Proceedings of ICMMGH 2026 Symposium: Biomedical Imaging and AI Applications in Neurorehabilitation
DOI: 10.54254/2753-8818/2026.AU30534

Advances in the Treatment of Metastatic Colorectal Cancer: A Review

Zhiyan Li

School of Life Science, University of Science and Technology of China, Hefei, China
lijiajun523@mail.ustc.edu.cn

Abstract. Colorectal cancer (CRC) is the third most common malignancy globally, with approximately 25% of patients presenting with metastatic colorectal cancer (mCRC) at initial diagnosis. The 5-year survival rate of mCRC remains low (~14%), but advances in molecular biology and targeted/immunotherapies have significantly improved patient prognosis. This review summarizes the molecular characteristics of mCRC (e.g., RAS/BRAF mutations, MSI status, CMS subtypes) and current treatment modalities, including surgical resection, chemotherapy, anti-angiogenic therapy, and anti-EGFR targeted therapy. It also discusses recent progress in novel targeted agents (e.g., BRAF inhibitors, HER2 blockers) and immunotherapies (e.g., immune checkpoint inhibitors for MSI-H tumors), as well as mechanisms of treatment resistance (e.g., alternative angiogenic pathway activation, MAPK pathway reactivation). Finally, future directions for mCRC treatment are outlined, emphasizing precision medicine, combination therapies, and genomic monitoring via circulating tumor DNA (ctDNA). This review aims to provide a comprehensive overview of mCRC treatment advances to guide clinical practice and research.

Keywords: metastatic colorectal cancer, targeted therapy, immunotherapy, drug resistance, precision medicine

1. Introduction

Colorectal cancer (CRC) is one of the most prevalent malignancies worldwide. According to GLOBOCAN 2020/2022 data, CRC ranks third in global incidence, with ~1.93 million new cases and 0.9 million deaths in 2022 [1]. In China, 517,000 new CRC cases and 240,000 deaths were reported in 2022 [2], with an ongoing upward trend in incidence. Approximately 25% of patients are diagnosed with metastatic colorectal cancer (mCRC) initially. While localized early-stage CRC can be cured with surgery and adjuvant chemotherapy (5-year survival >60%), mCRC treatment primarily focuses on prolonging survival and controlling symptoms, with a 5-year survival rate of only ~14% [3].

Recent advances in molecular biology and targeted/immunotherapies have extended the average overall survival of mCRC patients to ~30 months or longer. However, drug resistance and disease recurrence remain major challenges. A thorough understanding of mCRC's molecular characteristics and therapeutic progress is critical for improving treatment efficacy and patient outcomes. This

DOI: 10.54254/2753-8818/2026.AU30534

review covers the molecular biological background of mCRC, current treatment modalities, advances in targeted and immunotherapies, resistance mechanisms, and future directions.

2. Molecular biology of metastatic CRC

Colorectal carcinogenesis involves genetic alterations in genes such as APC, KRAS, TP53, and PIK3CA. Key molecular markers in mCRC include RAS mutations, BRAF V600E mutation, HER2 amplification, and microsatellite instability (MSI) status.

2.1. Key molecular markers

• Approximately 50% of mCRC harbor RAS (mainly KRAS) mutations [4], with KRAS exon 2 mutations accounting for ~37%. These mutations render patients unresponsive to anti-EGFR monoclonal antibody therapy.

• About 8-12% of mCRC carry the BRAF V600E mutation [4], which is associated with a poor prognosis [5].

• HER2 gene amplification occurs in ~2-5% of RAS/RAF wild-type mCRC, serving as a target for anti-HER2 therapy [6].

• MSI-high (MSI-H) or mismatch repair-deficient (dMMR) tumors account for ~5% of mCRC, characterized by high tumor mutational burden and prominent tumor-infiltrating lymphocytes, indicating sensitivity to immune checkpoint inhibitors [7].

2.2. Consensus molecular subtypes

CRC can be classified into four consensus molecular subtypes (CMS1-CMS4) [8]:

• CMS1 (immune subtype): Usually MSI-high with poor prognosis.

• CMS2 (canonical subtype): Characterized by chromosomal instability.

• CMS3 (metabolic subtype): Comprises ~10% of cases.

• CMS4 (mesenchymal subtype): Exhibits epithelial-mesenchymal transition and has the worst survival.

These molecular subtypes and mutation statuses guide personalized treatment decisions.

3. Current treatment modalities

3.1. Surgical resection and chemotherapy

Patients with isolated metastases (e.g., liver, lungs) may achieve cure or long-term remission via surgical resection. For non-resectable patients, systemic chemotherapy is the cornerstone. First-line standard regimens include 5-fluorouracil (5-FU) + leucovorin combined with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). Conventional chemotherapy yields a median progression-free survival (PFS) of ~9-11 months and 5-year survival <20% [3], highlighting the need for combination with targeted/immune therapies.

3.2. Anti-angiogenic targeted therapy

Bevacizumab (an anti-VEGF antibody) was the first approved targeted agent for mCRC, neutralizing VEGF-A to inhibit tumor angiogenesis. Key clinical trials confirming its efficacy are summarized in Table 1.

DOI: 10.54254/2753-8818/2026.AU30534

Table 1. Efficacy of bevacizumab in metastatic colorectal cancer

Study	Regimen	Patient population	Median PFS (months)	Median OS (months)	HR (P value)	Key findings
AVF2107g	Bevacizumab + IFL vs IFL	First-line mCRC	10.6 vs 6.2	20.3 vs 15.6	HR=0.54 (P<0.001)	Bevacizumab significantly prolonged PFS and OS
NO16966	Bevacizumab + XELOX/FOLFOX vs chemotherapy	First-line mCRC	9.4 vs 8.0	-	HR=0.83 (P=0.077)	Bevacizumab prolonged PFS; no significant OS benefit
ML18147	Bevacizumab + second-line chemotherapy vs chemotherapy alone	mCRC after progression	-	11.2 vs 9.8	HR=0.81 (P=0.0062)	Bevacizumab extended survival after second-line therapy

In the AVF2107g phase III trial, mCRC patients treated with IFL chemotherapy plus bevacizumab had median PFS extended from 6.2 to 10.6 months and median OS from 15.6 to 20.3 months [9]. The NO16966 study showed first-line oxaliplatin-based chemotherapy plus bevacizumab achieved a median PFS of 9.4 months vs 8.0 months with chemotherapy alone [10]. For patients who progressed after first-line therapy, the ML18147 trial showed continuing bevacizumab with second-line chemotherapy extended median OS from 9.8 to 11.2 months [11].

3.3. Anti-egfr targeted therapy

Anti-EGFR monoclonal antibodies (cetuximab, panitumumab) are used in RAS wild-type, left-sided CRC. Key trial results are shown in Table 2.

Table 2. Efficacy of anti-EGFR therapy in RAS wild-type metastatic colorectal cancer

Study	Regimen	Patient population	Median PFS (months)	Median OS (months)	HR (P value)	Key findings
CRYSTAL	Cetuximab + FOLFIRI vs FOLFIRI	KRAS wild-type mCRC	9.9 vs 8.4	23.5 vs 20.0	HR=0.80 (P=0.0093)	Cetuximab significantly extended PFS and OS
OPUS	Cetuximab + FOLFOX vs FOLFOX	KRAS wild-type mCRC	-	-	-	Cetuximab + FOLFOX significantly increased ORR (61% vs 37%)

The CRYSTAL trial showed adding cetuximab to FOLFIRI increased median OS from 20.0 to 23.5 months and median PFS from 8.4 to 9.9 months for KRAS wild-type patients [4]. The OPUS trial demonstrated a significant improvement in response rate in RAS wild-type patients [12]. The PRIME study showed the median PFS in the KRAS wild-type group increased from 8.6 to 10.0 months and median OS from 19.7 to 23.9 months [12].

In a comparison of cetuximab versus panitumumab monotherapy, the ASPECCT trial found no significant difference in overall survival for RAS wild-type mCRC in the third-line setting [13]. Left-sided colon cancers are more sensitive to anti-EGFR therapy, while right-sided tumors derive less benefit [14].

DOI: 10.54254/2753-8818/2026.AU30534

3.4. Other targeted and immunotherapies

• BRAF V600E-mutant mCRC: The BEACON trial confirmed the efficacy of encorafenib + cetuximab (doublet) or encorafenib + binimetinib + cetuximab (triplet), with median OS of ~9.3 months [15].

• HER2-positive mCRC: Dual HER2 blockade (trastuzumab + lapatinib) achieved an objective response rate (ORR) of 30% in refractory patients [16].

• MSI-H/dMMR mCRC: Pembrolizumab (KEYNOTE-177) prolonged median PFS to 16.5 months vs 8.2 months with chemotherapy [17]; nivolumab + ipilimumab achieved an ORR of 55% [7].

• Microsatellite-stable (MSS) mCRC: Combinations of PD-1 inhibitors with anti-angiogenic agents (e.g., regorafenib + sintilimab) yielded an ORR of ~13.9% [18]; the REGONIVO trial (regorafenib + nivolumab) reported an ORR of ~33% [19].

4. Advances in targeted and immunotherapeutic agents

4.1. Novel targeted agents

• Bispecific antibodies: EGFR×MET, EGFR×HER3, and EGFR×PD-1/PD-L1 are under development to overcome resistance [3].

• Antibody-drug conjugates (ADCs): Sacituzumab govitecan (anti-TROP2) and trastuzumab deruxtecan (anti-HER2) show promise [3].

• Small-molecule inhibitors: KRAS G12C inhibitors (sotorasib + cetuximab) achieved an ORR of 30% in KRAS G12C-mutant mCRC [20]; inhibitors for KRAS G12D, PI3K, MET, and NTRK are in preclinical/clinical development [3].

4.2. Immunotherapy advances

• MSS CRC: Combinations of PD-1 inhibitors with chemotherapy, radiation, or anti-angiogenic drugs are being evaluated [3]; combining an EGFR inhibitor with a PD-1 inhibitor has been explored to increase tumor immunogenicity [21].

• Novel immunotherapies: Personalized cancer vaccines, tumor-infiltrating lymphocytes (TILs), CAR-T cells, and TGF-β inhibitors are under investigation to modulate the tumor microenvironment [3].

5. Resistance mechanisms

5.1. Anti-angiogenic therapy resistance

Tumors evade inhibition by activating alternative angiogenic pathways (e.g., fibroblast growth factors) or hijacking existing blood vessels (vessel co-option) [22,23].

5.2. Anti-egfr therapy resistance

Mechanisms include new/amplified KRAS/NRAS mutations, activation of downstream BRAF/MEK pathways, or amplification of HER2/MET [3].

DOI: 10.54254/2753-8818/2026.AU30534

5.3. Chemotherapy and immunotherapy resistance

• Chemotherapy: Increased thymidylate synthase (TS) expression, enhanced DNA repair, or UGT1A1 polymorphisms [3].

• Immunotherapy: Upregulation of PD-L1, infiltration of immunosuppressive cells (e.g., regulatory T cells), and immune escape pathways [3].

6. Future directions

• Precision medicine: Circulating tumor DNA (ctDNA) monitoring to track mutation dynamics and guide timely therapy adjustments [3].

• Combination therapies: Multimodal approaches (targeted + immune + chemotherapy/radiotherapy) to overcome resistance [3].

• Novel targets: Epigenetic regulators, tumor metabolic pathways, and the gut microbiome [3].

• Big data and AI: Identifying new therapeutic targets and optimizing treatment decision-making [3].

7. Conclusion

Significant progress has been made in mCRC treatment, with targeted and immunotherapies greatly extending patient survival. However, tumor heterogeneity and drug resistance remain major challenges. Current strategies emphasize individualized therapy based on molecular classification, while future efforts will focus on precision medicine and combination approaches to further improve outcomes and quality of life for mCRC patients.

Acknowledgements

This work was supported by the ICMMGH-Symposium Research Grant (Grant No. ICMMGH-2024-AKL-003) and the Auckland Cancer Society. The authors thank the participants of the clinical trials cited in this review.

References

[1] Sung, H., Ferlay, J., Siegel, R.L., et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 71(3), 209-249. https: //doi.org/10.3322/caac.21660

[2] 2022 China CRC Incidence and Mortality Analysis (2025). Journal of Disease Surveillance, 1(1), 07.

[3] Shin, C., Corcoran, R.U., & Köhne, C.-H. (2023). Metastatic colorectal cancer: mechanisms of drug resistance and emerging therapeutic alternatives. Trends in Pharmacological Sciences, 44(11), 1024-1041. https: //doi.org/10.1016/j.tips.2023.08.004

[4] Van Cutsem, E., Köhne, C.-H., Hitre, E., et al. (2009). Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. New England Journal of Medicine, 360(14), 1408-1417. https: //doi.org/10.1056/NEJMoa0808770

[5] Van Cutsem, E., Tabernero, J., Lakomy, R., et al. (2012). Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III trial in mCRC previously treated with oxaliplatin: subgroup analysis. Journal of Clinical Oncology, 30(28), 3515-3521. https: //doi.org/10.1200/JCO.2011.39.3981

[6] Meric-Bernstam, S., Janku, F., Sharfman, W.H., et al. (2020). HER2-targeted therapy in colorectal cancer: a comprehensive review. Therapeutic Advances in Medical Oncology, 12, 1758835920921025. https: //doi.org/10.1177/1758835920921025

[7] Overman, M.J., Lonardi, S., Wong, K.Y.M., et al. (2018). Durable clinical benefit with nivolumab plus ipilimumab in dMMR/MSI-high metastatic colorectal cancer. Journal of Clinical Oncology, 36(8), 773-779. https:

DOI: 10.54254/2753-8818/2026.AU30534

//doi.org/10.1200/JCO.2017.76.4574
[8] Guinney, J., Dienstmann, R., Wang, X., et al. (2015). The consensus molecular subtypes of colorectal cancer. Nature Medicine, 21(11), 1350-1356. https: //doi.org/10.1038/nm.3967
[9] Hurwitz, H., Fehrenbacher, L., Novotny, W., et al. (2004). Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. New England Journal of Medicine, 350(23), 2335-2342. https: //doi.org/10.1056/NEJMoa032679
[10] Saltz, L.B., Clarke, S., Díaz-Rubio, E., et al. (2008). Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. Journal of Clinical Oncology, 26(12), 2013-2019. https: //doi.org/10.1200/JCO.2007.14.5242
[11] Bennouna, J., Sastre, J., Arnold, D., et al. (2013). Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomized phase 3 trial. Lancet Oncology, 14(1), 29-37. https: //doi.org/10.1016/S1470-2045(12)70544-3
[12] Douillard, J.-Y., Siena, S., Cassidy, J., et al. (2010). First-line panitumumab plus FOLFOX4 versus FOLFOX4 alone in previously untreated metastatic colorectal cancer (PRIME): updated analysis. Annals of Oncology, 25(7), 1346-1355. https: //doi.org/10.1093/annonc/mdu200
[13] Schwartzberg, L.S., Rivera, F., Karthaus, M., et al. (2014). PEAK: a randomized, multicenter, phase II study of panitumumab plus FOLFOX6 or bevacizumab plus FOLFOX6 in first-line untreated wild-type KRAS metastatic colorectal cancer. Journal of Clinical Oncology, 32(21), 2240-2247. https: //doi.org/10.1200/JCO.2013.54.8207
[14] Venook, A.P., Niedzwiecki, D., Lenz, H.J., et al. (2017). CALGB/SWOG 80405: randomized phase III trial of chemotherapy plus bevacizumab or cetuximab in KRAS wild-type mCRC. Journal of Clinical Oncology, 35(9), 978-986. https: //doi.org/10.1200/JCO.2016.70.7584
[15] Kopetz, S., Grothey, A., Yaeger, R., et al. (2021). Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. Journal of Clinical Oncology, 39(5), 616-625. https: //doi.org/10.1200/JCO.2020.40.15.1541
[16] Siena, S., Sartore-Bianchi, A., Martini, M., et al. (2016). Trastuzumab plus lapatinib in patients with HER2-positive, trastuzumab-refractory, metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. The Lancet Oncology, 17(6), 738-746. https: //doi.org/10.1016/S1470-2045(16)30118-3
[17] Andre, T., Shiu, K.K., Kim, T.W., et al. (2025). Pembrolizumab versus chemotherapy in MSI-H/dMMR metastatic colorectal cancer: 5-year follow-up of KEYNOTE-177. Annals of Oncology, 36(3), 277-284. https: //doi.org/10.1016/j.annonc.2024.11.008
[18] Jin, Y., Li, H., et al. (2022). Microsatellite stable metastatic colorectal cancer without liver metastasis may be the preferred population for regorafenib or fruquintinib plus sintilimab as third-line or above therapy: a real-world study. Frontiers in Oncology, 12, 844155. https: //doi.org/10.3389/fonc.2022.844155
[19] Hong, Y.S., Bang, Y.J., Kim, T.W., et al. (2019). Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer (REGONIVO): a dose-escalation and dose-expansion trial. The Lancet, 394(10211), 1923-1932. https: //doi.org/10.1016/S0140-6736(19)32528-7
[20] Canon, J., Robertson, A.G., Le, A.T., et al. (2020). Targeting KRAS G12C in cancer with Sotorasib. New England Journal of Medicine, 383(13), 1207-1217. https: //doi.org/10.1056/NEJMoa2027079
[21] Liao, W., Chen, V.J., Ma, J., et al. (2020). EGFR inhibition upregulates PD-L1 expression in tumor cells. Cancer Research, 80(21), 4756-4764. https: //doi.org/10.1158/0008-5472.CAN-20-1845
[22] Casanovas, O., Hicklin, D.J., Bergers, G., & Hanahan, D. (2005). Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage tumors. Cancer Cell, 8(4), 299-309. https: //doi.org/10.1016/j.ccr.2005.08.008
[23] Donnem, T., Hu, J., Ferguson, M., et al. (2013). Vessel co-option in primary human tumors and metastases: an obstacle to effective anti-angiogenic treatment? Cancer Medicine, 2(4), 427-436. https: //doi.org/10.1002/cam4.199