**Supplementary Table 1- Completed clinical trials using ICI in CRC.**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Intervention and combination treatment** | **Trial Title** | **Phase** | **Actual Enrollment (# of participants)** | **Main Findings** | **NCT number** | **Year/ Actual Study Completion Date** | **Ref.** |
| PembrolizumabmFOLFOX6 | Study of Pembrolizumab in Combination With Chemotherapy for Patients With Advanced Colorectal Cancer | II | 30 | T cells and myeloid cells did not influence the treatment outcomes, and this combination did not yield a superior anti-tumor effect compared to previously tested ones. Further research utilizing a more effective combination could be achieved by focusing on biomarkers associated with positive treatment responses. | NCT02375672 | October 8, 2020 | (1) |
| CyclophosphamideGVAXPembrolizumab | Study of GVAX (With CY) and Pembrolizumab in MMR-p Advanced Colorectal Cancer | II | 17 | The combination fell short of the initial objectives in MMR-p CRC. However, an improvement in the anti-tumor effect was observed compared to pembrolizumab treatment alone, possibly caused by GVAX. | NCT02981524 | March 20, 2018 | (2) |
| PembrolizumabAzacitidine | A Phase 2 Study of Pembrolizumab (MK-3475) in Combination With Azacitidine in Subjects With Chemo-refractory Metastatic Colorectal Cancer | II | 31 | This combination demonstrated reasonable disease control and a safe, tolerable effect in chemotherapy-refractory mCRC.It is suggested that tumor immunomodulation is positively correlated with the use of the DNA demethylation agent azacitidine | NCT02260440 | September 2017 | (3) |
| Oral CC-486 (5-azacitidine)RomidepsinMK-3475 | A Study of Enhancing Response to MK-3475 in Advanced Colorectal Cancer | I | 27 | The combination of Pembrolizumab with 5-azacitidine and romidepsin was found to be well-tolerated in patients with MMR-proficient CRC.Further research is required to determine the regimen's predictive responses both before and after treatment | NCT02512172 | November 20, 2021 | (4) |
| CetuximabPembrolizumab | Cetuximab and Pembrolizumab in Treating Patients With Colorectal Cancer That is Metastatic or Cannot Be Removed by Surgery | I & II | 45 | This regimen modified the TME by recruiting CTL and expanding their population, as evidenced by the observed reduction in their numbers in PB. There was a noticeable decrease in PD1+ expressing cells within the TME, supported by an increase in CD4+CTLA4+ T-cells in peripheral blood. However, the results are not yet conclusive, and further research using clinical data is necessary to gain better insights | NCT02713373 | July 20, 2021 | (5) |
| Pembrolizumab | Study of Pembrolizumab (MK-3475) as Monotherapy in Participants With Previously-Treated Locally Advanced Unresectable or Metastatic Colorectal Cancer (MK-3475-164/KEYNOTE-164) | II | 124 | Pembrolizumab is effective and safe in treating MSI-CRC | NCT02460198 | February 19, 2021 | (6) |
| PembrolizumabIbrutinib | Pembrolizumab in Combination With Ibrutinib for Advanced, Refractory Colorectal Cancers | I & II | 40 | This combination was found to be tolerated, but it exhibited low anti-tumor activity in mCRC | NCT03332498 | September 9, 2021 | (7) |
| Pembrolizumab Maraviroc | Combined PD-1 and CCR5 Inhibition for the Treatment of Refractory Microsatellite Stable mCRC | I | 20 | -In this heavily pretreated cohort, the effectiveness of poststudy salvage treatment exceeded expectations. -The combination of pembrolizumab and maraviroc proved to be safe, with a positive toxicological impact and stabilized MMR CRC diesase. does this paragraph mean the same as the above one | NCT03274804 | March 1, 2020 | (8) |
| Olaptesed (NOX-A12)Pembrolizumab Combination Therapy | Olaptesed (NOX-A12) Alone and in Combination With Pembrolizumab in Colorectal and Pancreatic Cancer | I & II | 20 | This combination has a safety record comparable to pembrolizumab in advanced cancer. The regimen induced an immune response in 25% of the patients and led to a prolonged treatment duration compared to prior treatments in 35% of the patients | NCT03168139 | March 25, 202 | (9) |
| AMG820 and pembrolizumab | Safety and Efficacy Study of AMG 820 and Pembrolizumab Combination in Select Advanced Solid Tumor Cancer | I & II | 117 | This regimen demonstrated a favorable safety profile at a dose of 1100 mg for AMG 820 and 200 mg for pembrolizumab. However, due to the low anti-tumor activity observed with this combination, further research does not appear promising | NCT02713529 | May 17, 2019 | (10) |
| MK-3475(Pembrolizumab) | Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C) | II | 113 | The treatment of mismatch instable tumors with immune checkpoint blockade, Pembrolizumab, is highly beneficial as it leads to an increase in progression-free survival.Disease control rate (DCR) is 90% in dMMR.At week 20, the progression-free survival (PFS) was 78% in dMMR, but overall survival (OS) had not been reached in this cohort | NCT01876511 | August 2019 | (11,12) |
| Epacadostat in combination with Immunotherapeutic drugs (including Pembrozulimab ) and chemotherapies | A Study of Epacadostat in Combination With Pembrolizumab and Chemotherapy in Participants With Advanced or Metastatic Solid Tumors (ECHO-207/KEYNOTE-723) | I & II | 70 | The concurrent use of these drugs, pembrolizumab and chemotherapy, with Epacadostat administered at a dosage of 100 mg twice daily, showed a favorable safety profile. Results also indicated that this treatment is effective against advanced and metastatic tumors. | NCT03085914 | July 13, 2020 | (13) |
| Avelumab | Avelumab and Cetuximab in Combination With FOLFOX in Patients With Previously Untreated Metastatic Colorectal Cancer - The Phase II AVETUX-CRC Trial. | II | 43 | A 79.5% objective response rate (ORR) to estimated time of surgery (ETS) ratio is promising for further investigations. The AVETUX regimen is feasible and produces a significant response, especially within the first 8 weeks, in MSS patients.Through central radiological review, TIL clonality and diversity can be used as possible indicators of the response to the combination of chemotherapy and immunotherapy. | NCT03174405 | July 16, 2021 | (14,15) |
| eFT508Avelumab | A Study to Evaluate eFT508 Alone and in Combination With Avelumab in Subjects With MSS Colorectal Cancer | II | 56 | This combination is safe, with a strong target interaction initially, and the results show some level of effectiveness. | NCT03258398 | May 13, 2019 | (16) |
| AvelumabCetuximab | Avelumab Plus Cetuximab in Pre-treated RAS Wild Type Metastatic Colorectal Cancer | II | 77 | In RAS wild-type mCRC patients, this combination is effective and well tolerated. Patients who can benefit from this treatment can be identified using plasma ctDNA analysis. | NCT04561336 | November 14, 2021 | (17) |
| Avelumab | Avelumab Plus Autologous Dendritic Cell Vaccine in Pre-treated Metastatic Colorectal Cancer Patients | I & II | 28 | This study represents a novel therapeutic approach that sensitizes tumors through therapeutic-induced metabolic reprogramming. The combination of Avelumab plus the ADC (Autologous dendritic cells) vaccine is safe, well tolerated, but shows limited clinical efficacy. | NCT03152565 | October 5, 2020 | (18) |
| TemozolomideNivolumabIpilimumab | Nivolumab Plus IPILIMUMAB and TEMOZOLOMIDE in Microsatellite Stable, MGMT Silenced Metastatic Colorectal Cancer (MAYA)   | II | 135 | A significant clinical effect is to be seen upon priming with temozolomide followed by a combination of low-dose ipilimumab and nivolumab in this proof of concept study in MSS and MGMT-silenced mCRC. | NCT03832621 | September 30, 2021 | (19) |
| NivolumabOxaliplatinLeucovorinFluorouracilBevacizumab | An Investigational Immunotherapy Study of Nivolumab With Standard of Care Therapy vs Standard of Care Therapy for First-Line Treatment of Colorectal Cancer That Has Spread (CheckMate 9X8) | II & III | 195  | In mCRC, the combination of NIVO with SOC has been determined to be safe. There was an increase in PFS after 12 months and long-lasting disease control compared to SOC alone. | NCT03414983 | December 28, 2022 | (20) |
| Liver radiation therapyNivolumab InjectionIpilimumab Injection [Yervoy]CMP-001 | Combined Immunotherapy and Radiosurgery for Metastatic Colorectal Cancer | I | 19  | Intolerable liver toxicity is caused by this combination, intratumoral vidutolimod, radiosurgery, nivolumab, and ipilimumab,; hence, this combination is not effective. | NCT03507699 | May 25, 2022 | (21) |
| Biological: GRT-C901Biological: GRT-R902Biological: nivolumabBiological: ipilimumab | A Study of a Personalized Neoantigen Cancer Vaccine | I & II | 214  | This study has two endpoints. The first endpoint demonstrated that the regimen is safe and tolerable, with no dose-dependent toxicity observed. Regarding the second endpoint, the vaccine elicited a CD8+ T cell response and improved overall survival (OS) in some patients with MSS-CRC. Consequently, these results warrant further research to explore this regimen | NCT03639714 | November 10,2022 | (22) |
| Drug: Based on sensitivity analysis | Predictive Value of Drug Sensitivity Testing Tumorspheres From Patients With Metastatic Colorectal Cancer | II | 90  | In mCRC patients, in vitro responsiveness and patient-specific organoids were feasible. No disease progression was observed in half of the patients for 2 months, meeting the first endpoint. This suggests the potential benefits of functional testing using tumor-derived organoids for cancer patient. | NCT03251612 | March 21,2022 | (23) |
| Drug: Part 1 TPST-1120Drug: Part 2 TPST-1120 + nivolumabDrug: Part 3 TPST-1120Drug: Part 4 TPST-1120 + nivolumab | TPST-1120 as Monotherapy and in Combination With Nivolumab in Subjects With Advanced Cancers | I | 138  | The treatment alone or in combination has shown to be well tolerated and measurable improvement or reduction in the size or activity of tumors in the combination setting including responders in late-line RCC and heavily pretreated CCA, resistant to anti-PD-1 therapy. | NCT03829436 | September 7, 2022 | (24) |
|  Regorafenib (Stivarga, BAY73-4506)Nivolumab (Opdivo) | Study on the Effectiveness and Safety of the Combination of the Two Drugs Regorafenib and Nivolumab in Patients With Colorectal Cancer (Cancer of the Colon or Rectum Classified as Proficient Mismatch Repair and Microsatellite Stable) | II | 70  | For this combination to be more effective, further research is warranted to discover patients subgroups with biomarkers or clinical traits. | NCT04126733 | March 28, 2022 | (25) |
| TAS-102nivolumab | A Study Evaluating TAS-102 Plus Nivolumab in Patients With MSS CRC | II | 18  | Although the combination showed to be feasible and tolerable, no therapeutic effect was seen in MSS-CRC. | NCT02860546 | September 7, 2017 | (26) |
| enadenotucirevnivolumab | Phase I Study of Enadenotucirev and PD-1 Inhibitor in Subjects With Metastatic or Advanced Epithelial Tumors (SPICE) | I | 51  | This combinatorial regimen has been shown to have enduring tolerability, enhance immune cell tumor infiltration, and improve OS.  | NCT02636036 | October 8, 2021 | (27) |
| Combination of varlilumab and nivolumab | A Dose Escalation and Cohort Expansion Study of Anti-CD27 (Varlilumab) and Anti-PD-1 (Nivolumab) in Advanced Refractory Solid Tumors | I & II | 175 | The combination is well tolerated with minimal side effects. While there was no significant response observed overall, there was a notable response in patients refractory to anti-PD-1 therapy. Treatment resulted in changes in the tumor microenvironment in ovarian cancer patient. | NCT02335918 | December 12, 2018 | (28) |
| Drug: Nivolumab (Phase 1)Drug: Epacadostat (Phase 1)Drug: Chemotherapy (Phase 1)Drug: Nivolumab (Phase 2)Drug: Epacadostat (Phase 2) | A Study of the Safety, Tolerability, and Efficacy of Epacadostat Administered in Combination With Nivolumab in Select Advanced Cancers (ECHO-204) | I & II | 307  | This combination is well tolerated and shows potential anti-cancer activity in melanoma patients. However, no final data have been provided for this study  | NCT02327078 | July 10, 2020 | (29) |
| Combination of NKTR-214 + nivolumab | A Dose Escalation and Cohort Expansion Study of NKTR-214 in Combination With Nivolumab and Other Anti-Cancer Therapies in Patients With Select Advanced Solid Tumors (PIVOT-02) | I & II | 557  | BEMPEG plus nivolumab was well endured with antitumor activity as first-line treatment in patients with locally advanced/mUC. | NCT02983045 | April 28, 2022 | (30) |
| INCAGN01876NivolumabIpilimumab | Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 Combined With Immune Therapies in Advanced or Metastatic Malignancies | I & II | 145  | INCAGN01876, in combination with NIVO and/or IPI treatments, was well tolerated with no major toxicity observed. The recommended phase 2 dose for INCAGN01876 is 300 mg administered every two weeks (Q2W) | NCT03126110 | November 9, 2021 | (31) |
| Talimogene LaherparepvecAtezolizumab | Study of Talimogene Laherparepvec With Atezolizumab for Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases | I | 36 | No unprecedented safety issues were recorded after treatment with T-Vec or after the combination with atezolizumab. Low anti-tumor activitiy was observed.  | NCT03256344 | December 3, 2021 | (32) |
| Atezolizumab (MPDL3280A), an Engineered Anti-PDL1 AntibodyCobimetinibRegorafenib | A Study to Investigate Efficacy and Safety of Cobimetinib Plus Atezolizumab and Atezolizumab Monotherapy Versus Regorafenib in Participants With Metastatic Colorectal Adenocarcinoma (COTEZO IMblaze370) | III | 363 | IMblaze370 did not meet its primary endpoint of improved overall survival with atezolizumab plus cobimetinib or atezolizumab versus regorafenib. The safety of atezolizumab plus cobimetinib was consistent with those of the individual drugs. These results underscore the challenge of expanding the benefit of immunotherapy to patients whose tumours have lower baseline levels of immune inflammation, such as those with microsatellite-stable metastatic colorectal cancer. | NCT02788279 | December 26, 2018 | (33) |
| AtezolizumabBevacizumabCobimetinib | Study of Cobimetinib in Combination With Atezolizumab and Bevacizumab in Participants With Gastrointestinal and Other Tumors | I | 51 | The combination is safe, and better outcomes were observed in patients with RAS mutations compared to those with wild-type genes | NCT02876224 | June 25, 2019 | (34) |
| BevacizumabIrinotecanOxaliplatinL-Leucovorin5-fluorouracilAtezolizumab | FOLFOXIRI + Bev + Atezo vs FOLFOXIRI + Bev as First-line Treatment of Unresectable Metastatic Colorectal Cancer Patients | II | 201  | Combining atezolizumab to the initial regimen (FOLFOXIRI plus bevacizumab) is safe and escalated the PFS in previously untreated mCRC.Survival improvement was observed in patients with high immune score (IS) pMMR mCRC using this combination as upfront treatment. The results need further investigation in a phase III study | NCT03721653 | August 31,2023 | (35,36) |
| PexidartinibDurvalumab | Evaluation of Safety and Activity of an Anti-PDL1 Antibody (DURVALUMAB) Combined With CSF-1R TKI (PEXIDARTINIB) in Patients With Metastatic/Advanced Pancreatic or Colorectal Cancers (MEDIPLEX) | I | 48 | Toxicity was consistent with the expected profiles of the individual drugs and no unexpected events were seen with the combination. Updated data will be presented at the meeting.A restricted tumor response was observed, attributed to the use of the FLT3 inhibitor pexidartinib, which had a detrimental effect on dendritic cells (DCs). subsequently , FLT3 inhibition should be considered when combining tyrosine kinase inhibitors (TKIs) with anti-PD-L1 therapy | NCT02777710 | December 2019 | (37,38) |
| CetuximabFOLFOX induction regimen Fluoropyrimidine (5-FU/LV or capecitabine) AtezolizumabVemurafenibBevacizumabTrastuzumabPertuzumabCobimetinib5-FU/LV | A Study of Biomarker-Driven Therapy in Metastatic Colorectal Cancer (mCRC) | II | 609 | Primary results suggested that in BRAF wild-type mCRC, PD-L1, CD8/GrB, and FoxP3 are not potential prognostic indicators. For this setting, further exploration is needed to determine the predictive indicators and factors.In BRAFmut mCRC, Vemurafenib plus cetuximab plus 5-FU/LV merit further exploration and MAPK- pathway cutting edge genetic modification could offer a new therapeutic opportunity. Further combination should be tested in MSS mCRC as Cobimetinib plus atezolizumab showed undesirable results. | NCT02291289 | March 24,2021 | (39,40) |
| AZD4635DurvalumabAbiraterone AcetateEnzalutamideOleclumabDocetaxel | A Phase 1 Clinical Study of AZD4635 in Patients With Advanced Solid Malignancies | I | 313 | AZD4635 was well-tolerated both as a single agent and in combination therapy. In metastatic castration-resistant prostate cancer (mCRPC), further combinations warrant investigation in a phase II study. | NCT02740985 | March 31, 2023 | (41) |
| DurvalumabTremelimumab | Tremelimumab and Durvalumab in Treating Patients With Colorectal Cancer With Liver Metastases That Can Be Removed by Surgery | I | 22 | The activation of T and B cells was evident upon the use of this combination, and the safety level was apparent before liver resection in patients with pMMR mCRC | NCT02754856 | January 30,2023 | (42) |
| Standard of CareExperimentalChemotherapy and Bevacizumab | COLUMBIA-1: Novel Oncology Therapies in Combination With Chemotherapy and Bevacizumab as First- Line Therapy in MSS-CRC | I & II | 61 | This combination, consistent with the previous safety profile, has been deemed safe.Following the addition of durvalumab and oleclumab to bevacizumab and FOLFOX (standard of care), a slight improvement was observed in comparison to the standard of care alone | NCT04068610 | October 10, 2022 | (43) |
| durvalumabTremelimumab | Study of Durvalumab and Tremelimumab After Radiation for Microsatellite Stable Metastatic Colorectal Cancer Progressing on Chemotherapy | II | 33 | The combination of two ICB with SBRT (palliative hypofractionated radiotherapy) was found to be safe and well-tolerated. In this regimen, two patients exhibited partial improvement, with response durations of 44 and 44+ weeks, in the context of treatment-resistant MSS CRC. | NCT03007407 | August 9, 2019 | (44) |
| durvalumabtremelimumabRadiation: Radiotherapy (RT)Procedure: ablation | A Clinical Trial of Durvalumab and Tremelimumab, Administered with Radiation Therapy or Ablation in Patients with Colorectal Cancer | II | 25 | The study combination does not warrant further investigation after not meeting the predefined endpoints. However, the occurrence of an abscopal response in non-irradiated areas and a systemic escalation in the immune response is uncommon. In p-MSS CRC, combining durvalumab and tremelimumab is feasible with a tolerable safety profile. Future studies involving new combinations and predictive markers for abscopal responses are required. | NCT03122509 | April 28, 2021 | (45) |
| Durvalumab(Anti-PD-L1)Tremelimumab (Anti-CTLA-4) | A Pilot Feasibility Study of Yttrium-90 Liver Radioembolization Followed by Durvalumab and Tremelimumab in Patients with Microsatellite Stable Colorectal Cancer Liver Metastases | II | 9 | No tumor-guided immune response was noticed in MSS CRC that is metastasized to liver; however, Y90 radioembolization can be harmlessly combined with durvalumab and tremelimumab | NCT03005002 | November 26, 2019 | (46) |
| MEDI4736 | Evaluate the Efficacy of MEDI4736 in Immunological Subsets of Advanced Colorectal Cancer | II | 16 | In patient with MSI CRC, durvalumab was found to have a manageable safety profile, anti-tumor activity, and favorable overall survival. | NCT02227667 | June 29, 2020  | (47) |
| TremelimumabDurvalumabOther: Best Supportive Care | Durvalumab and Tremelimumab and Best Supportive Care vs Best Supportive Care in Patients With Advanced Colorectal Cancer | II | 180 | In advanced unresponsive CRC, prolonged overall survival could be associated with the combination of durvalumab plus tremelimumab. Patients who can benefit from this regimen are to be identified by elevated plasma levels of tumor mutation burden (TMB).Enhanced OS is more prominent in CMS2 than CMS4 when using this combination. The immune characteristics specific to each CMS type are crucial in determining the appropriate approach for targeting the desired immune regulation. | NCT02870920 |  June 7, 2022 | (48,49) |
| DurvalumabTrametinib | Study of Durvalumab (MEDI4736) (Anti-PD-L1) and Trametinib (MEKi) in MSS Metastatic Colon Cancer | II | 29 | In unresponsive mCRC, this combination demonstrated acceptable tolerability. However, the study will not progress to stage 2 due to the response rate not meeting the effectiveness benchmarks in stage 1. | NCT03428126 | May 5, 2022 | (50) |
| ONCOS-102DurvalumabCyclophosphamide | A Study to Investigate ONCOS-102 in Combination With Durvalumab in Subjects With Advanced Peritoneal Malignancies | I & II | 67 | Combining durvalumab with IP ONCOS-102 was proven to be safe with no dose-limiting toxicity. Both biological and clinical activities were noticeable from preliminary evaluations.The study did not meet its efficacy endpoint; however, the combination was well-tolerated. | NCT02963831 | June 25, 2022 | (51) |
| AzacitidineDurvalumab | Study of Azacitidine and Durvalumab in Advanced Solid Tumors | II | 28 | In immunologically cold tumor, this combination did not show any pharmacological or clinical effect. This study supports further drug developments and studies to be done using these drugs. | NCT02811497 | August 4, 2020 | (52) |
| DurvalumabTremelimumab | A Phase 1 Study to Evaluate MEDI4736 in Combination With Tremelimumab | I | 104 | The combination regimen of Durva and Treme demonstrated a tolerable safety profile with indications of clinical effectiveness. These results warrant further investigation of this combination. | NCT01975831 | July 2, 2021 | (53) |
| Ticilimumab (CP-675,206)Anti-CTLA-4 | Phase 2, Single Arm Study Of Ticilimumab In Patients With Refractory Metastatic Adenocarcinoma Of The Colon Or Rectum | Phase 2 | 47 | Despite the survival of 21 patients for more than six months and the interesting moderate response of one patient, Ticilimumab has shown no significant activity. In combination with other ICI, it could be promising. | NCT00313794 | June 2008 | (54) |
| XmAb20717PD-1 x CTLA-4 Bispecific antibody | A Phase 1 Multiple Dose Study to Evaluate the Safety and Tolerability of XmAb®20717 in Subjects With Selected Advanced Solid Tumors | Phase 1 | 150 | This bispecific antibody is safe and showed pharmacodynamic activity in patients with advanced solid tumors who have undergone intensive pretreatment. | NCT03517488 | September 6, 2022 | (55) |

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