# Immunotherapy of Colorectal Cancer

Subjects: Oncology

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Immunotherapy has become one of the pillars of treatmemt of Colorectal Cancer. This entry explains what Immune Checkpoint Inhibitors are, how they work and which patients are most likely to benefit from them. You will get an overview of the current (2020) scientific evidence on their efficacy in terms of objective tumor response, progression free survival and overall survival, as well as on safety, adverse effects and potential impact on quality of life indicators. Furthermore, ongoing or planned trials are listed.

Keywords: colorectal cancer ; metastatic colorectal cancer ; advanced colorectal cancer ; treatment refractory colorectal cancer ; immunotherapy ; checkpoint inhibitors ; pembrolizumab ; nivolumab ; atezolizumab ; ipilimumab

## 1. Background

Cancer immunotherapy aims to enhance the natural capability of the immune system to fight cancer cells and has already become one of the pillars of cancer treatment in advanced stages [1]. Immune checkpoint inhibitors (ICI) have demonstrated ground-breaking results in tumors with a high burden of genetic mutations such as melanoma or lung cancer [2]. Due to their high mutagenic level, these tumors generate many neoantigens and provoke a strong immunogenic reaction driven by T-cells. Programmed death cell protein 1 (PD-1) is expressed on the surface of these T-cells and interacts with programmed death-ligand 1 or 2 (PD-L1, PD-L2), leading to a suppression of the immune response by transmitting an inhibitory signal to the cytotoxic T-cells and reducing apoptosis in regulatory T-cells. Cancers use this mechanism to evade the immune response by over-expressing programmed cell death ligand-1/2 (PD-L1/2) on their cell surface [3]. In a similar way, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptors are up-regulated on the surface of activated T-lymphocytes and compete with CD28 receptors for the ligands CD80/86 expressed on antigen presenting cells (APCs). While CD28 is a co-activating factor for T-cells, CTLA-4 sends an inhibitory signal to T-cells and outcompetes CD28 as it binds with higher affinity and avidity to its ligands CD80/86. Immune checkpoint inhibitors (ICI) are monoclonal antibodies that block these pathways by binding to the PD-1 receptor (i.e., nivolumab, pembrolizumab), to PD-L1 (i.e., atezolizumab), or to CTLA-4 (i.e., ipilimumab) and thus enhance the immune response against cancer cells.

Recent evidence indicates that in metastatic colorectal cancer (mCRC) patients, ICIs' response is limited to those with high mutational burden showing mismatch repair deficiency (MMRd). Professional organizations recommend testing all newly diagnosed CRCs for MMRd either by immunohistochemistry (IHC) to detect loss of expression of the mismatch repair (MMR) proteins (MLH1, MSH2, MSH6 or PMS2) or by polymerase chain reaction (PCR) or next generation sequencing (NGS) of microsatellite instability (MSI) markers [4][5][6][7][8]. MMRd CRC tumors have a high mutational load (and specially frame-shift mutations) that creates many neoantigens which are presented on major histocompatibility complex (MHC) molecules and are recognized as foreign by T-cells. As a consequence, MMRd tumors have much higher PD-L1 expression in tumoral cells and tumor associated macrophages (TAMs) and a higher presence of tumor-infiltrating lymphocytes (TIL) than MMR proficient (MMRp) tumors. This subtype of CRC accounts for approximately 5% of all mCRC and has shown an impressive benefit of treatment with ICIs, which led to their accelerated approval by the U.S. Food and Drug Administration (FDA) in 2017 [9][10].

## 2. Current scientific evidence (2020)

Most of the scientific evidence on the efficacy of ICIs in CRC derives from phase II clinical trials (e.g. Keynote 164, Checkmate 142) that focus on patients with metastatic disease and who had multiple previous lines of chemotherapy. The primary endpoint in these studies was the rate of objective response (ORR) measured by imaging techniques and evaluated by the RECIST v1.1 criteria. As secondary endpoints, progression free survival (PFS) and overall survival (OS) rates were analyzed. For Pembrolizumab monotherapy, between 33 and 52% of the cases with MMR deficient tumors showed an objective response [11][12][13][14]. Neither the median PFS nor the median OS was reached in none of the studies with estimates at one year between 34 and 78% for PFS and about 70 to 80% for OS. For nivolumab, 32% of

MMR deficient cases showed an objective response [15], rising up to 49% when combined with ipilimumab [16]. Taken into account that these were all heavily pretreated patients, these results indicate a significant improvement in responses and survival rates. Recently, at the 2020 Meeting of the American Society of Clinical Oncology (ASCO), unpublished data of a well designed phase III clinical trial were presented and provide the first evidence that pembrolizumab as a first line therapy may be superior to standard of care chemotherapy in the metastatic setting of MMR deficient tumors (44% vs. 33%, respectively) [17]. On the other hand, MMR proficient tumors are considered to be naturally resistant to ICI therapy due to a lower mutational burden and subsequently a less dense immune infiltrate. However, when the combination of nivolumab and ipilimuab was administered to early stage CRC (stage I, II and III) as a neoadjuvant treatment (before surgery), surprisingly, with only 3 doses of treatment about 25% of patients with MMR proficient tumors experienced an objective response and, more strikingly, in 13% of cases the tumor had disappeared completely [18]. Moreover, MMR proficient tumors showed a significant increase of tumor infiltrating T cells in the surgical specimen (compared to pretreatment tumor biopsies) even though they had not experienced a pathological response. These (unpublished) data are very promising yet need to be confirmed in larger trials.

## 3. Predictive Biomarkers

To date, the only predictor of response to checkpoint inhibitors is the presence of MMR deficiency in the tumor. In the Checkmate study with nivolumab, none of the assessed biomarkers (PD-L1 expression, mutation status of the oncogenes *BRAF* and *KRAS*, history of Lynch syndrome) were predictive for response. In the case of pembrolizumab, the study from Le and colleagues [19] showed that a high number of mutations was associated with a longer PFS, while the presence of CD8+ lymphocytes and expression of PD-L1 showed a trend toward objective response, although differences in PFS and OS were not statistically significant. In the same study, a substantial decrease of the levels of the tumor marker ‘carcinoembryonic antigen' (CEA) was only observed in MMRd CRCs and was predictive for both PFS and OS. There are preliminary results that CD8+/PD-1+ T-cell infiltration may be predictive of response in MMRp early CRC in the neoadjuvant setting, but this needs to be confirmed in larger trials.

## 4. Quality of Life Indicators

The Checkmate 142 study assessed quality of life indicators using the EORTC-QLQ-C30 and the EQ-5D questionnaires. Results from the nivolumab in monotherapy or combination with ipilimumab were similar with more than 50% of patients maintaining functioning and global health without worsening of symptoms. Moreover, both schemes showed statistically significant and clinically meaningful improvements in functioning, symptoms and quality of life observed as early as week thirteen and were maintained for some indicators beyond week 37. Regarding the EQ-5D test, a clinically meaningful improvement of all five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) was observed also as early as week thirteen and was maintained during the treatment (up to 67 weeks in the combination arm).

## 5. Safety and Security

Overall tolerability of all checkpoint inhibitors was favorable with most of the adverse effects being mild (grade one and two) and not leading to treatment discontinuation nor withdrawal from the study. Since ICIs block a pathway that is thought to prevent autoimmunity, any relevant autoimmune precondition or immunosuppressive treatment were exclusion criteria as well as active or chronic hepatitis B/C or human immunodeficiency virus (HIV) infection. Drug related adverse effects (DRAE) grade three or four ranged from 20% to 41% and were mainly manageable. In the two Checkmate study arms, 6.8% and 13% discontinued treatment for any grade of adverse effect, respectively. The most frequent grade three and four adverse effects reported were fatigue, nausea/vomiting, anemia, lymphopenia, hyponatremia, colitis/diarrhea, gastritis/ulcer, arthritis/arthralgia, elevated liver enzymes, acute kidney injury and asymptomatic pancreatitis, most of which were either auto-limited, reversed after discontinuation or were treatable. Drug related adverse effects with potential immunologic etiology affected the skin (rash), liver, thyroid (hypothyroidism), GI tract (colitis), adrenal glands (adrenal insufficiency) or the lungs (pneumonitis). All were manageable with treatment discontinuation, short-term corticosteroid therapy or replacement therapy (in case of hypothyroidism). No drug related deaths occurred. In the Checkmate study, one sudden death occurred ten days after therapy discontinuation and under steroid therapy for colitis. After the autopsy, this death was not attributed to drug toxicity. All other reported deaths were caused by disease progression or other causes. Despite the overall excellent tolerability, anecdotally one case of pneumonitis was reported related to pembrolizumab and we found one case report in the literature of a severe necrotizing myositis associated with long term efficacy following nivolumab and ipilimumab combination therapy [20]. Regarding atezolizumab, patients had more grade 3–4 adverse effects when combined with cobimetinib compared to atezolizumab monotherapy, but a similar rate when

compared with standard of care regorafenib (61, 31 and 58%, respectively) [21]. The most frequent adverse effects in the combination group were diarrhea (11%), anemia (6%), elevated creatine phosphokinase levels (7%) and fatigue (4%). Fatal events were rare and occurred in 3% of both the combination group (2 × sepsis) and the regorafenib group (1 × perforation), while there was no fatal event in the atezolizumab monotherapy group.

## 6. Future Studies

The results of the first studies with ICIs presented in this article have raised new hope for the treatment of CRC. As a consequence, numerous further studies are ongoing or planned to corroborate these data, test ICIs in different settings and investigate new ICI antibodies. Many ongoing studies seek to enhance treatment efficacy by combining ICIs with other therapeutic modalities such as chemotherapy (e.g., with pembrolizumab, NCT02375672, or with atezolizumab, NCT02912559), radiotherapy (e.g., with pembrolizumab, NCT02437071), or other targeted therapies such as regorafenib (with pembrolizumab, NCT03657641), binimetinib and bevacizumab (with pembrolizumab, NCT03475004), cetuximab (with pembrolizumab, NCT02713373), bevacizumab (with atezolizumab, NCT02982694) or cobimetinib (with ipilimumab and nivolumab, NCT02060188). Another focus is to assess ICI efficacy in the setting of microsatellite stable (MSS), mismatch repair proficient (MMRp) tumors, which were thought be naturally resistant to ICIs until Chalabi and colleagues showed this year that there might be a subset of patients that could benefit from them [22]. In this sense, studies are ongoing or planned that assess the usefulness of ICIs in MSS/MMRp patients particularly when combined with other treatments, for instance nivolumab with regorafenib (NCT04126733), nivolumab and ipilimumab combined with radiotherapy (NCT04575922) or nivolumab and regorafenib combined with radiotherapy (NCT04030260). For the combination of nivolumab and ipilimumab, Chalabi and colleagues also showed that ICIs could be very useful in the neoadjuvant setting. Trials are now on their way to determine the role of neoadjuvant pembrolizumab in mCRC (e.g., NCT03984578, NCT04231526). The neoadjuvant use of ICIs could also be interesting for rectal cancers following the rationale that radiotherapy increases the mutational burden and subsequent generation of neoantigens boosting the cytotoxic T-cell immune response against the tumor. All four ICIs are under investigation for that purpose: pembrolizumab (NCT04109755), nivolumab and ipilimumab (NCT04124601) and atezolizumab (NCT04017455, combined with bevacizumab). Another potentially useful approach is to pretreat MSS/MMRp tumors with temozolomide—an alkylating agent—to trigger a hypermutation status and make MSS/MMRp tumors more amenable to ICI treatment, for instance with pembrolizumab (NCT03519412) or nivolumab and ipilimumab (NCT03832621). Lastly, ICIs are also being investigated as combination partners for chemotherapy in the first line of treatment, e.g., nivolumab (NCT04072198) and atezolizumab (NCT03721653). In addition to the ICIs discussed so far in this article, new antibodies are on the horizon that have shown promising results in other cancers: durvalumab and avelumab (both anti-PD-L1) and tremelimumab (anti-CTLA-4). For instance, the combination of tremelimumab and durvalumab is actually under investigation in three different settings: in MSS mCRC after palliative radiotherapy (NCT03007407), as a combination partner for chemotherapy in the first line treatment of *KRAS* mutant mCRC (NCT03202758), and in advanced unresectable and treatment-refractory CRC in a randomized, open-label trial comparing with best supportive care (NCT02870920). Most of the ongoing or planned studies discussed here are small-to-medium sized, single arm, open-label phase two trials that seek to confirm objective responses, safety and tolerability. Thus, interpretation of efficacy, especially when compared to standard treatment, should be done cautiously. However, some phase three trials with adequate comparators are now on their way and the first results are expected within the next two years: standard of care chemotherapy (SOC) and nivolumab vs. SOC alone (NCT03414983), nivolumab and ipilimumab vs. nivolumab alone vs. SOC alone (NCT04008030) and SOC and atezolizumab vs. SOC alone (NCT02912559).

## 7. General Recommendation

Immunotherapy based on ICIs in monotherapy (anti-PD-1) or combination therapy (anti-PD-1 and anti-CTLA-4) should be offered as a second line therapy to mCRC patients with tumors that display MMRd demonstrated by either microsatellite instability and/or by immunohistochemistry (loss of expression of MLH1, MSH2, MSH6 or PMS2). Unpublished data suggest moderate evidence that pembrolizumab may be superior to standard of care chemotherapy as a first line treatment in MMRd mCRC and therefore should be considered as an option. There is preliminary evidence that ICIs may also be helpful in the neoadjuvant setting of early tumors, but this needs to be confirmed in larger future trials.

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