

# Overview of Frontline Therapy for Metastatic Colorectal Cancer

## MEBEA AKLILU, MD

*Assistant Professor, Hematology & Oncology  
Comprehensive Cancer Center  
Wake Forest Baptist Health  
Wake Forest University Health Sciences  
Winston-Salem, North Carolina*

## CATHY ENG, MD, FACP

*Associate Professor  
Department of Gastrointestinal Medical Oncology  
The University of Texas MD Anderson  
Cancer Center  
Houston, Texas*



Colorectal cancer (CRC) is the third most common cancer in the United States and remains the second most common cause of cancer-related death, with 142,570 new cases of CRC and 51,370 CRC-related deaths estimated for 2010.<sup>1</sup> In the past decade, the introduction of several new drugs and the results of pivotal clinical trials have transformed the management paradigm of metastatic CRC.

Traditionally, the treatment of metastatic CRC consisted of 5-fluorouracil (5-FU) monotherapy, which yielded a 10% to 15% response rate and a 10-month median overall survival (OS).<sup>2,3</sup> The addition of cytotoxic chemotherapy (irinotecan and oxaliplatin) to the 5-FU backbone led to encouraging tumor responses and OS results, providing additional treatment options. The addition of molecular-targeted agents to combination cytotoxic agents has further altered the treatment landscape of metastatic CRC. The increasing therapeutic effectiveness has led to more patients with incurable disease being able to achieve palliation with therapy and more patients previously considered to have incurable

disease being able to receive therapy with a curative intent. This review describes the pivotal trials that have established our present standards for frontline treatment of metastatic CRC.

### Combination Cytotoxic Chemotherapy

Initial explorations in combination cytotoxic chemotherapy evaluated the addition of irinotecan to the 5-FU backbone. The results of 3 Phase III trials established the superiority of this combination over 5-FU alone (Table 1).<sup>4-6</sup> The trials differed in the way the 5-FU was given (bolus vs bolus plus 24-hour infusion vs bolus plus two 22-hour infusions), but they all demonstrated

an 18% to 19% improvement in response rate (RR) and a 2- to 3-month improvement in OS with the addition of irinotecan. The use of irinotecan with bolus 5-FU (IFL) was associated with a greater 60-day mortality, mainly because of a syndrome characterized by diarrhea, neutropenia, and sepsis.<sup>7</sup> The use of infusional 5-FU with irinotecan (FOLFIRI) avoided this risk and became accepted as the preferred regimen of the combination.

The oxaliplatin and 5-FU combination was explored in 2 published Phase III trials (Table 1).<sup>8,9</sup> One looked at the addition of oxaliplatin to chronomodulated 5-FU, while the other trial looked at the addition of oxaliplatin to infusional 5-FU (FOLFOX). These trials demonstrated 28% and 37% improvements in RR and approximately 3-month improvements in progression-free survival (PFS;  $P=0.048$  and  $P=0.0003$  for oxaliplatin/infusional 5-FU and oxaliplatin/chronomodulated 5-FU, respectively), but no statistically significant improvement in median OS was seen ( $P$ =not significant and  $P=0.12$ , respectively). Although diarrhea was more frequent in the oxaliplatin-treated arms, the most common dose-limiting toxicity was neuropathy, which increased in frequency when cumulative doses above 540 mg/m<sup>2</sup> were given.<sup>10</sup>

The Phase III GI Intergroup N9741 trial compared IFL with FOLFOX and IROX (every 3 weeks combination of irinotecan and oxaliplatin).<sup>11</sup> When FOLFOX was compared with IFL, RR (45% vs 31%;  $P=0.002$ ), time to progression (TTP; 8.7 vs 6.9 months;  $P=0.0014$ ), and OS (19.5 vs 15 months;  $P=0.0001$ ) all favored FOLFOX. However, some argued that the comparison was flawed because FOLFOX was compared with IFL rather than FOLFIRI. Tournigand et al reported the results of a Phase III trial of FOLFOX followed by FOLFIRI at progression versus FOLFIRI followed by FOLFOX at progression (Table 1).<sup>12</sup> There was no statistical difference in terms of RR (54% vs 56%;  $P$ =not significant), PFS (8 vs 8.5 months;  $P=0.26$ ) or OS (20.6 vs 21.5 months;  $P=0.99$ ). There were differences in toxicity, with more frequent grade 3/4 mucositis, nausea and vomiting, and grade 2 alopecia with FOLFIRI, and more frequent grade 3/4 neutropenia and neurotoxicity with FOLFOX. Thus, at present both sequences are deemed equally efficacious for frontline therapy, but they have differing toxicity profiles.

### Choice of Fluoropyrimidine For Combination Therapy

In the single-agent setting, infusional 5-FU provides a small (1-month) but real survival advantage over bolus 5-FU,<sup>13</sup> and when combined with irinotecan, infusional 5-FU consistently has demonstrated improved OS and toxicity compared with bolus 5-FU.<sup>5,6</sup> This has led to the uniform adoption of infusional 5-FU as the fluorouracil backbone of combinational therapy.

The oral fluoropyrimidine capecitabine (Xeloda, Roche) was compared with bolus 5-FU in 2 large Phase III trials and resulted in improved RR, tolerability, and ease of administration but no OS benefit.<sup>14,15</sup> This led to trials that tried to substitute capecitabine for fluorouracil in combinational therapy.

**Table 1. Cytotoxic Combinational Chemotherapy Trials**

Author/Regimen	RR, %	PFS/ TTP, mo	OS, mo
<b>Douillard et al<sup>5</sup></b>			
Infusional 5-FU	23	4.4 <sup>a</sup>	14.1
FOLFIRI	41	6.7	17.4
<b>DeGramont et al<sup>9</sup></b>			
Infusional 5-FU	22	6.0	14.7
FOLFOX	50	9.0	16.2
<b>Giacchetti et al<sup>8</sup></b>			
Chronomodulated 5-FU	16	6.1	19.9
Chronomodulated 5-FU/oxaliplatin	53	8.7	19.4
<b>Goldberg et al<sup>11</sup></b>			
IFL	31	6.9 <sup>a</sup>	15.0
FOLFOX	45	8.7	19.5
<b>Kohne et al<sup>4</sup></b>			
AIO 5-FU	34	6.1	16.9
AIO/5-FU/irinotecan	53	8.5	20.1
<b>Saltz et al<sup>6</sup></b>			
Bolus 5-FU	21	4.3	12.6
IFL	39	7.0	14.8
<b>Tournigand et al<sup>12</sup></b>			
FOLFIRI	56	8.5	21.5
FOLFOX	54	8.0	20.6

<sup>a</sup> Trial reported TTP not PFS.

**AIO**, weekly 24-h infusion of 5-FU; **FOLFIRI**, leucovorin/5-FU/irinotecan; **FOLFOX**, leucovorin/5-FU/oxaliplatin; **5-FU**, 5-fluorouracil; **OS**, overall survival; **PFS**, progression-free survival; **TTP**, time to progression

Several Phase II trials have explored the capecitabine and irinotecan combination (CAPIRI/XELIRI). They reported RRs ranging from 35% to 61%, TTP of 6.6 to 9.2 months, and median OS of 17 to 25 months, but the toxicity of this combination was significant, with grade 3/4 diarrhea reported in 19% to 28% of patients and grade 3/4 neutropenia in 5% to 25%.<sup>16-18</sup> The Phase III BICC-C trial studied the safety and efficacy of 3 irinotecan-containing regimens—FOLFIRI, modified IFL, and CAPIRI (Table 2). Patients also were randomized to celecoxib or placebo. FOLFIRI showed statistically significant improvement in PFS over modified IFL and CAPIRI (7.6 vs 5.9 vs 5.8 months;  $P=0.004$  and  $P=0.015$ , respectively), translating into a numerical, but not statistically significant, improvement in OS (23.1 vs 17.6 vs 18.9 months;  $P=0.09$  and  $P=0.27$ , respectively). CAPIRI was associated with significantly higher rates of severe diarrhea, vomiting, and dehydration. This led to a protocol amendment that discontinued the CAPIRI arm.<sup>19</sup>

Capecitabine also has been explored in combination

**Table 2. Trials Evaluating Different Fluoropyrimidines**

Trial/Regimen	RR, %	PFS/TTP, mo	OS, mo
<b>BICC-C (period 1)<sup>19</sup></b>			
FOLFIRI	—	7.6	23.1
mIFL	—	5.9 ( <i>P</i> =0.004)	16.6 ( <i>P</i> =0.09)
CAPIRI	—	5.8 ( <i>P</i> =0.015)	18.9 ( <i>P</i> =0.27)
<b>N016966<sup>25</sup></b>			
CAPOX	—	8.0	19.8
FOLFOX	—	8.5 (HR, 1.04; 92.5% CI, 0.93-1.16)	19.6 (HR, 0.99; 92.5% CI, 0.88-1.12)
<b>TREE (Phase II study)<sup>24</sup></b>			
FOLFOX	41	—	19.2
Bolus 5-FU/ oxaliplatin	20	—	17.9
CAPOX	27	—	17.2

CAPIRI, capecitabine/irinotecan; CAPOX, capecitabine/oxaliplatin; HR, hazard ratio; FOLFIRI, leucovorin/5-FU/irinotecan; FOLFOX, leucovorin/5-FU/oxaliplatin; 5-FU, 5-fluorouracil; mIFL, irinotecan/bolus 5-FU/leucovorin; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression

with oxaliplatin (CAPOX/XELOX) and found to have similar results to FOLFOX. The results of several Phase II trials that explored different capecitabine schedules reported response rates of 42% to 55% and median OS of 19.5 to 20 months, confirming the activity of the regimen.<sup>20-23</sup> TREE-1 (Three Regimens of Eloxatin Evaluation) was a randomized Phase II study exploring the safety and efficacy of 3 oxaliplatin combinations—FOLFOX, bolus 5-FU and oxaliplatin, and CAPOX.<sup>24</sup> Following the approval of bevacizumab, the study later was amended to include bevacizumab (TREE-2). The results of the TREE-1 cohort showed RRs of 41%, 20%, and 27%, respectively. OS for the TREE-1 cohort was 19.2, 17.9, and 17.2 months for FOLFOX, bolus 5-FU and oxaliplatin, and CAPOX, respectively. Of those in the CAPOX arm, 31% had grade 3/4 diarrhea and 27% had grade 3/4 dehydration, which led to the reduction of the dose of the capecitabine (from 1,000 to 850 mg/m<sup>2</sup> twice daily, days 1-14, repeated every 21 days) in the TREE-2 cohort, resulting in improved tolerance in that study.

N016966 was an international Phase III trial initially designed to explore the noninferiority of CAPOX to FOLFOX. It was later amended to be a 2 × 2 analysis of patients assigned to either CAPOX or FOLFOX, and then to bevacizumab or placebo.<sup>25</sup> In the pooled CAPOX-alone arms, the median PFS was 8, versus 8.5 months in the pooled FOLFOX-alone arms (hazard ratio [HR], 1.04; 97.5% confidence interval [CI], 0.93-1.16), and the median OS was 19.8 vs 19.6 months, respectively

(HR, 0.99; 97.5% CI, 0.88-1.12). FOLFOX was associated with more grade 3/4 neutropenia and febrile neutropenia and CAPOX had more grade 3 diarrhea and hand-foot syndrome.

What appears clear is that the tolerance of capecitabine is different in the United States than in Asia and Europe. It is uncertain if the differences are based on dietary variables or are the result of underlying differences in genetic polymorphisms that alter the pharmacokinetics of the drug in varying populations. Based on these tolerance issues, routine use of CAPIRI in the United States should be discouraged. CAPOX is a reasonable alternative to FOLFOX, but has differing toxicity profiles that warrant attention when selecting patients.

### Antiangiogenic Therapy

Vascular endothelial growth factor (VEGF) has been shown to be an important proangiogenic protein and a viable target for drug development. Bevacizumab is a monoclonal antibody that targets VEGF, and its role in the treatment of metastatic CRC has been refined through a series of randomized clinical trials (RCTs) (Table 3).<sup>24,26-28</sup> The initial 3-arm Phase II study by Kabbinavar et al compared bolus 5-FU with 2 different doses of bevacizumab (5 and 10 mg/kg every 2 weeks) in combination with bolus 5-FU.<sup>28</sup> The arm containing 5 mg/kg of bevacizumab produced a doubling of the RR (*P*=0.029) and an approximately 4-month improvement in PFS (*P*=0.005). This result led to the pivotal AVF 2107 Phase III trial, conducted by Hurwitz et al.<sup>27</sup> This initially was a 3-arm trial, comparing the efficacy of IFL with or without bevacizumab. The third arm of bolus 5-FU plus bevacizumab was closed early after planned interim analysis showed no increase in toxicity of IFL plus bevacizumab. The addition of bevacizumab increased RRs from 34.8% to 44.8% and increased TTP from 6.3 to 10.6 months (*P*<0.001). The median survival also improved from 15.6 with IFL alone to 20.3 months with the combination (*P*<0.001). Of note, this is likely the last metastatic CRC frontline randomized trial in which OS can serve as a surrogate marker of efficacy. The commercial availability of several drugs and use of subsequent lines of therapy make PFS a more reliable surrogate of efficacy.

After data from the Hurwitz trial became available, the BICC-C trial (discussed earlier) had a second phase; it became a 2-arm trial of FOLFIRI/bevacizumab and modified IFL/bevacizumab after the CAPIRI arm was discontinued because of toxicity. Analysis of these data revealed that the FOLFIRI/bevacizumab arm had a median survival of 28 months, versus 19.2 months in the modified IFL/bevacizumab arm (*P*=0.007).<sup>26</sup>

The addition of bevacizumab to oxaliplatin-based chemotherapy was explored in the TREE and N016966 trials. The TREE study (discussed earlier) had a protocol amendment that accrued a sequential cohort of patients (TREE-2) with the 3 oxaliplatin-containing

**Table 3. Selected Studies Evaluating Angiogenesis Inhibitors**

Trial/Regimen	RR, %	PFS/TTP, mo	OS, mo
<b>AVF 2107<sup>27</sup></b>			
IFL	34.8	6.2	15.6
IFL/bevacizumab	44.8 ( <i>P</i> =0.004)	10.6 ( <i>P</i> <0.001)	20.3
Bolus 5-FU/bevacizumab	40.0 ( <i>P</i> =0.66)	8.8 ( <i>P</i> =0.4192)	18.3 ( <i>P</i> =0.2521)
<b>BICC-C (period 2)<sup>26</sup></b>			
FOLFIRI/bevacizumab	—	—	28.0
CAPIRI/bevacizumab	—	—	19.2 ( <i>P</i> =0.037)
<b>Kabbonavar et al<sup>28</sup></b>			
Bolus 5-FU	17	5.2	13.8
Bolus 5-FU/bevacizumab 5 mg/kg	40 ( <i>P</i> =0.029)	9.0 ( <i>P</i> =0.005)	21.5
Bolus 5-FU/bevacizumab 10 mg/kg	24 ( <i>P</i> =0.434)	7.2 ( <i>P</i> =0.217)	16.1
<b>N016966<sup>29</sup></b>			
FOLFOX or CAPOX	38	8	19.9
FOLVOX/CAPOX + Bev	38 ( <i>P</i> =0.99)	9.4 ( <i>P</i> =0.0023)	21.3 ( <i>P</i> =0.077)
<b>TREE-2 (Phase II study)<sup>24</sup></b>			
FOLFOX/Bev	52	—	26.1
Bolus 5-FU/oxaliplatin/bevacizumab	39	—	20.4
CAPOX/bevacizumab	46	—	24.6

CAPIRI, capecitabine/irinotecan; CAPOX, capecitabine/oxaliplatin; FOLFIRI, leucovorin/5-FU/irinotecan; FOLFOX, leucovorin/5-FU/oxaliplatin; 5-FU, 5-fluorouracil; IFL, irinotecan/5-FU/leucovorin; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression

regimens—FOLFOX, bolus 5-FU/oxaliplatin, and CAPOX—plus bevacizumab.<sup>24</sup> The addition of bevacizumab to any of the 3 arms generally resulted in a 10% improvement in RR and increased TTP by 2 months. The median OS for FOLFOX, bolus 5-FU/oxaliplatin, and CAPOX in TREE-2 were 26.1, 20.4, and 24.6 months, respectively. In comparison, during the TREE-1 period, median OS was 19.2, 17.9, and 17.2 months, respectively. Saltz et al conducted the analysis of the second portion of the N016966 trial (discussed earlier).<sup>29</sup> They looked at the addition of bevacizumab or placebo to the oxaliplatin-containing regimens (FOLFOX or CAPOX) and found that bevacizumab led to similar RRs (38%), an increase in PFS from 8 to 9.4 months (*P*=0.0023), and a nonsignificant increase in median OS (21.3 vs 19.9 months; *P*=0.077). One possible explanation for the less-than-impressive survival benefit was that a majority of patients (71%) stopped all treatment for nonprogressive events, which were primarily oxaliplatin-related neurotoxicity.

### Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) and its associated downstream signaling pathways are important in the maintenance of several characteristics displayed by neoplastic cells and are felt to be an important therapeutic target.<sup>30</sup> Cetuximab (chimeric immunoglobulin G1 [IgG1] antibody) and panitumumab (fully humanized IgG2 antibody) both target EGFR with high

affinity. The results of a pivotal randomized Phase II study (BOND [Bowel Oncology and Cetuximab Antibody]) demonstrating the ability of cetuximab to overcome chemotherapy resistance led to a series of Phase II/III studies exploring the role of EGFR inhibitors in the frontline treatment of metastatic CRC (Table 4).<sup>31</sup>

The Phase III CRYSTAL (Cetuximab combined with irinotecan in first line therapy for metastatic colorectal cancer), Phase II OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer), and Phase II SAKK (Swiss Group for Clinical Cancer Research) trials were randomized studies that examined the addition of cetuximab to frontline treatment with FOLFIRI and FOLFOX. In the CRYSTAL trial, the addition of cetuximab increased RR (38.7% vs 46.9%; *P*=0.004) and PFS (8 vs 8.9 months; *P*=0.048) but resulted in no statistically significant improvement in OS (18.6 vs 19.9 months; *P*=0.31).<sup>32</sup> In the OPUS trial, the addition of cetuximab to FOLFOX improved the RR (36% vs 46%; *P*=0.064) but had no impact on PFS (7.2 vs 7.2 months; *P*=0.62).<sup>33</sup> The SAKK trial was a small study looking at the addition of cetuximab to CAPOX. This trial noted an improvement in RRs (14% vs 41%), PFS (5.8 vs 7.2 months), and median OS (16.5 vs 20.5 months).<sup>34</sup> These trials supported the clinical activity of cetuximab, but the clinical benefit appeared modest at best.

Data indicating that *KRAS*-mutant (MT) tumors are resistant to cetuximab therapy<sup>35</sup> led to a retrospective analysis of the outcomes in CRYSTAL and OPUS with

**Table 4. Selected Studies Evaluating EGFR Inhibitors**

Trial/Regimen	RR, %	PFS/TTP, mo	OS, mo
<b>CRYSTAL (unselected)<sup>32</sup></b>			
FOLFIRI	38.7	8.0	18.6
FOLFIRI/cetuximab WT	46.9 ( <i>P</i> =0.004)	8.9 ( <i>P</i> =0.048)	19.9 ( <i>P</i> =0.31)
<b>OPUS (Phase II study, unselected)<sup>33</sup></b>			
FOLFOX	36	7.2	—
FOLFOX/cetuximab	46 ( <i>P</i> =0.064)	7.2 ( <i>P</i> =0.62)	—
<b>CRYSTAL<sup>32</sup></b>			
FOLFIRI <i>KRAS</i>	43.2	8.7	21.0
FOLFIRI/cetuximab WT	59.3 ( <i>P</i> =0.0025)	9.9 ( <i>P</i> =0.02)	24.9 (HR 0.84; 95% CI, 0.64-1.1)
FOLFIRI <i>KRAS</i>	40.2	8.1	17.7
FOLFIRI/cetuximab MT	36.2 ( <i>p</i> =0.46)	7.6 ( <i>P</i> =0.75)	17.5 (HR 1.03; 95% CI, 0.74-1.44)
<b>OPUS (Phase II study)<sup>33</sup></b>			
FOLFOX <i>KRAS</i>	37	7.2	—
FOLFOX/cetuximab WT	61 ( <i>P</i> =0.011)	7.7 ( <i>P</i> =0.0163)	—
FOLFOX <i>KRAS</i>	49	8.6	—
FOLFOX/cetuximab MT	33 ( <i>P</i> =0.106)	5.5 ( <i>P</i> =0.0192)	—
<b>MRC COIN<sup>37</sup></b>			
FOLFOX/CAPOX <i>KRAS</i>	57	8.6	17.9
FOLFOX/CAPOX + cetuximab WT	64 ( <i>P</i> =0.049)	8.6	17.0 ( <i>P</i> =0.68)
<b>PRIME<sup>38</sup></b>			
FOLFOX <i>KRAS</i>	48	8.0	19.7
FOLFOX/panitumumab WT	55	9.6 ( <i>P</i> =0.02)	23.9
FOLFOX <i>KRAS</i>	—	8.8	—
FOLFOX/panitumumab MT	—	2.3 ( <i>P</i> =0.02)	—

CI, confidence interval; FOLFIRI, leucovorin/5-FU/irinotecan; FOLFOX, leucovorin/5-FU/oxaliplatin; HR, hazard ratio; MT, mutant type; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression; WT, wild-type

respect to *KRAS* mutation status. In the CRYSTAL study, for those who were *KRAS* wild-type (WT), the addition of cetuximab to FOLFIRI led to an improvement in RR (43.2% vs 59.3%; *P*=0.0025) and PFS (8.7 vs 9.9 months; *P*=0.02) but no statistical difference in the median OS (21 vs 24.9 months; HR, 0.84; 95% CI, 0.64-1.11).<sup>32</sup> The investigators subsequently released an update of their data showing that with longer follow-up, the addition of cetuximab led to an improvement in OS that was statistically significant (20 vs 23.5 months; *P*=0.0094).<sup>36</sup> For patients who had *KRAS*-MT tumors, the addition of cetuximab had no impact on RR, PFS, or OS. Similarly, in the OPUS study, the addition of cetuximab to FOLFOX in patients with *KRAS*-WT tumors resulted in an improvement in RR (37% vs 61%; *P*=0.011) and PFS (7.2 vs 7.7 months; *P*=0.0163).<sup>33</sup> For the *KRAS*-MT tumors, the addition of cetuximab led to a decrease in RR (49% vs 33%; *P*=0.106) and a worsening in PFS (8.6 vs 5.5 months; *P*=0.0192).

The UK Medical Research Council (MRC)/COIN (Combination Chemotherapy With or Without Cetuximab as First-Line Therapy in Treating Patients With Metastatic

Colorectal Cancer) study explored the addition of cetuximab to CAPOX or FOLFOX (investigator's choice) in patients with untreated metastatic CRC.<sup>37</sup> For the *KRAS*-WT group, the addition of cetuximab resulted in an improvement in RR (50% vs 59%; *P*=0.049) but no improvement in PFS (8.6 vs 8.6 months; *P*=0.60) or OS (17.9 vs 17 months; *P*=0.68). There were no differences seen in RR, PFS, or OS with the addition of cetuximab to the *KRAS*-MT population.

Panitumumab also has been explored in frontline therapy of metastatic CRC. PRIME (Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) was a randomized Phase III trial of FOLFOX with or without panitumumab.<sup>38</sup> The findings were similar to those of cetuximab-based frontline trials with FOLFOX. In the *KRAS*-WT population, the addition of panitumumab led to an improvement in RR (48% vs 55%; *P*=0.068) and PFS (8 vs 9.6 months; *P*=0.02), as well as a numeric difference in OS that was not statistically significant (19.7 vs 23.9 months; *P*=0.072). For the *KRAS*-MT population,

**Table 5. Studies Evaluating Dual VEGF and EGFR Inhibitors**

Trial/Regimen	RR, %	PFS/TTP, mo	OS, mo
<b>BOND-2 (Phase II study)<sup>40</sup></b>			
Irinotecan/cetuximab/bevacizumab	37	7.3 <sup>a</sup>	14.5
Cetuximab/bevacizumab	20	4.9	11.4
<b>PACCE<sup>41</sup></b>			
FOLFOX/bevacizumab unselected	48	11.4	24.5
FOLFOX/bevacizumab + panitumumab <sup>w</sup>	46	10.0 (HR, 1.27; 95% CI, 1.06-1.52)	19.4 (HR, 1.43; 95% CI, 1.11-1.83)
FOLFIRI/bevacizumab unselected	40	11.7	20.5
FOLFIRI/ bevacizumab + panitumumab	43	10.1 (HR, 1.19; 95% CI, 0.29-1.29)	20.7 (HR, 1.42; 95% CI, 0.77-2.62)
FOLFOX/bevacizumab <i>KRAS</i>	56	11.5	24.5
FOLFOX/bevacizumab + panitumumab WT	50	9.8 (HR, 1.36; 95% CI, 1.04-1.77)	20.7 ( <i>P</i> =0.45)
FOLFIRI/ bevacizumab <i>KRAS</i>	48	12.5	19.8
FOLFIRI/bevacizumab + panitumumab WT	54	10.0	NE
FOLFOX/bevacizumab <i>KRAS</i>	44	11	19.3
FOLFOX/bevacizumab + panitumumab MT	47	10.4	19.3
FOLFIRI/bevacizumab <i>KRAS</i>	38	11.9	20.5
FOLFIRI/bevacizumab + panitumumab MT	30	8.3	12.8
<b>CAIRO-2<sup>42</sup></b>			
CAPOX/ bevacizumab unselected	50	10.7	20.3
CAPOX/ bevacizumab + panitumumab	52.7 ( <i>P</i> =0.49)	9.4 ( <i>P</i> =0.01)	19.4 ( <i>P</i> =0.16)
CAPOX/ bevacizumab <i>KRAS</i>	50.0	10.6	22.4
CAPOX/ bevacizumab + panitumumab WT	61.4 ( <i>P</i> =.06)	10.5 ( <i>P</i> =0.030)	21.8 ( <i>P</i> =0.64)
CAPOX/ bevacizumab <i>KRAS</i>	59.2	10.5	24.9
CAPOX/ bevacizumab + panitumumab MT	45.9	8.1 ( <i>P</i> =0.003)	17.2 ( <i>P</i> =0.03)

<sup>a</sup> TTP reported

**CAPOX**, capecitabine/oxaliplatin; **EGFR**, endothelial growth factor receptor; **FOLFIRI**, leucovorin/5-FU/irinotecan; **FOLFOX**, leucovorin/5-FU/oxaliplatin; **HR**, hazard ratio; **MT**, mutant type; **OS**, overall survival; **PFS**, progression-free survival; **RR**, response rate; **TTP**, time to progression; **VEGF**, vascular endothelial growth factor; **WT**, wild-type

the addition of panitumumab produced no difference in RR (40% vs 40%; *P*=0.98), but there appeared to have been a worsening in PFS (8.8 vs 7.3 months; *P*=0.02) and OS (19.3 vs 15.5 months; *P*=0.068).

*KRAS* has demonstrated its ability to serve as a predictive biomarker of response for EGFR-targeted agents. Generally, anti-EGFR antibodies only are offered to patients with *KRAS*-WT tumors. The results of RCTs suggest that there may be a negative interaction between oxaliplatin and anti-EGFR antibodies and that irinotecan may be a better partner. Recent provocative data from De Roock et al question the validity of treating all *KRAS*-mutated tumors in a similar fashion.<sup>39</sup> The *KRAS* mutation is found in 30% to 50% of CRC, commonly in codons 12, 13, and 61 (in decreasing order of incidence). De Roock et al conducted a retrospective pooled analysis of 579 patients with chemotherapy-refractory metastatic CRC treated with cetuximab and found that

patients with a mutation in codon 13 (p.G13d, n=32) had a longer PFS (4 vs 1.9 months; *P*=0.004) and OS (7.6 vs 5.7 months; *P*=0.005) compared with patients with other *KRAS*-mutated tumors. There was no difference in PFS or OS between *KRAS*-WT tumors and those that had the p.G13d mutation. The study was limited by the small sample size of the p.G13d group and the retrospective nature of the analysis. It will require further validation in an adequately powered trial before routine implementation of EGFR inhibitors in this population can be recommended.

### Dual Therapy With Targeted Agents

The activity of VEGF and EGFR inhibitors naturally led to exploration of regimens incorporating dual VEGF and EGFR blockade in metastatic CRC (Table 5). The results of the randomized Phase II BOND-2 trial in irinotecan-refractory metastatic CRC demonstrated that

dual biologic inhibition improved the RR, PFS, and OS in the irinotecan/cetuximab plus bevacizumab arm as well as the cetuximab and bevacizumab arm.<sup>40</sup> Patients had received a median of 3 lines of prior therapy. This trial was unique because the investigational arm of combined biologic therapy without cytotoxic therapy resulted in an impressive RR of 20%.

The preliminary results of BOND-2 served as the impetus for the creation of 2 large Phase III trials exploring the benefit of dual inhibition for patients with metastatic CRC. The PACCE (Panitumumab Advanced Colorectal Cancer Evaluation) trial explored the addition of panitumumab to FOLFOX or FOLFIRI plus bevacizumab in *KRAS*-unselected metastatic CRC, with the end point limited to patients treated with FOLFOX.<sup>41</sup> The addition of panitumumab to FOLFOX resulted in statistically significant worsening of PFS and OS. When the results were analyzed based on *KRAS* status, similar results were seen. Similar, but less pronounced, findings were seen in the FOLFIRI-based population. CAIRO2 also explored the role of dual inhibition.<sup>42</sup> Patients with unselected metastatic CRC were treated with CAPOX/bevacizumab with or without the addition of cetuximab. This trial also reported a significantly worse PFS in the arm treated with cetuximab and no benefit with respect to RR or OS.

Surprisingly, unlike in BOND-2, in the PACCE and CAIRO2 trials, combined biologic therapy added to the cytotoxic chemotherapy backbone appeared to result in a detrimental outcome. As a result, the CALGB (Cancer and Leukemia Group B) 80405 study was amended to exclude *KRAS*-MT tumors as well as dual biologic inhibition with bevacizumab and cetuximab (Figure).<sup>43</sup> At present, there are no data to support the routine use of dual VEGF and EGFR inhibition in metastatic CRC, but as investigators identify more predictive biomarkers, a subset of patients with metastatic CRC who would benefit from dual inhibition with other biologic agents might be uncovered.

### Alternative Treatment Schedules

Pooled analysis from several clinical trials suggested that there was an association with improved outcome with exposure to all active agents in metastatic CRC.<sup>44</sup> Investigators began to explore alternative treatment schedules that questioned sequential versus combination therapy, as well as duration of exposure to key chemotherapy agents.

The MRC FOCUS (Fluorouracil, Oxaliplatin and Irinotecan: Use and Sequencing) trial explored different sequential and combination chemotherapy regimens for patients with untreated metastatic CRC (N=2,135).<sup>45</sup> Patients on strategy A were treated with 5-FU monotherapy, followed by single-agent irinotecan at progression (control arm). Strategy B patients were treated with 5-FU monotherapy, followed by FOLFOX or FOLFIRI at progression. Strategy C patients were treated with FOLFOX or FOLFIRI. The median OS for strategy A patients was 13.9 months; the median OS for strategy B patients were

15.2 and 15 months for FOLFOX and FOLFIRI, respectively; the median OS for strategy C patients were 15.4 and 16.7 months for FOLFOX and FOLFIRI, respectively. Log-rank comparison of each group demonstrated superiority only for patients treated on strategy C with FOLFIRI ( $P=0.01$ ). Comparison of strategies B and C demonstrated noninferiority (HR, 1.06; 95% CI, 0.97-1.17). Quality-of-life analysis revealed no significant differences between the 3 approaches.

The original CAIRO study explored a similar question.<sup>46</sup> Patients were assigned to either capecitabine followed by irinotecan followed by CAPOX, or CAPIRI followed by CAPOX. Despite improvements in RR or PFS in favor of up-front combinational therapy, there was no difference in median OS, which was 16.3 months for sequential treatment and 17.4 months for combination treatment ( $P=0.3281$ ). Quality-of-life analysis suggested a decrease in all functional domains in the combination arm.

Results from FOCUS and CAIRO challenged the paradigm of combination therapy for all patients and suggested that an alternative option is warranted for some patients. However, neither trial included biologic agents, and in the FOCUS trial, only 23% of patients received all available cytotoxic agents. Sequential therapy is not accepted as a routine standard option for all patients, but it is a viable alternative. The criteria to select patients who would benefit from sequential treatment is not defined. Generally, those patients who present with potentially resectable disease, are symptomatic, or have a heavy tumor burden appear more appropriate for up-front combination therapy.

A review conducted by Folprecht et al demonstrated an association between RR to neoadjuvant chemotherapy and the rate of liver resection with curative intent.<sup>47</sup> Furthermore, there is consistent evidence that exposure to all 3 active cytotoxic drugs can result in a greater fraction of patients undergoing secondary surgery on metastasis. But, with less-intense chemotherapy schedules, fewer patients are receiving subsequent lines of therapy. The Gruppo Oncologico Nord Ovest conducted a Phase III trial comparing infusional 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI) with FOLFIRI.<sup>48</sup> FOLFOXIRI resulted in an improved RR (60% vs 34%;  $P=0.0002$ ). The clear resection margin (RO stage) rate was greater in the FOLFOXIRI arm overall (15% vs 6%;  $P=0.033$ ) and in those with only liver disease (36% vs 12%;  $P=0.017$ ). Treatment with FOLFOXIRI improved PFS (9.8 vs 6.9 months;  $P=0.0006$ ) and OS (22.9 vs 16.7 months;  $P=0.032$ ) when compared with FOLFIRI alone. This trial highlights the concept of dose intensification as a treatment option for select patients.

With increased use of oxaliplatin-based frontline chemotherapy, the development of cumulative neuropathy associated with prolonged exposure to oxaliplatin is a concern. One strategy that addresses this problem is the stop-and-go approach that has gained popularity as a result of the OPTIMOX (Optimized LV-5FU-Oxaliplatin Strategy in Metastatic Colorectal Cancer) studies. The

OPTIMOX1 study randomized patients to FOLFOX until progression or FOLFOX for 6 cycles, 5-FU/leucovorin maintenance without oxaliplatin for 12 cycles, and reintroduction of FOLFOX.<sup>49</sup> There was no difference between the 2 arms with respect to RR (58.5% vs 58.2%), PFS (9 vs 8.7 month;  $P=0.47$ ), and OS (19.3 vs 21.2 months;  $P=0.49$  for the continuous and intermittent arms, respectively). Grade 3 neuropathy was observed in 17.9% of those treated continuously versus 13.3% of those in the intermittent arm. Of note, only 40.1% of patients in the intermittent arm were able to have oxaliplatin reintroduced.

OPTIMOX2 was a follow-up randomized Phase II study that evaluated planned complete chemotherapy discontinuation.<sup>50</sup> Patients were randomized to receive 6 cycles of FOLFOX followed by 5-FU monotherapy until progression, or 6 cycles of FOLFOX before a complete discontinuation of all chemotherapy, with reintroduction of FOLFOX after tumor progression in both arms. The primary end point was duration of disease control, which was 13.1 months in those assigned to the maintenance arm versus 9.2 months ( $P=0.046$ ) for those who took a planned chemotherapy holiday. Similarly, both PFS (8.6 vs 6.6 months) and OS (23.8 vs 19.5 months) were worse for those who discontinued all chemotherapy. There was no difference in RR between the 2 arms (59.2% vs 59.6%). Based on these results, prolonged chemotherapy breaks with no treatment cannot be recommended.

## Conclusion

The past decade has significantly altered the treatment paradigm of metastatic CRC. The proliferation of active agents and the emergence of predictive biomarkers has made the management of CRC quite complex. 5-FU remains the backbone of cytotoxic chemotherapy, and infusional 5-FU or capecitabine are the preferred agents. Irinotecan and oxaliplatin are equally efficacious agents in combination with 5-FU in the frontline therapy of metastatic CRC.

The addition of bevacizumab to cytotoxic chemotherapy has improved outcomes compared with chemotherapy alone. However, the magnitude of benefit appears modest at best in modern clinical trials using optimal chemotherapy platforms. Similarly, EGFR inhibition appears to have a modest benefit in the frontline setting. More importantly, the development in predictive biomarkers such as *KRAS* has helped identify those who would potentially not benefit from EGFR inhibition. There are still a large number of patients with *KRAS*-WT tumors who do not respond to EGFR inhibition, and identification of additional predictive markers is greatly needed to minimize exposure to ineffective chemotherapy. There are no reliable predictive markers to help select those who may benefit from VEGF-targeted agents.

The progress in the treatment of metastatic CRC is encouraging, but challenges remain for patients with surgically incurable disease. Trials with novel approaches and agents that attempt to minimize toxicity and improve efficacy are urgently needed. Additional

biologic markers will continue to be identified and used to aid in treatment decisions. However, the underlying biology of CRC is complex and heterogeneous, making it one of the most interesting malignancies for clinical research at this time.

## References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277-300, PMID: 20610543.
2. Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol*. 1992;10(6):896-903, PMID: 1534121.
3. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. *BMJ*. 2000;321(7260):531-535, PMID: 10968812.
4. Kohne CH, van Cutsem E, Wils J, et al. Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. *J Clin Oncol*. 2005;23(22):4856-4865, PMID: 15939923.
5. Douillard J-Y, 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(9209):1041-1047, PMID: 10744089.
6. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2000;343(13):905-914, PMID: 11006366.
7. Rothenberg ML, Meropol NJ, Poplin EA, van Cutsem E, Wadler S. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol*. 2001;19(18):3801-3807, PMID: 11559717.
8. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol*. 2000;18(1):136-147, PMID: 10623704
9. de Gramont A, Figuer A, Homerin M, Seymour M. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18:2938-2947, PMID: 10944126.
10. Extra JM, Marty M, Brienza S, Misset JL. Pharmacokinetics and safety profile of oxaliplatin. *Semin Oncol*. 1998;25(2 suppl 5):13-22, PMID: 9609104.
11. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol*. 2004;22(1):23-30, PMID: 14665611.
12. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*. 2004;22(2):229-237, PMID: 14657227.
13. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. Meta-analysis Group In Cancer. *J Clin Oncol*. 1998;16(1):301-308, PMID: 9440757.
14. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol*. 2001;19(8):2282-2292, PMID: 11304782.
15. Van CE, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol*. 2001;19(21):4097-4106, PMID: 11689577.
16. Bajetta E, Di Bartolomeo M, Mariani L, et al. Randomized multicenter Phase II trial of two different schedules of irinotecan combined with capecitabine as first-line treatment in metastatic colorectal carcinoma. *Cancer*. 2004;100(2):279-287, PMID: 14716761.

17. Borner MM, Bernhard J, Dietrich D, et al. A randomized phase II trial of capecitabine and two different schedules of irinotecan in first-line treatment of metastatic colorectal cancer: efficacy, quality-of-life and toxicity. *Ann Oncol*. 2005;16(2):282-288, PMID: 15668285.
18. Tewes M, Schleucher N, Achterrath W, et al. Capecitabine and irinotecan as first-line chemotherapy in patients with metastatic colorectal cancer: results of an extended phase I study. *Ann Oncol*. 2003;14(9):1442-1448, PMID: 12954586.
19. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol*. 2007;25(30):4779-4786, PMID: 17947725.
20. Borner MM, Dietrich D, Stupp R, et al. Phase II study of capecitabine and oxaliplatin in first- and second-line treatment of advanced or metastatic colorectal cancer. *J Clin Oncol*. 2002;20(7):1759-1766, PMID: 11919232.
21. Cassidy J, Taberero J, Twelves C, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. *J Clin Oncol*. 2004;22(11):2084-2091, PMID: 15169795.
22. Scheithauer W, Kornek GV, Raderer M, et al. Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2003;21(7):1307-1312, PMID: 12663719.
23. Zeuli M, Nardoni C, Pino MS, et al. Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer. *Ann Oncol*. 2003;14(9):1378-1382, PMID: 12954576.
24. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol*. 2008;26(21):3523-3529, PMID: 18640933.
25. Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol*. 2008;26(12):2006-2012, PMID: 18421053.
26. Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. *J Clin Oncol*. 2008;26(4):689-690, PMID: 18235136.
27. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335-2342, PMID: 15175435.
28. Kabbinnar F, Hurwitz HI, Fehrenbacher L, 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(1):60-65, PMID: 12506171.
29. Saltz LB, Clarke S, Diaz-Rubio E, 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(12):2013-2019, PMID: 18421054.
30. Mendelsohn J. Targeting the epidermal growth factor receptor for cancer therapy. *J Clin Oncol*. 2002;20(18 suppl):1S-13S, PMID: 12235219.
31. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351(4):337-345, PMID: 15269313.
32. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360(14):1408-1417, PMID: 19339720.
33. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol*. 2009;27(5):663-671, PMID: 19114683.
34. Borner M, Koeberle D, Von Moos R, et al. Adding cetuximab to capecitabine plus oxaliplatin (XELOX) in first-line treatment of metastatic colorectal cancer: a randomized phase II trial of the Swiss Group for Clinical Cancer Research SAKK. *Ann Oncol*. 2008;19(7):1288-1292, PMID: 18349029.
35. Lievre A, Bachet JB, Le CD, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res*. 2006;66:3992-3995, PMID:
36. Van Cutsem E, Lang I, Folprecht G, et al. Cetuximab plus FOLFIRI in the treatment of metastatic colorectal cancer (mCRC): The influence of KRAS and BRAF biomarkers on outcome: Updated data from the CRYSTAL trial. Gastrointestinal Cancers Symposium, 2010. Abstract 281.
37. Maughan TS, Adams R, Smith CG, et al. Oxaliplatin and fluoropyrimidine chemotherapy plus or minus cetuximab: the effect of infusional 5-FU or capecitabine on the outcomes of the MRC COIN trial in advanced colorectal cancer (ACRC). Gastrointestinal Cancers Symposium, 2010. Abstract 402.
38. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28(31):4697-4705, PMID: 20921465.
39. De Roock W, Jonker DJ, Di NF, et al. Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. *JAMA*. 2010;304(16):1812-1820, PMID: 20978259.
40. Saltz LB, Lenz HJ, Kindler HL, et al. Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 study. *J Clin Oncol*. 2007;25(29):4557-4561, PMID: 17876013.
41. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase III trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol*. 2009;27(5):672-680, PMID: 19114685.
42. Tols J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med*. 2009;360(6):563-572, PMID: 191966731.
43. NCT00265850. Cetuximab and/or bevacizumab combined with combination chemotherapy in treating patients with metastatic colorectal cancer. <http://www.clinicaltrials.gov/ct2/show/study/NCT00265850?term=NCT00265850&rank=1>. Accessed April 14, 2011.
44. Grothey A, Sargent D. Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardless of whether doublet or single-agent therapy is used first line. *J Clin Oncol*. 2005;23(36):9441-9442, PMID: 16361649.
45. Seymour MT, Maughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet*. 2007;370(9582):143-152, PMID: 17630037.
46. Koopman M, Antonini NF, Douma J, 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(9582):135-142, PMID: 17630036.
47. Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH. Neo-adjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol*. 2005;16(8):1311-1319, PMID: 15870084.
48. Falcone A, Ricci S, Brunetti I, 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(13):1670-1676, PMID: 17470860.
49. Tournigand C, Cervantes A, Figuer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer--a GERCOR study. *J Clin Oncol*. 2006;24(3):394-400, PMID: 16421419.
50. Chibaudel B, Maindrault-Goebel F, Lledo G, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol*. 2009;27(34):5727-5733, PMID: 19786657.