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CED-CCO Special Advice Report 8 EDUCATION AND INFORMATION 2012

The Use of Epidermal Growth Factor Receptor Inhibitors in Advanced Colorectal Cancer

D. Jonker, J. Biagi, and A.E. Haynes

Report Date: July 9, 2008

This CED-CCO Special Advice Report was put in the Education and Information section in 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).
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SUMMARY

The 2008 guideline recommendations were put in the

Education and Information section

This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes.

QUESTIONS

Primary Research Question:

- Is treatment with epidermal growth factor receptor (EGFR) inhibitors in patients with advanced colorectal cancer (CRC) recommended? Outcomes of interest: overall survival, progression-free survival, objective tumour response rates, quality of life, and adverse events.
- Can *K-RAS* testing be used to identify patients with advanced CRC who may benefit from treatment with EGFR inhibitors? Outcomes of interest: overall survival, progression-free survival, objective tumour response rates, quality of life, and adverse events.

Secondary Research Question:

- Is one EGFR inhibitor superior or inferior to another when used to treat patients with advanced CRC? Outcomes of interest: overall survival, progression-free survival, objective tumour response rates, quality of life, and adverse events.

TARGET POPULATION

Adult patients with advanced CRC who are suitable candidates for therapy (ECOG performance status grade 0-2)

RECOMMENDATIONS

- **The two clinically available EGFR inhibitors, cetuximab and panitumumab, are recommended for patients with advanced CRC after failure of standard chemotherapy and whose tumours have tested negative for *K-RAS* gene mutations (i.e. patients with *K-RAS* wild-type). The recommended dose of cetuximab is a loading dose of 400 mg/m^2 of body surface area (BSA) intravenously (iv) followed by a weekly 250 mg/m^2 infusion; pre-medication with an antihistamine is required. The dose of panitumumab is 6 mg/kg iv every two weeks; no pre-medication is required.**

  Key Evidence

  - A randomized phase III study that compared cetuximab plus best supportive care (BSC) versus (vs.) BSC alone (1) demonstrated response rates of 8.0% in the cetuximab group vs. 0% in the BSC group (p<0.001) and stable disease in 31.4% vs. 10.9% (p<0.001), respectively. Progression-free survival was superior for the cetuximab arm (hazard ratio [HR] 0.68, p<0.001), as was overall survival (HR 0.77, p=0.005). Quality of life was superior for physical function and global health status scores (both p<0.05).
    - ⇒ Sixty-nine percent of the intent-to-treat population was retrospectively analyzed according to *K-RAS* status. In the *K-RAS* wild-type population, cetuximab treatment resulted in an increase of median progression-free survival 3.8 vs. 1.9 months (HR 0.40, p<0.001), median overall survival 9.5 vs. 4.8 months (HR 0.55, p<0.0001) (2). Within the *K-RAS* mutant population, no effect of cetuximab was apparent on progression-free survival (HR 0.99) or overall survival (HR 0.98).
  - A randomized phase III study compared panitumumab plus BSC versus BSC alone (3). The response rate was 10% for panitumumab vs. 0% for BSC (p<0.0001); stable disease 27% vs. 10%. Progression-free survival was superior for the panitumumab arm (HR 0.54, p<0.0001). There was no difference in overall survival (HR 1.0), which may have been affected by the high proportion of patients undertaking the protocol-sanctioned crossover to panitumumab after progression on the BSC arm. Quality of life was not reported. Toxicities of panitumumab treatment were manageable.
    - ⇒ Ninety-two percent of the intent-to-treat population was retrospectively analyzed according to *K-RAS* status (4). In the *K-RAS* wild-type population, panitumumab treatment resulted in an increase of median progression-free survival 2.8 vs. 1.7 months (HR 0.45, p<0.0001) and response rate (17% vs. 0%). Median overall survival was not significantly different (HR 1.02); however, it was likely affected by crossover. Within the *K-RAS* mutant population, no effect of panitumumab was apparent on progression-free survival (HR 0.99), response rate, or overall survival (HR 1.02).

- **For patients who have not yet failed chemotherapy treatment, there is mounting evidence that EGFR inhibitors are safe and effective when combined with chemotherapy in advanced CRC patients who are confirmed to be *K-RAS* gene wild-type. However, at this time there is insufficient evidence to recommend it over the current standards of care.**

  Key Evidence

  - There are two trials published in abstract form involving the addition of cetuximab to chemotherapy in previously untreated patients, for which exploratory *K-RAS* mutation analysis have been reported: one in combination with folinic acid plus fluorouracil plus irinotecan (FOLFIRI) and the other with folinic acid plus fluorouracil plus oxaliplatin (FOLFOX). In these trials, there was a statistically significant reduction of the risk of

progression of 32% and 43% with the addition of cetuximab to FOLFIRI and FOLFOX, respectively (5,6).

- In patients with one prior line of chemotherapy, there are two trials examining the addition of cetuximab to second-line chemotherapy. In the Erbitux® (ImClone Systems Incorporated and Bristol-Myers Squibb Company; cetuximab) Plus Irinotecan for Metastatic Colorectal Cancer (EPIC) study, 1,298 patients who received first-line oxaliplatin-based chemotherapy were randomized to cetuximab plus irinotecan versus irinotecan alone (7). Superior response rate (16.4% vs. 4.2%, p<0.0001) and progression-free survival (median 4.0 vs. 2.6 months, HR 0.692; p<0.0001) were demonstrated. Median overall survival was not statistically different (HR 0.98), a possible effect of the crossover by 47% of the monotherapy arm to receive subsequent cetuximab. The quality of life scores were superior for global health status (p=0.047). An analysis by *K-RAS* status has not been reported. In the Cetuximab Plus FOLFOX For Colorectal Cancer (EXPLORE) study, 102 patients who had first-line irinotecan-based chemotherapy were randomized to cetuximab plus FOLFOX versus FOLFOX alone (8). This study was terminated early for poor accrual. No differences in outcomes were noted between arms for progression-free survival.

- **For patients who have not yet failed chemotherapy treatment, the combination of EGFR inhibitors with both chemotherapy and the vascular endothelial growth factor (VEGF) antibody bevacizumab is not recommended outside of a clinical trial.**

  Key Evidence

  - There are two trials published in abstract form that suggest a detrimental effect of the dual EGFR-VEGF inhibition plus oxaliplatin-based chemotherapy (9-11). In these *K-RAS* unselected populations, the risk of progression with the addition of EGFR antibody therapy was increased by between 17 to 22%.

- **The two agents that are clinically available, panitumumab and cetuximab, have not been directly compared for efficacy or toxicity in a randomized clinical trial. Therefore, neither agent can be recommended over the other after failure of standard chemotherapy.**

Qualifying Statements

- There are no clinical trials of EGFR inhibitor efficacy where patients were prospectively tested for *K-RAS* status and selected, based on these results. Observations of benefit for EGFR inhibitors in *K-RAS* wild-type patients are based on retrospective tumour assessment from prospective trials; nonetheless, the consistency of the demonstrated effect across multiple trials is sufficient to strongly recommend restricting the use of EGFR inhibitors to *K-RAS* wild-type patients.
- Although not the topic of this systematic review, the addition of irinotecan to cetuximab resulted in superior progression-free survival and response rate in the randomized phase II Bowel Oncology and Cetuximab Antibody (BOND) study with a primary endpoint of response rate (12). This study assigned 329 patients who progressed on irinotecan to cetuximab plus irinotecan vs. cetuximab alone. The response rate was 22.9% vs. 10.8% (p=0.007); median time to progression was 4.1 vs. 1.5 months (p<0.001); median overall survival was 8.6 vs. 6.9 months (p=0.48). Patients on the cetuximab monotherapy arm were permitted to cross over at the time of progression to receive the combination. **The opinion of the authors is that irinotecan should be added to cetuximab for suitable patients.** The authors are not

aware of any clinical trials of irinotecan combined with panitumumab. Therefore, this combination is not currently recommended.

- Standard first-line therapy for advanced CRC is either FOLFOX or 5-fluorouracil/irinotecan regimen in combination with bevacizumab, where the addition of bevacizumab results in an improved progression-free survival (HR=0.83 and 0.54, respectively) (13,14). The improvement in progression-free-survival in *K-RAS* wild-type patients with the addition of cetuximab to FOLFOX or FOLFIRI is of a similar magnitude (HR 0.57 or HR 0.68, respectively). Determining whether cetuximab is superior to bevacizumab as an adjunct to first-line chemotherapy in the wild-type population will require the results of ongoing trials (i.e. CALGB 80405: A Phase III Trial of Irinotecan / 5-FU / Leucovorin or Oxaliplatin / 5-FU/ Leucovorin With Bevacizumab, or Cetuximab (C225), or With the Combination or Bevacizumab and Cetuximab for Patients With Untreated Metastatic Adenocarcinoma of the Colon or Rectum).

RELATED GUIDELINES

- **Practice Guideline #2-16:** Use of Irinotecan in the Second-line Treatment of Metastatic Colorectal Carcinoma.
- **Practice Guideline #2-16b:** Use of Irinotecan (Camptosar®, CPT-11) Combined with 5-Fluorouracil and Leucovorin (5FU/LV) as First-line Therapy for Metastatic Colorectal Cancer.
- **Practice Guideline #2-22:** The Role of Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in the First and Second-line Treatment of Advanced Colorectal Cancer.
- **Practice Guideline #2-25:** The Role of Bevacizumab (Avastin™) Combined with Chemotherapy in the Treatment of Patients with Advanced Colorectal Cancer.

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For information about the PEBC and the most current version of all reports, please visit the CCO web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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FULL REPORT

I. QUESTIONS

Primary Research Question:

- Is treatment with epidermal growth factor receptor (EGFR) inhibitors in patients with advanced colorectal cancer (CRC) recommended? Outcomes of interest: overall survival, progression-free survival, objective tumour response rates, quality of life, and adverse events.
- Can *K-RAS* testing be used to identify patients with advanced CRC who may benefit from treatment with EGFR inhibitors? Outcomes of interest: overall survival, progression-free survival, objective tumour response rates, quality of life, and adverse events.

Secondary Research Question:

- Is one EGFR inhibitor superior or inferior to another when used to treat patients with advanced CRC? Outcomes of interest: overall survival, progression-free survival, objective tumour response rates, quality of life, and adverse events.

II. CHOICE OF TOPIC AND RATIONALE

Colorectal cancer is the second leading cause of cancer death in Canada. In 2008, approximately 20,000 Canadians will be diagnosed with CRC, and there will be close to 8,000 deaths, affecting men and women roughly equally (1).

When CRC reaches an advanced stage, only a small minority of patients can be cured with surgical excision of metastases. For the remaining patients, survival can be prolonged with chemotherapy (e.g. 5-fluorouracil, capecitabine, irinotecan, oxaliplatin) with or without the vascular endothelial growth factor (VEGF) inhibitor bevacizumab. Untreated, the median survival for advanced CRC is six months, but with combination chemotherapy, the median survival is two years (2). However, chemotherapy resistance develops over time in almost all cases, and for these patients new treatments are required.

Monoclonal antibodies directed against the EGFR have demonstrated activity in CRC and are the subject of recent randomized trials. Anti-EGRF agents include the chimeric murine-human IgG1 antibody cetuximab and the fully human IgG2 antibody panitumumab.

While the EGRF inhibitors are similar, they have somewhat different immunology, toxicity profiles, and schedules of administration and have undergone clinical development through different trial designs.

Although these agents were initially studied exclusively in patients with overexpression of the EGFR receptor by immunohistochemistry, it has now been demonstrated that EGFR inhibitors are also effective in patients with tumours that are EGFR-"undetectable," suggesting that the threshold for the presence of EGFR by commercial EGFR tests are not useful in patient selection (3,4). However, recent analyses have suggested that the presence or absence of mutations of *K-RAS*, a downstream G-protein in the EGFR signalling cascade, can be used as a biomarker to predict which patients are likely to benefit from cetuximab or panitumumab therapy. The activating mutations in exon 2 of the *K-RAS* gene can be reliably detected from tumour-derived genomic DNA by direct gene sequencing, using commercially available kits (DxS), and are available through commercial laboratories in the United States. Efforts are underway in several hospital molecular diagnostics laboratories across Canada to make testing available in the near future.

III. METHODS

This advice report, produced by the PEBC, is a convenient and up-to-date source of the best available evidence on the role of EGFR inhibitors in the treatment of advanced CRC, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

A systematic search of the published literature identified all reports relating to the use of EGFR inhibitors for the treatment of patients with advanced CRC. The MEDLINE (2003 to May Week 4, 2008 [June 6]), EMBASE (2003 to 2008, Week 23 [June 6]), MEDLINE Daily Update (June 2008), MEDLINE In-Process & Other Non-Indexed Citations (June 2008), and the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (2008, Issue 2) databases were searched according to the strategies in Appendix 1. One search strategy was developed to identify randomized controlled trials (RCTs) in MEDLINE and EMBASE, while another was developed to identify reports that assessed the affect of *K-RAS* status on outcomes of interest in patients with advanced CRC enrolled in RCTs assessing an EGFR inhibitor. Abstracts from the American Society of Clinical Oncology (ASCO) (2003-2008) annual conference proceedings and the ASCO Gastrointestinal Cancers Symposium (2004-2008) were also searched. The National Cancer Institute (NCI) Clinical Trials Register and the United States National Institutes of Health (NIH) Clinical Trials databases were searched to identify ongoing clinical trials, and the National Guidelines Clearinghouse and the CMA Infobase were searched for clinical practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers (DJ and AH), and the reference lists from those sources were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review if they met the following criteria:

1. Studies were prospective, randomized phase II or III clinical trials that compared an EGFR inhibitor, alone or in combination with other agents (i.e. chemotherapy, bevacizumab), to the same therapy without an EGFR inhibitor.
2. Studies included adult patients with advanced CRC.
3. Results were reported for any of the following outcomes of interest: overall survival, progression-free survival, objective tumour response rates, quality of life, and adverse events.
4. Studies were systematic reviews, meta-analyses, or evidence-based practice guidelines that assessed the use of an EGFR inhibitor in patients with advanced CRC.
5. The studies were retrospective, post hoc, or unplanned analyses of randomized trials (as defined by 1 and 2, above) assessing the affect of *K-RAS* status on the outcomes of interest (as defined by 3, above).

Exclusion Criteria

1. Reports published in a language other than English.
2. Letters, editorials, notes, comments, and books.

Synthesizing the Evidence

The authors considered the appropriateness of a meta-analysis of the results of the identified trials. Although adequate data were available, a meta-analysis was not conducted due to the clinical heterogeneity between those trials.

IV. RESULTS

Literature Search Results

A total of 408 citations were retrieved from the MEDLINE, MEDLINE Daily Update, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, and the Cochrane Library databases. Nine citations met the inclusion criteria. In addition, 33 abstracts from the conference proceedings of the ASCO Annual Meeting and the ASCO Gastrointestinal Cancers Symposium were identified that met inclusion criteria. Many of the identified abstracts were of trials that have since been fully published or for which more up-to-date abstracts were available. Only the full publication or most up-to-date abstract has been referenced for each trial. One additional abstract publication, presented at the European Society for Medical Oncology (ESMO) International Symposium 10th World Congress on Gastrointestinal Cancer, was identified in the personal files of one author (DJ). That abstract reported the results of an analysis of *K-RAS* status with survival and response outcomes based on an RCT that was fully published in 2007. In total, eight RCTs of cetuximab and four RCTs of panitumumab in patients with advanced CRC were identified. For a list of the identified trials, associated publications referenced in this systematic review, and publication types see Table 1. One systematic review and one health technology assessment of cetuximab and one systematic review of panitumumab were identified (5-7). No evidence-based practice guideline documents were identified.

Table 1. Primary and additional publications for identified RCTs of EGFR inhibitors in patients with advanced CRC.

Study	Primary publication [FP/abs]	Additional publications	*K-RAS* status analysis
Cetuximab			
EPIC	Sobrero, 2008 [FP] (8)	None	None
CO.17	Jonker, 2007 [FP] (9)	None	Karapetis, 2008 [abs] (10)
EXPLORE	Jennis, 2005 [abs] (11)	None	Mitchell, 2008 [abs] (12)
CAIRO2	Punt, 2008 [abs] (13)	Tol, 2008 [FP] (14)	Punt, 2008 [abs] (13)[a]
COIN	Maughan, 2007 [abs] (15)	None	None
CRYSTAL	Van Cutsem, 2007 [abs] (16)	None	Van Cutsem, 2008 [abs] (17)
OPUS	Bokemeyer, 2007 [abs] (18)	None	Bokemeyer, 2008 [abs] (19)
Borner, 2006	Borner, 2006 [abs] (20)	None	None
Panitumumab			
Van Cutsem, 2007	Van Cutsem, 2007 [FP] (21)	Siena, 2007 [FP] (22)	Amado, 2008 [FP] (23)
Peeters, 2008	Peeters, 2008 [abs] (24)	None	None
PRIME	Siena, 2008 [abs] (25)	None	None
PACCE-Iri/Bev	Hecht, 2008 [abs] (26)	None	None
PACCE-Ox/Bev	Hecht, 2008 [abs] (27)	None	None

Notes: abs=abstract; Bev=bevacizumab; FP=full publication; Iri=irinotecan; Ox=oxaliplatin.

[a] *K-RAS* status and the effect on efficacy outcomes was reported in the abstract presentation of the primary publication for the CAIRO2 trial.

Systematic Reviews

Frieze et al (5) systematically reviewed MEDLINE up to December 2005 for randomized trials of cetuximab in metastatic CRC. Only two trials were identified, and results for efficacy were not available for either. Given the fact that no data for any randomized trials were presented in that systematic review, we do not discuss the review further.

Tappenden et al (6) reported a health technology assessment of the clinical effectiveness and cost effectiveness of bevacizumab and cetuximab; however, no trials of

cetuximab met the authors' eligibility criteria. Therefore, that systematic review is not considered further.

Saadeh et al (7) reported a systematic review of panitumumab for solid tumours. The authors searched MEDLINE up to February 2007 and identified two randomized trials of panitumumab in advanced CRC. Both trials were reported in abstract form only; however, only one trial had efficacy data available. That trial compared panitumumab plus best supportive care (BSC) to BSC alone. As the authors only reported the results of that single trial, and as our literature search identified abstract reporting efficacy data for three additional randomized trials, we do not discuss that systematic review further.

Trial Characteristics and Quality

Cetuximab

Eight trials of cetuximab in patients with advanced CRC were identified (8-20). The EPIC and CO.17 trials were both fully published (8,9). The remaining six trials were published in abstract form only (11,13,15,16,18,20). In general, more details on trial design and quality were available for the EPIC and CO.17 trials than were available for the remaining six trials as the latter were reported in abstract form only. Details of study quality are illustrated in Table 2.

Table 2. Quality characteristics of RCTs examining EGFR inhibitors in patients with advanced CRC.

Trial name, Author, year (ref)	A priori sample size requirement met	Primary outcome	Double blinding	Randomization method	Allocation concealment	ITT analysis	Final analysis	Early termination	Losses to follow-up	Ethical approval
Fully published trials										
Cetuximab										
EPIC, Sobrero, 2008 (8)	Yes	OS	-	Yes	Yes	Yes	Yes	No	-	Yes
CO.17, Jonker, 2007 (9)	Yes	OS	No	Yes	-	Yes	Yes	No	-	Yes
Panitumumab										
Van Cutsem, 2007 (21)	Yes	PFS	No	-	-	Yes	Yes	No	-	Yes
Abstracts										
Cetuximab										
CAIRO2, Punt, 2008 (13)	-	PFS	-	Yes	Yes	No	-	No	-	-
COIN, Maughan, 2007 (15)	No	OS	-	-	-	No	No	No	-	-
CRYSTAL, Van Cutsem, 2007 (16)	Yes	PFS	-	Yes	-	Yes	Yes	No	-	-
OPUS, Bokemeyer, 2007 (18)	-	OR	-	-	-	-	-	-	-	-
Borner, 2006 (20)	Yes	OR	-	-	-	-	-	-	-	-
EXPLORE, Jennis, 2005 (11)	No	OS	-	-	-	-	No	Yes[a]	-	-
Panitumumab										
PACCE, Hecht, 2008 (26,27)	No	PFS	No	-	-	No	No	No	-	-
PRIME, Siena, 2008 (25)	No	PFS	No	-	-	No	No	No	-	-
Peeters, 2008 (24)	No	OS/PFS	-	-	-	No	No	No	-	-

Notes: "-" indicates that the published report did not describe this characteristic of the trial; ITT=intention-to-treat; OR=objective response rate; OS=overall survival.

[a]Trial was terminated early due to changes in clinical practice such that irinotecan was replaced with oxaliplatin in the first-line treatment of patients with metastatic CRC.

Both the EPIC and CO.17 trials met their a priori sample size requirement, which was based on overall survival as the primary outcome in both trials (8,9). In addition, the results

of both trials were reported as final analyses. Double-blinding was either not used or not reported in the two trials. Overall survival was also a primary outcome in two trials reported in abstract form only (11,15). The remaining trials used progression-free survival or response as primary outcomes. In addition, two of six abstracts reported that the a priori sample size requirement had been met (16,20); however only the results of the CRYSTAL trial were reported as a final analysis (14). That trial, as well as EPIC and CO.17 used intent-to-treat analyses. Of note, the EXPLORE trial was terminated early due to an inability to enrol patients as changes in clinical practice resulted in irinotecan being replaced by oxaliplatin in the first-line treatment of metastatic CRC.

Panitumumab

Four trials of panitumumab were identified: one was fully published (21), and three were available only in abstract form (24,26,27). All four trials reported progression-free survival as the primary outcome; however, Peeters et al also reported that overall survival was a co-primary outcome (24). Only Van Cutsem et al reported that their a priori sample size requirement had been met and that the analysis was final and intent-to-treat (21).

Trial Characteristics

Cetuximab

The trials of cetuximab in advanced CRC were divided into those that enrolled previously treated patients and those that enrolled previously untreated patients. Patient eligibility criteria for each trial as well as the interventions and comparisons can be found in Table 3. Full dose and schedule information can be found in Appendix 2.

The three trials of cetuximab in previously treated patients enrolled different patient populations: EPIC enrolled patients who had failed treatment with a fluoropyrimidine and oxaliplatin (8); CO.17 enrolled patients who had failed fluoropyrimidine, irinotecan, and oxaliplatin (9); and EXPLORE enrolled patients who had received irinotecan as first-line treatment (11). All three trials investigated cetuximab combined with different regimens (Table 3).

All five trials of cetuximab in previously untreated patients were reported in abstract form, and only the CRYSTAL trial reported a final analysis (16). That trial randomized patients to cetuximab combined with FOLFIRI compared to FOLFIRI alone. The remaining trials all administered different regimens combined with cetuximab (Table 3).

Panitumumab

The trials of panitumumab in advanced CRC were also grouped into those that enrolled previously treated patients and those that enrolled previously untreated patients (Table 3).

Van Cutsem et al (21) randomized patients who failed treatment with fluoropyrimidine, irinotecan, and oxaliplatin to panitumumab combined with BSC compared to BSC alone. Peeters et al (24) reported an interim analysis of patients with one or less prior treatments with fluoropyrimidine-based chemotherapy randomized to panitumumab combined with FOLFIRI compared to FOLFIRI alone.

The PRIME and PACCE trials enrolled patients with previously untreated metastatic CRC. PRIME randomized patients to panitumumab combined with FOLFOX-4 compared to FOLFOX-4 (25). PACCE randomized patients to receive panitumumab combined with bevacizumab and chemotherapy compared to bevacizumab and chemotherapy. Patients and physicians jointly decided whether the patient would receive irinotecan plus bevacizumab (Iri/Bev stratum) or oxaliplatin plus bevacizumab (Ox/Bev stratum). The results for each stratum were reported in two separate abstracts (26,27).

Table 3. Patient and trial characteristics of RCTs examining EGFR inhibitors in patients with advanced CRC.

Author, year (ref)	Patient characteristics	Intervention[a]	N	Age, mdn (y)
Cetuximab				
Previously treated				
EPIC Sobrero, 2008 (8)	EGFR+ metastatic CRC who had failed fluoropyrimidine/Ox in last six months	Iri + cetuximab	648	61
		Iri	650	62
CO.17 Jonker, 2007 (9)	EGFR+ advanced CRC who had been treated with fluoropyrimidine/Iri/Ox with no response within six months of treatment	BSC + cetuximab	287	63.0
		BSC	285	63.6
EXPLORE Jennis, 2005 (11) [abstract]	EGFR+ metastatic CRC who received Iri in first-line treatment	FOLFOX-4 + cetuximab	50	59
		FOLFOX-4	52	63
Previously untreated				
CAIRO2 Punt, 2008 (13) [abstract]	Previously untreated advanced CRC Patients could have previous adjuvant treatment for non-advanced disease if more than six months prior	Cap/Ox/Bev + cetuximab	368	62
		Cap/Ox/Bev	368	62
COIN Maughan, 2007 (15) [abstract]	Previously untreated advanced CRC, PS 0-2	FOLFOX or XELOX + cetuximab	248	NR
		FOLFOX or XELOX Intermittent FOLFOX or XELOX	502[b]	NR
CRYSTAL Van Cutsem, 2007 (16) [abstract]	Previously untreated EGFR+ metastatic CRC	FOLFIRI + cetuximab	599	61
		FOLFIRI	599	61
OPUS Bokemeyer, 2007 (19) [abstract]	Previously untreated EGFR+ metastatic CRC not resectable with curative intent	FOLFOX-4 + cetuximab	169	NR
		FOLFOX-4	168	NR
Borner, 2006 (20) [abstract]	Previously untreated metastatic CRC	XELOX + cetuximab	37	NR
		XELOX	37	NR
Panitumumab				
Previously treated				
Van Cutsem, 2007 (21)	EGFR+ metastatic CRC who failed previous fluoropyrimidine/Iri/Ox treatment in last six months, ECOG PS 0-2	BSC + panitumumab	231	62
		BSC	232	63
Peeters, 2008 (24) [abstract]	Metastatic CRC with no more than one prior fluoropyrimidine-based CT for metastatic CRC, ECOG PS 0-2	FOLFIRI + panitumumab	352	61
		FOLFIRI	349	
Previously untreated				
PRIME Siena, 2008 (25) [abstract]	Previously untreated metastatic CRC, ECOG PS 0-2	FOLFOX-4 + panitumumab	455	62
		FOLFOX-4	448	
PACCE - Iri/Bev Hecht, 2008 (26) [abstract]	Previously untreated metastatic CRC, ECOG PS 0-1	Iri/Bev + panitumumab	115	60.0
		Iri/Bev	115	59.0
PACCE - Ox/Bev Hecht, 2008 (27) [abstract]	Previously untreated metastatic CRC, ECOG PS 0-1	Ox/Bev + panitumumab	413	NR
		Ox/Bev	410	NR

Notes: Bev=bevacizumab; BSC=best supportive care; Cap=capecitabine; CRC=colorectal cancer; CT=chemotherapy; EGFR=epidermal growth factor receptor; ECOG=Eastern Cooperative Oncology Group; Iri=irinotecan; mdn=median; N=number of patients randomized; NR=not reported; Ox=oxaliplatin; PS=performance status; ref=reference; y=year(s).

[a]Full dose and schedule information for each regimen can be found in Appendix 2.

[b]Patient data were only available for the FOLFOX/XELOX and intermittent FOLFOX/XELOX arms combined. Therefore, in subsequent tables the data for these regimens are presented together and referred to as a single arm, FOLFOX or XELOX.

Clinical Efficacy

Data on the clinical efficacy of cetuximab and panitumumab can be found in Table 4.

Cetuximab

Previously treated

Overall survival

After a median follow-up of 14.6 months in the CO.17 trial (9), overall survival was significantly higher for BSC plus cetuximab (median 6.1 months) compared to BSC alone (median 4.6 months, HR 0.77, 95% confidence interval [CI] 0.64 – 0.92) (Table 4). In the EPIC trial there was a difference in median overall survival for irinotecan plus cetuximab compared to irinotecan alone (10.7 months vs. 10.0 months, respectively); however, that difference was not statistically significant (HR 0.975, 95% CI 0.854 – 1.114) (8).

Progression-free survival

In both EPIC and CO.17, progression-free survival was significantly higher in the cetuximab arm compared to the control arm (Table 4). In a much smaller trial that was terminated early due to an inability to enrol patients, progression-free survival was not significantly different (median 4.4 months for cetuximab plus FOLFOX-4 vs. 4.1 months for FOLFOX-4 alone; p=0.4861) (11).

Response

EPIC and CO.17 reported that objective and partial response rates were significantly higher in the cetuximab arm compared to the control arm (Table 4).

Previously untreated

Overall survival

No significant differences in overall survival were reported (Table 4); however, only one trial reported a final analysis (16).

Progression-free survival

The CRYSTAL trial reported a significant difference in progression-free survival for the FOLFIRI plus cetuximab arm (median 8.9 months) compared to the FOLFIRI-alone arm (median 8.0 months, HR 0.851, 95% CI 0.726 – 0.998) (16). The CAIRO2 trial reported a significant difference in progression-free survival for patients that received capecitabine/oxaliplatin/bevacizumab plus cetuximab (median 9.6 months) compared to the capecitabine/oxaliplatin/bevacizumab alone (median 10.7 months, HR 1.21, p=0.018). Of note, the authors did not report whether the analysis was final or if an a priori sample size requirement had been met. None of the remaining trials reported a significant difference in progression-free survival; however, none of those trials reported a final analysis.

Response

The CAIRO2 trial (13) reported no significant difference in objective response rates (Table 4). None of the remaining trials reported statistical comparisons on response rates for cetuximab compared to control.

Table 4. Efficacy outcomes of RCTs examining EGFR inhibitors in advanced CRC.

Author, year (ref)	Intervention	N	OS mdn (mos)	PFS mdn (mos)	OR (%)	CR (%)	PR (%)	Follow-up mdn (mos)
Cetuximab								
Previously treated								
EPIC Sobrero, 2008 (8)	Iri + Cetux	648	10.7	4.0	16.4	1.4	15.0	NR
	Iri	650	10.0 HR 0.975 (95% CI 0.854-1.114)	2.6 HR 0.692 (95% CI 0.617-0.776)	4.2 p<0.0001	0.2	4.0	NR
CO.17 Jonker, 2007 (9)	BSC + Cetux	287	6.1	NR	NR	NR	8.0	14.6
	BSC	285	4.6 HR 0.77 (95% CI 0.64-0.92)	NR HR 0.68 (95% CI 0.57-0.80)	NR	NR	0 p<0.001	
EXPLORE Jennis, 2005 (11) [abstract]	FOLFOX-4 + Cetux	50	NR	4.4	NR	NR	18.0	NR
	FOLFOX-4	52	NR	4.1 p=0.4861	NR	NR	7.7	NR
Previously untreated								
CAIRO2 Punt, 2008 (13) [abstract]	Cap/Ox/Bev + Cetux	368	20.3	9.6	44	NR	NR	18.7
	Cap/Ox/Bev	368	20.4 HR 1.15 p=0.21	10.7 HR 1.21 p=0.018	44 p=0.88	NR	NR	
COIN Maughan, 2007 (15) [abstract]	FOLFOX or XELOX + Cetux	248	NR	NR	NR	NR	NR	NR
	FOLFOX or XELOX	502	NR	NR	NR	NR	NR	NR
CRYSTAL Van Cutsem, 2007 (16) [abstract]	FOLFIRI + Cetux	599	NR	8.9	46.9	0.5	46.4	NR
	FOLFIRI	599	NR	8.0 HR 0.851 (95% CI 0.726-0.998)	38.7 p=0.0038	0.3	38.4	NR
OPUS Bokemeyer, 2007 (18) [abstract]	FOLFOX-4 + Cetux	169	NR	NR	45.6	1.2	44.4	NR
	FOLFOX-4	168	NR	NR	35.7	0.6	35.1	NR
Borner, 2006 (20) [abstract]	XELOX + Cetux	67	NR	NR	NR	NR	53	NR
	XELOX		NR	NR	NR	NR	33	NR
Panitumumab								
Previously treated								
Van Cutsem, 2007 (21)	BSC + Pan	231	NR	8 wks	10	NR	NR	35 wks[b]
	BSC	232	NR HR 1.00 (95% CI 0.82-1.22)	7.3 wks HR 0.54 (95% CI 0.44-0.66)	0 p<0.0001[a]	NR	NR	
Peeters, 2008 (24) [abstract]	FOLFIRI + Pan	352	NR	NR	NR	NR	NR	15 wks
	FOLFIRI	349	NR	NR	NR	NR	NR	
Previously untreated								
PRIME Siena, 2008 (25) [abstract]	FOLFOX-4 + Pan	455	NR	NR	NR	NR	NR	15 wks
	FOLFOX-4	448	NR	NR	NR	NR	NR	
PACCE - Iri/Bev Hecht, 2008 (26) [abstract]	Iri/Bev + Pan	115	20.7	10.1	43	0	43	37.6 wks
	Iri/Bev	115	20.5	11.7 HR 1.21 (95% CI 0.80-1.82)	39	0	39	40.3 wks
PACCE - Ox/Bev Hecht, 2008 (27) [abstract]	Ox/Bev + Pan	413	19.3	9.5	45	0	45	12.2
	Ox/Bev	410	20.6 HR 1.4 (95% CI 1.09-1.81)	11 HR 1.29 (95% CI 1.06-1.56)	46	<1	45	

Notes: Bev=bevacizumab; BSC=best supportive care; Cap=capecitabine; Cetux=cetuximab; CI=confidence interval; CR=complete response; HR=hazard ratio; Iri=irinotecan; mdn=median; mos=months; N=number of patients evaluated; NR=not reported; OR=objective response; OS=overall survival; Ox=oxaliplatin; Pan=panitumumab; PFS=progression-free survival; PR=partial response; ref=reference; wks=weeks. [a]Objective response was significantly different between the two arms after a minimum of 12 months follow-up. [b]Median follow-up was 61 weeks after crossover of 76% of patients to the panitumumab arm.

K-RAS status

Five trials of cetuximab reported efficacy outcomes compared by *K-RAS* status (Table 5). All five reports are in abstract form only; however, two of those reports (10,17), are based on trials for which a final analysis has been reported (9,16). No significant differences in overall survival or objective response rates were reported for cetuximab compared to the control in patients with mutant-type *K-RAS*. The CAIRO2 trial reported significantly lower progression-free survival for mutant *K-RAS* patients who received capecitabine/oxaliplatin/bevacizumab plus cetuximab (median 8.6 months) compared to the capecitabine/oxaliplatin/bevacizumab alone (median 12.5 months, p=0.043) (13). The OPUS trial also reported significantly lower progression survival for mutant K-RAS patients in the FOLFOX-4 plus cetuximab arm (median 5.5 months) compared to the FOLFOX-4 alone arm (median 8.6 months, HR 1.83, p=0.0192) (19). None of the remaining trials reported significant differences in progression-free survival for cetuximab compared to control.

For 250 wild-type *K-RAS* patients in the CO.17 trial, overall survival was significantly higher in the cetuximab plus BSC arm (median 9.5 months) compared to BSC alone (median 4.8 months, HR 0.55, 95% CI 0.41 – 0.74) (10). In addition, progression-free survival was also significantly higher in the cetuximab plus BSC arm (Table 5).

For trials of previously untreated patients, the CRYSTAL trial (17) and OPUS trial (19) reported significantly higher progression-free survival in patients with wild-type *K-RAS* in the cetuximab arm compared to the control arm (CRYSTAL HR 0.68, p=0.017; OPUS HR 0.57, p=0.016). The CAIRO2 trial reported no significant difference in either overall or progression-free survival for patients with *K-RAS* wild-type (13).

Table 5. Efficacy outcomes by *K-RAS* status.

Author, year (ref)	Intervention	Wild Type *K-RAS*				Mutant *K-RAS*			
		N	OS mdn (mos)	PFS mdn (mos)	OR (%)	N	OS mdn (mos)	PFS mdn (mos)	OR (%)
Cetuximab									
Previously treated									
CO.17 Karapetis, 2008 (10) [abstract]	BSC + Cetux	230	9.5	3.8	NR	164	4.6	1.8	NR
	BSC		4.8 HR 0.55 (95% CI 0.41-0.74)	1.9 HR 0.40 (95% CI 0.30-0.54)	NR		4.5 HR 0.98 (95% CI 0.70-1.37)	1.8 HR 0.99 (95% CI 0.73-1.35)	NR
EXPLORE Mitchell, 2008 (12) [abstract]	FOLFOX-4 + Cetux	NR	NR	162 days	NR	NR	NR	68 days	NR
	FOLFOX-4	NR	NR		NR	NR	NR		NR
Previously untreated									
CAIRO2 Punt, 2008 (13) [abstract]	Cap/Ox/Bev + Cetux	153	22.2	10.5	NR	93	19.1	8.6	NR
	Cap/Ox/Bev	152	23.0 p=0.49	10.7 p=0.1	NR	103	24.9 p=0.35	12.5 p=0.043	NR
CRYSTAL Van Cutsem, 2008 (17) [abstract]	FOLFIRI + Cetux	172	NR	9.9	59.3	105	NR	7.6	36.2
	FOLFIRI	176	NR	8.7 HR 0.68 p=0.017	43.2	87	NR	8.1 HR 1.07 p=0.47	40.2
OPUS Bokemeyer, 2008 (19) [abstract]	FOLFOX-4 + Cetux	61	NR	7.7	60.7	52	NR	5.5	32.7
	FOLFOX-4	73	NR	7.2 HR 0.57 p=0.016	37.0	47	NR	8.6 HR 1.83 p=0.0192	48.9
Panitumumab									
Previously treated									
Amado, 2008 (23) (Van Cutsem study)	BSC + Pan	124	8.1	12.3 wks	17	84	4.9	7.4 wks	0
	BSC	119	7.6 HR 0.99 (95% CI 0.75-1.29)	7.3 wks HR 0.45 (95% CI 0.34-0.59)	0	100	4.4 HR 1.02 (95% CI 0.75-1.39)	7.3 wks HR 0.99 (95% CI 0.73-1.36)	0

Notes: Bev=bevacizumab; BSC=best supportive care; Cap=capecitabine; Cetux=cetuximab; CI=confidence interval; HR=hazard ratio; mdn=median; mos=months; N=number of patients evaluated; NR=not reported; OR=objective response; OS=overall survival; Ox=oxaliplatin; Pan=panitumumab; PFS=progression-free survival; ref=reference.

Adverse events

Only the EPIC (8), CO.17 (9), CAIRO2 (13), and COIN (15) trials reported statistical comparisons of adverse events for cetuximab compared to a control (Table 6). Three of those trials reported that a significantly greater proportion of patients in the cetuximab arm experienced at least one grade 3 or 4 adverse event compared to the control arm (9,13,15). Grade 3 or 4 adverse events occurred in 50.9% to 82% of cetuximab-treated patients compared to 30% to 72% of control patients (Table 6). The rates of any grade and grade 3/4 hypomagnesemia were significantly higher in the cetuximab arm compared to the control arm in the EPIC and CO.17 trials (Table 6). Grade 3/4 hypomagnesemia occurred in 3.3% to 5.2% of patients receiving cetuximab and in 0 to 0.4% of patients in the control arms. Grade 3/4 skin reactions were significantly higher for cetuximab (8.2% to 12.1%) compared to control (0 to 0.6%) in the EPIC, CO.17, and COIN trials (Table 6). Grade 3/4 fatigue (7.7% vs. 3.3%) and grade 3/4 lethargy (FOLFOX, 21.2% vs. 7.9%; XELOX, 18.1% vs. 8.5%) were significantly higher for cetuximab in EPIC and COIN, respectively. Grade 3/4 diarrhea was significantly higher for cetuximab (13.1% to 28.4%) than control (6.8% to 19%) in EPIC, CAIRO2, and COIN. A significantly higher rate of infusion-related reactions and grade 3/4 infections occurred in the cetuximab plus BSC arm compared to the BSC-alone arm in the CO.17 trial (Table 6). The EPIC trial reported a significantly higher rate of both any grade (62.4% vs. 55.6%) and grade 3/4 (31.8% vs. 25.4%) neutropenia for patients receiving cetuximab compared to control (8).

Table 6. Adverse events in RCTs examining EGFR inhibitors in patients with advanced CRC.

Author, year (ref)	Intervention	N (eval)	Grade 1-4 adverse events [%] (Grade 3/4 [%])							
			Hypo-magnesemia	Infusion reaction	Skin reaction	Diarrhea	Fatigue	Infection	Neutropenia	Any AE
Cetuximab										
EPIC Sobrero, 2008 (8)	Iri + Cetux	638	33.8* (3.3)*	(1.4)	76.3* (8.2)*	81.2* (28.4)*	40.3 (7.7)*	NR	62.4* (31.8)*	62.1
	Iri	629	8.4* (0.4)* *p<0.05	(0.8)	4.9* (0.2)* *p<0.05	71.9* (15.7)* *p<0.05	35.1 (3.3)* *p<0.05	NR	55.6* (25.4)* *p<0.05	43.6
CO.17 Jonker, 2007 (9)	BSC + Cetux	288	47.9 (5.2)	20.5 (4.5)	(11.8)	NR	(33.0)	(12.8)[a]	NR	(78.5)
	BSC	274	10.9 (0) p<0.001	0 (0) p<0.001	(0.4) p<0.001	NR	(25.9) p=0.09	(5.5)[a] p=0.003	NR	(59.1) p<0.001
EXPLORE Jennis, 2005 (11) [abstract]	FOLFOX-4 + Cetux	NR	NR	NR	NR	NR	NR	NR	NR	NR
	FOLFOX-4	NR	NR	NR	NR	NR	NR	NR	NR	NR
CAIRO2 Punt, 2008 (13) [abstract]	Cap/Ox/Bev + Cetux	365	38 (2)[b]	NR	84 (25)	(26)	NR	25 (5)[b]	NR	(82)
	Cap/Ox/Bev	366	15 (1)[b]	NR	4 (0.5)	(19) p=0.026	NR	26 (4)[b]	NR	(72) p=0.0013
COIN Maughan, 2007 (15) [abstract]	FOLFOX or XELOX + Cetux	96/152	NR	(0/3.0)	(12.1/10.1)	(13.1/25.8)	(21.2/18.1)[c]	NR	(25.7/0.6)	(54.0/50.9)
	FOLFOX or XELOX	186/316	NR	(0/1.2)	(0/0.6) p<0.001	(6.8/15.2) p<0.05	(7.9/8.5)[c] p<0.001	NR	(18.3/1.6)	(31.6/30.0) p<0.001
CRYSTAL Van Cutsem, 2007 (16) [abstract]	FOLFIRI + Cetux	600	NR	(2.3)	(18.7)	(15.2)	(5.0)	NR	(26.7)	(78.0)
	FOLFIRI	602	NR	(0)	(0.2)	(10.5)	(4.5)	NR	(23.3)	(59.5)
OPUS Bokemeyer, 2007 (18) [abstract]	FOLFOX-4 + Cetux	170	(2.0)	(4.1)	(14.1)	(7.1)	(3.5)	NR	(27.6)	NR
	FOLFOX-4	168	(0)	(1.8)	(0)	(6.0)	(3.0)	NR	(31.5)	NR
Borner, 2006 (20) [abstract]	XELOX + Cetux	67	NR	NR	(6)	NR	NR	NR	NR	NR
	XELOX		NR	NR	(0)	NR	NR	NR	NR	NR
Panitumumab										
Van Cutsem, 2007 (21)	BSC + Pan	229	NR	NR	90	21 (1)	24 (4)	NR	NR	100 (35)
	BSC	234	NR	NR	9	11 (0)	15 (3)	NR	NR	86 (20)
Peeters, 2008 (24) [abstract]	FOLFIRI + Pan	352	7 (1)	NR	61 (12)	55 (9)	28 (4)	1 (<1)	27 (15)	NR
	FOLFIRI	349								
PRIME Siena, 2008 (25) [abstract]	FOLFOX-4 + Pan	455	11 (2)	NR	56 (10.6)	47 (11)	27 (4)	<1 (0)	44 (28)	NR
	FOLFOX-4	448								
PACCE - Iri/Bev Hecht, 2008 (26) [abstract]	Iri/Bev + Pan	111	(5)	NR	(37)	(28)	NR	(14)	(17)	99 (79)
	Iri/Bev	113	(1)	NR	(0)	(9)	NR	(9)	(21)	100 (58)
PACCE - Ox/Bev Hecht, 2008 (27) [abstract]	Ox/Bev + Pan	413	NR	NR	(39)	(24)	NR	(19)	NR	NR
	Ox/Bev	410	NR	NR	(2)	(13)	NR	(10)	NR	NR

Notes: AE=adverse event; Bev=bevacizumab; BSC=best supportive care; Cap=capecitabine; Cetux=cetuximab; Iri=irinotecan; N=number of patients evaluated; NR=not reported; Ox=oxaliplatin; Pan=panitumumab; ref=reference;.
[a]Non-neutropenic infection.
[b]Hypomagnesemia and infection adverse events were reported in a full publication by Tol et al (14) with 192 patients in the panitumumab arm and 197 patients in the control arm.
[c]Lethargy (grade 3/4).

Panitumumab

Previously treated

Overall survival

Van Cutsem et al (21) reported no significant difference in overall survival (HR 1.00, 95% CI 0.82 – 1.22) (Table 4); however, as the study was powered to detect differences in progression-free survival, it is unknown whether the study was sufficiently powered to detect a difference in overall survival. The remaining trial (24) did not report on overall survival.

Progression-free survival

Van Cutsem et al (21) reported a significant difference in progression-free survival for patients receiving panitumumab and BSC (median eight weeks) compared to BSC alone (7.3 weeks) (HR 0.54, 95% CI 0.44 – 0.66). Peeters et al (24) did not report on progression-free survival.

Response

Van Cutsem et al (21) reported a significant difference in objective response rates (Table 4). Again, Peeters et al (24) did not report tumour response rates.

Previously untreated

Overall survival

Hecht et al (26,27) reported overall survival data for both strata of the PACCE trial (Table 4). In the irinotecan plus bevacizumab stratum (26), overall survival was 20.7 months in the panitumumab arm compared to 20.5 months in the control arm. In the oxaliplatin plus bevacizumab stratum (27), overall survival was significantly decreased for patients that received panitumumab (HR 1.4, 95% CI 1.09 – 1.81). No data on overall survival were reported for the PRIME trial (25).

Progression-free survival

Progression-free survival was reported for both strata of the PACCE trial (26,27). In the irinotecan plus bevacizumab stratum, no statistically significant difference in progression-free survival reported (Table 4). However, patients in the oxaliplatin plus bevacizumab stratum who received panitumumab had a statistically significant decrease in progression-free survival compared to those who did not receive panitumumab (HR 1.29, 95% CI 1.06 – 1.56). No data on progression-free survival were reported for the PRIME trial (25).

Response

No statistically significant differences in objective response rates were reported in the PACCE or PRIME trials (25-27).

K-RAS status

Data on efficacy outcomes compared by *K-RAS* status were available for only the Van Cutsem trial (21) in a separate full publication (23) and are presented in Table 5. The authors reported that among patients with mutant *K-RAS*, there were no significant differences in overall survival (HR 1.02, 95% CI 0.75 – 1.39) or progression-free survival (HR 0.99, 95% CI 0.73 – 1.36) (23).

Progression-free survival in wild-type *K-RAS* patients was significantly higher for panitumumab plus BSC (median 12.3 weeks) compared to BSC alone (median 7.3 weeks; HR 0.45, 95% CI 0.34 – 0.59). However, there was no significant difference in overall survival (HR 0.99, 95% CI0.75 – 1.29) (23).

Adverse events

No trials of panitumumab reported statistical differences between patients receiving panitumumab compared to control, although no trial reported whether they undertook any statistical comparisons of adverse events between the intervention and control arms. In general, more adverse events were noted in the panitumumab arms than in the control arms (Table 6) in the Van Cutsem (21) and PACCE trials (26,27).

V. DISCUSSION

Patient selection by *K-RAS* status

Although in each randomized trial where *K-RAS* status was assessed as a predictor of benefit, it was done in an exploratory analysis; there is now consistent and compelling data to recommend these agents only for patients with *K-RAS* wild-type status and advise against their use in those expressing activating *K-RAS* mutations. In several trials, particularly where these agents were used in combination with oxaliplatin-based chemotherapy, there is evidence to suggest that the addition of cetuximab or panitumumab in patients with mutant *K-RAS* tumours results in a worsening of outcomes. Therefore, *K-RAS* is recommended as a biomarker, with only patients selected for wild-type tumour status proceeding to receive EGFR inhibitors.

EGFR antibody monotherapy in chemotherapy refractory patients

There is good evidence that both cetuximab and panitumumab improve progression-free survival and objective response rate compared to BSC alone in chemotherapy refractory patients. Although effective in an unselected population, this benefit is most pronounced when evaluating the subset of patients with *K-RAS* wild-type tumours. In *K-RAS* wild-type patients, cetuximab monotherapy resulted in a 60% reduction in risk of progression (HR 0.40, 95% CI 0.30 to 0.54) (10), and panitumumab resulted in a 55% reduction in risk of progression (HR 0.45, 95% CI 0.34 to 0.59) (23). Where no objective tumour responses occurred in patients on BSC, the objective response rate in wild-type selected populations was 17% with panitumumab (23).

In addition to the response and progression benefits in *K-RAS* wild-type patients, cetuximab was also demonstrated to result in a near doubling of median overall survival (4.8 vs. 9.5 months, HR 0.55, $p<0.0001$) (10). The trial with panitumumab did not demonstrate a survival improvement (7.6 vs. 8.1 months median overall survival), although crossover by 76% of patients in the panitumumab study may explain the absence of effect on overall survival (19,21). The trial with cetuximab also demonstrated better preservation of quality of life compared to BSC alone (9). This was not assessed in the panitumumab monotherapy trial.

Is one EGFR inhibitor inferior or superior to another?

The high level of consistency between the two monotherapy trials for certain endpoints (progression-free survival, response rate, many toxicities) suggests trial design issues alone (i.e. crossover) might account for the differences in overall survival outcomes. However, as the drugs also differ in structural backbone (IgG1 vs. IgG2), immunogenicity, pharmacokinetics, and toxicity, only a direct comparison of the agents could clearly evaluate superiority. The schedule (every two weeks instead of weekly) and toxicity (low rate of hypersensitivity reactions with panitumumab) profile of panitumumab might otherwise lead to a preference for this agent over cetuximab, but the overall survival improvement is currently only clearly demonstrated for cetuximab. The safety and efficacy of combining panitumumab with irinotecan has also not been established.

Adding an EGFR antibody to bevacizumab plus chemotherapy

There are now two trials published in abstract form that suggest a detrimental effect of the double biologics plus oxaliplatin-based chemotherapy combination (13,26,27). In these *K-RAS* unselected populations, the risk of progression with the addition of EGFR antibody therapy was increased between 17 to 22%. Outside of a clinical trial, and then only for *K-RAS* wild-type patients, the strategy of combining EGFR and VEGF inhibitors with chemotherapy should not be used.

Adding an EGFR antibody to chemotherapy

As earlier mentioned, there is now evidence of a potential detrimental effect of adding an EGFR antibody to chemotherapy in patients with *K-RAS* mutant tumours. There was an 83% increase in risk of progression when cetuximab was added to first-line FOLFOX in *K-RAS* mutants (19). The addition of cetuximab to FOLFIRI in a *K-RAS* mutant population was less clearly detrimental (HR 1.07) but suggested no advantage (17).

In *K-RAS* wild-type patients in the first-line setting, two trials, published in abstract form only, of an EGFR antibody added to chemotherapy involved the addition of cetuximab, one in combination with FOLFIRI, and the other with FOLFOX. In those trials, there was a reduction of the risk of progression of 32% and 43% with the addition of cetuximab to FOLFIRI and FOLFOX respectively (17,19). Those reductions in risk of progression compare favourably with the results of adding bevacizumab to FOLFOX or 5-fluorouracil/irinotecan regimen in the same setting (HR=0.83 and 0.54, respectively) (28,29). Determining if cetuximab is superior to bevacizumab as an adjunct to first-line chemotherapy in the wild-type population will require the results of ongoing trials (i.e. CALGB 80405). While awaiting this data, the toxicity profile and the administration schedule currently favour bevacizumab, suggesting EGFR monoclonal antibodies are justifiably reserved for patients in the chemotherapy-refractory setting.

Although not the topic of this systematic review, the addition of irinotecan to cetuximab resulted in superior progression-free survival and response rate in a randomized phase II study (BOND) with a primary endpoint of response rate (30). This study assigned 329 patients who progressed on irinotecan to cetuximab plus irinotecan vs. cetuximab alone. Response rate was 22.9 % vs. 10.8 percent (P=0.007); median time to progression was 4.1 vs. 1.5 months ($p<0.001$); median overall survival was 8.6 vs. 6.9 months ($p=0.48$). Patients on the cetuximab monotherapy arm were permitted to cross over at the time of progression to receive the combination. A meta-analysis from seven series of irinotecan-refractory patients treated with cetuximab plus irinotecan, determined the role of *K-RAS* status (31). Median progression-free and overall survival were significantly higher in the *K-RAS* wild-type patients, 24 vs. 12 weeks ($p<0.0001$) and 44 vs. 36 weeks ($p<0.0001$), respectively. Based on these studies, the opinion of the authors is that irinotecan should be added to cetuximab for suitable patients. The authors are not aware of any clinical trials of irinotecan combined with panitumumab; therefore, this combination is not currently recommended.

VI. ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (http://clinicaltrials.gov/) were searched for reports of new or ongoing randomized trials investigating the use of EGFR inhibitors in advanced CRC that met our eligibility criteria. Appendix 3 details the identified ongoing trials.

VII. RECOMMENDATIONS AND EVIDENCE

Recommendations

- **The two clinically available EGFR inhibitors, cetuximab and panitumumab, are recommended for patients with advanced CRC after failure of standard chemotherapy and whose tumours have tested negative for *K-RAS* gene mutations (i.e. patients with *K-RAS* wild-type). The recommended dose of cetuximab is a loading dose of 400 mg/m^2 of body surface area (BSA) intravenously (iv) followed by a weekly 250 mg/m^2 infusion; pre-medication with an antihistamine is required. The dose of panitumumab is 6 mg/kg iv every two weeks; no pre-medication is required.**

  Key Evidence

  - A randomized phase III study that compared cetuximab plus best supportive care (BSC) versus (vs.) BSC alone (9) demonstrated response rates of 8.0% in the cetuximab group vs. 0% in the BSC group (p<0.001) and stable disease in 31.4% vs. 10.9% (p<0.001). Progression-free survival was superior for the cetuximab arm (HR 0.68, p<0.001) as was overall survival (HR 0.77, p=0.005). Quality of life was superior for physical function and global health status scores (both p<0.05).
    - ⇒ Sixty-nine percent of the intent-to-treat population was retrospectively analyzed according to *K-RAS* status (10). In the *K-RAS* wild-type population, cetuximab treatment resulted in an increase of median progression-free survival 3.8 vs. 1.9 months (HR 0.40, p<0.001), median overall survival 9.5 vs. 4.8 months (HR 0.55, p<0.0001). Within the *K-RAS* mutant population, no effect of cetuximab was apparent on progression-free survival (HR 0.99) or overall survival (HR 0.98).
  - A randomized phase III study compared panitumumab plus BSC versus BSC alone (21). The response rate was 10% for panitumumab vs. 0% for BSC (p<0.0001); stable disease 27% vs. 10%. Progression-free survival was superior for the panitumumab arm (HR 0.54, p<0.0001). There was no difference in overall survival (HR 1.0), which may have been affected by the high proportion of patients undertaking the protocol-sanctioned crossover to panitumumab after progression on the BSC arm. Quality of life was not reported. Toxicities of panitumumab treatment were manageable.
    - ⇒ Ninety-two percent of the intent-to-treat population was retrospectively analyzed according to *K-RAS* status (23). In the *K-RAS* wild-type population, panitumumab treatment resulted in an increase of median progression-free survival 2.8 vs. 1.7 months (HR 0.45, p<0.0001) and response rate (17% vs. 0%). Median overall survival was not significantly different (HR 1.02); however, it was likely affected by crossover. Within the *K-RAS* mutant population, no effect of panitumumab was apparent on progression-free survival (HR 0.99), response rate, or overall survival (HR 1.02).

- **For patients who have not yet failed chemotherapy treatment, there is mounting evidence that EGFR inhibitors are safe and effective when combined with chemotherapy in advanced CRC patients who are confirmed to be *K-RAS* gene wild-type. However, at this time there is insufficient evidence to recommend it over the current standards of care.**

  Key Evidence

  - There are two trials published in abstract form involving the addition of cetuximab to chemotherapy in previously untreated patients, for which exploratory *K-RAS* mutation analysis have been reported: one in combination with FOLFIRI and the other with FOLFOX. In these trials, there was a statistically significant reduction of the risk of

progression of 32% and 43% with the addition of cetuximab to FOLFIRI and FOLFOX, respectively (17,19).

- In patients with one prior line of chemotherapy, there are two trials examining the addition of cetuximab to second-line chemotherapy. In the EPIC study, 1,298 patients who had first-line oxaliplatin-based chemotherapy were randomized to cetuximab plus irinotecan versus irinotecan alone (8). Superior response rate (16.4% vs. 4.2%, p<0.0001) and progression-free survival (median 4.0 vs. 2.6 months, HR 0.692, p<0.0001) were demonstrated. Median overall survival was not statistically different (HR 0.98), a possible effect of the crossover by 47% of the monotherapy arm to receive subsequent cetuximab. The quality of life scores were superior for global health status (p=0.047). An analysis by *K-RAS* status has not been reported. In the EXPLORE study, 102 patients who had first-line irinotecan-based chemotherapy were randomized to cetuximab plus FOLFOX versus FOLFOX alone (11). This study was terminated early for poor accrual. No differences in outcomes were noted between arms for progression free survival.

- **For patients who have not yet failed chemotherapy treatment, combination of EGFR inhibitors with both chemotherapy and the vascular endothelial growth factor (VEGF) antibody bevacizumab are not recommended outside of a clinical trial.**

  Key Evidence
  - There are two trials published in abstract form which suggest a detrimental effect of the dual EGFR-VEGF inhibition plus oxaliplatin-based chemotherapy (13,26,27). In these *K-RAS* unselected populations, the risk of progression with the addition of EGFR antibody therapy was increased between 17 to 22%.

- **The two agents that are clinically available, panitumumab and cetuximab, have not been directly compared for efficacy or toxicity in a randomized clinical trial. Therefore, neither agent can be recommended over the other after failure of standard chemotherapy.**

Qualifying Statements

- There are no clinical trials of EGFR inhibitor efficacy where patients were prospectively tested for *K-RAS* status and selected based on these results. Observations of benefit for EGFR inhibitors in *K-RAS* wild-type patients are based on retrospective tumour assessment from prospective trials; nonetheless, the consistency of the demonstrated effect across multiple trials is sufficient to strongly recommend restricting the use of EGFR inhibitors to *K-RAS* wild-type patients.
- Although not the topic of this systematic review, the addition of irinotecan to cetuximab resulted in superior progression-free survival and response rate in a randomized phase II study (BOND) with a primary endpoint of response rate (30). This study assigned 329 patients who progressed on irinotecan to cetuximab plus irinotecan vs. cetuximab alone. The response rate was 22.9 % vs. 10.8 percent (p=0.007); median time to progression was 4.1 vs. 1.5 months (p<0.001); median overall survival was 8.6 vs. 6.9 months (p=0.48). Patients on the cetuximab monotherapy arm were permitted to cross over at the time of progression to receive the combination. **The opinion of the authors is that irinotecan should be added to cetuximab for suitable patients.** The authors are not aware of any clinical trials of irinotecan combined with panitumumab. Therefore, this combination is not currently recommended.

- Standard first line therapy for advanced CRC is either FOLFOX or 5-fluorouracil/irinotecan regimen in combination with bevacizumab, where the addition of bevacizumab results in an improved progression-free survival (HR=0.83 and 0.54, respectively) (28,29). The improvement in progression-free survival in *K-RAS* wild-type patients with the addition of cetuximab to FOLFOX or FOLFIRI is of a similar magnitude (HR 0.57 or HR 0.68, respectively). Determining whether cetuximab is superior to bevacizumab as an adjunct to first-line chemotherapy in the wild-type population will require the results of ongoing trials (i.e. CALGB 80405: A Phase III Trial of Irinotecan / 5-FU / Leucovorin or Oxaliplatin / 5-FU/ Leucovorin With Bevacizumab, or Cetuximab (C225), or With the Combination or Bevacizumab and Cetuximab for Patients With Untreated Metastatic Adenocarcinoma of the Colon or Rectum).

Related Guidelines

- **Practice Guideline #2-16:** Use of Irinotecan in the Second-line Treatment of Metastatic Colorectal Carcinoma.
- **Practice Guideline #2-16b:** Use of Irinotecan (Camptosar®, CPT-11) Combined with 5-Fluorouracil and Leucovorin (5FU/LV) as First-line Therapy for Metastatic Colorectal Cancer.
- **Practice Guideline #2-22:** The Role of Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in the First and Second-line Treatment of Advanced Colorectal Cancer.
- **Practice Guideline #2-25:** The Role of Bevacizumab (Avastin™) Combined with Chemotherapy in the Treatment of Patients with Advanced Colorectal Cancer.

VIII. CONFLICTS OF INTEREST

Two authors (JB, AH) reported no conflicts of interest. One author (DJ) served on an advisory board of Bristol-Myers Squibb.

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Appendix 1. Literature search strategies.

Search strategies for systematic reviews, meta-analyses, and randomized trials of patients treated with EGFR inhibitors:

MEDLINE (OVID), MEDLINE Daily Update (OVID), and MEDLINE In-Process & Other Non-Indexed Citations (OVID)

1. exp colorectal neoplasms/
2. cetuximab.mp.
3. c225:.mp.
4. erbitux.mp.
5. panitumumab.mp.
6. abx-egf:.mp.
7. vectibix.mp.
8. or/2-7
9. 1 and 8
10. meta-analysis as topic/
11. meta analysis.pt.
12. meta analy$.tw.
13. metaanaly$.tw.
14. (systematic adj (review$1 or overview$1)).tw.
15. or/10-14
16. cochrane.ab.
17. embase.ab.
18. (cinahl or cinhal).ab.
19. science citation index.ab.
20. bids.ab.
21. cancerlit.ab.
22. or/16-21
23. reference list$.ab.
24. bibliograph$.ab.
25. hand-search$.ab.
26. relevant journals.ab.
27. manual search$.ab.
28. or/23-27
29. selection criteria.ab.
30. data extraction.ab.
31. 29 or 30
32. review.pt.
33. review literature as topic/
34. 32 or 33
35. 31 and 34
36. comment .pt.
37. letter.pt.
38. editorial.pt.
39. or/36-38
40. 15 or 22 or 28 or 35
41. 40 not 39
42. randomized controlled trials as topic/
43. randomized controlled trial.pt.
44. random allocation/
45. double blind method/

46. single blind method/
47. clinical trials, phase II as topic/
48. clinical trial, phase II.pt.
49. clinical trials, phase III as topic/
50. clinical trial, phase III.pt.
51. (clinic$ adj trial$1).tw.
52. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
53. placebos/
54. placebo$.tw.
55. (allocated adj2 random$).tw.
56. random allocation.tw.
57. randomly allocated.tw.
58. or/42-57
59. case report.tw.
60. letter.pt.
61. historical article.pt.
62. or/59-61
63. 58 not 62
64. 41 or 63
65. 9 and 64
66. limit 65 to (English language and humans)
67. limit 66 to yr="2003 – 2008"

EMBASE (OVID)

1. exp colon cancer/
2. exp rectum cancer/
3. 1 or 2
4. cetuximab.mp.
5. c225:.mp.
6. erbitux.mp.
7. panitumumab.mp.
8. abx-egf:.mp.
9. vectibix.mp.
10. or/4-9
11. 3 and 10
12. exp meta-analysis/
13. ((meta adj analy$) or metaanaly$).tw.
14. (systematic ad (review$1 or overview$1)).tw.
15. or/12-14
16. cancerlit.ab.
17. cochrane.ab.
18. embase.ab.
19. (cinahl or cinhal).ab.
20. science citation index.ab.
21. bids.ab.
22. or/16-21
23. reference list$.ab.
24. bibliograph$.ab.
25. hand-search$.ab.

26. manual search$.ab.
27. relevant journals.ab.
28. or/23-27
29. data extraction.ab.
30. selection criteria.ab.
31. 29 or 30
32. review.pt.
33. 31 and 32
34. letter.pt.
35. editorial.pt.
36. 34 or 35
37. 15 or 22 or 28 or 33
38. 37 not 36
39. randomized controlled trial/
40. randomization/
41. single blind procedure/
42. double blind procedure/
43. placebo/
44. randomi?ed control$ trial$.tw.
45. RCT.tw.
46. random allocation.tw.
47. randomly allocated.tw.
48. allocated randomly.tw.
49. (allocated adj2 random$).tw.
50. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
51. placebo$.tw.
52. or/39-51
53. case study/
54. case report.tw.
55. abstract report/
56. letter/
57. or/53-56
58. 52 not 57
59. 38 or 58
60. 11 and 59
61. limit 60 to (human and English language)
62. limit 61 to yr="2003 – 2008"

Search strategies for K ras mutation testing in patients treated with EGFR inhibitors:
MEDLINE (OVID), MEDLINE Daily Update (OVID), and MEDLINE In-Process & Other Non-Indexed Citations (OVID)

1. exp colorectal neoplasms/
2. cetuximab.mp.
3. c225:.mp.
4. erbitux.mp.
5. panitumumab.mp.
6. abx-egf:.mp.
7. vectibix.mp.
8. or/2-7
9. 1 and 8
10. ras proteins/
11. genes, ras/
12. kras$.mp.
13. k-ras$.mp.
14. k ras.mp.
15. exp protein-tyrosine kinases/
16. (mutation$ adj2 test$).tw.
17. 15 and 16
18. or/10-14,17
19. 9 and 18
20. limit 19 to (English language or humans)
21. limit 20 to yr="2003 – 2008"

EMBASE (OVID)

1. exp colon cancer/
2. exp rectum cancer/
3. 1 or 2
4. cetuximab.mp.
5. c225:.mp.
6. erbitux.mp.
7. panitumumab.mp.
8. abx-egf:.mp.
9. vectibix.mp.
10. or/4-9
11. 3 and 10
12. oncogene k ras/
13. k ras protein/
14. k-ras$.mp.
15. kras$.mp.
16. k ras .mp.
17. or/12-16
18. epidermal growth factor receptor/
19. tyrosine kinase receptor/
20. (mutation$ adj2 test$).tw.
21. (18 or 19) and 20
22. 17 or 21
23. 11 and 22
24. limit 23 to (human and English language)

25. limit 24 to yr=”2003 – 2008”

Search strategies in other databases:
Cochrane Central Register of Controlled Trials (CCTR) and Cochrane Database of Systematic Reviews (CDSR)
1. panitumumab.mp.
2. vectibix.mp.
3. abx-egf.mp.
4. cetuximab.mp.
5. erbitux.mp.
6. c225:.mp.
7. egfr.mp.
8. epidermal growth factor receptor:.mp.
9. or/1-8
10. colorectal.mp.
11. colon.mp.
12. rectal.mp.
13. rectum.mp.
14. or/10-13
15. cancer.mp.
16. 14 and 15
17. 9 and 16
18. limit 17 to yr="2003 - 2008"
19. limit 18 to medline records
20. limit 18 to embase records
21. 19 or 20
22. 18 not 21

Annual Conference Proceedings of the American Society of Clinical Oncology (ASCO) and the ASCO Gastrointestinal Cancers Symposia
Search terms used: Vectibix, panitumumab, abx-egf, Erbitux, cetuximab, c225, EGFR, colorectal cancer.

Appendix 2. Dose and schedule information for trials of EGFR inhibitors in advanced CRC.

Author, year (ref)	Treatment Arms	Treatment details
Cetuximab		
Previously treated		
EPIC Sobrero, 2008 (8)	Iri + Cetux	**Cetux** loading dose 400 mg/m^2 (iv, 120 minutes), then 250 mg/m^2 (iv, 60 minutes) weekly, preceeded by premedication with an antihistamine followed 1 hour later by **Iri** 350 mg/m^2 (iv, 90 minutes)[a]; every 3 weeks. Treatment continued until disease progression or unacceptable toxicity.
	Iri	**Iri** 350 mg/m^2 (iv, 90 minutes)[a]; every 3 weeks. Treatment continued until disease progression or unacceptable toxicity.
CO.17 Jonker, 2007 (9)	BSC + Cetux	**Cetux** loading dose 400 mg/m^2 of BSA (iv, 120 minutes), then 250 mg/m^2 (iv, 60 minutes) weekly, preceeded by premedication with an anithistamine 30-60 minutes before each cetuximab dose + **BSC:** defined as measures designed to provide palliation of symptoms and improve QOL. Treatment continued until death, presence or occurrence of unacceptable AE, tumour progression, worsening cancer symptoms, or patient choice.
	BSC	**BSC:** defined as measures designed to provide palliation of symptoms and improve QOL. Treatment continued until death, presence or occurrence of unacceptable AE, tumour progression, worsening cancer symptoms, or patient choice.
EXPLORE Jennis, 2005 (11) [abstract]	FOLFOX-4 + Cetux	**Cetux** loading dose 400 mg/m^2, then 250 mg/m^2 weekly + **FOLFOX-4:** Ox 85 mg/m^2 d1 + LV 200 mg/m^2 d1,2 + 5-FU 400 mg/m^2 bolus then 600 mg/m^2 d1,2 (civ, 22 hours).
	FOLFOX-4	**FOLFOX-4:** Ox 85 mg/m^2 d1 + LV 200 mg/m^2 d1,2 + 5-FU 400 mg/m^2 bolus then 600 mg/m^2 d1,2 (civ, 22 hours).
Previously untreated		
CAIRO2 Punt, 2008 (13) [abstract]	Cap/Ox/Bev + Cetux	**Cetux** loading dose 400 mg/m^2 iv, then 250 mg/m^2 iv weekly + **Cap** 1000 mg/m^2 orally bid d1-14 + **Ox** 130 mg/m^2 d1 + **Bev** 7.5 mg/kg d1; every 3 weeks for cycles 1-6, then **Cetux** 250 mg/m^2 iv weekly + **Cap** 1250 mg/m^2 orally bid d1-14 + **Bev** 7.5 mg/kg d1; every 3 weeks for subsequent cycles.
	Cap/Ox/Bev	**Cap** 1000 mg/m^2 orally bid d1-14 + **Ox** 130 mg/m^2 d1 + **Bev** 7.5 mg/kg d1; every 3 weeks for cycles 1-6, then **Cap** 1250 mg/m^2 orally bid d1-14 + **Bev** 7.5 mg/kg d1; every 3 weeks for subsequent cycles.
COIN Maughan, 2007 (15) [abstract]	FOLFOX or XELOX + Cetux	**Cetux** loading dose 400 mg/m^2 d1, then 250 mg/m^2 weekly, preceded by premedication with chlorphenamine 10 mg iv, paracetamol 1 g orally, ranitidine 150 mg orally + either: **FOLFOX: LV** 175 mg (iv, 120 minutes) + **Ox** 85 mg/m^2 (iv, 120 minutes) + **5-FU** 400 mg/m^2 bolus then 2400 mg/m^2 (civ, 46 hours); every 2 weeks, until progression, cumulative toxicity or patient choice, or; **XELOX: Ox** 130 mg/m^2 d1 (iv, 120 minutes) + **Cap** 1000 mg/m^2 orally bid d1-14; every 3 weeks, until progression, cumulative toxicity or patient choice.
	FOLFOX or XELOX	**FOLFOX: LV** 175 mg (iv, 120 minutes) + **Ox** 85 mg/m^2 (iv, 120 minutes) + **5-FU** 400 mg/m^2 bolus then 2400 mg/m^2 (civ, 46 hours); every 2 weeks, until progression, cumulative toxicity or patient choice, or; **XELOX: Ox** 130 mg/m^2 d1 (iv, 120 minutes) + **Cap** 1000 mg/m^2 orally bid d1-14; every 3 weeks, until progression, cumulative toxicity or patient choice.
	Intermittent FOLFOX or XELOX	**FOLFOX: LV** 175 mg (iv, 120 minutes) + **Ox** 85 mg/m^2 (iv, 120 minutes) + **5-FU** 400 mg/m^2 bolus then 2400 mg/m^2 (iv, 46 hours); every 2 weeks, stopped at 12 weeks in stable or responding patients and restarted following progression, or; **XELOX: Ox** 130 mg/m^2 d1 (iv, 120 minutes) + **Cap** 1000 mg/m^2 orally bid d1-14; every 3 weeks, stopped at 12 weeks in stable or responding patients and restarted following progression.
CRYSTAL Van Cutsem, 2007 (16)	FOLFIRI + Cetux	**Cetux** loading dose 400 mg/m^2 iv, then 250 mg/m^2 iv weekly + **FOLFIRI: Iri** 180 mg/m^2 + **5-FU** 400 mg/m^2 bolus then 2400 mg/m^2 (civ, 46 hours) + **FA**;

Author, year (ref)	Treatment Arms	Treatment details
[abstract]		every 2 weeks.
	FOLFIRI	**FOLFIRI: Iri** 180 mg/m^2 + **5-FU** 400 mg/m^2 bolus then 2400 mg/m^2 (civ, 46 hours) + **FA**, every 2 weeks.
OPUS Bokemeyer, 2007 (19) [abstract]	FOLFOX-4 + Cetux	**Cetux** loading dose 400 mg/m^2 iv, then 250 mg/m^2 iv weekly + **FOLFOX-4: Ox** 85 mg/m^2 d1 + **FA** 200 mg/m^2 d1,2 + **5-FU** 400 mg/m^2 bolus then 600 mg/m^2 d1,2 (civ, 22 hours); every 2 weeks.
	FOLFOX-4	**FOLFOX-4: Ox** 85 mg/m^2 d1 + **FA** 200 mg/m^2 d1,2 + **5-FU** 400 mg/m^2 bolus then 600 mg/m^2 d1,2 (civ, 22 hours); every 2 weeks.
Borner, 2006 (20) [abstract]	XELOX + Cetux	**Cetux** loading dose 400 mg/m^2, then 250 mg/m^2 weekly + **XELOX: Ox** 130 mg/m^2 d1 + **Cap** 1000 mg/m^2 orally bid d1-14; every 3 weeks up to 6 cycles maximum.
	XELOX	**XELOX: Ox** 130 mg/m^2 d1 + **Cap** 1000 mg/m^2 orally bid d1-14; every 3 weeks up to 6 cycles maximum.
Panitumumab		
Previously treated		
Van Cutsem, 2007 (21)	BSC + Pan	**Pan** 6 mg/kg (iv, 60 minutes) every 2 weeks until disease progression or unacceptable toxicity + **BSC**
	BSC	**BSC**
Peeters, 2008 (24) [abstract]	FOLFIRI + Pan	**Pan** 6.0 mg/kg + **FOLFIRI**; every 2 weeks
	FOLFIRI	**FOLFIRI** every 2 weeks
Previously untreated		
PRIME Siena, 2008 (25) [abstract]	FOLFOX-4 + Pan	**Pan** 6.0 mg/kg (iv, 60 minutes) + **FOLFOX-4: Ox** 85 mg/m^2 (iv, 2 hours) d1 + **LV** 200 mg/m^2 (iv, 2 hours) d1,2 + **5-FU** 400 mg/m^2 bolus then 600 mg/m^2 (civ, 22 hours) d1,2; every 2 weeks.
	FOLFOX-4	**FOLFOX-4: Ox** 85 mg/m^2 (iv, 2 hours) d1 + **LV** 200 mg/m^2 (iv, 2 hours) d1,2 + **5-FU** 400 mg/m^2 bolus then 600 mg/m^2 (civ, 22 hours) d1,2; every 2 weeks.
PACCE - Iri/Bev Hecht, 2008 (26) [abstract]	Iri/Bev + Pan	**Pan** 6 mg/kg, every 2 weeks + **Iri**-based CT[b] (e.g. **FOLFIRI: Iri** 180 mg/m^2 d1 (iv, 90 minutes) + **LV** 200 mg/m^2 d1 (iv, 60 minutes) + **5-FU** 400 mg/m^2 bolus then 2400 mg/m^2 (civ, 46 hours) for first 2 cycles then increased to 3000 mg/m^2 if no toxicity higher than grade 1 + **Bev** (dose NR); until disease progression or intolerability.
	Iri/Bev	**Iri**-based CT[b] (e.g. **FOLFIRI: Iri** 180 mg/m^2 d1 (iv, 90 minutes) + **LV** 200 mg/m^2 d1 (iv, 60 minutes) + **5-FU** 400 mg/m^2 bolus then 2400 mg/m^2 (civ, 46 hours) for first 2 cycles then increased to 3000 mg/m^2 if no toxicity higher than grade 1 + **Bev** (dose NR); until disease progression or intolerability.
PACCE - Ox/Bev Hecht, 2008 (27) [abstract]	Ox/Bev + Pan	**Pan** 6 mg/kg, every 2 weeks + **Ox**-based CT[c] (e.g. **FOLFOX**) + **Bev** (dose NR); until disease progression or intolerability.
	Ox/Bev	**Ox**-based CT[c] (e.g. **FOLFOX**) + **Bev** (dose NR); until disease progression or intolerability.

Notes: AE=adverse event(s); Bev=bevacizumab; bid=twice daily; BSC=best supportive care; Cap=capecitabine; Cetux=cetuximab; civ=continuous intravenous infusion; CT=chemotherapy; d=day(s); FA=folinic acid; Iri=irinotecan; iv=intravenous; LV=leucovorin; NR=not reported; Ox=oxaliplatin; Pan=panitumumab; QOL=quality of life; ref=reference; 5-FU=5-fluorouracil.

[a]Patients 70 years of age or older, ECOG performance status of 2, or with prior pelvic/abdominal irradiation received irinotecan 300 mg/m^2.

[b]Irinotecan-based chemotherapy regimens were offered to patients based on investigator choice.

[c]Oxaliplatin-based chemotherapy regimens were offered to patients based on investigator choice.

Appendix **3. Ongoing trials.**

A randomized, multicenter phase 3 study to compare the efficacy of panitumumab in combination with chemotherapy to the efficacy of chemotherapy alone in patients with previously treated metastatic colorectal cancer.	
Protocol ID:	NCT00339183, NCI 20050181
Last date modified:	April 10, 2008
Trial type:	Phase III, randomized, open-label, multicenter
Accrual:	1,100
Primary outcome:	Overall survival and progression-free survival
Sponsorship:	Amgen
Status:	Ongoing, not accruing

A Randomised Clinical Trial of Treatment for Fluorouracil-Resistant Advanced Colorectal Cancer Comparing Standard Single-Agent Irinotecan Versus Irinotecan Plus Panitumumab and Versus Irinotecan Plus Ciclosporin [Panitumumab, Irinotecan & Ciclosporin in COLOrectal Cancer Therapy (PICCOLO)].	
Protocol ID:	NCT00389870, CTRU-PICCOLO_MO-05-7289, EUDRACT-2005-003492-20, CTAAC-CTRU-PICCOLO-MU-05-7289, EU-20647
Last date modified:	July 2007
Trial type:	Phase III, randomized, open-label, multicenter
Accrual:	1,269
Primary outcome:	Objective response and stable disease rate and overall survival
Sponsorship:	University of Leeds
Status:	Accruing

A Randomized Phase II Clinical Trial of IMC-A12, as a Single Agent, or in Combination Wih Cetuximab, in Patients With Metastatic Colorectal Cancer With Disease Progression on Prior Anti-EGFr Therapy.	
Protocol ID:	NCT00503685, CP13-0605
Last date modified:	May 19, 2008
Trial type:	Phase II, randomized, open-label, multicenter
Accrual:	72
Primary outcome:	Objective response rate
Sponsorship:	ImClone Systems
Status:	Accruing

A Randomized Phase II Study of Modified FOLFOX6 (Infusional 5-Fluorouracil/Leucovorin, Oxaliplatin) and Bevacizumab With or Without Cetuximab in Patients With Metastatic Colorectal Cancer.	
Protocol ID:	NCT00193219, SCRI GI 64, CA225-115
Last date modified:	June 10, 2008
Trial type:	Phase II, randomized, open-label, multicenter
Accrual:	70
Primary outcome:	Objective response rate
Sponsorship:	Sarah Cannon Research Institute, SCRI Oncology Research Consortium, Bristol-Myers Squibb
Status:	Ongoing, not accruing

Randomized Phase II Trial of Cetuximab/Bevacizumab (CB) as Palliative First-Line Therapy in Patients With Advanced Colorectal Cancer Followed by FOLFOX+CB vs. FOLFOX+B.	
Protocol ID:	NCT00571740, NCCTG-N0548
Last date modified:	June 11, 2008
Trial type:	Phase II, randomized
Accrual:	100
Primary outcome:	Progression-free survival
Sponsorship:	North Central Cancer Treatment Group, NCI
Status:	Accruing

Open-Label, Phase II, Randomised, Pilot Study to Evaluate the Safety and Efficacy of Combination Therapy With Cetuximab and FOLFOX4 or FOLFOX4 Alone in Patients Colorectal Cancer and Initially Non-Resectable.	
Protocol ID:	NCT00202787, TTD-04-02
Last date modified:	July 6, 2008
Trial type:	Phase II, randomized, open-label
Accrual:	136
Primary outcome:	Objective response rate
Sponsorship:	Spanish Cooperative Group for Gastrointestinal Tumour Therapy, Merck
Status:	Ongoing, not accruing

A Multi-Center, Open-Label, Randomized, Phase 2 Clinical Trial Evaluating Safety and Efficacy of FOLFIRI With Either Panitumumab or Bevacizumab as Second-Line Treatment in Subjects With Metastatic Colorectal Cancer.	
Protocol ID:	NCT00418938, 20060141, SPIRITT
Last date modified:	June 27, 2008
Trial type:	Phase II, randomized, open-label, multicenter
Accrual:	200
Primary outcome:	Objective response rate
Sponsorship:	Amgen
Status:	Accruing

Multicenter Randomized Trial Evaluating FOLFIRI Plus Cetuximab Versus Bevacizumab in First Line Treatment of Metastatic Colorectal Cancer.	
Protocol ID:	NCT00433927, FIRE-3
Last date modified:	February 9, 2007
Trial type:	Phase II, randomized, open-label, multicenter
Accrual:	NR
Primary outcome:	Objective response rate
Sponsorship:	Ludwig-Maximilians – University of Muich, Merck, Hoffmann-La Roche
Status:	Accruing

A Phase III Trial of Irinotecan / 5-FU / Leucovorin or Oxaliplatin / 5-FU/ Leucovorin With Bevacizumab, or Cetuximab (C225), or With the Combination or Bevacizumab and Cetuximab for Patients With Untreated Metastatic Adenocarcinoma of the Colon or Rectum.	
Protocol ID:	NCT00265850, CALGB-C80405, SWOG-C80405
Last date modified:	June 19, 2008
Trial type:	Phase III, randomized, open-label, multicenter
Accrual:	2,300
Primary outcome:	Overall survival
Sponsorship:	Cancer and Leukemia Group B, Southwest Oncology Group, NCI
Status:	Suspended

A Randomized Phase III Trial of Cetuximab, Bevacizumab and Biweekly Infusional 5FU/Leucovorin (FOLF-CB) Versus Oxaliplatin, Bevacizumab, and Biweekly Infusional 5FU/Leucovorin (Bev-FOLFOX) in First Line Treatment of Metastatic Colorectal Cancer	
Protocol ID:	NCT00252564, CA225251
Last date modified:	Februaary 27, 2008
Trial type:	Phase III, randomized, open-label, multicenter
Accrual:	120
Primary outcome:	Progression-free survival
Sponsorship:	US Oncology Research, Bristol-Myers Squibb, Memorial Sloan-Kettering Cancer Center, Prologue Research International
Status:	Ongoing, not accruing

Notes: NR=not reported.