Review Article

Decoding the Complexities of Colorectal Cancer Treatment: Modalities and Outcomes

Abstract

Colorectal cancer (CRC) is the third most common cancer worldwide, remains a major cause of cancer-related morbidity and mortality globally. It has diverse treatment modalities including chemotherapy, immunotherapy, and targeted therapies. Chemotherapy remains a cornerstone of CRC management, either as adjuvant therapy post-surgery or as palliative treatment for advanced disease. Recent advancements in immunotherapy have transformed treatments particularly in subsets characterized by microsatellite instability-high (MSI-H) or deficient DNA mismatch repair (dMMR). Targeted therapies have revolutionized the management of CRC by specifically targeting molecular pathways involved in tumor growth and progression. This review provides a comprehensive overview of current guidelines and emerging strategies in CRC treatment, focusing on chemotherapy regimens, immune checkpoint inhibitors (ICIs), targeted therapies, biomarkers for treatment selection, and ongoing challenges.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with a significant portion of patients diagnosed at advanced stages [1]. Patients with CRC typically present with rectal bleeding, microcytic anemia, altered bowel habits, and chronic abdominal pain, with median age at onset is 67 years [2]. Advances in understanding molecular pathways and tumor biology have revolutionized treatment strategies beyond traditional chemotherapy and surgery. Immunotherapy, particularly ICIs targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), has emerged as a promising strategy [3]. The management of CRC involves multimodal treatment approaches, with chemotherapy playing a crucial role in both early-stage and metastatic disease settings. Targeted therapies, such as monoclonal antibodies and small molecule inhibitors, aim to improve outcomes by selectively inhibiting oncogenic signaling pathways. This review aims to summarize current guidelines and novel approaches in CRC therapy, encompassing chemotherapy, immunotherapy with ICIs, and targeted therapies tailored to specific molecular alterations.

Methods

A systematic search of PubMed, clinical trial databases, and oncology society guidelines up to was conducted. Search terms included "colorectal cancer," "microsatellite instability," "chemotherapy," "immunotherapy," "immune checkpoint inhibitors," "targeted therapy,"

"monoclonal antibodies," "PD-1," "PD-L1," “small molecule inhibitors," and specific molecular targets in CRC (e.g., EGFR, HER2, BRAF).and combinations thereof. Studies, guidelines, and systematic reviews addressing chemotherapy, immunotherapy, and targeted therapies in CRC were included for analysis and synthesis.

Results and Discussion

Systemic chemotherapy is the primary treatment for metastatic CRC. Based on population-based data from the National Cancer Institute, 5-year survival for metastatic CRC is 16% [2]. Integration of chemotherapy, immunotherapy, and targeted therapies in CRC treatment requires biomarker-driven precision medicine approaches. Biomarkers such as MSI status, RAS/BRAF mutations, and HER2 amplification play pivotal roles in treatment decision-making. Challenges include primary and acquired resistance mechanisms, treatment-related toxicities, and optimizing sequencing of therapies in the continuum of care [4].

Chemotherapy

The optimization of chemotherapy in CRC involves balancing efficacy, toxicity, and patient-specific considerations. Biomarkers such as RAS status, MSI status, and tumor sidedness are increasingly used to guide treatment decisions and predict response to therapy [5]. Challenges include primary and acquired resistance, treatment-related toxicities, and the need for continuous adaptation based on evolving clinical evidence. For the 50% of patients with metastatic CRC with KRAS/NRAS/BRAF wild-type tumors, cetuximab and panitumumab (monoclonal antibodies to the epithelial growth factor receptor [EGFR]), in combination with chemotherapy, can extend median survival by 2 to 4 months compared with chemotherapy alone [6]. In the 1990s, fluorouracil-based chemotherapy improved the OS of patients with mCRC to 14 months. Later, the additional combination of leucovorin and oxaliplatin (FOLFOX) prolonged the OS to 19.5 months [7]

Adjuvant chemotherapy plays a crucial role in managing stage III and potentially high-risk stage II colon cancer [8]. In both younger and older patients, 5-FU/LV adjuvant chemotherapy demonstrates comparable benefits in terms of progression-free survival (PFS), disease-free survival (DFS), and overall survival (OS) [9]. For metastatic colorectal cancer (CRC), cytotoxic chemotherapy remains the cornerstone of treatment. Options include single-agent weekly or every three weeks irinotecan, as well as oxaliplatin-containing regimens such as FOLFOX, XELOX (capecitabine plus oxaliplatin), or combinations like irinotecan plus oxaliplatin [10][11]. BRAFV600E mutations in CRC correlate with advanced age, right-sided colon primaries, and female gender, and are associated with reduced chemotherapy response and poorer prognosis [12][13].

Despite the challenging prognosis linked to BRAFV600E-mutant mCRC, aggressive first-line chemotherapy has not shown improved outcomes. Meta-analysis results suggest that for

these patients, combining bevacizumab with a chemotherapy regimen like FOLFOXIRI optimizes clinical activity and quality of life [14][15]. In the BEACON CRC trial involving 665 patients with BRAFV600E-mutant mCRC, second- or third-line treatment with anti-BRAF/MEK/EGFR triplet therapy (encorafenib, binimetinib, and cetuximab) or anti-BRAF/EGFR doublet therapy (encorafenib and cetuximab) was compared with standard care options [16]. The trial established that the doublet regimen of encorafenib plus cetuximab is now a recommended standard of care for previously treated patients with BRAFV600E-mutant mCRC, receiving FDA approval on April 8, 2020 [17].

Recent advances include the integration of targeted therapies and immunotherapy into chemotherapy regimens, particularly in biomarker-selected patient populations (e.g., RAS wild-type tumors for anti-EGFR therapy, MSI-H tumors for immunotherapy). These approaches aim to improve efficacy and minimize toxicity through personalized treatment strategies.

Targeted therapies

The integration of targeted therapies into CRC treatment algorithms has significantly enhanced survival outcomes, particularly in biomarker-selected patient populations. These therapies primarily target EGFR, VEGF, and other critical signaling pathways involved in tumor proliferation and angiogenesis. Monoclonal antibodies such as cetuximab and panitumumab, which inhibit the EGFR pathway, are recommended for RAS wild-type metastatic CRC [18]. Bevacizumab, an anti-VEGF antibody, is utilized in combination with chemotherapy as a first-line treatment for metastatic CRC [19]. Despite these advancements, acquired resistance to targeted therapies remains a challenge in CRC, driven by mechanisms such as secondary mutations in target genes, activation of alternative signaling pathways, and changes in the tumor microenvironment. Ongoing research is focused on developing combination therapies, novel agents targeting resistance pathways, and exploring immunotherapy combinations to overcome resistance and improve treatment outcomes.

Targeted therapies for colorectal cancer (CRC) are tailored to specific molecular alterations. RAS and BRAF mutations dictate the use of anti-EGFR therapies, while HER2 amplification suggests HER2-targeted agents may be beneficial. Regorafenib and TAS-102 are approved for refractory CRC, targeting angiogenesis and cell cycle pathways, respectively. Cetuximab, the first FDA-approved targeted drug for CRC in 2004 [20], marked the beginning of a growing array of FDA-approved therapies for metastatic CRC (mCRC).

The progression of mCRC involves interactions with various receptor-mediated signaling pathways, including EGFRs, FGFRs, VEGFRs, and TRKs [21][22]. Immune evasion mechanisms mediated by molecules like PD-L1 and CTLA-4 necessitate inhibition by targeted drugs [22]. Cetuximab and panitumumab, monoclonal antibodies targeting EGFR, are used alone or with chemotherapy for RAS wild type mCRC [18]. VEGF/VEGFR-targeted strategies are employed in CRC, especially for patients with or without RAS mutations and considerations of

tumor location [19]. Bevacizumab, an anti-VEGF-A monoclonal antibody, is FDA-approved for mCRC [23]. Aflibercept, functioning as a decoy receptor for VEGF-A, has demonstrated efficacy in mCRC as well [24]. In the VELOUR trial, compared to placebo plus FOXFIRI, the combination of aflibercept and FOXFIRI significantly enhanced overall survival (OS) (13.5 months vs. 12.06 months), progression-free survival (PFS) (6.9 months vs. 4.67 months), and response rate (RR) (19.8% vs. 11.1%) in metastatic colorectal cancer (mCRC) patients who had previously received oxaliplatin-based therapy. These findings support the recommendation for aflibercept-based regimens in second-line treatment settings [25].

Ramucirumab, another anti-VEGF-A monoclonal antibody, improves outcomes in combination with chemotherapy for mCRC patients who have progressed on previous therapies. In the RAISE study, ramucirumab combined with FOLFIRI showed substantial improvements in overall survival (OS) (13.3 months vs. 11.7 months) and progression-free survival (PFS) (5.7 months vs. 4.5 months) compared to FOLFIRI alone [26]. This regimen received FDA approval for second-line treatment in combination with FOLFIRI for metastatic colorectal cancer (mCRC) patients who experienced disease progression following or during treatment with bevacizumab, oxaliplatin, and fluoropyrimidine therapies [27]. Regorafenib, inhibiting multiple kinases including VEGFR and FGFR, is effective in previously treated mCRC, demonstrating improved survival outcomes [28]. Regorafenib has been FDA-approved for the treatment of metastatic colorectal cancer (mCRC) in patients who have undergone prior therapies. Clinical trials such as CORRECT and CONCUR have shown significant improvements in overall survival (OS) compared to placebo [29][30]. The neurotrophic tropomyosin receptor kinases (NTRK) operate through homodimerization, activating downstream pathways such as RAS/Raf/MEK/ERK, PI3K/Akt, and PLC-γ/PKC. These pathways promote gene transcription, cell survival, and cancer progression [31][32]. In addition to NTRK, anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) fusions also occur in colorectal cancer (CRC) [33].

ALK and ROS1 encode tyrosine kinases that are persistently activated through fusion events, thereby stimulating downstream signaling pathways crucial for tumor cell growth and progression [34]. Larotrectinib and entrectinib represent first-generation TRK inhibitors, approved by the FDA for solid tumors harboring NTRK gene fusions [35]. Entrectinib, a potent inhibitor of TRK, ROS1, and ALK kinases, demonstrated efficacy in phase I/II trials involving 54 cancer patients with NTRK fusions across a wide age range (1 month to 84 years), achieving an impressive overall response rate (ORR) of 57% alongside good tolerability [36]. BRAF acts as a downstream effector in the RAS/Raf/MEK/ERK signaling pathway and is a significant oncogenic driver [37]. Mutations like BRAF V600E are found in about 10% of metastatic colorectal cancers (mCRCs) and are linked to chemotherapy resistance and poorer prognosis [38][39]. Encorafenib, a kinase inhibitor targeting BRAF V600E and wild-type BRAF, exhibits prolonged pharmacodynamic activity compared to other BRAF inhibitors [40]. In the BEACON trial, an open-label phase III study, encorafenib combined with cetuximab significantly improved median overall survival (OS) (8.4 months vs. 5.4 months) and response rates (RR) (20% vs. 2%)

compared to cetuximab plus chemotherapy [41]. Based on these findings, the FDA approved encorafenib in 2020 for the treatment of mCRC with a BRAF V600E mutation following prior therapy [19].

Immunotherapy

Immune Checkpoint Inhibitors (ICIs) have revolutionized cancer treatment by targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways [42]. Pembrolizumab and nivolumab, anti-PD-1 antibodies, have demonstrated significant efficacy in microsatellite instability-high (MSI-H) or deficient DNA mismatch repair (dMMR) colorectal cancer (CRC), with durable responses observed in clinical trials [43]. Key studies like CheckMate 142 and KEYNOTE-164 reported objective response rates (ORRs) of up to 50% in heavily pretreated metastatic CRC patients [44][45]. Pembrolizumab is FDA-approved for MSI-H/dMMR metastatic CRC, underscoring the importance of biomarker-driven treatment selection. Tumor immunotherapy induces immune cell-mediated responses against neoantigens expressed on various tumors [46]. Approximately 5% of metastatic CRC cases exhibit MSI/dMMR status, making MSI-high tumors particularly responsive to immunotherapy [47]. PD-1 and CTLA-4 are immune checkpoint molecules expressed on activated T-cells that regulate immune responses through distinct mechanisms [48].

Pembrolizumab and nivolumab are FDA-approved for MSI-H/dMMR metastatic CRC [49]. In the open-label phase III KEYNOTE-177 trial, pembrolizumab as first-line treatment for MSI-H/dMMR metastatic CRC showed superior progression-free survival (PFS) (16.5 months vs. 8.2 months) and ORR (43.8% vs. 33.1%) compared to chemotherapy, with lower incidence of grade 3 or higher treatment-related adverse effects (22% vs. 66%) [50]. Similarly, in the CheckMate 142 trial, second-line nivolumab treatment in MSI-H/dMMR metastatic CRC demonstrated an ORR of 31% and disease control for 12 weeks or longer in 69% of patients [45]. Both agents have shown efficacy and manageable safety profiles in this patient population.

Ipilimumab, a fully human anti-CTLA-4 monoclonal antibody, is FDA-approved in combination with nivolumab for MSI-H/dMMR metastatic CRC after progression following chemotherapy [51]. In the CheckMate-142 trial, combination therapy with nivolumab and ipilimumab improved 1-year overall survival (85% vs. 73%), ORR (55% vs. 31%), and disease control for 12 weeks or longer (80% vs. 69%) compared to nivolumab alone [45]. These results highlight the favorable impact of combination therapy on quality of life for patients with MSI-H/dMMR metastatic CRC [52]. The incorporation of immunotherapy into colorectal cancer (CRC) treatment protocols marks a transformative shift, particularly in cohorts selected based on biomarkers. Challenges encompass identifying predictive biomarkers extending beyond MSI/dMMR, managing immune-related adverse events, and comprehending mechanisms underpinning primary and acquired resistance [53]. Tailored precision medicine strategies are pivotal for optimizing patient selection and therapeutic outcomes.

Conclusion

Chemotherapy remains a cornerstone of treatment in colorectal cancer, both in adjuvant and metastatic settings. Immunotherapy represents a significant advancement in the treatment of CRC, particularly in MSI-H/dMMR subtypes. Targeted therapies have transformed the treatment of CRC by targeting specific molecular aberrations driving tumor growth. Current guidelines advocate for a multidisciplinary approach integrating chemotherapy, immunotherapy, and targeted therapies tailored to CRC molecular profiles. Advances in biomarker identification and therapeutic combinations offer new opportunities to improve outcomes for CRC patients. Future directions include the development of predictive biomarkers, optimizing biomarker-driven patient selection, exploring rational combinations, and overcoming resistance mechanisms, refinement of combination strategies into early-stage CRC treatment algorithms.

References

1. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145-164. doi:10.3322/caac.21601
2. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer stat facts: colorectal cancer. Accessed August 10, 2024.https://seer.cancer.gov/statfacts/html/colorect.html
3. Guo Y, Shi M, Shen X, Yang C, Yang L, Zhang J. Capecitabine plus irinotecan versus 5-FU/leucovorin plus irinotecan in the treatment of colorectal cancer: a meta-analysis. Clin Colorectal Cancer. 2014;13(2):110-118. doi: 10.1016/j.clcc.2013.12.004
4. Guo Y, Xiong BH, Zhang T, Cheng Y, Ma L. XELOX vs. FOLFOX in metastatic colorectal cancer: an updated meta-analysis. Cancer Invest. 2016;34(2):94-104. doi:10.3109/07357907.2015.1104689
5. Biller LH, Schrag D. Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. JAMA. 2021;325(7):669–685. doi:10.1001/jama.2021.0106
6. Douillard, J.Y.; Cunningham, D.; Roth, A.D.; Navarro, M.; James, R.D.; Karasek, P.; Jandik, P.; Iveson, T.; Carmichael, J.; Alakl, M.; et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. Lancet 2000, 355, 1041–1047.
7. Goldberg, R.M.; Sargent, D.J.; Morton, R.F.; Fuchs, C.S.; Ramanathan, R.K.; Williamson, S.K.; Findlay, B.P.; Pitot, H.C.; Alberts, S.R. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J. Clin. Oncol. 2004, 22, 23–30.

8. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, Hill M, Gilberg F, Rittweger K, Schmoll HJ. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011;29:1465–1471.
9. Iwashyna TJ, Lamont EB. Effectiveness of adjuvant fluorouracil in clinical practice: a population-based cohort study of elderly patients with stage III colon cancer. J Clin Oncol. 2002;20:3992–3998.
10. Figer A, Perez-Staub N, Carola E, Tournigand C, Lledo G, Flesch M, Barcelo R, Cervantes A, André T, Colin P, et al. FOLFOX in patients aged between 76 and 80 years with metastatic colorectal cancer: an exploratory cohort of the OPTIMOX1 study. Cancer. 2007;110:2666–2671.
11. Seymour MT, Thompson LC, Wasan HS, Middleton G, Brewster AE, Shepherd SF, O'Mahony MS, Maughan TS, Parmar M, Langley RE. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. Lancet. 2011;377:1749–1759.
12. Bokemeyer C, Cutsem EV, Rougier P, et al: Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer 48:1466-1475, 2012
13. Pietrantonio F, Perrone F, Biondani P, et al: Single agent panitumumab in KRAS wild-type metastatic colorectal cancer patients following cetuximab-based regimens: Clinical outcome and biomarkers of efficacy. Cancer Biol Ther 14:1098-1103, 2013
14. Karapetis CS, Jonker D, Daneshmand M, et al: PIK3CA, BRAF, and PTEN status and benefit from cetuximab in the treatment of advanced colorectal cancer—Results from NCIC CTG/AGITG CO.17. Clin Cancer Res 20:744-753, 2014
15. Pietrantonio F, Petrelli F, Coinu A, et al: Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: A meta-analysis. Eur J Cancer 51:587-594, 2015
16. Tabernero J, Grothey A, Van Cutsem E, et al: Encorafenib plus cetuximab as a new standard of care for previously treated BRAF V600e-mutant metastatic colorectal cancer: Updated survival results and subgroup Analyses from the BEACON study. J Clin Oncol 39:273-284, 2021
17. FDA Approves Encorafenib in Combination with Cetuximab for Metastatic Colorectal Cancer with a BRAF V600E Mutation. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-combination-cetuximab-metastatic-colorectal-cancer-braf-v600e-mutation, 2020
18. Van Cutsem, E.; Cervantes, A.; Adam, R.; Sobrero, A.; Van Krieken, J.H.; Aderka, D.; Aranda Aguilar, E.; Bardelli, A.; Benson, A.; Bodoky, G.; et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann. Oncol. 2016, 27, 1386–1422.

19. Ohishi T, Kaneko MK, Yoshida Y, Takashima A, Kato Y, Kawada M. Current Targeted Therapy for Metastatic Colorectal Cancer. Int J Mol Sci. 2023 Jan 15;24(2):1702. doi: 10.3390/ijms24021702. PMID: 36675216; PMCID: PMC9864602.
20. Caballero Servin, I.A. Evaluation and application of microbiological methods to the sanitary control of restaurants. Salud Publica Mex. 1967, 9, 221–235.
21. Kheder, E.S.; Hong, D.S. Emerging Targeted Therapy for Tumors with NTRK Fusion Proteins. Clin. Cancer Res. 2018, 24, 5807–5814.
22. Guler, I.; Askan, G.; Klostergaard, J.; Sahin, I.H. Precision medicine for metastatic colorectal cancer: An evolving era. Expert Rev. Gastroenterol. Hepatol. 2019, 13, 919–931.
23. Wang Y., Fei D., Vanderlaan M., Song A. Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. Angiogenesis. 2004;7:335–345. doi: 10.1007/s10456-004-8272-2.
24. Papadopoulos N., Martin J., Ruan Q., Rafique A., Rosconi M.P., Shi E., Pyles E.A., Yancopoulos G.D., Stahl N., Wiegand S.J. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis. 2012;15:171–185. doi: 10.1007/s10456-011-9249-6.
25. Van Cutsem E., Tabernero J., Lakomy R., Prenen H., Prausova J., Macarulla T., Ruff P., van Hazel G.A., Moiseyenko V., Ferry D., et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J. Clin. Oncol. 2012;30:3499–3506. doi: 10.1200/JCO.2012.42.8201.
26. Tabernero J., Yoshino T., Cohn A.L., Obermannova R., Bodoky G., Garcia-Carbonero R., Ciuleanu T.E., Portnoy D.C., Van Cutsem E., Grothey A., et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): A randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015;16:499–508. doi: 10.1016/S1470-2045(15)70127-0.
27. Debeuckelaere C., Murgioni S., Lonardi S., Girardi N., Alberti G., Fano C., Gallimberti S., Magro C., Ahcene-Djaballah S., Daniel F., et al. Ramucirumab: The long and winding road toward being an option for mCRC treatment. Expert Opin. Biol. Ther. 2019;19:399–409. doi: 10.1080/14712598.2019.1600505.
28. Carter N.J. Regorafenib: A review of its use in previously treated patients with progressive metastatic colorectal cancer. Drugs Aging. 2014;31:67–78. doi: 10.1007/s40266-013-0140-6.
29. Grothey A., Van Cutsem E., Sobrero A., Siena S., Falcone A., Ychou M., Humblet Y., Bouche O., Mineur L., Barone C., et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381:303–312. doi: 10.1016/S0140-6736(12)61900-X.

30. Li J., Qin S., Xu R., Yau T.C., Ma B., Pan H., Xu J., Bai Y., Chi Y., Wang L., 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;16:619–629. doi: 10.1016/S1470-2045(15)70156-7.
31. Amatu, A.; Sartore-Bianchi, A.; Bencardino, K.; Pizzutilo, E.G.; Tosi, F.; Siena, S. Tropomyosin receptor kinase (TRK) biology and the role of NTRK gene fusions in cancer. Ann. Oncol. 2019, 30 (Suppl. 8), viii5–viii15.
32. Cho, H.; Kim, N.; Murakami, T.; Sim, T. Anti-Tumor Activity of AZD4547 Against NTRK1 Fusion Positive Cancer Cells Through Inhibition of NTRKs. Front. Oncol. 2021, 11, 757598.
33. Hallberg, B.; Palmer, R.H. The role of the ALK receptor in cancer biology. Ann. Oncol. 2016, 27 (Suppl. 3), iii4–iii15.
34. Akhoundova, D.; Hussung, S.; Sivakumar, S.; Topfer, A.; Rechsteiner, M.; Kahraman, A.; Arnold, F.; Angst, F.; Britschgi, C.; Zoche, M.; et al. ROS1 genomic rearrangements are rare actionable drivers in microsatellite stable colorectal cancer. Int. J. Cancer 2022, 151, 2161–2171.
35. Ratti, M.; Grizzi, G.; Passalacqua, R.; Lampis, A.; Cereatti, F.; Grassia, R.; Hahne, J.C. NTRK fusions in colorectal cancer: Clinical meaning and future perspective. Expert Opin. Ther. Targets 2021, 25, 677–683.
36. Doebele, R.C.; Drilon, A.; Paz-Ares, L.; Siena, S.; Shaw, A.T.; Farago, A.F.; Blakely, C.M.; Seto, T.; Cho, B.C.; Tosi, D.; et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020, 21, 271–282.
37. He, Z.; Thorrez, L.; Siegfried, G.; Meulemans, S.; Evrard, S.; Tejpar, S.; Khatib, A.M.; Creemers, J.W.M. The proprotein convertase furin is a pro-oncogenic driver in KRAS and BRAF driven colorectal cancer. Oncogene 2020, 39, 3571–3587.\
38. Jones, J.C.; Renfro, L.A.; Al-Shamsi, H.O.; Schrock, A.B.; Rankin, A.; Zhang, B.Y.; Kasi, P.M.; Voss, J.S.; Leal, A.D.; Sun, J.; et al. (Non-V600) BRAF Mutations Define a Clinically Distinct Molecular Subtype of Metastatic Colorectal Cancer. J. Clin. Oncol. 2017, 35, 2624–2630.
39. Chu, J.E.; Johnson, B.; Kugathasan, L.; Morris, V.K.; Raghav, K.; Swanson, L.; Lim, H.J.; Renouf, D.J.; Gill, S.; Wolber, R.; et al. Population-based Screening for BRAF (V600E) in Metastatic Colorectal Cancer Reveals Increased Prevalence and Poor Prognosis. Clin. Cancer Res. 2020, 26, 4599–4605.
40. Delord, J.P.; Robert, C.; Nyakas, M.; McArthur, G.A.; Kudchakar, R.; Mahipal, A.; Yamada, Y.; Sullivan, R.; Arance, A.; Kefford, R.F.; et al. Phase I Dose-Escalation and -Expansion Study of the BRAF Inhibitor Encorafenib (LGX818) in Metastatic BRAF-Mutant Melanoma. Clin. Cancer Res. 2017, 23, 5339–5348.

41. Kopetz, S.; Grothey, A.; Yaeger, R.; Van Cutsem, E.; Desai, J.; Yoshino, T.; Wasan, H.; Ciardiello, F.; Loupakis, F.; Hong, Y.S.; et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. N. Engl. J. Med. 2019, 381, 1632–1643.
42. Goey KKH, Elias SG, van Tinteren H, et al. Maintenance treatment with capecitabine and bevacizumab versus observation in metastatic colorectal cancer: updated results and molecular subgroup analyses of the phase 3 CAIRO3 study. Ann Oncol. 2017;28(9):2128-2134. doi:10.1093/annonc/mdx322
43. André T, Shiu K-K, Kim TW, et al; KEYNOTE-177 Investigators. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020;383(23):2207-2218. doi:10.1056/NEJMoa2017699
44. Le DT, Kim TW, Van Cutsem E, et al. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: KEYNOTE-164. J Clin Oncol. 2020;38(1):11-19. doi:10.1200/JCO.19.02107
45. Overman, M.J.; McDermott, R.; Leach, J.L.; Lonardi, S.; Lenz, H.J.; Morse, M.A.; Desai, J.; Hill, A.; Axelson, M.; Moss, R.A.; et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): An open-label, multicentre, phase 2 study. Lancet Oncol. 2017, 18, 1182–1191.
46. Hu, L.F.; Lan, H.R.; Huang, D.; Li, X.M.; Jin, K.T. Personalized Immunotherapy in Colorectal Cancers: Where Do We Stand? Front. Oncol. 2021, 11, 769305.
47. Colle, R.; Cohen, R.; Cochereau, D.; Duval, A.; Lascols, O.; Lopez-Trabada, D.; Afchain, P.; Trouilloud, I.; Parc, Y.; Lefevre, J.H.; et al. Immunotherapy and patients treated for cancer with microsatellite instability. Bull Cancer 2017, 104, 42–51.
48. Myint, Z.W.; Goel, G. Role of modern immunotherapy in gastrointestinal malignancies: A review of current clinical progress. J. Hematol. Oncol. 2017, 10, 86.
49. Sun, J.; Zheng, Y.; Mamun, M.; Li, X.; Chen, X.; Gao, Y. Research progress of PD-1/PD-L1 immunotherapy in gastrointestinal tumors. Biomed. Pharmacother. 2020, 129, 110504.
50. Andre, T.; Shiu, K.K.; Kim, T.W.; Jensen, B.V.; Jensen, L.H.; Punt, C.; Smith, D.; Garcia-Carbonero, R.; Benavides, M.; Gibbs, P.; et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N. Engl. J. Med. 2020, 383, 2207–2218.
51. Garcia, C.R.; Jayswal, R.; Adams, V.; Anthony, L.B.; Villano, J.L. Multiple sclerosis outcomes after cancer immunotherapy. Clin. Transl. Oncol. 2019, 21, 1336–1342.
52. Overman, M.J.; Lonardi, S.; Wong, K.Y.M.; Lenz, H.J.; Gelsomino, F.; Aglietta, M.; Morse, M.A.; Van Cutsem, E.; McDermott, R.; Hill, A.; et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. J. Clin. Oncol. 2018, 36, 773–779.
53. Shulman K, Barnett-Griness O, Friedman V, et al. Outcomes of chemotherapy for microsatellite instable-high metastatic colorectal cancers. JCO Precis Oncol. 2018;2:2. doi:10.1200/PO.17.00253