Acta Oncologica, 2005; 44: 203–217

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AN ACTA ONCOLOGICA EXPERT REPORT

Targeted drugs in metastatic colorectal cancer with special emphasis on guidelines for the use of bevacizumab and cetuximab: An Acta Oncologica expert report

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Abstract

From having been a 'single-drug not very interesting cancer type' from a medical treatment perspective, treatment of colorectal cancer (CRC) has during the past five years become a more complex issue of the appropriate use of several cytotoxic drugs sometimes integrated with advanced metastatic surgery with curative intent. The new drugs have provided significant benefit to the patients, so far mostly in the metastatic setting but also in adjuvant treatment. The significant progress in molecular and tumour biology has produced a great number of new 'targeted' drugs that are now in various stages of clinical development. Two of these drugs, the monoclonal antibodies bevacizumab (Avastin™) and cetuximab (Erbitux™), directed against VEGF and EGFR, respectively, have recently been approved within the EU for use in metastatic CRC. This Nordic Expert Consensus Report summarizes the current status of chemotherapy in metastatic CRC, overviews the clinical status of targeted drugs in CRC and, finally, provides guidelines for the routine clinical use of bevacizumab and cetuximab based on the most recently available clinical data.

In colorectal cancer (CRC), surgery is the mainstay of treatment but during the past decade the role of chemotherapy has expanded considerably, both in the adjuvant and the advanced settings. From being dominated by bolus injections of 5-fluorouracil (5-FU), chemotherapy has made considerable progress in CRC by biochemical modulation from leucovorin (LV) of the 5-FU effect [1], the development of infused 5-FU/LV regimens [2,3] and the introduction of two new cytotoxic drugs, irinotecan and oxaliplatin [4–7]. In CRC, two targeted drugs have recently become available within the EU; cetuximab (CX; Erbitux™), a monoclonal antibody blocking the epidermal growth factor receptor [EGFR; 8,9] and the first drug targeting angiogenesis, the monoclonal antibody bevacizumab [BV: Avastin™; 9,10]. Given their price tag, they will also add to the already ongoing discussion on health-economics and, more specifically, cost-benefit aspects of medical treatment in CRC.

Given this scenario, the aims of the present report are to overview the current status of the clinical development of targeted drugs for treatment of CRC and to provide Nordic Expert Recommendations for the routine clinical use of CX and BV in CRC. To fully understand the clinical role of these antibodies and since they are to be combined with chemotherapy, it was also considered necessary to summarize the current principles of chemotherapy in metastatic CRC.

Methods

Principles for retrieval of published data and assessment of scientific evidence

To identify data on targeted drugs and chemotherapy, the medical database Medline was searched for relevant publications using the search words 'chemotherapy/targeted drugs and colorectal cancer'. Drugs were also identified in relevant publications

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(Received 1 March 2005; accepted 19 March 2005)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860510029798

and from listings in a recent overview [11], from relevant reviews in Nature Reviews Cancer, Nature Reviews Drugs Discovery and Lancet Oncology as well as from the 2002–2004 conference proceedings from the annual meetings of American Association of Clinical Oncology (ASCO) and the 2004 and 2005 ASCO gastrointestinal cancer symposiums. In addition, the cumulated knowledge within the expert group also added to literature identification. Since full reporting of final results from clinical trials considerably lags behind more preliminary reports in the abstract form, the present report included abstracted reporting to be able to consider the most recent information on the new drugs. Last revision of the paper was completed on March 18th 2005.

There are several formalized systems for assessment of scientific evidence and classification of recommendations. These were felt to be somewhat rigid and not fully applicable. Instead the support and scientific reasoning for the recommendations on the clinical use of CX and BV are given in text immediately after each statement.

Current status of chemotherapy in metastatic colorectal cancer

During the past years chemotherapy of CRC has moved from being a fairly simple question of if and how to use 5-FU and LV to become a quite complicated matter of how to most efficiently utilize the potential of the new drugs, taking into consideration the many combinations possible, the considerably different tolerance profiles, ways of administration, the matter of most appropriate sequencing of drugs/drug combinations and, finally, cost aspects [5,6,12,13].

First line therapy. Compared with best supportive care, 5-FU/LV based chemotherapy produces objective tumour response rates of approximately 20% and prolongs median survival by 4–6 months, i.e. from about 6–8 to 10–12 months [14]. Compared with bolus 5-FU/LV (Mayo regimen), infused administration of 5-FU/LV increases the tumour response rate, prolongs time to tumour progression (TTP) and marginally prolongs survival with reduced or similar severe toxicity [3,15]. Across trial comparisons also support the notion that infused 5-FU/LV regimens are somewhat more effective and less toxic than bolus regimens [16–19]. Efficacy and toxicity of bolus Nordic 5-FU/LV is seemingly comparable to infused regimens [20,21]. However, there is not yet any publication on a direct comparison between this regimen and infused 5-FU/LV, but results from a randomized trial comparing these regimens when combined with irinotecan (NordicVI) are awaited.

The oral alternative drugs, capecitabine and UFT seem to be as effective and less toxic as the Mayo regimen [6,22,23]. Capecitabine also seems to be as effective as infused 5-FU/LV in drug combinations [24,25]. Thus, capecitabine might come to substitute infused 5-FU/LV, but final comparative data on this issue are pending.

The addition of irinotecan to bolus or infused 5-FU/LV significantly improves the response rate to 40–50%, prolongs median TTP by approximately 3 months and the median overall survival (OS) with 2–3 months compared with 5-FU/LV alone [16,17]. Similarly, the addition of oxaliplatin to infused 5-FU/LV significantly improves response rate and TTP whereas significant prolongation of survival has not been shown, perhaps due to cross-over and use of 2nd line therapy [26,27].

Direct comparison between the irinotecan/infused 5-FU/LV (FOLFIRI) and oxaliplatin/infused 5-FU/LV (FOLFOX) shows that these combinations are equally effective with response rates of approximately 55% and median TTP and OS of approximately 8 and 20 months, respectively [19].

The general notion at present is that the 1st line choice between irinotecan or oxaliplatin and the selection of the 5-FU/LV schedule is mainly a matter of the adverse effects profile that differs between these combinations [5–7,19,21,28,29].

Second line therapy. After failure on 5-FU/LV, 2nd line therapy with an alternative 5-FU/LV regimen (oral or iv), produces very little anti-tumour efficacy and this strategy seems futile [30,31].

After 5-FU/LV failure, irinotecan alone increased the median OS by 2–3 months from the 6–8 months in patients treated with best supportive care or infused 5-FU/LV despite a very low response rate [30,32]. There is no data to support that combining irinotecan with a fluoropyrimidine improves the results in the 2nd line setting [33].

Following progression on infused 5-FU/LV, addition of oxaliplatin to the previous 5-FU/LV regimen resulted in objective tumour remissions of approximately 20%, a median TTP of approximately 5 months and median OS of approximately 11 months [34]. Following progression on bolus 5-FU/LV/irinotecan (IFL), FOLFOX resulted in a response rate of 10% and prolonged median TTP from 2.7 to 4.6 months compared with infused 5-FU/LV with a trend also to improved survival for FOLFOX [35]. Single agent oxaliplatin was essentially as inactive as infused 5-FU/LV. These data were essentially con-

firmed when infused 5-FU/LV was compared with FOLFOX after progression on sequential fluoropyrimidine and irinotecan [36]. Similar data were also reported for treatment with oxaliplatin in combination with capecitabine (Xelox) after progression on irinotecan/5-FU/LV [37].

Given the sequence of development of irinotecan and oxaliplatin there are less data on the efficacy of irinotecan after progression on oxaliplatin. However, 2nd line FOLFIRI after FOLFOX resulted in 4% tumour responses and a median TTP of 2.5 months according to a recent randomized cross-over trial [19].

With respect to drug sequencing, a randomized cross-over trial comparing FOLFIRI 1st line and FOLFOX 2nd line or the reverse sequence [19], showed that the sequences are similar in terms of tumour response rates 1st line and OS. Thus, sequencing is mostly a matter of tolerance rather than efficacy. In addition, a recent review suggests that the more patients who receive all active cytotoxic drugs the longer the median survival [7]

The introduction of new agents for treatment of metastatic CRC and their application in sequence has moved the median OS for patients in clinical trials from slightly above 6 months to more than 20 months and it is now a general view that optimal OS is achieved by sequential use of all three drugs, preferably in combinations [5–7,13,38].

It has to be acknowledged, though, that factors such as earlier start of treatment and a very strict selection of patients before inclusion in clinical trials may account for some of this progress [5,39]. However, median OS of more than 20 months seems to be achievable also in the routine clinical setting [40].

Targeted drugs in colorectal cancer

There has been major scientific progress in the understanding of tumour biology during the past decades and cancer is no longer a biologic mystery [41]. As a consequence, a number of new potential targets for medical treatment of cancer have been identified and a great number of drug candidates are already in various stages of clinical trials but still the evidence for clinical benefit from most of these new drugs and approaches is very limited [11]. These new drugs are often denoted 'targeted' which is intuitively easy to understand, yet no unequivocal definition for this term exists despite several proposals [42].

This section will briefly overview the clinical status of new drugs from various mechanistic groups provided that they have shown some advancement in their clinical development towards use in CRC. Thus, drugs in phase I clinical trials as well as drugs not yet studied in CRC are disregarded in this summary.

Chemotherapy resistance reversing drugs and mechanistically new cytotoxics

The idea of pharmacological reversal of cytotoxic drug resistance, e.g. by interaction with drug transport across the cell membrane, was considered highly promising approximately a decade ago and early clinical trials were performed also in CRC [43,44]. After failure of the approach in the most promising tumour types [11], this field seems less fruitful for further development.

E7070 is a new agent inhibiting cell cycle progression and has shown activity against CRC in a small phase II trial but no more mature data are available [45].

Signal transduction inhibition

Interference with tumour cell signal transduction is an interesting approach considering the many observations of increased activity in various such signal systems in tumour compared with normal cells. There are a great number of approaches within this group and with different types of drugs, from small molecules to macromolecular antibodies. This is clearly the group of new drugs with the greatest clinical development activity in CRC at present. Key findings are summarized in Tables I and II.

Except for CX, no convincing effects in CRC from this group of drugs have been observed so far. CX is an IgG1 monoclonal antibody that binds to EGFR with higher affinity than the natural ligands. This results in reduced receptor activated tyrosine kinase activity and subsequently to, e.g. reduced cell proliferation, cell survival and cell invasion. CX also induces antibody–dependent cell mediated cytotoxicity and show synergistic effects when combined with cytotoxic drugs and radiotherapy [8]. The clinical effects of CX are further detailed and discussed below.

Gene targeting drugs

Although a number of approaches for gene therapy are in early development in CRC [59], no data on clinical efficacy were retrieved.

Metastasis inhibitors

Although very promising from the conceptual and preclinical points of view, clinical trials with matrix metalloproteinase inhibitors have been disappointing in CRC. Thus, *marimastat* provided no survival

Table I. Efficacy of small molecules interacting with signal transduction.

Mechanism of action	Drug	Clinical phase	Efficacy in CRC	References
RAS farnesyl-transferase inhibition	R115777 (Zarnestra™)	III	No benefit over placebo in refractory CRC	[46]
RAS farnesyl-transferase inhibition	SCH66336	II	No responses in refractory CRC	[47]
EGFR tyrosine kinase inhibition	Gefitinib (Iressa™)	II	No responses in 2nd line. High response rates when combined with FOLFOX in 1st and 2nd line	[48,49]
EGFR tyrosine kinase inhibition	Erlotinib (Tarceva™)	II	No responses in 2nd line. 23% responses when combined with FOLFOX in refractory CRC	[9,50]
EGFR tyrosine kinase inhibition	EKB-569	II	38% responses when combined with FOLFIRI 1st line	[51]
Proteasome inhibition	Bortezomib (Velcade™)	II	No responses in 2nd line	[52]
PKC antisense	ISIS-3521	II	No responses in 1st line	[53)
RAF antisense	ISIS-5132	II	No responses in 1st line	[53]
Inhibition of cycloxygenase-2	Celecoxib	II	Potential benefit with respect to safety and efficacy when added to chemotherapy	[54]

benefit over placebo in metastatic CRC [60]. This approach seems to be futile in the metastatic setting and might be more relevant in early disease.

Differentiation inducing agents

These drugs often have multiple effects in addition to differentiation induction. Clinical studies in CRC are few. Neither *bryostatin* nor *troglitazone* showed any anti-tumour activity as single agents in phase II [61,62].

Angiogenesis inhibitors

Besides the signal transduction inhibitors, angiogenesis inhibition is the group of drugs that has focused most interest, clearly fueled by the efficacy shown for BV. This group contains a number of drugs and approaches, but is dominated by antibody targeting of vascular endothelial growth factor (VEGF) or small molecule inhibition of the VEGF-receptor (VEGFR) tyrosine kinase. Several drugs are in clinical development but the clinical data are yet fairly limited [63]. The clinical findings in CRC are summarized in Table III.

Thus, BV is so far the only drug targeting angiogenesis with evidence of clinical benefit as detailed further below. VEGF ligands expressed by tumour or host stromal cells stimulate VEGFR-1, VEGFR-2 or VEGFR-3 expressed by endothelial, lymphoendothelial and hematopoietic cells. This leads to activation of endothelial cell proliferation, migration and survival and but also to increased vascular permeability and increased interstitial pressure.

Besides a pure effect on angiogenesis, VEGF reduction by, e.g. BV, will lead to vessel normalization and decreased intratumoural pressure and might increase tumour cell access to chemotherapy. The role of the VEGF pathway in tumour growth and angiogenesis has been excellently reviewed recently [67]. The preclinical findings on the pharmacodynamics of BV were confirmed in rectal cancer in patients that obtained a single infusion of BV [68].

Immune therapy

Cancer therapy by active or passive immune therapy is conceptually interesting but has, despite efforts

Table II. Efficacy of monoclonal antibodies interacting with signal transduction.

Mechanism of action	Drug	Clinical phase	Efficacy in CRC	Reference
EGFR binding	Cetuximab (Erbitux™)	II	Clinical benefit in terms of response and TTP when combined with irinotecan over cetuximab alone	[55]
EGFR binding	ABX-EGF	II	13% responses in 2ndline	[56]
EGFR binding	EMD72000	I/II	Responses observed in early trials	[57]
Her-2 binding	Trastuzumab (Herceptin™)	II	Response in 5/7 patients when combined with irinotecan 2nd line	[58]

Table III. Efficacy of angiogenesis inhibitors.

Mechanism of action	Drug	Clinical phase	Efficacy in CRC	Reference
Antibody binding of VEGF	Bevaxizumab (Avastin™)	III	Improvement in tumour response, TTP and OS when added to chemotherapy 1st line	[64]
VEGFR tyrosine kinase inhibition	SU55416	III	No survival benefit when added to chemotherapy in 1st line	[9]
VEGFR tyrosine kinase inhibition	PTK/ZK	III	Trend to prolonged TTP when added to 5-FU/LV/oxoliplatin 1st line	To be presented at ASCO 2005
VEGFR tyrosine kinase inhibition	ZK 222584	II	54% reponses when combined with 5-FU/LV/ oxoliplatin 1st line	[65]
VEGFR tyrosine kinase inhibition	Angiozyme	II	43% responses when combined with 5-FU/LV/ irinotecan in 1st line	[66]

during many years, not yet proven to be of clinical benefit in CRC. In fact, the amount of clinical data is limited. The 17-1A antibody edrecolomab seemed promising in early clinical trials but phase III trials with the antibody alone or combined with chemotherapy have essentially been negative [57]. Vaccination with the anti-idiotypic CD55 antibody 105AD7 provided no benefit over placebo in metastatic CRC [69]. Finally, the oncolytic adenovirus ONYX-015 induced no tumour responses in 18 patients with metastatic CRC that had failed chemotherapy [70].

Overall conclusions on targeted drugs in CRC

Except for BV and CX that are already approved, no targeted drug seems to be close to an introduction for routine treatment of CRC. Rather the contrary, most clinical data on other 'targeted' drugs are negative or at least not very impressive. Thus, the therapeutic armamentarium in CRC may now have reached a steady-state that will last for some time. The issue right now seems to be how to use these drugs in the most optimal way.

Monoclonal antibodies for treatment of metastatic colorectal cancer

It is evident that so far and perhaps a bit unexpected, among the ill defined group of 'targeted drugs', anti-tumour monoclonal antibodies are in the lead with respect to advancement into the routine health-care and number of patients being candidates for treatment [11,71]. As evident from the above, this is especially so in CRC in which there is now two EU approved monoclonal antibodies available, i.e. BV and CX. Whereas the mechanistic principles of these antibodies have been outlined previously, the following sections will summarize the available data on their clinical efficacy and safety as a basis for the subsequent guidelines regarding their use in routine care.

Table IV. Efficacy of bevacizumab added to 5-fluorouracil/leucovorin (n = 104).

Endpoint	5-FU/LV alone	5-FU/LV/ BV 5mg/kg	5-FU/LV/ BV 10 mg/kg
Response rate (%)	17	40*	24
Median TTP (months)	5,2	9.0*	7,2
Median OS (months)	13,8	21,5	16,1

*Statistically significant vs 5-FU/LV alone.

Efficacy and safety of bevacizumab in metastatic CRC

Randomized studies have investigated the effect of BV in combination with 5-FU/LV and IFL as 1st line therapy and in combination with FOLFOX and CX/ irinotecan as 2nd line therapy.

First line therapy. Kabbinavar et al. randomized 104 patients to bolus 5-FU/LV alone or 5-FU/LV in combination with low- (5 mg/kg every 2 weeks) or high-dose (10 mg/kg every 2 weeks) BV [72]. Compared with 5-FU/LV alone, addition of low dose BV improved the efficacy as detailed in Table IV. High dose BV produced intermediate results.

Cross-over from 5-FU/LV to high dose BV alone produced partial response (PR) in 2 among 22 patients. Increased potentially severe toxicity from the addition of BV was observed for hypertension and thrombosis and epistaxis was observed in approximately half of the patients on BV.

Kabbinavar et al. also randomized 209 patients not considered optimal candidates for 1st line irinotecan-containing therapy, to bolus 5-FU/LV alone or 5-FU/LV combined with low-dose BV [73]. The patients had at least one of the following characteristics: age $\geq$65 years, ECOG performance status of 1 or 2, serum albumin $\leq$35 g/l or prior radiotherapy to the abdomen or pelvis. A number of exclusion criteria were applied [73]. Mean age was 71 years, almost all patients had a performance

status of 0 or 1 and, to be noted, 38% of the patients in the BV group and 46% in the placebo group received oxaliplatin and/or irinotecan following 1st line 5-FU/LV.

Addition of BV significantly prolonged progression free survival (PFS) but not tumour response rate or OS as detailed in Table V. BV treatment increased grade 3–4 toxicity with 16%, and 87 of the 100 patients given BV had a grade 3–4 event. Of special concern is the observation that 10% of the BV patients had a grade 3–4 arterial thrombotic event.

Hurwitz et al. in a pivotal trial randomized 813 patients to IFL or IFL in combination with low-dose BV [64]. Initially the trial also included a third arm treated with 5-FU/LV/BV but this arm was terminated after inclusion of 110 patients following a safety analysis. Notably, the mean patient age was only 59 years and approximately 55% of the patients had ECOG performance status 0. Efficacy data are summarized in Table VI.

Approximately 55% in both treatment groups had post-progression chemotherapy [74]. Despite this second line therapy OS was, thus, significantly prolonged for all patients (20.3 versus 15.6 months). Survival improvement was also observed in the subgroup receiving oxaliplatin as 2nd line treatment (25 versus 22 months) and in patients who did not receive 2nd line oxaliplatin (20 versus 16 months).

The combination arm was significantly more toxic with grade 3/4 adverse events in 85 versus 74% of the patients. However, there was no difference with respect to fatal adverse events. Outstanding and potentially serious adverse effects in the BV arm were hypertension in 22% (grade 3 in 11%) and gastrointestinal perforation in 1.5%. There were no clear differences in thromboembolic events, serious bleeding or proteinuria. This is in some contrast to the finding of a few cases of severe bleeding in non-small-cell lung cancer patients treated with BV in combination with chemotherapy [75].

The data from this trial have subsequently been further analyzed. Prolonged survival was observed in multiple subgroups [76]. There was no increased risk of bleeding in patients in the BV arm that were on full-dose anticoagulation due to thrombosis emerging during the trial [77]. Compromised wound healing or increased bleeding for primary cancer surgery performed 28–60 days before start of trial treatment was not clearly observed in the BV compared with the IFL alone arm [78]. At the other end, an increase in wound healing/bleeding complications, from 0/25 patients in the IFL arm to 4/40 patients in the BV arm, was observed when surgery was performed closely to BV/IFL treatment [79]. BV did not increase venous thromboembolism whereas arterial thromboembolism was increased; from 1 to 3% in the pivotal trial and from 5 to 10% in the trial on less fit patients receiving 5-FU/LV alone or 5-FU/LV/BV [80].

A randomized trial investigating the efficacy of adding BV to FOLFOX or Xelox in the 1st line setting is ongoing.

Second line therapy. Chen et al. studied the efficacy of the combination of bolus or infused 5-FU/LV and low-dose BV in patients progressing after irinotecan and oxaliplatin based regimens [81]. The response rate of approximately 2% and median TTP of 3.7 months indicate very limited activity of this combination in this setting.

Giantonio et al. randomized 579 patients previously treated with 5-FU/LV and irinotecan to FOLFOX alone or in combination with high-dose BV [82]. Median age was approximately 62 years and almost all had performance status 0 or 1. OS was significantly improved (12.5 months versus 10.7 months) in the BV arm. Grade 3 nausea (10% versus 5%), vomiting (8% versus 3%), hypertension (5% versus 2%) and sensory neuropathy (15% versus 9%) were significantly more frequent in patients receiving FOLFOX and bowel perforation was observed only in the BV arm in 1% of the patients.

Saltz et al. recently presented the first data from the BOND II trial in which 74 patients with irinotecan resistant and also mostly oxaliplatin treated disease were randomized to receive irinotecan (same schedule as given prior to entry) in combination with CX and low-dose BV or BV and CX without irinotecan [83]. It was concluded that concurrent administration of CX and BV is feasible and that toxicity is as would be predicted from the individual agents, without clear indication of syner-

Table V. Efficacy of bevacizumab added to 5-fluorouracil/leucovorin in patients unsuitable for 1st line irinotecan (n = 209).

Endpoint	5-FU/LV alone	5-FU/LV/BV
Response rate (%)	15	26
Median PFS (months)	5,5	9,2*
Median OS (months)	12,9	16,6

*Statistically significant vs 5-FU/LV alone.

Table VI. Efficacy of bevacizumab added to 5-fluorouracil, leucovorin and irinotecan (n = 813).

Endpoint	IFL alone	IFL plus BV
Response rate (%)	35	45*
Median PFS (months)	6,2	10,6*
Median OS (months)	15,6	20,3*

*Statistically significant vs IFL alone.

gistic toxicity. Addition of BV seemed to add efficacy in terms of response rate and TTP in both regimens compared with historical controls. However the use of historical data for comparison does not allow the question of improved efficacy to be answered.

With respect to safety, the cumulated experience in CRC indicate that addition of BV to chemotherapy in metastatic CRC leads to a rather high incidence (5 to 20%) of hypertension that seems manageable with standard medications, minor bleeding (epistaxis), proteinuria of unclear significance, a slight increase in risk for potentially serious arterial thrombosis and gastrointestinal perforation and a somewhat increased risk for wound healing/bleeding complications from surgery after BV treatment.

BV was granted marketing authorization within the EU in January 2005 with the approved indication "*Avastin (bevacizumab) in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum*".

Efficacy and safety of cetuximab in metastatic CRC

First line therapy. There are not yet reliable data available on the efficacy of CX in the 1st line setting. A large randomized trial investigating the effect of adding CX to FOLFIRI or FOLFOX has been started but was temporarily stopped for a protocol revision to allow for inclusion of a BV containing arm.

Small preliminarily reported phase II trials indicate high tumour response rates (70–80%) from CX in combination with irinotecan/5-FU/LV or oxaliplatin/5-FU/LV in first line treatment of patients with EGFR-expressing tumours [84,85].

Second line therapy. Saltz et al. observed a 9% tumour response rate of CX alone in 57 patients progressing on irinotecan and with EGFR-expressing tumours in a phase II trial [86]. In another phase II study the response rate was 23% when CX and irinotecan was combined in 121 irinotecan resistant patients [87].

These results were confirmed and expanded in the pivotal BOND I study reported by Cunningham et al. [55]. In this study, 329 patients whose disease had progressed during or within three months after treatment with an irinotecan-based regimen and whose tumours expressed any level of EGFR were randomized to receive either CX (400 mg/m^2 loading dose, followed by 250 mg/m^2 weekly) and irinotecan (same schedule as before; 218 patients) or CX alone. Notably the median age of patients included was only 59 years and only 29% of the patients were >65 years. Almost 90% had a Karnofsky performance status of 80–100. Response rate was higher (23% versus 11%) and TTP was longer (4.1 months versus 1.5 months) in patients receiving CX plus irinotecan as detailed in Table VII.

Table VII. Efficacy of cetuximab and cetuximab/irinotecan in irinotecan resistant patientsn (n = 329).

Endpoint	CX alone	CX plus irinotecan
Response rate (%)	11	23*
Median TTP (months)	1.5	4.1*
Median OS (months)	6.9	8.6

*Statistically significant vs CX alone.

Subgroup analyses indicated preserved efficacy for the combination in patients strictly refractory to irinotecan and in those with prior oxaliplatin treatment. In 56 patients progressing on CX alone, the addition of irinotecan resulted in two PRs. Efficacy for both the combination and CX alone was unrelated to percentage of EGFR-expressing cells or staining intensity but strongly related to degree of skin rash. Thus, for patients treated with CX and irinotecan, response rate was 6% for patients without skin reaction, 20% for patients with mild and 55% for patients with severe skin reaction. In patients with severe skin reaction TTP was 8.2 months and OS 13.7 months.

Severe hypersensitivity reactions occurred in 1.2% of the patients, mostly during or after the first infusion of CX. Eighty per cent developed any grade of skin rash (5–10% grade 3–4). Other adverse events were those expected from irinotecan treatment.

Lenz et al. observed a tumour response rate of 12% from CX alone in 346 patients with EGFR-expressing tumours resistant to both irinotecan and oxaliplatin [88]. Interestingly, out of 9 erroneously EGFR-negative patients enrolled, 2 had PR. A recent retrospective study by Chung et al. confirmed activity of CX/irinotecan or CX alone in EGFR negative metastatic CRC [89]. PR was observed in 4 of 14 patients. The recommended practice of testing EGFR status by immunohistochemistry to select for CX therapy is clearly inappropriate and other predictive tests are needed [90].

Taken together the clinical data indicate clinical efficacy of CX/irinotecan after failure on irinotecan or irinotecan and oxaliplatin (2nd and 3rd line settings) at least as good as that observed from infused 5-FU/LV/oxaliplatin after irinotecan failure. The tolerance to CX is generally good but with high incidence of skin rash and, more bothersome, occasional serious hypersensitivity reactions.

CX (Erbitux) was granted marketing authorization within the EU in June 2004, with the indication "*Erbitux in combination with irinotecan is indicated in the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy*."

Principle aspects on guideline formulation for cancer treatment

There are a number of factors that need to be considered when making conclusions on the role of new drugs in cancer chemotherapy. Those most important are briefly discussed below.

Are there sufficient clinical data to make firm conclusions on the role of the drug within the current treatment context?

With respect to amount of data considered sufficient, the principle of having at least two independent high-quality clinical trials supporting each other seems now infrequently applied at drug approval in the EU. This trend towards earlier approval based on less and unconfirmed data is probably stimulated by the regulatory principles at the US Food and Drug Administration (FDA) and probably also by indirect pressure from industry and well-informed patients, relatives and patient associations. Expert groups writing clinical guidelines for new drugs are certainly not refractory to such trends.

Is there evidence of sufficient efficacy?

With respect to efficacy the limit for when this is sufficient to warrant routine use of a new drug can always be debated. The following limits were proposed by Swedish and Norwegian authorities: for life prolongation in cancer, a median survival prolongation of at least 20% or three months and if the goal is to alleviate symptoms, at least 20% of patients treated should experience substantial improvement in major disease related symptoms [91,92]. Considering the more recent approvals of new cytotoxic drugs for treatment of CRC, i.e. irinotecan, oxaliplatin and capecitabine, it is clear that they balance close around these limits.

CX was approved without a statistically significant effect on survival but on a tumour response rate and TTP prolongation considered to be relevant. Without cross-over and effective further-line treatment, TTP was recently found to adequately reflect survival effects [93]. Still, this 'standard' for assessment of efficacy will also tend to move clinical expert guidelines in the same direction.

Is there an acceptable safety profile?

The safety profiles for the new anti-cancer antibodies and their impact on the final benefit/risk assessments are different from those of most cytotoxic drugs. Thus, neither BV nor CX add very much of toxicity to their treatment regimens in most cases. However, a few per cent of patients treated may experience potentially fatal adverse events. In comparison to more common but less serious adverse events as we know from most cytotoxic drugs, such low-frequent but very serious adverse events will have limited bearing on the final benefit/risk assessment.

Is the cost of the drug reasonable in relation to the benefit?

Given the difficulties for funding of health-care that is based on taxes and with an outspoken ambition to provide the best health-care available to all citizens, as in the Nordic countries, drug prizes should reasonably be an important issue in writing treatment guidelines. There are yet no health-economy analyses made on BV and CX but inclusion of the new antibodies into the current treatment strategies will raise drug-costs considerably [94].

The expert group has not, in its formulation of the present guidelines, considered health-economy aspects. Given the complexity of health-economy analyses, the NEC group focused on making a comprehensive medical benefit/risk assessment. However, the group encourages an independent health-economy analysis to take place as soon as possible.

Has the drug passed the benefit/risk assessment made by competent authorities, i.e. has the drug been granted marketing authorization?

An easy way out when formulating clinical guidelines would be to rely on the assessment made at drug approval and as expressed in the indication text. However, authorities do not comprehensively consider all treatment options and current treatment strategies for the treatment setting in question but rather assess whether the filed data comply with the indication proposed by the pharmaceutical company. Additional factors need to be considered when formulating guidelines, e.g. the overall treatment context, emerging scientific evidence and alternative data interpretation.

Are there predictive factors for treatment effects that allow for a rational use of the drug in routine health-care?

With the introduction of new and more 'targeted' drugs, there has been well motivated hope that they would be accompanied by valid tests being predictive for the drugs' effects and that could be used for patient selection. The reason for this hope is heralded within the 'targeted' concept implying that the presence of the target is necessary for the drug to work.

Unfortunately, there are no predictive tests or factors of use for selection of patients for treatment with BV or CX. While awaiting such tests, a conservative approach to new and expensive drugs with limited effects would be to withhold their use with the motivation that they cannot be properly used. A more liberal approach would be to use these drugs as chemotherapy has been used for many decades now, i.e. based on an empirical and statistical approach.

Do the prognostic characteristics of the patients included in the pivotal trials reflect those of the majority of patients considered for treatment in routine health-care, i.e. is the external validity of the pivotal trial data sufficient?

The many and detailed eligibility criteria in most clinical trials have become even more strict when it has come to trials of 'targeted' drugs. This is driven by the fear of unacceptable toxicity in patients compromised in specific ways. A possible consequence is that the treatment effects and the benefit/risk balance as observed in the trials are more favourable than what will be obtained in routine-health care. How much patients can be moved away from the properties of the trial population but still retain substantial benefit might take many years of further clinical trials to collect data on. Thus, until more data on the generalizability of the drug effects are at hand, patients in routine health-care considered for the new expensive and potentially harmful drugs with limited benefit should essentially comply with the major eligibility criteria.

How much of extrapolation from the clinical trial data is necessary to bridge the gap to routine health-care and the treatment context that has emerged since the design of the clinical trials?

At the time of marketing authorisation, the knowledge on the effects of the new drug mostly cover only a limited number of the many treatment situations that need to be considered in routine health-care, e.g. there might only be data for 1st line cancer therapy whereas the treatment context covers both 2nd and perhaps even 3rd line treatments. Thus, there are always uninvestigated fields that need to be bridged by extrapolation to be able to use the drug in the full clinical context. Extrapolation is a key aspect of clinical skill and well-founded scientific reasoning for bridging of information gaps is necessary, also in guideline writing. However, in this setting it has to be kept to a minimum.

What is the role a clinical guideline?

A clinical guideline can mostly not provide more than general statements on the treatment principles recommended to apply for typical treatment settings. In routine health-care there are a number of situations that cannot be covered in detail by the guidelines. Thus, the guidelines form a basis to which clinical factors and individual patient characteristics and preferences have to be added to form a treatment decision.

Guidelines for the routine use of bevacizumab in metastatic CRC

1. *There is strong, yet circumstantial, support for the use of BV in first line therapy in combination with an optimal 5-FU/LV/irinotecan combination in younger medically fit patients without risk factors for BV toxicity.*

This conclusion is compatible with the approved labelling for BV. There is one large high-quality randomized trial showing statistically convincing and clinically relevant benefits in terms of tumour response, PFS and OS from this approach. In this trial, BV was combined with IFL, a bolus 5-FU/LV/irinotecan combination that seems less efficient than infused 5-FU/LV/irinotecan [FOLFIRI; 18,19]. The question is then whether BV merely compensated for sub-optimal chemotherapy and, thus, that BV would not provide survival benefit if used together with more optimal chemotherapy. It is acknowledged that there is no evidence excluding this possibility but according to the expert group there is strong circumstantial evidence sufficient to conclude that BV has an add–on effect.

Firstly, BV has, at least partly, other modes of action than chemotherapy, targeting blood vessels, perfusion and intra-tumoural pressure, proven also in patients [68] and they reasonably add effect to chemotherapy. Secondly, clinically relevant additive/synergistic effects between BV and chemotherapy have been observed for other regimens than IFL [72,73,75,82,83]. Thirdly, in the pivotal trial, slightly more than half of the patients had 2nd line chemotherapy, evenly distributed between the con-

trol and BV groups and including oxaliplatin for part of the patients [74]. Despite this, the OS benefit was observed. Thus, it seems reasonable to believe that BV would also add survival benefit to a more optimal 1st line 5-FU/LV/irinotecan regimen, e.g. FOLFIRI or FLIRI, i.e. the Nordic schedule 5-FU/LV/irinotecan [29].

The question then appears whether the extrapolation could also include 1st line treatment with 5-FU/LV/oxaliplatin regimens. Although this is probable, based on the reasoning above as well as the finding of a statistically significant OS benefit from the addition of BV to FOLFOX 2nd line [82], this is not supported until more clinical data are at hand. A large prospective randomized trial that will provide data on this issue has recently finished patient inclusion.

The above guidelines regarding use of BV do not exclude that oxaliplatin based therapy without BV can be used as 1st line therapy based on individual patient characteristics (see below) and/or preferences [28].

With respect to patient selection there are yet no clinically relevant factors that can predict for benefit from BV. In this situation it is recommended that patients suitable for BV are selected to mimic the trial population. In essence this means that suitable patients should be comparatively young, have a performance status of 0–1, preserved major organ function and being without risk factors for serious toxicity, i.e. not have recently performed or planned surgery (approximate safety limit of 1 month), recent hemoptysis, CNS metastases, nephritic syndrome, NSAID treatment or cardio-/cerebrovascular disease or history. The recommendation regarding patient age could perhaps be questioned given the experience of retained activity in elderly patients of 5-FU/LV based regimens in metastatic CRC [95]. However, while awaiting more data, a conservative approach on this issue is reasonable.

2. *There is insufficient support for the addition of BV to 5-FU/LV in first line therapy in patients medically unsuitable for combination chemotherapy.*

This conclusion is not in line with the approved labelling for BV. There is one small [72] and one medium-sized [73] randomized trial showing numerically relevant benefit from addition of BV in terms of tumour response and PFS/TTP and with trends to improved OS. However, the internal and/or external validity of the results from these trials might be questioned. Thus, there were potentially important group imbalances [72] and the patients included had better prognostic characteristics than expected from a patient population not considered suitable for combination 1st line therapy in routine care [73,96]. Thus, there are no convincing data from patients for which 1st line 5-FU/LV would truly be the first therapeutic choice. Also, true contraindications to 1st line irinotecan combination therapy would in most cases probably also contraindicate use of BV. The lack of statistically significant differences and the overall small number of patients studied for this combination further add to the notion of insufficient support for 1st line 5-FU/LV/BV. Furthermore, grade 3–4 toxicity was increased, especially arterial thrombotic events.

Still, the available 5-FU/LV/BV data, together with the overall notion that BV seems to add efficacy when given together with active chemotherapeutic regimens used in metastatic CRC, give reasonable support for the addition of BV to 5-FU/LV in younger medically fit patients that for some reason do not want to be treated with an irinotecan/5-FU/LV or oxaliplatin/5-FU/LV combination.

3. *There is insufficient support for the use of BV in 2nd line treatment in combination with oxaliplatin/5-FU/LV following progression on irinotecan and 5-FU/LV.*

Such use of BV is not part of the approved labelling for BV. Data from the large randomized trial [82] showed a 1.8 month median OS benefit from the addition of BV in a medically 'fit' patient population. The data has only been reported in the abstract form, the benefit is small to modest and non-authorised high-dose BV was used. Furthermore, no data on tumour response rate and TTP has been presented. A more comprehensive report on these data is necessary prior to a change in this conclusion.

4. *There is no support for the use of BV in 2nd line treatment in combination with irinotecan following progression on oxaliplatin/5-FU/LV.*

There are yet no clinical data from this setting.

5. *There is no support for the use of BV in 3rd line treatment after progression on irinotecan and oxaliplatin*.

Such use of BV is not part of the approved labelling for BV. Preliminary data from a non-randomized phase II trial indicate very modest anti-tumour activity in this setting [81] and single agent BV seems poorly active as discussed above. BV seems to add to the activity of CX in terms of tumour response and TTP after progression on irinotecan and oxaliplatin [83]. However, these data are yet insufficient for a more positive view.

6. *There is insufficient support for the addition of BV to the CX/irinotecan combination after progression on irinotecan.*

Compared with historical data (see above), BV seems to add to the activity of CX in terms of tumour response and TTP [83]. However, these data are yet insufficient for a more positive view.

7. *There is no support for the use of single drug BV or continuous administration of BV after stopping chemotherapy.*

Single drug use of BV is not part of the approved labelling. A relevant question is whether BV should be continued in the case that chemotherapy have to be stopped, e.g. due to intolerance. In the pivotal study, this was the case which would argue for a similar approach in clinical routine. On the other hand, the true benefit from this is not proven and the anti-tumour efficacy of BV alone seems low [72,81] and the BV alone arm was terminated due to inferior survival in the 2nd line FOLFOX ±BV study.

Guidelines for the routine use of Cetuximab in metastatic CRC

1. *There is modest, yet sufficient, support for the use of CX in therapy in combination with irinotecan in younger medically fit patients following progression on irinotecan/5-FU/LV (2nd line setting) and oxaliplatin/5-FU/LV (3rd line setting).*

Such use of CX is compatible with the approved labelling. There is one medium sized randomized trial showing clinically relevant anti-tumour efficacy and prolonged TTP in comparison with CX alone [55]. A question is whether optimal use of CX/irinotecan is in the 2nd or 3rd line setting. Extrapolation could give some support for 3rd line use since oxaliplatin/5-FU/LV 2nd line provides a prolongation of TTP [35]. This effect seems to be similar to that provided by CX/irinotecan but this combination is active also following progression on oxaliplatin/5-FU/LV [55] whereas it is not known if oxaliplatin/5-FU/LV is active in the 3rd line following progression on CX/irinotecan. However, this reasoning is not considered sufficient for a recommendation regarding choice of 2nd or 3rd line treatment. Rather, many clinicians seem to argue for the 2nd line use of CX/irinotecan and then oxaliplatin/5-FU/LV. The target population for CX, in line with patient eligibility in the clinical trials, is younger patients in performance status 0–1 with preserved major organ function.

2. *There is insufficient support for the use of CX as single drug following progression on irinotecan based chemotherapy.*

Single drug CX consistently produce an approximately 10% objective tumour response rate in the 2nd and 3rd line settings [55,86,88]. A median TTP of 1.5 months reveals that most patients had PD on the first evaluation after 6 weeks of treatment. Since convincing data on effects and/or survival are lacking, this anti-tumour effect is considered to be insufficient for routine use.

3. *There is no support for the use of CX in the 1st line setting.*

There are not yet any clinical data supporting 1st line use.

4. *There is no support that the decision to use CX should rely on immunohistochemical detection of EGFR expression.*

This conclusion is not compatible with the approved labelling stating that the tumour should express EGFR. However, the overall clinical experience [55,88,89] and the scientific reasoning on this issue [90] clearly argue against the use of immunohistochemical staining of EGFR as a predictive test.

5. *There is insufficient support for the dosing of CX based on skin toxicity.*

Efficacy of CX is strongly associated with skin toxicity as detailed above. However, whether a dose escalation of CX would produce more skin toxicity and anti-tumour efficacy is unknown and presently focus for a randomized trial. Early evaluation of tumour response, e.g. by imaging after 6–8 weeks of treatment, is recommended both for CX and BV to be able to terminate treatment in the case of tumour progression.

Concluding remarks

There has been a dramatic change in the medical treatment of CRC during the past five years making such treatment considerably more complex than previously and with much more to offer patients with metastatic CRC. Development of 'targeted' drugs is in progress in CRC and so far the monoclonal antibodies BV and CX are clearly in

the lead with justified use in some clinical situations as detailed above. Although the contribution from these antibodies should not be denied, the therapeutic improvement is still small in absolute terms and comes at a price that will be difficult to handle in tax funded health-care systems. From a principle point of view, it is interesting to note that the recent progress in CRC treatment comes both from the new 'targeted' and the 'old' cytotoxic drugs and that they need to be combined to produce optimal activity. Only future can tell, but by extrapolation from the development so far, a steady but slow progress in the treatment of CRC with contributions both from 'old' cytotoxics and new 'targeted' drugs is expected.

BV and CX provide clinically relevant, yet marginal, patient benefit at seemingly high cost in some settings in metastatic CRC. Their routine use in the large group of patients with metastatic CRC met in daily clinical practice without reliable cost-benefit analyses might be questioned. Thus, an independent health-economy analysis of the cost-benefit balance of these drugs is encouraged.

Guideline summary

Bevacizumab

1. *There is strong, yet circumstantial, support for the use of BV in first line therapy in combination with an optimal 5-FU/LV/irinotecan combination in younger medically fit patients without risk factors for BV toxicity.*
2. *There is insufficient support for the addition of BV to 5-FU/LV in first line therapy in patients medically unsuitable for combination chemotherapy.*
3. *There is insufficient support for the use of BV in 2nd line treatment in combination with oxaliplatin/5-FU/LV following progression on irinotecan and 5-FU/LV.*
4. *There is no support for the use of BV in 2nd line treatment in combination with irinotecan following progression on oxaliplatin/5-FU/LV.*
5. *There is no support for the use of BV in 3rd line treatment after progression on irinotecan and oxaliplatin.*
6. *There is insufficient support for the addition of BV to the CX/irinotecan combination after progression on irinotecan.*
7. *There is no support for the use of single drug BV or continuous administration of BV after stopping chemotherapy.*

Cetuximab

1. *There is modest, yet sufficient, support for the use of CX in therapy in combination with irinotecan in younger medically fit patients following progression on irinotecan/5-FU/LV (2nd line setting) and oxaliplatin/5-FU/LV (3rd line setting).*
2. *There is insufficient support for the use of CX as single drug following progression on irinotecan based chemotherapy.*
3. *There is no support for the use of CX in the 1st line setting.*
4. *There is no support that the decision to use CX should rely on immunohistochemical detection of EGFR expression.*
5. *There is insufficient support for the dosing of CX based on skin toxicity.*

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