Colorectal Cancer: Scientific and Competitive Landscape

Presented by – Arkodipto Mallick
MBA HM – 25
Under the guidance of Dr. Piyusha Majumdar

Introduction

- **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
  - Analytics Team
  - Primary Research Team
  - Software Team
  - Business Operations Team
- 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

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.

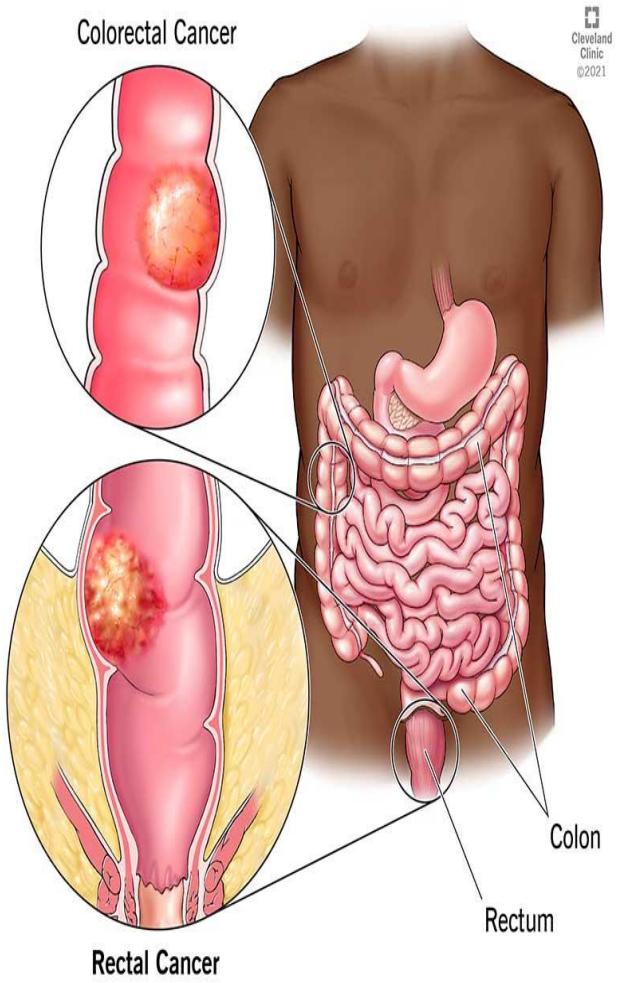
- **Data collection method:** Web-based data collection.

- **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

Disease Overview And Epidemiology

Disease Overview Colorectal Cancer (1/2)`



Description

- Colorectal cancer in the gastrointestinal tract starts as a growth, called a polyp, on the inner lining of the colon or rectum; some polyps are pre-cancerous, such as adenomatous polyps, sessile polyps and traditional serrated adenomas1. Most of the CRC (about 70%) tend to occur in the left side, whereas a small percentage (about 10%) occurs in the right side

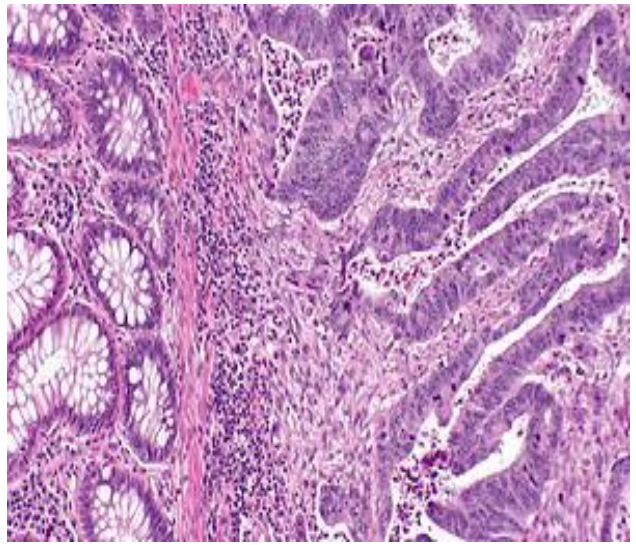
Onset/Risk Factors

- There are changeable lifestyle-related risk factors and non-changeable known risk factors for CRC1
  - Age: CRC is most common in people older than 50
  - 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 disease: 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[1]

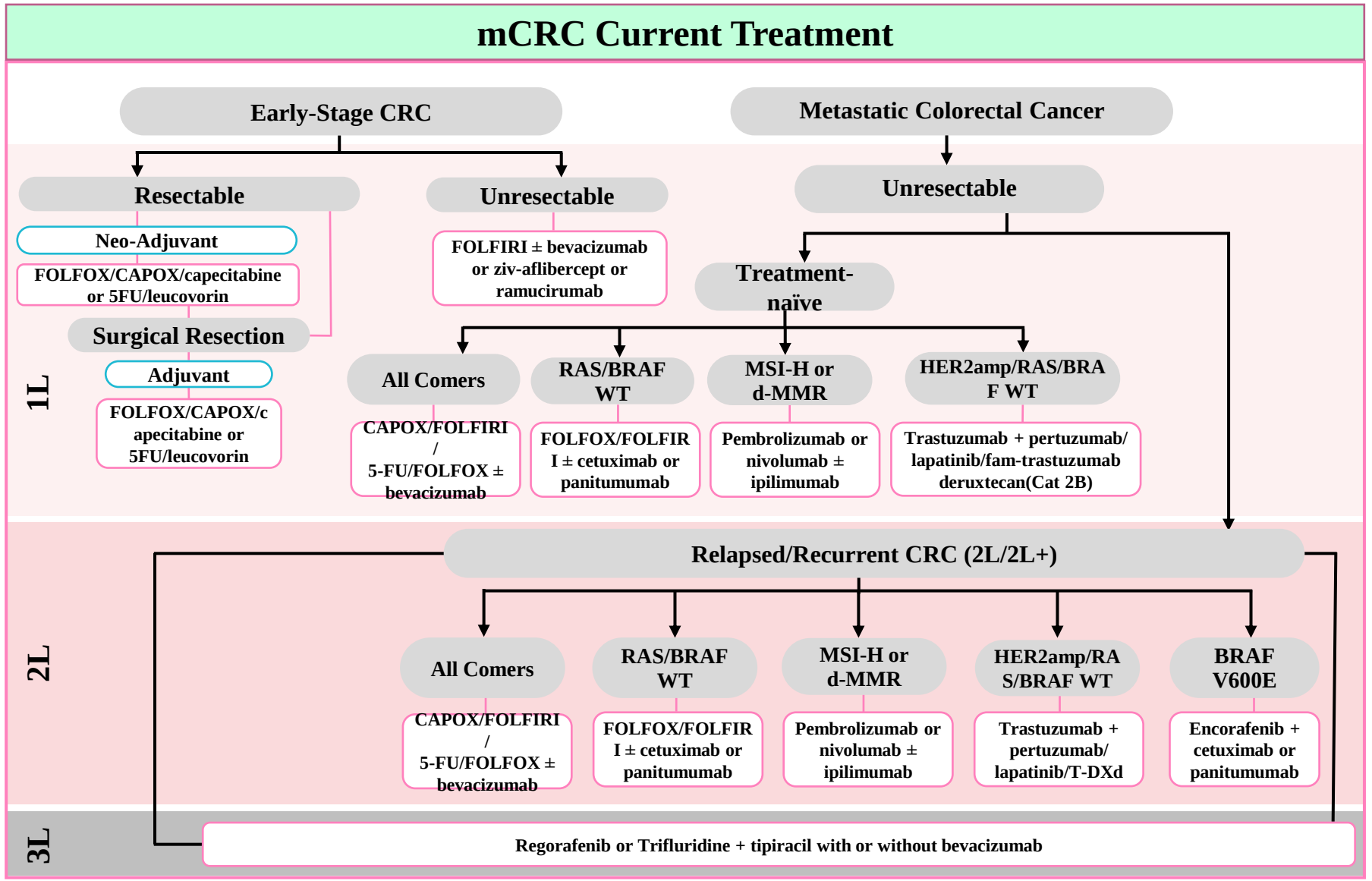
Disease Overview Colorectal Cancer (2/2)



Treatments	• Resectable, localized tumors can be removed either with surgery, a polypectomy, or a hemi, partial or segmental colectomy • Systemic part of 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 unresectable1
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, 14% for distant and 63% combined. For rectal cancer, the survival rate is 89% for localized disease, 72% for regional, 16% for distant and 67% combined
Unmet Needs	• Curative therapy for metastatic advanced CRC • Emotional, psychological and informational domain for the patient
Epidemiology	• Median age of diagnosis: 693 • Male predominance is seen in CRC4 • Estimated new cases in 2021: 149,500 (US), accounting for 7.9% of all new cancer cases5

Current Treatment Algorithm

Current Treatment Algorithm Overview for CRC



Sources: Top image: NCCN and ESMO

Treatment Paradigms – Colorectal Cancer

Most Commonly Used Regimens (MAT Ending September 2021)

	US	EU4+UK	JP
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)
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)
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)
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)

The treatment paradigms between the US, EU5 and Japan for metastatic CRC are similar among all lines

- In 1L patients in the US, EU5 and JP, bevacizumab/fluorouracil/oxaliplatin was among the top 3 regimens
- In 2L patients in the US, EU5 and JP, bevacizumab/fluorouracil/irinotecan was among the top 3 regimens
- In 3L patients in the US, EU5 and JP, regorafenib and trifluridine-tipiracil were among the top 3 regimens
- In 4L+ patients in the US, EU5 and JP, regorafenib and trifluridine-tipiracil were among the top 3 regimens

Abbreviations:
Fluorouracil/Oxaliplatin - **FOLFOX**
Fluorouracil/Irinotecan - **FOLFIRI**
Capecitabine/Oxaliplatin – **CAPOX**
Irinotecan/S-1 – **IRIS**
Capecitabine/Irinotecan – **CAPIRI**
Oxaliplatin/ S-1 - **SOX**

Treatment Paradigms – Colorectal Cancer – RAS WT

Most Commonly Used Regimens (MAT Ending September 2021)

	US	EU4+UK	JP
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)
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)
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)
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)

The treatment paradigms between the US, EU5 and Japan for metastatic CRC with RAS wild type are similar in later lines but differ in 1L
In 1L patients in the US and JP, bevacizumab/fluorouracil/oxaliplatin was among the top 3 regimens
In 2L patients in the US, EU5 and JP, bevacizumab/fluorouracil/irinotecan was among the top 3 regimens
In 3L patients in the US, EU5 and JP, regorafenib was among the top 3 regimens
In 4L+ patients in the US, EU5 and JP, trifluridine-tipiracil was among the top 3 regimens

Abbreviations:
Fluorouracil/Oxaliplatin - FOLFOX
Fluorouracil/Irinotecan - FOLFIRI
Capecitabine/Oxaliplatin – CAPOX
Irinotecan/S-1 – IRIS
Capecitabine/Irinotecan – CAPIRI
Oxaliplatin/ S-1 - SOX

Treatment Paradigms – Colorectal Cancer – RAS Mutant

Most Commonly Used Regimens (MAT Ending September 2021)

	US	EU4+UK	JP
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)
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)
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)
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)

The treatment paradigms between the US, EU5 and Japan for metastatic CRC with RAS mutant are similar among all lines
In 1L patients in the US, EU5 and JP, bevacizumab/fluorouracil/oxaliplatin and bevacizumab/fluorouracil/irinotecan were among the top 3 regimens
In 2L patients in the US, EU5 and JP, bevacizumab/fluorouracil/irinotecan was among the top 3 regimens
In 3L patients in the US, EU5 and JP, regorafenib and trifluridine-tipiracil were among the top 3 regimens
In 4L+ patients in the US, EU5 and JP, trifluridine-tipiracil and regorafenib were among the top 3 regimens

Abbreviations:
Fluorouracil/Oxaliplatin - FOLFOX
Fluorouracil/Irinotecan - FOLFIRI
Capecitabine/Oxaliplatin – CAPOX
Irinotecan/S-1 – IRIS
Capecitabine/Irinotecan – CAPIRI
Oxaliplatin/ S-1 - SOX

Treatment Paradigms – Colorectal Cancer – MSI - High

Most Commonly Used Regimens (MAT Ending September 2021)

	US	EU4+UK	JP
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)
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)
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)
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)

The treatment paradigms between the US, EU5 and Japan for metastatic CRC MSI-High are similar among 1L but differ in later lines
In 1L patients in the US, and EU5, bevacizumab/fluorouracil/oxaliplatin was among the top 3 regimens
In 2L patients in the US and JP, pembrolizumab was among the top 3 regimens
In 3L patients in the US, EU5 and JP, regorafenib was among the top 3 regimens
In 4L+ patients in the US and EU5, regorafenib was among the top 3 regimens

Abbreviations:
Fluorouracil/Oxaliplatin - FOLFOX
Fluorouracil/Irinotecan - FOLFIRI
Capecitabine/Oxaliplatin – CAPOX
Irinotecan/S-1 – IRIS
Capecitabine/Irinotecan – CAPIRI
Oxaliplatin/ S-1 - SOX

Treatment Paradigms – Colorectal Cancer – MSS

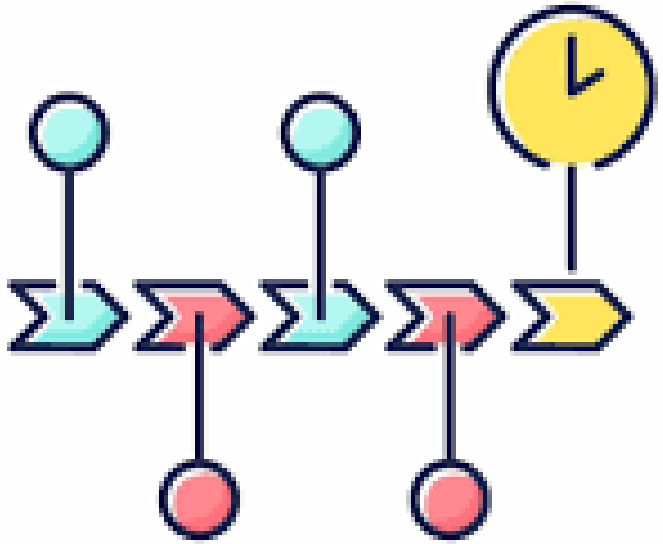
Most Commonly Used Regimens (MAT Ending September 2021)

	US	EU4+UK	JP
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)
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)
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)
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)

The treatment paradigms between the US, EU5 and Japan for metastatic CRC MS stable are similar among 1L and 2L but differ in later lines
In 1L patients in the US, EU5 and JP, bevacizumab/fluorouracil/oxaliplatin was among the top 3 regimens
In 2L patients in the US, EU5 and JP, bevacizumab/fluorouracil/irinotecan was among the top 3 regimens
In 3L patients in the US and EU5, regorafenib and trifluridine-tipiracil were among the top 3 regimens
In 4L+ patients in the US and EU5, trifluridine-tipiracil was among the top 3 regimens

Abbreviations:
Fluorouracil/Oxaliplatin - FOLFOX
Fluorouracil/Irinotecan - FOLFIRI
Capecitabine/Oxaliplatin – CAPOX
Irinotecan/S-1 – IRIS
Capecitabine/Irinotecan – CAPIRI
Oxaliplatin/ S-1 - SOX

Competitive Heat Map and Timeline



All Comers

Competitive Heat Map for Current & Emerging Therapies in mCRC

Marketed, registration-seeking, or FDA Breakthrough / Fast Track designation therapies (1/4)

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) ⃠		

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

APPROVED Phase III Phase II

All Comers

Competitive Heat Map for Current & Emerging Therapies in mCRC

Marketed, registration-seeking, or FDA Breakthrough / Fast Track designation therapies (1/4)

Agent	ROA & MOA	1st Line	2nd Line	3rd line and Beyond
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 1º endpoint ⦸ did not meet 1º endpoint

APPROVED | Phase III | Phase II

RAS WT

Competitive Heat Map for Current & Emerging Therapies in mCRC

Marketed, registration-seeking, or FDA Breakthrough / Fast Track designation therapies (1/4)

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 1º endpoint ⦸ did not meet 1º endpoint

APPROVED | Phase III | Phase II

MSI-High

Competitive Heat Map for Current & Emerging Therapies in mCRC

Marketed, registration-seeking, or FDA Breakthrough / Fast Track designation therapies (2/4)

Agent	ROA & MOA	1st Line	2nd line	3rd line and Beyond
KEYTRUDA (pembrolizumab) Merck	IV PD-1	**MARKETED IN US, EU, JP** SA (Keynote 177: ▲ +)	**MARKETED IN US, EU, JP** SA (Keynote 177: ▲ +)-**2L+**	
OPDIVO (nivolumab) BMS	IV PD-1		**MARKETED IN US, EU, JP** Nivolumab in combination with ipilimumab (CHECKMATE-142: +)-**2L+**	
JEMPERLI (dostarlimab) GSK	IV PD-1			**MARKETED IN US** (GARNET: +)- MSI-H Solid tumors - Last line

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

APPROVED | Phase III | Phase II

RAS-mutant

Competitive Heat Map for Current & Emerging Therapies in mCRC

Marketed, registration-seeking, or FDA Breakthrough / Fast Track designation therapies (2/4)

Agent	ROA & MOA	1st Line	2nd line	3rd line and Beyond
BRAFTOVI (Encorafenib) Pfizer	Oral BRAF + MEK	**Phase III, started in Q4 2020** encorafenib + cetuximab +/- CT); BRAF V600E (BREAKWATER: ▲)	**MARKET US, EU, JP (in Q4 2020)** Encorafenib + cetuximab 2L BRAF V600E (BEACON CRC: ▲ +)-**2L**	
Encorafenib (Pfizer-Ono Pharma)	BRAF Inhibitor	**Ph III: BREAKWATER** + cetuximab + chemo vs. SOC		
Sotorasib (Amgen)	KRAS G12C inhibitor		**Ph III: CodeBreaK 300** Sotorasib + Panitumumab vs. SOC	
Adagrasib (Mirati Therapeutics)	KRAS G12C inhibitor		**Ph III: KRYSTAL-10** Adagrasib (MRTX849) + cetuximab vs. chemo	

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

APPROVED | Phase III | Phase II

MSS

Competitive Heat Map for Current & Emerging Therapies in mCRC

Marketed, registration-seeking, or FDA Breakthrough / Fast Track designation therapies (2/4)

Agent	ROA & MOA	1st Line	2nd line	3rd line and Beyond
Favezelimab (Merck)	LAG-3 inhibitor		**Ph III: NCT05064059 2L+** Favezelimab + pembrolizumab coformulation v. Stivarga or Lonsurf	
Lenvatinib (Merck/Eisai)	Multi-Kinase Inhibitor			**Ph III: LEAP-017 3L+** Len + pembro vs. regorafenib

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

APPROVED | Phase III | Phase II

HER2+

Competitive Heat Map for Current & Emerging Therapies in mCRC

Marketed, registration-seeking, or FDA Breakthrough / Fast Track designation therapies (2/4)

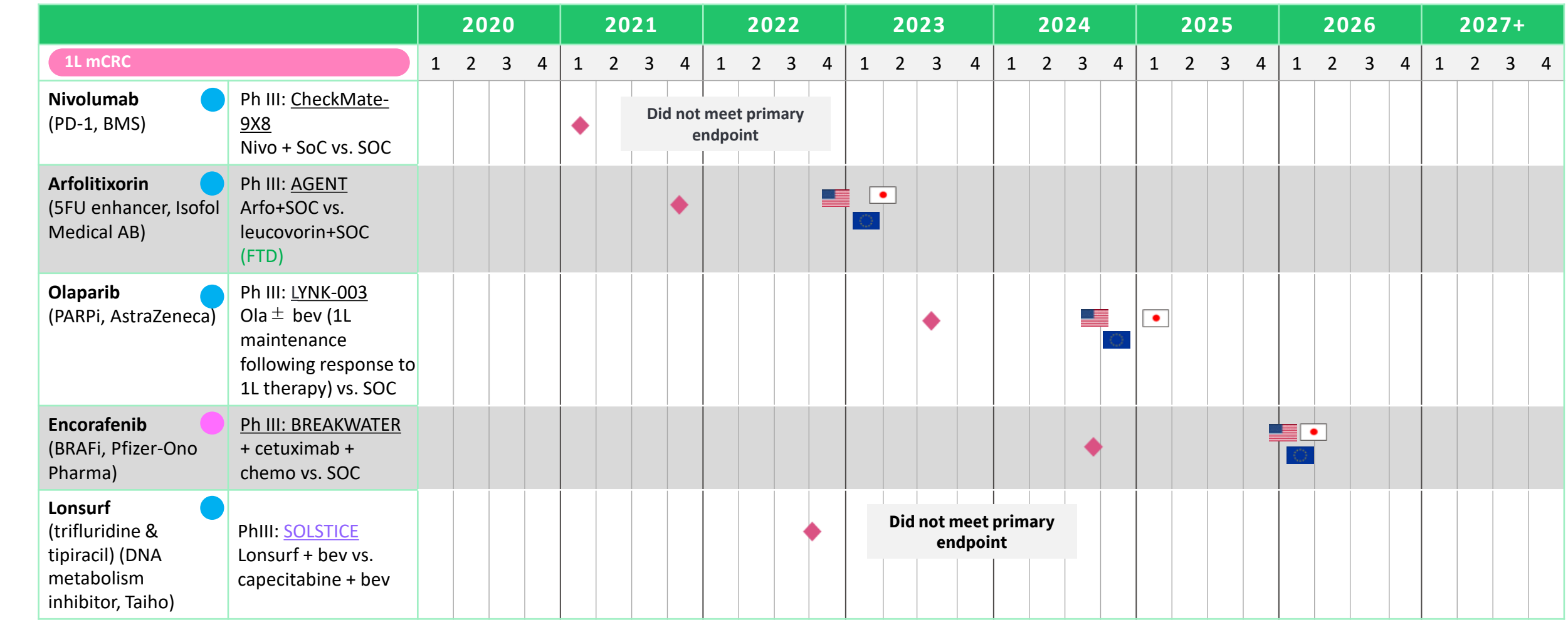
Agent	ROA & MOA	1st Line	2nd line	3rd line and Beyond
Tucatinib (Seagen)	HER2 inhibitor			**Ph II: MOUNTAINEER Last line HER2+** Tuca ± trastuzumab Multiple dose arms
Trastuzumab deruxtecan (Daiichi-AstraZeneca)	HER2 ADC			**Ph II: DESTINY-CRC01** Multiple dose arms
				Ph II: DESTINY-CRC02 Multiple dose arms

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

APPROVED | Phase III | Phase II

Competitive Timeline for Current & Emerging Therapies in mCRC

Registration-seeking, or FDA Breakthrough / Fast Track designation therapies (1/3)



Topline Results/ Primary Completion Date

US EU Japan Approval

FTD – Fast Track Designation

RAS or/and BRAF WT

MSI-H or dMMR

MSS

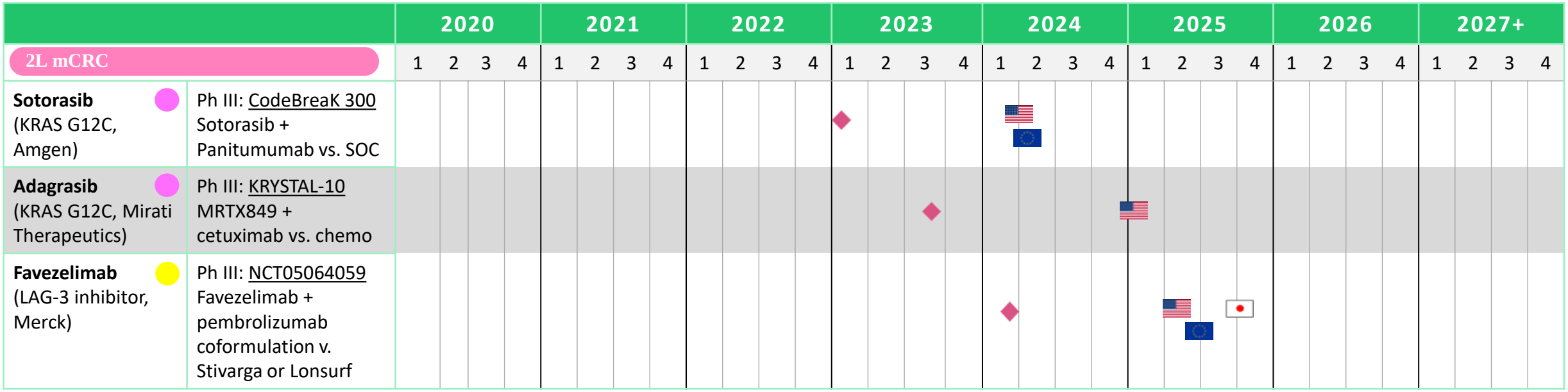
BRAF V600E / KRAS

All Comers/ no mutation

HER2+

Competitive Timeline for Current & Emerging Therapies in mCRC

Registration-seeking, or FDA Breakthrough / Fast Track designation therapies (2/3)



Topline Results/ Primary Completion Date

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FTD – Fast Track Designation

RAS or/and BRAF WT

MSI-H or dMMR

MSS

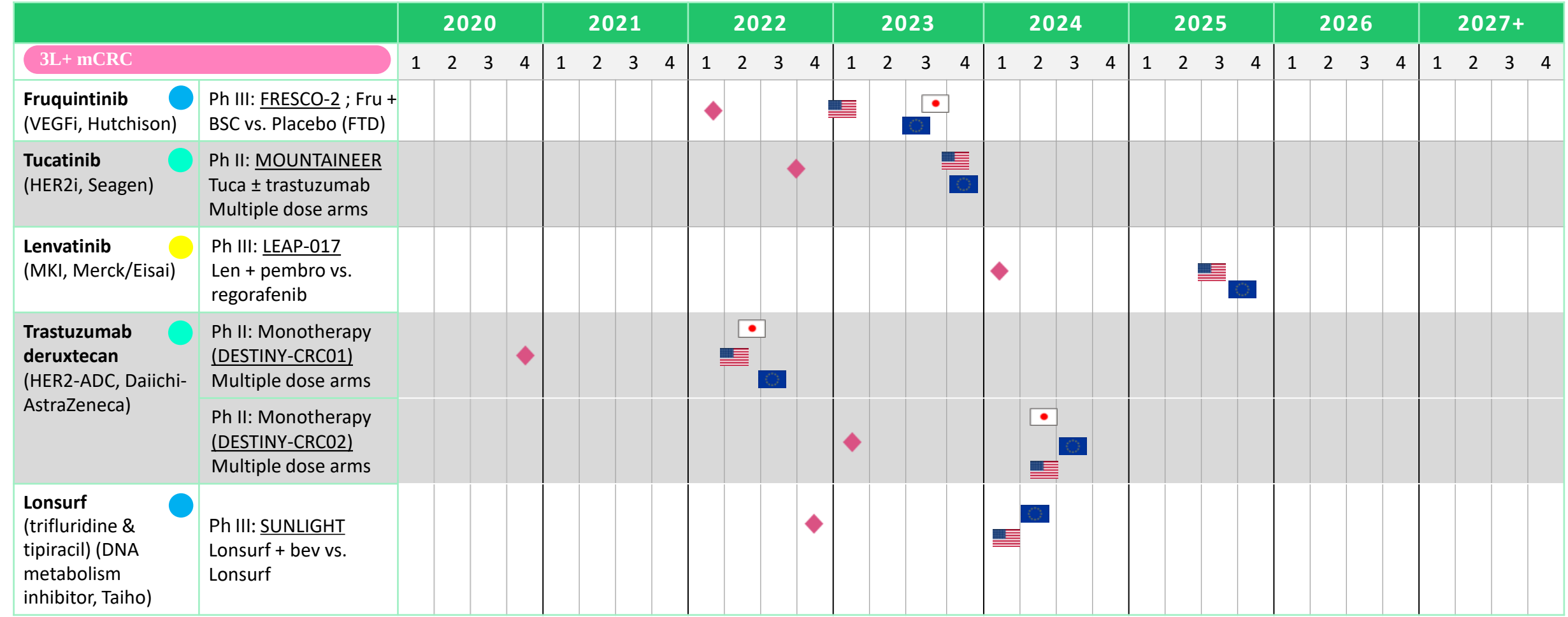
BRAF V600E / KRAS

All Comers/ no mutation

HER2+

Competitive Timeline for Current & Emerging Therapies in mCRC

Registration-seeking, or FDA Breakthrough / Fast Track designation therapies (3/3)



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+

Other Potential Upcoming Therapies

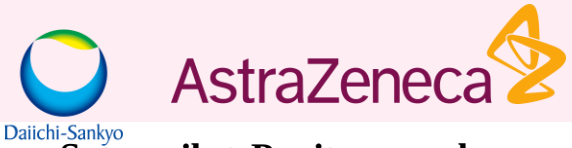
Non-registrational P2+ for new molecular or biologic entities

Product	Interventional Arms	Company	Disease Area	LoT	Developmental Phase	MoA	Trial ID
AlloStim	**Single arm:** AlloStim	Immunovative Therapies	MSS/pMMR mCRC	3L	Phase IIb	T-cell stimulant	NCT04444622
RXC-004	**Arm 1**: RXC-004 mono **Arm 2:** RXC004 + nivolumab	Redx	MSS/pMMR mCRC	2L+	Phase II	PORCN inhibitor	NCT04907539
Vicriviroc	**Multiple dose arms**: Vicri+Pembro	Merck & Co.	MSS/pMMR mCRC	3L+	Phase II	CCR5 antagonist	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	CD8+ T lymphocyte stimulants	NCT05141721
Belzutifan	**Single arm:** Pembrolizumab + Belzutifan + Lenvatinib	Merck & Co.	Non-MSI-H/dMMR mCRC	3L+	Phase II	EPAS protein 1 inhibitor	NCT04976634
Trilaciclib	**Experimental arm :** Trilaciclib + FOLFOXIRI/bevacizumab **Comparator arm:** placebo + FOLFOXIRI/bevacizumab	G1 Therapeutics	MSS/pMMR mCRC	1L	Phase III	CDK4/6 inhibitor	NCT04607668
Tepotinib	**Single arm:** Tepotinib + Cetuximab	EMD Serono	MET+	1L	Phase II	MET TKI inhibitors	NCT04515394

Recent Trial Data for Current & Emerging Therapies in metastatic Colorectal Cancer (1/2)

Agent / Company	LoT	MoA	Headline	Key Takeaways
Fruquintinib + BSC (FRESCO-2 Ph 3) Hutchison Medi Pharma	3L+	VEGF	Study of efficacy and safety of fruquintinib in patients with **metastatic colorectal cancer**	Results from previous FRESCO Ph 3 study: • **Efficacy** :ORR=4.7%, DCR=62.2%, OS=9.3mo, PFS=3.7mo • **Safety** : Gr3-5 =61.1%
Tucatinib+ trastuzumab (MOUNTANEER Ph 2) Seagen®	3L+	HER2	Tucatinib plus trastuzumab in patients with **HER2+ colorectal cancer**	Preliminary Results from MOUNTANEER Ph 2: • **Efficacy:** ORR=55%, mOS=17.3 mos, mPFS=6.2 mos • **Safety:** Gr3=9%
Lenvatinib + pembro (LEAP-005 Ph 2) MERCK	3L+	MKI + PD-1	Efficacy and safety of pembrolizumab plus lenvatinib in **previously treated participants with select solid tumors**	Results from previous LEAP-005 Ph 2 study: • **Efficacy** (from prior studies): ORR=21.9%, DCR=47% • **Safety** (from prior studies): Gr3-5 =50%

Recent Trial Data for Current & Emerging Therapies in metastatic Colorectal Cancer (2/2)

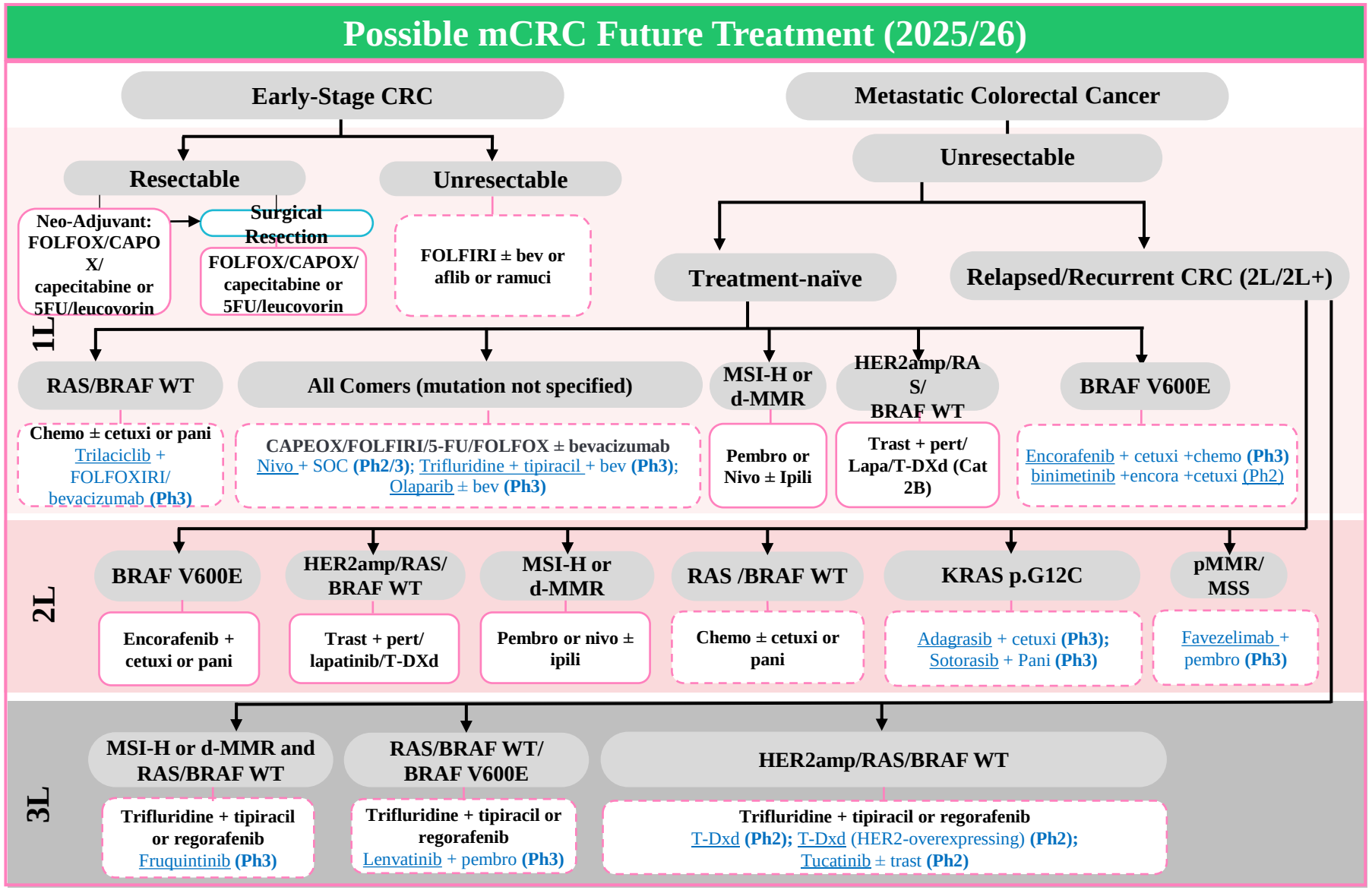
Agent / Company	LoT	MoA	Headline	Key Takeaways
Trastuzumab deruxtecan (DS-8201a) (DESTINY-CRC01 Ph 2) 	3L+	HER2-ADC	DS-8201a in Human Epidermal Growth Factor Receptor2 (HER2)-Expressing Colorectal Cancer	Results from DESTINY-CRC01 study: • **Efficacy** (from prior studies): Cohort A - ORR=45.3%, DCR=83%, mDOR=7 mos, mPFS=6.9 mos, mOS=15.5 mos • **Safety** (from prior studies): TEAE Gr ≥3 in 65.1% (56/86), TEAE discontinuation in 13 pts, 8 pts (9.3%; 4 Gr 2, 1 Gr 3, 3 Gr 5) had interstitial lung disease

Sotorasib + Panitumumab CodeBreaK 300 (Ph 3) 	2L	KRAS G 12C inhibitor	Activity of AMG 510, a Novel Small Molecule Inhibitor of KRASG12C, in Patients With **Advanced Colorectal Cancer**	Results from previous Ph 1/2 **CodeBreaK 100** basket study across multiple advanced solid tumors:
				• In 42 heavily pretreated KRAS G12C-mutant CRC pts., receiving 960 mg:
				  • Efficacy: ORR=12%, DCR=80%, mPFS=4.2mo
				  • Safety (overall): 4.8% Gr. 3 TRAEs

Adagrasib + cetuximab (KRYSTAL-10 Ph 3) 	2L	KRAS G 12C inhibitor	MRTX849 With Cetuximab vs Chemotherapy in Patients With Advanced Colorectal Cancer With **KRAS G12C Mutation**	Results from Ph 1/2 KRISTAL-1 study: • **Efficacy** : At a median follow up of 7 mos, RR = 43%, (including two unconfirmed PRs and a DCR rate of 100%) • **Safety** (from prior studies): Grade 3/4 TRAEs in 16% pts, TREAEs discontinuation in 6% of pts

Emerging Treatment Algorithms

Potential Future Treatment Algorithm for CRC



Bev: Bevacizumab, **Trast:** Trastuzumab, **Pert:** Pertuzumab, **Lapa:** Lapatinib, **T-Dxd:** Trastuzumab deruxtecan **Cetuxi:** Cetuximab **Pani:** Panitumumab, **Pembro:** Pembrolizumab, **Nivo:** Nivolumab, **Ipili:** Ipilimumab, **Oxa:** Oxaliplatin

Current Clinical Benchmarks

All Comers

Current Clinical Benchmarks
Marketed Products – mCRC (1/2)

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%)

All Comers

Current Clinical Benchmarks
Marketed Products – mCRC (2/2)

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%)

RAS WT

Current Clinical Benchmarks
Marketed Products – mCRC (1/2)

First-line Regimens	Trial Description	Efficacy		Safety
ERBITUX® (cetuximab) **(in combination with FOLFIRI)** *(EGFR Inhibitor)* s 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)* s 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)

RAS WT

Current Clinical Benchmarks
Marketed Products – mCRC (2/2)

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%)

MSI-High

Current Clinical Benchmarks Marketed Products – mCRC

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%)

Note that Opdivo ± Yervoy are FDA approved in 2L settings post-chemo but are recommended in 1L per NCCN guidelines

RAS

Current Clinical Benchmarks Marketed Products – mCRC

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 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 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.

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Thank
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