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REVIEW

Advances in the Use of Immune Checkpoint Inhibitors for Colorectal Cancer Treatment

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Purpose: Colorectal cancer (CRC) is a highly prevalent malignant tumor worldwide, and the emergence of immune checkpoint inhibitors (ICIs) has changed CRC immunotherapy. This systematic review aims to provide a comprehensive overview of registered clinical trials on ICIs in CRC worldwide, with a focus on major molecular targets, combination therapy strategies, geographic distribution patterns, and future directions for precision immunotherapy.

Methods: All clinical trials related to ICIs in CRC were retrieved. Trials were screened according to inclusion and exclusion criteria, and core information such as trial phase, conducting country, mechanism targets, and combination therapy, was systematically organized for retrospective and trend analyses.

Results: A total of 1,479 eligible clinical trials were included. There has been a steady increase in the number of registered trials, with Phase II trials being the most numerous. The United States and China lead globally in the number of trials reported. Key research targets included PD-1, PD-L1, CTLA-4, and molecules related to the tumor microenvironment. Combination therapies involving ICIs, anti-angiogenic agents, and targeted drugs across multiple pathways emerged as a new research focus.

Conclusion: ICIs have driven the development of precision immunotherapy for CRC, and multi-target combination therapies hold promise for improving outcomes. However, clinical translation and efficacy improvements remain challenging. Future studies should focus on the mechanisms involved and accumulating clinical data to guide more effective immunotherapy strategies.

Keywords: colorectal cancer, immune checkpoint inhibitors, clinical trials, combination therapy, tumor microenvironment

Introduction

Colorectal cancer (CRC) is a common malignant tumor with persistently high incidence and mortality rates worldwide. There are approximately 1.9 million new CRC cases and nearly 916,000 related deaths each year globally, ranking third among all malignant tumors in terms of incidence and second in terms of mortality.[1] With population aging and changes in lifestyle, the incidence and mortality of CRC are expected to continue rising.[2] Therefore, the prevention and treatment of CRC have become a critical issue in global cancer control.

Currently, the main treatment modalities for CRC include surgery, chemotherapy, radiotherapy, and targeted therapy. For patients with early-stage CRC, surgical resection is the most effective treatment approach and can offer a high cure rate. However, as the disease progresses, especially in cases of locally advanced and metastatic CRC, the efficacy of surgical treatment becomes limited and complete eradication is often unachievable.[3] Chemotherapy and radiotherapy are commonly used as adjuvant therapies; they primarily aim to reduce the risk of recurrence and improve survival. Nevertheless, these treatment methods are also associated with significant side effects, particularly with prolonged therapy, which may greatly impact patients' quality of life, highlighting the urgent need for new therapeutic approaches.[4]

In recent years, the emergence of immunotherapy, especially immune checkpoint inhibitors (ICIs), has brought significant breakthroughs to cancer treatment. ICIs restore and enhance the body's immune response against tumors by blocking inhibitory signals between tumor cells and T cells, thereby effectively increasing antitumor activity.[5] Particularly in

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microsatellite instability-high (MSI-H) or DNA mismatch repair-deficient (dMMR) colorectal cancer, ICIs have demonstrated excellent efficacy and tolerability. This subgroup of patients is characterized by high tumor mutational burden, abundant tumor neoantigens, and increased T-cell infiltration, making them ideal candidates for immunotherapy, with some patients achieving durable survival (5). PD-1/PD-L1 inhibitors such as pembrolizumab and nivolumab have been approved for first-line and subsequent-line treatment in patients with advanced or metastatic MSI-H/dMMR CRC, significantly improving the long-term survival of this subtype of patients.[6]

However, the efficacy of ICIs varies among the overall CRC patient population. Recent studies have revealed that tumor immune evasion is not only related to the abnormal expression of conventional immune checkpoints but also closely associated with multiple mechanisms within the tumor microenvironment (TME), such as abnormal tumor angiogenesis, infiltration of immunosuppressive cells, signal pathway alterations, and metabolic reprogramming. These factors collectively influence both the therapeutic response and resistance to ICIs. On this basis, an increasing number of clinical studies are focusing on the combined regulation of angiogenesis, signaling pathways, and immune metabolism, leading to the identification of a series of potential immunotherapeutic targets and providing both theoretical and molecular foundations for multi-target combination therapy.[7]

Therefore, systematically reviewing the recent clinical studies on ICIs for CRC, and exploring molecular targets roles in combination immunotherapy, is of great significance for advancing precision immunotherapy in CRC. To this end, we used the Trialtrove website (https://clinicalintelligence.citeline.com/) to systematically integrate and review global clinical trial data related to the use of ICIs in CRC treatment. This platform provides the latest and most comprehensive trial information, enabling an in-depth evaluation of the efficacy, safety, and clinical progress of ICIs at different trial stages.[8] Through the analysis of these data, we have deepened our understanding of the mechanisms of ICIs and their roles in CRC and provided robust support for future evidence-based clinical applications and further research. In the future, the combination of ICIs, anti-angiogenic agents, and novel targeted therapies is expected to further expand the population benefiting from immunotherapy and improve overall treatment outcomes.

Materials and Methods

Data Source and Selection Criteria

Clinical trial information related to the mechanism of action of ICIs in CRC was collected from Trialtrove (https://clinicalintelligence.citeline.com/). All pertinent studies registered up to July 1, 2025, were included. The search term used was "Mechanism Of Action: 'Immune checkpoint inhibitor' Therapeutic area: 'Oncology: Colorectal'." To guarantee data accuracy and pertinence, only interventional clinical trials were selected for analysis.

Inclusion and Exclusion Criteria

To maintain the rigor of this review, explicit inclusion and exclusion criteria were established. The inclusion criteria required that: (i) studies investigated the mechanism of action of ICIs in CRC; (ii) each trial possessed a clearly specified therapeutic mechanism or target; and (iii) the design was a clinical trial. Exclusion criteria included: (i) trials without well-defined therapeutic targets or mechanisms; (ii) studies with incomplete or inadequate data; and (iii) non-interventional research, such as observational studies, which are insufficient for assessing the efficacy of ICIs. For trials with unclear or partially described therapeutic targets, further assessment was conducted to decide on their inclusion. Any study that did not provide enough information to accurately identify the therapeutic targets was ultimately omitted from the final analysis.

Handling Incomplete Data

A rigorous methodology was implemented to detect and assess gaps in the dataset, thereby strengthening the credibility and accuracy of the review. Studies that failed to provide essential outcome information—especially those missing explicit definitions of primary or secondary endpoints—were omitted from further consideration. Additionally, research with vague therapeutic objectives was typically excluded; however, if therapeutic targets could be specifically determined through independent sources or databases, those studies were evaluated for potential inclusion. Ultimately, prioritizing

studies with well-defined therapeutic goals and robust, complete datasets promoted data integrity and facilitated more reliable comparisons and conclusions.

Results

Clinical Trial Phases

In this study, we systematically reviewed clinical trials investigating the mechanisms of action of ICIs in CRC that were registered up to July 1, 2025. A total of 1,665 studies were initially identified. After applying strict exclusion criteria, we excluded 100 studies that did not specify drug targets, 56 studies without start dates, 19 studies missing country information, 3 studies categorized as "Other" for trial phase, and 56 studies without sponsor information. As a result, 1,479 clinical trials met the inclusion criteria and were included in the final analysis (Figure 1). The registration of relevant clinical trials started in 1997. Since then, the number of newly registered studies has steadily increased, peaking in 2023. Phase II trials were the most common, with a total of 611 studies registered. Early-phase studies included 449 Phase I trials and 322 Phase I/II trials, both of which were less frequent than Phase II studies. In contrast, late-phase trials were relatively uncommon, comprising 15 Phase II/III, 52 Phase III, and 30 Phase IV studies (Figure 2). These findings highlight the evolving landscape of clinical trial registration in the field of ICIs for CRC over the past decades.

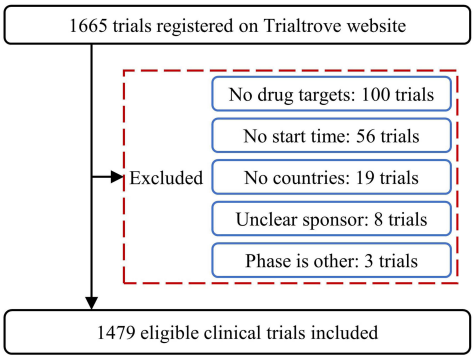

Figure 1 Flowchart of clinical trial selection process.

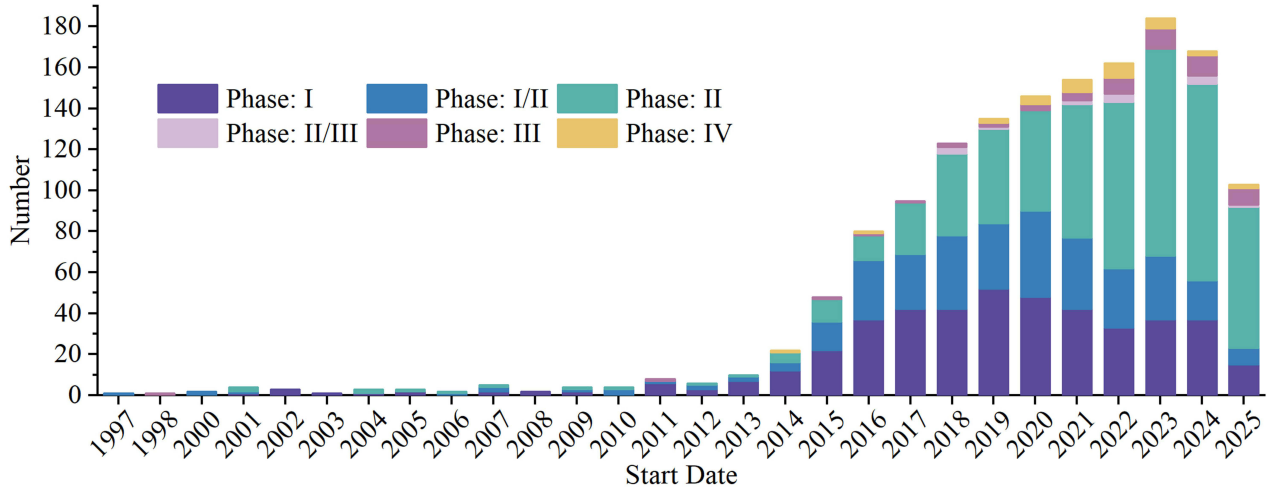

Figure 2 Phases and start dates of clinical trials with ICIs in CRC.
Abbreviations: ICI, immune checkpoint inhibitor; CRC, colorectal cancer.

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Clinical Trial Status and Countries

In this study, we investigated the current status of clinical trials. Among the 1,479 clinical trial records identified, 495 have reached completion, which highlights significant advancements in this research field. At present, 476 clinical trials remain in progress. This ongoing activity highlights sustained research efforts and a continued commitment to elucidating the mechanisms of action of ICIs in CRC. Conversely, 136 trials have been closed and 192 have been terminated. These outcomes may reflect challenges associated with the mechanisms of action of ICIs, including difficulties in patient recruitment or failure to meet predetermined efficacy endpoints (Figure 3). Regarding geographic distribution, the United States led with 672 clinical trials. China followed with 637 trials, while Spain, Australia, and France reported 218, 178, and 173 trials, respectively (Figure 4). These findings illustrate the global commitment and ongoing challenges in advancing the knowledge of mechanisms of action of ICIs in CRC.

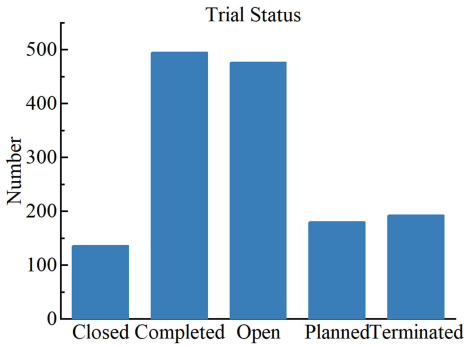

Figure 3 Status of clinical trials with ICIs in CRC.
Abbreviations: ICI, immune checkpoint inhibitor; CRC, colorectal cancer.

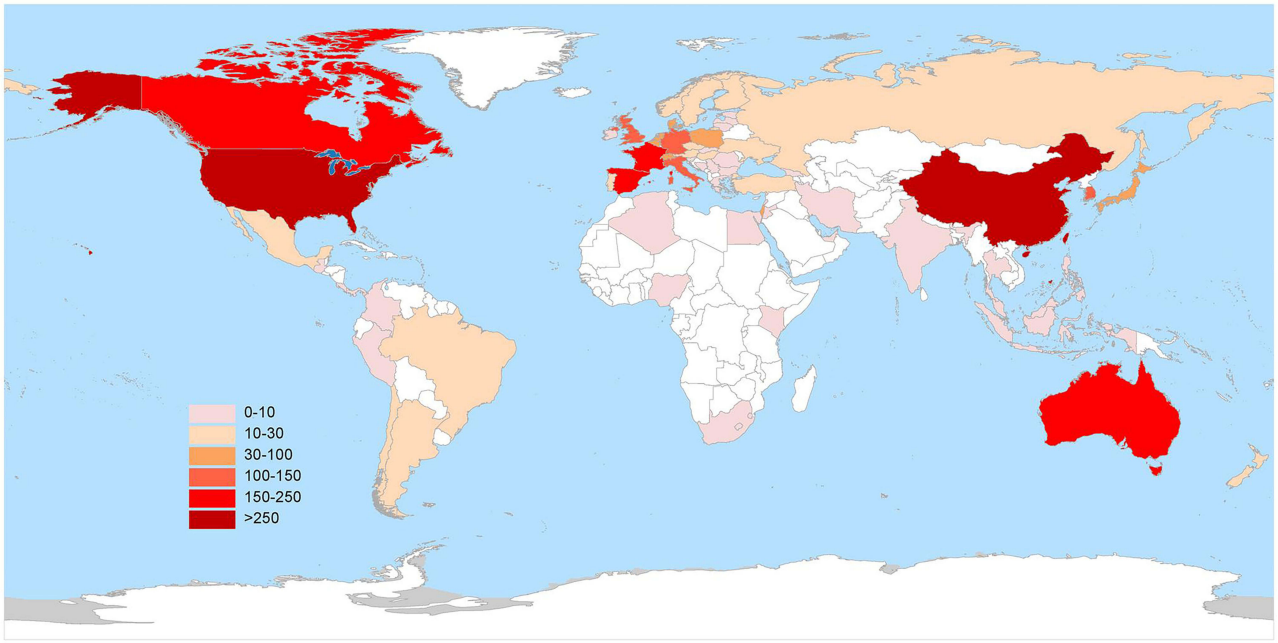

Figure 4 Global distribution of clinical trials with ICIs in CRC.
Abbreviations: ICI, immune checkpoint inhibitor; CRC, colorectal cancer.

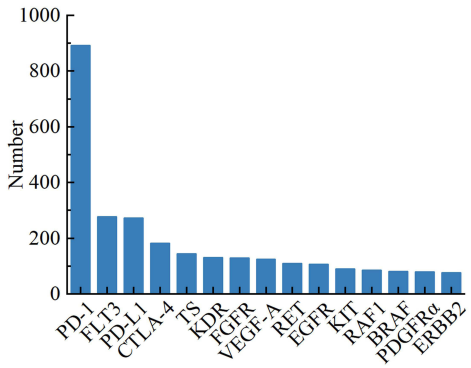

Figure 5 Molecular targets of clinical trials with ICIs in CRC. The figure illustrates the frequency of therapeutic targets mentioned across all clinical trials for colorectal cancer (CRC) indications included in the Trialtrove database. Immune checkpoint targets such as PD-1, PD-L1, and CTLA-4 represent the predominant therapeutic approaches. FLT exhibits a relatively high frequency in the reported statistics, primarily due to its inclusion in multi-tumor platform trials or non-CRC-specific studies containing CRC subgroups, potentially reflecting non-specific confounding effects across indications. Meanwhile, the TYMS frequency stems mainly from the combined annotation of chemotherapy targets within ICI-combined chemotherapy regimens. Consequently, its results are retained and explicitly noted within the assessment of immune-related targets.

Abbreviations: ICI, immune checkpoint inhibitor; CRC, colorectal cancer.

Target Analysis in Clinical Trials

Figure 5 illustrates the distribution of different targets investigated in clinical trials. The 10 most frequently investigated targets for the mechanisms of action of ICIs in CRC include programmed cell death 1 (PD-1), fms-related tyrosine kinase (FLT), CD274 molecule (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), thymidylate synthetase (TYMS), kinase insert domain receptor (KDR), fibroblast growth factor receptor (FGFR), vascular endothelial growth factor A (VEGFA), RET proto-oncogene (RET), and epidermal growth factor receptor (EGFR).

In target distribution analysis, PD-1 is the most common target, which is in line with the current dominant direction of immunotherapy. However, the emergence of FLT as the second high-frequency target may be partly due to the inclusion of non-CRC specific or combined therapy platforms in the database. We reviewed the relevant entries and found that some studies were multi-indications or platform trials, which affected the frequency ranking of FLT in statistics. In addition, TYMS belongs to the class of anti-metabolic chemotherapy targets, and its appearance in statistics mainly comes from studies on immunotherapy combined with chemotherapy design. Therefore, although it is not a traditional immune target, there are still sources of data for its appearance in specific combination strategies.

Discussion

CRC is a highly heterogeneous malignancy of the digestive system. During its development and progression, tumor cells employ diverse mechanisms to establish an immunosuppressive TME, thereby evading detection and elimination by the host immune system.[9] Although conventional treatments such as surgery, chemotherapy, and molecular targeted therapies have improved patient survival to some extent, approximately 40% of patients with CRC still experience recurrence and metastasis. This persistent high rate of disease relapse underscores the limitations of traditional therapeutic approaches and the urgent need for more effective interventions.[10] In recent years, ICIs have revolutionized the landscape of cancer immunotherapy. Several ICIs have been incorporated into standard CRC treatment regimens, marking a significant shift in clinical practice.[11] As a result, both the clinical application and mechanistic investigation of ICIs in CRC have emerged as key areas of ongoing research.

To provide a comprehensive overview, we systematically analyzed global clinical trial data on the use of ICIs in CRC. Since 1997, there has been a steady increase in the number of registered clinical trials examining the mechanisms of ICIs in CRC, reflecting the sustained commitment of both academia and industry to advance immunotherapy in this field. Notably, trial registrations peaked in 2023, a surge likely driven by rapid advances in precision medicine and immunotherapeutic technologies, which have dramatically transformed cancer treatment paradigms. In this context, exploring

the global distribution of these clinical trials is essential to understanding how different regions contribute to the development of ICI-based therapies for CRC.

Geographically, the United States leads the world in the number of CRC ICI trials, with 672 studies, owing to its substantial investment in biomedical research and robust research infrastructure. China follows closely, conducting 637 trials, highlighting its rapid progress and strong commitment to both basic and clinical research in cancer immunotherapy.[12] In Europe, Spain and France have made notable contributions, with 218 and 173 trials respectively, while Australia has also emerged as a significant participant, with 178 studies. These countries are recognized for their expertise in conducting standardized clinical trials and their active engagement in international research collaborations.[13]

Beyond regional differences, evaluating the status of these trials offers valuable insights into the current progress and ongoing challenges in ICI research for CRC. To date, 495 clinical trials investigating ICI mechanisms in CRC have been completed, reflecting meaningful advancements in our understanding of these therapies.[14] Meanwhile, 476 trials are ongoing as investigators continue to pursue novel strategies for modulating immune responses in CRC. However, 136 and 192 trials have been closed and terminated, respectively, frequently due to issues related to safety or poor efficacy. Analyses of these failures reveal that immune-related adverse events and disappointing response rates are frequent barriers to trial success. Understanding these reasons is critical for optimizing future trial design, such as improving patient stratification, developing predictive biomarkers, and enhancing management of immune-related side effects. These outcomes underscore the inherent complexity of deciphering ICI mechanisms in CRC and provide important lessons for ongoing and future research.[15]

Further insight can be gained by examining the distribution of these studies across different clinical trial phases, which highlights both the scientific advancements achieved and the practical challenges that remain. These mid-stage trials are pivotal for determining the therapeutic potential of ICIs and guiding progression to later-phase studies. At the same time, the current scarcity of early-phase trials underscores ongoing challenges in advancing from early- and mid-stage trials to late-stage clinical development. This scarcity underscores ongoing challenges in advancing from early- and mid-stage trials to late-stage clinical development. The observed imbalance across trial phases highlights the necessity of addressing barriers that hinder the successful translation of promising early findings into practice-changing therapies.

Last but not least, we analyzed the clinical trial targets of ICIs in CRC. Among these, immune checkpoint molecules such as PD-1, PD-L1, and CTLA-4 are the most frequently studied and therapeutically relevant. PD-1 is predominantly expressed on immune cells, including T cells, B cells, and macrophages, whereas PD-L1 is upregulated in various normal tissues and is frequently overexpressed on tumor cells.[16] The interaction between PD-L1 and PD-1 inhibits T-cell proliferation and activation, suppresses cytokine secretion, and ultimately dampens antitumor immune responses.[17] This mechanism allows tumor cells to escape immune surveillance and establish an immunosuppressive TME.[18]

Numerous studies and clinical trials have consistently demonstrated that patients with MSI-H or dMMR CRC exhibit a high tumor mutational burden and abundant neoantigens, making them particularly responsive to PD-1/PD-L1 inhibitors. For this subgroup, immune checkpoint blockade leads to significant and durable survival benefits, and these patients represent the main population for which ICIs are currently approved by the Food and Drug Administration.[19] However, the majority of patients with microsatellite stable (MSS) or proficient mismatch repair CRC show limited responses to PD-1/PD-L1 monotherapy, highlighting the complex mechanisms of resistance and heterogeneity of the tumor immune microenvironment in CRC. A clinical trial (NCT02563002) demonstrated that in patients with MSI-H/dMMR metastatic CRC, pembrolizumab as first-line therapy achieved an objective response rate (ORR) of 43.8% with a median progression-free survival (PFS) of 16.5 months, significantly outperforming the chemotherapy group ORR of 33.1% and median PFS of 8.2 months.[20] By contrast, MSS patients typically exhibit an ORR below 5% and a median PFS of less than 3 months under monotherapy with PD-1 inhibitors.[21] For this disease, the RENMIN-215 study (ChiCTR2100046768) used fecal microbiota transplantation combined with the PD-1 inhibitor tislelizumab and the VEGFR-TKI fruquintinib as third-line or subsequent therapy. Among 20 MSS patients, it achieved an ORR of 20%, with a median PFS of 9.6 months and a median overall survival (OS) of 13.7 months. These outcomes significantly outperformed those of previous monotherapy regimens for MSS patients while demonstrating a manageable side-effect profile. The study further identified recognizable immunological signatures in the gut microbiota profiles and TCR clonal architecture of responders.[22]

In addition to the PD-1/PD-L1 axis, CTLA-4 represents another crucial immune checkpoint. CTLA-4 exerts immunosuppressive effects by competitively binding to the costimulatory molecules CD80 and CD86, thereby blocking the signals necessary for early T-cell activation.[23] Importantly, combined blockade of PD-1/PD-L1 and CTLA-4 has demonstrated synergistic enhancement of antitumor immune responses and has shown the potential to overcome resistance to single-agent immunotherapy in certain patients. Clinical studies have confirmed that this dual-checkpoint inhibition strategy yields higher objective response rates and disease control rates, particularly among patients with MSI-H/dMMR CRC.[24]

In addition to immune checkpoint molecules, our research reveals that targets such as VEGFA, KDR, EGFR, and FGFR are frequently investigated in clinical trials. The focus on these molecules is largely attributable to the multilayered and complex immunosuppressive mechanisms within the TME, which often render ICI monotherapy insufficient to achieve durable and broad-spectrum antitumor effects.[25] Thus, increasing attention has shifted toward combination strategies that integrate ICIs with anti-angiogenic agents or inhibitors targeting EGFR, FGFR, and other pathways. The rationale is to overcome the tumor immune barrier through multi-pathway synergy.

Combination therapies involving ICIs and multi-targeted agents offer several advantages. Firstly, anti-angiogenic drugs help normalize the aberrant tumor vasculature, thereby improving immune cell infiltration and activation.[26] Additionally, these regimens can decrease the accumulation of immunosuppressive cells within the TME such as myeloid-derived suppressor cells and regulatory T cells, ultimately enhancing the antitumor immune response and improving the clinical efficacy of ICIs.[27] Importantly, key signaling molecules such as VEGFA, FGFR, and EGFR are highly expressed in CRC, where they not only promote angiogenesis and tumor proliferation but also reshape the TME by impeding immune cell infiltration and fostering an immunosuppressive milieu.[28] A single-arm phase II study in MSS and RAS wild-type patients (ChiCTR2000035642) evaluated the efficacy of tislelizumab in combination with cetuximab and irinotecan. Among 33 patients receiving third-line or later treatment, the confirmed ORR was 33%, with median PFS of 7.3 months and median OS of 17.4 months, exceeding the benchmark efficacy reported for existing chemotherapy or targeted therapies. The study further revealed, through ctDNA and peripheral immune proteome analysis, that low baseline mutational burden, marked ctDNA decline during treatment, and immune protein activation signatures were significantly associated with improved prognosis.[29]

Furthermore, evidence suggests that activation of pathways involving EGFR and FGFR can upregulate PD-L1 expression on tumor cells, thereby promoting immune escape. These molecular characteristics underscore the rationale for developing ICI-based combination therapies targeting these pathways, which have emerged as promising strategies to overcome the therapeutic limitations of conventional ICI monotherapy, particularly in CRC.[30]

Recent clinical and preclinical studies reinforce the benefits of such multi-targeted combination approaches. For instance, in one clinical trial (NCT02060188), nivolumab combined with ipilimumab was administered to previously treated MSI-H/dMMR mCRC patients, yielding an ORR of 55%, a 12-month PFS rate of 71%, and a 24-month OS rate of 79%.[21] Furthermore, a clinical trial (NCT02992912) report described a patient with metastatic dMMR CRC who achieved a response and remained progression-free. Nivolumab combined with low-dose ipilimumab achieved an ORR of 55% in comparable patient cohorts, with a one-year PFS rate as high as 77%.[31] Another clinical trial (2017–000977-35) suggested the potential benefit of ICIs combinations in CRC; the median PFS for first-line treatment of CRC with the combination of FOLFOXIRI and bevacizumab exceeded 12 months.[32]

Supporting these clinical observations, basic research has elucidated the underlying mechanisms of synergy. For example, Xu et al found that the anti-angiogenic agent endostatin, when combined with a PD-1 antibody, markedly inhibited tumor growth by enhancing immune cell recruitment and activation within the TME. Collectively, these findings highlight that multi-targeted combination therapies not only address the efficacy bottlenecks of ICI monotherapy but also represent innovative strategies for reprogramming the TME and optimizing immunotherapy in CRC.[33]

Our study also found that metabolic enzyme targets such as thymidylate synthetase (TS) are frequently mentioned in clinical trials. TS is the primary molecular target of chemotherapeutic agents such as 5-fluorouracil (5-FU) and has traditionally been regarded as a key regulator of cell proliferation.[34] With the rise of immunotherapy, increasing evidence suggests that conventional chemotherapy drugs such as 5-FU, oxaliplatin, and irinotecan can induce immunogenic cell death, promote the release of tumor-associated antigens, thereby enhancing tumor immunogenicity, and promote more

effective anti-immune responses when used in combination with ICIs. Recent clinical studies have evaluated the efficacy of combining ICIs, such as anti-PD-1 antibodies, with standard chemotherapy regimens in the treatment of metastatic CRC. These studies have demonstrated that chemo-immunotherapy combinations significantly improve progression-free survival and OS compared to chemotherapy or immunotherapy alone. The therapeutic benefit of this approach is particularly notable in patients with specific molecular subtypes.[35] Notably, next-generation ICIs targeting lymphocyte-activation gene 3, T-cell immunoreceptor with Ig and ITIM domains, and other emerging molecules have entered Phase I/II clinical development for CRC. These agents represent promising strategies to overcome resistance mechanisms and expand the efficacy of immunotherapy beyond current standards. Incorporating these new targets is expected to further diversify combination regimens and shape the future landscape of precision immunotherapy in CRC.[36]

Beyond traditional tumor biological factors, recent research has increasingly focused on the influence of lifestyle and environmental factors on host immune status, the TME, and responses to immunotherapy. Chronic stress, dietary patterns, obesity, gut microbiota, smoking, and physical activity can alter the composition of the TME through inflammatory mediators, metabolic pathways, and immune cell infiltration, thereby regulating responses to immunotherapy. For instance, a high-fat diet can suppress dendritic cell activity and diminish the efficacy of immune checkpoint inhibitors.[37]

Molecular pathological epidemiology (MPE) is an emerging interdisciplinary field that integrates traditional epidemiology with molecular pathology to elucidate the complex interactions among lifestyle, environmental factors, immune biomarkers, and clinical outcomes in colorectal cancer.[38] MPE research enables the investigation of how specific exposures interact with molecular features of tumors to influence disease risk, progression, and response to immunotherapy. Recent studies have demonstrated that MPE approaches can uncover novel etiologic pathways, identify subgroups of patients who may benefit from tailored interventions, and inform biomarker-driven clinical trials.[39] Integrating MPE frameworks into future research will facilitate more personalized prevention and treatment strategies by accounting for individual variability in both exposures and tumor biology. These advances have substantial implications for clinical practice and precision immunotherapy in CRC.

This study presents a comprehensive and systematic analysis of global clinical trials investigating the mechanisms and therapeutic strategies of ICIs in CRC. By leveraging the Trialtrove database, the review encompassed 1479 interventional trials registered from 1997 to 2025, thus providing a broad temporal and geographical perspective on the evolving landscape of ICI-based therapy. In addition, our study reported the major molecular targets and development trends of multi-target combination therapy. The analysis highlights the changes across trial phases and global regions, underscoring both the expanding research investment and the innovative approaches being pursued to overcome resistance and heterogeneity in CRC immunotherapy. Furthermore, the study provides valuable theoretical support for precision immunotherapy and future translational research in this field. Nevertheless, there are several limitations to this study that merit consideration. First, the data source was restricted to the Trialtrove database, which may not capture all relevant trials, particularly those registered in other platforms or unpublished studies, potentially introducing selection bias. Second, the analysis primarily relied on registered information regarding mechanisms and targets, rather than granular clinical outcomes such as efficacy or safety, thus limiting direct insights into the real-world impact of various therapeutic strategies. Additionally, while we acknowledge the challenges posed by tumor heterogeneity and immunoresistance, we did not perform an in-depth exploration of subgroup-specific responses or translational barriers from early-phase research to late-stage clinical application. Finally, there is a lack of forward-looking discussion on policy development, collaborative frameworks, and strategies to accelerate the clinical translation and adoption of innovative immunotherapeutic approaches for CRC.

Conclusion

This study systematically integrated clinical trial data on ICIs in CRC from around the world, comprehensively revealing the distribution of major molecular targets, geographical regional differences, and the development trends of multi-target combination therapy. The study showed that multi-pathway synergistic regimens combining ICIs with anti-angiogenic and molecularly targeted drugs have become an important direction for overcoming the limitations of traditional immunotherapy, improving efficacy, and expanding the beneficiary population. Future efforts should focus on clarifying

the mechanisms involved, optimizing combination therapy strategies, and promoting large-scale, high-quality, multi-center clinical trials to validate and refine the application of immunotherapy in CRC.

Data Sharing Statement

Data available on request from the Ying Tong.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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