The past decade has seen major advances in the treatment options for colorectal cancer. The second part of this month’s special feature focuses on the current and future drug treatment of the disease.

**ADJUVANT CHEMOTHERAPY**

The initial treatment of colorectal cancer is surgery, but the disease recurs in about half of patients. Adjuvant chemotherapy is given after surgery with the aim of “mopping” up any cancer cells that are not removed during the operation.

Because of the proximity to surrounding tissues, the local recurrence rates are generally higher for rectal tumours. The adjuvant treatment of colon and rectal tumours are therefore considered separately. The adjuvant treatment of rectal cancers (usually with a combination of chemotherapy and radiotherapy) is beyond the scope of this article.

**Colon cancer** By assessing the stage of the tumour at the time of surgery it is possible to identify patients who are more likely to progress either locally or with metastatic disease and thus identify those who are likely to benefit from adjuvant chemotherapy. Patients who are at higher risk of having residual disease or developing metastatic disease are those with stage II or Dukes B2 tumours with full thickness penetration of the bowel wall, or patients with lymph node involvement (stage III or Dukes C). Prognostic factors can also be used to identify patients with a higher risk of recurrence. These include obstruction or perforation of the bowel wall,2 poorly differentiated histology and tumours not demonstrating microsatellite instability [an abnormal number of base pair repeats in regions of DNA which have short repeating segments].3

Although the role of adjuvant chemotherapy for stage III tumours is well established,14 the value of adjuvant chemotherapy for Dukes’ B/stage II disease has not yet been proven.1 This may be due to the good prognosis of patients with stage II disease and the large number of patients who would need to be treated in the context of a clinical trial to show a significant difference in survival. Although there is a lack of evidence to support the use of adjuvant chemotherapy in patients with stage II disease, it may be an option in higher risk patients (eg, those who present with intestinal obstruction or perforation or with a poorly differentiated tumour).3

**Choice of adjuvant therapy** In the 1990s, 5-FU/levamisole was the standard treatment for patients receiving adjuvant chemotherapy for colon cancer. However, following the change in practice in advanced colorectal cancer to using 5-FU with calcium folinate (calcium leucovorin, LV), the use of this combination for adjuvant treatment was the next logical area for investigation. The efficacy of this regimen was subsequently confirmed.6–8 High dose LV does not provide any extra benefit over low dose LV in terms of survival or recurrence9 and there is no additional benefit in giving 12 months’ rather than six months’ treatment.10 Three months of continuous 5-FU has been shown to produce similar overall survival and relapse-free survival when compared with six months of bolus 5-FU/LV11 and provides an alternative treatment schedule. However, while continuous 5-FU is associated with a more favourable toxicity profile, it requires the insertion of an indwelling central venous catheter, which may be associated with inconvenience, extra costs and complications relating to the line.

The role of oxaliplatin in the adjuvant treatment of colon cancer has been investigated in the MOSAIC study.12 This large European phase III trial compared the de Gramont schedule of 5-FU/LV with FOLFOX4 (see Table 1, p184) in patients with stage II or III colon cancer. At three years follow-up, disease-free survival was...
significantly superior for patients on FOLFOX4. Overall survival data are not yet available. FOLFOX4 appears to be safe in this group of patients with a similar rate of death from any cause in each arm of the trial.

The efficacy of irinotecan with 5-FU/LV for adjuvant treatment is currently being assessed in the context of phase III trials.

### Advanced Disease

Colorectal cancer is defined as advanced if, at the time of presentation or recurrence, it has either metastasised to distant organs or is so locally invasive as to make curative surgical resection impossible. Common sites of disease recurrence are the liver, lung, lymph nodes, bones or pelvis.

Approximately 30 per cent of patients present with advanced colorectal cancer and the most commonly used drugs in the treatment of advanced disease are the fluoropyrimidines.

The fluoropyrimidines, such as 5-FU, are antimetabolite drugs that inhibit DNA synthesis by several mechanisms including inhibition of thymidylate synthase. They also inhibit RNA synthesis by mis-incorporation into RNA. The oral fluoropyrimidines, capecitabine and tegafur, offer patients the advantage of being able to take chemotherapy orally, which is less disruptive to their lifestyle than intravenous treatment.

However, agents such as oxaliplatin and irinotecan have provided new treatment options.

The goal of chemotherapy is to increase survival, improve or maintain quality of life and control symptoms.

5-FU 5-FU is usually administered by intravenous injection or infusion. It is converted to 5-fluorodeoxyuridine monophosphate (FdUMP) by a variety of different metabolic pathways. FdUMP combines with methylenetetrahydrofolate (CH$_2$FH$_4$) to form a stable complex with thymidylate synthase, thus inhibiting the enzyme. Fluorouracil as a stable complex with thymidylate synthase, inhibits the enzyme principally located in the liver and in tumour tissue. The final conversion to 5-fluorouracil is catalysed by the enzyme thymidine phosphorylase, which is present at higher levels in tumour tissue than in normal tissue. Through this activation cascade, 5-FU is preferentially released at the tumour site, thereby minimising systemic exposure to 5-FU.

5-FU has a short half-life and acts on the S phase of the cell cycle [a phase of DNA synthesis]. There have been attempts to utilise these properties with the aim of improving clinical outcomes by altering the administration schedule of 5-FU.

In a 1998 meta-analysis, higher response rates were seen with continuous infusion 5-FU when compared with bolus 5-FU, and there was a significantly improved overall survival. While the incidence of diarrhoea, mucositis and nausea was similar with either schedule, haematological toxicity was greater for bolus 5-FU and hand-foot syndrome greater for continuous infusion 5-FU. When 5-FU and LV given in the “Mayo” or “NCCTG” schedule (see Table 1) was compared with 5-FU and LV in the de Gramont schedule (see Table 1), higher response rates and progression free survival were seen with the de Gramont schedule. However, while there was a trend towards improved survival, the result was not statistically significant. In practice both infused 5-FU (usually delivered via an indwelling central venous catheter) and bolus 5-FU are used. These are usually given in combination with either high or low dose LV. Continuous infusion 5-FU has been increasingly used in Europe, whereas in the United States, the inconvenience, cost and complications relating to central venous catheters have maintained the popularity of bolus 5-FU/LV.

Capecitabine Because 5-FU has unreliable bioavailability and undergoes rapid catabolic clearance by dihydropyrimidine dehydrogenase (DPD), it is unsuitable for oral delivery. Capecitabine is a pro-drug which is absorbed unchanged from the gastrointestinal tract. It undergoes a three step enzymatic conversion to 5-FU. It is primarily metabolized in the liver by the enzyme carboxylesterase to 5'-deoxy-5-fluorocytidine (5'-DFCR), which is then converted to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase, an enzyme principally located in the liver and in tumour tissue. The final conversion to 5-fluorouracil is catalysed by the enzyme thymidine phosphorylase, which is present at higher levels in tumour than in normal tissue. Through this activation cascade, 5-FU is preferentially released at the tumour site, thereby minimising systemic exposure to 5-FU.

Side effects are similar to those of 5-FU and include myelosuppression, mucositis, diarrhoea, nausea, hand-foot syndrome and, rarely, cerebellar syndrome and chest pain.

5-FU has been increasingly used in Europe, whereas in the United States, the inconvenience, cost and complications relating to central venous catheters have maintained the popularity of bolus 5-FU/LV.
There is currently no randomised study to support the routine substitution of infused 5-FU with capecitabine in combination with other agents such as oxaliplatin and irinotecan. However, ongoing clinical trials will help demonstrate whether these combinations will provide clinical benefits.

Capecitabine is currently licensed for first-line monotherapy treatment of colorectal cancer. NICE recommend capecitabine as an option for the first-line treatment of metastatic colorectal cancer.

**Tegafur/uracil (UFToral)**

UFToral is a combination of tegafur and uracil at a molar ratio of 1:4. Tegafur is a pro-drug of 5-FU which is reliably absorbed from the gastrointestinal tract. Uracil is a competitive inhibitor of DPD thus inhibiting the degradation of 5-FU. Side effects are similar to those with 5-FU, including myelosuppression, mucositis, diarrhoea, asthenia, rash and, rarely, angina.

Trials of tegafur/uracil (UFT) plus oral LV versus bolus 5-FU/LV have demonstrated similar efficacy in terms of response rate and overall survival. However, time to progression in one trial favoured 5-FU/LV. UFT/LV was associated with less stomatitis, myelosuppression, incidence of infection, diarrhoea, nausea and vomiting. In contrast UFT/LV was associated with more hyperbilirubinaemia.

Tegafur/uracil is licensed as first-line monotherapy treatment of colorectal cancer. NICE recommend tegafur/uracil in combination with LV as an option for the first-line treatment of metastatic colorectal cancer.

**Irinotecan**

Irinotecan (CPT-11) is a camptothecin analogue. It is an inhibitor of topoisomerase I, an enzyme responsible for the unwinding of DNA during DNA replication and therefore essential for cell division. It is metabolised by carboxyl esterase to the active metabolite SN-38 in most tissues. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces replication arrest with breaks in single-strand DNA.

Side effects of irinotecan include delayed onset diarrhoea occurring from 24 hours after the infusion, myelosuppression, nausea and vomiting, alopecia and acute cholinergic syndrome (characterised by early onset diarrhoea, salivation, lacrimation and abdominal cramps within 24 hours of administration).

Irinotecan has demonstrated statistically significant survival benefits when compared with best supportive care or 5-FU based chemotherapy in patients with 5-FU refractory colorectal cancer. In addition, irinotecan in combination with 5-FU/LV for the first-line treatment of advanced disease has been shown to produce statistically significant advantages in response rate, time to progression and median survival when compared with 5-FU/LV. In one of these trials, a regimen of bolus 5-FU/LV in combination with irinotecan (IFL, see Table 1) was used. There have since, however, been
concerns regarding the toxicity of this regimen, due to a disproportionate number of deaths in the first 60 days of study entry in the IFL arm of two recent adjuvant and metastatic clinical trials. This death rate has largely been attributed to gastrointestinal toxicity and an increased incidence of thromboembolic events.\textsuperscript{30} 

This concern has not been raised for the combination of irinotecan with infused 5-FU. Irinotecan is licensed for the first-line treatment of advanced colorectal cancer in combination with 5-FU/LV and as a single agent for patients who have failed 5-FU.\textsuperscript{25} 

NICE currently does not recommend irinotecan in combination with 5-FU/LV for routine first-line therapy of advanced colorectal cancer.\textsuperscript{31} It does, however, recommend irinotecan monotherapy for patients who have failed 5-FU.\textsuperscript{31} 

Oxaliplatin 

Oxaliplatin is a third-generation platinum derivative. The mechanism of action of oxaliplatin includes inter and intra cross-links, which result in the disruption of DNA synthesis and leads to cytotoxic and antitumour effects. Unlike other platinum compounds it causes no significant nephrotoxicity, ototoxicity or alopecia.\textsuperscript{32} Its side effect profile includes haematological and gastrointestinal toxicity.\textsuperscript{33} However, the dose limiting toxicity of oxaliplatin is neurological, occurring in 95 per cent of patients on oxaliplatin. It comprises acute paraesthesias and dysaesthesias (often cold-related) and cumulative sensory neuropathy. 

Acute paraesthesias and dysaesthesias occur during or soon after the infusion and usually resolve over the course of a few hours or days. A rare pharyngolaryngeal dysaesthesia may occur and is characterised by a subjective sensation of dysphagia or dyspnoea, jaw spasm or an abnormal tongue sensation. The incidence of this syndrome is estimated to be between 1 and 2 per cent.\textsuperscript{33} Increasing the infusion rate from two to six hours may improve the symptoms associated with this syndrome. Patients should be advised to avoid cold drinks or exposure to cold weather immediately following the infusion. The cumulative sensory neuropathy is a delayed reaction and may result in impaired sensation or secondary ataxia. This effect does, however, appear to be at least partly reversible in 75 per cent of affected patients within three to five months of therapy discontinuation.\textsuperscript{34} 

The response rate for oxaliplatin monotherapy in patients with 5-FU refractory disease is low at only 10 per cent.\textsuperscript{35} However, the combination of oxaliplatin with 5-FU does appear to be synergistic, resulting in response rates of 20 per cent in patients refractory to 5-FU who were treated with oxaliplatin in combination with 5-FU/LV.\textsuperscript{36} 

Two randomised controlled trials of oxaliplatin plus 5-FU/LV versus 5-FU/LV as first-line treatment of advanced colorectal cancer demonstrated an increase in progression free survival and response rate for the
Neither trial demonstrated a survival advantage.37,38

A recent study compared irinotecan plus bolus 5-FU/LV (IFL) versus irinotecan plus oxaliplatin (IROX) versus oxaliplatin plus infused 5-FU/LV (FOLFOX4) as first-line treatment of metastatic colorectal cancer.39

Time to progression and response rates in patients on the FOLFOX4 arm significantly exceeded both IFL and IROX. In terms of median survival FOLFOX4 exceeded IFL but did not differ from IROX.39

Oxaliplatin is licensed for the treatment of metastatic colorectal cancer in combination with 5-FU/LV.33 NICE does not recommend oxaliplatin in combination with 5-FU/LV for routine first-line treatment of advanced colorectal cancer. It recommends

<table>
<thead>
<tr>
<th>Regimen</th>
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<th>Interval</th>
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<tbody>
<tr>
<td>NCCTG/Mayo clinic schedule</td>
<td>LV 20mg/m² 5-FU 425mg/m²</td>
<td>iv bolus iv bolus</td>
<td>On days 1–5, repeated every 28 days</td>
</tr>
<tr>
<td>LV5FU2/de Gramont</td>
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<td>iv bolus ivi over 2 hours ivi over 22 hours</td>
<td>On days 1 &amp; 2, repeated every 14 days</td>
</tr>
<tr>
<td>MdG (modified de Gramont as per the MRC CR08 FOCUS trial)</td>
<td>Calcium levofolinate 175mg 5-FU 400mg/m² 5-FU 2800mg/m²</td>
<td>ivi over 2 hours iv bolus ivi over 46 hours</td>
<td>On day 1, repeated every 14 days</td>
</tr>
<tr>
<td>AIO</td>
<td>LV 500mg/m² 5-FU 2,600mg/m²</td>
<td>ivi over 2 hours ivi over 24 hours</td>
<td>Once a week for 6 weeks, repeated every 8 weeks</td>
</tr>
<tr>
<td>Lokich</td>
<td>5-FU 300mg/m²/day</td>
<td>ivi over 24 hours</td>
<td>Continuous infusion days 1–21, without interruption, repeat every 21 days</td>
</tr>
<tr>
<td>Capecitabine</td>
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<td>Tegafur/uracil + calcium folinate</td>
<td>300mg/m²/day tegafur 672mg/m²/day uracil LV 90mg/day</td>
<td>orally in 3 divided doses for 28 days followed by a 7 day break</td>
<td>Repeated every 35 days</td>
</tr>
<tr>
<td>Raltitrexed</td>
<td>3mg/m²</td>
<td>ivi over 15 minutes</td>
<td>Repeated every 21 days</td>
</tr>
</tbody>
</table>

**Irinotecan-containing regimens**

| | | |
| Irinotecan | 350mg/m² | ivi over 30–90 minutes | Repeated every 21 days |
| FOLFIRI | LV 400mg/m² 5-FU 400mg/m² | ivi over 2 hours ivi over 90 minutes | On day 1, repeated every 14 days |
| | Irinotecan 180mg/m² 5-FU 2,400 (– 3,000)mg/m² | iv bolus ivi over 46 hours | |
| IFL | Irinotecan 125mg/m² LV 20mg/m² 5-FU 500mg/m² | ivi over 90 minutes iv bolus iv bolus | Once a week for 4 weeks repeated every 6 weeks |

**Oxaliplatin-containing regimens**

| | | |
| FOLFOX4 | LV 200mg/m² Oxaliplatin 85mg/m² 5-FU 400mg/m² 5-FU 600mg/m² | ivi over 2 hours ivi over 2 hours iv bolus ivi over 22 hours | On days 1 and 2 (oxaliplatin on day 1 only), repeated every 14 days |
| FOLFOX6 | LV 400mg/m² Oxaliplatin 100mg/m² 5-FU 400mg/m² 5-FU 2,400 (– 3,000)mg/m² | ivi over 2 hours ivi over 2 hours ivi over 22 hours | On day 1, repeated every 14 days |

**Table 1: Commonly used chemotherapy regimens for colorectal cancer**

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**Irinotecan-containing regimens**

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**Oxaliplatin-containing regimens**

| | | |
| FOLFOX4 | LV 200mg/m² Oxaliplatin 85mg/m² 5-FU 400mg/m² 5-FU 600mg/m² | ivi over 2 hours ivi over 2 hours iv bolus ivi over 22 hours | On days 1 and 2 (oxaliplatin on day 1 only), repeated every 14 days |
| FOLFOX6 | LV 400mg/m² Oxaliplatin 100mg/m² 5-FU 400mg/m² 5-FU 2,400 (– 3,000)mg/m² | ivi over 2 hours ivi over 2 hours ivi over 22 hours | On day 1, repeated every 14 days |

LV = calcium folinate (calcium leucovorin), 5-FU = 5-fluorouracil, iv = intravenous, ivi = intravenous infusion. The dose of calcium levofolinate is generally half that of calcium folinate. Some of these regimens are not used according to the licensed indication for the drug(s). In addition, some of the above regimens are not described in the text of the article, although they are commonly used in clinical practice.
Panel 1: NICE guidance on the treatment of colorectal cancer

<table>
<thead>
<tr>
<th>Technology appraisal</th>
<th>Date</th>
<th>Guidance</th>
</tr>
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<tbody>
<tr>
<td>Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer (no 33)</td>
<td>March 2002</td>
<td>Neither irinotecan nor oxaliplatin in combination with 5-FU/LV is recommended for routine first-line therapy for advanced colorectal cancer. Oxaliplatin should be considered for use as first-line therapy, in combination with 5-FU/LV, in advanced colorectal cancer in patients with metastases that are confined solely to the liver and may become resectable following treatment. Irinotecan monotherapy is recommended in patients who have failed an established 5-FU containing treatment regimen. Raltitrexed is not recommended for the treatment of advanced colorectal cancer. Its use for this patient group should be confined to appropriately designed clinical studies.</td>
</tr>
<tr>
<td>Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer (no 61)</td>
<td>May 2003</td>
<td>Oral therapy with either capecitabine or tegafur uracil (in combination with calcium folinate [folic acid]) is recommended as an option for the first-line treatment of metastatic colorectal cancer. The choice of regimen (5-FU/LV or oral treatment) should be made jointly by the individual and the clinician(s) responsible for treatment. The use of capecitabine or tegafur/uracil should be supervised by oncologists who specialise in colorectal cancer.</td>
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A trial published this year, compared irinotecan in combination with infused 5-FU/LV (FOLFIRI) versus oxaliplatin in combination with infused 5-FU/LV (FOLFOX6) as first-line treatment in patients with advanced colorectal cancer. On disease progression patients crossed over to the other regimen, ie, patients on FOLFOX6 crossed to FOLFIRI and patients on FOLFIRI crossed to FOLFOX6. The objective was to determine the best therapeutic sequence. Response rate, first-line progression free survival, second progression free survival and overall survival did not differ between the two arms. Therefore, the superiority of oxaliplatin plus 5-FU/LV or irinotecan plus 5-FU/LV as first-line therapy cannot be concluded at this time.

Current NICE guidance restricts the use of irinotecan to second-line therapy and stipulates that oxaliplatin can only be used as first-line therapy in combination with 5-FU/LV in advanced colorectal cancer in patients with liver metastases that may become resectable following treatment.

We await the results of the MRC CR08 FOCUS trial to see if any conclusions can be made with regard to whether use of either of these drugs initially is more advantageous to using them sequentially following 5-FU/LV.

Liver confined metastases Of the patients that present with advanced colorectal cancer, 11 per cent have liver metastases which are suitable for “downstaging”, ie, giving chemotherapy with the aim of shrinking the metastases to make them resectable. In addition, 50 per cent of patients whose disease recurs after surgery will have metastases in the liver. The surgical removal of liver metastases has a significant effect on patients’ long-term survival. The five-year survival for patients with advanced colorectal cancer with unresectable liver metastases is approximately 3 per cent. This increases to 28–34 per cent when oxaliplatin and 5-FU/LV are given to shrink metastases so that surgery is possible. Unfortunately two thirds of patients have recurrence of their disease after resection of liver metastases. The role of adjuvant therapy following metastectomy has not been established. NICE has approved oxaliplatin as first-line therapy, in combination with 5-FU/LV, in patients with advanced colorectal cancer with potentially resectable metastases confined solely to the liver. |

NICE guidance There are two NICE technology appraisals which give guidance on the use of certain drugs in colorectal cancer:

- Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer (March 2002)
- Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer (May 2003)

A summary of the guidance is given in Panel 1. Neither irinotecan nor oxaliplatin are recommended for routine first-line treatment of advanced colorectal cancer.

New therapies Of the agents under development for the treatment of colorectal cancer, two monoclonal antibodies, cetuximab and bevacizumab, are the most advanced in terms of development.

Cetuximab The epidermal growth factor receptor (EGFR) is a transmembrane
receptor which possesses tyrosine kinase activity. EGFR is overexpressed in 25–80 per cent of colorectal cancers and is associated with advanced disease. Activation of the EGFR leads to a down-stream signalling cascade, with multiple effects, including cell proliferation, inhibition of apoptosis, angiogenesis, invasion and metastasis.

Cetuximab (Erbitux) is a chimeric monoclonal antibody that binds to the EGFR, and has demonstrated efficacy in tumour types which overexpress EGFR, for example head and neck, and colorectal cancer.

The Bowel Oncology and Cetuximab Antibody (BOND) study was a randomised, multicentre trial in patients with metastatic colorectal cancer whose disease had progressed on irinotecan-based regimens. Patients were randomised to cetuximab plus irinotecan versus cetuximab alone. Only patients with EGFR expression on tumour tissue were entered into the study. Results presented last year showed higher response rates and longer time to disease progression in the combination arm compared with cetuximab alone. Median survival durations were 8.6 and 6.9 months' respectively.

The most common grade 3/4 adverse events occurring in patients receiving cetuximab monotherapy were asthenia, acne-like rash, abdominal pain, nausea and vomiting. The incidence of hypersensitivity reactions was 3.5 per cent. The most common grade 3/4 adverse events reported by patients receiving cetuximab in combination with irinotecan were diarrhoea, asthenia, neutropenia, acne-like rash and nausea and vomiting. There does, however, appear to be a correlation between the incidence of skin rash and response to treatment. In the patients who had no rash, the response rates were 6.3 per cent for the combination arm and 0 per cent for the monotherapy arm. In patients who had a grade 2 or greater skin rash, the response rate was 33.6 per cent for the combination arm and 20 per cent for the monotherapy arm.

The commonly used dose of cetuximab is 400mg/m² initially, followed by 250mg/m² administered each week. An antihistamine such as chlorphenamine given before the infusion helps to prevent hypersensitivity reactions. The initial loading dose should be given over 120 minutes with subsequent infusions over 60 minutes, and patients observed for signs of hypersensitivity during and 60 minutes after the infusion. Cetuximab is currently licensed in Switzerland and is in the preregistration phase in the EU. It recently received Food and Drug Administration (FDA) approval in the United States.

**Bevacizumab** Angiogenesis or new blood vessel formation is essential for tumour development and the formation of metastasis. Bevacizumab is a recombinant humanised monoclonal antibody to vascular endothelial cell growth factor (VEGF), an angiogenic factor which stimulates angiogenesis. In a phase III trial of irinotecan plus bolus 5-FU/LV (IFL) versus IFL plus...
bevacizumab 5mg/kg, the combination of bevacizumab and IFL was associated with statistically significant higher response rates, progression free survival and overall survival. The incidence of hypertension was greater in the combination arm. Bevacizumab (Avastin) has recently received FDA approval in the United States.

**REFERENCES**


**DISCUSSION**

The introduction of new drugs for the treatment of colorectal cancer has extended the life-expectancy for patients with this disease. Ongoing trials will further clarify the optimal scheduling of the available cytotoxic agents.

The first of a new generation of agents targeting specific abnormalities in the pathway of carcinogenesis have demonstrated exciting potential in initial randomised clinical trials. The funding of these drugs within the NHS will remain a significant health economic challenge for the foreseeable future.


