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EDITORIAL

Anti program death-1/anti program death-ligand 1 in digestive cancers

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Abstract

Human tumors tend to activate the immune system regulatory checkpoints as a means of escaping immunosurveillance. For instance, interaction between program death-1 (PD-1) and program death-ligand 1 (PD-L1) will lead the activated T cell to a state of anergy. PD-L1 is upregulated on a wide range of cancer cells. Anti-PD-1 and anti-PD-L1 monoclonal antibodies (mAbs), called immune checkpoint inhibitors (ICIs), have consequently been designed to restore T cell activity. Accumulating data are in favor of an association between PD-L1 expression in tumors and response to treatment. A PD-L1 expression is present in 30% to 50% of digestive cancers. Multiple anti-PD-1 (nivolumab, pembrolizumab) and anti-PD-L1 mAbs (MPDL3280A, Medi4736) are under evaluation in digestive cancers. Preliminary results in metastatic gastric cancer with pembrolizumab are highly promising and phase Ⅱ will start soon. In metastatic colorectal cancer (CRC), a phase Ⅲ trial of MPDL3280A as maintenance therapy will shortly be initiated. Trials are also ongoing in metastatic CRC with high immune T cell infiltration (*i.e.*, microsatellite instability). Major challenges are ahead in order to determine how, when and for which patients we should use these ICIs. New radiologic criteria to evaluate tumor response to ICIs are awaiting prospective validation. The optimal therapeutic sequence and association with cytotoxic chemotherapy needs to be established. Finally, biomarker identification will be crucial to selection of

patients likely to benefit from ICIs.

Key words: Program death-1; Program death-ligand 1; Antibody; Digestive cancer

Core tip: Anti-program death-1 and anti-program death-ligand 1 (PD-L1) monoclonal antibodies have been designed to restore T cell activity, since human tumors tend to activate this immune regulatory checkpoint as a means of escaping immunosurveillance. A PD-L1 expression is present in 30% to 50% of digestive cancers and accumulating data are in favor of an association between this PD-L1 expression and response to treatment, which make digestive cancers promising candidates for those breakthrough immunotherapies. We review the ongoing clinical trials and the major challenges ahead of us in order to learn how, when and for which patients we should use these therapeutics.

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TUMOR IMMUNOLOGY

Up until recently, only melanoma and renal cell cancer (RCC) were considered as immunogenic tumors. But in 2012 the results of a phase I study with nivolumab, an anti program death-1 (PD-1) monoclonal antibody (mAb), showed clinical responses in non-small cell lung cancers (NSCLC), thereby introducing the notion that any tumor can respond to the immune checkpoint inhibition strategy[1]. To prevent autoimmunity, to allow peripheral tolerance (during a woman's pregnancy, for instance) or to permit negative feed-back on immune reactions and secure immune system homeostasis, multiple immune checkpoints must be crossed so that immune response can occur and last. Human tumors tend to activate these immune checkpoints as a means of escaping immunosurveillance. That is one reason why new therapeutics called immune checkpoints inhibitors (ICIs) have been designed.

Cancer immunoediting

Cancer immunoediting is currently defined by three E's: elimination, equilibrium and escape[2]. The first phase reflects active immunosurveillance, which facilitates tumor eradication and is mostly mediated by tumor-associated antigen-specific lymphocytes. The second phase refers to the period during which tumor growth is still prevented by the host immune system even though the surviving tumor and its stroma are also shaped by the immune response, which they learn how to downsize. Lastly, the escape phase describes tumor growth notwithstanding an immunologically intact environment due to selection of tumor cell variants during the equilibrium phase.

T cell activation

In order to be activated, a T lymphocyte needs an association of triggering signals. Antigen coupled with major histocompatibility complex recognition is the first step toward activation. A second signal arising from the interaction of co-stimulatory molecules of activation must occur, avoiding T cell anergy. CD28 is the most commonly cited example of co-stimulatory molecules, and it is constitutively expressed on the T cell surface. It binds to B7.1 (CD80) or B7.2 (CD86), which are primarily expressed on activated antigen-presenting cells. B7 molecules also interact with cytotoxic T lymphocyte associated antigen 4 (CTLA-4), which is expressed on T cells. CTLA-4 transmits an inhibitory signal to T cells to prevent early excessive T cell activation. The molecules involved are called immune checkpoint. PD-1 is more widely expressed than CTLA-4 and can be detected not only on T cells but also on B lymphocytes and natural killer cells. Program death-ligand 1 (PD-L1) expression is up-regulated by interferon-γ production, which follows T cell activation. PD-1/PD-L1 interaction allows for negative feedback on the immune response regulating effector T cell responses in peripheral tissues and leads to peripheral T cell tolerance[3,4] (Figure 1). PD-L1 expression is up-regulated on a wide range of cancer cells and tumor-infiltrating immune cells strongly involved in tumor immunosurveillance escape. Several ICIs have been developed so as to prevent those negative regulations of the host immune system.

IMMUNE CHECKPOINT INHIBITORS

To boost immune responses, ipilimumab, an anti-CTLA-4 mAb has been designed and has produced good results in cases of melanoma. Its limiting toxicities are mostly autoimmunity since it seems to upregulate all immune reactions. The PD-1/PD-L1 axis can be targeted by either anti-PD-1 mAbs or anti-PD-L1 mAbs (Figure 2). Anti PD-1 mAbs target PD-1 interactions with both PD-L1 and program death-ligand 2 (PD-L2), while PD-L1 mAbs target interactions between PD-L1 and either PD-1 or B7.1. PD-1 mAbs have been approved for the treatment of unresectable melanoma and NSCLC and their development for bladder cancer and RCC is well-advanced. Targeting of the CTLA-4 pathway has changed the melanoma treatment landscape[5,6] but PD-1/PDL1 axis targeting is also highly promising in multiple tumors[1,7].

Association between PD-L1 expression and treatment response

Several studies have demonstrated an association

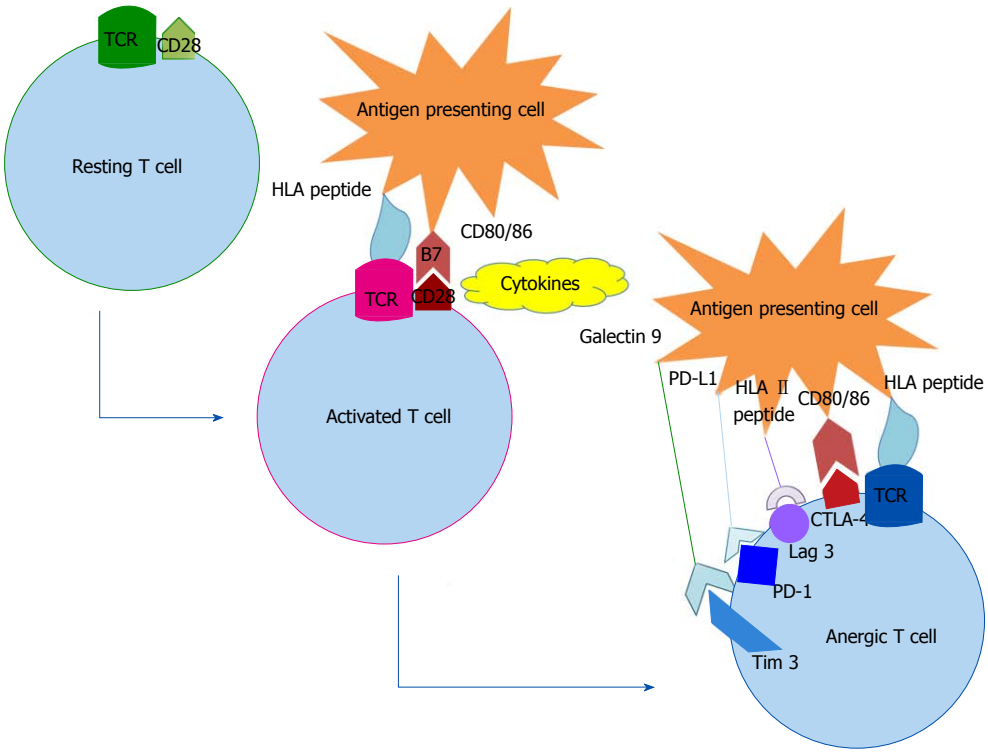

Figure 1 From a resting T cell to an activated or an anergic T cell. To be activated a T cell lymphocyte needs recognition of an antigen coupled with major histocompatibility complex by its specific TCR, adequate cytokines and activation of co-stimulatory molecules such as CD28. An inhibitory signal can instead be transmitted by co-inhibitory molecules (PD-1, CTLA-4, Lag 3, Tim 3…) and lead to T cell anergy. TCR: T cell receptor; CD28: Cluster of differenciation 28; HLA: Human leucocyte antigen; CD80/86: Cluster of differenciation CD80/86; PD-1: Program death-1; PD-L1: Program death-ligand 1; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4.

between pretreatment PD-L1 expression and tumor responses to anti-PD-1/PD-L1 therapies in melanoma, bladder cancer and NSCLC[1,8]. A PD-L1/PD-1 positive tumor should consequently be a good candidate for these treatments. For example, Dong *et al*[9] found 53% of PD-L1 positive colon carcinomas. Later, Droeser *et al*[10] studied PD-L1 expression in 1420 colorectal cancer (CRC). Strong PD-L1 positivity was found in 36% and 29%, respectively in mismatch repair (MMR)-proficient and deficient (dMMR) CRC. dMMR CRC has been associated with high level of tumor-infiltrating lymphocytes (TIL) and a good prognosis[11]. In other digestive cancers, especially in esophageal, gastric and pancreatic cancers, a PD-L1 expression was found in 30%-50% of cases[12-15].

Anti-PD-1 mAbs

Preliminary results are available for two anti-PD-1 mAbs (nivolumab and pembrolizumab) in digestive cancers. Nineteen patients with CRC were enrolled in the phase Ⅰ study of nivolumab, but no efficacy was demonstrated[1]. However, nivolumab is currently being evaluated in multiple digestive cancers both alone and in combination with other ICIs (such as ipilumumab or anti-Lag 3) or with immune system stimulators. A phase Ⅱ clinical trial of nivolumab *vs* nivolumab plus ipilimumab in recurrent and metastatic colon cancer with a stratification between dMMR and pMMR status is ongoing. Pembrolizumab has been evaluated in gastric cancer and preliminary results were presented at the 2014 European Society for Medical Oncology meeting and updated at the 2015 American Society of Clinical Oncology Gastro Intestinal symposium[14]. In this trial, only PD-L1 positive tumors were eligible. Thirty-nine patients were enrolled and 67% had received at least two prior chemotherapy regimens. The overall response rate was 22%. The 6-mo progression-free survival and overall survival rates were 24% and 69%, respectively. Four patients experienced grade 3 to 4 adverse events and one patient died due to treatment-related hypoxia. A phase Ⅱ study will shortly be initiated with pembrolizumab monotherapy or in combination with cisplatin and 5 fluoro-uracil (5FU) in advanced gastric cancer treatment. Pembrolizumab is also currently under investigation in pancreatic cancer and in combination with aflibercept in CRC.

Anti-PD-L1 mAbs

Now focusing on anti-PD-L1 mAbs (BMS936559, MPDL-3280A and MEDI4736) results in digestive cancers, the phase Ⅰ study with BMS936559 enrolled eighteen patients with CRC, fourteen with pancreatic cancer and seven with gastric cancer. None of the gastric cancer patients could be included in the efficacy analysis and no objective response was observed in either CRC or in pancreatic cancer[7]. MPDL3280A showed very promising

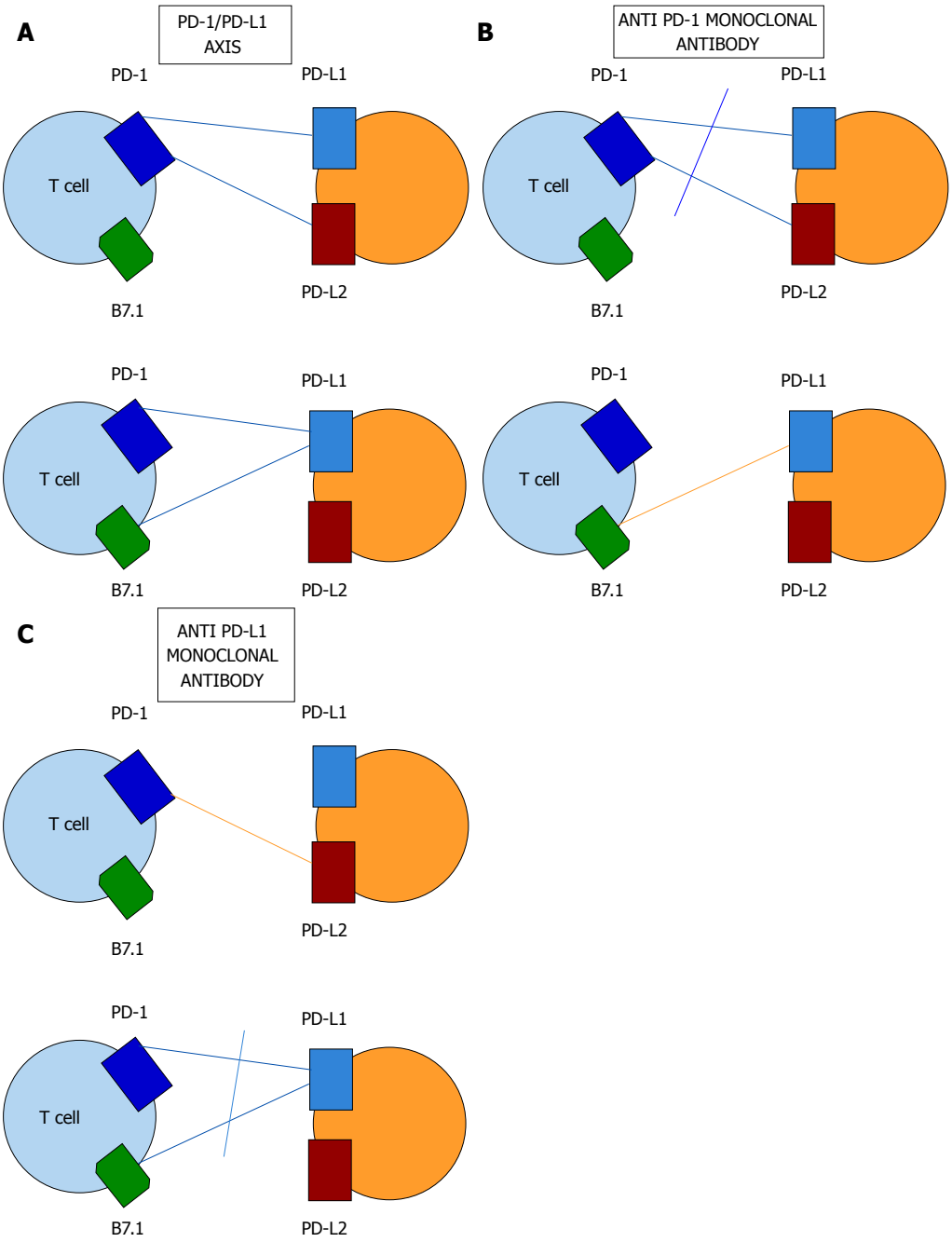

Figure 2 The program death-1 and program death-ligand 1 axis blockade. A: The PD-1 and PD-L1 interactions: PD1 has two ligands called PD-L1 and PD-L2. PD-L1 can interact either with PD-1 or B7.1; B: Anti PD-1 monoclonal antibody blockade prevents PD-L1 and PD-L2 ligation to PD-1 but not the B7.1 and PD-L1 interaction; C: Anti PD-L1 monoclonal antibody blockade prevents PD-1 and B7.1 ligation to PD-L1 but not the PD-1 and PD-L2 interaction. PD-1: Program death-1; PD-L1: Program death-ligand 1; PD-L2: Program death-ligand 2.

results in metastatic bladder cancer[8], NSCLC and RCC[16] but so far no result has been presented in digestive cancer. However, clinical trials are ongoing in combination with immune-modulating therapies (ipilumumab or interferon-α) and in combination with bevacizumab, MEK inhibitor or CD40 agonist. Finally, the MODUL trial is a randomized phase Ⅲ multicenter trial with biomarker-driven maintenance therapy in metastatic CRC first-line treatment (Figure 3). After a four-month FOLFOX plus bevacizumab induction therapy, patients with disease control will be treated by maintenance therapy with 5FU, cetuximab and vemurafenib in *BRAF* mutated tumors or with 5FU, bevacizumab and MPDL3280A in *BRAF* wild-type tumors (the control arm will be 5FU and bevacizumab in both cohorts). MPDL3280A and MEDI4736 are both human IgG1 PD-L1 mAbs whose Fc domain has been engineered to prevent antibody-dependent cell-mediated cytotoxicity (ADCC). Indeed, PD-L1 can be expressed by the tumor-infiltrating immune cells, including T cells and if ADCC was induced, the latter would be killed, which would be counterproductive. The results of the MEDI4736

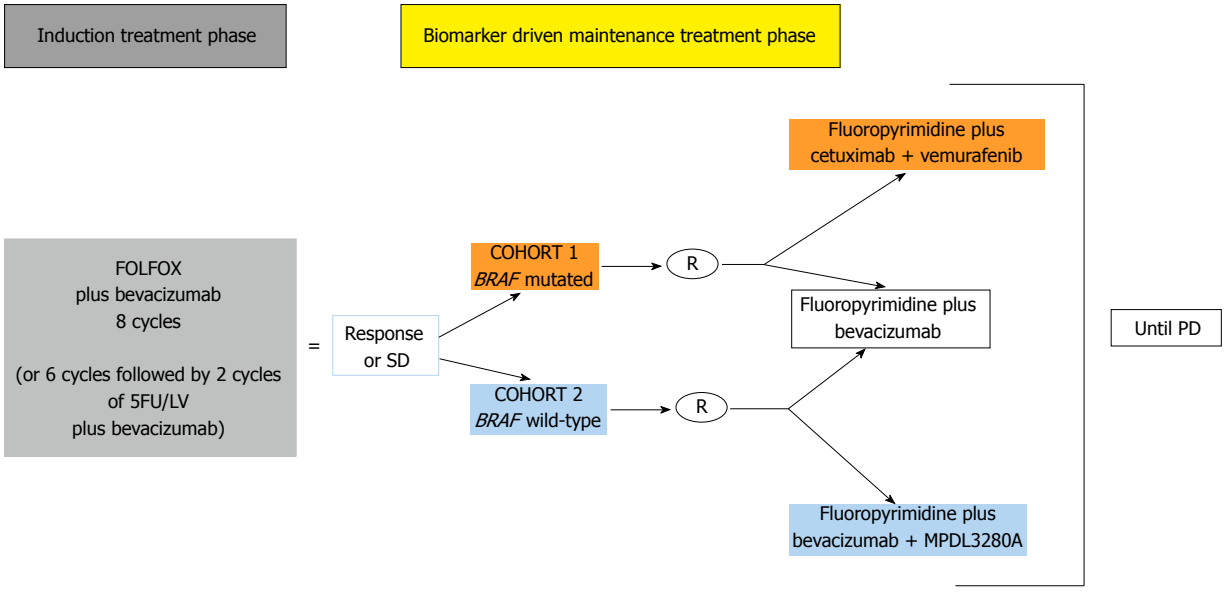

Figure 3 MODUL Phase Ⅲ trial design. 5FU: 5-Fluoro-Uracil; LV: Leucovorin; SD: Stable disease; R: Randomization; PD: Progressive disease.

Table 1 Ongoing anti program death-1 or anti program death-ligand 1 monoclonal antibodies clinical trials in digestive cancers

Monoclonal antibody	Antibody description	Association	Tumors
MPDL3280A	Anti-PD-L1 Engineered Human IgG1[1]	MODUL trial: Phase Ⅲ biomarker driven maintenance therapy	Metastatic colorectal cancer
Medi 4736	Anti-PD-L1 Engineered Human IgG1[1]	None	Immunological subsets of advanced colorectal cancer
Nivolumab	Anti-PD-1 Fully human IgG4[2]	Nab-paclitaxel +/- Gemcitabine	Pancreatic cancer
		GVAX pancreas vaccine + CRS-207	Pancreatic cancer
		None	Squamous cell carcinoma of the anal canal
		Ipilimumab	Recurrent and metastatic colon cancer
		None	Hepatocellular carcinoma
		None	Advanced or recurrent gastric cancer
Pembrolizumab	Anti-PD-1 Humanized IgG4[2]	None	Resectable or borderline resectable pancreas cancer
		None	Advanced gastro-intestinal cancers
		None	Metastatic colorectal cancer with and without microsatellite instability

[1]Engineered Fc domain prevent antibody dependent cell mediated cytotoxicity (ADCC); [2]IgG4 antibody do not induce ADCC. PD-1: Program death-1; PD-L1: Program death-ligand 1; Ig: Immunoglobulin; GVAX: Granulocyte-macrophage colony-stimulating factor–secreting allogeneic pancreatic tumor cells, induces T-cell immunity to cancer antigens, including mesothelin; CRS-207: Live-attenuated L monocytogenes-expressing mesothelin.

multi-arm dose expansion study were presented at the 2014 ASCO meeting and updated at the 2014 ESMO meeting. A disease control rate of approximately 20% was observed across all relevant histology (10 mg/kg every two weeks), especially in hepatocellular carcinoma (19 patients), gastro-esophageal cancer (28 patients) and pancreatic cancer (29 patients)[15]. Tolerance was acceptable with 5.6% grade 3-4 adverse events, and no autoimmunity was reported. A study with MEDI4736 in dMMR CRC and pMMR CRC presenting with high TIL infiltration is scheduled to start.

UPCOMING THERAPEUTIC CHALLENGES

Since ICIs seem as promising in digestive cancer as in other tumors, the same major challenges will be faced. Firstly, since initial progression is not rare, there arises the need for novel criteria to evaluate tumor response to immunotherapeutic agents. As with anti-angiogenic therapies, a tumor burden increase or appearance of new lesions can precede objective response and caution should be used before drawing any conclusion on disease progression[1,6,8,16]. Immune cell

infiltration can explain these features. Recently, immune-related response criteria have been defined and await prospective validation[17]. In any case, progression should be confirmed by a new radiological evaluation four weeks later. Secondly, optimal therapeutic sequences need to be established since most studies have included patients with advanced tumors. As of now no data are available in first-line therapy or in the adjuvant setting, but promising results with ipilimumab in melanoma have been reported[18]. Thirdly, in solid tumors, ICIs will probably need to be combined with chemotherapy, which could cause some problems, given the detrimental effects that chemotherapy can exert on the immune system. Combination with an immunogenic chemotherapy such as oxaliplatin should nonetheless be a good option. Finally, biomarkers are eagerly awaited to enable selection of the patients most likely to benefit from these ICIs. Only 20% to 30% of patients show objective response and in addition to inefficacy, patients are exposed to unnecessary toxicity. PD-L1 expression seems to correlate with clinical outcome but objective responses have been observed in PD-L1 negative tumors. Moreover, definition of a PD-L1 positive tumor needs standardization, given that the threshold of positivity varies between 1% and 5% across different studies and also given that PD-L1 expression can be analyzed either on tumor cells or on tumor-infiltrating cells[16,19]. In melanoma, a predictive model using CD8, PD-1 and PD-L1 positive cells at invasive margins and the tumor center has been correlated with a treatment response but requires prospective validation[20]. In addition, the expression of PD-L1 could be different in primary tumors at the beginning of the disease compared to metachronous metastasis several months later.

CONCLUSION

Many digestive cancers are candidates for the anti-PD-1/PD-L1 axis blockade (Table 1) but we have still got to elucidate for whom, when and how to use them. dMMR CRCs are good candidates due to their high TIL infiltration associated with their high load of frameshift mutations[21]. dMMR CRCs are associated with high-CD8 cytotoxic T cells but also with up-regulation of at least five negative regulatory immune checkpoint molecules (PD-1, PD-L1, CTLA-4, LAG-3, IDO)[22]. One limit to use of ICIs in dMMR CRC could be that it represents only 5% of stage Ⅳ CRCs. Nevertheless, both nivolumab and pembrolizumab are currently being tested in this particular subset.

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