CLINICAL INVESTIGATION

Recent advances in treatment of metastatic colorectal cancer

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Metastatic colorectal cancer is the second leading cause of cancer-related death in the Western population. New therapies have been developed at a rapid pace in the past 15 years with six new agents being approved since 1996, with the most recent addition approved in August 2012. These new cytotoxic and biologic agents have increased median overall survival from 12 to 24 months. Over 50 experimental agents are currently in clinical trials with one expected to be approved by the US FDA in the next year. The overall 5-year survival in patients with liver-isolated metastasis has improved with more aggressive surgical approaches and new chemotherapy regimens. Elderly patients with a good performance status are increasingly being given chemotherapy for metastatic disease with recent studies showing them to benefit in a similar manner to younger patients from combinations of chemotherapy and biological agents with similar toxicities.

Keywords: cytotoxic therapy • elderly • experimental agents • liver-isolated metastasis • metastatic colorectal cancer • personalized therapy • targeted therapy

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the Western population and results in approximately 50,000 deaths annually in the USA [1]. New diagnoses of CRC in the USA are estimated at 143,460 cases in 2012 [2]. The incidence and mortality has decreased from 1999–2006, which is attributed to improvements in surgical and adjuvant therapy as well as increasing the use of screening methods leading to earlier detection. The incidence of CRC steadily increases after the age of 50 years, with approximately 60% of cases diagnosed in patients 65 years and older; 40% are diagnosed in patients 75 years and older [101]. Approximately 20% of patients present with metastatic CRC (mCRC) and untreated, this group has a median overall survival (OS) of 7 months [3] and, with therapy, a 5-year survival rate of 10% [4]. The most common sites of metastasis are liver, lymph nodes, lung and peritoneum. The 2-year survival rate has improved significantly in the past decade with new agents and regimens, while 5-year survival rates have only changed modestly.

Recent advances in the understanding of tumor characteristics have paved the way for targeted therapies and led to improvements in cytotoxic regimens. 5-fluorouracil (5-FU) has been available for use in CRC for over 60 years and six additional agents have been approved since 1996, three of which are targeted therapies.

This article provides an overview of the most recent developments in treatment, including cytotoxic therapies and targeted therapies, and discusses the potential for surgical removal for isolated liver metastasis, as well as giving an insight into promising experimental agents undergoing evaluation in clinical trials.

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Chemotherapy backbones

5-FU

5-FU was the first cytotoxic agent approved for mCRC and has been the backbone of treatment for over 60 years. Given alone, it offers a median OS of 12–15 months. Adding leucovorin (LV) to bolus 5-FU further strengthens the bond between 5-FU and its main target, the enzyme thymidylate synthase, improving response rates (RR) to 23% from the 11% RR observed when the single agent 5-FU is delivered by bolus administration [5]. 5-FU was historically delivered as a bolus, despite its brief half life of less than 15 min. This practice changed largely as a consequence of the study by de Gramont showing superior RR and decreased toxicities when the bolus of 5-FU (400 mg/m^2) was given with intravenous LV of 200 mg/m^2, followed by a 22-h infusion of 5-FU (600 mg/m^2) compared with the historical 5-day 5-FU bolus regimen known commonly as the Mayo Clinic regimen [6]. Furthermore, the 5-FU bolus has been shown to increase toxicities and mortality when given with oxaliplatin or irinotecan, presumably because of the effects of higher peak-drug levels on the vulnerable GI tract mucosa and bone marrow [7]. Consequently, there is a low threshold for omitting the 5-FU bolus in patients with mCRC who have had, or are believed to be at risk for, grade 3 or 4 toxicities.

Capecitabine is an oral prodrug of 5-FU that can be given twice daily. It is believed to be equivalent to 5-FU, although no head-to-head comparisons have been made with infusional 5-FU. Although it is approved at a dose of 1250 mg/m^2 twice a day on days 1–14 of a 21-day cycle, American patients have tolerated this dosing poorly compared with other ethnicities, more likely due to their folate-enriched diet. Consequently, a starting dose of 850–1000 mg/m^2 twice daily has been more widely adapted in North American populations.

Irinotecan

Irinotecan was initially shown to have a response rate of 20% as a single agent [8]; however, it was not until the late 2000s that the modern day FOLFIRI regimen (5-FU bolus 400 mg/m^2 with LV 400 mg/m^2, irinotecan 180 mg/m^2, 5-FU infusion 2400 mg/m^2 over 46 h every 2 weeks) was established and found to be superior to the modified irinotecan, LV (folinic acid), and 5-FU (IFL) regimen (5-FU bolus 500 mg/m^2 with LV 20 mg/m^2, irinotecan 125 mg/m^2, given on days 1 and 8 every 3 weeks) with the publication of the BICC-C trial. In this Phase III trial, FOLFIRI demonstrated a significant improvement in a progression-free survival (PFS) in untreated mCRC patients when compared with irinotecan administered with either bolus 5-FU plus LV or capecitabine (7.6 vs 5.9 vs 5.8 months) as well as a better toxicity profile [9].

Oxaliplatin

Oxaliplatin does not appear to have significant single-agent activity in mCRC; however, when combined with 5-FU/LV it significantly improved PFS (9.0 vs 6.2 months) and RR (51 vs 22%) compared with 5-FU/LV alone [10]. In the N9741 Phase III trial, three different two-drug regimens were compared: IFL (5-FU bolus 500 mg/m^2 with LV 20 mg/m^2, irinotecan 125 mg/m^2 given on days 1, 8, 15 and 22 every 6 weeks), FOLFOX4 (5-FU bolus 400 mg/m^2 with LV 400 mg/m^2 followed by 5-FU 600 mg/m^2 in 22-h infusion, oxaliplatin 85 mg/m^2 every 2 weeks) and IROX (oxaliplatin 85 mg/m^2, irinotecan 200 mg/m^2 every 3 weeks) in untreated patients. A total of 795 patients were enrolled and FOLFOX had a significantly superior RR of 45 versus 34% with IROX and 31% with IFL. Median survival time was also significantly improved (19.5 months with FOLFOX vs 17.4 months with IROX and 14.8 months with IFL) [11].

5-FU containing regimens

While capecitabine given with irinotecan (XELIRI/CAPIRI) has been shown to be poorly tolerated due to significant GI toxicities [9], capecitabine with oxaliplatin (XELOX/CAPEOX) is a reasonable alternative to FOLFOX. A pooled analysis of six randomized Phase II and III trials showed similar PFS and OS in the CAPEOX and FOLFOX groups with less prominent grade 3/4 thrombocytopenia and hand–foot syndrome in the FOLFOX group, but higher incidence of neutropenia compared with the CAPEOX group [12]. FOLFOX and FOLFIRI have been shown to be equivalent regimens in first-line therapy of mCRC and the sequence by which they are given does not seem to have an impact on the outcome as explored in a GERCOR study. A total of 200 untreated patients were randomized to receive FOLFIRI followed by FOLFOX at the time of progression (arm A) versus the reverse sequence of FOLFOX followed by FOLFIRI upon progression (arm B). There was no significant difference in median survival (21.5 vs 20.6 months), PFS (14.2 vs 10.9 months) or RR in the first-line setting (56 vs 54%). There was a difference in toxicity profiles with the oxaliplatin regimen causing more neuropathy and neutropenia and the irinotecan regimen causing more GI toxicities and alopecia [13].

FOLFOXIRI (combination of 5-FU, LV, oxaliplatin and irinotecan) has been explored in two Phase III trials with conflicting results. In the HORG trial, 283 patients received FOLFOXIRI versus FOLFIRI in the first-line setting, with no significant difference

in the OS, time to progression or RR, but a significant increase in toxicities, mainly alopecia, diarrhea and neuropathy [14]. In the GONO trial, 244 patients with untreated disease were randomized to FOLFOXIRI versus the less dose-intense regimen of 5-FU plus irinotecan, known as the Douillard regimen, and results showed improvement in PFS (6.9 vs 9.8 months; p = 0.0006) and the median OS (17 vs 23 months; p = 0.032) with increased, but not prohibitive, toxicities for the four-drug regimen [15]. Of note, the FOLFOXIRI arm on the GONO trial received 5-FU 3200 mg/m^2 as a continuous infusion over 48 h while the FOLFOXIRI arm on the HORG trial and the FOLFIRI arms on both the trials received 5-FU 400 mg/m^2 bolus followed by 600 mg/m^2 given over 22 h, possibly explaining the better RR with FOLFOXIRI in the GONO trial. Given the increased toxicities caused by FOLFOXIRI, this regimen is not used widely by US clinicians, although it is listed as a potential treatment option in the National Comprehensive Cancer Network (NCCN) guidelines [102]. It may, however, add benefit to patients with potentially resectable liver metastasis as further discussed below.

Combination versus sequential administration

Combination- versus sequential-chemotherapy approaches were explored in the CAIRO and MRC FOCUS trials. In CAIRO, sequential therapy with capecitabine, followed by irinotecan on progression followed by CAPEOX on progression was compared with CAPIRI followed by CAPEOX and found to be equivalent, with median OS of 16.3 versus 17.4 months. Interestingly, grade 3 and 4 toxicities did not differ between the two arms with the exception of more frequent grade 3 hand–foot syndrome in the combination arm [16]. The MRC FOCUS trial compared three different treatment arms – infusional 5-FU followed by irinotecan on progression (arm A), infusional 5-FU followed by combination with either FOLFOX or FOLFIRI on progression (arm B) or combination chemotherapy with FOLFOX or FOLFIRI upfront (arm C). Salvage chemotherapy was changed halfway through the trial (from infusional 5-FU with mitomycin-C to combination FOLFOX or FOLFIRI) as new data were emerging on the sequential use of FOLFOX and FOLFIRI. Arm A had inferior survival compared with arm B and C or 13.9 versus 15.0–16.7 months on arms B and C. Although only 23% of patients received salvage chemotherapy with FOLFOX or FOLFIRI, the highest rate was in arm C or 33%, possibly explaining the improved OS in that arm [17]. This is in concordance with a meta-analysis of 21 arms of 11 published Phase III trials with 5768 patients, which showed that the single most important factor in OS was exposure to three active cytotoxic agents (5-FU, oxaliplatin, irinotecan), irrespective of whether they were given as singlets or doublets [18].

Established biological agents

VEGF-targeted therapy

Bevacizumab (bev) is the first FDA-approved VEGF inhibitor, a humanized monoclonal antibody, with high affinity to soluble VEGF-A. It has a half-life of 20 days allowing for dosing every 2–3 weeks. Hurwitz *et al.* reported the first trial to indicate a survival advantage when bev was added to first-line IFL therapy and this led to the agent's FDA approval in 2004 [19]. A total of 813 patients were randomized to IFL with bev versus placebo and median OS was 20.3 versus 15.6 months (p <0.001) [19]. Similarly, bev was found to be beneficial when added to FOLFOX as second-line therapy after progression on an irinotecan-based regimen, as shown in the Phase III E3200 trial where patients treated with bev with FOLFOX4 had a median OS of 12.9 versus 10.8 months for those treated with FOLFOX4 alone (p = 0.0011). A third arm in the E3200 trial tested bev as a single agent with a response rate of 3.3% and PFS of 2.7 months suggesting that bev has minimal activity when given alone [20]. The NO16966 Phase III randomized study did not show a statistical OS benefit with the addition of bev to FOLFOX4 as first-line therapy, but a has been criticized for having high numbers of patients who had early discontinuation of treatment contrary to the protocol's specifications as only 29 and 47% of the bev and placebo recipients, respectively, were treated until progression [21]. In the observational community-based BRiTE registry, 1953 patients were enrolled with patients receiving first-line FOLFOX, with bev having a median OS of 24.4 months, while patients on first-line FOLFIRI with bev had a median OS of 22.9 months [22]. The abovementioned trials, therefore, suggest that adding bev to standard therapy will improve RR by approximately 10% and increase median OS by approximately 2–6 months.

The authors of the BRiTE registry looked at the continuation of bev with second-line chemotherapy after progression on first-line chemotherapy with bev and revealed that patients whose regimen included continuous bev had a significantly longer median OS, or 31.8 versus 19.9 months (p <0.001) [23]. In the TML study presented at American society of Clinical Oncology (ASCO) in 2012, highly selected patients with no evidence of rapidly progressive disease on first-line therapy with bev who were noted to have progressive disease within 3 months of stopping first-line treatment, manifested a 9.8 month median overall survival when

on chemotherapy alone as compared with 11.2 months (p = 0.0062) when bev was continued with second-line chemotherapy [24]. The modest difference in the randomized trial highlights the pitfalls of attempting to use retrospective data to determine best practices. The DREAM trial preliminary results were presented at the annual ASCO meeting in 2012. In total, 446 patients were randomized to either bev versus bev and erlotinib maintenance therapy after induction therapy with FOLFOX/bev, CAPEOX/bev or FOLFIRI/bev. Median PFS was 4.6 versus 5.8 months in the two arms while median PFS from inclusion were 9.2 versus 10.2 months. Grade 3 skin toxicities (0 vs 19%) and diarrhea (<1 vs 9%) were increased in the combination maintenance therapy group [25].

Aflibercept is a fully humanized recombinant fusion protein that functions as a VEGF-A, -B and PIGF trap, preventing the growth factors from binding to their specific receptors. It received FDA approval in August 2012 for use in combination with FOLFIRI for patients who have previously progressed on an oxaliplatin-containing regimen [103]. It is composed of part of the extracellular domains of VEGFR-1 and -2 fused to the constant region of human IgG1 and binds VEGF-A with higher affinity than bev [26]. The VELOUR trial, which led to FDA approval, was a Phase III second-line clinical trial, where 1226 patients who had progressed on oxaliplatin-based therapy, were randomized to FOLFIRI with aflibercept versus FOLFIRI alone. In total, 30% of patients had been previously treated with bev. After a median follow up of 22 months, median OS was 13.5 months in the combined treatment arm versus 12 months in the FOLFIRI-alone arm (p = 0.0032), with an overall response rate of 20 versus 11%. Discontinuation of therapy due to adverse events occurred in 27% of patients on aflibercept versus 12% in the placebo-controlled group [27].

EGFR-targeted therapy

Cetuximab is a chimeric antibody that binds to and inhibits the EGFR pathway. It was FDA approved in 2004 as a second-line therapy in mCRC in combination with chemotherapy or as a single agent. Although promising effects were seen in several trials, its full effects were not known until mutations in the *KRAS* gene were found to have a negative impact on EGFR therapy, either rendering the drug to lack benefit or even to cause shorter times to disease progression in patients with tumors that carry *KRAS* mutations [28]. As a single agent compared with best supportive care, cetuximab significantly improved OS and PFS and had a RR of 13% in *KRAS* wild-type patients [29]. The CRYSTAL trial recently published an updated OS analysis that showed an OS benefit in the *KRAS* wild-type population (23.5 vs 20 months; p = 0.0093) when cetuximab was added to FOLFIRI versus FOLFIRI alone [30]. Data on adding cetuximab to FOLFOX have been more conflicting. The randomized Phase II OPUS trial showed a significant improvement in response rate and PFS in *KRAS* wild-type patients when cetuximab was combined with FOLFOX4 versus FOLFOX4 but no significant difference in OS [31]. Similarly, the Phase III COIN trial (with CAPEOX or mFOLFOX6) [32] and NORDIC VII trial (which used FLOX [bolus 5-FU] and not the more traditionally recognized FOLFOX regimen) showed no significant benefit in PFS or OS with the addition of cetuximab to FOLFOX in *KRAS* wild-type patients [33]. A recent presentation at ASCO 2012 pooled together the OPUS trial data with the mFOLFOX6 arms from COIN and suggested an improved RR (odds ratio: 1.87; 95%CI: 1.07–3.28) and PFS (hazard ratio [HR]: 0.69; 95%CI: 0.52–0.92) with no significant improvement in OS [34]. As no single trial has shown improvement in OS, cetuximab with FOLFOX in the first-line setting has been removed from the NCCN guidelines [102] but is still licensed in Europe. It appears that the interactions between cetuximab and FOLFIRI differ from the interactions with FOLFOX, suggesting that irinotecan-based regimens may be a better partner with the EGFR inhibitor.

Panitumumab is a fully humanized monoclonal antibody targeting EGFR and was FDA approved in 2006 as a monotherapy in mCRC patients who have failed prior to therapy. It had a RR of 17% and improved PFS and OS compared with best supportive care in wild-type *KRAS* patients in an updated publication of the initial single-agent trial published in 2007 [35]. The PRIME study looked at adding panitumumab to FOLFOX in the first-line setting. PFS was improved with the addition of panitumumab (9.6 vs 8.0 months; p = 0.02) in patients with *KRAS* wild-type tumors with a trend towards prolonged OS (23.9 vs 19.7 months; p = 0.072); while patients with *KRAS* mutant tumors had worse PFS and OS [36]. Peeters *et al.* reported that combining panitumumab with FOLFIRI as second-line therapy increased RR from 10 to 35% and PFS from 3.9 to 5.9 months (p = 0.004) as well as OS from 12.5 to 14.5 months (p = 0.12) in *KRAS* wild-type tumors when compared with FOLFIRI alone [37].

In summary, adding EGFR-targeted therapy to cytotoxic therapy for *KRAS* wild-type tumors increases RR by approximately 20% (~10–15% as a single agent) and OS by 2–4 months (Table 1). Panitumumab, a fully humanized monoclonal antibody,

Table 1. Clinical trials with EGFR inhibitors, *KRAS* wild-type patients only.

Trial	Patients (n)	Line of therapy	Phase	Regimen	First degree end point	Primary outcome	Secondary outcome	Ref.
CO.17	215	Refractory	III	BSC +/- Cmab	OS	9.5 vs 4.8 mo (HR: 0.55; p <0.001)	PFS 3.7 vs 1.9 mo (HR: 0.40; p <0.001); RR 13 vs 0%	[29]
CRYSTAL	666	First	III	FOLFIRI +/- Cmab	PFS	9.9 vs 8.4 mo (p = 0.0012)	OS 23.5 vs 20 mo (p = 0.0093); ORR 57 vs 40% (p <0.001)	[30]
OPUS	134	First	II	FOLFOX4 +/- Cmab	ORR	57 vs 34% (OR 2.55; p = 0.0027)	PFS 8.3 vs 7.2 mo (HR: 0.57; p = 0.0064); OS 22.8 vs 18.5 mo (HR: 0.86; p = 0.39)	[31]
COIN	729	First	III	mFOLFOX6/ CAPEOX +/- Cmab	OS	17.9 vs 17 mo (ns)	PFS 8.6 vs 8.6 mo; ORR 64 vs 57% (p = 0.049)	[32]
NORDIC VII	303	First	III	FLOX/FLOX + Cmab†	PFS	8.7 vs 7.9 mo (ns)	ORR 47 vs 46% (ns); OS 22 vs 20.1 mo (ns)	[33]
Amado *et al.*	243	Refractory	III	BSC +/- Pmab	PFS	12.3 vs 7.3 w	OS 8.1 vs 7.6 mo; RR 17 vs 0%	[35]
20050181	597	Second	III	FOLFIRI +/- Pmab	PFS/OS	5.9 vs 3.9 mo (p = 0.004)/14.5 vs 12.5 mo (ns)	ORR 35 vs 10% (p <0.001)	[37]
PRIME	656	First	III	FOLFOX4 +/- Pmab	PFS	9.6 vs 8.0 mo (p = 0.02)	OS 23.9 vs 19.7 mo (p = 0.072)	[36]

†Third arm with intermittent FLOX and Cmab is not presented here.

BSC: Best supportive care; Cmab: Cetuximab; HR: Hazard ratio; mo: Month; ns: Not significant; ORR: Overall-response rate; OS: Overall survival; PFS: Progression-free survival; Pmab: Panitumumab; RR: Response rate; w: Weeks.

is rarely associated with infusion reactions, whereas cetuximab, a murine based protein, causes grade 3 or 4 infusion reactions in up to 22% of patients in certain geographical areas, namely North Carolina and Tennessee (USA) [38]. Other areas in the USA and Europe have not seen frequent infusion reactions with grade 3 or 4 being reported in 2.3% of patients in the CRYSTAL trial [30]. Panitumumab is administered every 2 weeks, while cetuximab is given weekly. We would, therefore, commonly choose panitumumab over cetuximab. Figure 1 provides an overview of our proposed combination of cytotoxic and biologic agents at different stages of treatment.

The combination of two biological agents with cytotoxic therapy has not been shown to improve outcomes and may in fact worsen them as shown in the CAIRO-2 trial where the addition of cetuximab to CAPEOX with bev worsened skin toxicities, worsened quality of life and shortened PFS [39]. In the PACCE trial, the addition of panitumumab to FOLFOX or FOLFIRI with bev led to a worse PFS and increased toxicities [40]. ASPECCT is a Phase III trial currently in progress comparing panitumumab directly with cetuximab in refractory mCRC, and is estimated to complete accrual in 2013 [104].

■ Are chemotherapy holidays or reduced-intensity maintenance therapies a safe option?

The OPTIMOX-2 trial looked at chemotherapy holidays versus reduced-intensity maintenance therapy and randomized 212 patients to receive either six cycles of mFOLFOX7 followed by maintenance 5-FU/LV until disease progression (arm 1) or the same six cycles of mFOLFOX7 followed by observation only (arm 2). In both arms, mFOLFOX7 was restarted upon disease progression. 5-FU maintenance therapy was associated with a significant improvement in the duration of disease control (13.1 vs 9.2 months; p = 0.046) as well as PFS (8.6 vs 6.6 months; p = 0.0017). A total of 80% of patients were reintroduced to chemotherapy at the time of progression [41]. The fact that patients only received 3 months of chemotherapy before initiating a chemotherapy-free interval has been criticized in this study as less than an optimal duration for the more intensive treatment. The fact that the novel construct of duration of disease control was used as a primary end point makes comparison of these results with other trials problematic.

The OPTIMOX-1 trial explored whether oxaliplatin could be stopped after 6 cycles with plans to reintroduce it at progression. Over 600 patients with previously untreated mCRC were randomized to receive

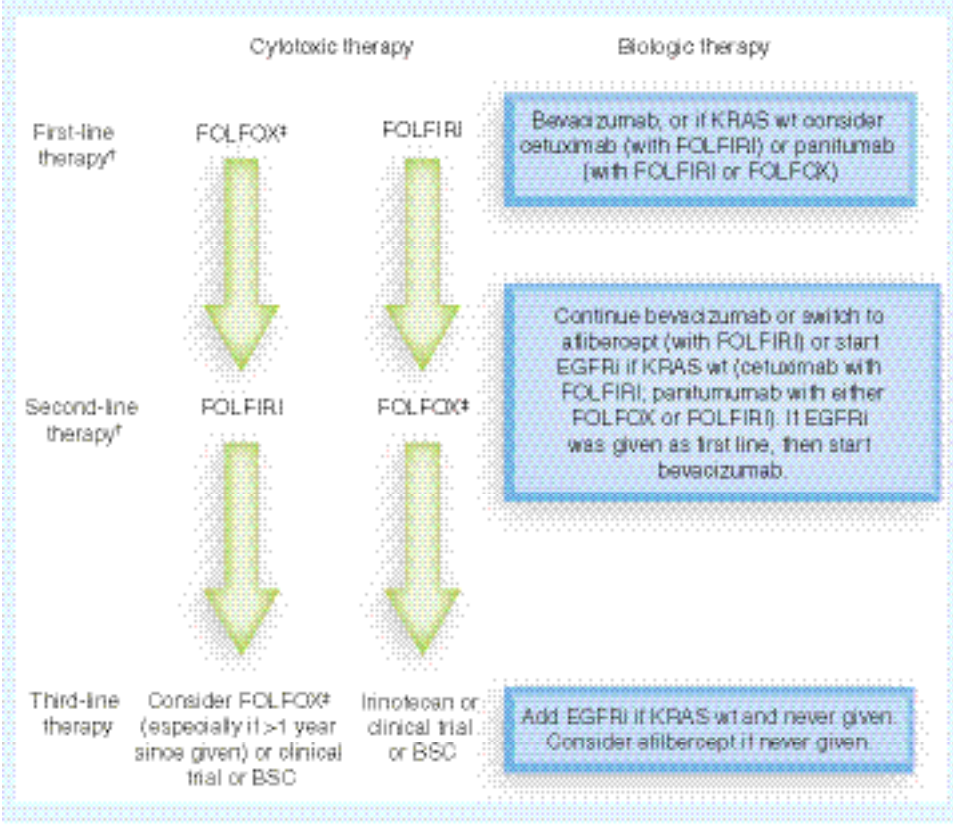

Figure 1. Proposed management of a patient with unresectable metastatic colorectal cancer.

†Can consider maintenance 5-FU with a biological agent if minimal disease burden and partial response/stable disease after 4–6 cycles of therapy.

‡5-FU can be substituted with capecitabine.

5-FU: 5-fluorouracil; BSC: Best supportive care; EGFRi: EGFR inhibitor; wt: Wild-type.

FOLFOX4 until progression (arm A) or FOLFOX7 for six cycles followed by maintenance 5-FU/LV for 12 cycles, at which point FOLFOX7 was reintroduced for six additional cycles (arm B). The median PFS and OS were not significantly different between the groups (PFS: 9.0 vs 8.7 months; OS: 19.3 vs 21.2 months) but stopping oxaliplatin after six cycles did lower the incidence of grade 3/4 toxicities, mainly during cycles 7–12. Approximately 40% of patients in arm B were retreated later with oxaliplatin due to early progression, death or treatment-related toxicity; however, of the 125 patients who were retreated, 70% had either tumor response or stabilization. However, since 30% of patients in arm A were eventually retreated with oxaliplatin off study, comparison between the study's two arms in isolating the benefits derived from oxaliplatin reintroduction are difficult to discern [42].

The COIN trial looked at administering FOLFOX/CAPEOX for 12 weeks and then randomizing patients to continuous chemotherapy versus a chemotherapy break with restarting chemotherapy on progression. Median OS was 15.8 months in continuous arm versus 14.4 months in the intermittent-chemotherapy arm (HR: 1.084; 80% CI: 1.008–1.165). Elevated platelet count >400.000/µl at baseline was associated with a poor survival on the intermittent-chemotherapy arm and a subgroup analysis identified patients with liver metastases only to benefit more from continuous chemotherapy (HR: 1.43; 95% CI: 1.03–1.97). Patients on the continuous chemotherapy arm had more toxicities, in particular grade 3 or worse hematologic toxicities and peripheral neuropathy [43].

Therefore, we believe it is reasonable to continue with 5-FU/LV or capecitabine maintenance therapy with bev after completion of six or more cycles of conventional FOLFOX or FOLFIRI with bev, depending on the individual patient's burden of disease and experience with toxicity. Patients should be closely monitored with repeat imaging every 2 months. Observation after six cycles is also a potential strategy in patients with low disease burden, who have had a good response to treatment and are compliant with an intensive follow-up schedule. Since patients with extensive peritoneal disease may have bowel obstruction as their first manifestation of progressive disease, we tend to be less comfortable with a surveillance-alone strategy in that subgroup. There are at least two ongoing clinical trials to further address the questions of maintenance therapy with a biologic agent versus observation alone following induction chemotherapy with an oxaliplatin-based regimen (CAIRO3 [105] and AIO KRK [106]). Maintenance therapy has been less well studied in cohorts of patients treated initially with FOLFIRI.

Experimental biological agents

The development of biological targeted therapies has been rapid in the past few years and, today, at least five novel agents are in Phase III trials. Over 50 Phase II trials are being conducted world wide with over 50 different targeted agents [44]. Data regarding selected agents that are further along in their development are presented below.

Regorafenib is a multityrosine kinase inhibitor (VEGFR1–3, PDGFR-β, TIE2, FGFR, KIT, PDGFR, RET), structurally comparable to sorafenib [43]. The results from the CORRECT trial were presented at the annual ASCO meeting in 2012. In total, 760 patients who had progressed on standard therapy were randomized in a two-to-one fashion to regorafenib or placebo. At the primary end point, OS was 6.4 months in the regorafenib group versus 5.0 months in the placebo group ($p < 0.00001$) with a median PFS of 1.9 versus 1.7 months in the two groups. *KRAS* mutational status did not predict response to regorafenib [45].

Ramucirumab is a human monoclonal antibody that inhibits VEGFR-2, thereby blocking the binding of VEGF to the receptor. It is currently being investigated in a Phase III trial as second-line therapy in combination with FOLFIRI with an estimated study completion date of April 2016 [107].

Brivanib is a tyrosine kinase inhibitor that targets VEGF- and FGF-signaling pathways. A Phase III trial with 750 *KRAS* wild-type patients randomized to cetuximab with either brivanib or placebo showed an improved median PFS (5.0 vs 3.4 months; $p < 0.0001$) but no significant change in OS [46].

Perifosine targets NF-κB, AKT and JNK had shown intriguing results in a Phase II trial, which led to an expedited FDA-approved mechanism to initiate a Phase III trial with results presented at the ASCO annual meeting in 2012. A total of 468 patients were randomized to capecitabine with perifosine or placebo. After 6.6 months of median follow up, median OS was 6.4 months in the combined group versus 6.8 months in the capecitabine-only group ($p = 0.15$), so no difference was observed between the two groups [47].

Treatment strategies for isolated liver metastasis

Approximately a third of patients with mCRC have isolated liver metastasis. Historically, approximately 10–15% of these patients have been considered candidates for resection and older studies reported a 5-year OS of 25–40% [48,49]. More recently, with multimodality therapy, resectability rates have increased to 20–30%, with a 5-year OS of approximately 33 and 25% of patients surviving more than 10 years. Hepatic resection is the treatment of choice for patients with isolated resectable liver metastasis, but other methods, including radiofrequency ablation, radioactive yttrium^{90} microspheres (SIR-spheres), hepatic intraaarterial chemotherapy and transarterial chemoembolization, are available. These modalities, however, have not been shown to improve OS.

Fong *et al.* published a clinical risk score to predict which patients would benefit most from surgery and found five factors to have a negative predictive value: <12 months from primary resection to liver metastasis; >1 tumor; node-positive primary; hepatic tumor >5 cm; and carcinoembryonic antigen level >200 ng/ml. The 5-year OS went from 16% if all of the factors were present to 40% with none of these factors present [50]. Although commonly cited, clinical risk scores are of limited clinical utility when choosing patients for surgery, particularly in the era of preoperative chemotherapy. It is generally agreed that patients with extensive unresectable extrahepatic disease, involvement of the hepatic artery, major bile ducts or main portal vein, celiac/aortic lymph node involvement, >70% liver involvement (or more than six segments involved or involvement of all three hepatic veins) or inadequate postresection functional reserve, would not be considered eligible for surgical resection upfront [51].

Resectable liver metastasis

It is still debated whether chemotherapy before resection of liver metastasis that are resectable upfront, will improve outcomes or not. The only Phase III trial addressing perioperative chemotherapy was the EORTC 40983 trial, which randomized 364 patients with up to four resectable liver metastasis to undergo surgery alone versus receiving 6 cycles of preoperative and postoperative FOLFOX4. Although absolute PFS (the primary end point) was increased in the chemotherapy group (by 9.2% in all resected patients; $p = 0.025$), the PFS curves parallel each other after a fall out of 9% of patients immediately following surgery suggesting that the 9% increase was due to patients who were not good operative candidates. Preoperative chemotherapy caused a median of 30% decrease in size of liver metastasis and 44% of patients had an objective response (4% CR, 40% PR). Postoperative complications were higher in the chemotherapy group (25 vs 16%) but did not affect postoperative mortality rates [52]. A recent report on the OS after a median follow up of 8.5 years showed no significant difference between the two groups [53].

While it is an important perioperative chemotherapy trial, Nordlinger's trial did not answer the question of whether patients with upfront resectable liver metastasis benefit from preoperative chemotherapy. Concerns of missing the 'window of opportunity' for surgery while administering chemotherapy are valid, although patients who progress on neoadjuvant chemotherapy are likely to have aggressive disease and surgery might therefore not provide benefit to them. It is also increasingly being recognized that preoperative chemotherapy can cause liver toxicities and, therefore, potentially limit the resectability of tumors and cause postoperative liver failure. Irinotecan-based therapy is

associated with an increased incidence of steatohepatitis and an increased 90 day mortality while oxaliplatin is associated with an increased risk of sinusoidal dilatation but not increased mortality [54]. The number of preoperative chemotherapy cycles should be limited to 12 weeks or less as more has been associated with more postsurgical complications, higher rates of reoperation and a longer hospital stay. An interval of less than 4 weeks between chemotherapy and resection has also been associated with increased complication rates [55]. Of note, patients who obtain a complete response on imaging after receiving preoperative chemotherapy will still require resections to achieve optimal outcomes as 83% are found to have residual microscopic disease [56].

Postoperative chemotherapy is commonly used, although it has not been clearly shown to improve survival, likely partly due to poor accrual to trials and published trials using outdated chemotherapy regimens. Two randomized trials (both closed prematurely due to poor accrual) showed better median PFS (28 vs 19 months; p = 0.058) with postoperative chemotherapy compared with observation and a trend towards better survival (62 vs 47 months; p =0.095) in a combined analysis of both trials [57].

FOLFIRI cannot be recommended as postoperative chemotherapy after liver resection as shown in a trial comparing FOLFIRI with 5-FU/LV, which demonstrated no significant change in median disease-free survival (22 vs 25 months) in the 306 patients treated [58]. Similarly, irinotecan has failed to demonstrate a benefit as adjuvant therapy in resected stage II/III CRC when compared with 5-FU alone. There are no good data on whether to include biological agents in the postoperative chemotherapy regimen. The current NCCN guidelines suggest conventional adjuvant therapy for stage II/III disease in patients with resected liver metastasis for a total of 6 months as an option [102].

It is our belief that if a patient has resectable disease (<4–6 liver metastasis) and is a good operative candidate, surgery should not be delayed to administer chemotherapy. Chemotherapy should be given preoperatively for any residual microscopic disease comparable to administration of chemotherapy after resection in stage III CRC.

■ Unresectable liver metastasis

Patients who present with metastatic disease isolated to the liver, but who are not deemed resectable, should be considered for conversion chemotherapy to obtain resectability with R_0 margins (R_0 margins are the most important predictive factor of PFS). In a study by Adam *et al.*, 184 patients underwent resection after receiving conversion chemotherapy (5-FU/LV, FOLFOX, FOLFIRI or FOLFIRINOX); the OS at 5 and 10 years was 33 and 27%, respectively [59].

Two studies have been conducted comparing FOLFOXIRI with FOLFIRI. Falcone *et al.* published a Phase III trial (GONO trial) in 244 patients with initially unresectable disease [15]. RR and R_0 resection rates were higher in the FOLFOXIRI arm compared with FOLFIRI (RR 60 vs 34%; p <0.0001; R_0 rates 36 vs 12%; p = 0.017) in patients with liver metastases only [15]. In the HORG trial, 283 patients were randomized to the same regimens with no difference in PFS and OS and no significant change in the rate of surgical resection or 10% in the patients treated with FOLFOXIRI and 4% in the patients treated with FOLFIRI (p = 0.08) [14]. These conflicting trial results were discussed further in the previous section 'Chemotherapy backbones'.

The addition of targeted therapies to improve rates of surgical resection is not of clear benefit. The Phase II CELIM trial investigated cetuximab in combination with either an oxaliplatin- or irinotecan-based regimen in initially unresectable patients. R_0 resection rates were high or 38 and 30% in the two groups, but as no comparison was made with a group without cetuximab, the benefit of adding it is not clear [60]. Bev only moderately improved resectability rates when given with FOLFOX/CAPEOX in the NO16966 trial or from 6.1% with chemotherapy alone to 8.4% in the combination arm [21]. Similarly, the CRYSTAL trial showed a modest increase in rate of surgery and R_0 resection in *KRAS* wild-type patients who received FOLFIRI with cetuximab versus FOLFIRI alone (surgery rate 7.9 vs 4.6%; p = 0.0633; R_0 resections 5.1 vs 2.0%; p = 0.0265), respectively [30]. Biologic agents can, therefore, be considered in addition to cytotoxic chemotherapy for conversion but should be explored further in trials to determine the effect better.

Personalized therapy

Fearon and Vogelstein described the molecular basis of CRC as a multistep process in 1990 [61] but even though 22 years have passed since, only three biological therapies that target this process have been approved. The search continues to try to find molecular markers and elucidate pharmacogenetics with the hope that these factors could help guide and individualize therapy. Even though gene expression profiling is available and does help determine prognosis, it has not been shown to impact therapy choices and, therefore, survival with the exception of *KRAS* status and EGFR-targeted therapy. Therefore, *KRAS* testing is the only molecular testing currently recommended in the NCCN guidelines (*BRAF* testing can be considered if *KRAS* is wild-type) [102].

Approximately 40% of all mCRC have mutations in codons 12, 13 or 61 of the *KRAS* gene [31,62,63], which predicts for a nonresponse to EGFR-targeted therapy. Patients with *KRAS* mutations should not be considered for EGFR-targeted therapy, although this might not be true for all *KRAS* mutations. A recent retrospective study from the CRYSTAL and OPUS studies showed improved RR and PFS in patients with tumors exhibiting the codon 13 (G13D) mutation who received cetuximab compared with those who did not receive cetuximab [64]. It is still debated whether *KRAS* mutations confer a worse prognosis than wild-type *KRAS*. A recently published updated analysis of the MRC COIN trial showed both *BRAF* and *KRAS* mutations to negatively impact survival compared with wild-type tumors (OS – BRAF mutation: 8.8 months; KRAS mutation: 14.4 months; all wild type: 20.1 months) irrespective of the therapy patients received [32]. *BRAF* mutations are detected in 5–10% of mCRC [65] and confer a poorer prognosis but do not predict independently whether patients respond to EGFR-targeted therapy in the first-line setting [30], although in the second-line setting this is less clear. VEGF is over expressed in approximately 50% of colon cancer and has some association to worse survival [66]. Even though this is the case, there are no good biological markers to indicate which patients will benefit the most from VEGF-targeted therapy. *KRAS* and *BRAF* mutational status do not predict benefit with bev [67].

Patients with mismatch repair deficiency characterized by microsatellite instability or Lynch syndrome, have been found to have a good prognosis in early-stage disease and do not appear to benefit from 5-FU adjuvant chemotherapy. Approximately 15% of early-stage CRC patients have microsatellite instability from epigenetic changes causing silencing of the mismatch repair genes through hypermethylation, but this appears to be less frequent or approximately 3.5% in patients with mCRC [68]. It is not clear whether these patients should be treated differently in the metastatic setting. A recently published study on hypermethylation of *TFAP2E* (gene encoding transcription factor AP-2 epsilon) showed this to be related to a decrease in RR to 5-FU based chemotherapy in mCRC and rectal cancer [69].

Intratumor heterogeneity has been shown to be a potential problem when using targeted therapies with up to 70% discordance between primary tumor and metastasis reported in patients with metastatic renal cell carcinoma [70]. Results in mCRC have been relatively consistent with a recent study showing >90% concordance between both primary and metastatic sites (84 patients) and different metastatic sites (31 patients) when mutations in *KRAS*, *NRAS*, *BRAF* and *PIK3CA* were tested. The exception to this was p53, which was more frequently mutated in metastatic versus primary tumors (53.1 vs 30.3%; p <0.001) [71].

Several different pharmacogenetic polymorphisms and their effects on chemotherapy responses and toxicities have been investigated. The UGT1A1*28 polymorphism was observed as homozygous in 9% of 520 patients tested on the N9741 study and was associated with an increased risk of grade 4 neutropenia in patients, irrespective of study arm (18% in the IFL group; 36% in the FOLFOX group; 55% in the IROX group) [72].

The discovery of deficiencies in dihydropyrimidine dehydrogenase, a rate-limiting step in 5-FU catabolism in the liver, has shed light on the severe and at times fatal 5-FU toxicities (diarrhea, severe myelosuppression) that are seen in 2–12% of patients. Dihydropyrimidine dehydrogenase deficiency prevalence is three-times higher in African–Americans when compared with other ethnicities [73].

Obese patients have historically been dose-reduced for a body-surface area >2.0 m^2. Recent evidence suggests that this does not need to be done and can negatively impact their OS as seen in the retrospective study by Chambers *et al.* [74]. In total, 54% of obese patients (BMI >30) were dose reduced compared with 16% of overweight and 4% of normal-weight patients in the FOCUS, FOCUS2 and COIN trials. Dose-reduced obese patients had significantly worse PFS at 1 year compared with fully dosed obese patients (PFS 14.8 vs 21.2%) and had a trend towards worse OS at 2 years (29.5 vs 35%; p = 0.152) [74].

Elderly patients & patients with poor performance status

Choosing chemotherapy regimens for the elderly (>70 years old) can be challenging as the risks and benefits of treatment must be weighed in the context of the estimated life expectancy. Even though 40% of CRC cases present in patients older than 75 years, this group is under represented in clinical trials. Elderly patients have age-related organ-function decline including liver- and kidney-function impairments, bone marrow suppression, increased incidence of cardiovascular disease and an increasing number of comorbid conditions that can all influence the choice of chemotherapy.

When giving 5-FU to the elderly, the de Gramont regimen has been shown to be very well tolerated, while the older Mayo Clinic regimen was associated with significantly more toxicities. A retrospective analysis of four clinical trials administering bimonthly FOLFOX4 in the adjuvant and metastatic setting, compared toxicities, PFS, RR and OS in

patients <70 versus ≥70 years of age. Elderly patients did not have an increased 60-day mortality and had an equal efficacy from chemotherapy with no significant differences in OS, PFS or RR. They did, however, have an increased rate of ≥grade 3 neutropenia (49 vs 43%; p = 0.04) and thrombocytopenia (5 vs 2%; p = 0.04).

Executive summary

Background
- Colorectal cancer is the second leading cause of cancer-related mortality in USA.
- A total of 20% present with metastatic disease.
- Incidence and mortality has decreased in the past 10 years, related to increasing use of screening methods and improvements in surgical and adjuvant therapy.

Chemotherapy backbones
- Single agents offer a median survival of 12–15 months, while doublet therapy has a median survival of 20–24 months when both oxaliplatin- and irinotecan-based regimens are given.
- 5-fluorouracil (5-FU) should be administered via the infusional regimen (22- or 46-h infusion) due to better response rates (RR) and less toxicities compared with bolus 5-FU.
- FOLFOX and FOLFIRI are equivalent first-line regimens.
- FOLFOXIRI should be used with caution as a first-line regimen due to conflicting trial results and increased toxicities but should be considered if the goal of therapy is to convert unresectable liver metastasis to resectable disease.

Established biological agents
- Aflibercept was US-FDA approved for use with FOLFIRI as a second-line therapy in August 2012.
- Initial studies showed bevacizumab to improve survival by 5–6 months but later trials have demonstrated less of an effect on survival or ranging from 2–6 months and improving RR by approximately 10%.
- EGFR-targeted therapy should only be given to patients with *KRAS* wild-type tumors (G13D *KRAS* mutations need further investigation).
- Cetuximab may have more synergistic effects and efficacy when combined with irinotecan or FOLFIRI rather than FOLFOX. It improves RR by 10–20% and overall survival (OS) by 3–4 months when combined with FOLFIRI.
- Panitumumab is a humanized antibody and has far less infusion reactions than cetuximab. It improves RR by 10–20% and OS by 2–4 months when combined with either FOLFIRI or FOLFOX.
- The use of two targeted therapies simultaneously has not been shown to be beneficial in Phase III trials and has been associated with shorter progression-free survival and OS in some studies.

Are chemotherapy holidays or reduced intensity maintenance therapies a safe option?
- 5-FU/leucovorin maintenance therapy is a reasonable approach after initial conventional FOLFOX or FOLFIRI for 6 cycles.
- Close observation following conventional 6 cycles of FOLFOX or FOLFIRI with repeat imaging every 2 months is an option if the patient has a low burden of disease.

Experimental biological agents
- Regorafenib is furthest along in clinical trials and is expected to be reviewed by the FDA in 2012.
- Brivanib and perifosine, although initially promising agents, failed to show improvement in OS in recent reports.

Treatment strategies for isolated liver metastasis
- 5- and 10-year OS rates are 33 and 25% in properly selected liver resection candidates, respectively.
- There is no good data to support preoperative chemotherapy in patients with upfront resectable liver metastasis.
- Patients who get conversion chemotherapy should have the most aggressive regimen they can tolerate (preferably FOLFOXIRI) to optimally improve responses and resection rates.

Personalized therapy
- *KRAS* mutations are found in 40% of metastatic colorectal cancer (mCRC).
- *BRAF* mutations are found in 5–10% of mCRC cases and are associated with a poor survival.
- VEGF is overexpressed in 50% of mCRC tumors, there are no good biomarkers to predict which patients benefit the most from VEGF-inhibitor therapy.
- Obese patients should probably not be dose reduced based on a high body surface area alone as it has been associated with worse survival.

Elderly patients and patients with poor performance status
- Elderly patients (>70 years old) are under represented in clinical trials.
- Elderly patients with good performance status (PS; 0–1) have been shown to benefit from chemotherapy, almost equally so to younger patients.
- Patients with a PS of 2 could be considered for chemotherapy if it is related to the cancer, patients with a PS 3–4 should not be given chemotherapy.

The rates of nausea, vomiting, diarrhea, infection or neurologic adverse events including neuropathy were not increased and treatment-related death was not increased in the elderly [75]. Of note, only 16% of patients enrolled onto these four trials were aged ≥70 years so these results should be applied cautiously when making treatment decisions.

The MRC FOCUS2 trial enrolled 459 patients who were considered to be unfit for full-dose first-line chemotherapy (due to advanced age [29%], frailty [32%] or both [38%]) and randomized them in a 2 × 2 design to short-term infusional 5-FU/LV or capecitabine with or without oxaliplatin (5-FU/LV, FOLFOX, capecitabine or CAPEOX). The chemotherapy starting doses were 80% of conventional doses with escalation to full dose in 6 weeks if tolerated. The median age was 74 years (range 35–87) and a third of the patients had an Eastern Cooperative Oncology Group performance status (PS) of 2. The addition of oxaliplatin to the fluoropyrimidine did improve RR (35 vs 13%; p <0.0001) and provided a nonsignificant improvement in PFS (5.8 vs 4.5 months; p = 0.07). The addition of oxaliplatin was not associated with increased ≥ grade 3 toxicity but capecitabine did increase toxicities when compared with 5-FU alone (40 vs 30%; p = 0.03) [76].

The efficacy of adding irinotecan to 5-FU was explored in a pooled analysis of four studies by Folprecht *et al.* Patients ≥70 years old had a significant benefit in response rate (50.5 vs 30.3%) and PFS (9.2 vs. 7.0 months). A trend towards OS was seen (17.6 vs 14.2 months; p = 0.15) whereas there was a significant OS benefit in those <70 years old [77].

Bev should be considered as a first-line treatment with a fluoropyrimidine-based regimen but in the elderly it has been associated with a higher incidence of arterial thromboembolic events [78] and hypertension, so the decision to add bev should be weighed carefully in each patient. Both cetuximab and panitumumab have been found to be efficacious and relatively well tolerated in small cohorts of elderly patients [79]. Patients ≥65 years had a similar PFS as those <65 years in a Phase III trial comparing panitumumab with best supportive care [80].

Resection of liver metastasis in the elderly seems to be a safe option in fit patients. The LiverMetSurvey registry in Europe showed a 3-year survival rate of 57% in patients >70 years with a 60-day perioperative mortality of 4%, which is relatively comparable to outcomes in patients <70 years old with 60-day mortality being 3.8 versus 1.6% in the two age groups and 3-year OS 57 versus 60%, respectively [81].

It is generally accepted that frail older patients with significant functional impairment and/or a PS of 3–4 should receive palliative care support with focus on quality of life rather than chemotherapy administration.

Most Phase III trials enrol a small fraction of patients with poor PS with <10% of patients having a PS of 2. Regardless of age, PS does influence survival and the ability to tolerate chemotherapy regimens as explored in a pooled analysis of nine trials with 6286 patients receiving first-line therapy. Compared with patients with PS of 0–1, patients with PS of 2 (a total of 509 patients) had a significantly higher 60-day all-cause mortality (12 vs 2.8%; p <0.0001), shorter median OS (8.5 vs 17.3 months; p <0.0001), shorter median PFS (4.9 vs 7.6 months; p <0.0001), lower RR (32 vs 44%; p <0.0001) and higher rates of ≥grade 3 nausea and vomiting [82]. If the poor PS is entirely related to the cancer, treatment should be considered, otherwise caution should be used and single agents or no chemotherapy might be more reasonable options than attempting doublet chemotherapy.

Future perspective

It is evident that the research conducted during the first decade of the 21st century will be very focused on finding targets and creating targeted therapies and it is expected that several such therapies will get approval in the next 5–10 years. It is important to keep in mind that, so far, such therapies have only improved survival by a few months at most. Even though this is a positive development we must take a multipronged approach to significantly advance the field. For example, improvement in liver resections for isolated liver metastasis has significantly improved survival in selected patients and the benefits of improved surgical techniques have outstripped those of targeted therapies to date. Furthermore, identifying markers that might predict response and toxicities from current cytotoxic and biologic therapies is a worthy goal.

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