

Third and Later Line Therapy in Metastatic Colorectal Cancer – Current Landscape and Future Perspectives

Marjanovic Marko¹, Biljana Kukic^{1,2}, Kolarov Bjelobrk Ivana^{1,2}, Petrovic Nemanja^{1,2}, Djurić Aleksandar^{1,2}, Novak Stela¹, Urosevic Teodora¹

1 Clinic for Internal Oncology, Institute of Oncology Vojvodina, Sremska kamenica, Serbia

2 Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

doi: 10.53011/JMRO.2025.02.03

ISSN: 2784 – 0131

Received October 21, 2025

Revised December 30, 2025

Accepted December 31, 2025

Available online December 31, 2025

*Corresponding author:

Marko Marjanovic

Email: markom.95.ns@gmail.com

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ABSTRACT

Background: Colorectal cancer (CRC) is the third most common malignancy globally, with metastatic disease (mCRC) carrying a poor prognosis. Despite advances in first- and second-line therapies, long-term survival in later-line (≥ 3 L) mCRC remains limited. Molecular profiling has enabled personalized treatment strategies, yet optimal sequencing and therapy selection in refractory disease are still evolving.

Aim: This review summarizes current treatment options for ≥ 3 L mCRC, highlighting recent advances in targeted therapies, biomarker-driven rechallenge strategies, and unmet clinical needs in this setting.

Main Body: Regorafenib, an oral multikinase inhibitor, was the first agent approved for ≥ 3 L mCRC, providing modest survival benefits primarily through disease stabilization. Trifluridine/tipiracil (FTD/TPI), alone or combined with bevacizumab, improves overall survival (OS) and disease control with manageable hematologic toxicity. Fruquintinib, a selective VEGFR inhibitor, has shown efficacy similar to that of other VEGFR inhibitors, with a favorable safety profile. Molecularly guided therapies, including anti-EGFR rechallenge based on circulating tumor DNA (ctDNA), demonstrate promising clinical activity in RAS/BRAF wild-type tumors. BRAF V600E-mutated mCRC benefits from encorafenib plus cetuximab, HER2-amplified tumors respond to trastuzumab-based combinations or antibody–drug conjugates, and KRAS G12C mutations can be targeted using dual inhibition with KRAS G12C inhibitors plus anti-EGFR therapy. Across these agents, preserved performance status consistently predicts clinical benefit.

Conclusion: Significant advances in later-line mCRC therapy, particularly molecularly tailored approaches, have expanded treatment options and improved outcomes for select patients. However, response rates remain modest, resistance ultimately develops, and many patients have limited options due to poor functional status or comorbidities. Future research must focus on predictive biomarkers, optimal sequencing strategies, and combination therapies to further extend survival and quality of life in this challenging patient population.

KEYWORDS: metastatic colorectal cancer, molecularly targeted therapy, third-line therapy

1. Introduction

Colorectal cancer (CRC) is the most common malignancy of the gastrointestinal tract and remains one of

the leading causes of cancer-related morbidity and mortality worldwide. With more than 1.9 million new cases and approximately 850,000 deaths annually, CRC represents a major global health burden (1). Survival outcomes vary widely and are strongly

influenced by disease stage and molecular characteristics. While early-stage disease is potentially curable, metastatic colorectal cancer (mCRC) remains largely incurable, with long-term survival achieved in only a minority of patients (3).

Management of localized CRC is based on surgery with or without adjuvant chemotherapy and radiotherapy. In contrast, treatment of metastatic or unresectable CRC relies on systemic therapy, including cytotoxic chemotherapy, targeted agents, and immunotherapy. Current international guidelines recommend mandatory molecular testing prior to initiating systemic treatment, including RAS and BRAF V600E mutations and microsatellite instability (MSI) status, with additional recommended testing for HER2 amplification, KRAS G12C mutation, and NTRK or RET fusions where appropriate (4,5).

Advances in systemic therapy have significantly improved overall survival (OS) in mCRC, leading to an increasing number of patients eligible for third-line and later (≥ 3 L) treatment (6). However, optimal selection and sequencing of therapies in this setting remain unresolved.

2. Regorafenib

Regorafenib is an oral multikinase inhibitor targeting angiogenic (VEGFR1–3, TIE2/angiopoetin), stromal (PDGFR- β , FGFR), and oncogenic (KIT, BRAF, RET) pathways. Its antitumor activity is primarily mediated by inhibiting angiogenesis and tumor cell proliferation.

Regorafenib was the first agent approved for ≥ 3 L treatment of mCRC based on the pivotal phase III CORRECT trial (7), a randomized, double-blind, placebo-controlled study including 760 heavily pretreated patients. Regorafenib significantly improved OS compared with placebo (median OS 6.4 vs. 5.0 months; HR 0.77, 95% CI 0.64–0.94, $p = 0.0052$), with a modest improvement in progression-free survival (PFS). Objective response rates (ORR) were low (1%), while disease control rate (DCR) reached 41%, reflecting disease stabilization rather than tumor shrinkage. Treatment-related toxicity was substantial, with frequent grade ≥ 3 adverse events (AEs), most commonly hand–foot syndrome, fatigue, and hypertension, often necessitating dose modifications.

Subsequent real-world studies, including REBECCA, CONSIGN, CONCURE, and CORRELATE (8–11), confirmed the survival benefit and

safety profile observed primarily in the CORRECT trial. These studies consistently demonstrated that regorafenib provides a modest but clinically meaningful benefit, predominantly through disease stabilization. Approximately 15–20% of patients experience durable disease control, although no validated predictive biomarkers have been identified (12). Preserved performance status remains the strongest predictor of benefit, with ECOG PS ≥ 2 consistently associated with inferior outcomes. Timing of regorafenib initiation appears clinically relevant. Observational data suggest improved outcomes when regorafenib is used earlier in the ≥ 3 L setting while patients retain good functional status, reserving chemotherapy rechallenge for later lines (13).

3. Trifluridine/Tipiracil (FTD/TPI)

Trifluridine/tipiracil (FTD/TPI) is an oral cytotoxic agent combining trifluridine, a thymidine analog, with tipiracil, a thymidine phosphorylase inhibitor that increases trifluridine bioavailability. Unlike fluoropyrimidines, trifluridine directly incorporates into DNA, disrupting DNA synthesis and inhibiting tumor cell proliferation.

Approval of FTD/TPI was based on the phase III RECURSE trial (17), which enrolled 800 patients with refractory mCRC. Compared with placebo, FTD/TPI significantly improved OS (7.1 vs. 5.3 months; HR 0.68; 95% CI 0.58–0.81, $p < 0.0001$) and PFS (2 vs 1.7 months, HR 0.48, 95% CI 0.41–0.57, $p < 0.0001$), with consistent benefit across all subgroups, regardless of RAS mutation status. ORR remained low, but disease control was achieved in a substantial proportion of patients. Toxicity, as expected, was primarily hematologic, with neutropenia, anemia, and leukopenia being the most common grade ≥ 3 AEs. Non-hematologic toxicity was generally mild and manageable.

Building on the success of RECURSE, the phase III SUNLIGHT trial (18) evaluated the combination of FTD/TPI with bevacizumab, reflecting established synergy between chemotherapy and VEGF inhibition in earlier treatment lines. SUNLIGHT demonstrated a clinically and statistically significant improvement in OS (10.8 vs. 7.5 months; HR 0.44; 95% CI 0.36–0.54, $p < 0.001$) and PFS (5.6 vs 2.4 months; HR 0.61; CI 0.49–0.77, $p < 0.001$) with combination therapy compared with FTD/TPI alone. Disease control rates exceeded 75%, with

acceptable toxicity and no unexpected safety signals. These findings were practice-changing and rapidly incorporated into international guidelines, establishing FTD/TPI plus bevacizumab as a preferred $\geq 3L$ option.

Post-SUNLIGHT meta-analyses and real-world studies have confirmed the efficacy and safety of this combination, including in patients previously treated with bevacizumab (19-21). The majority of studies reported non-significant toxicity in the combination group compared with FTD/TPI alone, except for neutropenia, which ranged up to 45% of patients and remains manageable with appropriate monitoring. Exploratory studies evaluating inflammatory markers, such as the neutrophil-to-lymphocyte and lymphocyte-to-monocyte ratios, as predictive biomarkers are ongoing but not yet validated for routine use (22, 23).

4. Fruquintinib

Fruquintinib is a highly selective oral tyrosine kinase inhibitor targeting VEGFR1–3, designed to provide potent and sustained inhibition of tumor angiogenesis, thereby depriving cancer cells of nutrients and oxygen.

Its approval for refractory mCRC was based on the phase III FRESCO-2 trial (24), which included 691 heavily pretreated patients who had progressed after standard therapies, including regorafenib or FTD/TPI. Fruquintinib significantly improved OS (7.4 vs. 4.8 months; HR 0.66; 95% CI, 0.55–0.80; $p < 0.001$) and PFS (3.7 months vs 1.8 months, with a HR 0.32; 95% CI 0.26–0.38; $p < 0.001$) compared with placebo. While ORR was low (1.5%), disease control was achieved in over half of treated patients. Benefit was observed irrespective of RAS mutation status or prior anti-VEGF therapy.

The safety profile of fruquintinib was favorable, with grade ≥ 3 AEs comparable to placebo. The most common toxicities included hypertension, fatigue, and hand–foot syndrome, which are generally manageable with dose adjustments.

Real-world studies (25-27) have further supported these findings, reporting median OS values equal to or greater than those observed in FRESCO-2, with consistent safety outcomes. As with other $\geq 3L$ agents, preserved ECOG performance status emerged as the most important predictor of benefit, while poor functional status was associated with inferior outcomes (25).

5. Anti-EGFR rechallenge guided by liquid biopsy

Anti-EGFR rechallenge represents a biomarker-driven therapeutic strategy for patients with mCRC who harbor RAS- and BRAF-wild-type tumors and previously derived clinical benefit from anti-EGFR agents in first-line treatment. Acquired resistance to cetuximab or panitumumab most commonly arises through emergent mutations in RAS, BRAF, or the EGFR extracellular domain (EGFR-ECD) (28). Importantly, these resistant subclones have been shown to decay after discontinuation of anti-EGFR therapy, often within four months, providing a strong biological rationale for rechallenge strategies in later treatment lines. The advent of circulating tumor DNA (ctDNA) analysis has enabled real-time, non-invasive monitoring of tumor molecular status and has become central to identifying patients who may regain sensitivity to EGFR inhibition in the $\geq 3L$ setting.

Prospective clinical evidence supports the utility of ctDNA-guided anti-EGFR rechallenge. In the phase II CRICKET trial (29), patients with RAS wild-type ctDNA at the time of rechallenge achieved significantly improved progression-free survival (PFS) and disease control with cetuximab plus irinotecan compared with those harboring RAS mutations (median PFS 4.0 vs 1.9 months; HR 0.44; 95% CI 0.18–0.98; $P = 0.03$). These findings established ctDNA RAS status as a predictive biomarker for rechallenge benefit. The CHRONOS trial (30) further refined patient selection by enrolling only patients with no detectable RAS, BRAF, or EGFR-ECD mutations in ctDNA. Panitumumab monotherapy achieved durable disease control, with a disease control rate exceeding four months in 63% of patients (95% CI 41–78%).

Additional strategies have explored combination approaches. The phase II CAVE trial (31) evaluated cetuximab combined with the PD-L1 inhibitor avelumab as a chemotherapy-free rechallenge regimen in heavily pretreated RAS wild-type mCRC. mPFS of 5.4 months (HR: 0.62; 95% CI: 0.42–0.92; $P=0.017$) and mOS of 15.0 months (HR: 0.61; 95% CI: 0.39–0.97; $P=0.037$) were achieved, demonstrating manageable toxicity and encouraging survival outcomes, suggesting potential synergy between EGFR inhibition and immune modulation.

More recently, a pooled analysis of four Italian phase II trials (31) confirmed the clinical relevance of

anti-EGFR rechallenge in molecularly selected patients. In ctDNA-confirmed RAS/BRAF wild-type mCRC, rechallenge achieved an overall response rate of approximately 17.5%, a disease control rate exceeding 70%, a median PFS of around 4 months, and a median overall survival of approximately 13 months.

The aforementioned studies were all phase II, conducted on a relatively small cohort, while phase III studies (e.g., the FIRE-4 study) are ongoing. Therefore, although anti-EGFR rechallenge based on ctDNA shows encouraging results, it cannot yet be recommended for routine clinical use.

6. BRAF V600E–mutated metastatic colorectal cancer

BRAF V600E mutations occur in approximately 8–10% of metastatic colorectal cancers and are associated with aggressive disease biology and poor prognosis (32). Targeting the MAPK pathway has proven effective in this subgroup, particularly through combined inhibition strategies. While BRAF-targeted therapy may be used earlier when feasible, it remains a recommended and relevant option in the third-line setting for patients with progressive disease.

The phase III BEACON CRC trial (33) established the combination of a BRAF inhibitor (encorafenib) with an anti-EGFR antibody (cetuximab) as a standard of care in previously treated BRAF V600E–mutated mCRC. This regimen significantly improved overall survival (HR=0.60; 95% CI, 0.45–0.79; $P<0.001$), ORR of 20%, and quality of life compared with standard chemotherapy. The addition of a MEK inhibitor did not confer additional benefit and increased toxicity, leading to adoption of the doublet as the preferred approach.

More recently, the phase III BREAKWATER trial (34) evaluated encorafenib plus cetuximab combined with chemotherapy as first-line treatment for BRAF V600E–mutated mCRC. The regimen significantly improved progression-free survival, overall survival, and response rates compared with standard chemotherapy $\pm$ bevacizumab, supporting its emerging role as a first-line option. Early results show very high response rates and promising efficacy (ORR 60.9%; odds ratio, 2.443; 95% CI 1.403–4.253; $P=0.0008$), but final mature PFS/OS results and guideline changes are pending publication and longer follow-up.

7. Anti-HER2–targeted therapy

HER2 amplification or overexpression occurs in approximately 2–5% of metastatic colorectal cancers and is associated with resistance to anti-EGFR therapy (35). In HER2-positive, RAS/BRAF wild-type mCRC, HER2-targeted therapy has emerged as an effective third-line alternative to conventional cytotoxic or antiangiogenic approaches in this molecularly defined subgroup.

Multiple phase II studies have established the efficacy of HER2-directed regimens in ≥ 3 L mCRC. The HERACLES trial (36) demonstrated durable responses with trastuzumab plus lapatinib, while the MyPathway (37) study reported significant activity with trastuzumab combined with pertuzumab. More recently, antibody–drug conjugates have shown particularly promising results. Trastuzumab deruxtecan demonstrated an objective response rate in one third of patients, and prolonged disease control in heavily pretreated patients in the DESTINY-CRC02 phase II trial (38), leading to its inclusion in current treatment guidelines for HER2-positive mCRC after failure of standard therapies. These regimens are generally well tolerated, though interstitial lung disease remains a notable toxicity requiring careful monitoring, occurring in about 10% of patients. Phase III trials (e.g., DESTINY-CRC03) are currently active and aim to further demonstrate the effectiveness of anti-HER2 therapy in the treatment of mCRC, with prolongation of OS as the primary objective.

8. KRAS G12C–mutated metastatic colorectal cancer

KRAS G12C mutations are present in approximately 3–4% of metastatic colorectal cancers and define a distinct molecular subgroup with historically limited targeted treatment options. Unlike in non-small cell lung cancer, single-agent KRAS G12C inhibition has demonstrated modest activity in mCRC due to adaptive resistance mechanisms, particularly through EGFR-mediated reactivation of the pathway (38). As a result, combination strategies targeting both KRAS G12C and EGFR have emerged as the preferred therapeutic approach in the refractory setting.

Clinical evidence supporting this strategy has led to its inclusion in current treatment recommendations

for previously treated KRAS G12C–mutated mCRC. The combination of adagrasib, a selective KRAS G12C inhibitor, with cetuximab demonstrated clinically meaningful antitumor activity in heavily pretreated patients, with improved objective response rates (46% of patients) and a median progression-free survival of 7 months, compared with historical outcomes of standard ≥ 3 L therapies (39). Similar efficacy has been observed with sotorasib combined with panitumumab, with an ORR of over 25% and mPFS of more than 5 months (HR=0.49; 95% CI, 0.30-0.80; P = 0.006), further supporting the biological rationale of dual pathway inhibition (40). These combinations are generally better tolerated than conventional chemotherapy, with manageable gastrointestinal, dermatologic, and hepatic toxicities.

While KRAS G12C–targeted therapy represents a significant advance, responses remain less durable. Resistance eventually develops, and long-term disease control remains uncommon. Nevertheless, in the third-line or later setting, KRAS G12C inhibitor–based combinations provide a valuable, molecularly tailored option with superior efficacy compared to the previous standard of care.

9. Unmet needs and future directions

Despite recent advances, several unmet needs persist in ≥ 3 L mCRC. First, overall response rates remain low for most later-line therapies, with disease stabilization rather than tumor shrinkage being the predominant outcome. Second, predictive biomarkers for patient selection are limited; aside from RAS/BRAF ctDNA-guided anti-EGFR rechallenge, no validated markers reliably identify patients most likely to benefit from regorafenib, fruquintinib, or FTD/TPI. Third, resistance mechanisms emerge rapidly, particularly in targeted therapies such as KRAS G12C inhibitors or HER2-directed regimens, limiting the durability of responses. Fourth, clinical trial populations often exclude patients with poor performance status, leaving a gap in evidence for a substantial proportion of real-world patients who may not tolerate intensive therapy. Finally, sequencing and combination strategies remain poorly defined; while data suggest earlier use of certain agents may be beneficial, standardized algorithms integrating molecular profiling, prior therapy exposure, and patient fitness are lacking. Addressing these gaps through biomarker discovery, novel combination approaches, and adaptive trial designs is essential to improve outcomes and provide truly personalized therapy in later-line mCRC.

ABBREVIATIONS

≥ 3 L – Third-line or later treatment

AE – Adverse event

BRAF – v-raf murine sarcoma viral oncogene homolog B

CRC – Colorectal cancer

ctDNA – Circulating tumor DNA

DCR – Disease control rate

ECOG – Eastern Cooperative Oncology Group

EGFR – Epidermal growth factor receptor

EGFR-ECD – EGFR extracellular domain

FTD/TPI – Trifluridine/tipiracil

HER2 – Human epidermal growth factor receptor 2

KRAS – Kirsten rat sarcoma viral oncogene homolog

mCRC – Metastatic colorectal cancer

mOS – Median overall survival

mPFS – Median progression-free survival

MSI – Microsatellite instability

NTRK – Neurotrophic tropomyosin receptor kinase

ORR – Objective response rate

OS – Overall survival

PDGFR – Platelet-derived growth factor receptor

PFS – Progression-free survival
PS – Performance status
RAS – Rat sarcoma viral oncogene homolog
VEGF – Vascular endothelial growth factor
VEGFR – Vascular endothelial growth factor receptor

STATEMENTS

Authors' contributions: MM conceptualized the study and wrote part of the manuscript. KBI and KB reviewed and edited the manuscript. PN and DA performed the literature search. NS and UT were involved in writing the manuscript. All authors read and approved the final version of the manuscript.

Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all named authors.

Conflict of interests: The authors declare no conflict of interest.

Funding Sources: None

Statement of Ethics: The manuscript does not contain any studies carried out by the authors on humans or animals.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71(3):209-49.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018 Jan;68(1):7-30.
3. Biller LH, Schrag D. Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. *JAMA.* 2021 Feb 16;325(7):669-85.
4. Morris VK, Kennedy EB, Baxter NN, Benson AB 3rd, Cercek A, Cho M, et al. Treatment of metastatic colorectal cancer: ASCO guideline. *J Clin Oncol.* 2023 Jan 20;41(3):678-700.
5. Candia L, Cervantes A, Martinelli E; ESMO Guidelines Committee. Updated treatment recommendations for third and further lines of treatment in advanced colorectal cancer: from the ESMO Metastatic Colorectal Cancer Living Guideline. *Ann Oncol.* 2025 Mar;36(3):342-4.
6. Loupakis F, Antonuzzo L, Bachet JB, Kuan FC, Macarulla T, Pietrantonio F, et al. Practical considerations in the use of regorafenib in metastatic colorectal cancer. *Ther Adv Med Oncol.* 2020 Oct 31;12:1758835920956862.
7. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013 Jan 26;381(9863):303-12.
8. Adenis A, de la Fouchardière C, Paule B, Burtin P, Tougeron D, Waller J, et al. Survival, safety, and prognostic factors for outcome with Regorafenib in patients with metastatic colorectal cancer refractory to standard therapies: results from a multicenter study (RE-BECCA). *BMC Cancer.* 2016 Jul 7;16:412.
9. Van Cutsem E, Martinelli E, Cascinu S, Sobrero A, Banzi M, Seitz JF, et al. Regorafenib for Patients with Metastatic Colorectal Cancer Who Progressed After Standard Therapy: Results of the Large, Single-Arm, Open-Label Phase IIIB CONSIGN Study. *Oncologist.* 2019 Feb;24(2):185-92.
10. Ducreux M, Petersen LN, Öhler L, Bergamo F, Metges JP, de Groot JW, et al. Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer in routine clinical practice in the prospective, observational CORRELATE study. *Eur J Cancer.* 2019 Dec;123:146-54.
11. Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2015 Jun;16(6):619-29.
12. Loupakis F, Antonuzzo L, Bachet JB, Kuan FC, Macarulla T, Pietrantonio F, et al. Practical considerations in the use of regorafenib in metastatic colorectal cancer. *Ther Adv Med Oncol.* 2020 Oct 31;12:1758835920956862.
13. Arnold D, Prager GW, Quintela A, Stein A, Moreno V, van Cutsem E, et al. Beyond second-line therapy in patients with metastatic colorectal cancer: a systematic review. *Ann Oncol.* 2018;29(4):835-56.
14. Rais T, Riaz R, Siddiqui T, Shakeel A, Khan A, Zafar H. Innovations in colorectal cancer treatment: trifluridine and tipiracil with bevacizumab for improved outcomes – a review. *Front Oncol.* 2024 Jul 12;14:1296765.
15. Lenz HJ, Stintzing S, Loupakis F. TAS-102, a novel antitumor agent: a review of the mechanism of action. *Cancer Treat Rev.* 2015;41(9):777-83.
16. Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol.* 2012;13(10):993-1001.
17. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med.* 2015 May 14;372(20):1909-19.

18. Prager GW, Taieb J, Fakih M, Ciardiello F, Van Cutsem E, Elez E, et al. Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. *N Engl J Med*. 2023 May 4;388(18):1657-67.
19. Aquino de Moraes FC, Dantas Leite Pessoa FD, Duarte de Castro Ribeiro CH, Rodrigues Fernandes M, Rodriguez Burbano RM, Carneiro dos Santos NP. Trifluridine-tipiracil plus bevacizumab versus trifluridine-tipiracil monotherapy for chemorefractory metastatic colorectal cancer: a systematic review and meta-analysis. *BMC Cancer*. 2024 Jun 3;24(1):674.
20. Voutsadakis IA. A Systematic Review and Meta-Analysis of Trifluridine/Tipiracil plus Bevacizumab for the Treatment of Metastatic Colorectal Cancer: Evidence from Real-World Series. *Curr Oncol*. 2023 May 24;30(6):5227-39.
21. Yoshino T, Taieb J, Kuboki Y, Pfeiffer P, Kumar A, Hochster HS. Trifluridine/tipiracil with or without bevacizumab in metastatic colorectal cancer: results of a systematic review and meta-analysis. *Ther Adv Med Oncol*. 2023 Jan 21;15:17588359221146137.
22. Matsuda A, Yamada T, Matsumoto S, Sakurazawa N, Kawano Y, Shinozuka E, et al. Pretreatment Neutrophil-to-Lymphocyte Ratio Predicts Survival After TAS-102 Treatment of Patients With Metastatic Colorectal Cancer. *Anticancer Res*. 2019 Aug;39(8):4343-50.
23. Kuramochi H, Yamada T, Yoshida Y, Matsuda A, Kamiyama H, Kosugi C, et al. The Pre-treatment Lymphocyte-to-Monocyte Ratio Predicts Efficacy in Metastatic Colorectal Cancer Treated With TAS-102 and Bevacizumab. *Anticancer Res*. 2021 Jun;41(6):3131-7.
24. Dasari A, Lonardi S, García-Carbonero R, Elez E, Yoshino T, Sobrero A, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. *Lancet*. 2023 Jul 1;402(10395):41-53.
25. Liu S, Lu L, Pan F, Yang C, Liang J, Liu J, et al. Real-World Data: Fruquintinib in Treating Metastatic Colorectal Cancer. *Oncol Res*. 2022 May 4;29(1):25-31.
26. Xu D, Zeng S, Qiu W, Wang G, Qin Z, Liu Y, et al. Fruquintinib in refractory metastatic colorectal cancer: a multicenter real-world study. *ESMO Open*. 2024 Nov;9(11):103702.
27. Zhang Q, Niu H, Cheng K, Qian X. Efficacy and safety of dose adjustment for fruquintinib in the third-line treatment of metastatic colorectal cancer: a retrospective study with real-world settings. *J Gastrointest Oncol*. 2025 Apr 30;16(2):42-54.
28. Tonini G, Imperatori M, Vincenzi B, Frezza AM, Santini D. Rechallenge therapy and treatment holiday: different strategies in management of metastatic colorectal cancer. *J Exp Clin Cancer Res*. 2013 Nov 18;32(1):92.
29. Cremolini C, Rossini D, Dell'Aquila E, Lonardi S, Conca E, Del Re M, et al. Rechallenge for Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer With Acquired Resistance to First-line Cetuximab and Irinotecan: A Phase 2 Single-Arm Clinical Trial. *JAMA Oncol*. 2019 Mar 1;5(3):343-50.
30. Sartore-Bianchi A, Pietrantonio F, Lonardi S, Mussolin B, Rua F, Crisafulli G, et al. Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial. *Nat Med*. 2022 Aug;28(8):1612-8.
31. Ciardiello D, Martini G, Bielo LB, Pietrantonio F, Raimondi A, Manca P, et al. Cetuximab rechallenge in molecularly selected metastatic colorectal cancer: the randomized CAVE-2 GOIM trial. *Ann Oncol*. 2025 Dec 22;36(12):S0923-7534(25)06334-3.
32. Guerrero RM, Labajos VA, Ballena SL, Macha CA, Lezama MS, Roman CP, et al. Targeting BRAF V600E in metastatic colorectal cancer: where are we today? *Eccancermediscience*. 2022 Dec 15;16:1489.
33. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. *N Engl J Med*. 2019 Oct 24;381(17):1632-43.
34. Elez E, Yoshino T, Shen L, Lonardi S, Van Cutsem E, Eng C, et al. Encorafenib, Cetuximab, and mFOLFOX6 in BRAF-Mutated Colorectal Cancer. *N Engl J Med*. 2025 Jun 26;392(24):2425-37.
35. Singh H, Kang A, Bloudek L, Hsu LI, Palanca-Wessels MC, Stecher M, et al. Systematic literature review and meta-analysis of HER2 amplification, overexpression, and positivity in colorectal cancer. *JNCI Cancer Spectr*. 2024 Jan 4;8(1):pkad082.
36. Sartore-Bianchi A, Trusolino L, Martino C, Bencardino K, Lonardi S, Bergamo F, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016 Jun;17(6):738-46.
37. Meric-Bernstam F, Hurwitz H, Raghav KPS, McWilliams RR, Fakih M, VanderWalde A, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol*. 2019 Apr;20(4):518-30.
38. Raghav K, Siena S, Takashima A, Kato T, Van den Eynde M, Pietrantonio F, et al. Trastuzumab deruxtecan in patients with HER2-positive advanced colorectal cancer (DESTINY-CRC02): primary results from a multicentre, randomised, phase 2 trial. *Lancet Oncol*. 2024 Sep;25(9):1147-62.
39. Yaeger R, Weiss J, Pelster MS, Spira AI, Barve M, Ou SI, et al. Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated KRAS G12C. *N Engl J Med*. 2023 Jan 5;388(1):44-54.
40. Fakih MG, Salvatore L, Esaki T, Modest DP, Lopez-Bravo DP, Taieb J, et al. Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated KRAS G12C. *N Engl J Med*. 2023 Dec 7;389(23):2125-39.