Chapter 2
Immunotherapy in Gastrointestinal Malignancies

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Abstract Gastrointestinal (GI) tumors present a high rate of morbidity and mortality worldwide. Currently used treatment modalities include surgical resection, chemotherapy, and radiation therapy, and offer modest or poor overall outcomes. The success of immunotherapy in the treatment of solid tumors such as melanoma and lung cancer in the last decade has galvanized the investigative immunotherapeutic approaches in patients with gastrointestinal malignancies. The GI tumors with high microsatellite instability (MSI) have particularly been responsive to the immunotherapeutic approaches prompting the use of precision medicine in reducing the tumor burden globally. Various combination strategies in clinical trials currently are aiming to study the effect of various targeted monoclonal antibody-based or immune checkpoint inhibitor-based approaches to improve the overall outcome in GI malignancies.

Keywords Gastrointestinal tumors · Immunotherapy · Monoclonal antibody · Checkpoint inhibitor

Abbreviations

CAR-T cells	Chimeric antigen receptor carrying-T cells
CR	Complete response
CRC	Colorectal cancer
DCR	Disease control rate

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EAC	Esophageal adenocarcinoma
EC	Esophageal cancer
ESCC	Esophageal squamous cell carcinoma
GC	Gastric cancer
hEGFR2	Human epidermal growth factor receptor 2
HNPCC	Hereditary non-polyposis colorectal cancer
mAb	Monoclonal antibody
MSI	Microsatellite instability
MSS	Microsatellite stable disease
NKs	Natural killer cells
ORR	Objective response rate
OS	Overall survival
PC	Pancreatic cancer
PFS	Progression-free survival
TILs	Tumor infiltrating lymphocytes
VEGF	Vascular endothelial growth factor
VV	Vaccinia virus

2.1 Introduction

Gastrointestinal malignancies include the cancers of organs that aid in digestion and absorption of nutrition. These include esophagus, gastric, intestine (colon), rectum, anus, pancreas, and liver. Gastric, colorectal, and liver malignancies are among the five most common cancers worldwide. Among these, colorectal cancer presents the highest incidence in developed countries, and stomach and liver cancers are predominant in developing nations [1, 2]. According to a recent report published by *American Cancer Society*, 2020, gastrointestinal malignancies are the third most leading cause of death in males and females in the United States [3]. The risk factors for these malignancies include, but are not limited to, poor diet, chronic inflammation, genetics, and infection with *Helicobacter pylori*. Current GI malignancies' treatment modalities include surgery, radiation, chemotherapy, molecular targeted therapy, and combination approach [4]. Despite several treatment approaches, the overall survival of GI cancer patients has improved modestly [5]. The imminent and ever-increasing global tumor burden due to GI malignancies has pressured the scientific and clinical community to look for alternative strategies to reduce the burden and improve overall treatment outcome.

The seeds of immunotherapy were laid by the pivotal work of William Bradley Coley in 1891 when he demonstrated the ability of the immune system to treat bone cancer [6]. More recently, significant work by James Allison and Tasuku Honjo in identifying immune checkpoint molecules as potential cancer treatment modality won them the 2018 Nobel Prize. Current cancer immunotherapeutic approaches aim toward overcoming the inhibitory blockade on the immune system in malignant condition either by resetting the immune response to tumor antigens or by mitigating

the immunosuppressive effects of the tumor microenvironment. The success of immunotherapy in improving the prognosis of patients in a broad range of solid and hematologic tumors in the last decade has brought immunotherapy to the forefront in treating GI malignancies. The results have been promising, with many studies researching the role of immunotherapy alone or as a combination therapy.

Cancer immunotherapy involves molecular targeted antibodies, cancer vaccines, adoptive cell transfer (ACT), tumor cytolytic viruses, immune checkpoint inhibitors (ICN), cytokines, and adjuvants [7]. These are currently being used as either monotherapies or as a combination treatment.

2.2 Current Immunotherapeutic Strategies

2.2.1 Immune Modulators

(a) *Immune check point inhibitors*: CTLA-4, PD-1, and its ligand PD-L1 are immune checkpoint molecules that play a role in preventing autoimmunity and promoting self-tolerance. Tumor cells evade the immune cells by overexpression of these immune checkpoint molecules. CTLA-4 functions by inhibiting naïve T cell activation and promoting suppression through T reg cells whereas PD-1 and PD-L1 function by inhibiting the activation of effector T cells [8, 9].
Anti-immune checkpoint immune modulators are targeted against these checkpoint proteins and act by lifting the brakes on the immune T cells. Anti-CTLA-4 (Ipilimumab) has been shown to provide clinical benefits in most and durable response in a portion of patients with metastatic melanoma; however, it has not had much success in gastric malignancies [10, 11]. Anti-PD1 inhibitors (Pembrolizumab and Nivolumab), on the other hand, work by inhibiting the immune checkpoint targeting the PD-1/PD-L1 pathway that promotes self-tolerance, and hence lifting the brakes on the effector T cells. Anti-PD1/PD-L1 inhibitors have had greater overall success in the treatment of malignancies and have proven to be effective in treating gastric malignancies, resulting in longer progression-free survival [10, 12]. Anti-CTLA-4 and anti-PD-1/PD-L1 combination therapies have also proven to be more effective than monotherapies [10].

(b) *Immune costimulators*: OX-40 is a costimulatory molecule on T-cells that binds to OX-40L on antigen-presenting cells to provide activating signals to the T cells. OX-40/OX-40L-based costimulation exerts its activating effects in a bidirectional approach specifically enhancing the Th_1 and Th_{17} cell-mediated responses and antagonizing T-reg-mediated suppression. Agonistic anti-OX-40 monoclonal antibody ligation to OX-40 molecule on T cells provides activating signals to T cells, enabling their potential anti-tumorigenic activity in the tumors. PF-04518600 (PF-8600) is an investigational, fully human, monoclonal antibody (mAb) immunotherapeutic OX-40 (CD134) agonist developed by Pfizer and is presently under many clinical studies for its efficacy against solid tumors.

2.2.2 Targeted Antibodies

(a) *Antiangiogenic monoclonal antibody*: Vascular endothelial growth factor (VEGF) is critical to tumor angiogenesis. Monoclonal antibodies that target the VEGF/VEGF-R pathway have demonstrated success with inhibiting tumor growth. Monoclonals under this category include bevacizumab, a recombinant humanized anti-VEGF-A antibody, and ramcirumab, which targets the VEGF/VEGF-R2 pathway. A meta-analysis of bevacizumab from four clinical studies that enrolled 2101 unresectable lung cancer patients predicted its efficacy in improving progression-free survival when administered at low doses, whereas administration at high doses was predicted to increase two-year overall survival rate thus stimulating efforts to study its safety and value in the treatment of various other malignancies including gastric malignancies [13].

(b) *Anti-Her2 mAb*: Human epidermal growth factor receptor 2 (hEGFR2) uses the tyrosine kinase-based signaling pathway. hEGFR2 is overexpressed on many cancer cell types and the dimerization of the receptor causes autophosphorylation of tyrosine residues within the cytoplasmic area of the receptor prompting cellular proliferation and enhanced tumorigenesis [14]. Anti-Her2 (Herceptin or Trastuzumab) is used for inhibiting the growth of Her2+/neu+ tumors. Other monoclonal antibodies in this category include cetuximab, a human/mouse panitumumab, and chimeric, a fully human mAb that blocks EGFR. Both the monoclonal antibodies have demonstrated modest improvements in survival.

(c) *TROP2 Abs*: TROP2 is encoded by the TACSTD2 gene. It is a transmembrane protein that is also a transducer of intracellular calcium-signaling pathway, and it is overexpressed on a variety of tumors and is understood to play a role in tumor progression, renewal, and survival. IMMU-132 (Sacituzumab govitecan) that targets TROP2 is an investigational anti-Trop-2-SN-38 Ab-drug conjugate currently under many clinical trials to study its efficacy in improving overall response and survival outcomes [15].

(d) *Bispecific Abs (BiTE/bsAb)*: Two monoclonal antibodies targeted against two unique tumor antigens are fused together to make BiTE or bispecific antibodies [16].

2.2.3 Cancer Vaccines

Tumor cells express unique tumor-connected antigens and that differentiate them from normal cells. This has potential for prophylactic as well as therapeutic vaccination. The aim of malignance vaccination is to boost the preexisting immunity or induce a strong anti-tumor response against the neo-antigens or targeted differentiation antigens [17]. Current vaccination strategies include injecting peptides resultant from the patient's tumor connected antigens or tumor connected antigen encoding gene with in vitro generated DCs. Currently, OncoVax and dendritic cell

vaccines such as autologous TriMix DCs in combination therapy are being explored in clinical trials [18].

OncoVax requires patients' own tumor cells with BCG as an adjuvant. Sipuleucel-T was the first dendritic cell-based vaccine filled with a protein combination of prostatic acid phosphatase and a macrophage-colony stimulating factor. Sipuleucel-T was approved by FDA for use in asymptomatic or minimally symptomatic castration-resistant prostate malignance. A lack of clinical benefits, especially during late-stage cancer with Sipuleucel-T led to the discontinuation of its use in clinical setting [19] and led to more recent approaches directed toward creating optimally neo or tumor-antigen-loaded more mature DCs.

2.2.4 Oncolytic Viruses

Oncolytic viruses are used to supplement the effect of immunotherapeutic agents. These viruses specifically attack tumor cells and reveal hidden tumor antigens during the process of their lytic cycle, thus acting as potential in situ therapeutic agents [20].

2.2.5 Adoptive T cell therapy

Another approach uses introducing the patient's whole immune cells expanded in vitro to destroy the tumors. In more recent approaches, a chimeric antigen receptor carrying T cells (CAR-T cells) was reprogrammed to identify the target tumor cells and destroy them. The main adverse events associated with this are cytokine release syndrome and neurological toxicity. Other immune cells that are currently being investigated for their potential in killing the tumor are natural killer cells (NKs) and tumor infiltrating lymphocytes (TILs).

2.3 Current Immunotherapeutic Approaches in GI Malignancies

2.3.1 Esophageal Cancer (EC)

Esophageal cancer (EC) is the seventh most common malignancy ranking as the eighth leading cause of death worldwide [21, 22]. Esophageal cancer may present in either of two types:

Esophageal squamous cell carcinoma (ESCC)—cancer in the squamous cell lining, or
Esophageal adenocarcinoma (EAC)—cancer in the mucus producing cells.

Current therapeutic options comprise surgical resection, radiation, chemotherapy, or combination for localized cancer treatment. In early stages with localized cancer, surgery remains the most common treatment choice; however, in advanced stages of EC, combination chemo and radiotherapy has an improved overall survival. However, the prognosis is not favorable with either ESCC or EAC to either form of systemic therapy due to the resistance of cancer caused by the high rate of mutation [23]. The high rate of mutation though makes it a favorable target for immunotherapeutic approach [24]. Further evidence regarding the abscopal effect of radiation in other cancer types suggests that immune cells may be effective in overcoming the tumor burden (TMB), thus forming a rationale for immunotherapy in ESCC or EAC [25]. The treatment of esophageal cancer that has progressed to advanced stages and is resistant to surgery is done using commonly used three immunotherapeutic approaches.

Pembrolizumab and Nivolumab are two FDA-approved anti-PD1 inhibitors for the advanced stages of treatment. The success of pembrolizumab in Keynote 180 (overall response rate ORR: 9.9%), a Phase II multicentric clinical study on patients with advanced and metastatic EAC and ESCC [26], and Keynote 181, a Phase III randomized multicentric clinical study [27], led to the its approval by FDA as a second line of treatment for recurrent esophageal cancer that progressed following systemic chemotherapy administration. Similarly, a phase II study with Nivolumab that enrolled esophageal carcinoma patients that had been pretreated also showed anti-carcinoma effects. Anti-CTLA-4 (tremelimumab) is another checkpoint inhibitor that is currently being used in combination therapy in various clinical trials. Immune-linked adverse events of immune checkpoint inhibitors generally may cause colitis, pneumonitis, hepatitis, nephritis, renal dysfunction, endocrinopathies, and severe dermatologic reactions.

Ramucirumab has also been approved as an orphan drug by FDA for the treatment of patients with advanced gastric cancer (GC) or gastroesophageal junction adenocarcinoma as either a monotherapy or in combination with nivolumab. In advanced gastroesophageal cancer due to low toxicity and increased tumor cell toxicity, it is considered as a second line of treatment [28].

Overexpression of Her2 is particularly observed in gastric and gastroesophageal cancers. In advanced gastroesophageal cancer patients that are molecularly selected for the expression of Her2 on the surface of cancer cells, anti-Her2 mAb is being used as first line of treatment. Trastuzumab (Herceptin) was adopted as choice treatment in Her2 positive patients based on improved overall success in terms of response and progression-free survival in the ToGA study, a phase III investigation that combined trastuzumab with chemotherapy in patients with Her2 positive and as monotherapy in metastatic gastroesophageal cancer patients [29].

2.3.2 Colorectal Cancer (CRC)

Colorectal cancer (CRC), the malignancy of colon and rectum occurs, mostly in the mucus-producing glands (>95%). It is the third most common malignancy worldwide [3, 30]. CRC patients are commonly associated with the occurrence of Lynch syndrome, hereditary non-polyposis colorectal cancer (HNPCC), demonstrate high microsatellite instability due to germ line mutations in one of the following mismatch repair genes—MSH2, MLH1, PMS2, and HSH6 [31]—and are associated with an improved diagnosis compared to the microsatellite stable disease (MSS) [32]. Several FDA-approved options exist for the treatment of MSI CRC cases. These range from immunomodulators to targeted mono or combination therapies. Due to an increased level of expression of PD-L1, PD-1, Lymphocyte activating gene-3, CTLA-4, and IDO, immunotherapeutic modulators including the checkpoint inhibitors can be used to activate the immune system [33]. Phase I clinical investigation of 39 patients with an anti-PD1 inhibitor produced durable complete response against CRC [34]. Pembrolizumab and Nivolumab are approved for MSI-H advanced colorectal cancer patients. Cetuximab has been approved by the FDA for the treatment of metastatic CRC with wild type KRAS. Bevacizumab is being used as a first line of therapy for patients with advanced colorectal cancer. Panitumumab is approved for patients with advanced EGFR positive colorectal cancer. Combination therapy that includes several viral platforms is currently being tried in clinical settings to study their oncolytic activity on colorectal tumors.

These include:

1. Adenovirus (common cold virus): The Ad11p/Ad3 chimeric adenovirus, in combination with nivolumab, is being verified as phase I dose-escalation trial (NCT02636036) and the LOAd703 oncolytic adenovirus monotherapy is being tested in a phase I/II trial of CRC patients.
2. Herpes simplex viruses have shown oncolytic effect on CRC stem cells, New-Castle virus (conjunctivitis and flu-like symptoms causing virus), and Reovirus (gastrointestinal and respiratory tract symptoms causing viruses). Injection of Pexa-Vec (JX-594), an oncolytic and immunotherapeutic vaccinia virus (VV), in CRC has been shown to be safe with fewer immune-adverse events. The Pexa-Vec-durvalumab combination is in phase I and with tremelimumab is in phase II in patients with refractory metastatic CRC (NCT03206073).
3. Reovirus, double-stranded RNA oncolytic virus—It preferentially replicates and causes apoptosis in colorectal cancer KRAS mutant cells forming crystalline arrays of virions within viral inclusions and causing lysis of the host cell [35]. In a phase I dose escalation study, Reovirus serotype 3—Dearing Strain (Reolysin)—has been studied in combination with FOLFIRI (Folinic acid, Leucovorin, and Irinotecan) and bevacizumab, an anti-VEGF-A agent, in FOLFIRI-naive patients with KRAS mutant metastatic CRC (NCT01274624). This was particularly effective where cetuximab and bevacizumab have failed due to KRAS mutations in the tumor.

2.3.3 *Hepatocellular Cancer and Biliary Tract Cancer (Cholangiocarcinoma)*

Hepatocellular carcinomas are one of the leading causes of cancer-related mortality globally with an estimated 0.8 million deaths annually (https://www.cancerresearch.org/immunotherapy/cancer-types/liver-cancer). In 2019, hepatocellular and biliary tract cancers accounted for a total of 2.4% of newly reported cancer cases and caused 31,780 cancer-related deaths (5.2%) in the U.S. (https://seer.cancer.gov/statfacts/html/livibd.html). The common risk factors for HCC include viral infection with Hepatitis, B or C virus, obesity, autoimmune hepatitis, and alcoholic cirrhosis [36]. Less than half of the liver cancer cases are diagnosed early; the surgical treatment of these cases therefore presents challenges, with over 70% cases being unresectable or unsuitable as transplantation candidates due to increased tumor burden or impaired liver function. The treatment regimen for unresectable HCCs has included the cytotoxic chemotherapeutic agents: single agent (doxorubicin and 5-fluorouricil) and more recently tyrosine kinase inhibitors such as sorafenib as a first line of treatment. Failure of sorafenib as a second line of treatment, and increasing data on the success of immunomodulators, prompted the approval of ramucirumab, a direct VEGFR2 antagonist, for treating advanced, unresectable HCC in patients with at least 400 ng/mL of detectable alpha fetoprotein levels [37]. Current data on FDA-approved immune checkpoint inhibitors in the treatment of HCCs or BTCs comes from the results of three published studies. In 2017, a phase 1/2 dose-escalation and dose-expansion study, CheckMate-040 (NCT01658878), led to the approval of nivolumab for use in advanced HCC with or without chronic hepatitis as a second line of treatment. The study reported an objective response rate (ORR) of 20%; complete response (CR) 1%; disease control rate (DCR) 64%; median progression free survival, 4 months; grade 3–5 adverse events, 19% [38].

In 2017, another key study led to the approval of the anti-PD1 inhibitor pembrolizumab in non-CRC patients with advanced MMR-deficient cancer. The phase II study that also included solid unresectable mismatch repair-deficient tumors from cholangiocarcinoma patients showed promising results. Two-year overall survival (OS), Progression-free survival (PFS) and estimates measured using the Response Evaluation Criteria In Solid Tumors (RECIST v1.1) guidelines were 53% and 64%, respectively. The complete response and disease control rates measured in the study following the anti-PD1 treatment were 21% and 77%, respectively underscoring the efficacy of pembrolizumab based treatment [39].

In Keynote-224, a phase II clinical study that enrolled 104 patients with advanced hepatocellular carcinoma, the efficacy of pembrolizumab was tested as a second line of treatment. The study demonstrated an ORR of 17%; CR, 1%, DCR, 69%; median progression free survival, 7 months, and grade 3–5 adverse events, 26%.

The role of non-FDA-approved Tremelimumab, an anti-CTLA-4 monoclonal antibody in the treatment of HCC and Cholangiocarcinoma, is currently under investigation in many studies. Tremelimumab resulted in a partial response of 17.6% and DCR of 76.4% in a phase II trial pilot study that recruited patients with

advanced HCC and HCV infection [40]. Combination studies of tremelimumab with durvalumab in patients with advanced HCC or BTC as a second line of treatment or after previous therapy are currently underway. Oncolytic viral platforms currently under clinical trials for the treatment of liver cancer include adenoviruses, herpes simplex viruses, and vaccinia viruses.

2.3.4 Pancreatic Cancer (PC)

Pancreatic cancer (PC) has the greatest fatality rate worldwide and is the third leading cause of malignance-related deaths in the USA [41]. Globally, PC is the seventh foremost cause of malignance-related deaths. The risk issues include diabetes, chronic pancreatitis, tobacco use, and inherited genetic syndromes [42, 43]. Traditionally, patients with unresectable pancreas have been treated with chemotherapy including gemcitabine and FOLFIRINOX [44]. Immunotherapeutic advances and success met with clinical trials in other cancers have galvanized the investigative approaches in the treatment of PC. However, due to the poor antigenicity and a strong immune-suppressive tumor microenvironment of pancreatic tumors, immunotherapy has not currently met with success as in other GI malignancies [45].

Immune checkpoint inhibitor blockade has met with limited success in the treatment of PC. The Ipilimumab (anti-CTLA-4 blockade) monotherapy proved ineffective in the treatment of advanced PC. Similarly, the phase I trial with anti-PDL1 in a dose escalation study showed no clinical benefit in patients with advanced PC [46].

The safety and efficacy of a whole cell-based cancer vaccine approach that employs GM-CSF-expressing engineered pancreatic cancer cells to further induce APC antigen uptake and T-cell priming (GVAX) was assessed in a phase I study. The phase I study confirmed that GVAX was safe and effective in promoting anti-tumor immunity. A phase II trial using GVAX showed limited effectiveness in a subgroup of patients with extended disease-free survival had improved tumor antigen-specific CD8+ T cells [47]. Currently, many clinical trials that employ GVAX and combination therapy are underway to study their efficacy in the treatment of locally advanced or metastatic pancreatic cancers.

Adjuvant multipeptide-based vaccines as an alternative approach to whole cell vaccines is also being investigated in the treatment of PC. An adjuvant multipeptide KRAS vaccine has also shown some success with anti-RAS response in 58% of the patients in a phase I/II trial [48]. A phase II study of 30 Japanese patients who were administered the peptide cocktail vaccine OCV-C01 containing epitope peptides derived from KIF20A, VEGFR1, and VEGFR2, together with gemcitabine in the adjuvant treatment for resected PC patients showed 58.6% of patients developed cytotoxic CD8+ T lymphocytes.

Combination therapies using immune checkpoint inhibitor blockade and vaccines have also met with some success. A phase I study studied the efficacy and safety of ipilimumab in combination with GVAX in PC comparison to ipilimumab alone. The

study, conducted on 30 patients, displayed that the combination treatment was safe with improved efficacy [49].

Studies in mice models of PC injected with GVAX in combination with anti-PD-1 showed an increased preponderance of IFN-γ-producing CD8+ in the tumor-infiltrating lymphocytes at the tumor sites, underscoring the status of combination treatment regimens for Pancreatic Adenocarcinoma (PAC) [50]. Vaccination with GVAX two weeks prior to surgical resection also resulted in increased PD-1-expressing tumor frequency. Based on these, GVAX is currently being investigated for its potential in improving patient survival outcomes in immunotherapeutic trials with or without immune checkpoint blockade, nivolumab for patients with resectable PC (NCT02451982; clinicaltrials.gov).

Studies of the pancreatic tumor microenvironment have shown increased colony-stimulating factor-1 expression by pancreatic tumor cells and its receptor CSFR1 expression on tumor-linked macrophages and myeloid-derived suppressor cells implicating its role in immune suppression. Blockade of the CSFR1-CSF pathway was revealed to progress chemotherapy-stimulated antitumor immunity in animal models [51]. Preclinical PC models further showed that prior treatment with tyrosine kinase inhibitors to block CSF-CSFR1 interaction increased PD-1 and CTLA-4 expression, making them better candidates for immune checkpoint blockade. Consistently, combination treatment with gemcitabine, CSF1R blockade, and either anti-PD1 or anti-CTLA4 treatment caused a synergistic effect. Currently, clinical trials with IMC-CS4, anti-CSF1R in conjunction with anti-PD1 and GVAX treatment for borderline resectable PC; PLX-3397 (Pexidartinib), another anti-CSF1R agent in combination with anti-PD-L1 for patients with advanced PC and CRC are underway. In PC, CXCR4 is expressed on endothelial and cancer cells and causes carcinoma-associated fibroblast immunosuppression. A dose escalation trial for the CXCR4 antagonist (Plerixafor) is also currently in phase I test for patients with PC (NCT03277209) to target CXCL12/CXCR4 interaction in order to reverse malignance-linked fibroblast immunosuppression. In yet another approach, triggering CD40, a molecule expressed on the surface of CD4+ T cells, has been revealed to improve the efficacy of vaccines in aiding anti-tumor immunity [52], leading to the phase I trial of a CD40-agonist (R07009789) for patients with resectable pancreatic cancer.

Other tumor-associated antigens that are presently being examined in clinical trials include ERBB/HER receptors, PDGFRα, VEGF/VEGF-R, and mesothelin for the treatment of PC. Oncolytic viruses under clinical studies for the treatment of PC include Adenovirus, simplex virus, Herpes, Reovirus, Parvovirus, and Vaccinia virus.

2.4 Combining Immunotherapy with Precision Medicine

Although the first immunotherapeutic treatment for cancer was approved in 2011, four immune checkpoint inhibitors received FDA approval for treatment not very long ago [53, 54]. While there are over 70 immunotherapy drugs are in clinical

investigations, it remains to be seen why some individuals respond better to these compared to others. The increasing number of studies showed that tumors with mutations in DNA mismatch repair or dMMR (microsatellite instability MSI) respond better to immune checkpoint inhibitors. The clinical data from a study to determine the efficacy of anti-PD1 blockade conducted on 12 different tumor types based on their dMMR status indicated that the tumors were susceptible to the blockade consistent with the deficiency in the DNA mismatch repair system [39]. Similarly, recently, identified MR1-restricted pan tumor targeting T cells could be studied in more detail regarding their numbers and origin in different types of tumors [55]. Combination therapy using the pan-T cells and immune check-point inhibitors may even unleash their potential in the treatment of metastasized tumors.

It is thus apparent that individualized or personalized medicine could play a significant role at the forefront of immunotherapy enabling identification of tumor mutation burden, genetic or epigenetic profile of tumors that renders them susceptible to the immunotherapeutics. Tissue agnostic drug approvals could be more relevant given the heterogenous nature of the tumors and the efficacy of immune checkpoint blockade therapy. Future approaches may rely on the identification of immunogenic neoantigens or tumor mutational burden to have deeper insights into understanding the tumor microenvironment and its role in causing immune suppression. Such information on tumor neoantigens and mutations could be vital to breaking the immunosuppression using combination therapy with immune therapeutics paving the path toward optimal patient outcomes.

2.5 Conclusions

Immunotherapy is emerging as a cornerstone of ongoing treatment strategies in GI malignancies. Combination approaches that combine the traditionally favored surgical resection to non-metastasized tumors with radiation or chemotherapy hold promise. Identification of biomarkers, protein expression profiles, and genetic and epigenetic profiles with advances in next-generation sequencing technology may be useful in providing agnostic therapies that treat cancer based on their genetic and molecular profiles rather than their type, stage, or origin. Precision medicine along with immunotherapy may thus hold the key to unlock the treatment strategy for the prolonged battle against cancer.

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