

KRAS Testing for Anti-EGFR Therapy in Advanced Colorectal Cancer

An Evidence-Based and Economic Analysis

*Presented to the Ontario Health Technology
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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is considered for the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practising medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

If you are aware of any current additional evidence to inform an existing evidence-based analysis, please contact the Medical Advisory Secretariat: MASinfo.moh@ontario.ca. The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

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Table of Contents

LIST OF ABBREVIATIONS	6
EXECUTIVE SUMMARY	8
Objective	8
Clinical Need: Condition and Target Population	8
KRAS Mutation Testing in Advanced Colorectal Cancer	9
Research Question	9
Research Methods	9
Literature Search	9
Summary of Findings of Systematic Review	10
Economic Analysis	10
CONCLUSIONS	11
KRAS STATUS IS PREDICTIVE OF OUTCOMES IN CETUXIMAB AND PANITUMUMAB MONOTHERAPY, AND IN CETUXIMAB-IRINOTECAN COMBINATION THERAPY.	11
WHILE KRAS TESTING IS COST-EFFECTIVE FOR ALL STRATEGIES CONSIDERED, IT IS NOT EQUALLY COST-EFFECTIVE FOR ALL TREATMENT OPTIONS.	11
BACKGROUND	12
Objective of Analysis	12
Clinical Need and Target Population	12
Ontario Context	13
KRAS Mutation Testing	13
EVIDENCE-BASED ANALYSIS	14
Research Question	14
Research Methods	14
Literature Search Strategy	14
Statistical Analysis	15
Results of Literature Review and Evidence-Based Analysis	15
Quality of Evidence	25
EXISTING GUIDELINES FOR KRAS TESTING IN ANTI-EGFR TARGETED THERAPY	29
ECONOMIC ANALYSIS	30
Study Question	30
Economic Analysis Overview	30
Economic Literature Review	31
Target Population	31
Perspective	32
Comparators	32
Time Horizon	32
Discounting	32
Model Structure	32
Outcomes	33
Resource Use and Costs	33
Parameter Estimates	34

Sensitivity Analysis.....	37
Results and Discussion.....	37
Budget Impact Analysis.....	38
CONCLUSIONS	40
Appendix 1: Literature Search Strategies.....	41
Appendix 2: Study and Patient Characteristics	42
REFERENCES	46

List of Abbreviations

AE	Adverse event
AUC	Area under the curve
BIA	Budget impact analysis
BSC	Best supportive care
BSA	Body surface area
CAD	Canadian dollars
CCO	Cancer Care Ontario
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CI	Confidence interval(s)
EBA	Evidence-based analysis
EGFR	Epidermal growth factor receptor; cell-surface receptor for members of the epidermal growth factor family
HTA	Health technology assessment
HR	Hazard ratio
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (protein coded by KRAS gene); k-RAS oncogene
KRAS WT	KRAS wildtype
MAS	Medical Advisory Secretariat
mCRC	Metastatic colorectal cancer
MoAb	Monoclonal anti-body (for anti-EGFR treatment / as EGFR inhibitor)
MOHLTC	Ontario Ministry of Health and Long-Term Care
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NDFP	New Drug Funding Program
OHTAC	Ontario Health Technology Advisory Committee
OR	Odds ratio
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RR	Relative risk

QOL	Quality of life
SD	Standard deviation
WTP	Willingness-to-pay

Executive Summary

In February 2010, the Medical Advisory Secretariat (MAS) began work on evidence-based reviews of the literature surrounding three pharmacogenomic tests. This project came about when Cancer Care Ontario (CCO) asked MAS to provide evidence-based analyses on the effectiveness and cost-effectiveness of three oncology pharmacogenomic tests currently in use in Ontario.

Evidence-based analyses have been prepared for each of these technologies. These have been completed in conjunction with internal and external stakeholders, including a Provincial Expert Panel on Pharmacogenomics (PEPP). Within the PEPP, subgroup committees were developed for each disease area. For each technology, an economic analysis was also completed by the Toronto Health Economics and Technology Assessment Collaborative (THETA) and is summarized within the reports.

The following reports can be publicly accessed at the MAS website at:
www.health.gov.on.ca/mas or at
www.health.gov.on.ca/english/providers/program/mas/mas_about.html

1. Gene Expression Profiling for Guiding Adjuvant Chemotherapy Decisions in Women with Early Breast Cancer: An Evidence-Based and Economic Analysis
2. Epidermal Growth Factor Receptor Mutation (EGFR) Testing for Prediction of Response to EGFR-Targeting Tyrosine Kinase Inhibitor (TKI) Drugs in Patients with Advanced Non-Small-Cell Lung Cancer: an Evidence-Based and Economic Analysis
3. K-RAS testing in Treatment Decisions for Advanced Colorectal Cancer: an Evidence-Based and Economic Analysis.

Objective

The objective of this systematic review is to determine the predictive value of KRAS testing in the treatment of metastatic colorectal cancer (mCRC) with two anti-EGFR agents, cetuximab and panitumumab. Economic analyses are also being conducted to evaluate the cost-effectiveness of KRAS testing.

Clinical Need: Condition and Target Population

Metastatic colorectal cancer (mCRC) is usually defined as stage IV disease according to the American Joint Committee on Cancer tumour node metastasis (TNM) system or stage D in the Duke's classification system. Patients with advanced colorectal cancer (mCRC) either present with metastatic disease or develop it through disease progression.

KRAS (Kristen-RAS, a member of the rat sarcoma virus (ras) gene family of oncogenes) is frequently mutated in epithelial cancers such as colorectal cancer, with mutations occurring in mutational hotspots (codons 12 and 13) of the KRAS protein. Involved in EGFR-mediated signalling of cellular processes

such as cell proliferation, resistance to apoptosis, enhanced cell motility and neoangiogenesis, a mutation in the KRAS gene is believed to be involved in cancer pathogenesis. Such a mutation is also hypothesized to be involved in resistance to targeted anti-EGFR (epidermal growth factor receptor with tyrosine kinase activity) treatments such as cetuximab and panitumumab, hence, the important in evaluating the evidence on the predictive value of KRAS testing in this context.

KRAS Mutation Testing in Advanced Colorectal Cancer

Both cetuximab and panitumumab are indicated by Health Canada in the treatment of patients with metastatic colorectal cancer whose tumours are WT for the KRAS gene. Cetuximab may be offered as monotherapy in patients intolerant to irinotecan-based chemotherapy or in patients who have failed both irinotecan and oxaliplatin-based regimens and who received a fluoropyrimidine. It can also be administered in combination with irinotecan in patients refractory to other irinotecan-based chemotherapy regimens. Panitumumab is only indicated as a single agent after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

In Ontario, patients with advanced colorectal cancer who are refractory to chemotherapy may be offered the targeted anti-EGFR treatments cetuximab or panitumumab. Eligibility for these treatments is based on the KRAS status of their tumour, derived from tissue collected from surgical or biopsy specimens. It is believed that KRAS status is not affected by treatments, therefore, for patients for whom surgical tissue is available for KRAS testing, additional biopsies prior to treatment with these targeted agents is not necessary. For patients that have not undergone surgery or for whom surgical tissue is not available, a biopsy of either the primary or metastatic site is required to determine their KRAS status. This is possible as status at the metastatic and primary tumour sites is considered to be similar.

Research Question

To determine if there is predictive value of KRAS testing in guiding treatment decisions with anti-EGFR targeted therapies in advanced colorectal cancer patients refractory to chemotherapy.

Research Methods

Literature Search

The Medical Advisory Secretariat followed its standard procedures and on May 18, 2010, searched the following electronic databases: Ovid MEDLINE, EMBASE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and The International Network of Agencies for Health Technology Assessment database.

The subject headings and keywords searched included colorectal cancer, cetuximab, panitumumab, and KRAS testing. The search was further restricted to English-language articles published between January 1, 2009 and May 18, 2010 resulting in 1335 articles for review. Excluded were case reports, comments, editorials, nonsystematic reviews, and letters. Studies published from January 1, 2005 to December 31, 2008 were identified in a health technology assessment conducted by the Agency for Healthcare Research and Quality (AHRQ), published in 2010. In total, 14 observational studies were identified for inclusion in this EBA: 4 for cetuximab monotherapy, 7 for the cetuximab-irinotecan combination therapy, and 3 to be included in the review for panitumumab monotherapy

Inclusion Criteria

- English-language articles, and English or French-language HTAs published from January 2005 to May 2010, inclusive.
- Randomized controlled trials (RCTs) or observational studies, including single arm treatment studies that include KRAS testing.
- Studies with data on main outcomes of interest, overall and progression-free survival.
- Studies of third line treatment with cetuximab or panitumumab in patients with advanced colorectal cancer refractory to chemotherapy.
- For the cetuximab-irinotecan evaluation, studies in which at least 70% of patients in the study received this combination therapy.

Exclusion Criteria

- Studies whose entire sample was included in subsequent publications which have been included in this EBA.
- Studies in pediatric populations.
- Case reports, comments, editorials, or letters.

Outcomes of Interest

- Overall survival (OS), median
- Progression-free-survival (PFS), median.
- Response rates.
- Adverse event rates.
- Quality of life (QOL).

Summary of Findings of Systematic Review

Cetuximab or Panitumumab Monotherapy

Based on moderate GRADE observational evidence, there is improvement in PFS and OS favouring patients without the KRAS mutation (KRAS wildtype, or KRAS WT) compared to those with the mutation.

Cetuximab-Irinotecan Combination Therapy

There is low GRADE evidence that testing for KRAS may optimize survival benefits in patients without the KRAS mutation (KRAS wildtype, or KRAS WT) compared to those with the mutation.

However, cetuximab-irinotecan combination treatments based on KRAS status discount any effect of cetuximab in possibly reversing resistance to irinotecan in patients with the mutation, as observed effects were lower than for patients without the mutation. Clinical experts have raised concerns about the biological plausibility of this observation and this conclusion would, therefore, be regarded as hypothesis generating.

Economic Analysis

Cost-effectiveness and budget impact analyses were conducted incorporating estimates of effectiveness from this systematic review. Evaluation of relative cost-effectiveness, based on a decision-analytic cost-utility analysis, assessed testing for KRAS genetic mutations versus no testing in the context of treatment

with cetuximab monotherapy, panitumumab monotherapy, cetuximab in combination with irinotecan, and best supportive care.

Of importance to note is that the cost-effectiveness analysis focused on the impact of testing for KRAS mutations compared to no testing in the context of different treatment options, and does not assess the cost-effectiveness of the drug treatments alone.

Conclusions

KRAS status is predictive of outcomes in cetuximab and panitumumab monotherapy, and in cetuximab-irinotecan combination therapy.

While KRAS testing is cost-effective for all strategies considered, it is not equally cost-effective for all treatment options.

Background

In February 2010, the Medical Advisory Secretariat (MAS) began work on evidence-based reviews of the literature surrounding three pharmacogenomic tests. This project came about when Cancer Care Ontario (CCO) asked MAS to provide evidence-based analyses on the effectiveness and cost-effectiveness of three oncology pharmacogenomic tests currently in use in Ontario.

Evidence-based analyses have been prepared for each of these technologies. These have been completed in conjunction with internal and external stakeholders, including a Provincial Expert Panel on Pharmacogenomics (PEPP). Within the PEPP, subgroup committees were developed for each disease area. For each technology, an economic analysis was also completed by the Toronto Health Economics and Technology Assessment Collaborative (THETA) and is summarized within the reports.

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3. *K-RAS testing in Treatment Decisions for Advanced Colorectal Cancer: an Evidence-Based and Economic Analysis*

Objective of Analysis

The objective of this systematic review is to determine the predictive value of KRAS testing in the treatment of metastatic colorectal cancer (mCRC) with two anti-EGFR agents, cetuximab and panitumumab. Economic analyses are also being conducted to evaluate the cost-effectiveness and budget impact of KRAS testing.

Clinical Need and Target Population

Metastatic colorectal cancer (mCRC) is usually defined as stage IV disease according to the American Joint Committee on Cancer tumour node metastasis (TNM) system or stage D in the Duke's classification system. (1) Patients with advanced colorectal cancer (mCRC) either present with metastatic disease or develop it through disease recurrence.

KRAS (Kristen-RAS, a member of the rat sarcoma virus (ras) gene family of oncogenes) is frequently mutated in epithelial cancers such as colorectal cancer, with mutations occurring in mutational hotspots (codons 12 and 13) of the KRAS protein. (2) Involved in EGFR-mediated signalling of cellular

processes such as cell proliferation, resistance to apoptosis, enhanced cell motility and neoangiogenesis, a mutation in the KRAS gene is believed to be involved in cancer pathogenesis. Such a mutation is also hypothesized to be involved in resistance to targeted anti-EGFR (epidermal growth factor receptor with tyrosine kinase activity) treatments such as cetuximab and panitumumab, hence, the important in evaluating the evidence on the predictive value of KRAS testing in this context.

Ontario Context

Both cetuximab and panitumumab are indicated by Health Canada in the treatment of patients with metastatic colorectal cancer whose tumours are wildtype (WT) for the KRAS gene. A tumour that is WT means that a KRAS mutation has not been identified through mutation testing as described in the next section.

Cetuximab may be offered as monotherapy in patients intolerant to irinotecan-based chemotherapy or in patients who have failed both irinotecan and oxaliplatin-based regimens and who received a fluoropyrimidine. It can also be administered in combination with irinotecan in patients refractory to other irinotecan-based chemotherapy regimens. Panitumumab is only indicated as a single agent after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

In Ontario, patients with advanced colorectal cancer who are refractory to chemotherapy may be offered the targeted anti-EGFR treatments cetuximab or panitumumab. Eligibility for these treatments is based on the KRAS status of their tumour, derived from tissue collected from surgical or biopsy specimens. It is believed that KRAS status is not affected by treatments, therefore, for patients for whom surgical tissue is available for KRAS testing, additional biopsies prior to treatment with these targeted agents is not necessary. For patients that have not undergone surgery or for whom surgical tissue is not available, a biopsy of either the primary or metastatic site is required to determine their KRAS status. This is possible as status at the metastatic and primary tumour sites is considered to be similar. (3)

The Ontario prevalence of KRAS mutations in advanced colorectal cancer patients in Ontario, based on 1000 samples, is 43%. The remaining 57% have a non-mutated KRAS gene, or are KRAS wild-type (KRAS WT).

KRAS Mutation Testing

KRAS testing is presently being conducted by many laboratories in Ontario. Laboratories require a licence for KRAS testing which they obtain from the Ministry of Health and Long-Term Care. KRAS testing costs vary depending on methods used (Expert consultation, April 2010) and are currently funded by Amgen and Bristol Myers Squibb, manufacturers of cetuximab and panitumumab, respectively.

The laboratory procedures for testing are based on polymerase chain reaction (PCR) methods. These include direct sequencing (DR), RFLP, allele-specific probes, high resolution melting analysis confirmed by DR, amplification refractory mutation system (ARMS), and pyrosequencing. Advantages and disadvantages of these tests include turnaround time (from days to weeks) and sensitivity (ranging from 1% to 25%). A sensitivity of 1%, which is the better measure compared to 25% sensitivity, means that mutations can be detected in the presence of only 1% affected cells. Details of these laboratory procedures can be found in a thorough review by Soulieres et al. (4)

The TheraScreen KRAS mutation kit, a commercial kit from DxS, Manchester, UK, is also available in Canada though distribution by Roche Diagnostics. A combination of ARMS and real-time PCR technology, it can detect KRAS mutations in codons 12 and 13 with a sensitivity of 1 to 5 %. Approved by Health Canada in 2009, it is licenced as a Class 3 device (Licence number 79697).

Evidence-Based Analysis

Research Question

To determine if there is predictive value of KRAS testing in guiding treatment decisions with anti-EGFR targeted therapies in advanced colorectal cancer.

Research Methods

Literature Search Strategy

The Medical Advisory Secretariat followed its standard procedures and on May 18, 2010, searched the following electronic databases: Ovid MEDLINE, EMBASE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and The International Network of Agencies for Health Technology Assessment database.

The subject headings and keywords searched included colorectal cancer, cetuximab, panitumumab, and KRAS testing. The search was further restricted to English-language articles published between January 1, 2009 and May 18, 2010 resulting in 1335 articles for review. Excluded were case reports, comments, editorials, nonsystematic reviews, and letters. The detailed search strategy can be viewed in Appendix 1.

Studies published from January 1, 2005 to December 31, 2008 were identified in a health technology assessment published by the Agency for Healthcare Research and Quality (AHRQ) in 2010. (2)

In total, 14 observational studies were identified for inclusion in this EBA: 4 for cetuximab monotherapy, 7 for the cetuximab-irinotecan combination therapy, and 3 to be included in the review for panitumumab monotherapy.

Inclusion Criteria

- English-language articles, and English or French-language HTAs published from January 2005 to May 2010, inclusive.
- Randomized controlled trials (RCTs) or observational studies, including single arm treatment studies that include KRAS testing.
- Studies with data on main outcomes of interest, overall and progression-free survival.
- Studies of third line treatment with cetuximab or panitumumab in patients with advanced colorectal cancer refractory to chemotherapy.
- For the cetuximab-irinotecan evaluation, studies in which at least 70% of patients in the study received this combination therapy.

Exclusion Criteria

- Studies whose entire sample was included in subsequent publications which have been included in this EBA.
- Studies in pediatric populations.
- Case reports, comments, editorials, or letters.

Intervention

- KRAS mutation testing.

Outcomes of Interest

- Overall survival (OS), median
- Progression-free-survival (PFS), median.
- Response rates.
- Adverse event rates.
- Quality of life (QOL).

Statistical Analysis

Data for median overall and progression-free-survival between KRAS mutated and wildtype patients treated with cetuximab or panitumumab monotherapy, or the cetuximab-irinotecan combination therapy are presented as reported in the existing literature. Pooling of studies was only possible when 95% confidence intervals of the median survival were available, for conversion of medians to mean survival times by the method of Hozo et al. (5) Pooling of studies was based on the random effects model comparing mean survival times in months between KRAS mutated and wildtype patients. Pooling was conducted in Review Manager 5.

Results of Literature Review and Evidence-Based Analysis

Two recent health technology assessments, one by the Agency for Healthcare Research and Quality (AHRQ) and the other by Blue Cross Blue Shield (6), were identified in the literature from 2005 to 2010. The HTA by AHRQ, published in 2010 (2), was used as a source of studies from 2005 to 2008. A literature search for studies from January 1 2009 to May 18 2010 gave rise to a total of 1335 references, although no further studies were identified for inclusion in this MAS EBA.

Table 1: Summary and Focus of Previous Health Technology Assessments on KRAS Testing

Year	Author	Focus of Assessment
2010	Agency for Healthcare Research and Quality (AHRQ)(2)	To evaluate whether KRAS testing predicts response to cetuximab or panitumumab therapy.
2009	Blue Cross Blue Shield (6)	To evaluate and summarize the evidence of using KRAS mutation status as a predictor of non-response to EGFR targeted therapy with cetuximab and panitumumab in patients with metastatic colorectal cancer.

EGFR epithelial growth factor receptor;

The AHRQ review (2) found that a substantial body of evidence consisting of small retrospective analyses and analyses based on RCTs suggests that the presence of a KRAS mutation predicts differential response to anti-EGFR therapy in colorectal cancer patients. The review by Blue Cross Blue Shield (6) concluded similarly that there is sufficient evidence of the clinical validity of KRAS mutation testing and its clinical utility in guiding anti-EGFR therapy selection in patients with metastatic colorectal cancer.

Medical Advisory Secretariat Review

The Medical Advisory Secretariat review includes 14 retrospective analyses by KRAS status within 2 previously conducted anti-EGFR therapy RCTs and 12 single arm treatment studies. In total, 4 studies were included in the cetuximab review, and 3 studies in the panitumumab monotherapy review. These numbers are similar to those identified in the AHRQ review. For the cetuximab-irinotecan combination therapy, 7 studies in which at least 70% of the study sample received irinotecan were included. Excluded from the combination therapy review were also studies whose entire sample was subsequently published in an article included in this review. A thorough clinical review of all studies was also conducted to ensure similarities in treatment regimens, outcomes and timing of measurements, and patient characteristics. Details of patient and study characteristics for studies included in this MAS review are available in Appendix 2.

Table 2: Quality of Evidence of Included Studies (7)

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	
Large RCT unpublished but reported to an international scientific meeting	1(g)	
Small RCT	2	
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3a	2 + 12
Non-RCT with historical controls	3b	
Non-RCT presented at international conference	3(g)	
Surveillance (database or register)	4a	
Case series (multisite)	4b	
Case series (single site)	4c	
Retrospective review, modelling	4d	
Case series presented at international conference	4(g)	
	Total	

RCT refers to randomized controlled trial;

Cetuximab Monotherapy

Four observational studies were included in the review of KRAS testing in the context of treatment with cetuximab as a monotherapy. The study by Karapetis et al. (8) is a retrospective analysis (stratified by KRAS status) of the CO.17 RCT by Jonker et al. (9) which compared the effectiveness of cetuximab and best-supportive care (BSC) compared to BSC in the treatment of patients with advanced colorectal cancer refractory to chemotherapy. The original CO.17 trial included 572 patients and did not allow cross-over from the BSC arm to the treatment arm, whereas the Karapetis data included 394 patients (or 68.8% of the Jonker et al. sample) for whom KRAS status was available. Nevertheless, data are presented within the context of the original CO.17 trial arms of cetuximab and best-supportive care (BSC) or BSC, further stratified by KRAS status. This feature of the Karapetis data allows for the testing of an interaction between KRAS and the treatment options in relation to the outcomes of interest, OS and PFS. Considered an observational study as randomization was not based on KRAS status, this retrospective analysis of a prospective study, which allows for testing of the interaction mentioned, is considered higher quality evidence than the remaining observational studies which are single arm studies (with no comparison). For this reason, The GRADE evaluation which is seen in the section on ‘Quality of Evidence’, is based on

this higher quality evidence and not on the single arm studies.

Furthermore, the Karapetis data is presented first in this section in that it is the only study with a comparison group (BSC) thus allowing for an examination of the presence of a prognostic and/or predictive effect of KRAS status. With respect to the prognostic value of KRAS status, there was no evidence of a prognostic effect as survival times were similar in the BSC arm for OS (4.6 and 4.8 months) and PFS (1.8 and 1.9 months) for KRAS mutated and WT patients, respectively. Therefore, all assessments in this EBA are based on the predictive value and not the prognostic value of KRAS status.

With respect to the treatment-KRAS interaction effect, Karapetis et al. showed a significant KRAS-treatment interaction ($p < 0.05$) for both OS and PFS. This significant interaction indicates that the effect of cetuximab differs by KRAS status, with improved OS and PFS favouring the KRAS WT compared to the mutated patients treated with cetuximab.

In an effort to include all relevant studies in this systematic review, the treatment arm of the Karapetis study is presented in Tables 3 and 4 in addition to the remaining 3 observational (single arm) treatment studies. As seen in Table 3, the median PFS is approximately 2.0 months and 4.0 months for the KRAS mutated and WT patients, respectively. Hazard ratios (HR) and/or p-values of comparisons of median survival between the two groups, KRAS mutated and WT, are also reported where available. Hazard ratios and p-values presented indicate a better PFS for patients without the mutation (WT) compared to those with the mutation. Similarly, the median OS was in favour of the KRAS WT patients, with an approximate median survival of 5.5 months and 8.0 months for the KRAS mutated and WT patients, respectively. Hazard ratios (HR) and/or p-values of comparisons of median OS between the two groups were also in favour of KRAS WT patients. (Table 4)

Table 3: Median Progression-Free-Survival by KRAS Status in Advance Colorectal Cancer Patients Treated with Cetuximab

Study (N patients)	Median PFS in mos. (95%CI)			HR (95% CI), p-value
	N KRAS tests, % mutated	KRAS Mutated	KRAS WT	
Karapetis et al. 2008 (287) (8)	198 42.3%	1.8	3.7	NR, NR
Lurje et al. 2008 (346) (10)	130 32.3%	1.3	1.4	RR=1.49 (1.01- 2.20), p=0.02
Cappuzzo et al. 2008 (85) (11)	80 52.5%	4.4	5.4	NR, p=0.02
Khambata-Ford et al. 2007 (110) (12)	80 37.5%	1.97	2.03	1.4 (0.87-2.6), p= 0.14

NR: not reported.

Table 4: Median Overall Survival by KRAS Status in Advance Colorectal Cancer Patients Treated with Cetuximab

Study (N patients)	Median OS in mos. (95%CI)			HR (95% CI), p-value
	N KRAS tests, % mutated	KRAS Mutated	KRAS WT	
Karapetis et al. 2008 (287) (8)	198 42.3%	4.5	9.5	NR, NR
Lurje et al. 2008 (346) (10)	130 32.2%	4.9	6.6	RR=1.59 (1.05-2.40), p=0.02
Cappuzzo et al. 2008 (85) (11)	80 52.5%	9.5	10.8	NR, p=0.3
Khambata-Ford et al. 2007 (110) (12)	80 37.5%	NR	NR	NR, NR

NR: not reported.

Cetuximab-Irinotecan Combination Therapy

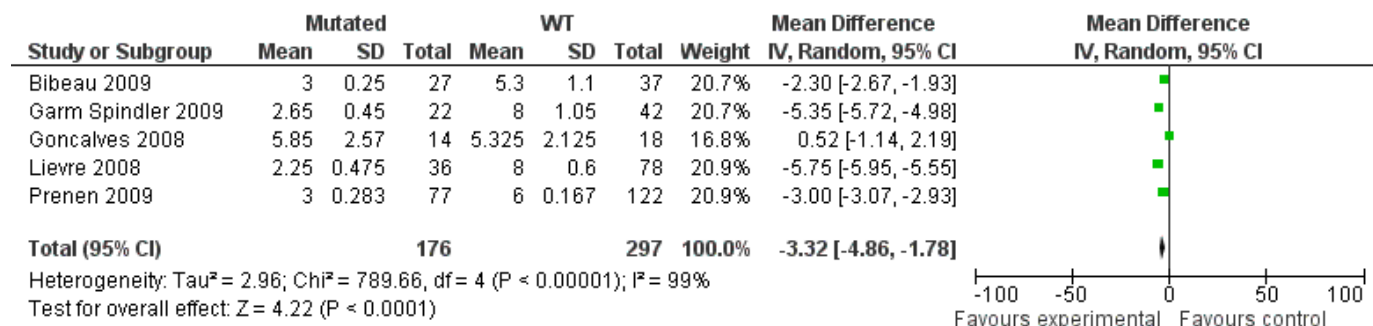
In assessing the predictive value of KRAS testing in the context of patients treated with the cetuximab-irinotecan combination therapy, the PFS was approximately 3.0 and 6.0 months for the mutated compared to the WT patients. (Table 5) In pooling 5 of 7 studies for whom relevant data was available, a mean difference of 3.32 months (95%CI: 1.78-4.86) was significantly in favour of the KRAS WT patients ($p < 0.00001$). (Figure 1) However, the test for heterogeneity was significant ($p < 0.00001$, $I^2 = 99\%$) which suggests important heterogeneity in the data, in spite of considerable efforts to minimize the clinical heterogeneity in the data. Efforts to minimize clinical heterogeneity included a review of all studies with an expert in colorectal cancer treatment for similarities in treatment regimens, including dosages, patient characteristics with respect to stage of disease and previous treatments to ensure that studies were assessing effects of third line therapies. Studies were also reviewed with an expert in laboratory medicine with specific expertise in genetic testing to ensure that laboratory methods used in testing for KRAS and the prevalence of mutations were compatible across studies, and not likely to contribute to analytic and clinical heterogeneity.

Table 5: Median Progression-Free-Survival by KRAS Status in Advance Colorectal Cancer Patients Treated with Cetuximab-Irinotecan Combination Therapy

Study (N patients)	Median PFS in mos. (95%CI)			
	N KRAS tests, % mutated	KRAS Mutated	KRAS WT	HR (95% CI), p-value
Bibeau et al. 2009 (69) (13)	64 42.2%	3	5.3	1.8 (1.1-3.1), p=0.024
Oden-Gangloff et al. 2009 (64) (14)	64 28%	3	5	NR, p=0.034
Garm Spindler et al. 2009 (71) (15)	64 34%	2.3	8.0	NR, p=<0.009
Goncalves et al., 2008 (32) (16)	32 43.8%	4.7	3.9	NR, p=0.97
Prenen et al., 2009 (200) (17)	199 38.7%	3	6	0.56 (0.41-0.77), mutant referent, p= <0.0001
Loupakis et al. 2009 (102) (18)	88/96 primary, 48/59 mets 40% (n=88)	3.1	4.2	2.2 (1.4-3.7), p=0.003
Lievre et al. 2008 (234) (19)	114 27% (n=89)	2.25	8	3.3 (2.0-5.4), p=0.0001

NR: not reported.

Figure 1: Pooling of Studies for Cetuximab-Irinotecan Combination Therapy: Mean Progression-Free-Survival



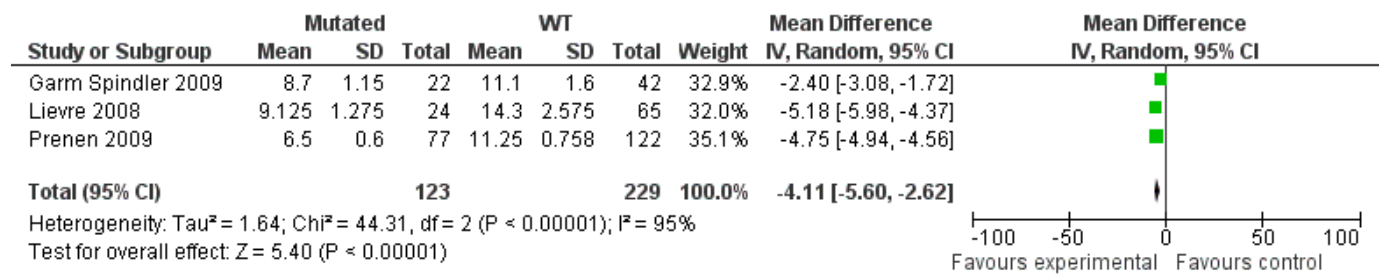
The median OS was also highest for patients without the mutation (approximately 14 months) compared to those with the mutation (8 months) (Table 6) with a pooled mean difference of 4.11 months (95%CI: 2.62-5.60) in favour of the WT patients. Similar to the pooled estimates of the PFS data, there was significant heterogeneity in the pooling of the OS data ($p < 0.00001$, $I^2 = 95\%$, Figure 2).

Table 6: Median Overall Survival by KRAS Status in Advance Colorectal Cancer Patients Treated with Cetuximab-Irinotecan Combination Therapy

Study (N patients)	Median OS in mos. (95%CI)			
	N KRAS tests, % mutated	KRAS Mutated	KRAS WT	HR (95% CI), p-value
Bibeau et al. 2009 (69) (13)	64 42.2%	8.7	10.8	1.6 (0.8-2.9), p=0.147
Oden-Gangloff et al. 2009 (64) (14)	64 28%	NR	NR	NR, NR
Garm Spindler et al. 2009 (71) (15)	64 34%	8.7	11.1	NR, p=0.46
Goncalves et al. 2008 (32) (16)	32 43.8%	13.8	20.8	NR, p=0.47
Prenen et al. 2009 (200) (17)	199 38.7%	6.5	11.25	0.50 (0.37-0.69), mutant referent p=<0.0001
Loupakis et al. 2009 (102) (18)	88/96 primary 48/59 mets 40% (n=88)	6.1	13.5	2.2 (1.5-4.5), p=0.0004
Lievre et al. 2008 (234) (19)	114 27% (n=89)	10.1	14.3	2.4 (1.4-4.1), p=0.0001

NR: not reported.

Figure 2: Pooling of Studies for Cetuximab-Irinotecan Combination Therapy: Mean Overall Survival



Panitumumab Monotherapy

Similar to the analysis of Karapetis et al. for cetuximab monotherapy, Amado et al. published in 2008 (20) a retrospective analysis (stratified by KRAS status) of a previously conducted RCT of panitumumab compared to BSC by Van Cutsem et al. (21) Similar to the cetuximab monotherapy assessment of quality of data, the GRADE evaluation as presented in the 'Quality of Evidence' section is based on this study mainly and not on the single arm studies which are considered lower quality observational data.

In the Amado study, 427 of the 463 patients in the Van Cutsem trial with known KRAS status were included. Testing of the KRAS-treatment interaction term was significant, although not for the outcome of OS. These results suggest a benefit with respect to PFS for KRAS WT patients in being treated with panitumumab. The lack of a significant effect for OS, however it likely attributable to the fact that cross-over was allowed in this RCT, with approximately 76% of the BSC patients receiving treatment.

When the treatment arm of the Amado et al. study was included with the remaining single arm studies of patients treated with panitumumab, overall survival (Table 8) and PFS (Table 7) were both improved for patients without the mutation. The survival times were similar to that of cetuximab monotherapy, and lower for both outcomes than that observed for the cetuximab-irinotecan combination therapy. This observation of increased survival in the cetuximab-irinotecan combination therapy for patients with and without the KRAS mutation lead to a further examination of response rates to determine if any additional effects could be observed.

Whereas the response rates (partial response) were approximately 1% for the mutated and 10-15% for the WT groups for both cetuximab and panitumumab monotherapies, the stable disease rates were similar for both the mutated and non-mutated patients treated with the cetuximab-irinotecan combination. The response rates for the cetuximab-irinotecan combination studies presented in Table 10, however, are suggestive of similar partial response rates to the monotherapies, although stable disease rates are approximately 45% and appear to be higher in the mutated patients (range 37-64%) than in the WT patients (range 26.2%-51.6%). This is in contrast to the stable disease rates for the monotherapies that are between 8% and 53%, although much higher for the WT than the mutated patients.

There was much discussion of the interpretation of these response rate data for the cetuximab-irinotecan combination which are suggestive of a role of cetuximab in the reversal of resistance to irinotecan as all treated patients had previously received irinotecan. This possible reversal of resistance was also mentioned by Cunningham et al. (22) Clinical experts, however, indicate that it is unclear how irinotecan resistance is defined in these patients, which could include failure of treatment or toxicity at different time points prior to initiation of the cetuximab-irinotecan combination therapy. In addition, it was suggested that since these studies were conducted prior to the availability of oxaliplatin as a further treatment option, the increased OS and PFS compared to the monotherapies may be due to the expected survival advantage for patients at an earlier stage in their treatment process.

Table 7: Median Progression-Free-Survival by KRAS Status in Advance Colorectal Cancer Patients Treated with Panitumumab

Study (N patients)	Median PFS in mos. (95% CI)			
	N KRAS tests, % mutated	KRAS Mutated	KRAS WT	HR (95% CI), p-value
Amado et al. 2008 (231) (20)	208 43%	1.85	3.08	NR, NR
Freeman et al. 2008 (533) (23)	62 38.7%	1.85	4.05	2.50 (1.43-5.00), p=<0.002
Muro et al. 2009 (60) (24)	24 42%	1.83	3.30	NR, NR

NR: not reported.

Table 8: Median Overall Survival by KRAS Status in Advance Colorectal Cancer Patients Treated with Panitumumab

Study (N patients)	Median OS in mos. (95% CI)			
	KRAS tests, % mutated	KRAS Mutated	KRAS WT	HR (95% CI), p-value
Amado et al. 2008 (231) (20)	208 43%	4.9	8.1	NR, NR
Freeman et al. 2008 (533) (23)	62 38.7%	5.55	10.73	2.00 (1.11-3.33), p=<0.015
Muro et al. 2009 (60) (24)	24 42%	NR	NR	NR, NR

NR: not reported.

Table 9: Response Rates for Cetuximab-Irinotecan Combination Therapy by KRAS Status

Study	N tests Response	KRAS Mutated	KRAS WT
Bibeau et al. (13)	N PR SD PD	27 4% 37% 59%	37 27% 41% 32%
Oden-Gangloff et al. (14)	N CR + PR SD PD	18 0% 38.9% 61.1%	46 34.8% 34.8% 30.4%
Garm Spindler et al. (15)	N PR SD PD	22 0% 54.5% 45.5%	42 40% 26.2% 33.3%
Goncalves et al. (16)	N PR SD PD	14 14.3% NR NR	18 38.9% NR NR
Prenen et al. (17)	N CR + PR SD PD	77 0% + 1.3% 63.6% 57.4%	122 0.8% + 29.5% 51.6% 18.0%
Loupakis et al. (18)	Primary (N) Response Non-response Mets (N) Response Non-response	53 6% 94% 27 10% 90%	35 25% 75% 21 41% 59%
Lievre et al. (19)	N CR + PR SD PD	36 0% + 0% 38.9% 61.1%	78 2.6% + 41.0% 33.3% 23.1%

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NR: not reported..

Adverse Events and Quality of Life

Adverse events data was reported in both Karapetis et al. (8) and Amado et al. (20) Karapetis et al reported rash during or within 30 days of cetuximab treatment at a rate of 94.9% in WT patients compared to 84.0% in those with the KRAS mutation (p=0.02). Although rates are high in both groups, quality of life (QOL) data from this study (Table XX) suggests that KRAS WT patients confer an improvement in their measures in spite of adverse events whereas patients with the mutation experience deterioration in their QOL. Global health status (including role function, fatigue, nausea, pain, sleep, financial impact, social function, appetite and constipation) derived from the European Organization for Research and Treatment of Cancer (EORTC) questionnaire (QLQ-C30) was significantly better for patients treated with cetuximab + BSC compared to BSC at 8 weeks (mean change in score of 3.2 versus -7.7, p<0.05) and 16 weeks (mean change in score of -0.2 versus -18.1, p<0.05) from baseline among KRAS WT patients only. Among patients with the mutation, the deterioration in QOL was not significantly different between the treated and BSC patients at 8 weeks (mean change in score of -4.7 versus -9.6, p>0.05) and at 16 weeks (mean change in score of -9.5 versus -13.9, p>0.05). It is thought

that the benefit that drives the utility in WT patients is likely attributable to a treatment response that mutated patients do not experience (Expert opinion, August 2010).

Table 10: Quality of Life Measures by KRAS Status

QOL Measure in Global Health Status	KRAS Mutated (n=81)	KRAS WT (n=117)
Mean change in score at 8 wks		
Cetuximab	-4.7	3.2
BSC	-9.6	-7.7
Mean change in score at 16 wks		
Cetuximab	-9.5	-0.2
BSC	-13.9	-18.1

QOL: quality of life; BSC: best supportive care.

Adverse events data was also reported by Amado et al. (Table 11) for treatment with panitumumab. Mutated patients received on average 5 infusions and WT patients received a mean of 10 infusions. The grade 3 or 4 adverse event rate (which includes multiple events per patient) was 28% and 44% for mutated and WT patients, respectively. These rates include grade 3 treatment- and integument-related events and grade 3 diarrhea. In addition, there was a 3% rate of hypomagnesemia (any grade) among WT and 1% of grade 2 infusion reactions in the KRAS mutated patients.

Table 11: Adverse Events (Amado et al. 2008)

Adverse Event Rates	KRAS Mutated (5 infusions)	KRAS WT (10 infusions)
Grade 3 or 4	28%	44%
Grade 3 treatment related	12%	25%
Grade 3 integument-related	13%	25%
Grade 4 integument-related	1%	0%
Diarrhea any grade	19%	24%
Grade 3 diarrhea	1%	2%
Hypomagnesemia any grade	0%	3%
Grade 2 infusion reaction	1%	0%

Quality of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (25) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Table 12: GRADE Quality of Evidence for the Predictive Value of KRAS Mutation Testing for Treatment with Cetuximab Monotherapy

Outcome	Explanation	GRADE
Design	4 observational studies, 1 as subgroup analyses of prior drug RCT.	Moderate
Quality	Subgroup analysis within RCT is well conducted, within original arms of RCT.	Moderate
Consistency	Consistent for PFS, OS, and response rates.	Moderate
Directness	Treatments and outcomes of interest were specific to the objectives of this EBA.	Moderate
Quality of evidence		Moderate

Table 13: Factors Affecting GRADE Quality of Evidence for Cetuximab Monotherapy

Factor	Explanation	Effect on GRADE
Risk of Bias		
Study design	Observational studies with one retrospective analysis of KRAS status within context of arms of an RCT.	Moderate
Limitations	One retrospective analysis of RCT-based drug trial. Retrospective single arm studies with no comparison group.	Unchanged
Indirectness		
Outcomes	Main outcomes were overall survival and progression-free-survival. Studies included these outcomes directly.	Unchanged
Patient populations, diagnostic test, comparison test, and indirect comparisons	Study population was advanced colorectal cancer with similar patient characteristics and treatment regimens.	Unchanged
Important inconsistency in study results	No inconsistency.	Unchanged
Imprecise evidence	Survival (PFS and OS) were sufficiently precise.	Unchanged
Publication bias	No known publication bias	Unchanged
Quality of evidence		Moderate

Table 14: GRADE Quality of Evidence for the Predictive Value of KRAS Mutation Testing for Treatment with Cetuximab-Irinotecan Combination Therapy

Outcome	Explanation	GRADE
Design	7 observational single arm treatment studies.	Moderate
Quality	No comparison group.	Moderate → Low
Consistency	Consistent for PFS, OS, and response rates.	Low
Directness	Treatments and outcomes of interest were specific to the objectives of this EBA.	Low
Quality of evidence		Low

Table 15: Factors Affecting GRADE Quality of Evidence for Treatment with Cetuximab-Irinotecan Combination Therapy

Factor	Explanation	Effect on GRADE
Risk of Bias		
Study design	Observational studies.	Moderate
Limitations	Retrospective single arm studies with no comparison group.	Moderate → Low
Indirectness		
Outcomes	Main outcomes were overall survival and progression-free-survival. Studies included these outcomes directly.	Unchanged
Patient populations, diagnostic test, comparison test, and indirect comparisons	Study population was advanced colorectal cancer with similar patient characteristics and treatment regimens.	Unchanged
Important inconsistency in study results	No inconsistency.	Unchanged
Imprecise evidence	Survival (PFS and OS) were sufficiently precise.	Unchanged
Publication bias	No known publication bias	Unchanged
Quality of evidence		Low

Table 16: GRADE Quality of Evidence for the Predictive Value of KRAS Mutation Testing for Panitumumab Monotherapy

Outcome	Explanation	GRADE
Design	3 observational studies, 1 as subgroup analyses of prior drug RCT.	Moderate
Quality	Subgroup analysis within RCT is well conducted, within original arms of RCT.	Moderate
Consistency	Consistent for PFS, OS, and response rates.	Moderate
Directness	Treatments and outcomes of interest were specific to the objectives of this EBA.	Moderate
Quality of evidence		Moderate

Table 17: Factors Affecting GRADE Quality of Evidence for Panitumumab Monotherapy

Factor	Explanation	Effect on GRADE
Risk of Bias		
Study design	Observational studies. One retrospective analysis of RCT-based drug trial.	Moderate
Limitations	One retrospective analysis of RCT-based drug trial. Retrospective single arm studies with no comparison group.	Unchanged
Indirectness		
Outcomes	Main outcomes were overall survival and progression-free-survival. Studies included these outcomes directly.	Unchanged
Patient populations, diagnostic test, comparison test, and indirect comparisons	Study population was advanced colorectal cancer with similar patient characteristics and treatment regimens.	Unchanged
Important inconsistency in study results	No inconsistency.	Unchanged
Imprecise evidence	Survival (PFS and OS) were sufficiently precise.	Unchanged
Publication bias	No known publication bias	Unchanged
Quality of evidence		Moderate

Summary of Findings

Cetuximab or Panitumumab Monotherapy

Based on moderate GRADE observational evidence, there is improvement in PFS and OS favouring patients without the KRAS mutation (KRAS wildtype, or KRAS WT) compared to those with the mutation.

Cetuximab-Irinotecan Combination Therapy

There is low GRADE evidence that testing for KRAS may optimize survival benefits in patients without the KRAS mutation (KRAS wildtype, or KRAS WT) compared to those with the mutation.

However, cetuximab-irinotecan combination treatments based on KRAS status discount any effect of cetuximab in possibly reversing resistance to irinotecan in patients with the mutation, as observed effects were lower than for patients without the mutation. Clinical experts have raised concerns about the biological plausibility of this observation and this conclusion would, therefore, be regarded as hypothesis generating.

Existing Guidelines for KRAS Testing in Anti-EGFR Targeted Therapy

Clinical guidelines from Cancer Care Ontario (CCO) published in 2008 (26) and the American Society of Clinical Oncology (ASCO) published in 2009 (27) were identified for this review.

The CCO review reviewed studies to 2008 and conclude, with respect to treatment with cetuximab or panitumumab by KRAS status that there is good evidence that both cetuximab and panitumumab improve PFS and objective response rate compared to BSC alone in chemotherapy refractory patients. This benefit is most pronounced in patients with K-RAS wild-type tumours.

The ASCO provisional clinical opinion, based on a systematic review of the relevant literature, concludes that all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR monoclonal antibody therapy should have their tumour tested for KRAS mutations in a CLIA-accredited laboratory. If KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR monoclonal antibody therapy as part of their treatment.

Economic Analysis

DISCLAIMER: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents *an estimate only*, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Study Question

The objective of the current economic analysis was to determine the cost effectiveness of k-RAS oncogene (KRAS) testing for the third-line treatment of (stage IV) metastatic colorectal cancer (mCRC) in Ontario. Third-line treatments used in this analysis consisted of the following drug regimens: cetuximab and panitumumab monoclonal anti-body (MoAb) anti-EGFR monotherapies, and cetuximab used in combination with irinotecan chemotherapy. Note that the comparative cost-effectiveness analysis focuses on the benefit of KRAS genetic testing – comparison was made between strategies showing the benefit of KRAS testing and not necessarily the benefit of drug treatments alone.

Economic Analysis Overview

A decision-analytic cost-utility analysis (CUA) was conducted to evaluate the relative cost-effectiveness of testing for KRAS genetic mutations with subsequent treatment by four options: cetuximab monotherapy, panitumumab monotherapy, cetuximab in combination with irinotecan, and best supportive care (BSC). Best supportive care was defined identically as Jonker et al. 2007 as being: "... those measures designed to provide palliation of symptoms and improve quality of life as much as

possible". (9) As the definition of BSC was synonymous with that defined by Jonker et al. 2007, cost parameters used for BSC as taken from Mittmann et al. 2009 were consistent in terms of the definition of patient population. (28)

The physician and hospital costs for the non-invasive imaging tests were taken from 2009 Ontario Health Insurance Plan (OHIP) and the Ontario Case Costing Initiative (OCCI) administrative databases. (29;30) Costs of drug treatments were taken from publicly listed prices provided by the New Drug Funding Program (NDFP) as administered by Cancer Care Ontario (CCO); values provided were based on consultations with experts.

A budget impact analysis (BIA) was performed assessing the effect of replacing a certain proportion of patients (cases) with the drug regimen of interest; either cetuximab, panitumumab, or cetuximab in combination with irinotecan. The costs and volume of patients presented in this BIA were estimated from expert consultation and CCO data sources from 2009.

Economic Literature Review

A literature search was performed on May 20th, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, and EconLit. The range of dates used for the systematic search was: 1996 to Week 2 2010 for MEDLINE, and 1980 to Week 19 2010 for EMBASE. Included studies were those with full economic evaluations describing both costs and consequences of KRAS genetic testing for (stage IV) mCRC patients.

According to the systematic review performed, there were no health economic evaluations found comparing the relative cost-effectiveness of KRAS genetic testing for the population and therapies of interest. However, a CUA was done by Mittmann et al. in 2009 related to the results of the CO-17 trial conducted by Jonker et al. in 2007, which included patients from Ontario. (9;28) Costs and effects (health-related quality-of-life utilities) specific to mCRC third-line patients receiving, separately, cetuximab monotherapy and BSC were taken from Mittmann et al. 2009 and used in the current economic evaluation and decision-analytic model.

Target Population

The target population in this economic evaluation was defined as patients diagnosed with (stage IV) metastatic colorectal cancer (mCRC) from whom cetuximab or panitumumab monotherapies, or cetuximab and irinotecan combination therapy were indicated as third-line treatments. According to Health Canada this indication requires certain restrictions for patients for each treatment option as follows: a) for cetuximab monotherapy, patients must be intolerant to irinotecan, or have failed on both irinotecan- and oxaliplatin-based regimens and have received a fluoropyrimidine (chemotherapy) as previous treatments; b) for panitumumab monotherapy, patients must have failed on fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens; and c) for cetuximab and irinotecan combination therapy, patients must be refractory to other irinotecan-based chemotherapy regimens. (31;32)

In addition to the restrictions listed above for the three treatment options considered in the current evaluation, patients must have tested negative for KRAS mutations (i.e. KRAS wild-type). It is important to note that for comparison purposes, certain strategies consisted of treating patients with KRAS mutations; while the benefit of KRAS genetic testing was the focus of the evaluation, treating mCRC patients with KRAS mutations using the three treatments above is not indicated in Ontario.

Perspective

The analytic perspective was that of the Ontario Ministry of Health and Long-Term Care (MOHLTC).

Comparators

The seven strategies listed in Table 18 were used to evaluate the benefit of KRAS genetic testing for third-line treatment(s) of mCRC:

Table 18: Cost-effectiveness strategies evaluating the benefit of KRAS testing

Number	Label	Description
0	Best supportive care (No KRAS test; No treatment)	All patients were treated with BSC (i.e. no MoAb anti-EGFR therapy or chemotherapy)
1a	Cetuximab (Perform KRAS test)	In addition to BSC treatment, patients with KRAS wild-type received cetuximab monotherapy; patients with KRAS mutations received only BSC
1b	Cetuximab (No KRAS test)	All patients received both BSC and cetuximab monotherapy (i.e. this includes both KRAS wild-type and KRAS mutated patients)
2a	Panitumumab (Perform KRAS test)	In addition to BSC treatment, patients with KRAS wild-type received panitumumab monotherapy; patients with KRAS mutations received only BSC
2b	Panitumumab (No KRAS test)	All patients received both BSC and panitumumab monotherapy (i.e. this includes both KRAS wild-type and KRAS mutated patients)
3a	Cetuximab + Irinotecan (Perform KRAS test)	In addition to BSC treatment, patients with KRAS wild-type received cetuximab and irinotecan combination treatment; patients with KRAS mutations received only BSC
3b	Cetuximab + Irinotecan (No KRAS test)	All patients received both BSC and cetuximab and irinotecan combination treatment (i.e. this includes both KRAS wild-type and KRAS mutated patients)

Time Horizon

The time horizon used in the model was life-time in length (i.e. the model's patient cohort was followed until death).

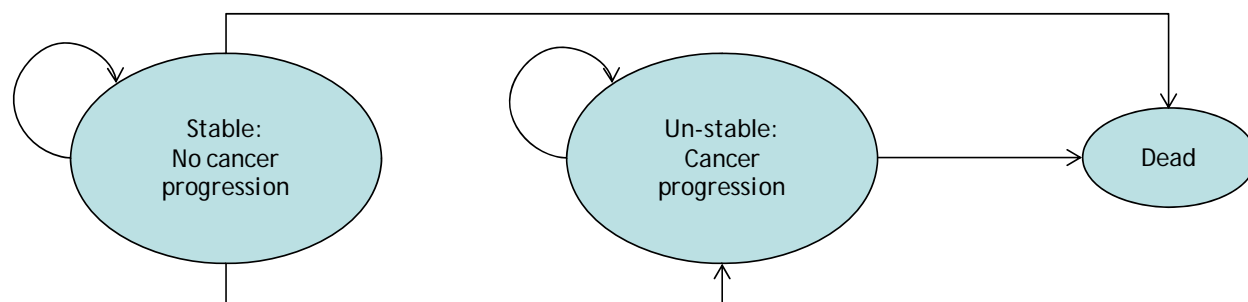
Discounting

All costs and effects (quality-adjusted life years, or QALYs) were discounted at a common rate of 5% per annum.(33)

Model Structure

A schematic of the Markov model is shown in Figure 3. Metastatic CRC Patients receiving third-line treatment with cetuximab, panitumumab or cetuximab and irinotecan combination therapy begin the Markov process in the health state labelled "Stable: No cancer progression". Subsequent state transitions were informed by the median overall survival time (OS) and progression-free survival time (PFS) for transitions to the "Dead" and "Un-stable: Cancer progression" health states, respectively. The model also incorporated adverse events (AEs) specific to each treatment as summarized in the Parameter Estimates section. Note that the cycle length in the Markov model was one month.

Figure 3: KRAS CEA Markov model showing the three health states and possible state transitions



Outcomes

The outcome of interest was the lifetime-aggregated QALYs (per patient) associated with each strategy.

Resource Use and Costs

Costs were reported in 2009 Canadian dollars (CAD) and were taken from literature, 2009 OHIP and OCCI administrative databases. Table 19 summarizes the drug costs used in current the CUA, where an average value of 1.75 m² was used for Body Surface Area (BSA) and an average value of 64.1 kg was used for mass (body weight). The CCO prices listed under the “Reference” column were obtained through consultation with experts and publicly listed NDFP drug prices. Note that the cost per “cycle” refers to the one-month cycle used in the Markov model; actual drug cycles are listed under “Drug dose”. The cost of the KRAS genetic test was taken from expert consultations and estimated as being \$500 (range \$150-\$500).

Table 19: Drug costs (CAD) used in the Markov model for third-line treatment of mCRC

Treatment	Drug dose	Drug cost	Cost per cycle (month)	Reference
Cetuximab	400 mg/m ² initial; 250 mg/m ² weekly	\$2,345; \$1,466	\$2,345; \$5,862	CCO (NDFP price); \$3.35/mg; BSA=1.75m ²
Panitumumab	6 mg/kg every 2 weeks	\$2,308	\$4,615	CCO (NDFP price); \$6/mg; Average mass=64.1kg
Irinotecan	180 mg/m ² every 2 weeks	\$158	\$315	CCO (NDFP price); \$0.50/mg; BSA=1.75m ²

Note: NDFP prices listed are public prices derived from consultations with CCO experts.

Other treatment costs were estimated for patient management and the administration of MoAb and chemotherapy. BSC management costs were estimated from Mittmann 2009: approximately \$61/month, based on an aggregated average of \$1,093 over 18 months per patient. (28) The hospital cost of outpatient administration of MoAb treatment (cetuximab or panitumumab monotherapy) was estimated from FY2008 OCCI data as being \$118. This was derived by subtracting the average drug cost per oncology visit (\$92; (34)) from the average cost reported for oncology outpatient functional centres (\$210; (29)), where patients had: a most responsible diagnosis of chemotherapy (ICD-10-CA code of Z51.1 or Z51.2), and a principal procedure of monoclonal antibody targeted injection (CCI code of 8.NZ.70.HZ-CC).

(35;36) In a similar way, the hospital cost of outpatient administration of a MoAb with chemotherapy (cetuximab with irinotecan) was estimated as being \$329 per patient (i.e. subtraction of \$92 from \$421, reported for ICD-10-CA codes of Z51.1 or Z51.2, together with CCI codes of 1.ZZ.35.HA-M0 to 1.ZZ.35.HA-M9).(35;36) Oncology physician costs were estimated as being \$132.50 per consultation and \$64.05 per additional assessment, related to patient follow up and the treatment of potential adverse events.

The costs for certain AEs were estimated from the literature and hospital administrative databases. The cost of grade 3 or 4 AEs, as defined by criteria published by the National Cancer Institute Common Toxicity Criteria (37), was estimated for the following AEs: rash (\$992.50; (28)), pain (\$27; (28)), non-neutropenic infection (\$2,340; (28)), neutropenia (\$4,645; medical oncology inpatient diagnosis code of D70.0; (36)), hypomagnesemia (\$318; outpatient diagnosis code of E83.4; (36)), and diarrhea (\$357; outpatient dehydration diagnosis code of E86.0 with infusion procedure codes 1.LZ.35.XX-C7, 1.LZ.35.XX-T9 and 1.LZ.35.XX-Z9, where “XX” can be HH, HA or HR; (35)).

Parameter Estimates

The effectiveness of treatments for third-line therapy for mCRC patients was summarized from the literature and shown in Table 20. Adverse events parameters are summarized in Table 21 and show the proportion of patients with the specified AE (grade 3 or 4 as defined by NCI-CTC). Note that the percentages were “normalized” and re-calculated such that the totals sum to 100% for the given list of AEs. Values related to BSC were taken from Jonker et al. 2007 and Karapetis 2008; values for cetuximab-related therapies were taken from Cunningham 2004, Jonker et al. 2007, Karapetis et al. 2008, and Loupakis et al. 2009; and values for panitumumab were taken from Van Cutsem et al. 2008 and Amado et al. 2008.(8;9;20;22;38)

Table 20: Treatment effectiveness parameters used in the Markov model

Treatment	KRAS status	Median PFS (months)	Median OS (months)	Reference
Best supportive care	WT + Mutated	1.8	4.6	(9)
Best supportive care	WT	1.9	4.8	(8)
Best supportive care	Mutated	1.8	4.6	(8)
Cetuximab	WT + Mutated	1.9	6.1	(9)
Cetuximab	WT	3.7	9.5	(8)
Cetuximab	Mutated	1.8	4.5	(8)
Panitumumab	WT + Mutated	2.4	6.3	(39)
Panitumumab	WT	3.1	8.1	(20)
Panitumumab	Mutated	1.8	4.9	(20)
Cetuximab + Irinotecan	WT + Mutated	4.1	8.6	(22)
Cetuximab + Irinotecan	WT	5.1	14.7	(38)
Cetuximab + Irinotecan	Mutated	3.8	9.7	(38)

Note: “WT” denotes KRAS wild-type genetic status and “Mutated” denotes a KRAS genetic mutation.

Quality-of-life utility weights used to calculate patient QALYs were based on literature estimates. A baseline utility value of 0.71 was assigned to all patients and was based on utility values reported for mCRC patients treated by only BSC as third-line therapy. (28) A utility increase of 0.07 associated

cetuximab, panitumumab or cetuximab with irinotecan treatments was applied to patients for all strategies *except* BSC, and was calculated from Mittmann et al. using 4-24 week averaged utility values. (28) In a separate sensitivity analysis, the utility increase for panitumumab was estimated at 0.12 and taken from Siena et al.(40)

Table 21: Selected grade 3 or 4 (NCI-CTC) adverse events and treatment-specific percent occurrences (normalized)

Treatment	Source	Rash	Abdominal Pain	Non-neutro. Infection	Neutropenia	HypoMg	Diarrhea	Total %
Best supportive care	Original % from study	0.4%	15.7%	5.5%				21.6%
	Re-calculated % from selection of AE's	1.9%	72.7%	25.5%				100.0%
Cetuximab	Original % from study	11.8%	13.2%	12.8%		5.2%	2.0%	45.0%
	Re-calculated % from selection of AE's	26.2%	29.3%	28.4%		11.6%	4.4%	100.0%
Panitumumab	Original % from study	8.4%	7.4%				1.0%	
	Re-calculated % from selection of AE's	50.0%	44.1%				5.9%	
Cetuximab + Irinotecan	Original % from study	9.4%	3.3%		9.4%		21.0%	43.2%
	Re-calculated % from selection of AE's	21.9%	7.6%		21.9%		48.6%	100.0%

Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the relative percentage cost-effectiveness of the KRAS testing strategies listed in the Comparators section for different willingness-to-pay (WTP) thresholds. The following is a list of strategies considered in the PSA: 0) Best supportive care (No KRAS test; No treatment); 1a) Cetuximab (Perform KRAS test); 2a) Panitumumab (Perform KRAS test); and 3a) Cetuximab + Irinotecan (Perform KRAS test). The range of parameter values used in the PSA is summarized in Table 22.

Table 22: Effectiveness, cost and utility parameter ranges used in the PSA analysis

Parameter	PFS Range (months)	OS Range (months)	Cost Range (per cycle)	Utility Range
Cetuximab - WT	1.40 - 5.40	6.60 - 10.80	\$2,931 - \$5,862	
Cetuximab - Mutated	1.30 - 4.40	4.50 - 9.50		
Panitumumab - WT	3.08 - 4.50	8.10 - 10.73	\$2,308 - \$4,615	0.07 - 0.12
Panitumumab - Mutated	1.83 - 1.85	4.90 - 5.55		
Cetuximab + Irinotecan - WT	3.90 - 8.00	10.80 - 20.80	\$158 - \$315	
Cetuximab + Irinotecan - Mutated	2.25 - 4.70	6.10 - 13.80		

Note: The cost ranges specified are general drug costs; the range specified for “Cetuximab + Irinotecan” actually refers to the cost of irinotecan only.

Results and Discussion

A summary of the results showing the benefit of KRAS genetic testing is presented in Table 23. All strategies considering KRAS testing for third-line treatment of mCRC disease were found to be cost-effective when compared to the corresponding strategies of no KRAS testing. Specifically, KRAS testing was found to be cost-effective for cetuximab monotherapy (at a WTP threshold of \$54,802); KRAS testing was found to be cost-effective for panitumumab monotherapy (at a WTP threshold of \$47,795); and KRAS testing was found to be cost-effective for cetuximab with irinotecan combination therapy (at a WTP threshold of \$42,701).

When all treatment strategies were considered in the CUA simultaneously (Table 24), performing KRAS testing for cetuximab with irinotecan combination therapy was the preferred cost-effective option (at a WTP threshold of \$42,710). For a WTP threshold of \$50K, this strategy yielded the greatest effect (QALYs) and had the lowest ICER value. If a higher WTP threshold is considered, the strategy of not testing for KRAS genetic mutations is cost-effective at a WTP threshold of \$163,396. This latter result was due to the combination treatment contributing QALYs (having beneficial effect) to both the KRAS wild-type and mutated patient groups. However, further research may be needed to determine the exact benefit of using cetuximab with irinotecan therapy on mCRC patients (both KRAS wild-type and mutated).

Table 23: Cost-effectiveness of KRAS genetic testing - treatment-specific results

Strategy	Cost	Incremental Cost	Effect (QALY)	Incremental Effect	ICER (\$/QALY)
Cost-effectiveness of KRAS testing for cetuximab monotherapy					
0: BSC (No KRAS test; No treatment)	\$1,414		0.7455		
1a: Cetuximab (Perform KRAS test)	\$18,305	\$16,891	1.0537	0.3082	54,802
1b: Cetuximab (No KRAS test)	\$29,399	\$11,094	1.0447	-0.0090	(Dominated)
Cost-effectiveness of KRAS testing for panitumumab monotherapy					
0: BSC (No KRAS test; No treatment)	\$1,414		0.7455		
2a: Panitumumab (Perform KRAS test)	\$12,236	\$10,821	0.9719	0.2264	47,795
2b: Panitumumab (No KRAS test)	\$20,424	\$8,188	0.9985	0.0266	308,236
Cost-effectiveness of KRAS testing for cetuximab with irinotecan combination therapy					
0: BSC (No KRAS test; No treatment)	\$1,414		0.7455		
3a: Cetuximab + Irinotecan (Perform KRAS test)	\$23,373	\$21,959	1.2596	0.5141	42,710
3b: Cetuximab + Irinotecan (No KRAS test)	\$44,798	\$21,425	1.3907	0.1311	163,396

Table 24: Relative cost-effectiveness of KRAS genetic testing for all treatment strategies

Strategy	Cost	Incremental Cost	Effect (QALY)	Incremental Effect	ICER (\$/QALY)
0: BSC (No KRAS test; No treatment)	\$1,414		0.7455		
2a: Panitumumab (Perform KRAS test)	\$12,236	\$10,821	0.9719	0.2264	(Ext.Dom.)
1a: Cetuximab (Perform KRAS test)	\$18,305	\$6,069	1.0537	0.0818	(Ext.Dom.)
2b: Panitumumab (No KRAS test)	\$20,424	\$2,119	0.9985	-0.0552	(Dominated)
3a: Cetuximab + Irinotecan (Perform KRAS test)	\$23,373	\$5,068	1.2596	0.2059	42,710
1b: Cetuximab (No KRAS test)	\$29,399	\$6,026	1.0447	-0.2149	(Dominated)
3b: Cetuximab + Irinotecan (No KRAS test)	\$44,798	\$21,425	1.3907	0.1311	163,396

Note: "Ext. Dom." represents strategies which are ruled out due to extended dominance.

Results of the PSA showed that for all strategies involving KRAS genetic testing, cetuximab with irinotecan combination therapy was the cost-effective option for increasing values of WTP. For lower WTP values, the probability of specific KRAS testing strategies being cost-effective varied. At a WTP of \$50K, the probabilities of cetuximab monotherapy, panitumumab monotherapy and cetuximab with irinotecan combination therapy being cost-effective were approximately 14%, 44% and 42%, respectively. The strategy of not performing the KRAS test and treating patients with BSC alone was not cost-effective (zero probability) for WTP values greater than \$45K.

Budget Impact Analysis

The BIA calculation of the current CUA was based on the number of drug claims reported by the NDFP and through consultations with experts. The number of mCRC patients using panitumumab as third-line therapy in Ontario in FY2009 was 145 according to the NDFP. The corresponding number of cetuximab with irinotecan patients was about 38, however, the number of cetuximab monotherapy patients was unavailable as this treatment option is not funded by the NDFP and is available only out-of-country. It was assumed (expert consultation) that the distribution of treatments for third-line treatment of mCRC was approximately 30% for cetuximab, 20% for panitumumab and 30% for cetuximab with irinotecan combination therapy (and 30% for BSC for a total of 100%). Using these proportions, it was estimated that the number of patients using cetuximab monotherapy in 2009 was 218.

Using the average cost of treatments reported in Tables 23 and 24, the impact of having 50% of patients

on any given therapy was calculated for the BIA. The results are summarized in Table 25, where the “estimated FY2009 costs” were calculated from the current distribution of mCRC patients using third-line therapy (i.e. 30% cetuximab, 20% panitumumab, 30% cetuximab with irinotecan), and the “Re-calculated FY2009” costs were based on the re-calculated patient proportions or number of patients for the impact analysis. The effect of shifting patients, where 50% of mCRC patients would use the indicated third-line therapy in Table 25, was estimated as the simple difference between the estimated costs given the current distribution and the estimated (re-calculated) costs given the new distribution. As a result, estimates of the yearly cost savings (if any) of the different distributions of patients on a given third-line therapy were: a yearly increase of \$0.07M for cetuximab, a yearly decrease of \$1.76M for panitumumab, and a yearly increase of \$1.63M for cetuximab with irinotecan combination therapy.

Table 25: Cost differences between the current distribution of treatments and future 50%-distributions

Strategy	Patients (%)	Re-calculated patients (N)	Estimated FY2009 costs	Re-calculated FY2009 costs	Impact (cost difference)
Assuming 50% of patients are using cetuximab monotherapy					
1a: Cetuximab (Perform KRAS test)	50%	363	\$3.98M	\$6.64M	\$2.65M
2a: Panitumumab (Perform KRAS test)	10%	73	\$1.77M	\$0.89M	-\$0.89M
3a: Cetuximab + Irinotecan (Perform KRAS test)	10%	73	\$3.39M	\$1.69M	-\$1.69M
<i>Total</i>	<i>70%</i>	<i>508</i>	<i>\$9.14M</i>	<i>\$9.22M</i>	<i>\$0.07M</i>
Assuming 50% of patients are using panitumumab monotherapy					
1a: Cetuximab (Perform KRAS test)	12%	87	\$3.98M	\$1.59M	-\$2.39M
2a: Panitumumab (Perform KRAS test)	50%	363	\$1.77M	\$4.44M	-\$2.66M
3a: Cetuximab + Irinotecan (Perform KRAS test)	8%	58	\$3.39M	\$1.38M	-\$2.03M
<i>Total</i>	<i>70%</i>	<i>508</i>	<i>\$9.14M</i>	<i>\$7.38M</i>	<i>-\$1.76M</i>
Assuming 50% of patients are using cetuximab with irinotecan combination therapy					
1a: Cetuximab (Perform KRAS test)	12%	87	\$3.98M	\$1.59M	-\$2.39M
2a: Panitumumab (Perform KRAS test)	8%	58	\$1.77M	\$0.71M	-\$1.06M
3a: Cetuximab + Irinotecan (Perform KRAS test)	50%	363	\$3.39M	\$8.47M	\$5.08M
<i>Total</i>	<i>70%</i>	<i>508</i>	<i>\$9.14M</i>	<i>\$10.77M</i>	<i>\$1.63M</i>

Conclusions

KRAS status is predictive of outcomes in cetuximab and panitumumab monotherapy, and in cetuximab-irinotecan combination therapy.

While KRAS testing is cost-effective for all strategies considered, it is not equally cost-effective for all treatment options.

Appendix 1: Literature Search Strategies

Search date: May 18, 2010

Databases searched: Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1996 to May Week 1 2010>

Search Strategy:

-
- 1 exp Colorectal Neoplasms/ or crc.ti,ab. (67094)
 - 2 ((colorectal or colon or rectal or rectum) adj2 (cancer* or carcinoma* or neoplas* or adenocarcinoma* or tumo?r*)).ti,ab. (60335)
 - 3 1 or 2 (79670)
 - 4 exp Genes, ras/ or exp ras Proteins/ (13387)
 - 5 (Therascreen or k-ras or kras or Kirsten-RAS or Kirsten rat sarcoma 2 viral oncogene).af. (4204)
 - 6 (cetuximab or erbitux or panitumumab or vectibix or abx-egf).af. (1873)
 - 7 or/4-6 (16083)
 - 8 3 and 7 (2515)
 - 9 limit 8 to (english language and humans and yr="2009 -Current") (384)
 - 10 limit 9 to (case reports or comment or editorial or letter) (59)
 - 11 9 not 10 (325)
 - 12 from 11 keep 1-325 (325)

Database: EMBASE <1980 to 2010 Week 19>

Search Strategy:

-
- 1 exp colon tumor/ (102815)
 - 2 ((colorectal or colon or rectal or rectum) adj2 (cancer* or carcinoma* or neoplas* or adenocarcinoma* or tumo?r*)).ti,ab. (80141)
 - 3 1 or 2 (120553)
 - 4 exp oncogene k ras/ (3703)
 - 5 exp K ras protein/ (2039)
 - 6 (Therascreen or k-ras or kras or Kirsten-RAS or Kirsten rat sarcoma 2 viral oncogene).af. (6807)
 - 7 exp cetuximab/ (7002)
 - 8 exp panitumumab/ (1777)
 - 9 (cetuximab or erbitux or panitumumab or vectibix or abx-egf).af. (7310)
 - 10 or/4-9 (13551)
 - 11 3 and 10 (5122)
 - 12 limit 11 to (human and english language and yr="2009 -Current") (1010)

Appendix 2: Study and Patient Characteristics

Cetuximab Monotherapy

Study	Patient and Sample Characteristics	Treatments Received
Karapetis, 2008	N=394 of 572 pts (68.9%) in CO.17 RCT of cetux + BSC vs. BSC. Advanced crc in whom all chemo had failed and no other standard anticancer therapy available. Kras mutation 42.3%. PCR: direct sequencing 2.	IV loading dose of 400 mg/sq m body-surface area, administered over 120 mins, on day 1, followed by infusion of 250 mg/sq m, administered over 60 mins, weekly. Continued until disease progression or intolerable toxicity. Tumour response or progression assessed every 8 wks.
Lurje, 2008	N=130 of 346 pts (38%) in open-label multi-center study. Histopathologically confirmed metastatic crc who had failed at least 2 prior chemo or an adjuvant therapy plus one chemo regimen(s). Kras mutation 32.3%. PCR: direct sequencing 12/13.	2 wks initial treatment followed by formal skin rash evaluation. Treatment continued in absence of intolerable or progressive disease, defined as at least 25% increase in measurable disease, unequivocal growth of existing nonmeasurable disease, appearance of one or more new lesions, or reappearance of old lesions assessed every 6 wks based on modified WHO criteria.
Cappuzzo, 2008	N=80 of 85 pts. with chemo-refractory (including irinotecan and oxaliplatin) metastatic crc exposed to cetuximab therapy and previously evaluated for EGFR. Kras mutation 52.5% (42/80). PCR: surveyor @ DNA endonuclease.	400 mg/sq m, followed by weekly infusion of 250 mg/sq m. Disease assessment every 2 mos. based on RECIST criteria.
Khambata-Ford, 2007	N=80 of 110 pts. with metastatic crc having received at least one prior chemo regimen for advanced disease or refused prior treatment. At least 18 yrs of age with life expectancy of 4 mos, ECOG score of 0 to 2 and standard lab values within normal limits. Kras mutation 37.5%. PCR: direct sequencing 2.	Standard dosing regimen (400 mg/sq m loading dose, followed by 250 mg/sq m weekly) for first 3 wks; thereafter, pts eligible for dose escalation every 3 wks to maximum of 400 mg/sq m if less than grade 3 rash. Tumour response assessed every 9 wks (one cycle of therapy) based on modified WHO criteria.

Cetuximab-Irinotecan Combination Therapy

Study	Patient and Sample Characteristics	Treatments Received
Bibeau, 2009	N=64 of 69 pts. (92.8%) with histologically proven crc., Irinotecan resistant. 78% had at least 2 previous lines for metastatic disease. Kras mutation 42.2%. (27/64) PCR: multiplex primer extension method sequencing.	Standard cetuximab dosage + irinotecan. Tumor response evaluated every 2 to 3 months by RECIST criteria.
Oden-Gangloff, 2009	N=64 chemorefractory metastatic crc (90% irinotecan refractory). 44 pts from Di Fiore 2007 study. Kras mutation 28% (19/64). PCR: multiplex primer extension method sequencing.	Cetux + irinotecan (n=62), cetux + irinotecan + oxaliplatin-based chemo (n=1), cetuximab alone (n=1). Tumor response according to response criteria in solid tumors.
Garm Spindler, 2009	N=64 of 71 pts (90.1%) with histologically confirmed metastatic crc referred for 3 rd line cetux + irinotecan. Refractory to prior fluoropyrimidine, oxaliplatin, and irinotecan, age over 18 yrs. Kras mutation 34%. (22/64). PCR: direct sequencing (DxS) with PCR kit.	Irinotecan 350 mg/sq m every 3 wks + cetuximab 400 mg/sq m loading dose followed by weekly 250 mg/sq m, until disease progression as assessed by RECIST.
Goncalves, 2008	N=32 EGFR positive metastatic crc . Kras mutation 43.8% (14/32) codons 12/13. PCR: direct sequencing.	In 26 pts: cetux (loading dose 400 mg/sq m, followed by 250 mg/sq m weekly until progression) + irinotecan (180 mg/sq m every other week). 6 pts from specific trials evaluating dose escalation of cetux mono-therapy (3), cetux+FOLFIRI as 1 st line (2), or 2 nd line after failure with fluoropyrimidine/oxaliplatin (1). Tumor evaluation at 4 wks, then every 2 mos for 6 mos, then every 3 mos until disease progression, by WHO criteria.
Prenen, 2009	N=199 of 200 (99.5%) irinotecan-refractory pts. with metastatic crc. 184 pts. on cetux+ irinotecan, 16 on cetux alone. Pts. pooled from 4 clinical trials (Babel, Everest, Bond salvage) and outside trials in same setting. Kras mutation 38.7% (77/199). PCR: allele-specific PCR.	Dosages not reported. May be similar to De Rook et al. 2008. Tumor response assessed by RECIST.

Loupakis, 2009	<p>N=102 pts with irinotecan-refractory metastatic crc whose disease had progressed during or within 3 mos after treatment with an irinotecan-based regimen. 18% received cetux-based therapy as 2nd line, 82% treated after failure of at least 2 line of chemo. Kras tests available on 88/96 primary tumours, 48/59 mets. Kras mutation 40.0% (35/88). PCR: direct sequencing 12/13.</p>	<p>Cetux + irinotecan reported, no dosages.</p> <p>Response evaluated every 8 wks based on RECIST criteria.</p>
Lievre, 2008	<p>N=114 of 234 (48.7%) metastatic crc. 89 as independent series from 6 centers, then pooled pts. from Lievre 2006. Cetux mono (n=2), cetux+irinotecan (n=88), cetux + irinotecan+FOLFIRI (n=10). Kras mutation 27% (24/89). PCR: TaqMan® allelic discrimination assay.</p>	<p>Dosages not reported. Disease assessment based on RECIST criteria.</p>

Panitumumab Monotherapy

Study	Patient and Sample Characteristics	Treatments Received
Amado, 2008	<p>N=427 of 463 pts (92%) in Van Cutsem 2007 RCT of panitum + BSC vs. BSC.</p> <p>Metastatic crc with EGFR expression in $\geq 1\%$ of tumor cells and documented evidence of disease progression after failure with fluoropyrimidines and prespecified exposure to oxaliplatin and irinotecan.</p> <p>Race: Caucasian.</p> <p>Kras mutation 43% (184/427).</p> <p>PCR: allele-specific PCR.</p>	<p>6 mg/kg + BSC every 2 wks or BSC. BSC could receive panitum after disease progression. Tumor status assessed every 4 to 8 wks from week 8 until disease progression using RECIST criteria.</p>
Freeman, 2008	<p>N=62 of 533 pts (11.6%) with metastatic crc from 3 phase II clinical trials: 15/182 Berlin et al. 2006, 12/203 Mitchell et al. 2007, 35/148 Hecht et al. 2007.</p> <p>Radiographic or pathologic confirmation of metastatic crc, treatment refractory (disease progression after fluoro-pyrimidine-, oxaliplatin-, and/or irinotecan-containing chemo)</p> <p>Race: 75%-80% Caucasian.</p> <p>Kras mutation 38.7% (24/62).</p> <p>PCR: direct sequencing.</p>	<p>Two studies: panitum 6 mg/kg every 2 wks.</p> <p>One study: 2.5 mg/kg weekly.</p> <p>Tumor assessments at 8 or 9 wks and at scheduled time points, based on RECIST or WHO criteria.</p>
Muro, 2009	<p>N=24: 16/52 (30.8%) metastatic crc pts (Muro et al. 2008) from phase I study with EGFR expression in $\geq 1\%$ of tumor cells and disease progression during or after fluoro-pyrimidine-, oxaliplatin-, and/or irinotecan-containing chemo. PLUS 8 pts. (Doi et al. 2009) from phase I study.</p> <p>Race: Asian (Japanese).</p> <p>Kras mutation 42.0%. (10/24).</p> <p>PCR: DxS (direct sequencing?)</p>	<p>Panitum IV infusion of 6 mg/kg every 2 wks over 60 min, until disease progression or intolerable toxicity.</p> <p>Tumor response assessed at 8, 12, 16, 24, 32, 40, 48 wks and every 8 weeks thereafter until disease progression. .</p>

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