. 2003; 21:60-65. Doi: 10.1200/JCO.2003.10.066. [PubMed] [CrossRef] [Google Scholar]
7. Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR, *et al*. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: Results of a randomized phase II trial. J. Clin. Oncol. 2005; 23:3697-3705. Doi: 10.1200/JCO.2005.05.112. [PubMed] [CrossRef] [Google Scholar]
8. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N. Engl. J. Med. 2004; 350:2335-2342. Doi: 10.1056/NEJMoa032691. [PubMed] [CrossRef] [Google Scholar]
9. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, *et al*. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. J. Clin. Oncol. 2008; 26:2013-2019. Doi: 10.1200/JCO.2007.14.9930. [PubMed] [CrossRef] [Google Scholar]
10. Tebbutt NC, Wilson K, Gebski VJ, Cummins MM, Zannino D, van Hazel GA, *et al*. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: Results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. J. Clin. Oncol. 2010; 28:3191-3198. Doi: 10.1200/JCO.2009.27.7723 [PubMed] [CrossRef] [Google Scholar]
11. Stathopoulos GP, Batziou C, Trafalis D, Koutantos J, Batzios S, Stathopoulos J, *et al*. Treatment of colorectal cancer with and without bevacizumab: A phase III study. Oncology. 2010; 78:376-381. Doi: 10.1159/000320520. [PubMed] [CrossRef] [Google Scholar]
12. Guan ZZ, Xu JM, Luo RC, Feng F-y, Wang L-W, Shen L, *et al*. Efficacy and safety of bevacizumab plus chemotherapy in Chinese patients with metastatic colorectal cancer: A randomized phase III ARTIST trial. Chin. J. Cancer. 2011; 30:682-689. Doi: 10.5732/cjc.011.10188. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
13. Passardi A, Nanni O, Tassinari D, Petracci R, Scarp E, Biggeri A, *et al*. Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: Final results for first-line treatment from the ITACa randomized clinical trial. Ann. Oncol. 2015; 26:1201-1207. Doi: 10.1093/annonc/mdv130. [PubMed] [CrossRef] [Google Scholar]
14. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, *et al*. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N. Engl. J. Med. 2014; 371:1609-1618. Doi: 10.1056/NEJMoa1403108 [PubMed] [CrossRef] [Google Scholar]
15. Van Cutsem E, Lenz HJ, Köhne CH, Heinemann V, Tejpar S, Melezinek I, *et al*. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. J. Clin. Oncol. 2015; 33:692-700. Doi: 10.1200/JCO.2014.59.4812. [PubMed] [CrossRef] [Google Scholar]
16. Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, *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; 377:2103-2114. Doi: 10.1016/S0140-6736(11)60613-2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
17. Tveit KM, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Sigurdsson SPF, *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; 30:1755-1762. Doi: 10.1200/JCO.2011.38.0915. [PubMed] [CrossRef] [Google Scholar]
18. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, *et al*. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N. Engl. J. Med. 2013; 369:1023-1034. Doi: 10.1056/NEJMoa1305275. [PubMed] [CrossRef] [Google Scholar]
19. Bokemeyer C, Köhne CH, Ciardiello F, Lenzd H-J, Heinemanne V, Klinkhardtf U, *et al*. FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer. Eur. J. Cancer. 2015; 51:1243-1252. Doi: 10.1016/j.ejca.2015.04.007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
20. Qin S, Li J, Wang L, Xu J, Cheng Y, Bai Y, *et al*. Efficacy and Tolerability of First-Line Cetuximab Plus

Leucovorin, Fluorouracil, and Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 in Patients with RAS Wild-Type Metastatic Colorectal Cancer: The Open-Label, Randomized, Phase III TAILOR Trial. J. Clin. Oncol. 2018; 36:3031-3039. Doi: 10.1200/JCO.2018.78.3183. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
21. Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyerhardt JA, *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. Doi: 10.1001/jama.2017.7105. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
22. Heinemann V, Von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, *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; 15:1065-1075. Doi: 10.1016/S1470-2045(14)70330-4. [PubMed] [CrossRef] [Google Scholar]
23. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon J-L, Hecht JR, *et al*. PEAK: A randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J. Clin. Oncol. 2014; 32:2240-2247. Doi: 10.1200/JCO.2013.53.2473. [PubMed] [CrossRef] [Google Scholar]
24. Souglakos J, Androulakis N, Syrigos K, Polyzos A, Ziras N, Athanasiadis A, *et al*. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs. FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): A multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG) Br. J. Cancer. 2006; 94:798-805. Doi: 10.1038/sj.bjc.6603011. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
25. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, *et al*. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The Gruppo Oncologico Nord Ovest. J. Clin. Oncol. 2007; 25:1670-1676. Doi: 10.1200/JCO.2006.09.0928. [PubMed] [CrossRef] [Google Scholar]
26. Sastre J, Vieitez JM, Gomez-España MA, Gil S, Salud A, Graña B, *et al*. Randomized phase III study comparing FOLFOX + bevacizumab versus folfoxiri + bevacizumab (BEV) as 1st line treatment in patients with metastatic colorectal cancer (mCRC) with ≥3 baseline circulating tumor cells (bCTCs) J. Clin. Oncol. 2019; 37:3507. Doi: 10.1200/JCO.2019.37.15_suppl.3507. [CrossRef] [Google Scholar]
27. Cremolini C, Antoniotti C, Rossini D, Lonardi S, Loupakis F, Pietrantonio F, *et al*. Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): A multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2020; 21:497-507. Doi: 10.1016/S1470-2045(19)30862-9. [PubMed] [CrossRef] [Google Scholar]
28. Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard J-Y, *et al*. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann. Oncol. 2017; 28:2340-2366. Doi: 10.1093/annonc/mdx310. [PubMed] [CrossRef] [Google Scholar]
29. Sorich MJ, Wieses MD, Rowland A, Kichenadasse G, Mckinnon RA, Karapetis CS. Extended RAS mutations and antiEGFR monoclonal antibody survival benefit in metastatic colorectal cancer: Meta-analysis of randomized, controlled trials. Ann. Oncol. 2015; 26:13-21. Doi: 10.1093/annonc/mdu378. [PubMed] [CrossRef] [Google Scholar]
30. Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, *et al*. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J. Clin. Oncol. 2009; 27:672-680. Doi: 10.1200/JCO.2008.19.8135. [PubMed] [CrossRef] [Google Scholar]
31. Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJM, Schrama JG, *et al*. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N. Engl. J. Med. 2009; 360:563-572. Doi: 10.1056/NEJMoa0808268. [PubMed] [CrossRef] [Google Scholar]
32. Arnold D, Lueza B, Douillard J-Y, Peeters M, Lenz H-J, Venook A, *et al*. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann. Oncol. 2017; 28:1713-1729. Doi: 10.1093/annonc/mdx175. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
33. Loupakis F, Cremolini C, Masi G, Leonardi S, Zagonel V, Salvatore L, *et al*. Initial Therapy with FOLFOXIRI and Bevacizumab for Metastatic Colorectal Cancer. N. Engl. J. Med. 2014; 23:371-317.
34. Modest DP, Martens UM, Riera-Knorrenschild J, Greeve J, Florschutz A, Wessendorf S, *et al*. FOLFOXIRI Plus Panitumumab As First-Line Treatment of RAS Wild-Type Metastatic Colorectal Cancer: The Randomized, Open-Label, Phase II VOLFI Study (AIO KRK0109) J. Clin. Oncol. 2020; 37:3401-3411. Doi: 10.1200/JCO.19.01340. [PubMed] [CrossRef] [Google Scholar]
35. Andre T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt CJ, *et al*. Pemnrolizumab versus chemotherapy for microsatellite instability-hgh/mismatch repair deficient metastatic colorectal cancer: The phase 3 KEYNOTE-177 study. J. Clin. Oncol. 2020; 38:LBA4. Doi: 10.1200/JCO.2020.38.18_suppl.LBA4. [CrossRef] [Google Scholar]
36. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, *et al*. PD-1 blockade in tumors with mismatch-repair deficiency. N. Engl. J. Med. 2015;

372:2509-2520. Doi: 10.1056/NEJMoa1500596. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
37. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, *et al*. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer. N. Engl. J. Med. 2019; 381:1632-1643. Doi: 10.1056/NEJMoa1908075. [PubMed] [CrossRef] [Google Scholar]
38. Sartore-Bianchi A, Trusolino L, Marttino C, Bencardino K, Lonardi S, Bergamo F, *et al*. Dual-targeted therapy with tratuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild type, HER2-positive metastatic colorectal cancer (HERACLES): A proof-of-concept, multicentre, open label, phase 2 trial. Lancet Oncol. 2016; 17:738-746. Doi: 10.1016/S1470-2045(16)00150-9. [PubMed] [CrossRef] [Google Scholar]
39. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, *et al*. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N. Engl. J. Med. 2018; 378:731-739. Doi: 10.1056/NEJMoa1714448. [PMC free article] [PubMed] [CrossRef] [Google Scholar]