



pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Cetuximab (Erbitux) for Metastatic Colorectal Cancer

January 10, 2014

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

TABLE OF CONTENTS

DISCLAIMER AND FUNDING	ii
INQUIRIES	iii
TABLE OF CONTENTS.....	iv
1 GUIDANCE IN BRIEF	1
1.1. Background	1
1.2. Key Results and Interpretation.....	1
1.3. Conclusions	5
2 CLINICAL GUIDANCE	6
2.1 Context for the Clinical Guidance	6
2.2 Interpretation and Guidance.....	12
2.3 Conclusions	13
3 BACKGROUND CLINICAL INFORMATION	15
4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT	17
5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT.....	22
6 SYSTEMATIC REVIEW.....	24
6.1 Objectives.....	24
6.2 Methods.....	24
6.3 Results	27
6.4 Ongoing Trials	42
7 SUPPLEMENTAL QUESTIONS	43
7.1 Summary of KRAS Mutation Testing in Metastatic Colorectal Carcinoma	43
7.2 Critical Appraisal of Indirect Comparison of Cetuximab plus FOLFIRI with Bevacizumab plus FOLFIRI and Bevacizumab plus FOLFOX in the Treatment of metastatic Colorectal Carcinoma.....	46
8 ABOUT THIS DOCUMENT	51
APPENDIX A: LITERATURE SEARCH STRATEGY	52
REFERENCES	58

1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of cetuximab in combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) as first-line treatment in patients who have epidermal growth factor receptor-expressing *K-RAS* wild-type metastatic colorectal cancer (mCRC).

Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR) with an affinity higher than endogenous ligands.

Cetuximab has a Health Canada approved indication for use in patients with EGFR-expressing *KRAS* wild-type mCRC:

- in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment.
- in combination with irinotecan in patients who are refractory to other irinotecan-based chemotherapy regimens.
- as a single agent in patients who are intolerant to irinotecan-based chemotherapy.
- as a single agent for the treatment of patients who have failed both irinotecan- and oxaliplatin-based regimens and who have received a fluoropyrimidine.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two phase 3 studies, CRYSTAL (Van Cutsem 2009, 2013) and FIRE-3 (Heinemann 2013).

- CRYSTAL was a randomized, open-label, phase 3 RCT that randomised patients to cetuximab plus FOLFIRI (N=599), given once weekly or to FOLFIRI alone (N=599). Patients had a median age: 61 years, were 60.5% (61.6 and 59.5 % in two arms) male and EGFR-expressing with first occurrence of metastatic confirmed adenocarcinoma of the colon or rectum. Most patients were of ECOG performance status of 0 (53-55%) and 1 (41-43%) (4% of patients had ECOG 2). The tumors were not curatively resectable. The primary site of tumors was colon (60%) and rectum (38%). The majority of patients (84-86%) had metastases at one or two sites, and 21% had metastasis confined to the liver. The majority of patients had wild-type *KRAS* tumors (666/1063, 63%) and 37% (397/1063) had mutant *KRAS* tumors.
- FIRE-3 was an open-label, multicenter, phase 3 RCT that randomised patients to cetuximab plus FOLFIRI or bevacizumab plus FOLFIRI. Data from a subgroup analysis of 592 patients with *KRAS* wild-type (297 in cetuximab plus FOLFIRI and 295 in bevacizumab plus FOLFIRI) were reported only in a conference abstract,¹ while data from an unplanned subgroup analysis of 96 patients with *KRAS* mutant tumors (50 in cetuximab plus FOLFIRI and 61 in bevacizumab plus FOLFIRI) were reported in a published article.² Patients had a median age of 64 years, 64% to 66% were male, and ECOG performance status of 0 and 1 was found in 94% to 98% of patients.

Overall, patient populations of CRYSTAL and FIRE 3 studies were similar in terms of age, gender, ECOG performance status and colon primary site.

Efficacy

In the CRYSTAL study the primary efficacy endpoint was progression free survival (PFS). As of the May 31, 2009 data cut-off, the median PFS in patients with KRAS wild-type tumours was 9.9 vs 8.4 months in the cetuximab plus FOLFIRI arm vs. FOLFIRI arm, respectively (HR 0.70; p=0.0012) while in the ITT population, median PFS was 8.9 vs 8.0 months in the cetuximab plus FOLFIRI arm vs. FOLFIRI arm, respectively (HR 0.85; p=0.048).

Secondary efficacy endpoints included overall survival (OS) and best overall response rate (ORR). In patients with KRAS wild-type tumours, the median OS was 23.5 vs 20 months in the cetuximab plus FOLFIRI arm and FOLFIRI arm, respectively (HR 0.80; p=0.0093). In the ITT population, median OS was 19.9 vs. 18.6 months in the cetuximab plus FOLFIRI vs. FOLFIRI arm (HR 0.88; p=0.042). Cetuximab plus FOLFIRI had significant improvements in ORR in ITT population (OR 1.40; p=0.004), in total KRAS population (OR 1.41; p=0.005) and in patients with wild-type KRAS (OR 2.07; p<0.001).

In patients with KRAS wild-type disease, the rate of surgery for metastasis (7.9% [n=25] vs. 4.6% [n=16]; OR 1.82 [95% CI 0.96, 3.47], p=0.063) and the rate of R0 resection (5.1% [n=16] vs. 2.0% [n=7]; OR 2.65 [95% CI 1.08, 6.49], p=0.027) were both higher in cetuximab plus FOLFIRI group compared with FOLFIRI alone, respectively.

For HRQoL determined by EORTC QLQ-C30, there were no statistically significant differences between groups for global health status and other functioning scores including physical, role, emotional, cognitive and social.

In the FIRE-3 study, the primary efficacy endpoint was ORR in the ITT patient population. In the KRAS wild-type population, the ORR was 62% and 57% in cetuximab and bevacizumab arm, respectively while in the KRAS mutant population, ORR was 44% and 48% in cetuximab and bevacizumab arm, respectively.

Secondary efficacy outcomes included OS and PFS. The median OS times were 28.8 vs 25.0 months (HR 0.77; p=0.0164) for KRAS wild-type patients and 22.7 vs. 18.7 months (HR 0.86; 95% CI 0.55, 1.35) for the KRAS mutant patients in the cetuximab compared to bevacizumab arms, respectively. The median PFS times were 10.3 vs. 10.4 months (HR 1.04; p=0.69) in the KRAS wild-type patients and 7.5 vs. 8.9 months (HR 1.00; 95% CI 0.66, 1.53) in the KRAS mutant patients for the cetuximab and bevacizumab arms, respectively.

No HRQoL data was reported for FIRE-3.

Harms

In the CRYSTAL study, cetuximab plus FOLFIRI had higher incidence of any grade skin reaction (88% vs. 16%), any grade acne-like rash (86% vs. 13%), any grade infusion reaction (14% vs. 0%) and any grade palmar-plantar erythrodysesthesia (19% vs. 4%) in KRAS wild-type population compared with FOLFIRI alone. The incidence of grade 3-4 AE's for these adverse events was also higher in cetuximab plus FOLFIRI arm.

In the KRAS wild-type population, the incidence of serious adverse events was higher in patients receiving cetuximab plus FOLFIRI than in patients receiving FOLFIRI alone (43% vs. 32%). Cetuximab plus FOLFIRI also had higher incidence of adverse events leading to discontinuation (30% vs. 13%), higher incidence of adverse events leading to dose reduction (29% vs. 18%) or delay treatment (72% vs. 51%) compared with FOLFIRI.

In FIRE-3, patients receiving cetuximab had higher incidence of acneiform exanthema (grade 3-4: 20% vs. 0%) than those receiving bevacizumab. Neutropenia was also higher in cetuximab group (grade 3-4: 28% vs. 17%). By contrast, hypertension was more frequent in patients receiving bevacizumab (grade 3-4: 22% vs. 8%).

1.2.2 Additional Evidence

pCODR received input on cetuximab (Erbix) for metastatic colorectal cancer from one patient advocacy group, Colorectal Cancer Association of Canada (CCAC). Provincial Advisory group input was obtained from eight of the nine provinces participating in pCODR.

In addition, two supplemental questions were identified during the development of the review protocol as relevant to the pCODR review of cetuximab and are discussed as supporting information.

- Summary of KRAS Mutation Testing in Metastatic Colorectal Carcinoma
- Summary of Critical Appraisal of Indirect Comparison of Cetuximab plus FOLFIRI with Bevacizumab plus FOLFIRI and Bevacizumab plus FOLFOX in the Treatment of Metastatic Colorectal Carcinoma

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Colorectal cancer represents a significant burden of illness in Canada, accounting for the second most common cause of cancer-related death.³ The majority of patients with mCRC present with unresectable metastatic colorectal cancer.

In patients with unresectable metastatic colorectal cancer (mCRC), accepted standard practice for the first-line management of patients is chemotherapy (typically FOLFOX or FOLFIRI) in combination with bevacizumab. The use of the Epidermal Growth Factor Receptor inhibitors (EGFRi) such as cetuximab and panitumumab is based upon tumour KRAS status. The presence of a KRAS mutation, observed in 40% of CRCs, is a negative predictor of EGFRi benefit and hence a contraindication to the use of cetuximab and panitumumab. Currently, the use of cetuximab and panitumumab in Canada is primarily limited to the third-line setting of chemotherapy-refractory, wtKRAS mCRC. While the availability of newer systemic therapies has translated into meaningful improvements in survival and other patient outcomes, the overwhelming majority of patients will die of their disease. In this context, there remains both a medical and patient expressed need for improved cancer therapies.

Effectiveness

Based on the results of the CRYSTAL study, the addition of cetuximab to FOLFIRI was associated with significant improved OS, PFS and ORR. Among patients with wtKRAS liver-limited disease, R0 resections were achieved in 5.1% on cetuximab + FOLFIRI compared with 2% on FOLFIRI alone. The findings of this study are considered generalizable to the majority of patients in this setting, despite no Canadian patient enrolment in this trial and only 4% of patients having an ECOG PS of 2. This study is however not generalizable to patients with initially resectable mCRC. As the standard arm of FOLFIRI alone does not reflect the current first-line standard of care in Canada which includes chemotherapy plus bevacizumab, there remain limitations in determining the applicability of this study to patients.

Based on the results of the FIRE-3 study, median OS was significantly higher in patients receiving first-line cetuximab plus FOLFIRI compared to bevacizumab plus FOLFIRI. No significant differences were however observed for ORR or PFS between both study arms. The discordant efficacy results between CRYSTAL and FIRE-3 are not explained and while

this may be related to a differential impact of subsequent lines of therapies, uncertainty remains regarding the overall survival benefit observed in FIRE-3.

The indirect comparative analysis of cetuximab plus FOLFIRI with chemotherapy plus bevacizumab presents several methodological and analytic challenges that preclude its applicability to this clinical guidance. A head-to-head comparison of chemotherapy plus bevacizumab versus chemotherapy plus cetuximab is awaited when the results of the phase 3 Intergroup C80405 (NCIC.CRC5) become available. Accrual to this study was completed last year.

Safety

Established adverse effects related to cetuximab include acneiform rash, diarrhea and hypomagnesemia. In CRYSTAL, the increased grade 3-4 adverse events associated with cetuximab + FOLFIRI compared with FOLFIRI alone were skin reaction, acne-like rash, infusion reaction and palmar-plantar erythrodysesthesia. In FIRE-3, cetuximab was associated with a acneiform exanthema (grade 3-4) and neutropenia while bevacizumab was associated with hypertension.

Based on the current use of EGFR inhibitors in the third-line setting in Canada, it can be expected that the majority of Canadian medical oncologists are familiar with the assessment and management of EGFR-related toxicities.

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit with the use of cetuximab in combination with FOLFIRI chemotherapy as compared to FOLFIRI alone in patients with treatment-naïve, wt KRAS unresectable mCRC with an ECOG performance status of 0-2 who would otherwise be ineligible or unsuitable for first-line bevacizumab use. This conclusion is primarily based on the findings of the well-conducted phase 3 CRYSTAL trial which demonstrated a significant meaningful improvement in OS, PFS and ORR with the addition of cetuximab to first-line FOLFIRI chemotherapy.

The Clinical Guidance Panel also considered that from a clinical perspective:

- In clinical practice, the use of FOLFIRI + cetuximab in the first-line treatment of patients with wtKRAS unresectable mCRC would be limited to patients with a contraindication to the use of bevacizumab and for patients with initially unresectable metastases where the higher response and R0 resection rates, as per the CRYSTAL trial, may allow for a higher rate of resectability in a small proportion of selected patients.
- There is currently insufficient evidence to evaluate the clinical benefit of first-line cetuximab in combination with chemotherapy as compared with the current standard of first-line bevacizumab in combination with chemotherapy.
- Despite having no Canadian patient enrolment in this trial and only 4% of patients having an ECOG PS of 2, the findings of this study are considered generalizable to the majority of patient population in this setting.
- These findings are however not generalizable to patients with initially resectable MCRC.
- As no benefit is observed in KRAS mutant disease, the key efficacy and safety data for this review pertain to the wtKRAS population.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding cetuximab (Erbix) for metastatic colorectal cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding cetuximab (Erbix) conducted by the Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on cetuximab (Erbix) and a summary of submitted Provincial Advisory Group Input on cetuximab (Erbix) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR) with an affinity higher than endogenous ligands. EGFR signaling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis and cellular invasion/metastasis. Cetuximab induces the internalization of EGFR, leading to down-regulation of the receptor. It also targets cytotoxic immune effector cells towards EGFR-expressing tumor cells.

On December 20, 2012, Health Canada issued a Notice of Compliance stating that Erbix (cetuximab) was approved in combination with FOLFIRI for the first-line treatment of EGFR-expressing *KRAS* wild-type mCRC.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the efficacy and safety of cetuximab in combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) as first-line treatment in patients who have epidermal growth factor receptor-expressing *K-RAS* wild-type metastatic colorectal cancer (mCRC).

2.1.3 Highlights of Evidence in the Systematic Review

This review included two phase 3 studies: CRYSTAL and FIRE-3.

CRYSTAL⁴⁻⁷ was a randomized, open-label, multicenter, multinational (without Canada and USA) trial. Cetuximab given once weekly in combination with FOLFIRI (N=599) was compared with FOLFIRI alone (N=599). The study recruited patients (median age: 61 years; 60.5% (61.6 and 59.5 % in two arms) male) who were EGFR-expressing with first occurrence of metastatic confirmed adenocarcinoma of the colon or rectum. The tumors were not curatively resectable. Most patients were of ECOG performance status of 0 (53-55%) and 1 (41-43%), only 4% of patients had ECOG performance status of 2. The primary site of tumors was colon (60%) and rectum (38%). 84-86% of patients had metastases at one or two sites, and 21% had metastasis confined to the liver. The primary endpoint was progression

free survival (PFS) and the secondary endpoints were overall survival (OS) and best overall response rate (ORR). Safety outcomes included death, on treatment death, adverse events (AEs) leading to death, serious AEs, AEs leading to discontinuation, AEs leading to dose reduction/delay, and any AEs. The study did not allow for cross-over.

Retrospective KRAS mutation analyses were conducted twice. At cut-off date of July 27, 2006, KRAS mutation analyses were conducted on 540 samples obtained at baseline. On May 31, 2009, KRAS mutation analyses were updated. The samples were increased from 540 (45%) to 1,063 (89% of ITT population). There were 666 (63%) wild-type KRAS tumors and 397 (37%) mutant KRAS tumors.

Table 1 presents key efficacy and safety data for KRAS wild-type population as of May 31, 2009.

On May 31, 2009, there were 989 deaths (cetuximab plus FOLFIRI: 487; FOLFIRI: 502). The median OS times for ITT population were 19.9 months in the cetuximab plus FOLFIRI arm and 18.6 months in the FOLFIRI arm (HR 0.88; $p=0.042$). For patients with KRAS wild-type, the median OS times were 23.5 months in the cetuximab plus FOLFIRI arm and 20.0 months in the FOLFIRI arm (HR 0.80; $p=0.0093$). The median PFS times for ITT population were 8.9 months in the cetuximab plus FOLFIRI arm and 8.0 months in the FOLFIRI arm (HR 0.85; $p=0.048$). For patients with KRAS wild-type, the median PFS times were 9.9 months in the cetuximab plus FOLFIRI arm and 8.4 months in the FOLFIRI arm (HR 0.70; $p=0.0012$). Cetuximab plus FOLFIRI had significant improvements in ORR in ITT population (OR 1.40; $p=0.004$), in total KRAS population (OR 1.41; $p=0.005$) and in patients with wild-type KRAS (OR 2.07; $p<0.001$).

For HRQoL determined by EORTC QLQ-C30, there were no statistically significant differences between groups for global health status and other functioning scores including physical, role, emotional, cognitive and social.

As of May 31, 2009, there were 243 (77%) deaths in the cetuximab plus FOLFIRI group and 288 (82%) deaths in the FOLFIRI group of KRAS wild-type population. There were no differences between groups for on treatment death or adverse events leading to death. Compared with FOLFIRI alone, cetuximab plus FOLFIRI had higher incidence of any grade skin reaction (88% vs. 16%), any grade acne-like rash (86% vs. 13%), any grade infusion reaction (14% vs. 0%) and any grade palmar-plantar erythrodysesthesia (19% vs. 4%) in KRAS wild-type population. The incidences of grade 3-4 of those adverse events were also higher in cetuximab plus FOLFIRI. In the KRAS wild-type population, the incidence of serious adverse events was higher in patients receiving cetuximab plus FOLFIRI than in patients receiving FOLFIRI alone (43% vs. 32%). The most frequent SAEs showing notable difference between groups were diarrhea (7% vs. 3%), dehydration (4% vs. 1%), pulmonary embolism (4% vs. 2%) and hypomagnesemia (2% vs. 0%). Cetuximab plus FOLFIRI had higher incidence of adverse events leading to discontinuation (30% vs. 13%), higher incidence of adverse events leading to dose reduction (29% vs. 18%) or delay treatment (72% vs. 51%) compared with FOLFIRI.

Table 1: Key Results from CRYSTAL Study

Efficacy data for KRAS wild-type population (as of May 31, 2009)		
	Median (95% CI); months	HR (95% CI) P-value
OS	C + F (N=316): 23.5 (21.2, 26.3)	0.80 (0.67, 0.95) 0.0093
	F (N=350): 20.0 (17.4, 21.7)	
PFS	C + F (N=316): 9.9 (9.0, 11.3)	0.70 (0.56, 0.87) 0.0012
	F (N=350): 8.4 (7.4, 9.2)	
	Percent (95% CI)	OR (95% CI) P-value
ORR	C + F (N=316): 57.3 (51.6, 62.8)	2.07 (1.52, 2.83) <0.001
	F (N=350): 39.7 (34.6, 45.1)	
Safety data for KRAS wild-type population (as of May 31, 2009)		
	C + F (N=317)	F (N=350)
All deaths, n (%)	243 (77)	288 (82)
SAEs, n (%)	136 (43)	111 (32)
AEs leading to discontinuation, n (%)	94 (30)	44 (13)
Grade 3-4 AEs, n (%)		
Skin reaction	70 (22)	2 (1)
Acne-like rash	56 (18)	1 (0)
Infusion reaction	6 (2)	0
Palmar-plantar erythrodysesthesia	13 (4)	1 (0)
AEs=adverse events; C=cetuximab; CI=confidence interval; F=FOLFIRI; HR=hazard ratio; OS=overall survival; ORR=overall response rate; OR=odds ratio; PFS=progression free survival; SAEs=serious adverse events		

FIRE-3^{1,2,8} was an open-label, multicenter, phase 3 RCT conducted in Germany and Austria. Cetuximab plus FOLFIRI was compared with bevacizumab plus FOLFIRI. Data from subgroup analysis of 96 patients with *KRAS* mutant tumors (50 in cetuximab plus FOLFIRI and 61 in bevacizumab plus FOLFIRI) were first reported in a published article,² while the data from subgroup analysis of 592 patients with *KRAS* wild-type (297 in cetuximab plus FOLFIRI and 295 in bevacizumab plus FOLFIRI) were reported in conference abstracts.^{1,8} The primary end point was ORR in the ITT patient population. Secondary outcomes were OS and PFS. For the subgroup analysis of *KRAS* mutant tumors, 9 patients (18%) in the cetuximab plus FOLFIRI arm dropped out before first tumor assessment.

For *KRAS* mutant patients, the median OS times were 22.7 months for cetuximab plus FOLFIRI and 18.7 months for bevacizumab plus FOLFIRI (HR 0.86; 95% CI 0.55, 1.35). The median PFS times were 7.5 months for cetuximab plus FOLFIRI and 8.9 months for bevacizumab plus FOLFIRI (HR 1.00; 95% CI 0.66, 1.53). The ORR was 44% and 48% in cetuximab arm and bevacizumab arm, respectively. The difference in ORR was not statistically significant.

For *KRAS* wild-type patients, the median OS times were 28.8 months for cetuximab plus FOLFIRI and 25.0 months for bevacizumab plus FOLFIRI (HR 0.77; p=0.0164). The median PFS times were 10.3 months for cetuximab plus FOLFIRI and 10.4 months for bevacizumab plus FOLFIRI (HR 1.04; p=0.69). The ORR was 62% and 57% in cetuximab arm and bevacizumab arm, respectively; p=0.183 (not statistically significant).

Further analysis of *RAS* wild-type (N=334), which consisted of *KRAS* exon 2/3/4 and *NRAS* exon 2/3/4 wild-type, had median OS of 33.1 months in cetuximab plus FOLFIRI and 25.9 months in bevacizumab plus FOLFIRI group; HR was 0.69 (95% CI 0.52, 0.92), p=0.01. The

median PFS was 10.5 months in cetuximab plus FOLFIRI and 10.4 months in bevacizumab plus FOLFIRI group; HR was 0.94 (95% CI 0.75, 1.19), $p=0.63$. The median ORR was 76% in cetuximab plus FOLFIRI and 65.2% in bevacizumab plus FOLFIRI group, $p=0.044$.

Patients receiving cetuximab had higher incidence of acneiform exanthema (grade 3-4: 20% vs. 0%) than those receiving bevacizumab. Neutropenia was also higher in cetuximab group (grade 3-4: 28% vs. 17%). By contrast, hypertension was more frequent in patients receiving bevacizumab (grade 3-4: 22% vs. 8%).

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

Summary of KRAS Mutation Testing in Metastatic Colorectal Carcinoma

The predictive diagnostic value of *KRAS* mutation status testing and its role in identifying mCRC patients who may benefit from treatment with cetuximab is widely accepted among clinicians.⁹⁻²⁰ The various methods of *KRAS* mutation testing have differing strength in terms of sensitivity, specificity and mutant DNA detection limits. Several of these diagnostic techniques are available for used in Canada without any streamlined official guideline except that an employed method should be validated and be performed in an experienced laboratory. *KRAS* testing is prone to biases from several factors including: selection of patients to test; methods of test samples acquisition; DNA extraction procedures; protocols for the determination of *KRAS* status, and reporting/interpretation of test results.^{14,15} Improper patient selection may result in improper patient management decisions in colorectal cancer treatment with cetuximab. While treatment may be withheld from patients who might have benefitted, it could wrongfully be administered to patients who are not expected to benefit, but who could potentially suffer any adverse side effects associated with treatment. Current publicly available information provides only a general range of costs for *KRAS* testing with no price delineation of the individual methods used. See section 7.1 for more information.

Summary of Critical Appraisal of Indirect Comparison of Cetuximab plus FOLFIRI with Bevacizumab plus FOLFIRI and Bevacizumab plus FOLFOX in the Treatment of Metastatic Colorectal Carcinoma

The comparative efficacies of cetuximab plus FOLFIRI, bevacizumab plus FOLFIRI, and bevacizumab plus FOLFOX were indirectly assessed in patients with mCRC using relative ratio of effect estimate method. Sensitivity analysis to derive OS and PFS measures for bevacizumab plus FOLFIRI was performed using a non-comparative, non-RCT study 4. The indirect analysis and derivations from it are not appropriate because the import of survival studies is not properly derived with a model using median time to event or relative risk analysis and instead uses relative ratio. Secondly, comparing a non-comparative, non-RCT trial with RCT studies is not an appropriate analytical approach. In addition, the manufacturer's use of outcome data from NO16996 as if it were bevacizumab plus FOLFOX is misleading since the NO16966 study reports a combined outcome of bevacizumab plus FOLFOX or XELOX but not outcome for bevacizumab plus FOLFOX alone. These shortfalls, together with others discussed above, indicate that the indirect comparison and sensitivity analysis have numerous limitations rendering conclusions from them non-interpretable. See section 7.2 for more information.

2.1.6 Other Considerations

Patient Advocacy Group Input

From a patient perspective, accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival is extremely important, and that patients should be afforded the opportunity to have a choice in the selection of the best therapeutic option in the treatment of their mCRC. According to the patient survey and informal patient conversations, the most frequently reported disease-related symptoms were fatigue, abdominal pain, bloody stools, painful diarrhea/constipation; all of which impact a patient's QoL significantly. Respondents reported that it would be very important to access additional treatments even though the benefits might only be short term and despite treatment adverse effects. According to CCAC, 60% of respondents would not refuse taking a cancer therapy based on a severe toxicity profile of the therapy.

PAG Input

Input on cetuximab (Erbix) for mCRC was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, cetuximab already being used for third-line setting and KRAS testing already being in place are enablers. The key barriers to implementation are the weekly dosing schedule, the one hour infusion time, and KRAS testing in a larger patient population because these factors have an impact on resources and accessibility. PAG noted that bevacizumab, in combination with FOLFOX or FOLFIRI, is the standard of care for first-line mCRC which is administered every two weeks. As such, PAG indicated the current treatment algorithms, specifically sequential therapy with bevacizumab and cetuximab, will need to be evaluated.

Other

- Serious warnings and precautions from Product Monograph: *"Severe infusion reactions occurred with the administration of Erbitux in approximately 3% of patients in clinical trials, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with first infusion of Erbitux. Severe infusion reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction and/or cardiac arrest. Fatal anaphylactic reactions may occur despite the use of prophylactic premedications. Severe infusion reactions require immediate interruption of the Erbitux infusion and permanent discontinuation from further treatment."*
- On May 19, 2011, the EMA/CHMP approved Erbitux for the treatment of patients with EGFR-expressing, KRAS wild-type mCRC in combination with irinotecan-based chemotherapy or FOLFOX4. On November 17, 2011, the EMA/CHMP approved Erbitux for the treatment of patients with EGFR-expressing, KRAS wild-type mCRC in first line in combination with FOLFOX.
- In 2004, US FDA approved Erbitux (cetuximab) in combination with FOLFIRI for first-line treatment of patients with EGFR-expressing, KRAS wild-type mCRC. FDA had warning box about serious infusion reactions and cardiopulmonary arrest upon Erbitux administration. Close monitoring of serum electrolytes including magnesium, potassium and calcium during and after Erbitux administration is required.

2.2 Interpretation and Guidance

Burden of Illness and Need

Colorectal cancer represents a significant burden of illness in Canada, accounting for the second most common cause of cancer-related death.³ In patients with unresectable metastatic colorectal cancer (MCRC), accepted standard practice for the first-line management of patients is chemotherapy (typically FOLFOX or FOLFIRI) in combination with bevacizumab. While the availability of newer systemic therapies has translated into meaningful improvements in survival and other patient outcomes, the overwhelming majority of patients will die of their disease. In this context, there remains both a medical and patient expressed need for improved cancer therapies.

Cetuximab is a therapeutic cancer agent currently used in the third-line setting of chemotherapy-refractory disease. It is a chimeric monoclonal antibody to the Epidermal Growth Factor Receptor (EGFR). As the presence of a KRAS mutation is a negative predictor of cetuximab benefit, its use is restricted to the estimated 60% of patients with wtKRAS MCRC. The objective of this pCODR review is to evaluate the efficacy and safety of cetuximab in combination with FOLFIRI as first-line treatment in patients with treatment-naïve, wt KRAS unresectable MCRC.

Effectiveness

The systematic review included two phase 3 studies: CRYSTAL and FIRE-3.

CRYSTAL is a randomized, multinational study of cetuximab with FOLFIRI versus FOLFIRI alone in 1,198 patients with unresectable MCRC and a preserved ECOG performance status of 0 to 2.^{4,6} The findings of this study are considered generalizable to the majority of our patient population in this setting, despite no Canadian patient enrolment in this trial and only 4% of patients having an ECOG PS of 2. This study is not generalizable to patients with initially resectable MCRC. In the CRYSTAL ITT population, 37% of patients had mutant KRAS tumours. As no benefit is observed in mutant KRAS disease, the key efficacy and safety data for this review pertains to the wtKRAS analysis (n=667). The addition of cetuximab to FOLFIRI was associated with significant improved OS 23.5 vs. 20 months, (HR 0.80, 95%CI: 0.67, 0.95), PFS 9.9 vs. 8.4 months, (HR 0.70: 56, 0.87) and ORR 57.3% vs. 39.7%, (OR 2.07: 1.52, 2.83). Among patients with wtKRAS liver-limited disease, R0 resections were achieved in 5.1% on cetuximab + FOLFIRI compared with 2% on FOLFIRI alone. The main limitation in determining the applicability of this study to our patient population is that the standard arm of FOLFIRI alone does not reflect the current first-line standard of care in Canada which includes chemotherapy plus bevacizumab.

FIRE-3 is a phase 3 European trial conducted in a similar patient population, randomizing participants to first line FOLFIRI + cetuximab or to FOLFIRI plus bevacizumab.¹ The key efficacy and safety data come from the wtKRAS analysis presented as an oral abstract at ASCO 2013. The median OS was significantly higher with in patients receiving first-line cetuximab compared to bevacizumab 28.8 vs 25 mos, (HR 0.77; p=0.0164). No significant differences however were observed in ORR (62% vs 57%) or PFS (10.3 vs 10.4 mos) between both study arms. The discordant efficacy results are not explained and while this may be related to a differential impact of subsequent lines of therapies, uncertainty remains regarding the overall survival benefit observed in FIRE-3. The study has not yet been subject to peer-review publication.

It is further noted that the supplementary indirect comparative analysis of cetuximab plus FOLFIRI with chemotherapy plus bevacizumab presents several methodological and analytic challenges that preclude its applicability to this clinical guidance. A head-to-head comparison of chemotherapy plus bevacizumab versus chemotherapy plus cetuximab is awaited when the results

of the phase 3 Intergroup C80405 (Section 6.4) become available. Accrual to this study was completed last year.

It is expected that the use of FOLFIRI + cetuximab in the first-line treatment of patients with wtKRAS unresectable MCRC in clinical practice would be limited to patients with a contraindication to the use of bevacizumab and for patients with initially unresectable metastases where the higher response and R0 resection rates as per the CRYSTAL trial may allow for a higher rate of resectability in a small proportion of selected patients.

Safety

The addition of cetuximab to FOLFIRI is associated with toxicity. The established adverse effects related to cetuximab include acneiform rash, diarrhea and hypomagnesemia. In CRYSTAL, the increased grade 3-4 adverse events associated with cetuximab + FOLFIRI compared with FOLFIRI alone were skin reaction (22% vs 1%), acne-like rash (18% vs 0%), infusion reaction (2% vs 0%) and palmar-plantar erythrodysesthesia (4% vs 0%). In FIRE-3, cetuximab was associated with a acneiform exanthema (grade 3-4; 20% vs 0%) and neutropenia (28% vs 17%) while bevacizumab was associated with hypertension (22% vs 8%).

Input from the Patient Advocacy Group survey indicates 60% of patients would not refuse a cancer therapy based on severe toxicity concerns. Respondents treated with cetuximab reported that they tolerated the side effects well. In addition, these side effects are well known. Based on the current use of EGFR inhibitors in the third-line setting in Canada, it can be expected that the majority of Canadian medical oncologists are familiar with the assessment and management of EGFR-related toxicities.

In terms of resource impact, the use of cetuximab in the first-line setting would require upfront KRAS testing which would represent a change in the current testing paradigm wherein mutation testing is typically performed beyond first-line therapy in most provinces. As noted by PAG, this could be associated with concerns regarding increased resource demands. Current KRAS testing turnaround times are 10 to 15 working days. Upfront testing in all patients with newly diagnosed MCRC may lead to further pressures and delayed turnaround times. Weekly cetuximab administration would be expected to also impact on cancer care resources, however this can largely be mitigated with q2weekly cetuximab administration which has already been adopted in practice in several jurisdictions.²¹

2.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit with the use of cetuximab in combination with FOLFIRI chemotherapy as compared to FOLFIRI alone in patients with treatment-naïve, wt KRAS unresectable mCRC with an ECOG performance status of 0-2 who would otherwise be ineligible or unsuitable for first-line bevacizumab use. This conclusion is primarily based on the findings of the well-conducted phase 3 CRYSTAL trial which demonstrated a significant meaningful improvement in OS, PFS and ORR with the addition of cetuximab to first-line FOLFIRI chemotherapy.

The Clinical Guidance Panel also considered that from a clinical perspective:

- In clinical practice, the use of FOLFIRI + cetuximab in the first-line treatment of patients with wtKRAS unresectable mCRC would be limited to patients with a contraindication to the use of bevacizumab and for patients with initially unresectable metastases where the higher response and R0 resection rates, as per the CRYSTAL trial, may allow for a higher rate of resectability in a small proportion of selected patients.
- There is currently insufficient evidence to evaluate the clinical benefit of first-line cetuximab in combination with chemotherapy as compared with the current standard of first-line bevacizumab in combination with chemotherapy.
- Despite having no Canadian patient enrolment in this trial and only 4% of patients having an ECOG PS of 2, the findings of this study are considered generalizable to the majority of patient population in this setting.
- These findings are however not generalizable to patients with initially resectable mCRC.
- As no benefit is observed in KRAS mutant disease, the key efficacy and safety data for this review pertain to the wtKRAS population.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Gastrointestinal Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

An estimated 23,300 Canadians will be diagnosed with colorectal cancer and 9,200 will die as a consequence of colorectal cancer in 2013.³ Metastatic Colorectal Cancer (MCRC) represents a significant burden of disease with an estimated 25% of all new cases presenting with disseminated disease and an additional 30% of patients with early-stage disease subsequently relapsing with metastatic disease. The majority of patients with MCRC present with unresectable metastatic colorectal cancer. While systemic chemotherapy can significantly prolong survival in this setting, currently available therapies are not curative. Approximately 60% of patients are estimated to have wildtype KRAS status. Based on clinical opinion, median survival for unresectable MCRC irrespective of KRAS status is estimated to be 24 - 28 months. It is likely 3-4 months shorter for mutant KRAS patients because they do not benefit from anti- EGFR therapy.

3.2 Accepted Clinical Practice

Management of metastatic colorectal cancer involves consideration of patient factors (including performance status, age, comorbidities), disease-related factors (resectable metastases versus potentially resectable metastases versus unresectable disease, and KRAS status) and sequencing strategies of available cytotoxic chemotherapies (5-fluorouracil/capecitabine, irinotecan and oxaliplatin) and targeted agents (bevacizumab, cetuximab, panitumumab). The availability of new therapies over the past decade has translated into significant improvements in survival with median survival estimates of less than 12 months in the era of 5-fU alone as compared to contemporary median survival estimates of 24 to 26 months.²²

Patients with initially unresectable liver and/or lung-limited metastatic disease who are converted to resectability with chemotherapy treatment would be referred for surgical consideration.

Accepted clinical practice for the chemotherapeutic management of patients with unresectable MCRC in Canada in 2013

First-Line	Second-Line	Third-Line - wt KRAS	Third-Line - mut KRAS Fourth-Line - wt KRAS
FOLFIRI/CAPIRI	FOLFOX/CAPOX	Irinotecan + Cetuximab	Regorafenib
or	or	or	or
FOLFOX/CAPOX	FOLFIRI/CAPIRI	Cetuximab	Clinical Trial
or	or	or	or
Capecitabine	Irinotecan	Panitumumab	Best Supportive Care
PLUS	PLUS/MINUS		
Bevacizumab	Bevacizumab		

FOLFIRI - 5FU/irinotecan; CAPIRI - capecitabine/irinotecan

FOLFOX - 5FU/oxaliplatin; CAPOX - capecitabine/oxaliplatin

Patients are typically switched to a subsequent line of therapy due to treatment failure defined as either disease progression or treatment intolerance. Suitability for the next line of therapy is determined by patient status, anticipated tolerability of the subsequent therapy and patient preference. Based on clinical experience, approximately two-thirds of patients on first-line therapy will go on to second-line therapy and approximately half of those patients will go on to third-line therapy.

The use of the Epidermal Growth Factor Receptor inhibitors (EGFRi) such as cetuximab and panitumumab is based upon tumour KRAS status. The presence of a KRAS mutation, observed in 40% of CRCs, is a negative predictor of EGFRi benefit and hence a contraindication to the use of cetuximab and panitumumab. Currently, the use of cetuximab and panitumumab in Canada is primarily limited to the third-line setting of chemotherapy-refractory, wtKRAS MCRC. Common toxicities with this class of agents include papulopustular rash and skin reactions, diarrhea and hypomagnesemia. Access to KRAS testing is widely available in Canada however the timing and turnaround times are variable across provinces. In British Columbia, KRAS testing is only permitted after failure of first-line therapy and can typically take 10-15 working days to obtain a result. In Ontario, KRAS testing is permitted after failure of second-line therapy. Tumour mutation testing beyond KRAS (including NRAS and BRAF) is not readily available.

Cetuximab is a chimeric monoclonal antibody to EGFR. Consideration for the use of cetuximab in combination with FOLFIRI chemotherapy as first-line treatment in patients with wtKRAS unresectable MCRC is under PCODR review based upon the findings of two phase III studies.

The US Intergroup trial C80405 (NCIC.CRC5) randomized patients with wtKRAS MCRC to cetuximab or bevacizumab with first-line FOLFIRI or FOLFOX. The results of this large trial (n=1,172 for the wtKRAS population) are expected within the next year and will further inform the issue of optimal first-line biologic therapy in patients with unresectable MCRC.

3.3 Evidence-Based Considerations for a Funding Population

The population considered for treatment with FOLFIRI and cetuximab would be patients with an ECOG PS of 0-2 with treatment-naïve, wtKRAS, and initially unresectable MCRC.

3.4 Other Patient Populations in Whom the Drug May Be Used

The scope of this pCODR evaluation is limited to the indication for use of FOLFIRI + cetuximab as first-line treatment in unresectable MCRC. This evaluation should not be extrapolated to patient populations with initially resectable or potentially resectable liver-limited MCRC.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

A patient advocacy group, Colorectal Cancer Association of Canada (“CCAC”), provided input on cetuximab (Erbix) in combination with FOLFIRI for the first line treatment of metastatic colorectal cancer (mCRC), which is summarized below.

CCAC conducted online surveys for metastatic colorectal cancer patients and caregivers in Canada who were contacted through the CCAC Medical Advisory Board of medical oncologists who treat mCRC, as well as through CCAC’s database of registered colorectal cancer patients and their respective caregivers residing in Canada. The survey received a total of 37 responses. CCAC noted that due to access limitations, there was a lack of robust patient/caregiver input as it related specifically to the Cetuximab + FOLFIRI experience in first line therapy.

Recognizing the importance of providing a robust patient perspective, the input included past conversations with patients and caregivers, as well as publications focusing on the treatment in question. An additional Quality of Life (QoL) survey conducted by the CCAC in March 2011 was also included.

From a patient perspective, accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival is extremely important, and that patients should be afforded the opportunity to have a choice in the selection of the best therapeutic option in the treatment of their mCRC. According to the patient survey and informal patient conversations, the most frequently reported disease-related symptoms were fatigue, abdominal pain, bloody stools, painful diarrhea/constipation; all of which impact a patient’s QoL significantly. Respondents reported that it would be very important to access additional treatments even though the benefits might only be short term and despite treatment adverse effects. According to CCAC, 60% of respondents would not refuse taking a cancer therapy based on a severe toxicity profile of the therapy.

Please see below for a summary of specific input received from the patient advocacy group.

4.1 Condition and Current Therapy Information

4.1.1 Experiences patients have with mCRC

Depending upon the metastatic site, CCAC reports that symptoms of metastatic colorectal cancer (“mCRC”) include but are not limited to severe abdominal pain, shortness of breath, coughing, fatigue, bloating and loss of appetite.

According to the patient survey and informal patient conversations, the most frequently reported disease-related symptoms were: fatigue, abdominal pain, bloody stools, painful diarrhea/constipation; all of which reported to impact a patient’s QoL significantly.

Approximately 95% of the respondents identified the following aspects of colorectal cancer as being the most important and difficult to control:

- Fatigue
- Pain
- Weakness
- Diarrhea

The limitations resulting from those symptoms included but are not limited to the following:

- Work cessation
- Cessation of physical activity/lack of mobility
- Inability to meet family and social obligations
- Stress induction/psychological impact

Some of the comments from the respondents included:

"I am not able to work. I am constantly fatigued and it gets in the way of doing anything. I also cannot partake in my two passions, dancing and swimming. I also have difficulty helping my mother who is my caregiver and does everything for me."

"I became tired more easily, could not eat as much and at some point could hardly walk."

From a patient perspective, first and second line therapy (FOLFIRI/FOLFOX) in combination with a biologic therapy (bevacizumab) has proven to successfully shrink tumours and stop the progression of the disease for a period of time for a subset of the population. According to the survey, 33.3% of the respondents reported an improvement in the symptoms resulting from their colorectal cancer after accessing these systemic therapies. However, there were some patients who were unable to tolerate, or have a contraindication to bevacizumab as well as oxaliplatin, and for these patients, the most appropriate comparators may be cetuximab and FOLFIRI.

CCAC suggests that patients with KRAS wild type tumors comprise approximately 60% of all colorectal cancer cases, and would support the need for EGFR agents, such as, cetuximab administered in combination with FOLFIRI in first line therapy.

4.1.2 Patients' Experiences with Current Therapy for mCRC

CCAC notes that standard treatment for mCRC, which is used by approximately 50% of the colorectal cancer population, involves chemotherapy based on fluoropyrimidines, oxaliplatin and irinotecan - used in combination i.e. FOLFIRI and FOLFOX, and sequentially; and monoclonal antibodies (MAB) targeting vascular endothelial growth factor (VEGF; bevacizumab). In patients with KRAS wild type tumours, monoclonal antibodies targeting epidermal growth factor receptor (EGFR; cetuximab) and panitumumab) may also be used.

For patients, current treatment-related toxicities often necessitate cessation of therapy. According to the survey results, neurotoxicity is the most frequent dose-limiting toxicity of oxaliplatin. A cumulative sensory peripheral neuropathy may also develop with prolonged treatment with oxaliplatin. Respondents report tingling or a feeling of pins and needles in hands and feet with severe numbness and find it difficult to do small tasks with their hands like buttoning a shirt. In some cases, neuropathy can cause pain and difficulty with daily life, including walking or balancing. Diarrhea, nausea and vomiting were the most frequently reported side effects of irinotecan which can cause dehydration and once again necessitate cessation of therapy.

33.3% of surveyed respondents report an improvement in the symptoms resulting from their colorectal cancer after accessing therapies such as FOLFIRI/FOLFOX in combination

with bevacizumab. However, there were some respondents who were unable to tolerate, or have a contraindication to bevacizumab as well as oxaliplatin.

CCAC reports that differences exist across Canada as they relate to access to treatments both to the therapy itself and in some cases, the line of treatment in which it is available. This was supported by the QoL Survey results conducted by CCAC in March 2011, which showed regional disparities in the confidence levels of Canadians regarding access to therapies. According to that survey, over 50% of the respondents believed that geographical location impacted their quality of treatment when diagnosed with cancer.

Patients have also reported forfeiting the addition of bevacizumab in the first line treatment of their mCRC so that it may be introduced in second line. The addition of cetuximab in first line therapy in combination with FOLFIRI may help address this funding issue in respect of bevacizumab.

In addition, 52.6% of respondents surveyed reported financial implications associated with the management of their disease. They cited travel-related and parking costs as the most highly incurred expenditures when accessing their drug therapies. When asked if patients would be willing to pay out of pocket to access new drug therapies for the treatment of their mCRC, 68% replied "Yes". Some of the comments were:

- *"Yes, but with great difficulty"*
- *"Anything to fight the cancer I would do and you cannot put a price tag on extending your life or someone else's"*
- *"Given no other option, I would pay"*

It was noted that 43.8% of respondents surveyed also identified the following needs currently not being met by current therapy:

- The funding of bevacizumab in second line therapy
- More treatment options to help manage their mCRC
- Unsuccessful treatment of their mCRC

Over 80% of respondents surveyed reported that it would be very important to access additional treatments whose benefits might only be short term despite treatment adverse effects. A survey conducted by the CCAC in March 2011 indicated that patients were interested in treatment even in the end of life situations when the benefit may be just a few weeks provided there was good QoL. The results of the CCAC QoL Survey determined that part of maintaining QoL is linked to providing greater access to therapies that treat mCRC. In view of the above, CCAC submits that access to new treatments for mCRC would be paramount to manage the progression of this disease.

4.1.3 Impact of mCRC and Current Therapy on Caregivers

According to the survey, patients and caregivers have both reported a significant impact on the caregiver in caring for patients with mCRC. Caregivers provide supportive care to the patient in managing adverse side effects, providing emotional support and assuming additional unpaid work duties in the home. Additionally, caregivers of mCRC patients may be burdened with financial challenges relating to disability and cost of accessing treatments in those provinces that have reimbursement restrictions. Travel and parking costs are also often assumed by the caregiver when accessing drug therapies. Respondents reported the following difficulties in caring for mCRC patients:

"Being able to truly understand what the patient is going through. Being able to attend all medical appointments and have all the information the patient has is hard for caregivers. It is vitally important for caregivers and patients to decide who will fill important roles like regularly communicating with doctors, who will change appointments, etc."

"Loss of pay due to absence from work, burnout, other expenses, i.e. parking, nutritional supplements, over the counter meds, etc."

"Anxiety, having to clean up after patient (vomit, stool, spills); having to manage everything the patient did before getting sick, stress from worry about the patient..."

Caregivers also reported that accessing drug therapies significantly impacted their daily routine as follows:

- *"Plenty of lost work time"*
- *"Preparing appropriate meals, ensure meds are taken on time"*
- *"Taking a leave of absence from work"*
- *"...had to constantly cook food that he might like only to find out that he couldn't eat it."*
- *"Driving the patient to all the appointments, thereby disrupting regular routine and then must be with the patient during treatment as well..."*

Additionally, 81.3% of caregivers surveyed reported the following challenges in dealing with adverse effects from the current therapies:

- *"Frustrating at not being able to help"*
- *"Extra expenses, nutritional supplements, over the counter meds, burnout"*
- *"Must help the patient manage the side effects when the oncologists cannot provide assistance"*
- *"Frustration with not being adequately equipped to help patient deal with complications"*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Cetuximab

Respondents have expressed their desire to continue accessing therapies to help control their mCRC with respect to quality of life (QoL), progression free survival (PFS) and overall survival (OS) as reported by anecdotal and survey input.

CCAC submits that patients are well aware of the fact that all drug therapies have associated risks. 60% of patients surveyed would not refuse taking a cancer therapy based on a severe toxicity profile of the therapy. Respondents reported that together with their treating oncologist, 85% of patients would very much appreciate choosing the best therapeutic option for the management of their disease. Respondents also noted that any extension in life is considered an extension in long term health.

One respondent surveyed had received cetuximab + FOLFIRI therapy and reported that it successfully treated their mCRC. The only reported side effect was dermal toxicity which

was considered by the respondent to be an acceptable side effect. The respondent also found cetuximab easier to administer.

CCAC submits that the majority of the metastatic colorectal cancer population is fraught with colorectal liver metastases. Fewer than 20% of these patients are considered candidates for surgical resection. Reducing tumour burden in this patient population may increase resection rates, a benefit which may be obtained by administering cetuximab + FOLFIRI in the first line treatment of kras wild type mCRC patients.

CCAC believes that the addition of cetuximab to FOLFIRI as first line treatment of KRAS wild type unresectable colorectal liver metastases may result in a higher rate of resection and longer survival when compared to chemotherapy alone. The CCAC referenced the study by Xu et al.,²³ and noted that although it was a small study population and relatively short follow up time, CCAC believed that the key finding was that adding cetuximab to FOLFIRI may effectively reduce tumour burden and increase the possibility of surgically removing confined liver metastases, thereby improving survival and QoL. CCAC also cited the CRYSTAL study,²⁴ and in their opinion, they believed that it showed that by adding cetuximab to first line FOLFIRI in patients with KRAS wild type mCRC significantly improved treatment outcome compared with FOLFIRI alone, and supported the consistency of the benefit obtained across all efficacy end points. CCAC also referenced the German FIRE-3 study,¹ which they acknowledged was small in size and did not meet its primary endpoint; however, they believed that the study showed that frontline cetuximab plus FOLFIRI improved OS when compared to bevacizumab plus FOLFIRI in patients with KRAS wild type mCRC. Accordingly, CCAC suggests that this is encouraging data for the subset of the mCRC patient population who may have a contraindication to bevacizumab therapy or lack of provincial reimbursement.

4.3 Additional Information

The Colorectal Cancer Association of Canada ("CCAC") also surveyed 11 medical oncologists from the CCAC Medical Advisory Board and other affiliated experts from within Canada who treat mCRC. The survey included input on prescribing decisions for first line therapy, key factors contributing to treatment choice and challenges in preventing best outcomes for their patient populations. This survey and the summary of results were provided to pCODR along with this patient advocacy group's input.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for cetuximab (Erbix) for first-line treatment of mCRC in combination with chemotherapy. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on cetuximab (Erbix) for mCRC was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, cetuximab already being used for third-line setting and KRAS testing already being in place are enablers. The key barriers to implementation are the weekly dosing schedule, the one hour infusion time, and KRAS testing in a larger patient population because these factors have an impact on resources and accessibility. PAG noted that bevacizumab, in combination with FOLFOX or FOLFIRI, is the standard of care for first-line mCRC which is administered every two weeks. As such, PAG indicated the current treatment algorithms, specifically sequential therapy with bevacizumab and cetuximab, will need to be evaluated.

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that bevacizumab in combination with FOLFOX/FOLFIRI is a standard of care in most jurisdictions. PAG indicated that results from the direct comparison trial of cetuximab and bevacizumab would be more relevant and noted this trial recently reported some results at ASCO 2013.

5.2 Factors Related to Patient Population

PAG identified barriers related to patient population include the potential for use as second line after bevacizumab, the timing of treatment (initiation and stopping) in relation to surgical resection and the potential for physicians seeking single agent first-line use.

If cetuximab is used in the first-line setting, sequential therapy with bevacizumab as second-line therapy would need to be evaluated.

5.3 Factors Related to Accessibility

Patients would need to travel once a week to and from outpatient clinics for intravenous administration of cetuximab. This is a significant barrier for patients who cannot travel easily, have far to travel, or live in communities where satellite clinics/outreach centres may not have the resources to implement weekly infusion.

Cetuximab being in use in the third-line setting is an enabler since healthcare staff are familiar with the protocols established for preparation, administration and monitoring.

5.4 Factors Related to Dosing

PAG identified that the weekly administration of cetuximab would be a barrier. Additional resources and clinic chair time are required to prepare and administer cetuximab weekly, where concomitant chemotherapy and alternate treatments are administered every 2 or 3 weeks.

PAG noted that cetuximab is given every two weeks in the third-line setting and questioned whether this dosing schedule could be adopted in the first-line setting. The ability to synchronize the administration of cetuximab with the administration of FOLFOX or FOLFIRI would be an enabler from both the patient and healthcare system perspectives.

5.5 Factors Related to Implementation Costs

PAG also identified the need for resources to monitor and manage toxicities, particularly skin reactions and infusion related reactions, in a larger patient population as a potential barrier to implementation. PAG also noted that cetuximab infusion is over one hour and would require more clinic chair time in comparison to the 10 minute bevacizumab infusion time. PAG identified larger cold storage requirements for treatment centers as a possible new resource also.

PAG noted that KRAS testing has already been established in most of the jurisdictions. However, KRAS testing would be done earlier for patients, prior to initiating therapy. PAG has concerns on whether there is the capacity for the increased number of testing as more resources and time are required to coordinate testing in a larger patient population. There are also concerns with potential delays to initiation of any first-line treatment at centres where KRAS testing is conducted in another city or province while waiting for test results.

5.6 Other Factors

None identified.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of cetuximab (Erbix) in combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) as first-line treatment in patients who have epidermal growth factor receptor-expressing *K-RAS* wild-type metastatic colorectal cancer (mCRC) (see Table 2 in Section 6.2.1 for outcomes of interest and comparators).

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Genetic testing of KRAS mutation status to select mCRC patients for whom cetuximab (Erbix) would be an effective treatment.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 2: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCT	<p>Previously untreated adult patients (≥ 18 years) with metastatic colorectal cancer (mCRC) and <i>K-RAS</i> wild-type tumors</p> <p>Subgroups:</p> <ul style="list-style-type: none"> ECOG performance status: 0 or 1 vs. 2 Other RAS wild-type (N-RAS, H-RAS) 	<p>Erbix (Cetuximab) in combination with FOLFIRI (irinotecan, fluorouracil, leucovorin)</p> <p><u>Dosage:</u> Erbix: 400 mg/m², 120-min infusion; followed by 250 mg/m², 60-min infusion QW</p>	<p>FOLFIRI (irinotecan, fluorouracil, leucovorin) alone</p> <p>or</p> <p>Bevacizumab plus FOLFIRI</p>	<ul style="list-style-type: none"> OS PFS HRQoL CBR ORR TTP Proportion of patients undergoing resection SAE AE WDAE
<p>AE=adverse events; CBR=clinical benefit rate; HRQoL=health-related quality of life; ORR=overall response rate; OS=overall survival; PFS= progression-free survival; QW=once weekly; RCT=randomized controlled trial; SAE=serious adverse events; TTP=time to progression; WDAE=withdrawal due to adverse events</p>				

* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 7) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were cetuximab and Erbitux.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of August 26, 2013.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

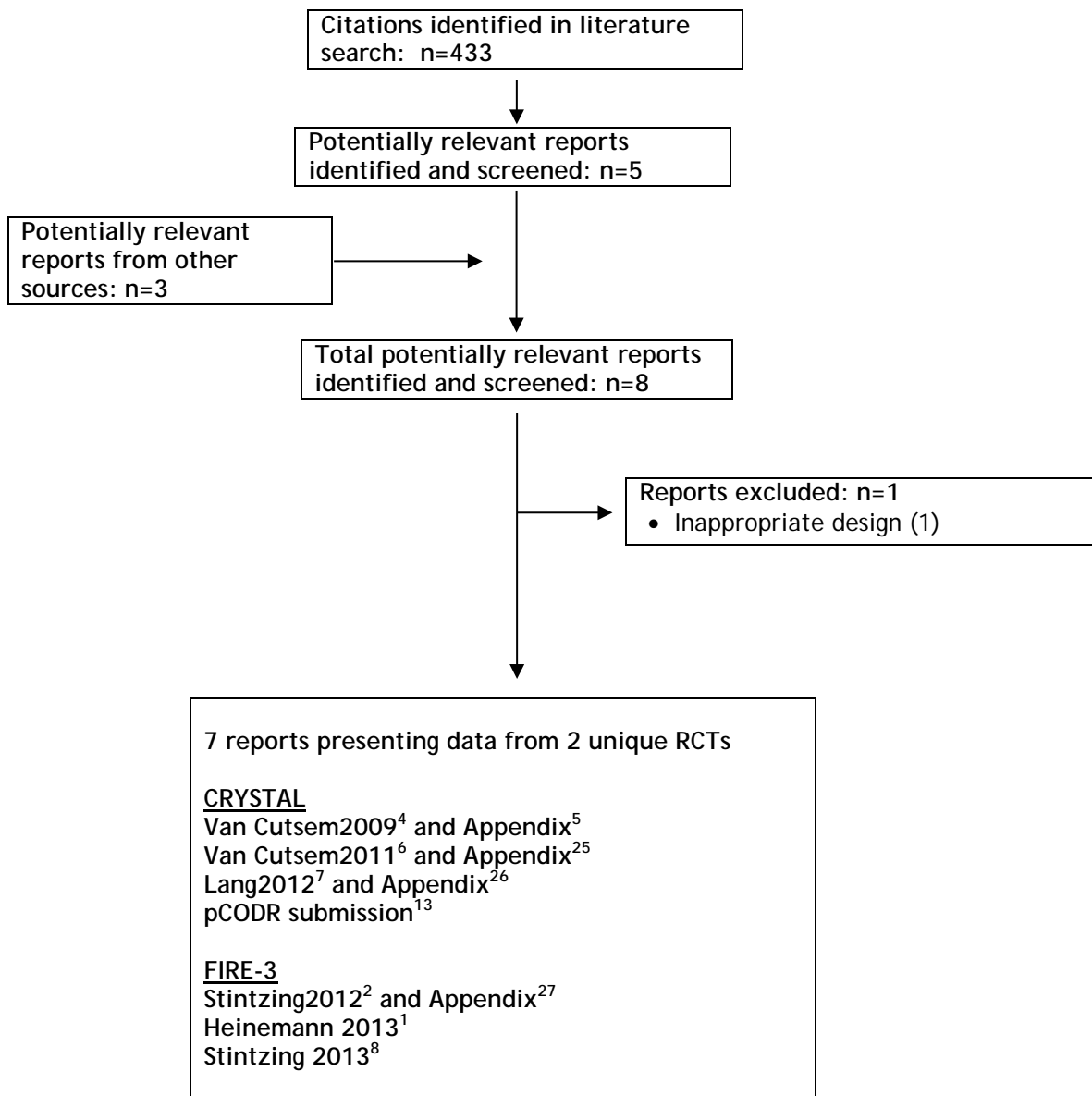
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the eight potentially relevant reports identified, seven reports presenting data for two unique studies were included in the pCODR systematic review^{1,2,4,6-8} and one study was excluded. This study was excluded because it was an inappropriate design (phase I/II that led to the pivotal phase 3 CRYSTAL study)⁴ which has been included in this review. Regulatory reports from FDA or EMA were not available for the indication at the time of this review.

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 3: Summary of Trial characteristics of the included Studies^{1,2,4-8,27}

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
<p>CRYSTAL⁴⁻⁷</p> <p>Open-label, multicenter, multinational, phase 3 RCT</p> <p>189 centers, 28 countries (no Canada and USA)</p> <p>Randomization period: Jul 2004 - Nov 2005</p> <p>Randomization at 1:1 ratio was stratified on the basis of:</p> <ul style="list-style-type: none"> • ECOG performance status (0 or 1 vs. 2) • Region <p>Date cut-off for PFS: 27 Jul 2006</p> <p>Date cut-off for OS: Dec 31, 2007 (828 deaths)</p> <p>Date of updated analysis: 31 May 2009 (989 deaths)</p> <p>N=2,020 enrolled N=1,217 randomized N=1,198 analyzed (ITT)</p> <p>Retrospective subgroups:</p> <ul style="list-style-type: none"> • <i>KRAS</i> wild-type • <i>KRAS</i> mutant <p>Sponsored: Merck</p>	<p>Patients (≥ 18 years) with confirmed adenocarcinoma of the colon or rectum, first occurrence of metastatic disease (not curatively resectable), evidence of EGFR-expression, ECOG performance status ≤ 2.</p> <p>Exclusion criteria: Previous exposure to EGFR-targeting therapy or iritonecan-based chemotherapy, previous chemotherapy for metastatic colon rectal cancer, adjuvant treatment that was terminated ≤ 6 months before the trial, and the use of radiotherapy, surgery or any investigational drug in the 30-day period before the trial.</p>	<p>Cetuximab plus FOLFIRI (irinotecan, fluorouracil, leucovorin)</p> <p>FOLFIRI alone</p> <p>Dosage: Cetuximab: 400 mg/m², 120-min infusion; followed by 250 mg/m², 60-min infusion QW Irinotecan: 180 mg/m², 30-min to 90-min infusion Rac-leucovorin: 400 mg/m² or L-leucovorin : 200 mg/m², 120-min infusion Flurouracil : bolus, 400 mg/m²; 2400 mg/m² for 46 h</p>	<p>Primary</p> <ul style="list-style-type: none"> • PFS <p>Secondary</p> <ul style="list-style-type: none"> • OS • ORR (CR or PR) • QoL (EORTC QLQ-C30) • Safety (AEs, SAEs)
<p>FIRE-3^{1,2,8,27}</p> <p>Open-label, multicenter phase 3 RCT</p> <p>177 centers, Germany and Austria</p> <p>Randomization period: Dec 2006 to Oct 2008²</p> <p>Recruitment completed: October 2012¹</p> <p>Randomization at 1:1</p>	<p>Patients (18-75 years) with confirmed stage IV colorectal adenocarcinoma, <i>KRAS</i> mutation on codon 12 or 13, ECOG performance status ≤ 2, life expectancy ≥ 3 months.</p> <p>Exclusion criteria: Previous treatment with topoisomerase-1</p>	<p>Cetuximab plus FOLFIRI (irinotecan, fluorouracil, leucovorin)</p> <p>Bevacizumab plus FOLFIRI</p> <p>Dosage: Cetuximab: 400 mg/m², 120-min infusion; 250</p>	<p>Primary</p> <ul style="list-style-type: none"> • ORR (CR or PR) <p>Secondary</p> <ul style="list-style-type: none"> • PFS • OS • Safety (AEs)

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
ratio was stratified on the basis of: <ul style="list-style-type: none"> • ECOG performance status (0 or 1 vs. 2) • White blood cell count • Alkaline phosphatase level • Number of metastatic sites N=336 randomized N=96 analyzed Retrospective subgroups: <ul style="list-style-type: none"> • KRAS codon 12-mutated • KRAS codon 13-mutated • KRAS wild-type Sponsored: Merck	inhibitors, anti-VEGF agents or anti-EGFR agents, prior cytotoxic treatment of colorectal cancer with adjuvant chemotherapy <6 months before randomization, and surgery or radiation therapy within 6 weeks before randomization.	mg/m ² , 60-min infusion weekly Bevacizumab: 5 mg/kg, 90-min infusion; 5 mg/kg, 60-min infusion 2 weeks later; 5 mg/kg, 30-min infusion every 2 weeks. Irinotecan: 180 mg/m ² , 60-90-min infusion Folinic acid: 400 mg/m ² , 120-min infusion Flurouracil : bolus, 400 mg/m ² ; 2400 mg/m ² , 46 h infusion	
AEs=adverse events;CR= complete response; ECOG=Eastern Cooperative Oncology Group; EGFR=epithelial growth factor receptor; EORTC QLQ-C30= the European Organization for Research and Treatment of Cancer quality of life questionnaire-core 30;OR=overall survival; ORR=overall response rate; PFR=progression free survival; PR= partial response; RCT= randomized controlled trial			

Definition:

- PFS: time from randomization to disease progression or death from any cause within 60 days after the last tumor assessment or after randomization.
- OS: time from randomization to the date of death.
- ORR: the proportion of patients with a confirmed complete response or partial response, defined as a response persisting for at least 28 days.

a) Trials

Two phase 3 studies were included in this review (see Table 3).

CRYSTAL⁴ was a randomized, open-label, multicenter (189 centers), multinational (28 countries, without Canada and USA) trial. The study was conducted by Merck to evaluate the efficacy and safety of cetuximab plus FOLFIRI compared with FOLFIRI alone as first-line treatment of metastatic colorectal cancer (mCRC) with EGF-receptor positive and unresectable metastasis. The study was designed to test the superiority of combination therapy (cetuximab plus FOLFIRI) over FOLFIRI alone.

Patients were randomized in a 1:1 ratio to receive treatment with cetuximab plus FOLFIRI or FOLFIRI alone. The dosage and mode of administration were indicated in the Table 3. Randomization was stratified, using permuted-block procedure, by ECOG performance status (0 or 1 vs. 2) and by region (sites in the Western Europe vs. Eastern Europe vs. outside Europe). The study did not allow for cross-over.

A total of 633 progression events were required to have 80% power to detect difference in progression free survival (PFS) between the two treatment arms. A cut-off date of July 27, 2006 was for analyses of PFS and overall response rate (ORR). Overall survival (OS) analysis

was conducted when at least 705 deaths were reached. December 31, 2007 was the cut-off date for collection of OS. Subgroup analysis according to *KRAS* mutation status (codon 12 or 13) was performed retrospectively on 540 patients (45% of ITT population), whose samples were available.

On May 31, 2009, an updated analysis of OS was carried out with an additional 523 tumors for *KRAS* mutation to increase from 540 to 1,063 samples (89% of ITT population). The DNA materials were recovered from slides used for immunohistochemical analysis of EGFR expression.

FIRE-3^{1,2} was an open-label, multicenter (177 centers) phase 3 RCT conducted in German and Austria. The study was supported by Merck to evaluate the efficacy and safety of cetuximab plus FOLFIRI compared with bevacizumab plus FOLFIRI in first-line treatment of mCRC. The study was designed to test superiority of combination therapy (cetuximab plus FOLFIRI) compared with bevacizumab plus FOLFIRI in patients with wild-type *KRAS* tumors. The primary end point was ORR in the ITT patient population. Secondary outcomes were OS, PFS and safety outcomes.

From December 2006 to October 2008, patients were randomly assigned in a 1:1 ratio to receive cetuximab plus FOLFIRI or bevacizumab plus FOLFIRI. Randomization was stratified by ECOG performance status (0-1 vs. 2), white blood cell counts (<8,000/ μ l vs. \geq 8,000/ μ l), alkaline phosphatase level (<300 vs. \geq 300 U/ml) and number of metastatic sites (1 vs. >1). In October 2008, recruitment of patients with *KRAS* mutated tumors were terminated, and only patients with *KRAS* wild-type tumors continued to enroll.² Recruitment was completed in October 2012.^{1,8}

FIRE-3 was reported in a published article² and in two conference abstracts.^{1,8} The published articles reported only the findings derived from unplanned subgroup analysis based on *KRAS*-mutated tumors.² Therefore there was insufficient power to detect a significant difference between the two treatment arms in the population of patients with *KRAS*-mutated tumors. Two recent conference abstracts reported the findings involving patients with *KRAS* wild-type tumors from the completed study.^{1,8}

b) Populations

The CRYSTAL study⁴ enrolled 2,020 patients, of which 1,198 EGFR-expressing patients were randomized and treated (n=599 in each treatment group). Full analysis set population consisted of all randomized patients (intention-to-treat, ITT, N=1,198). Four additional patients (two in each arm) were treated but not randomized. Safety analysis set population consisted of all patients who received at least one dose of study treatment (N=1,202).

In the primary analysis population, the two treatment arms were balanced for baseline characteristics and demographics. Median age was 61 years (range 19-84) and 60.5% (61.6 and 59.5 % in two arms) of patients were male. Most patients were of ECOG performance status of 0 (53% to 55%) and 1 (41% to 43%), with only 4% of patients having ECOG performance status of 2. The primary site of tumors was colon (60%) and rectum (38%). 84% to 86% of patients had metastases at one or two sites, and 20% to 22% had metastasis confined to the liver.

At the cut-off date of July 27, 2006, tumors samples obtained at baseline from 540 patients were available for the analysis of *KRAS* mutation status. There were 348 (64%) wild-type *KRAS* tumors and 192 (36%) mutant *KRAS* tumors. On May 31, 2009, an updated report included an additional 523 samples, to increase to a total of 1,063 *KRAS* population. At this time, there were 666 (63%) wild-type *KRAS* tumors and 397 (37%) mutant *KRAS* tumors. The two treatment arms were also balanced for baseline characteristics and

demographics in the *KRAS* population, as well as in the *KRAS* wild-type and *KRAS* mutant populations.

At the time of this review, the evidence from the FIRE-3 study was available from a published article by Stintzing et al,² which reported the subgroup analysis of 96 patients with *KRAS*-mutant tumors (50 in cetuximab plus FOLFIRI and 46 in bevacizumab plus FOLFIRI), and from conference abstracts by Heinemann et al,¹ and by Stintzing et al,⁸ which reported the subgroup analysis of 592 patients with *KRAS* wild type (297 in cetuximab plus FOLFIRI and 295 in bevacizumab plus FOLFIRI). The two treatment arms were balanced for demographic characteristics in *KRAS* mutant and *KRAS* wild-type populations. Median age was 64 years, 64% to 66% were male, and ECOG performance status of 0 and 1 was found in 94% to 98% of patients. Colon primary site was 56% to 67% in the *KRAS* mutant population.

Overall, patient populations of CRYSTAL and FIRE 3 studies were similar in terms of age, gender, ECOG performance status and colon primary site.

c) Interventions

In the CRYSTAL and FIRE-3 studies, patients in the FOLFIRI group received irinotecan (180 mg/m², 30-min to 90-min infusion), followed by racemic leucovorin or L-leucovorin (400 mg/m² or 200 mg/m², respectively, 120-min infusion) followed by 5-fluorouracil (400 mg/m² bolus and 2400 mg/m² for 46 h continuous infusion) on day 1 of each 14-day period. Treatment cycle was repeated every 2 weeks.

In both studies, patients in the cetuximab plus FOLFIRI received cetuximab at an initial dose of 400 mg/m² as a 120-min infusion followed by weekly infusions of 250 mg/m² over 60 min. In FIRE3 patients in the bevacizumab plus FOLFIRI received bevacizumab 5 mg/kg over 90 min followed by 5 mg/kg over 60 min 2 weeks later followed by every 2-week infusions of 5 mg/kg over 30 min.

In the CRYSTAL study,⁴ the median durations of treatment exposure are shown in Table 4. The median duration of follow-up was 29.9 months (95% CI 29.1, 30.5) with cetuximab plus FOLFIRI and 29.4 months (95% CI 28.8, 30.4) with FOLFIRI alone. In the cetuximab plus FOLFIRI arm, post-study chemotherapy with or without EGFR antibody was given to 63.9% and 6.2% of patients, respectively. In the FOLFIRI arm, post-study chemotherapy with or without EGFR antibody was given to 68.8% and 25.4% of patients, respectively.

Table 4: Median Duration of Treatment Exposure (CRYSTAL)

Treatment	Median duration (interquartile range), weeks	
	Cetuximab + FOLFIRI (n=599)	FOLFIRI (n=599)
Cetuximab	25.0 (12.9 to 40.4)	--
Irinotecan	26.0 (14.0 to 40.3)	25.7 (15.1 to 35.9)
Fluorouracil	26.0 (13.8 to 40.4)	25.7 (14.9 to 36.0)

Source: Van Cutsem et al. 2009⁴

In FIRE-3, the median duration of treatment for the *KRAS* wild-type population was 4.7 months and 5.3 months for the cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI group, respectively.¹ Other details of treatment exposure for the wild-type population were not available in the abstract form.

d) Patient Disposition

CRYSTAL

In the CRYSTAL study, of the 2,020 patients screened for participation,⁴ 803 were excluded and 1,217 underwent randomization, of which 1,198 were subsequently treated (599 in each of the two groups), which comprises the ITT population. The safety analysis population consisted of 1,221 patients, of which 4 additional patients (2 in each arm) were treated but not randomized. As of November 30, 2007, 9 patients were still on treatment (7 in the cetuximab plus FOLFIRI and 2 in FOLFIRI group). As shown in Table 5, almost all patients of the primary analysis population discontinued the study treatment at the indicated date. The main reason for discontinuation of treatment was disease progression (70% in both arms). Discontinuation due to adverse events was slightly higher in the cetuximab plus FOLFIRI (8.8%) compared to the FOLFIRI alone (5.2%). There were no notable differences in discontinuation of treatment due to symptomatic deterioration, death, lost of follow-up, non-compliance, consent withdrawal and other. Follow-up of patients discontinued from treatment was not reported.

Table 5: Patient Disposition in the CRYSTAL Study⁴ (as of November 30, 2007)

	Cetuximab + FOLFIRI	FOLFIRI
Received randomized therapy, n	599	599
Discontinued treatment, n (%)	592 (98.8)	597 (99.7)
• Disease progression, n (%)	412 (69.6)	420 (70.4)
• Symptomatic deterioration, n (%)	13 (2.2)	14 (2.3)
• Adverse events, n (%)	52 (8.8)	31 (5.2)
• Death, n (%)	26 (4.4)	24 (4.0)
• Lost to follow-up, n (%)	2 (0.3)	5 (0.8)
• Non-compliance, n (%)	4 (0.7)	10 (1.7)
• Consent withdrawal, n (%)	16 (2.7)	24 (4.0)
• Other, n (%)	67 (11.2)	69 (11.6)

Source: Van Cutsem et al. 2009, Figure 2 of Supplementary Appendix⁵

FIRE-3

In the FIRE-3 study,² 336 patients were randomly assigned to cetuximab plus FOLFIRI (n=169) and bevacizumab plus FOLFIRI (n=167) from December 2006 to October 2008. Retrospective *KRAS* mutational analysis was possible on 292 (87%) patients, of which 100 (34%) patients had a *KRAS* mutated tumors (53 patients in cetuximab plus FOLFIRI arm and 47 patients in the bevacizumab plus FOLFIRI arm). Due to the study amendment in October 2008 to stop recruiting patients with *KRAS* mutant tumors, 3 patients in the cetuximab plus FOLFIRI arm were not treated, giving 96 patients receiving at least one cycle of treatment (ITT population).

For patients with *KRAS* mutant, the rate of early dropout was higher in the cetuximab plus FOLFIRI arm (18% vs. 0%) due to retrospective detection of *KRAS* mutation that led to discontinuation of study medication. About 20% of patients in each arm discontinued treatment due to progression of disease. Treatment discontinuation due to toxicity was similar in both arms, but the rate of patient wish to discontinue was twice as high in the bevacizumab plus FOLFIRI arm (24% vs. 12%). Follow-up of patients discontinued from treatment was not reported.

Patient disposition in the FIRE-3 study for patients with *KRAS* wild-type tumors was not available from the conference abstracts.

e) *Limitations/Sources of Bias*

Potential limitations of the CRYSTAL study:

- CRYSTAL was an open-label study, in which both patients and investigators were not blinded. The study was designed by the study sponsor (Merck) and primary academic investigator. It is not known if the study sponsor and the assessors of the endpoint were blinded. The study may therefore have potential biases.
- Progression free survival (PFS) was the primary endpoint in this study. Overall survival (OS) and overall response rate (ORR) were secondary endpoints. The positive findings of these endpoints in the *KRAS* wild-type population were derived from a retrospective subgroup analysis to *KRAS* mutation status that was conducted twice. Statistically, the study was not originally designed to test the superiority of cetuximab plus FOLFIRI over FOLFIRI alone in the *KRAS* wild-type population.
- Long-term risk-benefit of the drug, subsequent therapies after progression, and early discontinuation of treatment may affect the generalizability of OS results. As of the first cut-off date (July 27, 2006), almost all patients ended the treatment and about 70% of patients discontinued the treatment due to disease progression. Adverse event was a second main reason for end of treatment.
- Most patients included in this study were of ECOG performance status of 0 [53-55%] (patient is fully active) and 1 [41-43]; only 4% of patients having ECOG performance status of 2 (the patient is ambulatory and capable of all self-care but unable to work). The high proportion of patients with good performance status in this study raises concern about the generalizability of the findings. The effectiveness and safety of the study drug in combination with first-line chemotherapy in patients with ECOG performance status ≥ 2 remain unknown.
- The HRQoL, as measured by EORTC QLQ-C30, should be interpreted with caution, due to high drop-out rates in both groups and no post-progression/long-term QoL data.

Potential limitations of the FIRE-3 study:

- Although it was reported that the study was designed to test the superiority cetuximab over bevacizumab in the *KRAS* wild-type population, *KRAS* mutational analysis was performed retrospectively while the trial was still ongoing. In October 2008, an amendment was made to restrict recruitment of patients with *KRAS* mutant. The study was then continued to analyze *KRAS* wild-type population only.
- Full published report for the findings of *KRAS* wild-type population was not available. The results would have been accessible by the submitter because the study was funded by Merck
- The study was open-label, which may have potential biases in favor toward the intervention group.
- There was a lack of information regarding subsequent therapy, which may have confounded OS results.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

In the CRYSTAL study, the primary endpoint was progression free survival (PFS) and the secondary endpoints were overall survival (OS) and best overall response rate (ORR). The

analysis of PFS was conducted on the intention-to-treat (ITT) population, i.e. all patients who received at least one dose of study drug. The assessments of efficacy were performed at baseline and every 8 weeks until disease progression. Follow-up evaluations for survival were performed every 3 months. Adverse events and concomitant medication use were recorded continuously. Quality of life (QoL) was assessed using the European Organization for Research and Treatment of Cancer QoL questionnaire-core 30 (EORTC QLQ-C30).

Tumor assessments were performed using computed tomography or magnetic resonance imaging every 6-10 weeks until the occurrence of disease progression. Follow-up evaluation was performed every 3 months. Treatment was continued until progression, unacceptable toxicity, or withdrawal of consent.

PSF and ORR were first analyzed at the cut-off date of July 27, 2006, and OS was analyzed at December 31, 2007. The findings were published in the *New England Journal of Medicine* by Van Cutsem et al. 2009,⁴ in which a retrospective subgroup analysis for *KRAS* mutation status was performed on 540 patient samples (45%). An updated analysis was then followed to include additional 523 samples to increase *KRAS* population from 540 to 1,063 (89%). The findings were published two years later in the *Journal of Clinical Oncology* by Van Cutsem et al. 2011.⁶ **Table 6** presents the key efficacy outcomes and **Table 7** presents the key safety outcomes from the CRYSTAL study. **Figure 1** shows the Kaplan-Meier Estimates of PFS and OS in the primary analysis population and wild-type *KRAS* population.

In the FIRE-3 study, ORR was the primary endpoint in the ITT population. PFS and OS were secondary endpoints. While the study was ongoing, an amendment was made in October 2008 to end the inclusion of *KRAS* mutant patients and only *KRAS* wild-type patients were recruited at this point in time. The findings of the subgroup analysis of patients with *KRAS* mutant that had been previously recruited was reported in the published article by Stintzing et al. 2012.² The findings of the sub-group analysis of patients with *KRAS* wild-type was recently found in two conference abstracts by Heinemann et al. 2013,¹ and by Stintzing et al. 2013.⁸

Table 6: Summary of Key Efficacy Outcomes from CRYSTAL Study (cetuximab plus FOLFIRI, N=599; FOLFIRI, N=599)

December 31, 2007 ^a			
Overall Survival	Median (95% CI); months	HR (95% CI)	P-value
• ITT population	C + F (N=599): 19.9 (18.5, 21.3)	0.93 (0.81, 1.07)	0.31
	F (N=599): 18.6 (16.6, 19.8)		
• Wild-type KRAS	C + F (N=172): 24.9 (nr)	0.84 (0.64, 1.11)	nr
	F (N=176): 21.0 (nr)		
Progression-free Survival	Median (95% CI); months	HR (95% CI)	P-value
• ITT population	C + F (N=599): 8.9 (8.0, 9.5)	0.85 (0.72, 0.99)	0.048
	F (N=599): 8.0 (7.6, 9.0)		
• Wild-type KRAS	C + F (N=172): 9.9 (nr)	0.68 (0.50, 0.94)	nr
	F (N=176): 8.7 (nr)		
Overall response rate	Percent (95% CI)	OR (95% CI)	P-value
• ITT population	C + F (N=599): 46.9 (42.9, 51.0)	1.40 (1.12, 1.77)	0.004
	F (N=599): 38.7 (34.8, 42.8)		
• Wild-type KRAS	C + F (N=172): 59.3 (nr)	1.91 (1.24, 2.93)	nr
	F (N=176): 43.2 (nr)		
Surgery (ITT)	Percent (95% CI)	OR (95% CI)	P-value
For metastasis	C + F (N=599): 7.0 (nr)	nr	
	F (N=599): 3.7 (nr)		
R0 resection	C + F (N=599): 4.8 (nr)	3.02 (1.45, 6.27)	0.002
	F (N=599): 1.7 (nr)		
May 31, 2009 (updated) ^b			
Overall Survival	Median (95% CI); months	HR (95% CI)	P-value
• ITT population	C + F (N=599): 19.9 (18.5, 21.3)	0.88 (0.77, 0.99)	0.042
	F (N=599): 18.6 (16.7, 19.8)		
• Wild-type KRAS	C + F (N=316): 23.5 (21.2, 26.3)	0.80 (0.67, 0.95)	0.0093
	F (N=350): 20.0 (17.4, 21.7)		
Progression-free Survival	Median (95% CI); months	HR (95% CI)	P-value
• ITT population	C + F (N=599): 8.9 (8.0, 9.5)	0.85 (0.72, 0.99)	0.048
	F (N=599): 8.0 (7.6, 9.0)		
• Wild-type KRAS	C + F (N=316): 9.9 (9.0, 11.3)	0.70 (0.56, 0.87)	0.0012
	F (N=350): 8.4 (7.4, 9.2)		
Overall response rate	Percent (95% CI)	OR (95% CI)	P-value
• ITT population	C + F (N=599): 46.9 (42.9, 51.0)	1.40 (1.12, 1.77)	0.004
	F (N=599): 38.7 (34.8, 42.8)		
• Wild-type KRAS	C + F (N=316): 57.3 (51.6, 62.8)	2.07 (1.52, 2.83)	<0.001
	F (N=350): 39.7 (34.6, 45.1)		
Surgery (KRAS wild-type)	Percent (95% CI)	OR (95% CI)	P-value
For metastasis	C + F (N=316): 7.9 (nr)	1.82 (0.96, 3.47)	0.063
	F (N=350): 4.6 (nr)		
R0 resection	C + F (N=316): 5.1 (nr)	2.65 (1.08, 6.49)	0.027
	F (N=350): 2.0 (nr)		

C=cetuximab; CI=confidence interval; F=FOLFIRI; HR=hazard ratio; ITT=intention-to-treat; nr=not reported; OR=odds ratio

^aSource:Van Cutsem et al. 2009⁴

^bSource :Van Cutsem et al. 2011⁶

Table 7: Summary of Key Safety Outcomes from CRYSTAL Study*

Category	KRAS wild-type population		Safety population	
	Cetuximab plus FOLFIRI (N=317) n (%)	FOLFIRI (N=350) n (%)	Cetuximab plus FOLFIRI (N=600) n (%)	FOLFIRI (N=602) n (%)
All deaths	243 (77)	288 (82)	488 (81)	505 (84)
On treatment death	15 (5)	16 (5)	35 (6)	28 (5)
AEs leading to death	15 (5)	14 (4)	33 (6)	25 (4)
SAEs	136 (43)	111 (32)	263 (44)	205 (34)
Treatment related	83 (26)	61 (17)	156 (26)	117 (19)
AEs leading to discontinuation	94 (30)	44 (13)	180 (30)	74 (13)
Any AEs	316 (100)	347 (99)	599 (100)	597 (99)
Treatment related	316 (100)	328 (94)	589 (98)	571 (95)
Any grade skin reaction	278 (88)	55 (16)	510 (85)	107 (18)
Grade 3-4 skin reaction	70 (22)	2 (1)	124 (21)	2 (0)
Any grade acne-like rash	272 (86)	47 (13)	499 (83)	94 (16)
Grade 3-4 acne-like rash	56 (18)	1 (0)	106 (18)	1 (0)
Any grade infusion reaction	43 (14)	1 (0)	80 (13)	2 (0)
Grade 3-4 infusion reaction	6 (2)	0	15 (3)	0
Any grade PED	60 (19)	14 (4)	100 (17)	27 (4)
Grade 3-4 PED	13 (4)	1 (0)	--	--
AEs leading to dose reduction	92 (29)	62 (18)	178 (30)	115 (19)
AEs leading to delay treatment	227 (72)	180 (51)	417 (70)	308 (51)

AEs=adverse events; PED=palmar-plantar erythrodysesthesia; SAEs=serious adverse events

*Cut-off date May 31, 2009

These safety data were from the Summary of Clinical Safety submitted by the manufacturer and were not publically available.

Efficacy Outcomes

a) Overall Survival

CRYSTAL study: Overall survival (OS) was the secondary endpoint. It was defined as time from randomization to the date of death. Kaplan-Meier methods were used to estimate the distribution function of OS. A stratified log-rank test was performed to compare differences between treatment groups. Analysis of OS was conducted when at least 705 deaths had been reported. There was no statistically significant difference between groups in the total *KRAS* population or *KRAS* mutant population.

At the cut-off date of December 31, 2007, there were 828 deaths (412 in cetuximab plus FOLFIRI group and 416 in FOLFIRI group). The median OS times were 19.9 months for cetuximab plus FOLFIRI group and 18.6 months for FOLFIRI alone. The adjusted hazard ratio (HR) for death with cetuximab plus FOLFIRI was 0.93 (95% CI 0.81, 1.07). At that time, *KRAS* mutation status was available in 540 samples, of which 348 were *KRAS* wild-type. In this *KRAS* wild-type population, the median OS times were 24.9 months for cetuximab plus FOLFIRI group and 21.0 months for FOLFIRI alone. HR was 0.84 (95% CI 0.64, 1.11).

At the cut-off date of May 31, 2009, there were 989 deaths (487 in cetuximab plus FOLFIRI group and 502 in FOLFIRI group). An updated analysis was conducted with an additional 523 tumor samples to increase the *KRAS* population from 540 (45% of ITT) to 1063 (89% of ITT). The median OS times were unchanged, but HR for death with cetuximab plus FOLFIRI

was 0.88 (95% CI 0.77, 0.99), which was statistically significant ($p=0.042$). In this *KRAS* wild-type population, the median OS times were 23.5 months for cetuximab plus FOLFIRI group and 20.0 months for FOLFIRI alone; difference was 3.5 months. HR was 0.80 (95% CI 0.67, 0.95), which was statistically significant ($p=0.0093$).

Subgroup analyses in the CRYSTAL *KRAS* wild-type population revealed that OS was numerically favored by the cetuximab plus FOLFIRI treatment in all subgroups, except ECOG performance status 2 (N=27). The HR for ECOG 2 was 1.31 compared with 0.78 for ECOG 0-1 (N=639).

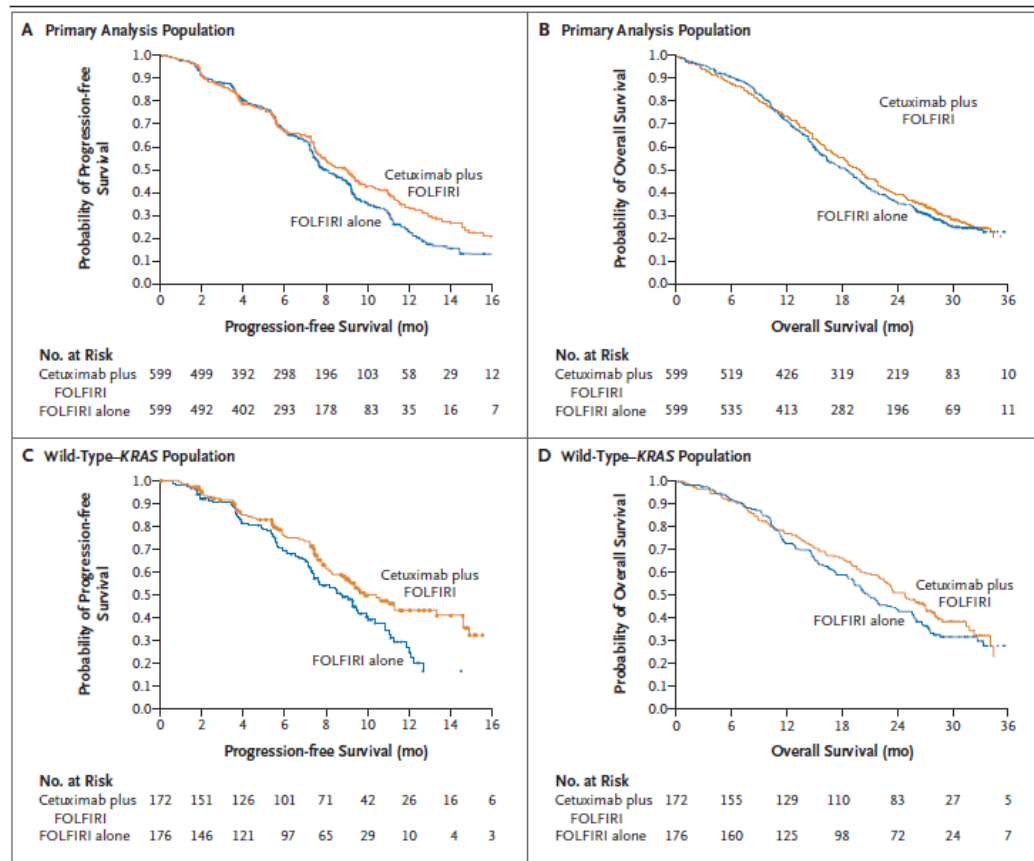


Figure 1: Kaplan-Meier Estimates of PFS and OS in the Primary Analysis Population and Wild-type *KRAS* Population in the CRYSTAL Study (cut-off date December 31, 2007 from Van Cutsem et al. 2009⁴)

FIRE-3 study: At the time of analysis for *KRAS* mutant patients (N=96), the median OS was 22.7 months (95% CI 18.3, 27.0) in cetuximab plus FOLFIRI and 18.7 months (95% CI 13.0, 24.4) in bevacizumab plus FOLFIRI group; HR 0.86 (95% CI 0.55, 1.35), which was not statistically significant. There was also no statistical significant difference between groups in either *KRAS* 12 or *KRAS* 13 mutant subtype.

For *KRAS* wild-type patients (N=592), the median OS was 28.8 months in cetuximab plus FOLFIRI and 25.0 months in bevacizumab plus FOLFIRI group; difference was 3.8 months. HR was 0.77 (95% CI 0.62, 0.95), $p=0.0164$. Further analysis of *RAS* wild-type (N=334), which consisted of *KRAS* exon 2/3/4 and *NRAS* exon 2/3/4 wild-type, had median OS of

33.1 months in cetuximab plus FOLFIRI and 25.9 months in bevacizumab plus FOLFIRI group; difference was 7.2 months. HR was 0.69 (95% CI 0.52, 0.92), $p=0.01$.

b) Progression Free Survival

CRYSTAL study: Progression free survival (PFS) was the primary endpoint. It was defined as time from randomization to disease progression or death from any cause within 60 days after the last tumor assessment or after randomization. At the cut-off date of December 31, 2007, there were 620 progression events (298 in cetuximab plus FOLFIRI group and 322 in FOLFIRI group). The median PFS times were 8.9 months for cetuximab plus FOLFIRI group and 8.0 months for FOLFIRI alone. HR for cetuximab plus FOLFIRI was 0.85 (95% CI 0.72, 0.99), which was statistically significant ($p=0.048$). In the *KRAS* wild-type population, the median PFS times were 9.9 months for cetuximab plus FOLFIRI group and 8.7 months for FOLFIRI alone. HR was 0.68 (95% CI 0.50, 0.94), which was statistically significant (p value not reported). There was no statistically significant difference between groups in the total *KRAS* population or *KRAS* mutant population.

At the cut-off date of May 31, 2009, with the increase of *KRAS* population from the retrospective analysis of *KRAS* mutation status, the median PFS times in the *KRAS* wild-type population were 9.9 months for cetuximab plus FOLFIRI group and 8.4 months for FOLFIRI alone; difference was 1.5 months. HR was 0.70 (95% CI 0.56, 0.87), which was statistically significant ($p=0.0012$).

Subgroup analyses in the CRYSTAL *KRAS* wild-type population revealed that PFS was numerically favored by the cetuximab plus FOLFIRI treatment in all subgroups, except ECOG performance status 2 (N=27). The HR for ECOG 2 was 1.03 compared with 0.67 for ECOG 0-1 (N=639).

FIRE-3 study: For *KRAS* mutant patients (N=96), the median PFS was 7.5 months (95% CI 5.7, 10.4) in cetuximab plus FOLFIRI and 8.9 months (95% CI 7.3, 11.4) in bevacizumab plus FOLFIRI group; HR 1.00 (95% CI 0.66, 1.53). There was also no difference between groups in either *KRAS* 12 subtype or *KRAS* 13 mutant subtype.

For *KRAS* wild-type patients (N=592), the median PFS was 10.3 months in cetuximab plus FOLFIRI and 10.4 months in bevacizumab plus FOLFIRI group; HR was 1.04, $p=0.69$ (not statistically significant). Further analysis of *RAS* wild-type (N=334), which consisted of *KRAS* exon 2/3/4 and *NRAS* exon 2/3/4 wild-type, had median PFS of 10.5 months in cetuximab plus FOLFIRI and 10.4 months in bevacizumab plus FOLFIRI group; HR was 0.94 (95% CI 0.75, 1.19), $p=0.63$ (not statistically significant).

c) Overall Response Rate

CRYSTAL study: Overall response rate (ORR) was the secondary endpoint. It was defined as the proportion of patients with a confirmed complete response or partial response, defined as a response persisting for at least 28 days. Cochrane-Mantel-Haenszel test was used to compare the rates of ORR between groups.

At the cut-off date of December 31, 2007, there were 5 complete (3 in cetuximab plus FOLFIRI group and 2 in FOLFIRI group) and 508 partial (278 in cetuximab plus FOLFIRI group and 230 in FOLFIRI group) responses. Thus, the ORR was 46.9% for cetuximab plus FOLFIRI and 38.7% for FOLFIRI alone, for ITT population. The adjusted odds ratio (OR) for a tumor response with cetuximab plus FOLFIRI compared with FOLFIRI alone was 1.40 (95% CI 1.12, 1.77), which was statistically significant ($p=0.004$). In the *KRAS* wild-type population, ORR was also higher in cetuximab plus FOLFIRI compared with FOLFIRI alone (59.3% vs. 43.2%, difference 16.1%). OR was 1.91 (95% CI 1.24, 2.93), which was statistically significant (p

value not reported). There was no statistically significant difference between groups in the total *KRAS* population or *KRAS* mutant population.

At the cut-off date of May 31, 2009, the ORR in the *KRAS* wild-type population was 57.3% for cetuximab plus FOLFIRI and 39.7% for FOLFIRI alone. OR was 2.07 (95% CI 1.52, 2.83), which was statistically significant ($p < 0.001$). There was no statistically significant difference between groups in the *KRAS* mutant population, but there was statistically significant difference in favor of cetuximab plus FOLFIRI for total *KRAS* population; HR 1.41 (95% CI 1.11, 1.80), $p = 0.05$.

Subgroup analyses in the CRYSTAL *KRAS* wild-type population revealed that ORR was numerically favored by the cetuximab plus FOLFIRI treatment in all subgroups.

FIRE-3 study: For *KRAS* mutant patients (N=96), the ORR was 44% (95% CI 29, 59) in cetuximab plus FOLFIRI and 48% (95% CI 33, 62) in bevacizumab plus FOLFIRI group.

For *KRAS* wild-type patients (N=592), the ORR was 62% in cetuximab plus FOLFIRI and 57% in bevacizumab plus FOLFIRI group, OR was 1.25, $p = 0.183$ (not statistically significant). Further analysis of *RAS* wild-type (N=301), which consisted of *KRAS* exon 2/3/4 and *NRAS* exon 2/3/4 wild-type, had ORR of 76% in cetuximab plus FOLFIRI and 65.2% in bevacizumab plus FOLFIRI group, $p = 0.044$.

d) Surgery + R0 Resection

In the CRYSTAL study, the rate of surgery for metastasis in the ITT population was 7.0% (n=42) for cetuximab plus FOLFIRI group and 3.7% (n=22) in the FOLFIRI group. The rate of R0 resection with curative intent before disease progression was 4.8% (n=29) for cetuximab plus FOLFIRI group and 1.7% (n=10) in the FOLFIRI group; OR was 3.02 (95% CI 1.45, 6.27), $p = 0.002$.

For patients with *KRAS* wild-type, the rate of surgery for metastasis and the rate of R0 resection were also both higher in cetuximab plus FOLFIRI group compared with FOLFIRI alone group (7.9% [n=25] vs. 4.6% [n=16]; OR 1.82 [95% CI 0.96, 3.47], $p = 0.063$; 5.1% [n=16] vs. 2.0% [n=7]; OR 2.65 [95% CI 1.08, 6.49], $p = 0.027$, respectively).

e) Health-Related quality of Life

CRYSTAL: The health-related quality of life (HRQoL) was a secondary outcome in the CRYSTAL study and the scores were analyzed over time using the European Organization for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire (EORTC QLQ-C30). The QLQ-C30 consists of 30 items combined into 15 subscales including a Global Health Status (GHS) subscale; total scores range from 0 to 100, with higher scores indicating better HRQoL.²⁸ The accepted minimal important difference (MID) values for different subscales of the EORTC QLQ-C30 range from 5% to 10%.²⁹⁻³¹

In CRYSTAL, HRQoL was evaluated in 627 of 666 patients (94%) with *KRAS* wild-type tumors (301 in cetuximab plus FOLFIRI and 326 in FOLFIRI). HRQoL was assessed at randomization, every 8 weeks prior to the beginning of the next treatment cycle and at final tumor assessment.

- Compliance rates deteriorated over time, but were similar between treatment arms.
- There were no significant differences between groups for GHS and other functioning scores including physical, role, emotional, cognitive and social.²⁶
- For worst post-baseline symptom scores, nausea and vomiting was higher in FOLFIRI than the cetuximab plus FOLFIRI (20.07 vs. 15.93, $p = 0.032$), while dyspnoea was higher in the combined group than the FOLFIRI arm ($p = 0.020$); incidence 10% vs. 5%.

- In patients receiving cetuximab plus FOLFIRI, early skin reaction at week 8 did not significantly affect GHS and social functioning. Mean (SD) changes from baseline for GHS in Grade II-IV skin reaction compared with no skin reaction were -0.51 (20.81) vs. 3.00 (26.67), $p=0.49$. Mean (SD) changes from baseline for social functioning in Grade II-IV skin reaction compared with no skin reaction were 1.48 (22.20) vs. -6.41 (27.11), $p=0.14$.

FIRE-3: No HRQoL data was reported.

f) Clinical Impact of Tumor BRAF Mutation in Patients with KRAS Wild-Type Tumors

From an updated report of CRYSTAL study as of May 31, 2009,⁶ *BRAF* V600E mutations were found in 60 (6%) of 999 tumor samples, and of which 59 cases were identified in tumors which were wild-type *KRAS*.

In patients whose tumors were wild-type for both genes, cetuximab plus FOLFIRI had significantly reduced risk of disease progression (HR, 0.64; $p=0.0013$) and significantly increased odds of overall response rate (OR, 2.18; $p<0.001$) compared to FOLFIRI alone. The overall survival benefit was not statistically significant (HR, 0.83; $p=0.0547$).

In patients whose tumors were *KRAS* wild-type/*BRAF* mutant, there were no statistically significant differences between cetuximab plus FOLFIRI and FOLFIRI alone for PFS (median 8.0 vs. 5.6 months; HR, 0.93; $p=0.87$), for OS (median 14.1 vs. 10.3 months; HR 0.91; $p=0.74$), and for ORR (19.2% vs. 15.2%; OR 1.08; $p=0.91$).

Harms Outcomes

CRYSTAL: The safety analysis population comprised 1,202 patients (600 in cetuximab plus FOLFIRI group and 602 in FOLFIRI group).

The median durations of exposure to cetuximab are shown in **Table 4**. Results of key safety outcomes for safety population and *KRAS* wild-type population are shown in **Table 7**.

a) Death

As of May 31, 2009, there were 488 deaths (81%) in the cetuximab plus FOLFIRI group and 505 deaths (84%) in the FOLFIRI group for safety population. For the *KRAS* wild-type population, there were 243 deaths (77%) in the cetuximab plus FOLFIRI group and 288 deaths (82%) in the FOLFIRI group. The main reason for death was disease progression. The incidence of death on-treatment and within 30 days after last dose of study medication and the incidence of adverse events leading to death were balanced between groups in both safety population and *KRAS* wild-type population.

b) Serious Adverse Events

The incidence of serious adverse events (SAEs) was higher in patients receiving cetuximab plus FOLFIRI than in patients receiving FOLFIRI alone for both safety population (44% vs. 34%) and *KRAS* wild-type population (43% vs. 32%). In the *KRAS* wild-type population, the most frequent SAEs showing notable difference between groups were diarrhea (7% vs. 3%), dehydration (4% vs. 1%), pulmonary embolism (4% vs. 2%) and hypomagnesemia (2% vs. 0%).

The incidence of treatment related serious adverse events (SAEs) was also higher in patients receiving cetuximab plus FOLFIRI than in patients receiving FOLFIRI alone for both safety population (26% vs. 19%) and *KRAS* wild-type population (26% vs. 17%). In the *KRAS*

wild-type population, the most frequent treatment related SAEs showing notable difference between groups were diarrhea (7% vs. 3%) and hypomagnesemia (2% vs. 0%).

c) Adverse Events Leading to Discontinuation

The incidence of AEs leading to discontinuation of treatment was higher in patients receiving cetuximab plus FOLFIRI than in patients receiving FOLFIRI alone for both safety population (30% vs. 13%) and *KRAS* wild-type population (30% vs. 13%). In *KRAS* wild-type population, diarrhea (4% vs. 1%), rash (4% vs. 0%), fatigue (3% vs. 2%) and dermatitis (2% vs. 0%) were the main AEs leading to treatment discontinuation.

d) Any Adverse Events

There were no apparent differences between groups for the incidences of any AEs or any treatment related AEs. However, combination of cetuximab and FOLFIRI had higher incidence of skin reaction, acne-like rash, infusion reaction and palmar-plantar erythrodysesthesia compared with FOLFIRI alone. The incidences of all grade and grade 3-4 toxicity for specific AEs are shown in Table 7.

e) Adverse Events Leading to Dose Reduction or Delay Treatment

The incidence of AEs leading to dose reduction or delay treatment was higher in patients receiving cetuximab plus FOLFIRI than in patients receiving FOLFIRI alone for both safety population and *KRAS* wild-type population (Table 7).

FIRE-3: Patients receiving cetuximab had higher incidence of acneiform exanthema (grade 3-4: 20% vs. 0%) than those receiving bevacizumab. Neutropenia was also higher in cetuximab group (grade 3-4: 28% vs. 17%). By contrast, hypertension was more frequent in patients receiving bevacizumab (grade 3-4: 22% vs. 8%). There were no notable differences for other hematological and non-hematological AEs.

6.4 Ongoing Trials

One related on-going trial was identified.³²

Status	Study
Closed	<p><u>Title:</u> A Phase III Trial of Irinotecan / 5-FU / Leucovorin or Oxaliplatin / 5-FU / Leucovorin with Bevacizumab, or Cetuximab (C225), or with the Combination of Bevacizumab and Cetuximab for patients with Untreated Metastatic Adenocarcinoma of the colon or Rectum</p> <p><u>Study ID:</u> NCT00265850; CALGB-C80405</p> <p><u>Design:</u> Phase 3, open-label, multicenter RCT</p> <p><u>Primary Objective:</u> Compare overall survival of patients with previously untreated metastatic colorectal cancer treated with cetuximab and/or bevacizumab in combination with either oxaliplatin, fluorouracil, and leucovorin calcium (FOLFOX) or irinotecan hydrochloride, fluorouracil, and leucovorin calcium (FOLFIRI).</p> <p><u>Treatment arms:</u> Arm I: Bevacizumab in combination FOLFOX or FOLFIRI Arm II: Cetuximab in combination FOLFOX or FOLFIRI Arm III (closed to accrual as of 09/10/2009): as in arm I plus arm II</p> <p><u>Primary outcome:</u> Overall survival</p> <p><u>Secondary outcomes:</u> Overall response rate (complete and partial); progression-free survival; time to treatment failure; duration of tumor response</p> <p><u>Duration:</u> Treatment continued until disease progression, unacceptable toxicity or planned surgery with curative intent. After completion of study treatment, patients are followed up every 2 months for 5 years and then every 6 months for 5 years.</p> <p><u>Start date:</u> 30 November 2005</p> <p><u>End date:</u> 31 March 2013 (estimated)</p>

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of cetuximab (Erbix) for EGFR-expressing *KRAS* wild-type metastatic colorectal carcinoma (mCRC), in combination with FOLFIRI for first-line treatment:

- Summary of *KRAS* mutation testing in mCRC patients

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary of *KRAS* Mutation Testing in Metastatic Colorectal Carcinoma

7.1.1 Objective

To summarize *KRAS* mutation testing and its role in identifying mCRC patients who may benefit from treatment with cetuximab.

The provincial advisory group (PAG) is interested in the implementation and additional costs of *KRAS* mutation testing, including different test methods available, cost differences, differences with respect to the level of evidence to support them, and issues associated with test accessibility (See Section 5 of the report).

7.1.2 Findings

*a) Description and clinical utility of *KRAS* testing*

The *KRAS* proto-oncogene encodes the K-ras protein, which is a downstream effector in the EGFR signaling pathway and helps to modulate EGFR-mediated cell proliferation and growth. It is also involved with activation and regulation of cell survival and/or apoptosis and angiogenesis.⁹ Perturbations in EGFR-dependent intracellular signaling have been implicated in multiple aspects of the malignant process, including enhanced tumor cell survival and proliferation, tumor-induced angiogenesis and metastasis.¹² In the *KRAS* wild-type tumors, signaling in the epidermal growth factor pathway requires activation through appropriate ligand-receptor binding. Mutations in the *KRAS* gene induce continuous signaling in the pathway, even without any upstream stimulation of the epidermal growth factor receptors.¹² Cetuximab is an anti-EGFR antibody therapy which works through direct inhibition of the EGFR and indirectly through antibody-dependent cellular cytotoxicity.⁹ It is ineffective in tumors expressing mutant *KRAS* genes because EGFR is not required for the tumor-engendering signaling produce in *KRAS* mutant type mCRC. It has been reported that approximately 40% to 50% of colorectal tumors have *KRAS* mutations in codons 12 and 13.¹⁰ Therefore, anti-EGFR antibody therapy with cetuximab could be ineffective in up to 50% of colorectal carcinoma patients and potentially expose patients to adverse effects.

*b) Description of *KRAS* testing*

KRAS mutation testing is typically performed with samples taken from formalin-fixed paraffin-embedded tissue blocks. Mutations usually occur early in the development and progression of colorectal cancers with high concordance of *KRAS* mutations in either primary or metastatic tumors from CRC patients.¹² *KRAS* mutation testing is preferably performed on primary tumor tissue, provided that the tissue area holds more than 70% invasive carcinoma cells, considered adequate tumor density.¹² Macrodissection of the area underlined by a pathologist is recommended to improve the percentage of detected mutations. For patients who present with metastatic disease at diagnosis biopsy material from representative tissue sample of the metastatic lesion, but not the primary tumor, is required for analysis. Sample acquired by fine-

needle aspiration of a metastasis is frequently not enough to proceed with a mutational analysis and should be avoided.¹²

Two commonly used procedures to evaluate samples for *KRAS* mutations are:

1. Real-Time PCR in which fluorescent probes specific for the most common mutations in codons 12 and 13 are utilized. When a mutation is present, the probe binds and fluorescence is detected; and,
2. Direct Sequencing Analysis of exon 2 in the *KRAS* gene which identifies all possible mutations in the exon. This method has lower analytical sensitivity than some of the real time PCR assays.

Variations of these major testing procedures are used in several testing methods including Restriction Fragment Length Polymorphism (RFLP), allele-specific probes, High Resolution Melting analysis (HRM) confirmed by direct sequencing, Amplification Refractory Mutation System (ARMS), and pyrosequencing. Test techniques have varying merits in terms of detection limits, sensitivity and specificity.

A high ratio of benign stromal cells can dilute out mutant DNA making detection difficult. The difficulty is heightened in post-chemotherapy tumors and in tumors where the number of cells can be very low.¹⁸ Therefore, *KRAS* testing requires methods that can detect mutant DNA even in highly diluted circumstances. Sequencing analysis, which identifies all possible mutations in the exon, requires at least 15% to 50% of sample DNA to be mutant for a reliable test.¹⁸ Array or strip assays and allele-specific PCR techniques have detection limits of between 0.1% and 1% of mutant DNA in samples, and have reported sensitivity and specificity of up to 100%. HRM methods have a detection limit range of 3% to 10% of mutant DNA in samples with a reported sensitivity and specificity of 88% and 80%, respectively.¹⁸ High Resolution Melting analysis methods are commonly used to analyze *KRAS* mutation because of their suitability and cost effectiveness. However, they are prone to relatively high false-positive rates. Therefore, it is recommended that positive HRM results be confirmed by sequencing or allele-specific PCR.¹⁸

TheraScreen®: K-RAS Mutation Kit was approved and licensed by Health Canada in 2009 as a Class 3 device. Manufactured by UK-based DxS Limited, the kit is a CE-marked product commercially available in Canada through distributorship of Roche Diagnostics.¹⁶ It is for in vitro diagnostic use on either the Roche Diagnostics LightCycler® 480 Real-Time PCR System or Applied BioSystems 7500 Real-Time PCR System.¹⁶ In June 2012, the US Food and Drugs Administration (FDA) approved a similar kit; *therascreen*® *KRAS* RGQ PCR Kit, as a companion diagnostic device for cetuximab. It is manufactured by QIAGEN Manchester Limited to be used on the Rotor-Gene Q MDx instrument.²⁰ Currently, it is the only FDA approved test for *KRAS* mutation testing. Both kits utilize ARMS and Scorpions real-time PCR technologies for the detection of 7 somatic mutations in the *KRAS* oncogene in codons 12 and 13. Overall agreement between the *therascreen*® RGQ PCR *KRAS* Kit and Sanger bi-directional sequencing (reputed for its ability to identify all mutated base pairs, and small insertions and deletions)¹⁷ is 96.4 %; with 99.07 % positive percent agreement (sensitivity) and 96.4% negative percent agreement (specificity).¹⁹ However, the kits have more sensitive detection limits (1% to 5%) compared to sequencing (15% to 50%).¹⁷ While the US product information for cetuximab specifically requires testing for *KRAS* mutation status using an "FDA-approved test", the Canadian product monograph states that assessment of *KRAS* mutation should be performed by an experienced laboratory using a validated method.

c) Current practice regarding KRAS testing

Based on level 2A evidence (low-level evidence including clinical practice), the Canadian Expert Group consensus recommendation on *KRAS* testing in colorectal Cancer¹⁷ states that any validated test strategy is deemed acceptable provided that it satisfies the minimal requirements of between 95% and 99% mutation-detection sensitivity, and 100% specificity.¹⁷

The Canadian consensus recommendation states - among other things - that tumour *KRAS* status should be determined whenever anti-EGFR therapy is considered in the treatment of mCRC. This position is in consonance with the American Society of Clinical Oncology (ASCO) recommendation for all patients with mCRC to be specifically tested for *KRAS* mutations status at codons 12 and 13, if they are being considered for EGFR antagonist treatment.¹²

The Ontario Health Technology Assessment Committee review of December 2010 reports that the cost of *KRAS* testing ranges between \$150 and \$500 per test depending on the methods used, while the Canadian consensus recommendation on *KRAS* testing states that general costs range from \$300 to \$450 depending on the method used (excluding pre- or post-test costs associated with getting the tissue to the lab and assessing its tumour cellularity).^{16,17}

KRAS testing is available in many but not all provinces in Canada. For example, samples from patients in Manitoba who need testing services are sent to Toronto for evaluation, via drug company funding.¹³ There is no public record indicating availability of *KRAS* testing in Prince Edward Island (PEI) and Newfoundland. In provinces with availability, facilities for testing are few and concentrated in urban areas.¹³ Reliance on laboratories far removed from patient locations can adversely affect turnaround time for *KRAS* mutation testing and delay initiation of therapy unduly.

Funding for *KRAS* testing is not uniform. While the manufacturer of cetuximab claims that it covers funding for the test, it is ambiguous on source of funding for some provinces. For instance Nova Scotia has recently begun funding *KRAS* testing through the Capital District Health Authority (CDHA)/ hospital budget with availability of fee for service at site outside the CDHA.¹³

Knowledge of *KRAS* mutation status is currently only directly relevant for the clinical management of metastatic carcinomas. Routine testing for *KRAS* mutations might not be beneficial for patients with stage I CRC. Therefore, restricting testing to the metastatic setting is the generally accepted practice.¹⁷

7.1.3 Summary

The predictive diagnostic value of *KRAS* mutation status testing and its role in identifying mCRC patients who may benefit from treatment with cetuximab is widely accepted among clinicians.⁹⁻²⁰ The various methods of *KRAS* mutation testing have differing strength in terms of sensitivity, specificity and mutant DNA detection limits. Several of these diagnostic techniques are available for used in Canada without any streamlined official guideline except that an employed method should be validated and be performed in an experienced laboratory. *KRAS* testing is prone to biases from several factors including: selection of patients to test; methods of test samples acquisition; DNA extraction procedures; protocols for the determination of *KRAS* status, and reporting/interpretation of test results.^{14,15} Improper patient selection may result in improper patient management decisions in colorectal cancer treatment with cetuximab. While treatment may be withheld from patients who might have benefitted, it could wrongfully be administered to patients who are not expected to benefit, but who could potentially suffer any adverse side effects associated with treatment. Current publicly available information provides only a general range of costs for *KRAS* testing with no price delineation of the individual methods used.

7.2 Critical Appraisal of Indirect Comparison of Cetuximab plus FOLFIRI with Bevacizumab plus FOLFIRI and Bevacizumab plus FOLFOX in the Treatment of metastatic Colorectal Carcinoma

7.2.1 Objective

To summarize and critically appraise the methods and findings of the manufacturer-submitted indirect comparison and sensitivity analysis of cetuximab plus FOLFIRI with Bevacizumab plus FOLFIRI and with Bevacizumab plus FOLFOX for the treatment of mCRC

7.2.2 Findings

The manufacturer provided an indirect comparison of effectiveness between cetuximab plus FOLFIRI with Bevacizumab plus FOLFOX, and Bevacizumab plus FOLFIRI as the base case comparator in their model for economic evaluation. No network diagram was provided.

Data from two Phase III studies^{6,33} constitute the major basis for the indirect comparison, though the content of the model is formed by a total of 8 papers. The CRYSTAL study⁶ has FOLFIRI alone as the comparator to cetuximab plus FOLFIRI, and the NO16996 trial³³ compares a combination of two chemotherapies (FOLFOX or XELOX) plus placebo to bevacizumab plus FOLFOX or XELOX. The indirect comparison is inappropriate because the manufacturer's portrayal of the combined outcome of FOLFOX or XELOX in the second study,³³ as being the same as the outcome of FOLFOX to be compared with FOLFIRI, is a misrepresentation. For sensitivity analysis, data from a head-on comparison between bevacizumab + FOLFIRI and bevacizumab + FOLFOX from the BEAT³⁴ study were used. It must be noted that the BEAT study is non-comparative, and non-randomized (non-RCT) unlike the others which are randomized controlled trials (RCTs). Lack of adequate homogeneity between this study and the others precludes comparison of the studies, making derivations from such inappropriate. All the studies and a summary of study characteristics are listed in Table 1. The study by Okines et al.³⁵ analyses data from the BEAT and NO16966 studies further and provides complementary information for resection and R0 rates. The GERCOR study³⁶ is used to derive second-line efficacy for FOLFOX versus FOLFIRI and the remaining three studies³⁷⁻³⁹ are used as sources for third-line treatment. Exclusion criteria were similar for all the studies.

Relative ratio approach, in which the ratio of point estimates between the intervention and comparator is calculated from one source and applied to another source to derive respective values, is used to perform the indirect comparison. The manufacture argued that since each source had different assumptions for calculating and reporting relative risks, this approach allowed for consistency between sources. Table 2 presents details and commentary on relevant items appraised according to the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparison.⁴⁰

Table 1 Summary of studies used for indirect comparison and sensitivity analysis

Trial, First author, Publication	Study design	Patient population	Intervention, and Comparator	Outcomes
CRYSTAL, Van Cutsem et al. J Clin Oncol, 2011 ⁶	Phase III, multicenter, multinational, Open-label, RCT	1,198 Patients, ≥ 18 yrs., with EGFR-expression mCRC not curatively resectable, not previously exposed to EGFR-targeting therapy or irinotecan-based chemotherapy, with adjuvant chemotherapy completed at least 6 months. ECOG 0-2	Erbitux (Cetuximab) plus FOLFIRI (irinotecan, fluorouracil, leucovorin) FOLFIRI alone	Primary: PFS Secondary: OS, ORR, QoL Safety (AEs, SAEs)
NO16966 Salts et al. J Clin Oncol 2008 ³³	Phase III, multicenter, open-label RCT	1,400 patients, ≥ 18 yrs., with unresectable mCRC and without prior systematic treatment for mCRC or previous treatment with oxaliplatin or Bevacizumab. ECOG ≤ 1	Bevacizumab plus FOLFOX-4 or XELOX, and Placebo plus FOLFOX-4 or XELOX	Primary: PFS Secondary: On-treatment PFS, OS, RR, DR, TTF
Okines et al. Br J Cancer ^a 2009 ³⁵	Phase III, multinational, multicenter, open-label, non-comparative, non-RCT	225 out of 1914 patients, ≥ 18 yrs., with unresectable mCRC and without previous treatment for mCRC (adjuvant treatment for CRC allowed) ECOG ≤ 1,	Bevacizumab plus fluoropyrimidine-based chemotherapy, and Treatment with Different regimens	Primary: Resection rate, R0 Secondary: Safety
Okines et al. Br J Cancer ^b 2009 ³⁵	Phase III, multicenter, open-label RCT	1,400 patients, ≥ 18 yrs., with unresectable mCRC and without prior systematic treatment for mCRC or previous treatment with oxaliplatin or Bevacizumab. ECOG ≤ 1	Bevacizumab plus FOLFOX or XELOX, and Placebo Plus FOLFOX or XELOX	Primary: Resection rate Secondary: PFS OS
BEAT, Van Cutsem et al. Ann Oncol 2009 ³⁴	Phase III, multinational, multicenter, open-label, non-comparative, non-RCT	1,914 patients, ≥ 18 yrs., with unresectable mCRC and without previous treatment for mCRC (adjuvant treatment for CRC allowed) ECOG ≤ 1,	Bevacizumab plus fluoropyrimidine-based chemotherapy, and N/A	Primary: Safety Secondary: PFS OS
GERCOR, Tourigard et al. J Clin Oncol 2004 ³⁶	Phase III, multicenter, open-label RCT	220 patients, 18 to 75 yrs., with untreated mCRC or adjuvant chemotherapy completed at least 6 months before inclusion WHO PS 0-2,	Arm A: FOLFIRI followed by FOLFOX6, and Arm B: FOLFOX6 followed by FOLFIRI	Primary: PFS Secondary: OS, RR, toxicity
Jonker et al. N Engl J Med 2007 ³⁷	Phase III, multinational, multicenter, open-label RCT	572 patients, ≥ 16 yrs., with EGFR-expressing mCRC and failed treatment (within 6 months of last dose) with	Cetuximab plus BSC, and BSC alone	Primary: OS Secondary: PFS, RR, QOL

Trial, First author, Publication	Study design	Patient population	Intervention, and Comparator	Outcomes
		fluoropyrimidine, irinotecan, and oxaliplatin, or for whom these drugs are contraindicated, ECOG 0-2,		
Sobrero et al. J Clin Oncol 2008 ³⁸	Phase III, multinational, multicenter, open-label RCT	1,298 patients ≥ 18 yrs., with EGFR-expressing mCRC and failed first-line treatment (within 6 months of last dose) with fluoropyrimidine and oxaliplatin, ECOG 0-2,	Cetuximab plus irinotecan, and Irinotecan alone	Primary: OS Secondary: PFS, RR, QoL
Van Cutsem et al. J Clin Oncol 2007 ³⁹	Phase III, multinational, multicenter, open-label RCT	463 patients ≥ 18 yrs., with ≥ 1% EGFR expressing mCRC, with disease progression during or within 6 months of most recent chemotherapy using fluoropyrimidine, irinotecan, and oxaliplatin. ECOG 0-2,	Panitumumab (panitumumab) plus BSC, and BSC alone (BSC)	Primary: PFS Secondary: OR, OS, safety

a = derived from BEAT study, b = derived from NO16966 study

Abbreviations: AE = adverse events, SAE = serious adverse events, OS = overall survival, PFS = progression free survival, RR = response rate, QoL = quality of Life, ORR = objective response rate, DR = Duration of response, TTF = Time to treatment failure R0 = complete removal of all the tumor, ECOG = Eastern Cooperative Oncology Group performance scale, WHO PS = World Health Organization performance scale

Limitations

The manufacturer stated that with regards to model data sources, comparators, and treatment flow for this indirect comparison, it followed the recommendations of one expert based experience and practice patterns at once faculty. Considering the great deal of variety in treatment of mCRC throughout Canada, the generalizability of conclusions of this comparison is uncertain. Furthermore, restricting study sources to the recommendations of one expert has the potential of omitting potentially higher quality source that could afford greater robustness to the comparison.

The NO16966 study³³ from which clinical parameters were drawn for base case comparison and sensitivity analysis was not selective for Bevacizumab + FOLFOX, or FOLFOX alone. The study allocated equal number of patients (n = 350) to XELOX plus Bevacizumab arm as it did to FOLFOX-4 plus Bevacizumab arm. However, outcomes from the 2 arms were pooled and reported as Bevacizumab plus FOLFOX or XELOX, because the study aimed to evaluate the safety and efficacy of bevacizumab when added to oxaliplatin-based chemotherapy. Thus, FOLFOX, as used by the manufacturer to refer to data from the NO16966 study used in this indirect comparison, assumes an expanded meaning beyond the putative definition. Since the manufacturer seeks to compare cetuximab plus FOLFIRI with Bevacizumab plus traditional FOLFOX, the appropriateness of using the outcome of the dual oxaliplatin-based chemotherapy comprising FOLFOX and XELOX in place of FOLFOX is uncertain. Therefore, reported and derived values from the indirect comparison such

as OS and PFS for bevacizumab plus FOLFOX, bevacizumab plus FOLFIRI, as well as the sensitivity analysis can be misleading.

Another source of caution is that the relative ratios for overall survival (OS) and of progression free survival (PFS) between the cetuximab + FOLFIRI and FOLFIRI alone from the CRYSTAL study was applied to the “FOLFOX” arm of the NO16966 study to derive prospective OS and PFS outcomes for cetuximab + FOLFOX. In survival analysis the acceptable practice is to employ median time to event or relative risk, not relative ratio, as effect evaluators. Therefore, the indirect comparison is inappropriate. In addition, there is a breach of homogeneity between the non-comparative, non-RCT BEAT study and the other RCT studies used in the sensitivity analysis, which decrease the confidence in the reliability of the results.

Table 2 Appraisal of the indirect comparison analyses using ISPOR criteria⁴⁰

Item	Detail to focus on	Comments
Introduction	Are the rationale for the study and the objectives stated clearly?	<ul style="list-style-type: none"> The rationale for conducting an indirect comparison analysis and the study objectives were stated.
Methods	Does the methods section include the following? <ul style="list-style-type: none"> Eligibility criteria Information sources Search strategy Study selection process Data extraction Description of outcome measures Description of method including analysis/synthesis of evidence and description of analyses method/models Handling of Potential bias/inconsistency Analysis of framework 	<ul style="list-style-type: none"> Since both RCT and non-RCT studies were used the eligibility criteria is not clear. Model data sources, comparators, and treatment flow were recommended by an expert to reflect practice patterns in his practice. It is not stated whether a systematic review of literature was performed. Outcome measures overall survival (OS), and progression free survival (PFS) were stated. Relative ratio approach (instead of time to median survival of relative risk), in which the ratio of point estimates between the regimen and the comparator was calculated from one source and applied to another source, was used for base comparison and sensitivity analysis. There is no discussion of potential bias/inconsistency
Results	Do the results include a summary of the studies included in the network of evidence? <ul style="list-style-type: none"> Individual study data? Network of studies? Does the study describe an assessment of model fit? Are competing models being compared? Are the results of the evidence synthesis presented clearly?	<ul style="list-style-type: none"> No clear selection process of included studies reported except to say it followed expert recommendation. There is no table/list of information on study design and patient characteristics that might act as effect modifiers. Effect estimates are reported without confidence intervals. No figure showing the network of studies was provided. Assessing model fit or comparing models do not apply to this indirect comparison The results of the analysis are clearly presented
Discussion	Does the discussion include the following?	<ul style="list-style-type: none"> There is no discussion on how differences across the individual trials might violate consistency of

Item	Detail to focus on	Comments
	<ul style="list-style-type: none"> • Summary of main findings • Internal Validity • External validity • Implication of results for target audience 	<p>assumptions and affect the internal validity of the analysis.</p> <ul style="list-style-type: none"> • There is no discussion regarding generalizability of findings. • Interpretation of finding from biological and clinical perspective has been provided but their appropriateness is in doubt given the limitations discussed above.

7.2.3 Summary

The comparative efficacies of cetuximab plus FOLFIRI, bevacizumab plus FOLFIRI, and bevacizumab plus FOLFOX were indirectly assessed in patients with mCRC using relative ratio of effect estimate method. Sensitivity analysis to derive OS and PFS measures for bevacizumab plus FOLFIRI was performed using a non-comparative, non-RCT study.³⁴ The indirect analysis and derivations from it are not appropriate because the import of survival studies is properly derived with a model using median time to event or relative risk analysis and not relative ratio. Secondly, comparing a non-comparative, non-RCT trial with RCT studies is not an appropriate analytical approach. In addition, the manufacturer's use of outcome data from NO16996 as if it were bevacizumab plus FOLFOX is misleading since the NO16966 study reports a combined outcome of bevacizumab plus FOLFOX or XELOX but not outcome for bevacizumab plus FOLFOX alone. These shortfalls, together with others discussed above, indicate that the indirect comparison and sensitivity analysis have numerous limitations rendering conclusions from them non-interpretable.

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR Gastrointestinal Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on cetuximab (Erbix) for metastatic colorectal cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Gastrointestinal Clinical Guidance Panel is comprised of cetuximab (Erbix) for metastatic colorectal cancer. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): Embase 1974 to present, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	(Cetuximab* or Erbitux* or C225 or "c 225" or "IMC 225" or IMC225 or "IMCC 225" or IMCC225 or MAbC225 or HSDB-7454 or HSDB7454).ti,ot,ab,sh,rn,hw,nm.	21040
2	205923-56-4.rn,nm.	12728
3	or/1-2	21040
4	(Folfiri or IFL).ti,ot,ab,sh,rn,hw,nm.	2776
5	(1000669-05-5 or C480833000).rn,nm.	0
6	4 or 5	2776
7	Fluorouracil/	137123
8	(fluracedyl* or fluorouracil* or fluoruracil* or fluoracil* or efudex or FU or 5-fu or 5fu or 5-faracil or 5-fluor* or haemato-fu or neofluor or onkofluor or fluoroplex or 5-hu or 5hu or carac or flurodex or ribofluor or efudix or effluderm or fluoro-uracil* or fluroblastin or fluoroblastin or fluril or fluro-uracil or adrucil or ulup or timazin or queroplex or arumel or carzonal or phthoruracil or queroplex).ti,ot,ab,sh,rn,hw,nm.	172251
9	51-21-8.rn,nm.	133307
10	or/7-9	172251
11	Leucovorin/	34025

12	(LV or leucovor* or leukovor* or lenkovor* or citrovorum factor or "5 formyltetrahydrofolate" or "n(5) formyltetrahydrofolate" or leukovorum or factor citrovorum or folinic acid or "5 formyltetrahydropteroylglutamate" or folinate or "5 formyltetrahydrofolate" or wellcovorin or HSDB-6544 or HSDB6544 or Leucal).ti,ot,ab,sh,rn,hw,nm.	118524
13	58-05-9.rn,nm.	33267
14	or/11-13	118524
15	*Camptothecin/aa [Analog & Derivatives]	3976
16	(Irinotecan* or Camptosar or Campto or Topotecin or irinotel or SN-38* or SN38 or CPT11 or CPT-11 or camptothecin-11 or HSDB7607 or HSDB-7607).ti,ot,ab,sh,rn,hw,nm.	41717
17	(97682-44-5 or 100286-90-6).rn,nm.	20756
18	or/15-17	41717
19	10 and 14 and 18	9754
20	6 or 19	10972
21	and/3,20	3267
22	21 use pmez	447
23	*cetuximab/	2912
24	(Cetuximab* or Erbitux* or C225 or "c 225" or "IMC 225" or IMC225 or "IMCC 225" or IMCC225 or MAbC225 or HSDB-7454 or HSDB7454).ti,ab.	10824
25	or/23-24	11200
26	(Folfiri or IFL).ti,ab.	2722
27	*Fluorouracil/	52653

28	(fluracedyl* or fluorouracil* or fluoruracil* or fluoracil* or efudex or FU or 5-fu or 5fu or 5-faracil or 5-fluor* or haemato-fu or neofluor or onkofluor or fluoroplex or 5-hu or 5hu or carac or flurodex or ribofluor or efudix or effluderm or fluoro-uracil* or fluoblastin or fluoroblastin or fluril or fluoro-uracil or adrucil or ulup or timazin or queroplex or arumel or carzonal or phthoruracil or queroplex).ti,ab.	94736
29	or/27-28	113451
30	*folinic acid/	8970
31	(LV or leucovor* or leukovor* or lenkovor* or citrovorum factor or "5 formyltetrahydrofolate" or "n(5) formyltetrahydrofolate" or leukovorum or factor citrovorum or folinic acid or "5 formyltetrahydropteroylglutamate" or folinate or "5 formyltetrahydrofolate" or wellcovorin or HSDB-6544 or HSDB6544 or Leucal).ti,ab.	96052
32	or/30-31	98919
33	*irinotecan/	4696
34	(Irinotecan* or Camptosar or Campto or Topotecin or irinotel or SN-38* or SN38 or CPT11 or CPT-11 or camptothecin-11 or HSDB7607 or HSDB-7607).ti,ab.	17849
35	or/33-34	18534
36	29 and 32 and 35	3348
37	or/26,36	4981
38	and/25,37	831
39	38 use oomezd	496
40	or/22,39	943
41	exp animals/	35909864
42	exp animal experimentation/ or exp animal experiment/	1706241

43	exp models animal/	1111323
44	nonhuman/	4079753
45	exp vertebrate/ or exp vertebrates/	34977793
46	animal.po.	0
47	or/41-46	37097195
48	exp humans/	27727583
49	exp human experimentation/ or exp human experiment/	325464
50	human.po.	0
51	or/48-50	27729663
52	47 not 51	9369121
53	40 not 52	943
54	limit 53 to english language	736
55	remove duplicates from 54	438

2. Literature search via PubMed

Search	Query	Items found
#7	Search #5 AND #6	4
#6	Search publisher[sb]	432944
#5	Search #1 AND #4	283
#4	Search #2 OR #3	2015

Search	Query	Items found
#1	Search cetuximab OR Erbitux OR C225 OR c-225 OR IMC-225 OR IMC225 OR IMCC-225 OR IMCC225 OR MAbC225 OR HSDB-7454 OR HSDB7454	3701
#3	Search (FU OR fluracedyl OR fluorouracil OR fluoruracil OR fluoracil OR 5-FU OR 5FU OR 5-faracil OR 5-HU OR 5HU OR fluoro-uracil OR fluoro-racil OR fluoro-uracil) AND (LV OR leucovorin OR leukovorin OR lenkovorin OR folinic acid OR folinate) AND (irinotecan OR camptothecin-11 OR CPT11 OR CPT-11)	1462
#2	Search IFL OR FOLFIRI	1008

3. Cochrane Central Register of Controlled Trials (Central)

Issue 7 of 12, August 2013

There are 22 results from 704315 records for your search on #12 - #1 and #11 in Trials in the strategy currently being edited

ID	Search	Hits
#1	cetuximab* or Erbitux* or C225 or c-225 or IMC-225 or IMC225 or IMCC-225 or IMCC225 or MAbC225 or HSDB-7454 or HSDB7454	362
#2	IFL or FOLFIRI	154
#3	MeSH descriptor: [Fluorouracil] explode all trees	3674
#4	FU or fluracedyl or fluorouracil* or fluoruracil* or fluoracil* or 5-FU or 5FU or 5-faracil or 5-fluor* or 5-HU or 5HU or fluoro-uracil* or fluoro-racil* or fluoro-uracil*	9259
#5	#3 or #4	9464
#6	MeSH descriptor: [Leucovorin] explode all trees	954
#7	LV or leucovor* or leukovor* or lenkovor* or folinic acid* or folinate	4971
#8	irinotecan* or camptothecin-11 or CPT11 or CPT-11	798
#9	#6 or #7	4971
#10	#5 and #9 and #8	346
#11	#2 or #10	397
#12	#1 and #11	49

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
<http://www.clinicaltrials.gov/>

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
<http://www.canadiancancertrials.ca/>

Search terms: Cetuximab or Erbitux or C225 or IMC 225 or MAbC225 or HSDB-7454 or HSDB7454

Select international agencies including:

Food and Drug Administration (FDA):
<http://www.fda.gov/>

European Medicines Agency (EMA):
<http://www.ema.europa.eu/>

Search terms: Cetuximab or Erbitux

Conference abstracts:

American Society of Clinical Oncology (ASCO)
<http://www.asco.org/>

Search terms: Cetuximab or Erbitux or C225 or IMC 225 or MAbC225 or HSDB-7454 or HSDB7454/ last 5 years

REFERENCES

1. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE. LBA3506: randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). *J Clin Oncol* [Internet]. 2013 [cited 2013 Jul 9];31(suppl). Available from: <http://meetinglibrary.asco.org/print/1158611> (Presented at Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, May 31 - June 4, 2013).
2. Stintzing S, von Weikersthal LF, Decker T, Vehling-Kaiser U, Jager E, Heintges T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer-subgroup analysis of patients with KRAS: mutated tumours in the randomised German AIO study KRK-0306. *Ann Oncol*. 2012 Jul;23(7):1693-9.
3. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2013 [Internet]. Toronto: Canadian Cancer Society; 2013 May. [cited 2013 Oct 3]. Available from: <http://www.cancer.ca/~media/cancer.ca/CW/publications/Canadian%20Cancer%20Statistics/canadian-cancer-statistics-2013-EN.pdf>
4. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009 Apr 2;360(14):1408-17.
5. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Supplementary appendix: cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009 Apr 2;360:1408-17.
6. Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* [Internet]. 2011 May 20 [cited 2013 Jul 4];29(15):2011-9. Available from: <http://jco.ascopubs.org/content/29/15/2011.full.pdf+html>
7. Lang I, Kohne CH, Folprecht G, Rougier P, Curran D, Hitre E, et al. Quality of life analysis in patients with KRAS wild-type metastatic colorectal cancer treated first-line with cetuximab plus irinotecan, fluorouracil and leucovorin. *Eur J Cancer*. 2013 Jan;49(2):439-48.
8. Stintzing S, Jung A, Rossius L, Modest DP, von Weikersthal LF, Decker T, et al. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: a randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. Abstract presented at: European Cancer Congress 2013. 2013 September 27 - October 1; Amsterdam, The Netherlands. Abstract LBA17.

9. Lyseng-Williamson KA. Cetuximab: a guide to its use in combination with FOLFIRI in the first-line treatment of metastatic colorectal cancer in the USA. *Mol Diagn Ther*. 2012 Oct;16(5):317-22.
10. Ocvirk J, Brodowicz T, Wrba F, Ciuleanu TE, Kurteva G, Beslija S, et al. Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial. *World J Gastroenterol* [Internet]. 2010 Jul 7 [cited 2013 Oct 3];16(25):3133-43. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2896750>
11. Yen LC, Uen YH, Wu DC, Lu CY, Yu FJ, Wu IC, et al. Activating KRAS mutations and overexpression of epidermal growth factor receptor as independent predictors in metastatic colorectal cancer patients treated with cetuximab. *Ann Surg*. 2010 Feb;251(2):254-60.
12. Russo A, Rizzo S, Bronte G, Silvestris N, Colucci G, Gebbia N, et al. The long and winding road to useful predictive factors for anti-EGFR therapy in metastatic colorectal carcinoma: the KRAS/BRAF pathway. *Oncology*. 2009;77(Suppl 1):57-68.
13. pan-Canadian Oncology Drug Review manufacturer submission: Erbitux (cetuximab); Company: Bristol-Myers Squibb Canada. Saint-Laurent (QC): Bristol-Myers Squibb Canada; 2012 Dec 20.
14. van Krieken JH, Jung A, Kirchner T, Carneiro F, Seruca R, Bosman FT, et al. KRAS mutation testing for predicting response to anti-EGFR therapy for colorectal carcinoma: proposal for an European quality assurance program. *Virchows Arch*. 2008 Nov;453(5):417-31.
15. Bellon E, Ligtenberg MJ, Tejpar S, Cox K, De Hertogh G, de Stricker K, et al. External quality assessment for KRAS testing is needed: setup of a European program and report of the first joined regional quality assessment rounds. *Oncologist* [Internet]. 2011 [cited 2013 Jul 15];16(4):467-78. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3228116/pdf/onc467.pdf>
16. Medical Advisory Secretariat. KRAS testing for anti-EGFR therapy in advanced colorectal cancer: an evidence-based and economic analysis. *Ont Health Technol Assess Ser* [Internet]. 2010 Dec [cited 2013 Jul 15];10(25):1-49. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377508/pdf/ohtas-10-49.pdf>
17. Aubin F, Gill S, Burkes R, Colwell B, Kamel-Reid S, Koski S, et al. Canadian Expert Group consensus recommendations: KRAS testing in colorectal cancer. *Curr Oncol* [Internet]. 2011 Aug [cited 2013 Oct 4];18(4):e180-e184. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149550>
18. Shackelford RE, Whitling NA, McNab P, Japa S, Coppola D. KRAS testing: a tool for the implementation of personalized medicine. *Genes Cancer* [Internet]. 2012 Jul [cited 2013 Jul 18];3(7-8):459-66. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3527988/pdf/10.1177_1947601912460547.pdf
19. Summary of safety and effectiveness data (SSED): real-time PCR test, theascreen® KRAS RGQ PCR Kit [Internet]. Silver Spring (MD): U.S. Food and Drug Administration;

2012. [cited 2013 Jul 18]. Available from:
http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110030b.pdf
20. U.S. Food and Drug Administration [Internet]. Silver Spring (MD): FDA. Companion diagnostic devices: in vitro and imaging tools; 2013 Aug 26 [cited 2013 Oct 4]. Available from:
<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>
 21. BC Cancer Agency. BCCA protocol summary third line treatment of metastatic colorectal cancer using cetuximab in combination with irinotecan: GIAVCETIR [Internet]. Vancouver: BC Cancer Agency; 2013 Sep 1. [cited 2013 Oct 4]. Available from:
http://www.bccancer.bc.ca/NR/rdonlyres/COA8933B-3AAD-4EBA-A95C-4552A0A060C9/66038/GIAVCETIR_Protocol_1Sep2013.pdf
 22. Grothey A, Sugrue MM, Purdie DM, Dong W, Sargent D, Hedrick E, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). *J Clin Oncol*. 2008 Nov 20;26(33):5326-34.
 23. Ye LC, Liu TS, Ren L, Wei Y, Zhu DX, Zai SY, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol* [Internet]. 2013 Jun 1 [cited 2013 Oct 4];31(16):1931-8. Available from:
<http://jco.ascopubs.org/content/31/16/1931.full.pdf+html>
 24. Bokemeyer C, Van Cutsem E, Rougier P, Ciardiello F, Heeger S, Schlichting M, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. *Eur J Cancer*. 2012 Jul;48(10):1466-75.
 25. Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. Appendix: cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol*. 2011 May 20;29:2011-9.
 26. Lang I, Kohne CH, Folprecht G, Rougier P, Curran D, Hitre E, et al. Supplementary data: quality of life analysis in patients with KRAS wild-type metastatic colorectal cancer treated first-line with cetuximab plus irinotecan, fluorouracil and leucovorin. *Eur J Cancer*. 2013 Jan;49:439-48.
 27. Stintzing S, von Weikersthal LF, Decker T, Vehling-Kaiser U, Jager E, Heintges T, et al. Supplementary data: FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer-subgroup analysis of patients with KRAS: mutated tumours in the randomised German AIO study KRK-0306. *Ann Oncol*. 2012 Jul;23:1693-9.
 28. Fayers PM, Aaronson NK, Bjorgal K, Curran D, Groenvold M. EORTC QLC-30 scoring manual. 2nd edition. Brussels: EORTC Quality of Life Study Group; 1999.

29. Maringwa JT, Quinten C, King M, Ringash J, Osoba D, Coens C, et al. Minimal important differences for interpreting health-related quality of life scores from the EORTC QLQ-C30 in lung cancer patients participating in randomized controlled trials. *Support Care Cancer*. 2011 Nov;19(11):1753-60.
30. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998 Jan;16(1):139-44.
31. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer*. 2007 Jul 1;110(1):196-202.
32. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT00265850, Cetuximab and/or bevacizumab combined With combination chemotherapy in treating patients with metastatic colorectal cancer; 2012 Mar [cited 2013 Jul 26]. Available from: <http://clinicaltrials.gov/show/NCT00265850>
33. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2008 Apr 20;26(12):2013-9.
34. Van Cutsem E, Rivera F, Berry S, Kretzschmar A, Michael M, DiBartolomeo M, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Ann Oncol*. 2009 Nov;20(11):1842-7.
35. Okines A, Puerto OD, Cunningham D, Chau I, Van Cutsem E, Saltz L, et al. Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer First BEAT and the randomised phase-III NO16966 trial. *Br J Cancer* [Internet]. 2009 Oct 6 [cited 2013 Oct 4];101(7):1033-8. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2768086>
36. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*. 2004 Jan 15;22(2):229-37.
37. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcborg JR, Tu D, Au HJ, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med*. 2007 Nov 15;357(20):2040-8.
38. Sobrero AF, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, Lutz MP, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008 May 10;26(14):2311-9.
39. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol*. 2007 May 1;25(13):1658-64.
40. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision

making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good
Research Practices: part 1. Value Health. 2011 Jun;14(4):417-28.