Review

The Interplay between Anti-Angiogenics and Immunotherapy in Colorectal Cancer

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Simple Summary: Colorectal cancer is a frequent and lethal neoplasm. The tumor often creates new vessels to grow and spread—a process called ‘angiogenesis’. Therefore, drugs blocking angiogenesis are effective against this malignancy. On the other side, immune checkpoint inhibitors, which unleash the immune system to fight against tumors, have limited efficacy in patients carrying instability of DNA regions called microsatellites. However, there is an interaction between angiogenic factors and the immune system. This gives a chance to combine anti-angiogenic agents and immune checkpoint inhibitors to improve the efficacy of treating this malignancy.

Abstract: Angiogenesis, a hallmark of cancer, plays a fundamental role in colorectal cancer (CRC). Anti-angiogenic drugs and chemotherapy represent a standard of care for treating metastatic disease. Immune checkpoint inhibitors (ICIs) have changed the therapeutic algorithm of many solid tumors. However, the efficacy of ICIs is limited to mCRC patients carrying microsatellite instability (MSI-H), which represent approximately 3–5% of mCRC. Emerging evidence suggests that anti-angiogenic drugs could exhibit immunomodulatory properties. Thus, there is a strong rationale for combining anti-angiogenics and ICIs to improve efficacy in the metastatic setting. Our review summarizes the pre-clinical and clinical evidence regarding the combination of anti-angiogenics and ICIs in mCRC to deepen the possible application in daily clinical practice.

Keywords: colorectal cancer; CRC; anti-angiogenics; angiogenesis; immune checkpoint inhibitors; ICIs; immunotherapy; bevacizumab; pembrolizumab; nivolumab

1. Introduction

Colorectal cancer (CRC) represents the third most common cancer and the second leading cause of cancer-related deaths worldwide, with an increasing incidence in the last decades [1]. Around 20% of patients are diagnosed in the metastatic stage; moreover, 50% of patients with localized disease will develop metastases eventually [2].

Starting from the late 1950s, when 5-fluorouracil (5-FU) was tested, the therapeutic scenario of metastatic CRC (mCRC) evolved from monotherapy to combinations of 5-fluorouracile (5-FU), oxaliplatin, and irinotecan as doublets or triplets; this significantly moved forward mCRC survival. A subsequent fundamental improvement for mCRC patients derived from a personalized approach, consisting of administering agents targeting specific mutations, such as epidermal growth factor receptor (EGFR), B-Raf, and v-Raf murine sarcoma viral oncogene homolog B (BRAF), or anti-angiogenic drugs [2,3]. Effectively, angiogenesis has been indicated as one of the hallmarks of cancer, involved in the development and spread of CRC [4]. Starting in the 2000s, the clinical development of
anti-angiogenic drugs, including bevacizumab, ramucirumab, aflibercept, and regorafenib, represented a benchmark for the treatment of mCRC [5–15]. Presently, anti-angiogenics can be used in both the first and subsequent lines of mCRC treatments. Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor A (VEGF-A). In several phase III trials, when bevacizumab was added to first-line chemotherapy, progression-free survival (PFS) was prolonged up to 12 months, and overall survival (OS) reached 31 months [6–9]. Bevacizumab was also effective in later lines after the progression to front-line treatment reaching around one year of OS [13]. The other anti-angiogenics have been tested after progression to first-line therapy in patients that also received bevacizumab. Aflibercept is a fusion protein directed against VEGF, and ramucirumab binds VEGF-Receptor 2 (VEGFR-2); they determined an OS of around 13 months combined with FOLFIRI in pre-treated patients [14,15]. Furthermore, the tyrosine kinase inhibitor (TKI) regorafenib proved anti-tumor activity in patients with refractory mCRC and is used as a standard of care (SOC) as a later-line treatment [16].

Immunotherapy profoundly transformed the therapeutic scenario of several malignancies; in fact, in the last two decades, the use of immune checkpoint inhibitors (ICIs) spread in many solid tumors after achieving meaningful improvements in survival and quality of life [17–24]. Finding predictive biomarkers for ICIs to allow a better patient selection remains one of the most critical unanswered questions in contemporary immune oncology. Microsatellite instability (MSI) has been addressed as a possible predictive biomarker for ICIs in mCRC. Microsatellites are repeated sequences of one to six nucleotides, often altered during DNA replication. The mismatch repair system (MMR) is a group of proteins (including MutL Homolog [MLH] 1, MLH3, MutS Homolog [MSH] 2, MSH6, MSH3, Protein homolog [PMS] 1, PMS2, and Exonuclease 1 [Exo1]) that can detect and repair microsatellites errors, thus maintaining genome integrity. Hence, an alteration of this system leads to MSI [25,26]. The accumulation of mutations eventually determines a high neo-antigen load, leading to the activation of the immune system, representing a possible explanation for the higher efficacy of ICIs in these patients compared to MS stable (MSS) [27]. Effectively, MSI-H tumors express higher levels of tumor-infiltrating lymphocytes (TILs), cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed cell death 1 (PD1)/PD-ligand 1 (PD-L1), indoleamine 2,3-dioxygenase (IDO), and lymphocyte-activation gene 3 (LAG-3) [28].

Initial studies of ICIs in mCRC included pre-treated patients with MSI. Both KEYNOTE-016 and KEYNOTE-164 demonstrated the efficacy of pembrolizumab as monotherapy in chemo-resistant patients, with an overall response rate (ORR) up to 40% and over 31 months of mOS [29,30]. In phase III KEYNOTE-177 trial, patients were randomized to pembrolizumab or chemotherapy as first-line treatment. Pembrolizumab boosted ORR to 43.8% and doubled mPFS to 16.5 (vs. 8.2) months, and was therefore approved by the Food and Drug Administration (FDA) and European Medical Agency (EMA) [31]. Similar results were observed with nivolumab in pre-treated MSI patients [32]. Interestingly, a combination of Nivolumab plus the anti-CTLA4 Ipilimumab led to an increased response rate and durable response both in untreated and refractory MSI mCRC [32,33].

However, MSI is observed only in 3–5% of mCRC. The vast majority of patients with proficient MMR or microsatellite stable (MSS) tumors do not benefit from ICIs [34]. In this scenario, different combinatory strategies have been investigated to convert MSS ‘cold tumors’ into ‘immune-competent malignancies’, and therefore are amenable to benefit from immunotherapy. Notably, anti-angiogenic drugs are associated with immunomodulatory properties [35,36]. As a consequence, an exciting possibility is represented by the association of anti-angiogenic with immunotherapeutic agents. Our review aims to summarize the available evidence of this combination to define better the pre-clinical rationale that underlies this novel treatment strategy to elicit an immune response in MSS mCRC patients, its clinical application in daily clinical practice, and future directions for research in this field.
2. Rationale to Combine Anti-Angiogenics and ICIs in mCRC

Angiogenesis is a complex process of forming new blood vessels that differentiate from existing endothelial cells (ECs), used as a mechanism of growth and spread by all types of solid tumors [37]. Six ligands and three receptors constitute the VEGF pathway involved in the angiogenetic process regulation [38]. Hypoxia, which often characterizes solid tumors, leads to the activation of the hypoxia-inducible factors (HIF), leading to the transcription of genes, VEGF-A included, aiming to ensure adequate tissue oxygenation [39]. The tumor cells themselves can produce VEGF-A, which binds VEGFR-2 of nearby blood vessels and stimulates the differentiation and growth of EC: the ECs’ shift from a dormant to an active state has been described as the ‘angiogenic swift’ [5]. These changes occur in blood vessels and extracellular matrix, with vasodilatation, permeabilization, and EC migration leading to the formation of new blood vessels [37]. The increased production of VEGF-A triggered by the hypoxic stimulus during neo-angiogenesis shifts the tumor microenvironment (TME) towards immune suppression. VEGF-A can inhibit the maturation and function of dendritic cells (DCs), upregulating PD-L1 expression on DCs, and finally induce T-cell suppression [40–43]. The abnormal architecture of new blood vessels induces an increase in interstitial fluid pressure that, together with the lack of adhesion molecules (such as vasculature cell adhesion molecule [VCAM]-1), reduces the TILs infiltration at tumor sites. Moreover, hypoxia regulates some immune suppressive signals, such as PD-L1, IDO, interleukin-6 (IL-6), and IL-10. It induces the upregulation of chemokines such as chemokine (C-C motif)-ligand (CCL)-22 and CCL28, that recruit Tregs at tumor sites, altering the equilibrium between T-effectors and Tregs [43–45]. Another effect of hypoxia is macrophage polarization towards the M2-like phenotype. Furthermore, ECs express Fas ligand (FasL) that reduces CD8+ T cells but not Tregs, as the latter express FLICE-inhibitory protein (c-FLIP) [43]. As a result, the TME balance is shifted towards immune suppression. The combined restoration of immune responsiveness induced by ICIs and inhibition of angiogenesis after anti-angiogenic therapy could revert this effect on the TME and restore the reciprocal efficacy of the two treatments (Figure 1).

![Diagram](image-url)

**Figure 1.** Effects of hypoxia/neo-angiogenesis on tumor microenvironment.

The increased production of vascular endothelial growth factor A (VEGF-A), triggered by the hypoxic stimulus during neo-angiogenesis, shifts the tumor microenvironment...
(TME) towards immune suppression. VEGF-A inhibits the maturation and function of dendritic cells (DCs), upregulating programmed death ligand 1 (PD-L1) expression on DCs, and finally induces T-cell suppression. Another effect of hypoxia is macrophage polarization towards the M2-like phenotype. Moreover, hypoxia regulates some immune suppressive signals, such as PD-L1, indoleamine 2,3-dioxygenase (IDO), interleukin-6 (IL-6), IL-10, and induces the upregulation of chemokines such as chemokine (C-C motif)-ligand (CCL)-22 and CCL28, that recruit Tregs at tumor sites, altering the equilibrium between T-effectors and Tregs. The abnormal architecture of new blood vessels induces an increase in interstitial fluid pressure that, together with the lack of adhesion molecules (such as vasculature cell adhesion molecule [VCAM]-1), reduces the TILs infiltration at tumor sites. Moreover, endothelial cells express Fas ligand (FasL) that reduces CD8+ T cells but not Tregs, as the latter express FLICE-inhibitory protein (c-FLIP). As a result, the TME balance is shifted towards immune suppression.

3. Clinical Trials of Anti-Angiogenics Plus ICIs in mCRC

As the potential synergism between anti-angiogenics and ICIs was effective and was approved in several solid tumors, several trials were also carried out in mCRC. As ICIs efficacy was restricted to MSI-H patients, many combination trials focused on MSS subjects. Most studies included pre-treated patients, but only five trials were conducted on naïve patients. (Table 1).

In the phase Ib NCT01633970 study, atezolizumab was co-administered with bevacizumab in pre-treated mCRC patients (Arm A), and with bevacizumab and FOLFOX in naïve (Arm B) mCRC patients. Patients were not selected for RAS-mutational status. ORR was 8% among the 13 patients of Arm A, and 36% among the 26 patients in Arm B. G3 or more AEs occurred in 64% of Arm A and 73% of Arm B patients [46]. In the MODUL trial, 445 BRAF wild-type patients received 5-FU + bevacizumab with or without atezolizumab as maintenance after induction with first-line FOLFOX + bevacizumab. Although ORR and DCR were numerically but not statistically significantly higher in the experimental arm compared with SOC, no difference in PFS or OS was observed [47]. Biomarker analyses are currently ongoing and will be presented. In the phase II BACCI trial (NCT02873195), 133 heavily pre-treated MSS mCRC patients were randomized to capecitabine plus bevacizumab plus/minus atezolizumab. Patients could have progressed on previous chemotherapy and anti-VEGF agents in case of RAS mutations. In the atezolizumab group, mPFS was 4.4 months vs. 3.6 in the PBO group. ≥G3 AEs occurred as hypertension (7 vs. 4.3%), diarrhea (7 vs. 4.3%), and hand-foot syndrome (HFS)(7 vs. 4.3%). An exploratory analysis showed that patients without liver metastases had a higher ORR than those with liver metastases (23.1% vs. 5.8%) and tended to have better PFS and OS [48].

In the AtezoTRIBE trial, a multicenter phase II study, naïve mCRC patients were randomized 1:2 to FOLFOXIRI plus bevacizumab without or with atezolizumab, independently from RAS or BRAF mutational status. PFS was the primary endpoint. At the data cut-off, 73 patients had received the standard treatment and 145 atezolizumab. The trial met its primary endpoint, as atezolizumab improved mPFS to 13.1 vs. 11.5 months (HR 0.69, 95% CI 0.56–0.85; p = 0.012). OS data are still immature. The most frequent ≥G3 AEs were neutropenia and diarrhea in both groups. The authors conducted a translational analysis to identify possible biomarkers of response. Interestingly, patients with higher tumor mutational burden (TMB) and Immunoscore IC showed a prolonged PFS [49].
Table 1. Clinical trials of anti-angiogenics plus ICIs in mCRC.

| Trial Name            | First Author | Year | Phase | Nr. of Patients | Treatment                                                                 | ORR, % | mPFS, Months | mOS, Months | Safety                                                                 |
|-----------------------|--------------|------|-------|-----------------|---------------------------------------------------------------------------|--------|--------------|-------------|-----------------------------------------------------------------------|
| NCT01633970           | Bendell      | 2015 | 1b    | Arm A (pre-treated): 13 Arm B (naïve): 26 | Arm A: atezolizumab + bevacizumab Arm B: atezolizumab + FOLFOX + bevacizumab | Arm A: 8% Arm B: 36% | NA           | NA          | >G3 AEs: 64% (Arm A), 73% (Arm B)                                     |
| MODUL (NCT02291289)   | Grothey      | 2018 | 2     | 445 (naïve, BRAF wt) | Maintenance bevacizumab +/- atezolizumab after FOLFOX + bevacizumab       | NA     | Not met      | NA          | Immature data                                                        |
| CheckMate 9X8 (NCT03414983) | Lenz         | 2022 | 2     | Experimental Arm: 127 Control Arm: 68 | Experimental Arm: FOLFOX + Bevacizumab + Nivolumab Control Arm: FOLFOX + Bevacizumab | 60% vs. 48% | 11.9 months in both Arm | NA          | Immature data; Grade 3–4 AEs 75% experimental Arm Vs. 48% control Arm |
| BACCI (NCT0287319)    | Mettu        | 2019 | 2     | 133 (pre-treated) | Capecitabine and bevacizumab + atezolizumab or placebo                   | NA     | 4.4 vs. 3.6  | NA          | >G3 AEs: hypertension (7 vs. 4.3%), diarrhea (7 vs. 4.3%), HFS (7 vs. 4.3%) |
| Atezo TRIBE (NCT03721653) | Antoniotti   | 2022 | 2     | 218 (naive) | FOLFOXIRI + bevacizumab +/- atezolizumab                                | NA     | 13.1 vs. 11.5 (p = 0.012) | NA          | >G3 AEs: neutropenia, diarrhea; 2 treatment-related deaths          |
| CheckMate 9X8 (NCT03414983) | Lenz         | 2022 | 2     | 195 (naive) | FOLFOX + bevacizumab +/- nivolumab                                     | 60% vs. 46% | 11.9 vs. 11.9 | NA          | >G3 AEs 75% vs. 48%                                                  |
| NIVACOR (NCT04072198) | Damato       | 2022 | 2     | 73 (naïve, RAS/BRAF mut) | FOLFOXIRI + bevacizumab + nivolumab                                    | 76.7%  | 10.1 months  | NA          | >G3 AEs: neutropenia, diarrhea, fatigue and hypertension             |
| NCT03946917           | Wang         | 2021 | 1b/2  | 42 (MSS pre-treated) | Toripalimab + regorafenib                                              | 15.2   | 2.1          | 15.5        | >G3 AEs: Hand-foot syndrome; Rash; impaired liver function            |
Table 1. Cont.

| Trial Name | First Author | Year | Phase | Nr. of Patients | Treatment | ORR, % | mPFS, Months | mOS, Months | Safety |
|------------|--------------|------|-------|-----------------|-----------|--------|-------------|-------------|--------|
| LEAP-005 (NCT03797326) | Gomez-Roca | 2021 | 2 | 32 (MSS, pre-treated) | Pembrolizumab + lenvatinib | 22 | 2.3 | 7.5 | 50% AEs |
| NCT03396926 | Bocobo | 2022 | 2 | 44 (MSS, pre-treated) | Pembrolizumab + capecitabine + bevacizumab | 5 | 4.3 | 9.6 | 28% ≥G3 AEs, 58% dose reduction/interruption |
| NCT03050814 | Redman | 2022 | 2 | 26 (MSS, naïve) | mFOLFOX6 + bevacizumab +/− avelumab + CEA-targeted vaccine | 50% vs. 50% | No differences | NA | NA |
| REGONIVO (EPOC1603) | Fukuoka | 2020 | 1b | 25 (pre-treated) | Nivolumab + regorafenib | 36 | 7.9 |NA | ≥G3 AEs: rash (12%), proteinuria (12%), PPED (10%) |
| NCT03712943 | Kim | 2022 | 1b | 51 (MSS, pre-treated) | Nivolumab + regorafenib | 10 | 4.3 | 11.1 | ≥G3 AEs: hypertension (16%), rash (19%), anemia (6%) |
| NCT04126733 | Fakih | 2021 | 2 | 70 (MSS, pre-treated) | Nivolumab + regorafenib | 21.7 | 15 weeks | 52 weeks | ≥G3 AEs: rash (14%), fatigue (7%), pneumonia (6%), increased bilirubin (6%) |
| NCT03657641 | Barzi | 2022 | 1/2 | 73 (MSS, pre-treated) | Pembrolizumab + regorafenib | 0 | 2.8 | 9.6 | ≥G3 rash 20%; ≥G3 HFS 7% |
| REGOMUNE (NCT03475953) | Cousin | 2021 | 2 | 48 (MSS, pre-treated) | Avelumab + regorafenib | 0 | 3.6 | 10.8 | ≥G3 AEs: PPED (29.8%), hypertension (23.4%), diarrhea (12.8%) |
| (Wang et al.) | | 2021 | 1b/2 | 42 (MSS, pre-treated) | Toripalimab + regorafenib | 15.2 | 2.1 | 15.5 | ≥G3 AEs: 38.5% |
| NCT03239145 | Rahma | 2020 | 1b | 18 (MSS, pre-treated) | Pembrolizumab + trebananib | NA | NA | 9 | AEs: diarrhea, limber edema, proteinuria, transaminase increase |

AEs: adverse events; BRAF: v-raf murine sarcoma viral oncogene homolog B1; FOLFOX: folinic acid, 5-fluorouracil, and oxaliplatin; FOLFOXIRI: folinic acid, 5-fluorouracil, oxaliplatin, irinotecan; HFS: hand-foot syndrome; ICIs: immune checkpoint inhibitors; mCRC: metastatic colorectal cancer; mPFS: median progression-free survival; mOS: median overall survival; MSI-H: microsatellite instability-high; MSS: microsatellite stability; NA: not available; NR: not reached; ORR: overall response rate; PPED: palmar-plantar erythrodysesthesia; wt: wild-type.
CheckMate 9X8 is a randomized phase II study that investigates the addition of nivolumab to the standard of care (SOC—FOLFOX + bevacizumab) as a first-line treatment for mCRC, independently from RAS, BRAF, or MS status [50]. The primary endpoint was not met, as mPFS was 11.9 months in both experimental and SOC arms. However, adding nivolumab to FOLFOX + bevacizumab correlated with a higher ORR (60% vs. 46%) and more durable responses than SOC. These data suggest that there is a subset of patients that could benefit from ICIs.

The NIVACOR trial is a single-arm, phase II study evaluating the combination of nivolumab with FOLFOXIRI + bevacizumab followed by maintenance with bevacizumab plus nivolumab in patients with RAS/BRAF mutant untreated mCRC [51]. Of the 73 patients enrolled, 10 were MSI, and for 11 patients, microsatellite instability was not assessed. ORR was 76.7% in the overall population, with a DCR of 97.3%; 2 (2.7%) pts were not evaluable. The mDOR was 8.4 (95% CI, 7–NE) months. In the subset of MSS patients, ORR was 78.9% with an mDOR of 7.59 (95% CI 6.21–11.43) months, DCR of 96.2%, and mPFS of 9.8 (95% CI 8.18–15.24) months.

In a single-center phase II trial, 44 MSS mCRC patients with SD or PD on previous fluoropyrimidine-based therapy received capecitabine plus bevacizumab plus pembrolizumab. Patients were enrolled independently from RAS/BRAF status. ORR was 5%, mPFS 4.3 months, 6 mos PFS 31.1%, mOS 9.6 months. ≥G3 AEs occurred in 28% of patients, with the requirement of dose reduction/interruption in 58% of cases [52].

In the NCT03050814 phase II trial, patients with untreated MSS mCRC (independently from RAS/BRAF status) were randomized to mFOLFOX6 + bevacizumab with or without avelumab plus a CEA-targeted vaccine. No differences emerged between the two arms regarding PFS (HR = 1.06, 95% CI, 0.38–2.96; p = 0.91), and ORR was 50% in both groups [53].

There is emerging evidence that regorafenib with ICIs could exert an anti-tumor activity by various mechanisms, including the activation of the immune system [54]. In this regard, OU and colleagues observed that regorafenib could influence the polarization of tumor-associated macrophages. Based on this rationale, different studies evaluated the combination of regorafenib with ICIs.

Nivolumab was tested with regorafenib in two phase Ib and one phase II studies. In the phase Ib REGONIVO (EPOC1603) trial, 25 pre-treated mCRC patients were included, independently from RAS/BRAF mutational status. ORR was 36%, and mPFS was 7.9 months. Patients with lung metastases tended to have better outcomes compared with liver metastases [55]. Among 51 patients with mismatch repair proficient (pMMR) mCRC of NCT03712943 study, 10% achieved PR, 53% SD with an mPFS of 4.3 months, and an mOS of 11.1 months. The most common G3/G4 AEs were hypertension (16%), rash (19%), and anemia (6%) [56]. Among 70 mCRC patients of the NCT03712943 study, an ORR of 21.7% was achieved. Higher baseline levels of cytotoxic T cells, FoxP3+ Tregs, and macrophages tended to better outcomes. Lower plasma levels of VEGF-D, Angiopoietin-2 (Ang-2), and von Willebrand factor (VWF) correlated with longer PFS. The most common G3/G4 AEs were rash (14%), fatigue (7%), and increased bilirubin (6%) [57]. In the phase I/II NCT03657641 study, 73 patients with MSS mCRC were treated with pembrolizumab plus regorafenib, reaching an mPFS of 4.3 months and an ORR of 0%, with 49% of patients having SD. ≥G3 rash occurred in 20% of patients, ≥G3 HFS in 7% [58].

In the REGOMUNE (NCT03475953) phase II trial, 48 patients received the combination of regorafenib and avelumab 10 mg/kg q2w. Patients were eligible if MSS, but independently from RAS/BRAF mutational status. mPFS was 3.6 mos, mOS 10.8 mos. PPES (29.8%), hypertension (23.4%), and diarrhea (12.8%) were the most common ≥G3 AEs. High infiltration of tumor-associated macrophages (TAMs) at baseline was significantly associated with shorter PFS (1.9 vs. 3.7 mos; p = 0.045) and OS (4.8 mos vs. NR, p = 0.027). On the contrary, increased CD8+ after treatment starting was significantly associated with better PFS (p = 0.011) [59].
In a phase Ib/II study, the safety and activity of regorafenib plus the anti-PD1 toripalimab were tested in 42 MSS pre-treated mCRC patients, independently from RAS/BRAF status [60]. The ORR was 15.2% and the DCR was 36.4% in evaluable patients with recommended phase II dose (80 mg regorafenib plus toripalimab). mPFS and mOS were 2.1 months and 15.5 months, respectively. Similarly to previous findings, patients with liver metastases exhibited lower ORR than those without (8.7% versus 30.0%).

In the LEAP-005 phase II study (NCT03797326), patients with MSS/pMMR (but independently from RAS/BRAF status) mCRC were treated with pembrolizumab 200 mg q3w plus lenvatinib 20 mg daily. Among the 32 treated patients, ORR was 22%, and 50% of patients experienced AEs, with three treatment discontinuation. DCR was 47%, mDOR was not reached (NR), mPFS 2.3 months, and mOS 7.5 months [61]. Based on these results, an ongoing randomized phase III study evaluating pembrolizumab plus lenvatinib in pre-treated patients with mCRC is ongoing [62].

In the NCT03239145 phase Ib trial, 18 MSS (independently from RAS/BRAF status) heavily pre-treated mCRC patients received pembrolizumab plus trebananib, an anti-Ang 1/2 antibody. DCR was 33%, median time-to-progression (TTP) was 2.8 months, and mOS 9 months. The most common AEs of the combination were diarrhea, limber edema, proteinuria, and transaminase increase; only two pembrolizumab-related G3/G4 AEs were reported (pneumonitis and transaminase increase) [63,64].

4. Discussion

Angiogenesis represents a hallmark of cancer, also in mCRC; therefore, anti-angiogenic drugs are regularly used in clinical practice in different settings [4,6–16,65]. On the other hand, even if immunotherapy is one of the significant achievements of modern oncology, in mCRC its use is still limited to MSI-H patients. Based on the potential interaction with the immune response, there is a rationale to combine anti-angiogenic with ICIs. Despite the solid biological rationale and robust pre-clinical evidence, further studies are needed to find the best combinatory strategies and potential biomarkers of response to improve patients’ selection.

Endothelial cells (ECs) share common ancestors with immune cells, which is why they play a role in immune modulation, acting as a sort of gatekeeper controlling the passage of patrolling immune cells from circulation into tissues [66–68]. E-selectin and P-selectin on ECs interact with T-cell ligands. T cells attracting chemokines, such as CCL2 and CXCL9-10-11, interact with their receptors on T-cells (such as CCL2 receptor [CCR2] and CXCR receptor 3 [CXCR3]), activating them [67–69]. After activation, T-cell integrins interact with surface adhesion molecules, very late antigen-4 (VLA4) with vascular cell adhesion molecule 1 (VCAM1), lymphocyte function-associated antigen 1 (LFA-1) with intercellular adhesion molecule (ICAM) [67,68,70]. ECs activation and expression of adhesion molecules can be induced by cytokines, such as IL-6, IL-1b, IFNγ, and TNFα, or pathogen-associated molecular patterns, such as lipopolysaccharide. Inflammatory cytokines, and the same VEGF, act as proangiogenic but also immunomodulatory molecules. For example, VEGF inhibits the expression of surface adhesion molecules and T cells recruiting chemokines such as CXCL9-10-11; moreover, it induces the ECs expression of FasL that causes T-cell apoptosis and recruits Tregs. Therefore, during inflammation, ECs can recruit different immune cells, such as T-effectors, monocytes, and neutrophils [66–68,71]. Furthermore, as tumor vessels are structurally and functionally abnormal, they contribute to immune suppression by implementing necrosis-hypoxia-acidosis. In fact, the production of immune suppressive lactate, nitric oxide, and reactive oxygen species suppresses T-effectors. Moreover, MDSCs and Tregs are recruited, and macrophages shift towards an M2-like subtype, reducing the activity of cytotoxic T cells. Furthermore, ECs can express inhibitory checkpoints such as PD-L1/2, IDO, and T-cell immunoglobulin and mucin domain-containing protein 3 (TIM3), even leading to T-cell death or anergy [66–68]. Finally, a shift towards major histocompatibility complex (MHC)-I overexpression and MHC-II decrease can be associated with the lack of co-stimulatory molecules, such as CD80/CD86, and a higher immune.
tolerogenicity [66–68,72]. As a result, the inhibition of tumor angiogenesis through anti-angiogenic drugs could contribute to a more immune-responsive TME and act in synergy with ICIs. It has been previously demonstrated that there is an interplay between T cells and tumor vascularization inducing CD4+ T-cell activation, IFN\(_\gamma\) production, and subsequent boosting angiogenesis homeostasis, but also immune response [66–68] (Table 2).

Table 2. Endothelial cells (ECs) as checkpoint for immunological patrolling. Receptors expressed by ECs, or circulating factors interacting with ECs, and relative functions in immunological patrolling are listed.

| Molecule | Role |
|----------|------|
| Chemokines (e.g., CCL2, CXCL4/10) | Attracting and binding immune cells with ECs |
| Circulating pro-inflammatory cytokines (IFN\(\gamma\), TNF\(\alpha\)) | Favoring the activation of ECs with exposure of cell adhesion molecules, immune modulation recruiting MDSCs, Tregs, macrophages shifting towards M2-like subtype |
| VEGF | Recruiting immune suppressive cells such as Tregs, inhibiting expression of cell surface adhesion molecules, reducing T cells recruiting chemokines, inducing FasL expression on ECs |
| Adhesion molecules (E-/P-selectin, VCAM, ICAM) | Recruiting and binding immune cells |
| MHC-I | Overexpression associated with lack of co-stimulatory molecules (CD80/CD86) |
| MHC-II | Decrease on tumor vessels, contributing to immune tolerogenicity |
| PD-L1/2 | Creating an immune suppressive tumor microenvironment through the crosstalk between immune cells, cancer cells, and vessels |
| NO, ROS | Altering immune cells infiltration and suppressing CD8+ T cells |
| IDO, TIM3 | After stimulation of ECs by cytokines such as IFN\(\gamma\) inducing T-cell death, cell cycle arrest, and anergy |
| FasL | Causing T-cell apoptosis |

CCL2: chemokine (C-C motif) ligand 2; CD: cluster of differentiation; CXCL4/10: CXC chemokine ligand 4/10; ECs: endothelial cells; ICAM: intercellular adhesion molecule; IDO: Indoleamine 2,3-dioxygenase; IFN\(\gamma\): Interferon gamma; MDSCs: myeloid-derived suppressive cells; MHC: major histocompatibility complex; NO: nitric oxide; PD-L1/2: programmed death ligand 1/2; ROS: reactive oxygen species; TIM3: T-cell immunoglobulin and mucin domain-containing protein 3; TNF\(\alpha\): tumor-necrosis factor alpha; VEGF: vascular endothelial growth factor; VCAM: vascular cell adhesion molecule.

To date, the combination of chemotherapy plus ICIs appears less effective than expected within most studies, with no clear advantage over standard treatment. Nevertheless, in the AtezoTRIBE study, adding PD-1/PD-1 blockade to the intensive chemotherapy FOL-FOXIRI plus bevacizumab seemed to prolong PFS compared with SOC [49]. The authors conducted an exploratory analysis to investigate the role of different potential biomarkers, including the microsatellite instability status, tumor mutational burden (TMB), and Immunoscore IC, as predictive of ICIs response. Interestingly, among patients with MSS tumors, those with Immunoscore IC and TMB high displayed a prolonged PFS. With the limits of a small number of patients included in the biomarker analysis, these results could be considered hypothesis-generating for future investigation. Another study conducted on 18 CRC patients, and CRC cell lines, showed a higher expression of CTLA4 in CRC tissues compared to adjacent non-CRC ones and that this expression could be altered after administering capecitabine, opening up the way for further investigations regarding treatment combinations for improving ICIs efficacy in this malignancy [73]. Effectively, angiogenesis itself can interact with TME, inducing a shift toward immune suppression: DCs are reduced and upregulated the expression of tolerogenic signals such as PD-L1, T cells are suppressed, and TILs infiltration is reduced at tumors sites [40–43]. Immune suppression is further potentiated by hypoxia, which reinforces immune suppressive signals, PD-L1, IDO, IL-6,
IL-10, recruits Tregs, and stimulates macrophage polarization towards M2-like rather than M1-like subtype [43–45].

Effectively, an immune suppressive TME has a crucial role in CRC liver metastasis (CRC-LM) [60,74,75]. A weakened liver’s immune-killing ability promotes the development of CRC-LM. Thus, the overexpression of immune checkpoints (PD1/ PD-L1), immunosuppressive cytokines such as transforming growth factor (TGF)-beta and IL-10, and the subsequent activation of Tregs and TAMs, lead to an immunosuppressive TME and favor the CRC-LM growth. In a monocenter retrospective study, the prognostic role of CRC-LM was assessed in a cohort of 95 patients with MSS refractory mCRC treated with ICIs [74]. The ORR in the overall population was 8.4% (8/95). Interestingly, 8 out of 41 (19.5%) patients without CRC-LM achieved a CR/PR, whereas no response was observed in 54 patients with liver metastases. The DCR was 58.5% (24 out of 41) in patients without liver metastases and 1.9% (1 out of 54) in patients with liver metastases. Moreover, patients without CRC-LM displayed a statistically significant increase in PFS compared with patients with CRC-LM (4.0 vs. 1.5 months; p < 0.001). On the same line, different studies investigating the use of TKIs with ICIs showed that patients with CRC-LM were less likely to respond to combinatory strategies [55,59]. Considering the small number of trial patients, this observation should be taken with caution. The ongoing randomized phase III study LEAP-17 will lighten the efficacy of pembrolizumab plus lenvatinib in this subset of patients [61]. Similarly, further attempts to combine anti-angiogenic/TKI with ICIs and chemotherapeutic regimens are ongoing at different stages. Their results could better clarify the efficacy of the combined mechanisms and eventually improve the therapeutic options in daily clinical practice (Table 3). Up to now, no particular safety concerns have emerged from the combination studies, as the primary toxicity derives from the administered anti-angiogenics. In contrast, ICIs do not seem to raise specific safety concerns. Ongoing studies will also shed light on the safety profile of the different agents when used in combination. Finally, beyond the RAS/BRAF mutational status, which does not seem to influence the response to this combination, and MSS status, a deep investigation regarding biomarkers for treatment response should be conducted in order to allow an optimal patients selection towards a tailored therapeutic approach, combined with sequencing strategies.

### Table 3. Ongoing trials of immune checkpoint inhibitors and anti-angiogenics combination.

| Trial Identification | Phase | Drug Combination | Primary Endpoint |
|----------------------|-------|-----------------|-----------------|
| NCT03657641          | I/II  | Pembrolizumab + Regorafenib | Safety, RD |
| NCT03475004          | II    | Pembrolizumab + bevacizumab + binimetinib | Safety |
| NCT03396926          | II    | Pembrolizumab + bevacizumab + capecitabine | DLT, ORR |
| NCT04776148          | III   | Pembrolizumab + lenvatinib vs. SOC (Regorafenib or TAS-102) | OS |
| NCT05035381          | II    | Pembrolizumab + FOLFIRI + bevacizumab | ORR |
| NCT02298959          | I     | Sintilimab + regorafenib + cetuximab | OS |
| NCT04745130          | II    | Nivolumab + Regorafenib | MTD |
| NCT03712943          | I     | Nivolumab + cabozantinib | DCR |
| NCT04963283          | I     | Nivolumab + ipilimumab + regorafenib | RD |
| NCT03475953          | I/II  | Avelumab + regorafenib | RP2D, ORR |
| NCT02997228          | III   | mFOLFOX6 + bevacizumab vs. atezolizumab vs. mFOLFOX6 + bevacizumab + atezolizumab | PFS |
### Table 3. Cont.

| Trial Identification | Phase | Drug Combination | Primary Endpoint |
|----------------------|-------|-----------------|------------------|
| NCT02873195          | II    | Capecitabine + bevacizumab + atezolizumab vs. PBO | PFS              |
| NCT04659382(SIRTCI)  | II    | Atezolizumab + XELOX + bevacizumab + SIRT         | 9 months-PFS     |
| NCT02777710(MEDIplex)| I     | Durvalumab + pexidartinib                         | DLT, ORR         |
| NCT03555149(Morpheus-CRC)| I/II | Atezolizumab + bevacizumab or regorafenib combinations | ORR              |
| NCT03170960          | I/II  | Atezolizumab + cabozantinib                       | MTD, ORR         |
| NCT03539822          | I/II  | Durvalumab + cabozantinib                         | MTD, ORR         |
| NCT05485909          | II    | Toripalimab + regorafenib + RFA                   | ORR              |
| NCT04110093          | I/II  | Nivolumab or camrelizumab or sintilimab or toripalimab + regorafenib | ORR, PFS |
| NCT04866862          | II    | Camrelizumab + fruquitinib                        | ORR              |
| NCT04695470          | II    | Sintilimab + fruquitinib                          | PFS              |
| NCT04194359          | III   | Xelox + bevacizumab + sintilimab vs. PBO         | PFS              |
| NCT04764006          | II    | Sintilimab + surufatinib                         | ORR              |
| NCT05438108          | II    | SBRT + Xelox + sintilimab + bevacizumab          | ORR, AEs         |
| NCT04271813(APICAL-CR)| II   | Sintilimab + anlotinib                           | ORR              |
| NCT04745130          | II    | Sintilimab + regorafenib + cetuximab             | ORR              |
| NCT05524155          | II    | Sintilimab + regorafenib + HAIC                  | ORR, AEs         |
| NCT05292417          | II    | Sintilimab + fruquitinib + GM-CSF                | PFS              |
| NCT04948034(RIFLE)   | II    | SABR+ tislelizumab + fruquitinib                 | ORR              |
| NCT05314101          | II    | Tislelizumab + bevacizumab + TAS-102            | PFS              |
| NCT04924179          | II    | Tislelizumab + fruquitinib + SBRT                | PFS              |
| NCT04777162          | II    | Tislelizumab + anlotinib                        | ORR              |
| NCT05435313          | II    | Tislelizumab + fruquitinib + HAIC                | ORR              |
| NCT04577963          | I/II  | Tislelizumab + fruquitinib                       | RP2D, AEs, ORR   |
| NCT04579757          | I/II  | Tislelizumab + surufatinib                      | DLT, ORR         |

AEs: adverse events; DLT: dose-limiting toxicity; HAIC: hepatic arterial infusion chemotherapy; MTD: maximum tolerated dose; ORR: overall response rate; OS: overall survival; PBO: placebo; PFS: progression-free survival; RD: recommended dose; RFA: radiofrequency ablation; RP2D: recommended phase II dose; SABR: stereotactic ablative radiotherapy; SIRT: selective internal radiation therapy; SOC: standard of care.

An emerging amount of evidence indicates that the gut microbiome could regulate the homeostasis of different physiological conditions. Alteration of the composition and biodiversity of gut microbiota, a condition called dysbiosis, is involved in different pathological conditions, including CRC [76]. Although the role of specific microbes in modulating the efficacy and tolerability of immunotherapy has been addressed in different malignancies, little evidence is currently available for mCRC patients [77–79]. To assess the potential role of gut microbiota in response to ICIs, we conducted a retrospective analysis on available pre-treatment stool samples of mCRC and non-small cell lung cancer (NSCLC) patients treated with cetuximab plus avelumab [80–82]. Fascinatingly, in five long-term responding patients with MSS mCRC, PFS (9–24 months) was significantly increased in two butyrate-producing bacteria, *Agathobacter* M104/1 ($p = 0.018$) and *Blautia* SR1/5 ($p = 0.023$) compared...
with nine patients with shorter PFS (2–6 months). These results were consistent with the validation cohort of NSCLC patients that received the combination of cetuximab and avelumab. In the phase Ib/II study evaluating the combination of regorafenib plus toripalimab, a gut microbiome analysis of the baseline fecal samples was performed [83]. Notably, a significantly increased relative abundance and positive detection rate of *Fusobacterium* was observed in non-responders compared with responders. Moreover, patients with a high abundance of *Fusobacterium* exhibited a shorter PFS than those with low abundance (mPFS = 2.0 vs. 5.2 months; \( p = 0.002 \)).

**5. Conclusions**

Following the robust results of blocking the angiogenesis and PD1/PD-L1 axis in hepatocarcinoma and renal cell carcinoma, there was great interest in this therapeutic strategy for CRC. Unfortunately, preliminary results were more disappointing than expected. Whereas a small subset of mCRC is experiencing tumor regression with ICIs plus anti-angiogenic drugs, most patients do not benefit from the treatment. The commonly used molecular classifications are not prognostic for this combination of treatments. Therefore, further translational studies are needed to identify clinical, immunological, and molecular predictive biomarkers of response.

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**References**

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer statistics, 2022. *CA Cancer J. Clin.* 2022, 72, 7–33. [CrossRef] [PubMed]

2. Biller, L.H.; Schrag, D. Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. *JAMA* 2021, 325, 669–685. [CrossRef]

3. Ciardiello, F.; Ciardiello, D.; Martini, G.; Napolitano, S.; Tabernero, J.; Cervantes, A. Clinical management of metastatic colorectal cancer in the era of precision medicine. *CA Cancer J. Clin.* 2022, 72, 372–401. [CrossRef] [PubMed]

4. Hanahan, D. Hallmarks of Cancer: New Dimensions. *Cancer Discot.* 2022, 12, 31–46. [CrossRef] [PubMed]

5. Hanahan, D.; Folkman, J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 1996, 86, 353–364. [CrossRef]

6. Hurwitz, H.; Fehrenbacher, L.; Novotny, W.; Cartwright, T.; Hainsworth, J.; Heim, W.; Berlin, J.; Baron, A.; Griffin, S.; Holmgren, E.; et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N. Engl. J. Med.* 2004, 350, 2335–2342. [CrossRef] [PubMed]

7. Saltz, L.B.; Clarke, S.; Diaz-Rubio, E.; Scheithauer, W.; Figer, A.; Wong, R.; Koski, S.; Lichinitser, M.; Yang, T.S.; Rivera, F.; et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J. Clin. Oncol.* 2008, 26, 2013–2019. [CrossRef] [PubMed]

8. Cremolini, C.; Loupakis, F.; Antoniotti, C.; Lupi, C.; Sensi, E.; Lonardi, S.; Mezi, S.; Tommasello, G.; Ronzoni, M.; Zaniboni, A.; et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: Updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol.* 2015, 16, 1306–1315. [CrossRef]

9. Cremolini, C.; Marmorino, F.; Loupakis, F.; Masi, G.; Antoniotti, C.; Salvatore, L.; Schirripa, M.; Boni, L.; Zagonel, V.; Lonardi, S.; et al. all the investigators of the Gruppo Oncologico del Nord Ovest. TRIBE-2: A phase III, randomized, open-label, strategy trial in unresectable metastatic colorectal cancer patients by the GONO group. *BMC Cancer* 2017, 17, 408. [CrossRef]

10. Hegewisch-Becker, S.; Graeven, U.; Lerchenmüller, C.A.; Killing, B.; Depenbusch, R.; Steffens, C.C.; Al-Batran, S.E.; Lange, T.; Dietrich, G.; Stoehlmacher, J.; et al. Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for
patients with metastatic colorectal cancer (AIO 0207): A randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol.* **2015**, *16*, 1355–1369. [CrossRef]

11. Simkens, L.H.J.; van Tinteren, H.; May, A.; Tije, A.J.T.; Creemers, G.-J.M.; Loosveld, O.J.L.; E de Jongh, F.; Erdkamp, F.L.G.; Erjavec, Z.; E van der Torren, A.M.; et al. Maintenance treatment with capectabine and bevacizumab in metastatic colorectal cancer (CAIRO3): A phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. *Lancet* **2015**, *385*, 1843–1852. [CrossRef]

12. Giantonio, B.J.; Catalano, P.J.; Meropol, N.J.; O’Dwyer, P.J.; Mitchell, E.P.; Alberts, S.R.; Schwartz, M.A.; Benson, A.B., III. Eastern Cooperative Oncology Group Study E3200. Bevacizumab in combination with oxalaplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. *J. Clin. Oncol.* **2007**, *25*, 1539–1544. [CrossRef] [PubMed]

13. Bennouna, J.; Sastre, J.; Arnold, D.; Österlund, P.; Greil, R.; Van Cutsem, E.; von Moos, R.; Véitez, J.M.; Bouché, O.; Borg, C.; et al. ML18147 Study Investigators. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): A randomised phase 3 trial. *Lancet Oncol.* **2013**, *14*, 29–37. [CrossRef]

14. Van Cutsem, E.; Tabernero, J.; Lakomy, R.; Preven, H.; Prausová, J.; Macarulla, T.; Ruff, P.; van Hazel, G.A.; Moiseyenko, V.; Ferry, D.; et al. Addition of afilbercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxalaplatin-based regimen. *J. Clin. Oncol.* **2012**, *30*, 3499–3506. [CrossRef] [PubMed]

15. Tabernero, J.; Yoshino, T.; Cohn, A.L.; Obermannova, R.; Bodoky, G.; Garcia-Carbonero, R.; Cituleanu, T.E.; Portnoy, D.C.; Van Cutsem, E.; Grothey, A.; et al. RAISE Study Investigators. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with meta-static colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxalaplatin, and a fluoropyrimidine (RAISE): A randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol.* **2015**, *16*, 499–508, Erratum in: *Lancet Oncol.* **2015**, *16*, e262. [CrossRef] [PubMed]

16. Grothey, A.; Van Cutsem, E.; Sobrero, A.; Siena, S.; Falcone, A.; Ychou, M.; Humblet, Y.; Bouché, 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 Oncol.* **2013**, *14*, 303–312. [CrossRef]

17. Pradeep, J.; Win, T.T.; Aye, S.N.; Sreeramareddy, C.T. Efficacy and Safety of Immune Checkpoint Inhibitors for Advanced Malignant Melanoma: A Meta-Analysis on Monotherapy Vs Combination Therapy. *J. Cancer* **2022**, *13*, 3091–3102. [CrossRef] [PubMed]

18. Lavacchi, D.; Pellegrini, E.; Palmieri, V.E.; Doni, L.; Mela, M.M.; Di Maida, F.; Amedei, A.; Pillozzi, S.; Carini, M.; Antonuzzo, L. Immune Checkpoint Inhibitors in the Treatment of Renal Cancer: Current State and Future Perspective. *Int. J. Mol. Sci.* **2020**, *21*, 4691. [CrossRef]

19. Maiorano, B.A.; De Giorgi, U.; Ciardiello, D.; Schinzari, G.; Cisternino, A.; Tortora, G.; Maiello, E. Immune-Checkpoint Inhibitors in Advanced Bladder Cancer: Seize the Day. *Biomedicines* **2022**, *10*, 411. [CrossRef] [PubMed]

20. Maiorano, B.A.; Maiorano, M.F.P.; Cormio, G.; Maglione, A.; Lorusso, D.; Maiello, E. How Immunotherapy Modified the Therapeutic Scenario of Endometrial Cancer: A Systematic Review. *Front. Oncol.* **2022**, *12*, 844801. [CrossRef] [PubMed]

21. Ciardiello, D.; Guerrera, L.P.; Maiorano, M.F.P.; Cormio, G.; Maglione, A.; Lorusso, D.; Maiello, E. Immunotherapy in advanced anal canc: Is the beginning of a new era? *Cancer Treat Rev.* **2022**, *105*, 102373. [CrossRef] [PubMed]

22. Ciardiello, D.; Maiorano, B.A.; Parente, P.; Parente, P.; Pia Latiano, T.; Mela, M.M.; Di Maio, M.; Ciardiello, F.; Troiani, T.; Martinelli, E.; Maiello, E. Immunotherapy for Biliary Tract Cancer in the Era of Precision Medicine: Current Knowledge and Future Perspectives. *Int. J. Mol. Sci.* **2022**, *23*, 820. [CrossRef]

23. Maiorano, B.A.; Maiorano, M.F.P.; Lorusso, D.; Maiello, E. Ovarian Cancer in the Era of Immune Checkpoint Inhibitors: State of the Art and Future Perspectives. *Cancers* **2021**, *13*, 4438. [CrossRef] [PubMed]

24. Tang, S.; Qin, C.; Hu, H.; Liu, T.; He, Y.; Guo, H.; Yan, H.; Zhang, J.; Tang, S.; Zhou, H. Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer: Progress, Challenges, and Prospects. *Cells* **2022**, *11*, 320. [CrossRef] [PubMed]

25. Hause, R.J.; Pritchard, C.C.; Shendure, J.; Salipante, S.J. Classification and characterization of microsatellite instability across 18 cancer types. *Nat. Med.* **2016**, *22*, 1342–1350. [CrossRef] [PubMed]

26. Amato, M.; Franco, R.; Facchini, G.; Addeo, R.; Ciardiello, F.; Berretta, M.; Zito Marin, F. Microsatellite Instability: From the Implementation of the Detection to a Prognostic and Predictive Role in Cancers. *Int. J. Mol. Sci.* **2022**, *23*, 8726. [CrossRef]

27. Xiao, Y.; Freeman, G.J. The microsatellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. *Cancer Discov.* **2015**, *5*, 16–18. [CrossRef] [PubMed]

28. Drescher, K.M.; Sharma, P.; Watson, P.; Gatalica, Z.; Thibodeau, S.N.; Lynch, H.T. Lymphocyte recruitment into the tumor site is altered in patients with MSI-H colon cancer. *Fam. Cancer* **2009**, *8*, 231–239. [CrossRef] [PubMed]

29. Le, D.T.; Uram, J.N.; Wang, H.; Bartlett, B.R.; Kemberling, H.; Eyring, A.D.; Skora, A.D.; Luber, B.S.; Azad, N.S.; Laheru, D.; et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N. Engl. J. Med.* **2015**, *372*, 2509–2520. [CrossRef] [PubMed]

30. Le, D.T.; Kim, T.W.; Van Cutsem, E.; Geva, R.; Jäger, D.; Hara, H.; Burge, M.; O’Neil, B.; Kavan, P.; Yoshino, T.; 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*, 11–19. [CrossRef] [PubMed]
31. André, T.; Shiue, K.K.; Kim, T.W.; Geva, R.; Jäger, D.; Harra, H.; Burge, M.; O'Neil, B.; Kavan, P.; Yoshino, T.; et al. KEYNOTE-177 Investigators. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N. Engl. J. Med.* 2020, 383, 2207–2218. [CrossRef] [PubMed]

32. 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. [CrossRef]

33. Lenz, H.J.; Van Cutsem, E.; Luisa Limon, M.; Wong, K.Y.M.; Hendliss, A.; Aglietta, M.; García-Alfonso, P.; Neyns, B.; Lupp, G.; Cardin, D.B.; et al. First-Line Nivolumab Plus Low-Dose Ipiilimumab for Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. *J. Clin. Oncol.* 2022, 40, 161–170. [CrossRef] [PubMed]

34. Ciardiello, D.; Vitiello, P.P.; Cardone, C.; Martini, G.; Troiani, T.; Martinelli, E.; Ciardiello, F. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019, 76, 22–32. [CrossRef] [PubMed]

35. Chen, D.S.; Hurwitz, H. Combinations of Bevacizumab with Cancer Immunotherapy. *Cancer J.* 2018, 24, 193–204. [CrossRef] [PubMed]

36. García, J.; Hurwitz, H.I.; Sandler, A.B.; Miles, D.; Coleman, R.L.; Deurloo, R.; Chinot, O.L. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat. Res.* 2020, 86, 102017. [CrossRef]

37. Carmeliet, P. Angiogenesis in health and disease. *Nat. Med.* 2003, 9, 653–660. [CrossRef]

38. Dvorak, H.F. Vascular permeability factor/vascular endothelial growth factor: A critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. *J. Clin. Oncol.* 2002, 20, 4366–4380. [CrossRef]

39. Fang, J.; Yan, L.; Shing, Y.; Moses, M.A. HIF–1alpha–mediated up–regulation of vascular endothelial growth factor, independent of basic fibroblast growth factor, is important in the switch to the angiogenic phenotype during early tumorigenesis. *Cancer Res.* 2001, 61, 5731–5735.

40. Ramjiawan, R.R.; Griffioen, A.W.; Duda, D.G. Anti–angiogenesis for cancer revisited: Is there a role for combinations with immunotherapy? *Angiogenesis* 2017, 20, 185–204. [CrossRef]

41. Gabrilovich, D.I.; Chen, H.L.; Girgis, K.R.; Cunningham, H.T.; Meny, G.M.; Nadaf, S.; Kavanaugh, D.; Carbone, D.P. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. *Nat. Med.* 1996, 2, 1096–1103. [CrossRef] [PubMed]

42. Curiel, T.J.; Wei, S.; Dong, H.; Alvarez, X.; Cheng, P.; Mottram, P.; Krzysiek, R.; Knutson, K.L.; Daniel, B.; Zimmermann, M.C.; et al. Blockade of B7–H1 improves myeloid dendritic cell–mediated antitumor immunity. *Nat. Med.* 2003, 9, 562–567. [CrossRef] [PubMed]

43. Yi, M.; Jiao, D.; Qin, S.; Chu, Q.; Wu, K.; Li, A. Synergistic effect of immune checkpoint blockade and anti–angiogenesis in cancer treatment. *Mol. Cancer* 2019, 18, 60. [CrossRef]

44. Curiel, T.J.; Coukos, G.; Zou, L.; Alvarez, X.; Cheng, P.; Mottram, P.; Evdemon-Hogan, M.; Conejo-Garcia, J.R.; Zhang, L.; Burow, M.; et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat. Med.* 2004, 10, 942–949. [CrossRef] [PubMed]

45. Facciabene, A.; Peng, X.; Hagemann, I.S.; Balint, K.; Barchetti, A.; Wang, L.P.; Gimotty, P.A.; Gilks, C.B.; Lal, P.; Zhang, L.; et al. Tumour hypoxia promotes tolerance and angiogenesis via CCL28 and T(reg) cells. *Nature* 2011, 475, 226–230. [CrossRef] [PubMed]

46. Bendell, J.C.; Powderly, J.D.; Lieu, C.H.; Eckhardt, S.G.; Hurwitz, H.; Hochster, H.S.; Murphy, J.E.; Funke, R.P.; Rossi, C.; Wallin, J.; et al. Safety and efficacy of MPDL3280A (anti–PD–L1) in combination with bevacizumab (bev) and/or FOLFOX in patients (pts) with metastatic colorectal cancer (mCRC). *J. Clin. Oncol.* 2015, 33, 704. [CrossRef]

47. Tabernerio, J.; Grotchey, A.; Arnold, D.; de Gramont, A.; Dueurx, M.; O'Dwyer, P.; Tahirri, A.; Gilberg, F.; Irahara, N.; Schmoll, H.-J.; et al. MODUL cohort 2: An adaptable, randomized, signal-seeking trial of fluoropyrimidine plus bevacizumab with or without atezolizumab maintenance therapy for BRAF metastatic colorectal cancer. *ESMO Open* 2022, 7, 100559. [CrossRef]

48. Mettu, N.; Twohy, E.; Ou, F.-S.; Halldanarson, T.; Lenz, H.; Breakstone, R.; Boland, P.; Crysler, O.; Wu, C.; Grothey, A.; et al. BACCI: A phase II randomized study of fluoropyrimidine and bevacizumab maintenance plus atezolizumab (A) or placebo (P) in refractory metastatic colorectal cancer (mCRC): A CCRU network study. *Ann. Oncol.* 2019, 30 (Suppl. 5), v198–v252. [CrossRef]

49. Antoniotti, C.; Rossi, D.; Pietrantonio, F.; Catteau, A.; Salvatore, L.; Lonardi, S.; Boquet, I.; Tamberi, S.; Marmorino, F.; Moretto, R.; et al. GONO Foundation Investigators. Uptight FOLFOXIRI plus bevacizumab with or without atezolizumab in the treatment of patients with metastatic colorectal cancer (AtezoTRIBE): A multicentre, open-label, randomised, controlled, phase 2 trial. *Lancet Oncol.* 2022, 23, 876–887. [CrossRef]

50. Lenz, H.-J.; Parikh, A.R.; Spigel, D.R.; Cohn, A.L.; Yoshino, T.; Kochenderfer, M.D.; Elez, E.; Shao, S.H.; Deming, D.A.; Holdridge, R.C.; et al. Nivolumab (NIVO) + 5-fluorouracil/leucovorin/oxaliplatin (mFOLFOX6)/bevacizumab (BEV) versus mFOLFOX6/BEV for first-line (1L) treatment of metastatic colorectal cancer (mCRC): Phase 2 results from CheckMate 9X8. *J. Clin. Oncol.* 2022, 40 (Suppl. 4), 8. [CrossRef]

51. Damato, A.; Bergamo, F.; Antonuzzo, L.; Nasti, G.; Pietrantonio, F.; Tonini, G.; Maiello, E.; Bordonaro, R.; Rosati, G.; Romagnani, A.; et al. Phase II study of nivolumab in combination with FOLFOXIRI/bevacizumab as first-line treatment in patients with
advanced colorectal cancer RAS/BRAF mutated (mut): NIVACOR trial (GOIRC-03-2018). J. Clin. Oncol. 2022, 40 (Suppl. 16), 3509. [CrossRef]

Bocobo, A.G.; Wang, R.; Behr, S.; Carnevale, J.C.; Cinar, P.; Colisson, E.A.; Fong, L.; Keenan, B.P.; Kidder, W.A.; Ko, A.H.; et al. Phase II study of pembrolizumab plus capicitabine and bevacizumab in microsatellite stable (MSS) metastatic colorectal cancer (mCRC). J. Clin. Oncol. 2022, 40 (Suppl. 16), 3565. [CrossRef]

Redman, J.M.; Tsai, Y.T.; Weinberg, B.A.; Donahue, R.N.; Gandhy, S.; Gatti-Mays, M.E.; Abdul Sater, H.; Bilusic, M.; Cordes, L.M.; Steinberg, S.M.; et al. A Randomized Phase II Trial of mFOLFOX6 + Bevacizumab Alone or with AdCEA Vaccine + Avelumab Immunotherapy for Untreated Metastatic Colorectal Cancer. Oncologist 2022, 27, 198–209. [CrossRef]

Ou, D.; Chen, C.; Hsu, C.; Chung, C.H.; Peng, Z.R.; Lee, B.S.; Cheng, A.L.; Yang, M.H.; Hsu, C. Regorafenib enhances antitumor immunity via inhibition of p38 kinase/Creb1/Klf4 axis in tumor-associated macrophages. J. Immunother. Cancer 2021, 9, e001657. [PubMed]

Fukuoka, S.; Hara, H.; Takahashi, N.; Kojima, T.; Kawazoe, A.; Asayama, M.; Yoshii, T.; Kotani, D.; Tamura, H.; Mikamoto, Y.; et al. Regorafenib Plus Nivolumab in Patients with Advanced Gastric or Colorectal Cancer: An Open-Label, Dose–Escalation, and Dose–Expansion Phase Ib Trial (REGONIVO, EPOC1603). J. Clin. Oncol. 2020, 38, 2053–2061. [CrossRef] [PubMed]

Kim, R.D.; Kovari, B.P.; Martinez, M.; Xie, H.; Sahin, I.H.; Mehta, R.; Strosberg, J.; Imanirad, I.; Ghayouri, M.; Kim, Y.C.; et al. A phase I/ib study of regorafenib and nivolumab in mismatch repair proficient advanced refractory colorectal cancer. Eur. J. Cancer 2022, 169, 93–102. [CrossRef] [PubMed]

Fakhri, M.; Raghav, K.P.S.; Chang, D.Z.; Bendell, J.C.; Larson, T.; Cohn, A.L.; Huyck, T.K.; Cosgrove, D.; Fiorillo, J.A.; Garbo, L.E.; et al. Single-arm, phase 2 study of regorafenib plus nivolumab in patients with mismatch repair proficient (pMMR)/microsatellite stable (MSS) colorectal cancer (CRC). J. Clin. Oncol. 2021, 39 (Suppl. 15). [CrossRef]

Barzi, A.; Azad, N.S.; Yang, Y.; Tsao-Wei, D.; Rehan, R.; Fakhri, M.; Iqbal, S.; El-Khoueiry, A.B.; Millstein, J.; Jayachandran, P.; et al. Phase I/II study of regorafenib (rego) and pembrolizumab (pembro) in refractory microsatellite stable colorectal cancer (MSSCRC). J. Clin. Oncol. 2022, 40 (Suppl. 4), 15. [CrossRef]

Cousin, S.; Cantarel, C.; Guegan, J.P.; Gomez-Roca, C.; Metges, J.P.; Adenis, A.; Perlot, S.; Bellera, C.; Kind, M.; Auzanneau, C.; et al. Regorafenib-Avelumab Combination in Patients with Microsatellite Stable Colorectal Cancer (REGOCURE): A Single-arm, Open-label, Phase II Trial. Clin. Cancer Res. 2021, 27, 2139–2147. [CrossRef] [PubMed]

Wang, F.; He, M.M.; Yao, Y.C.; Zhao, X.; Wang, Z.Q.; Jin, Y.; Luo, H.Y.; Li, J.B.; Wang, F.H.; Qiu, M.Z.; et al. Regorafenib plus toripalimab in patients with metastatic colorectal cancer: A phase Ib/II clinical trial and gut microbiome analysis. Cell Rep. Med. 2021, 2, 100383. [CrossRef] [PubMed]

Gomez-Roca, C.; Yanez, E.; Im, S.-A.; Alvarez, E.C.; Senellart, H.; Doherty, M.; Garcia-Corbacho, J.; Lopez, J.S.; Basu, B.; Maurice-Dror, C.; et al. LEAP-005: A phase II multicohort study of lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors—Results from the colorectal cancer cohort. J. Clin. Oncol. 2021, 39, 94. [CrossRef]

Yoshino, T.; Fu, R.; Hawk, N.; Adelberg, D.E.; Norwood, K.G.; Heinemann, V. 506TIP Pembrolizumab plus lenvatimib versus standard of care for previously treated metastatic colorectal cancer (mCRC): Phase III LEAP-017 study. Ann. Oncol. 2021, 32, S580. [CrossRef]

Rhama, O.E.; Cleary, J.M.; Schlechter, B.L.; Ng, K.; Eno, J.; Stroinee, A.; Giobbe-Hurder, A.; McDermott, D.F.; Hodi, F.S. Phase Ib study of pembrolizumab and tebananib (angiopoietin-2 inhibitor [Ang-2]): Preliminary analysis of the colorectal cancer (CRC) cohort. J. Clin. Oncol. 2019, 37, e14160. [CrossRef]

Rhama, O.E.; Cleary, J.M.; Ng, K.; Schlechter, B.L.; Eno, J.; Maloney, A.; Giobbe-Hurder, A.; McDermott, D.F.; Hodi, F.S. Phase Ib study to test the safety and activity of pembrolizumab (anti-PD-1) and tebananib (angiopoietin-2 inhibitor [Ang-2]) in patients with advanced solid tumors: Updated analysis of the colorectal cancer (CRC) cohort. J. Clin. Oncol. 2020, 38 (Suppl. 4), 155. [CrossRef]

Van Custem, 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. [CrossRef]

Solimando, A.G.; Summa, S.; Vacca, A.; Ribatti, D. Cancer-Associated Angiogenesis: The Endothelial Cell as a Checkpoint for Immunological Patrolling. Cancers 2020, 12, 3380. [CrossRef] [PubMed]

Duru, G.; van Egmond, M.; Heemskerk, N. A Window of Opportunity: Targeting Cancer Endothelium to Enhance Immunotherapy. Front. Immunol. 2020, 11, 584723. [CrossRef]

Amersfoort, J.; Eelen, G.; Carmeliet, P. Immunomodulation by endothelial cells—Partnering up with the immune system? Nat. Rev. Immunol. 2022, 22, 576–588. [CrossRef]

Springer, T.A. Traffic signals for lymphocyte recirculation and leukocyte emigration: The multistep paradigm. Cell 1994, 76, 301–314. [CrossRef]

Carman, C.V.; Martinielli, R. T lymphocyte–endothelial interactions: Emerging understanding of trafficking and antigen-specific immunity. Front. Immunol. 2015, 6, 603. [CrossRef]

Motz, G.T.; Santoro, S.P.; Wang, L.P.; Garaabrant, T.; Lastra, R.R.; Hagemann, I.S.; Lal, P.; Feldman, M.D.; Benencia, F.; Coukos, G. Tumor endothelium Fasl establishes a selective immune barrier promoting tolerance in tumors. Nat. Med. 2014, 20, 607–615. [CrossRef] [PubMed]
72. Griffioen, A.W.; Damen, C.A.; Martinotti, S.; Blijham, G.H.; Groenewegen, G. Endothelial intercellular adhesion molecule-1 expression is suppressed in human malignancies: The role of angiogenic factors. *Cancer Res.* 1996, 56, 1111–1117. [PubMed]

73. Derakhshani, A.; Hashemzadeh, S.; Asadzadeh, Z.; Shadbad, M.A.; Rasibonab, F.; Safarpour, H.; Jafarlou, V.; Solimando, A.G.; Racanelli, V.; Singh, P.K.; et al. Cytotoxic T-Lymphocyte Antigen-4 in Colorectal Cancer: Another Therapeutic Side of Capcitabine. *Cancers* 2021, 13, 2414. [CrossRef] [PubMed]

74. Zhou, H.; Liu, Z.; Wang, Y.; Wen, X.; Amador, E.H.; Yuan, L.; Ran, X.; Xiong, L.; Ran, Y.; Chen, W.; et al. Colorectal liver metastasis: Molecular mechanism and interventional therapy. *Sig. Transduct. Target. Ther.* 2022, 7, 70. [CrossRef]

75. Wang, C.; Sandhu, J.; Ouyang, C.; Ye, J.; Lee, P.P.; Fakih, M. Clinical Response to Immunotherapy Targeting Programmed Cell Death Receptor 1/Programmed Cell Death Ligand 1 in Patients With Treatment-Resistant Microsatellite Stable Colorectal Cancer With and Without Liver Metastases. *JAMA Netw. Open* 2021, 4, e2118416. [CrossRef]

76. Panebianco, C.; Ciardiello, D.; Villani, A.; Maiorano, B.A.; Latiano, T.P.; Maiello, E.; Perri, F.; Pazienza, V. Insights into the role of gut and intratumor microbiota in pancreatic ductal adenocarcinoma as new key players in preventive, diagnostic and therapeutic perspective. *Semin. Cancer Biol.* 2021, 25. [CrossRef] [PubMed]

77. Zhou, C.B.; Zhou, Y.L.; Fang, J.Y. Gut Microbiota in Cancer Immune Response and Immunotherapy. *Trends Cancer* 2021, 7, 647–660. [CrossRef] [PubMed]

78. Derosa, L.; Routy, B.; Fidelle, M.; Iebba, V.; Alla, L.; Pasolli, E.; Segata, N.; Desnoyer, A.; Pietrantonio, F.; Ferrere, G.; et al. Gut Bacteria Composition Drives Primary Resistance to Cancer Immunotherapy in Renal Cell Carcinoma Patients. *Eur. Urol.* 2020, 78, 195–206. [CrossRef]

79. Baruch, E.N.; Youngster, I.; Ben-Betzalel, G.; Ortenberg, R.; Lahat, A.; Katz, L.; Adler, K.; Dick-Necula, D.; Raskin, S.; Bloch, N.; et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 2021, 371, 602–609. [CrossRef]

80. Fasano, M.; Della Corte, C.M.; Di Liello, R.; Barra, G.; Sparano, F.; Viscardi, G.; Iacovino, M.L.; Paragliola, F.; Famiglietti, V.; Ciaramella, V.; et al. Induction of natural killer anti-body-dependent cell cytotoxicity and of clinical activity of cetuximab plus avelumab in non-small cell lung cancer. *ESMO Open* 2020, 5, e000753. [CrossRef]

81. Martinelli, E.; Martini, G.; Famiglietti, V.; Troiani, T.; Napolitano, S.; Pietrantonio, F.; Ciardiello, D.; Terminiello, M.; Borrelli, C.; Vitiello, P.P.; et al. Cetuximab Rechallenge Plus Avelumab in Pretreated Patients With RAS Wild-type Metastatic Colorectal Cancer: The Phase 2 Single-Arm Clinical CAVE Trial. *JAMA Oncol.* 2021, 7, 1529–1535. [CrossRef] [PubMed]

82. Ciardiello, D.; Famiglietti, V.; Napolitano, S.; Esposito, L.; Pietrantonio, F.; Avallone, A.; Maiello, E.; Cremolini, C.; Troiani, T.; Martinelli, E.; et al. Final results of the CAVE trial in RAS wild type metastatic colorectal cancer patients treated with cetuximab plus avelumab as rechallenge therapy: Neutrophil to lymphocyte ratio predicts survival. *Clin. Colorectal Cancer* 2022, 21, 141–148. [CrossRef] [PubMed]

83. Martini, G.; Ciardiello, D.; Dallio, M.; Famiglietti, V.; Esposito, L.; Corte, C.M.D.; Napolitano, S.; Fasano, M.; Gravina, A.G.; Romano, M.; et al. Gut microbiota correlates with antitumor activity in patients with mCRC and NSCLC treated with cetuximab plus avelumab. *Int. J. Cancer* 2022, 151, 473–480. [CrossRef] [PubMed]