Treatment in advanced colorectal cancer: what, when and how?

I Chau*,1 and D Cunningham1
1Department of Medicine, Royal Marsden Hospital, London and Surrey, UK

Treatment of advanced colorectal cancer (CRC) increasingly requires a multidisciplinary approach and multiple treatment options add to the complexity of clinical decision-making. Recently novel targeted therapy against angiogenesis and epidermal growth factor receptor (EGFR) completed a plethora of phase III studies. The addition of bevacizumab to chemotherapy improved the efficacy over chemotherapy alone in both first and second line settings, although the magnitude of benefit may not be as great when a more optimal chemotherapy platform is used. Studies performed thus far did not address conclusively whether bevacizumab should be continued in subsequent lines of treatment. Anti-angiogenesis tyrosine kinase inhibitors have not shown any additional benefit over chemotherapy alone so far. Although some benefits were seen with cetuximab in all settings of treating advanced CRC, K-ras mutation status provides an important determinant of who would not benefit from such a treatment. Caution should be exercised in combining anti-angiogenesis with anti-EGFR strategy until further randomised data become available. In this review, we have focused on the implications of these trial results on the everyday management decisions of treating advanced CRC. Review

WHAT IS AN APPROPRIATE PRIMARY END POINT IN ADVANCED CRC TRIALS?

Improvement in overall survival (OS) has traditionally been regarded as the most important end point in assessing experimental therapy. Yet reliant on this end point may require many years of follow-up and may delay the introduction of effective treatment into routine clinical practice. Furthermore, with effective post-trial treatment, the beneficial effect of experimental therapy may be diluted, especially if the experimental therapy is made available to the trial patients after failing control treatment. Intermediate end points, in particular progression-free survival (PFS), have been generally used as a surrogate for OS. Indeed, in a recent pooled analysis of 39 randomised controlled trials (RCTs) of first line therapy (Tang et al, 2007), there was a strong relationship between hazard ratios for PFS and OS. A novel therapy, which produced a 10% reduction in risk of progression would yield an estimated 5.4 ± 1% reduction in risk of death. However, reliance on PFS in assessing a novel treatment effect is not without pitfalls (Panageas et al, 2007). The date with radiological progression first evident is often used as a proxy for the true progression, when in fact the true progression time lies somewhere between this date and the last radiological assessment date. As a result, the protocol-specified time interval between radiological assessments used in clinical trials (for example, every 6 weeks vs every 12 weeks) may have an impact on the PFS, thus making cross-trial comparisons of clinical benefits with treatment particularly problematic. In addition, definition of PFS is also not universal among phase III trials and this potentially leads to different magnitudes of benefit from the same agent (for example, bevacizumab) seen in advanced CRC (Hurwitz et al, 2004; Saltz et al, 2008).

ANGIOGENESIS

Vascular endothelial growth factor (VEGF) represents one of the most important pro-angiogenic proteins. Bevacizumab is a humanised monoclonal antibody against VEGF. A series of randomised studies has initially established and subsequently refined the role of bevacizumab and anti-angiogenic therapy as treatment for advanced CRC. Table 1 shows the efficacy results of these studies (Kabbinavar et al, 2003, 2005a, b; Hurwitz et al, 2004; Giantonio et al, 2007; Hecht et al, 2007, 2009; Kohne et al, 2007; Saltz et al, 2007, 2008; Berry et al, 2008; Cunningham et al, 2008; Reinacher-Schick et al, 2008; Grothey et al, 2008b; Tol et al, 2009).

Initially a randomised phase II study compared bolus 5-FU/leucovorin (LV) alone with 5-FU/LV combined with two different doses of bevacizumab (5 and 10 mg kg⁻¹ every 2 weeks) (Kabbinavar et al, 2003). Interestingly, only the lower dose of bevacizumab (5 mg kg⁻¹) significantly improved the objective
response rate (ORR) and time to tumour progression (TTP) over chemotherapy alone. As a result, this lower dose was chosen in the pivotal study, although there is still much debate about the optimal dose of bevacizumab in solid tumours (Hurwitz et al., 2004; Sandler et al., 2006; Giantonio et al., 2007; Miller et al., 2007). The pivotal study showed a significant improvement in ORR, PFS and OS with the addition of bevacizumab to irinotecan/bolus 5-FU/leucovorin (IFL) compared to IFL alone (Hurwitz et al., 2004), although it is now recognised that IFL was not an optimal chemotherapy platform in advanced CRC (Fuchs et al., 2007). Bevacizumab plus

| Study | Treatment arms | Number of patients | Response rates (%) | Median progression-free survival (months) | Median overall survival (months) |
|-------|----------------|--------------------|-------------------|------------------------------------------|---------------------------------|
| First line | Kabbinavar et al (2003) | 36 | 17 | 5.2 | 13.8 |
| | 5-FU/LV | | | | |
| | 5-FU/LV/BEV (5 mg kg\(^{-1}\)) | 35 | 40 | 9.0 | 21.5 |
| | 5-FU/LV/BEV (10 mg kg\(^{-1}\)) | 33 | 24 | 7.2 | 16.1 |
| | Hurwitz et al (2004) | IFL | 411 | 34.8 | 6.2 | 15.6 |
| | AVF 2107 | IFL/BEV | 402 | 44.6 | 10.6 | <0.001 |
| | 5-FU/LV/BEV | 110 | 40.0 | 8.8 | 0.4192 |
| | Kabbinavar et al (2005b) | 5-FU/LV | 105 | 15.2 | 5.5 | 12.9 |
| | 5-FU/LV/BEV | 104 | 26.0 | 9.2 | 0.0002 |
| | Kabbinavar et al (2005a) | 5-FU/LV or IFL | 241 | 24.5 | 5.55 | 14.6 |
| | 5-FU/LV/BEV | 249 | 34.1 | 9.4 | 0.01 |
| | Saltz et al (2008) | FOLFOX or CAPOX | 701 | 38 | 8.0 | 19.9 |
| | XELOX-1/ N016966 | FOLFOX/CAPOX + BEV | 699 | 38 | 9.4 | 21.3 |
| | Tol et al (2009) | CAPOX + BEV | 368 | 50 | 10.7 | 20.3 |
| | CAIRO 2 | CAPOX + BEV + cetuximab | 368 | 52.7 | 9.4 | 19.4 |
| | Hecht et al (2009) | FOLFOX + BEV | 410 | 48 | 11.4 | 24.5 |
| | PACCE | FOLFOX + BEV + PAN | 413 | 46 | 10.0 | 19.4 |
| | Hecht et al (2009) | FOLFIRI + BEV | 115 | 40 | 11.7 | 20.5 |
| | PACCE | FOLFIRI + BEV + PAN | 115 | 43 | 10.1 | 20.7 |
| | Reinacher-Schick et al (2008)* | CAPOX + BEV | 127 | 53 | 10.4 | 26.7 |
| | AIO 0604 | CAPRI + BEV | 120 | 55 | 12.1 | 26.7 |
| | Hecht et al (2009) | FOLFOX | 583 | 46 | 7.7 | 20.5 |
| | CONFIRM 1 | FOLFOX + PTK/ZK | 585 | 42 | 9.1 | 21.4 |
| | Grothey et al (2008b) | Chemotherapy + BEV (non-randomised US cohort study) | 1953 | NR | 9.9 | 25.1 |
| | BritE* | Chemotherapy + BEV (non-randomised non-US cohort study) | 1914 | NR | 10.8 | 22.7 |
| Second line | Giantonio et al (2007) | ECOG E3200 | FOLFOX | 291 | 8.6 | 4.7 | 10.8 |
| | | FOLFOX/BEV (10 mg kg\(^{-1}\)) | 289 | 22.7 | <0.0001 | 7.3 |
| | | BEV (10 mg kg\(^{-1}\)) | 243 | 3.3 | 2.7 | 10.2 |
| | Kohne et al (2007) | CONCERT 2 | FOLFOX | 429 | 18 | 4.1 | 11.8 |
| | | FOLFOX + PTK/ZK | 426 | 19 | 5.6 | 0.026 |
| | Cunningham et al (2008)* | A. FOLFOX + BEV | 66 | 27 | 7.8 | B vs A |
| | | B. FOLFOX + cetirizanib (low dose) | 71 | 18 | 5.8 | 0.29 |
| | | C. FOLFOX + cetirizanib (high dose) | 73 | 19 | 7.2 | C vs A 0.79 |
| | Saltz et al (2007)* | irinotecan/cetuximab/ BEV | 43 | 37 | 7.3 | 14.5 |

\(LV = \) leucovorin; FOLFOX: oxaliplatin/infused 5-FU/LV; BEV = bevacizumab; CAPOX: capecitabine/oxalaplatin; IFL = irinotecan/bolus 5-FU/LV; FOLFIRI = irinotecan-infused 5-FU/LV; CAPRI: capecitabine/irinotecan; PAN = panitumumab; NR = not reported; NS = Not significant; HR = hazard ratio; CI = confidence interval. The first treatment arm of each study was the control arm. Unless stated, all bevacizumab was given at 2.5 mg kg\(^{-1}\)/C\(0\)1 per week. All \(P\)-values were compared with control arms. *Randomised phase II studies. **Observational registry studies.
5-FU/LV also showed a non-significant trend towards better survival compared with IFL alone (Hurwitz et al, 2005a). Notably this pivotal bevacizumab study only included patients with performance status (PS) 0 or 1. Another randomised trial was performed in patients deemed to be unsuitable for first line irinotecan-based combination chemotherapy regimens (Kabbavavar et al, 2005b). In addition, they were required to have at least one of the following characteristics: age ≤ 65 years, PS 1 or 2, serum albumin ≤ 3.5 g dl⁻¹ or prior radiotherapy to abdomen or pelvis. In this study, patients were randomised to either 5-FU/LV/bevacizumab or 5-FU/LV/placebo. The addition to bevacizumab to 5-FU/LV resulted in a non-significant prolongation of survival. To more reliably quantify the benefit of adding bevacizumab to 5-FU/LV, two further non-randomised studies were performed (Kabbinavar et al, 2005a). There was an improvement for 5-FU/LV/bevacizumab over control group (5-FU/LV or IFL) in terms of OS, PFS and ORR. Most recently, a large RCT (NO16966) was published (Saltz et al, 2008). Although the addition of bevacizumab to oxaliplatin–fluoropyrimidine chemotherapy significantly improved PFS compared with oxaliplatin–fluoropyrimidines alone, no significant differences were seen in terms of ORR and OS. The magnitude of benefit was less than expected from previous studies. One of the reasons cited for the relative small survival benefit for bevacizumab in the NO16966 study was the fact that large proportion of patients (71%) discontinued treatment due to non-progression events (Saltz et al, 2008) with many patients stopping oxaliplatin/fluoropyrimidines due to adverse events. Similar proportion (71%) of patients from the FOLFOX + bevacizumab control arm in PACCE study also stopped treatment due to non-progression events (Hecht et al, 2009), whereas 64% of patients died so in the German AIO study (Reinacher-Schick et al, 2008). With preclinical data suggesting rapid tumour blood vessel regrowth following cessation of VEGF inhibition (Mancuso et al, 2006), one may advocate the continuation of bevacizumab alone until disease progression in the event of cytotoxic drug-induced adverse events. However, re-introduction of VEGF inhibition resulted in the same degree of reduced tumour vasculature as initial VEGF inhibition, suggesting much of the regrown tumour vasculature was still VEGF-dependent (Mancuso et al, 2006). Similar observations were also made clinically (Cacheux et al, 2008). There are therefore no definitive direct clinical evidence to support the necessity of continuing bevacizumab when chemotherapy needs to be stopped due to adverse events. Some preliminary published data support continuing bevacizumab beyond disease progression when second and subsequent lines of chemotherapy were instituted, suggesting a role of continued suppression of the VEGF pathway (Grothey et al, 2008b). However, the improved survival seen with continuing bevacizumab beyond disease progression seen in this observational study might only reflect a fitter group of patients being retreated with combination chemotherapy, rather than bevacizumab-specific (Kopez and Abbruzzese, 2009). Therefore, these non-randomised data should be viewed as hypothesis generating and need confirmation in a randomised trial setting. Curiously South West Oncology Group 0600 trial is testing this hypothesis and until results from this RCT are available, first line use of bevacizumab should be discontinued at the time of disease progression. Another large scale study evaluated bevacizumab in a second line setting (Giantonio et al, 2007). In patients previously treated with irinotecan and fluoropyrimidine, the addition of bevacizumab to oxaliplatin-infused 5-FU/leucovorin (FOLFOX) significantly improved ORR, PFS and OS compared with FOLFOX alone. However, bevacizumab monotherapy was ineffective in this situation and should not be used routinely.

Tyrosine kinase inhibitors (TKIs) targeting at least partly VEGF have recently been shown to be effective in other solid tumours (Demetri et al, 2006; Escudier et al, 2007; Motzer et al, 2007). Several oral anti-angiogenesis inhibitors have also entered clinical development in CRC. Among these, vatalanib underwent phase III trial testing in both first and second line treatment. In both of these studies, no improvement in efficacy was seen with adding vatalanib to FOLFOX chemotherapy (Hecht et al, 2007; Kohne et al, 2007).

**EPIDERMAL GROWTH FACTOR RECEPTOR**

The EGFR-signalling pathway regulates the processes involved in cell differentiation, proliferation, migration, angiogenesis and apoptosis, all of which become dysregulated in cancer cells. Cetuximab is a chimeric monoclonal antibody that specifically targets EGFR with high affinity. After the initial pivotal randomised phase II BOND study which demonstrated the ability of cetuximab to circumvent chemotherapy resistance (Cunningham et al, 2004), a series of randomised phase II–III trials for EGFR-targeted monoclonal antibodies (mAbs) have been reported. Table 2 shows the results of these trials (Cunningham et al, 2004; Jonker et al, 2007; Tejpar et al, 2007; Van Cutsem et al, 2007, 2009; Borner et al, 2008; Ciuleanu et al, 2008; Heinemann et al, 2008; Sobrero et al, 2008; Wilke et al, 2008; Bokemeyer et al, 2009; Hecht et al, 2009). All these studies supported the biological activity of cetuximab in advanced CRC. The benefit of adding cetuximab to first line FOLFIRI in prolonging DFS was relatively small and no improvement in OS results was seen (Van Cutsem et al, 2009). In the second line setting, cetuximab/irinotecan significantly improved ORR and PFS (Sobrero et al, 2008), but with the commercial availability of cetuximab to patients in the irinotecan control arm on disease progression during the trial, no benefits were seen with OS, although other factors might have contributed to the lack of OS improvement. Forty-seven percent of patients in the control arm received subsequent cetuximab and had a median survival of 13 months, identical to patients who were randomised to irinotecan plus cetuximab and received subsequent treatment without cetuximab (Sobrero et al, 2008). One must therefore balance the adverse, but manageable effect of prolonged skin rash with some improvement in remaining progression-free and improvement in at least some domains of quality of life (QoL). In a chemotherapy–refractory situation, cetuximab did show statistically significant improved survival and QoL over best supportive care (BSC) (Jonker et al, 2007), but the cost-effectiveness of this approach will need to be carefully evaluated. Notably, no crossover was allowed in the BSC arm to receive cetuximab on disease progression.

Panitumumab, a fully human monoclonal antibody against EGFR was also evaluated against BSC (Van Cutsem et al, 2007). Although a significant improvement in PFS was seen with panitumumab, a large proportion of patients (76%) in the BSC arm crossed over to the panitumumab arm on disease progression and precluded any OS benefit to be seen. Nevertheless, this improvement in PFS led to the licensing of panitumumab by the Food and Drug Administration in September 2006. In Europe, the same data was originally rejected for licensing of panitumumab within the European Union. However, with further data available for K-ras (Kirsten rat sarcoma viral oncogene homologue) mutation in this study (Amado et al, 2008), the licensed indication for panitumumab within EU is treatment of patients with metastatic colorectal carcinoma after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens whose tumours contain non-mutated (wild-type) K-ras.

EGFR TKI currently has no role in advanced CRC with only two randomised studies showing little clinical benefit (Rothenberg et al, 2005; Santoro et al, 2008). Several phase II studies found little additional benefit of EGFR TKI on a conventional chemotherapy platform (Hoheinz et al, 2006; Chau et al, 2007; Gelibter et al,
More importantly, excessive toxicities were encountered in a number of these studies, especially with irinotecan combinations. The lack of EGFR mutations in CRC and supra-additive toxicity of EGFR TKI to chemotherapy regimens may partly explain why development of EGFR TKI in advanced CRC would be unlikely to be fruitful.

With encouraging results seen with individually targeting VEGF and EGFR as successful treatment strategies in advanced CRC, it would be logical to consider dual inhibition of angiogenesis and EGFR with support from preclinical data (Ciardiello et al., 2004; Tonra et al., 2006). The BOND-2 study showed encouraging results with this approach (Saltz et al., 2007). Recruiting similar irinotecan–refractory population to the original BOND study, the BOND-2 study randomised patients between cetuximab plus bevacizumab vs irinotecan, cetuximab plus bevacizumab. The efficacy seen with dual inhibition of VEGF and EGFR in the BOND-2 study had improved by 2- to 3-fold in ORR, PFS and OS compared with BOND study, although BOND study had a much larger sample size and this was a cross trial comparison.

However, two large phase III studies have been published disputing the benefit of dual EGFR/VEGF inhibition in combination with chemotherapy (Hecht et al., 2009; Tol et al., 2009). In the PACCE study, the addition of panitumumab to oxaliplatin-based chemotherapy plus bevacizumab resulted in significantly inferior PFS and OS compared with chemotherapy plus bevacizumab (Hecht et al., 2009). A further study, CAIRO 2, also reported a significantly worse PFS with the addition of cetuximab to chemotherapy in advanced CRC.

### Table 2: Randomised studies evaluating epidermal growth factor receptor inhibitors in advanced colorectal cancer

| Study | Treatment arms | Number of patients | Response rates (%) | Median progression-free survival (months) | Median overall survival (months) |
|-------|----------------|--------------------|--------------------|------------------------------------------|---------------------------------|
| **First line** | | | | | |
| Van Cutsem et al (2009) | FOLFIRI | 599 | 38.7 | — | 8.0 |
| | FOLFIRI + cetuximab | 599 | 46.9 | 0.004 | 8.9 | 0.048 |
| Bokemeyer et al (2009)* | FOLFOX | 168 | 36 | — | 7.2 |
| | FOLFOX + cetuximab | 169 | 46 | 0.064 | 7.2 | 0.62 |
| Borner et al (2008)* | CAPOX | 37 | 14 | — | 5.8 |
| | CAPOX + cetuximab | 37 | 41 | NR | 7.2 | NR |
| Heinemann et al (2008)* | CAPOX + cetuximab | 93 | 47 | — | 6.7 |
| German AIO | CAPOX + cetuximab | 92 | 48 | NR | 7.9 | NR |
| Ciuleanu et al (2008)* | FOLFIRI + cetuximab | 78 | 45 | — | 8.3 |
| | FOLFIRI + cetuximab | 77 | 43 | NR | 8.6 | NS |
| Hecht et al (2009) | FOLFOX | 410 | 48 | — | 11.4 |
| | FOLFOX + BEV | 413 | 46 | NS | 10.0 | 1.06 – 1.52 |
| PACCE | FOLFOX + BEV + PAN | 115 | 40 | — | 11.7 |
| | FOLFOX + BEV + PAN | 115 | 43 | NS | 10.1 | 0.79 – 1.79 |
| **Second line** | | | | | |
| Sobrero et al (2008) | Irinotecan | 650 | 4.2 | <0.0001 | 2.6 |
| | Irinotecan + cetuximab | 648 | 16.4 | 4.0 | <0.0001 | 9.99 |
| EPIC | | | | | |
| | Cetuximab + BSC | 285 | 0 | <0.0001 | 1.8 |
| | Cetuximab + BSC | 287 | 8 | 1.9 | <0.0001 | 4.6 |
| Jonker et al (2007) | BSC | 232 | 0 | <0.0001 | 1.8 |
| | Panitumumab + BSC | 231 | 10 | 2 | <0.0001 | NR |
| Van Cutsem et al (2007) | BSC | 111 | 10.8 | 0.0074 | 1.5 |
| | Cetuximab + cetuximab | 218 | 22.9 | 0.0001 | 4.1 |
| Cunningham et al (2004) | Cetuximab | 45 | 16 | — | 3.9 |
| BOND* | Panitumumab + cetuximab (standard dose) | 44 | 30 | NR | 4.8 |
| | Panitumumab + cetuximab (escalating dose) | 44 | 30 | NR | 8.6 |
| Tejpur et al (2007) | Panitumumab + cetuximab | 1147 | 20.1 | — | 3.2 |
| EVEREST* | | | | | |
| | | | | | |

LV = leucovorin; FOLFOX = oxaliplatin/infused F-U/LV; BEV = bevacizumab; FOLFIRI = irinotecan/infused F-U/LV; CAPOX = capecitabine/oxaliplatin; BSC = best supportive care; PAN = panitumumab; NR = not reported; HR = hazard ratio; CI = confidence interval. The first treatment arm of each study was the control study. All P-values were compared with control arms. *Randomised phase II studies. **Observational registry studies.
biacucizumab plus oxaliplatin/capecitabine (CAPOX). No ORR or OS benefit was seen with adding cetuximab in this study (Tol et al., 2009). The reasons behind this detrimental effect of adding EGFR antibody to bevacizumab are currently unclear. Additional toxicities were observed with adding panitumumab to bevacizumab/oxaliplatin-based chemotherapy resulting in a lower dose intensity in the PACCE study (Hecht et al., 2009). Pharmacokinetic as well as pharmacodynamic interactions could occur between bevacizumab and cetuximab/panitumumab. On the other hand, bevacizumab-associated hypertension, a putative marker for bevacizumab efficacy, was less frequent with CAPOX plus bevacizumab/panitumumab in the CAIRO 2 study (Tol et al., 2009). Both PACCE and CAIRO 2 did not pre-select patients with wild-type K-ras tumours, the US Intergroup study, CALGB 80405, had amended the entry criteria to exclude patients with K-ras mutations and hopefully this would be able to answer definitely whether synergy exists between cetuximab and bevacizumab in wild-type K-ras patients.

Aside from combined inhibition of VEGF and EGFR, there are other potential strategies to improve on the efficacy of EGFR-targeted therapy. In a study with patients receiving cetuximab for advanced CRC, 23% of patients were found to have HER2 fluorescent in-situ hybridisation positive disease (Finocchio et al., 2007). Patients with HER2-positive disease had a significantly worse TTP and OS compared to those with HER2-negative disease. Dual targeting treatment is now available for EGFR and HER2 (Geyer et al., 2006) and this might be a strategy worth pursuing in advanced CRC.

Preclinical evidence suggested that mAb and TKI against EGFR might not have a completely overlapping mechanism of action and synergistic actions had been observed for administering cetuximab and gefitinib simultaneously in human xenograft models (Matar et al., 2004). A phase I study has established that cetuximab and gefitinib can be administered in combination at full individual agent dose in patients who had failed chemotherapy treatment (Baselga et al., 2006). Preliminary results showed an encouraging 50% response rate in CRC patients.

**TOXICITIES FROM TARGETED AGENTS**

Table 3 and 4 show toxicities seen with agents targeting VEGF and EGFR respectively. Whereas bevacizumab in general does not increase the toxicities from the cytotoxic agents, it does have unique serious side effects, which thankfully are uncommon. However, awareness about hypertension, thromboembolism, bowel perforation and rarely reversible posterior leucoencephalopathy syndrome should be raised to the patients’ primary care physician and other allied health professionals for prompt treatment of these complications. Cetuximab and panitumumab do, however, increase incidences of some side effects (e.g., diarrhoea) from cytotoxic drugs. Nevertheless, integument-related toxicities are very common and may adversely affect patients’ QoL if used on a long-term basis, although oral minocycline may be helpful in some patients (Scope et al., 2007). Furthermore, preemptive skin treatment (using skin moisturisers, sunscreen, topical steroid and oral doxycycline) starting before panitumumab-based treatment has recently been shown to reduce skin toxicity by >50% with improved QoL compared with reactive skin treatment, that is, starting treatment after development of skin rash (Lacouture et al., 2009). There is also a hint that K-ras wild-type patients might experience more side effects from cetuximab compared to those treated without cetuximab. The increased toxicity from combining panitumumab and bevacizumab is noteworthy (Hecht et al., 2009). However, the CAIRO 2 study did not report any safety concern (Tol et al., 2009), further safety data are awaited from cetuximab plus bevacizumab.

**BIOMARKERS FOR EFFICACY AND TOXICITY**

Until recently, the most consistent predictor for response and survival to EGFR mAb is the development of skin rash. Multiple RCTs showed a correlation between survival and severity of skin reaction (Cunningham et al., 2004; Jonker et al., 2007; Van Cutsem et al., 2007, 2009). Because no dose-limiting toxicity was observed in phase I studies of cetuximab with the current recommended dosing regimen, individualised dose titration based on the occurrence and severity of skin rash may improve the effectiveness of cetuximab treatment. EVEREST study randomized patients with <grade 2 skin reaction after 3 weeks of cetuximab to either continue on the same dose of cetuximab or escalate dose up to 500 mg m^{-2} (Tejpar et al., 2007). Although this study was small, there was nearly a doubling of ORR (16% standard dose vs 30% escalating dose). However, due to the small sample size, 95% confidence interval for the ORR overlapped between the two arms. Furthermore, PFS and OS did not show any improvement in dose escalation of cetuximab.

However, skin rash could only be assessed after treatment had been commenced. More than 90% of patients destined to develop rash would only do so after 4 weeks of cetuximab (i.e. after four infusions already) (Jonker et al., 2007). Other biomarkers that could predict efficacy before commencing on cetuximab or panitumumab would be more desirable. A number of RCTs evaluating panitumumab/cetuximab has reported their data on a K-ras analysable population. Table 5 shows the results of these studies (Amado et al., 2008; Karapetis et al., 2008; Tejpar et al., 2008; Van Cutsem et al., 2009; Bokemeyer et al., 2009; Hecht et al., 2009; Tol et al., 2009). K-ras mutation occurred in about 35–43% of patients. Patients with wild-type K-ras and treated with panitumumab or cetuximab enjoyed generally longer PFS and better ORR compared with those not treated by these antibodies, but those patients with mutant K-ras did not derive any benefit from panitumumab/cetuximab. As all of these studies reported K-ras data as a retrospective subgroup analysis, no OS benefit has been demonstrated yet in K-ras wild-type patients receiving chemotherapy plus cetuximab/panitumumab over those receiving chemotherapy alone. This might be due to underpowered sample sizes in these subgroup analyses. With these emerging data, patients should be tested for K-ras mutation before commencing on cetuximab/panitumumab treatment and only those with wild-type tumours should be started on such treatment. Facilities to test for K-ras mutation in routine clinical practise are lacking in many institutions. Quality assurance for such testing would be required and central reference laboratories with rapid turnover would be essential, similar to HER 2 testing (Perez et al., 2006).

K-ras mutation appeared to have no impact on patients treated with bevacizumab. The ORR, PFS and OS benefits of adding bevacizumab to chemotherapy were independent to K-ras mutation status (Hurwitz et al., 2009). Interestingly, despite patients with K-ras wild-type tumours could benefit from cetuximab/panitumumab, when these patients were treated with oxaliplatin-based chemotherapy plus bevacizumab plus cetuximab/panitumumab, no additional benefit was seen over chemotherapy plus bevacizumab (Hecht et al., 2009; Tol et al., 2009). Indeed they appeared to have worse OS outcome with panitumumab (Hecht et al., 2009). For patients with K-ras mutant tumours, treatment with CAPOX plus bevacizumab plus cetuximab resulted in worse survival outcome (Tol et al., 2009), similar to other studies where chemotherapy plus cetuximab had the worst outcome in K-ras mutant patients (Van Cutsem et al., 2008; Bokemeyer et al., 2009). Therefore, for K-ras mutant patients, it would appear to be potentially harmful to treat them with EGFR-targeted therapy.

Further biomarkers have also been evaluated to predict responsiveness to cetuximab/panitumumab. BRAF mutation had been found to be mutually exclusive to K-ras mutation and BRAF mutation was found in 11–14% of K-ras wild type patients.
Patients with KRAS wild-type tumours but harbouring BRAF mutations did not show any responses to cetuximab/panitumumab and had inferior survival compared to those without BRAF mutations (Di Nicolantonio et al, 2008; Cappuzzo et al, 2008b). In another retrospective study, nuclear factor kappa B positivity by immunohistochemistry also appeared to have worse ORR, PFS and OS in irinotecan-refractory patients receiving irinotecan plus cetuximab (Scartozzi et al, 2007), whereas patients with EGFR gene amplification were more likely to respond to cetuximab/panitumumab (Moroni et al, 2005; Lievre et al, 2006; Sartore-Bianchi et al, 2007; Personeni et al, 2008; Cappuzzo et al, 2008a).

For conventional cytotoxics, a large number of studies has been performed evaluating variations in genes associated with drug metabolism and targets and the effects of these variations on treatment outcome and toxicities. This has been systematically reviewed (Funke et al, 2008). Most of these studies were small (<200 patients), retrospective and non-randomised; included a heterogeneous patient population and utilised a variety of laboratory techniques and biological materials including primary tumours, metastasis and peripheral blood. Few genetic variants have therefore been shown to be unequivocally associated with treatment outcome. Overall, the homozygous UGT1A1*28 insertion polymorphism was associated with increased risk of irinotecan-related toxicities. XPD gene (ERCC 2) variations led to differences in DNA-repair capability. Glutathione-S-transferases (GST) are phase II metabolising enzymes involved in detoxification of platinum compounds. GSTP1-105 mutations were associated with improved outcome (Funke et al, 2008).

Recently, the largest published RCT in advanced CRC, FOCUS (Seymour et al, 2007a), reported the first results of a nested prospective search for biomarkers within the FOCUS study (Braun et al, 2008). Topo 1, a molecular target of SN38 (active metabolite of irinotecan), was found to be a predictive biomarker to irinotecan therapy in the assessable 1313 patients. Patients with low Topo 1 (below the median) had a significantly worse outcome, with a major improvement in survival for the highest expressing patients. This observation was seen with the addition of either irinotecan or oxaliplatin, but the association with improved survival was stronger with irinotecan. None of the other biomarkers studied, including ERCC1, MLH1/MSH2, p53, MGMT, COX-2 protein expression as assessed by tumour immunohistochemistry or GST-P1, ABCB1, XRCC1, ERCC2, UGT1A1 germ-line

| Study                        | Treatment arms                  | Number of evaluable patients | Grade 3/4 hypertension (%) | Venous thrombosis (%) | Arterial thrombosis (%) | Grade 3/4 bleeding (%) | Grade 2-4 proteinuria (%) | GI perforation (%) |
|------------------------------|---------------------------------|------------------------------|---------------------------|-----------------------|-------------------------|------------------------|--------------------------|---------------------|
| Kabbinavar et al (2003)      | 5-FU/LV                         | 35                           | 0                         | 6                     | 3                       | 0                      | NR                      | NR                  |
|                              | 5-FU/LV/BEV (5 mg kg−1)         | 35                           | 9                         | 26                    | 0                       | 0                      | NR                      | NR                  |
|                              | 5-FU/LV/BEV (10 mg kg−1)        | 32                           | 25                        | 6                     | 6                       | 9                      | NR                      | NR                  |
| Hurwitz et al (2004)         | IFL                            | 397                          | 2                         | 11.4                  | 1                       | 2.5                    | 6.6                     | 0                   |
|                              | AVF 2107                        | 393                          | 11                        | 12.5                  | 3.3                     | 3.1                    | 3.9                     | 1.5                 |
| Kabbinavar et al (2005b)     | 5-FU/LV                         | 104                          | 3                         | 11                    | 5                       | 3                      | 4                      | 0                   |
|                              | 5-FU/LV/BEV                     | 100                          | 16                        | 9                     | 10                      | 5                      | 8                      | 2                   |
| Kabbinavar et al (2005a)     | 5-FU/LV or IFL                  | 237                          | 3                         | 9                     | 3                       | 2                      | 4                      | 0                   |
|                              | 5-FU/LV/BEV                     | 244                          | 16                        | 10                    | 5                      | 5                      | 9                      | 1                   |
| Gianantonio et al (2007)     | FOLFOX                          | 285                          | 1.8                       | 2.5                   | 0.4                     | 0.4                    | 0                      | 0                   |
|                              | ECOG E200                       | 287                          | 6.2                       | 3.4                   | 0.9                     | 3.4                    | 0.7                     | 1                   |
|                              | BEV (10 mg kg−1)                | 234                          | 7.3                       | 0.4                   | 0.4                     | 2.1                    | 0                      | 1.3                 |
| Saltz et al (2007)           | FOLFOX or CAPOX                 | 675                          | 1                         | 5                     | 1                       | 1                      | NR                      | <1                  |
|                              | XELOX-I/NO16966                 | 694                          | 4                         | 8                     | 2                       | 2                      | <1                     | <1                  |
| Hecht et al (2009)           | FOLFOX + BEV                    | 397                          | 5                         | 12                    | NR                      | NR                     | NR                      | 0                   |
|                              | PACE                          | 407                          | 4                         | 13                    | NR                      | NR                     | NR                      | 0                   |
| Hecht et al (2009)           | FOLFIRI + BEV + panitumumab     | 113                          | 2                         | 11                    | NR                      | NR                     | NR                      | NR                  |
|                              | PACCE                         | 111                          | 3                         | 24                    | NR                      | NR                     | NR                      | NR                  |
| Tol et al (2009)             | CAPOX + BEV                    | 366                          | 148                       | 6.8                   | 3.3                     | 1.6                    | NR                      | 0.3                 |
|                              | CAIRO 2                       | 366                          | 9.3                       | 8.2                   | 2.2                     | 0.5                    | 1.6                     |                    |
| Berry et al (2008) BEAT      | Chemotherapy + BEV             | 1914                         | 5.3                       | NR                    | 1.5                     | 3.4                    | 1.1                     | 1.8                 |
| Grothey et al (2007)         | BrITE Chemotherapy + BEV       | 1953                         | NR                        | 1.8                   | 2.4                     | NR                     | 1.8                     |                    |

*Only grade 3 toxicity was reported. LV = leucovorin; FOLFOX = oxaliplatin infused 5-FU/LV; BEV = bevacizumab; CAPOX = capecitabine/oxaliplatin; IFL = irinotecan bolus 5-FU/LV; NR = not reported.
polymorphism as assessed by macrodissected normal tissue, were found to be associated with treatment outcome from 5-FU plus either irinotecan or oxaliplatin (Braun et al, 2008). Within the same group of patients in FOCUS, those with KRAS and/or BRAF mutation had a significantly worse OS compared to patients with no mutation. However, treatment efficacy from oxaliplatin or irinotecan was not impacted by the KRAS/BRAF mutation status (Richman et al, 2008).

**SHOULD ORAL FLUOROPYRIMIDINES SUBSTITUTE INFUSED FLUOROURACIL IN ADVANCED CRC?**

Only capecitabine has been evaluated as combination treatment regimens in randomised phase III trials in conjunction with oxaliplatin, irinotecan and bevacizumab. Such data are currently lacking with UFT and S-1. Five phase III RCTs have been reported to establish non-inferiority of CAPOX compared with FOLFIRI. Table 6 shows the efficacy results of these studies (Diaz-Rubio et al, 2007; Ducrueux et al, 2007; Porschgen et al, 2007; Cassidy et al, 2008; Rothenberg et al, 2008). Two studies did not meet the primary objective of demonstrating non-inferiority in PFS with CAPOX compared with FOLFIRI, although the convenience of capecitabine did come with a price of nearly doubling of grade 3–4 diarrhoea (20% CAPOX vs 11% FOLFIRI) in the dose schedule used in NO16966 (Cassidy et al, 2008). A meta-analysis of the above studies plus two further randomised phase II studies reported a significantly reduced ORR with CAPOX compared with FOLFIRI (Arkenau et al, 2008). However, CAPOX was non-inferior in PFS and OS compared with FOLFIRI.

Two studies have also been reported comparing capecitabine/irinotecan (CAPIRI) with FOLFIRI – both of which did not reach their recruitment targets. In the first EORTC 40015 study, recruitment was suspended after 85 patients (originally planned recruitment n = 629) because of the frequent occurrence of grade 3/4 diarrhoea (CAPIRI 37% vs FOLFIRI 13%) and more fatal events occurring in the CAPIRI arm (CAPIRI n = 6 vs FOLFIRI n = 2). Five deaths in the CAPIRI arm and both deaths in the FOLFIRI arm were considered to be treatment-related. PFS and OS were all worse with CAPIRI compared with FOLFIRI (Kohne et al, 2008). In the second study BICC-C (Fuchs et al, 2007), CAPIRI was associated with a significantly worse PFS compared with FOLFIRI, when associated with higher rates of severe vomiting, diarrhoea and dehydration. In view of the toxicity concerns, further enrolment into CAPIRI arm in this study was discontinued after the first period of the study (pre-bevacizumab) with 430 patients randomised. However, both the EORTC 40015 and BICC-C had one further complicating factor – a second randomisation to either celecoxib or placebo. Coxibs have been associated with an increased risk of cardiovascular thrombotic events in colorectal neoplasia (Solomon et al, 2005; Kerr et al, 2007). There might be an interaction between celecoxib with CAPIRI that compromised CAPIRI’s efficacy and increased its toxicity. A further large randomised study (CAIRO) evaluating CAPIRI completed patient recruitment (Koopman et al, 2007). CAPIRI treatment did result in grade 3–4 diarrhoea incidence of 27%. A further randomised study of CAPOX plus bevacizumab vs CAPIRI plus bevacizumab using a lower dose of capecitabine and irinotecan resulted in a more tolerable grade 3–4 rate of 16% (CAPOX) and 13% (CAPIRI) respectively (Reinacher-Schick et al, 2008).

Taken together, when using an irinotecan-based regimen in the treatment of first line metastatic CRC, FOLFIRI is the preferred approach unless there is a clear contraindication to continuous infusion 5-FU. Further development in alternative dosing schedule of CAPIRI could provide a better efficacy and safety profile than that used in these three published trials. When using an oxaliplatin-based regimen, capecitabine could substitute infused 5-FU. However, the relative benefit/cost-effectiveness may also depend on the health care system and reimbursement pattern of individual countries (Mayer, 2007).

**SHOULD WE USE SEQUENTIAL TREATMENT OR FIRST LINE COMBINATION CHEMOTHERAPY?**

In a pooled analysis of 11 phase III trials in CRC including 5768 patients (Grothey and Sargent, 2005), there was a strong...
| Study                        | No. of patients evaluable for K-ras mutation/No. of patients in the ITT study population | Proportion of patients with K-ras mutations | Treatment by mutation status | Response rates (%) | P-value | Median progression-free survival | P-value | Median overall survival | P-value |
|-----------------------------|----------------------------------------------------------------------------------------|---------------------------------------------|-------------------------------|-------------------|---------|---------------------------------|---------|--------------------------|---------|
| First line                  |                                                                                        |                                             |                               |                   |         |                                 |         |                          |         |
| Van Cutsem et al (2009)     | 540/1198 (45%)                                                                         | 35.6% mutant                                | Wild type                    | 43.2              | 0.0025  | 8.7 months                      | 0.02    | 21.0 months               | HR: 0.84 |
|                            |                                                                                        |                                             | FOIRI + cetuximab            | 59.3              |         | 9.9 months                      |         | 24.9 months               |         |
|                            |                                                                                        |                                             | Mutant                       | 40.2              | 0.46    | 8.1 months                      | 0.75    | 17.7 months               | HR: 1.03 |
|                            |                                                                                        |                                             | FOIRI + cetuximab            | 36.2              | 0.76    | 7.6 months                      |         | 17.5 months               |         |
| Bokemeyer et al (2009)      | 233/337 (69%)                                                                          | 42% mutant                                  | Wild type                    | 37                | 0.011   | 7.2 months                      | 0.0163  | NR                       | NR      |
|                            |                                                                                        |                                             | FOIRI + cetuximab            | 61                |         | 7.7 months                      |         | NR                       | NR      |
|                            |                                                                                        |                                             | Mutant                       | 49                | 0.106   | 8.6 months                      | 0.0192  | NR                       | NR      |
|                            |                                                                                        |                                             | FOIRI + cetuximab            | 33                |         | 5.5 months                      |         | NR                       | NR      |
| Hecht et al (2009)          | 865/1053 (82%)                                                                         | 40% mutant                                  | Wild type                    | 56                | NR      | 11.5 months                     | HR: 1.36 (95% CI: 1.04–1.77) 24.5 | 0.045   |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 50                | 9.8     | 9.6 months                      |         | 20.7                     |         |
|                            |                                                                                        |                                             | Mutant                       | 44                | NR      | 11.0 months                     |         | 19.3                     |         |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 47                | 10.4    | 10.4 months                     |         | 19.3                     |         |
| Tol et al (2009)            | 528/736 (72%)                                                                          | 39.6% mutant                                | Wild type                    | 50.0              | 0.06    | 10.6 months                     | 0.03    | 22.4 months               | 0.64    |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 61.4              |         | 10.5 months                     |         | 21.8 months               |         |
|                            |                                                                                        |                                             | Mutant                       | 59.2              | 0.03    | 12.5 months                     | 0.003   | 24.9 months               | 0.03    |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 45.9              |         | 8.1 months                      |         | 17.2 months               |         |
| Hecht et al (2009)          | 865/1053 (82%)                                                                         | 40% mutant                                  | Wild type                    | 48                | NR      | 12.5 months                     | NR      | 19.8                     | NR      |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 54                |         | 10.0 months                     |         | NE                       |         |
|                            |                                                                                        |                                             | Mutant                       | 38                | NR      | 11.9 months                     | 0.03    | 20.5 months               | 17.8 months |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 30                | 8.3     | 8.3 months                      |         | 17.8 months               |         |
| Subsequent lines            |                                                                                        |                                             |                               |                   |         |                                 |         |                          |         |
| Tepari et al (2008)         | 148/157 (94%)                                                                          | 39% mutant                                  | Wild type                    | 30.4              | 0.396   | 5.7 months for all wild-type patients 0.014 (in favour of wild type in standard dose) | NR      | NR                       | NR      |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 41.9              |         | (in favour of wild type in standard dose) | NR      | NR                       | NR      |
|                            |                                                                                        |                                             | Mutant                       | 0                 | NR      | 2.7 months for all mutant patients | <0.001  | NR                       | NR      |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 0                 |         | (in favour of wild type in escalating dose) | NR      | NR                       | NR      |
|                            |                                                                                        |                                             | Mutant                       | 0                 |         |                                 |         | NR                       | NR      |
| Amado et al (2008)          | 427/463 (92%)                                                                          | 43% mutant                                  | Wild type                    | 17                | NR      | 12.3 weeks                      | <0.0001 | 8.1 months               | NS      |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 0                 |         | 7.3 weeks                       |         | 7.6 months               | NS      |
|                            |                                                                                        |                                             | Mutant                       | 0                 | NR      | 7.4 weeks                       | 0.99    | 4.9 months               | NS      |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 0                 |         | 7.3 weeks                       |         | 4.4 months               | NS      |
| Karpetis et al (2008)       | 394/572 (69%)                                                                         | 42.3% mutant                                 | Wild type                    | 12.8              | NR      | 3.7 months                      | <0.001  | 9.5 months               | <0.00   |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 0                 |         | 1.9 months                      |         | 4.8 months               | 1       |
|                            |                                                                                        |                                             | Mutant                       | 1.2               | NR      | 1.8 months                      | 0.96    | 4.5 months               | 0.89    |
|                            |                                                                                        |                                             | FOIRI + bevacizumab          | 0                 |         | 1.8 months                      |         | 4.6 months               |         |

ITT = intention to treat; FOLFOX = oxaliplatin-infused 5-FU/LV; FOLFIRI = irinotecan-infused 5-FU/LV; BSC = best supportive care; NR = not reported; NS = not significant; NE = not estimable.
correlation between improved OS and percentage of patients treated with 5-FU/LV, irinotecan and oxaliplatin at some point in their disease. However, combination doublet therapy was not always beneficial in the first line treatment of advanced CRC. Although this analysis was not a formal meta-analysis using individual patient data, it gave a timely indication to clinicians of the importance of having access to all three active drugs – fluoropyrimidines, irinotecan and oxaliplatin in advanced CRC. Several RCTs had attempted to determine whether upfront combination chemotherapy offers any advantage over giving these agents in a sequential manner. Table 7 shows the results of three studies (Koopman et al, 2007; Seymour et al, 2007a; Cunningham et al, 2009).

FOCUS trial is the largest RCT conducted to date in advanced CRC (Seymour et al, 2007). 2135 patients were randomly allocated patients to sequential LV5FU2 followed by irinotecan or first line CAPIRI followed by second line FOLFOX. Combination treatment did not significantly improve OS over sequential treatment, despite an improvement in ORR and PFS with first line combination treatment. Interestingly, the deterioration in QoL functioning was on average more for combination treatment. Another study (CAIRO) randomly allocated patients to sequential capecitabine followed by irinotecan followed by CAPOX (sequential arm) or first line CAPOX followed by second line CAPOX (combination arm) (Koopman et al, 2007). Again combination treatment did not significantly improve OS over sequential treatment, despite an improvement in ORR and PFS with first line combination treatment. Furthermore, the deterioration in QoL functioning was on average more for combination treatment in all domains in this study. LIFE study randomly allocated patients to sequential LV5FU2 followed by irinotecan or FOLFIRI followed by irinotecan. Upfront combination FOLFIRI significantly improved response rate and PFS, but no improvement of OS was seen over sequential treatment (Cunningham et al, 2009).
over single agent. This study also commenced with a reduced starting dose of 80% standard dose. With a median age of 75 and 30% of patients with PS 2, this represented an older and frailer population compared with other RCTs. Only 30–50% of patients escalated to a 100% dose. Addition of oxaliplatin increased ORR (P < 0.0001), but did not significantly improve PFS (P = 0.06) or OS (P = 0.61). In this patient population, substituting 5-FU with capecitabine did not result in any significant differences in PFS or OS. Interestingly in some measures of QoL, capecitabine-containing regimen was worse than infused 5-FU. Capecitabine also led to significantly increased incidences of nausea, diarrhoea, lethargy and hand foot syndrome.

Currently in patients with unresectable metastasis, it would be reasonable to consider first line monotherapy to maintain QoL, but these patients must be monitored closely during treatment in order not to miss the therapeutic window for exposure to other active agents. However, both FOCUS and CAIRO studies utilised treatment strategies without bevacizumab and cetuximab and thus support for sequential treatment might not apply for patients with access to these biological agents. On the other hand, there have been no RCT to demonstrate OS benefit to give combination chemotherapy, oxaliplatin-induced cumulative neuropathy is becoming a significant clinical problem. It can cause substantial impairment of patients' QoL as well as potentially compromising efficacy due to reduced dose intensity. Randomised trials have so far suggested potential benefits of calcium/magnesium infusion, glutamine and glutathione in preventing oxaliplatin-induced peripheral neuropathy (Wolf et al., 2008), but few drugs are effective to treat established peripheral neuropathy. One of the strategies that had been tested in a phase III setting to address this issue was the 'stop and go' strategy. The OPTIMOX 1 study randomised 620 patients to FOLFOX 4 till disease progression or FOLFIRI 7 (high dose of oxaliplatin and omission of bolus 5-FU) for 12 weeks followed by LVSFU2 followed by oxaliplatin reintroduction at the time of disease progression (Tournigand et al., 2006). Overall, no differences were seen in response rates, durations of disease control or overall survival between the two arms, but the incidence of neurotoxicity was markedly reduced in the FOLFOX 7 stop and go arm during oxaliplatin omission phase of LVSFU2, suggesting a novel way to reduce toxicity for patients. However, large variations among treatment centres in reintroducing oxaliplatin might have explained the lack of efficacy differences between the two arms as oxaliplatin reintroduction had a significant positive impact on survival (de Gramont et al., 2007).

A further study from the United States followed similar trial design of assessing intermittent oxaliplatin vs continuous oxaliplatin in the FOLFOX plus bevacizumab regimen (Grothey et al., 2008a). This study also assessed the use of calcium/magnesium infusion in a 2 × 2 factorial design. However, this study was discontinued early due to an unplanned interim analysis of ORR showing worse results with patients receiving calcium/magnesium infusion based on data collected through the clinical research organisation. These inferior results with calcium/magnesium infusion were not confirmed subsequently by either investigator-reported or centrally reviewed ORR. Interestingly, in this study, intermittent oxaliplatin was associated with a significant prolongation of time to treatment failure as well as PFS.

Following on from the OPTIMOX study, a randomised phase II study was performed evaluating the OPTIMOX 1 strategy vs FOLFOX 7 for 3 months only and then reintroduced FOLFOX 7 on disease progression (thus a complete chemotherapy-free period) (Maindrault-Goebel et al., 2007), there was no significant differences in OS, PFS, ORR or duration of disease control between the two arms, although there was a trend towards a benefit with continuous chemotherapy. However, this may simply be a reflection that 3 months of initial chemotherapy were not sufficient and patients should be treated for longer periods (at least 6 months) before contemplating a treatment break. Another GISCAD study randomised 266 patients to either intermittent FOLFIRI (alternating FOLFIRI for 2 months and stopping chemotherapy for 2 months) or continuous FOLFIRI till disease

### Table 7: Randomised studies evaluating combination vs sequential treatment in advanced colorectal cancer

| Study                  | Treatment arms                                                                 | Number of patients | First line response rates | P-value | Median progression-free survival from first line treatment (months) | P-value | Median overall survival (months) | P-value |
|------------------------|---------------------------------------------------------------------------------|--------------------|---------------------------|---------|-------------------------------------------------------------------|---------|-------------------------------|---------|
| Seymour et al (2007a,b) | FOCUS Strategy A 5-FU/LV → irinotecan                                          | 710                | 28% (5-FU/LV)             | <0.001  | 6.3 (5-FU/LV)                                                    | <0.001  | 13.9                          |         |
|                        | Strategy B 5-FU/LV → FOLFIRI or FOLFOX                                          | 356 (FOLFIRI)      | 13% (5-FU/LV)             |         | 356 (FOLFIRI)                                                    | <0.001  | 13.9                          |         |
|                        | Strategy C FOLFIRI → FOLFOX                                                     | 356 (FOLFIRI)      | 13% (5-FU/LV)             |         | 356 (FOLFIRI)                                                    |         | 13.9                          |         |
| Koopman et al (2007)   | CAIRO Strategy A capectabine → irinotecan                                       | 410                | 20% (capectabine)         |         | 410 (FOLFIRI)                                                    |         | 15.9                          |         |
|                        | Strategy B CAPOX → CAPOX                                                        | 357 (CAPOX)        | 20% (capectabine)         |         | 357 (CAPOX)                                                     |         | 15.9                          |         |
| Cunningham et al (2009) | LIFE Strategy A 5-FU/LV → irinotecan                                            | 363                | 29.8% (5-FU/LV)           |         | 363 (5-FU/LV)                                                    |         | 15.9                          |         |
|                        | Strategy B FOLFIRI → irinotecan                                                 | 362                | 54.1% (FOLFIRI)           |         | 362 (FOLFIRI)                                                    |         | 15.9                          |         |

LV = leucovorin, FOLFOX = oxaliplatin/infused 5-FU/LV, FOLFIRI = irinotecan/infused 5-FU/LV, CAPOX = capectabine/oxaliplatin, CAPIRI = capectabine/irinotecan, NR = not reported, NS = non-significant.
to be initiated immediately or whether an expectant policy can be adopted for a period of time. Whereas the original Nordic study concluded that early treatment in asymptomatic patients with advanced CRC prolonged survival, asymptomatic period and time to progression (1992), a meta-analysis of two subsequent studies conducted in Canada and Australasia did not show significant improvement in survival and QoL. To commence early treatment in asymptomatic patients (Ackland et al, 2005). Notably, the latter two studies terminated prematurely due to poor accrual. It is unlikely further studies would be performed to address this issue. However, biological agents as monotherapy with relatively fewer side effects to conventional cytotoxic treatment might be considered to stabilise the disease (Pessino et al, 2008) and delay the introduction of combination cytotoxic drugs with biological agents.

WHAT ARE THE CURRENT CONTROVERSYS WITH RESECTION OF COLORECTAL METASTASIS?

Aggressive surgical approaches to metastatic disease are increasingly practised with a proportion of patients enjoying long-term survival. Five-year survival rates of 30–40% are seen with resection of liver metastasis (Fernandez et al, 2004), despite a lack of randomised data to support surgery. Introduction of new drugs such as oxaliplatin and more recently monoclonal antibodies have allowed sufficient downsizing of ‘unresectable’ liver metastases to convert them to resectable following therapy.

For patients with resectable liver metastasis, the role of peri-operative chemotherapy is still controversial. The European Organisation for Research and Treatment of Cancer (EORTC) 40983 study randomised 364 patients to either peri-operative FOLFOX or surgery alone (Nordlinger et al, 2008). Ninety-two percent of patients had 1–3 liver metastasis and 75% had >2 years between original diagnosis and development of liver metastasis. Three-year PFS benefit from peri-operative FOLFOX did not reach the conventional level of significance in all randomised patients (P = 0.058; absolute difference: 7.2%), although 3-year progression-free survival was significantly improved in those receiving peri-operative FOLFOX in the eligible population (P = 0.041; absolute difference in 3-year PFS: 8.1%) and in the resected patients (P = 0.025; absolute difference in 3-year PFS: 9.2%).

In patients with resectable liver metastasis, a proportion of patients would achieve sufficient downsizing after a period of conversion chemotherapy to allow liver resection. In one study, 13% of patients were converted from unresectable to resectable after chemotherapy (Adam et al, 2004). Although OS was significantly worse in this group of patients (P = 0.01) compared with those who were primarily resectable, this former group of initially unresectable patients still had a respectable 5-year OS rate of 33%.

The rate of liver resection correlated significantly with the ORR of neoadjuvant chemotherapy (Folprecht et al, 2005). FOLFOXIRI (5-FU/LV/oxaliplatin/irinotecan) resulted in a higher response rate compared with FOLFIRI (60 vs 34% respectively; P < 0.0001) (Falcone et al, 2007). This improved response rate led to an increased rate of surgical resection of metastasis. R0 resection was achieved in a higher proportion of patients receiving FOLFOXIRI, which might have contributed to the significant improvement of PFS and OS with FOLFOXIRI compared with FOLFIRI. The addition of cetuximab to FOLFIRI also significantly improved ORR and thus R0 resection of metastasis compared with FOLFIRI alone (4.8 vs 1.7% respectively; P = 0.002) (Van Cutsem et al, 2009). This improvement in ORR with cetuximab was even more pronounced in the K-ras wild-type population (Van Cutsem et al, 2008). In the subgroup of patients with liver metastasis only, R0 resection was increased and PFS significantly improved when cetuximab was added to FOLFIRI. Although bevazucizumab did not significantly improve ORR when added to oxaliplatin/fluoropyrimidine com-

HOW DO WE TREAT THE ELDERLY, POOR PERFORMANCE STATUS OR ASYMPTOMATIC PATIENTS?

Elderly patients represent an increasing challenge. Declining organ reserve may lead to an increased risk and decreased tolerance to chemotherapy-induced side effects. However, recent pooled analyses on elderly patients (aged 70 or more) with both oxaliplatin-based and irinotecan-based chemotherapy showed similar benefit from chemotherapy in terms of ORR, PFS and OS compared with those aged <70 years (Goldberg et al, 2006; Folprecht et al, 2008). Toxicity was similar when treated with irinotecan-based chemotherapy, but more neutropenia, thrombocytopenia was seen in the elderly when treated with FOLFOX. Caution needs to be exercised to extrapolate these data to routine clinical practise, as patients enrolled into these RCTs were fit older patients with better PS. In another pooled analysis of nine first line chemotherapy RCTs (Sargent et al, 2009), patients with PS 2 did experience more toxicity and thus R0 resection of metastasis compared with younger patients and only 0.9–2% of patients were octogenarians. Similar proportion (17%) of patients was progression-free after 6 months of irinotecan, thus eligible for randomisation. Nevertheless, there was no detriment to QoL for those patients who continued irinotecan after an appropriate dose reduction in the initial phase of treatment.

There is currently no detrimental survival effect for treatment for a defined duration (at least 6 months) followed by a treatment break compared with continuous treatment until disease progression. Prolonged continuous treatment may be associated with side effects such as venous thromboembolism.

In conjunction with the previously mentioned FOCUS 2 study, which recruited elderly or poor PS patients, sequential or combination strategies are both reasonable in these patients and there is no evidence that efficacy is compromised or toxicity more pronounced in these groups of elderly or PS 2 patients.

For patients with unresectable but low volume, asymptomatic disease, there is some controversy about whether treatment needs...
pared with oxaliplatin/fluoropyrimidine alone in the NO16966 study, there was a numerical increase in the curative surgery rate in the bevacizumab-containing arm (19.2% vs 12.9%), although this was a post hoc analysis. Even in patients resistant to initial chemotherapy, one study showed that subsequent addition of cetuximab to chemotherapy induced a response and allowed 12% of patients to proceed to surgery with a median OS of 20 months (Adam et al, 2007) and no increase in peri-operative mortality. Currently there is no universally agreed optimal conversion chemotherapy before resection of liver metastasis. FOLFOXIRI or chemotherapy plus cetuximab in K-ras wild-type patients represent attractive options.

Liver injury secondary to chemotherapeutic agents is increasingly recognized. Hepatic vascular lesions could be seen more frequently in patients receiving neoadjuvant oxaliplatin-based chemotherapy (Aloia et al, 2006) leading to higher red blood transfusion requirement. In addition, more prolonged neoadjuvant treatment led to a higher rate of re-operation and a longer hospital stay (Aloia et al, 2007). Pre-operative irinotecan was associated with steatohepatitis and patients with this liver injury had higher 90-day mortality (Vauthey et al, 2006). Neoadjuvant cetuximab was not found to be associated with specific pathological liver damage yet (Adam et al, 2007). These studies highlighted the importance of chemotherapy-induced damage on the non-tumour bearing liver – a complication that needs to be carefully assessed in future studies.

Although lung metastasis is less common than liver involvement, similar long-term survival has been observed after complete resection with a 5-year survival rate of 48% in a recent systematic review of 20 surgical retrospective series (Pflanenschmidt et al, 2007). However, similar to liver resection, it would be difficult to conduct a randomised trial against no resection nowadays. Similar approach of neoadjuvant chemotherapy in liver metastasis may be beneficial in CRC lung metastasis.

CONCLUSIONS

The addition of bevacizumab to chemotherapy improved the efficacy over chemotherapy alone in both first and second line settings, although the magnitude of benefit may not be as great when a more optimal chemotherapy platform is used. Studies performed thus far did not address conclusively whether bevacizumab should be continued in subsequent lines of treatment. Anti-angiogenesis TKI has not shown any additional benefit over chemotherapy alone so far. Although some benefits were seen with cetuximab in all settings of treating advanced CRC, K-ras mutation status provides an important determinant of who would not benefit from such treatment. Caution should be exercised when combining anti-angiogenesis with anti-EGFR strategy until further randomised data become available. In totality of randomised evidence, capecitabine is non-inferior to intravenous fluorouracil when combined with oxaliplatin, although not all study results were consistent. On the other hand, the dose schedule used in randomised trials of irinotecan plus capecitabine might be too toxic, hampering the potential use of this combination.

In patients with extensive unresectable metastasis, a staged strategy of a single agent followed by a combination treatment might be an alternative to upfront combination treatment, whereas in patients with resectable metastasis, a combination therapy with a high response rate appears to be essential. Sequential or combination strategies are both reasonable in elderly or PS 2 patients. There is no evidence that the efficacy is compromised or toxicity more pronounced in elderly or PS 2 patients. Currently the optimal duration of treatment remains uncertain, but there does not appear to be clearly detrimental effect to stop treatment after a defined duration of at least 6 months.

Management of advanced colorectal cancer has become increasingly complex with our expanding (and improved) array of medical, radiation and surgical treatment. What is certain, however, is that our patients are benefiting from this intense research focusing on colorectal cancer.

ACKNOWLEDGEMENTS

We acknowledge National Health Service funding to the National Institute for Health Research Biomedical Research Centre.

REFERENCES

Ackland SP, Jones M, Tu D, Simes J, Yuen J, Sargeant AM, Dhillon H, Goldberg RM, Abdi E, Shepherd L, Moore MJ (2005) A meta-analysis of two randomised trials of early chemotherapy in asymptomatic metastatic colorectal cancer. Br J Cancer 93: 1236 – 1243

Adam R, Aloia T, Levi F, Wicherts DA, de Haas RJ, Paule B, Bralet MP, Bouchahda M, Machover D, Ducreux M, Castagne V, Azoulay D, Castaing D (2007) Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. J Clin Oncol 25: 4593 – 4602

Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghemard O, Levi F, Bismuth H (2004) Rescue surgery for unresectable colorectal metastases downwards by chemotherapy: a model to predict long-term survival. Ann Surg 240: 644 – 657

Aloia T, Sebagh M, Piasse M, Karam V, Levi F, Giacchetti S, Azoulay D, Bismuth H, Castaing D, Adam R (2006) Liver histology and surgical outcomes after prooperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol 24: 4983 – 4990

Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, Juan T, Sikorski R, Suggs S, Radinsky R, Patterson SD, Chang DD (2008) Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 26: 1626 – 1634

Andre T, Quinaux E, Louvet C, Colin P, Gamelin E, Bouche O, Achille E, Piedbois P, Tubiana-Mathieu N, Flesch M, Lledo G, Raoul Y, Debrix I, Buyse M, de Gramont A (2007) Phase III study comparing a semimonthly with a monthly regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: final results of GERCOR C96.1. J Clin Oncol 25: 3732 – 3738

Arkenau HT, Arnold D, Cassidy J, Diaz-Rubio E, Douillard JY, Hochster H, Martoni A, Grothey A, Hinke A, Schmiegel W, Schmoll HJ, Porschen R (2008) Efficacy of oxaliplatin plus bevacizumab or infusional fluorouracil/leucovorin in patients with metastatic colorectal cancer: a pooled analysis of randomized trials. J Clin Oncol 26: 5910 – 5917

Baselga J, Schoffski P, Rojo F, Dunne H, Ramos FJ, Macarulla T, Cajar R, Kisker O, Van Oosterom A, Tabernero J (2006) A phase I pharmaco-kinetic (PK) and molecular pharmacodynamic (PD) study of the combination of two anti-EGFR therapies, the monoclonal antibody (MAb) cetuximab (C) and the tyrosine kinase inhibitor (TKI) gefitinib (G), in patients (pts) with advanced colorectal (CRC), head and neck (HNC) and non-small cell lung cancer (NSCLC). J Clin Oncol (Meeting Abstracts) 24: 3006

Berry SR, Van Cutsem E, Kretzschmar A, Michael M, Rivera F, DiBartolomeo M, Mazier M, Andre N, Cunningham D (2008) Final efficacy results for bevacizumab plus standard first-line chemotherapies in patients with metastatic colorectal cancer: First BEAT. J Clin Oncol (Meeting Abstracts) 26: 4025

Bokemeyer C, Bondarenko I, Makson H, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludvig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 27: 663 – 671

Borner M, Koeberle D, Von Moos R, Saleti P, Rauch D, Hess V, Trojan A, Helbing D, Pestalozzi B, Caspar C, Ruhiestablish T, Roth A, Kappeler A, Dietrich D, Lanz D, Mingrone W (2008) Adding cetuximab to capectabine plus oxaliplatin (XELOX) in first-line treatment of metastatic colorectal cancer: a randomized phase II trial of the...
Cunningham D, Sirohi B, Pluzanska A, Utracka-Hutka B, Zaluski J, Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets

Cunningham D, Wong RP, D'haens G, Douillard J, Robertson J, Ciardiello F, Bianco R, Caputo R, Caputo R, Damiano V, Troiani T, Melisi

Ciuleanu TE, Kurteva G, Ocvirk J, Beslija S, Koza I, Papamichael D, British Journal of Cancer (2009) 100

Cappuzzo F, Finocchiaro G, Rossi E, Janne PA, Carnaghi C, Calandri C, Chau I, Cunningham D, Hickish T, Massey A, Higgins L, Osborne R, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Vrbanec D, Brodowicz T, Scheithauer W, Zielinski CC (2008) A phase II study including a biological analysis of EGFR overexpression, vs randomization, open-label CECOG phase II study evaluating the efficacy of 5-fluorouracil-refractory colorectal cancer patients. Br J Cancer 99: 717 – 723.

Cappuzzo F, Varella-Garcia M, Finocchiaro G, Skokan M, Gajajapathy S, Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets

Cascino S, Berardi R, Salvagni S, Beretta GD, Catalano V,ucci F, Sobrero A, Tagliaferri P, Labanca R, Scartozzi M, Crociocchio F, Mari E, Aridizzoni A (2008) A combination of gefitinib and FOLFLOX-4 as first-line treatment in advanced colorectal cancer patients. A GISCAD multicentre phase II study including a biological analysis of EGFR overexpression, amplification and NF-KB activation. Br J Cancer 98: 71 – 76.

Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzen F, Saltz L (2008) Randomized phase III study of capcitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 26: 2006 – 2012.

Chau I, Cunningham D, Hickish T, Massey A, Higgins L, Osborne R, Botwood N, Swainland A (2007) Gefitinib and irinotecan in patients with fluoropyrimidine-refractory, irinotecan-naive advanced colorectal cancer: a phase I – II study. Ann Oncol 18: 730 – 737.

Chau I, Norman AR, Cunningham D, Tait D, Ross PJ, Iveson T, Hill M, Hickish T, Lofos F, Jodrell D, Webb A, Oates J (2005) A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. Ann Oncol 16: 549 – 557.

Ciardiello F, Bianco R, Caputo R, Damiano V, D’haens G, Douillard J, Robertson J, Sikic BI (2008) A phase II study of gefitinib, 5-fluorouracil, leucovorin, and oxaliplatin in previously untreated patients with metastatic colorectal cancer. J Clin Oncol (Meeting Abstracts) 26: 4021.

Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG (2006) Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 368: 1329 – 1338.

Di Nicolantonio F, Martini M, Molinari F, Sartore-Bianchi A, Arena S, Saletti P, De Dosso S, Mazzucchelli L, Frattini M, Siena S, Bardelli A (2008) Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 26: 5705 – 5712.

Diaz-Rubio E, Tabernero J, Gomez-Espana A, Massuti B, Sastre J, Chaves M, Abad A, Carrato A, Queralt B, Reina JJ, Maurel J, Gonzalez-Flores E, Aparicio J, Rivera F, Losa F, Aranda E (2007) Phase III study of capcitabine plus oxaliplatin compared with continuous-infusion fluoropyrimidin plus irinotecan 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: 4224 – 4230.

Ducreux M, Bournouna M, Hebbard M, Ychou M, Lledo G, Conroy T, Adenis A, Faroux R, Rebischung C, Douillard J (2007) Efficacy and safety findings from a randomized phase III study of capcitabine (X) vs oxaliplatin (O) (XELOX) vs infusional 5-FU/LV + O (FOLFLOX-6) for metastatic colorectal cancer (MCRC). J Clin Oncol (Meeting Abstracts) 25: 4029.

Escudier B, Eisen T, Stadler WM, Szczylzik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356: 125 – 134.

Falcone A, Ricci S, Brunetti I, Pfeiffer E, Allegrini G, Barbiera C, Crino L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Graneto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFORI) combined with infusional fluorouracil, leucovorin, and irinotecan (FOLFOXIRI) as first-line treatment for metastatic colorectal cancer: the Group Oncologico Nord Ovest. J Clin Oncol 25: 1670 – 1676.

Fernandez FG, Drebis JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM (2004) Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg 240: 438 – 447.

Finocchiaro G, Cappuzzo F, Janne PA, Bencardino K, Carnaghi C, Franklin WA, Roncalli M, Crino L, Santoro A, Varella-Garcia M (2007) EGFR, HER2 and KRas as predictive factors for cetuximab sensitivity in colorectal cancer. J Clin Oncol (Meeting Abstracts) 25: 4021.

Fisher GA, Kuo T, Ramsey M, Schwartz E, Rove RV, Cho CD, Halsey J, Sikic BI (2008) A phase II study of gefitinib, 5-fluorouracil, leucovorin, and oxaliplatin in previously untreated patients with metastatic colorectal cancer. Clin Cancer Res 14: 7074 – 7079.

Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH (2005) Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol 16: 1311 – 1313.

Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG, Sikic BI, Thomson A, Venkatraman M, Davies RH, Muehling JA, Verweij J, Siena S, Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets

Fuske S, Brenner H, Chang-Claude J (2008) Pharmacogenetics in colorectal cancer: a systematic review. Pharmacogenomics 9: 1079 – 1099.

Gelber AJ, Gamucci T, Pollera CF, Di Costanzo F, Nuzzo C, Gabriele A, Signorelli C, Gasperoni S, Ferrari V, Giannarelli D, Cognetti F, Zeuli M (2007) A phase II trial of gefitinib in combination with capcitabine and oxaliplatin as first-line chemotherapy in patients with advanced colorectal cancer. Curr Med Res Opin 23: 1117 – 1123.

Geyer CE, Forster J, von Pawel J, Siewert JE, Pfeiffer DG, Pignoli PK, Gajajapathy S, Cunningham D, Humblet Y, Siena S, Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets

Gore M, Osborne R, Schwartz B, Shan M, Simantov R, Bukowski RM (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356: 125 – 134.

Gustafsson S, de la Monte S, Basu M, Abrahantes JC, Bzurykowski T, Quinna E, Cervantes A, Figer A, Lledo G, Fliesch M, Mineur L, Carola E, Ettorre PL, Rivera F, Chiarella I, Perez-Staub N, Louvet C, Andre T, Tahab-Fisch I, Tourignand C (2007) Reinroduction of oxaliplatin is associated with improved survival in advanced colorectal cancer. J Clin Oncol 25: 3224 – 3229.
with oxaliplatin, fluorouracil, and leucovorin (FOLFIRI4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 25: 1539 – 1544
Goldberg RM, Tabah-Fisch I, Bleiberg H, de Gramont A, Tournigand C, Andre T, Rothenberg ML, Green E, Sargent DJ (2006) Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. J Clin Oncol 24: 4085 – 4091.
Grothey A, Hart LL, Rowland KM, Marshall J, Cohn A, McCollum D, Stella P, Deeter R, Shahin S, Amado RG (2003) A phase II, randomized trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone in patients with metastatic colorectal cancer. J Clin Oncol 21: 672 – 670.
Grothey A, Trarbach T, Jaeger E, Hainsworth J, Wolf RA, Lloyd K, Bodoky G, Borner M, Laurent D, Jacques C. (2007) Final overall survival results of CONFIRM 1, a randomized, double-blind, placebo-controlled phase III trial in patients with metastatic adenocarcinoma of the colon or rectum receiving first line chemotherapy with oxaliplatin/S-fluorouracil/leucovorin (FOLFOX 4) and PTX7/7ZK222584 (PTX/ZK) or placebo. Euro J Cancer 5:4 Suppl): 3010
Hofheinz RD, Kubica S, Wollert J, Arnold D, Hochhaus A (2006) Gefitinib in combination with S-fluorouracil/S-5FU/folinic acid and irinotecan in patients with S-5FU/oxaliplatin- refractory colorectal cancer: a phase II/III study of the Arbeitsgemeinschaft für Internistische Onkologie (AGO). Onkologie 29: 563 – 567.
Hospers GA, Schraeppe M, Notiert JW, Wils J, van Bochove A, de Jong RS, Rodenburg CJ, Hartmann JT, Lang I, Vergauwe P, Becker K, Braunmiller D, Jossaens E, Muller L, Janssens B, Bokemeyer C, Reimer P, Link H, Spatz-Schwalbe W, Wilke HJ, Bleiberg H, Van Den BJ, Debois M, Bette U, Van Cutsem E (2005) Irinotecan combined with infusional S-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: 920 – 926.
Kohne C, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreudenhil G, Loosveld OJ, van Bochove A, Sinnige HA, Creemers GJ, Tsetse SL, Sle PH, Werter MJ, Møl L, Dalesio O, Punt CJ. (2007) Sequential vs combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. Lancet 370: 135 – 142.
Kopetz S, Abbruzzese JL (2009) Hidden Biases in an Observational Study of Bevacizumab Beyond Progression. J Clin Oncol 27(10): 1732 – 1733.
Lecomte M, Mitchell EP, Shearer H, Iannotti N, Pieribelli B, Pillai MV, Xu F, Yassine M (2009) Impact of pre-emptive skin toxicity treatment on panitumumab-related skin toxicities quality of life in patients with metastatic colorectal cancer: Results from STEPP. Proc 2009 Gastrointestinal Cancers Symposium 291.
Lai R, Dickson J, Cunningham D, Chau I, Norman AR, Ross PJ, Topham C, Middleton G, Hill M, Oates J (2004) A randomized trial comparing defined-duration with continuous irinotecan until disease progression in fluoropyrimidine and thymidylate synthase inhibitor-resistant advanced colorectal cancer. J Clin Oncol 22(10): 2003 – 2010.
Lievre A, Bachet JB, Le Normand C, Chevalier S, Beige V, Landi B, Emile JF, Cot JF, Tommasi G, Penna C, Dureux M, Rouvier P, Penault-Llorca F, Laurent-Puig P (2006) KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res 66: 3992 – 3995.
Maindrou-Goebel F, Lledo G, Chibaudel B, Mineur L, Andre T, Bennamoun M, Mahbo M, Artru P, Louvet C, de Gramont A (2007) Final results of OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC): A GERCOR study. J Clin Oncol (Meeting Abstracts) 25: 4013.
Mancuso MR, Davis R, Norberg SM, O’Brien S, Sennino B, Nakaahara T, Yao VJ, Inai T, Brooks F, Freimark B, Shalinsky DR, Hsu-Lowe DD, McDonald DM (2006) Rapid vascular regrowth in tumors after reversal of VEGF inhibition. J Clin Invest 116: 2610 – 2612.
Mandala M, Barni S, Floriani I, Isa L, Fornarini G, Marangolo M, Mosconi S, Corsi D, Rulli E, Frontini L, Cortesi E, Zaniboni A, Aglietta M, Labianca R (2009) Incidence and clinical implications of venous thromboembolism in advanced colorectal cancer patients: the GIS-CAT study. Eur J Cancer 45: 65 – 71.
Matar P, Rojo F, Cassia R, Moreno-Bueno G, Di Cosimo S, Tabernero J, Guzman M, Rodriguez S, Arribas J, Palacios J, Baselga J (2004) Combined epidermal growth factor receptor targeting with the tyrosine kinase inhibitor gefitinib (ZD1839) and the monoclonal antibody cetuximab (IMC-C225): superiority over single-agent receptor targeting, Clin Cancer Res 10: 6487 – 6501.
Maughan TS, James RD, Kerr DJ, Ledermann JA, Seymour MT, Topham C, Mc Ardle C, Craft D, Stephens RJ (2003) Comparison of intermittent and continuous palliative chemotherapy for advanced colorectal cancer: a multicentre randomised trial. *Lancet* 361: 457–464

Mayer RJ (2007) Should capcitabine replace infusional fluorouracil and leucovorin when combined with oxaliplatin in metastatic colorectal cancer? *J Clin Oncol* 25: 4165–4167

Miller K, Wang M, Gralow J, Dickler M, Coleghie M, Perea EA, Shenker T, Cella D, Davidson NE (2007) Paclitaxel plus bevacizumab vs paclitaxel alone for metastatic breast cancer. *N Engl J Med* 357: 2666–2676

Moroni M, Veronese S, Benvenuti S, Marrappese G, Sartore-Bianchi A, Di Nicolantonio F, Gambacorta M, Siena S, Bardelli A (2005) Gene copy number for epidermal growth factor receptor (EGFR) and clinical response to antiEGFR treatment in colorectal cancer: a cert study. *Lancet Oncol* 6: 279–286

Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA (2007) Sunitinib vs interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 356: 115–124

Nordic Gastrointestinal Tumour Adjuvant Therapy Group (1992) Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomised trial. *J Clin Oncol* 10: 904–911

Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Nordic Gastrointestinal Tumor Adjuvant Therapy Group (1992) Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomised trial. *J Clin Oncol* 10: 904–911

O’Connell MJ, Laurie JA, Kahn M, Fitzgibbons Jr RJ, Erlitchman C, Shepherd L, Moertel CG, Kocha WI, Pazdur R, Wianez HS, Rubin J, Vukov AM, Donohue JH, Krook JE, Figueroed A (1998) Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. *J Clin Oncol* 16: 295–300

Panagias KS, Ben Porat L, Dickler MN, Chapman PB, Schrag D (2007) When you look matters: the effect of assessment schedule on progression-free survival. *J Natl Cancer Inst* 99: 428–432

Perea EA, Suman VJ, Davidson NE, Martino S, Kaufman PA, Lingle WL, Panageas KS, Sobrero AF, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, Lorusso V, Oliva C, Ronzoni M, Siena S, Zuradelli M, Mari E, Presssiani T, Carnaghi C (2008) A phase II randomized multicenter trial of gefitinib plus FOLFIRI and FOLFOX in patients with metastatic colorectal cancer. *Ann Oncol* 19: 1886–1893

Sargent DJ, Kohnne CH, Sanoff HK, Bot BM, Seymour MT, de Gramont A, Porschen R, Saltz LB, Rougier P, Tournigand C, Douillard YJ, Stephens RJ, Grothey A, Goldberg RM (2009) Pooled Safety and Efficacy Analysis Examining the Effect of Performance Status on Outcomes in Nine First-Line Treatment Trials Using Individual Data From Patients With Metastatic Colorectal Cancer. *J Clin Oncol* 27(12): 1948–1955

Sartore-Bianchi A, Moroni M, Veronese S, Carnaghi C, Bajetta E, Lorusso V, Cristofori S, Bajetta E, Luppi G, Sobrero A, Barone C, Saccucchi S, Colucci G, Cortesi E, Nichelli M, Gambacorta M, Siena S (2007) Epidermal growth factor receptor gene copy number and clinical outcome of metastatic colorectal cancer treated with panitumumab. *J Clin Oncol* 25: 3238–3245

Scartozzi M, Beazzi I, Pierantoni C, Mandolesi A, Loupakis F, Zaniboni A, Catalano V, Quadri A, Zorai F, Berardi R, Biscotti T, Labianca R, Falcone A, Cascinu S (2007) Nuclear factor-kB tumor expression predicts response and survival in irinotecan-refractory metastatic colorectal cancer treated with cetuximab-irinotecan therapy. *J Clin Oncol* 25: 3930–3935

Scope A, Agero AL, Dusza SW, Myskowski PL, Lieb JA, Saltz L, Kemeny NE, Halpern AC (2007) Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol* 25: 5390–5396

Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, Zhang ZYJ, Daniel S, Thrasher DB, Ashcroft A, Moyney A, Perry DR, Meade AM, Thompson L, Griffiths GO, Parmar MK, Stephens RJ (2007a) Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 370: 143–152

Seymour MT, Maughan TS, Wasan HS, Brewster AE, Shepherd SF, O’Mahoney MS, May BR, Thompson LC, Meade AM, Langley RE, on behalf of the FOCUS (2007b) Capecitabine (Cap) and oxaliplatin (Ox) in elderly and/or frail patients with metastatic colorectal cancer: The FOCUS2 trial. *J Clin Oncol (Meeting Abstracts)* 25: 9030

Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zaubier A, Hawk E, Bertagnolli M (2005) Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 352: 1071–1080

Stebbing J, Harrison M, Glyne-Jones R, Bridgewater J, Propper D (2008) A phase II study to determine the ability of gefitinib to reverse fluoropyrimidine resistance in metastatic colorectal cancer (the INFOMY study). *Br J Cancer* 98: 716–719

---

*British Journal of Cancer (2009) 100(11), 1704–1719 © 2009 Cancer Research UK*
Tang PA, Bentzen SM, Chen EX, Siu LL (2007) Surrogate end points for median overall survival in metastatic colorectal cancer: literature-based analysis from 39 randomized controlled trials of first-line chemotherapy. *J Clin Oncol* 25: 4562 – 4568

Tejpar S, Peeters M, Humblet Y, Gelderblom H, Vermorken J, Viret F, Glimelius B, Ciardiello F, Kisker O, Van Cutsem E (2007) Phase I/II study of cetuximab dose-escalation in patients with metastatic colorectal cancer (mCRC) with no or slight skin reactions on cetuximab standard dose treatment (EVEREST): Pharmacokinetic (PK), Pharmacodynamic (PD) and efficacy data. *J Clin Oncol (Meeting Abstracts)* 25: 4037

Tejpar S, Peeters M, Humblet Y, Vermorken J, De Hertogh G, De Roock W, Nippgen J, von Heydebreck A, Stroh C, Van Cutsem E (2008) Relationship of efficacy with KRAS status (wild type vs mutant) in patients with irinotecan-refractory metastatic colorectal cancer (mCRC), treated with irinotecan (q2w) and escalating doses of cetuximab (q1w): The EVEREST experience (preliminary data). *J Clin Oncol (Meeting Abstracts)* 26: 4001

Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG, Erdkamp FL, Vos AH, van Groeningen CJ, Sinnige HA, Richel DJ, Voest EE, Dijkstra JR, Vink-Borger ME, Antonini NF, Mol L, van Krieken JH, Dalesio O, Punt CJ (2009) Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 360: 563 – 572

Tonra JR, Deevi DS, Corcoran E, Li H, Wang S, Carrick FE, Hicklin DJ (2006) Synergistic antitumor effects of combined epidermal growth factor receptor and vascular endothelial growth factor receptor-2 targeted therapy. *Clin Cancer Res* 12: 2197 – 2207

Tournigand C, Achille E, Lledo G, Quinaux E, Couteau C, Buyse M, Landi B, Colin P, Louvet C, de Gramont A (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 22: 229 – 237

Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, Andre T, Tabah-Fisch L, de Gramont A (2006) OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer–a GERCOR study. *J Clin Oncol* 24: 394 – 400

Van Cutsem E, Kohnle CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D’haens G, Pinter T, Lim B, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 360: 1408–1417

Van Cutsem E, Lang J, D’haens G, Moiseyenko V, Zaluski J, Folprecht G, Tejpar S, Nippgen J, Stroh C, Rougier P (2008) Kras status and efficacy in the Crystal study: 1-st line treatment of patients with metastatic colorectal cancer receiving FOLFIRI with or without cetuximab. *Ann Oncol* 19: viii44

Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendilsz A, Neyns B, Canon J, Van Laethem JL, Maurel J, Richardson G, Wolf M, Amado RG (2007) 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: 1658 – 1664

Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, Eng C, Lauwers GY, Mino-Kenudson M, Risio M, Muratore A, Capussotti L, Curley SA, Abdalla EK (2006) Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 24: 2065 – 2072

Wilke H, Glynne-Jones R, Thaler J, Adenis A, Preusser P, Aguilar EA, Aapro MS, Esser R, Loos AH, Siena S (2008) Cetuximab plus irinotecan in heavily pretreated metastatic colorectal cancer progressing on irinotecan: MABEL Study. *J Clin Oncol* 26: 5335 – 5343

Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C (2008) Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. *Eur J Cancer* 44: 1507 – 1515

Zampino MG, Magni E, Massacesi C, Zaniboni A, Martignetti A, Zorzino L, Lorizzo K, Santoro L, Boselli S, de Braud F (2007) First clinical experience of orally active epidermal growth factor receptor inhibitor combined with simplified FOLFIRX as first-line treatment for metastatic colorectal cancer. *Cancer* 110: 752 – 758