* Aim:
  + Determie t
* Hypothesis:
  + Resistant BRAF mutant colon cancer cells express high levels of other kinases that can overcome the effect of the BRAF inhibiting drugs.
  + Upregulation of transporter proteins confers innate resistance to BRAF inhibitors in BRAF mutant colorectal cancer cell lines.
  + pERK levels increase in BRAF mutant colorectal cancer cell lines

**To do list:**

* Plan:
  + Step 1. Research Keywords
  + Step 2. Relationships between key words
  + Step 3. Determine gap in knowledge (STUCK here)
  + Step 4. Address knowledge (Experiments)
* 1. BRAF inhibitors work in melanoma (PROVE IT)
* 2. BRAF inhibitors get partial response in Colorectal cancer
* 3. BRAF mutant colorectal cancer populations have reduced responses to BRAF inhibition (PROVE IT)

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6. **Colorectal cancer**
   1. **Epidemiology (word count = 345)**

Colorectal cancer (CRC) is among the most common cancers globally, accounting for 10.0% of cancers diagnosed in men and 9.2% of cancers diagnosed in women. Approximately 746,000 men and 614,000 women suffered from colorectal cancer in 2012, making it the third most common form of cancer in men and the second most common form of cancer in women.

The inverse relationship between rates of incidence and mortality based on geographical locations is demonstrated by the fact 55% of cases are diagnosed in more developed regions, while only accounting for 48% of deaths. This relationship suggests survivability is heavily dependant on regional origin. This seems to be predicated more on the development of the region than the geographic location. For instance, while Northern, Western and Southern Europe are geographically connected to Central and Eastern Europe, they have higher rates of incidence and lower rates of mortality.

Incidence and mortality rates of CRC have similar degrees of variance for both sexes depending on geographical context. There is a variation of approximately 10 fold in age-standardized rate (ASR) of incidence, with Australia/New Zealand having the highest ASR of incidence in the world, at 44.8-32.2 per 100,000 men and women respectively, and Western Africa having the lowest, at 4.5-3.8 per 100,000 men & women respectively.

Variations in mortality rates are less severe than that of incidence rates, with ASR of mortality only exhibiting a 6-4-fold difference among men and women respectively based on geographical location. Western Africa has the lowest ASR of mortality, at 3.5-3 per 100,000 men and women respectively. Central and Eastern Europe have the highest rates of mortality at 20.3-11.7 per 100,000 men and women, respectively.

CRC diagnosis in Australia has increased by 17.2 % from 2012 to 2016, with an estimated 13.4% of new cancer diagnoses and 8.7% of cancer deaths, making it the 2nd most common cancer in Australia. CRC is also estimated to be the 2nd most deadly cancer in Australia in 2016. However, a 1.3% decrease in deaths attributed to CRC has occurred between 2013 (4,162 deaths) and 2016 (4,094 deaths).

* <http://www.aihw.gov.au/cancer/bowel/>
* <http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=colorectal>
* NEED TO PUT THESE REFERENCES IN ENDNOTE
  + 1. **Genetic tumorigenesis (Word count = 305)**

Multiple pathways have been well characterized as carcinogenic in colonic epithelial tissue, with each pathway leading to slight variations in both genotype and histology. Genetic instability is an early hallmark of colorectal cancer, with adenomas exhibiting both chromosomal and microsatellite instability.

The Chromosomal instability pathway describes a series of events impacting chromosomal stability during the progression from early adenomas to adenocarcinomas.

These events typically include RAS-gene mutations, inactivation of tumour suppressor genes and loss of chromosomal heterozygosity.

It is strongly believed that the initial event in the formation of carcinomas via this pathway is the loss of Adenomatous Polyposis Coli (APC) gene functionality. APC is and important regulator of the Wnt signalling pathway, which is responsible for the maintenance of native stem cell populations in the proximal colon. Wild-type APC inhibits cell cycle progression, specifically from G1 to S phase, through the degradation of β-catenin. β-catenin is involved heavily in Wnt signalling and the migration of colonic stem cells and the accumulation of β-catenin leads to an increased population of undifferentiated stem cells that remain undifferentiated and are therefor unable to migrate out of colonic crypts.

This pathway is strongly associated with activating-mutations in proto-oncogenes such as K-RAS and the loss of tumour suppressor genes APC, p53 and DCC located on the chromosome 5q, 17p, and 18q respectively. Tumour progression is associated with the accumulation of these chromosomal deletions.

The MSI pathway typically involves errors in the mismatch repair (MMR) pathways. MMR pathways are responsible for correcting errors made in DNA replication by DNA polymerase and are integral in maintaining genomic stability. Irregular or lack of MMR activity is concomitant with positive MSI status. The key MMR genes being mutated in CRC are MLH1, MSH2, MSH6 and PMS2, with the majority of sporadic CRC’s exhibiting MMR defect being caused by the epigenetic silencing of MLH1.

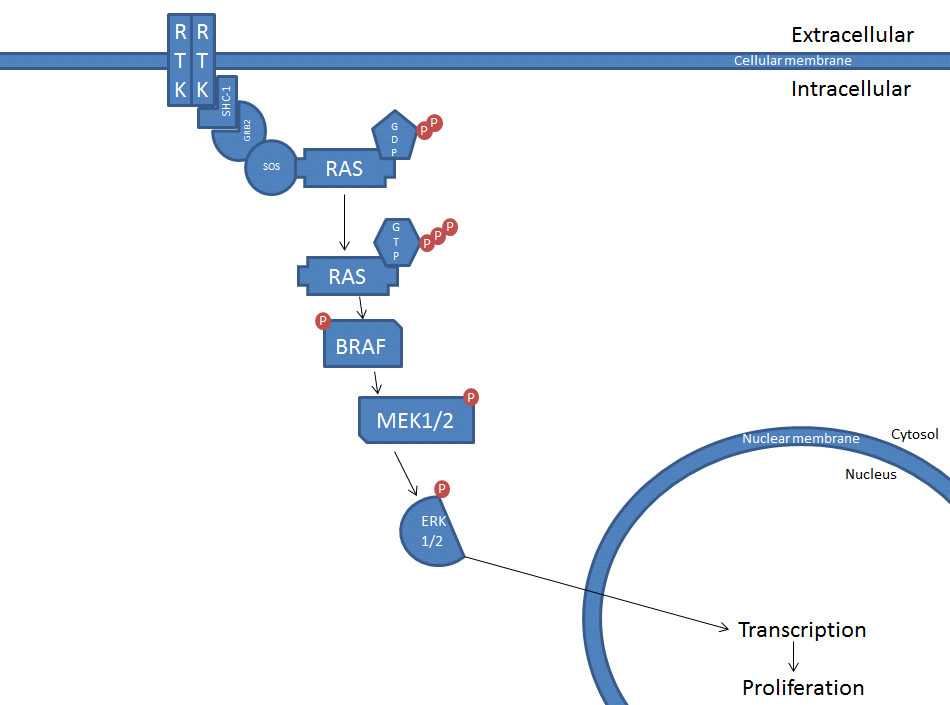
1. **MAPK pathways**
   1. **RAS-RAF-MEK-ERK signaling (Word count = 416)**

The RAS-RAF-MEK-ERK pathway outlines specific interactions involved in signal transduction between transmembrane receptors and genomic DNA. The pathway begins with an initial interaction between transmembrane receptor tyrosine kinases (RTKs) and a specific ligand, typically growth factors such as EGFR, leading to receptor dimerization and trans-phosphorylation of cytosolic tyrosine residues. These phosphorylated tyrosine residues act as binding sites for proteins containing Src-2 homology (SH2) binding sites. Proteins recruited upon EGFR RTK stimulation include SHC-1, GRB2 and SOS. SHC-1 family proteins, specifically p46SHC and p54SHC, contains an n-terminal phosphotyrosine-binding domains and a C-terminal SH2 domain. SHC-1 goes on to recruit Guanine-Exchange Factor (GEF), namely Growth factor Receptor-Bound protein 2 (Grb2). Grb2 consists of two SH3 binding domains located at either terminus, separated by a SH2 binding domain in the centre. The n-terminus contains a SH3 binding site responsible for SOS binding, which in turn allows SOS to activate RAS.  
RAS family proteins act as binary molecular switches, with their position determined by the species of guanine-nucleotide associated with the protein, with RAS-GDP being the inactive form and RAS-GTP as the active form. The binding of SOS to RAS-GDP causes the dissociation of GDP, therefor activating RAS by allowing it to bind GTP. Unoccupied RAS proteins spontaneously associate with GTP due to higher cytosolic concentrations of GTP compared to GDP. RAS activation can also be the result of GTPase activating protein (GAP) activity, which typically increases enzymatic activity by 100 fold. RAS-GTP has intrinsic enzymatic activity and therefor uses the energy associated with the hydrolysis of GTP to facilitate the phosphorylation of RAF family proteins, or Mitogen-Activating Protein Kinase-Kinase-Kinase (MAPKKK), activating their kinase functions. However, RAS-GTP has a wide specificity and acts on multiple effectors, such as PI3k, suggesting RAS kinase activity is not limited to activating RAF proteins.

RAF-family proteins (ARAF, BRAF and CRAF/RAF-1) are proto-oncogenes. While BRAF and CRAF have been well characterized, less is known about ARAF. RAF regulation is a product of homo-heterodimerization with BRAF or other RAF isotypes.

Activated RAF family proteins phosphorylate downstream targets such as MEK1/2. All RAF family members display the ability to phosphorylate MEK, however their kinase activity varies. BRAF and CRAF have much higher kinase activity regarding MEK/ERK phosphorylation than ARAF. Due to the restricted specificity of BRAF/CRAF kinases, they selectively phosphorylate and activate MEK1 and MEK2 (A.K.A Mitogen-Activating Protein kinase-kinase, MAPKK).   
MEK1/2 then phosphorylates ERK1/2 (Mitogen-Activating Protein Kinase (MAPK)). ERK proteins are protein-serine/threonine kinases heavily involved in the regulating of events throughout the cell cycle, such as mitosis and meiosis. ERK1 and ERK2 share 85% homology, suggesting similar functionality. Studies have shown that selective ERK2 silencing is lethal in early development, where as ERK1 silencing has no discernible impact, suggesting redundancy. The culmination of ERK1/2 signalling is cellular proliferation, increasing the appeal for cancer cells to utilize this pathway .

Figure 1. Receptor-ligand interactions initiate a kinase cascade culminating cellular proliferation. The extracellular signal generated by the receptor binding a ligand causes the activation of GTPase switches (RAS) which in turn initiates a series of phosphorylation events that begins with BRAF and terminates with ERK1/2 translocating to the nucleus to promote gene transcription.



1. **BRAF mutants**
   1. **Epidemiology (Word count = 123)**

Activating BRAF mutations occur in several cancers including melanoma, colorectal cancer, glioma, sarcoma, papillary thyroid cancer, ovarian & non-small cell lung cancer. The frequency of BRAF mutation varies depending on histology.   
Melanomas are more frequently mutated with 59% of cases exhibiting activating BRAF mutations, followed by colorectal cancer at 18%.   
The most common BRAF mutations typically occur at the activation segment, of which the majority describe a single substitution at V600, for example V600E substitutions account of 82% of all BRAF mutations.   
Less common BRAF mutations have been observed at in the kinase domain, typically in the glycine-rich loop at residues G463, G465 and G468. 7.9% of diagnosed Phase II/III CRC exhibit BRAF V600E mutations. MSI-H tumours display increased frequencies of BRAF mutations.

* 1. **Clinico-pathological features (Word count= 43)**

BRAF mutations are enriched in colorectal cancer populations that are poorly differentiated and exhibit hyper-methylation of CpG islands (CIMP-H), microsatellite instability (MSI-H) and KRAS wildtype status. BRAF mutations also lead to increased dependency on metastasis via peritoneal disease and distant lymph nodes. BRAF mutations in CRC occur more frequently in females, patients over 70, right-sided, proximal, colonic tumours.

* 1. **Predictive and Prognostic roles (Word count = 379)**

BRAF status typically denotes poorer prognosis in patients treated with traditional chemotherapy agents. This trend is maintained even in the presence of anti-EGFR monoclonal antibodies ([Kalady et al., 2012](#_ENREF_5)). BRAF status is a prognostic marker of reduced Overall Survival (OS) in patients with MSI-L and MSS phenotypes {Roth, 2010 #2}.BRAF mutations in malignant melanoma and metastatic colorectal cancer are predictive of anti-EGFR monoclonal antibody resistance ([Prahallad et al., 2012](#_ENREF_7)). BRAF mutations are predictive of poorer outcomes for patients undertaking metastasectomy due to increased peritoneal spread and decreased liver involvement ([Yaeger et al., 2014](#_ENREF_9)).

1. **BRAF inhibitors**
   1. **Classes**

Type 1 BRAF inhibitors such as Vemurafenib (PLX4032) act via ATP competition. They work by locking BRAF in a DFG-in conformation, or always active.

Type 2 BRAF inhibitors act by causing a DFG-out conformation.

|  |  |  |  |
| --- | --- | --- | --- |
| **Class** | **Drug I.D** | **Clinical Trials** | **Clinical Trials (CRC)** |
| 1 | Vemurafenib | [NCT01006980](https://clinicaltrials.gov/ct2/show/results/NCT01006980), NCT00405587, NCT01006980, |  |
| 1 | Dabrafenib | [NCT01227889](https://clinicaltrials.gov/show/NCT01227889) |  |
| 1 | Encorafenib | [NCT01436656](https://clinicaltrials.gov/ct2/show/NCT01436656) |  |
| 2 | Sorafenib | [NCT00119249](https://clinicaltrials.gov/ct2/show/NCT00119249), [NCT00105443](https://clinicaltrials.gov/ct2/show/results/NCT00105443?sect=X01256) |  |
| 2 | XL281 | [NCT00451880](https://clinicaltrials.gov/ct2/show/NCT00451880) | [NCT01086267](https://clinicaltrials.gov/ct2/show/NCT01086267) |
| 2 | Regorafenib | [NCT01068769](https://clinicaltrials.gov/ct2/show/NCT01068769), [NCT01271712](https://clinicaltrials.gov/ct2/show/NCT01271712) | [NCT01103323](http://clinicaltrials.gov/show/NCT01103323) |
| 3 | CEP-32496 (RXDX105) | ([James et al., 2012](#_ENREF_4)) |  |

* 1. **Efficacy**

Clinical trials show a reduced response to BRAF inhibition in colorectal tumors when compared to melanoma with similar genomic subtypes.

* 1. **Resistance**

Proposed mechanisms of innate resistance in colorectal cancer tumors include feedback activation of EGFR. Depending on whether or not activation is due to activating BRAF mutations or upstream events, like RAS mutations or constitutive receptor signaling, the presence of first and second generation BRAF inhibitors can lead to the paradoxical activation or inactivation of MAPK pathways. A new class of inhibitor known as Paradox Breakers exhibit the ability to illicit responses in cell lines resistant to first/second generation BRAF inhibitors.

1. **Combination treatment**

|  |  |  |
| --- | --- | --- |
| **Targets** | **Drug combination** | **Clinical Trials** |
| RAF-MEK |  |  |
| EGFR-RAF | Panitumumab-Vemurafenib  Cetuximab-XL281 | [NCT01791309](https://clinicaltrials.gov/ct2/show/NCT01791309)  [NCT01086267](https://clinicaltrials.gov/ct2/show/NCT01086267) |
| EGFR-RAF-MEK |  |  |
| EGFR-RAF-PI3K | Cetuximab-Encorafenib-BYL719 | [NCT01719380](https://clinicaltrials.gov/ct2/show/NCT01719380) |
| 2 |  |  |
| 2 |  |  |
| 3 |  |  |

* 1. **Established targets** 
     1. **RAF-MEK**
     2. **RTK-RAF-MEK**
     3. **RTK-RAF-PI3k**
  2. **Candidate targets**
     1. **MAP3k2**
     2. **MAP3k1**
     3. **MAP3k8**
     4. **MAGI3**
     5. **PIK3R1**

* Genetic Alterations in Colorectal Cancer: [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3348713/pdf/gcr19.pdf>]
* Adenoma-to-carcinoma: [[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4671844/#\_\_sec3title](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4671844/) ]
* Genetic alterations during colorectal-tumor development: [<https://www.ncbi.nlm.nih.gov/pubmed/2841597/>]
* A Big Bang model of human colorectal tumor growth: [<https://www.ncbi.nlm.nih.gov/pubmed/25665006/>]
* Mutations of the BRAF gene in human cancer [<http://www.nature.com/nature/journal/v417/n6892/full/nature00766.html>]
* Prognostic and Predictive Biomarkers in Resected Colon Cancer: Current Status and Future Perspectives for Integrating Genomics into Biomarker Discovery [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227961/>]
* Comprehensive molecular characterization of human colon and rectal cancer [<http://www.nature.com/nature/journal/v487/n7407/full/nature11252.html>]
* Optimizing targeted therapeutic development: analysis of a colorectal cancer patient population with the BRAF V600E mutation [<http://onlinelibrary.wiley.com.ez.library.latrobe.edu.au/doi/10.1002/ijc.25555/epdf>]
* BRAF-Mutated Colorectal Cancer Exhibits Distinct Clinicopathological Features from Wild-Type BRAF-Expressing Cancer Independent of the Microsatellite Instability Status [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5143296>]
* Patient and Tumor Characteristics and BRAF and KRAS Mutations in Colon Cancer, NCCTG/Alliance N0147 [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110470/>]
* Poor Survival Associated with the BRAF V600E Mutation in Microsatellite-Stable Colon Cancers [<http://cancerres.aacrjournals.org/content/65/14/6063.long>]
* BRAF mutations in colorectal cancer are associated with distinct clinical characteristics and worse prognosis. [<https://www.ncbi.nlm.nih.gov/pubmed/22228154>]
* Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer [<https://www.ncbi.nlm.nih.gov/pubmed/19001320>]
* BRAF Mutation Predicts for Poor Outcomes After Metastasectomy in Patients With Metastatic Colorectal Cancer [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4928876/>]
* Molecular Cell Biology. 4th edition. [<https://www.ncbi.nlm.nih.gov/books/NBK21720/>]
* The MAPK (ERK) Pathway: Investigational Combinations for the Treatment Of BRAF-Mutated Metastatic Melanoma [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628180/>]
* Inhibition of Mutated, Activated BRAF in Metastatic Melanoma [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3724529/>]
* Vemurafenib and Panitumumab Combination Therapy in Patients With BRAF V600E Mutated Metastatic Colorectal Cancer [<https://clinicaltrials.gov/ct2/show/NCT01791309>]
* [Review] Vemurafenib: a new treatment for BRAF-V600 mutated advanced melanoma [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3421463/>]
* Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial [<https://www.sciencedirect.com/science/article/pii/S014067361260868X>]
* Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial [<https://www.ncbi.nlm.nih.gov/pubmed/23177514/>]
* Efficacy and safety of Regorafenib in patients with metastatic and/or unresecable GI stromal tumor after failure of Imatinib and Sunitinib: A phase II trial [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3675695/>]
* Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib: an international, multicentre, prospective, randomised, placebo-controlled phase III trial (GRID) [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3819942/>]
* Discovery of RAF265: A Potent mut-B-RAF Inhibitor for the Treatment of Metastatic Melanoma [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4569875/>]
* CEP-32496: A Novel Orally Active BRAFV600E Inhibitor with Selective Cellular and *In Vivo* Antitumor Activity [<http://mct.aacrjournals.org/content/11/4/930.long>]
* Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2268581/>]
* Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma [<https://www.ncbi.nlm.nih.gov/pubmed/20823850>]
* The RAF inhibitor PLX4032 inhibits ERK signaling and tumor cell proliferation in a V600E BRAF-selective manner [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2930420/>]
* A selective Raf kinase inhibitor induces cell death and tumor regression of human cancer cell lines encoding B‐RafV600E mutation [<http://mct.aacrjournals.org/content/8/12_Supplement/B88>]
* [Review] Dabrafenib and its potential for the treatment of metastatic melanoma [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3523565/>]
* Encorafenib (LGX818), a potent BRAF inhibitor, induces senescence accompanied by autophagy in BRAFV600E melanoma cells [<https://www.ncbi.nlm.nih.gov/pubmed/26586345>]
* Sorafenib Inhibits Growth and MAPK Signaling in Malignant Peripheral Nerve Sheath Cells [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3267321/>]
* BAY 43-9006 Exhibits Broad Spectrum Oral Antitumor Activity and Targets the RAF/MEK/ERK Pathway and Receptor Tyrosine Kinases Involved in Tumor Progression and Angiogenesis [<http://cancerres.aacrjournals.org/content/64/19/7099.long>]
* Regorafenib (BAY 73-4506): A new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity [<http://onlinelibrary.wiley.com/doi/10.1002/ijc.25864/full>]
* Phase I study of XL281 (BMS-908662), a potent oral RAF kinase inhibitor, in patients with advanced solid tumors [<https://www.ncbi.nlm.nih.gov/pubmed/25476894>]
* Phase II Pilot Study of Vemurafenib in Patients With Metastatic BRAF-Mutated Colorectal Cancer [<http://ascopubs.org/doi/full/10.1200/jco.2015.63.2497>]
* Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation (BRIM-3) [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3549296/>]
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* A Phase II Trial of Sorafenib in Metastatic Melanoma with Tissue Correlates [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3012061/>]
* EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3308191/>]
* Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR [<https://www.ncbi.nlm.nih.gov/pubmed/22281684/>]
* Clinical acquired resistance to RAF inhibitor combinations in BRAF-mutant colorectal cancer through MAPK pathway alterations [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4390490/>]
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* PTEN loss confers BRAF inhibitor resistance to melanoma cells through the suppression of BIM expression [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3070772/>]
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* (Review) BRAF Inhibitor Resistance Mechanisms in Metastatic Melanoma: Spectrum and Clinical Impact [<http://clincancerres.aacrjournals.org/content/20/7/1965>]
* Phase 1-2 trial of the BRAF inhibitor Dabrafenib and MEK inhibitor Trametinib in BRAF V600 mutant CRC [<http://meetinglibrary.asco.org/content/131743-144>]
* Fluorouracil and Leucovorin With or Without Irinotecan in Treating Patients Following Surgery for Stage III Colorectal Cancer [<https://clinicaltrials.gov/ct2/show/NCT00026273t>]
* Prognostic Role of KRAS and BRAF in Stage II and III Resected Colon Cancer: Results of the Translational Study on the PETACC-3, EORTC 40993, SAKK 60-00 Trial [<http://ascopubs.org/doi/full/10.1200/JCO.2009.23.3452>]

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