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Evidence-Based Series 2-6 Version 2

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

Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer

S. Berry, R. Cosby, T. Asmis, K. Chan, M.K. Krzyzanowska, N. Hammad, and the Gastrointestinal Disease Site Group

September 15, 2022

An assessment conducted in December 2023 deferred the review of Evidence Based Series (EBS) 2-6. 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)

EBS 2-6 Version 2 is comprised of 4 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/411

Section 1:	**Guideline Recommendations**
Section 2:	**Evidentiary Base**
Section 3:	**Development Methods, Recommendations Development and External Review Process**
Section 4:	**Document Assessment and Review**

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Evidence-Based Series 2-6

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Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version January 8, 2014	2000-2013	Full Report	Web publication	NA
Current Version 2 September 15, 2022	2013-2021	New data found in section 4: Document Assessment and Review	Updated Web publication	2014 recommendations are **ENDORSED**

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Evidence-Based Series 2-6: Section 1

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

Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer: Guideline Recommendations

S. Berry, R. Cosby, T. Asmis, K. Chan, M.K. Krzyzanowska, N. Hammad, and the Gastrointestinal Disease Site Group

The 2014 guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Assessment and Review for a summary of updated evidence published between 2013 and 2022, and for details on how this guideline was ENDORSED.

QUESTION

What is the impact of intermittent strategies of administering systemic therapy on length and quality of survival in patients with untreated, unresectable metastatic colorectal cancer?

TARGET POPULATION

These recommendations apply to adult patients (≥18 years old) with inoperable, advanced (Stage IV) colorectal cancer.

INTENDED USERS

This guideline is intended for use by clinicians and healthcare providers involved in the management of patients with advanced colorectal cancer.

RECOMMENDATIONS AND KEY EVIDENCE

Intermittent strategies of administering first-line systemic therapies to patients with unresectable metastatic colorectal cancer (mCRC) do not result in a statistically significant reduction in overall survival and either improve or maintain quality of life compared to continuous administration of therapy. Patients who want a break from treatment can be reassured that intermittent strategies of administering first-line therapy are a reasonable alternative to continuous administration. Intermittent systemic treatment strategies should be part of an informed discussion of treatment options for this group of patients.

Ten trials (1-10) were identified, and seven (1,2,5-9) had published overall survival hazard ratios (HRs) that could be used for the meta-analysis. Meta-analysis demonstrates no clinically significant survival difference between the continuous and intermittent

chemotherapy strategies (HR, 1.02; 95%CI, 0.95-1.10, p=0.62). No subgroup of trials based on the type of induction or maintenance therapy in the intermittent arm demonstrates a significant difference in overall survival between the two chemotherapy strategies (Figures 2, 3, and 6). Toxicity assessments revealed differential toxicity patterns for the two strategies. However, these toxicity assessments reflect maximal levels of toxicity experienced during exposure to the treatment on that arm of the trial. These measures are important, but for patients on intermittent treatment, duration of exposure to toxicity, or ability of patients to recover from the toxicities after induction treatment, are also important and are likely better captured in quality-of-life (QOL) assessments. Of the two trials that measured quality of life, the Maughan et al. (1) trial demonstrated no difference in QOL, and several benefits were demonstrated for the intermittent chemotherapy arm at 24 weeks in the COIN (6) trial. Specifically, there were statistically significant benefits with respect to role functioning (OR, 0.82; 95%CI, 0.70-0.96, p=0.015) and social functioning (OR, 0.82; 95%CI, 0.70-0.96, p=0.016) as well as for several symptom scales including fatigue, nausea and vomiting, appetite loss, constipation, diarrhea, dry or sore mouth, eating or drinking problems, problems handling small objects, and treatment interfering with activities of daily living (all p<0.04).

QUALIFYING STATEMENTS

- Given that the trials included in this systematic review included a variety of maintenance strategies, a definitive recommendation regarding an optimal maintenance strategy is not possible. However, our analyses of strategies that did not use any maintenance systemic therapy did not demonstrate any statistically significant detriment in overall survival. Therefore, this approach may be preferred by patients, as it offers them a complete break from treatment.
- All but one of the intermittent strategies offered 12 to 18 weeks of induction treatment and were monitored with imaging at least every 8 to 12 weeks during the intermittent phase of treatment, with reintroduction of the induction chemotherapy at disease progression. These represent reasonable guidelines to consider when using an intermittent strategy, but adaptation of a strategy to individual circumstances should always be considered. A longer induction period or closer clinical monitoring of patients on maintenance therapy or chemotherapy-free interval might be appropriate for patients with very bulky or symptomatic disease. For some patients like this, an intermittent strategy may not be appropriate.
- Five of the seven trials that contributed to the meta-analyses were based on treatments with FOLFOX chemotherapy, one of the commonly used first-line chemotherapy regimens for mCRC in Ontario. The other two trials included in the meta-analyses used fluoropyrimidine monotherapy or FOLFIRI as induction chemotherapy regimens. Given the acceptability of fluoropyrimidine monotherapy as one of the options for first-line therapy (see EBS #2-5) and the accepted equivalence of FOLFIRI and FOLFOX as first-line therapies (11,12), extrapolation of our conclusions to all commonly used induction chemotherapy regimens is reasonable.
- During maintenance therapy or a chemotherapy-free interval, best supportive care should be continued for patients.

FUTURE RESEARCH

Future research should include a population study to evaluate the impact of intermittent strategies of administering first-line therapy for mCRC on outcomes in routine practice.

RELATED GUIDELINES

- PEBC Evidence-based Series #2-5: *Strategies of Sequential Therapies in Unresectable, Metastatic Colorectal Cancer Treated with Palliative Intent* (currently under development)

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Evidence-Based Series 2-6: Section 2

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

Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer: Evidentiary Base

S. Berry, R. Cosby, T. Asmis, K. Chan, M.K Krzyzanowska, N. Hammad and the Gastrointestinal Disease Site Group

Original Report Date: January 8, 2014

QUESTION

What is the impact of reducing exposure to systemic therapy with intermittent administration strategies on efficacy and toxicity (including length and quality of survival) in inoperable advanced colorectal cancer?

INTRODUCTION

Colorectal cancer is the third most common cancer in Ontario in both sexes, with an estimated 8700 new cases in 2012. Mortality rates have been declining since 1997, but it is estimated that there will be 3450 colorectal cancer deaths in Ontario in 2011, representing 12.4% of all cancer deaths (1). Therefore, improving outcomes for people with colorectal cancer remains a priority.

Since the late 1990s, new effective cytotoxic and biologic agents have emerged for the treatment of unresectable mCRC, and randomized trials demonstrate the benefits of adding these agents to the traditional standard fluoropyrimidine therapy. The median survival of patients treated with these regimens is 20 to 23 months in randomized trials. As patients live longer, it also means a longer exposure to the toxicities of systemic therapies. A number of randomized trials have now studied strategies to ameliorate the toxicities that patients experience. These intermittent chemotherapy strategies involve an induction period with chemotherapy (with or without a biologic) followed by a period during which one or all of the chemotherapy drugs are discontinued, followed by re-introduction of the induction chemotherapy at some point. While one of the important goals of these "stop-and-go" strategies is to reduce side effects and improve patients' quality of life, it is also important to understand the impact of these strategies on efficacy. The Gastrointestinal Disease Site Group (GI DSG) of the PEBC decided that a systematic review of the evidence and a synthesis of the available data would be useful in helping clinicians recommend appropriate treatment strategies for patients with mCRC.

METHODS

The evidence-based series (EBS) guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (2). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one member of the PEBC Gastrointestinal Disease Site Group (GI DSG) working group and one methodologist (Appendix 1).

The systematic review is a convenient and up-to-date source of the best available evidence on intermittent strategies of administering chemotherapy in advanced colorectal cancer. The body of evidence in this review is primarily comprised of mature, randomized controlled trial data. That evidence forms the basis of the recommendations developed by the GI DSG (Appendix 2) presented in Section 1. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

Literature Search Strategy

The MEDLINE (2000 through July [week4] 2013) and EMBASE (2000 through week 30 2013) databases were searched for relevant evidence. The full MEDLINE and EMBASE literature search strategies can be found in Appendix 3. The reference lists from retained articles were also searched for additional relevant trials. In addition, the proceedings of the 2000-2013 American Society of Clinical Oncology (ASCO) and the 2000-2012 European Society of Medical Oncology (ESMO) annual meetings were searched for abstract reports of relevant studies.

Study Selection Criteria

Articles were included if they were published English-language abstracts or fully published reports of Phase II or III randomized controlled trials (RCTs) comparing continuous chemotherapy to an intermittent strategy of chemotherapy, with or without maintenance chemotherapy, in adult patients with metastatic colorectal cancer and included at least one of the outcomes of interest. Syntheses of RCTs in the form of systematic review or meta-analyses were also eligible. If more than one study evaluated the same data set, only the most recent paper was selected for inclusion.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, the data was pooled using the Review Manager software (RevMan 5.1) provided by the Cochrane Collaboration (3). Since hazard ratios (HRs), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes (4), those were extracted directly from the most recently reported trial results. The variances of the hazard ratio estimates were calculated from the reported confidence intervals (CIs) using the methods described by Parmar et al. (4). A random effects model was used for all pooling.

Statistical heterogeneity was calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% were considered indicative of statistical heterogeneity. Results are expressed as hazard ratios with 95%CIs. An HR <1.0 indicates that patients receiving intermittent chemotherapy had a lower probability of experiencing an event (death); conversely, an HR >1.0 suggests that patients receiving continuous chemotherapy experienced a lower probability of an event.

Meta-analyses were only conducted on the overall survival outcome. Given the number of induction and maintenance strategies used in the included trials, after a meta-analysis was conducted on all trials, sensitivity analyses were conducted to determine the robustness of findings across the spectrum of strategies. Some of these sensitivity analyses were suggested during the review process. Patients may prefer intermittent strategies that offer complete breaks from treatment, so several sensitivity analyses were conducted on subsets of these types of trials. Given that combination chemotherapy is most commonly used in clinical practice in Ontario, several sensitivity analyses were also done among these trials.

Meta-analyses conducted were as follows:

- All trials included
- All trials with maintenance therapy
- All trials with no maintenance therapy
    - All trials with no maintenance therapy excluding Labianca et al. (a trial with a unique design – 2 months on and 2 months off treatment in the intermittent arm – that is unlikely to be used in clinical practice)
- All combination chemotherapy induction trials
- Combination chemotherapy trials by Maintenance Strategy as follows:
    - Combination trials with no maintenance therapy
    - Combination trials with no maintenance therapy excluding Labianca et al.
    - Combination trials with a biologic maintenance therapy.

RESULTS

Literature Search Results

The MEDLINE search yielded 532 hits, of which 23 were potentially relevant and were fully reviewed. Five were retained (Table 1, Appendix 4). The EMBASE search yielded 1485 hits, of which 9 were potentially relevant and were fully reviewed. Two of these were retained. Eight abstracts from ASCO were retrieved, and three were retained. No abstracts from ESMO were retained.

Table 1. RCTs selected for inclusion.

Database	Dates searched	Hits	Fully reviewed	Retained
MEDLINE	2000 - July [week4] 2013	532	23	5
EMBASE	2000 - week 30 2013	1485	9	2
ASCO	2000-2013	8	8	3
ESMO	2000-2012	9	9	0
Reference Mining	Not Applicable	0	0	0

Study/Trial Design and Quality

Randomized trials were assessed for key methodological characteristics, using information provided in the trial reports. The following elements were assessed: generation of allocation sequence, allocation concealment, blinding, intention-to-treat analysis, withdrawals, loss to follow-up, funding source, statistical power calculations, length of follow-up, differences in baseline patient characteristics, and early termination.

Outcomes

Study/Trial Design and Quality

All ten trials (5-14) involved adult patients with inoperable locoregional or metastatic colorectal cancer comparing continuous first-line chemotherapy until disease progression (PD) to a planned intermittent chemotherapy strategy, with or without maintenance therapy (Table 2). Of the nine trials (5-13) that reported on performance status (PS) as an eligibility criteria, all allowed patients with a PS of 0-1 or 0-2 to be included. One abstract (14) did not report on the PS of participants. Seven of the trials were superiority trials (5-9,13,14), and three were non-inferiority trials (10-12). The primary outcome of the trials varied. Overall survival (OS) was the primary outcome for three of the trials (5,10,11), progression-free survival (PFS) or time-to-treatment failure (TTF) for four of the trials (7,12-14) and duration of disease control

(DDC) for two of the trials (6,9). The Alexopoulos abstract (8) did not report the primary outcome of the trial. Of the ten trials that comprise this systematic review, there is one single-agent trial (5) and nine combination chemotherapy trials (6-14). Of the combination chemotherapy trials, there were two trials in which the intermittent chemotherapy strategy arm contained 5FU maintenance therapy (6,7), four trials in which the intermittent arm contained no maintenance therapy (8-11), two trials in which the intermittent arm contained a biologic maintenance therapy (12,13) and one trial in which the intermittent chemotherapy arm contained a fluoropyrimidine and a biologic as maintenance therapy (14).

The intermittent chemotherapy arms in each of the trials varied on some key features. All trials continued the intermittent component of the strategy until disease progression except the Labianca trial, which used an "8 week on, 8 week off" treatment schedule after starting. The duration of induction in the intermittent arm varied from 12 (5,6,8-10) up to 18 weeks (12,14), except for the Labianca trial (11) (8-week induction). The induction chemotherapy was re-introduced either at disease progression (5,8-10,13), after completion of a set number of chemotherapy cycles (6,7,11) or was not included as part of the study protocol (12,14). OPTIMOX2 (9) did allow patients' tumours to return to their baseline measurements before re-introducing the induction chemotherapy. RECIST criteria was used to define disease progression (PD) in four trials (9,10,12,13), whereas Tournigand et al. (6) defined PD as an increase of 25% or more of measurable lesions or the appearance of new malignant lesion(s). The definition of PD was not reported in the other five trials (5,7,8,11,14). Frequency of imaging after induction varied from every 8 weeks (9) to every 16 weeks (11), with 3 trials not reporting this variable (7,8,14) (Table 3).

With respect to trial quality, seven trials (5,6,9-13) reported on the generation of allocation sequences, although none reported on allocation concealment. Seven of the trials were open-labelled (i.e., not blinded) (5,6,9-13), and eight were funded by industry (5-7,9,10,12-14). Six of the trials describe an intent-to-treat (ITT) analysis (5,6,10-13). Power calculations were reported for all the trials except for two reported in abstract form (7,8). Similarly, all trials except the CONcePT (7) and Alexopoulos (8) abstracts report that baseline characteristics of participants were balanced. Only three of the studies reported on loss to follow-up (8,10,11), and two of the studies were known to be terminated early (5,7) (Table 4).

Table 2. Characteristics of identified randomized controlled trials.

Trial	Patient characteristics	Site of tumour (%)	Primary outcome	Type of trial	Treatment	Number of patients randomized (evaluated)
SINGLE-AGENT TRIAL						
Maughan 2003 (5)	Primary carcinoma of colon or rectum Inoperative local or metastatic disease No prior chemo for metastatic disease WHO PS 0-2	Colon – 59 Rectum – 31 Rectosigmoid – 1 Other – 1 Unknown - 7	Overall Survival	Superiority	**Intermittent** (12 wks deGramont (15) or Lokich (16) or raltitrexed; CFI; restart at PD) **Continuous** (12 wks deGramont (15) or Lokich (16) or raltitrexed until PD)	178 176
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH 5FU MAINTENANCE THERAPY						
Tournigand 2006 (OPTIMOX1) (6)	Colon or rectal adenocarcinoma Unresectable metastases No prior chemo for metastatic disease Age 18-80, WHO PS 0-2	Colon – 63 Rectum – 34 Other - 3	Duration of Disease Control	Superiority	**Intermittent** (FOLFOX7 – 6 cycles; sLV5FU2 – 12 cycles; FOLFOX7 - 6 cycles) **Continuous** (FOLFOX4 every 2 weeks until PD)	309 311
Grothey 2008 (CONcePT) (7) *Abstract*	Metastatic colorectal cancer No prior therapy for metastatic disease Age ≥18, ECOG PS 0-1 No neuropathy	Colon – 80 Other – NR	Time-to-Treatment Failure	Superiority	**Intermittent** (mFOLFOX 7 + BEV alternate every 8 cycles with and without oxaliplatin) ± CaMg **Continuous** (mFOLFOX7 + BEV every 2 weeks ± CaMg until PD)	180(139) (in total)
COMBINTATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH NO MAINTENANCE THERAPY						
Alexopoulos 2006 (8) *Abstract*	Metastatic colorectal cancer No prior chemo for metastatic disease ECOG PS 0-2	NR	NR	Superiority	**Intermittent** (FOLFIRI – 6 cycles; CFI; restart FOLFIRI at PD) **Continuous** (FOLFIRI – 12 cycles)	20 19
Chibaudel 2009 (OPTIMOX2) (9)	Colon or rectal adenocarcinoma Unresectable metastases No prior chemo for metastatic disease Age 18-80, WHO PS 0-2	Colon – 66 Rectum – 31 Both - 3	Duration of Disease Control	Superiority	**Intermittent** (mFOLFOX7 – 6 cycles; CFI; restart mFOLFOX7 at PD – 6 cycles) **Continuous** (mFOLFOX7 – 6 cycles; sLV5FU2; restart mFOLFOX7 at PD- 6 cycles)	108 (104) 108 (98)
Adams 2011 (COIN) (10)	Adenocarcinoma of the colorectum Inoperatable metastatic or locoregional measurable disease No prior chemo for metastatic disease ≥ 18 years old, WHO PS 0-2	Rectum – 30 Other - NR	Overall Survival	Non-inferiority	**Intermittent** (FOLFOX or CapeOx – 12 weeks; CFI; restart same chemo at PD) **Continuous** (FOLFOX or CapeOx until PD)	815 815
Labianca 2011 (11)	Colorectal cancer Advanced phase of disease No prior chemo for metastatic disease >18 years old, ECOG PS 0-2	Colon – 73 Rectum - 27	Overall Survival	Non-inferiority	**Intermittent** (FOLFIRI every 2 weeks and 2 mos on, 2 mos off until PD) **Continuous** (FOLFIRI every 2 weeks until PD)	167 (147) 170 (146)
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH A BIOLOGIC MAINTENANCE THERAPY						
Diaz-Rubio 2012 (MACRO) (12)	Metastatic colorectal cancer No prior chemo for metastatic disease Age ≥18, ECOG PS 0-2	Colon – 62 Rectum – 27 Both - 11	Progression Free Survival	Non-inferiority	**Intermittent** (BEV + CapeOx – 6 cycles; BEV only until PD) **Continuous** (BEV + CapeOx until PD)	241 239
Tveit 2012 (NORDIC VII) (13)	Metastatic colorectal cancer No prior chemo for advanced or metastatic disease Age 18-75, ECOG PS 0-2	Colon – 59 Rectum – 41	Progression Free Survival	Superiority	**Intermittent** (Cetuximab + FLOX – 16 weeks; Cetuximab; reintroduce FLOX at PD) **Continuous** (FLOX until PD or unacceptable toxicity)	187 185
COMBINATION TRIALS: INTERMITTENT CHEMOTERHAPY WITH A FLUOROPYRIMIDINE AND BIOLOGIC MAINTENANCE THERAPY						
Yalcin 2012 (14) *Abstract*	Metastatic colorectal cancer No prior therapy for metastatic disease	NR	Progression Free Survival	Superiority	**Intermittent** (BEV + CapeOx – 6 cycles; BEV + cape until PD) **Continuous** (BEV + CapeOx until PD)	61 62

BEV = bevacizumab; CaMg = calcium magnesium; cape = capecitabine; CapeOx = capecitabine/oxaliplatin; CFI = chemotherapy-free interval; ECOG = Eastern Cooperative Oncology Group; FLOX = 5-FU/leucovorin/oxaliplatin; FOLFIRI = folinic acid(leucovorin)/5-FU/irinotecan; FOLFOX = folinic acid(leucovorin)/5-FU/oxaliplatin; m = modified; mos = months; NR = not reported; PD = disease progression; PS = performance status; WHO = World Health Organization; 5FU = 5-fluorouracil

Table 3. Characteristics of intermittent chemotherapy strategy in identified randomized controlled trials.

Trial	Treatment	Duration of induction in intermittent arm	Median CFI in trials with no maintenance therapy (months)	Criteria for re-introduction of chemotherapy in intermittent arm	Definition of disease progression	Frequency of Imaging Post Induction
SINGLE-AGENT TRIAL						
Maughan 2003 (5)	**Intermittent** (12 wks deGramont (15) or Lokick (16) or raltitrexed; CFI: restart at PD) **Continuous** (12 wks deGramont (15) or Lokick (16) or raltitrexed, continue until PD)	12 weeks	NA	PD	NR	12 weeks
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH 5FU MAINTENANCE THERAPY						
Tournigand 2006 (OPTIMOX1) (6)	**Intermittent** (FOLFOX7 – 6 cycles; sLV5FU2 – 12 cycles; FOLFOX7 - 6 cycles) **Continuous** (FOLFOX4 every 2 weeks until PD)	12 weeks (6 cycles)	NA	Completion of 24 weeks (12 cycles) of chemotherapy without oxaliplatin	Increase of ≥25% of measurable lesions or appearance of new malignant lesion(s).	12 weeks
Grothey 2008 (CONcePT) (7) *Abstract*	**Intermittent** (mFOLFOX 7 + BEV alternate every 8 cycles with and without oxaliplatin) ± CaMg **Continuous** (mFOLFOX7 + BEV ± CaMg)	16 weeks (8 cycles)	NA	Completion of 16 weeks (8 cycles) of chemotherapy without oxaliplatin (earlier reintroduction of oxaliplatin if tumour progression >50% in maintenance phase)	NR	NR
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH NO MAINTENANCE THERAPY						
Alexopoulos 2006 (8) *Abstract*	**Intermittent** (FOLFIRI – 6 cycles; CFI; restart FOLFIRI at PD) **Continuous** (FOLFIRI – 12 cycles)	12 weeks (6 cycles)	NR	PD	NR	NR
Chibaudel 2009 (OPTIMOX2) (9)	**Intermittent** (mFOLFOX7 – 6 cycles; CFI; restart mFOLFOX7 at PD – 6 cycles) **Continuous** (mFOLFOX7–6 cycles; sLV5FU2 ; restart mFOLFOX7 at PD-6 cycles)	12 weeks (6 cycles)	3.9 NA	PD (or at least before the tumour reached baseline measures in case of previous response)	RECIST criteria	8 weeks
Adams 2011 (COIN) (10)	**Intermittent** (FOLFOX or CapeOx – 12 weeks, CFI, restart same chemo at PD) **Continuous** (FOLFOX or CapeOx until PD)	12 weeks	3.7 NA	PD	RECIST criteria	12 weeks
Labianca 2011 (11)	**Intermittent** (chemotherapy every 2 weeks and 2 mos on, 2 mos off until PD) **Continuous** (chemotherapy every 2 weeks until PD)	8 weeks (4 cycles)	3.5 NA	Completion of 8 weeks (4 cycles) off chemotherapy	NR	16 weeks
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH A BIOLOGIC MAINTENANCE THERAPY						
Diaz-Rubio 2012 (MACRO) (12)	**Intermittent** (BEV + CapeOx- 6 cycles, then BEV only until PD) **Continuous** (BEV + CapeOx until PD)	18 weeks (6 cycles)	NA	Re-introduction not included as part of study protocol	RECIST criteria	9 weeks
Tveit 2012 (NORDIC VII) (13)	**Intermittent** (Cetuximab + FLOX – 16 weeks; Cetuximab; restart FLOX at PD) **Continuous** (FLOX until PD or unacceptable toxicity)	16 weeks (8 cycles)	NA	PD	RECIST criteria	8 weeks
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH A FLUOROPYRIMIDINE AND BIOLOGIC MAINTENANCE						
Yalcin 2012 (14) *Abstract*	**Intermittent** (BEV + CapeOx – 6 cycles; BEV + cape until PD) **Continuous** (BEV + CapeOx until PD)	18 weeks (6 cycles)	NR	Re-introduction not included as part of study protocol	NR	NR

BEV = bevacizumab; CapeOx = capecitabine/oxaliplatin; CFI = chemotherapy-free interval; FOLFOX = folinic acid(leucovorin)/5-fluorouracil/oxaliplatin; m = modified; mos = months; NA = not applicable; NR = not reported; PD = disease progression; 5FU = 5-fluorouracil

Table 4. Methodological quality characteristics of identified randomized controlled trials.

Trial	Generation of allocation sequence reported	Allocation concealment	Blinding	ITT	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
SINGLE-AGENT TRIAL										
Maughan 2003 (5)	Yes	NR	No	Yes	No	Yes	90% power to detect 10% improvement in survival with continuing chemotherapy with 420 pts. Actual accrual 354 pts.	NR	Yes	Yes, for slow accrual
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH 5FU MAINTENANCE THERAPY										
Tournigand 2006 (OPTIMOX1) (6)	Yes	NR	No	Yes	No	Yes	80% power to detect 3-month increase in DDC with 560 pts. Actual accrual 620 pts.	NR	Yes	No
Grothey 2008 (CONcePT) (7) *Abstract*	No	NR	NR	NR	No	Yes	NR	NR	NR	Yes
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH NO MAINTENANCE THERAPY										
Alexopoulos 2006 (8) *Abstract*	No	NR	NR	NR	Yes	NR	NR	Yes	NR	NR
Chibaudel 2009 (OPTIMOX2) (9)	Yes	NR	No	NR	Yes	Yes	Unknown power to detect a 15% increase in DDC at 9 months with 200 pts. Actual accrual 202 pts.	NR	Yes	No
Adams 2011 (COIN) (10)	Yes	NR	No	Yes	Yes	Yes	90% power to detect non-inferiority with respect to survival with 1420 pts and a non-inferiority boundary of 1.162, one-sided log-rank test. Actual accrual 1630 pts.	Yes	Yes	No
Labianca 2011 (11)	Yes	NR	No	Yes	Yes	No	80% power to detect non-inferiority with respect to survival with 310 events and a non-inferiority boundary of 1.36. Actual accrual 337 pts.	Yes	Yes	No
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH A BIOLOGIC MAINTENANCE THERAPY										
Diaz-Rubio 2012 (MACRO) (12)	Yes	NR	No	Yes	Yes	Yes	80% power to detect non-inferiority with respect to PFS with 470 pts and a non-inferiority boundary of 1.32, one-sided, $\alpha = 0.025$, assuming PFS of 10 months in both arms. Actual accrual 480 pts.	NR	Yes	No
Tveit 2012 (NORDIC VII) (13)	Yes	NR	No	Yes	Yes	Yes	80% power to detect an increase in PFS from 7 to 10 months, allowing for two pair-wise analyses at the 2.5% significance level with 550 pts. Actual accrual 566 pts.	NR	Yes	No
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH A FLUOROPYRIMIDINE AND BIOLOGIC MAINTENANCE										
Yalcin 2012 (14) *Abstract*	NR	NR	NR	NR	No	Yes	80% power to detect a 1.5-month increase in median PFS with 118 pts and a SD of 3.9 months, $\alpha = 0.05$, 10% dropout rate.	NR	Yes	NR

DDC = duration of disease control; PFS = progression-free survival; pts = patients; SD = standard deviation

Response and Survival

Seven of the trials report overall response rate (ORR) for the ITT population (5,6,9,10,12-14). In all seven of these trials, overall response rate was similar for the intermittent and continuous chemotherapy arms, although only three (6,10,14) report that the difference found is non-significant (Table 5). Progression-free survival (PFS) for the ITT population is reported in six trials (5,6,9,12-14) but is only significantly different in two of the trials (9,14). Specifically, in the OPTIMOX2 trial (9), PFS was significantly longer in the continuous chemotherapy arm (p=0.0017), whereas in the Yalcin et al. (14) abstract, PFS was significantly longer in the intermittent arm (p=0.002).

Definitions

- **Duration of Disease Control (DDC)** – the progression-free survival (PFS). If FOLFOX was re-introduced, DDC was the initial PFS plus the PFS of the re-introduction of FOLFOX in the case of no progression at the first evaluation after re-introduction. Please refer to Figure 2 in OPTIMOX1 (6).
- **Time-to-Treatment Failure (TTF)** – the time from randomization to treatment discontinuation for any reason.

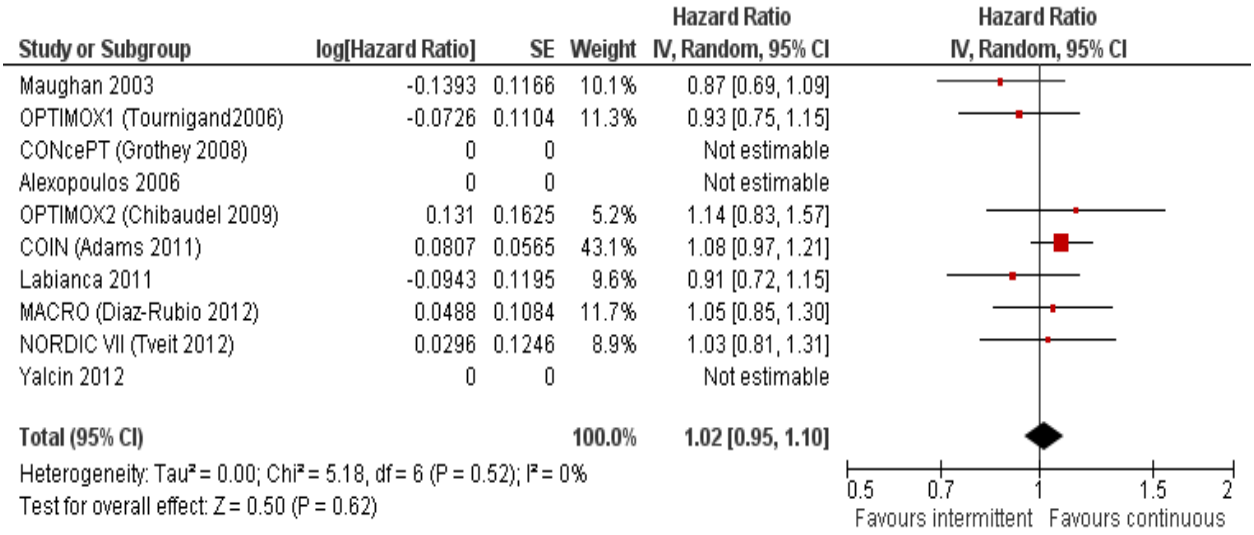
Table 5. Outcomes of identified first-line randomized controlled trials.

Trial	Treatment	N	Overall Survival			Progression-Free Survival		Failure-Free Survival		ORR (%)	Median F/U (mos)
			2-year (%)	Median (mos)	HR (95%CI)	Median (mos)	HR (95%CI)	Median (mos)	HR (95%CI)		
SINGLE-AGENT TRIAL											
Maughan 2003 (5)	Intermittent Continuous	178 176	19 13	10.8 11.3	0.87 (0.69-1.09), p=ns	3.7 4.9	1.20 (0.96-1.49), p=ns	NR	NR	39.0 37.5	16.6
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH 5FU MAINTENANCE THERAPY											
Tournigand 2006 (OPTIMOX1) (6)	Intermittent Continuous	309 311	NR	21.2 19.3	0.93 (0.72-1.11), p=ns	8.7 9.0	1.06 (0.89-1.20), p=ns	**DDC** 10.6 9.0	**DDC** 0.99 (0.81-1.15), p=ns	59.2 58.5 p=ns	31
Grothey 2008 (CONcePT) (7) *Abstract*	Intermittent Continuous	NR NR Total=139	NR	NR	NR	NR	NR	**TTF** 25 18 (wks)	**TTF** 0.58 (0.41-0.83), p=0.0025	NR	NR
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH NO MAINTENANCE THERAPY											
Alexopoulos 2006 (8) *Abstract*	Intermittent Continuous	20 19	NR	15 21	NR, p=ns	NR	NR	**TTF** 9 8	**TTF** NR, p=ns	NR	13
Chibaudel 2009 (OPTIMOX2) (9)	Intermittent Continuous	104 98	39.4 50.0	19.5 23.8	1.14[a] (NR), p=ns	6.6 8.6	1.64[a] (NR), p=0.0017	**DDC** 9.2 13.1	**DDC** 1.41 (1.01-1.96)[a], p=0.046	59.6 59.2 (first 3 mos)	NR
Adams 2011 (COIN) (10)	***ITT*** Intermittent Continuous	 815 815	 26.5 28.7	 14.4 15.8	 1.084 (0.970-1.211)[b], p=NR	 NR	 NR	 7.4 8.4	 NR	 52 51 p=ns	NR
	Per Protocol Intermittent Continuous	 511 467		 18.0 19.6	 1.087 (0.936-1.262)[c], p=NR	 NR	 NR	 8.7 9.2	 NR	 NR	
Labianca 2011 (11)	***ITT*** Intermittent Continuous	 167 170	 NR	 NR	 0.91 (0.72-1.15), p=NR	 NR	 0.98 (0.79-1.21), p=NR	 NR	 NR	 NR	41
	Per Protocol Intermittent Continuous	 147 146	 34 30	 18 17	 0.88 (0.69-1.14), p=0.0008	 6 6	 1.03 (0.81-1.29), p=ns	 NR	 NR	 34 67 p=NR	
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH A BIOLOGIC MAINTENANCE THERAPY											
Diaz-Rubio 2012 (MACRO) (12)	Intermittent Continuous	241 239	NR	20.0 23.2	1.05 (0.85-1.30), p=ns	9.7 10.4	1.10 (0.89-1.35), p=ns	NR	NR	49 47	29.0
Tveit 2012 (NORDIC VII) (13)	Intermittent Continuous	187 185	NR	20.3 20.4	1.03 (0.81-1.32), p=ns	7.3 7.9	NR	NR	NR	47 41	NR
COMBINATION TRIALS: INTERMITTENT CHEMOTERHAPY WITH A FLUOROPYRIMIDINE AND BIOLOGIC MAINTENANCE											
Yalcin 2012 (14) *Abstract*	Intermittent Continuous	NR NR Total=123	NR	23.8 20.2	NR, p=ns	11.0 8.3	NR, p=0.002	NR	NR	66.7 58.9 p=ns	NR

[a]Chibaudel 2009 reports HRs and CIs based on a continuous versus intermittent analysis. This data was inverted so that all the data from each trails was in the same direction (i.e., intermittent versus continuous).
[b]Primary analysis for OS was at 90% level of significance, one-sided and with a calculated 80%CI of 1.008-1.165.
[c]Primary analysis for OS was at 90% level of significance, one-sided and with a calculated 80%CI of 0.986-1.198.
CI = confidence interval; DDC = duration of disease control; F/U = follow-up; HR = hazard ration; ITT = intent-to-treat analysis; mos = months; NR = not reported; ns = non-significant; ORR = objective response rate; TTF = time-to-treatment failure

Median overall survival data were available for nine of the ten trials (5,6,8-14), and HRs were available for seven trials (5,6,9-13). There was no significant difference between intermittent and continuous chemotherapy in the ITT population in any of these trials. Meta-analysis of all the trials includes more than 3000 patients and demonstrates no statistically significant difference between chemotherapy strategies (HR, 1.02; 95%CI, 0.95-1.10, p=0.62) (Figure 1).

Figure 1: Meta-analysis for Overall Survival: All Trials



Several additional subgroup analyses were conducted as follows. Table 6 summarizes the results of all the meta-analysis conducted.

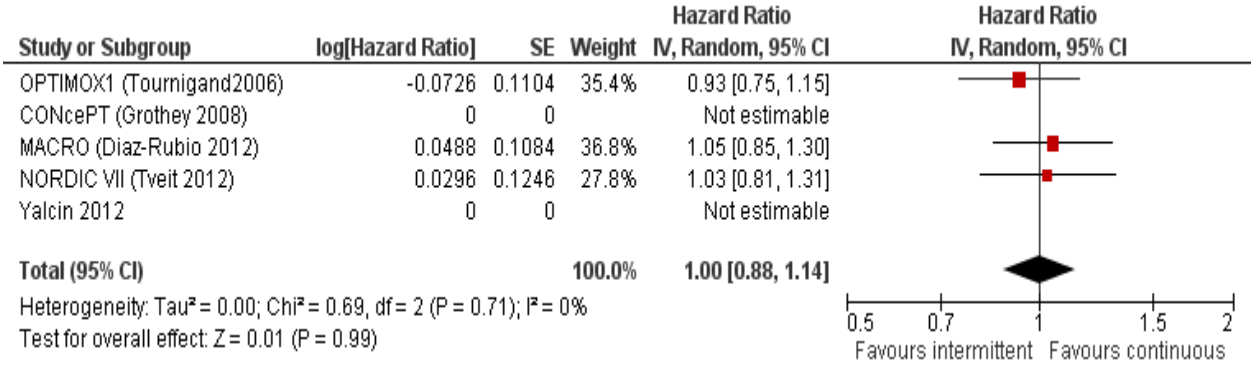
Table 6. Summary of overall survival hazard ratios, 95% confidence intervals and p-values for all meta-analyses conducted.

Analysis	Hazard Ratio	95% Confidence Interval	p-value
All trials	1.02	0.95-1.10	0.62
All trials with maintenance therapy	1.00	0.88-1.14	0.99
All trials with no maintenance therapy	1.01	0.89-1.14	0.92
All trials with no maintenance therapy excluding Labianca (11)	1.03	0.89-1.19	0.69
All combination chemotherapy trials	1.04	0.96-1.12	0.35
Combination chemotherapy trials by maintenance strategy			
Combination trials with no maintenance therapy	1.06	0.96-1.16	0.25
Combination trials with no maintenance therapy excluding Labianca (11)	1.09 1.04	0.98-1.21 0.89-1.22	0.11 0.62
Combination Trials with biologic maintenance therapy			

All Trials with Maintenance Therapy (Figure 2, Table 6)

A meta-analysis of all trials with maintenance therapy (single-agent and combination trials) (Figure 2) demonstrates no significant difference between continuous and intermittent chemotherapy with respect to overall survival (HR, 1.00; 95%CI, 0.88-1.14, p=0.99) and no heterogeneity.

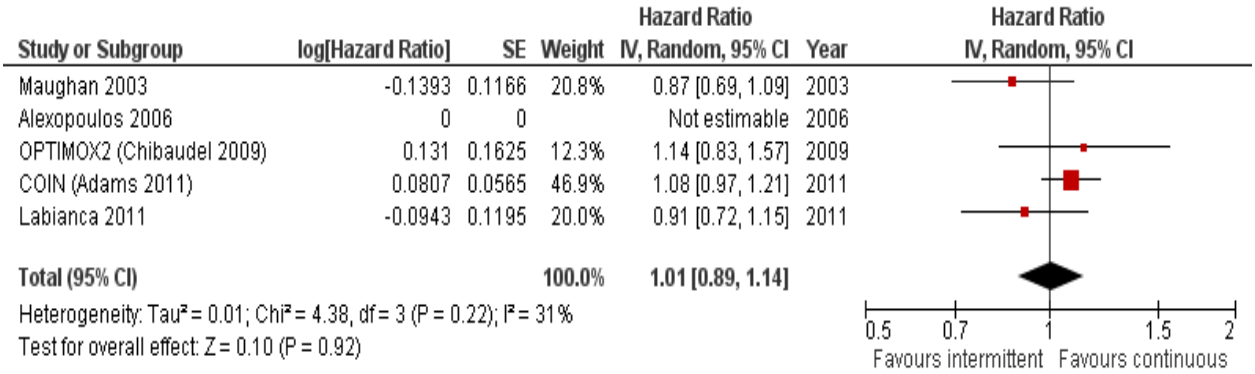
Figure 2: Meta-analysis for Overall Survival: All Trials with Maintenance Therapy



All Trials with No Maintenance Therapy (Figure 3, Table 6)

Meta-analysis of all trials with no maintenance therapy (single-agent and combination chemotherapy induction trials) (Figure 3) demonstrates no statistically significant difference in overall survival (HR, 1.01; 95%CI, 0.89-1.14, p=0.92). There is low heterogeneity (17) in this meta-analysis (31%, p=0.22).

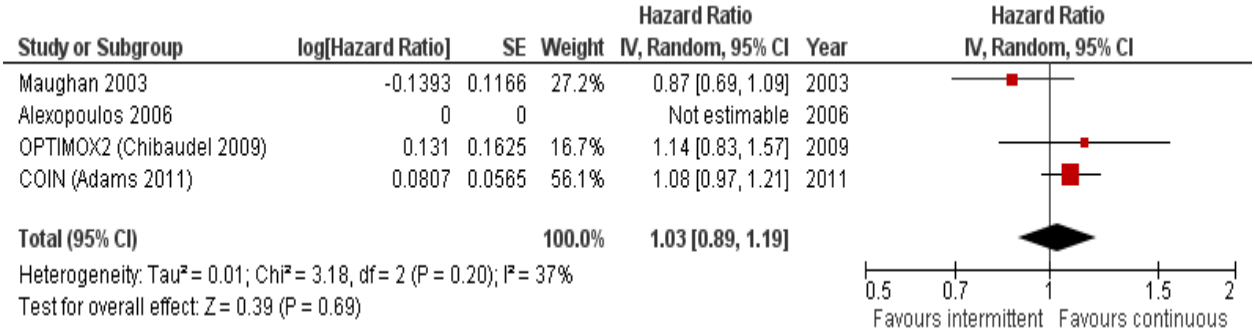
Figure 3: Meta-analysis for Overall Survival: All Trials with No Maintenance Therapy



All Trials with No Maintenance Therapy [excluding Labianca et al. (11)] (Figure 4, Table 6)

A subsequent analysis of trials with no maintenance therapy excluding the Labianca et al. trial (11), owing to its unique approach to the stop-and-go principle compared to the other trials (Figure 4), demonstrates similar non-significant results (HR, 1.03, 95%CI, 0.89-1.19, p=0.69). There is low heterogeneity (17) in this meta-analyses as well (I^2=37%; p=0.20).

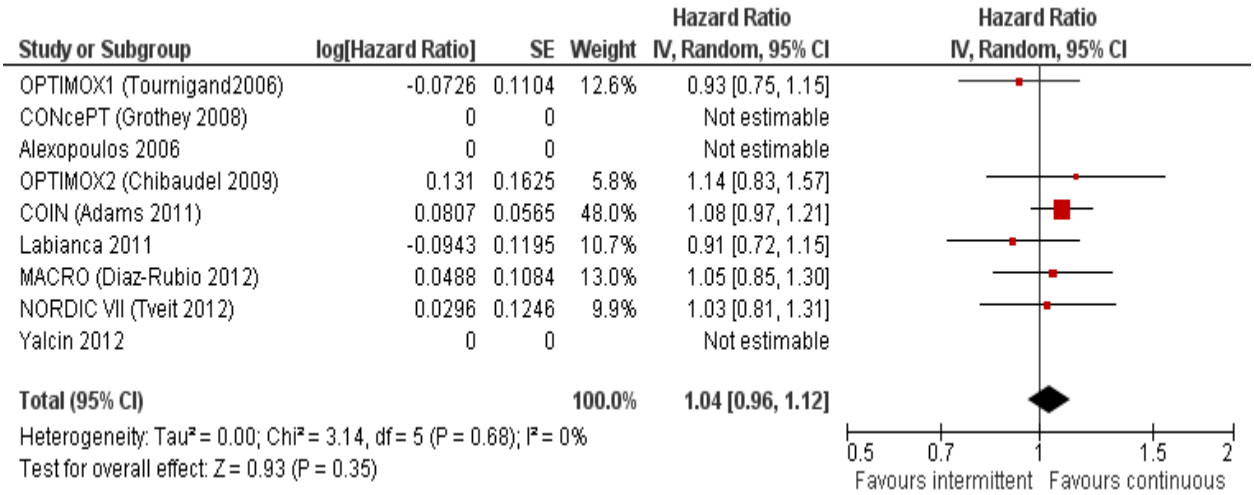
Figure 4: Meta-analysis for Overall Survival: All Trials with No Maintenance Therapy Excluding Labianca (11)



All Combination Trials (Figure 5, Table 6)

Meta-analysis of all combination chemotherapy trials demonstrates no significant difference between intermittent and continuous chemotherapy strategies (HR, 1.04; 95%CI, 0.96-1.12, p=0.35).

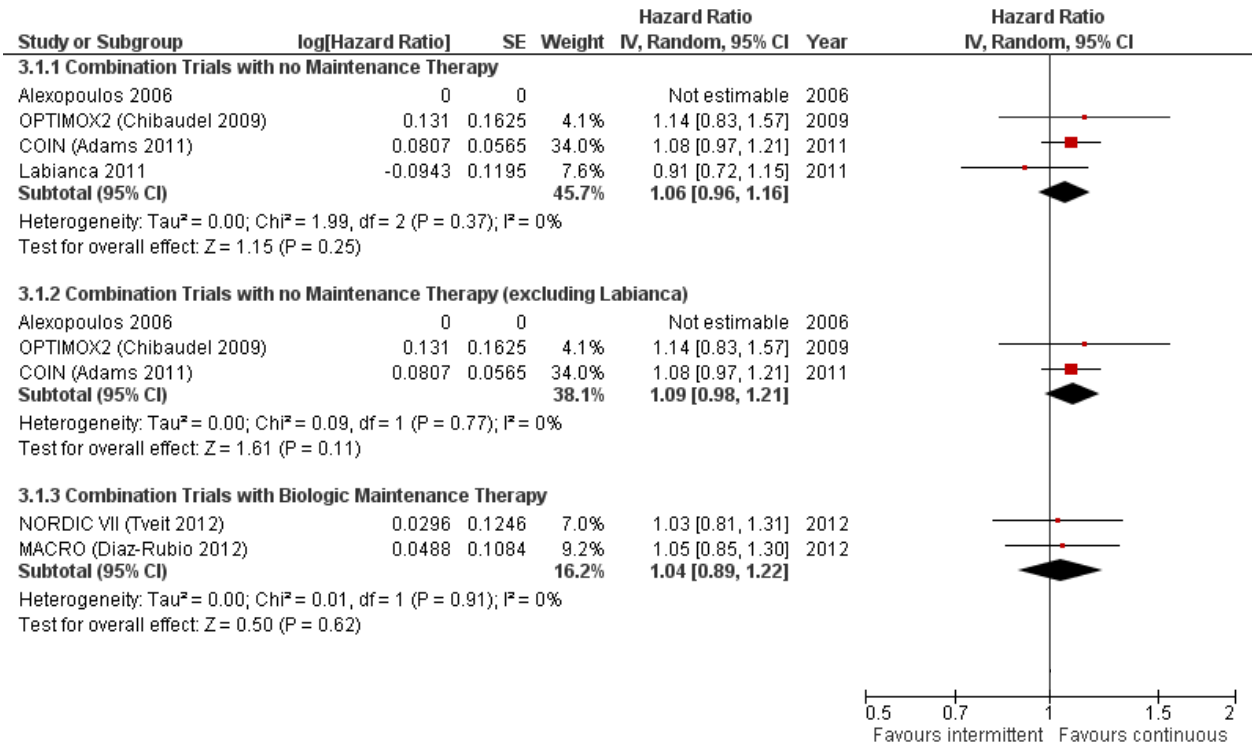
Figure 5: Meta-analysis for Overall Survival: All Combination Chemotherapy Trials



Combination Trials by Maintenance Strategy (Figure 6, Table 6)

Figure 6 shows the subgroup analyses performed to examine the impact of the different induction and maintenance strategies on OS. Only those subgroups with at least two studies for which HRs are available are shown (i.e., combination trials with no maintenance, combination trials with no maintenance excluding Labianca et al. (11) owing to its unique strategy and combination trials with a biologic maintenance). None of these subgroup analyses demonstrate a significant difference in overall survival between continuous and intermittent chemotherapy strategies, and none of these meta-analyses demonstrates any heterogeneity. The other subgroups (i.e., single-agent trials, combination trials with 5FU maintenance, and combination trials with a fluoropyrimidine and biologic maintenance) are not shown, as these subgroups had either only one trial within the subgroup or only one of the trials within the subgroup had an HR available.

Figure 6: Meta-analysis for Overall Survival: Combination Trials by Maintenance Strategy



Toxicity

With respect to grade 3-4 hematologic toxicity, there were similar rates of anemia with both chemotherapy strategies in all the trials that reported this outcome. There were more cases of neutropenia with continuous chemotherapy in OPTIMOX1 (6) and OPTIMOX2 (9), although it was only significant in OPTIMOX 1 (p=0.002) (Table 7). Thrombocytopenia results were mixed. Of the five trials that reported this outcome, the incidence was similar for both chemotherapy strategies in three of the trials (5,11,13), non-significantly increased in the continuous chemotherapy arm of OPTIMOX2 (9), and significantly increased for the intermittent chemotherapy arm in OPTIMOX1 (6). Febrile neutropenia and leucopenia were rarely reported (Table 7).

Incidence of grade 3-4 non-hematologic toxicities tended to be similar for both chemotherapy strategies, with the following notable exceptions (Table 7). The intermittent strategy resulted in significantly more cases of the following outcomes in the trials noted: nausea/vomiting (6), mucositis (6) and hand-foot syndrome/rash (6,13). The continuous chemotherapy strategy resulted in significantly more cases of the following outcomes in the trials noted: fatigue (12), neurologic toxicity (12) and hand-foot syndrome (12).

Table 7. Grade 3-4 hematologic and non-hematologic toxicities of identified randomized controlled trials.

TRIAL	TREATMENT	HEMATOLOGIC TOXCITY (%)					NON-HEMATOLOGIC TOXICITY (%)										
		Anemia	Neutropenia	Febrile Neutropenia	Leucopenia	Thrombo-cytopenia	Diarrhea	Nausea	Vomiting	Stomatitis	Anorexia	Alopecia	Fatigue	Infection	Mucositis	Neurologic	Hand-Foot Syndrome/ Rash
SINGLE-AGENT TRIAL																	
Maughan 2003 (5)	Intermittent Continuous	1 5	4 2	NR	4 2	1 1	6 10	9 6	7 5	2 4	13 12	2 2	24 26	NR	NR	NR	2 4
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH 5FU MAINTENANCE THERAPY																	
Tournigand 2006 (OPTIMOX1) (6)	Intermittent Continuous	1 2 p=ns	21 32 p=0.002	NR	NR	9 4 p=0.006	10 11 p=ns	10 5 p=0.040		NR	NR	NR	NR	NR	6 3 p=0.031	13 18 p=ns	3 0 p=0.006
Grothey 2008 (CONcePT) (7) *Abstract*	Intermittent Continuous	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH NO MAINTENANCE THERAPY																	
Alexopoulos 2006 (8) *Abstract*	Intermittent Continuous	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chibaudel 2009 (OPTIMOX2)[a] (9)	Intermittent Continuous	0.0 0.0	11.7 21.4 p=ns	NR	NR	3.9 8.2 p=ns	3.9 3.1	NR	3.9 1.0	NR	NR	NR	NR	NR	1.9 1.0	4.9 2.9	0.0 0.0
Adams 2011 (COIN) (10)	Intermittent Continuous	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Labianca 2011 (11)	Intermittent Continuous	0 1 p=ns	2 2 p=ns	NR	NR	3 3 p=ns	13 13 p=ns	3 3 p=ns	1 3 p=ns	NR	NR	1 2 p=ns	NR	NR	0 0 p=ns	NR	NR
COMBINATION TRIALS: INTERMITTENT CHEMOTHERAPY WITH A BIOLOGIC MAINTENANCE THERAPY																	
Diaz-Rubio 2012 (MACRO) (12)	Intermittent Continuous	NR	NR	NR	NR	NR	13 11 p=ns	NR	NR	NR	NR	NR	4 10 p=0.01	NR	NR	8 26 p<0.0001	7 13 p=0.003
Tviet 2012 (NORDIC VII) (13)	Intermittent Continuous	2 1	49 47	11 9	17 21	2 3	16 10 p=ns	5 3	2 0	2 1	NR	NR	11 10	10 5	NR	14 22	29 1 p<0.01
COMBINATION TRIALS: INTERMITTENT CHEMOTERHAPY WITH A FLUOROPYRIMIDINE AND BIOLOGIC MAINTENANCE																	
Yalcin 2012 (14) *Abstract*	Intermittent Continuous	NR	NR	NR	NR	NR	3.3 9.7	NR	NR	NR	NR	NR	NR	NR	NR	3.3 4.8	1.6 3.2

[a]Toxicity during cycles 1-6.

Quality of Life

Only two of the trials identified for this systematic review reported quality-of-life (QOL) data (5,10). Maughan et al. (5) administered the Hospital Anxiety and Depression Scale (HADS) and the European Organization for Research Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ C30) as well as six other questions to trial patients prior to randomization and every six weeks thereafter. They report that the patients in the intermittent and continuous chemotherapy arms of the trial were similar with respect to physical functioning, overall health, general symptoms and psychological distress (5). In addition, most of the patients in both groups reported that they felt that their treatment was worthwhile.

COIN (10) administered the EORTC QLQ C30 as well as five other questions to patients at baseline, six weeks, 12 weeks and every 12 weeks thereafter. These authors note that the QOL questionnaires were completed by less than 67% of patients. They also report that there were no clear differences in the baseline characteristics between those who completed the QOL questionnaires and all patients randomized, but note that they cannot eliminate the risk of differences existing. At baseline, there were no significant differences between patients in the two arms of the trial. At 12 weeks, there were still no differences between patients in the two arms of the trial except for a significant detriment with respect to problems in eating or drinking for those in the intermittent chemotherapy arm (OR, 1.23; 95%CI, 1.00-1.50, p=0.045). At 24 weeks, there were significant benefits for the intermittent chemotherapy arm for role functioning (OR, 0.82; 95%CI, 0.70-0.96, p=0.015) and social functioning (OR, 0.82; 95%CI, 0.70-0.96, p=0.016). At this time point, there were also significant benefits for the intermittent chemotherapy arm for several symptom scales including fatigue, nausea and vomiting, appetite loss, constipation, diarrhea, dry or sore mouth, eating or drinking problems, problems handling small objects, and treatment interfering with activities of daily living (all $p<0.04$). At 12 weeks, there was a significant detriment for intermittent chemotherapy for pain (OR, 1.38; 95%CI, 1.16-1.64), p=0.00029).

ONGOING TRIALS

The NCI® database of ongoing clinical trials (http://clinicaltrials.gov/ct2/search) was searched on August 6, 2013. Six relevant Phase II, III and IV clinical trials were found and are described in Table 8 below.

Table 8. Ongoing randomized trials of intermittent strategies of systemic therapy administration for untreated, unresectable metastatic colorectal cancer.

Title	OPTIMOX1 in Chinese mCRC patients
Protocol ID	NCT01023633
Study start date	October 2009
Date last modified	December 2009
Type of trial	Phase IV RCT, open-label, active control, parallel assignment, safety/efficacy study
Comparison	FOLFOX4 until PD (max 24 cycles) vs. FOLFOX4 (6 cycles), followed by 5FU/LV (12 cycles), reintroduce FOLFOX4 (6 cycles)
Primary endpoint	Duration of disease control
Accrual	Target enrolment = 300
Sponsorship	Nanjing Medical University
Status	Recruiting
Title	Safety and efficacy study of mFOLFOX-6 plus cetuximab for 8 cycles followed by mFOLFOX-6 plus cetuximab or single agent cetuximab as maintenance therapy in patients with metastatic colorectal cancer and WT KRAS tumours (MACRO-2)
Protocol ID	NCT01161316
Study start date	August 2010
Date last modified	February 2013
Type of trial	Phase II RCT, open-label, active control, parallel assignment, safety/efficacy study
Comparison	mFOLFOX6 + cetuximab until PD vs. mFOLFOX6 (8 cycles) + cetuximab, followed by cetuximab alone until PD
Primary endpoint	Progression free survival
Accrual	Target enrollment = 192
Sponsorship	Spanish Cooperative Group for Gastrointestinal Tumour Therapy
Status	Ongoing but not recruiting
Title	Avastin and chemotherapy followed by a KRAS stratified randomization to maintenance treatment for first line treatment of metastatic colorectal cancer (ACT2)
Protocol ID	NCT01229813
Study start date	October 2010
Date last modified	November 2012
Type of trial	Phase III RCT, open-label, active control, parallel assignment, efficacy study
Comparison	KRAS WT – Bevacizumab + erlotinib vs. bevacizumab alone; KRAS mutated – Bevacizumab vs. low dose capecitabine
Primary endpoint	Progression free survival
Accrual	Target enrolment = 181
Sponsorship	Lund University Hospital; Hoffman-La Roche
Status	Ongoing but not recruiting
Title	Maintenance treatment versus observation after induction in advanced colorectal carcinoma (CAIRO3)
Protocol ID	NCT00442637
Study start date	January 2007
Date last modified	August 2012
Type of trial	Phase III RCT, open-label, observational control, parallel assignment, safety/efficacy study
Comparison	Capecabine/bevacizumab vs. Observation following induction chemotherapy
Primary endpoint	Progression free survival after re-introduction of chemotherapy; Secondary endpoints are overall survival, toxicity and quality of life
Accrual	Target enrolment = 635
Sponsorship	Dutch Colorectal Cancer Group; Koningin Wilhelmina Fonds, Sanofi-Aventis, Hoffman-La Roche
Status	Ongoing but not recruiting
Title	A study of avastin (bevacizumab) and xeloda (capecitabine) as maintenance treatment in patients with metastatic colorectal cancer
Protocol ID	NCT00623805
Study start date	February 2008
Date last modified	July 2013
Type of trial	Phase III RCT, open-label, active control, parallel assignment, efficacy study
Comparison	Avastin/Oxaliplatin/Xeloda until PD vs. Xeloda (6 cycles) + Avastin/Xeloda until PD
Primary endpoint	Progression free survival
Accrual	Enrollment = 123
Sponsorship	Hoffman-La Roche
Status	Completed

Title	Combination chemotherapy and bevacizumab with or without bevacizumab maintenance therapy in treating patients with metastatic colorectal cancer
Protocol ID	NCT00952029
Study start date	March 2010
Date last modified	June 2013
Type of trial	Phase III RCT, open-label, active control, parallel assignment, efficacy study
Comparison	FOLFIRI/Bevacizumab (12 cycles) followed by bevacizumab maintenance vs. FOLFIRI/Bevacizumab (12 cycles) followed by chemotherapy-free interval
Primary endpoint	Duration of disease control
Accrual	Target Enrollment = 492
Sponsorship	Federation Francophone de Cancerologie Digestive
Status	Recruiting

DISCUSSION

Since the late 1990s, many new effective cytotoxic and biologic agents have emerged for the treatment of unresectable mCRC. Randomized trials have demonstrated the benefits of adding these agents to the traditional standard fluoropyrimidine therapy. Subsequently, randomized trials were designed that assessed whether different strategies of administering these drugs would maintain efficacy while reducing toxicity from prolonged exposure to these agents and improving QOL. One strategy that emerged was using intermittent systemic therapy administration with scheduled breaks from one or more of the agents used during an "induction period." This systematic review and meta-analysis of ten randomized trials using a variety of intermittent strategies confirmed that regardless of intermittent strategy used, survival was not compromised.

With respect to survival, none of the seven individual trials (5,6,9-13) that reported hazard ratios on this outcome demonstrated a statistically significant difference between continuous and intermittent chemotherapy strategies. Meta-analysis of these trials for overall survival also demonstrates no statistically significant difference (Figure 1; HR, 1.02; 95%CI, 0.95-1.10, p=0.62). Additionally, no subgroup of trials based on the type of induction or maintenance therapy in the intermittent arm demonstrates a statistically significant difference in overall survival between the intermittent and continuous chemotherapy arms (Figure 6). Similarly, grouping of trials based on the presence or absence of maintenance therapy demonstrates no significant difference with respect to overall survival between intermittent and continuous chemotherapy strategies (Figures 2-6).

In contrast to this finding, another recent systematic review and meta-analysis by Pereira et al. (18) comparing intermittent and continuous chemotherapy strategies concludes that continuous chemotherapy has a significant, albeit modest, improvement in survival (HR, 0.90; 95%CI, 0.82-0.99, p=0.03) over intermittent chemotherapy. However, there are two main concerns with the systematic review. It only included five trials, one of which being the COIN-B (19) trial. COIN-B does not have a true continuous chemotherapy arm. After a 12-week induction with combination chemotherapy and cetuximab, patients were randomized to either single-agent cetuximab as maintenance versus a complete break from therapy. Therefore, it was not included in the present systematic review. Secondly, the forest plot of the Pereira et al. (18) meta-analysis shows the Maughan et al. trial (5) to have an overall survival HR of 0.87 in favour of continuous chemotherapy when, in fact, the overall survival HR in this trial is 0.87 in favour of intermittent chemotherapy. Given that the Maughan et al. (5) trial accounts for 17.1% of the result and the confidence interval for the HR is so close to 1.00, it is likely that the conclusion of the Pereira et al. (18) systematic review will not be maintained when this error is corrected.

Quality of life (QOL) was only reported in two of the trials identified for this systematic review (5,10). Maughan et al. (5) report that the patients in the intermittent and continuous chemotherapy arms of the trial were similar with respect to physical functioning, overall health, general symptoms and psychological distress. In addition, most of the patients in both groups reported that they felt that their treatment was worthwhile. In the COIN trial (10), there were no significant differences between patients in the two arms of the trial at baseline. Although there was a detriment seen in the pain control domain for patients on intermittent therapy at 12 weeks (OR, 1.38, p=0.00029), by 24 weeks, several benefits for the intermittent chemotherapy arm had emerged: specifically, there were statistically significant benefits with respect to role functioning (OR, 0.82; 95%CI, 0.70-0.96, p=0.015) and social functioning (OR, 0.82; 95%CI, 0.70-0.96, p=0.016) as well as for several symptom scales including fatigue, nausea and vomiting, appetite loss, constipation, diarrhea, dry or sore mouth, eating or drinking

problems, problems handling small objects, and treatment interfering with activities of daily living (all $p<0.04$).

Hematological toxicity data shows similar rates of grade 3-4 anemia with both chemotherapy strategies in trials reporting this outcome. There were more cases of neutropenia with continuous chemotherapy in OPTIMOX1 (6) and OPTIMOX2 (9), although it was only significant in OPTIMOX 1 ($p=0.002$) (Table 6). Thrombocytopenia was significantly increased for the intermittent chemotherapy arm in OPTIMOX1 (6). The intermittent strategy resulted in significantly more grade 3-4 cases of nausea/vomiting (6), mucositis (6) and hand-foot syndrome/rash (6,13). The continuous chemotherapy strategy resulted in significantly more cases of fatigue (12), neurologic toxicity (12) and hand-foot syndrome (12).

Non-hematologic toxicities tended to be similar for both chemotherapy strategies. There are limitations in interpreting this type of toxicity data for randomized trials of continuous versus intermittent systemic therapy. These toxicity assessments reflect maximal levels of toxicity experienced during exposure to the treatment on that arm of the trial. These measures are important, but for patients on intermittent treatment, duration of exposure to toxicity, or ability of patients to recover from the toxicities after induction treatment, are also important and are likely better captured in QOL assessments, as described above.

An intermittent strategy did not compromise response rates observed, and a PFS detriment was only seen in two of the six trials where this outcome was reported. In one trial, PFS was shorter in the intermittent arm (9), and in the other trial, PFS was shorter in the continuous arm (14).

In summary, this meta-analysis demonstrates that there is no statistically significant difference in survival between intermittent and continuous strategies of delivering chemotherapy for first-line treatment of mCRC. Two trials assessed QOL. The single-agent induction trial (5) showed no differences in QOL between arms, and the QOL of patients on the intermittent arm of the COIN trial with combination chemotherapy as induction showed that patients on the intermittent arm benefited in terms of better functioning and fewer symptoms related to treatment. The findings for overall survival were robust across a broad range of induction therapies, chemotherapy backbones and maintenance treatments.

Clinicians, therefore, have a range of acceptable strategies that they could consider and offer patients who want to consider breaks from treatment. Patients may prefer strategies that offer a true break from all systemic therapies, so the analyses of these strategies warrant closer consideration. The meta-analysis of the subset of all trials with no maintenance therapy in the intermittent arm (Figure 3) demonstrates that the hazard ratio for overall survival is 1.01. Further sensitivity analyses demonstrated no detriment in OS for any subset of this group of trials, suggesting that patients can be offered strategies with complete breaks from chemotherapy without compromising their survival (Table 6).

All intermittent strategies offered 12 to 18 weeks of induction treatment and were monitored with imaging at least every 8 to 12 weeks during the intermittent phase of treatment. These represent reasonable guidelines to consider when using an intermittent strategy, but adaptation of a strategy to individual circumstances need always be considered (for instance, a longer induction period or closer clinical monitoring of patients on maintenance therapy if they have very bulky or symptomatic disease). For some patients like this, an intermittent strategy may not be appropriate. Five of the seven trials that contributed to the meta-analyses were based on treatments with FOLFOX chemotherapy, one of the commonly used first-line chemotherapy regimens for mCRC in Ontario. The other two trials included in the meta-analyses used fluoropyrimidine monotherapy or FOLFIRI as induction chemotherapy regimens. Given the acceptability of fluoropyrimidine monotherapy as one of the options for first-line therapy (see EBS #2-5) and the accepted equivalence of FOLFIRI and FOLFOX as first-

line therapies (20,21), extrapolation of our conclusions to all commonly used induction chemotherapy regimens is reasonable.

Preliminary results of the CAIRO3 trial (22) were presented at the 2013 ASCO annual meeting. In this trial, 558 patients with unresectable mCRC had 12 weeks of CapeOx + Bev induction and were then randomized to maintenance treatment with reduced dose, continuous capecitabine with bevacizumab, or no maintenance treatment. This trial cannot be formally included in the current systematic review and meta-analysis at this time, as only preliminary OS data are available. However, as a large trial of an intermittent chemotherapy strategy, the results of this trial are relevant to our analysis, in particular the sensitivity analyses of trials that included complete breaks from treatment. The OS hazard ratio for the intermittent arm in CAIRO3 (22) presentation at ASCO 2013 was 1.15 (p=0·156). One of the sensitivity analyses (Figure 6 – part 3.1.2) in the current systematic review includes the two trials most similar in design to CAIRO3. These three trials with chemotherapy-free intervals, COIN (10), OPTIMOX2 (9), and CAIRO3 (22), are the most relevant to current practice in that they use a combination chemotherapy induction (unlike Maughan at al.) and have maintenance periods that continue until progression of disease in the intermittent arm (unlike Labianca et al.). The hazard ratio for OS in the sensitivity analysis that included only COIN (10) and OPTIMOX2 (9) was 1.09 (95%CI, 0.98–1.21, p=0.11), therefore it is possible that including the CAIRO3 (22) trial in this sensitivity analysis could demonstrate a statistically significant detriment in OS. However, there are two caveats. First, even if statistically significant, the OS HR would be somewhere between 1.09 and 1.15, and the clinical significance of this detriment would be questionable. Second, these conclusions would only apply to the results of one sensitivity analysis, albeit the most clinically relevant one. Ultimately, any definitive conclusions await the final OS results of CAIRO3.

Finally, a recent analysis of population-based data on the use of intermittent strategies (23) in the "real world" concludes that the use of complete chemotherapy breaks as an intermittent strategy is associated with lower toxicity, without any apparent evidence of negative impact on survival. This study suggests that clinicians are making correct decisions, in concert with their patients, regarding the use of chemotherapy breaks.

CONCLUSIONS

This meta-analysis demonstrates that intermittent strategies of administering first-line systemic therapies to patients with unresectable, metastatic colorectal cancer do not result in a statistically significant reduction in overall survival, and either improve or maintain quality of life compared to continuous administration of therapy. Patients who want a break from treatment can be reassured that intermittent strategies of administering first-line therapy are a reasonable alternative to continuous administration. Intermittent systemic treatment strategies should be part of an informed discussion of treatment options for this group of patients.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, GI DSG members, and internal and external reviewers were asked to disclose potential conflicts of interest. Four authors declared they had no conflicts (RC, KC, MKK, NH). Two authors (SB and TA) declared conflicts. One author (SB) reported receiving more than $5000 in a single year for consulting work and/or honoraria from Sanofi and Roche pharmaceutical companies. Another author (TA) reported receiving more than $5000 in a single year and/or other support from Sanofi-Aventis, Pfizer and Roche pharmaceutical companies. This author also declared receiving grant support from Sanofi-Aventis, Roche and Pfizer, being the principal investigator for ImClone CP-120709, and publishing an editorial and providing an opinion piece for the Globe and Mail.

For the expert Panel 18 members declared they had no conflicts of interest and six (NC, DJ, CB, SW, KZ and PK) declared conflicts. NC reported receiving a $1000 education grant from Novartis in 2009. DJ reported receiving a $100,000 grant from Sanofi-Aventis to study triple combination (IXO) as induction therapy for rectal cancer. This member is a local principal investigator (PI) on many mCRC studies and the overall study PI on a trial comparing cetuximab versus best supportive care in refractory CRC (NCIC C017). CB reported receiving $5000 or more in a single year to act in a consulting capacity (Advisory Boards) for Amgen and Roche and $6000 from Roche for travel support to several conferences. CB also holds a grant from CIHR-Roche for $76,000 as well as consortium funding of $40,000. SW reported receiving honoraria from Roche and Amgen for speaking and being on advisory boards as well as receiving grant support from Amgen. KZ received travel support from Sanofi of $5000 or more in a single year to attend an international meeting. PK received a research grant from Sanofi-Aventis for $25,000.

All three RAP reviewers declared they had no conflicts.

There were three Targeted Peer Reviewers. One reviewer (WC) declared he had no conflicts of interest. Two reviewers did declare conflicts. JM is the principal investigator for the following trials: CALGB 80702, a phase II trial of vandetanib plus cetuximab and irinotechan in 2nd and 3rd line mCRC, phase II trial of 5-FU/cetuximab/XRT as neoadjuvant therapy in stage II and III rectal cancer, MEGF0444AG, and FOLFIRI +/- G6624 and 2nd line therapy in KRAS mutant CRC. This reviewer also spoke at the 2012 ASCO conference on the topic of this guideline. LS has received $5000 or more in a single year to participate in several scientific advisory boards for Roche and has also led studies involving bevacizumab and cetuximab.

The COIs declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.

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1. Hans Messersmith, PEBC Assistant Director, Quality and Methods
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5. Internal Peer Reviewers: Rovena Tey and Norma Varela
6. Bruce Histed for copy editing
7. Report Approval Panel Reviewers: Melissa Brouwers, Gail Darling and Laurie Elit
8. Targeted Peer Reviewers: Winson Cheung, Jeffrey Meyerhardt and Leonard Saltz

For a complete list of the GI DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/

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Appendix 1. Members of the Start/Stop Strategies in Advanced Colorectal Cancer Working Group.

Chair:

Scott Berry	Medical Oncologist, Odette Cancer Centre, Toronto, ON

Panel Members:

Tim Asmis	Medical Oncologist, Ottawa Hospital Cancer Centre, Ottawa, ON
Kelvin Chan	Medical Oncologist, Odette Cancer Centre, Toronto, ON
Roxanne Cosby	Methodologist, McMaster University, Hamilton, ON
Nazik Hammad	Medical Oncologist, Kingston, ON
Monika Krzyzanowska	Medical Oncologist, Princess Margaret Hospital, Toronto, ON

Appendix 2. Members of the Gastrointestinal Disease Site Group

Co-Chairs:

Jim Biagi	Medical Oncologist
Rebecca Wong	Radiation Oncologist

Members:

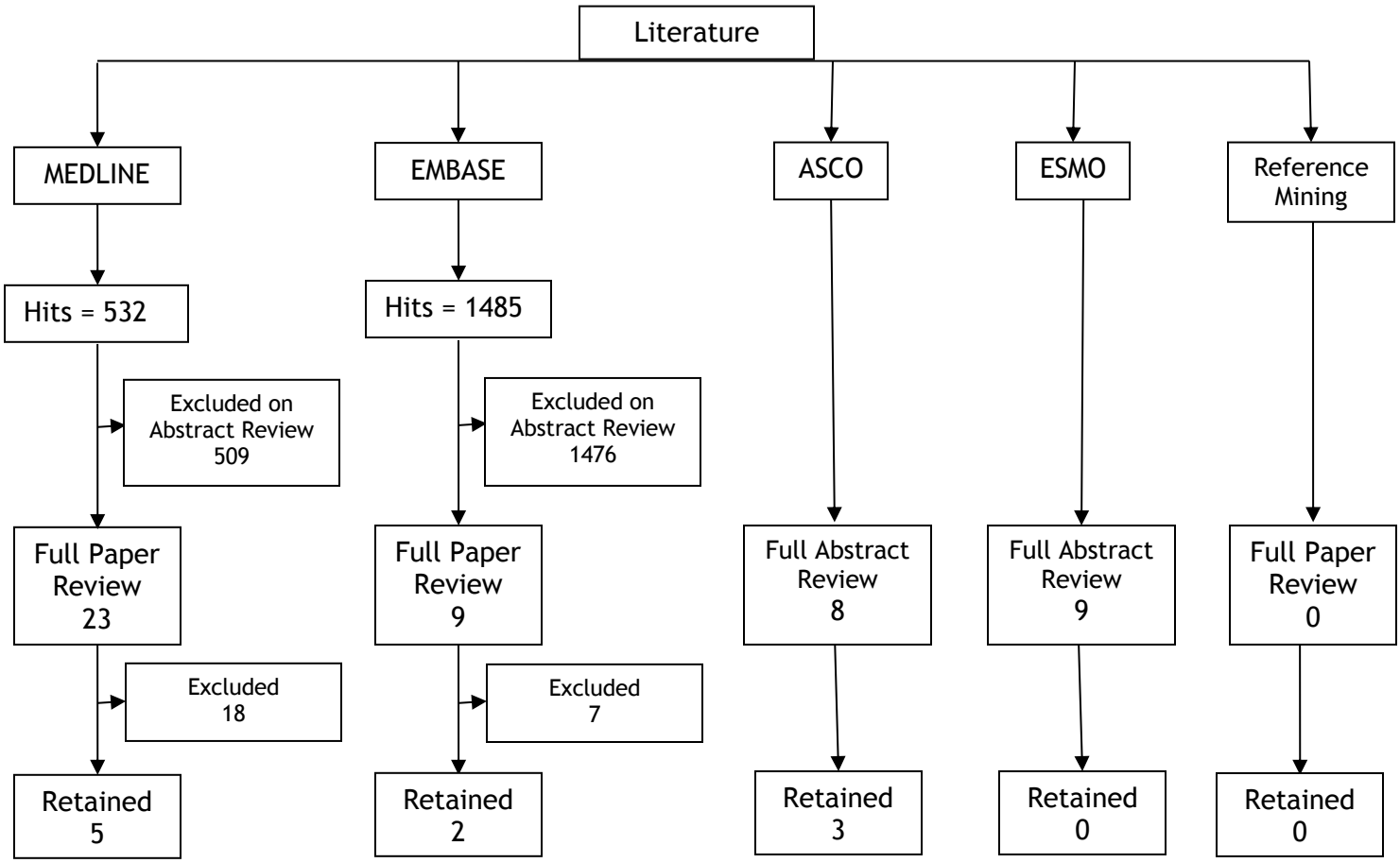
Belal Ahmad	Radiation Oncologist
Tim Asmis	Medical Oncologist
Scott Berry	Medical Oncologist
Christine Brezden-Masley	Medical Oncologist
Kelvin Chan	Medical Oncologist
Charles Cho	Radiation Oncologist
Murray Citron	Patient Representative
Natalie Coburn	Surgical Oncologist
Roxanne Cosby	Methodologist
Craig Earle	Medical Oncologist
Tarek Elfiki	Medical Oncologist
Nazik Hammad	Medical Oncologist
Derek Jonker	Medical Oncologist
Paul Karanicolas	Surgical Oncologist
Gregory Knight	Medical Oncologist
Jennifer Knox	Medical Oncologist
Aamer Mahmud	Radiation Oncologist
Richard Malthaner	Surgical Oncologist
Jason Pantarotto	Radiation Oncologist
Jolie Ringash	Radiation Oncologist
Mark Rother	Medical Oncologist
Marko Simunovic	Surgical Oncologist
Simron Singh	Medical Oncologist
Stephen Welch	Medical Oncologist
Raimond Wong	Radiation Oncologist
Youssef Youssef	Radiation Oncologist
Kevin Zbuk	Medical Oncologist

Appendix 3. Literature search strategy.

MEDLINE
1. exp Colorectal Neoplasms/
2. metastat$.mp.
3. advanced.mp.
4. 2 or 3
5. 1 and 4
6. exp Antineoplastic Combined Chemotherapy Protocols/
7. exp Antineoplastic Agents/
8. 6 or 7
9. continuous versus intermittent chemotherapy.mp.
10. intermittent versus continuous chemotherapy.mp.
11. stop-and-go.mp.
12. exp Drug Administration Schedule/
13. or/9-12
14. 5 and 8 and 13
15. limit 14 to yr="2000 - 2011"
16. limit 15 to english language

EMBASE
1. exp colorectal cancer/
2. exp colorectal tumor/
3. exp colorectal carcinoma/
4. or/1-3
5. metastas$.mp.
6. advanced.mp.
7. 5 or 6
8. 4 and 7
9. exp combination chemotherapy/
10. exp cancer combination chemotherapy/
11. chemotherapy/
12. or/9-11
13. exp drug intermittent therapy/
14. exp continuous infusion/
15. continuous versus intermittent chemotherapy.mp.
16. stop-and-go.mp.
17. exp drug dose reduction/
18. exp drug dose regimen/
19. exp drug withdrawal/
20. exp maintenance therapy/
21. drug administration schedule.mp.
22. or/13-21
23. 8 and 12 and 22
24. limit 23 to yr="2000 - 2011"
25. limit 24 to english language

Appendix 4. Literature search results flow diagram.



Evidence-Based Series 2-6: Section 3

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

Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer: Development Methods, Recommendations Development and External Review Process

S. Berry, R. Cosby, T. Asmis, K. Chan, M. Krzyzanowska, N. Hammad, and the Gastrointestinal Disease Site Group

Report Date: January 8, 2014

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) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Gastrointestinal Disease Site Group of the CCO PEBC (see Section 2, Appendices 1 and 2 for a complete list of working group and DSG members, respectively). The series is a convenient and up-to-date source of the best available evidence on continuous versus intermittent chemotherapy strategies in inoperable, advanced colorectal cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. There was no controversy within the working group or the DSG with respect to the recommendation made in this guidance document. Interestingly though, another recent systematic review and meta-analysis by Pereira et al. presented at ESMO 2012, and comparing intermittent and continuous chemotherapy strategies, concluded that continuous chemotherapy had a significant, albeit modest, improvement in survival over intermittent chemotherapy. This is in direct contrast to the findings of the current document. However, there are two issues with the Pereira et al. (3) review. It only included five trials, one of which was the COIN-B trial. COIN-B does not have a true continuous chemotherapy arm and was, therefore, not included in the present systematic review. Secondly, the forest plot of the Pereira et al. meta-analysis shows the Maughan et al. (4) trial to have an overall survival HR of 0.87 in favour of continuous chemotherapy when, in fact, the overall survival HR in this trial is 0.87 in favour of intermittent chemotherapy. Given that the Maughan et al. trial accounts for 17.1% of the result and the confidence interval for the HR is so close to 1.00, it is likely that the conclusion of the Pereira et al. (3) systematic review will not be maintained when this error is corrected. The working group performed its due diligence and contacted the senior author of the Pereira et al. systematic review to inform them of this error. They maintain that their meta-analysis is correct. All members of the working group rechecked the data to ensure that we were representing the Maughan et al. (4) data correctly. The Maughan et al. trial does indeed clearly favour intermittent chemotherapy.

Report Approval Panel Review and Approval

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise. Key issues raised by the Report Approval Panel included the following:

- a concern that the question should be clearer that this guideline addresses first-line treatment of mCRC. *The question was revised to reflect this request*.
- a query that the GI DSG has no allied health personnel or a lay member. *DSGs do not necessarily have allied health personnel unless needed for a particular guideline. If they are needed, they are brought in to join the working group. The GI DSG does have a patient/community representative as noted in Section 2 - Appendix 2.*
- a concern that the toxicity benefits are unclear. It was suggested that a table of the significant differences in toxicity would be helpful as well as presenting the QOL data in tabular form. *The working group decided that all the toxicity data should be presented, not just the significantly different ones. Also, there was too little QOL data to make a table feasible*.
- a suggestion that a more in-depth discussion of the QOL issues would be helpful. *This was done*.
- a suggestion that the guideline should specify who should get continuous or intermittent chemotherapy. *A population-based analysis of intermittent chemotherapy was recently presented at ASCO 2013. This information was added to the discussion.*
- a suggestion that the recommendation should be clearer. *Additional qualifying statements were added to the recommendation in Section 1. In addition, the discussion was revised to address this suggestion.*
- a concern that it was unclear if the included trials were superiority or non-inferiority trials. *This information is included in Section 2 – Table 2.*
- a suggestion that more should be included in the methods sections to address why so many meta-analyses were done. *This was done*.
- a suggestion to better address the small amount of QOL date. *This was done*.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Gastrointestinal Disease Site Group (GI DSG) circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GI DSG.

BOX 1:
QUESTION

What is the impact of intermittent strategies of administering systemic therapy on length and quality of survival in patients with untreated, unresectable metastatic colorectal cancer?

TARGET POPULATION

These recommendations apply to adult patients (≥18 years old) with inoperable, advanced (Stage IV) colorectal cancer.

DRAFT RECOMMENDATIONS and KEY EVIDENCE (approved for external review September 26, 2013)

Intermittent strategies of administering first-line systemic therapies to patients with unresectable metastatic colorectal cancer (mCRC) do not result in a statistically significant reduction in overall survival and either improve or maintain quality of life compared to continuous administration of therapy. Patients who want a break from treatment can be reassured that intermittent strategies of administering first-line therapy are a reasonable alternative to continuous administration. Intermittent systemic treatment strategies should be part of an informed discussion of treatment options for this group of patients.

Ten trials (1-10) were identified, and seven (1,2,5-9) had published overall survival hazard ratios (HRs) that could be used for the meta-analysis. Meta-analysis demonstrates no clinically significant survival difference between the continuous and intermittent chemotherapy strategies (HR, 1.02; 95%CI, 0.95-1.10, p=0.62). No subgroup of trials based on the type of induction or maintenance therapy in the intermittent arm demonstrates a significant difference in overall survival between the two chemotherapy strategies (Figures 2, 3, and 6). Toxicity assessments revealed differential toxicity patterns for the two strategies. However, these toxicity assessments reflect maximal levels of toxicity experienced during exposure to the treatment on that arm of the trial. These measures are important, but for patients on intermittent treatment, duration of exposure to toxicity, or ability of patients to recover from the toxicities after induction treatment, are also important and are likely better captured in quality-of-life (QOL) assessments. Of the two trials that measured quality of life, the Maughan et al (1) trial demonstrated no difference in QOL, and several benefits were demonstrated for the intermittent chemotherapy arm at 24 weeks in the COIN (6) trial. Specifically, there were statistically significant benefits with respect to role functioning (OR, 0.82; 95%CI, 0.70-0.96, p=0.015) and social functioning (OR, 0.82; 95%CI, 0.70-0.96, p=0.016) as well as for several symptom scales including fatigue, nausea and vomiting, appetite loss, constipation, diarrhea, dry or sore mouth, eating or drinking problems, problems handling small objects, and treatment interfering with activities of daily living (all p<0.04).

QUALIFYING STATEMENTS

- Given that the trials included in this systematic review included a variety of maintenance strategies, a definitive recommendation regarding an optimal maintenance strategy is not possible. However, our analyses of strategies that did not use any maintenance systemic therapy did not demonstrate any statistically

significant detriment in overall survival. Therefore, this approach may be preferred by patients, as it offers them a complete break from treatment.

- All but one of the intermittent strategies offered 12 to 18 weeks of induction treatment and were monitored with imaging at least every 8 to 12 weeks during the intermittent phase of treatment, with reintroduction of the induction chemotherapy at disease progression. These represent reasonable guidelines to consider when using an intermittent strategy, but adaptation of a strategy to individual circumstances should always be considered. A longer induction period or closer clinical monitoring of patients on maintenance therapy or chemotherapy-free interval might be appropriate for patients with very bulky or symptomatic disease. For some patients like this, an intermittent strategy may not be appropriate.
- Five of the seven trials that contributed to the meta-analyses were based on treatments with FOLFOX chemotherapy, one of the commonly used first-line chemotherapy regimens for mCRC in Ontario. The other two trials included in the meta-analyses used fluoropyrimidine monotherapy or FOLFIRI as induction chemotherapy regimens. Given the acceptability of fluoropyrimidine monotherapy as one of the options for first-line therapy (see EBS #2-5) and the accepted equivalence of FOLFIRI and FOLFOX as first-line therapies (11,12), extrapolation of our conclusions to all commonly used induction chemotherapy regimens is reasonable.

During maintenance therapy or a chemotherapy-free interval, best supportive care should be continued for patients.

Methods

Targeted Peer Review: During the guideline development process, three targeted peer reviewers from British Columbia and the USA considered to be clinical and/or methodological experts on the topic were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on September 26, 2013. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The working group from the GI DSG reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Medical oncologists known to treat colorectal cancer and any medical oncologist for whom their treatment speciality was unknown from the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on October 21, 2013. The consultation period ended on November 11, 2013. The working group from the GI DSG reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				2	1
2. Rate the guideline presentation.				2	1
3. Rate the guideline recommendations.					3
4. Rate the completeness of reporting.			1		2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				1	2
6. Rate the overall quality of the guideline report.				1	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.					3
8. I would recommend this guideline for use in practice.					3

9. What are the barriers or enablers to the implementation of this guideline report?
Only one barrier was noted by one reviewer who identified the preconceived notion on the part of some clinicians against treatment interruptions as a possible barrier to implementation. The reviewer further notes that the guidance document makes a strong case against that preconceived idea.

Summary of Written Comments

Most of the comments were quite positive with respect to the content and quality of the document. The main points contained in the written comments along with the discussion or modification(s) made by the working group (*in italics*) were:

i. A concern that the report is quite lengthy which might distract from the key messages. *The working group decided that a systematic review was supposed to provide all the details used to formulate the recommendations. This leads to transparency. Those not wishing to read all the details can read Section 1 only which includes the recommendations as well as a very brief summary of the key evidence.*

ii. A suggestion that population-based studies, if they exist, should be included. *Such studies would not meet the inclusion criteria set out for the systematic review. However, they are included in the discussion.*

iii. A suggestion to add in the results of CAIRO3. *Only preliminary results of CAIRO3 in abstract form are currently available and, therefore, cannot be part of the included studies. However, the results of CAIRO3 are provided in the discussion section.*

Professional Consultation: Thirteen responses were received. Key results of the feedback survey are summarized in Table 2.

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

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. **Rate the overall quality of the guideline report.**	1(8)	1(8)	2(15)	4(31)	5(38)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. **I would make use of this guideline in my professional decisions.**			1(8)	4(31)	8(62)
3. **I would recommend this guideline for use in practice.**			2(15)	2(15)	9(69)

4. **What are the barriers or enablers to the implementation of this guideline report?**
   Several reviewers commented that clinicians' and patients' views that continuous treatment is necessary could be a barrier. There was also the comment that the document provides assurance when providing patients with breaks from chemotherapy that it is not detrimental to overall survival.

Summary of Written Comments

The main points contained in the written comments were:

i. A concern that most of the trials in the meta-analysis are treated with oxaliplatin-based chemotherapy and not irinotecan-based chemotherapy.
ii. A concern that CAIRO3 was not one of the included studies.

Modifications/Actions

i. This is addressed in the document in the discussion in Section 2.
ii. Only preliminary results of CAIRO3 in abstract form are currently available and, therefore, cannot be part of the included studies. However, the results of CAIRO3 are provided in the discussion section.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GI DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

Funding

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Ontario Health
Cancer Care Ontario

Evidence-based Series 2-6 Version 2: Section 4

Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer

Document Assessment and Review

S. Berry, S. Kellett,
and the Gastrointestinal Disease Site Group

September 15, 2022

The 2014 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2014.

In 2021/2022, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (SK) conducted an updated search of the literature. A clinical expert (SB) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. An expert panel selected from the Gastrointestinal Disease Site Group (DSG) (Appendix 1), endorsed the recommendations found in Section 1 (Clinical Practice Guideline) in September 2022.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

What is the impact of intermittent strategies of administering systemic therapy on length and quality of survival in patients with untreated, unresectable metastatic colorectal cancer?

Literature Search and New Evidence
Medline and Embase were searched from July 2013 to December 1, 2021 (Search details in Appendix 2). Articles were included if they were published English-language abstracts or fully published reports of phase II or III randomized controlled trials (RCTs) comparing continuous chemotherapy with an intermittent strategy of chemotherapy, with or without maintenance chemotherapy, in adult patients with metastatic colorectal cancer and included at least one of the outcomes of interest. Syntheses of RCTs in the form of systematic reviews (SRs) or meta-analyses were also eligible.

Impact on Guidelines and Its Recommendations
The new data support existing recommendations. Hence, the expert panel ENDORSED the 2014 recommendations on continuous versus intermittent chemotherapy strategies in inoperable, advanced colorectal cancer.

DOCUMENT REVIEW TOOL

Number and Title of Document under Review	2-6 Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer
Original Report Date	January 8, 2014
Date Assessed (by DSG or Clinical Program Chairs)	December 5, 2018
Health Research Methodologist	Sarah Kellett
Clinical Expert	Dr. Scott Berry
Approval Date and Review Outcome	September 15, 2022 ENDORSE

Original Question(s):
What is the impact of intermittent strategies of administering systemic therapy on length and quality of survival in patients with untreated, unresectable metastatic colorectal cancer?

Target Population:
These recommendations apply to adult patients (≥18 years old) with inoperable, advanced (Stage IV) colorectal cancer.

Study Selection Criteria:
Articles were included if they were published English-language abstracts or fully published reports of Phase II or III RCTs comparing continuous chemotherapy to an intermittent strategy of chemotherapy, with or without maintenance chemotherapy, in adult patients with metastatic colorectal cancer and included at least one of the outcomes of interest. Syntheses of RCTs in the form of systematic reviews or meta-analyses were also eligible.

Search Details:
Medline and Embase were searched from July 2013 to December 1, 2021 (Search details in Appendix 2). Ongoing trials are listed in Appendix 3.

Summary of new evidence:
Literature Search Results

There were no new guidelines that met the original study inclusion criteria. Two new SRs were included (1, 2). Details of these two SRs are found in Table 1. One new Phase III RCT evaluating intermittent chemotherapy regimens with or without maintenance chemotherapy was included (3). In addition, two trials that were included in the original guideline based on abstract data were published in full (4, 5). Details of these three studies can be found in Table 2. The study by Yalcin et al was not included in the overall survival (OS) meta-analysis in the original guideline because it did not include a hazard ratio (HR) for OS differences between the continuous and intermittent arms. The full publication also did not include an HR for OS but as was observed in the abstract, there was no statistically significant difference between the two arms.

Literature Review Summary

One SR including a meta-analysis of individual patient data (IPD) was found (1). The authors were able to obtain patient data from nine of 17 eligible studies which consisted of 73% of all eligible patients. The OS meta-analysis in this paper included seven of the eight studies that were included in the OS meta-analysis in the original guideline in addition to the one new study that was identified for this review (3). They also included a study, COIN-B (6), that did not meet the inclusion criteria for the original guideline. Adams et al found no detriment to OS (HR, 1.03; 95% CI 0.93 to 1.14) from either a complete break in therapy (HR, 1.04; 95% CI, 0.87 to 1.25) or from maintenance therapy (HR, 0.99; 95% CI, 0.87 to 1.13) compared with the continuous chemotherapy which is consistent with the OS meta-analysis in the original guideline (1). Another systematic review with a network meta-analysis was also included (2). The inclusion criteria for studies included in this SR differed from the original guideline. For a study to be included in the original guideline, one arm had to include continuous chemotherapy. Sonbol et al (2) included a specific analysis of four studies that compared continuous chemotherapy with either observation (7) or maintenance therapy (5, 8, 9). All four studies (5, 7-9) were included in the OS meta-analysis of the original guideline. When these four studies were evaluated separately, there was no detriment to OS when continuous chemotherapy was compared with either a complete break (HR, 0.95; 95% CI, 0.85 to 1.07) or maintenance therapy (HR, 1.04; 95% CI, 0.92 to 1.17) which is consistent with the OS meta-analysis in the original guideline (2).

Clinical Expert and HRM Interest Declaration(s):

S. Berry declares the following conflicts:

1. $500 or more in a single year to act in a consulting capacity? “Consulting capacity” includes such work as consultant, investigator, advisory board member, lobbyist, speaker."
    a. Consulting / advisory work for Merck, Amgen, Bayer, Apobiologix, MD Briefcase.

S. Kellet has no conflicts to declare.

Conflict of interest declarations for the expert panel can be found in Appendix 1.

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No.
2. Does the newly identified evidence support the existing recommendations?	Yes. The new evidence in this review supports the existing recommendations.
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes. No further recommendations are necessary.
Review Outcome as recommended by the Clinical Expert	**ENDORSE**

DSG/Expert Panel Commentary	None. All DSG Expert Panel members approved of the Endorsement without further comments.

Table 1. SRs meeting inclusion criteria for EBS 2-6 (chronological order)				
Author, year, reference	**Procedure and Population**	**Methods**	**Outcomes of interest**	**Brief results**
Adams et al, 2021 (1)	Individual Patient data meta-analysis from multiple clinical trials (9/17, 53%) evaluating the intermittent strategies.	SR to search for eligible studies, contacted authors to obtain IPD. Authors did not separate type of treatments but did separate the trials into those with a complete stop and a maintenance strategy	OS, exploratory analysis of PFS	Authors were able to obtain IPD from 9 of 17 eligible trials (53%, 73% of relevant patients).(**some studies were included in the original 2-6 Guideline as well as this update**) OS: Analysis of IPD from 7 studies did not demonstrate a detriment to OS (HR=1.03, I^2=23.4%) with a complete break in treatment (HR-1.04; I^2=46.3 (moderate)) or maintenance strategy omitting oxaliplatin (HR=0.99, I^2:0%) PFS: Studies with a treatment break had a 2 month improvement in PFS with continuous therapy (HR = 1.53) and 1 month improvement in PFS for continuous maintenance strategy omitting oxaliplatin (HR 1.17) – *large heterogeneity in the trials evaluated, I^2 87.4%)*
Sonbol et al, 2021 (2)	SR including 12 RCTs comparing continuous induction chemotherapy until progression with an intermittent strategy of observation, or chemotherapy with or without maintenance therapy. trials had to include at least 1 of the following strategies: (1) observation; (2) maintenance treatment with a fluoropyrimidine (FP; fluorouracil or capecitabine), bevacizumab (Bev), or both FP + Bev; or continuous induction treatment until progression	Systematic review	OS and PFS	Disruption of Treatment and Loss of Benefit: Network Meta-analysis: PFS (HR 0.71; 95% CI 0.46-1.09)); OS (HR, 0.95; 95% CI 0.85-1.07) – no benefit to continuous induction chemotherapy until progression compared with observation Maintenance therapy versus observation Network Meta-analysis: PFS (HR 0.58; 95% CI 0.43-0.77)); OS (HR, 0.91; 95% CI 0.83-1.01) – PFS benefit to maintenance therapy, OS no benefit to maintenance therapy

It should be noted that these results also included studies that did not have a continuous chemotherapy arm. Details of the studies that had a continuous chemotherapy arm are included in Table 2

IPD: individual patient data; OS: overall survival; PFS: progression free survival; HR: hazard ratio

Table 2. RCTs meeting inclusion criteria for EBS 2-6 (chronological order)					
Author, year, reference	**Procedure and Population**	**Methods**	**Intervention/ Comparison**	**Outcomes of interest**	**Brief results**
Yalcin et al, 2013*, ** *(5)*	Aim of the study was to evaluate maintenance therapy with bevacizumab + capecitabine following induction with bevacizumab + capecitabine + oxaliplatin (XELOX) versus bevacizumab + XELOX until progression as first-line therapy in mCRC	Phase III RCT	**BOTH GROUPS:** 6 cycles of XELOX (oxaliplatin 130 mg/m^2 IV on day 1 and capecitabine 1,000 mg/m^2 orally twice daily on days 1–14 every 3 weeks) + bevacizumab 7.5 mg/ kg intravenously on day 1 of the 3-week cycle. **ARM A:** After 6 cycles, patients received maintenance therapy comprising XELOX + bevacizumab 7.5 mg/kg intravenously every 3 weeks (n=56) **ARM B:** After 6 cycles, patients received maintenance therapy comprising capecitabine 1,000 mg/m^2 orally twice daily on days 1–14 + bevacizumab 7.5 mg/kg intravenously on day 1 every 3 weeks until disease progression, severe toxicity or withdrawal of consent (n=54)	Primary endpoint: PFS Secondary endpoints: OS, ORR and safety	Primary Endpoint: The primary endpoint, median PFS, was statistically significantly greater for **ARM B** (11.0 months, 95% CI 9.1– 12.9) than for **ARM A** (8.3 months, 95% CI 7.1–9.5; logrank test, p = 0.002; hazard ratio 0.6) Secondary Endpoints: **ARM A**: ORR: 59.0 (CR – 5.4; PR: 53.6); SD: 35.7; PD: 5.4 **ARM B**: ORR: 66.7 (CR – 5.6; PR: 61.1); SD: 29.6; PD: 3.7 OS (23.8 vs. 20.2 months; p = 0.100). Safety: Tolerability was acceptable in both treatment arms; the most frequent grade 3/4 treatment-related adverse events (arm B vs. arm A) were fatigue (6.6 vs. 16.1%), diarrhea (3.3 vs. 11.3%), anorexia (3.3 vs. 11.3%), and neuropathy (1.6 vs. 8.1%). *Brief conclusions:* Maintenance therapy with bevacizumab + capecitabine can be considered an appropriate option following induction bevacizumab + XELOX in patients with mCRC instead of continuation of bevacizumab + XELOX.
Simkens et al, 2015 (CAIRO3 trial)*, ** (4)	Previously untreated mCRC pts, PS 0–1, with stable disease or better after 6 cycles of CAPOX-B, not eligible for metastasectomy and eligible for future treatment with oxaliplatin	Phase III RCT; CAIRO 3 Trial	**ARM A:** observation **ARM B:** maintenance treatment with capecitabine 625 mg/m^2 bid daily continuously and bevacizumab 7.5 mg/kg iv q 3 weeks Upon first progression (PFS1), pts in both arms were treated with CAPOX-B until second progression (PFS2, primary endpoint).	Primary Endpoint: PFS2 Secondary Endpoints: OS, time to second progression	The median PFS1 in **ARM A vs B** was 4.1 vs 8.5 months (HR 0.44, 95% CI 0.37–0.53, p < 0.0001). PFS1, 75% of pts received CAPOX-B in arm A and 47% in arm B. The median PFS2 was 10.5 vs 11.5 months (HR 0.81, 95% CI 0.67–0.98, p = 0.03). The median TTP2 and OS in **ARM A vs B** were 14.1 vs 18.7 months (HR 0.67, 95%

Table 2. RCTs meeting inclusion criteria for EBS 2-6 (chronological order)					
Author, year, reference	**Procedure and Population**	**Methods**	**Intervention/ Comparison**	**Outcomes of interest**	**Brief results**
					CI 0.56– 0.82, p < 0.0001), and 18.0 vs 21.7 months (HR 0.87, 95% CI 0.71–1.06, p = 0.16), respectively. The overall quality of life (QoL) was not significantly different between the 2 treatment arms
Hegewisch_Becker (AIO 0207 trial) *, ** (3)	no continuation of therapy or bevacizumab alone are non-inferior to fluoropyrimidine plus bevacizumab, following induction treatment with a fluoropyrimidine plus oxaliplatin plus bevacizumab	Phase III RCT (AIO 0207 Trial)	After 24 weeks of induction therapy with either fluorouracil plus leucovorin plus oxaliplatin or capecitabine plus oxaliplatin, both with bevacizumab, patients without disease progression were randomly assigned (1:1:1) to **ARM A**: standard maintenance treatment with a fluoropyrimidine plus bevacizumab **ARM B**: bevacizumab alone **ARM C**: no treatment	Primary Endpoint: TTF of strategy Secondary Endpoints: time to failure of strategy from enrolment, PFS, OS (low power, update planned)	TTF **ARM A**: 6.9 months (95% CI 6.1–8.5) **ARM B**: 6.1 months (5.3–7.4) **ARM C:** 6.4 months (4.8–7.6) Bevacizumab alone was non-inferior to standard fluoropyrimidine plus bevacizumab (HR 1.08 [95% CI 0.85–1·37]; p=0.53; upper limit of the one-sided 98·8% CI 1.42), whereas no treatment was not (HR 1.26 [0·99–1·60]; p=0.056; upper limit of the one-sided 98·8% CI 1.65). PFS: All patients: 4.5 months (95% CI 4.1–5.2) for all patients bevacizumab alone versus fluoropyrimidine plus bevacizumab (HR 1.34 [95% CI 1.06–1.70]; p=0·015); no treatment versus fluoropyrimidine plus bevacizumab (HR 2.09 [95% CI 1.64–2.67]; p<0·0001); and no treatment versus bevacizumab alone (HR 1.45 [95% CI 1.15–1.82]; p=0.0018). *Brief conclusions:* Although non-inferiority for bevacizumab alone was demonstrated for the primary endpoint,

Table 2. RCTs meeting inclusion criteria for EBS 2-6 (chronological order)					
Author, year, reference	**Procedure and Population**	**Methods**	**Intervention/ Comparison**	**Outcomes of interest**	**Brief results**
					maintenance treatment with a fluoropyrimidine plus bevacizumab may be the preferable option for patients following an induction treatment with a fluoropyrimidine, oxaliplatin, and bevacizumab, as it allows the planned discontinuation of the initial combination without compromising time with controlled disease

*Study included in Adams et al , **Study Included in Sonbol et al

PFS: Progression Free Survival, RCT: randomized controlled trial, IUPD: individual patient data, HR: hazard ratio; OS: overall survival; TTF: time to failure; TTP: time to progression; ORR: overall response rate; SD: stable disease; PD: progressive disease

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Appendix 1. Members of the Expert Panel

Name	Affiliation	Conflict of Interest Declaration
Dr. Rachel Goodwin	University of Ottawa Division of Medical Oncology Ottawa, Ontario	$500 or more in a single year to act in a consulting capacity: member and/or speaker of the following boards with compensation for each totalling less than $1500 annually: Novartis- adv, boards, speaker; Onivyde- adv boards; Bayer- Adv Boards; Amgen-Adv Boards, Speaker; Ipsen-Adv. Boards, Speaker; Pfizer-Adv. Boards, Speaker; Eisai-Adv. Boards, Speaker; Roche- Adv. Boards; AAA- Adv. Boards; Apobiologix- Adv. Boards; Merck- Adv. Boards, Speaker; Viatris or Mylan- Advisory Boards, Speaker; Knight Therapeutics- Adv. Received grants or other research support, either as principal or co-investigator from Ipsen, Novartis, Apotex, Pfizer.
Dr. Asma Ali	Northeast Cancer Center Health Sciences North Sudbury, Ontario	Employment, regardless of salary and benefits: Medical Oncologist, Northeast Cancer Center; Health Sciences North. Sudbury, Ontario
Dr. Tim Asmis	The Ottawa Hospital Cancer Centre Ottawa, Ontario	$500 or more in a single year to act in a consulting capacity: member and/or speaker of the following boards with compensation for each totalling less than $1500 annually: Ipsen- advisory board, speaker; Eisai-advisory boards; BMS- advisory boards; Medison- speaker; Taiho-advisory boards; Amgen-advisory boards, speaker; Novartis- advisory board, consultant, speaker; Bayer-advisory board; Roche-consultant;

		Shire-advisory board; Apobiologix-advisory board; Celgene-advisory boards.
Dr. Kelvin Chan	Sunnybrook Odette Cancer Centre Toronto, Ontario	No conflicts to declare
Dr. Joe Del Paggio	Thunder Bay Regional Health Sciences Centre Thunder Bay, Ontario	No conflicts to declare
Dr. Shiva Jayaraman	St. Joseph's Health Centre Toronto, Ontario	No conflicts to declare

Appendix 2

2-6 EMBASE Search Strategy
Search run December 1, 2021 (95 hits)

1. exp colorectal cancer/
2. exp colorectal tumor/
3. exp colorectal carcinoma/
4. or/1-3
5. metastas$.mp.
6. advanced.mp.
7. 5 or 6
8. 4 and 7
9. exp combination chemotherapy/
10. exp cancer combination chemotherapy/
11. chemotherapy/
12. or/9-11
13. exp drug intermittent therapy/
14. exp continuous infusion/
15. continuous versus intermittent chemotherapy.mp.
16. stop-and-go.mp.
17. exp drug dose reduction/
18. exp drug dose regimen/
19. exp drug withdrawal/
20. exp maintenance therapy/
21. drug administration schedule.mp.
22. or/13-21
23. 8 and 12 and 22
24. (201307$ or 201308$ or 201309$ or 201310$ or 201311$ or 201312$ or 2014$ or 2015$ or 2016$ or 2017$ or 2018$ or 2019$ or 20$0 or 2021$).dd
25. 23 and 24
26. limit 25 to english language

MEDLINE Search Strategy – Update
Ran December 1, 2021 (203 hits)
1. exp Colorectal Neoplasms/
2. metastat$.mp.
3. advanced.mp.
4. 2 or 3
5. 1 and 4
6. exp Antineoplastic Combined Chemotherapy Protocols/
7. exp Antineoplastic Agents/
8. 6 or 7
9. continuous versus intermittent chemotherapy.mp.
10. intermittent versus continuous chemotherapy.mp.
11. stop-and-go.mp.
12. exp Drug Administration Schedule/
13. or/9-12
14. 5 and 8 and 13

15. (201307$ or 201308$ or 201309$ or 201310$ or 201311$ or 201312$ or 2014$ or 201$: or 2016$ or 2017$ or 2018$ or 2019$ or 2020$ or 2021$).ed
16: 14 and 15
16. limit 16 to english language

Appendix 3. Ongoing Clinical Trials

Title	Status	Study Results	Conditions	Interventions	URL
Fruquintinib Plus Capecitabine Versus Bevacizumab Plus Capecitabine as Maintenance Therapy Following First-line Treatment for Metastatic Colorectal Cancer	Recruiting	No Results Available	Colorectal Cancer	Drug: Fruquintinib Plus Capecitabine|Drug: Bevacizumab Plus Capecitabine	https://ClinicalTrials.gov/show/NCT04733963
Consolidative Radiotherapy Plus Maintenance Chemotherapy for Metastatic Colorectal Cancer	Not yet recruiting	No Results Available	Metastatic Colorectal Cancer|Radiotherapy	Drug: maintenance chemotherapy|Radiation: Consolidative Radiotherapy	https://ClinicalTrials.gov/show/NCT03142282
Cetuximab Plus Capecitabine as Maintenance Treatment in RAS and BRAF wt Metastatic Colorectal Cancer	Not yet recruiting	No Results Available	Colorectal Cancer	Drug: Cetuximab, Capecitabine|Drug: Cetuximab	https://ClinicalTrials.gov/show/NCT04262635
Fruquintinib as a Maintenance Therapy Following First-line Treatment for Metastatic Colorectal Cancer	Not yet recruiting	No Results Available	Colo-rectal Cancer	Drug: Fruquintinib	https://ClinicalTrials.gov/show/NCT04296019
A Study of Cetuximab Plus Raltitrexed for Maintenance Treatment in Advanced Colorectal Cancer	Recruiting	No Results Available	Colorectal Cancer	Drug: Raltitrexed|Drug: Cetuximab	https://ClinicalTrials.gov/show/NCT04241731
Predictors of Physical Activity Maintenance in Colorectal Cancer Survivors	Recruiting	No Results Available	Colorectal Cancer	Behavioral: Group Exercise	https://ClinicalTrials.gov/show/NCT03781154
Fruquintinib Plus Capecitabine as Maintenance Treatment of RAS / BRAF Wild-type Metastatic Colorectal Cancer	Recruiting	No Results Available	Metastatic Colorectal Cancer	Drug: fruquintinib plus capecitabine	https://ClinicalTrials.gov/show/NCT05016869

A Randomized Phase III Study Comparing Maintenance Treatment With Fluoropyrimidine + Bevacizumab Versus Fluoropyrimidine After Induction Chemotherapy for a Metastatic Colorectal Cancer	Not yet recruiting	No Results Available	Patients With Metastatic Colorectal Cancer	Drug: Fluoropyrimidine|Drug: Bevacizumab	https://ClinicalTrials.gov/show/NCT04188145
Cetuximab Maintenance Treatment Versus Continuation After Induction Therapy in mCRC	Not yet recruiting	No Results Available	Colorectal Cancer	Drug: Cetuximab|Drug: mFOLFOX6|Drug: FOLFIRI	https://ClinicalTrials.gov/show/NCT02942706
FOLFOX + Panitumumab According to a "Stop and go" Strategy With a Reintroduction Loop After Progression on Fluoropyrimidine as Maintenance Treatment, as the First Line in Patients With Metastatic Colorectal Adenocarcinoma Without a RAS Mutation	Recruiting	No Results Available	Metastatic Colorectal Cancer	Combination Product: FOLFOX + panitumumab	https://ClinicalTrials.gov/show

DEFINITIONS OF REVIEW OUTCOMES

1. ARCHIVE – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "ARCHIVE."

2. ENDORSE – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. UPDATE – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.