PCORI Topic Brief:

Comparative Effectiveness of Second-line therapies for Patients with Metastatic Colorectal Cancer

Prepared by

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1. Background

Adenocarcinoma of the colon or rectum originates in the epithelial lining and is the most commonly diagnosed malignant histology of the large bowel.[1] Colorectal cancers identified at early stages (before spread to distant sites) are amenable to surgical resection with curative intent. However, the treatment of metastatic colorectal cancer remains a significant health issue in the United States. Of the approximately 130,000 cases of colorectal cancer diagnosed each year in the United States, approximately 30% are metastatic to distant organs at the time of diagnosis and an additional 50% of persons in whom colorectal cancer was diagnosed at a loco-regional stage will go on to develop metastatic disease.[2]

For patients with metastatic disease, systemic therapy is the standard of care with the goal of prolonging life, limiting disease progression, and maintaining quality of life by controlling disease symptoms.[1,3,4] Multiple anticancer drugs have been approved for use in the treatment of colorectal cancer (see Appendix Table 1). Individual lines of treatment typically consist of combinations of multiple agents, and the majority of patients with metastatic disease receive multiple lines of therapy.[5] Anti-cancer drugs for treating colorectal cancer are generally classified as either chemotherapies (i.e., cytotoxic drugs) or targeted therapies (i.e., drugs targeting molecular pathways thought to play a role in cancer pathogenesis). Targeted therapies for colorectal cancer typically biologics and fall into one of two categories: (1) EGFR pathway inhibitors (e.g., cetuximab, panitumumab), which are effective in RAS wild-type cancers (i.e., cancers that do not harbor activating mutations in either KRAS or NRAS) only, and (2) antiangiogenics (e.g., bevacizumab, ramucirumab, ziv-aflibercept, regorafenib). Typical first-line chemotherapy regimens include oxaliplatin- or irinotecan-based chemotherapy with or without a targeted agent. In the United States, oxaliplatin-based chemotherapy (e.g., FOLFOX, CapeOX) and bevacizumab are the most commonly used first-line chemotherapy and targeted therapies, respectively.[5] However, alternative sequences of chemotherapy and targeted agents are also accepted treatment options.[6] While a response to first-line treatment regimens is common, the majority of patients will experience progressive disease.[7]

For these patients, the choice of second-line therapy (or choice to discontinue treatment) depends on a number of factors including, response to previous therapy, patient performance status, and presence of residual toxicity from previous therapy.[3,4] In general, patients who were treated with oxaliplatin-based chemotherapy in the first-line setting will be treated with irinotecan-based chemotherapy in the second-line setting, and vice versa. The addition of a targeted agent to this chemotherapy regimen may also be used in the second line setting. In the United States, the most commonly prescribed second-line chemotherapy and targeted agent are FOLFIRI and bevacizumab, respectively.[5] However, many active regimens are available for use in this setting (see Current Guidelines, below). This topic brief is intended to summarize current treatment options in the second-line setting and identify potential research questions relevant to choosing among these treatment options.

2. Patient-centeredness of the topic

Metastatic colorectal cancer that has progressed following first-line chemotherapy imposes a substantial burden on patients in terms of both mortality and quality of life. Patients undergoing second-line regimens have a median overall survival of approximately 1 year.[8] Simultaneously, health-related quality of life tends to deteriorate during the course of the patient's disease with physical functioning, fatigue, pain, dyspnea, and appetite steadily worsening as patients advance to later stages of treatment.[9] Systemic treatments may alleviate some of the symptom burden in metastatic colorectal cancer patients; an observational study reported that patients undergoing second-line chemotherapy for colorectal cancer reported a stabilization in quality of life scores. Additionally, patients who experience a response to treatment frequently report improvements in pain and appetite.[9] However, multi-agent systemic therapy regimens frequently employed in treating metastatic colorectal cancer also carry the risk for treatment-related toxicity. Treatment-related toxicities are cumulative, which may also contribute to decreased patient quality-of-life in patients who have undergone multiple lines of therapy.

3. Impact/burden of the condition

The American Cancer Society estimates that 135,430 cases of colorectal cancer (95,520 and 39,910 cases of colon and rectal cancer, respectively) will be diagnosed in the United States in 2017, the majority of which are diagnosed in persons 50 years of age or older.[10] The incidence of colorectal cancer in those over 50 years has fallen approximately 3% per year between 2004 and 2012.[2,10] However, among individuals aged 50 years or younger, the incidence rate has been increasing by approximately 2% per year, driven mainly by an increase in rectal cancer diagnoses.[10]

ACS estimates that 50,260 persons in the United States will die of colorectal cancer in 2017, and colorectal cancer represents the second most common cause of cancer-related death. Yet ACS also reports that the colorectal cancer death rate fell from 28 per 100,000 persons in 1975 to 14 per 100,000 in 2014, a change thought to be driven by improvements in colorectal cancer screening and treatment.[10]

4. Ongoing evidence gaps

A systematic review of second-line therapies was published by Cochrane Collaboration in January 2017.[7] In this review, Mocellin and colleagues identified 34 randomized controlled trials (RCTs) of 25 combinations of 17 anti-cancer agents to assess the survival effects of second-line systemic therapy for metastatic colorectal cancer. The main conclusions of the systematic review were typically supported by moderate to high levels of evidence and are summarized in Table 1, below.

Table 1: Main Conclusions from Mocellin et al. 2017

Conclusion	Regimens Compared in RCTs	Outcomes (Relative Effect [95% CI])	Level of Evidence
Chemotherapy is more effective than best supportive care	Irinotecan vs. Best Supportive Care	OS HR 0.58 (0.43 to 0.80) PFS – Not Reported ORR – Not Reported SAE RR 1.19 (1.01 to 1.40)	Moderate 279 participants
Modern chemotherapy is more effective than outdated chemotherapy	FOLFOX vs. 5-FU Irinotecan vs. 5-FU	OS HR 0.69 (0.51 to 0.94) PFS HR 0.59 (0.49 to 0.73) ORR RR 2.96 (1.66 to 5.27) SAE RR 1.39 (1.22 to 1.58)	High 726 participants
Irinotecan-based combinations are more effective than irinotecan alone	FOLFIRI vs. Irinotecan (2 RCTs) Irinotecan + Hyaluronan vs. Irinotecan Irinotecan + Oxaliplatin vs. Irinotecan Panitumumab + Irinotecan vs. Irinotecan Cetuximab + Irinotecan vs. Irinotecan	OS HR 0.91 (0.79 to 1.04) PFS HR 0.68 (0.60 to 0.76) ORR RR 2.87 (2.10 to 3.93) SAE RR 1.18 (0.96 to 1.45)	Moderate 2,615 participants
Addition of bevacizumab to chemotherapy is more effective than chemotherapy alone	Bevacizumab + Irinotecan- or Oxaliplatin-Based Chemotherapy vs. Irinotecan or Oxaliplatin-Based Chemotherapy Bevacizumab + FOLFIRI vs. FOLFIRI Bevacizumab + FOLFOX vs. FOLFOX Bevacizumab + FOLFIRI or FOLFOX vs. FOLFIRI or FOLFOX	OS HR 0.79 (0.70 to 0.88) PFS HR 0.67 (0.60 to 0.75) ORR RR 1.72 (1.23 to 2.43) SAE RR 1.07 (0.93 to 1.25)	High 1,723 participants
Addition of targeted agents to FOLFIRI is more effective than FOLFIRI alone	Conatumumab + FOLFIRI vs. FOLFIRI Ganitumab + FOLFIRI vs. FOLFIRI Panitumumab + FOLFIRI vs. FOLFIRI Bevacizumab + Panitumumab + FOLFIRI vs. FOLFIRI Trebananib + FOLFIRI vs. FOLFIRI Ramucirumab + FOLFIRI vs. FOLFIRI Ziv-Aflibercept + FOLFIRI vs. FOLFIRI	OS HR 0.84 (0.77 to 0.91) PFS HR 0.78 (0.71 to 0.87) ORR RR 2.07 (1.31 to 3.28) SAE RR 1.30 (1.17 to 1.45)	High 3,335 participants
Addition of targeted agents to FOLFOX is more effective than FOLFOX alone	Bevacizumab + FOLFOX vs. FOLFOX Vatalanib + FOLFOX vs. FOLFOX	OS HR 0.92 (0.82 to 1.04) PFS HR 0.76 (0.66 to 0.86) ORR RR 2.64 (1.71 to 4.06) SAE RR 1.20 (1.13 to 1.28)	Low 1,432 participants

GRADE Levels of Evidence:

- High: Further research is very unlikely to change our confidence in the estimate of effect
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very Low: We are very uncertain about the estimate

Abbreviations: HR – Hazard Ratio; OS – Overall Survival; PFS – Progression-Free Survival; ORR – Overall Response Rate; RR – Risk Ratio; SAE – Severe Adverse Events

In addition to these main conclusions, the authors also identified multiple comparisons for which data from only a single trial was available and, therefore, they were unable to reach definitive conclusions on the relative efficacy of the investigated regimens. Conclusions based on data from single trials included:[7]

- Oral (instead of intravenous) fluoropyrimidines (i.e., XELOX as compared to FOLFOX) significantly reduced the incidence of adverse effects (without compromising efficacy) in people treated with oxaliplatin-based regimens (627 participants, GRADE Level of Evidence – Moderate)
- FOLFOX compared to Irinotecan improved upon PFS and ORR without a significant increase in toxicity; however, no significant difference in OS was observed (491 participants, GRADE Level of Evidence – Low)
- Comparison of two different bevacizumab doses (5 mg/kg vs 10 mg/kg) in combination with FOLFIRI did not detect a significant difference in the rate of OS, PFS, ORR, or SAEs (369 participants, GRADE Level of Evidence – Low)

Mocellin and colleagues noted several limitations of the data available regarding second-line treatment options for patients with colorectal cancer.[7] First, data from multiple RCTs testing the same regimens were rarely available for pooling and, therefore, the systematic review addressed questions that were less specific. To do so, they combined various therapies and patient populations that ideally would be examined separately. For example, the review attempted to answer whether addition of any targeted therapy to chemotherapy improved patient outcomes. Targeted therapies included in this comparison came from multiple therapeutic classes (i.e., anti-angiogenic drugs, anti-EGFR drugs), which may themselves exhibit differences in efficacy. Additionally, these comparisons combined both FDA-approved targeted therapies routinely used in treating colorectal cancer (e.g., bevacizumab, cetuximab, panitumumab, ramucirumab, ziv-aflibercept) and still investigational targeted therapies not routinely used in treating colorectal cancer (e.g., conatumumab, ganitumab, hyaluronan, trebabanib, vatalanib). Pooling the limited studies available also led to the inclusion of patients with differing first-line treatment histories within the same comparison (e.g., the inclusion of both bevacizumab-naïve and bevacizumab-experienced patients in a pool looking at addition of bevacizumab to chemotherapy).

Second, the authors noted that not all potential comparisons have been evaluated in head-to-head randomized trials, precluding a full ranking of all tested regimens. As an example, study authors noted that no RCT had investigated the relative efficacy of bevacizumab plus irinotecan to that of irinotecan alone in the second-line setting. Additional comparisons that might be worthy of study in a RCT include a comparison of anti-angiogenic drugs used in combination with FOLFIRI (e.g., bevacizumab vs. ramucirumab vs. ziv-aflibercept) or comparison of the addition of antiangiogenic drugs to chemotherapy versus the addition of anti-EGFR antibodies to chemotherapy.

Lastly, the authors identified topics for further research in the second-line treatment of colorectal cancer, as follows:[7]

- Other targeted agents, in particular targeted agents being used successfully against other tumor types should be investigated in the treatment of colorectal cancer.
- Identification of novel biomarkers (i.e., markers other than RAS status for EGFR pathway inhibitors) capable of predicting response to treatment with a given anticancer agent should be pursued.

- Quality of life data was infrequently available from RCTs in second-line colorectal cancer, and the authors suggest that quality of life should be a mandatory outcome included in the design of future oncology clinical trials to formally investigate the balance between survival benefits and treatment-related toxicity.

In addition to the limitations of the available data identified by the systematic review authors, the National Comprehensive Cancer Network guidelines for treating colon and rectal cancer[3,4] include several treatments as options in the second-line setting that are not addressed by RCTs identified in the review by Mocellin et al.[7] Such treatment options include the following:

(1) Checkpoint inhibitors (e.g., the PD-1 inhibitors nivolumab and pembrolizumab) as a second-line treatment option for the approximately 4% of patients whose tumors exhibit high microsatellite instability (MSI), a molecular marker of an underlying defect in DNA mismatch repair. Data on the use of these agents in patients with MSI-high cancers come from non-RCTs with the majority of patients receiving treatment in the salvage setting (i.e., patients who have undergone at least 2 prior rounds of treatment).[11] Data on the efficacy of these treatments in the second-line setting is lacking.
(2) Irinotecan with or without EGFR pathway inhibitor; regorafenib monotherapy; and co-formulated trifluridine and tipiracil as second-line treatment options for patients who received a chemotherapy regimen containing both irinotecan and oxaliplatin (e.g., FOLFIRINOX) in the first-line setting. Patients whose disease progresses following such a first-line regimen do not have available the standard switch between irinotecan- and oxaliplatin-based chemotherapy and little data is available to guide treatment selection for this patient population

5. Current guidelines

The National Comprehensive Cancer Network (NCCN) maintains separate guidelines on colon cancer and rectal cancer, both of which were last updated in March 2017.[3,4] Systemic therapies recommended for treatment of advanced/metastatic disease are identical for colon and rectal cancer. The guidelines indicate that the recommended second-line treatment regimens for advanced/metastatic colorectal cancer differ based on the therapy received in the first-line setting.

For patients who were eligible to receive intensive chemotherapy in the first-line setting and underwent oxaliplatin-based chemotherapy without irinotecan (e.g., FOLFOX), NCCN recommends the following treatment options:

- FOLFIRI with or without antiangiogenic targeted therapy (i.e., bevacizumab, ramucirumab, ziv-aflibercept). Note: ramucirumab is only FDA-approved for treating patients with metastatic colorectal cancer who have received prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.[12]
- Irinotecan with or without antiangiogenic targeted therapy
- FOLFIRI with or without anti-EGFR targeted therapy (i.e., cetuximab or panitumumab) – only intended for patients with wild-type KRAS/NRAS
- Irinotecan with or without anti-EGFR targeted therapy – only intended for patients with wild-type KRAS/NRAS

- Immune checkpoint inhibitor (i.e., nivolumab, pembrolizumab) – only intended for patients exhibiting DNA mismatch repair deficiency (dMMR)/high microsatellite instability (MSI-H)

For patients who were eligible to receive intensive chemotherapy in the first-line setting and underwent irinotecan-based chemotherapy without oxaliplatin (e.g., FOLFIRI), NCCN recommends the following treatment options:

- FOLFOX or CapeOX with or without bevacizumab
- Irinotecan with or without anti-EGFR targeted therapy (i.e., cetuximab or panitumumab) – only intended for patients with wild-type KRAS/NRAS
- Immune checkpoint inhibitor (i.e., nivolumab, pembrolizumab) – only intended for patients exhibiting dMMR/MSI-H

For patients who were eligible to receive intensive chemotherapy in the first-line setting and underwent oxaliplatin and irinotecan-based chemotherapy (e.g., FOLFOXIRI), NCCN recommends the following treatment options:

- Irinotecan with or without anti-EGFR targeted therapy (i.e., cetuximab or panitumumab) – only intended for patients with wild-type KRAS/NRAS
- Regorafenib
- Trifluridine/tipiracil
- Immune checkpoint inhibitor (i.e., nivolumab, pembrolizumab) – only intended for patients exhibiting dMMR/MSI-H

For patients who were eligible to receive intensive chemotherapy in the first-line setting and underwent fluoropyrimidine treatment without irinotecan or oxaliplatin, NCCN recommends the following treatment options:

- FOLFOX with or without bevacizumab
- CapeOX with or without bevacizumab
- FOLFIRI with or without antiangiogenic targeted therapy (i.e., bevacizumab, ramucirumab, ziv-aflibercept)
- Irinotecan with or without antiangiogenic targeted therapy
- Irinotecan/oxaliplatin with or without bevacizumab
- Immune checkpoint inhibitor (i.e., nivolumab, pembrolizumab) – only intended for patients exhibiting dMMR/MSI-H

For patients who were ineligible to receive intensive chemotherapy in the first-line setting and who demonstrate improvement in functional status post-treatment, NCCN recommends one of the intensive chemotherapy options typically utilized in the first-line setting.

For patients who were ineligible to receive intensive chemotherapy in the first-line setting and who demonstrate no improvement in functional status post-treatment, NCCN recommends that these patients receive best supportive care.

6. Ongoing research

Recently Published Results

To identify any RCTs published after the cut-off date for the systematic review by Mocellin et al. (May 2016), we searched Ovid Embase and PubMed in process on March 23. 2017, for RCTs in second-line colorectal cancer. Three publications regarding RCTs in the second-line setting were published between May 2016 and March 2017. Two of the studies identified potential predictive biomarkers for EGFR pathway inhibitors.[7,13] The third study reported negative results for the addition of two antiangiogenic pathway inhibitors to FOLFOX.[14]

Ciardiello and colleagues[7] published data from a phase II trial investigating the continuation of the anti-EGFR monoclonal antibody in patients with wild-type KRAS colorectal cancer who had undergone first-line treatment with FOLFIRI and cetuximab.[7] Patients (n=153) were randomly assigned to treatment with either FOLFOX plus cetuximab or FOLFOX alone. FOLFOX+cetuximab did not demonstrate improved progression-free survival in the overall patient population (HR 0.81, 95% CI 0.58 to 1.12, p=0.19). However, 117 of 153 patients underwent genetic testing and within a subpopulation of 66 patients with wild-type KRAS, NRAS, BRAF, and PIK3CA, progression-free survival was improved in FOLFOX+cetuximab-treated patients (HR 0.56, 95% CI 0.33 to 0.94). Authors suggest that the efficacy of cetuximab be tested in phase III RCTs enrolling these ‘quadruple-positive’ colorectal cancer patients.

Shitara and colleagues[13] published data from a phase II trial comparing FOLFIRI plus panitumumab to FOLFIRI plus bevacizumab in patients (n=121) with wild-type KRAS colorectal cancer previously treated with oxaliplatin-based chemotherapy and bevacizumab. No significant difference in overall survival or progression-free survival was observed between the two arms. Genetic testing of circulating tumor cells identified KRAS, NRAS, and BRAF mutations as potential negative predictive markers for panitumumab.

Moore and colleagues[14] published data from a phase II trial investigating the combination of the anti-VEGFR2 monoclonal antibody ramucirumab with a modified FOLFOX regimen (mFOLFOX) or the combination of the anti-VEGFR1 monoclonal antibody icrucumab with mFOLFOX to mFOLFOX alone in patients (n=153) with metastatic colorectal cancer previously treated with an irinotecan-based chemotherapy regimen with or without bevacizumab. Ramucirumab is FDA approved for use in the second-line setting in combination with FOLFIRI. Icrucumab is an investigational drug not FDA approved for any indication. Both combinations failed to demonstrate improved progression-free survival in this patient population compared to FOLFOX alone (Ramucirumab+mFOLFOX versus mFOLFOX, HR 1.116, 95% CI 0.713-1.745; Icrucumab+mFOLFOX versus mFOLFOX, HR 1.603, 95% CI 1.011-2.543).

Additionally, analyses recently published[15] or presented at scientific meetings[16,17] have suggested that the anatomic location of the primary tumor has important implications for the efficacy of certain treatments. In particular, the biology of right-sided tumors (i.e., tumors located proximal to the hepatic flexure) appears different from that of left-sided tumors (i.e., tumors located distal to the splenic flexure). Retrospective analyses of patients receiving cetuximab plus chemotherapy for treatment of metastatic colorectal cancer have suggested that cetuximab is less effective in treating patients whose primary tumor was right-sided.[15-17] These observations await confirmation in prospective clinical trials.

Ongoing Trials

To identify ongoing trials, we searched ClinicalTrials.gov on March 28, 2017, and identified 111 studies involving second-line treatments for metastatic colorectal cancer. Among these 111 studies, 17 studies were identified as ongoing. This includes three RCTs comparing established second-line treatments (see Appendix Table 2); seven trials comparing non-established second-line treatments to established second-line treatments (see Appendix Table 3); one non-RCT of an established second-line treatment (see Appendix Table 4); and six non-RCTs of non-established second-line treatments (see Appendix Table 5).

With regards to areas for future research identified in Mocellin et al., four of the 17 trials (NCT00940316, NCT01298570, NCT02450656, NCT01139138) are investigating classes of targeted therapies known to have efficacy in other cancer types, including EGFR inhibitors (afatinib and erlotinib); MEK inhibitors (selumetinib); mTOR inhibitors (everolimus). Additionally, five of the 17 trials (NCT02414009, NCT00940316, NCT02450656, NCT02619435, NCT02906059) included a genetic marker other than wild-type KRAS intended to predict response to treatment and/or toxicity of specific drugs. Genetic markers in these trials included activating mutations in BRAF, KRAS, or NRAS, MGMT promoter methylation, UGT1A1 diplotype, and wild-type PIK3CA. Lastly, five of the 17 trials (NCT01442649, NCT02605044, NCT02414009, NCT01532804, NCT0293576) explicitly included quality of life as a secondary outcome measure for the trial.

In addition to these trials of various systemic therapies, our searches identified two RCTs (NCT01483027 and NCT03069950) investigating multidisciplinary approaches in the second-line treatment setting combining systemic therapy with localized treatment for liver metastasis (See Appendix Table 6). The liver is the most common site for colorectal cancer metastases, and the progression of liver metastases contributes substantially to the morbidity and mortality associated with colorectal cancer.[18] Therefore, localized therapies targeting liver metastases have the potential to alleviate symptoms and/or prolong survival while limiting systemic toxicity due to their localized mechanism of action.

Lastly, our searches identified one trial (NCT02246725) investigating the impact of early contact with a palliative care unit on quality of life in patients undergoing treatment for various advanced cancers, including patients receiving second-line treatment for metastatic colorectal cancer.

7. Likelihood of implementation in practice and feasibility of carrying out the research

No significant advances have been made in second-line treatment of colorectal cancer in recent years. Therefore, physicians and patients are eager for improvements in this treatment setting and comparative effectiveness research demonstrating improved patient outcomes would likely be implemented in practice.

Multiple treatment options exist in the second-line treatment setting with comparable efficacy.[3,4] Comparative effectiveness trials investigating differences in the efficacy of these treatments might need to recruit a large number of patients in order to achieve sufficient statistical power to demonstrate such a difference.

8. Durability of information

It is likely that the results of comparative effectiveness studies investigating second-line treatments for colorectal cancer would remain relevant for some time. No new classes of anticancer drug have become available for treating colorectal cancer since the approval of the anti-EGFR monoclonal antibody cetuximab in 2004. Ongoing RCTs appear to be further extensions of established paradigms and are unlikely to cause a dramatic shift in practice patterns.

Checkpoint inhibitors, for which initial results have recently been reported in colorectal cancer, have the potential to bring an immunotherapy approach to colorectal cancer treatment. However, unlike other cancer types (e.g., melanoma, non-small cell lung cancer), these drugs do not appear to have widespread activity outside of patients with a subtype of colorectal cancer defined by MSI-H.[11] Therefore, any disruptive effect of these drugs would be limited to the small minority of patients (approximately 4%) that exhibit this molecular phenotype.

9. Potential research areas and comparative effectiveness research questions

(1) Identification of biomarkers aside from wild-type KRAS for anti-EGFR monoclonal antibodies.

- Expanding testing for anti-EGFR monoclonal antibody treatment to NRAS, BRAF, and/or PIK3CA
- Investigation of alternative methods for targeting BRAF mutation-positive colorectal cancer, an aggressive form of colorectal cancer with a poorer prognosis than BRAF-wild-type colorectal cancer. BRAF inhibitors have demonstrated efficacy in other BRAF-mutation-positive cancers, in particular melanoma.[19] However, single-agent vemurafenib has not demonstrated efficacy in treating BRAF mutation-positive colorectal cancer.[20] One hypothesis is that compensatory signaling through EGFR is responsible for BRAF-mutation-positive colorectal cancer's resistance to BRAF inhibitors,[21] and a phase II trial investigating the combination of the anti-EGFR antibody cetuximab, the BRAF inhibitor vemurafenib, and irinotecan is ongoing (NCT02164916).
- Additional predictive genetic markers may arise from basket trials testing multiple targeted therapies in different cancers with various somatic mutations (e.g., NCI Match, NCT02465060)

(2) Investigation of targeted therapies being used successfully in treating other cancers in colorectal cancer, in particular immunooncology approaches using checkpoint inhibitors

- Determine appropriate treatment setting (if any) for use of checkpoint inhibitors (e.g., nivolumab, pembrolizumab) in high microsatellite instability colorectal cancer.
- Investigate alternative methods of expanding efficacy of immunotherapy to microsatellite stable tumors. For example, inhibiting the kinase MEK has been hypothesized to lead to increased expression of major-histocompatibility complex I in tumor cells and increased T-cell infiltration in tumors, both of which could potentiate the effects of checkpoint inhibitor-based immunotherapy.[22] A phase I trial combining a checkpoint inhibitor (atezolizumab) with a MEK inhibitor (cobimetinib) produced promising results in a small number of colorectal cancer patients,[22] and a phase III trial investigating this combination is ongoing in the third-line setting (NCT02788279).

(3) Investigation of role for liver-directed localized therapies (e.g., chemoembolization, radioembolization, radiofrequency ablation, hepatic artery chemoinfusion) in combination with second-line treatments.

(4) Performance of RCTs for established second-line treatment options that have not been studied in head-to-head clinical trials.
    - Irinotecan plus bevacizumab vs. irinotecan in the second-line setting
    - FOLFIRI+bevacizumab vs. FOLFIRI+ramucirumab vs. FOLFIRI+ziv-aflibercept in the second-line setting
    - Studies intended to optimize the sequencing of anticancer agents in the first-, second-, and third-line settings.

(5) Study the relative safety/efficacy of treatment options for patients who have received irinotecan and oxaliplatin (e.g., FOLFOXIRI) in the first-line setting
    - Regorafenib vs. tipiracil/trifluridine vs. irinotecan plus/minus bevacizumab

(6) Investigation of influence of primary tumor location on management of patients with metastatic disease
    - Prospectively enrolled trials to investigate the efficacy of anti-cancer agents in left-sided vs. right sided tumors (in particular confirmation of observations regarding reduced efficacy of cetuximab in right-sided tumors)
    - Studies to investigate the underlying biological basis for the differences observed between left-sided and right-sided tumors (i.e., identification of a biomarker or biomarkers). One potential biomarker is a set of four consensus molecular subtypes defined by gene expression analysis,[23] which appear to be differentially distributed between right- and left-sided tumors.[24]
    - Assessment of whether stratification of patients based on anatomic location of the primary tumor should be included in future colorectal cancer trials.

10.Conclusions

- Colorectal cancer represents the second-leading cause of cancer-related death in the United States. Patients with metastatic colorectal cancer that has progressed following first-line systemic therapy have a median overall survival of approximately 1 year and this stage of the disease also carries a substantial symptom burden.
- Systemic therapy is the standard of care in the second-line treatment of metastatic disease and multiple accepted treatment regimens are available. Few of the currently accepted treatment regimens have been compared to one another in randomized control trials and, therefore, questions remain regarding the selection of therapies in the second-line treatment setting.
- In addition to established therapies for treating colorectal cancer in the second-line setting, substantial interest exists in the development of new treatments for this disease. In particular, the success of immunooncology approaches to treating other solid tumors (e.g., lung cancer, melanoma) has created substantial interest using such an approach in colorectal cancer.

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Glossary

Activating Mutation – A change in the DNA sequence of a gene resulting in an altered protein that has higher levels of activity (i.e., hypermorphic mutation) or new activity (i.e., neomorphic mutation). Activating mutations occurring in oncogenes contribute to the pathogenesis of cancer.

Anti-Angiogenic – Larger tumors require that new blood vessels be created to supply oxygen to tumor cells, a process known as angiogenesis. Anti-angiogenic drugs are a class of pharmaceuticals intended to interfere with the formation of new blood vessels.

Basket Trial – A clinical trial design that enrolls patients with cancers of different tissues of origin (e.g., bladder cancer, lung cancer) but sharing a common genetic change (i.e., activating mutation in a specific oncogene). These trials are based on the concept that the shared genetic make-up of these cancers may make them susceptible to treatment with the same molecularly directed therapy despite the cancers' different tissue of origin. These trials are intended to allow study of rare cancers that may not be amenable to study in enrichment trials because of the small number of patients.

Biologics – Therapeutics using living organisms or substances derived from living organisms. Biologics used in the treatment of colorectal cancer are frequently cell line-generated monoclonal antibodies that are specific for molecules involved in cancer pathogenesis.

Checkpoint Inhibitor - a class of anti-cancer drugs that targets negative regulators of immune responses (e.g., CTLA-4, PD-1), potentially activating an immune response against the cancer.

Cytotoxic Chemotherapy – broad class of anti-cancer drugs intended to kill cancer cells, typically by interfering with the cell cycle or DNA replication.

Targeted therapy—a cancer therapy targeting a biomolecule or process thought to be important in sustaining the cancer (e.g., bevacizumab used to target angiogenesis). Targeted therapies may be biologic agents (e.g., monoclonal antibodies) or small molecules (e.g., kinase inhibitors). While these drugs have a specific molecular 'target,' the drugs are not necessarily intended for use in specific subgroup characterized by a biomarker.

Wild-Type – the predominant sequence of a gene present in the human population, which is considered to lack deleterious alterations (i.e., mutations)

Abbreviations:

BRAF: B-Raf Proto-Oncogene, Serine/Threonine Kinase

DCR: Disease Control Rate (a combination of complete response, partial response, and stable disease)

dMMR: Deficient Mismatch Repair

EGFR: Epidermal Growth Factor Receptor

KRAS: Kirsten Rat Sarcoma Proto-Oncogene, GTPase

MEK: Mitogen-Activated Protein Kinase Kinase

MGMT: O-6-methylguanine-DNA methyltransferase

MSI-H: High-Frequency Microsatellite Instability

mTOR: Mammalian Target of Rapamycin

NRAS: Neuroblastoma RAS Viral Oncogene Homolog

ORR: Overall Response Rate (combination of complete and partial responses to treatment)

OS: Overall Survival (time from treatment initiation to death by any cause)

PD-1: Programmed-Death Receptor 1

PFS: Progression-Free Survival (time from treatment initiation to disease progression)

PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha

RAS: Rat Sarcoma Proto-Oncogene, GTPase

SAE: Severe Adverse Event (treatment-related grade 3 to 5 toxicity)

TTF: Time to Treatment Failure (time from treatment initiation to treatment discontinuation for any reason)

UGT1A1: UDP glucuronosyltransferase family 1 member A1

Appendices

Appendix Table 1. Anticancer Agents Used in Treating Colorectal Cancer

Name	Class	Description
5-Fluorouridine (5-FU)	Chemotherapy	Antimetabolite (intravenously administered fluoropyrimidine)
Bevacizumab (Avastin)	Targeted Therapy	Anti-VEGF-A Monoclonal Antibody
Capecitabine (Xeloda)	Chemotherapy	Antimetabolite (orally administered fluoropyrimidine)
Cetuximab (Erbitux)	Targeted Therapy	Anti-EGFR Monoclonal Antibody - intended for use in patients with RAS wild-type tumors
FOLFIRI	Chemotherapy	Multiagent chemotherapy regimen containing folinic acid (FOL), fluorouracil (F), and irinotecan (IRI)
FOLFOX	Chemotherapy	Multiagent chemotherapy regimen containing folinic acid (FOL), fluorouracil (F), and oxaliplatin (OX)
FOLFOXIRI	Chemotherapy	Multiagent chemotherapy regimen containing folinic acid (FOL), fluorouracil (F), irinotecan (IRI), and oxaliplatin (OX)
Irinotecan	Chemotherapy	Camptothecan Analog
Nivolumab (Opdivo)	Immunotherapy	Anti-PD1 Monoclonal Antibody
Oxaliplatin	Chemotherapy	Alkylating Agent
Panitumumab (Vectibix)	Targeted Therapy	Anti-EGFR Monoclonal Antibody - intended for use in patients with RAS wild-type tumors
Pembrolizumab (Keytruda)	Immunotherapy	Anti-PD1 Monoclonal Antibody
Ramucirumab (Cyramza)	Targeted Therapy	Anti-VEGFR2 Monoclonal Antibody
Regorafenib (Stivarga)	Targeted Therapy	Multikinase Inhibitor (VEGFR2, TIE-2)
Trifluridine and Tipiracil (Lonsurf)	Chemotherapy	Antimetabolite
XELIRI	Chemotherapy	Multiagent chemotherapy regimen containing capecitabine and irinotecan
XELOX (CapeOx)	Chemotherapy	Multiagent chemotherapy regimen containing capecitabine and oxaliplatin
Ziv-Aflibercept (Zaltrap)	Targeted Therapy	VEGF Trap Peptibody

Appendix Table 2. Ongoing Trials – RCTs of Established Treatments

NCT Number/Title	Patient Population	Intervention/Comparators	Outcome Measures	Completion Date
NCT0293576 FOLFIRI Versus Irinotecan as Second-Line Treatment in Metastatic Colorectal Cancer Patients	Patients with metastatic colorectal cancer who have undergone first-line treatment with either XELOX or FOLFOX (n=164)	Patients randomly assigned to treatment with either irinotecan or FOLFIRI	Primary: PFS Secondary: OS; ORR; Adverse Event Rate; Quality of Life	Oct-2019
NCT01442649 Phase II, Multicentric Randomized Trial, Evaluating the Efficacy of Fluoropyrimidine-based Standard Chemotherapy, Associated to Either Cetuximab or Bevacizumab, in KRAS Wild-type Metastatic Colorectal Cancer Patients With Progressive Disease After Receiving First-line Treatment With Bevacizumab	Patients with wild-type KRAS metastatic colorectal cancer previously treated with chemotherapy (5-FU with irinotecan or oxaliplatin) plus bevacizumab (n=133)	Patients randomly assigned to treatment with fluoropyrimidine-based chemotherapy (FOLFIRI or FOLFOX) plus bevacizumab or fluoropyrimidine chemotherapy plus cetuximab	Primary: PFS Secondary: ORR; OS; Treatment Tolerance; Quality of Life	Dec-2018
NCT01878422 Sequential Treatment Strategy for Metastatic Colorectal Cancer	Patients with wild-type KRAS unresectable, locally advanced or metastatic colorectal cancer previously treated with chemotherapy (FOLFIRI or FOLFOX) plus or minus bevacizumab (n=104)	Patients who received FOLFOX/FOLFIRI+bevacizumab randomly assigned to treatment with FOLFIRI/FOLFOX plus cetuximab or FOLFIRI/FOLFOX alone. Patients who received FOLFOX/FOLFIRI randomly assigned to treatment with FOLFIRI/FOLFOX plus bevacizumab and cetuximab or FOLFIRI/FOLFOX plus bevacizumab.	Primary: PFS Secondary: ORR, OS, SAE rate	Mar-2017

Appendix Table 3. Ongoing Trials – RCTs of Non-Established Treatments

NCT Number/Title	Patient Population	Intervention/Comparators	Outcome Measures	Completion Date
NCT00940316 Dual Epidermal Growth Factor Receptor Inhibition With Erlotinib and Panitumumab With or Without Chemotherapy for Advanced Colorectal Cancer	Patients with metastatic colorectal cancer who have progressive disease within 3 months of treatment with first-line 5-FU and oxaliplatin-based chemotherapy or developed metastatic disease within 6 months of completing adjuvant therapy with 5-FU and oxaliplatin. Patients' tumors must harbor wild-type KRAS (n=96)	Patients with UGT1A1 genotype 6/6 or 6/7 randomly assigned to treatment with either (A) erlotinib, panitumumab, and irinotecan or (B) erlotinib and panitumumab followed by irinotecan upon disease progression. Patients with UGT1A1 genotype 7/7 assigned to treatment with erlotinib and panitumumab	Primary: ORR Secondary: Time to Disease Progression; Time to Disease Failure; Toxicity	Jul-2018
NCT01298570 Multi-Center, Randomized, Placebo-Controlled Phase II Study of Regorafenib in Combination With FOLFIRI Versus Placebo With FOLFIRI as Second-Line Therapy in Patients With Metastatic Colorectal Cancer	Patients with metastatic colorectal cancer not amenable to surgical resection with curative intent who previously received oxaliplatin-based chemotherapy (FOLFOX, CapeOx) with or without bevacizumab (n=181)	Patients randomly assigned to treatment with either FOLFIRI + regorafenib or FOLFIRI + placebo.	Primary: PFS Secondary: ORR, DCR; OS; Toxicity per NCI CTCAE	Feb-2021
NCT01532804 2nd-line Treatment of Metastatic Colorectal Cancer (BEVATOMOX)	Patients with metastatic colorectal cancer who have undergone first-line chemotherapy with an irinotecan-based chemotherapy regimen (n=124)	Patients randomly assigned to treatment with either FOLFOX plus bevacizumab or combination therapy with ralitrexed, oxaliplatin, and bevacizumab	Primary: Disease-free survival Secondary: Treatment-related toxicity; ORR; OS; Cost-Effectiveness; Quality of Life	Dec-2018
NCT01996306 A Multinational, Randomized, Phase III Study of XELIRI With/Without Bevacizumab Versus FOLFIRI With/Without Bevacizumab As Second-line Therapy in Patients With Metastatic Colorectal Cancer	Patients with metastatic colorectal cancer who had withdrawn from first-line chemotherapy due to disease progression or toxicity and patients with colorectal cancer whose disease had relapsed within 180 days of receiving adjuvant chemotherapy. (n=650)	Patients randomly assigned to treatment with either XELIRI plus or minus bevacizumab or FOLFIRI plus or minus bevacizumab	Primary: OS Secondary: PFS; TTF; ORR; DCR; Relative Dose Intensity; Incidence of Adverse Events; Correlation between UGT1A1 Genotype and Safety	Jan-2017
NCT02414009 Study to Compare CAPTEM vs FOLFIRI as Second Line Treatment in Advanced, Colorectal Cancer Patients (CAPTEM)	Patients with metastatic colorectal cancer who have undergone first-line chemotherapy with an oxaliplatin-containing chemotherapy regimen. Patients' tumor must exhibit MGMT promoter methylation and RAS mutation. (n=82)	Patients randomly assigned to treatment with either CAPTEM (capecitabine plus temozolomide) or FOLFIRI	Primary: PFS Secondary: ORR; OS; Adverse Event Rate; Quality of Life	Sep-2017
NCT02450656 Afatinib and Selumetinib in Advanced KRAS Mutant and PIK3CA Wildtype Colorectal,	Patients with colorectal cancer, non-small cell lung cancer, or pancreatic cancer who have underfone first-line therapy for metastatic disease. Patients' tumors must have a known pathogenic KRAS	Patients randomly assigned to treatment with either the EGFR inhibitor afatinib in combination with the MEK inhibitor selumetinib or standard chemotherapy.	Primary: PFS Secondary: OS; ORR; Duration of Response; Time to Response	Dec-2019

NCT Number/Title	Patient Population	Intervention/Comparators	Outcome Measures	Completion Date
Non-small Cell Lung and Pancreatic Cancer (M14AFS)	mutation and be wild-type at the PIK3CA locus (i.e., absence of mutations in exon 9 and 20). (n=320)			
NCT02605044 Study to Compare the Efficacy and Safety of Masitinib in Combination With FOLFIRI to Placebo in Combination With FOLFIRI in Second Line Treatment of Patients With Metastatic Colorectal Cancer	Patients with non-resectable, metastatic colorectal cancer who are eligible for second-line treatment with FOLFIRI (n=550)	Patients randomly assigned to treatment with either FOLFIRI + masitinib or FOLFIRI + placebo	Primary: OS Secondary: PFS; ORR; Quality of Life: Safety Profile	Jun-2018

Appendix Table 4. Ongoing Trials – Non-RCTs of Established Treatments

NCT Number/Title	Patient Population	Intervention/Comparators	Outcome Measures	Completion Date
NCT02322736 Prospective Observational Study of 1st and 2nd Line Vectibix® Use in RAS-wt mCRC Pts to Evaluate Pattern of Use and ORR (VISION)	Patients with metastatic colorectal cancer receiving panitumumab in either the first-line or second-line setting. Patients' tumors must be RAS wild-type (n=218)	Observational study of patients receiving treatment with panitumumab.	Primary: Pattern of use of Panitumumab Secondary: ORR	Jul-2018

Appendix Table 5. Ongoing Trials – Non-RCTs of Non-Established Treatments

NCT Number/Title	Patient Population	Intervention/Comparators	Outcome Measures	Completion Date
NCT0303525 A Study of OMP-305B83 in Subjects With Metastatic Colorectal Cancer	Patients with metastatic colorectal cancer in whom second-line therapy with FOLFIRI is appropriate. (n=30)	All patients will receive treatment with FOLFIRI plus the DLL4/VEGF bi-specific monoclonal antibody OMP-305B83.	Primary: Dose-Limiting Toxicities Secondary: Safety; Immunogenicity of OMP-305B83; ORR; Response Rate by CEA; PFS	Jan-2019
NCT01139138 Safety Study of the Combination of Panitumumab, Irinotecan and Everolimus in the Treatment of Advanced Colorectal Cancer (PIE)	Patients with metastatic colorectal cancer who have undergone first-line fluoropyrimidine-based therapy. Patients' tumors must be KRAS wild-type. (n=49)	All patients will receive treatment with irinotecan, panitumumab, and the mTOR inhibitor everolimus.	Primary: Dose-Limiting Toxicities Secondary: Safety & Toxicity; ORR; PFS; OS	Jun-2017
NCT01803282 Safety and Tolerability Study in Solid Tumors	Patients with various solid tumors including patients with metastatic colorectal cancer who have undergone first-line therapy with oxaliplatin- and fluoropyrimidine-based chemotherapy with or without bevacizumab (n=250)	Patients will receive treatment with either the anti-matrix metallopeptidase 9 monoclonal antibody andecaliximab (GS-5745) or andecaliximab in combination with FOLFIRI plus bevacizumab	Primary: Safety and Tolerability	Feb-2019
NCT02619435 Regorafenib Monotherapy as Second-line Treatment of Patients With RAS-mutant Advanced Colorectal Cancer (STREAM)	Patients with metastatic colorectal cancer that has progressed following treatment with first-line therapy consisting of oxaliplatin-based chemotherapy plus bevacizumab. Patients' tumors must harbor an activating KRAS mutation. (n=46)	All patients will receive treatment with regorafenib	Primary: PFS at 6 months Secondary: Toxicity; ORR; PFS; OS	Nov-2018
NCT02906059 Study of Irinotecan and AZD1775, a Selective Wee 1 Inhibitor, in RAS or BRAF Mutated, Second-line Metastatic Colorectal Cancer	Patients with metastatic colorectal cancer that has progressed following treatment with first-line therapy consisting of oxaliplatin-based chemotherapy plus bevacizumab or who have experienced progressive disease within 12 months of completing adjuvant treatment with FOLFOX. Patients' tumors must harbor an activating mutation in KRAS, NRAS, or BRAF. (n=32)	All patients will receive treatment with irinotecan and the wee1 inhibitor AZD1775	Primary: Dose-Limiting Toxicities Secondary: ORR	Sep-2019
NCT03053167 Irinotecan Plus Raltitrexed as Second-line Treatment in Advanced Colorectal Cancer Patients	Patients with metastatic colorectal cancer that has progressed following treatment with first-line therapy consisting of an oxaliplatin- and fluoropyrimidine based chemotherapy regimen or who have experienced progressive disease within 6 months of completing adjuvant therapy consisting of an oxaliplatin- and fluoropyrimidine based chemotherapy regimen. (n=100)	All patients will receive treatment with irinotecan and raltitrexed.	Primary: PFS Secondary: OS; ORR; DCR	Dec-2020

Appendix Table 6. Ongoing Trials – Multidisciplinary Approaches to Liver Metastatic Disease

NCT Number/Title	Patient Population	Intervention/Comparators	Outcome Measures	Completion Date
NCT01483027 Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer (EPOCH)	Patients with metastatic colorectal cancer that have exhibited disease progression in unresectable liver metastases after first-line treatment with oxaliplatin-based or irinotecan-based chemotherapy (n=340)	Patients will be randomly assigned to treatment with either radioembolization with yttrium 90 microspheres in combination with standard second-line chemotherapy or to standard second-line chemotherapy alone.	Primary: PFS	Feb-2019
NCT03069950 Study of Chemotherapy With or Without Hepatic Arterial Infusion for Patients With Unresectable Metastatic Colorectal Cancer to the Liver	Patients with RAS/RAF wild-type metastatic colorectal cancer with unresectable liver metastases and no radiographic evidence of extrahepatic disease who have previously received oxaliplatin-based systemic therapy.	Patients will be randomly assigned to either treatment with hepatic arterial infusion of floxuridine and dexamethasone in combination with systemic chemotherapy consisting of FOLFIRI+panitumumab or to treatment with FOLFIRI+panitumumab alone	Primary: Number of patients whose liver disease becomes resectable	Feb-2020

Literature Search:

In March 2017, we conducted a literature review to identify evidence-based research around the comparative effectiveness of second-line therapies for metastatic colorectal cancer. We used PubMed, EMBASE, and the Cochrane Library to identify systematic reviews, meta-analyses and research reports, and the most current reviews, including those published by the Cochrane collaboration. We also searched the National Guideline Clearinghouse to identify clinical practice guidelines that addressed this topic. These strategies are provided in the tables below.

Clinical Trials and NIH Funding Announcements:

To identify ongoing trials, we searched ClinicalTrials.gov on March 28, 2017. A total of 111 studies were found using the search terms:

((colorectal neoplasms OR ((colorectal OR colon) AND (cancer* OR carcinoma* OR adenocarcinoma* OR tumor* OR tumour*)))
AND
("2nd-line" OR "2nd line" OR "second-line" OR "second line")

Bibliographic search strategies:

Embase.com [1/1/14 – 3/23/17 – Systematic review search], [1/1/16 – 3/23/17 – RCT search]

Set Number	Concept	Search statement	# identified
1	Colorectal cancer	'colorectal cancer'/exp OR 'colorectal cancer' OR 'colon tumor'/exp OR 'benign colon tumor' OR 'benign colon tumour' OR 'colon neoplasm' OR 'colon sigmoid tumor' OR 'colon sigmoid tumour' OR 'colon tumor' OR 'colon tumour' OR 'colon villous tumor' OR 'colon villous tumour' OR 'colonic neoplasms' OR 'colonic tumor' OR 'colonic tumour' OR 'mesocolon tumor' OR 'mesocolon tumour' OR 'sigmoid colon tumor' OR 'sigmoid colon tumour' OR 'sigmoid neoplasms' OR 'sigmoid tumor' OR 'sigmoid tumour' OR 'rectum tumor'/exp OR 'mass, rectum' OR 'neoplasma recti' OR 'pararectal tumor' OR 'pararectal tumour' OR 'rectal mass' OR 'rectal neoplasm' OR 'rectal neoplasms' OR 'rectal tumor' OR 'rectal tumour' OR 'rectum mass' OR 'rectum neoplasm' OR 'rectum tumor' OR 'rectum tumour' OR 'retrorectal tumor' OR 'retrorectal tumour' OR 'tumor recti' OR 'tumour recti'	305,855
2		(colorect* OR colon* OR rectum OR rectal OR anal* OR anus* OR intestine* OR bowel*) NEAR/3 (carcinom* OR neoplas* OR adenocarcinom* OR cancer* OR tumor* OR tumour* OR sarcom*)	511,185
3		#1 OR #2	520,989
4		'second line chemotherapy'/exp OR 'second line chemotherapy'	3,376

Set Number	Concept	Search statement	# identified
5	Second-line therapy	'second line' OR 'second-line' OR '2nd line' OR '2nd-line'	29,374
6		#4 OR #5	29,374
7	Combine sets	#3 AND #6 [limited to English language, humans, 2014 – present]	1,044
8	Systematic reviews	#7 AND (‘systematic review’/de OR ‘systematic review’ OR (meta NEAR/1 analy*) OR ‘meta analysis’/de	104
9	RCTs	#7 AND ('randomized controlled trial'/exp OR 'randomization'/de OR 'double blind procedure'/de OR 'single blind procedure'/de OR 'placebo'/de OR 'crossover procedure'/de OR placebo* OR random*:de,ti OR crossover* OR 'cross over' OR (singl* OR doubl* OR tripl* OR trebl* AND (blind* OR mask* OR sham*)) OR 'latin square' OR isrtcn* OR actrn* OR (nct* NOT nct)) AND [1-1-2016]/sd	115
10	Combine sets	#8 OR #9	293

PubMed [In process citations – 2016 – 3/23/17]

Set Number	Concept	Search statement	# identified
1	1st approach	(((("colorectal cancer"[ti] OR "colorectal neoplasm"[ti] OR "colorectal tumor"[ti] OR "colorectal tumors"[ti] OR "colorectal tumour"[ti] OR "colorectal tumours"[ti]) AND (publisher[sb] OR pubmednotmedline[sb] OR in process[sb])) OR (("colorectal cancer"[ti] OR "colorectal neoplasm"[ti] OR "colorectal tumor"[ti] OR "colorectal tumors"[ti] OR "colorectal tumour"[ti] OR "colorectal tumours"[ti]) AND inprocess[sb])) AND (random* OR "systematic review" OR "meta-analysis" OR "meta analysis" OR pooled[ti]) AND (("2016/01/01"[PDat] : "2017/12/31"[PDat]))) AND ("second-line" OR "2nd-line" OR "second line" OR "2nd line") Filters: Publication date from 2016/01/01 to 2017/12/31	17
2	2nd approach	"second-line"[ti] OR "second line"[ti] OR "2nd line"[ti] OR "2nd-line"[ti] Filters: Publication date from 2016/01/01 to 2017/12/31 AND (inprocess[sb] OR pubmednotmedline[sb] OR publisher[sb])	18
3	Combine sets	#1 OR #2	29

Cochrane Library [2016 – 3/23/17]

Set Number	Concept	Search statement	# identified
1	Colorectal cancer	[Colorectal neoplasms] explode all trees	6320
2		(Colorectal or colon or rectal):ti	12168
3		#1 OR #2	
4	Second line	("second-line" or "second line" or "2nd line" or "2nd-line"):ti	1119
5	Combine sets	#3 AND #4	108
6		Limit #4 to Reviews and trials published 2016 – 2017	13

National Guideline Clearinghouse

MeSH browse – colorectal neoplasms – 34 – 2 selected

Search:

S1: "second-line" OR "2nd-line" – 128

Limited to clinical specialty oncology – 60 – 0 unique relevant summaries identified

S2: "colon cancer" – 34 – 0 unique relevant summaries identified