Guideline Endorsement 2-31

## A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

# The Role of Primary Tumour Location in the Selection of Biologics for the Treatment of Unresectable Metastatic Colorectal Cancer: An Endorsement of a Canadian Consensus Statement

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**This document describes the CCO-Gastrointestinal Cancer Disease Site Group endorsement of The predictive effect of primary tumour location in the treatment of metastatic colorectal cancer: a Canadian consensus statement published in 2017 by Abrahao et al. The original publication is available at Current Oncology Vol 24, No 6 (2017)**

**An assessment conducted in December 2023 deferred the review of Guideline Endorsement 2-31. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)**

**You can access the full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/53941**

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## **Section 1:** Guideline Endorsement

**GUIDELINE OBJECTIVES**

The objective of this guideline is to make recommendations with respect to the role of primary tumour location (PTL) in the selection of epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) and vascular endothelial growth factor (VEGF) inhibitors (first-line/second-line) in addition to chemotherapy for the treatment of unresectable metastatic colorectal cancer (mCRC).

**RESEARCH QUESTION(S)**

Are there survival and/or quality of life benefits related to the selective use of EGFR monoclonal antibodies (mAbs) and VEGF inhibitors based on PTL for the first and second-line treatment of *RAS* wild-type, unresectable mCRC?

**TARGET POPULATION**

The target population consists of adult patients with RAS wild-type unresectable mCRC who are undergoing first-line or second-line chemotherapy.

**INTENDED USERS**

This guideline is targeted to clinicians involved in the management of patients with mCRC.

**RECOMMENDATIONS**

The Gastrointestinal Disease Site Group of Cancer Care Ontario endorses the following recommendations from *The Predictive Effect of Primary Tumour Location in the Treatment of Metastatic Colorectal Cancer: a Canadian Consensus Statement* [1]. Rectal cancer was included in the analysis of left-sided colon cancer. See Abrahao et al [1] for more details on the development of the recommendations and the evidence that supports them.

1. **First-Line**
   a. In patients with *RAS* wild-type left-sided colon cancer, standard chemotherapy (FOLFOX or FOLFIRI) in combination with an EGFR mAb (cetuximab or panitumumab) is recommended in the first-line setting.

      **Qualifying statement**

      Standard chemotherapy in combination with an EGFR mAb is the preferred option over the current standard of standard chemotherapy and bevacizumab.

   b. In patients with *RAS* wild-type right-sided colon cancer, the use of an EGFR mAb first-line is not recommended. The combination of bevacizumab plus standard chemotherapy remains the standard of care for these patients.

c. Extended *RAS* testing should be available in a timely manner to allow for the appropriate selection of biologic for first-line treatment decisions.

**2. Second-Line**

a. At this time, there is no evidence to recommend the selective use of EGFR mAbs in the second-line setting based on PTL.
b. In the second-line setting, patients who were treated with an EGFR mAb instead of bevacizumab in the first line of therapy can be considered to receive bevacizumab in combination with standard chemotherapy.

**3. Third-Line**

All patients with *RAS* wild-type disease who have not previously been treated with an EGFR mAb should be offered one.

**4. Tumour Response**

At this time, in cases where tumour response is the primary goal of therapy, the evidence is insufficient for the selective use of EGFR mAbs based on PTL.

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## **Section 2:** Endorsement Methods Overview

### THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

### GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was sponsored by the Gastrointestinal Cancer Disease Site Group, a group organized by CCO's Gastrointestinal Cancer Disease Site Group. The group was comprised of medical, surgical and radiation oncologists (see Appendix 1 for membership). The project was led by a small Working Group, comprised of three medical oncologists, one, radiation oncologist, one surgical oncologist and one research methodologist, who were responsible for reviewing the recommendations in '*The predictive effect of primary tumour location in the treatment of metastatic colorectal cancer: a Canadian consensus statement'* in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and leading the response to the internal review. The Working Group members are noted in Appendix 1. All members of the Gastrointestinal Cancer Disease Site Group made contributions to the endorsement process, refinement of the endorsement document, and approval of the final version of the document. Conflict of interest declarations for all members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

### CHOICE OF GUIDELINE FOR ENDORSEMENT

The endorsed guidance document was identified by the Working Group. In order to avoid the duplication of guideline development efforts across jurisdictions, the following databases were searched for existing guidelines

- Practice guideline databases: Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- The websites of guideline developers such as the National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), New Zealand Guidelines Group (NZGG), and National Health and Medical Research Council – Australia (NHMRC) were also searched.

Guidelines considered relevant were evaluated for quality using the AGREE II instrument [2]. The Identified guidance documents [3-7] were excluded because they did not address treatment based on primary tumour location (PTL). However, the Working Group members recommended Abrahao et al [1], a guidance document that was in press at the planning stage of this project. Once published, it was reviewed and considered eligible for endorsement.

## DESCRIPTION OF THE CANDIDATE GUIDELINE FOR ENDORSEMENT

Abrahao et al, 2017 [1] is an evidence-based Canadian Consensus Statement that addressed the predictive effect of PTL in the treatment of metastatic colorectal cancer (mCRC) with the purpose of developing a set of national evidence-based guidelines for the treatment of mCRC based on PTL. The authors are experts in gastrointestinal medical oncology from Ontario and Nova Scotia and the expert panel was made up of 12 Oncologist from across Canada. The recommendations were developed based on a consensus agreement of the panel members after discussion of available evidence. The AGREE II instrument was used to ascsess the document and it scored 57%. The details of the assessment can be found in Appendix 2. One major limitation of the consensus guidance document as identified by the AGREE II assessment was that the evidence supporting the recommendations was not retrieved through a systematic review process.

### Confirmatory Search for Systematic Reviews and Primary Literature

The Working Group members decided to conduct a confirmatory literature search (described below) to ensure that no relevant studies were omitted from the source document.

#### *Literature Search*

Using the search strategy outlined in Appendix 3, the confirmatory search for primary literature in MEDLINE and EMBASE (January 2008 through October 2017) was conducted. A search for existing systematic reviews on the role of PTL in the selection of biologics for the treatment of unresectable mCRC was also conducted. Systematic reviews published as a component of practice guidelines that were not considered suitable for adaptation or endorsement were also considered eligible for inclusion. The Cochrane Database of Systematic Reviews was also searched using a combination of the following search terms: metastatic colorectal cancer. The year 2008 was used as the cut-off because the Working Group members agreed that studies that attempt to analyze the predictive role of PTL in the treatment of mCRC are relatively new. Moreover, none of the referenced studies in the consensus guidance document was published before 2008.

The Ovid interface was used to search MEDLINE and EMBASE for existing systematic reviews in this topic area. Three references [8-10] that reported on four meta-analyses were already included in the source document. The other identified systematic reviews did not meet the inclusion criteria.

#### *Study Selection Criteria and Process*

A review of the titles and abstracts that resulted from the electronic searches was conducted by one reviewer (CA). For those items that appeared to meet the inclusion criteria, CA obtained and reviewed the full text of each item. Studies were included if they were systematic reviews, meta-analyses, or randomized controlled trials evaluating the role of biologics (first-line/second-line) in the treatment of unresectable mCRC with specific focus on PTL. The studies had to report at least one of the following outcomes: overall survival rate (OS), disease-free survival rate, tumour response rate, grade 3/4 toxicity, or quality of life.

*Exclusion Criteria*

The following exclusion criteria were applied to the entire literature search:

- Abstracts, case reports, news reports, notes, commentaries, opinions, letters, editorials, qualitative studies.
- Studies on cost-effectiveness, utility, and economics.
- Studies with fewer than 30 participants.
- Studies published in a language other than English, due to the lack of funding and resources for translation.

***Results***

Abrahao et al [1] reported the results of ten RCTs [11-20] that investigated and summarized the available evidence on the effects of PTL on the first, second and third line therapy with EGFR mAbs and/or VEGFR inhibitors. The effect of PTL on therapy with Bevacizumab was also analysed. In the first line setting, the Crystal and Prime trials showed that the addition of cetuximab or panituzumab to a chemotherapy regimen improved the progression-free survival (PFS), OS, and ORS [17,19,21]. In the second line setting, the combination of FOLFIRI and EGFR mAb also demonstrated improvement in the overall response rate (ORR) and PFS but not in OS [11,14]. They also reported the results of four meta-analyses of trials with EGFR mAb [8-10]. See Appendix 4 & 5 for more details on the included studies and the results of the analyses. The results of these studies and the associated meta-analyses formed the evidentiary base for the recommendations in Section 1.

The confirmatory search retrieved 450 articles, of which 70 were retained for full-text review. Sixteen references were already included in the source document [8-23] and two new studies were identified: Japan Clinical Cancer Research Organization (JACCRO) CC-05/06 and Arbeitsgemeinschaft Internistische Onkologie (AIO) KRK-0104 Trials [24,25]. The remaining 52 references did not meet the inclusion criteria.

Sunakawa et al [24] conducted a subgroup analysis on 110 mCRC patients with KRAS exon 2 wild-type tumours who were enrolled in the JACCRO trials CC-05 (cetuximab plus FOLFOX) and CC-06 (cetuximab plus SOX). The aim of the analysis was to evaluate the prognostic impact of tumour location on the clinical outcome. The results showed that left-sided tumours were significantly associated with longer OS (36.2 vs. 12.6 months; hazard ratio [HR], 0.28; $p<0.0001$) and progression-free survival (PFS) (11.1 vs. 5.6 months; HR, 0.47; $p=0.041$) than the right-sided tumours. The AIO KRK-0104 [25] is a randomized phase II trial that investigated the addition of cetuximab to CAPIRI or CAPOX as first-line treatment in 146 mCRC patients with KRAS codon 12/13 wild-type. Left-sided tumours were associated with better OS (HR, 0.63; $p=0.016$) and PFS (HR, 0.67; $p=0.02$). The Working Group did not believe that these new results were relevant to the current guideline as they represented information on the prognostic rather than the predictive role of PTL in this population.

None of the retrospective analyses based on PTL explicitly addressed QoL as a function of PTL. However, evidence, with analyses not selected by PTL, shows that in the treatment of patients with KRAS wild-type mCRC, the addition of EGFR to a chemotherapy regimen or best supportive care does not have a detrimental effect on overall QoL irrespective of early skin reactions [26-33]. Qol was measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), the Dermatology Life Quality Index (DLQI), dermatology specific Quality of Life (DSQL), EuroQual 5-domain Health State Index (HSI) and Overall Health Rating (OHR) scales. There was also a prospective evaluation of QoL in Cetuximab alone or Cetuximab plus Bevacizumab and there were no significant differences in the global QoL [34]. Patients receiving Cetuximab had more skin related QoL concerns and in most of the studies, skin reaction correlated with survival.

*Conclusion*
The review confirmed that no relevant studies had been omitted from the source guideline.

**ENDORSEMENT PROCESS**
The Working Group reviewed the recommendations in '*The predictive effect of primary tumour location in the treatment of metastatic colorectal cancer: a Canadian consensus statement'* in detail to determine whether they could be endorsed, endorsed with changes, or rejected. This determination was based on the agreement of the Working Group with the interpretation of available evidence presented in the guideline, and whether it was applicable and acceptable to the Ontario context, and feasible for implementation.

**ENDORSEMENT REVIEWS**
The draft endorsement document was evaluated and approved by the gastrointestinal cancer DSG members (see Appendix 1) that provided PEBC with their conflict of interest declaration (see the PEBC Conflict of Interest (COI) Policy). One member of the PEBC Report Approval Panel (RAP) also reviewed the document and suggested that a brief summary of the evidence considered in the source document will help contextualize the 2 new studies found through the confirmatory search. In response, the WG added a brief summary of the evidence that supports the recommendation.

**Expert Panel Review and Approval**
In March 2018, 20 (83%) of the 24 panel members (excluding the WG) cast votes of approval. Of those that cast votes, 19 (95%) approved the document with no additional comment. One member gave a conditional approval and advised that the wording of the research question could lead one to expect that the recommendations are based on evidence from direct comparison of EGFR mAb versus bevacizumab. He also noted that there was no recommendation on rectal cancer. The WG reviewed the feedback and acknowledged that rectal cancer was represented in the analysis of left sided colon cancer. The qualifying statement 'Standard chemotherapy in combination with an EGFR mAb is the preferred option over the current standard of standard chemotherapy and bevacizumab' was added to support the recommendation for first line treatment.

**Professional Consultation**
Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Professionals in the PEBC database with an interest in colorectal cancer, systemic (chemotherapy), colposcopy, and surgery were contacted by email to inform them of the survey. Ninety professionals who practice in Ontario (96%) and other provinces (4%) were contacted. Eleven (12%) responses were received. Two of the respondents were unavailable to review the guideline. The results of the feedback survey from remaining nine people are summarized in Table 2-1. The main comments from the consultation and the Working Group's responses are summarized in Table 2-2.

**Table 2-1. Responses to four items on the professional consultation survey.**

| | Number 9 (10%) | | | | |
|---|---|---|---|---|---|
| **General Questions: Overall Guideline Assessment** | Lowest Quality (1) | (2) | (3) | (4) | Highest Quality (5) |
| **Rate the overall quality of the guideline report.** | 0 | 0 | 1 | 6 | 2 |

| | Strongly Disagree (1) | (2) | (3) | (4) | Strongly Agree (5) |
|---|---|---|---|---|---|
| **I would make use of this guideline in my professional decisions.** | 0 | 0 | 1 | 3 | 5 |
| **I would recommend this guideline for use in practice.** | 0 | 0 | 1 | 5 | 3 |
| **What are the barriers or enablers to the implementation of this guideline report?** | • Cost of biological therapy and the availability in smaller communities<br>• Funding of these drugs outside of accepted present day guidelines. For example, funding of EGFR inhibitors in bevacizumab eligible patients<br>• Ready availability of KRAS status at diagnosis<br>• Toxicity of combination therapy | | | | |

**Table 5-2. Modifications/Actions taken/Responses regarding main written comments from professional consultants.**

| Comments | WG Responses |
|---|---|
| 1. The research question seems to suggest that the issue of QOL related to selection of biologics based on PTL would be addressed in the guideline; however this isn't the case. The "QOL" question could perhaps be omitted.<br>2. Your research question suggests looking at QOL and OS - would you comment on these in the recommendations (e.g. we recommend EGFR mAbs in first line based on OS data? | None of the retrospective analyses based on PTL explicitly addressed QoL as a function of PTL. However, there is a prospective evaluation of QoL in EGFR versus VEGFR inhibitors and there seems to be no difference. The WG decided not to omit the QoL question. |
| 3. The recommendation to consider bevacizumab in second line is reasonable by expert opinion but not supported by RCT evidence.<br>4. The only change should be that in the 2nd-line setting if an EGFR mAb was used and there is no contraindication to bevacizumab the wording should be "should be used" not "can". | There is a PEBC guideline on the use of bevacizumab in second line [35] and the WG try to stay consistent with the language in that guideline. The population may not have included EGFR mAb but that could easily be extrapolated to this population. |
| 5. A summary of the relevant studies in a table would be helpful. | The table of included studies from the source document was added in the Appendix 4. |
| 6. Overall, the guideline is well written, but most of the evidence is largely based on subgroup analyses so this could affect its implementation. | The issues with using subgroup analyses were addressed in the source document and we agree with the authors. |

**CONCLUSION**

PTL has been shown to have a predictive effect on the outcomes of treatment for mCRC. This led Abrahao et al [1] to develop an evidences-based guidance document for the treatment of mCRC based on PTL. Rectal cancer was included in the analysis of left-sided colon cancer.

Brule et al [36] also conducted a sensitive analysis with or without rectal cancer in the left-sided colon cancer in the third line setting, and PTL remained predictive. The CCO GI cancer DSG reviewed the draft endorsement with respect to the recommendations, and provided feedback. Once a final endorsement was agreed upon, the panel voted to approve the endorsement of the recommendations in Section 1.

**UPDATING THE ENDORSEMENT**

CCO GI cancer DSG will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario.

**ACKNOWLEDGEMENTS**

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- Sara Miller for copy editing.
- Stacey Christie and Maria Cavicchioli for administrative assistance.

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## Appendix 1: Affiliations and Conflict of Interest Declarations.

| Name | Affiliation | COI Declared |
|---|---|---|
| **Working Group** | | |
| Rachel Goodwin | The Ottawa Hospital Regional Cancer Center, Ottawa, ON | Yes[1] |
| Chika Agbassi | McMaster University, Hamilton, ON | No |
| Erin Kennedy | Mount Sinai Hospital, Toronto, ON | Yes[2] |
| Jim Biagi | Queen's University, Kingston, ON | No |
| Raimond Wong | Hamilton Health Sciences, Hamilton, ON | No |
| Stephen Welch | London Health Sciences Centre, London, ON | Yes[3] |
| Scott Berry | Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON | Yes[4] |
| GI DSG Expert panel | | |
| Aamer Mahmud | Kingston General Hospital, Kingston, ON | No |
| Brandon Meyers | Hamilton Health Sciences, Hamilton, ON | No |
| Charles Cho | Southlake Regional Health centre | No |
| Derek Jonker | University of Ottawa, Ottawa, ON | No |
| Erin Kennedy | Princess Margaret Cancer Centre, Toronto, ON | No |
| Fayez Quereshy | University Health Network, Toronto, ON | No |
| Gonzalo Sapisochin | University Health Network, Toronto, ON | Yes[5] |
| Jolie Ringash | University Health Network, Toronto, ON | No |
| Kelvin Chan | Sunnybrook Health Sciences Centre, Toronto ON | No |
| Kevin Zbuk | Hamilton Health Sciences, Hamilton, ON | Yes[6] |
| Kristopher Dennis | University of Ottawa, Ottawa ON | No |
| Mala Bahl | Grand River Hospital, Kitchener, ON | No |
| Maria Kalyvas | Kingston General Hospital, Kingston, ON | No |
| Mark Doherty | Sunnybrook Health Sciences Centre, Toronto ON | No |
| Mark Rother | Trillium Health Partners. | Yes[7] |
| Natalie Coburn | Sunnybrook Health Sciences Centre, Toronto, ON | No |
| Nazik Hammad | Kingston General Hospital, Kingston, ON | No |
| Paul Karanicolas | Sunnybrook Health Sciences Centre, Toronto, ON | Yes[8] |
| Raymond Jang | University Health Network, Toronto, ON | Yes[9] |
| Rebecca Wong | University Health Network, Toronto, ON | No |
| Richard Malthaner | London Health Sciences Centre, London, ON | No |
| Robert Beecroft | Mount Sinai Hospital, Toronto, ON | Yes[10] |
| Robert Gryfe | Mount Sinai Hospital, Toronto, ON | No |
| Tarek Elfiki | Windsor Regional Cancer Centre, Windsor, ON | No |
| Tim Asmis | The Ottawa Hospital Regional Cancer Centre, Ottawa, ON | Yes[11] |
| **Report Approval Panel** | | |
| Melissa Brouwers | McMaster University,, Hamilton, ON | No |

[1] Conducted a retrospective analysis of CO.17 trial and received honorarium (<$5000) from AMGEN.
[2] The Ontario GI Cancers Lead for disease pathway management at CCO.
[3] Received honorarium (<$5000) from AMGEN for speaking engagements.
[4] AMGEN advisory board member; co-authored the endorsed guideline; received honorarium from AMGEN for speaking engagements.
[5] Received research support or grant ($10000) from Bayer
[6] Received travel support from AMGEN.
[7] Advisory board member for AMGEN and Roche received honorarium ($2000).
[8] Advisory board member and speaker for Sanofi; received honorarium/grant from Baxter and Sanofi; published editorial for HAIP.
[9] Principle investigator and received grants or other research support from AstraZeneca, Merck, Norvatis Lilly, and Boston Biomedical and Bristo-Myers Squibb.
[10] Principle investigator for UHN Site for the EPOCH trial studying Radioembolization as second line therapy for certain patients with metastatic colorectal cancer to liver
[11] Received grant or honorarium (>$5000) from Roche, AMGEN, and Novartis; published an editorial/commentary/opinion in the 2017 Eastern Canadian Colorectal Cancer Consensus.

## Appendix 2: AGREE II Score Sheet

| Domain | Item | AGREE II Rating | | |
|---|---|---|---|---|
| | | Appraiser 1 | Appraiser 2 | Appraiser 3 |
| Scope and purpose | The overall objective(s) of the guideline is (are) specifically described. | 7 | 6 | 7 |
| | The health question(s) covered by the guideline is (are) specifically described. | 6 | 6 | 6 |
| | The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described. | 7 | 6 | 6 |
| Stakeholder involvement | The guideline development group includes individuals from all the relevant professional groups. | 5 | 6 | 7 |
| | The views and preferences of the target population (patients, public, etc.) have been sought. | 1 | 1 | 1 |
| | The target users of the guideline are clearly defined. | 7 | 6 | 7 |
| Rigor of development | Systematic methods were used to search for evidence. | 3 | 3 | 1 |
| | The criteria for selecting the evidence are clearly described. | 1 | 1 | 1 |
| | The strengths and limitations of the body of evidence are clearly described. | 5 | 4 | 6 |
| | The methods for formulating the recommendations are clearly described. | 6 | 4 | 6 |
| | The health benefits, side effects and risks have been considered in formulating the recommendations. | 5 | 5 | 6 |
| | There is an explicit link between the recommendations and the supporting evidence. | 6 | 6 | 6 |
| | The guideline has been externally reviewed by experts prior to its publication. | 1 | 1 | 1 |
| | A procedure for updating the guideline is provided. | 1 | 1 | 1 |
| Clarity of presentation | The recommendations are specific and unambiguous. | 6 | 6 | 7 |
| | The different options for management of the condition or health issue are clearly presented. | 6 | 6 | 7 |
| | Key recommendations are easily identifiable. | 7 | 6 | 7 |
| Applicability | The guideline describes facilitators and barriers to its application. | 5 | 6 | 5 |
| | The guideline provides advice and/or tools on how the recommendations can be put into practice. | 1 | 2 | 1 |
| | The potential resource implications of applying the recommendations have been considered. | 5 | 5 | 3 |
| | The guideline presents monitoring and/or auditing criteria. | 1 | 3 | 1 |
| Editorial independence | The views of the funding body have not influenced the content of the guideline. | 5 | 4 | 3 |
| | Competing interests of guideline development group members have been recorded and addressed. | 7 | 7 | 7 |
| Overall Guideline Assessment | Rate the overall quality of this guideline. | 5 | 5 | 5 |
| Overall Guideline Assessment | I would recommend this guideline for use. | Yes | Yes | Yes |

$$\frac{\text{(Obtained score – Minimum possible score)}}{\text{(Maximum possible score – Minimum possible score)}}$$

(308-69) / (483-69) = 0.577 × 100 = 58%

## Appendix 3: Search Strategy

### MEDLINE and EMBASE

1. exp colon cancer/ or colorectal cancer/
2. (colon$ adj2 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp.
3. 1 or 2
4. (RAS Wild-Type or RAS or Wild-type or right side or left side or sided or sidedness or tumo$ sidedness or primary tumo$ location).tw.
5. 3 and 4
6. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
7. randomization/ or single blind procedure/ or double blind procedure/
8. ((phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/) and random$.tw.
9. ((allocat$ adj2 random$) or (clinic$ adj trial$1)).tw. or placebo/ or placebo?.tw.
10. 6 or 7 or 8 or 9
11. (editorial or note or letter erratum or short survey or abstract).pt. or abstract report/ or letter/ or case study/
12. Animal/ not Human/
13. 11 or 12
14. (5 and 10) not 13
15. limit 14 to (english language and yr="2008 -Current")

## Appendix 4: Studies included in Abrahao et al [1] as published in Current Oncology

**TABLE II** Trials with EGFR monoclonal antibodies

| Reference (*n*) analysis (%) | Treatment | Pts | *RAS* | *RAS* wild-type population | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Overall response rate | | | | Progression-free survival | | | | | Overall survival | | |
| | | | | (%) CI | HR/OR | 95% CI | *p* Value | (months) | HR/OR | 95% CI | *p* Value | (months) | HR/OR | 95% | |
| *First line* | | | | | | | | | | | | | | | |
| CRYSTAL, 2009 | FOLFIRI-Cmab | 599 | 45 | 46.9 | 1.4 | 1.12 to 1.17 | 0.004 | 8.9 | 0.85 | 0.72 to 0.99 | 0.048 | 19.9 | 0.93 | 0.81 to 1.07 | 0.31 |
| | FOLFIRI | 599 | (*KRAS*) | 38.7 | | | | 8.0 | | | | 18.6 | | | |
| CRYSTAL, 2015 (update) | FOLFIRI-Cmab | 316 | 64 | 66.3 | 3.11 | 2.03 to 4.78 | <0.001 | 11.4 | 0.56 | 0.41 to 0.76 | <0.001 | 28.4 | 0.69 | 0.54 to 0.89 | 0.002 |
| | FOLFIRI | 350 | (*KRAS*, *NRAS*) | 38.6 | | | | 8.4 | | | | 20.2 | | | |
| PRIME, 2010 | FOLFOX-Pmab | 593 | 93 | 55.0 | 1.55 | | 0.68 | 9.6 | 0.80 | 0.66 to 0.97 | 0.02 | 23.7 | 0.83 | 0.67 to 1.02 | 0.072 |
| | FOLFOX | 590 | (*KRAS*) | 48.0 | | | | 8.0 | | | | 19.7 | | | |
| PRIME, 2013 (update) | FOLFOX-Pmab | 546 | 90 | | Data | not available | | 10.1 | 0.72 | 0.58 to 0.90 | 0.004 | 26.0 | 0.78 | 0.62 to 0.99 | 0.04 |
| *Second line* | FOLFOX | 550 | (*KRAS*, *NRAS*) | | | | | 7.9 | | | | 20.2 | | | |
| 20050181, 2010 | FOLFIRI-Pmab | 591 | 91 | 35.0 | | <0.0001 | | 5.9 | 0.73 | 0.59 to 0.90 | 0.004 | 14.5 | 0.85 | 0.70 to 1.04 | 0.12 |
| | FOLFIRI | 595 | (*KRAS*) | 10.0 | | | | 3.9 | | | | 12.5 | | | |
| 20050181, 2014 (update) | FOLFIRI-Pmab | 591 | 91 | 36.0 | 5.50 | 3.32 to 8.87 | <0.0001 | 6.7 | 0.82 | 0.69 to 0.97 | 0.023 | 11.8 | 0.93 | 0.77 to 1.13 | 0.48 |
| | FOLFIRI | 595 | (*KRAS*) | 10.0 | | | | 4.9 | | | | 11.1 | | | |
| PICCOLO, 2013 | Irinotecan-Pmab | 230 | 100 | 34 | | <0.0001 | | Favours | 0·78 | 0·64 to 0·95 | 0·015 | 10.4 | 1.01 | 0.83 to 1.23 | 0.91 |
| | Irinotecan (2nd and 3rd | 230 | (*KRAS*) | 12 | | | | Irinotecan-Pmab | | | | 10.9 | | | |
| *Third line* | | | | | | | | | | | | | | | |
| CO.17, 2008 | Cetuximab | 287 | 69 | 12.8 | | Not reported | | 3.7 | 0.40 | 0.3 to 0.54 | <0.001 | 9.5 | 0.55 | 0.41 to 0.74 | <0.001 |
| | BSC | 285 | | 0 | | | | 1.9 | | | | 4.8 | | | |

Pts = patients; HR = hazard ratio; OR = odds ratio; CI = confidence interval; FOLFIRI = folinic acid-5-fluorouracil-irinotecan; Cmab = cetuximab; FOLFOX = folinic acid-5-fluorouracil-oxaliplatin; Pmab = panitumumab.

**TABLE IV** Trials with bevacizumab

| Study (*n*) | Treatment | Pts | *RAS* analysis (%) | *RAS* wild-type population | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Overall response rate | | | | Progression-free survival | | | | Overall survival | | |
| | | | | (%) | HR/OR | 95% CI | *p* Value | (months) | HR/OR | 95% CI | *p* Value | (months) | HR/OR | 95% CI | *p* Value |
| AGITG MAX, 2010 | Capecitabine | 578 | NA | 30.0 | 0.16 | | | 5.7 | 0.63 | 0.50 to 0.79 | <0.001 | 18.9 | 0.87 | 0.67 to 1.35 | 10.31 |
| | Capecitabine-Bev | 559 | | 38.1 | | | | 8.5 | | | | 18.9 | | | |

Pts = patients; HR = hazard ratio; OR = odds ratio; CI = confidence interval; AGITG = Australasian Gastrointestinal Trials Group; Bev = bevacizumab; NA = not available.

**TABLE V** Trials with bevacizumab and EGFR monoclonal antibodies

| Study (*n*) | Treatment | Pts | *RAS* analysis (%) | *RAS* wild-type population | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Overall response rate | | | | Progression-free survival | | | | Overall survival | | | |
| | | | | (%) | HR/OR | 95% CI | *p* Value | (months) | HR/OR | 95% CI | *p* Value | (months) | HR/OR | 95% CI | *p* Value |
| First line | | | | | | | | | | | | | | | |
| CALGB/SWOG 80405, 2014 | FOLFOX or FOLFIRI-Cmab | 578 | 100 | Data not available | | | | 10.4 | 1.04 | 0.91 to 1.17 | | 29.9 | 0.92 | 0.78 to 1.09 | |
| | FOLFOX or FOLFIRI-Bev | 559 | (*KRAS*) | | | | | 10.8 | | | | 29.0 | | | |
| FIRE-3, 2015 | FOLFIRI-Cmab | 297 | 69 | 62.0 | 1.18 | 0.85 to 1.64 | 0.18 | 10.4 | 1.06 | 0.88 to 1.26 | 0.55 | 33.1 | 0.77 | 0.62 to 0.96 | 0.02 |
| | FOLFIRI-Bev | 295 | (*KRAS*) | 58.0 | | | | 10.2 | | | | 25.6 | | | |
| PEAK, 2014 | FOLFOX-Pmab | 142 | 100 | 57.8 | | | | 10.9 | 0.87 | 0.85 to 1.17 | 0.35 | 34.2 | 0.62 | 0.44 to 0.89 | 0.009 |
| (phase II) | FOLFOX-Bev | 143 | (*KRAS*) | 53.3 | | | | 10.1 | | | | 24.3 | | | |

Pts = patients; HR = hazard ratio; OR = odds ratio; CI = confidence interval; FOLFOX = folinic acid-5-fluorouracil-oxaliplatin; FOLFIRI = folinic acid-5-fluorouracil-irinotecan; Cmab = cetuximab; Bev = bevacizumab; Pmab = panitumumab.

## Appendix 5: Analysis result from Abrahao et al[1] as published in Current Oncology

**TABLE III** Analysis of primary tumour location in trials with EGFR monoclonal antibodies

| Variable | Results of monoclonal antibody studies by tumour location | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CRYSTAL (FOLFIRI±cetuximab, first line) | | | | PRIME (FOLFOX±panitumumab, first line) | | | | 20050181 (FOLFIRI±panitumumab, second line) | | | | CO.17 (cetuximab vs. BSC, third line) | | | |
| | Cetuximab use | | | | Panitumumab use | | | | | | | | Cetuximab use | | | |
| | Panitumumab use | | | | | | | | | | | | Left-sided | | Right-sided | |
| | Left-sided | | Right-sided | | Left-sided | | Right-sided | | Left-sided | | Right-sided | | Yes (*n*=105) | No (*n*=105) | Yes (*n*=56) | No (*n*=56) |
| ORR (%) | 72.5 | 40.6 | 42.4 | 33.3 | 68.0 | 53.0 | 42.0 | 35.0 | 50.0 | 13.0 | 13.3 | 2.6 | Data not available | | | |
| OR | 3.99 | | 1.45 | | 1.9 | | 1.36 | | 6.49 | | 5.69 | | | | | |
| 95% CI | 2.40 to 6.62 | | 0.58 to 3.64 | | 1.30 to 2.27 | | 0.6 to 3.1 | | 3.73 to 11.3 | | 0.60 to 53.6 | | | | | |
| *p* Value | <0.001 | | 0.43 | | <0.001 | | 0.46 | | <0.001 | | 0.13 | | | | | |
| PFS (months) | 12.0 | 8.9 | 8.1 | 7.1 | 12.9 | 9.2 | 7.5 | 7.0 | 8.0 | 5.8 | 4.8 | 2.4 | 5.4 | 1.8 | 1.9 | 1.9 |
| HR | 0.50 | | 0.87 | | 0.72 | | 0.8 | | 0.88 | | 0.75 | | 0.28 | | 0.73 | |
| 95% CI | 0.34 to 0.72 | | 0.47 to 1.62 | | 0.57 to 0.90 | | 0.50 to 1.26 | | 0.69 to 1.12 | | 0.45 to 1.27 | | 0.18 to 0.45 | | 0.42 to 1.27 | |
| *p* Value | <0.001 | | 0.66 | | 0.005 | | 0.33 | | | | | | <0.0001 | | 0.26 | |
| OS (months) | 28.7 | 21.7 | 18.5 | 15.0 | 30.3 | 23.6 | 11.1 | 15.4 | 20.1 | 16.6 | 10.3 | 8.1 | 10.1 | 4.8 | 6.2 | 3.5 |
| HR | 0.65 | | 1.08 | | 0.73 | | 0.87 | | 0.96 | | 1.14 | | 0.49 | | 0.66 | |
| 95% CI | 0.50 to 0.86 | | 0.65 to 1.81 | | 0.57 to 0.93 | | 0.55 to 1.37 | | 0.74 to 1.23 | | 0.68 to 1.89 | | 0.31 to 0.77 | | 0.36 to 1.21 | |
| *p* Value | 0.002 | | 0.76 | | 0.012 | | 0.55 | | | | | | 0.002 | | 0.18 | |

FOLFIRI = folinic acid–5-fluorouracil–irinotecan; FOLFOX = folinic acid–5-fluorouracil–oxaliplatin; BSC = best supportive care; ORR = overall response rate; OR = odds ratio; CI = confidence interval; PFS = progression-free survival; HR = hazard ratio; OS = overall survival.

**TABLE VI** Analysis of primary tumour location in first-line trials comparing EGFR monoclonal antibodies with bevacizumab

| Variable | CALGB/SWOG 80405 (FOLFOX or FOLFIRI with cetuximab vs. FOLFOX or FOLFIRI with bevacizumab) | | | | FIRE-3 (FOLFIRI with cetuximab vs. FOLFIRI with bevacizumab) | | | | PEAK (FOLFOX with panitumumab vs. FOLFOX with bevacizumab) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Left-sided | | Right-sided | | Left-sided | | Right-sided | | Left-sided | | Right-sided | |
| | Cmab (*n*=152) | Bev (*n*=173) | Cmab (*n*=71) | Bev (*n*=78) | Cmab (*n*=157) | Bev (*n*=149) | Cmab (*n*=38) | Bev (*n*=50) | Pmab (*n*=53) | Bev (*n*=54) | Pmab (*n*=22) | Bev (*n*=14) |
| ORR (%) | 69.4 | 57.9 | 42.3 | 39.7 | 69.0 | 62.0 | 52.6 | 50.0 | 64.2 | 57.4 | 63.6 | 50.0 |
| OR | 1.65 | | 1.11 | | 1.37 | | 1.11 | | 1.33 | | 1.75 | |
| 95% CI | 1.16 to 2.34 | | 0.61 to 2.01 | | 0.85 to 2.19 | | 0.48 to 2.59 | | 0.57 to 3.11 | | 0.36 to 8.39 | |
| *p* Value | 0.005 | | 0.73 | | 0.23 | | 0.83 | | | | | |
| PFS (months) | 12.7 | 11.2 | 7.5 | 10.5 | 10.7 | 10.7 | 7.6 | 9.0 | 14.6 | 11.5 | 8.7 | 12.6 |
| HR | 0.84 | | 1.64 | | 0.90 | | 1.44 | | 0.68 | | 1.04 | |
| 95% CI | 0.66 to 1.06 | | 1.15 to 2.36 | | 0.71 to 1.14 | | 0.92 to 2.26 | | 045 to 1.04 | | 0.50 to 2.18 | |
| *p* Value | 0.15 | | 0.006 | | 0.38 | | 0.11 | | 0.07 | | 0.90 | |
| OS (months) | 39.3 | 32.6 | 13.9 | 29.2 | 38.3 | 28.0 | 18.3 | 23.0 | 43.4 | 32.0 | 17.5 | 21.0 |
| HR | 0.77 | | 1.36 | | 0.63 | | 1.31 | | 0.77 | | 0.67 | |
| 95% CI | 0.59 to 0.99 | | 0.93 to 1.99 | | 0.48 to 0.75 | | 0.81 to 2.11 | | 0.46 to 1.28 | | 0.30 to 1.50 | |
| *p* Value | 0.04 | | 0.10 | | 0.002 | | 0.28 | | 0.31 | | 0.32 | |

FOLFOX = folinic acid–5-fluorouracil–oxaliplatin; FOLFIRI = folinic acid–5-fluorouracil–irinotecan; Cmab = cetuximab; Bev = bevacizumab; Pmab = panitumumab; ORR = overall response rate; OR = odds ratio; CI = confidence interval; PFS = progression-free survival; HR = hazard ratio; OS = overall survival.

**TABLE VII** Analysis of primary tumour location in meta-analyses of trials with EGFR monoclonal antibodies (mAbs)

| Variable | Arnold *et al.*, 2017 (CRYSTAL, FIRE-3, PEAK, PRIME, PRIME) 20050181, CALGB/SWOG 80405) | | | | Li *et al.*, 2017 (CRYSTAL, NCIC CO.17) | | | | Holch *et al.*, 2017 (CRYSTAL, | | | | Holch *et al.*, 2017 (FIRE-3, PEAK, CALGB/SWOG 80405) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Use of *EGFR* mAb | | | | Use of *EGFR* mAb | | | | Use of *EGFR* mAb | | | | Use of *EGFR* mAb | | | |
| | Left-sided | | Right-sided | | Left-sided | | Right-sided | | Left-sided | | Right-sided | | Left-sided | | Right-sided | |
| | sided Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes Bev | No | Yes | No, |
| ORR (%) | Favours *EGFR* mAb | | No difference | | Favours *EGFR* mAb | | No difference | | Favours *EGFR* mAb | | No difference | | Favours *EGFR* mAb | | No difference | |
| OR | 2.12 | | 1.47 | | 1.37 | | 1.11 | | 2.45 | | 1.42 | | 1.49 | | 1.2 | |
| 95% CI | 1.77 to 2.55 | | 0.94 to 2.29 | | 0.85 to 2.19 | | 0.48 to 2.59 | | 1.82 to 3.3 | | 0.78 to 2.6 | | 1.19 to 1.9 | | 0.77 to 1.87 | |
| *p* Value | | | | | 0.23 | | 0.83 | | <0.00001 | | 0.25 | | 0.002 | | 0.43 | |
| PFS (months) | Data not available | | Data not available | | Favours *EGFR* mAb | | No difference | | Favours *EGFR* mAb | | No difference | | No difference | | Favours bevacizumab | |
| HR | | | | | 0.38 | | 0.79 | | 0.65 | | 0.82 | | 0.86 | | 1.53 | |
| 95% CI | | | | | 0.22 to 0.67 | | 0.52 to 1.19 | | 0.54 to 0.79 | | 0.57 to 1.19 | | 0.73 to 1.02 | | 1.16 to 2.01 | |
| *p* Value | | | | | 0.0008 | | 0.26 | | <0.0001 | | 0.30 | | 0.08 | | 0.003 | |
| OS (months) | Favours *EGFR* mAb | | No difference | | Favours *EGFR* mAb | | No difference | | Favours *EGFR* mAb | | No difference | | Favours *EGFR* mAb | | No difference | |
| HR | 0.75 | | 1.14 | | 0.60 | | 0.87 | | 0.69 | | 0.96 | | 0.71 | | 1.3 | |
| 95% CI | 0.67 to 0.84 | | 0.88 to 1.47 | | 0.47 to 0.77 | | 0.54 to 1.40 | | 0.58 to 0.83 | | 0.68 to 1.35 | | 0.58 to 0.85 | | 0.97 to 1.74 | |
| *p* Value | | | | | <0.0001 | | 0.56 | | <0.0001 | | 0.80 | | 0.0003 | | 0.08 | |

ORR = overall response rate; OR = odds ratio; CI = confidence interval; PFS = progression-free survival; HR = hazard ratio; OS = overall survival.