Special Review: Rectal Cancer-current Therapies and Emerging Concepts

Review of systemic therapies for locally advanced and metastatic rectal cancer

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Abstract: Rectal cancer, along with colon cancer, is the second leading cause of cancer-related deaths in the U.S. Up to a quarter of patients have metastatic disease at diagnosis and 40% will develop metastatic disease. The past 10 years have been extremely exciting in the treatment of both locally advanced and metastatic rectal cancer (mRC). With the advent of neoadjuvant chemoradiation, increased numbers of patients with locally advanced rectal cancer (LARC) are surviving longer and some are seeing their tumors shrink to sizes that allow for resection. The advent of biologics and monoclonal antibodies has propelled the treatment of mRC further than many could have hoped. Combined with regimens such as FOLFOX or FOLFIRI, median survival rates have been increased to an average of 23 months. However, the combinations of chemotherapy regimens seem endless for rectal cancer. We will review the major chemotherapies available for locally advanced and mRC as well as regimens currently under investigation such as FOLFOXIRI. We will also review vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors as single agents and in combination with traditional chemotherapy regimens.

Keywords: Systemic therapies; locally advanced and metastatic rectal cancer (mRC); chemotherapies

Submitted Apr 03, 2014. Accepted for publication Dec 13, 2014.

doi: 10.3978/j.issn.2078-6891.2014.112

View this article at: http://dx.doi.org/10.3978/j.issn.2078-6891.2014.112

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the U.S., with an estimated 142,820 newly diagnosed cases and an estimated 50,830 deaths in 2013. An estimated 40,000 new cases of rectal cancer will be diagnosed in the U.S. in 2014 (1). A total of 20-25% of patients will have metastatic disease at diagnosis and close to 40% will develop metastatic disease (2). Despite the significant proportion of metastatic disease, the 5-year survival for all stages of rectal cancer has significantly improved over the past 4 decades (3). These advances are in large part due to the development of new systemic therapies. Rectal cancer has seen impressive treatment developments over the past 20 years, including neoadjuvant chemoradiotherapy (CRT), novel biologic therapies and second generation chemotherapeutic agents. With these advances, rectal cancer management has evolved into a multidisciplinary approach involving surgery, radiotherapy, chemotherapy, and biologics.

This review will look the current systemic therapeutic options in treating locally advanced and metastatic rectal cancer (mRC). The review will also look at therapies and novel strategies that are currently active areas of research and debate.

Neoadjuvant therapy in locally advanced rectal cancer (LARC)

The last decade has seen a shift toward neoadjuvant therapy for the treatment of LARC. Previously, adjuvant CRT involving 5-fluorouracil (5-FU) following surgical resection was the cornerstone of advanced rectal cancer treatment. The first large scale trials performed in the 1980s, NSABP R-01 and GITSG, revealed that 5-FU based treatments combined with adjuvant radiotherapy following surgery had significant improvements in disease free survival

and local recurrence compared to surgery alone (4,5). Subsequently, the North Central Cancer Treatment Group (NCCTG) performed a trial comparing radiotherapy with and without 5-FU (6). The NCCTG found significantly improved rates of local recurrence, cancer-related deaths, and overall survival (OS) with CRT compared to radiation alone (6). Based on these studies, the National Institutes of Health (NIH) recommended the treatment of LARC be a combination of postoperative chemotherapy with 5-FU and radiation (7,8).

Following the NIH recommendations, shifts in the treatment paradigm for rectal cancer began and trials began looking at the role of neoadjuvant radiotherapy. The Swedish and Dutch rectal cancer trials established the benefit of neoadjuvant radiotherapy in local disease control (9,10). These trials showed that the local recurrence rate of rectal cancer was significantly lower in those that received preoperative radiotherapy followed by surgery compared to surgery alone (9,10). In the landmark German Rectal study (CAO/ARO/AIO-94), neoadjuvant CRT was superior to post-operative therapy (11). In 825 stage II or III patients, Sauer *et al.* compared neoadjuvant CRT with 5-FU followed by surgery with the same regimen in the adjuvant setting. There was significant differences in 5-year cumulative incidence of local relapse (6% *vs.* 13%, respectively), although, there was no significant difference in 5-year survival (76% *vs.* 74%, respectively). These results have persistent at 10-year follow-up and have led to the widespread adoption neoadjuvant CRT in the treatment of LARC (11).

Other studies have looked at preoperative *vs.* postoperative CRT in the treatment of LARC and confirmed the benefit of neoadjuvant therapy. The NSABP R-03 trial was one such trial that showed no significant difference in local relapse but did show a significant difference in 5-year disease free survival with neoadjuvant CRT compared to adjuvant CRT (12). This study was only able to accrue 277 patients out of the 900 originally planned and thus the study could not reach the same power as that of the German Rectal study thus limiting analysis of local recurrence and toxicities (11,12).

Xeloda *vs.* 5-FU in LARC

Fluoropyrimidines are the backbone of both neoadjuvant and adjuvant therapy for LARC. Through inhibition of thymidylate synthetase (TS), deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis is impaired (13). 5-FU is the most commonly used drug of this class. It is administered as an infusion in conjunction with leucovorin (LV) which stabilizes the tertiary complex between 5-FU and TS thus enhancing the efficacy of 5-FU (14,15). Given the inconvenience of infusion therapies, capecitabine, the first oral fluoropyrimidine, has been developed as a promising alternative. Capecitabine is a prodrug, which is converted to 5-FU via three enzymatic steps (16). Thymidylate phosphorylase plays a key role in the conversion of capecitabine to its active metabolite and is found in higher concentrations in the malignant tissue (16). Trials looking at the toxicity profile of the drug when compared to 5-FU have suggested an improved side effect profile compared to 5-FU/LV with decreased stomatitis, diarrhea, nausea and neutropenic sepsis (17,18). However, capecitabine did have higher rates of hyperbilirubinemia and hand-foot syndrome (17,18). Considering the potential benefits of an oral pro-drug, the efficacy of capecitabine in comparison to 5-FU as neoadjuvant therapy for rectal cancer was investigated (*Table 1*).

In the first-line monotherapy setting, the two randomized, prospective phase III trials enrolled a total number of 1,207 patients, who were randomized to receive either oral capecitabine (1,250 mg/m^2 bid 2 weeks on/1 week off in 3-week cycles) or the Mayo Clinic regimen (LV 20 mg/m^2 followed by 5-FU 425 mg/m^2 iv bolus on days 1-5 in a 4-week cycle) (18). The results suggested that capecitabine was equally effective with acceptable toxicity. Further retrospective data collected from small trials without treatment protocol standardization suggested that capecitabine had a higher complete response rate in the neoadjuvant setting (24).

The role of capecitabine as neoadjuvant treatment for rectal cancer became widely accepted with Hofheinz *et al.*'s findings in 2012 (25). This phase III non-inferiority trial evaluated capecitabine *vs.* 5-FU in the neoadjuvant and adjuvant settings in LARC (25). The primary endpoint was overall 5-year survival and capecitabine was found to be non-inferior to 5-FU (76% *vs.* 67%, respectively) (25). Post-hoc analysis for superiority showed capecitabine had significantly improved 5-year survival. Capecitabine had a better 5-year survival when compared 5-FU in both the neoadjuvant cohort (66% *vs.* 61%) and adjuvant cohort (81% *vs.* 71%) (25). Local recurrence rate, a secondary endpoint, was not significantly difference between capecitabine and 5-FU (6% *vs.* 7%) (25).

Recently, the NSABP R-04 trial was completed which looked at clinical complete response (cCR), pathologic complete response (pCR) and local-regional relapse in

Table 1 Synopsis of studies comparing capecitabine containing regimens to 5-FU containing regimens. Included are the dosing regimens, PFS statistics, median OS statistics, and toxicities observed in the treatment arms

Study	German AIO group (19)	Spanish group (20)	French study (21)	Tree-1-US study (22)	GOAM-Italian study (23)
Dosing regimen CAPOX/XELOX based treatment arm	CAPOX: oxaliplatin 70 mg/m^2 2-hour infusion days 1 and 8 every 3 weeks, capecitabine 1,000 mg/m^2 bid orally days 1-14 every 3 weeks	XELOX: oral capecitabine 1,000 mg/m^2 bid for 14 days plus oxaliplatin 130 mg/m^2 on day 1 every 3 weeks	XELOX: 2-hour iv of oxaliplatin 130 mg/m^2 on day 1 plus oral capecitabine 1,000 mg/m^2 twice daily on days 1-14 every 3 weeks	CapeOx: oxaliplatin 130 mg/m^2 iv on day 1 and capecitabine 1,000 mg/m^2 orally twice daily on days 1-15 every 3 weeks	XELOX: oxaliplatin as noted below and oral capecitabine at the dose of 1,000 mg/m^2 bid from the 1st to the 14th day
Dosing regimen FU + OX based treatment arm	FUFOX: oxaliplatin 50 mg/m^2 2-hour infusion, folinic acid 500 mg/m^2 2-hour infusion, FU 2,000 mg/m^2 22-hour infusion; days 1, 8, 15, and 22 every 5 weeks	FUOX: FU 2,250 mg/m^2 diluted in saline administered by civ during 48 hours on days 1, 8, 15, 22, 29, and 36, plus oxaliplatin 85 mg/m^2 on days 1, 15, and 29 every 6 weeks	FOLFOX6: 2-hour iv of oxaliplatin 100 mg/m^2 followed by a 2-hour infusion of LV 400 mg/m^2 followed by 5-FU 400 mg/m^2 given as an intravenous bolus injection and then 5-FU 2,400-3,000 mg/m^2 as a 46-hour civ every 2 weeks	mFOLFOX6: oxaliplatin 85 mg/m^2 iv with LV 350 mg iv over 2 hours plus FU 400 mg/m^2 iv bolus and 2,400 mg/m^2 civ over 46 hours every 2 weeks bFOL: oxaliplatin 85 mg/m^2 iv on days 1 and 15 and LV 20 mg/m^2 iv over 10-20 minutes followed by FU 500 mg/m^2 iv push on days 1, 8, and 15 every 4 weeks	PVIFOX: dexamethasone 20 mg in 100 cc of saline by the intravenous (iv) route in 15 min, granisetron 3 mg in 100 cc of saline iv in 15 min, oxaliplatin at the dose of 130 mg/m^2 in 500 cc of 5% glucose solution iv in 2 hours and, at the end, 5-FU at the dose of 250 mg/m^2/daily in civ from the 1st to the 21st day
Number of patients in CAPOX treatment arm	242	171	144	48	62
Number of patients in FU + OX treatment arm	234	171	140	50 (bFOL) & 49 (mFOLFOX)	56
PFS in treatment arms CAPOX/XELOX *vs.* FU + OX (months)	7.1 *vs.* 8.0 (P=0.117)	8.9 *vs.* 9.5 (P=0.153)	8.8 *vs.* 9.3	5.9 (CapeOx) *vs.* 6.9 (bFOL) *vs.* 8.7 (mFOLFOX)	9.0 *vs.* 7.0
OS in treatment arms CAPOX/XELOX *vs.* FU + OX (months)	16.8 *vs.* 18.8 (P=0.26)	18.1 *vs.* 20.8 (P=0.145)	19.9 *vs.* 20.5	17.2 (CapeOx) *vs.* 17.9 (bFOL) *vs.* 17.6 (mFOLFOX)	NA
RR in treatment arms CAPOX/XELOX *vs.* FU + OX	48% *vs.* 54%	37% *vs.* 46%	42% *vs.* 46%	27% (CapeOx) *vs.* 20% (bFOL) *vs.* 41% (mFOLFOX)	43% *vs.* 48%
Toxicity in treatment arms CAPOX/XELOX *vs.* FU + OX	Nausea, vomiting, and diarrhea were similar in both treatment groups. Only HFS grade 2/3 was significantly higher in the CAPOX arm (P=0.028)	Lower rates of grade 3/4 diarrhea (14% *vs.* 24%, P=0.027) and grade 1/2 mucositis (28% *vs.* 43%, P=0.005), with higher rates of grade 1/2 hyperbilirubinemia (37% *vs.* 21%, P=0.001) and grade 1/2 hand-foot syndrome (14% *vs.* 5%, P=0.009) with XELOX arm *vs.* FUOX arm, respectively	XELOX arm had significantly more grade 3/4 thrombocytopenia (12% *vs.* 5%) and diarrhea (14% *vs.* 7%), but significantly less grade 3/4 neutropenia (5% *vs.* 47%), febrile neutropenia (0% *vs.* 6%) and neuropathy (11% *vs.* 26%) than FOLFOX6 patients	Grade 3/4 treatment-related adverse events during the first 12 weeks of treatment were 59%, 36%, and 67% for mFOLFOX6, bFOL, and CapeOx, respectively. CapeOx toxicity included grade 3/4 diarrhea (31%) and dehydration (27%)	Grade 3/4 diarrhea was observed in 14.0% *vs.* 8.2%, grade 3 stomatitis in 3.7% *vs.* 0%, and grade 3 neurotoxicity in 18.5% *vs.* 24.6%, when comparing *vs.* PVIFOX *vs.* XELOX

AIO, Arbeitsgemeinschaft Internistische Onkologie; iv, intravenous infusion; 5-FU, 5-fluorouracil; LV, leucovorin; civ, continuous intravenous infusion; PFS, progression free survival; OS, overall survival; NA, not available; RR, response rate; HFS, hand foot syndrome.

patients who received neoadjuvant capecitabine/radiation *vs.* 5-FU/radiation (26-28). Preliminary data suggests that neoadjuvant capecitabine/radiation compared to 5-FU/radiotherapy have comparable outcomes particularly when looking at pCR, sphincter-saving surgery, and surgical down-staging (26-28). In a preliminary report presented at the 2014 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancer Meeting, patients receiving capecitabine had comparable rates of down-staging surgery and sphincter preservation, similar pCR rates (21% *vs.* 18% for capecitabine and infusional 5-FU), similar rates of locoregional control, the primary endpoint (3-year incidence of any locoregional event 12% *vs.* 11%) and comparable OS (81% *vs.* 80%). Preliminary data has also suggested there are significant differences in overall patient reported outcomes (PROs) and quality of life (QoL) indices favoring capecitabine (26-28). Additionally, the convenience of care noted by patients in the capecitabine treatment arms was also greater (26-28). No major differences were seen in patient reported functional assessment of cancer treatment-colorectal (FACT-C), trial outcome indices (TOI), and ultimately overall PROs (26-28). These data as well as those from the NSABP R-04 and Hofheinz *et al.* strongly support capecitabine as a reasonable alternative to 5-FU in LARC (25).

Oxaliplatin in LARC

Oxaliplatin is a platinum analog which functions as an alkylator (29). Thus, oxaliplatin forms inter- and intra-strand cross-links within DNA preventing replication and transcription (29). Oxaliplatin is highly effective in combination with 5-FU in the treatment of mRC and its efficacy in the neoadjuvant setting has been extensively investigated in several randomized controlled trials (30,31).

The aforementioned NSABP R-04 had two additional treatment arms added oxaliplatin to each of the original treatment regimens (capecitabine ± oxaliplatin and 5-FU ± oxaliplatin) (26). Preliminary data analysis showed no significant differences in cCR, pCR and local-regional relapse when oxaliplatin was added to each treatment arm (26). However, the rate significant toxicity and including neuropathy and diarrhea increased in the arms containing oxaliplatin (26). In addition to the NSABP R-04, four other large trials (ACCORD 12, STAR-01, PETACC-6 and CAO/ARO/AIO-04) have failed to demonstrate a role for oxaliplatin in the neoadjuvant setting for LARC (32-35). Of all these trials, only the CAO/ARO/AIO-04 showed a statistically significant change in pCR with the addition of oxaliplatin (17% *vs.* 13%) (35). There was also a significant incidence grade 3 and 4 neuropathy and diarrhea with the addition of oxaliplatin across all trials except for the CAO/ARO/AIO-04 trial (32-35). However, although 5-FU or capecitabine were included in all trials, dosing strategies and treatment regimens varied (32-35). Additionally, the adjuvant regimens varied with only the CAO/ARO/AIO-04 trial including oxaliplatin in the adjuvant treatment arm (32-35).

An important and relevant clinical outcome after neoadjuvant treatment that was not addressed in detail in these trials was the incidence of distant metastasis after neoadjuvant therapy and prior to surgical intervention (32-35). Overall trend analysis regarding the incidence of distant metastasis indicated a decrease in the rate of distant metastasis at the time of surgery in patients treated with neoadjuvant oxaliplatin (32,33,35). Comparing the incidence of distant metastasis in the neoadjuvant treatment arms containing oxaliplatin *vs.* those without, the ACCORD trial noted 2.8% *vs.* 4.2%, the STAR-01 noted 0.5% *vs.* 2.9% and the CAO/ARO/AIO-04 showed 4% *vs.* 6%, respectively (32,33,35). Both the NSABP R-04 and the PETACC-6 did not comment on distant metastasis (26,34).

More importantly, some of the trials have provided interval analysis on disease free survival and OS. The ACCORD trial at 3 years has noted no significant difference in disease free survival (67.9% *vs.* 72.7%, respectively) between the oxaliplatin and non-oxaliplatin treatment arms (87.6% *vs.* 88.3%, respectively) (32). Preliminary data from NSABP R-04 also has supported these conclusions (26). Outcome and primary end point analysis still remains to be seen regarding the CAO/ARO/AIO-04 and PETACC-6 trials (34,35). With the current data available, consensus among the oncologic community does not support the use of neoadjuvant oxaliplatin for LARC.

Metastatic rectal cancer (mRC)

Fluoropyrimidine based therapy has been the backbone of the systemic approach to CRC over the last 30 years. In the last 2 decades, there have been new classes of chemotherapeutic agents, as well as new biologic agents such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors approved for the treatment of CRC. These treatments have directly impacted the outcomes of our patients as CRC mortality in the United States has declined 3.0% from 2000 to 2009. This was among the highest rates of decline across all tumor types and likely reflects advances in detection

and the development of improved systemic treatments (1). Our current challenge lies in developing predictive and prognostic markers to enhance the activity of available agents as well as guiding the optimal sequence of treatment.

Oxaliplatin and metastatic CRC (mCRC)

Oxaliplatin is currently an important part of the systemic approach to advanced rectal cancer. It was originally studied in combination with 5-FU/LV in 1998 (36). De Gramont *et al.* subsequently randomized 420 patients to first line 5-FU/LV or FOLFOX4 (30). FOLFOX4 was found to be superior in terms of response rates (51% *vs.* 22%) and progression free survival (PFS) (9 *vs.* 6.2 months) but not in terms of OS (30). This study established FOLFOX's role as a first line therapy for mRC. FOLFOX further established its role in the treatment of mRC in 2004 when the INT 9471 trial was being conducted (31). The trial had to be unblinded early after FOLFOX4 significantly outperformed irinotecan/5-FU/LV (IFL) and irinotecan/oxaliplatin IROX (31). With 785 patients in the initial analysis, FOLFOX4 had improved objective response rates, time to tumor progression (TTP), and most importantly an improved median OS of 19.5 months (31). This is compared to IFL and IROX which had median OS times of 15 and 17.3 months, respectively (31). However, one potential flaw in the INT 9741 trial is that with the IFL regimen, 5-FU/LV are administered via bolus which had already been shown to have worse median survival compared to infusional regimens during initial investigations of 5-FU/LV in mRC (31,37). The FFCD 2000-05 trial followed in 2011 and randomized 410 patients to FOLFOX6 or infusional 5-FU/LV (38). The FOLFOX6 arm showed an improved objective response (58% *vs.* 24%) as well as TTP (7.6 *vs.* 5.3 months) (38). However, median survival was not significantly different between the two arms (38).

Following the success of oxaliplatin in combination with 5-FU, several studies have looked at the efficacy of oxaliplatin and capecitabine in combination. A meta-analysis of trials comparing capecitabine/oxaliplatin (CAPOX) to oxaliplatin/5-FU/LV regimens in the metastatic setting pooled 3,494 patients and found that although CAPOX had a lower response rate, there was no significant difference in median TTP or OS (39). Grade 3 and 4 thrombocytopenia as well as hand and foot syndrome were more common with capecitabine regimens (39). Thus, because of the toxicity profile CAPOX is an option for first line therapy in those who cannot receive or wish to avoid infusional regimens.

Oxaliplatin has also been investigated as second line therapy in advanced rectal cancer. Four multicenter trials have evaluated the efficacy of oxaliplatin after irinotecan failure. Rothenberg *et al.* randomized 463 patients who failed IFL to 5-FU/LV, or single agent oxaliplatin, or FOLFOX4 (40). FOLFOX4 was found to be superior to both 5-FU/LV and single agent oxaliplatin with a median TTP of 4.6 *vs.* 2.7 *vs.* 1.6 months, respectively (40). These findings were duplicated by Kemeny *et al.* when 214 patients were randomized to 5-FU/LV or FOLFOX4 after irinotecan failure (41). Again, FOLFOX4 was superior with a median TTP of 4.8 *vs.* 2.4 months (41). CAPOX has a role in second line therapy and has been found to have similar efficacy to FOLFOX when used as a second line agent after irinotecan failure (42). Rothenberg *et al.* randomly assigned 627 patients to FOLFOX or CAPOX and found that TTP was similar (4.8 *vs.* 4.7 months) as was median OS (12.5 *vs.* 11.9 months) (42). Toxicity profiles were also similar but there was a higher incidence of grade 3-4 diarrhea and hand/foot syndrome but fewer episodes of neutropenia in the CAPOX group (42). Given CAPOX was found to be non-inferior in the second line setting, it is an option for those who have failed irinotecan based regimens but is often deferred to FOLFOX given the side effect profile.

Neuropathy is the dose limiting toxicity of oxaliplatin (30,31,43-47). Oxaliplatin related neuropathy can present in one of two syndromes. The more common being a cumulative sensory neuropathy which begins distally and progresses proximally occurs in 10-15% of patients receiving cumulative oxaliplatin dosages of 850 mg/m^2 (48,49). The cumulative sensory neuropathy is largely reversible as 75% of patients recover roughly 13 weeks after treatment cessation (49). An acute sensory neuropathy can also occur and presents as paresthesias and dysesthesias which more commonly affect the hands, feet, and perioral region (44). This acute neuropathy can also involve jaw tightness and pharyngo-laryngo-dysesthesias (44).

Infusional reactions have been observed in up to 25% of patients receiving oxaliplatin and are characterized by fever, rash, respiratory, and ocular symptoms (50). Respiratory symptoms can be as mild as chest tightness to severe bronchospasm (50). Depending on the severity, oxaliplatin may be continued after the administration of steroids and diphenhydramine (50,51). Infusional reactions can be prevented with pre-medication with steroids and diphenhydramine as well as slowing the oxaliplatin infusion rate (50,51).

Irinotecan and mCRC

Irinotecan, a topoisomerase inhibitor, was first introduced as an active agent for mCRC in 1997 (52). Topoisomerase inhibitors function via preventing the unwinding of DNA via topoisomerase and thus prevent or halt DNA replication and thus prevent cell replication (53). The efficacy of irinotecan as a first line agent was initially defined in combination with 5-FU/LV (54-56). In three studies, irinotecan combined with 5-FU/LV had higher response rates and median TTP compared to 5-FU/LV alone (54-56). The first was performed by Douillard *et al.* where 387 patients were randomized to infusional 5-FU with or without irinotecan administered every 2 weeks (54). TTP (6.7 *vs.* 4.4 months) and median OS (17.4 *vs.* 14.1 months) were significantly improved with irinotecan (54). These results were replicated by Saltz *et al.* where IFL out performed 5-FU/LV and irinotecan as a single agent (56). Köhne *et al.* also showed improved TTP with IFL compared to 5-FU/LV (8.5 *vs.* 6.4 months) but there was only a trend towards improvement in OS in the irinotecan containing arm (20.1 *vs.* 16.9 months) (55). Toxicities were similar in all three trials and included grade 3 and 4 diarrhea and neutropenia, nausea, and mucositis (54-56).

Irinotecan in addition to capecitabine combination regimens have also been explored. A phase II study in 2007 showed promising results with a median OS of 16.8 months in the combination arm of irinotecan 250 mg/m^2 iv on day 1 + capecitabine 1,000 mg/m^2 orally twice daily on days 1 to 14, every 3 weeks (57). However, the phase III BICC-C trial in 2007 did not reflect these findings (58). This trial randomized 430 patients to capecitabine/irinotecan (CapeIRI), IFL, and FOLFIRI with the addition of bevacizumab to all arms during the trial (58). The CapeIRI arm not only had more side effects but also showed a worse PFS and trend towards worse OS compared to the other arms. Median PFS was 7.6 months for FOLFIRI, 5.9 months for irinotecan plus bolus 5-FU/LV (mIFL) (P=0.004 for the comparison with FOLFIRI), and 5.8 months for CapeIRI (58). Thus, it is currently recommended that irinotecan not be used in combination with capecitabine as first line therapy.

Irinotecan also has activity as second line therapy for mRC. Three meta-analyses pooled data on irinotecan use after failure with an oxaliplatin containing regimen (47,59,60). Within these three studies, response rates ranged 4-20% and PFS ranged 2.5-7.1 months (47,59,60). Furthermore, Grothey *et al.* pooled data and found that OS is significantly improved in patients receiving 5-FU/LV, oxaliplatin, and irinotecan at some point along their treatment course (61).

The dose limiting toxicities of irinotecan, especially in combination with 5-FU/LV, are diarrhea and neutropenia. Of important consideration, the pharmacokinetics of irinotecan can vary significantly between patients. Chemotherapies are traditionally dosed using body surface area but the pharmacokinetics of irinotecan poorly correlate with body surface based dosing (62-64). Bilirubin appears to be a better prognosticator of the incidence of neutropenia and diarrhea with irinotecan as is the presence of the UGT1A1*28 polymorphism (65-73). However, given the rarity of this polymorphism, the cost effectiveness of screening individuals for the UGT1A1*28 polymorphism is unknown (72). However, when the patients UGT1A1*28 status is known, it is recommended to dose reduce irinotecan in those that are homozygous for UGT1A1*28 (72).

FOLFOX *vs.* FOLFIRI

FOLFOX and FOLFIRI have been established as first line therapies for mRC and were compared head to head by Tournigand *et al.* in 2004 (47). Two hundred and twenty patients were randomized to FOLFIRI or FOLFOX6 and no difference between TTP (8.5 *vs.* 8.0 months, respectively) (47). At the time of progression, patients in the FOLFIRI arm were switched to FOLFOX6 and vice versa (47). As second line therapies, FOLFIRI and FOLFOX6 showed no significant difference in TTP (14.2 *vs.* 10.9 months) (47). Most importantly, there was no difference in median OS between either arm (21.5 and 20.6 months) (47). Colucci *et al.* also compared FOLFOX4 and FOLFIRI in 2005 when 360 patients were randomized (45). There was no significant difference between FOLFIRI or FOLFOX4 with median times to tumor progression of 7 months for both and a median OS of 14 and 15 months, respectively (45). The major differences between the groups were the toxicities. Gastrointestinal toxicities were more common with FOLFIRI while neuropathy and thrombocytopenia were more common with FOLFOX4 (45).

FOLFOXIRI

Given that Grothey *et al.* found that exposure to 5-FU/LV, oxaliplatin, and irinotecan at some point during the treatment course was key, the question was raised as to whether treating patients with all three agents as first line therapy would be more beneficial (61). Falcone *et al.*

conducted a trial on FOLFOXIRI *vs.* FOLFIRI as first line therapy for mRC in 244 patients (74). The results were promising with FOLFOXIRI being superior in PFS (9.8 *vs.* 6.9 months) and median OS (22.6 *vs.* 16.7 months) (74). FOLFOXIRI did have a less favorable toxicity profile with a higher rate of grade 2 and 3 neuropathy (19% *vs.* 0%) and neutropenia (50% *vs.* 28%) (74). There was no significant difference in febrile neutropenia and patients were able to tolerate the FOLFIRI with only a 9% treatment interruption rate compared to 4% in the FOLFIRI group (74). Recent data on the combination of FOLFOXIRI and bevacizumab, an antibody to the VEGF was presented at the ASCO Annual Conference in 2013. In a randomized study by Falcone *et al.*, 508 patients were randomized to FOLFIRI + bevacizumab *vs.* FOLFOXIRI + bevacizumab. In the primary analysis, FOLFOXIRI/bevacizumab had significantly greater PFS (median 12.1 months) compared with FOLFIRI/bevacizumab [9.7 months; stratified hazard ratio (HR) 0.75; 95% confidence interval (CI), 0.62-0.9; P=0.003]. Median OS for FOLFOXIRI/bevacizumab was 31.0 months compared with 25.8 months in the FOLFIRI/bevacizumab group (stratified HR 0.79; 95% CI, 0.63-1.00; P=0.054) (75). The FOLFOXFIRI/bevacizumab arm had a significantly better response rate measured by response evaluation criteria in solid tumours (RECIST) criteria (65%) compared with the FOLFIRI/bevacizumab arm (53%; P=0.006). With future studies, FOLFOXIRI combined with VEGF or EGFR inhibitors may become the first line therapy of choice in patients with mRC.

VEGF inhibitors: bevacizumab

Bevacizumab is a humanized monoclonal antibody which exerts its effect by inhibiting the effect of VEGF-A thus inhibiting its binding to the VEGF receptor and prevents angiogenesis (76). Thus, as the tumor grows, it is unable to keep up with its oxygen requirements making the tumor tissue exceedingly hypoxic, preventing further growth.

Hurwitz *et al.* demonstrated the impact of adding bevacizumab to irinotecan when they randomized 813 patients to first line IFL with or without bevacizumab (77). Those receiving bevacizumab had improved overall response, TTP, and more importantly improved median OS (20 *vs.* 16 months) (77). The BICC-C trial showed similar results with FOLFIRI combined with bevacizumab with median overall response rates of 28 months when FOLFIRI is combined with bevacizumab compared to 19.2 months with FOLFIRI alone (78). The TREE-2 trial later confirmed the benefits of adding bevacizumab to oxaliplatin containing regimens (22). With 223 patients randomized to one of three oxaliplatin/5-FU/LV regimens with or without bevacizumab, median OS with bevacizumab containing regimens was 23.7 months compared to 18.2 months in regimens without bevacizumab (22). The NO16966 trial again showed improved TTP with bevacizumab combined with XELOX or FOLFOX compared to XELOX or FOLFOX alone but no significant difference in median survival (79). More patients were noted to discontinue bevacizumab secondary to toxicities and thus lack of significant improvement in median OS could be related to patients not completing therapy (79).

Bevacizumab has also been shown to have efficacy with 5-FU/LV in patients that cannot tolerate oxaliplatin or irinotecan secondary to toxicities (80,81). Kabbinavar *et al.* found that of the 209 patients studied, those receiving bevacizumab/5-FU/LV had a median TTP of 9.2 months and OS of 16.6 months compared to 5-FU/LV in which these outcomes were 9.2 and 12.9 months, respectively (80).

Sub-analysis of the BRiTe cohort, the ARIES cohort, and a retrospective analysis of patients from community U.S. oncology practices looked at bevacizumab as a second line agent and demonstrated a survival benefit (82-84). Second line bevacizumab was directly studied in the European ML18147 study in which 820 patients who progressed on bevacizumab containing regimens were randomized to fluoropyrimidine based regimens with or without bevacizumab (85). Those receiving bevacizumab had improved median TTP (5.7 *vs.* 4.1 months) and OS (11.2 *vs.* 9.8 months) compared to those who did not receive bevacizumab (85). Thus, despite failing first line regimens that included bevacizumab, the benefit of bevacizumab was preserved when used in second line therapy. The Food and Drug Administration (FDA) approved the use of bevacizumab in this setting after these data were published.

Although generally well tolerated, side effects of bevacizumab include hypertension, proteinuria/nephrotic syndrome, bleeding, gastrointestinal (GI) tract perforation, and arterial and venous thromboembolic events (86-96). Bleeding most commonly involves epistaxis but rarely includes GI bleed, hematemesis, and intracerebral hemorrhage (89,95,96). Hypertension is the most common side effect and can be managed via regular blood pressure (BP) checks as well as antihypertensives to maintain a goal BP of <140/90 mmHg (97). Ranpura *et al.* performed a meta-analysis on bevacizumab related fatal adverse events which included 10,217 patients (98). Two point five percent

of patients experienced a fatal event related to bevacizumab with the most common being hemorrhage, neutropenia, and GI tract perforation (98).

EGFR inhibitors

Epidermal growth factor (EGF) and its receptor (EGFR) have been shown to play a role in sustaining and controlling CRCs (99,100). Messa *et al.* looked at the EGFR concentrations in 40 colorectal carcinoma specimens and found higher concentrations in tumor tissues especially those from the left side of the colon (100). EGFR has been found to play a key role in progression of cells through the G1 phase of mitosis as well as preventing apoptosis (101). This opened the door for the creation of EGFR inhibitors in the treatment of mRC.

Cetuximab is a mouse/human chimeric monoclonal Ab which is directed against the EGFR (102). Not only does cetuximab prevent binding of the EGF ligand to EGFR via binding the surface portion of the receptor, it also induces internalization of the receptor (102). In addition to direct EGFR inhibition, antibody-dependent cellular cytotoxicity (ADCC) is considered to be an important mechanism of action of cetuximab.

Cetuximab was first studied as a second line agent with one of the earliest studies in mRC in 2007 when 572 patients who failed irinotecan therapy were randomized to cetuximab or best supportive care (103). Cetuximab was found to have improved overall response, PFS, and median OS (6.1 *vs.* 4.6 months) (103). Health related QoL (HR-QoL) was also improved in those receiving cetuximab (103,104).

Cetuximab in combination with irinotecan was first investigated in the BOND trial where 329 patients who failed irinotecan were randomized to cetuximab alone or cetuximab with continued irinotecan (105). TTP was significantly improved with cetuximab/irinotecan combination compared to cetuximab as a single agent (4.1 *vs.* 1.5 months) (105). There was a trend towards improved OS with cetuximab/irinotecan combination (105). The EPIC trial followed with 1,298 patients who had failed oxaliplatin and were randomized to single agent irinotecan with or without cetuximab (106). Patients receiving cetuximab had improved PFS (4.0 *vs.* 2.6 months) and HR-QoL (106). Median OS was similar between the two arms but is likely related to a large volume of patients who were started on cetuximab after the study closed (106).

The CRYSTAL trial opened the door for cetuximab as a first line therapy (107). A total of 1,198 patients were randomized to FOLFIRI with or without cetuximab and the initial analysis showed a significantly improved overall response and PFS with cetuximab (107). Further analysis of the data which looked at wild type (WT) *KRAS* tumors showed cetuximab had improved overall response, PFS (9.9 *vs.* 8.4 months) and median OS (23.5 *vs.* 20.0 months) (108). The European phase II OPUS trial looked at FOLFOX4 with or without cetuximab as first line therapy (109). As with the CRYSTAL trial, FOLFOX4/cetuximab combination showed improved overall response and PFS with a trend towards improved OS even in the *KRAS* wild subgroup analysis (109). The CALGB trial has not published the final data yet but in the initial analysis, those receiving cetuximab with FOLFOX or FOLFIRI have shown improved response rates compared to those receiving FOLFOX or FOLFIRI alone (110). However, the United Kingdom MRC COIN and NORDIC-VII trials failed to show a difference PFS and median OS in oxaliplatin containing regimens with and without cetuximab (111,112). At this time, cetuximab is recommended in those with WT *KRAS* tumors who have failed or cannot tolerate irinotecan. It can be combined with irinotecan containing regimens but its use with oxaliplatin containing regimens has not been fully established. Currently the EXPLORE trial is underway and is comparing FOLFOX4 with and without cetuximab in those who have failed first line irinotecan (113).

Panitumumab is a fully humanized monoclonal antibody that is directed against the extracellular EGFR domain (reference). Van Cutsem *et al.* were the first to perform a phase III study with single agent panitumumab *vs.* best supportive care in 463 patients that failed 5-FU, irinotecan, and oxaliplatin (114). PFS was 13.8 weeks for those receiving cetuximab and 8.5 weeks for those receiving best supportive care (114). After the study closed, a large number of patients in the best supportive care arm were started on panitumumab which is likely why no difference in OS was observed between the two arms (114). The data was re-analyzed with those with WT *KRAS* and those that received panitumumab had improved OS (115). These mutations did predict lack of response to panitumumab.

The PRIME study looked at panitumumab in combination with FOLFOX4 as first line therapy compared to FOLFOX4 for mRC (116). In a subset of 1,183 patients with WT *KRAS*, panitumumab/FOLFOX4 had improved PFS (9.6 *vs.* 8.0 months) but no significant difference in median OS (23.9 *vs.* 19.7 months) (116). Further evaluation revealed that 108 patients that did not have *RAS* mutations at exon 2 actually did have mutations at *KRAS* exons 3 and

4 as well as *NRAS* exons 2, 3, and 4 (117). These mutations did predict a lack of tumor response to panitumumab (117).

The absence or presence of mutations in *KRAS* is extremely important when deciding whether to start EGFR inhibitors. In addition to the findings in subset analysis of the above trials involving cetuximab and panitumumab, a retrospective analysis of 394 tumors for *KRAS* mutations was performed and showed those that were WT *KRAS* had significant responses to EGFR inhibitors while those with mutated *KRAS* did not (118). KRAS is an intracellular protein downstream the EGFR pathway and mutations in the KRAS protein cause it to be turned on permanently. Thus the signal to proliferate and prevent apoptosis is propagated despite inhibition of EGFR.

To date, studies have shown the efficacy of cetuximab and panitumumab in the treatment of mRC and it can be extrapolated that they are equally efficacious. However, only one study has been designed to compare these two EGFR inhibitors head to head, the ASPECCT trial (119). The trial is still ongoing but prelim data was presented in the 4th annual ASCO GI cancer symposium in 2007 and showed that cetuximab and panitumumab are equally efficacious in terms of PFS (4.4 *vs.* 4.1 months) and OS (10.0 *vs.* 10.4 months) (119).

KRAS mutations in exon 2 (codons 12 and 13) are a successful predictive marker for cetuximab efficacy, researchers have identified additional mutations in *KRAS* and in *NRAS*, which is also mutated at a low frequency (<5%) (120,121). Retrospective analyses of tumor samples from the EGFR inhibitor studies have been expanded to include mutations in *KRAS* exon 3 codons 59 and 61 and exon 4 codons 117 and 146, as well as mutations in *NRAS* exons 2, 3, and 4 (116,117). In a retrospective analysis of the PRIME study, 17% of patients were identified too have a mutated *RAS* isoform outside of exon 2 (116,117). Use of the expanded version of *RAS*-mutation further identified a cohort of patients benefiting from EGFR inhibition (116,117). The PRIME study demonstrated improved OS for panitumumab plus FOLFOX4 *vs.* FOLFOX4 alone, specifically in first-line treatment of WT *RAS* patients (median OS, 26.0 *vs.* 20.2 months; HR 0.78; 95% CI, 0.62-0.99; P=0.04) (117).

Improved selection of *RAS* WT patients helped demonstrate a clear benefit of cetuximab in the FIRE-3 trial (122). OS was improved in patients with *RAS* WT tumors who were treated with cetuximab plus FOLFIRI, compared with the bevacizumab plus FOLFIRI arm (33.1 *vs.* 25.6 months, respectively; P=0.011) (122). Patients with *RAS*-mutant tumors showed worsened PFS when cetuximab was added to FOLFIRI (6.1 *vs.* 12.2 months in the bevacizumab arm; P=0.004), and cetuximab was not associated with an OS benefit in these patients (122). These results highlight the importance of providing EGFR inhibitors only to those patients with *RAS* WT tumors and consideration of using expanded criteria to identify *KRAS* mutations and patients not likely to benefit from this approach.

The role of EGFR inhibitors in front-line therapy and the value of expanded *RAS* testing will be validated with the release of data from the upcoming CALGB/SWOG 80405 trial. Like the retrospective analyses described above, this study will also review efficacy (bevacizumab plus FOLFOX or FOLFIRI *vs.* cetuximab plus FOLFOX or FOLFIRI) in light of the expanded mutational analysis.

Common EGFR inhibitor side effects include weakness, malaise, nausea, electrolyte abnormalities, and acneiform rashes. Infusion reactions occur in 25% of patients treated with cetuximab (123). These reactions are often severe, most common with the first infusion and within the first 3 hours of infusion (123).

Combined bevacizumab with EGFR inhibitors

Given the success of bevacizumab, EGFR inhibitors, and combination therapy in improving OS, combining the EGFR and VEGF inhibition has been studied. This question was addressed in the BOND-2, PACCE, and CAIRO2 trials (124-126). The BOND-2 trial, cetuximab and bevacizumab were combined with the addition of irinotecan to one of the arms in patients that failed oxaliplatin (124). The initial data was promising and showed significantly improved PFS (7.3 *vs.* 4.9 months, respectively) and OS (15.4 *vs.* 14.4 months, respectively) with cetuximab/bevacizumab/irinotecan compared to cetuximab/bevacizumab (124). However, the PACCE and CAIRO2 studies were larger and looked at the combination of EGFR inhibitors with bevacizumab as first line therapies (125,126). The PACCE trial compared bevacizumab with either oxaliplatin or irinotecan containing regimens with or without panitumumab (125). Hecht *et al.* had to close the study early after those receiving panitumumab with bevacizumab had worsened OS compared to those not receiving panitumumab (19.4 *vs.* 24.5 months respectively) (125). A significant increase in skin toxicities, diarrhea, infections, and pulmonary embolisms were also noted in those receiving panitumumab/bevacizumab/

oxaliplatin (125). The CAIRO2 study looked at combination XELOX and bevacizumab with and without cetuximab and had similar findings to the PACCE trial (126). PFS was significantly decreased with the cetuximab arm (9.4 *vs.* 10.7 months) and the toxicity profile was worse with cetuximab (126). Thus, given the lack of survival benefit and increased incidence of grade 3 and 4 toxicities, combination bevacizumab and EGFR inhibitors is not recommended.

Bevacizumab *vs.* EGFR inhibitors

The FIRE-3 trial presented at ASCO 2013 introduced data to challenge the use of bevacizumab over EGFR inhibitors in the first line metastatic setting (127). Five hundred and ninety-two patients with WT *KRAS* were randomized to FOLFIRI with either bevacizumab or cetuximab (127). The first analysis showed no difference in response rates or PFS between the two arms (127). However, the cetuximab arm had a significantly improved OS compared to bevacizumab (28.8 *vs.* 25.0 months, respectively) (127). Updated data were presented later in 2013 at the annual European Cancer Congress (ECC) forum and excluded patients with mutations in *KRAS* exon 2, but also those with mutations in *KRAS* exons 3 and 4 as well as *NRAS* exons 3 and 4 (122). With these exclusions, the difference in median OS was more pronounced with 33.1 months for the cetuximab arm compared to 25.9 months for bevacizumab (122). Although the trial has not published its final data, it has suggested that EGFR inhibitors may be appropriate for first line use. Both the final data from the FIRE-3 trial and the currently ongoing U.S. intergroup trial C80405 will help answer this question once the final data is published.

Summary

Since the introduction of 5-FU over 40 years ago there have been major advances in the treatment of locally advanced and mRC. The addition of neoadjuvant CRT has improved outcomes and QoL for our patients. This approach is now widely accepted and the standard of care throughout the world. Adding second-generation chemotherapeutics to the neoadjuvant setting has not improved outcomes to date, however, new approaches are under investigation in locally advanced disease.

Advances in treatment regimens for mRC have been extensive. Combination regimens with infusional 5-FU, such as FOLFOX and FOLFIRI, have significantly extended life. Currently the triplet combination FOLFOXIRI is showing additional promise but further studies are needed. The advent of EGFR and VEGF inhibitors has significantly improved outcomes in patients with advanced disease. These agents have demonstrated activity and reasonable toxicity profiles. Their addition to chemotherapy backbones has led to improved PFS and OS. Further development and expansion of our understanding of *KRAS* mutations and additional predictive and prognostic markers will continue to lead to improved outcomes. The future appears promising.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.
2. Glynne-Jones R, Kronfli M. Locally advanced rectal cancer: a comparison of management strategies. Drugs 2011;71:1153-77.
3. Howlader N, Noone AM, Krapcho M, et al. eds. SEER Cancer Statistics Review, 1975-2011, National Cancer Institute.
4. Prolongation of the disease-free interval in surgically treated rectal carcinoma. Gastrointestinal Tumor Study Group. N Engl J Med 1985;312:1465-72.
5. Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst 1988;80:21-9.
6. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-15.
7. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990;264:1444-50.
8. Petersen SH, Harling H, Kirkeby LT, et al. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev 2012;3:CD004078.
9. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23:5644-50.
10. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med

2001;345:638-46.
11. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-33.
12. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27:5124-30.
13. Sobrero AF, Aschele C, Bertino JR. Fluorouracil in colorectal cancer--a tale of two drugs: implications for biochemical modulation. J Clin Oncol 1997;15:368-81.
14. Mini E, Trave F, Rustum YM, et al. Enhancement of the antitumor effects of 5-fluorouracil by folinic acid. Pharmacol Ther 1990;47:1-19.
15. Thirion P, Michiels S, Pignon JP, et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. J Clin Oncol 2004;22:3766-75.
16. Schüller J, Cassidy J, Dumont E, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 2000;45:291-7.
17. 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;19:2282-92.
18. Cassidy J, Twelves C, Van Cutsem E, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 2002;13:566-75.
19. Porschen R, Arkenau HT, Kubicka S, et al. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. J Clin Oncol 2007;25:4217-23.
20. Díaz-Rubio E, Tabernero J, Gómez-España A, et al. Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. J Clin Oncol 2007;25:4224-30.
21. Ducreux M, Bennouna J, Hebbar M, et al. Efficacy and safety findings from a randomized phase III study of capecitabine (X) + oxaliplatin (O) (XELOX) vs. infusional 5-FU/LV + O (FOLFOX-6) for metastatic colorectal cancer (MCRC). J Clin Oncol 2007;25:abstr 4029.
22. 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;26:3523-9.
23. Martoni AA, Pinto C, Di Fabio F, et al. Capecitabine plus oxaliplatin (xelox) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (pvifox) as first-line treatment in advanced colorectal cancer: a GOAM phase II randomised study (FOCA trial). Eur J Cancer 2006;42:3161-8.
24. Saif MW, Hashmi S, Zelterman D, et al. Capecitabine vs continuous infusion 5-FU in neoadjuvant treatment of rectal cancer. A retrospective review. Int J Colorectal Dis 2008;23:139-45.
25. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-88.
26. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant therapy for rectal cancer: Mature results from NSABP protocol R-04. J Clin Oncol 2014;32:abstr 390.
27. Roh MS, Yothers G, O'Connell M, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. J Clin Oncol 2011;29:abstr 3503.
28. Yothers G, Ganz PA, Lopa SH, et al. Patient-reported outcomes (PROs) comparison of 5-FU and capecitabine (cape) with concurrent radiotherapy (RT) for neoadjuvant treatment of rectal cancer: Results of NSABP R-04. J Clin Oncol 2012;30:abstr 391.
29. Graham J, Mushin M, Kirkpatrick P. Oxaliplatin. Nat Rev Drug Discov 2004;3:11-2.
30. 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.
31. 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;22:23-30.
32. Gérard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012;30:4558-65.
33. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without

oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29:2773-80.
34. Schmoll HJ, Haustermans K, Price TJ, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: First results of the PETACC-6 randomized phase III trial. J Clin Oncol 2013;31:abstr 3531.
35. Rödel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012;13:679-87.
36. deBraud F, Munzone E, Nolè F, et al. Synergistic activity of oxaliplatin and 5-fluorouracil in patients with metastatic colorectal cancer with progressive disease while on or after 5-fluorouracil. Am J Clin Oncol 1998;21:279-83.
37. Delaunoit T, Goldberg RM, Sargent DJ, et al. Mortality associated with daily bolus 5-fluorouracil/leucovorin administered in combination with either irinotecan or oxaliplatin: results from Intergroup Trial N9741. Cancer 2004;101:2170-6.
38. Ducreux M, Malka D, Mendiboure J, et al. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial. Lancet Oncol 2011;12:1032-44.
39. Arkenau HT, Arnold D, Cassidy J, et al. Efficacy of oxaliplatin plus capecitabine or infusional fluorouracil/leucovorin in patients with metastatic colorectal cancer: a pooled analysis of randomized trials. J Clin Oncol 2008;26:5910-7.
40. Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol 2003;21:2059-69.
41. Kemeny N, Garay CA, Gurtler J, et al. Randomized multicenter phase II trial of bolus plus infusional fluorouracil/leucovorin compared with fluorouracil/leucovorin plus oxaliplatin as third-line treatment of patients with advanced colorectal cancer. J Clin Oncol 2004;22:4753-61.
42. Rothenberg ML, Cox JV, Butts C, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Ann Oncol 2008;19:1720-6.
43. Bécouarn Y, Ychou M, Ducreux M, et al. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. Digestive Group of French Federation of Cancer Centers. J Clin Oncol 1998;16:2739-44.
44. Argyriou AA, Cavaletti G, Briani C, et al. Clinical pattern and associations of oxaliplatin acute neurotoxicity: a prospective study in 170 patients with colorectal cancer. Cancer 2013;119:438-44.
45. Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol 2005;23:4866-75.
46. Ashley AC, Sargent DJ, Alberts SR, et al. Updated efficacy and toxicity analysis of irinotecan and oxaliplatin (IROX): intergroup trial N9741 in first-line treatment of metastatic colorectal cancer. Cancer 2007;110:670-7.
47. Tournigand C, André 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;22:229-37.
48. Gamelin E, Gamelin L, Bossi L, et al. Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. Semin Oncol 2002;29:21-33.
49. Cassidy J, Misset JL. Oxaliplatin-related side effects: characteristics and management. Semin Oncol 2002;29:11-20.
50. Polyzos A, Tsavaris N, Gogas H, et al. Clinical features of hypersensitivity reactions to oxaliplatin: a 10-year experience. Oncology 2009;76:36-41.
51. Suenaga M, Mizunuma N, Shinozaki E, et al. Management of allergic reactions to oxaliplatin in colorectal cancer patients. J Support Oncol 2008;6:373-8.
52. Rougier P, Bugat R, Douillard JY, et al. Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. J Clin Oncol 1997;15:251-60.
53. Pommier Y, Tanizawa A, Kohn KW. Mechanisms of topoisomerase I inhibition by anticancer drugs. Adv Pharmacol 1994;29B:73-92.
54. 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.
55. Köhne 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;23:4856-65.
56. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 2000;343:905-14.
57. Patt YZ, Lee FC, Liebmann JE, et al. Capecitabine plus 3-weekly irinotecan (XELIRI regimen) as first-line chemotherapy for metastatic colorectal cancer: phase II trial results. Am J Clin Oncol 2007;30:350-7.
58. 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;25:4779-86.
59. Bidard FC, Tournigand C, André T, et al. Efficacy of FOLFIRI-3 (irinotecan D1,D3 combined with LV5-FU) or other irinotecan-based regimens in oxaliplatin-pretreated metastatic colorectal cancer in the GERCOR OPTIMOX1 study. Ann Oncol 2009;20:1042-7.
60. Recchia F, Saggio G, Nuzzo A, et al. Multicentre phase II study of bifractionated CPT-11 with bimonthly leucovorin and 5-fluorouracil in patients with metastatic colorectal cancer pretreated with FOLFOX. Br J Cancer 2004;91:1442-6.
61. Grothey A, Sargent D, Goldberg RM, et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 2004;22:1209-14.
62. Felici A, Verweij J, Sparreboom A. Dosing strategies for anticancer drugs: the good, the bad and body-surface area. Eur J Cancer 2002;38:1677-84.
63. Mathijssen RH, Verweij J, de Jonge MJ, et al. Impact of body-size measures on irinotecan clearance: alternative dosing recommendations. J Clin Oncol 2002;20:81-7.
64. Ratain MJ. Irinotecan dosing: does the CPT in CPT-11 stand for "Can't Predict Toxicity"? J Clin Oncol 2002;20:7-8.
65. Mathijssen RH, Marsh S, Karlsson MO, et al. Irinotecan pathway genotype analysis to predict pharmacokinetics. Clin Cancer Res 2003;9:3246-53.
66. Michael M, Thompson M, Hicks RJ, et al. Relationship of hepatic functional imaging to irinotecan pharmacokinetics and genetic parameters of drug elimination. J Clin Oncol 2006;24:4228-35.
67. Raymond E, Boige V, Faivre S, et al. Dosage adjustment and pharmacokinetic profile of irinotecan in cancer patients with hepatic dysfunction. J Clin Oncol 2002;20:4303-12.
68. Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004;22:1382-8.
69. Carlini LE, Meropol NJ, Bever J, et al. UGT1A7 and UGT1A9 polymorphisms predict response and toxicity in colorectal cancer patients treated with capecitabine/irinotecan. Clin Cancer Res 2005;11:1226-36.
70. Côté JF, Kirzin S, Kramar A, et al. UGT1A1 polymorphism can predict hematologic toxicity in patients treated with irinotecan. Clin Cancer Res 2007;13:3269-75.
71. Liu CY, Chen PM, Chiou TJ, et al. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. Cancer 2008;112:1932-40.
72. Palomaki GE, Bradley LA, Douglas MP, et al. Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review. Genet Med 2009;11:21-34.
73. Toffoli G, Cecchin E, Corona G, et al. The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. J Clin Oncol 2006;24:3061-8.
74. 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;25:1670-6.
75. Falcone A, Cremolini C, Masi G, et al. FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group. J Clin Oncol 2013;31(suppl; abstr 3505).
76. Los M, Roodhart JM, Voest EE. Target practice: lessons from phase III trials with bevacizumab and vatalanib in the treatment of advanced colorectal cancer. Oncologist 2007;12:443-50.
77. 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.
78. 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;26:689-90.
79. Saltz LB, Clarke S, Díaz-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;26:2013-9.
80. Kabbinavar FF, Schulz J, McCleod M, 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;23:3697-705.
81. Vincenzi B, Santini D, Russo A, et al. Bevacizumab in association with de Gramont 5-fluorouracil/folinic acid in patients with oxaliplatin-, irinotecan-, and cetuximab-refractory colorectal cancer: a single-center phase 2 trial. Cancer 2009;115:4849-56.
82. Bekaii-Saab TS, Grothey A, Bendell JC, et al. Effectiveness and safety of second-line (2L) irinotecan- and oxaliplatin-based regimens after first-line (1L) bevacizumab (BV)-containing treatment (tx) for metastatic colorectal cancer (mCRC): Results from the ARIES observational cohort study. J Clin Oncol 2012;30:abstr 535.
83. Cartwright TH, Yim YM, Yu E, et al. Survival outcomes of bevacizumab beyond progression in metastatic colorectal cancer patients treated in US community oncology. Clin Colorectal Cancer 2012;11:238-46.
84. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol 2008;26:5326-34.
85. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 2013;14:29-37.
86. An MM, Zou Z, Shen H, et al. Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: an updated meta-analysis. Eur J Clin Pharmacol 2010;66:813-21.
87. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 2007;99:1232-9.
88. Schutz FA, Je Y, Azzi GR, et al. Bevacizumab increases the risk of arterial ischemia: a large study in cancer patients with a focus on different subgroup outcomes. Ann Oncol 2011;22:1404-12.
89. Hang XF, Xu WS, Wang JX, et al. Risk of high-grade bleeding in patients with cancer treated with bevacizumab: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 2011;67:613-23.
90. Hurwitz HI, Saltz LB, Van Cutsem E, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. J Clin Oncol 2011;29:1757-64.
91. Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA 2008;300:2277-85.
92. Ranpura V, Hapani S, Chuang J, et al. Risk of cardiac ischemia and arterial thromboembolic events with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis of randomized controlled trials. Acta Oncol 2010;49:287-97.
93. Shah SR, Gressett Ussery SM, Dowell JE, et al. Shorter bevacizumab infusions do not increase the incidence of proteinuria and hypertension. Ann Oncol 2013;24:960-5.
94. Wu S, Kim C, Baer L, et al. Bevacizumab increases risk for severe proteinuria in cancer patients. J Am Soc Nephrol 2010;21:1381-9.
95. Hapani S, Sher A, Chu D, et al. Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. Oncology 2010;79:27-38.
96. Kozloff M, Yood MU, Berlin J, et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. Oncologist 2009;14:862-70.
97. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst 2010;102:596-604.
98. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis. JAMA 2011;305:487-94.
99. el-Hariry I, Pignatelli M, Lemoine N. Fibroblast growth factor 1 and fibroblast growth factor 2 immunoreactivity in gastrointestinal tumours. J Pathol 1997;181:39-45.
100. Messa C, Russo F, Caruso MG, et al. EGF, TGF-alpha, and EGF-R in human colorectal adenocarcinoma. Acta Oncol 1998;37:285-9.
101. Wu X, Fan Z, Masui H, et al. Apoptosis induced by

an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin. J Clin Invest 1995;95:1897-905.
102. Goldstein NI, Prewett M, Zuklys K, et al. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. Clin Cancer Res 1995;1:1311-8.
103. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040-8.
104. Au HJ, Karapetis CS, O'Callaghan CJ, et al. Health-related quality of life in patients with advanced colorectal cancer treated with cetuximab: overall and KRAS-specific results of the NCIC CTG and AGITG CO.17 Trial. J Clin Oncol 2009;27:1822-8.
105. 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;351:337-45.
106. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:2311-9.
107. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408-17.
108. Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011;29:2011-9.
109. Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol 2011;22:1535-46.
110. Venook A, Niedzwiecki D, Hollis D, et al. Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) ± cetuximab for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results. J Clin Oncol 2006;24:abstr 3509.
111. 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.
112. 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.
113. Polikoff J, Mitchell E, Badarinath S, et al. Cetuximab plus FOLFOX for colorectal cancer (EXPLORE): Preliminary efficacy analysis of a randomized phase III trial. J Clin Oncol 2005;23:abstr 3574.
114. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-64.
115. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-34.
116. 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;28:4697-705.
117. 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.
118. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757-65.
119. Price TJ, Peeters M, Kim TW, et al. ASPECCT: a randomized, multicenter, open-label, phase 3 study of panitumumab (pmab) vs cetuximab (cmab) for previously treated wild-type (WT) KRAS metastatic colorectal cancer (mCRC). European Cancer Congress. Amsterdam, the Netherlands, 2013.
120. 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.
121. Vaughn CP, Zobell SD, Furtado LV, et al. Frequency of KRAS, BRAF, and NRAS mutations in colorectal cancer. Genes Chromosomes Cancer 2011;50:307-12.
122. Stintzing S, Jung A, Rossius L, et al. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. Presented at: European Cancer Congress 2013; September 27-October 1, 2013; Amsterdam, The

Netherlands. Abstract LBA17.
123. O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. J Clin Oncol 2007;25:3644-8.
124. 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;25:4557-61.
125. Hecht JR, Mitchell E, Chidiac T, 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;27:672-80.
126. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360:563-72.
127. Heinemann V, von Weikersthal LF, Decker T, et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). J Clin Oncol 2013;31:abstr LBA3506.

Cite this article as: Yaffee P, Osipov A, Tan C, Tuli R, Hendifar A. Review of systemic therapies for locally advanced and metastatic rectal cancer. J Gastrointest Oncol 2015;6(2):185-200. doi: 10.3978/j.issn.2078-6891.2014.112

