



Capecitabine in colorectal cancer

Capecitabine is an oral pro-drug that is converted, via a three-step enzymatic pathway, into the cytotoxic drug 5-fluorouracil. 5-fluorouracil has an established role in the management of patients with colorectal cancer in the adjuvant and advanced disease settings. In this article we review the available clinical data for the use of capecitabine as a single agent or in combination with other cytotoxic drugs (e.g., irinotecan or oxaliplatin), or targeted anticancer treatment (e.g., anti-EGF receptor or VEGF therapy), in patients with early-stage or advanced colorectal cancer.

KEYWORDS: 5FU ■ capecitabine ■ colorectal cancer ■ combination chemotherapy ■ oral chemotherapy

Background to colorectal cancer

Colorectal cancer is one of the three most commonly diagnosed cancers in the UK and western countries. A total of 13% of all cancers and 11% of all cancer-related deaths in the UK are attributable to colorectal cancer. This constitutes approximately 36,000 new patients and 16,000 deaths per year [1].

Systemic treatment options for patients with colorectal cancer have expanded rapidly over the last 10 years, with consequent improvements in the survival of those with either early-stage or advanced disease. For many years intravenous 5-fluorouracil (5-FU), given latterly in combination with the reduced folate leucovorin (LV) [2] and often as an infusion rather than a bolus, was the only cytotoxic agent with significant activity in colorectal cancer. 5-FU results in response rates of 15–25% in the metastatic setting and improves overall survival (OS) over best supportive care by 3.7 months [3]. The introduction of irinotecan and oxaliplatin into clinical practice in the late 1990s has resulted in a significant improvement in both response rates and survival in patients with metastatic disease [4–7]. OS of 15–20 months has been routinely observed in large randomized trials performed over the last 5 years. Targeted anti-cancer agents such as bevacizumab, a monoclonal antibody that binds to and blocks the activity of VEGF, has shown activity in colorectal cancer, and when added to combination chemotherapy further improved OS to beyond 20 months [8]. Panitumumab and cetuximab belong to a second family of monoclonal antibodies, targeting the EGF receptor (EGFR), and have shown promising activity as single agents [9] or in combination with chemotherapy [10].

Chemotherapy also has an established role in the adjuvant setting, with 5-FU/LV resulting in a 25% reduction in the risk of death for patients with stage 3 tumors [11,12], and also providing a modest benefit for those with stage 2 disease [13]. The addition of oxaliplatin to 5-FU in patients with stage 3 disease provides a further incremental improvement in disease-free survival (DFS) and OS [14,15].

The toxicity of 5-FU chemotherapy varies dependent upon the administration schedule, with hematological toxicity and diarrhea more commonly seen with bolus regimens, and hand-foot syndrome (HFS) more common with infusional schedules [16]. Infusional 5-FU-based regimens, such as the LV5FU2 regimen (LV 200 mg/m², 5-FU bolus 400 mg/m² and 5-FU 600 mg/m² 22-h infusion days 1 and 2, q14) have shown improved response rates and progression-free survival (PFS), as well as reduced rates of severe toxicity compared with bolus 5-FU regimens such as the Mayo clinic regimen (LV 20 mg/m², 5-FU bolus 425 mg/m², days 1–5, q28) [17]. Chemotherapy regimens of bolus 5-FU and irinotecan proved toxic, with high rates of severe toxicity and treatment-related deaths noted due to overlapping toxicity profiles [18,19]. The lower rates of severe toxicity seen with infusional 5-FU has made it the preferred drug for combination chemotherapy schedules. Schedules of 5-FU and oxaliplatin (FOLFOX) and 5-FU and irinotecan (FOLFIRI) have been developed based upon the LV5FU2 regimen. FOLFOX and FOLFIRI have similar efficacy [20,21] and have become internationally accepted as standard first-line chemotherapy options.

**Michael S Braun &
Chris J Twelves[†]**

[†]Author for correspondence:
Section of Oncology & Clinical
Research, Leeds Institute of
Molecular Medicine,
St. James's Institute of
Oncology, St. James's
University Hospital, Leeds, UK
Tel.: +44 113 206 8186
Fax: +44 113 206 8474
c.j.twelves@leeds.ac.uk

future
medicine part of fsg

Although infusional 5-FU regimens have become a standard of care they are cumbersome and require a central venous catheter to administer chemotherapy. These devices are associated with a variety of problems at the time of insertion (e.g., bleeding and pneumothorax), as well as longer term complications such as infection and thrombophlebitis. Additionally the two-weekly LV5FU2 regimen, and the original FOLFOX and FOLFIRI regimens, required the patient to attend for chemotherapy on day 1 and again on day 2 of each cycle. This was inconvenient for the patient and modified regimens omitting the day 2 bolus 5-FU dose have been developed [22,23].

In colorectal cancer, oral fluoropyrimidines dispense with the need for a central venous catheter and an infusion pump device. 5-FU has poor oral bioavailability, which has resulted in intravenous administration being preferred [24]. However, for the reasons outlined above, the development of oral fluoropyrimidines to safely and effectively replace infusional 5-FU has been an attractive prospect. Previous studies have shown that more than 80% of cancer patients would prefer oral chemotherapy, provided this is not at the expense of efficacy. However, oral therapy is not without problems. Under- and over-compliance has been documented in patients receiving oral chemotherapy, with potential implications for efficacy or toxicity, respectively [25]. The UK National Patient Safety Agency (NPSA) produced a Rapid Response Report on the risks of incorrect dosing of oral chemotherapy in January 2008 [101]. Between November 2003 and July 2007, the NPSA received reports of three deaths and 400 patient safety incidents involving oral chemotherapy. The prominence of capecitabine (42% of such safety incidents) probably reflects, at least in part, its widespread use and relatively recent introduction into clinical practice compared with other oral cytotoxics.

Capecitabine

Capecitabine (Xeloda®, Roche, Basel, Switzerland) is the best established of several oral fluoropyrimidines that have been developed as an alternative to intravenous 5-FU. After being absorbed intact, a three-step enzymatic process converts capecitabine into 5-FU, with the final step catalyzed by the enzyme thymidine phosphorylase (TP) (FIGURE 1). TP is often over-expressed in human tumors [26], so capecitabine has the potential advantage of being preferentially converted into 5-FU within tumor cells [27–29].

■ Metastatic colorectal cancer

Single-agent activity

Initial Phase I studies with capecitabine examined three treatment schedules that were then evaluated in a randomized Phase II study: continuous administration (1331 mg/m²/day), intermittent administration (2510 mg/m²/day on days 1–14, treatment break on days 15–21) and an intermittent schedule plus LV (capecitabine 1657 mg/m²/day, LV 60 mg/day) [30]. A total of 109 patients were randomized. All three schedules had similar activity levels, with response rates of 21, 24 and 23%, respectively. The main toxicities for all three schedules were nausea, diarrhea and HFS, but hematological toxicity was minimal. The patients receiving LV were administered a lower dose of capecitabine, but had the highest rates of grade 3 diarrhea and HFS. The total dose of capecitabine delivered per cycle in the intermittent arm was significantly higher than in the continuous or LV-treated arms (387 g compared with 307 and 218 g, respectively). Based on these results, the intermittent schedule was selected for further investigation due to the higher total dose of capecitabine delivered, the planned treatment breaks and acceptable levels of grade 3 and 4 toxicity.

Two key randomized Phase III trials in Europe [31] and North America [32] with identical protocols and statistical design compared the Mayo Clinic regimen with the intermittent capecitabine schedule (2500 mg/m²/day, day 1–14, q21). They clearly met their primary objective of showing capecitabine to be equivalent to 5-FU in terms of response rate, establishing it as a standard therapy in the metastatic setting. In a pre-planned integrated analysis of these trials, capecitabine use was associated with an improved response rate (26 vs 17%; $p = 0.00002$) and equivalent PFS or OS [33].

In these studies capecitabine was associated with significantly lower rates of severe diarrhea, stomatitis, nausea, neutropenia and neutropenic sepsis than the Mayo Clinic regimen. HFS was the only toxicity seen more frequently with capecitabine, being severe in 16–18% of patients receiving capecitabine and less than 1% of those receiving bolus 5-FU/LV. Although the Mayo clinic regimen was considered 'standard' for regulatory purposes when these trials were performed, it is accepted as causing high rates of hematological and gastrointestinal (GI) toxicity, and is infrequently used in UK practice. There has been no formal comparison of standard capecitabine with infusional 5-FU regimens, but recent data from the UK Medical Research

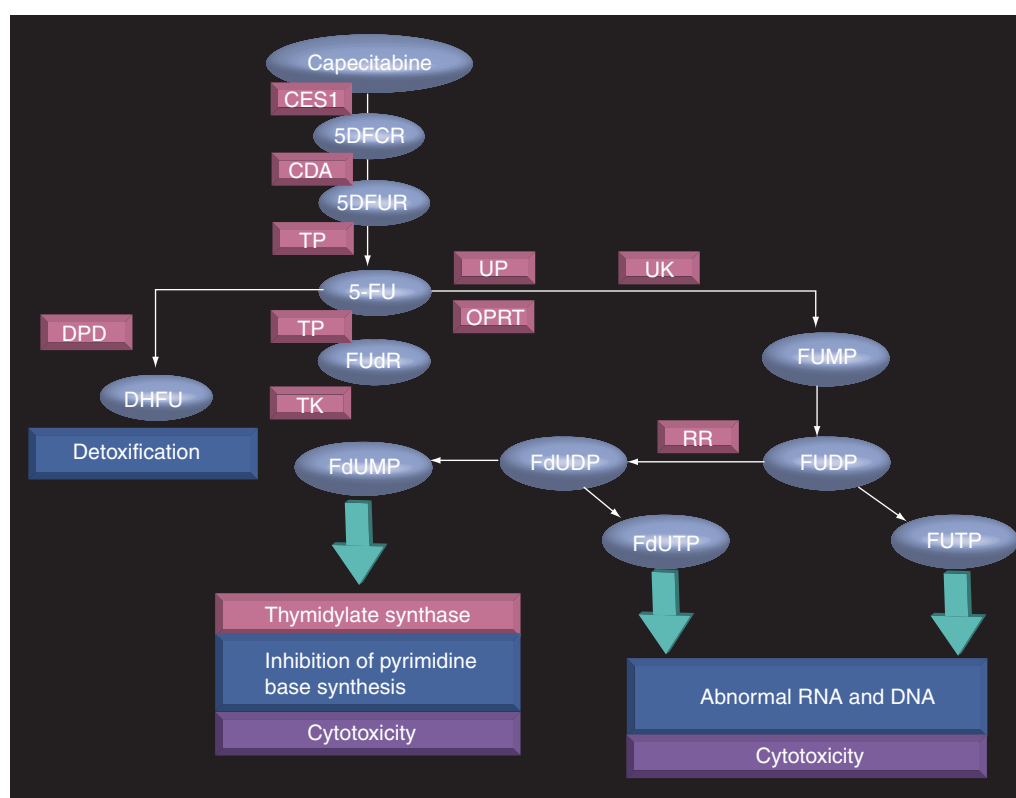


Figure 1. Metabolism of 5-fluorouracil and capecitabine. Capecitabine is converted into 5-FU via a three-step enzymatic process. The initial steps involving carboxylesterase-1 converts capecitabine into 5-deoxy-5-fluorocytidine. Cytidine deaminase then converts DFCR into 5DFUR. 5DFUR is then converted into 5-FU by thymidine phosphorylase. 5-FU is subsequently converted into three main metabolites: (1) An inactive metabolite, dihydrofluorouracil, is formed by the action of dihydropyrimidine dehydrogenase; (2) Two active metabolites are also formed, (a) fluorodeoxyuridine monophosphate is formed from 5-fluoro-2-deoxycytidine by the action of thymidine phosphorylase and thymidine kinase and can inhibit thymidylate synthase activity, (b) the metabolites fluorodeoxyuridine triphosphate and fluorouridine triphosphate can be misincorporated into DNA and RNA, respectively, resulting in instability and cytotoxicity.

5-FU: 5-fluorouracil; 5DFUR: 5-deoxy-5-fluorouridine; CDA: Cytidine deaminase; CES1: Carboxylesterase-1; DFCR: 5-deoxy-5-fluorocytidine; DHFU: Dihydrofluorouracil; DPD: Dihydropyrimidine dehydrogenase; FdUDP: Fluorodeoxyuridine diphosphate; FdUMP: Fluorodeoxyuridine monophosphate; FdUTP: Fluorodeoxyuridine triphosphate; FUDP: Fluorouridine diphosphate; FdUR: 5-fluoro-2-deoxycytidine; FUMP: Fluorouridine monophosphate; FUTP: Fluorouridine triphosphate; OPRT: Orotate phosphoribosyl transferase; RR: Ribonucleotide reductase; TK: Thymidine kinase; TP: Thymidine phosphorylase; TS: Thymidylate synthase; UK: Uridine kinase; UP: Uridine phosphorylase.

Council (MRC) FU, Oxaliplatin, CPT-11: Use and Sequencing – 2 (FOCUS2) trial provide interesting insights. FOCUS2 assessed the use of capecitabine or modified LV5FU2 (both given at a 80% of standard dose) in elderly or frail patients – the primary end point being quality of life. Both fluoropyrimidines were given with or without oxaliplatin in a 2 × 2 design [34]. With 460 patients randomized, there was no significant difference between infusional 5-FU and capecitabine in terms of response rate ($p = 0.98$) or PFS (hazard ratio [HR] = 1.00; $p = 0.96$). Lower rates of grade 3/4 nausea (1 vs 5%; $p = 0.032$), diarrhea (5 vs 13%; $p = 0.003$), lethargy (8 vs 14%; $p = 0.037$), HFS (0 vs 5%;

$p = 0.001$) and any grade 3/4 toxicity (27 vs 39%; $p = 0.006$) were observed for the modified LV5FU2 regimen in comparison with capecitabine, but there was no difference in quality of life assessed using the EORTC QLQ-C30.

Meta-analysis of trials using mainly bolus 5-FU regimens has shown that coadministration of LV improves response rate and OS compared with 5-FU alone [2]. LV also results in increased toxicity and a lower maximum tolerated dose (MTD) of 5-FU. Likewise, in the randomized capecitabine Phase II study described previously, increased rates of toxicity were seen in combination with LV, even though the dose of capecitabine itself was lower (1657

and 2510 mg/m²/day, respectively). This may have consequences for patients previously treated with 5-FU/LV who subsequently change onto a capecitabine-containing regimen. The results of the recently published Patient Preference in Adjuvant Colorectal Therapy (PACT) trial supports this notion [35]. Patients were randomized to receive a 6-week period of 5-FU/LV (425 mg/m² 5-FU/45 mg LV) or capecitabine (1250 mg/m² twice a day, days 1–14), then crossed over to the alternative therapy for a further 6 weeks; at that point they chose which regimen to receive for the final 12 weeks of planned adjuvant therapy. The trial closed early due to excessive toxicity in patients receiving capecitabine following 5-FU/LV. Five of the 18 patients (28%) receiving capecitabine first experienced grade 3/4 toxicity, but this was seen in 11 of 14 (79%) of patients who received capecitabine after 5-FU/LV. The 5-FU regimen used in this study provides comparable dose intensity with relatively low rates of toxicity compared with alternative 5-FU regimens [36]. This probably increases the apparent difference in toxicity observed between 5-FU and capecitabine. Nevertheless, the toxicity experienced with capecitabine following 5-FU/LV in PACT remains unexpectedly high.

Differences in the tolerability of capecitabine and 5-FU between patients treated in North America, Europe and Asia have been the subject of much speculation and were recently confirmed [37]. In both the metastatic and adjuvant settings, North American colorectal cancer patients treated with either capecitabine or bolus 5FU experienced increased rates of grade 3/4 toxicities. The reason for this difference is unknown [37], but dietary supplementation of folate [38] may be important.

In combination with oxaliplatin

Several regimens have been developed combining capecitabine with oxaliplatin. The XELOX regimen (oxaliplatin 130 mg/m², day 1; capecitabine 1000 mg/m² twice a day, days 1–14, q21) [39,40] has been established as safe and effective in Phase I and II studies. In the Phase II study, 96 patients received XELOX, with 53 responders (response rate: 55%), and encouraging time-to-progression (TTP) and OS times (7.7 and 19.5 months, respectively). Toxicity was manageable, with oxaliplatin-related neurotoxicity the most frequently observed grade 3/4 toxicity.

A randomized Phase II study of 147 patients, the Three Regimens of Eloxatin Evaluation (TREE-1) trial, combined oxaliplatin with different fluoropyrimidine partners: infusional 5-FU

(modified FOLFOX-6), bolus 5-FU (bFOL; oxaliplatin 85 mg/m² day 1 and 15, LV 20 mg/m² followed by bolus 5-FU 500 mg/m² days 1, 8 and 15, q28), and capecitabine (CapeOx; oxaliplatin 130 mg/m² day 1, capecitabine 1000 mg/m² twice a day, days 1–14, q21) [41]. The subsequent TREE-2 study assessed the addition of bevacizumab to this chemotherapy. In TREE-1, grade 3/4 toxicity during the first 12 weeks of treatment was seen in 67% of CapeOx and 59% of FOLFOX-6 patients, with response rates of 27 and 41%, and PFS of 5.9 and 8.7 months, respectively. However, TREE-1 was not powered to make statistical comparisons, and several well-designed, prospective, randomized Phase III studies have subsequently demonstrated noninferiority (albeit with differing statistical limits) of capecitabine and infusional 5-FU in combination with oxaliplatin.

The largest such study is XELOX-1 (NO16966A) [42], which was designed to assess whether XELOX was noninferior to the standard FOLFOX4 regimen as first-line treatment for metastatic colorectal cancer. After 634 patients had been randomized, the trial design was altered to a 2 × 2 factorial design incorporating a second randomization to bevacizumab or placebo. A further 1401 patients were randomized, giving a total of 2034 patients randomized overall. An interaction between bevacizumab and the efficacy of the XELOX and FOLFOX chemotherapy regimens was excluded, allowing data for the two XELOX regimens (± bevacizumab) and the two FOLFOX regimens (± bevacizumab) to be pooled. The primary end point of the study was noninferiority of PFS; this with defined as the upper limit of the 97.5% confidence interval (CI) of the HR for PFS being less than 1.23. The prespecified criteria for noninferiority were met, with median PFS of 8.0 and 8.5 months for XELOX and FOLFOX-4, respectively (HR: 1.04; 97.5% CI: 0.93–1.16). Additionally, no major differences were noted for the secondary end points of response rate and OS. The overall burden of toxicity was similar between the two treatments. The XELOX regimen had higher rates of grade 3/4 diarrhea (20 and 11%, respectively) and grade 3/4 HFS (6 and 1%), but FOLFOX-4 was associated with higher rates of neutropenia (44 and 7%), febrile neutropenia (4.8 and 0.9%) and grade 3/4 thromboembolic complications (6.3 and 3.8%).

Two smaller Phase III studies, with less statistical power than NO16966A, have also compared XELOX with 5-FU and oxaliplatin in the first-line setting [43,44]. Ducreux *et al.*

randomized 306 patients to XELOX or FOLFOX-6; response rates, the primary end point, were 42 and 46%, respectively [43]. This satisfied the predefined criteria for noninferiority for response rate, with PFS (9.3 vs 9.7 months) and OS (19.9 vs 18.4 months) also very similar for the two arms. In the second study, Diaz-Rubio *et al.* randomized 348 patients to receive XELOX or FUOX (5-FU 2250 mg/m² infusion over 48 h on days 1, 8, 15, 22, 29 and 36, plus oxaliplatin 85 mg/m² on days 1, 15 and 29 every 6 weeks) [44]. The primary end point of TTP was 8.9 months for XELOX and 9.5 months for FUOX, and the wide 95% CI exceeded the prespecified inferiority margin so noninferiority could not be concluded.

The second-line NO16967A study [45] randomized 627 patients between XELOX and FOLFOX-4, with TTP the primary end point. With a median TTP of 4.8 months for XELOX and 4.7 months for FOLFOX4, XELOX was judged noninferior to FOLFOX; OS and grade 3/4 adverse events were also similar between the two groups.

The CAPOX regimen (oxaliplatin 70 mg/m², days 1 and 8 and capecitabine 1000 mg/m², twice a day, days 1–14, q21), is an alternative to XELOX. CAPOX was compared with FUFOX (oxaliplatin 50 mg/m², folinic acid 500 mg/m², 5-FU 2000 mg/m² as 22-h infusions on days 1, 8, 15 and 22 every 5 weeks) by the German AIO group in a randomized trial of 476 chemo-naïve patients [46]. Median PFS times for CAPOX and FUFOX were 7.1 and 8.0 months, respectively (HR: 1.17, 95% CI: 0.96–1.43), but the predefined criteria for noninferiority were not satisfied. The median OS times for CAPOX and FUFOX were 16.8 and 18.8 months, respectively ($p = 0.26$).

These trials show that capecitabine in combination with oxaliplatin, in particular the XELOX regimen, is associated with similar efficacy and toxicity as combinations of 5-FU and oxaliplatin. A pooled analysis of a number of these trials showed noninferiority of PFS (HR: 1.05; $p = 0.25$) and OS providing further support for this conclusion [47]. Combination chemotherapy with XELOX, or alternative regimens, and targeted agents such as bevacizumab are likely to be increasingly used. Combining one or more targeted agents to overcome mechanisms of chemotherapy resistance and improve treatment efficacy is a promising strategy. However, as is discussed later, preliminary data from studies suggest that in some circumstances this approach may actually

increase rates of toxicity and shorten survival times in patients receiving combinations of targeted agents [48,49].

In combination with irinotecan

Several studies of combination chemotherapy with irinotecan and capecitabine have highlighted concerns over efficacy and toxicity [50,51]. The Bolus, Infusional, or Capecitabine with Camptosar-Celecoxib Trial (BICC-C) study randomized patients to FOLFIRI (irinotecan 180 mg/m² day 1, 5-FU 400 mg/m² bolus, 5-FU 600 mg/m² 22-h infusion on days 1 and 2, LV 200 mg/m² days 1 and 2, q14), bolus irinotecan and 5-FU (mIFL, irinotecan 125 mg/m², LV 20 mg/m², 5-FU bolus 500 mg/m², days 1 and 8, q21) and capecitabine and irinotecan (irinotecan 250 mg/m² on day 1, capecitabine 1000 mg/m² twice daily, days 1–14, q21) [50]. After 430 patients had been randomized, the capecitabine-containing arm was discontinued due to increased rates of grade 3/4 toxicity (nausea and vomiting, diarrhea, dehydration and HFS) and significantly shorter PFS than FOLFIRI (5.8 vs 7.6 months; $p = 0.015$). The same capecitabine/irinotecan (CAPIRI) regimen was also assessed in the EORTC 40015 trial, which aimed to demonstrate noninferiority with the FOLFIRI regimen [51]. After 85 patients had been randomized, the trial was stopped due to safety concerns. Six deaths, five thought to be treatment-related, were noted in the capecitabine arm compared with two deaths in the FOLFIRI arm. The combined frequency of grade 3/4 toxicity events was higher for CAPIRI than FOLFIRI (74 vs 49%), with diarrhea the most common severe toxicity experienced with CAPIRI. A number of the patient deaths in this trial were attributed to diarrhea and/or thrombo-embolic phenomena. CAPIRI also appeared to have inferior PFS to FOLFIRI (5.85 vs 9.6 months). Both these trials included a randomization to receive celecoxib or placebo, but there is no suggestion from the data presented thus far that celecoxib contributed to the toxicity of these regimens.

Interestingly, these problems echo those seen with bolus 5-FU in combination with irinotecan, where deaths due to gastrointestinal toxicity, neutropenic sepsis and thromboembolic phenomena have been noted [18,19]. However, the large randomized Phase III Capecitabine, Irinotecan, Oxaliplatin (CAIRO) trial comparing first-line combination chemotherapy to sequential administration of the same drugs used first-line CAPIRI in one of the treatment arms, and no efficacy or safety concerns were noted [52].

The AIO study presented at ASCO in 2008 also suggests there may be a place for capecitabine in combination with irinotecan [53]. A total of 255 patients received bevacizumab 7.5 mg/kg with either capecitabine (800 mg/m²/day for 14 days) plus irinotecan (200 mg/m²) or XELOX; treatment was repeated 3-weekly. Efficacy of the irinotecan and oxaliplatin-based regimens was very similar in terms of the primary end point of 6-month PFS (84 and 78%, respectively), median PFS (12.5 and 9.9 months) and response rate (55 and 54%); grade 3/4 diarrhea was seen in both arms (15 and 19%), but neuropathy only in the oxaliplatin arm (23%). This suggests that by modifying the dose capecitabine and irinotecan can be combined effectively.

Combinations with targeted agents

The targeted agents that have been evaluated in patients with colorectal cancer are the monoclonal antibodies bevacizumab [8], targeting VEGF, and cetuximab [10] and panitumumab [9], both directed at the EGF receptor.

The randomized Phase II TREE-2 study [41] assessed the addition of bevacizumab to the three TREE-1 regimens (mFOLFOX-6, bFOL and CapeOx, with capecitabine dose reduced from 1000 to 850 mg/m²) in 223 patients. CapeOx and mFOLFOX-6 were very similar with respect to grade 3/4 toxicity (56 and 59%), response rates (46 and 52%) and TTP (10.3 and 9.9 months).

The much larger Phase III XELOX-1 study, described above in the context of comparing XELOX to FOLFOX-4, recruited a total of 1401 patients after it had been modified to include a randomization to bevacizumab or placebo [54]. No interaction between the fluoropyrimidine used and the benefit of bevacizumab was noted by an interaction test. In the trial as a whole the addition of bevacizumab to chemotherapy (FOLFOX-4 and XELOX arms pooled) resulted in an improvement in PFS from 8.0 to 9.4 months (HR: 0.83; 97.5% CI: 0.72–0.95). In contrast to previous studies of bevacizumab, the improvement in OS did not reach statistical significance (21.3 vs 19.9 months, HR: 0.89; 97.5% CI: 0.76–1.03). A planned subset analysis of the FOLFOX-4- or XELOX-treated patients was subsequently performed. A significant improvement in PFS amongst patients receiving XELOX and bevacizumab, compared with placebo, was noted (HR: 0.77; 97.5% CI: 0.63–0.94), but no difference in PFS was noted for FOLFOX-4 ± bevacizumab (HR: 0.89; 97.5% CI: 0.73–1.08). An exploratory analysis suggested that patients

randomized to FOLFOX-4 who had not received prior adjuvant therapy may benefit from bevacizumab, but not those who had received adjuvant treatment; whether this effect is real or not remains unknown. The study also looked specifically at the safety of bevacizumab, but no safety concerns for its use in combination with XELOX were noted.

Combining targeted agents given with chemotherapy is an attractive approach. The CAIRO2 trial investigated targeting both the VEGF and EGFR pathways in patients randomized to receive XELOX and bevacizumab with or without cetuximab [55]. Combining several targeted agents to overcome mechanisms of resistance to chemotherapy is an attractive proposition. A manageable increase in the overall incidence of grade 3/4 toxicity events was noted in the cetuximab arm (81 vs 72%; $p = 0.03$). This was largely due to increased rates of skin and nail toxicity, but the rate of other hematological and nonhematological toxicities did not vary significantly. Efficacy data were presented at ASCO 2008 [48]. Surprisingly, PFS was significantly shorter in patients randomized to receive cetuximab (9.6 and 10.7 months, respectively). *RAS* genotyping was performed on the majority of tumors; the negative impact of cetuximab was seen in patients whose tumors carried *KRAS* mutations, but not those that were wild-type ($p = 0.04$ and $p = 0.1$, respectively). The Panitumumab Advanced Colorectal Cancer Evaluation Study (PACCE) randomized patients receiving chemotherapy (FOLFOX or FOLFIRI) and bevacizumab to receive panitumumab, a fully humanized anti-EGFR monoclonal antibody. PACCE was discontinued prematurely due to excessive toxicity and reduced PFS in the panitumumab-containing arm [49]. The similar results of CAIRO2 and PACCE suggest that there may be problems combining VEGF- and EGFR-targeted agents, and support the careful evaluation of each combination prior to widespread use.

■ Capecitabine in the adjuvant setting

The Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial randomized patients with stage 3 colon cancer to receive the Mayo Clinic bolus 5-FU/LV regimen or capecitabine (1250 mg/m², twice a day, days 1–14, q21) [56]. The primary end point of the trial was 3-year DFS and the study was powered to assess noninferiority of capecitabine over 5-FU. A noninferiority margin was defined by a HR with an upper limit

of 1.25 for DFS; a separate equivalence analysis was performed using a HR with an upper limit of 1.20. In the event of equivalence being shown, a test for superiority of capecitabine over 5-FU was planned.

The 3-year efficacy analysis demonstrated a HR of 0.87 (0.75–1.00) for capecitabine compared with 5-FU, meeting the prespecified criteria for both noninferiority and equivalence; results for OS were similar, with a HR of 0.84 (HR: 0.69–1.01). These data were recently updated with median follow-up of 6.8 years, and confirmed that capecitabine was at least equivalent to 5-FU, with a trend to superiority. With further follow-up DFS was 60.8 and 56.7% for capecitabine and 5-FU, respectively; this confirmed equivalence with a HR of 0.88 (95% CI: 0.77–1.01; $p = 0.0001$), although this improved DFS it did not reach statistical significance ($p = 0.07$). Similarly, OS was 71.4 and 68.4% for capecitabine and 5-FU, respectively (HR: 0.86; 95% CI: 0.74–1.01); again the benefit for capecitabine did not reach statistical significance ($p = 0.06$) [57]. Interestingly, an unplanned analysis suggested greater benefit from capecitabine in patients who experienced some degree of HFS.

Mirroring data from the metastatic setting, capecitabine was better tolerated than bolus 5-FU/LV. The incidence of diarrhea, nausea and vomiting, stomatitis, alopecia, neutropenia and neutropenic sepsis were all significantly lower in the capecitabine group. Consistent with the reduced rates of severe toxicity, the use of supportive treatments such as anti-diarrheals, anti-emetics and granulocyte colony-stimulating factor was significantly lower in patients receiving capecitabine. In the context of the UK National Health Service (NHS) capecitabine brought cost savings of approximately €5348/patient, the greater drug costs of capecitabine being more than outweighed by savings in the costs of drug administration [58]. An independent Health Technology Assessment (HTA) of capecitabine in the adjuvant setting [59] similarly concluded that the use of capecitabine was indeed cost-effective in comparison with bolus 5-FU/LV.

There is increasing use of adjuvant combination therapy since the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-O7 trials showed improvement in DFS with the addition of oxaliplatin to 5-FU [14,60]. Large adjuvant trials

of capecitabine in combination with oxaliplatin are in recruitment or follow-up. The XELOX-A trial compared bolus 5-FU/LV, (using either the Mayo Clinic or Roswell Park regimens) with XELOX in patients with stage 3 colon cancer [61]. Efficacy data are awaited, but analysis of toxicity showed XELOX to be safe and tolerable in the adjuvant setting. Accrual is also complete to the AVastin AdjuvaNt Trial (AVANT) study (Roche), again in patients with stage 3 disease, comparing FOLFOX-4 as standard therapy to the same regimen plus bevacizumab and to XELOX plus bevacizumab. By contrast, the ongoing UK Quick And Simple And Reliable (QUASAR2) trial in patients with stage 2 or 3 colorectal cancer compares single-agent capecitabine with and without bevacizumab.

Expert commentary

Capecitabine is an effective therapy in patients with colorectal cancer. As a single agent in patients with metastatic disease it shows similar activity to both bolus 5-FU and the LV5FU2 regimens, but with greater convenience to the patient. Capecitabine in combination with oxaliplatin, predominantly in the XELOX regimen, has been shown to be safe, effective and convenient. A number of studies have shown equivalence of XELOX compared with the standard FOLFOX regimen. The toxicity profiles of capecitabine and infusional 5-FU-based chemotherapy vary, with HFS, nausea and vomiting and diarrhea more frequently experienced with capecitabine. The extent to which capecitabine should replace intravenous 5-FU is debated, but capecitabine is already considered a standard therapeutic option in many clinical settings.

In the adjuvant setting, single-agent capecitabine is a proven alternative in patients with stage 3 colorectal cancer, and a very reasonable option in selected patients with stage 2 disease. Efficacy results of the XELOX regimen in stage 3 patients are awaited but, given the equivalence of this regimen with FOLFOX, it is likely that XELOX will become a standard adjuvant regimen.

In contrast to the encouraging data with XELOX, some safety concerns remain with respect to the combination of irinotecan and capecitabine, which has been associated with excess rates of severe toxicity and reduced efficacy; further clinical trial data are required before this combination can be considered safe and effective for routine clinical use. The finding of regional differences in the toxicity of fluoropyrimidine chemotherapy is intriguing, currently unexplained and requires further investigation.

Future perspective

The data presented above indicate that capecitabine can be considered as a safe, effective and convenient alternative to intravenous 5-FU in patients with early-stage and advanced colorectal cancer. There is accumulating evidence for the equivalence of capecitabine/oxaliplatin regimens compared with 5-FU/oxaliplatin. This is likely to lead to the increasing use of capecitabine regimens over the next few years. Many ongoing clinical trials are assessing capecitabine ± oxaliplatin in combination with targeted agents such as bevacizumab or cetuximab, and are also likely to establish capecitabine

in this context. We can therefore expect that capecitabine will become a more widely used and convenient alternative to intravenous 5-FU over the coming years.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Capecitabine is an oral fluoropyrimidine designed to be converted to 5-fluorouracil (5-FU) in a three-step enzymatic reaction. The final step is catalyzed by the enzyme thymidine phosphorylase, which is frequently overexpressed in tumor cells, and results in preferential production of 5-FU in tumor cells.
- Full-dose capecitabine is tolerated less well in North America compared with Europe and Asia; this may be explained by folate status, since the use of capecitabine immediately after 5-FU and leucovorin is also associated with increased toxicity.

Capecitabine has an established role in patients with metastatic disease

- Single-agent capecitabine achieves higher response rates and similar progression-free survival and overall survival compared with bolus 5-FU.
- The combination of capecitabine and oxaliplatin is safe and effective, with several trials showing noninferiority of capecitabine to 5-FU.
- The addition of bevacizumab adds significantly to the efficacy of capecitabine and oxaliplatin.
- Combining capecitabine and irinotecan has been associated with safety concerns, but recent data suggest this regimen may have a role in combination with bevacizumab.

Capecitabine is also an effective option as adjuvant therapy

- Updated results confirm that single-agent capecitabine is at least as effective as bolus 5-FU/leucovorin, with strong trends to superior disease-free and overall survival, and better tolerability.
- Preliminary data using capecitabine and oxaliplatin with bevacizumab have identified no additional safety concerns; efficacy data are awaited with interest.

Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest

- 1 Toms JR (Ed.): *Cancer Stats Monograph 2004*. Cancer Research UK, London, UK (2004).
- 2 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.* 22(18), 3766–3775 (2004).
- 3 Best L, Simmonds P, Baughan C *et al.*: Palliative chemotherapy for advanced or metastatic colorectal cancer. *Cochrane Database Syst. Rev.* 1(CD001545) (2000).
- 4 Cunningham D, Pyrhonen S, James RD *et al.*: Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 352(9138), 1413–1418 (1998).
- 5 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* 355(9209), 1041–1047 (2000).
- 6 de Gramont A, Figier A, Seymour M *et al.*: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J. Clin. Oncol.* 18(16), 2938–2947 (2000).
- 7 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.* 22(1), 23–30 (2004).
- 8 Hurwitz H, Fehrenbacher L, Novotny W *et al.*: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N. Engl. J. Med.* 350(23), 2335–2342 (2004).
- 9 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.* 25(13), 1658–1664 (2007).
- 10 Cunningham D, Humblet Y, Siena S *et al.*: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N. Engl. J. Med.* 351(4), 337–345 (2004).
- 11 Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. *Lancet* 345(8955), 939–944 (1995).
- 12 Gill S, Loprinzi CL, Sargent DJ *et al.*: Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? *J. Clin. Oncol.* 22(10), 1797–1806 (2004).

- 13 Quasar Collaborative G, Gray R, Barnwell J *et al.*: Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 370(9604), 2020–2029 (2007).
- 14 Andre T, Boni C, Mounedji-Boudiaf L *et al.*: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N. Engl. J. Med.* 350(23), 2343–2351 (2004).
- 15 de Gramont A, Boni C, Navarro M *et al.*: Oxaliplatin/5FU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of six years. *J. Clin. Oncol.* 25(18S), Abstract 4007 (2007).
- 16 Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. Meta-Analysis Group In Cancer. *J. Clin. Oncol.* 16(11), 3537–3541 (1998).
- 17 de Gramont A, Bosset JF, Milan C *et al.*: Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French Intergroup study. *J. Clin. Oncol.* 15(2), 808–815 (1997).
- 18 Ledermann JA, Leonard P, Seymour M: Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N. Engl. J. Med.* 345(2), 145–146 (2001).
- 19 Sargent DJ, Niedzwiecki D, O'Connell MJ, Schilsky RL: Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N. Engl. J. Med.* 345(2), 144–145 (Author reply 146) (2001).
- 20 Tournigand C, Andre T, Achille E *et al.*: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J. Clin. Oncol.* 22(2), 229–237 (2004).
- 21 Seymour MT, Maughan TS, Ledermann JA *et al.*: Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 370(9582), 143–152 (2007).
- 22 Cheeseman SL, Joel SP, Chester JD *et al.*: A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. *Br. J. Cancer* 87(4), 393–399 (2002).
- 23 Leonard P, Seymour MT, James R, Hochhauser D, Ledermann JA: Phase II study of irinotecan with bolus and high dose infusional 5-FU and folinic acid (modified de Gramont) for first or second line treatment of advanced or metastatic colorectal cancer. *Br. J. Cancer* 87(11), 1216–1220 (2002).
- 24 Chirstophidis N, Vajda FJ, Lucas I *et al.*: Fluorouracil therapy in patients with carcinoma of the large bowel: a pharmacokinetic comparison of various rates and routes of administration. *Clin. Pharmacokinet.* 3(4), 330–336 (1978).
- 25 O'Neill V, Twelves C: Oral cancer treatment: developments in chemotherapy and beyond. *Br. J. Cancer* 87, 933–937 (2002).
- 26 Miwa M, Ura M, Nishida M *et al.*: Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur. J. Cancer* 34(8), 1274–1281 (1998).
- 27 Schuller J, Cassidy J, Dumont E *et al.*: Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. *Cancer Chemother. Pharmacol.* 45(4), 291–297 (2000).
- 28 Longley D, Harkin D, Johnston P: 5-fluorouracil: mechanisms of action and clinical strategies. *Nat. Rev. Cancer* 3, 330–338 (2003).
- 29 Meropol NJ, Gold PJ, Diasio RB *et al.*: Thymidine phosphorylase expression is associated with response to capecitabine plus irinotecan in patients with metastatic colorectal cancer. *J. Clin. Oncol.* 24(25), 4069–4077 (2006).
- 30 Van Cutsem E, Findlay M, Osterwalder B *et al.*: Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: results of a randomized Phase II study. *J. Clin. Oncol.* 18(6), 1337–1345 (2000).
- 31 Van Cutsem E, Twelves C, Cassidy J *et al.*: Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J. Clin. Oncol.* 19(21), 4097–4106 (2001).
- 32 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.* 19(8), 2282–2292 (2001).
- Along with [31], key randomized, controlled trials demonstrating the equivalence of response rates for capecitabine compared with bolus 5-fluorouracil/leucovorin (5-FU/LV) in European and North American populations.
- 33 Van Cutsem E, Hoff PM, Harper P *et al.*: Oral capecitabine vs. intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, Phase III trials. *Br. J. Cancer* 90(6), 1190–1197 (2004).
- 34 Seymour MT, Maughan TS, Wasan HS *et al.*: Capecitabine (Cap) and oxaliplatin (Ox) in elderly and/or frail patients with metastatic colorectal cancer: The FOCUS2 trial. *J. Clin. Oncol.* 25(18S), Abstract 9030 (2007).
- 35 Hennig IM, Naik JD, Brown S *et al.*: Severe sequence-specific toxicity when capecitabine is given after fluorouracil and leucovorin. *J. Clin. Oncol.* 26(20), 3411–3417 (2008).
- 36 Patel K, Anthoney DA, Crellin AM *et al.*: Weekly 5-fluorouracil and leucovorin: achieving lower toxicity with higher dose-intensity in adjuvant chemotherapy after colorectal cancer resection. *Ann. Oncol.* 15(4), 568–573 (2004).
- 37 Haller DG, Cassidy J, Clarke SJ *et al.*: Potential regional differences for the tolerability profiles of fluoropyrimidines. *J. Clin. Oncol.* 26(13), 2118–2123 (2008).
- 38 Branda RF, Nigels E, Lafayette AR, Hacker M: Nutritional folate status influences the efficacy and toxicity of chemotherapy in rats. *Blood* 92(7), 2471–2476 (1998).
- 39 Cassidy J, Tabernero J, Twelves C *et al.*: XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. *J. Clin. Oncol.* 22(11), 2084–2091 (2004).
- 40 Diaz-Rubio E, Evans TR, Tabemero J *et al.*: Capecitabine (Xeloda) in combination with oxaliplatin: a phase I, dose-escalation study in patients with advanced or metastatic solid tumors. *Ann. Oncol.* 13(4), 558–565 (2002).
- 41 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.* 26(21), 3523–3529 (2008).
- 42 Cassidy J, Clarke S, Diaz-Rubio E *et al.*: Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J. Clin. Oncol.* 26(12), 2006–2012 (2008).
- Largest randomized, controlled trial conducted comparing oxaliplatin in combination with capecitabine or 5-FU, which demonstrated noninferiority of the two regimens.
- 43 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.* 25(18S), Abstract 4029 (2007).

- 44 Diaz-Rubio E, Tabernero J, Gomez-Espana 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.* 25(27), 4224–4230 (2007).
- 45 Rothenberg ML, Navarro M, Butts C *et al.*: Phase III trial of capecitabine + oxaliplatin (XELOX) vs. 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX4) as 2nd-line treatment for patients with metastatic colorectal cancer (MCRC). *J. Clin. Oncol.*, 25(18s), Abstract 4031 (2007).
- 46 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.* 25(27), 4217–4223 (2007).
- 47 Porschen R, Arkenau HT, Arnold D *et al.*: Capecitabine and oxaliplatin as first-line treatment in patients with metastatic colorectal cancer: a pooled analysis of randomized Phase 2–3 trials. *J. Clin. Oncol.* 26(15S), Abstract 4055 (2008).
- 48 Punt CJ, Tol J, Rodenburg CJ *et al.*: Randomized phase 3 study of capecitabine, oxaliplatin and bevacizumab with or without cetuximab in advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group. *J. Clin. Oncol.* 26(15S), LBA4011 (2008).
- 49 Hecht JR, Chidiac T, Mitchell E: An interim analysis of efficacy and safety from a randomized controlled trial of panitumumab with chemotherapy plus bevacizumab for metastatic colorectal cancer. *Ann. Oncol.* 18(vii21), Abstract 0-0033 (2007).
- 50 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.* 25(30), 4779–4786 (2007).
- Randomized, controlled trial assessing the CapeIRI combination regimen in comparison with the FOLFIRI, and highlighted concerns regarding the toxicity of capecitabine/irinotecan combinations.
- 51 Kohne CH, De Greve J, Hartmann JT *et al.*: Irinotecan combined with infusional 5-fluorouracil/folinic acid or capecitabine plus celecoxib or placebo in the first-line treatment of patients with metastatic colorectal cancer. EORTC study 40015. *Ann. Oncol.* 19(5), 920–926 (2008).
- 52 Koopman M, Antonini NF, Douma J *et al.*: Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a Phase III randomised controlled trial. *Lancet* 370(9582), 135–142 (2007).
- 53 Reinacher-Schick AC, Kubicka S, Freier W *et al.*: Activity of the combination of bevacizumab (Bev) with capecitabine/irinotecan (CapIri/Bev) or capecitabine/oxaliplatin (CapOx/Bev) in advanced colorectal cancer (ACRC): A randomized Phase II study of the AIO Colorectal Study Group (AIO trial 0604). *J. Clin. Oncol.* 26(15S), Abstract 4030 (2008).
- 54 Saltz LB, Clarke S, Diaz-Rubio E *et al.*: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized Phase III study. *J. Clin. Oncol.* 26(12), 2013–2019 (2008).
- 55 Tol J, Koopman M, Rodenburg CJ *et al.*: A randomised Phase III study of capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim analysis of toxicity. *Ann. Oncol.* 19(4), 734–738 (2008).
- 56 Twelves C, Wong A, Nowacki MP *et al.*: Capecitabine as adjuvant treatment for stage III colon cancer. *N. Engl. J. Med.* 352(26), 2696–2704 (2005).
- Large randomized, controlled trial that established that capecitabine was at least equivalent to bolus 5-FU/LV in the adjuvant setting.
- 57 Twelves C, Scheithauer W, McKendrick J *et al.*: Capecitabine versus 5-FU/LV in stage 3 colon cancer: updated 5-year efficacy data from X-ACT trial and preliminary analysis of relationship between hand-foot syndrome (HFS) and efficacy. Presented at: *ASCO 2008 Gastrointestinal Cancers Symposium*. Orlando, FL, USA, 25–27 January (2008) (Abstract 274).
- 58 Cassidy J, Douillard JY, Twelves C *et al.*: Pharmacoeconomic analysis of adjuvant oral capecitabine vs intravenous 5-FU/LV in Dukes' C colon cancer: the X-ACT trial. *Br. J. Cancer* 94(8), 1122–1129 (2006).
- 59 Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P: The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation. *Health Technol. Assess.* 10(41) (2006).
- 60 Wolmark N, Wieand HS, Kuebler JP, Colangelo L, Smith RE: A Phase 3 trial comparing FULV to FU/LV + oxaliplatin in stage 2 or 3 carcinoma of the colon: Results of NSABP Protocol C-07. *J. Clin. Oncol.* 23(18S), Abstract 3500 (2005).
- 61 Schmoll HJ, Cartwright T, Tabernero J *et al.*: Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. *J. Clin. Oncol.* 25(1), 102–109 (2007).

Website

- 101 Risks of incorrect dosing of oral anticancer medicines. Rapid Response Reports – NPSA/2008/RRR001. National Patient Safety Agency, 2008. www.npsa.nhs.uk/nrls/alerts-and-directives/rapidrr/