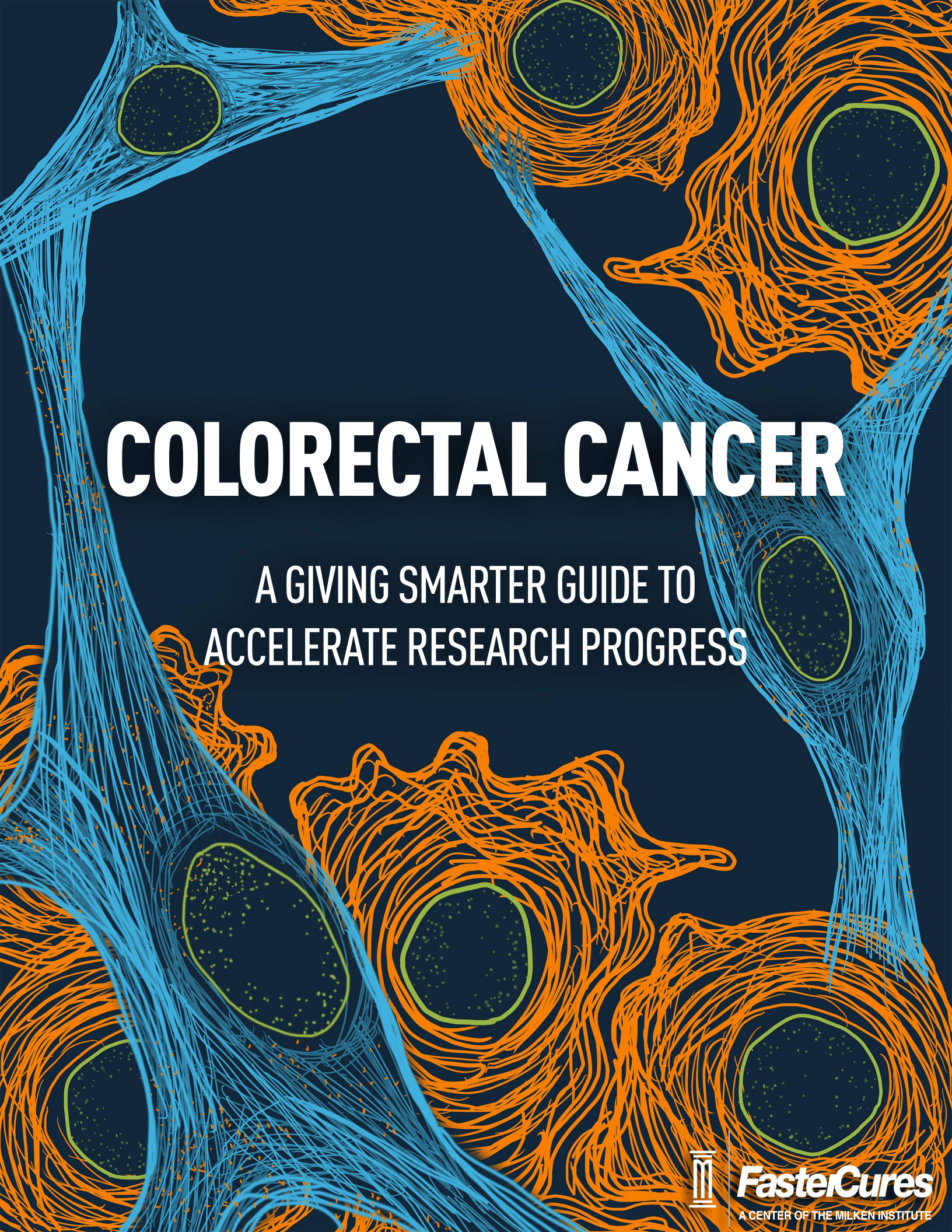

COLORECTAL CANCER

A GIVING SMARTER GUIDE TO ACCELERATE RESEARCH PROGRESS

FasterCures
A CENTER OF THE MILKEN INSTITUTE

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EXECUTIVE SUMMARY

Colorectal cancer (CRC) refers to cancer that originates from either the colon or rectum. Colorectal cancer is the second deadliest of cancers when the incidence in both men and women are combined. The American Cancer Society estimates that in 2015 nearly 50,000 patients in the United States will die from this disease. The disease is costly as well as deadly. In 2010, colorectal cancer was responsible for $14 billion in direct medical expenses to the U.S. healthcare system, and is projected to reach $20 billion by 2020 (DeBarros 2013).

Colorectal cancer is thought to be caused by mutations, which are either inherited or acquired, in several different genes. For many patients, colorectal cancer starts as a polyp (an abnormal growth on the mucous membrane of the colon or rectum). The polyp may remain benign (or noncancerous) or become malignant (cancerous). Several risk factors contribute to the development of colorectal cancer including age, race, personal disease history, family disease history, and lifestyle.

The primary method for preventing colorectal cancer is by screening (primarily conducted via colonoscopy) before symptoms appear. Early removal of polyps during regular screenings can help prevent disease. If cancer does develop, a combination of therapies (surgery, radiation, chemotherapy, and targeted therapies) can be administered. Some chemotherapy may not be effective based on certain genetic mutations, so testing should be done before they are prescribed.

As a result of improved screening and prevention methods, the incidence of colon and rectal cancers (per 100,000 people) have decreased from approximately 60 in 1976 to 46 in 2005 (Cheng 2005), and the mortality rate from colorectal cancer has decreased by nearly 35 percent from 1990 to 2007 (Siegel 2011). However, more effective treatment options are desperately needed in order to continue this downward trend in mortality.

There are significant efforts underway to shed additional light on the biology of the disease with the aim of developing more effective treatments and diagnostics. Recent studies have looked at the role of various genes, proteins, and cellular pathways involved in disease progression and mediation. Diagnostic research is focused on developing more sensitive, less invasive tests, while therapeutic research primarily involves new drugs or new combinations of existing drugs across various stages of disease.

There are quite a few areas of promising clinical research that could serve as the tipping point toward extending survival in colorectal cancer patients and potentially pave the way to a cure. These areas include but are not limited to translational research studies aiming to identify and inhibit aberrant molecular pathways that drive tumor resistance and metastasis. In addition, clinical research evaluating the use of immunotherapy strategies, and combinations of these treatments with chemo- and targeted therapies are also of tremendous value. While these research areas are indeed poised to have a high impact on colorectal treatment options, severe funding gaps threaten to delay acceleration of progress. As a result, medical philanthropy plays an increasingly important role in accelerating the translation of high-impact research into accessible medical solutions.

DISEASE OVERVIEW

ETIOLOGY

Cancer cells are characterized by uncontrollable growth and invasion of nearby tissues. Abnormal cell division and growth is caused by genetic mutations that either turn on oncogenes (genes that speed up cell division) or silence tumor suppressor genes (genes that slow down cell growth and control cell death). The accumulation of this type of genetic damage over time can lead to the progressive transformation and survival of abnormal cell populations that can form tumors.

Colorectal cancer develops in the colon or the rectum, both of which are essential components of the digestive system. Colorectal cancer usually develops very slowly, over a period of 10 to 15 years (Kozuka 1975). The tumor usually begins as a noncancerous polyp (a tissue growth that develops on the lining of the colon or rectum). Among the various types of polyps, those that are most likely to become cancerous are adenomas (Levine 2006).

Once cancerous the tumor can invade nearby cells in the wall of the colon and ultimately enter blood and lymphatic vessels. Once the cancer occupies these vessels the tumor cells can circulate throughout the body leading to metastasis (the movement of cancer cells to other parts of the body). Colorectal tumors are most likely to spread to the liver and the lungs.

RISK FACTORS

Several factors are linked to an increased risk for developing colorectal cancer including:

- Age – The chances of developing colorectal cancer increase significantly over age 50.
- Personal disease history – Patients who developed polyps or colon cancer at a young age are at greater risk for developing colorectal cancer again. Those who suffer from inflammatory bowel disease are also at greater risk due to prolonged inflammation.
- Family disease history – One in five people who develop colorectal cancer have family members who have had the disease. The risk increases with the number of family members with the disease. Additionally, 5 to 10 percent of colorectal cancer patients have inherited gene mutations that manifest themselves as familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC).
- Lifestyle – Diet (red and processed meats, high temperature cooking methods), smoking, alcohol, sedentary lifestyle, obesity, and use of postmenopausal hormones all contribute to greater risk for colorectal cancer.

PREVENTION

Several practices are recommended to prevent the development of colorectal cancer, including:

- Screening – Screening should be done before symptoms arise and can be helpful in averting disease if polyps are found and removed early. Screening techniques that can detect both polyps and cancer include sigmoidoscopy, colonoscopy, double-contrast barium enema, and computed tomography (CT colonography). Screening techniques that only detect cancer include fecal occult blood test, fecal immunochemical test, and stool DNA tests.

- Diet and Exercise – It is recommended to consume five or more servings of fruits and vegetables daily, limit red meat and alcohol, and engage in exercise for 45 minutes five days per week.

- Dietary Supplements – Studies suggest that the following can reduce risk of colorectal cancer: folic acid, vitamin D, and calcium.

- Anti-Inflammatory Drugs – Some studies show that regular use of anti-inflammatory drugs such as aspirin and ibuprofen prevents the development of polyps and thus colorectal cancer.

- Hormones – Use of combined hormone replacement therapy after menopause and oral contraceptives pre-menopause can reduce colorectal cancer in women.

- Genetic Testing – Genetic testing is particularly helpful in determining if family members are at high risk due to inherited syndromes like FAP or HNPCC. Those with mutations associated with HNPCC and FAP have an 80 percent and nearly 100 percent risk of developing colorectal cancer, respectively. People should begin screening for HNPCC in their early 20s and for FAP in their teens.

DIAGNOSIS AND TREATMENT

Colorectal cancer is diagnosed by extracting a biopsy of polyps identified during a colonoscopy or sigmoidoscopy. Once the polyps have been confirmed as cancerous, a pathologist will determine the primary cell type found within the colon cancer. According to the National Cancer Institute, the most common colon cancer cell type is adenocarcinoma, which accounts for 95 percent of cases (Cancer.gov 2013). The extent to which a colorectal cancer has spread is described as its stage. To evaluate whether the cancer has spread, physicians often use imaging tests such as a MRIs, X-rays, or CT scans.

STAGES OF COLORECTAL CANCER

According to the National Cancer Institute, colorectal cancer can be categorized by the following stages:

- Stage 0 – The cancer is found only in the innermost lining of the colon or rectum.
- Stage I – The tumor has grown into the inner wall of the colon or rectum, but not through the wall.
- Stage II – The tumor extends more deeply into or through the wall of the colon or rectum. Cancer cells may have invaded nearby tissue, but have not spread to the lymph nodes.
- Stage III – The cancer has spread to nearby lymph nodes, but not to other parts of the body.
- Stage IV – The cancer has spread to other parts of the body, such as the liver or lungs.
- Recurrence – This is cancer that has been treated and has returned after a period of time when the cancer could not be detected. The disease may return in the colon, rectum, or in another part of the body.

TREATMENT BY STAGE OF COLORECTAL CANCER

Surgery is the primary treatment for colorectal cancers that have not spread to distant parts of the body (generally stages I - III). The decision to treat with adjuvant (follow-up) chemotherapy is dependent on the stage of disease and the risk of tumor recurrence and/or metastasis (spreading). Table 1 provides a list of U.S. Food and Drug Administration (FDA)-approved therapies for colorectal cancer. The sections below outline how FDA-approved therapies should be administered depending on the stage of the disease as recommended by the National Comprehensive Cancer Network (NCCN Colon Cancer, 2013).

Table 1: FDA-approved therapies for colorectal cancer

Generic Name	Brand Name, Manufacturer	Year FDA Approved	Method of Action	Delivery	Notes and Considerations
CHEMOTHERAPIES *– drugs that deter the rapid cell division of cancer cells by interfering with the overall process of cell division of both cancer cells and normal cells*					
5-Fluorouracil (5-FU)	Adrucil, Teva Pharmaceuticals	1991	Antimetabolite that attacks the cell at specific points in its division cycle	IV infusion, often combined with leucovorin to enhance effectiveness	Part of most treatment regimens
Irinotecan	Camptosar, Pfizer	2000	Small molecule drug that prevents DNA processing	IV infusion, often combined with 5-FU and leucovorin	Some cannot break down drug, so patients should be tested for sensitivity prior to administering
Capecitabine	Xeloda, Genentech/Roche	2001	Small molecule drug that attacks the cell at specific points in its division cycle	Oral medication, changes to 5-FU at tumor	As effective as 5-FU and leucovorin together
Oxaliplatin	Eloxatin, Sanofi	2002	Small molecule drug that attacks the cell during resting phase of cell cycle	IV infusion, often combined with 5-FU and leucovorin	—

Generic Name	Brand Name, Manufacturer	Year FDA Approved	Method of Action	Delivery	Notes and Considerations
TARGETED THERAPIES *– drugs that inhibit specific molecular targets involved in abnormal cell signaling events and pathways that regulate cell development and behavior. Prominent molecular targets for CRC therapies include the epidermal growth factor receptor (**EGFR**) and vascular endothelial growth factor (**VEGF**) proteins, and their correlated pathways.*					
Cetuximab	Erbitux, Bristol-Myers Squibb	2004	Monoclonal antibody that binds to EGFR and prevents cell division	IV infusion, usually used with irinotecan or alone	40 percent of colorectal cancers have gene defects that make the drug ineffective, so patients should be tested prior to administering
Panitumumab	Vectibix, Amgen	2006	Monoclonal antibody that binds to EGFR and prevents cell division	IV infusion	40 percent of colorectal cancers have gene defects that make the drug ineffective, so patients should be tested prior to administering
Regorafenib	Stivarga, Bayer	2012	Small molecule drug that targets VEGF receptor-2 and tyrosine kinase, TIE2 to prevent angiogenesis	Oral administration	Can be severely toxic to the liver; patients should be monitored regularly for signs of liver toxicity
Bevacizumab	Avastin, Genentech/Roche	2013	Monoclonal antibody that targets VEGF and prevents angiogenesis	IV infusion	Accompanied by severe side effects

Generic Name	Brand Name, Manufacturer	Year FDA Approved	Method of Action	Delivery	Notes and Considerations
ziv-aflibercept	Zaltrap, Regeneron	2012	Recombinant fusion protein that acts as a decoy receptor for VEGF-A and PIGF ligands, to prevent angiogenesis	IV infusion	—

STAGE 0 AND I

Stages 0 and 1 CRCs generally do not require adjuvant chemotherapy after surgical resection via polypectomy (polyp removal) or colectomy (removal of malignant tissue from the colon).

STAGE II

Treatment plans for patients with stage II disease are dependent on whether the patient is categorized as high- or low-risk for recurrent disease.

High risks factors are considered as follows:

- The surgeon was unable to remove at least 12 lymph nodes during resection.
- The cancer has grown into nearby organs.
- The cancer has obstructed the bowel or colon.
- The cancer has caused a perforation in the colon wall.
- The cancer was found near the edge of the resected tissue, which may indicate that some residual tumor was left behind.

Additional treatment options for **high-risk** patients include, but are not limited to, the following:

- Observation without adjuvant chemotherapy
- Adjuvant chemotherapy with one of the following regimens:
  - 5-FU/LV
  - FOLFOX
  - Capecitabine
  - CapeOX

Commonly used regimen abbreviations:

- **5-FU/LV:** 5-Fluorouracil, leucovorin
- **FOLFOX:** leucovorin, 5-FU, and oxaliplatin (Eloxatin)
- **FOLFIRI:** leucovorin, 5-FU, and irinotecan (Camptosar)
- **CapeOX:** capecitabine and oxaliplatin
- **FOLFOXIRI:** leucovorin, 5-FU, oxaliplatin, and irinotecan

Additional treatment options for **low-risk** patients include, but are not limited to, the following:

- Observation without adjuvant chemotherapy
- Adjuvant chemotherapy with one of the following regimens:
    - 5-FU/LV
    - Capecitabine

According to experts, the definition currently used to distinguish between high-risk and low-risk patients is inadequate, in that some low-risk stage II CRC patients experience tumor recurrences, while many high-risk patients do not. Outside of anecdotal evidence, there are no concrete data that clearly denote clinical features that are predictive of benefit from adjuvant therapy. The current recommendations are based on evidence that stage III CRC patients benefit from adjuvant therapy. Consequently, key experts agree that it is reasonable to accept the relative benefit of adjuvant therapy in stage III disease as indirect evidence of benefit for stage II disease; however, determining risk for recurrent disease after surgery remains a major unmet need.

STAGE III

The current standard of care for patients with stage III CRC is surgical resection, followed by adjuvant chemotherapy. Chemotherapy regimens commonly used to treat stage III patients include, but are not limited to, the following:

- For patients with stage III disease, the panel recommends six months of adjuvant chemotherapy after primary surgical treatment. The treatment options are:
    - 5-FU/LV
    - FOLFOX
    - CapeOx
    - 5-FU/LV with capecitabine

STAGE IV

Patients with stage IV disease usually have significant metastasis of tumors to distant organs and tissues. This distant spreading of the cancer can preclude a patient from surgery if there are too many metastases or if they are inoperable due to location. In these cases, physicians may administer chemotherapy or targeted therapies to control the cancer. Commonly used treatment regimens include but are not limited to the following:

- 5-FU/LV
- FOLFOX
- FOLFIRI
- CapeOX
- Any of the above combinations plus either bevacizumab or cetuximab (but not both)
- 5-FU/LV with bevacizumab
- Capecitabine with or without bevacizumab
- FOLFOXIRI
- Irinotecan, with or without cetuximab

- Cetuximab
- Panitumumab
- Regorafenib

Overall, the choice of regimens will depend on previously administered treatments, overall health, and quality of life. Radiation therapy may also be used to shrink tumors and help prevent or relieve symptoms such as pain.

MOLECULAR DRIVERS OF COLORECTAL CANCER

Much research is linked to understanding more about colorectal cancer biology, the pathways of disease, and potential targets for drug development. The genomic changes that drive CRC pathogenesis are under intense investigation by researchers, as these are the key to both understanding CRC and developing more effective treatments for this invasive disease. There is a wide spectrum of genetic mutations and molecular pathways that contribute to the pathogenesis of CRCs, most of which are not well understood (Colussi 2013). These molecular drivers are discussed in more detail below.

CHROMOSOMAL INSTABILITY

The chromosomal instability (CIN) pathway involves the gain or loss of whole chromosomes or fractions of chromosomes in daughter cells. The result is that the daughter cells do not have the same number of chromosomes as the cell that they originated from.

There is an extensive collection of data that suggests that the CIN pathway is involved in CRC tumorigenesis (tumor formation); however, more concrete evidence is needed to clearly define this link (Colussi 2013).

A mutation in a gene called adenomatous polyposis coli (APC) is considered to be an important contributor to CIN (Rusan 2008). APC is a tumor suppressor gene that causes uncontrollable cell growth when mutated, resulting in the formation of hundreds of polyps, with ultimately some of the polyps becoming cancerous. APC mutations can be inherited or acquired. APC mutants are found in all forms of familial colon cancer, such as FAP. In addition, research shows that 75 percent of non-familial (sporadic) cases of colorectal cancer are driven by acquired mutations in the APC gene. Mutations in the APC gene are often accompanied by genetic mutations in several other genes such as KRAS, p53, SMAD4, and others.

MICROSATELLITE INSTABILITY

Microsatellite instability (MSI) refers to the incorrect replication of repetitive DNA sequences (microsatellites) throughout the genome. Usually, these types of DNA errors are corrected by repair molecules known as DNA mismatch repair (MMR) proteins; however, in cases of microsatellite instability, these MMR proteins are dysfunctional. These inoperative DNA repair mechanisms significantly increase the propensity of DNA mutations that drive the rate of tumor growth and pathologic change in CRC tumors (Kinzler 2002).

Microsatellite instability occurs in approximately 15 percent of sporadic CRCs and more than 95 percent of HNPCC syndrome cases (Colussi 2013). MSI is detected by comparing the lengths of microsatellite repeat sequences between tumor and normal cells. If the lengths differ by more than 30 percent, then the tumor is categorized as showing a high-level of microsatellite instability (MSI-H). Tumors with less than 30 percent MSI are categorized as low-level MSI (MSI-L), and tumors with no instability are referred to as microsatellite stable (MSS).

MSI is often used as a prognostic indicator of response to treatment. Counterintuitively, tumors with high microsatellite instability are associated with a better prognosis compared to microsatellite stable tumors (Popat 2005). MSI-H tumors are also less likely to metastasize to lymph nodes or distant sites compared to MSS tumors. However, a study published in 2011 by Tie et al. revealed that favorable prognosis conferred by MSI-H is muted by

a concurrent mutation in the BRAF gene (a gene involved in cell signaling and growth). It is also important to note that MSI-H CRCs do not respond to 5-FU based chemotherapies (Sinicrope 2012).

CPG ISLAND METHYLATION

Multiple studies show that CRC progression is partially due to the CpG island methylator phenotype (CIMP) (Colussi 2013). In this phenotype, special regions of DNA referred to as CpG islands (because they are rich in **C**ysteine and **G**uanine molecules connected by a **P**hosphodiester bond) are overpopulated by methyl groups. This overpopulation of methyl groups disables transcription of specific genes (Figure 1). In the context of CRC, the specific genes that are affected by CpG island methylation are involved in cell cycle regulation, apoptosis (cell death), angiogenesis (blood vessel development), DNA repair, cell invasion, and cell adhesion. CIMP is found in approximately 20 to 30 percent of CRCs.

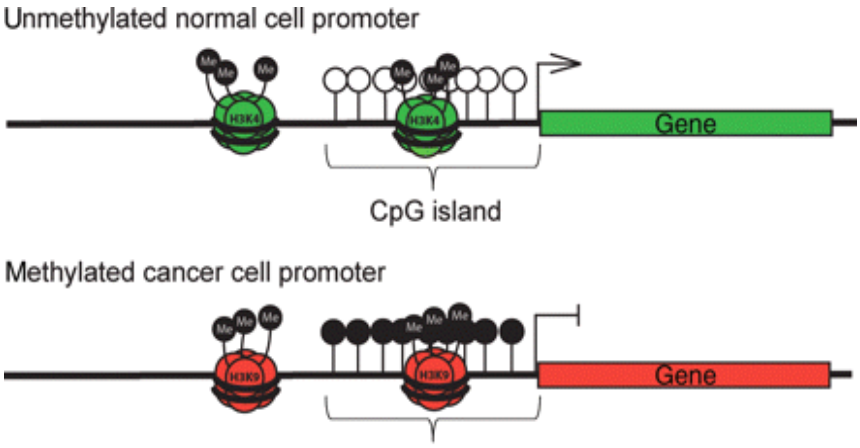


Figure 1: Unmethylated and Methylated CpG island DNA regions
Unmethylated CpG islands (white circles) allow genes to "turn on" or be transcribed. Densely methylated CpG islands (black circles) "silence" genes and do not allow for transcription. Adapted from J. Mol. Cell Biol.

Based on the number of methylations, the CIMP phenotype can be divided into CIMP-high and CIMP-low, both of which are associated with specific prognostic and clinical features. For example, BRAF mutations are often identified in CIMP-high CRCs and associated with increased cell growth, disease progression, and colon-specific mortality (Colussi 2013). On the contrary, KRAS mutations are often associated with CIMP-low CRCs.

MICRO RNA

MicroRNAs are short non-coding RNA molecules that regulate protein expression by inhibiting messenger RNA translation. MicroRNAs involved in CRC pathogenesis generally affect genes involved in cell differentiation, development, proliferation, and apoptosis. These microRNAs can be overactive (upregulated) or underactive (downregulated) throughout their various roles in the pathogenesis of CRC. There are a large number of microRNAs thought to be involved in CRC; however, some of the key microRNAs under intense investigation include miR-21, miR-31, miR-143, and miR-145.

TARGETING MOLECULAR PATHWAYS

The identification and targeting of specific molecules and cellular pathways altered in colorectal cancer has led to significant improvement in the outcome of CRC patients within the last two decades. Targeted therapies against

epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), such as cetuximab, panitumumab, and bevacizumab, have demonstrated clinical benefit in CRC patients and are commercially available for patients with advanced CRC. Unfortunately, efficacy of these drugs is limited in patients that have mutations in the KRAS gene or BRAF protein (Festino, 2013).

According to recent studies, up to 50 to 55 percent of colorectal cancers have mutations in RAS genes. These mutations are primarily observed in KRAS, but there are also a notable number of mutations observed in NRAS (Douillard 2013). Mutations in these genes often lead to unfavorable aberrations in the RAS signaling pathway, which can promote tumor development, growth, and maintenance.

The aforementioned data add to a growing body of research that strongly suggests that mutations in the RAS pathway may be a key driver in nearly 50 percent of colorectal cancers. Currently, there are no drugs that can successfully disrupt this pathway with the aim of treating patients with RAS mutations. **Targeted therapies against RAS and BRAF are desperately needed and would have a significant impact on the standard of care for advanced colorectal cancer patients.**

RAS Gene Family

RAS genes are the widely linked to human cancers. HRAS, KRAS, and NRAS are the most clinically notable members of the RAS family of genes; however, there are many others, which are listed below:

HRAS	***RAP1 A-B***
KRAS	***RAP2 A-C***
NRAS	***RASD 1-2***
DIRAS 1 -3	***RASL10 A-B***
ERAS	***RASL11 A-B***
GEM	***RASL12***
MRAS	***REM 1-2***
NKIRAS 1-2	***RERG***

UNMET NEEDS

While improvements in prevention and screening have had a significant impact on CRC incidence, prevalence, and mortality rates, new therapies by comparison have not had a proportional effect on these disease metrics. Targeted therapies such as cetuximab, panitumumab, and regorafenib only modestly improve survival in patients with advanced disease. In addition to needing new treatment options, the field also needs to evolve with respect to disease monitoring and prognostic biomarkers. In the sections below we discuss some of the most important unmet needs according to colorectal cancer experts.

UNDERLYING DISEASE BIOLOGY

According to experts, the poor understanding of the disease biology and genetic drivers of CRC pathogenesis is a huge obstacle to advancing research in this field and improving treatments. A better understanding of the complexity of the disease at the molecular level would have a significant effect on diagnosis, treatment, and monitoring of CRC.

High-impact accelerated research in this area could lead to the discovery of additional biomarkers that may improve screening and lead to a higher rate of early-stage diagnosis. Understanding more about the underlying biology may also provide additional prognostic factors that researchers can use to determine the likelihood of tumor recurrence and predict responses to treatment in patient subpopulations. Finally, new discoveries focused on the genetic drivers of CRC would enable researchers to develop more effective targeted therapies against these genetic drivers. While the currently approved targeted therapies cetuximab, panitumumab, and regorafenib are key weapons in the armamentarium against CRC, they are only moderately effective in advanced-stage patients and, more importantly, they are not curative.

To have a significant impact in this therapeutic area, there needs to be a major investment in the following:

- **Prospective genomic profiling** of a large number of CRC patients at various stages of disease. This would require an infrastructure that enables routine genomic analysis of patients before, during, and after treatment. The simultaneous collection of clinical data (tumor pathology, patient response, etc.) and genomic information will help researchers elucidate important connections between tumor phenotype and clinical outcomes. This information will also help to identify new molecular targets and pathways for follow-up study.

- A **centralized CRC database** that would support large-scale genomic efforts by serving as the primary infrastructure used to house the aforementioned clinically annotated CRC genomic data. This resource would not only provide researchers around the world a common repository for clinically annotated data, but will also allow them to analyze large data sets, thereby increasing the statistical significance of identified correlations. Centralizing this type of patient data may significantly accelerate discovery of individualized treatment approaches, biomarkers, diagnostics, and new drug targets. Successful examples of this type of research tool include the National Cancer Institute's Cancer Genome Atlas Project and the Multiple Myeloma Research Foundation's Centralized Data Platform.

- **New projects leveraging systems biology** to enable researchers to systematically follow up on new molecular leads identified using genomics and other research methods. Systems biology is quickly becoming a critical component of modern science as this approach mitigates researchers' previous reliance on descriptive science to explore and explain complex biological systems and instead provides a quantitative platform to achieve these tasks. This adds great value to any area of research because it is both time and cost effective, and it provides classical researchers more meaningful and advanced starting points to explore and validate hypotheses. Using systems biology approaches, researchers can simultaneously study multiple targets of CRC-relevant molecular pathways at the genetic, protein, and functional levels.

DETERMINING RISK FOR RESIDUAL DISEASE AFTER SURGERY

Determining which patients should receive adjuvant chemotherapy following surgical resection of CRC tumors is a major challenge for clinicians treating CRC patients. According to treatment guidelines, stage I patients should not be offered adjuvant chemotherapy, whereas stage III patients should always be offered adjuvant therapy. For stage II patients, this decision lies with the clinician and is solely dependent on whether the patient is considered high- or low-risk for tumor recurrence. Stage II patients that are considered high-risk should be offered adjuvant therapy, whereas patients that are low-risk should not.

While there are specific pathological and clinical factors affiliated with risk of recurrence, these factors are complex and do not offer clinicians a clear path toward accurately distinguishing high-risk and low-risk patients. Furthermore, these factors do not inform clinicians to the likelihood of residual disease. The implication of this challenge is that patients in various stages of CRC do not always receive the most appropriate care. Approximately 20 percent of patients with stage II and 5 percent of patients with stage I CRC experience tumor recurrence because they are not offered adjuvant chemotherapy. In addition, nearly 50 percent of patients with stage III disease unnecessarily receive chemotherapy. In order to address this issue and ensure that CRC patients are receiving the most appropriate course of care, there needs to be a change in the paradigm used to determine which patients are cured after surgery and those that have residual disease.

To address this unmet need, investment in the following areas could have a significant impact:

- Large randomized **clinical studies that focus on stratifying stage II CRC patients** based on risk of recurrence according to the current pathological and clinical factors associated with this risk. A key objective of these studies would be to identify biomarkers of residual disease.

- Research to **identify novel pathological and molecular features** indicative of residual disease after surgery in tumors at various stages of disease. Breakthrough discoveries in this area could significantly decrease the proportion of patients who die from recurrence due to lack of adjuvant therapy.

- Development of **molecular detection technologies** that can be used to validate novel residual disease markers and monitor patients for these markers after tumor resection, thereby eliminating the need for potentially invasive biopsies.

CLINICAL TRIALS

Clinical research is research in human subjects aiming toward approved products for use in patients. Clinical trials determine whether a particular product is as effective in people as it is in the laboratory or in animal models, which often fail to adequately mimic human responses. Clinical trials also provide information on potential adverse reactions or side effects that need to be weighed against the potential benefits.

Clinical research for drugs and vaccines is broken into four key phases. Each phase is described in the table below.

Table 2: Phases of clinical development

Clinical Phase	Description	Number of Patients
Phase I	Examines the safety of the product in a very small group of healthy volunteers or patients afflicted with a specific disease. Also used to determine appropriate dose ranges.	20-80
Phase II	Evaluates the safety and efficacy of the product at a pre-determined dose in comparison to the standard of care treatment (commercially available therapies commonly used to treat the same disorder or disease).	100-300
Phase III	Evaluates the product compared to the standard of care in a large diverse population to determine broader efficacy and develop usage guidelines.	1,000-3,000
Phase IV	Evaluates the long-term effects of a drug post-FDA approval for public use.	All patients prescribed the drug by a treating physician

As of March 2015, there were 158 distinct investigational agents in clinical development for CRC. Most of these agents are in pre-clinical or Phase II development. Meanwhile, only 16 agents are in Phase III development, which is indicative of the lean pipeline and the need for additional research around new therapies.

On the other hand, there is clearly no shortage of clinical trials for CRC. There are over 500 active clinical trials for colorectal cancer that were open or soon to be open, with the majority in Phase II development. Figure 2 illustrates the distribution of investigational agents and clinical trials by phase of clinical development.

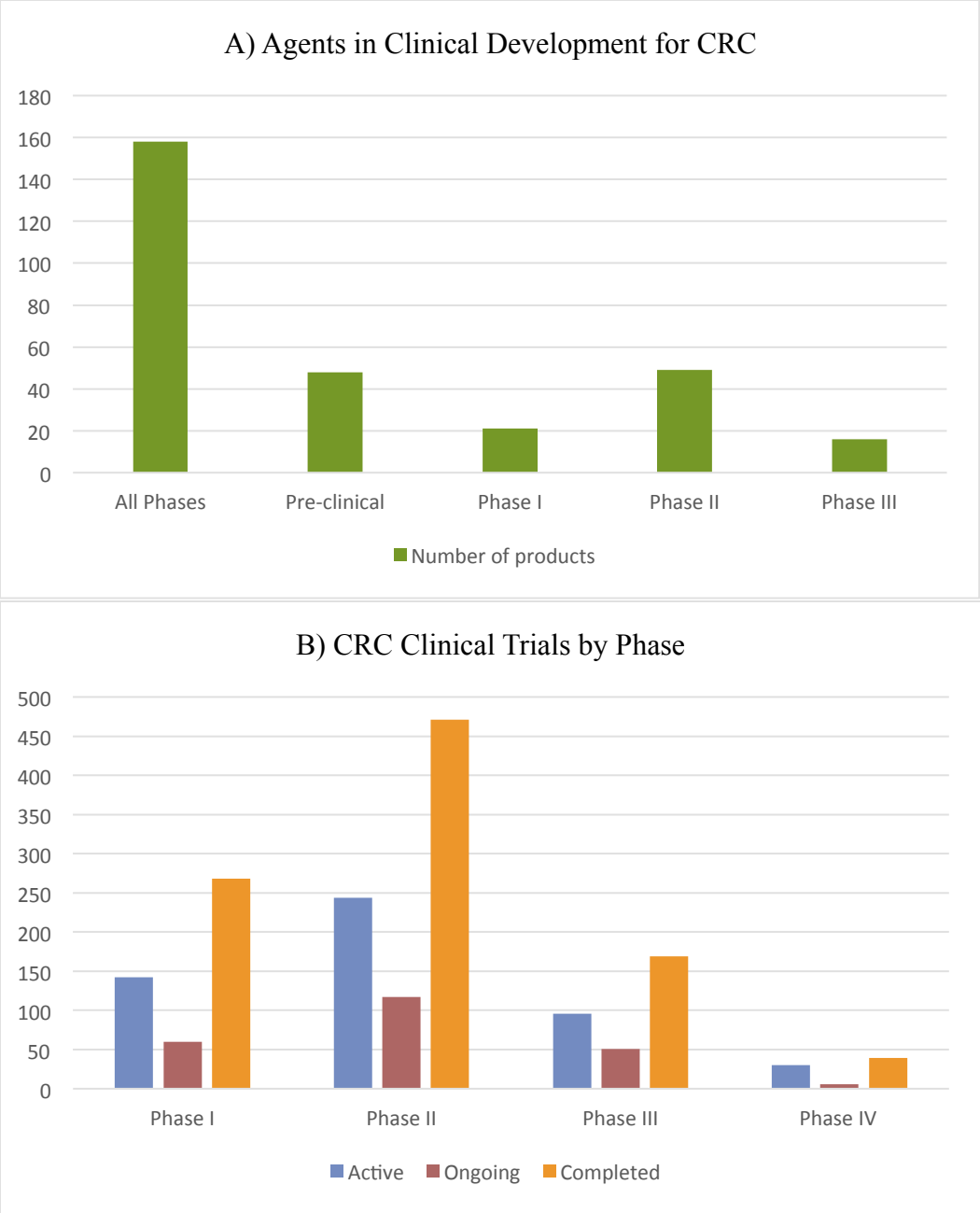


Figure 2: CRC Clinical Development Pipeline as of March 2015. A) *The number of distinct products currently in clinical trials for CRC at each phase of clinical development. The 158 distinct investigational agents in clinical development for CRC is inclusive of Discovery, Phase 0, Phase I/II and Phase II/III designations of clinical development, in addition to the other stages illustrated in the graph.* ***B)*** *The breakdown of active (recruiting or soon to recruit), ongoing (active but no longer recruiting patients), and completed trials by phase of clinical development.*

EMERGING THERAPY OUTLOOK

Although there are more than 150 distinct agents in clinical development for CRC, according to experts, very few show significant promise with respect to changing the standard of care for CRC patients. Novel drugs and therapeutic strategies that may provide clinical benefit are listed below.

TRASTUZUMAB

Trastuzumab (Genentech's Herceptin) is a monoclonal antibody currently approved to treat breast cancer and gastric cancers. Trastuzumab disrupts the function of the HER2/neu receptor. Research shows that this drug is most effective in patients with tumors that overexpress the Human Epidermal Growth Factor Receptor 2 (HER2, also known as HER2/neu, ErbB2, or p185), which is a protein encoded by the ErbB2 gene. It has been reported that only 5 percent of colorectal cancer tumors express extra copies of the ErbB2 gene, which can lead to the overexpression of HER2. Furthermore, the percentage of CRC tumors that overexpress HER2 protein is unclear as reports vary between 0 and 84 percent (Ross 2001).

While there are indeed some conflicting results about the prevalence of HER-2 neu overexpression in colorectal cancer, breakthrough results in targeting HER2 in breast cancer as well as positive results in gastric cancer have led researchers to evaluate HER2 targeting with trastuzumab in colorectal cancer.

Researchers are also considering the use of TDM-1 (Genentech's Kadcyla) to target HER2. TDM-1 is an enhanced form of trastuzumab and is colloquially referred to as Super Herceptin. This form is trastuzumab in combination with the chemotherapy drug emtansine. This agent provides advantages in that it more exclusively targets the tumor and is somewhat less toxic compared to trastuzumab. Additional research needs to be completed in order to thoroughly determine the clinical benefit offered by trastuzumab and TDM-1 compared to the standards of care for CRC; however, these drugs are poised to impact only 2 to 3 percent of colorectal cancer patients.

IMMUNOTHERAPY STRATEGIES

Immunotherapy refers to therapeutic strategies that stimulate a patient's immune response to attack and destroy tumor cells. The immune system works by actively surveilling cells in the body to detect and destroy cells that are foreign. Cells are identified as foreign or non-foreign based on molecules expressed on the surface of the cells called antigens. In the context of tumor cells, the immune system can naturally identify and eliminate some of these cells based on antigen expression; however, tumors are sophisticated such that they can change the expression of some of their surface antigens to resemble non-foreign cells. This process is often referred to as immune editing.

T cells are the primary arsenal of the immune system. These cells contribute to immune defense by either directing the immune response by sending signals to other molecules (helper T cells) or by directly attacking infected or cancerous cells (killer T cells). Cancer immunotherapy treatment strategies address this issue by boosting the immune system in a general way or by training the immune system to attack specific tumor cell antigens.

Recent approvals of two immunotherapeutic agents, sipuleucel-T (Provenge, Dendreon) and ipilimumab (Yervoy, Bristol-Myers Squibb) in prostate cancer and melanoma, respectively, have shown that these approaches can

extend patient survival. Numerous classes of immunotherapies are currently under development for treatment of colorectal cancer, including cancer vaccines, adapted cell transfer, immune checkpoint inhibitors, monoclonal antibodies, and combination therapies.

VACCINES

Cancer vaccines are active immunotherapeutic approaches that are intended to activate and expand tumor-specific T cells to induce an anti-tumor response. Active immunotherapeutic cancer vaccines are composed of tumor antigens, which are protein molecules expressed on the surface of tumor cells. CRC antigens that have been used in vaccine development include CEA, MUC-1, CD55, CD17-1A, Ras mutant, and p53, among others. A variety of methodologies and delivery mechanisms have been developed for cancer vaccines, including protein-based approaches, dendritic cells, recombinant DNA (often oncolytic viruses or bacteria used individually or in combination with dendritic cells), and whole cell therapy.

Many vaccine strategies use dendritic cells as a base for vaccine delivery, usually by treating them with a combination of tumor-targeting agents (i.e., tumor-associated antigens, tumor cells, recombinant DNA, or antigen-encoding DNA). The treatment of dendritic cells with tumor-targeting agents trains the dendritic cell to better recognize tumor cells as foreign, thus enhancing the immune effect. These vaccines are typically created using a patient's own cells (known as an autologous therapy), which begins with drawing a patient's blood to be used to produce immature dendritic cells that are then treated with tumor-specific antigens (or other tumor-targeting agents). When introduced back into the patient, the dendritic cells stimulate helper T cells or killer T cells to activate an immune response against the tumor.

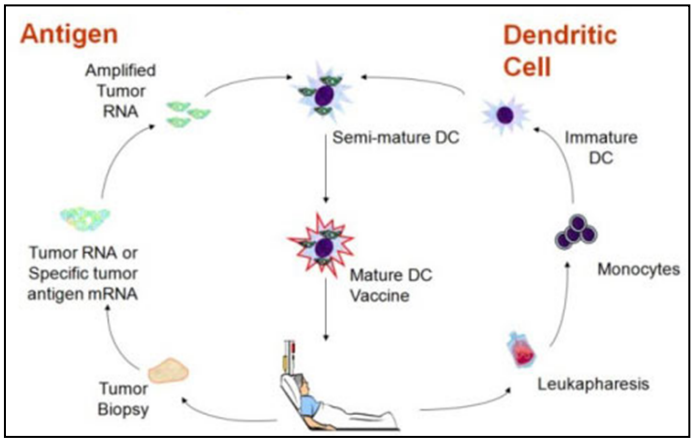


Figure 3: Dendritic cell vaccine preparation. *Adapted from www.sciences.surgery.duke.edu.*

Historically, vaccine strategies have not been very successful in CRC patients. According to experts, this is largely due to ineffective vaccine adjuvants – substances added to the vaccine to increase the body's immune response to the vaccine. **Investments in adjuvant technology research could have a significant impact on this area.**

Poor clinical trial design has also played a role in the diminished success of vaccines, as well as other immunotherapy strategies. This deficiency across the field can be heavily attributed to the lack of quality pre-clinical models to inform rational clinical trial design. CRC cell lines, which are often used in discovery and pre-clinical research, often do not recapitulate the mutations and overall heterogeneity of the disease. In addition, most CRC mouse models also do not adequately recapitulate disease heterogeneity. In order to equip researchers with the necessary data to design trials that are informative and clinically meaningful, there needs to be major improvement in the quality of pre-clinical data.

To effectively improve the quality of pre-clinical data, allocation of more research funds toward the following areas are critical:

- The development of **mouse xenograft (avatar mice) models.** Avatar mice are mice that are biologically engineered to grow implanted tumor cells taken directly from patient tumor biopsies. By directly modeling an individual patient's tumor in a mouse, researchers can better recapitulate disease heterogeneity and effectively observe tumor response to various interventions.

- A **centralized tissue repository (biobanking)** that will provide high-quality tissue specimens associated with clinical data to qualified researchers. This type of resource will enable a wide array of pre-clinical studies that can inform clinical trial design.

It is important to note that the impact of investment in the aforementioned areas is not limited to vaccines or immunotherapies, but rather extends to trial design for all types of CRC therapeutic strategies (chemotherapy, targeted therapy, combinatorial treatments, etc.).

ADOPTIVE CELL TRANSFER

Another common immunotherapy approach is adoptive cell transfer (ACT), which is a process through which antitumor T cells (usually tumor infiltrating lymphocytes, or TILs) are manipulated in vitro and then infused back into the body. The earliest form of this method was bone marrow transplants that were used to treat cancers of the blood. Principles of ACT have been established through research in metastatic melanoma, but the evidence of efficacy in other cancers is still in its nascent stages.

BISPECIFIC (FUSED) ANTIBODIES

Bispecific antibodies are fusions of two different monoclonal antibody fragments that bind to two different types of antigens. This idea draws from the development of drug-antibody conjugates. A new subclass of bispecific antibodies that are quickly gaining widespread attention are bi-specific T cell engagers (BiTEs). These monoclonal antibodies bind to both the T cell and tumor cell, causing the T cell to activate and kill the tumor cell. Phase I trials of BiTEs have been completed in blood cancers with a Phase II trial underway.

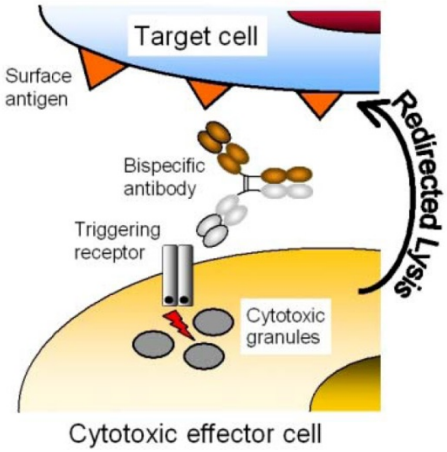


Figure 4: Bi-Specific Antibody. *The bispecific antibody (brown and white) binds to the target cell (tumor cell) and the killer T cell (cytotoxic effector cell). Adapted from www.discoverymedicine.com*

IMMUNE CHECKPOINT INHIBITORS

As mentioned previously, tumor cells can change the expression of some molecules on their cell surface antigens to resemble the surfaces of non-foreign cells. More specifically, tumor cells will often express molecules that serve as "immune checkpoints," meaning that when expressed these molecules send the message to the immune system that an immune response is not necessary. Researchers have discovered that developing drugs that can block these immune checkpoint molecules from binding to their molecular partners can effectively "release the brakes" on the immune system to allow the body to mount an immune response against the tumor. These types of drugs are called immune checkpoint inhibitors.

The two immune checkpoint molecules that have been most actively studied in the context of cancer immunotherapy are cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1). Checkpoint inhibitors currently in clinical development for various cancers are listed in Table 3.

Table 3: Immune checkpoint inhibitors currently in clinical development

Name	Manufacturer	Immune Checkpoint Target	Indications	Latest Phase of Clinical Development
Ipilimumab	Bristol-Myers Squibb	anti-CTLA-4	melanoma	Approved (melanoma)
Tremelimumab	Medimmune/AstraZeneca	anti-CTLA-4	melanoma, mesothelioma, and prostate, liver, renal, colorectal, and bladder cancers	Phase II (melanoma, mesothelioma, and colorectal and liver cancers)
BMS-936558	Bristol-Myers Squibb	anti-PD-1	melanoma, renal cell carcinoma, and non-small cell lung cancer	Phase III (melanoma and renal cell carcinoma)
BMS-936559	Bristol-Myers Squibb	anti-PDL-1	melanoma and non-Hodgkin's lymphoma	Phase I
MK-3475	Merck	anti-PD-1	melanoma and non-small cell lung and colorectal cancers	Phase III (melanoma and non-small cell lung cancer)
AMP224	Amplimmune/GlaxoSmithKline	anti-PD-1	solid tumors	Phase I
MPDL3280A	Genentech/Roche	anti-PDL-1	melanoma, non-small cell lung cancer, and solid tumors	Phase II (non-small cell lung cancer)
MEDI-4736	MedImmune/AstraZeneca	anti-PDL-1	Melanoma and renal cell, non-small cell lung, and colorectal cancers	Phase I

ANTI-CTLA-4

Ipilimumab (Yervoy, Bristol-Myers Squibb) is an antibody that binds to CTLA-4 on tumor cells (this agent and similar drugs are referred to colloquially as anti-CTLA-4). Ipilimumab was approved in 2012 for advanced melanoma after a Phase III trial demonstrated superior overall survival and progression-free survival compared to a peptide vaccine. In addition, approximately 20 percent of patients achieved long-term survival benefits, suggesting that ipilimumab may result in prolonged disease stabilization by inducing a state of equilibrium between the immune system and tumor.

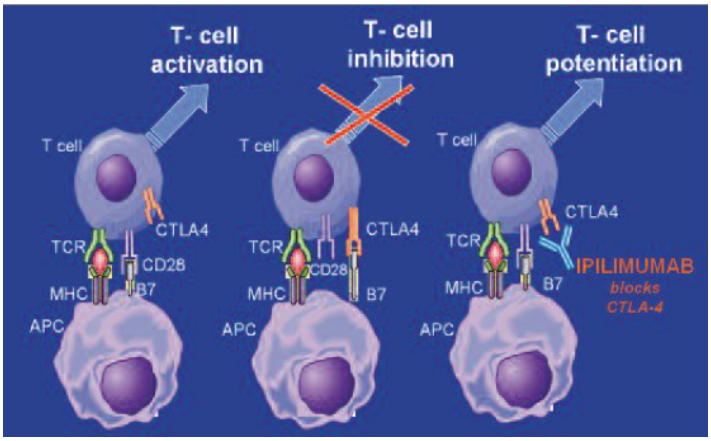


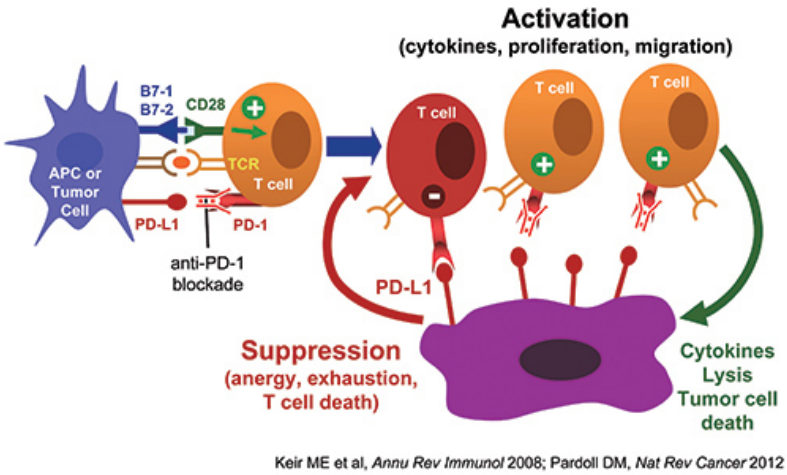
Figure 5: Anti-CTLA-4 *T cells are activated when B7 on the APC (antigen presenting cell or tumor cell) is allowed to bind to CD28 on T cells. When B7 is bound to CTLA-4 on T cells, T cells are inhibited and the immune system is suppressed. Anti-CTLA-4 agents such as ipilimumab block CTLA-4 binding to B7 and allows for T cell activation and immune response. Adapted from Lebbe et al. oral presentation 769O at the European Society for Medical Oncology conference in 2008.*

Multiple studies demonstrate that clinical response to anti-CTLA-4 therapy is usually observed well after dosing is complete and accompanied by toxicity. This can lead to delayed clinical response evaluation and the need for active response management after treatment is discontinued. The toxicities of these therapies are typically autoimmune-related adverse events, such as dermatitis and colitis. Severe immune-related adverse events have been observed in 10 to 35 percent of melanoma patients. In many of these cases the colon is frequently affected, which underscores the point that treatment may require active management, especially for colorectal cancer patients. Anti-CTLA-4 inhibitors have not been tested on a wide-scale basis in clinical trials for colorectal cancer.

ANTI-PD-1/ANTI-PD-L1

Similar to anti-CTLA-4 antibodies, anti-PD-1 and anti-PD-L1 antibodies also inhibit important immune checkpoints that enable tumors to evade immune response. PD-L1 is a ligand that is frequently expressed on tumor cells that counteract T cell activation; PD-1 is the corresponding receptor on the T cell. Monoclonal antibodies that inhibit both PD-L1 and PD-1 are currently in clinical trials for solid tumors.

Nivolumab (MDX-1106/BMS-936558, Bristol-Myers Squibb) is the anti-PD-1 therapy that is furthest along in the development pipeline and is currently in Phase III trials for melanoma, non-small cell lung cancer, and clear cell renal cell carcinoma. An early Phase I study evaluating nivolumab in patients with various types of solid tumors resulted in an objective positive response in a colorectal cancer patient (total n=39, OR=3) (NCT00441337). However, a follow-on Phase Ib trial with the same compound did not result in a response among any of the colorectal cancer patients (n=19) (NCT00730639), although of the 236 evaluable patients, responses were seen among the melanoma, non-small cell lung cancer, and renal cell cancer cohorts. Furthermore, PD-L1 expression was evaluated in tumor specimens from 42 patients; there were no objective responses among the 17 PD-L1 negative tumors, and 36 percent of the 25 PD-L1 positive tumors achieved objective responses. Based on the PD-L1 staining of the tumor specimens from this Phase I study, PD-L1 staining results are now being validated as a biomarker for clinical response in future studies.



Keir ME et al, *Annu Rev Immunol* 2008; Pardoll DM, *Nat Rev Cancer* 2012

Figure 6: Anti-PD-1/PD-L1 response. *PD-L1 expressed on the surface of the APC or tumor cell binds to PD-1 on the surface of T cells. This binding blocks T cell activation. When this binding is blocked by an anti-PD-1 or anti-PD-L1 agent, T cells become activated and can attack the tumor cells. Adapted from Keir ME et al. Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012.*

Currently, MDX1105-01 (Bristol-Myers Squibb) is the only anti-PD-L1 agent in clinical trials that has been tested in colorectal cancer patients. This agent was evaluated in a Phase I trial of 207 patients (NCT00729664), which included a cohort of 18 colorectal cancer patients (of which none responded). Objective responses for patients with other tumor types were observed.

ANTI-PD-1/ANTI-PD-L1 + ANTI-CTLA-4

Researchers are very interested in the potential therapeutic synergy of combining anti-PD-1 or anti-PD-L1 and anti-CTLA-4 agents. These agents inhibit T cells through non-overlapping pathways, which limit the ability of the tumor to use either pathway as an escape mechanism in response to treatment with either agent, and minimize the possibility of severe toxicity. Encouraging mouse data in melanoma have demonstrated synergistic activity with this type of combinatorial therapy. Bristol-Myers Squibb is currently recruiting for trials combining nivolumab with a variety of other therapies, including ipilimumab (Phase II, melanoma, NCT01783938); ipilimumab, sunitinib, or pazopanib (Phase I, renal cell carcinoma, NCT01472081); anti-KIR antibody (Phase I, solid tumors, NCT01714739); IL-2 (Phase I, solid tumors, NCT01629758); and multiple chemotherapies and targeted therapies (Phase I, non-small cell lung cancer, NCT01454102).

IMMUNOTHERAPY + TARGETED THERAPIES

Researchers are also looking toward the possible synergistic effects of combining targeted therapies with immunotherapies based on the strengths and weaknesses of each approach. Hypotheses of the immune response benefits of targeted therapies include that these therapies may:

- rapidly induce tumor regression, creating a window that will enable the enhanced effectiveness of immunotherapies;
- trigger an anti-tumor immune response by breaking oncogene addiction;
- cause the release of antigenic debris that may enhance vaccination at the tumor site;
- attenuate the activities of some T-cell populations;
- enhance augmentation of antigen presenting dendritic cells; and
- Sensitize tumor cells to immune destruction.

Based on these ideas, tumor-specific monoclonal antibodies such as rituximab (Rituxan, Biogen Idec/Genentech), trastuzumab (Herceptin, Genentech), and bevacizumab (Avastin, Genentech) are now being studied in in vitro assays for any potential role they may play in immune response, with the idea that they may be used in combination with traditional immunotherapies. Genentech is also currently recruiting for two Phase I trials for combining its anti-PD-L1 inhibitor with bevacizumab (Avastin, Genentech) and vemurafenib (Zelboraf, Roche), (NCT01633970 and NCT01656642, respectively).

Cetuximab (Erbitux, Bristol-Myers Squibb/Eli Lilly), the FDA-approved anti-EGFR therapy for colorectal cancer, has also been shown to play a role in anti-tumor immunity. A study evaluating the activity of dendritic cells that were incubated with cetuximab and tumor cells showed that these dendritic cells more effectively activated T cells than dendritic cells that were incubated with T cells alone. This finding partly contributed to its current use in a combinatorial cell vaccine trial for pancreatic cancer (NCT00305760). Also relevant to colorectal cancer may be the reported incidence of the inducement of tumor-infiltrating T cells using regorafenib (a BRAF inhibitor approved for use in colorectal cancer) in melanoma. Another BRAF inhibitor vemurafenib (Zelboraf, Roche) is now in a Phase I/II trial in combination with ipilimumab for metastatic melanoma to test out this combination (NCT01400451).

Overall, the exploration of combinatorial treatments represents an area of immense opportunity for significant advancement of CRC research; however, funding gaps, along with intellectual property concerns among pharmaceutical companies, have significantly limited the exploration of rational combinations of various immunotherapy agents with other immunotherapies, targeted therapies, and/or chemotherapies. **Other disease communities are working to overcome this issue and meet this unmet need by relying on venture philanthropy organizations to serve as "brokers" to negotiate intellectual property in a way that is mutually beneficial to the companies involved and the disease community.**

COLORECTAL CANCER FOUNDATIONS

There are a very limited number of nonprofit organizations specifically focused on charitable giving to support colon, rectal, or colorectal cancer. The majority of these organizations are focused on improving awareness, providing access to screening, and/or providing patient support.

Using desktop research and guidestar.org, we were able to identify seven national organizations that support colorectal or related cancers with revenues greater than $250,000 (see Table 4). Of these seven organizations, four provided direct support for colorectal cancer research. Additional information for these organizations is provided below.

Table 4: Charitable organizations supporting colon, rectal, or colorectal cancer with revenues greater than $250,000

Organization	Revenue (for most recent fiscal year available)	Research Support
Colon Cancer Alliance	**$3,561,110**	**Yes**
Fight Colorectal Cancer	**$1,328,406**	**Yes**
Colon Cancer Coalition Foundation	$1,132,954	No
Chris4Life Foundation	**$1,033,858**	**Yes**
Danny Butler Memorial Foundation	$692,879	No
Colon Cancer Challenge Foundation	$486,937	No
Susan Cohan Kasdas Colon Cancer Foundation	$438,304	No

COLON CANCER ALLIANCE

CEO: Eric Hargis
Founded: 1999
1025 Vermont Ave., NW, Suite 1066
Washington, DC 20005
Telephone: 202.628.0123

MISSION

To eradicate colon cancer as one of the top three cancer killers by championing prevention, providing the highest quality patient support services, and funding cutting-edge research.

Priority focus areas of the mission include the following:

- Advancing biomarker research
- Understanding why those under 50 are increasingly diagnosed with colon cancer
- Decreasing late-state diagnosis of high-risk populations
- Closing the referral gap for screening and diagnostic testing

FINANCIALS (FY2012)

Total Revenue:	$3,561,110
Total Expenses:	$4,124,773
Research Grants Awarded:	$12,904
Research/Expenses Ratio:	0.3%

FIGHT COLORECTAL CANCER

President: Anjee Davis
Founded: 2005
1414 Prince Street, Suite 204
Alexandria, VA 22314
Telephone: 703.548.1225

MISSION

To envision and demand a cure for colon and rectal cancer by being the leading patient advocacy group in colorectal cancer, and an active participant in cancer research and advocacy on Capitol Hill.

Priority focus areas of the mission include the following:

- Educating and supporting patients and caregivers
- Pushing for changes in policy that will increase and improve research
- Fund late-stage CRC research and bridge the gap between patients and scientists

FINANCIALS (FY2012)

Total Revenue:	$1,328,406
Total Expenses:	$1,339,232
Research Grants Awarded:	$173,347
Research/Expenses Ratio:	13%

CHRIS4LIFE COLON CANCER FOUNDATION

President and Founder: Michael Sapienza
Founded: 2011
8330 Boone Blvd., Suite 450
Vienna, VA 22182
Telephone: 1.855.610.1733

MISSION

To be a major catalyst in the fight against colon cancer, and become the preeminent national organization that empowers the community to find a cure for colon cancer by:

- Funding and facilitating cutting edge research programs across the nation
- Increasing awareness of the life-saving importance of early screening for colon cancer by using innovative strategies

FINANCIALS (FY2013)

Total Revenue:	$1,033,858
Total Expenses:	$1,111,135
Research Grants Awarded:	$102,223
Research/Expenses Ratio:	9%

COLORECTAL CANCER CONSORTIA

GENETICS AND EPIDEMIOLOGY OF COLORECTAL CANCER CONSORTIUM

The Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) is a collaborative effort of researchers from North America, Australia, and Europe, using genetic and epidemiology data from approximately 40,000 participants.

MISSION

GECCO aims to accelerate the discovery of colorectal cancer-related variants by replicating and characterizing Genome Wide Association Study (GWAS) findings, conducting a large-scale meta-analysis of existing and newly generated GWAS data, and investigating how genetic variants are modified by environmental risk factors. A crucial part of this work is the ongoing harmonization of detailed clinical, epidemiologic, and outcome data across the studies in the consortium. Recently, GECCO has begun to investigate rare variants, conduct survival studies, and incorporate gene-expression and tumor characteristics into its research.

LEADERSHIP

- Principal Investigator – Ulrike Peters, Associate Member, Fred Hutchinson Cancer Research Center; Professor, University of Washington
- Coordinating center for the international consortium - Fred Hutchinson Cancer Research Center

AFFILIATED STUDIES/CAMPAIGNS

- Identified a potential link between genetic mutations in PLA2G1B – an enzyme responsible for breaking down dietary fatty acids – and susceptibility to rectal cancer.
- Demonstrated that region 1 of chromosome 8q24 is a susceptibility locus for colorectal cancer. Also identified three additional CRC susceptibility loci in East Asian populations, which has shed additional insight into the genetics and biology of CRC.

CANCER IMMUNOTHERAPY TRIALS NETWORK

The Cancer Immunotherapy Trials Network (CITN) employs the collective expertise of top academic immunologists to design and conduct cancer therapy trials with the most promising immunotherapy agents prioritized for high potential in treating colorectal cancer and other types of cancer. This network is funded by the National Cancer Institute and the Fred Hutchinson Cancer Research Center as well as foundation and industry partners.

MISSION

The Mission of the CITN is to select, design, and conduct early phase trials using agents with known and proven biologic function and to provide the high quality immunogenicity and biomarker data essential to inform subsequent development pathways leading to the broad availability of these agents for treating patients with various cancers.

Funded by the National Cancer Institute and the Fred Hutchinson Cancer Research Center, the CITN employs the collective expertise of top academic immunologists to conduct multicenter research on immunotherapy agents capable of unleashing patient immunity to fight their cancer.

By collaborating with member institutions, industry sponsors, and philanthropic foundations, the primary focus is to spearhead the design and conduct of trials leading to ultimate regulatory approval of promising agents and to advance the knowledge of antitumor immunity and its application in immunotherapy.

LEADERSHIP

- Principal Investigator – Martin Cheever
- Coordinating center - Fred Hutchinson Cancer Research Center

AFFILIATED STUDIES/CAMPAIGNS

The studies below are not directly related to colorectal cancer; however, findings from these studies may inform potential efficacy in colorectal cancer and other gastrointestinal cancers.

- Evaluation of anti-CD40 in pancreatic cancer with the goal of establishing safety and identifying the presence of induced immune cell infiltrate within tumor and lymph nodes.
- Evaluation of E. coli-derived IL-15 in various advanced solid tumors with the goal of establishing a regimen that is effective for inducing growth of T cells and/or NK cells with a safety profile that is appropriate for combining with vaccines, antibodies, and other agents.

ACADEMIC MEDICAL CENTERS OF EXCELLENCE

The institutions listed in Table 5 have been designated as Academic Medical Centers of Excellence (AMCE) based on the awards and special designations described below.

- NCI Cancer Center Designation – This designation is granted by the National Cancer Institute (NCI) in recognition of scientific leadership, resources, and capabilities in laboratory, clinical, or population science, or some combination of these three components. The institution must also demonstrate reasonable depth and breadth of research in the scientific areas it chooses and trans-disciplinary research across these areas.

- Center Core Grant (P30) for GI Cancer Research – Cancer centers receiving P30 grants are medical research institutions recognized for their scientific excellence and extensive resources focused on cancer and cancer-related problems. These centers are recognized as major sources of discovery into the nature of cancer and development of effective approaches to cancer prevention, detection, diagnosis, and treatment. In addition, they deliver state-of-the-art medical care to patients and their families, educate healthcare professionals and the public, and reach out to underserved populations. They may be freestanding institutions, a center within a larger academic institution, or part of a consortium of institutions.

- Gastrointestinal (GI) Cancer Specialized Programs of Research Excellence (SPORE) Award – This award is granted by the National Institutes of Health to institutions and programs that are focused on translational research related to gastrointestinal cancers, including colorectal cancer, and multi-disciplinary collaboration. The institution must host at least four GI-related scientific projects, each reaching a human end-point within five years. The institution must also have an administrative and biospecimen core that collects and shares biospecimens among the scientific community.

- Member of the National Comprehensive Cancer Network (NCCN) – The National Comprehensive Cancer Network is a nonprofit alliance of 21 cancer centers throughout the United States. Experts from NCCN cancer centers diagnose and treat all cancers, with a particular focus on complex, aggressive, or uncommon cancers. The network also develops the NCCN Clinical Practice Guidelines in Oncology, a set of recommendations designed to help healthcare professionals diagnose, treat, and manage cancer patient care.

- U.S. News Ranking of Hospitals – Each year *U.S. News and World Report* surveys approximately 10,000 physicians and analyzes data for nearly 5,000 hospitals to rank the best in various specialties including cancer, gastroenterology, and GI surgery. Specific factors included in the analysis of hospitals are death rates, patient safety, and hospital reputation.

Institutions highlighted in Table 5 as an AMCE received a Cancer Core Grant (P30) greater than or equal to $500,000, at least two additional awards or special designations, and were ranked within the top 30 hospitals for cancer specialties. It is important to note that the list below is not a comprehensive list of institutions considered as Academic Medical Centers of Excellence. This list only includes AMCEs that meet *FasterCures*' predefined criteria outlined above; however, there are many other institutions that are considered AMCEs.

Table 5: Select Institutions Specializing in Gastrointestinal Cancers Identified as Academic Medical Centers of Excellence

Name	City, State	P30 Award ≥ $500,000	NCI Cancer Center	GI SPORE Award	NCCN Designation	US News Ranking - Cancer
Case Western Reserve University School of Medicine	Cleveland, OH	Yes	Yes	—	—	—
Dana-Farber, Harvard Cancer Center, Brigham and Women's Hospital	Boston, MA	Yes	Yes	Yes	Yes	5
Johns Hopkins Hospital	Baltimore, MD	Yes	Yes	Yes	Yes	4
Memorial Sloan Kettering Cancer Center	New York, NY	Yes	Yes	—	Yes	2
Robert H. Lurie Comprehensive Cancer Center of Northwestern University	Chicago, IL	Yes	Yes	—	Yes	14
University of Arizona Cancer Center	Tucson, AZ	Yes	Yes	Yes	—	—
University of Michigan Comprehensive Cancer Center	Ann Arbor, MI	Yes	Yes	Yes	Yes	24
University of Washington, Fred Hutchinson Cancer Research Center	Seattle, WA	Yes	Yes	Yes	Yes	7
Vanderbilt University School of Medicine	Nashville, TN	Yes	Yes	Yes	Yes	28

EVENT-DRIVEN CLINICAL UPDATES

Research on the latest approaches for the diagnosis, treatment, and management of gastrointestinal cancers were presented at recent conferences. Gastrointestinal cancers include those of the colon/rectum, stomach, pancreas, esophagus, small intestine, anus, and other digestive organs. Clinical data relevant to colorectal cancer are highlighted below.

GASTROINTESTINAL CANCERS SYMPOSIUM 2014

JANUARY 16-18, 2014 IN SAN FRANCISCO, CALIFORNIA

- ***Oral Chemotherapy Equivalent to Infusional Chemotherapy for Patients with Stage II or III Rectal Cancer:*** New findings from a phase III clinical trial indicate that combining pre-operative radiation with capecitabine is equally as effective as pre-operative 5-fluoraouracil (5-FU). This is the largest clinical study showing there is no difference in clinical benefit between oral and infusional treatments. The study also showed that adding oxaliplatin to either treatment did not increase clinical response.

- ***RAS Status Predicts Response to Combination Panitumumab Treatment in Patients with Metastatic Colorectal Cancer (mCRC):*** A genetic analysis of tumor samples collected as part of a large, phase III study demonstrates that tumors with RAS mutations are unlikely to benefit from the addition of panitumumab to second-line FOLFIRI chemotherapy. This analysis is the first to examine the effects of RAS mutations on second-line treatment.

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) ANNUAL MEETING 2014

MAY 30 - JUNE 3, 2014 IN CHICAGO, ILLINOIS

- ***Monitoring changes in circulating tumor DNA in gastrointestinal malignancies using a novel next-generation sequencing method:*** Circulating tumor DNA (ctDNA) is a promising cancer biomarker, and a new ctDNA assay was developed to evaluate recurrent cancer-associated mutations simultaneously in multiple genes without prior knowledge of the tumor's mutation profile. Results from a cohort of patients with GI malignancies indicate that this ctDNA assay may find clinical utility for non-invasive assessment of tumor mutation status and for monitoring of recurrence, progression, or therapeutic response.

- ***CA 11-19 as a tumor marker for the diagnosis of colorectal cancer:*** A new colon cancer antigen, CA 11-19, was measured in a 670-patient cohort and was determined as a serologic tumor marker for colorectal cancer with a demonstrated sensitivity of 95 percent and a specificity of 80 percent. Diagnostically, a positive CA 11-19 assay result increases the odds of finding colorectal cancer by a factor of five. The test appears to be highly sensitive for the detection of early-stage colorectal cancer.

GASTROINTESTINAL CANCERS SYMPOSIUM 2015

JANUARY 15-17, 2015 IN SAN FRANCISCO, CALIFORNIA

- ***Phase I study of anti-CD3 x anti-EGFR–armed activated T-cells for treatment of advanced colorectal or pancreatic cancer:*** New findings from a Phase I study indicate a novel immunotherapy with less toxicity. The study demonstrated that activated T cells armed with anti-CD3 x anti-EGFR can be produced and infused in patients with advanced colorectal and pancreatic cancers with minimal toxicity. Further studies in a larger patient cohort will test efficacy of this immunotherapy strategy.

ACRONYMS

5-FU	5-Fluorouracil
ACT	Adoptive Cell Transfer
AMCE	Academic Medical Center of Excellence
APC	Adenomatous Polyposis Coli
BiTEs	Bi-specific T cell Engagers
CapeOX	Capecitabine and oxaliplatin
CD17-1A	Cluster of Differentiation 17-1A
CD55	Cluster of Differentiation 55
CEA	Carcino Embryonic Antigen
CIMP	CpG Island Methylator Phenotype
CIN	Chromosomal Instability
CITN	Cancer Immunotherapy Trials Network
CRC	Colorectal Cancer
CT	Computed tomography
CTLA-4	Cytotoxic T Lymphocyte Antigen 4
EGFR	Epidermal Growth Factor Receptor
ErbB2	v-erb-b2 avian ErythroBlastic leukemia viral oncogene homolog 2
FAP	Familial Adenomatous Polyposis
FOBT	Fecal Occult Blood Test
FOLFIRI	Leucovorin, 5-FU, and irinotecan (Camptosar)
FOLFOX	Leucovorin, 5-FU, and oxaliplatin (Eloxatin)
FOLFOXIRI	Leucovorin, 5-FU, oxaliplatin, and irinotecan
GECCO	Genetics and Epidemiology of Colorectal Cancer Consortium
GWAS	Genome-Wide Association Study
HER2	Human Epidermal Growth Factor Receptor 2
HNPCC	Hereditary Non-Polyposis Colon Cancer
MMR	Mismatch Repair
MSI	Microsatellite Instability
MSI-H	High-level of MSI
MSI-L	Low-level of MSI
MSS	Microsatellite Stable
MUC-1	Mucin 1 (Cell Surface Associated)
NCCN	National Comprehensive Cancer Network
p185	Protein 185
p53	Protein 53
PD-1	Programmed Cell Death Protein 1
PDL-1	Programmed Cell Death Ligand 1
Ras	Rat Sarcoma identified protein
TIL	Tumor Infiltrating Lymphocytes
VEGF	Vascular Endothelial Growth Factor

GLOSSARY

Adjuvant Chemotherapy	Additional treatment given after surgery to lower the risk of the cancer returning
Angiogenesis	The physiological process through which new blood vessels form from pre-existing vessels
Apoptosis	Genetically determined process of cell self-destruction
Benign	Abnormal growth of body tissue that is not cancerous
Biobanking	A type of repository that stores biological samples
Chemotherapy	The use of one or more drugs that are toxic to cells with the purpose of preventing the spread or growth of tumor cells
Colectomy	Removal of malignant tissue from the colon
CT Colonography	Also known as virtual colonoscopy, uses low dose radiation CT scanning to obtain an interior view of the colon (the large intestine) that is otherwise only seen with a more invasive procedure where an endoscope is inserted into the rectum and passed through the entire colon
Downregulated	Refers to underactive expression of genes or proteins
Etiology	The cause or causes of a disease or abnormal condition
Genomic Profiling	Information about all the genes in an organism, including variations, gene expression, and the way those genes interact with each other and with the environment
Helper T cells	T-helper cells (Th cells) are a sub-group of white blood cells that help the activity of other immune cells by releasing T cell cytokines
Immunotherapy	Treatment of a disease by inducing, enhancing, or suppressing an immune response
Killer T cells	A subgroup of white blood cells that kill damaged, infected, and cancerous cells

Malignant Growth	A cellular growth that develops quickly and uncontrollably that has the ability to destroy tissues and/or travel to other parts of the body
Metastasis	The movement of cancer cells to other parts of the body
Molecular Pathway	A series of interactions within a cell that directs various cell processes and phenomena
Monoclonal Antibody	Antibody obtained from immune cells that were cloned from a unique parent cell
Mouse Xenograft (Avatar Mice)	Mice into which human tumor cells are transplanted either under the skin or into the organ
Neoadjuvant Chemotherapy	Treatment given to patients before the primary chemotherapy
Oncogenes	Genes that speed up cell division
Pathogenesis	The mechanism by which a disease is caused
Phase I	Examines the safety of the product in a very small group of healthy volunteers or patients afflicted with a specific disease. Also used to determine appropriate dose ranges
Phase II	Evaluates the safety and efficacy of the product at a predetermined dose in comparison to the standard of care treatment (commercially available therapies commonly used to treat the same disorder or disease)
Phase III	Evaluates the product compared to the standard of care in a large diverse population to determine broader efficacy and develop usage guidelines
Phase IV	Evaluates the long-term effects of a drug post-FDA approval for public use
Polypectomy	Removal of polyps
Polyps	Tissue growth on the lining of the colon that sometimes grows into cancers

Pre-clinical	A stage of research before clinical trials where feasibility and drug safety data are collected
Recombinant DNA	DNA molecules formed in the laboratory by bringing together genetic material from multiple sources
Tumor suppressor genes	Genes that slow down cell growth and control cell death
Non-familial CRC	Sporadic development of CRC
Standard of care treatment	Commercially available therapies commonly used to treat the same disorder or disease
Systems Biology	An interdisciplinary field of study that focuses on complex interactions within biological systems
T cells	A type of white blood cell (also called lymphocytes) that plays a central role in cell mediated immunity
Tumorigenesis	The formation of tumors tissue or cells
Upregulated	Refers to overactive expression of genes or proteins
Vaccine Adjuvants	A substance that is added to a vaccine to increase the body's immune response to the vaccine

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