The plan is complete and ready for final summarization to produce a professional research report covering all collected data on colon cancer immunotherapy, including modalities, regulatory status, clinical evidence, biomarkers, and outlook.

**Current Date: 2025-10-02**

**Comprehensive Overview of the Colon Cancer Immunotherapy Landscape**

This report provides a comprehensive overview of the immunotherapy landscape for colorectal cancer (CRC) in the United States (US) and European Union (EU) markets. It details approved products, the clinical-stage pipeline, and the forward-looking outlook for the next 2–3 years, with in-depth analysis of therapeutic modalities, mechanisms of action, combination strategies, and biomarker considerations.

**Executive Summary**

The colorectal cancer immunotherapy landscape is characterized by a distinct dichotomy. For the ~5% of patients with metastatic CRC (mCRC) whose tumors are mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H), immune checkpoint inhibitors (ICIs) have become the standard of care, displacing chemotherapy in the first-line setting. For the remaining 95% of patients with microsatellite stable (MSS) tumors, which are traditionally "cold" and unresponsive to ICIs, the landscape is one of intense clinical investigation. A robust and diverse pipeline of novel modalities—including bispecific antibodies, CAR-T cells, cancer vaccines, and oncolytic viruses—is aggressively being pursued, primarily through innovative combination strategies, with the goal of unlocking immunotherapy for the broader CRC population. The next 2–3 years will be pivotal, with multiple late-stage trial readouts expected to shape the future treatment paradigm.

**I. Approved Immunotherapy Landscape: The Era of Checkpoint Inhibition for MSI-H/dMMR CRC**

As of October 2025, regulatory approvals for immunotherapy in CRC are exclusively for immune checkpoint inhibitors and are strictly limited to the MSI-H/dMMR patient subpopulation. No CAR-T cell therapies, bispecific antibodies, or therapeutic cancer vaccines have secured FDA or EMA approval specifically for colorectal cancer [[3](https://www.fda.gov/media/165219/download)].

**Approved Checkpoint Inhibitors in the US & EU**

The table below summarizes the key approved agents that form the current standard of care for MSI-H/dMMR CRC.

| Agent (Brand Name) | Company | Target / Mechanism of Action | Key Approval & Setting (US/EU) | Geographic Coverage |
| --- | --- | --- | --- | --- |
| **Pembrolizumab** (Keytruda) | Merck & Co. | **PD-1 Inhibitor:** Blocks the interaction between PD-1 on T-cells and its ligands (PD-L1/L2), restoring anti-tumor T-cell activity. | **First-line** unresectable/metastatic MSI-H/dMMR CRC (FDA 2020, EMA 2021) [[3](https://www.fda.gov/media/165219/download)][[6](https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-first-line-treatment-msi-hdmmr-colorectal-cancer)]. | USA, UK, Germany, France, Italy, Spain [[20](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Approved%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)] |
| **Nivolumab** (Opdivo) | Bristol-Myers Squibb | **PD-1 Inhibitor:** Similar to pembrolizumab, it reinvigorates exhausted T-cells by blocking the PD-1/PD-L1 pathway. | **First-line** MSI-H/dMMR mCRC in combination with ipilimumab (FDA 2025, EMA 2025) [[5](https://www.cancer.gov/news-events/cancer-currents-blog/2025/fda-nivolumab-ipilimumab-dmmr-colorectal-cancer)][[7](https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-ipilimumab-unresectable-or-metastatic-msi-h-or-dmmr-colorectal-cancer)]. | USA, UK, Germany, France, Italy, Spain [[20](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Approved%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)] |
| **Ipilimumab** (Yervoy) | Bristol-Myers Squibb | **CTLA-4 Inhibitor:** Blocks the CTLA-4 protein on T-cells, a key negative regulator, promoting T-cell activation and proliferation. | **First-line** MSI-H/dMMR mCRC in combination with nivolumab (FDA 2025, EMA 2025) [[5](https://www.cancer.gov/news-events/cancer-currents-blog/2025/fda-nivolumab-ipilimumab-dmmr-colorectal-cancer)]. | USA, UK, Germany, France, Italy, Spain [[20](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Approved%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)] |
| **Dostarlimab** (Jemperli) | GSK / Tesaro | **PD-1 Inhibitor:** Another agent that blocks the PD-1/PD-L1 axis to enhance immune response. | **Tumor-agnostic** approval for dMMR recurrent/advanced solid tumors (including CRC) after prior therapy (FDA 2021, EMA 2022) [[4](https://www.sciencedirect.com/science/article/pii/S2049080122008068)][[8](https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dostarlimab-gxly-dmmr-advanced-solid-tumors)]. | USA, Italy, EU-wide [[8](https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dostarlimab-gxly-dmmr-advanced-solid-tumors)][[20](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Approved%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)] |
| **Nivolumab SC** (Opdivo Qvantig) | Bristol-Myers Squibb / Halozyme | **PD-1 Inhibitor:** A subcutaneous (SC) co-formulation of nivolumab with ENHANZE technology for faster administration. | Approved for all existing nivolumab indications, including CRC [[20](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Approved%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. | USA, Spain [[20](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Approved%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)] |

**Clinical Evidence & Biomarker Dominance**

The approval of these agents was driven by landmark clinical trials that established their superiority over chemotherapy for the MSI-H/dMMR population.

* **Pembrolizumab (KEYNOTE-177):** This trial established pembrolizumab as a first-line standard of care, demonstrating a median progression-free survival (PFS) of **16.5 months** versus 8.2 months for chemotherapy [[6](https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-first-line-treatment-msi-hdmmr-colorectal-cancer)].
* **Nivolumab + Ipilimumab (CheckMate-8HW):** This study validated the first dual-ICI combination in the first-line setting. The combination achieved a PFS that was not reached at the time of analysis, compared to 5.8 months for chemotherapy [[7](https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-ipilimumab-unresectable-or-metastatic-msi-h-or-dmmr-colorectal-cancer)]. The 3-year PFS rate was **68%** for the combination versus 51% for nivolumab alone, though this came at the cost of higher Grade ≥3 immune-related adverse events (22% vs. 14%) [[5](https://www.cancer.gov/news-events/cancer-currents-blog/2025/fda-nivolumab-ipilimumab-dmmr-colorectal-cancer)].
* **Dostarlimab (GARNET):** In a cohort of previously treated dMMR solid tumor patients, dostarlimab showed an impressive overall response rate (ORR) of **41.6%** and a median duration of response (DoR) of 34.7 months, securing its place as a later-line option [[8](https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dostarlimab-gxly-dmmr-advanced-solid-tumors)].

**Biomarker Imperative:** The MSI-H/dMMR biomarker is paramount. All current immunotherapy approvals in CRC hinge on this status. The CheckMate-8HW trial highlighted the criticality of accurate testing, revealing that over 10% of patients identified by local testing were false positives, prompting calls for dual-platform confirmation to ensure patients are correctly selected for these powerful therapies [[5](https://www.cancer.gov/news-events/cancer-currents-blog/2025/fda-nivolumab-ipilimumab-dmmr-colorectal-cancer)].

**II. Clinical-Stage Pipeline: Targeting the MSS-CRC Majority**

The vast majority of CRC research is focused on making immunotherapy effective for the 95% of patients with MSS tumors. This involves a multi-pronged approach using novel modalities and combination strategies.

**A. Bispecific Antibodies (bsAbs)**

Bispecific antibodies are engineered to simultaneously bind to two different targets, most commonly a tumor antigen and an immune cell receptor like CD3, thereby physically linking T-cells to cancer cells to induce killing.

* **CRC-Specific Clinical Data:** The Phase I/II trial of **Rybrevant (amivantamab)**, an EGFR/c-Met bispecific antibody, showed significant promise in combination with chemotherapy (FOLFOX/FOLFIRI) for RAS/BRAF wild-type mCRC. The study reported an **ORR of 49%** and a disease control rate (DCR) of 88%. Notably, 21% of patients were able to undergo curative-intent surgery after treatment [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)].
* **Broader Pipeline:** The landscape includes numerous agents targeting various antigens relevant to CRC, such as EpCAM, CEA, and Claudin18.2 [[11](https://www.cell.com/trends/cancer/fulltext/S2405-8033%2824%2900142-0)].
  + **QLS31905 (Claudin18.2/CD3):** In a Phase I study of solid tumors, this agent achieved an ORR of 18.18% and a DCR of 87.88%, though it was associated with a 21.5% incidence of cytokine release syndrome (CRS) [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)].
  + **BA3182 (EpCAM/CD3):** This T-cell engager demonstrated tumor reductions in 5 patients in its initial Phase I trial, with a dose expansion readout expected in 2026 [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)][[19](https://www.noahai.co/tool/catalyst/?search_param=%7B%22phases%22%3A%20%5B%22II%22%2C%20%22III%22%5D%2C%20%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)].
  + **REGN7075 (EGFR/CD28):** This costimulatory bispecific showed a 6% ORR in MSS CRC patients, indicating a potential, albeit modest, signal in this difficult-to-treat population [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)].

**B. CAR-T Cell & Adoptive Cell Therapies**

CAR-T therapy involves genetically engineering a patient's own T-cells to express Chimeric Antigen Receptors (CARs) that recognize tumor antigens. While transformative in hematologic cancers, its use in solid tumors like CRC is challenged by T-cell trafficking, persistence, and the immunosuppressive tumor microenvironment.

* **GUCY2C-Targeted CAR-T:** A Phase I study in the US and China of **GCC19CART** targeting the GUCY2C antigen, which is expressed in CRC, reported a promising **ORR of 60%** and a DCR of 80% in a small cohort of 13 patients, with manageable CRS [[9](https://ascopubs.org/doi/10.1200/JCO-24-02081)].
* **CEA-Targeted CAR-T (A2B530):** To mitigate on-target, off-tumor toxicity, this therapy uses a logic-gated design with an engineered "mask" to protect healthy tissues. It received FDA Orphan Drug Designation in 2024, highlighting its potential [[10](https://www.targetedonc.com/view/fda-grants-orphan-drug-designation-to-novel-car-t-cell-therapy-in-colorectal-cancer)].
* **Combination with ICIs:** The KEYNOTE-B79 trial is exploring the allogeneic (off-the-shelf) NKG2D-based CAR-T **CYAD-101** in combination with pembrolizumab for mCRC, aiming to leverage synergistic mechanisms [[9](https://ascopubs.org/doi/10.1200/JCO-24-02081)].

**C. Cancer Vaccines**

Therapeutic cancer vaccines are designed to train the immune system to recognize and attack cancer cells by presenting tumor-specific neoantigens.

* **Personalized mRNA Vaccines:** **Autogene cevumeran (BNT122)**, an individualized mRNA vaccine from BioNTech, is being evaluated in a randomized Phase II trial for patients with ctDNA-positive Stage II/III CRC after surgery, aiming to prevent recurrence [[13](https://www.biontech.com/int/en/home/pipeline-and-products/pipeline.html)].
* **Neoantigen Peptide Vaccines:** **GRANITE (GRT-C901/GRT-R902)** from Gritstone bio is a personalized vaccine platform. Phase II data in MSS-CRC showed a 21% relative risk reduction in disease progression (HR=0.79) and a 38% risk reduction in patients with low disease burden (HR=0.62). Mature overall survival (OS) data is a key upcoming catalyst expected in the second half of 2025. However, the company's bankruptcy filing in 2024 introduces significant execution risk [[19](https://www.noahai.co/tool/catalyst/?search_param=%7B%22phases%22%3A%20%5B%22II%22%2C%20%22III%22%5D%2C%20%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)].
* **Other Pipeline Vaccines:** **NOUS-209**, a gene therapy-based vaccine, is currently in Phase II trials across the US and EU [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%2C%20%22Approved%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Others%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22US%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)].

**D. Oncolytic Viruses (OVs)**

OVs are viruses engineered to selectively infect and kill cancer cells (oncolysis) while also triggering a potent anti-tumor immune response, effectively turning "cold" tumors "hot."

* **Pipeline Overview:** A 2025 review highlights six leading OV platforms under investigation for CRC, including adenovirus, HSV, and reovirus [[15](https://pmc.ncbi.nlm.nih.gov/articles/PMC12153852/)].
* **Pelareorep (Reolysin):** This oncolytic reovirus is in Phase II development in the UK and Phase I in the US for CRC [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%2C%20%22Approved%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Others%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22US%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)].
* **Combination with ICIs:** The Phase I/II trial of **Pexa-Vec** (a vaccinia virus) combined with a checkpoint inhibitor is exploring this strategy in refractory CRC, aiming to sensitize tumors to immunotherapy [[16](https://clinicaltrials.gov/study/NCT03206073)].

**E. Other Novel Immunomodulatory Agents**

The pipeline also includes other immunomodulatory classes in late-stage development.

| Modality | Agent | Target | Phase | Geographic Focus |
| --- | --- | --- | --- | --- |
| **TLR9 Agonist** | **Lefitolimod** (MGN-1703) | Toll-Like Receptor 9 | Phase III | USA, Germany, France, Italy, UK [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%2C%20%22Approved%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Others%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22US%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)] |
| **Antisense Oligonucleotide** | **Oblimersen sodium** (Genasense) | BCL2 Apoptosis Regulator | BLA/NDA | USA, Spain, France, UK, Germany, Italy [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%2C%20%22Approved%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Others%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22US%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)] |
| **Antisense Oligonucleotide** | **Trabedersen** (AP-12009) | TGF-β2 | Phase III | USA, Germany [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Colorectal%20cancer%22%2C%20%22Colon%20cancer%20recurrent%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%2C%20%22Approved%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Others%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22US%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)] |

**III. Key Development Trends and Future Outlook (2025–2027)**

**A. The Rise of Combination Strategies**

The future of CRC immunotherapy, especially for MSS tumors, lies in intelligent combinations.

* **Neoadjuvant Immunotherapy:** The **NICHE-2 trial** produced stunning results in dMMR colon cancer, where neoadjuvant (pre-surgical) treatment with ipilimumab and nivolumab led to a **98% pathological response** and a 68% pathological complete response (pCR), with low rates of severe toxicity (<4%) [[17](https://ascopubs.org/doi/10.1200/OA-24-00077)]. This is poised to change practice for early-stage dMMR disease.
* **ICI + Chemotherapy:** The **COMMIT trial** is evaluating the addition of atezolizumab to the standard FOLFOX-bevacizumab regimen in first-line mCRC, with PFS as the primary endpoint [[18](https://www.nrgoncology.org/Home/News/Post/pi-interview-the-commit-study-of-immunotherapy-for-dmmr-metastatic-colorectal-cancer-nrg-gi004swog-s1610)].
* **ICI + Targeted Therapy (TKI):** The Phase III **STELLAR-303** trial is testing **zanzalintinib** (a multi-targeted TKI) with atezolizumab. Phase Ib data showed an encouraging median OS of 14.3 months for the combination, with top-line results expected in H2 2025. However, the OS improvement did not achieve statistical significance in the early data (HR 0.75, 95% CI 0.45-1.26), representing a key risk [[19](https://www.noahai.co/tool/catalyst/?search_param=%7B%22phases%22%3A%20%5B%22II%22%2C%20%22III%22%5D%2C%20%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)].

**B. Forward-Looking Pipeline Catalysts (2025–2026)**

Several pivotal data readouts are expected to shape the landscape in the near term.

| Drug / Program | Company | Phase | Expected Timeline | Catalyst & Potential Impact |
| --- | --- | --- | --- | --- |
| **Zanzalintinib** | Exelixis | III | **July-Dec 2025** | Top-line results from STELLAR-303; could establish a new ICI + TKI combination for CRC [[19](https://www.noahai.co/tool/catalyst/?search_param=%7B%22phases%22%3A%20%5B%22II%22%2C%20%22III%22%5D%2C%20%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)]. |
| **GRANITE** | Gritstone bio | II/III | **July-Dec 2025** | Mature OS data; a positive result could validate personalized vaccines for MSS-CRC, pending resolution of corporate issues [[19](https://www.noahai.co/tool/catalyst/?search_param=%7B%22phases%22%3A%20%5B%22II%22%2C%20%22III%22%5D%2C%20%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)]. |
| **CFT-1946** | C4 Therapeutics | I/II | **July-Dec 2025** | Multiple updates for this first-in-class BRAF V600 protein degrader, including data in CRC combined with cetuximab [[19](https://www.noahai.co/tool/catalyst/?search_param=%7B%22phases%22%3A%20%5B%22II%22%2C%20%22III%22%5D%2C%20%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)]. |
| **Jemperli (Dostarlimab)** | GSK | II | **Jan-Dec 2026** | Top-line results from the AZUR-1 trial, potentially expanding its use in CRC [[19](https://www.noahai.co/tool/catalyst/?search_param=%7B%22phases%22%3A%20%5B%22II%22%2C%20%22III%22%5D%2C%20%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)]. |
| **BA3182** | BioAtla | I/II | **Jan-June 2026** | Dose expansion readout for this EpCAM/CD3 bispecific antibody, providing further proof-of-concept [[19](https://www.noahai.co/tool/catalyst/?search_param=%7B%22phases%22%3A%20%5B%22II%22%2C%20%22III%22%5D%2C%20%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)]. |

**C. Evolution of Biomarkers**

While MSI-H/dMMR remains the only validated biomarker for approved ICIs, the pipeline is exploring new selection strategies:

* **Circulating Tumor DNA (ctDNA):** The GRANITE vaccine program uses ctDNA levels to select patients and monitor response, with low baseline ctDNA correlating with better outcomes [[19](https://www.noahai.co/tool/catalyst/?search_param=%7B%22phases%22%3A%20%5B%22II%22%2C%20%22III%22%5D%2C%20%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)].
* **Tumor Antigens:** The success of CAR-T and bispecific antibodies will depend on the expression levels of targets like GUCY2C, CEA, and Claudin18.2.
* **Specific Mutations:** The KRAS-targeted vaccine (ELI-002) and BRAF-targeting degrader (CFT-1946) represent a move toward mutation-specific immunotherapies [[14](https://elicio.com/pipeline/eli-002/)][[19](https://www.noahai.co/tool/catalyst/?search_param=%7B%22phases%22%3A%20%5B%22II%22%2C%20%22III%22%5D%2C%20%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Other%20%28Colorectal%20tumor%29%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)].

**IV. Conclusion and Strategic Implications**

The colorectal cancer immunotherapy landscape is a field of stark contrasts and immense opportunity. For the biomarker-defined MSI-H/dMMR population, a competitive market of highly effective checkpoint inhibitors is now firmly established as the first-line standard of care in both the US and EU.

The primary strategic imperative for the entire field is to extend the benefits of immunotherapy to the 95% of patients with MSS-CRC. The next 2–3 years will be a critical period of validation for a host of innovative strategies. Success will likely come not from a single agent, but from personalized and multi-modal combination therapies that can overcome the immunosuppressive microenvironment of "cold" tumors. Key developments to watch include the maturation of data for personalized vaccines, the safety and efficacy of T-cell engagers and CAR-T cells, and the results of pivotal trials combining ICIs with TKIs and chemotherapy. While the path is challenging, the sheer breadth and depth of the clinical pipeline provide strong reason for optimism.