Disease Background and Unmet Need in mCRC

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Disease Background and Diagnosis

CRC: Key Global Statistics

3rd

most commonly diagnosed cancer*

~ 1.92 million

new cases in 2022[1-3]

Prevalence:

~11.68 million

cases in 2021[4]

2nd

leading cause of cancer-related mortality

~900,000

deaths in 2022[1,3]

By 2050:

CRC burden is projected to increase by **>85% to ~3.5 million** new cases[5]

Mortality is projected to increase by **>100% to ~1.8 million** deaths[5]

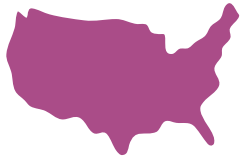
*Incidence varies widely (up to 10-fold) and is highest in countries with a "high" or "very high" human development index[1,2]

CRC, colorectal cancer

1. Bray F, et al. *CA Cancer J Clin* 2024;74:229–263. 2. World Health Organization Colorectal cancer: Key facts. Available at: https://www.who.int/news-room/fact-sheets/detail/colorectal-cancer#:~:text=Key%20facts,people%20aged%2050%20and%20above; accessed February 2026. 3. Cancer Today. Available at: https://gco.iarc.who.int/today/en/dataviz/bars?mode=population&group_populations=0&key=total&populations=900&types=0_1&sort_by=value1&cancers=41; accessed February 2026. 4. He Y, et al. *BMJ Open* 2025;15:e100042. 5. Cancer Tomorrow. Available at https://gco.iarc.fr/tomorrow/en/dataviz/tables?types=1&cancers=41&populations=903_904_905_908_909_935_900&years=2050; accessed February 2026.

CRC: Key Statistics in the US and Canada

USA



4th Most commonly diagnosed cancer

158,850 estimated new cases in 2026[1-3]

Prevalence: ~1.42 million cases in 2022[2]

2nd Leading cause of cancer-related mortality

55,230 estimated deaths in 2026[3]

By 2040:

~78,600 predicted deaths (44.0% increase in mortality) [4]

Canada

4th Most commonly diagnosed cancer

26,400 projected cases in 2025[5]

Prevalence: ~79,000 cases in 2022[6]

2nd Leading cause of cancer-related mortality

9,100 projected deaths in 2025[5]

By 2040:

~20,400 deaths predicted from CRC (76.9% increase in mortality)[7]

CRC, colorectal cancer

1. Morgan E et al. *Gut* 2023;72:338-344. 2. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. Available at https://seer.cancer.gov/statfacts/html/colorect.html. Accessed February 2026. 3. American Cancer Society. Colorectal Cancer Facts & Figures 2023-2025. Available at https://www.cancer.org/cancer/types/colon-rectal-cancer/about/key-statistics.html; accessed February 2026. 4. Cancer Tomorrow. Available at https://gco.iarc.fr/tomorrow/en/dataviz/bubbles?types=1&cancers=41&populations=840&years=2040&mode=population&group_populations=0&multiple_populations=1&single_unit=5000; accessed Mar 2026. 5. Canadian Cancer Statistics Dashboard. Available at: https://cancerstats.ca/?la=en#Welcome_to_the_Canadian_Cancer_Statistics_Dashboard_(CCSD); accessed February 2026. 6. Cancer Today. Available at: https://gco.iarc.fr/today/en/dataviz/bars-prevalence?mode=population&key=total&populations=124&sort_by=value1&cancers=41&group_cancers=1&multiple_cancers=1&prev_time=1_5_3; accessed February 2026. 7. Cancer Tomorrow. Available at: https://gco.iarc.who.int/tomorrow/en/dataviz/bubbles?types=1&cancers=41&populations=124&years=2040&mode=population&group_populations=0&multiple_populations=1&single_unit=500&multiple_cancers=0; accessed Mar 2026.

Risk Factors Associated with CRC

Non-modifiable risk factors[1-3]

Family or personal history of CRC

Radiation exposure to abdomen or pelvis

Personal history of IBD (UC or Crohn's disease)

Inherited syndromes*

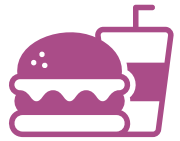
Age:

- >50 years
- Early-onset CRC†

Other factors:

- Male (at birth)
- Cholecystectomy
- Cystic fibrosis
- Ethnicity differences‡

Environmental and lifestyle (modifiable) risk factors[1-3]



Dietary habits (e.g., high levels of red/processed meat)

Smoking and alcohol consumption

Obesity

Diabetes mellitus Type 2

Low levels of Vitamin D

*Genetic conditions associated with higher risk, e.g., Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Peutz-Jeghers syndrome (PJS), MUTYH-associated polyposis (MAP). †Early-onset CRC is an emerging concern and is described in detail in the slide titled "Age as a Risk Factor: Early-Onset CRC (EOCRC)". ‡American Indian and Alaska Native people have the highest rates of colorectal cancer in the United States, followed by African American men and women in the US only.
CRC, colorectal cancer; IBD, inflammatory bowel disease; UC, ulcerative colitis.

1. American Cancer Society: Colorectal cancer risk factors. Available at https://www.cancer.org/cancer/types/colon-rectal-cancer/causes-risks-prevention/risk-factors.html; accessed February 2026. 2. Argilés G, et al. *Ann Oncol.* 2020;31:1291–1305; 3. Glynne-Jones R, et al. *Ann Oncol.* 2017;28(suppl_4):iv22–iv40.

Age as a Risk Factor: Early-Onset CRC (EOCRC)

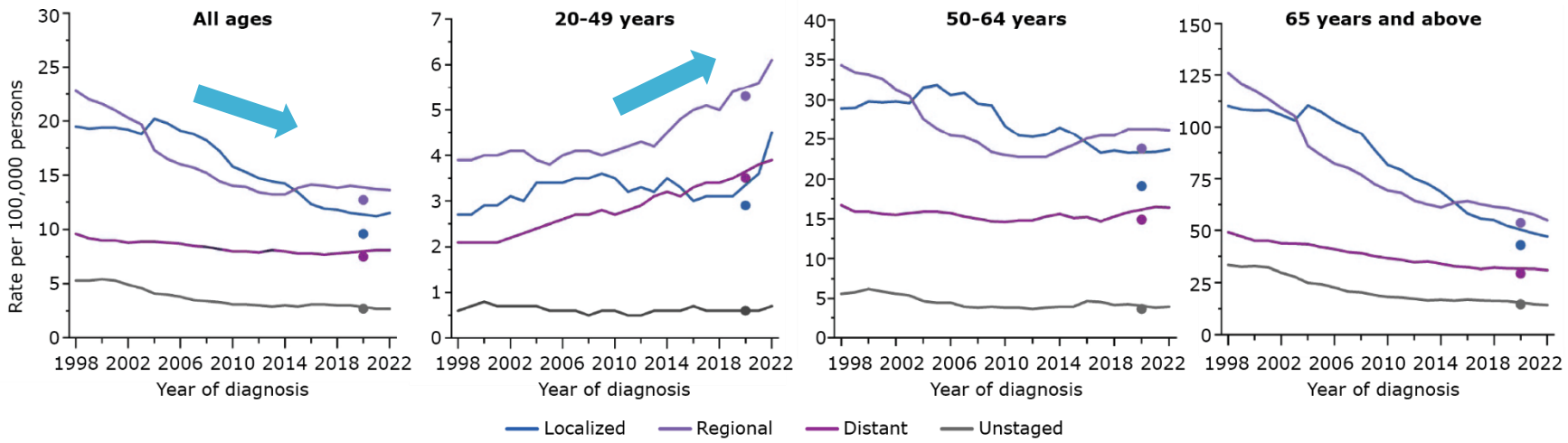
EOCRC is defined as CRC diagnosed before the age of 50 years[1,2]

Globally, rise in EOCRC is concerning and validated[2]

- Annual increase in EOCRC was 7.9% (20–29 years), 4.9% (30–39 years), and 1.6% (40–49 years) between 2004-2016[2]
- Rise in EOCRC is not confined to high-income western countries, and extends to diverse economies, including countries in eastern Europe, Asia, Latin America, and the Caribbean[3]

Trends in colorectal cancer incidence rates by age and stage at diagnosis in the US (1998–2022)*

- In the US, EOCRC has risen by ~3% annually since 2013, driven mostly by advanced-stage diagnoses and left-sided tumors[4]
- CRC is the leading cause of death in adults younger than 50 years in the US[5]



*Incidence rates exclude appendiceal cancer, are age adjusted to the 2000 US standard population, and adjusted for delays in case reporting. Incidence data for 2020 are shown as dots and are separate from trend lines.
CRC, colorectal cancer; EOCRC, early-onset CRC.

1. Pan H et al. *BMC Gastroenterol*. 2025 Jul 1;25(1):486. 2. Eng C et al. *Lancet* 2024; 404: 294–310. 3. Sung H et al. *The Lancet Oncology* 2025; 26(1): 51–63. 4. Siegel RL et al. *CA Cancer J Clin* 2026; e70067. 5. Siegel RL et al. *JAMA*. 2026;335(7):632–634.

CRC Symptoms and Screening

Signs and symptoms[1]

Cramping or abdominal pain

Weakness and fatigue

Unintended weight loss

Change in bowel habits

Rectal bleeding

Blood in the stool

Screening*[2,3]

Stool-based†

- Guaiac fecal occult blood
- Fecal immunochemical test
- Multi-target DNA or RNA testing

Blood-based

- cf-DNA

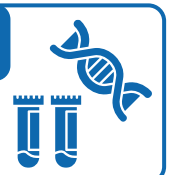


Image-based

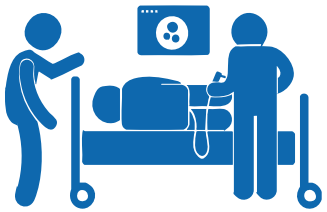
- CT colonography

Positive results from these screening tests to be confirmed with colonoscopy

(earlier and more frequent screening for high-risk patients [history of disease, genetic syndromes, IBD])

Endoscopy-based

- Colonoscopy: gold standard (may include biopsy; every 10 years)
- Flexible sigmoidoscopy (every 5 years)



*Routine screening for those at average risk and age ≥45 years. Earlier and more frequent screening for high-risk patients (history of disease, genetic syndromes, IBD). †More convenient, but can miss polyps and some cancers, higher rate of false-positives.
CRC, colorectal cancer; cf-DNA, cell-free DNA; CT, computed tomography; DNA, deoxyribonucleic acid; IBD, intestinal bowel disease; NCCN, National Comprehensive Cancer Network; RNA, ribonucleic acid.

1. American Cancer Society. 2026. Available at https://www.cancer.org/cancer/types/colon-rectal-cancer/detection-diagnosis-staging/signs-and-symptoms.html; accessed February 2026. 2. NCCN Guidelines: Colorectal Cancer Screening (V2.2025). Available at https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf; accessed February 2026. 3. ACS Colorectal Cancer Screening Guidelines. Available at https://www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines/colorectal-cancer-screening-guidelines.html; accessed February 2026.

CRC: Tumor Staging

Staging uses scales such as the TNM scale, which considers:[1]

- The extent of primary **t**umor growth **(T)**
- Involvement of regional lymph **n**odes **(N)**
- Presence of distant **m**etastasis **(M)**

TNM classification for CRC[2]

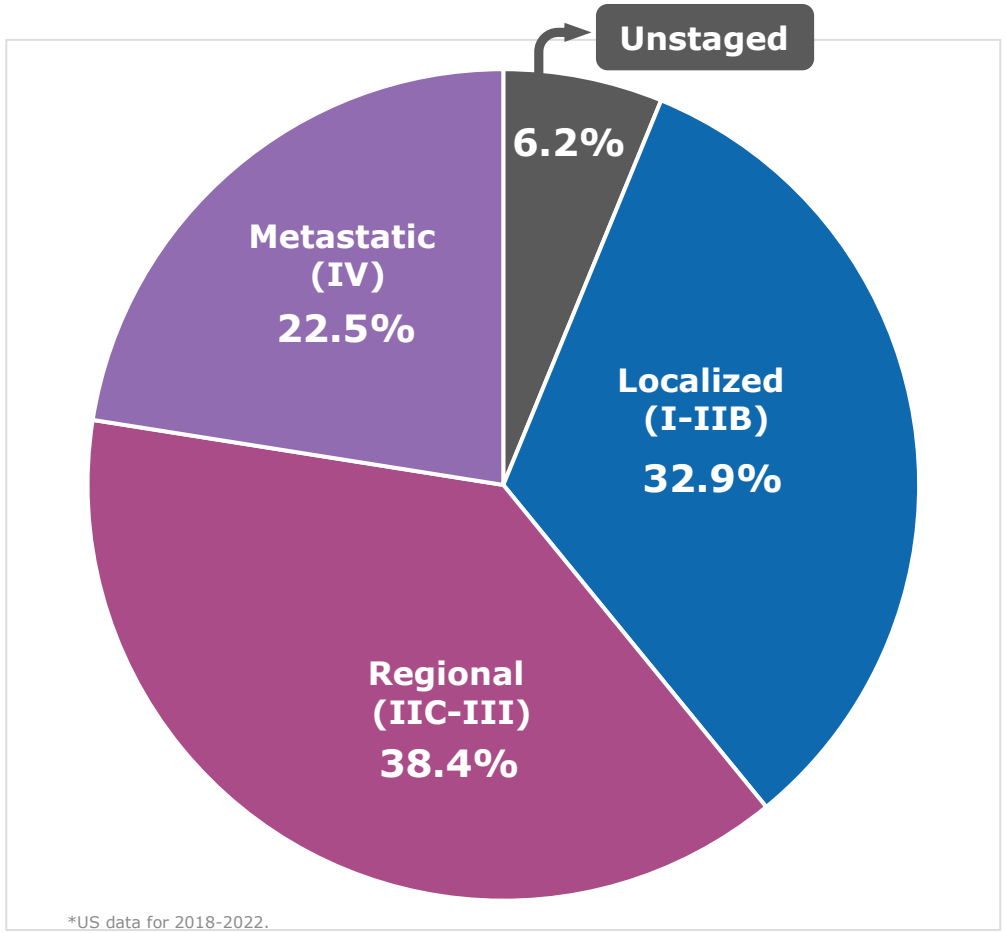
Stage	T	N	M	Description
I	T1–T2	N0	M0	Cancer has not spread outside of the bowel wall
II	T3–T4	N0	M0	Cancer has grown into or through the outer layer of the bowel wall
III	Any T	N1–2	M0	Cancer has spread to nearby lymph nodes
IV (mCRC)	Any T	Any N	M1	Cancer has spread to other parts of the body, most commonly, the liver, lung, peritoneum, and lymph nodes[3,4]

CRC, colorectal cancer; mCRC, metastatic colorectal cancer; TNM, tumor, node, metastasis.

1. American Cancer Society. Available at https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/staged.html; accessed February 2026. 2. PDQ® Adult Treatment Editorial Board. 2024. Available at https://www.cancer.gov/types/colorectal/hp/colon-treatment-pdq; accessed February 2026. 3. Hugen N et al. *Ann Oncol*. 2014;25(3):651-657. 4. Biller LH et al. *JAMA*. 2021;325(7):669-685.

CRC stage at diagnosis and prognosis

Staging at diagnosis[1-4]*



Recurrence based on staging at diagnosis

Localized (I–IIB) + Regional (IIC–III) → Tumor recurrence (~40%)[5,6]

Progression based on staging at diagnosis

- Localized (I–IIB) → metastatic (IV): 10-20% of patients[6,7]
- Regional (IIC–III) → metastatic (IV): 25-50% of patients[6,8]

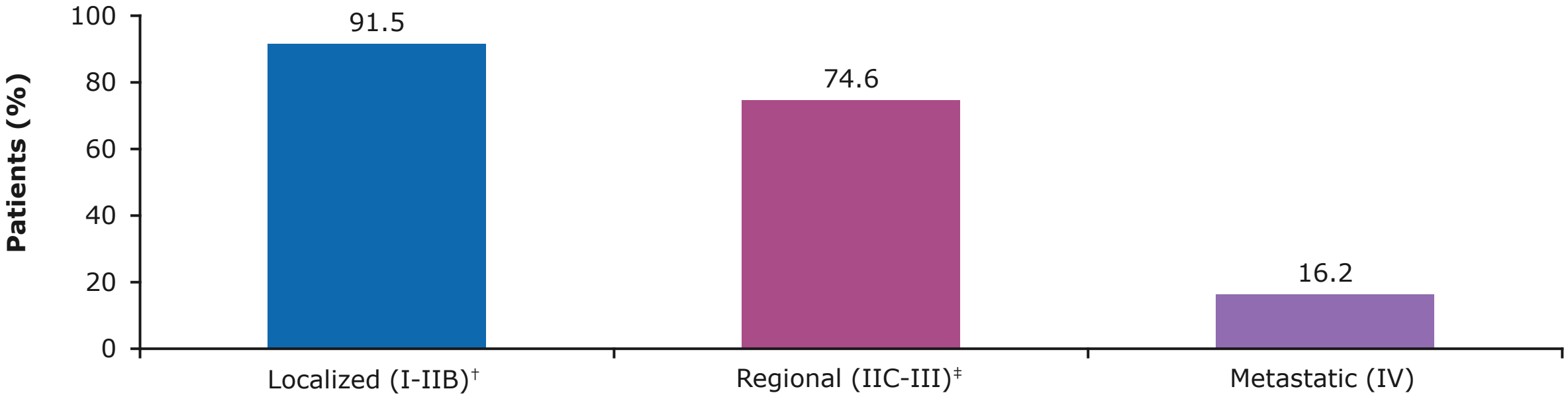
*US data for 2018-2022.
CRC, colorectal cancer; US, united States of America.

1. Centers for Disease Control and Prevention. U.S. Cancer Statistics Colorectal Cancer Stat Bite. U.S. Department of Health and Human Services; 2025. Available at https://www.cdc.gov/united-states-cancer-statistics/publications/colorectal-cancer-stat-bite.html#:~:text=Stage%20distribution,distant%20parts%20of%20the%20body); accessed February 2026. 2. Siegel RL et al. *CA Cancer J Clin*. 2023; 73(3): 233-254. 3. American Cancer Society - Colorectal Cancer stages. Available at https://www.cancer.org/cancer/types/colon-rectal-cancer/detection-diagnosis-staging/staged.html; accessed April 2026. 4. American Cancer Society – Cancer staging. Available at https://www.cancer.org/cancer/diagnosis-staging/staging.html; accessed April 2026. 5. Kahi CJ et al. *Gastroenterology*. 2016;150(3):758-768.e11. 6. Biller LH et al. *JAMA*. 2021;325(7):669-685. 7. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. Available at https://seer.cancer.gov/statfacts/html/colorect.html; accessed February 2026. 8. Bekaii-Saab T. *Am J Manag Care*. 2024;30:S23-S30.

CRC stage at diagnosis and survival

5-year relative survival* of patients with CRC

(based on stage at diagnosis: 2015–2021)[1]



*Survival relative to similar individuals who do not have cancer; †Confined to primary site; ‡Spread to regional lymph nodes.
CRC, colorectal cancer.

1. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. Available at https://seer.cancer.gov/statfacts/html/colorect.html; accessed February 2026.

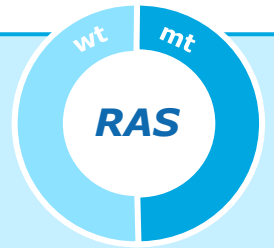
Genetic Biomarkers, Serum Biomarkers and Tumor Location (1/3)

Genetic Biomarkers

Serum Biomarkers

Tumor location

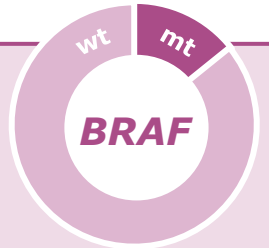
Three key molecular biomarkers can impact prognosis in patients with mCRC[1,2]



***RAS* mutations**

Frequency: around 45–50% of patients with mCRC[3,4]

Prognostic impact: negative[1]



***BRAF* mutations**

Frequency: around 5-10% of patients with mCRC[1,5]

Prognostic impact: negative[1]

MSI-H status

Frequency: around 5% of patients with mCRC[2]

Prognostic impact: negative in mCRC (positive in Stage II or III CRC)[2]

- Genetic biomarkers in mCRC are critical in 1L/2L as they can inform prognosis and help guide the use of targeted therapies[5-7]
- While biomarkers* are central to treatment selection in early-line CRC (1L/2L), their integration into later-line mCRC (≥3L) management remains less clearly defined[8,9]

*Other biomarkers used for treatment decisions in ≥2L include *NTRK*, HER2, and *RET* (as per NCCN guidelines V1. 2026).

BRAF, rapidly accelerated fibrosarcoma B-type gene; CRC, colorectal cancer; *HER2*, human epidermal growth factor receptor 2 gene; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; L, line of therapy; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; mt, mutant; *NTRK*, Neurotrophic tyrosine receptor kinase gene; *RAS*, Rat sarcoma virus gene; *RET,* rearranged during transfection gene (encodes a receptor tyrosine kinase); wt, wild-type.

1. Koncina E, et al. *Cancers* (Basel). 2020;12:319. 2. Colle R, et al. *Bull Cancer.* 2017;104:42–51. 3. Porru M, et al. *J Exp Clin Cancer Res.* 2018;13:57. 4. Zhao B, et al. *Oncotarget*. 2017;8:3980–4000. 5. NCCN Guidelines®: Colon Cancer (v.1.2026). https://www.nccn.org. 6. Cervantes A, et al. *Ann Oncol.* 2023;34:10–32. 7. Tabernero J, et al. *J Clin Oncol.* 2021;39:273–284. 8. Bekaii-Saab T, et al. *Clin Colorectal Cancer*. 2019;18(1):e117-e129. 9. Bekaii-Saab T. *Am J Manag Care*. 2024;30(2 Suppl):S23-S30.

Genetic Biomarkers, Serum Biomarkers and Tumor Location (2/3)

Genetic Biomarkers

Serum Biomarkers

Tumor location

Serum CEACAM5 (sCEA or CEA) is a standard biomarker in CRC*

- CEACAM5 is known to be (over)expressed in tumor tissue, including >90% of CRC tissue samples[1,2]
- CEACAM5 is secreted into the blood stream, resulting in an increase in sCEA concentration[2]
  - Serum CEA (sCEA) measurement is recommended in the NCCN Guidelines as part of the standard workup and surveillance for CRC[3]
  - Elevated preoperative sCEA is defined as >5 ng/ml[2,†]

Elevated serum CEACAM5 (sCEA) is associated with increased risk of recurrence and poorer survival in CRC[3]

*Assessed by blood-based immunoassays detecting circulating CEACAM5; †Pretreatment serum CEA levels 5-10 ng/mL suggest localized disease, a low likelihood of recurrence, and a favorable prognosis. A serum level above 10 µg/L indicates a higher probability of recurrence and poorer prognosis. This threshold of 10 µg/L has a sensitivity of 68% and a specificity of 97%.[2]

CEA, carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5); CRC, colorectal cancer; IHC, immunohistochemistry; NCCN, National Comprehensive Cancer Network.

1. Thomas J et al. *Genes Cancer*. 2023;14:12-29. 2. Aldilaijan, AF et al. *Sci Rep*. 2023;13:7616. 3. NCCN Guidelines®: Colon Cancer (v.1.2026). https://www.nccn.org.

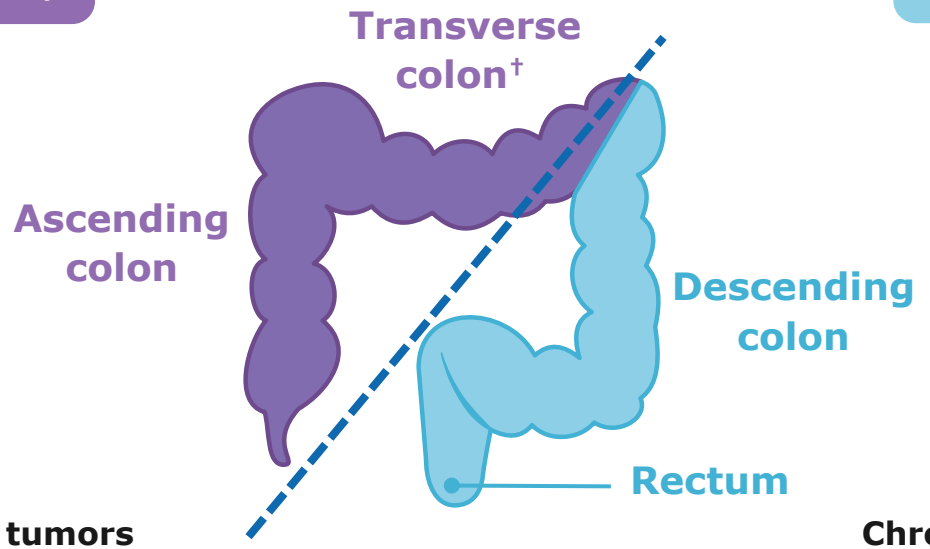
Genetic Biomarkers, Serum Biomarkers and Tumor Location (3/3)

Genetic Biomarkers

Serum Biomarkers

Tumor location

Right colon (proximal/midgut)	Left colon (distal/hindgut)
Incidence rate: 20–40%*[1,2]	**Incidence rate: 60–80%*[1,2]**
Predominantly Female	**Predominantly Male**
Higher TNM stage Larger tumors	**Lower TNM stage Smaller tumors**
MSI/*BRAF* positive tumors predominate	**Chromosomal instability tumors predominate**



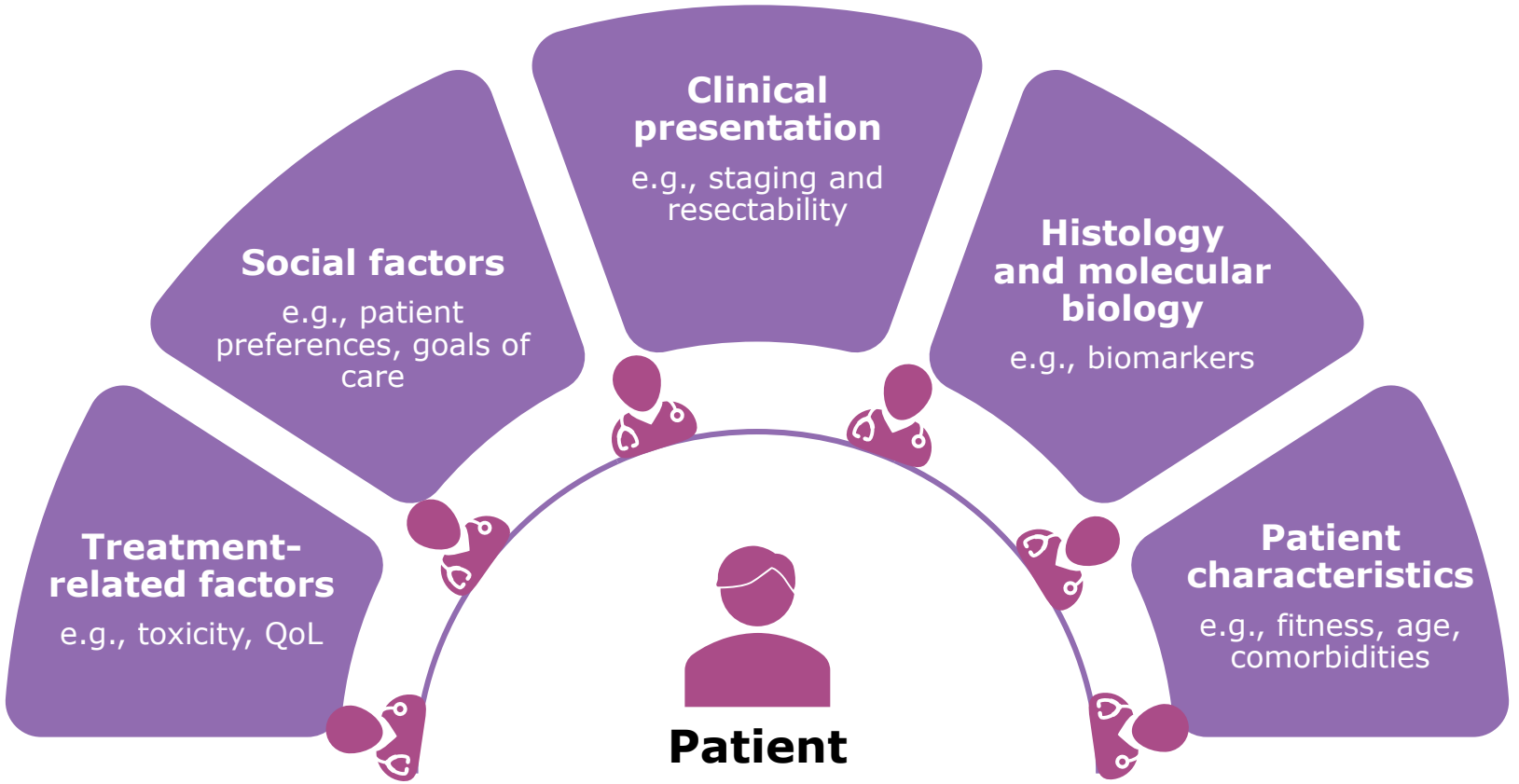
*Percentage of patients; left-sided includes patients with rectal cancer; †Classification of the transverse colon as right- or left-sided colon differs between studies.
BRAF, v-raf murine sarcoma viral oncogene homolog B1 gene; MSI, microsatellite instability; TNM, American Joint Committee on Cancer tumor–node–metastasis stage.

1. Maus MK, et al. *Pharmacogenomics J.* 2015;15:354–362. 2. Lee GH, et al. *Eur J Surg Oncol*. 2015;41:300–308.

Treatment Options for mCRC

Patient- and Disease-Specific Factors

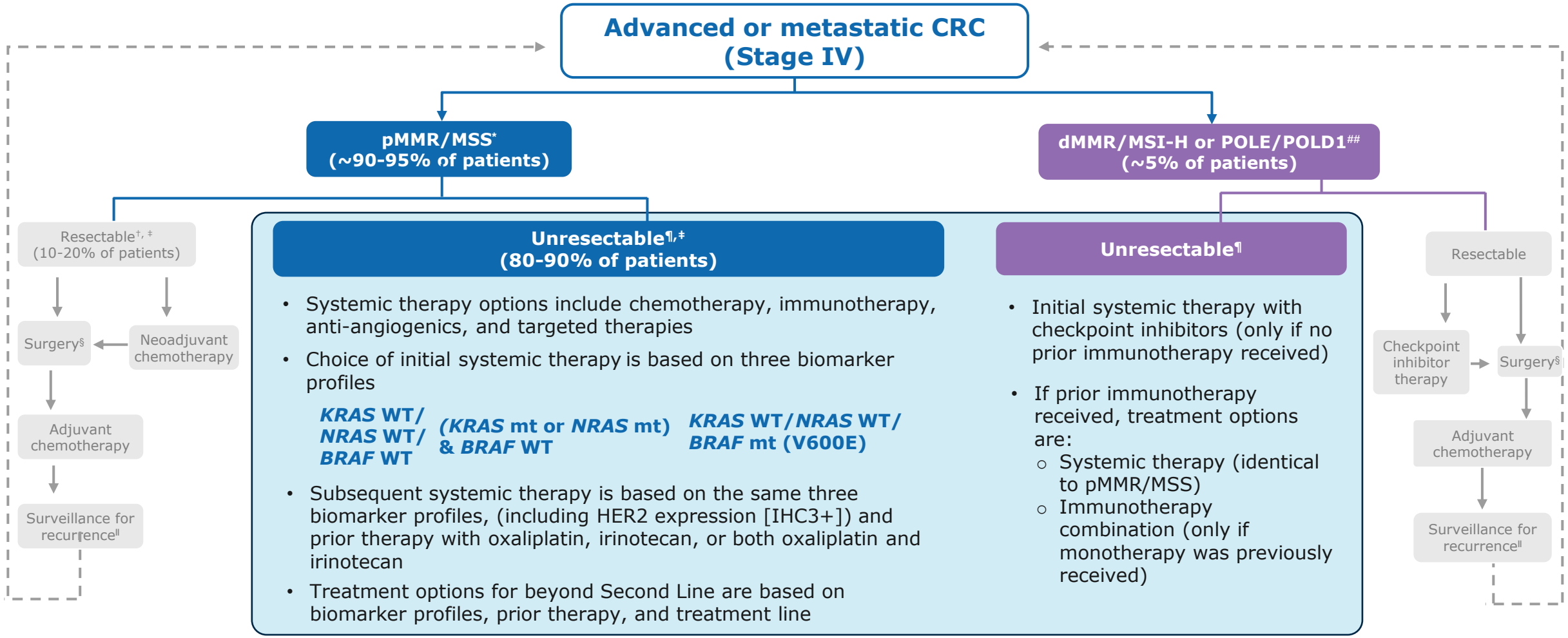
Treatment decisions are made by an MDT, considering a range of factors:[1,2]



mCRC, metastatic colorectal cancer; MDT, multidisciplinary team; QoL, quality of life.

1. Cervantes A, et al. *Ann Oncol* 2023;34:10–32. 2. Morris V K et al. *J Clin Oncol* 2023;41:678-700.

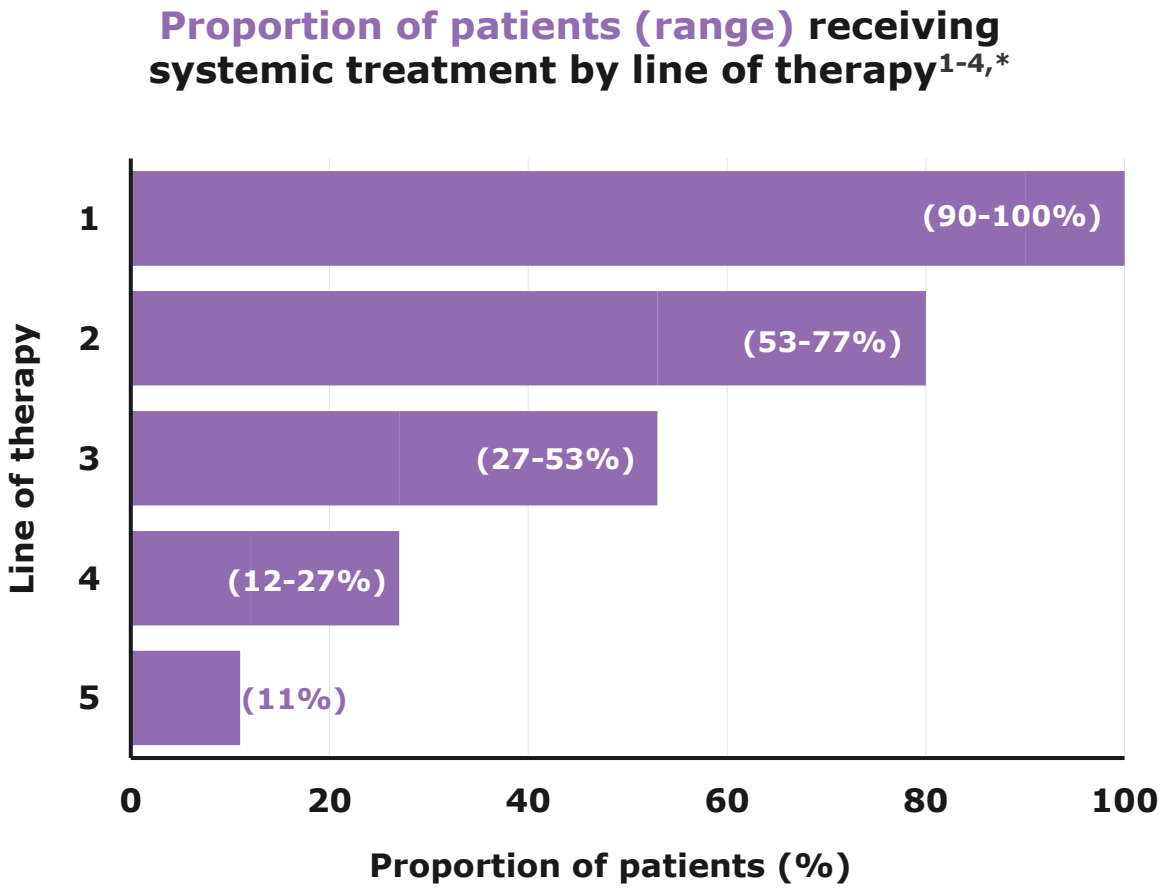
Treatment landscape of mCRC



*Can also include dMMR/MSI-H or POLE/POLD1 if patients are ineligible for or progressed on checkpoint inhibitor immunotherapy. †Synchronous liver only and/or lung only metastases. ‡Data on resectable vs unresectable for pMMR reflect overall rates as only ~5% of all mCRC patients have dMMR disease, and are not US-specific. §May also include local therapy. ‖Approach to surveillance varies dependent on pathologic stage of cancer. ¶Choice of systemic therapy should be tailored based on the goals of therapy, the type and timing of prior therapy, and the differing toxicity profiles of the drugs. *BRAF*, rapidly accelerated fibrosarcoma B-type gene; CRC, colorectal cancer; CT, chemotherapy; dMMR/MSI-H, deficient mismatch repair/microsatellite instability-high; IHC, immunohistochemistry; NCCN, National Comprehensive Cancer Network; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *NRAS*, Neuroblastoma RAS viral oncogene homolog; pMMR/MSS, proficient mismatch repair/microsatellite stable; POLD, DNA polymerase delta; POLE, DNA polymerase epsilon. NCCN Guidelines®: Colon Cancer [v.1.2026]. https://www.nccn.org. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colorectal Cancer V.1.2026.

Unmet Need in later-line mCRC

Treatment patterns in later lines of mCRC

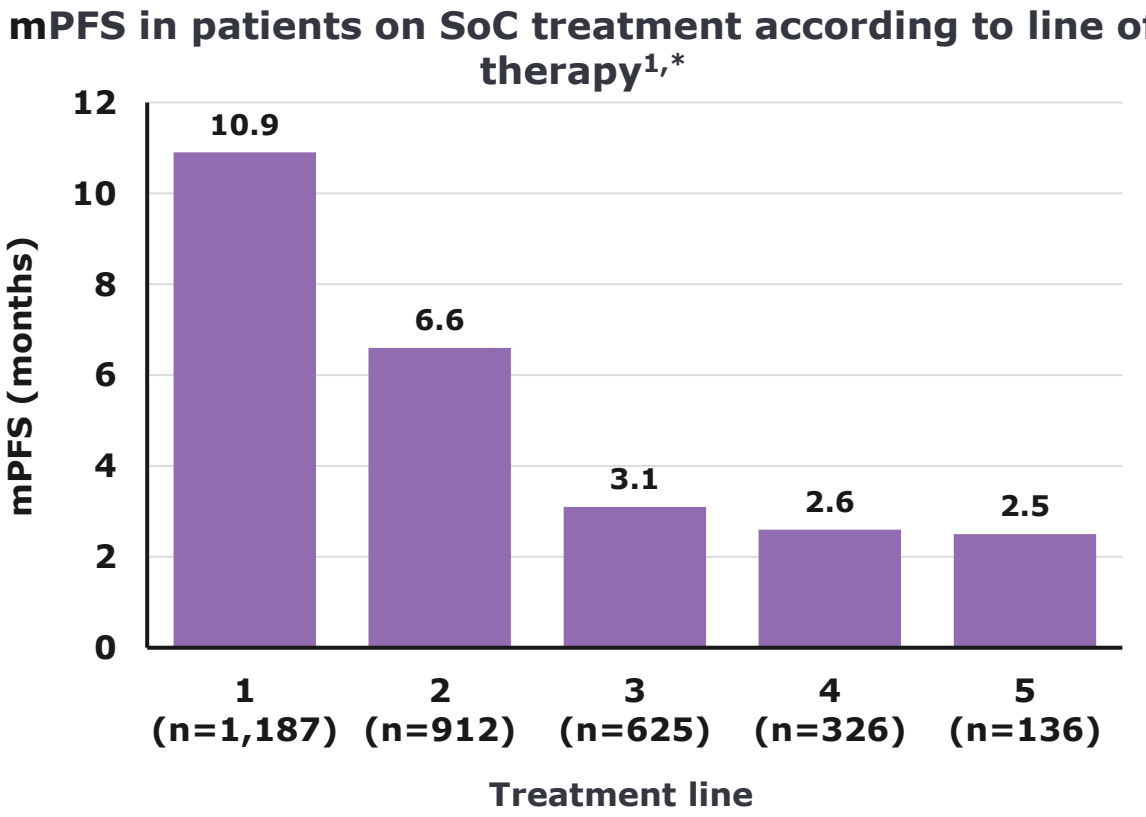


- Globally, among patients diagnosed with mCRC, 50-60% receive 2L treatment while 20-35% are treated in 3L[5,6]
  - In the US, real-world data show treatment rates of 53% in 2L, 28% in 3L, and 13% in 4L[4]
- Most likely causes of treatment attrition are cumulative toxicity, progressive disease, and reduced tolerability of therapies[7,8]
- Safety profile of ≥3L therapies is characterized by 54–72% of patients experiencing Grade ≥3 hematological or dermatological AEs[9-12]
- There are limited data to inform optimal treatment sequencing in later lines as choices are patient-specific and depend on prior therapy, patient performance status, and tolerability[8]

*Data from Italy, Canada, Spain and USA; data are range of the percentage of patients receiving treatment. Includes data from a post-hoc-analysis of TRIBE/TRIBE2-studies (n=1,187).
AE, adverse events, L, line of therapy; mCRC, metastatic colorectal cancer.

1. Rossini D, et al. *Eur J Cancer.* 2022;170:64–72; 2. Kennecke H, et al. *Curr Oncol.* 2019;26:e748–54; 3. Aranda E, et al. *Clin Transl Oncol.* 2020;22:1455–62; 4. Abrams TA, et al. *J Natl Cancer Inst.* 2014;106:djt371.
5. Bachet J-P, et al. *J Clin Oncol*. 2025; 43(18):2094–2106. 6. Ciraci P, et al. *Nat Rev Clin Oncol*. 2025; 22: 28–45. 7. Bahrabadi A, et al. *J Clin Oncol*. 2017;35:e18041-e18041. 8. Bekaii-Saab T. *Am J Manag Care*. 2024;30(2 Suppl):S23-S30. 9. Grothey A, et al. *Lancet.* 2013;381:303–312; 10. Dasari A, et al. *Lancet.* 2023;402:41–53; 11. Mayer RJ, et al. *N Engl J Med.* 2015;372:1909–1919; 12. Prager GW, et al. *N Engl J Med.* 2023;388:1657–1667.

Treatment in later lines of mCRC



- As patients advance through treatment lines (1L to 3L) in mCRC[2-4,8]
  - mPFS reduces from ~ 10 mo to <6 months
  - mOS shows reduction from ~30 mo to 6 mo
  - ORR drops from ~ 47-61% to ≤6%
- In the 3L+ setting:[5-8]
  - mOS is <12 months (range: 6.4–10.8)
  - mPFS is <6 months (range: 1.9–5.6)
  - ORR is ~6% (range 1–6.1%)

There is a high unmet need for more treatment options[1]

*Post-hoc-analysis of TRIBE/TRIBE2-studies including 1,187 mCRC pts.
L, line of therapy; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; SoC, standard of care.
1. Rossini D, et al. *Eur J Cancer*. 2022;170:64–72; 2. Koopeman M et al. *ESMO Gastrointestinal Oncology*. 2025; 9:100214. 3. Biller LH et al. *JAMA*. 2021;325(7):669-685. 4. Motta R et al. *J Clin Transl Res.* 2021 Nov 9;7(6):771–785. 5. Dasari A, et al. *Lancet*. 2023;402:41-53; 6. Mayer RJ, et al. *N Engl J Med*. 2015;372:1909-1919; 7. Grothey A, et al. *Lancet*. 2013;381:303-312; 8. Prager GW, et al. *N Engl J Med.* 2023;388:1657-1667.

Key Takeaways

Key Takeaways

Globally, CRC is the third most commonly diagnosed malignancy and has the second-highest mortality of any cancer, with particularly poor prognoses in the metastatic setting[1,2]

Diagnosis and staging are determined through multistep processes with MDT, including screening, biomarker assessment, and identification of tumor location[3,4]

Treatment options for mCRC include chemotherapy, targeted therapies, and immunotherapies, with selection guided by biomarker profile, prior treatment exposure, therapeutic goals, and anticipated toxicity[5]

There are limited data to inform optimal treatment sequencing in later lines as choices are patient-specific and depend on prior therapy, patient performance status, and tolerability[6]

Despite current therapies, only 20-35% of patients with mCRC progress to 3L, with a typical 5-year survival rate of 16.2%[7,8]

There is a high unmet need for more treatment options in the ≥3L setting in mCRC[6]

CRC, colorectal cancer; L, line of therapy; mCRC, metastatic colorectal cancer; MDT, multidisciplinaryy team; NCCN, National Comprehensive Cancer Network.

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