COLORECTAL CANCER: SCIENTIFIC AND COMPETITIVE LANDSCAPE

Dissertation submitted to

The IIHMR University, Jaipur

for the partial fulfilment for the award of the degree of

Master of Business Administration (MBA)

in

Hospital and Health Management

Submitted by

Dr Arkodipto Mallick

Under the supervision and guidance of

Dr Piyusha Majumdar

(Assistant Professor, IIHMR)

2022

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DECLARATION BY STUDENT

I hereby declare that this dissertation titled '**Colorectal Cancer: Scientific and Competitive Landscape'** is the bonafide record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

Dr Arkodipto Mallick

Date:

Certificate from organization

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TO WHOMSOEVER IT MAY CONCERN

This is to confirm that Arkodipto Mallick has successfully completed his dissertation in Intelligence & Insight team within Prescient Healthcare Group, from 21st March 2022 to 18th June 2022 under the guidance of Aviral Maheshwari (Vice President).

During this tenure, he was found to be hardworking and sincere.

We wish Arkodipto all the best for his future endeavours. Please feel free to contact me should you need any further confirmation.

Kind regards,

DocuSigned by:
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CERTIFICATE

This is to certify that dissertation titled "**Colorectal Cancer: Scientific And Competitive Landscape**" is a record of the research work undertaken by (Name of Student) in partial fulfillment of the requirements for the award of the degree of MBA (Hospital and Health Management)/MBA (Pharmaceutical Management)/MBA (Rural Management) from the IIHMR University, Jaipur under my guidance and supervision and his/her approach to the research study has been sincere, scientific, and analytical.

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ABSTRACT

Colorectal cancer (CRC) is the third most frequent malignancy and the fourth leading cause of death from cancer. The majority of CRC cases are found in Western countries, and its prevalence is increasing year by year. Colorectal cancer is estimated to affect 4% to 5% of people, and the chance of having CRC is linked to personal characteristics or habits such as age, chronic disease history, and lifestyle.

Mutations in oncogenes, tumour suppressor genes, and genes involved in DNA repair pathways cause CRC. There are three sorts of pathogenic pathways that might lead to this situation: chromosomal instability (CIN), microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP). Common mutations, chromosomal abnormalities, and translocations have been identified to disrupt critical pathways in different forms of CRC, and mutations in genes can be employed as predictive markers for patient outcome.

Changes in ncRNAs, such as lncRNA or miRNA, can also contribute to various stages of the carcinogenesis process and have predictive significance when utilized as biomarkers. As a result, various gene and mRNA panels are being created to better prognosis and treatment choices.

In CRC, the first-line treatment is a multimodal approach based on tumor-related characteristics, and typically consists of surgical resection followed by chemotherapy combined with monoclonal antibodies or proteins against vascular endothelial growth factor (VEGF) and epidermal growth receptor (EGFR) (EGFR). Alternative therapies, in addition to orthodox chemotherapy, are being researched to improve treatment efficacy and reduce adverse effects.

Development of newer therapies will provide better treatment for the CRC patients. Understanding the current and the future treatment landscape is crucial for development of treatments for colorectal cancers in future.

This study was undertaken to understand and analyze the treatment landscape by competitive analysis of the major pharmaceutical industries and the development of molecules for the treatment of CRC.

By secondary data analysis of the pipelines of the companies and web-based data collection of the ongoing clinical trials and upcoming therapies, I am going to assess the current and the future treatment paradigms in CRC.

ACKNOWLEDGEMENT

The opportunity to complete a dissertation at Prescient Healthcare Group was both enriching and valuable. I am grateful to have met so many knowledgeable professionals who guided me through my research. I sincerely thank them for guiding me.

First, I'd like to thank the entire Intelligence and Insight team, PHG. Dr Aviral Maheshwari (Vice President), Nishika Bhan (Associate Director), Tanya Upadhyay (Associate Engagement Manager), and Dr Karan Madhok (Senior Associate) who inspired, directed, and facilitated me in completing my research.

I am grateful to Dr Piyusha Majumdar (Assistant Professor) for her constant guidance and support throughout the project. Her valuable insights and suggestions were extremely beneficial to the successful completion of my project.

I am overwhelmed with humility and gratitude to recognize my significance to each and every one who has helped me in moving these thoughts beyond the level of straightforwardness and into something concrete. I would like to express my heartfelt appreciation to my parents and friends for their continuous support.

Sincerely

Dr Arkodipto Mallick

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LIST OF SYMBOLS AND ABBREVIATIONS

ABBREVIATIONS	FULL FORM
CRC	Colorectal Cancer
FOLFOX	Folinic acid, fluorouracil and oxaliplatin
FOLFIRI	Folinic acid-Fluorouracil-Irinotecan
FOLFOXIRI	Folinic acid, fluorouracil (5FU), oxaliplatin and irinotecan.
SEER staging	'Surveillance, Epidemiology, and End Results' staging
VEGF	Vascular endothelial growth factor
EGFR	Epidermal growth factor receptor
MSI-H	Microsatellite instability – High
dMMR	deficient Mis-Match Repair
MEK	Mitogen-activated protein kinase
HER2	Human epidermal growth factor receptor 2
CPI	Checkpoint inhibitor
PARP	Poly adenosine diphosphate-ribose polymerase
TKI	Tyrosine kinase inhibitor
PD-1	Programmed cell death protein 1
SOC	Standard of care
T-DXd	Trastuzumab deruxtecan

CHAPTER – 1: INTRODUCTION

Prescient Healthcare Group

A practical work background is essential while striving to enter the employment market. Internships are a crucial component of the MBA program. As part of my MBA education, I completed a three-month internship with Prescient Healthcare Group in Gurgaon.

- Objective of Dissertation:
  - For real-life working exposure
  - To promote personal development
  - To gain a better understanding of oneself
  - To build a professional network
  - To aid in the development of professional aptitude
  - To improve personal character
  - To open more doors to new opportunities
  - To understand an organization's work culture
  - To brainstorm to achieve good results

- Organization Profile

Prescient, which was founded in 2007, is a global firm with nine offices spread across three continents. Prescient has nearly 475 biopharma intelligence and strategy experts and is partnered with 23 of the top 25 biopharmaceutical companies, as well as the fastest-growing mid-caps and cutting-edge emerging biotech. Over the last five years, the company's CAGR has been 20%.

- Vision

“Our vision is to be the biopharma strategy partner most respected for its people, expertise, and impact.”

- Mission

"Our mission is to help biopharmaceutical companies develop, launch and market medicines that expand treatment options, optimize patient outcomes, and deliver high levels of return."

- Values

"We believe that the respect and trust of our clients must be continuously earned. We strive to achieve this by collectively challenging and supporting each other to be the best we can be and individually taking ownership, being accountable and making a difference."

- Different Teams of Prescient:
  - Intelligence & Insight Team: Helps clients to shape confident decisions by providing timely and in-depth insights into how changes in competitor activities, market dynamics and stakeholder behaviors may affect the strategy or performance of an asset, brand, or portfolio
  - Advisory Team: Helps to define client's success by using evidence to form the foundations of thinking, challenge the status quo and frame potential options, and channel cross-functional expertise to realize the potential of their brand
  - Analytics Team: Ensures depth, breadth, and timeliness of our secondary data analytics to provide client-facing teams with immediate access to relevant public domain intelligence
  - Primary Research Team: Works with Prescient Analytics team to support client-facing business units and handles collecting market, competitor and stakeholder evidence using primary research techniques
  - Software Team: Works to support proprietary software platform, Inflexion Rx and develops new tools and technologies that help drive clients' business excellence by helping them make quicker, more informed, and better-aligned decisions
  - Business Operations Team: Manages day-to-day global functions to run the business as efficiently as possible and helps businesses to continue to scale and grow

- **Office Locations:**

- San Francisco
- New York
- Boston
- Madrid
- Manchester
- London
- Munich
- New Delhi
- Beijing

- Key Learnings:
  - Research gathering experience in drug development, manufacturing, launch and marketing strategy across markets to support strategic analysis
  - Business research to deliver actionable insights to clients in therapeutic areas
  - Deep knowledge of the disease area as well as scientific expertise
  - Primary data collection, secondary data analysis, interviewing and tracking news to support strategic analysis
  - Coverage of conferences to gather the latest developments in the pharmaceutical industry
  - Assessment of competitor threat and market opportunity
  - Workshops on competitor simulation

‘

CHAPTER – 2: LITERATURE REVIEW

Sr. No.	Journal & Date	Title	Authors	Salient Features
1.	International Journal of Molecular Sciences (January 2017)	Colorectal Carcinoma: A General Overview and Future Perspectives in Colorectal Cancer(1)	Mármol et al.	This study explains the causes and risk factors of colorectal cancer and the various mutation that it presents with. It also sheds light on the developing treatment paradigms which can impact in the future
2.	Internet-based article (March 2020)	Comprehensive review of targeted therapy for colorectal cancer(2)	Xie et al.	This article explains the current treatment, chemotherapy, targeted therapy and the landscape of colorectal cancer. It also highlights the various pathways that are affected by colorectal cancer and the mechanism of action for the molecules
3.	The Lancet (October 2019)	Colorectal cancer(3)	Dekker et al.	This study focuses on the treatment and downstaging of advanced colorectal cancer. It highlights on the various treatment method available and the new emerging treatment option.

4.	Online publication (May 2018)	The molecular characteristics of colorectal cancer: Implications for diagnosis and therapy (Review)(4)	Nguyen et al.	This study highlights the molecular basis of colorectal cancer, various pathways and treatment focus. Also highlighting the clinical implication of the molecular genetics of colorectal cancer
5.	StatPearls Publishing (Internet) (January 2022)	Colon Cancer(5)	Recio-Boiles et al.	This study describes the pathophysiology, clinical presentation, risk factors and the role of early initiation of treatment in colorectal cancer
6.	Current Health Sciences Journal (April-June 2019)	Colorectal Cancer: An Update on Treatment Options and Future Perspectives(6)	Florescu-Ţenea et al.	This study highlights the genomic landscape through the sequencing techniques to understand mechanism behind the development of CRC and for refinement of the currently used techniques
7.	Online publication (November 2020)	Recent advances in clinical practice: colorectal cancer chemoprevention in the average-risk population	Chapelle et al.	This study focuses on the recent advanced in the treatment of colorectal cancer as well as prevention of colorectal cancer in patients at risk

CHAPTER 3 – METHODOLOGY

- **Key Research Question:**
  - What are the potential upcoming therapies for Colorectal Cancer?
  - What is the competitive timeline for current and emerging therapies in Colorectal Cancer?
- **Aim:**
  - The primary goal of this study is to gain a thorough understanding of the overview, current treatment algorithm, emerging treatment plans, and competitive timeline of colorectal cancer
  - The secondary goal is to comprehend the treatment landscape and competitive analysis, as well as to investigate the current colorectal cancer treatment algorithm

- **Study Design:** Cross sectional descriptive study and data was collected through secondary research

- **Study Setting:** Prescient Healthcare Group, Gurgaon

- **Study period:** 21st March 2022-18th June 2022

- **Trial Population/Sample size:** 689 trials of colorectal cancer

- **Data collection:** Data for the study was collected from clinicaltrials.gov for Colorectal Cancer.

- **Study research criteria was selected as follows:**

  - Status of the trial:
    - Not Yet Recruiting
    - Recruiting
    - Enrolling by invitation
    - Active not recruiting
    - Completed

  - Eligibility Criteria: All approved therapy and clinical trials on treatment of colorectal cancer.
  - Study type included all such as interventional (clinical trial), observational, patient registries and expanded access.
  - Study Phase: Phase 2 and 3

- Funder type: Industry

- **Data utilization:** An excel workbook was prepared in which two different sheets were made one for phase 2 and another phase 3. Relevant data was extracted on the basis of different criteria such as brand name, company name, phase, pipeline, special drug designation and results, etc. The relevant information was used to summarize heat map, current and emerging therapies and their timeline, potential upcoming therapy, emerging treatment algorithm and finally the current clinical benchmark.

- **Data collection method:** Web-based data collection.

- **Sampling technique:**

  - Inclusion criteria:
    - Trials from Phase II, Phase III and completed
    - Only industry-sponsored trials were considered (US, EU, and Japan)
  - Exclusion criteria:
    - Preclinical, Phase I/II, Phase I trials were excluded.
    - Studies that were suspended, discontinued, terminated, or whose status was unknown were excluded
    - Educational institutes, research centers, hospitals, and privately funded studies were excluded
  - Data analysis tools: MS Excel

CHAPTER – 4: RESULTS

Disease overview

Colorectal cancer in the gastrointestinal tract starts as a growth, which is called a polyp, on the inner lining of the colon or rectum. Some polyps are pre-cancerous such as adenomatous polyps, senile polyps and traditional serrated adenomas. Most of the CRC (about 70%) tend to occur in the left side, whereas a small percentage (approximately 10%) occur in the right side.

Onset/Risk factors

- There are changeable lifestyle related risk factors and non-changeable known risk factors for CRC –
  - Age: CRC is most common in people older than 50 years of age
  - Genetics: Family members may inherit a gene mutation that can lead to CRC, 1 in 3 patients with CRC have a family history, and 2-4% of CRC cases are attributable to Lynch syndrome
  - Medical history: Patients with a history of colorectal polyps, inflammatory bowel syndrome: ulcerative colitis or Crohn's disease are at risk of CRC
- Modifiable risk factors include obesity, smoking, alcoholism, and high intake of red meat

Symptoms and Diagnosis

- Symptoms include a change in bowel habits, diarrhea, constipation or incomplete evacuation of the bowels, rectal bleeding, cramps in the abdomen, unintended weight loss and fatigue
- CRC can be diagnosed with several tests: a physical digital rectal examination, liver function test (as colorectal cancer can spread to the liver), tumor marker CEA, colonoscopy, proctoscopy, USG, biopsy, CT scan, MRI or PET scan(7)

Treatment

- Resectable, localized tumors can be removed either with surgery, a polypectomy, or a hemi, partial or segmental colectomy
- Systemic part of the treatment: Chemotherapy is administered with FOLFOX, FOLFIRI or FOLFOXIRI combinations with leucovorin, oxaliplatin, irinotecan, 5-FU and capecitabine. Other options include hepatic artery infusion, target therapy or immunotherapy with pembrolizumab or nivolumab

- Ablation/ embolization can also be used to destroy the tumor as an adjuvant to localized resection, or if it has metastasized or is resectable(8)

Prognosis

- The prognosis of patients affected by CRC depends on the tumor size, location, and cellular division
- The 5-year survival rate based on SEER staging for patients with colon cancer for localized disease is 91%, 72% for regional, 16% for distant and 67% combined. For rectal cancer, the survival rate is 89% for localized disease, 72% for regional, 16% for distant and 67% combined(9)

Unmet Needs

- Curative therapy for metastatic advanced CRC
- Emotional, psychological and informational domain for the patient

Epidemiology

- Median age of diagnosis 69 years
- Male predominance is seen in CRC
- Estimated new cases in 2021: 149,500 (US), accounting for 7.9% of all newer cancer users(10)

Key Pathways and Drug Target in Colorectal Cancer (CRC)

VEGF/ EGFR Pathways

- Targeting the VEGF and EGFR pathways is the key approach in the current management of colorectal cancer with relevant therapies including bevacizumab, Cyramza, Erbitux and others
- While data suggest that right sided tumors respond better to VEGF-targeted therapies, no biomarker is yet available to guide the use of VEGF inhibitors and only patients without a RAS or BRAF mutation benefit from EGFR inhibitors as these other factors act downstream of VEGF/ EGFR

dMMR/MSI-H Status

- Approximately 12-15% of colorectal cancers are defined by a mismatch repair system (dMMR), which leads to high levels of microsatellite mutations (MSI-H)

- Colorectal cancer with the dMMR/MSI-H status has a distinct phenotype, including strong tumor-infiltrating lymphocytes, and it has prognostic and therapeutic implications, particularly indicating likely greater responsiveness to checkpoint inhibitors

BRAF Mutations

- BRAF mutations occur in 5-15% of colorectal cancers and historically confer a poor prognosis; however, the approval of BRAF/ MEK inhibitors is widening treatment options for refractory BRAF V600E-mutation-positive colorectal cancer patients

Other Targets

- The identification of HER2 overexpression in approximately 6% of colorectal cancers has led to the clinical investigation – and off-label use in certain markets – of HER2-targeted agents for a specific subset of patients; HER2-targeting agents are an active area of development
- There has been progress to target KRAS mutations, including KRAS G12C mutations, which occur in around 3-4% of colorectal cancer patients
- Other drug targets being investigated in clinical trials including IL-1α, MUC5AC, the JAK/STAT3, and PI3K/Akt pathways
- Exome sequencing has identified novel somatic mutations in genes such as FAT4, DOCK2, and CDH10 and in key pathways, including STING-controlled signalling pathways

Competitive Landscape Overview for colorectal cancer

Key Trends

Over the upcoming 5 years, CRC treatment will become increasingly personalised with the likely introduction of novel, biomarker-based therapies, most notably targeting HER2 and KRAS mutations.

While CPIs have historically failed outside of MSI-H CRC, novel combinations, including CPIs in combination with VEGF-targeted therapies and novel kinase inhibitors, are being investigated and early data suggest these approaches may be promising.

Colorectal Cancer Key Metrics

- Around 385,000 patients got diagnosed with colorectal cancer in 2021, globally.
- There are 10 approved therapies for colorectal cancer.
- 22 molecules in the company pipelines are in active development phase and 7 molecules are in phase III development.
- Forecasted global branded drug sales is around $7.8 billion by 2026 as compared to the global branded drug sales in 2021 was approximately $6.6 Billion.

DISCUSSION

Colorectal cancer has slowly become a worldwide health issue. While other types of cancer have seen a decrease in occurrences due to screening and vaccine programmes, colorectal cancer has increased to become the third most diagnosed cancer worldwide and, more concerning, the second biggest cause of cancer-related mortality. Targeted therapy has long been seen as a major paradigm change in the treatment of colorectal cancer, with drugs such as bevacizumab and cetuximab soon becoming standard alternatives in the treatment of locally progressed or metastatic illness. However, this sort of treatment has shown its limitations, with a huge percentage of patients seeing little or no benefit. About the molecular pathways that drive the malignant phenotype of colorectal cancer becomes available, scientists are working hard to create new medicines based on these discoveries.

Current Treatment Algorithm

Clinically, colorectal cancer can present in the early stage or at the late stage with metastasis. The treatment modalities also change with the presentation of colorectal cancer.

Early-Stage colorectal cancer

- In early-stage colorectal cancer it can be resectable or unresectable.
- In case of resectable case of colorectal cancer, treatment is done by neo-adjuvant therapy, which is with FOLFOX/ CAPOX/ capecitabine or 5FU/ leucovorin. After

doses of therapy has been given, the surgical resection is done. Following surgery adjuvant therapy with the same drugs are continued.

- In case of unresectable colorectal cancer treatment is done by FOLFIRI ± bevacizumab or ziv-aflibercept or ramucirumab. And is kept under regular radiological check-up to monitor the size of the tumor.

Metastatic colorectal cancer

- Metastatic colorectal cancer is already spread 1 or more parts of the body other than the primary tumor location. It generally presents as unresectable case.
- The treatment paradigm changes based on the mutation present in the cancer.
- For CRC with no mutation treatment is done by CAPOX/ FOLFIRI/ 5-FU/ FOLFOX ± bevacizumab
- With RAS mutation the treatment is done by FOLFOX/ FOLFIRI ± cetuximab or panitumumab OR Trastuzumab + pertuzumab/ lapatinib/ fam-trastuzumab deruxtecan

Relapsed/ Recurrent Colorectal cancer

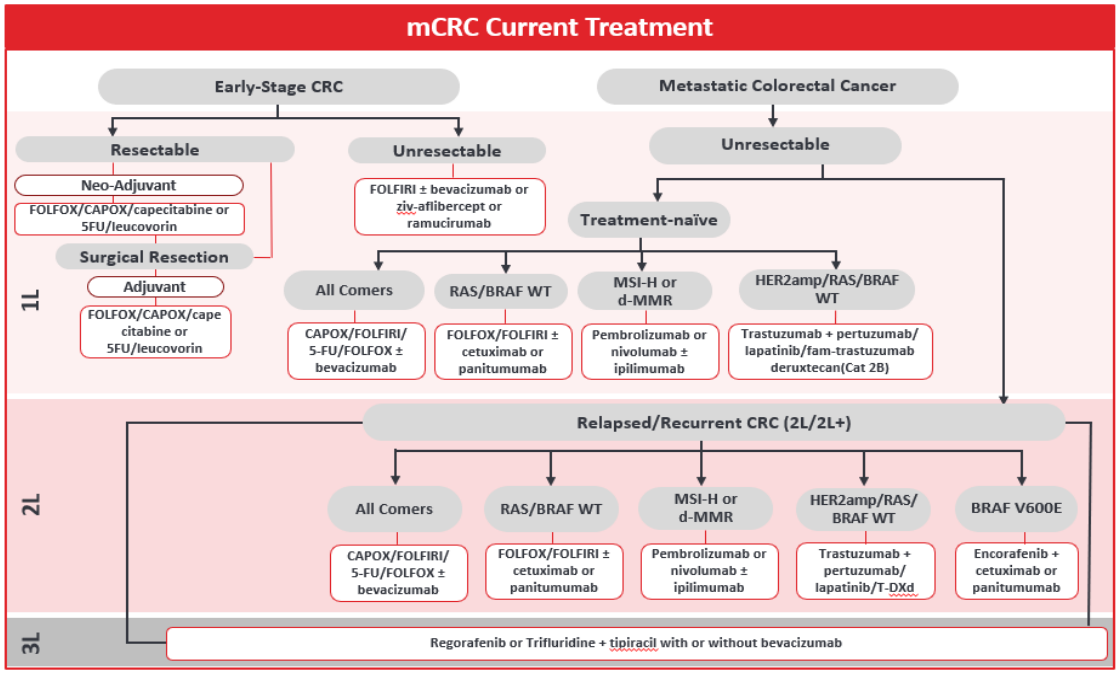
Relapsed cases have already been treated with at least 1 line of therapy or more and still colorectal cancer has reoccurred. In such cases the treatment paradigm is –

- **For no mutation:** CAPOX/ FOLFIRI/ 5-FU/ FOLFOX ± bevacizumab
- **For RAS/ BRAF WT/ RAS WT:** FOLFOX/ FOLFIRI ± cetuximab or panitumumab
- **For MSI-High:** Pembrolizumab or nivolumab ± ipilimumab
- **For HER2/ RAS/ BRAF WT:** Trastuzumab + pertuzumab/ lapatinib/ T-DXd
- **For BRAF V600E** - Encorafenib + cetuximab or panitumumab

Key Takeaways

- In FOLFOX vs. FOLFIRI, treatment choice depends on discussion with patients about toxicities and certain comorbidities that could restrict the use of one agent over the other
- Based on retrospective analysis, CAPOX regimen is preferred in older patients (>65-year-old) as compared to FOLFOX based regimens (<65-year-old)
- In the 1L setting, EGFR mAb (cetuximab and panitimumab) role is restricted to patients with RAS/BRAF wild type disease who have left-sided tumors or have contraindications to bevacizumab

- Newly approved MoAs include:
  - PD-1 inhibitor
  - BRAF/MEKi inhibitor
- Pembrolizumab and nivolumab/ ipilimumab were recently approved in the EU, the US and JP for patients with MSI-H mCRC in 1L settings
- Trastuzumab deruxtecan is not approved by the FDA, but it is recommended by the NCCN in 2L+ settings for HER2amp/RAS/ BRAF WT, based on the clinical benefit and safety profile of T-DXd from the DESTINY-CRC01 trial



<u>Most Commonly used treatment paradigms</u>
In USA

- For first line treatment 29% of the patients are treated with FOLFOX (Flurouracil + Oxaliplatin) as a single drug. 18% of the colorectal cancer cases are treated with FOLFOX in combination with Avastin (Bevacizumab). And around 7% of the cases are treated with Combination therapy of Avastin with FOLFIRI (Flurouracil + Irinotecan)
- For second line treatment 19% of colorectal cancer patients receive Avastin with combination with FOLFIRI, followed by FOLFIRI as a single drug which is about 9%. Around 6% cases receive Avastin/ CAPIRI (Capecitabine/Irinotecan) with Keytruda (Pembrolizumab)

- For third line treatment Stivarga (Regorafenib) is used in 24% of the cases, followed by Avastin (Bevacizumab)/Capecitabine at 16% of cases and Lonsurf (Trifluridine-tipiracil) at 9%
- For fourth line treatment Lonsurf (Trifluridine-tipiracil) is the main drug of choice at 21% followed by 18% receive Stivarga (Regorafenib) and 13% receive Vectibix (Panitumumab)/FOLFIRI

In EU+UK

- For first line treatment 22% of the colorectal cancer cases receive Avastin (Bevacizumab)/ FOLFOX, 11% for Avastin (Bevacizumab)/FOLFIRI and around 11% are treated only with FOLFOX
- For second line treatment Avastin (Bevacizumab)/FOLFIRI is used for around 15% of cases of colorectal cancer. Followed by Zaltrap (Aflibercept)/FOLFIRI around 13% and around 11% use Avastin (Bevacizumab)/FOLFOX
- For third line treatment the most common treatment option is Lonsurf (Trifluridine-tipiracil) which is around 39%. Stivarga (Regorafenib) is the second drug of choice at around 20% and around 12% use Capecitabine
- For fourth line treatment Lonsurf (Trifluridine-tipiracil) is used for 65% cases, followed by Stivarga (Regorafenib) in 12% and Zaltrap (Aflibercept)/FOLFIRI in 6% cases

In Japan

- For first line treatment Avastin (Bevacizumab)/CAPOX is used the most with around 17% of the cases receiving the combination. About 16% patients receive Avastin (Bevacizumab)/FOLFOX and 9% receive CAPOX
- For second line treatment comprise of Cyramza (Ramucirumab)/FOLFIRI (14%), Avastin (Bevacizumab)/FOLFIRI (13%) and Avastin (Bevacizumab)/Capecitabine (8%)
- For third line treatment 14% patients receive Stivarga (Regorafenib), following it is Lonsurf (Trifluridine-tipiracil), about 14% patient receiving the

combination and 11% receive Avastin (Bevacizumab)/Lonsurf (Trifluridine-tipiracil)

- For fourth line treatment Stivarga (Regorafenib), Lonsurf (Trifluridine-tipiracil) and Avastin (Bevacizumab)/Lonsurf (Trifluridine-tipiracil) at 15%, 14% and 9% respectively

	US	EU4+UK	JP
1. First Line	FOLFOX (34%) **Avastin** (Bevacizumab)/FOLFOX (18%) **Avastin** (Bevacizumab)/FOLFIRI (8%) N=40,585 (n=1,185)	**Avastin** (Bevacizumab)/FOLFOX (22%) **Avastin** (Bevacizumab)/FOLFIRI (11%) FOLFOX(11%) N=113,084 (n=6,321)	**Avastin** (Bevacizumab)/CAPOX (17%) **Avastin** (Bevacizumab)/FOLFOX (16%) CAPOX (9%) N=39,192 (n=761)
2. Second Line	**Avastin** (Bevacizumab)/FOLFIRI (19%) FOLFIRI (9%) **Avastin** (Bevacizumab)/CAPIRI (6%) & **Keytruda** (Pembrolizumab) (6%) N=19,150 (n=289)	**Avastin** (Bevacizumab)/FOLFIRI (15%) **Zaltrap** (Aflibercept)/FOLFIRI (13%) **Avastin** (Bevacizumab)/FOLFOX (11%) N=42,200 (n=1,544)	**Cyramza** (Ramucirumab)/FOLFIRI (14%) **Avastin** (Bevacizumab)/FOLFIRI (13%) **Avastin** (Bevacizumab)/Capecitabine (8%) N=16,958 (n=326)
3. Third Line	**Stivarga** (Regorafenib) (24%) **Avastin** (Bevacizumab)/Capecitabine (16%) **Lonsurf** (Trifluridine-tipiracil) (9%) N=15,601 (n=177)	**Lonsurf** (Trifluridine-tipiracil) (39%) **Stivarga** (Regorafenib) (20%) Capecitabine (12%) N=43,882 (n=1,451)	**Stivarga** (Regorafenib) (18%) **Lonsurf** (Trifluridine-tipiracil) (14%) **Avastin** (Bevacizumab)/**Lonsurf** (Trifluridine-tipiracil) (11%) N=8,922 (n=174)
4. Fourth Line	**Lonsurf** (Trifluridine-tipiracil) (21%) **Stivarga** (Regorafenib) (18%) **Vectibix** (Panitumumab)/FOLFIRI (13%) N=3,038 (n=83)	**Lonsurf** (Trifluridine-tipiracil) (65%) **Stivarga** (Regorafenib) (12%) **Zaltrap** (Aflibercept)/FOLFIRI (6%) N=4,230 (n=107)	**Stivarga** (Regorafenib) (15%) **Lonsurf** (Trifluridine-tipiracil) (14%) **Avastin** (Bevacizumab)/**Lonsurf** (Trifluridine-tipiracil) (9%) N=7,563 (n=147)

<u>Most Commonly used treatment paradigms in mutation cases</u>
RAS WT

- For first line treatment, FOLFOX, Avastin and keyruda are most commonly used in the US. In EU+UK Vectibix (panitumumab)/FOLFOX, Erbitux (cetuximab)/FOLFIRI and Erbitux (cetuximab)/FOLFOX are commonly used. In Japan, Vectibix (panitumumab)/FOLFOX, Avastin (Bevacizumab)/CAPOX and Avastin (Bevacizumab)/FOLFOX (11%) are used
- For second line treatment, Avastin (Bevacizumab)/FOLFIRI, Braftovi (Encorafenib)/Vectibix (panitumumab), Keytruda (Pembrolizumab) are the most common therapies used in the US. In EU+UK Avastin in combination with FOLFIRI or FOLFOX is used commonly. In Japan, Cyramza (Ramucirumab)/FOLFIRI, Avastin (Bevacizumab)/FOLFIRI, Vectibix (panitumumab)/FOLFIRI are the common choices
- For third line treatment, in the US, Stivarga (Regorafenib), Avastin (Bevacizumab)/Lonsurf (Trifluridine-tipiracil), Vectibix (Panitumumab)/FOLFIRI are the drug of choice. Lonsurf (Trifluridine-tipiracil), Stivarga (Regorafenib), Vectibix (Panitumumab) are used in EU+UK. In Japan, Stivarga (Regorafenib), Avastin (Bevacizumab)/Lonsurf (Trifluridine-tipiracil), Vectibix (Panitumumab)/FOLFIRI are common choices

- For fourth line of treatment, in US, Vectibix (Panitumumab)/FOLFIRI, Lonsurf (Trifluridine-tipiracil), Erbitux (cetuximab)/FOLFIRI are common drug of choice. In UK, Lonsurf (Trifluridine-tipiracil), Stivarga (Regorafenib), Zaltrap (Aflibercept)/FOLFIRI are used and in Japan, Lonsurf (Trifluridine-tipiracil), Vectibix (Panitumumab), Avastin (Bevacizumab)/Lonsurf (Trifluridine-tipiracil) are commonly used

	US	EU4+UK	JP
1. First Line	FOLFOX(29%) **Avastin** (Bevacizumab)/FOLFOX (18%) **Keytruda** (Pembrolizumab) (7%) N=19,553 (n=492)	**Vectibix** (panitumumab)/FOLFOX (13%) **Erbitux** (cetuximab)/FOLFIRI (10%) **Erbitux** (cetuximab)/FOLFOX(10%) N=36,186 (n=3,192)	**Vectibix** (panitumumab)/FOLFOX (18%) **Avastin** (Bevacizumab)/CAPOX (12%) **Avastin** (Bevacizumab)/FOLFOX (11%) N=17,916 (n=348)
2. Second Line	**Avastin** (Bevacizumab)/FOLFIRI (11%) **Braftovi** (Encorafenib)/**Vectibix** (panitumumab) (9%) **Keytruda** (Pembrolizumab) (8%) N=10,819 (n=159)	**Avastin** (Bevacizumab)/FOLFIRI (16%) **Avastin** (Bevacizumab)/FOLFOX(12%) FOLFIRI (10%) N=27,765 (n=1,189)	**Cyramza** (Ramucirumab)/FOLFIRI (15%) **Avastin** (Bevacizumab)/FOLFIRI (13%) **Vectibix** (panitumumab)/FOLFIRI(9%) N=8,400 (n=162)
3. Third Line	**Stivarga** (Regorafenib) (25%) **Avastin** (Bevacizumab)/**Lonsurf** (Trifluridine-tipiracil) (9%) **Vectibix** (Panitumumab)/FOLFIRI (8%) N=7,015 (n=81)	**Lonsurf** (Trifluridine-tipiracil) (35%) **Stivarga** (Regorafenib) (21%) **Vectibix** (Panitumumab) (11%) N=23,204 (n=1,038)	**Stivarga** (Regorafenib) (17%) **Avastin** (Bevacizumab)/**Lonsurf** (Trifluridine-tipiracil) (11%) **Vectibix** (Panitumumab)/FOLFIRI (10%) N=4,094 (n=79)
4. Fourth Line	**Vectibix** (Panitumumab)/FOLFIRI (25%) **Lonsurf** (Trifluridine-tipiracil) (23%) **Erbitux** (cetuximab)/FOLFIRI (12%) N=1,540 (n=35)	**Lonsurf** (Trifluridine-tipiracil) (56%) **Stivarga** (Regorafenib) (16%) **Zaltrap** (Aflibercept)/FOLFIRI (11%) N=2,151 (n=68)	**Lonsurf** (Trifluridine-tipiracil) (16%) **Vectibix** (Panitumumab) (11%) **Avastin** (Bevacizumab)/**Lonsurf** (Trifluridine-tipiracil) (9%) N=4,331 (n=84)

RAS Mutant

- In US, EU+UK and Japan the use of Avastin in combination with FOLFOX and FOLFIRI has been crucial for the first line treatment of colorectal cancer. In some cases, FOLFOX as a single agent is used. In Japan Avastin n combination with CAPOX is also used as first line treatment
- For second line treatment Avastin with combination with FOLFIRI or CAPIRI is used in US. Also, FOLFIRI with Keytruda is also used. In EU+UK the use of Zaltrap or Avastin with combination with FOLFOX or FOLFIRI is also commonly used. XELODA is also a drug of choice in the EU+UK. In Japan, the use of Avastin/ Cyramza with FOLFIRI is used. Also, Avastin is used with combination with Capecitabine (Xeloda)
- Third line treatment in US makes up of the Stivarga (Regorafenib), Lonsurf (Trifluridine-tipiracil), FOLFOX (9%) & CAPIRI. In EU+UK use of Lonsurf (Trifluridine-tipiracil), Stivarga (Regorafenib), Xeloda (capecitabine). In Japan, Lonsurf (Trifluridine-tipiracil), Stivarga (Regorafenib), Avastin (Bevacizumab)/Lonsurf (Trifluridine-tipiracil) are the drug of choice
- As fourth line treatment, Stivarga (Regorafenib), Avastin (Bevacizumab)/FOLFOX, Lonsurf (Trifluridine-tipiracil) is used in US. In EU+UK, Lonsurf (Trifluridine-tipiracil), Stivarga (Regorafenib), Avastin (Bevacizumab)/5FU (Fluorouracil) is used.

In Japan, Stivarga (Regorafenib), Lonsurf (Trifluridine-tipiracil), Avastin (Bevacizumab)/Lonsurf (Trifluridine-tipiracil) are used

	US	EU4+UK	JP
1. First Line	**Avastin** (Bevacizumab)/FOLFOX (30%) **Avastin** (Bevacizumab)/FOLFIRI (15%) FOLFOX (13%) N=6,766 (n=250)	**Avastin** (Bevacizumab)/FOLFOX (29%) **Avastin** (Bevacizumab)/FOLFIRI (14%) FOLFOX (11%) N=71,464 (n=2,896)	**Avastin** (Bevacizumab)/FOLFOX (28%) **Avastin** (Bevacizumab)/CAPOX (26%) **Avastin** (Bevacizumab)/FOLFIRI (7%) N=13,746 (n=266)
2. Second Line	**Avastin** (Bevacizumab)/FOLFIRI (35%) **Avastin** (Bevacizumab)/CAPIRI (10%) FOLFIRI (9%) & **Keytruda** (Pembrolizumab) (9%) N=4,317 (n=86)	**Zaltrap** (Aflibercept)/FOLFIRI (22%) **Avastin** (Bevacizumab)/FOLFIRI (14%) **Xeloda** (capecitabine) (12%) N=13,990 (n=339)	**Avastin** (Bevacizumab)/FOLFIRI (15%) **Cyramza** (Ramucirumab)/FOLFIRI (13%) **Avastin** (Bevacizumab)/Capecitabine) (10%) N=7,498 (n=144)
3. Third Line	**Stivarga** (Regorafenib) (35%) **Lonsurf** (Trifluridine-tipiracil) (30%) FOLFOX (9%) & CAPIRI (9%) N=4,275 (n=51)	**Lonsurf** (Trifluridine-tipiracil) (54%) **Stivarga** (Regorafenib) (15%) **Xeloda** (capecitabine) (9%) N=14,306 (n=308)	**Lonsurf** (Trifluridine-tipiracil) (23%) **Stivarga** (Regorafenib) (19%) **Avastin** (Bevacizumab)/**Lonsurf** (Trifluridine-tipiracil) (11%) N=4,316 (n=85)
4. Fourth Line	**Stivarga** (Regorafenib) (28%) **Avastin** (Bevacizumab)/FOLFOX (24%) **Lonsurf** (Trifluridine-tipiracil) (18%) N=1,300 (n=44)	**Lonsurf** (Trifluridine-tipiracil) (75%) **Stivarga** (Regorafenib) (5%) **Avastin** (Bevacizumab)/**5FU** (Fluorouracil)(4%) N=2,028 (n=37)	**Stivarga** (Regorafenib) (30%) **Lonsurf** (Trifluridine-tipiracil) (13%) **Avastin** (Bevacizumab)/**Lonsurf** (Trifluridine-tipiracil) (8%) N=2,617 (n=51)

MSI-High

- In US, Keyruda, Avastin/FOLFOX and CAPOX is used as first line treatment. For second line Keytruda (Pembrolizumab), Opdivo (Nivolumab) and Opdivo (Nivolumab)/Yervoy (Ipilimumab) is used. Commonly used third line drugs are Opdivo (Nivolumab), Avastin (Bevacizumab)/Irinotecan, Stivarga (Regorafenib) & Erbitux (cetuximab)/Braftovi (Encorafenib) us used. For fourth line treatment use of Stivarga (Regorafenib), Keytruda (Pembrolizumab), Opdivo (Nivolumab) is done.
- In EU+UK, FOLFOX (as single agent), Avastin (Bevacizumab)/FOLFOX, Xeloda (capecitabine) are used as first line drug. For second line treatment, Avastin (Bevacizumab)/FOLFOX, Vectibix (panitumumab)/FOLFIRI, Stivarga (Regorafenib) are used. For third line treatment, Lonsurf (Trifluridine-tipiracil), Stivarga (Regorafenib), Erbitux (cetuximab)/Braftovi (Encorafenib) are used. For fourth line treatment, Erbitux (cetuximab)/Braftovi (Encorafenib), Stivarga (Regorafenib), Erbitux (cetuximab) are used.
- In Japan, for first line treatment, Avastin with FOLFIRI or CAPOX is used. For second line treatment, Keytruda (Pembrolizumab), Opdivo (Nivolumab)/Yervoy (Ipilimumab) and Avastin (Bevacizumab)/CAPOX are used. For third line treatment, Opdivo (Nivolumab)/Yervoy (Ipilimumab), Keytruda (Pembrolizumab) and Stivarga (Regorafenib) is used. There is no available data for fourth line treatment.

	US	EU4+UK	JP
1. First Line	**Keytruda** (Pembrolizumab) (25%) **Avastin** (Bevacizumab)/FOLFOX (14%) CAPOX (14%) N=6,620 (n=155)	FOLFOX (12%) **Avastin** (Bevacizumab)/FOLFOX (11%) **Xeloda** (capecitabine) (9%) N=6,017 (n=812)	**Avastin** (Bevacizumab)/SOX (19%) **Avastin** (Bevacizumab)/CAPOX (12%) **Avastin** (Bevacizumab)/FOLFIRI (12%) N=466 (n=9)
2. Second Line	**Keytruda** (Pembrolizumab) (38%) **Opdivo** (Nivolumab) (24%) **Opdivo** (Nivolumab)/**Yervoy** (Ipilimumab) (13%) N=3,308 (n=51)	**Avastin** (Bevacizumab)/FOLFOX (15%) **Vectibix** (panitumumab)/FOLFIRI (12%) **Stivarga** (Regorafenib) (9%) N=2,312 (n=207)	**Keytruda** (Pembrolizumab) (28%) **Opdivo** (Nivolumab)/**Yervoy** (Ipilimumab) (27%) **Avastin** (Bevacizumab)/CAPOX (10%) N=592 (n=11)
3. Third Line	**Opdivo** (Nivolumab) (20%) **Avastin** (Bevacizumab)/Irinotecan (18%) **Stivarga** (Regorafenib) (13%) & **Erbitux** (cetuximab)/**Braftovi** (Encorafenib) (13%) N=1,532 (n=22)	**Lonsurf** (Trifluridine-tipiracil) (28%) **Stivarga** (Regorafenib) (17%) **Erbitux** (cetuximab)/**Braftovi** (Encorafenib) (13%) N=1,410 (n=154)	**Opdivo** (Nivolumab)/**Yervoy** (Ipilimumab) (28%) **Keytruda** (Pembrolizumab) (28%) **Stivarga** (Regorafenib) (22%) N=206 (n=4)
4. Fourth Line	**Stivarga** (Regorafenib) (46%) **Keytruda** (Pembrolizumab) (46%) **Opdivo** (Nivolumab) (8%) N=197 (n=17)	**Erbitux** (cetuximab)/**Braftovi** (Encorafenib)(47%) **Stivarga** (Regorafenib) (24%) **Erbitux** (cetuximab) (20%) N=197 (n=7)	N=0 (n=0)

MSS

- FOLFOX in combination with Avastin is used as first and second line treatment in US, EU+EK and Japan
- In US, Avastin with CAPIRI is used as second line treatment as well. In EU+UK, Zaltrap (Aflibercept)/FOLFIRI is also used for second line drug. In Japan, Avastin with Irinotican is also used
- For third line treatment, Avastin (Bevacizumab)/Capecitabine, Stivarga (Regorafenib) and Lonsurf (Trifluridine-tipiracil) are used in the US. In EU+UK, Lonsurf (Trifluridine-tipiracil), Stivarga (Regorafenib) and Vectibix (Panitumumab) are commonly used. In Japan, Avastin (Bevacizumab)/Lonsurf (Trifluridine-tipiracil), Avastin (Bevacizumab)/FOLFIRI and Cyramza (Ramucirumab)/FOLFIRI are used.
- For fourth line treatment Lonsurf (Trifluridine-tipiracil), Stivarga (Regorafenib) and Vectibix (Panitumumab)/FOLFIRI are used in the US. In EU+UK, Lonsurf (Trifluridine-tipiracil), Zaltrap (Aflibercept)/FOLFIRI and Avastin (Bevacizumab)/FOLFOX are commonly used. In Japan, Stivarga (Regorafenib), Vectibix (Panitumumab) and Avastin (Bevacizumab)/IRIS are used.

	US	EU4+UK	JP
1. First Line	FOLFOX (34%) **Avastin** (Bevacizumab)/FOLFOX (18%) **Avastin** (Bevacizumab)/FOLFIRI (10%) N=19,074 (n=711)	**Avastin** (Bevacizumab)/FOLFOX (21%) **Avastin** (Bevacizumab)/FOLFIRI (13%) FOLFOX (10%) N=49,911 (n=2,789)	**Avastin** (Bevacizumab)/CAPOX (15%) **Avastin** (Bevacizumab)/FOLFOX 14%) CAPOX (9%) N=4,955 (n=98)
2. Second Line	**Avastin** (Bevacizumab)/FOLFIRI (26%) FOLFIRI (10%) **Avastin** (Bevacizumab)/CAPIRI (10%) N=10,028 (n=174)	**Avastin** (Bevacizumab)/FOLFIRI (17%) **Zaltrap** (Aflibercept)/FOLFIRI (14%) FOLFIRI(11%) N=22,372 (n=774)	**Avastin** (Bevacizumab)/FOLFIRI (13%) **Avastin** (Bevacizumab)/Capecitabine (13%) **Avastin** (Bevacizumab)/IRIS (8%) N=2,978 (n=58)
3. Third Line	**Avastin** (Bevacizumab)/Capecitabine (26%) **Stivarga** (Regorafenib) (25%) **Lonsurf** (Trifluridine-tipiracil) (13%) N=9,053 (n=83)	**Lonsurf** (Trifluridine-tipiracil) (56%) **Stivarga** (Regorafenib) (13%) **Vectibix** (Panitumumab) (6%) N=21,723 (n=871)	**Avastin** (Bevacizumab)/**Lonsurf** (Trifluridine-tipiracil) (19%) **Avastin** (Bevacizumab)/FOLFIRI (13%) **Cyramza** (Ramucirumab)/FOLFIRI (10%) N=1,593 (n=31)
4. Fourth Line	**Lonsurf** (Trifluridine-tipiracil) (24%) **Stivarga** (Regorafenib) (18%) **Vectibix** (Panitumumab)/FOLFIRI (14%) N=2,396 (n=50)	**Lonsurf** (Trifluridine-tipiracil) (73%) **Zaltrap** (Aflibercept)/FOLFIRI (9%) **Avastin** (Bevacizumab)/FOLFOX (3%) N=3,093 (n=69)	**Stivarga** (Regorafenib) (24%) **Vectibix** (Panitumumab) (9%) **Avastin** (Bevacizumab)/IRIS (9%) N=1,714 (n=33)

Competitive Heat Map and Emerging Therapies

The molecules that are already marketed, registration seeking, or FDA breakthrough/ Fast track designation are included in the competitive heat map.

In the current heat map, therapies in US, EU+UK and Japan include –

For no mutation

- Avastin – It is being marketed as first and second line drug in combination Fluorouracil or fluoropyrimidine based chemotherapies
- Stivarga – It is currently being marketed for third line treatment or beyond
- Lonsurf – Is currently marketed as a third line drug. It is also under trials for use of Lonsurf in combination with Avastin (Bevacizumab) in the SOLSTICE trial (Phase III). Another clinical trial use of Lonsurf with Avastin as the third line medication is also underway (SUNLIGHT trial, Phase III)
- Cyramza – Is currently being marketed as second line treatment in combination with FOLFIRI
- Opdivo – Is currently under trial (CheckMate 9X8, Phase III) to use in combination with SOC (Oxaliplatin, Leucovorin, Fluorouracil and Bevacizumab)
- Zaltrap (aflibercept) – It is being marketed in combination with FOLFIRI
- Arfolitixorin – It is in phase III clinical trial (AGENT) for use with combination with SOC
- Olaparib – It is in trial with combination with bevacizumab in phase III clinical trial (LYNK-003)
- Fruquintinib – It is a approved therapy which is being marketed for treatment of colorectal cancer. In addition, it is also in clinical trials for use in third line medication and beyond (FRESCO-2)

Agent	ROA & MOA	1st Line	2nd Line	3rd line and Beyond
AVASTIN (bevacizumab) Roche	IV VEGF TKI	MARKETED IN US, EU, JP Bevacizumab with fluorouracil-based chemotherapy (AVF2107g: ▲ +)	MARKETED IN US, EU, JP Bevacizumab with fluoropyrimidine-based therapy OR with 5-FU + FOLFOX4 (ML18147, E3200: ▲+)	
STIVARGA (regorafenib) Bayer	Oral multikinase inhibitor			MARKETED IN US, EU, JP Regorafenib with tipiracil (CORRECT: ▲ +)
LONSURF (trifluridine and tipiracil) Taiho Oncology	Oral nucleoside analog and thymidine phosphorylase inhibitor	Phase III Lonsurf + bev vs. capecitabine + bev; ineligible for IC (SOLSTICE: ▲⃠)		MARKETED IN US, EU, JP Trifluridine with tipiracil (RECOURSE: ▲ +) Phase III Lonsurf + bev vs. Lonsurf; 3L (SUNLIGHT: ▲)
CYRAMZA (ramucirumab) BMS	IV VEGFR2		MARKETED IN US, EU, JP Ramucirumab with FOLFIRI (RAISE: ▲ +)-2L	
OPDIVO (nivolumab) BMS	IV PD-1	Phase II/III in combination with SoC v. SoC (CheckMate-9X8) ⃠		
ZALTRAP (ziv-aflibercept) Sanofi	IV VEGF inhibitor		MARKETED IN US, EU, JP ziv-aflibercept with FOLFIRI (VELOUR: ▲ +)	
Arfolitixorin (Isofol Medical AB) (FTD)	Folate-based 5-FU Enhancer	Ph III: AGENT Arfo+SOC (ARFOX) vs. leucovorin+SOC (mFOLFOX-6)		
Olaparib (AstraZeneca)	PARP Inhibitor	Ph III: LYNK-003 Ola ± bev (1L maintenance following response to 1L therapy) vs. SOC		
Fruquintinib (Hutchison)	VEGF Inhibitor			Ph III: FRESCO-2 Fru + BSC vs. Placebo (FTD) Post-Lonsurf or post-Stivarga

▲ randomized SA single agent + met 1° endpoint ⃠ did not meet 1° endpoint

APPROVED Phase III Phase II

For RAS WT mutation

- ERBITUX (cetuximab) – It is a marketed used in combination with FOLFIRI in the first line and as a single agent in second line medication
- VECTIBIX (panitumumab) – Marketed therapy used in combination with FOLFOX as first line therapy and as monotherapy as second line treatment

Agent	ROA & MOA	1st Line	2nd Line	3rd line and Beyond
ERBITUX (cetuximab) Eli Lilly	IV EGFR	MARKETED IN US, EU, JP Cetuximab in combination with FOLFIRI (CRYSTAL: ▲ +)	MARKETED IN US, EU, JP SA (CA225-025: ▲ +)	
VECTIBIX (panitumumab) Amgen	IV EGFR	MARKETED IN US, EU, JP Vectibix with FOLFOX (20050203: ▲ +)	MARKETED IN US, EU, JP Vectibix as monotherapy or with best supportive care (20100007: ▲ +)	

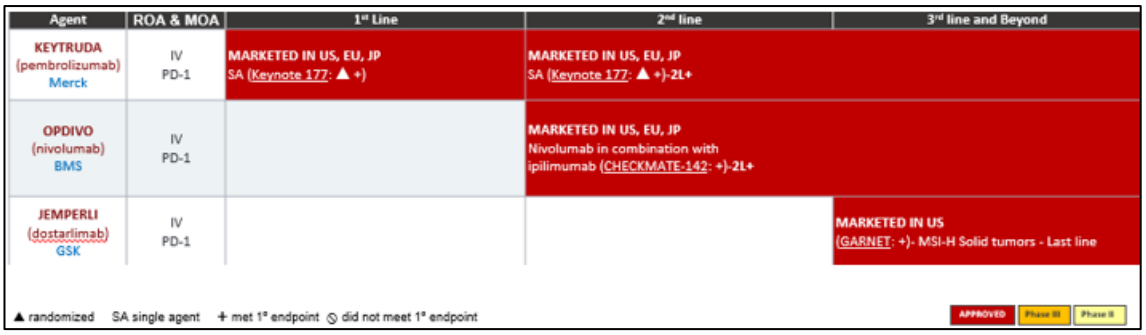
▲ randomized SA single agent + met 1° endpoint ⃠ did not meet 1° endpoint

APPROVED Phase III Phase II

For MSI-High

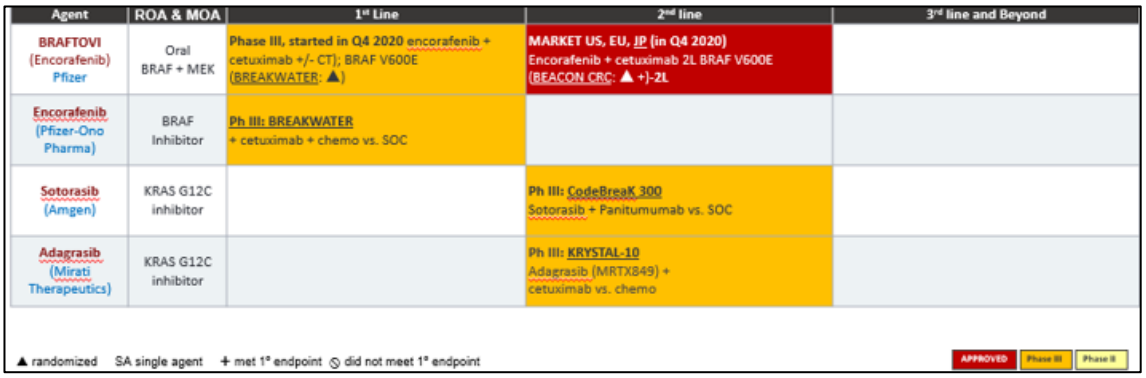
- KEYTRUDA (pembrolizumab) – Is the drug of choice for first line treatment and beyond as a single agent

- Opdivo (nivolumab) – It is marketed therapy used in second line treatment and beyond.
- Jemperli (dostarlimab) – It is the drug of choice for third line therapy in colorectal cancer



For BRAF/ RAS mutation

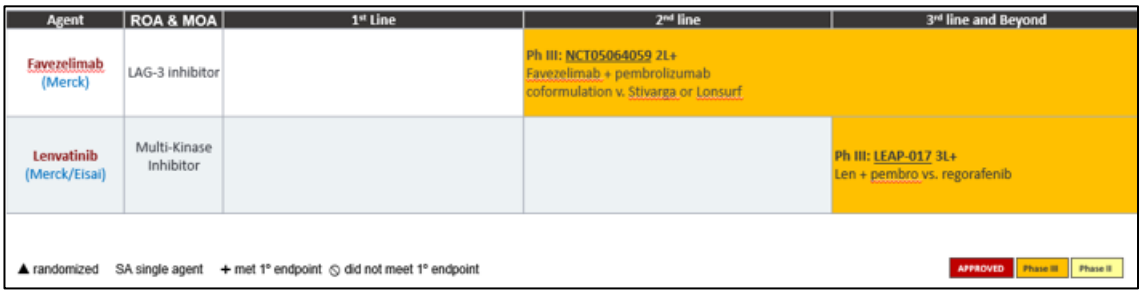
- BRAFTOVI (Encorafenib) – It is a approved and marketed second line therapy. For the use as first line therapy, it is currently under phase III randomized trial (BREAKWATER)
- Sotorasib – It is a drug currently under phase III trial (CodeBreak 300). It is checked for use with Panitumumab vs. SOC (Oxaliplatin, Leucovorin, Fluorouracil and Bevacizumab)
- Adagrasib – It is also a molecule under trial. It is currently in phase III trial (KRYSTAL-10) for used in combination with cetuximab



For MSS mutation

- Favezelimab – It is in phase II trial (NCT05064059) for use with pembrolizumab for use of second line and beyond as compared to Stivarga or Lonsurf

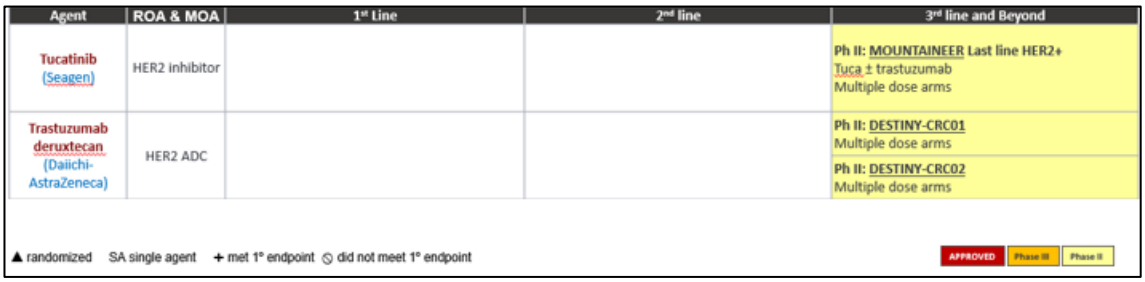
- Lenvatinib – It is in phase III trial (LEAP-017) for use with pembrolizumab for third line treatment and beyond as compared to regorafenib



For HER2+ mutation

The treatment of HER2+ colorectal cancer poses a challenge to treat. There are currently two molecule that are in trial phase for the use of the medication in HER2+ mutation

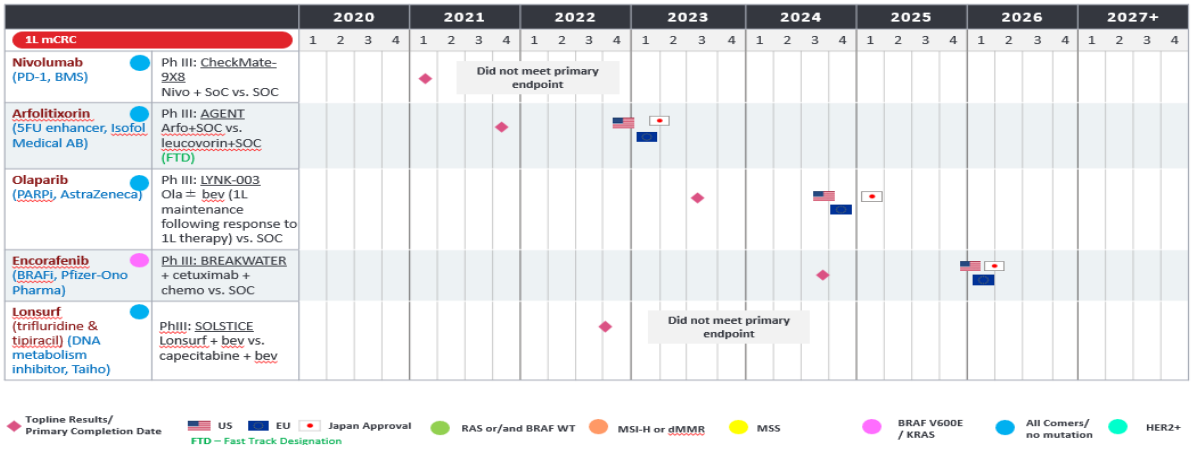
- Tucatinib – It is a HER2 inhibitor. Currently in phase II trial (MOUNTAINEER). It is trialed for use with trastuzumab and to be used as last line therapy in case of HER2+ is diagnosed
- Trastuzumab deruxtecan – There are currently two-phase II study trials underway for this molecule (DESTINY-CRC01)(DESTINY-CRC02)

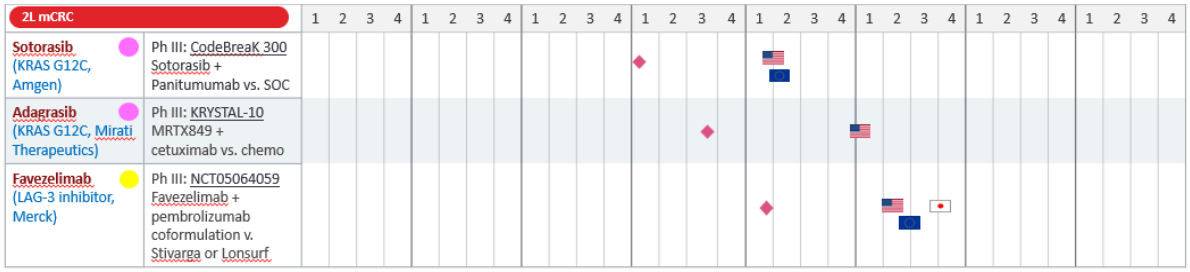


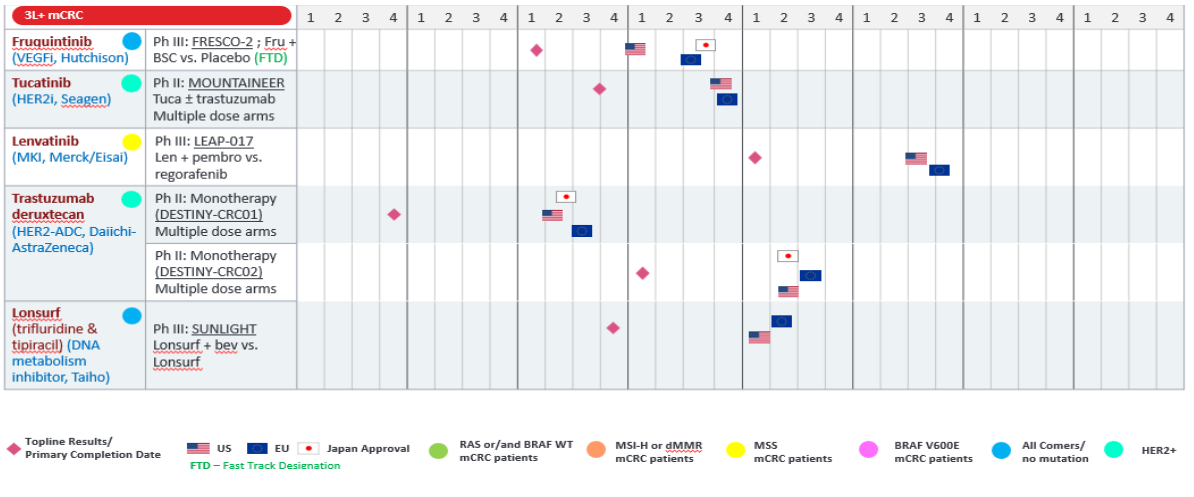
Competitive timeline for current and emerging therapies

The competitive timeline highlights the molecules which are currently under development which has received FDA breakthrough/ fast track designation or registration-seeking molecules. The FDA approval follows first marketing in the US. Following the approval from FDA then results are submitted to the European Medicines Agency (EMA) which provides the approval of the molecules in EU+UK with the next quarter of a year. The Pharmaceuticals and Medical Devices Agency (PMDA) is the regulatory agency in Japan. Approval will the PMDA also correlates with the European approval.

The molecules in the competitive timelines for first, second- and third-line treatment of colorectal cancer are listed in the figure below:


2020
2021
2022
2023
2024
2025
2026
2027+
1 2 3 4
1L mCRC
Nivolumab (PD-1, BMS)
Ph III: CheckMate-9X8 Nivo + SoC vs. SOC
Did not meet primary endpoint
Arfolitixorin (SFU enhancer, Isofol Medical AB)
Ph III: AGENT Arfo+SOC vs. leucovorin+SOC (FTD)
Olaparib (PARPi, AstraZeneca)
Ph III: LYNK-003 Ola ± bev (1L maintenance following response to 1L therapy) vs. SOC
Encorafenib (BRAFi, Pfizer-Ono Pharma)
Ph III: BREAKWATER + cetuximab + chemo vs. SOC
Lonsurf (trifluridine & tipiracil) (DNA metabolism inhibitor, Taiho)
PhIII: SOLSTICE Lonsurf + bev vs. capecitabine + bev
Did not meet primary endpoint
Topline Results/ Primary Completion Date
US
EU
Japan Approval
FTD – Fast Track Designation
RAS or/and BRAF WT
MSI-H or dMMR
MSS
BRAF V600E / KRAS
All Comers/ no mutation
HER2+


2L mCRC
1 2 3 4
Sotorasib (KRAS G12C, Amgen)
Ph III: CodeBreaK 300 Sotorasib + Panitumumab vs. SOC
Adagrasib (KRAS G12C, Mirati Therapeutics)
Ph III: KRYSTAL-10 MRTX849 + cetuximab vs. chemo
Favezelimab (LAG-3 inhibitor, Merck)
Ph III: NCT05064059 Favezelimab + pembrolizumab coformulation v. Stivarga or Lonsurf


3L+ mCRC
1 2 3 4
Fruquintinib (VEGFi, Hutchison)
Ph III: FRESCO-2 ; Fru + BSC vs. Placebo (FTD)
Tucatinib (HER2i, Seagen)
Ph II: MOUNTAINEER Tuca ± trastuzumab Multiple dose arms
Lenvatinib (MKI, Merck/Eisai)
Ph III: LEAP-017 Len + pembro vs. regorafenib
Trastuzumab deruxtecan (HER2-ADC, Daiichi-AstraZeneca)
Ph II: Monotherapy (DESTINY-CRC01) Multiple dose arms
Ph II: Monotherapy (DESTINY-CRC02) Multiple dose arms
Lonsurf (trifluridine & tipiracil) (DNA metabolism inhibitor, Taiho)
Ph III: SUNLIGHT Lonsurf + bev vs. Lonsurf
Topline Results/ Primary Completion Date
US
EU
Japan Approval
FTD – Fast Track Designation
RAS or/and BRAF WT mCRC patients
MSI-H or dMMR mCRC patients
MSS mCRC patients
BRAF V600E mCRC patients
All Comers/ no mutation
HER2+

Other pipeline therapies in colorectal cancer

Product	Interventional Arms	Company	Disease Area	Line of Treatment	Developmental Phase	Trial ID
AlloStim	**Single arm:** AlloStim	Immunovative Therapies	MSS/pMMR mCRC	3L	Phase IIb	NCT04444622
RXC-004	**Arm 1**: RXC-004 mono **Arm 2:** RXC004 + nivolumab	Redx	MSS/pMMR mCRC	2L+	Phase II	NCT04907539
Vicriviroc	**Multiple dose arms**: Vicri+Pembro	Merck & Co.	MSS/pMMR mCRC	3L+	Phase II	NCT03631407
GRT-C901/GRT-R902 +PD-1	**Experimental arm**: GRT-C901 + GRT-R902 + Atezo+ Bev+ ipili + SOC **Comparator arm**: SOC	Gritstone Bio	MSS/pMMR mCRC	1L	Phase II/III	NCT05141721
Belzutifan	**Single arm:** Pembrolizumab + Belzutifan + Lenvatinib	Merck & Co.	Non-MSI-H/dMMR mCRC	3L+	Phase II	NCT04976634
Trilaciclib	**Experimental arm :** Trilaciclib + FOLFOXIRI/bevacizumab **Comparator arm:** placebo + FOLFOXIRI/bevacizumab	G1 Therapeutics	MSS/pMMR mCRC	1L	Phase III	NCT04607668
Tepotinib	**Single arm:** Tepotinib + Cetuximab	EMD Serono	MET+	1L	Phase II	NCT04515394

Emerging Treatment Algorithms

Multiple development in the treatment of colorectal cancer is still ongoing to better tackle the disease. These upcoming treatment paradigms are for early-stage as well as the late-stage colorectal cancer.

The table below shows the emerging therapies that are under clinical trial.

Clinical Phase	Emerging Therapies	Mechanism of Action
Phase III	Fluquintinib (Hutchison)	VEGFR inhibitor
	Adagrasib (Mirati therapeutics)	KRAS inhibitor
	Arfolitixorin (Isofol)	Thymidylate synthase inhibitors
	Sotorasib (Amgen)	KRAS G12C inhibitors
	Olaparib (Merck/ AstraZeneca)	Oral PARP
Phase II	Tucatinib (Seagen)	HER2 inhibitor
	Trastuzumab deruxetan (AstraZeneca)	HER2-ADC

Early stage

If the tumor is surgically unresectable, then surgical resection is done and then followed up by treatment with FOLFIRI ± bevacizumab or aflibercept or Cyramza (ramucirumab)

If the tumor is resectable, surgical intervention is followed by treatment with FOLFOX/ CAPOX/ capecitabine or 5FU/ leucovorin. In case of the tumor size being large but has not spread to other system, treatment is done with FOLFOX/ CAPOX/ capecitabine or 5FU/ leucovorin. After the reduction in the size of the tumor surgical resection is done followed by the treatment with FOLFOX/ CAPOX/ capecitabine or 5FU/ leucovorin

Late Stage

Generally, late stage presents as unresectable cases. Medical treatment plays a crucial role in the treatment of such cases.

- **For first line treatment**
  - For All comers (No Specified mutation) - CAPEOX/FOLFIRI/5-FU/FOLFOX ± bevacizumab. there are 3 trials that are ongoing –
    - Nivolumab + SOC (CheckMate 9X8), Phase III
    - Trifluridine + tipiracil + bevacizumab (SOLSTICE), phase III
    - Olaparib ± bevacizumab (LYNK-003), phase III

- For RAS/ BRAF WT mutation - Chemo ± cetuximab or panitumumab. For future treatment, trilaciclib + FOLFOXIRI/ bevacizumab (PRESERVE1) is currently in phase III clinical trial
- For BRAF V600E mutation – Currently there is no specific treatment for the mutation. There are 2 ongoing clinical trials ongoing –
  - Encorafenib + cetuximab + chemotherapy (Phase-III)
  - binimetinib + encorafenib + cetuximab (ANCHOR-CRC)
- For MSI- High and HER2+ cases there is no ongoing clinical trials, use of the already available medications for the treatment is the only possibility

- **For second line treatment**
  - For KRAS mutation – There are currently two ongoing clinical trials for the indication
    - Adagrasib + cetuximab (KRYSTAL-10)
    - Sotorasib + panitumumab (CodeBreak 300)
  - There is no current development for second line treatment for BRAF V600E, HER2+, MSI-High and RAS/ BRAF WT mutations. Use of already available treatment paradigm is used for the treatment

- **For third line treatment**
  - For MSI-H or dMMR and RAS/BRAF WT –
    - Trifluridine + tipiracil or regorafenib is currently in use for the treatment
    - Fruquintinib (FRESCO-2)
    - Another potential future treatment for Ras/ BRAF WT/ BRAF V600E is Lenvatinib + pembrolizumab (LEAP-017)
  - For treatment on HER2/ RAS/ BRAF WT there are currently three molecules that are under trial –
    - Trastuzumab Deruxtecan (DESTINY-CRC01)
    - Trastuzumab Deruxtecan (HER2-overexpressing) (DESTINY-CRC02)
    - Tucatinib ± Trastuzumab (Phase II)

Current Clinical Benchmarks

For All comers

First-line Regimens	Trial Description	Efficacy		Safety
AVASTIN (bevacizumab) **(with fluorouracil-based chemotherapy)** *(VEGF inhibitor)* patients with metastatic colorectal cancer (mCRC)	AVF2107g N=923 (Experimental arm n=402)	Median follow-up: Not Reported (NR) mOS=20.3 mos mPFS=10.6 mos ORR=45% mDOR=10.4 mos	Comparator arm: Placebo with bolus-IFL mOS=15.6 mos mPFS=6.2 mos ORR=35% mDOR=7.1 mos	Most common Grade 3/4 AEs, (n=392): Leukopenia (37%), Neutropenia (21%), Hypertension (12%), Deep Vein Thrombosis (9%), Intra-abdominal Thrombosis (3%), Syncope (3%)
Second-line Regimens	**Trial Description**	**Efficacy**		**Safety**
AVASTIN (bevacizumab) **(with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin)** *(VEGF inhibitor)* patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab-containing regimen	ML18147 N=820 (Experimental arm n=409) EU, Saudi Arabia Primary Endpoint: OS	Median follow-up: NR mOS=11.2 mos mPFS=5.7 mos	Comparator arm: Chemotherapy mOS=9.8 mos mPFS=4.0 mos	Most common Grade 3-5 AEs: Neutropenia (16%), Diarrhea (10%), Asthenia (6%)
AVASTIN (bevacizumab) *(VEGF inhibitor)* **(with 5-FU + FOLFOX4)** patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab-containing regimen	Study E3200 N=829 (Experimental arm n=286) United States Primary Endpoint: OS	Median follow-up: NR mOS=13 mos mPFS=7.3 mos		Most common Grade 3/4 AEs: Sensory Neuropathy (17%), Hemorrhage (5%), Neurological Disorder (5%), Ileus (4%)

Second-line Regimens	Trial Description	Efficacy		Safety
ZALTRAP (ziv-aflibercept) **(with fluorouracil, leucovorin, irinotecan) (FOLFIRI)** *(VEGF Inhibitor)* patients with mCRC that are resistant to or have progressed following an oxaliplatin-containing regimen	VELOUR N=1,226 (Experimental arm n=612) Globally Primary Endpoint: OS	Median follow-up: NR mOS=13.50 mos mPFS=6.90 mos ORR=19.8% (16.4%, 23.2%)	Comparator arm: Placebo/FOLFIRI mOS=12.06 mos mPFS=4.67 mos ORR=11.1% (8.5%, 13.8%)	Most common Grade 3/4 AEs, (n=611): Leukopenia (16%), Neutropenia (37%), Thrombocytopenia (3%), Hypertension (41%), Proteinuria (8%) Deaths, n (%)=403/612 (65.8%)
CYRAMZA (ramucirumab) **(with FOLFIRI)** *(VEGFR2 Inhibitor)* Patients who had mCRC with disease progression on or after therapy with bevacizumab, oxaliplatin and a fluoropyrimidine	RAISE N=1,072 (Experimental arm n=536) Globally Primary Endpoint: OS	Median follow-up: NR mOS=13.3 (12.4, 14.5) mos mPFS=5.7 (5.5, 6.2) mos	Comparator arm: Placebo + FOLFIRI mOS=11.7 (10.8, 12.7) mos mPFS=4.5 (4.2, 5.4) mos	Most common Grade ≥3 AEs, (n=529): Neutropenia (59%), Thrombocytopenia (28%), Hypertension (26%), Proteinuria (17%) Deaths, n (%)=372/536 (69%)
Third-line Regimens	**Trial Description**	**Efficacy**		**Safety**
STIVARGA® (regorafenib) **(with tipiracil)** *(inhibits VEGFR2 and 3)* For patients with mCRC who have taken previous therapies and are RAS wildtype	CORRECT N=746 (Experimental arm n=505) Globally Primary Endpoint: OS	Median follow-up: NR mOS=6.4 mos mPFS=2.0 mos ORR = 1%	Comparator arm:Placebo mOS= 5.0 mos mPFS=1.7 mos ORR = 0.4%	Most common AEs, (n=500): Grade ≥3: Hemorrhage (21%) Grade 3: Anemia (5%), Lymphopenia (9%), Thrombocytopenia (2%) Grade 4: Anemia (1%)
LONSURF (trifluridine and tipiracil) *(nucleoside analog and thymidine phosphorylase inhibitor)* For patients with mCRC who have taken previous therapies and are RAS wildtype	RECOURSE N=800 (Experimental arm n=534) Globally Primary Endpoint: OS	Median follow-up: NR mOS=7.1 (6.5, 7.8) mos PFS no. of events= 88%	Comparator arm:Placebo mOS=5.3 (4.6, 6.0)mos PFS no. of events= 94%	Most common Grade 3/4 AEs, (n=533): Anemia (18%), Neutropenia (38%), Thrombocytopenia (5%)

For RAS WT

First-line Regimens	Trial Description	Efficacy		Safety
ERBITUX® (cetuximab) **(in combination with FOLFIRI)** *(EGFR Inhibitor)* indicated for the treatment of K-Ras wild-type, EGFR-expressing for mCRC	CRYSTAL N=1,217 (Experimental arm n=608) Globally Primary Endpoint: PFS	Median follow-up: NR All Randomized: mOS=19.6 mos, mPFS=8.9 mos, ORR=46% K-Ras Wild-type(n=320): mOS=23.5 mos mPFS=9.5 mos, ORR=57% Ras Mutant(n=216): mOS=16 mos mPFS=7.5 mos, ORR=31%	Comparator arm: FOLFIRI All Randomized: mOS=18.5mos, mPFS=8.1 mos, ORR=38% K-Ras Wild-type(n=320): mOS=23.5 mos mPFS=8.1 mos, ORR=39% K-Ras Mutant(n=187): mOS=16.7 =mos mPFS=8.2 mos, ORR=35%	Most common Grade 3/4 AEs, (n=317): Neutropenia (31), Conjunctivitis (<1), Diarrhea (16), Acne-like Rash (18)
VECTIBIX® (panitumumab) **(first-line in combination with FOLFOX)** *(EGFR antagonist)* indicated for the treatment of wild-type RAS defined as wild-type in both KRAS and NRAS mCRC	20050203 N=656 (Experimental arm n=325) Globally Primary Endpoint: PFS	Median follow-up: NR Wild-type KRAS mCRC: mPFS=9.6 mos ORR=54% Wild-Type RAS mCRC(n = 259) mPFS=10.1 mos ,mOS=25.8 mos ,ORR=58%	Comparator arm: FOLFOX Wild-type KRAS mCRC: mPFS=8.0 mos ORR=47% Wild-Type RAS mCRC(n = 253) mPFS=7.9 mos ,mOS=20.2 mos ,ORR=45%	Most common Grade 3/4 AEs, (n=322): Conjunctivitis (2%), Hypokalemia (10%), Acneiform Dermatitis (10%), Rash (17%), Paronychia (3%)
Second-line Regimens	**Trial Description**	**Efficacy**		**Safety**
ERBITUX® (cetuximab) **(as single agent)** *(VEGF Inhibitor)* indicated for the treatment of K-Ras wild-type, EGFR-expressing patients with mCRC who have failed chemotherapy	CA225-025 N=572 (Experimental arm n=287) Australia and Canada Primary Endpoint: OS	Median follow-up: NR All Randomized: mOS=6.1 mos K-Ras Wild-type: mOS=8.6 mos K-Ras Mutant: mOS=4.8 mos	Comparator arm: BSC All Randomized: mOS=4.6 mos K-Ras Wild-type: mOS=5.0 mos K-Ras Mutant: mOS=4.6 mos	Most common Grade 3/4 AEs, (n=118): Rash/Desquamation (16%), Dyspnea (16%), Pain-Other (18%)
VECTIBIX® (panitumumab) **(monotherapy or with BSC)** (EGFR antagonist) indicated for the treatment of wild-type RAS defined as wild-type in both KRAS and NRAS recurrent or refractory mCRC	20100007 N=377 (Experimental arm n=189) Globally Primary Endpoint: OS	Median follow-up: 41 weeks K-Ras Wild-type (n=189): mOS=10.0 mos, mPFS=3.6 mos, ORR=27% Wild-type RAS Mutant (n=142): mOS=10.0 mos mPFS=5.2 mos, ORR=31%	Comparator arm: BSC K-Ras Wild-type (n=189): mOS=7.4 mos, mPFS=1.7 mos, ORR=1.6% Wild-type RAS Mutant (n=142): mOS=6.9 mos mPFS=1.7 mos, ORR=2.3%	Most common Grade 3/4 AEs: Hypomagnesemia (6%), Skin Rash (6%) and Dermatitis Acneiform (6%) Number of deaths (%): K-Ras Wild-type=136/189 (72) Wild-type RAS Mutant=104/142 (73)

Third-line Regimens	Trial Description	Efficacy		Safety
STIVARGA® (regorafenib) **(with tipiracil)** *(inhibits VEGFR2 and 3)* for patients with mCRC who have taken previous therapies and are RAS wildtype	CORRECT N=746 (Experimental arm n=505) Globally Primary Endpoint: OS	Median follow-up: NR mOS=6.4 mos mPFS=2.0 mos ORR =1%	Comparator arm:Placebo mOS= 5.0 mos mPFS=1.7 mos ORR = 0.4%	Most common AEs, (n=500): Grade ≥3: Hemorrhage (21%) Grade 3: Anemia (5%), Lymphopenia (9%), Thrombocytopenia (2%) Grade 4: Anemia (1%)
LONSURF (trifluridine and tipiracil) *(nucleoside analog and thymidine phosphorylase inhibitor)* for patients with mCRC who have taken previous therapies and are RAS wildtype	RECOURSE N=800 (Experimental arm n=534) Globally Primary Endpoint: OS	Median follow-up: NR mOS=7.1 (6.5, 7.8) mos PFS no. of events= 88%	Comparator arm:Placebo mOS=5.3 (4.6, 6.0)mos PFS no. of events= 94%	Most common Grade 3/4 AEs, (n=533): Anemia (18%), Neutropenia (38%), Thrombocytopenia (5%)

For MSI-High

First-line Regimens	Trial Description	Efficacy		Safety
KEYTRUDA® (pembrolizumab) *(PD-1 inhibitor as a single agent)* for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer	Keynote 177 N=307 (Experimental arm n=153) Globally Primary Endpoints: PFS, OS	Median follow-up: 32.4 mos mPFS=16.5 (5.4, 32.4) mos ORR=44%, mDOR=NR, mOS=NR (49.2, NR)	Comparator arm: Chemotherapy mPFS=8.2 (6.1, 10.2) mos ORR=33%, mDOR=10.6, mOS=36.7 (27.6, NR)	AEs occurring in pts with MSI-H or dMMR CRC were similar to those occurring in 2,799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent Grade 3 Incidence (%): Pneumonitis (0.9%), Colitis (1.1%), Hepatitis (0.4%)
Opdivo (nivolumab) *(PD-1 inhibitor as a single agent)* adult and pediatric (12 years and older) patients with MSI-H or dMMR mCRC that has progressed following treatment with chemo	#CHECKMATE-142 N=193 (Experimental arm n=74) Globally Primary Endpoint: ORR	Median follow-up: 33.7 mos (n=74); ORR=38% mDOR: ≥6months=86%, ≥12months=82%		Most common Grade 3/4 AEs, (n=74): Musculoskeletal Pain (1.4%), Rash (1.4%), Decreased Appetite (1.4%)
Opdivo (nivolumab) *(PD-1)* **+ ipilimumab** *(CTLA-4))* adult and pediatric (12 years and older) patients with MSI-H or dMMR mCRC that has progressed following treatment with chemo	#CHECKMATE-142 N=193 (Experimental arm n=119) Globally Primary Endpoint: ORR	Median follow-up: 27.5 mos ORR=60% mDOR: ≥6 months =89%, ≥12months=77%		Most common Grade 3/4 AEs, (n=119): Musculoskeletal Pain (3.4%), Rash (4.2%), Decreased Appetite (1.7%)
Second-line Regimens	**Trial Description**	**Efficacy**		**Safety**
KEYTRUDA® (pembrolizumab) *(PD-1 inhibitor as a single agent)* for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer	KEYNOTE-164 N=124 (n=63; Cohort B: for patients who previously received chemo and anti-VEGF/EGFR mAb) Globally Primary Endpoint: ORR	Median follow-up: 24.2mos ORR=33% mDOR=NR, mOS=NR mPFS=4.1mos		Treatment-related grade 3-4 adverse events occurred in 8 (13%) in cohort B
Opdivo (nivolumab) *(PD-1)* **+ ipilimumab** *(CTLA-4))* adult and pediatric (12 years and older) patients with MSI-H or dMMR mCRC that has progressed following treatment with chemo	CHECKMATE-142 N=193 (Experimental arm n=119) Globally Primary Endpoint: ORR	Median follow-up: 27.5 mos ORR=60% mDOR: ≥6 months =89%, ≥12months=77%		Most common Grade 3/4 AEs, (n=119): Musculoskeletal Pain (3.4%), Rash (4.2%), Decreased Appetite (1.7%)

For BRAF/ RAS

Second-line Regimens	Trial Description	Efficacy		Safety
BRAFTOVI® (encorafenib) **(in combination with cetuximab)** *(BRAF kinase inhibitor)* for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation	BEACON CRC N=441 (Experimental arm n=220) Globally Primary Endpoints: DLTs, AEs, OS, ORR	mOS=8.4 (7.5, 11.0) mos mPFS=4.2 (3.7, 5.4) mos ORR=20% (13%, 29%)	Comparator arm: Irinotecan with cetuximab or FOLFIRI with cetuximab mOS=5.4 (4.8, 6.6) mos mPFS=1.5 (1.4, 1.7) mos ORR=2% (13%, 29%)	Most common Grade 3/4 AEs, (n=119): Anemia (4%), Lymphopenia (7%), Increased Alkaline Phosphatase (4%)

CONCLUSION

The understanding of the research and trials suggested that the treatment of colorectal cancer is characterized by late diagnosis of the cancer as the symptoms are not evident before the progression of the disease to higher stages. It gives rise to mutations which significantly reduces the success of the treatment. The understanding about the mutations have got better and with it newer treatment combinations are being tested to tackle this challenge. With fewer treatment options available and for treatment of these mutations and level of clinical unmet need in the disease area mainly with the mutations that has suffered from a high rate of late-stage clinical trial failure, resulting in a lack of targeted treatment option further research and trials on these disease areas is going to bring more

treatment options that can tackle the disease burden better. A deeper understanding of the subject and attempts to trace the competitive landscape through the available literature and clinical trial registry databases were made in order to identify the treatment gaps and the potential upcoming therapies that can support the overall quality of life of the patients suffering from the disease.

The open-source data available aided in the identification of the epidemiology of the disease to understand the extent and probability of wide-spreading, risk factors, available treatments, and unmet needs. Hence, it directed the research toward the two major goals - the identification of potential upcoming therapies and the competitive timeline.

The potential upcoming therapies treatment paradigm was promising and included a variety of molecules that are currently under later development phases. It was evident that the current R&D efforts are not limited to a single stage or single mutation of the disease and were rather distributed in early as well as later stages covering wide varieties of mutations which are seen in CRC. The most study on treatment with Trilaciclib, Nivolumab, Olaparib, Trifluridine + tipiracil and Encorafenib for first line treatment; Adagrasib, sotorasib and Favezelimab for second line; and, Fruquinitib, Lenvatinib for third line treatment of these mutation are already showing promising results and coming down the line these treatments will help with the treatment paradigm.

The overall emerging treatment algorithm comprised of both novel MoAs as well as the ones that have extensively been studied not in colorectal cancer combination of two medications or with chemotherapy the future of this disease. Moreover, immuno-oncology drugs are being aggressively pursued suggesting that this could be a potential target for the market players who might be interested in getting into the space.

The investigators have attempted to flourish the therapy area and, in that attempt, around half a dozen molecules are aligned for receiving regulatory approval worldwide amongst the ones that were under the scope of the research. Notably, the timeline seems to be more constricted in the next four years. Hence, the research can support potential players in the market to identify the most suitable time for planning their launch in order to have minimum competitors and maximum market share.

The upcoming treatment paradigm identified thus indicating that the unmet needs can be met in near future. However, concerted R&D efforts are required to stratify CRC by predictive biomarkers, which can also reveal novel therapeutic approaches

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