Review Article

Immune checkpoint inhibitors in gastrointestinal malignancies

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Abstract: Gastrointestinal (GIT) tumors are extremely fatal and lethal tumors with limited therapeutic options. Antitumor immunity is new line of research in management of solid tumors. Immune check points are negative regulators of immune system and control the immune response. These checkpoints are exploited by cancer cells. Cancer cells causes early activation of checkpoints and suppress the immune response, and therefore have unchecked growth and metastasis of malignant cells. Immune checkpoint inhibitors (ICIs), downregulates these checkpoints and activate the proliferation of cytotoxic T cells which helps in lysis of tumor cells. ICIs have shown the promising results in management of melanoma, non-small cell lung cancer and renal cell carcinoma. Encouraged by their recent success in solid tumors many clinical trials are ongoing to evaluate their efficacy in GIT tumors. In this article we will try to explain rationale for use of ICIs in GIT tumors. We will summarize the ongoing research, preliminary results and future aspects of ICIs in GIT malignancies.

Keywords: Ipilimumab; nivolumab; pembrolizumab; gastrointestinal (GIT) cancers

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Introduction

Immune checkpoint inhibitors (ICIs) in gastrointestinal (GIT) tumors—ICIs have revolutionized the cancer management and reignited the hope of treating cancers effectively. GIT tumors are one of the major causes of morbidity and mortality. Esophageal cancers, gastric cancers, pancreatic cancers, hepatocellular carcinoma (HCC) and colorectal cancers (CRC) are widely prevalent and lethal cancers. Currently there are not much effective treatment options for them. ICIs have shown some light and recently emerging data suggest that ICIs may be effective in GIT malignancies. ICIs were reported in 2010 (1) and 2012 (2). In clinical trials they have shown remarkable effect in management of various tumors even in advanced stages. Till now goal of immunotherapy is to enhance the immune system and help it fight against cancers. But it was not a big success due to immune check points. These check point act as brakes on immune system. Along with that, immune system is also suppressed by cancer cells and helps cancer cells in their growth and metastasis. ICIs release these breaks and enhance the activity of immune system to fight against cancers. ICIs act by suppressing the immune check point, which enhances the attachment of Antigen Presenting cells and cytotoxic T cells. This lead to proliferation and increased activity of T cells against cancers. Some of the targets of ICIs are programmed cell death 1 (PD-1), programmed death ligand 1 (PD-L1) and cytotoxic T lymphocyte associated protein 4 (CTLA-4). Cancer immunotherapy is new era in management of cancers and researches have shown its effect in treatment of cancers even in advanced stages. In this article we will discuss the effect of ICIs in GIT malignancies, ongoing research and their future aspects.

Esophageal and gastric cancers

Despite the recent advances in the field of oncology, prognosis of gastric and esophageal cancers is extremely poor. Esophageal cancer is 6th most common cause of cancer related death and 8th most common cancer worldwide (3). The prognosis of esophageal cancer is extremely poor as

generally patients present in advanced stages of cancer and therapeutic options are limited. Gastric cancer is 2nd most common cause of cancer related death worldwide in 2012 and 5th most common malignancy (3). Systemic therapy for metastatic disease is basically platinum/5 fluoropyrimidine based. With addition of anthracyclines/taxanes there is survival benefit in some patients (4-6). Anti Her-2 monoclonal antibody (7), trastuzumab and anti-vascular endothelial growth factor receptor 2 (VEGFR2) monoclonal antibody, ramucirumab (8) are important additions in the management of Esophageal and gastric cancers. But overall survival benefit is very low. Recent clinical experience, research and available data are showing that ICIs is the emerging therapy for esophageal and gastric cancers.

Rationale for ICIs in esophageal and gastric cancers

PD-L1/PD-L2 distribution

PD-L1 and PD-L2 are receptors present on tumor cells and on binding with PD-1, they inhibit the T cell activation and inactivates the immune system. ICIs acting on PD-L1 and PD-L2 inhibit this interaction and releases brakes of immune system and leads to activation and proliferation of cytotoxic T lymphocytes and helps in removing cancer cells. PD-L1 and PD-L2 are expressed on many cells like multiple myeloma, renal cell carcinoma, breast, colon bladder and lung cancer (9-11). Currently ICIs therapy is approved in melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma (12-14) and all three of them have shown high level of PD-L1 expression. Study done on esophageal squamous cell carcinoma patients has found that 43.9% patients had PD-L1 or PD-L2 expression (15). Similarly, in gastric carcinoma patients PD-L1 expression was 42.2% (16). Studies have shown convincing results regarding expression of PD-L1 and PD-L2 in esophageal and gastric cancers.

Tumor infiltration lymphocytes (TILs)

It is the microenvironment of the tumor which determines the effect of ICIs, especially TIL's. Multiple studies have shown a correlation between TILs density and favorable outcome in patients with breast ovarian and CRC (17-20). In esophageal and gastric cancers, it has been suggested through various preclinical models, that the density of TILs is higher in early stages of cancer but due to selection of least immunogenic cancer cell clones in advanced stages they are less immunogenic (21,22). Further studies are needed to understand the relationship of TILs density and immunotherapy response to define in which patients ICIs therapy will be helpful.

Clinical experience and ongoing research of ICIs in esophageal and gastric cancers

There are few studies regarding ICIs in esophageal and gastric cancers. In ASCO 2016, updated results of phase 1b KEYNOTE-28 study on advanced esophageal carcinoma cohort were presented (23). This study was for evaluation of pembrolizumab in solid tumors expressing PD-L1. It showed that in patients with PD-L1 positive heavily treated esophageal cancer, overall response rate was 30.4% and Progression free survival was 21.7% at 1 year. These are promising results. In ESMO conference, results of role of pembrolizumab in advanced PD-1 positive gastric cancers were presented (24). In that study total 39 patients were enrolled and analysis showed that overall response rate was 22% in median response duration was 24 weeks. After these results phase 2 trial was started, KEYNOTE-059 of cisplatin/5FU with pembrolizumab. It showed encouraging efficacy and manageable safety after 2 prior lines of therapy in patients with advanced gastric and gastroesophageal junction cancers. Currently phase 2 and phase 3 studies are going on regarding use of nivolumab and pembrolizumab in esophageal and gastric cancers. Their details are mentioned in (*Table 1*).

Future of ICIs in gastroesophageal cancers

Combination of PD-1 and CTLA-4 inhibitors

Both are ICIs and act on different receptors. There may be synergistic effect of their combination and it can enhance the efficacy of ICIs.

ICIs with chemotherapy

In esophageal cancer patients a study (NCT03143153) is going on which compares the effect of combination of ICIs (nivolumab and ipilimumab) with ICI (nivolumab) and chemotherapy (5FU plus cisplatin) with chemotherapy (5FU plus cisplatin) alone. Chemotherapy destroys tumor cells and releases intracellular RNA, peptides, proteins, DNA which act as a tumor antigen and increases the immune response of body against cancers. If ICIs are also given with them, they further enhance the immune system and helps in clearing cancer cells.

Table 1 Clinical trials of immune checkpoint inhibitors in gastroesophageal cancers (https://clinicaltrials.gov)

NCT number	Title	Phase	Conditions	Interventions	Outcome measures
NCT03322267	Adjuvant pembrolizumab for patients with locally advanced esophageal squamous cell carcinoma at high risk of recurrence	2	Esophageal squamous cell carcinoma	Pembrolizumab	RFS, OS, TEAE
NCT03278626	Immune checkpoint therapy with Nivolumab esophageal squamous cell carcinoma	1, 2	Esophageal squamous cell carcinoma	Nivolumab + carboplatin /paclitaxel + radiation	UT
NCT03189719	First line esophageal carcinoma study with chemo *vs.* Chemo plus Pembrolizumab (MK-3475-590/keynote-590)	3	Esophageal neoplasms	Pembrolizumab, cisplatin, drug: 5-FU	PFS, ORR, OS, DOR, AE
NCT03143153	A study to evaluate efficacy in subjects with esophageal cancer treated with nivolumab and ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin	3	Various advanced cancer	Nivolumab, ipilimumab, cisplatin, fluorouracil	OS, PFS, ORR
NCT03122548	Safety and efficacy of CRS-207 with pembrolizumab in gastric, gastroesophageal junction or esophageal cancers	2	Gastric and esophageal adenocarcinoma	CRS-207, pembrolizumab	TRAE, RR, OS
NCT03044613	Nivolumab or nivolumab/ipilimumab prior to chemoradiation plus nivolumab with II/III gastro/esophageal cancer	1	Gastric cancer, esophageal cancer, gastroesophageal cancer	Nivolumab, ipilimumab, carboplatin, paclitaxel, radiation	RR, TRAE,OS, RFS
NCT02998268	Study of pembrolizumab in locally advanced esophageal adenocarcinoma	2	Esophageal adenocarcinoma	Pembrolizumab, taxol, carboplatin	DFS, RR, OS
NCT02971956	Pembrolizumab in refractory advanced esophageal cancer	2	Esophageal cancer	Pembrolizumab	RR, OS, PFS, AE
NCT02954536	Phase II trial of pembrolizumab with trastuzumab and chemotherapy in advanced her2 positive esophagogastric cancer	2	Esophageal cancer, gastric cancer	Pembrolizumab, trastuzumab, capecitabine, cisplatin, oxaliplatin, 5-fluorouracil	PFS
NCT02918162	Perioperative chemo and pembrolizumab in gastric cancer	2	Gastric cancer	Pembrolizumab	DFS, pCR, OS, ORR
NCT02743494	An investigational immuno-therapy study of nivolumab or placebo in patients with resected esophageal or gastroesophageal junction cancer	3	Advanced cancer	Nivolumab	DFS, OS
NCT02689284	Combination margetuximab and pembrolizumab for advanced, metastatic her2(+) gastric or gastroesophageal junction cancer	1,2	Gastric cancer and esophageal cancer	Margetuximab, pembrolizumab	ATA, PFS, OS
NCT02642809	Pembrolizumab with locally delivered radiation therapy for the treatment of metastatic esophageal cancers	1	Esophageal cancer	Pembrolizumab, brachytherapy, endoscopic biopsy	ATA, PFS, OS
NCT02569242	Study of nivolumab in unresectable advanced or recurrent esophageal cancer	3	Esophageal cancer	Nivolumab, docetaxel/ paclitaxel	OS, PFS, RR, DOR AE
NCT01585987	An efficacy study in gastric and gastroesophageal junction cancer comparing Ipilimumab versus standard of care immediately following first line chemotherapy	2	Adenocarcinoma of the gastric and gastroesophageal junction	Ipilimumab	irPFS, PFS, OS, irBOR

UT, unacceptable toxicity; pCR, pathological complete response rate; ATA, antitumor activity; irBOR, immune-related best overall response; RFS, relapse free survival; OS, overall survival; TEAE, treatment-emergent adverse events; AE, adverse events; DOR, duration of response; ORR, overall response rate; RR, response rate; DFS, disease free survival; irPFS, immune related progression free survival; PFS, progression free survival; TRAE, treatment related adverse events.

ICIs with radiotherapy

Some trials regarding pembrolizumab with locally delivered radiation therapy for the treatment of metastatic esophageal cancers (NCT02642809) are also running. It will be a good combination therapy and will work on same principle as combination of chemotherapy with ICIs. Radiation therapy kills cancer cells and release inflammatory markers and if ICIs are also given along with them they will aggravate the immune response and will help in fighting cancer cells.

ICIs with Anti HER-2 monoclonal antibody

Currently phase II trial of pembrolizumab with trastuzumab and chemotherapy in advanced HER2 positive esophagogastric cancer (NCT02954536) is going on. Trastuzumab has immune modulating properties that may be helpful in more infiltration of tumor microenvironment with immune cells and increase efficacy of ICIs.

HCC

HCC is one of the most dreadful tumors, most of the times it is associated with chronic liver disease which make it more lethal and difficult to treat. Resection of the tumor is preferred therapy but most of the time, due to extent of disease and liver dysfunction, it's not an option. Patients who have advanced tumors, we go for radiofrequency ablation and chemoembolization. Liver transplantation is another option for locally extensive tumors, but chances of rejection and immunosuppression are some drawbacks of it. Chemotherapy is not used commonly as most of the HCC present in advanced stage and by that time they are refractory to treatment. Sorafenib (25) is the only FDA proved drug for HCC, but efficacy and overall response rate is very low. So in all we don't have enough tools in our armamentarium for effective management of HCC. ICIs have recently shown promising benefit in HCC patients a tumor which is resistant to traditional form of chemotherapy.

Rationale of ICIs in HCC

For a long time, our understanding regarding immune system was very limited. It was believed that primary role of immune system is to prevent invasion of body from foreign antigens. There is immune surveillance system which detects cancer cells and destroys them with the help of natural killer (NK) cells and cytotoxic T lymphocytes (CTLs). But now it has been well accepted that interactions between immune cells and cancer cells is complex and more dynamic than it was thought in the past. Host Immune system causes inflammation and infiltration of cancer tissue with myeloid derived suppressor cells (MDSCs), tumor-associated macrophages (TAM), regulatory T cells (Tregs) and cancer associated fibroblasts (CAF) (26). This infiltration of inflammatory cells has shown to promote proliferation of tumor cells along with that they also help in invasion and metastasis (27).

The intrinsic hepatic microenvironment has made liver an immune tolerogenic organ. There are multiple immune responses which promote the cancer progression like change in functional ability, change in cytokine level and expression of immune receptors or ligands. Due to Tregs, impairment of T cell function and upregulation of Immune check point pathways, immune system is unable to recognize tumor cells (28-34). These factors together downregulate immune response and promote activity of tumor cells. Therefore, immune system which is defense mechanism of body is modified by tumor cells, they make immune system work in their favor and promote growth of cancer cells. ICIs can reverse this effect, they can activate and proliferate CTLs and help in degradation and lysis of cancer cells.

Clinical experience and ongoing research in ICIs in HCC

In 2015ASCO, interim results of phase 1 and phase 2 trial of nivolumab in patients with advanced HCC were presented (35). In this trial, administered dose of nivolumab was 3 mL/kg in patients with hepatitis C virus, hepatitis B virus and uninfected patients, up to 10 mL/kg dose is safe in uninfected patients. Sample size of this study was 47 out of which 70% patients had extrahepatic metastasis, 13% had vascular invasion and 68% had history of use of Sorafenib treatment. Out of 47 patients therapy was discontinued in 30 patients. 26 developed progression of disease, 2 had adverse reaction and 2 patients had complete response. The therapy was continued in 17 patients. Approximately 19% (8 patients) responded to therapy with nivolumab. Among them, 2 had complete recovery while 6 patients had partial response. Progressive disease occurred in 33% (14 patients) and disease control rate was 67% (28 patients). Overall half of total patients had stable disease with longest lasting 17 months. At 12 months, 62% of people were surviving with HCC. Treatment related adverse events occurred in 68% of patients. Increase in liver enzymes was the most common side effect. Elevated aspartate aminotransferase is seen in 11%, elevated alanine transferase in 9% and elevated lipase in 2% of patients. Considering all together

Nivolumab produced durable response in HCC patients. Overall survival of 62% at 1 year, reduction in tumor size after 48 weeks, complete response in 3 months in 2 patients and maintainence of response at 18 months even after stopping nivolumab are promising results. Further clinical trials are going on regarding role of ICIs in HCC (*Table 2*).

Future of ICIs in HCC

Combination of ICIs

Combination of ICIs, acting on different receptors should have a synergistic effect combined therapy should enhance the activity of immune response to a greater extent and will have better response. Study evaluating Nivolumab alone versus Nivolumab plus Ipilimumab in patients with resectable and potentially resectable HCC is going on (NCT03222076).

ICIs combined therapy with transcatheter arterial trans-embolization

Their combination should have synergistic effects. Currently study is going on regarding combination of TATE Trans-arterial tirapazamine embolization and PD-1 Inhibitor in liver Cancer. (NCT03259867).

ICIs as neoadjuvant and adjuvant after resection and ablation

ICIs trials are also going on as adjuvant and neoadjuvant therapy after resection and ablation. A pilot study of combined immune checkpoint inhibition in combination with ablative therapies in patients with HCC or Biliary tract carcinomas (NCT02821754) is recruiting patients.

ICIs with chemotherapy

Trials on combination of chemotherapy and ICIs in HCC are also going on. One of them is Guadecitabine and Durvalumab in treating patients with advanced liver, pancreatic, bile duct, or gallbladder cancer (NCT03257761)

ICIs with radiotherapy

Actively recruiting study for this combination is Stereotactic body radiotherapy (SBRT) followed by nivolumab or ipilimumab with nivolumab in unresectable HCC (NCT03203304).

Pancreatic carcinoma

Across the world Pancreatic cancer is one of the most lethal malignant neoplasms and leading cause of mortality (3,36,37). Based on GLOBOCAN 2012 estimates, pancreatic cancer is 11th most common cancer and it is 7th most common cause of cancer mortality in both sexes together (3). It accounts for more than 331,000 deaths per year. Estimated 5-year survival rate is less than 5% (38). Pancreatic cancer is characterized by delayed diagnosis, resistance to therapy, highly metastatic and high mortality. Most of the time pancreatic cancer at time of diagnosis is advanced and metastasized to different organs so not amenable to surgery and most of these patients end up in getting palliative therapy. The existing treatment modalities, including chemotherapy and surgical resection, can prolong survival of patients but it cannot be curative. ICIs have revolutionized the cancer management and showed a promising response in advanced solid tumors. Some studies have shown the benefit of ICIs in pancreatic cancer and lot of studies are going on. If ICIs inhibitors improve survival of pancreatic cancer patients it will be a new paradigm.

Rationale of ICIs in pancreatic cancer

Similar to HCC, pancreatic cancer microenvironment consists of many inflammatory cells. This infiltration of inflammatory cells can promote the tumor growth and immunosuppressive in function. Some of them are MDSCs, TAM, Tregs, natural killer cells. Tumor cells also avoid detection by immune system by various mechanisms such as IL-10, Vascular endothelial growth factor, upregulation of immune check points, downregulation of major histocompatibility factor (MHC). Immune system plays a major role in pancreatic cancer and ICIs can enhance activity of immune system against cancer cells and therefore they can be a great treatment modality for pancreatic cancer.

Clinical experience and ongoing research

Currently lot of research is going on use of ICIs in pancreatic cancers. Initially a phase 2 trial was done for Ipilimumab on locally advanced and metastatic pancreatic cancer by Royal *et al.* (39) According to standard response evaluation criteria in solid tumors (RECIST) it did not show any benefit. But one patient showed delayed response in both metastatic and primary tumors. As per preclinical data ipilimumab has synergistic effect with GVAX. GVAX is a granulocyte macrophage colony stimulating factor (GM-CSF) gene transfected tumor cell vaccine which

Table 2 Clinical trials of immune checkpoint inhibitors in hepatocellular carcinoma (https://clinicaltrials.gov)

NCT number	Title	Phase	Conditions	Interventions	Outcome measures
NCT03299946	Feasibility and efficacy of neoadjuvant cabozantinib plus nivolumab (Cabonivo) followed by definitive resection for patients with locally advanced hepatocellular carcinoma	1	Locally advanced hepatocellular carcinoma	Cabozantinib, nivolumab	AE, CR, ORR, DFS
NCT03298451	Study of durvalumab and tremelimumab as first-line treatment in patients with unresectable hepatocellular carcinoma	3	Hepatocellular carcinoma	Durvalumab, tremelimumab	OS, TTP, ORR. DCR, DOR, PK
NCT03259867	Combination of TATE and PD-1 inhibitor in liver cancer	2	Hepatocellular, colorectal neoplasms	Nivolumab, pembrolizumab, trans-arterial tirapazamine embolization	RR, ORR, DOR, PFS, OS
NCT03257761	Guadecitabine and durvalumab in treating patients with advanced liver, pancreatic, bile duct, or gallbladder cancer	1	Liver, pancreatic, bile duct, gallbladder cancer	Durvalumab, guadecitabine	AE, OS, PFS
NCT03222076	Study evaluating nivolumab (anti-PD-1 antibody) alone versus nivolumab plus Ipilimumab (anti-CTLA-4 antibody) in patients with resectable and potentially resectable hepatocellular carcinoma	2	Hepatocellular carcinoma	Nivolumab, ipilimumab	ORR, PFS
NCT03203304	Study of stereotactic body radiotherapy (SBRT) followed by Nivolumab or Ipilimumab with nivolumab in unresectable hepatocellular carcinoma	1	Hepatocellular carcinoma	Nivolumab, ipilimumab	AE, ORR, PFS, OS
NCT03071094	A trial to evaluate the safety and efficacy of the combination of the oncolytic immunotherapy Pexa-Vec with the PD-1 receptor blocking antibody Nivolumab in the first-line treatment of advanced hepatocellular carcinoma	1,2	Hepatocellular carcinoma	Pexastimogene devacirepvec (Pexa Vec), nivolumab	Phase I part: DLT; Phase IIa part: ORR, DCR, OS
NCT03033446	Study of Y90-radioembolization with nivolumab in Asians with hepatocellular carcinoma	2	Hepatocellular carcinoma	Y-90, radioembolization, nivolumab	RR, DOR, PFS, OS,
NCT02837029	Nivolumab and Yttrium Y 90 glass microspheres in treating patients with advanced liver cancer	1	Hepatocellular carcinoma	Nivolumab	MTD, ORR, AE, PFS, DCR
NCT02821754	A pilot study of combined immune checkpoint inhibition in combination with ablative therapies in subjects with hepatocellular carcinoma or biliary tract carcinomas	1,2	Liver cancer, hepatocellular carcinoma	Durvalumab, tremelimumab	AE, PFS
NCT02576509	An investigational immuno-therapy study of Nivolumab compared to sorafenib as a first treatment in patients with advanced hepatocellular carcinoma	3	Hepatocellular carcinoma	Nivolumab, sorafenib	OS, ORR, PFS, PD
NCT02519348	A study of MEDI4736 with tremelimumab, MEDI4736 or tremelimumab monotherapy in unresectable hepatocellular carcinoma	2	Hepatocellular carcinoma	MEDI4736, tremelimumab	AE, DLT, DOR, OS, PFS, DCR
NCT01853618	Tremelimumab with chemoembolization or ablation for liver cancer	1	Liver cell carcinoma	Tremelimumab, radiofrequency ablation (RFA), SBRT, cryoablation	AE
NCT01658878	An immuno-therapy study to evaluate the effectiveness, safety and tolerability of nivolumab or nivolumab in combination with other agents in patients with advanced liver cancer	1, 2	Hepatocellular carcinoma	Nivolumab, sorafenib, ipilimumab, cabozantinib	AE, SAE, ORR,

DCR, disease control rate; AE, adverse events; SAE, serious adverse events; PFS, progression free survival; OS, overall survival; ORR, overall response rate; RR, response rate; DOR, duration of response; DLT, incidence of dose, limiting toxicities; CR, complete response; DFS, disease free survival; PD, pharmacodynamics; TTP, time to progression; PK, pharmacokinetics; DLT, dose limited toxicities; MTD, maximum tolerated dose.

stimulates immune response against cancer cells. So a study is conducted comparing combination of Ipilimumab and GVAX with Ipilimumab alone (40). It has two arms only Ipilimumab was given and in arm B Ipilimumab and GVAX was given to pancreatic cancer patients. In arm A, 2 patients had stable disease for 7 and 22 weeks and in arm B three patients had stable disease. Two of them had stabilization for 59 and 71 weeks, one has 17 weeks of regression. In arm A median overall survival was 3.6 months and 1-year survival was 7%. In arm B median overall survival was 5.7 months and 1-year survival was 27%. The study was inconclusive whether Ipilimumab alone or in combination has better outcome. But in patients with longer life expectancy ICIs can have some beneficial effects. List of clinical trials for ICI in pancreatic cancer is shown in *Table 3*.

Future of ICIs in pancreatic cancer

Combination therapy of ICIs

Active studies for this combination are nivolumab and ipilimumab and radiation therapy in high colorectal and pancreatic cancer (NCT03104439), durvalumab and tremelimumab in combination with first-line chemotherapy in advanced solid tumors (NCT02658214).

ICIs with chemotherapy

Active studies for this combination are azacitidine and pembrolizumab in pancreatic cancer (NCT03264404), defactinib combined with pembrolizumab and gemcitabine in patients with advanced cancer (NCT02546531),

ICIs with radiotherapy

Active study for this combination is immune checkpoint inhibition in combination with radiation therapy in pancreatic cancer patients (NCT02866383).

ICIs with vaccine

Active studies for combination of ICIs and vaccine are neoadjuvant/adjuvant GVAX pancreas vaccine with or without nivolumab trial for surgically resectable pancreatic cancer (NCT02451982), study of CRS-207, nivolumab, and ipilimumab with or without GVAX pancreas vaccine in patients with pancreatic cancer (NCT03190265).

CRC

It is one of the most prevalent and lethal cancer in the world. It is third most common diagnosed cancer in males and second in females (41). In USA approximately 135,430 new cases of large bowel cancer are diagnosed every year and out of that 95,520 are colon and rest are rectal cancers (42). CRC accounts for 8% of all cancer deaths. In addition to chemotherapy and surgical resection, recent therapeutic approaches are vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) targeted agents (43). These targeted therapies have improved survival to 30 months in patients with metastatic disease. However, lot of research is going on to further improve the outcome of advanced colorectal carcinoma. Early trial results of ICIs in CRC with micro satellite instability (MSI) are promising. Clinical trials are going on to confirm these preliminary results.

Rationale of ICIs in CRC

CRC is divided into three types sporadic, familial and hereditary. Sporadic is associated with lifestyle like alcohol, smoking, diet and obesity and it constitute 70–75%. Familial and hereditary is associated with germ line mutation and constitutes 20% and 5%, respectively (44-46). Mismatch repair (MMR) proteins function as security guard during cell replication, if there is any kind of mismatch due to insertion and deletion by DNA polymerase, these proteins correct it and decreases the chances of mutation in cell replication. These replication errors are more common in repetitive DNA sequences known as Microsatellites. Therefore, if there are mutation is MMR proteins, DNA replication will be inaccurate and it leads to MSI (47). Lynch syndrome is an autosomal dominant disorder, caused by germline mutation in MMR genes like MSH6, MLH1, MSH2 (48). These mutations play an important role in causation in CRC in Lynch syndrome patients by MSI (49). The molecular mechanism behind MSI is inactivation of MLH1 by hypermethylation of promoter area (50). Number of mutation required for CRC in MSI is much higher than microsatellite stability (MSS) (51). High no. of mutations increases the no. of neoantigen and enhances the immune response. This enhanced immune response increases the no of $CD4^+$ T cells, $CD8^+$ T cells, lytic enzymes and upregulates costimulatory molecules for Antigen presenting cells in the tumor microenvironment (52-57). Due to high immunogenic nature of CRC and high density of TILs, chances for success of ICIs in CRC is very high.

Table 3 Clinical trials of immune checkpoint inhibitors in pancreatic cancer (https://clinicaltrials.gov)

NCT number	Title	Phase	Conditions	Interventions	Outcome measures
NCT03336216	A study of cabiralizumab given with nivolumab with and without chemotherapy in patients with advanced pancreatic cancer.	2	Advanced pancreatic cancer	Cabiralizumab, nab-paclitaxel, onivyde, nivolumab, fluorouracil, gemcitabine, oxaliplatin, leucovorin	PFS, ORR, DOR, OS, AE, MDOR
NCT03264404	Azacitidine and pembrolizumab in pancreatic cancer	2	Pancreatic cancer	Pembrolizumab, azacitidine	PFS, ORR, DOR, DCR
NCT03245541	Study of durvalumab and stereotactic ablative body radiotherapy in advanced pancreatic adenocarcinoma	1, 2	Pancreatic cancer	Durvalumab, stereotactic ablative body radiotherapy	PFS
NCT03190265	Study of CRS-207, nivolumab, and ipilimumab with or without GVAX pancreas vaccine (with CY) in patients with pancreatic cancer	2	Pancreatic cancer	Cyclophosphamide, nivolumab, ipilimumab, GVAX pancreas vaccine, CRS-207	ORR, OS, PFS, DOR, TTP
NCT03168139	Olaptesed (NOX-A12) alone and in combination with Pembrolizumab in colorectal and pancreatic cancer	1, 2	Metastatic colorectal cancer, metastatic pancreatic cancer	Olaptesed pegol – monotherapy, olaptesed pegol + pembrolizumab – combination therapy	AE, DCR, PD
NCT03104439	Nivolumab and ipilimumab and radiation therapy in MSS and MSI high colorectal and pancreatic cancer	2	Colorectal Cancer, Pancreatic Cancer	Nivolumab, Ipilimumab, Radiation Therapy	DCR, MPFS, MOS
NCT03098160	Immunotherapy study of evofosfamide in combination with Ipilimumab	1	Pancreatic cancer	Evofosfamide, ipilimumab	RP2D, AE, MTD
NCT03038477	A study of durvalumab in patients with BR PDA following neoadjuvant therapy and successful surgical resection	2	Pancreatic cancer	Durvalumab	DFS, OS, AE
NCT02907099	Pembrolizumab and BL-8040 in metastatic pancreatic cancer	2	Metastatic pancreatic cancer	BL-8040, pembrolizumab	ORR, DOR
NCT02866383	Immune checkpoint inhibition in combination with radiation therapy in pancreatic cancer patients	2	Metastatic pancreatic cancer	Nivolumab, ipilimumab, radiotherapy	CBR, AE, ORR, PFS, OS
NCT02826486	Study assessing safety and efficacy of combination of BL-8040 and pembrolizumab in metastatic pancreatic cancer patients (combat/keynote-202)	2	Metastatic pancreatic adenocarcinoma	BL-8040, pembrolizumab	ORR, OS, PFS, DOR
NCT02777710	Evaluation of safety and activity of an anti-PD-L1 antibody (durvalumab) combined with CSF-1R TKI (Pexidartinib) in patients with metastatic/advanced pancreatic or colorectal cancers	1, 2	Colorectal cancer, pancreatic cancer	Pexidartinib, durvalumab	Part 1: DLT; part 2: ORR, DOR, PFS, AE
NCT02734160	A study of galunisertib (ly2157299) and durvalumab (MEDI4736) in participants with metastatic pancreatic cancer	1	Metastatic pancreatic cancer	Galunisertib, durvalumab	DLT, PK, PFS, ORR, CR,PR, DOR, DCR
NCT02658214	Durvalumab and tremelimumab in combination with first-line chemotherapy in advanced solid tumors	1	Carcinoma, pancreatic ductal, esophageal squamous cell carcinoma	Durvalumab, tremelimumab	AE

Table 3 (*continued*)

Table 3 (*continued*)

NCT number	Title	Phase	Conditions	Interventions	Outcome measures
NCT02648282	Study with CY, pembrolizumab, GVAX, and SBRT in patients with locally advanced pancreatic cancer	2	Pancreatic cancer	Cyclophosphamide, GVAX, pembrolizumab, SBRT	DMFS, OS, LPFS, irAE
NCT02558894	Phase II study of MEDI4736 monotherapy or in combinations with Tremelimumab in metastatic pancreatic ductal carcinoma	2	Metastatic pancreatic ductal adenocarcinoma	MEDI4736 monotherapy, tremelimumab	RR, DOR, DCR, PFS, PK
NCT02546531	Defactinib combined with pembrolizumab and gemcitabine in patients with advanced cancer	1	Advanced solid tumors, pancreatic cancer	Defactinib, pembrolizumab, gemcitabine	ORR, PFS, OS, irPFS
NCT02451982	Neoadjuvant/adjuvant GVAX pancreas vaccine (with CY) with or without nivolumab trial for surgically resectable pancreatic cancer	1, 2	Pancreatic cancer	Cyclophosphamide, GVAX, nivolumab	irAE, OS, DFS
NCT02311361	Immune checkpoint inhibition (tremelimumab and/or MEDI4736) in combination with radiation therapy in patients with unresectable pancreatic cancer	1	Pancreatic cancer	Durvalumab tremelimumab, stereotactic body radiation therapy (SBRT)	AE
NCT02305186	Safety and immunological effect of pembrolizumab in resectable or borderline resectable pancreatic cancer	1, 2	Pancreatic cancer	Pembrolizumab, neoadjuvant chemoradiation	DLTs, DFS, OS, RR
NCT00836407	Ipilimumab +/– vaccine therapy in treating patients with locally advanced, unresectable or metastatic pancreatic cancer	1	Pancreatic cancer	Ipilimumab	OS, ORR, irBOR, PFS, AE and ORR
NCT00112580	MDX-010 in treating patients with stage IV pancreatic cancer that cannot be removed by surgery	2	Pancreatic cancer	Ipilimumab	CR, PR

DCR, disease control rate; AE, adverse events; RP2D, recommended phase II dose; PFS, progression free survival; OS, overall survival; ORR, overall response rate; RR, response rate; DOR, duration of response; DLT, incidence of dose, limiting toxicities; CR, complete response; DFS, disease free survival; PD, pharmacodynamics; MPFS, median progression free survival; MOS, median overall survival; irORR, immune related overall response rate; PK, pharmacokinetics; MDOR, median duration of response; DCR, disease control rate TTP, time to progression; MTD, maximum tolerated dose; CBR, clinical benefit rate; DLT, dose limited toxicities; PR, partial response; DMFS, distant metastasis free survival; LPFS, local progression free survival; irAEs, number of participants experiencing immune-related toxicities.

Clinical experience and ongoing research

In patients with advanced CRC in which all chemotherapy has been failed, a clinical trial of tremelimumab was conducted. It is multicentric phase 2 trial (58). Results of study did not show any improvement in survival of patients as a single agent. This showed CTLA-4 inhibitors are not much useful in CRC. Recently updated results of 74 patients treated with monotherapy of nivolumab were presented at GIT cancer symposium. 28% patients had PD-L1 positive tumor, 16% had BRAF mutation, 35% had KRAS mutation, 31% had Lynch syndrome. The Disease control rate was 68.9% and overall response rate was 31.1% and median progression free survival was 9.6 months. Pembrolizumab- Deficient MMR status increases the efficacy of ICIs due to aggravated immune response (59-62). This hypothesis was checked by a phase 2 trial of pembrolizumab in deficient MMR CRC. In patients with deficient MMR the objective response rate was 40% and immune related Progression free survival was 20 weeks. These two indicators in proficient MMR were 0% and 11%. This showed that deficient MMR status is predictor of efficacy of pembrolizumab. Recently multiple trials have shown the beneficial effect of pembrolizumab in CRC (61-63), this result in FDA approval of pembrolizumab

for advanced CRC (adult and pediatric patients with unresectable or metastatic, MSI-high or deficient MMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or deficient MMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan). List of clinical trials of ICIs in CRC is shown in *Table 4*.

Table 4 Clinical trials of immune checkpoint inhibitors in colorectal cancers (https://clinicaltrials.gov)

NCT Number	Title	Phase	Conditions	Interventions	Outcome measures
NCT03332498	Pembrolizumab in combination with ibrutinib for advanced, refractory colorectal cancers	1, 2	Colorectal cancer	Pembrolizumab, ibrutinib	Phase I: RP2D; phase II: DCR
NCT03307603	Yttrium90 radioembolization + nivolumab for liver + extra hepatic metastases from colorectal cancer	1, 2	Metastatic colorectal cancer	yttrium-90 radioembolization, nivolumab	Phase I: SAE, PFS, OS, Phase II: RS, PFS, OS
NCT03271047	Study of Binimetinib + Nivolumab plus or minus Ipilimumab in patients with previously treated microsatellite-stable (MSS) metastatic colorectal cancer with RAS mutation	1, 2	MSS, RAS-mutant colorectal cancer	Binimetinib, nivolumab, ipilimumab	Phase Ib and phase II: DLTs, ORR, DOR, CR, AE
NCT03259867	Combination of TATE and PD-1 inhibitor in liver cancer and colorectal neoplasms	2	Hepatocellular, colorectal Neoplasms	Nivolumab, pembrolizumab trans-arterial tirapazamine embolization	RR, ORR, DOR, PFS, OS
NCT03233711	Nivolumab after combined modality therapy in treating patients with high risk stage II-IIIb anal cancer	2	Anal cancer	Biological: nivolumab	DFS, CFS, IOT, ORR, OS, STE
NCT03206073	A phase I/II study of Pexa-Vec oncolytic virus in combination with immune checkpoint inhibition in refractory colorectal cancer	1, 2	Colorectal cancer	Durvalumab, tremelimumab, Pexa-Vec	LAEF
NCT03202758	Evaluation of the safety and the tolerability of Durvalumab plus Tremelimumab combined with folfox in metastatic colorectal cancer	1, 2	Colorectal cancer metastatic	Durvalumab, tremelimumab and FOLFOX	EOS
NCT03182894	Epacadostat in combination with Pembrolizumab and Azacitidine in subjects with metastatic colorectal cancer	1, 2	Metastatic colorectal cancer	Epacadostat (INCB024360) in combination with pembrolizumab (MK-3475) and azacitidine (VIDAZA)	Phase Ib: RP2D; phase II: ORR, PFS, DOR, OS
NCT03168139	Olaptesed (nox-a12) alone and in combination with Pembrolizumab in colorectal and pancreatic cancer	1, 2	Metastatic colorectal cancer, metastatic pancreatic cancer	Olaptesed pegol – monotherapy and olaptesed pegol + pembrolizumab – combination therapy	Monotherapy: PD, AE; combination therapy: AE, DCR,
NCT03122509	A clinical trial of durvalumab and tremelimumab, administered with radiation therapy or ablation in patients with colorectal cancer	2	Metastatic colorectal cancer	Durvalumab tremelimumab radiotherapy (RT), procedure: ablation	ORR
NCT03104439	Nivolumab and ipilimumab and radiation therapy in MSS and MSI high colorectal and pancreatic cancer	2	Colorectal cancer, pancreatic cancer	Nivolumab, ipilimumab, radiation Therapy	DCR, MOS, MPFS
NCT03095781	Pembrolizumab and XL888 in patients with advan ced gastrointestinal cancer	1	Colorectal adenocarcinoma, and 38 more	XL888, pembrolizumab	ORR, OS, PFS, DOR
NCT03026140	Nivolumab, ipilimumab and COX2-inhibition in early stage colon cancer: an unbiased approach for signals of sensitivity	2	Colon carcinoma	Nivolumab, ipilimumab, celecoxib 200 mg	IAC, AE, RFS

Table 4 (*continued*)

Table 4 (*continued*)

NCT Number	Title	Phase	Conditions	Interventions	Outcome measures
NCT03007407	Study of durvalumab and tremelimumab after radiation for microsatellite stable metastatic colorectal cancer progressing on chemotherapy	2	Colorectal cancer metastatic	Durvalumab, tremelimumab	ORR, AE
NCT02981524	Phase 2 study of GVAX (with CY) and pembrolizumab in MMR-P advanced colorectal cancer	2	Metastatic colorectal cancer	CY, GVAX, pembrolizumab	ORR, OS, PFS
NCT02888743	Durvalumab and tremelimumab with or without high or low- dose radiation therapy in treating patients with metastatic colorectal or non-small cell lung cancer	2	Colorectal cancer non-small cell lung cancer	Durvalumab, radiation therapy, tremelimumab	ORR, AE, OS, PFS
NCT02860546	A study evaluating TAS-102 plus nivolumab in patients with MSS CRC	2	Refractory metastatic colorectal cancer	TAS-102 nivolumab	irORR, ORR, PFS, DCR, OS
NCT02851004	Special combination of BBI608 and pembrolizumab	1, 2	Metastatic colorectal cancer	BBI608 (napabucasin), pembrolizumab	irPFS, irORR, PFS, OS, DCR, TEAE, PK
NCT02837263	Pi Pembro in combination with stereotactic body radiotherapy for liver metastatic colorectal cancer	1	Colorectal cancer	Stereotactic body radiotherapy (SBRT), pembrolizumab	RR, DFS, OS
NCT02754856	Tremelimumab (anti-CTLA-4) plus durvalumab (MEDI4736) (anti-PD-L1) in the treatment of resectable colorectal cancer liver metastases	1	Colorectal cancer, liver metastases	Tremelimumab, MEDI4736, liver resection	RFS
NCT02713373	Cetuximab and pembrolizumab in treating patients with colorectal cancer that is metastatic or cannot be removed by surgery	1, 2	Colorectal carcinoma	Cetuximab, pembrolizumab	AE, PFS, OS, RR
NCT02600949	Peptide vaccine in advanced pancreatic ductal adenocarcinoma or colorectal adenocarcinoma	1	Pancreatic cancer, colorectal cancer	Pembrolizumab	PFS, AE
NCT02563002	Study of pembrolizumab (MK-3475) *vs.* standard therapy in participants with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) stage IV colorectal carcinoma (MK-3475-177/keynote-177)	3	Colorectal carcinoma	mFOLFOX6, FOLFIRI, pembrolizumab, bevacizumab, cetuximab	PFS, ORR, OS
NCT02437071	Assess the efficacy of Pembrolizumab plus radiotherapy or ablation in metastatic colorectal cancer patients	2	Metastatic colorectal cancer	Pembrolizumab radiotherapy, radiofrequency ablation	RR, AE
NCT02375672	Study of pembrolizumab in combination with chemotherapy for patients with advanced colorectal cancer	2	Colorectal cancer	Pembrolizumab, mFOLFOX6	MPFS, ORR, OS, AE, DCR
NCT02314169	Nivolumab in treating patients with refractory metastatic anal canal cancer	2	Anal canal	Nivolumab	ORR, AE, OS, PFS
NCT02060188	An investigational immuno-therapy study of nivolumab, and nivolumab in combination with other anti-cancer drugs, in colon cancer that has come back or has spread	2	Colorectal cancer	Ipilimumab, nivolumab, cobimetinib, daratumumab, anti-LAG-3 antibody	ORR

DCR, disease control rate; AE, adverse events; SAE, serious adverse events; RP2D, recommended phase II dose; PFS, progression free survival; OS, overall survival; ORR, overall Response rate; RR, response rate; DOR, duration of Response; DLT, incidence of dose, limiting toxicities; CR, complete response; DFS, Disease free survival; CFS, colostomy-free survival; IOT, incidence of toxicities; STE, severe toxicity interval; LAEF, list of adverse event frequency; EOS, evaluation of the safety; PD, pharmacodynamics; MPFS, median progression free survival; MOS, median overall survival; IAC, immune activating capacity; RFS, relapse free survival; irORR, immune-related overall response rate; TEAE, treatment-emergent adverse events; PK, pharmacokinetics; irPFS, immune related progression free survival.

Future of CRC

Combination therapy of ICIs- Active studies for combination therapies of ICIs are study of binimetinib + nivolumab with or without ipilimumab in patients with metastatic CRC with RAS mutation (NCT03271047), evaluation of the safety and the tolerability of durvalumab plus tremelimumab combined with FOLFOX in metastatic CRC (NCT03202758).

ICIs with chemotherapy

Active studies for combination of chemotherapy with ICIs are Epacadostat in combination with pembrolizumab and azacitidine in subjects with metastatic CRC (NCT03182894), olaptesed (NOX-A12) alone and in combination with pembrolizumab in CRC (NCT03168139).

ICIs with radiotherapy

Active studies for combination of ICIs with radiotherapy are nivolumab and ipilimumab and radiation therapy in MSS and MSI high colorectal and pancreatic cancer (NCT03104439), pembrolizumab in combination with stereotactic body radiotherapy for liver metastatic CRC (NCT02837263).

ICIs with vaccine

Active study for combination of ICIs with vaccine is phase 2 study of GVAX and pembrolizumab in MMR-p CRC (NCT02981524).

Conclusions

With ICIs, it's a beginning of new era for cancer treatment. By enhancing the immune system, it helps in degradation of cancer cells. After showing significant response in treatment of advanced melanoma, NSCLC, renal cancer now they are being tried in other catastrophic malignancies. GIT malignancies are extremely lethal, generally diagnosed in advanced stages and there are not much therapeutic options. ICIs in initial phases have shown promising effect in management of GIT tumors. Further research is going on ICIs individual and combination therapy with vaccines, chemotherapy, radiation therapy and surgical resection. Till now results are promising, if clinically proven beneficial, they will be a valuable tool in our armamentarium.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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