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*Review*

## **Innovative immunotherapeutic strategies for gastric cancer: A comprehensive review**

**Mujibullah sheikh\* and Pranita S. Jirvankar**

Datta Meghe College of Pharmacy DMIHER (Deemed to be University), Wardha, Maharashtra, 442001, India

**Correspondence:** Email: [mujib123sheikh@gmail.com](mailto:mujib123sheikh@gmail.com).

**Abstract:** Gastric cancer (GC) remains a significant global health challenge, ranking as the fifth most common cancer and the third leading cause of cancer-related deaths worldwide. Despite declining incidence rates in certain regions, such as the United States, mortality remains high, particularly in Eastern Asia. In this review, we explore innovative immunotherapeutic strategies for GC, including immune checkpoint inhibitors, CAR-T cell therapy, and therapeutic vaccines. The role of the tumor microenvironment (TME), immune cell interactions, tumor acidity, and microbial flora in shaping therapeutic responses is discussed. Emerging epidemiological trends, such as the rise of cardia gastric cancer and shifts in traditional risk factor profiles, underscore the need for targeted prevention strategies. While immunotherapy offers promising opportunities, challenges like therapeutic resistance and personalization of treatment persist. We aimed to highlight advancements in GC immunotherapy to promote research and improve patient outcomes.

**Keywords:** CAR-T-cell therapy; immune system modulation; chemotherapy; therapeutic vaccines

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**Abbreviations:** GC: Gastric cancer; GISTs: Gastrointestinal stromal tumors; M:I: Mortality-to-incidence ratio; CAFs: Carcinoma-associated fibroblasts; ICIs: Immune checkpoint inhibitors; TME: Tumor microenvironment; TAMs: Tumor-associated macrophages; MDSCs: Myeloid-derived suppressor cells; CSF1R: Colony-stimulating factor 1 receptor; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; TNBC: Triple-negative breast cancer; HCC: Hepatocellular carcinoma; RCC: Renal cell carcinoma; EC: Endometrial cancer

## 1. Introduction

Gastric cancer (GC), commonly referred to as stomach cancer, continues to be a major public health problem globally and is the fifth most prevalent cancer and third leading cause of cancer-related death globally. Histories indicating trends in the incidence of gastric cancer indicate that the incidence rate has decreased since the middle of the 20th century, and countries such as the United States have been experiencing declining incidence rates for the past few decades [1]. Nevertheless, this mortality trend is reversed by an increasing trend in gastroesophageal cancers. Adenocarcinoma is the most prevalent variety of gastric cancer that develops in the mucosa of the abdomen, and two more rare types are lymphomas and gastrointestinal stromal tumors (GISTs) [2]. Karimi et al. (2014) noted that it is important to study the incidence, survival and mortality rates of gastric cancer to address this cancer type [3]. According to GLOBOCAN 2018, GC ranks fifth among common malignant neoplasms and third in cancer mortality worldwide, mostly in males of advanced age; therefore, intervention-associated prevention is needed [4]. Furthermore, a general review of the literature revealed that GC-related factors depend on geographical location and lifestyle, including diet and *Helicobacter pylori* infection [5]. The increasing prevalence of cardia gastric cancer and the declining trend of noncardia types of gastric cancer suggest a changing pattern in the distribution of stomach cancer. These changes demand targeted preventive efforts, such as changing one's diet and quitting smoking [4].

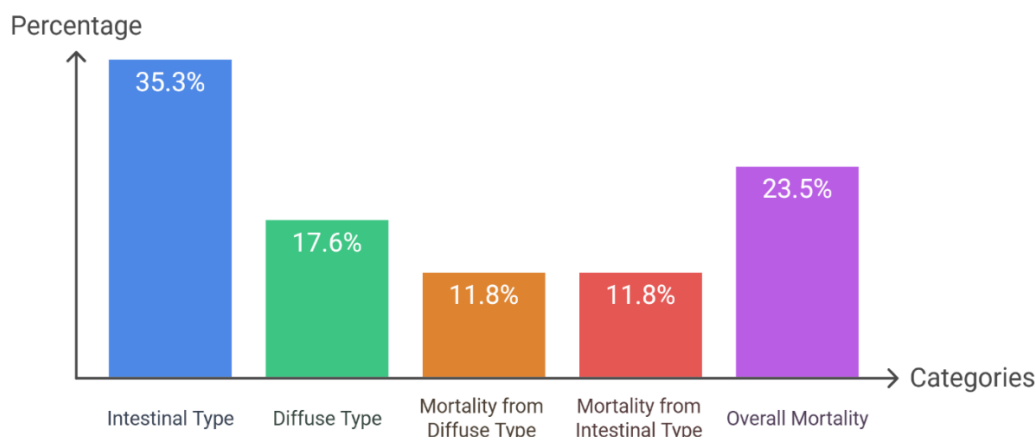
### 1.1. Overview of the prevalence and mortality of gastric cancer

Stomach cancer is one of the most life-threatening diseases in the world, with considerable geographic distinctions in incidence and mortality (Figure 1: Prevalence and mortality of gastric cancer). The number of new cases in the year has reached approximately 1.1 million, and the death toll is nearly 770,000; hence, cancer is prevalent globally [6]. These incidence rates are considerably higher among males, which are 15.8/100000 compared with 7.0/100000 among females, and the ranking countries are Eastern Asia, particularly Japan, as well as Korea [7]. For example, the incidence rate for males is 48.1 per 100000 for Japan, which clearly illustrates the geographical inequality of gastric cancer [6].

The mortality-to-incidence ratio (M:I) is also worrisome; gastric cancer is the second leading cause of cancer mortality in the world, with a high proportion of mortality in high-incidence areas of Eastern Asia [8]. For example, the mortality per 100,000 people in Mongolia is 36.5, which makes it even more crucial to devise efficient ways of prevention and early diagnosis in these countries. Additionally, forecasts suggest that if the trends persist, the rate of new cases could increase to 1.8 million for the year 2040, with a number of deaths of 1.3 million [9].

A study conducted by Miller et al. (2019) revealed that the global incidence of gastric cancer is decreasing; however, mortality from the disease is high, mainly because of regions with high incidences of *Helicobacter pylori* bacteria [10]. This highlights the need to understand the different epidemiology patterns related to gastric cancer, as noted by Karimi et al. (2014), who noted that risk factors for gastrointestinal cancers are multifactorial and can include diet, genetic, and immunological markers, with serologic detection being important [3]. The statistical overview of research data regarding gastric cancer is more upsetting in some directions; Miller et al. (2022) identified it as the third most lethal cancer globally, with a higher incidence of mortality among males aged over 60 years [11]. Emerging cases of cardia gastric cancer are worrisome and seem to change the epidemiology of gastric

malignancies (Rawla & Barsouk, 2018). These changes may represent new dietary and procurement risks and constitute one of the reasons, forcing a deeper investigation into these patterns [4].



**Figure 1.** Prevalence and mortality of gastric cancer [12–16].

The disparities in the incidence and mortality of cancer across the world imply that the causes of gastric cancer are diverse in nature. These factors, such as diet systems, attitudes, and hereditary qualities, strongly affect these trends. For example, Rugge et al. (2015) suggested that these regional differences must be further considered when designing prevention measures [17]. Cardia gastric cancer incidence is on the rise, whereas the overall rate is decreasing, and this phenomenon compels researchers to consider the shifts in gastric cancer epidemiology, suggesting the possibility that traditional risk factors are changing or that new factors indicating risk are being discovered [18]. Furthermore, a relationship between *Helicobacter pylori* infection and gastric cancer is clear; several works suggest that *Helicobacter pylori* infection continues to be one of the factors determining high mortality rates among patients with this pathology [19]. The discussion of serologic markers and the discussion of precursor lesions provides future possibilities for early detection, which could increase SC mortality rates [3]. Risk factor assessment is important because all these measures have the potential to substantially decrease the incidence of gastric cancer.

However, several questions about gastric cancer development and progression remain poorly understood, even in light of more recent findings. Specifically, studies aimed at evaluating the effect of combining genetic testing with other preventive measures, including dietary alterations and smoking cessation, are lacking [20]. Moreover, Miller et al. (2022) noted that there is a need to continue providing public health initiatives that address both incidence and deaths due to gastric cancer [11].

## 2. Search methodology

When searching for articles and studies to reference the topic of immunotherapeutic strategies in gastric cancer, a search was conducted in a way that identified both relevant and good quality articles. The choice of databases was crucial, and to ensure that a variety of sources were obtained, only those from PubMed, Scopus, and Web of Science were selected. The search was performed from the perspective of the following specific terms: gastric cancer, immunotherapy, immune checkpoint inhibitors, and adoptive cell therapy, which formed the basis of the review. The inclusion criteria were

formalized, and we focused on considering only the articles of the peer-reviewed journals and only the clinical trials that were published within the last five to ten years. The information was then extracted systematically, bearing in mind features such as efficacy, mode of action, and effects on patients. There were specific aspects that were followed during data collection and analysis: Diverse static data collection forms were utilized in each of the implemented strategies to ensure uniformity and minimize the effects of investigator-induced variability, and data extraction was performed independently by the different reviewers. Finally, this strict approach was designed to correlate data that might support subsequent studies and medical treatment of gastric cancer with immunotherapy.

### 3. Mechanisms of immunotherapy

Immunotherapy has become a promising therapeutic option in cancer management, with the principle of using the immune system to fight tumor development [21]. The immune–tumor interaction remains one of the key components of this therapeutic approach to consider if the anticancer effect is to be achieved [22]. The TME is underlain by diverse cell types embedded in a milieu of complementary cellular roles, such as immune cells, fibroblasts, and the ECM, all of which play major roles in modulating the immunological response to cancer. Researchers have therefore sought to reveal the multiple ways by which immunotherapy reprograms the TME and the consequences of such changes on treatment outcomes [23]. These include carcinoma-associated fibroblasts (CAFs) in the process of establishing an immunosuppressive TME, especially in the case of pancreatic cancer. Samstein et al. (2019) reported that FAP+ CAFs mediate the immune exclusion of T cells through the secretion of the chemokine CXCL12. These findings confirm that immunotherapeutic antibodies can be made more effective when directed at CAFs and that the identity of the TME should be considered when developing treatment plans. The removal of FAP+ CAFs not only enables better T-cell infiltration but also reveals which existing immunotherapies can be effective when the TME is enhanced [24].

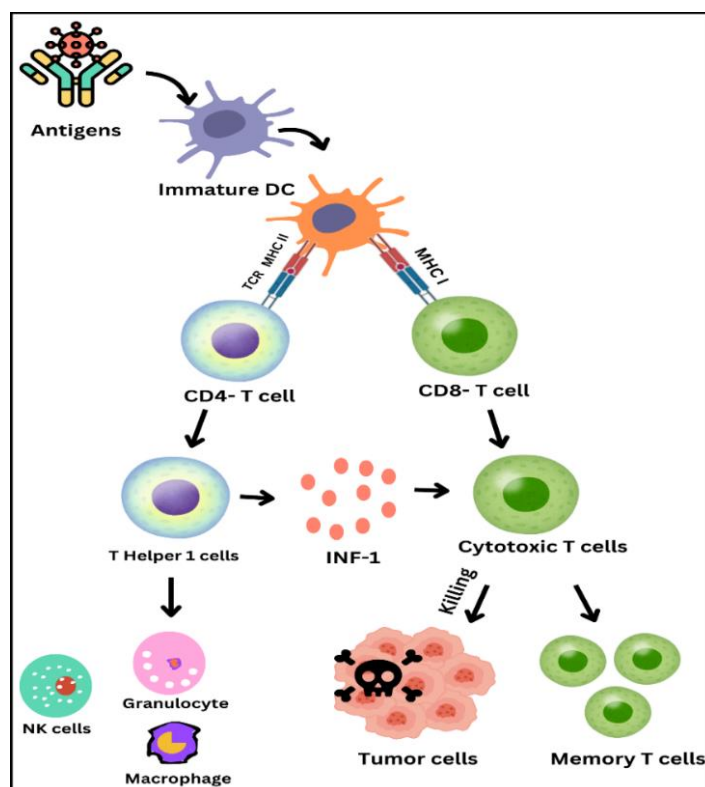
Moving from the effects of CAFs, the interactions of cancer cells with the immune system through immune checkpoint inhibitors (ICIs) are as follows. Ru and colleagues noted that although ICIs have revolutionized cancer treatment, resistance still poses a major problem. They are highly dependent on the TME, which either supports or negates immune response efforts. The investigation of local immune changes after receiving ICI therapy is critical for improving treatment plans, indicating that future research on the development of resistance mechanisms related to function and relevance to the TME is warranted [25]. Furthermore, the immune context of tumors is shaped by different immune cells, such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). Bagchi et al. (2020) mentioned clearly that such cells are involved in immune suppression and tumor advancement. Accordingly, trying on the colony-stimulating factor 1 receptor (CSF1R) can alter macrophage behavior to improve antigen presentation in addition to T cells. This finding highlights the need to elucidate the intricate TME immune cell interactions and ways to manipulate them to increase immunotherapy efficacy [26].

Thus, assessing cellular interactions also reveals that the physicochemical characteristics of the TME also regulate the immune response. Labani-Motlagh et al. (2020) noted that tumor acidity prevents T-cell activation, which limits immunotherapeutic approaches. In their study, they showed that elimination of tumor acidity improved T-cell penetration and the effectiveness of checkpoint inhibitors, which underlines the role of manipulation of TME properties in immunotherapy optimization [27]. In addition, evidence has revealed the effects of the microbiota on tumor immunity. Zhu et al. (2015) noted that individual bacterial

strains can increase T-cell proliferation by releasing metabolites such as inosine to improve immunotherapy outcomes. This has highlighted the unexplored strategy of developing combination therapy by adding microbiome manipulation to existing immunotherapeutic strategies [28].

However, this progress seems to leave some gaps in understanding regarding the relationships of the TME with immunoisolation and immune escape mechanisms. For example, the mechanisms by which tumors modulate PD-L1 to dampen T-cell activity are not fully defined. Research by Henke et al. (2020) revealed that several pathways impact the levels of PD-L1, the implication of which is that understanding these signaling pathways can provide insight into improving the effectiveness of anti-PD-L1 therapy [29]. More research on the role of the ECM should also be conducted in terms of modulating immune responses because, according to Mager et al. (2020), the role of the ECM has also been investigated, and the active participation of the ECM in tumor behavior and therapeutic reactions should be further investigated [30].

As illustrated by the immune response activation process shown in Figure 2, dendritic cells and T cells play crucial roles. It starts with the elimination of antigens by immature dendritic cells. These cells then mature and present the antigens to T cells in presenting the antigens, and most of the maturity occurs on the dendrite. This interaction occurs through the T-cell receptor and major histocompatibility complex molecules. Importantly, antigen presentation occurs through MHC II in T cells for immunoglobulin and MHC I for cytotoxic T cells; in this case, T helper 2 cells appear from  $CD4^+$  T cells and, in turn, release interferon-gamma to activate natural killer cells, granulocytes, and macrophages.  $CD8^+$  T cells further divide into cytotoxic T cells and kill these tumor cells. Additionally, some T cells become memory T cells with a high ability for immunity to pathogens or foreign substances. The ‘theater of immune response’ you see here identifies elements of the adaptive immune response and explains the actions of cell types and molecules in fighting infections and tumors.



**Figure 2.** Mechanisms of immunotherapy.

## 4. Types of immunotherapeutic approaches

### 4.1. Immune Checkpoint Inhibitors (ICIs)

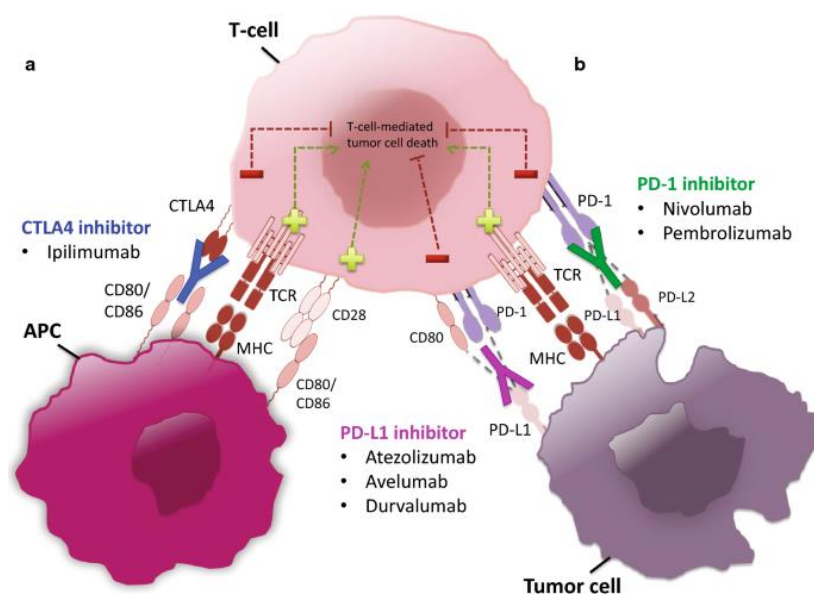
Known as immune-oncology agents, immune checkpoint inhibitors (ICIs) have radically altered approaches to cancer treatment by increasing the immune system's capacity to identify and destroy malignancies [31]. The development of ICIs dates to the discovery of immune checkpoints, which are regulatory mechanisms that tumors use to hide from the immune system. The first major step forward occurred in 2011, when the FDA gave ipilimumab (Yervoy), an antibody against CTLA-4, a green light, the beginning of the modern period of cancer therapy [32]. Pembrolizumab and nivolumab have emerged as PD-1/pD-L1 inhibitors that have revolutionized the treatment of several types of cancer. Immune checkpoint targeting was proposed on the basis of basic discoveries that were made in the late 1990s and early 2000s [33]. The work of James Allison and Tasuku Honjo identified CTLA-4 and PD-1 as avenues of interest for therapy [34]. Based on this work, he revealed that strengthening antitumor immunity with the help of blocking CTLA-4 was possible, which led to the development of ipilimumab. Similarly, young Honjo built upon another researcher's discoveries to establish subsequent PD-1 and PD-L1 inhibitors [35].

Table 1 lists approved immune checkpoint inhibitors from 2010–2024, targets, approval years, indications, and reference information. In this paper, we provide an outline of the state-of-the-art use of ICIs in treating cancer and points to further advancements in this area.

**Table 1.** Lists of immune checkpoint inhibitors approved from 2010–2024, including their targets, approval years, indications, and references for further information.

Drug Name	Brand Name	Target	Year Approved	Indications	Ref
Ipilimumab	Yervoy	CTLA-4	2011	Metastatic melanoma, renal cell carcinoma, colorectal cancer	[36,37]
Nivolumab	Opdivo	PD-1	2014	Melanoma, lung cancer, kidney cancer, bladder cancer	[38,39]
Pembrolizumab	Keytruda	PD-1	2014	Melanoma, lung cancer, head and neck cancer, Hodgkin's lymphoma	[40]
Atezolizumab	Tecentriq	PD-L1	2016	Bladder cancer, non-small cell lung cancer, breast cancer	[41]
Avelumab	Bavencio	PD-L1	2017	Merkel cell carcinoma, urothelial carcinoma	[42]
Durvalumab	Imfinzi	PD-L1	2017	Non-small cell lung cancer, small cell lung cancer	[43]
Cemiplimab	Libtayo	PD-1	2021	Squamous cell carcinoma of the skin, non-small cell lung cancer	[44]
Dostarlimab	Jemperli	PD-1	2021	Endometrial cancer	[45]
Tremelimumab	Imjudo	CTLA-4	2022	Hepatocellular carcinoma (in combination with Durvalumab)	[46]
Toripalimab	Loqtorzi	PD-1	2023	Nasopharyngeal carcinoma	[47]
Spartalizumab	PDR001	PD-1	TBD	Under investigation for various solid tumors and lymphomas	
Abemaciclib	Verzenio	CDK4/6	2017	Breast cancer (in combination with pembrolizumab)	[48]
Tislelizumab	Baiyin	PD-1	2022	Non-small cell lung cancer	[49]
Rovalpituzumab	Rova-T	DLL3	TBD	Small cell lung cancer	[50]

Programmed cell death protein 1 (PD-1) and its ligand (PD-L1) immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by engaging the immune system in identifying and eliminating cancer cells. The blockade of PD-1/PD-L1 interactions is of paramount importance during this process since it abrogates the inhibitory signals that otherwise reign in the T-cell response against tumors. A small study based on a multicenter phase 1 trial revealed that the application of an anti-PD-L1 antibody leads to long-term regression of the tumor mass in most advanced cancer patients, as evidenced by the objective response, which varies between 6% and 17% [51]. The historical development of ICIs describes a gradual step from the first approval of anti-CTLA-4 therapy for melanoma to the development of PD-1/PD-L1 inhibitors. These ICIs have been shown to be effective in treating various cancers. Nonetheless, the review highlights a significant challenge: Therapeutic failure and resistance to ICIs mean that the number of patients who can obtain a long-lasting therapeutic benefit remains limited. Understanding the nature of this resistance is critical for modulating treatment regimens, and the mechanisms involved in the development of this resistance remain to be characterized. For example, researchers conducting clinical trials, such as KEYNOTE-649, aim to study combined therapeutic approaches that potentiate PD-1/PD-L1 inhibition to further increase the survival status of patients [23]. A comprehensive understanding of the PD-1/PD-L1 pathway is crucial for the design of cancer immunotherapies. Strong evidence suggests that this pathway is an important way through which tumors are shielded from immune recognition. The presence of the PD-L1 protein on tumor cells can inhibit T cells, leading to an immune response-tolerant checkpoint with certain types of carcinogenesis [52]. As highlighted by findings from this review, it is important that the treatment of this axis calls for new strategies, especially for highly metabolic cancer types such as TNBC. Integrating PD-1/PD-L1 inhibitors with other drugs, including MEK inhibitors, increases the likelihood that the treatment efficiency and survival rates of patients will increase [53]. The combination strategies are summarized effectively in Figure 3 below. There is a new triple regimen of camrelizumab, an anti-PD-1 monoclonal antibody, apatinib, a newly approved angiogenesis inhibitor, and fuzuloparib, a newly formulated PARP inhibitor, which has recently exhibited acceptable safety and preliminary antitumor efficacy in TNBC [54]. The combination of PD-1/PD-L1 inhibitors with angiogenesis inhibitors has also demonstrated activity in third-line therapy for advanced hepatocellular carcinoma (HCC), third- and later-line therapy for renal cell carcinoma (RCC) and endometrial cancer (EC). Furthermore, combining ICIs with angiogenin inhibitors and chemotherapy might overcome the problems that NSCLC patients with EGFR mutations may encounter [55]. The FDA has approved the combination of PD-L1 inhibitors with BRAF-MEK inhibitors for advanced-stage melanoma with BRAFV600 [56]. Moreover, the addition of PD-L1 inhibitors with T-DM1 is favorable among patients with HER2-positive, PD-L1-positive advanced BC [57]. It also has clinically useful results when PD-1/PD-L1 inhibitors and PARP inhibitors are administered to breast cancer patients with germline BRCA1/2 mutations and ovarian cancer (OC) [58].



**Figure 3.** Overview of current strategies that combine immune checkpoint inhibitors (ICIs) and targeted therapies, is taken from the article distributed under the terms of the Creative Commons Attribution-Noncommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>).

There is an understanding of TMB and PD-L1 as predictive markers of ICI response in many papers. TMB is associated with better clinical results and lasting clinical benefits derived from PD-1/PD-L1 agents [59]. Consequently, these discoveries suggest that TMB and PD-L1 expression should complement the choice of predictive models to improve patient selection in routine care. The relevance for trials such as KEYNOTE-649 is significant since it sets out steps for selecting the patients who are most likely to derive advantages from these advanced treatment methods. Additionally, the combination of anti-PD-1/PD-L1 inhibitors and ibrutinib also suggests another direction for the intensification of antitumor immune reactions (source not provided). These combinations might enhance outcomes in various cancers because the mechanisms of PD-1/PD-L1 blockade are also in agreement. Emerging data suggest that further study of the factors and pathways affecting resistance mechanisms that might impair antigen presentation by HLA class I molecules will limit the efficacy of ICIs [60]. However, many unknowns remain in this area of study, including issues related to working against resistance and selecting the right patient reward profiles for different ICI treatments. Future work should focus on a better understanding of factors dependent on tumor characteristics and the immune milieu and their impact on treatment outcomes. This involves examining the use of biomarkers in prognostication and treatment planning for the neoadjuvant treatment of cancer types such as triple-negative breast cancer plus the identification of biomarkers that may be used to predict combination therapy reactions [61].

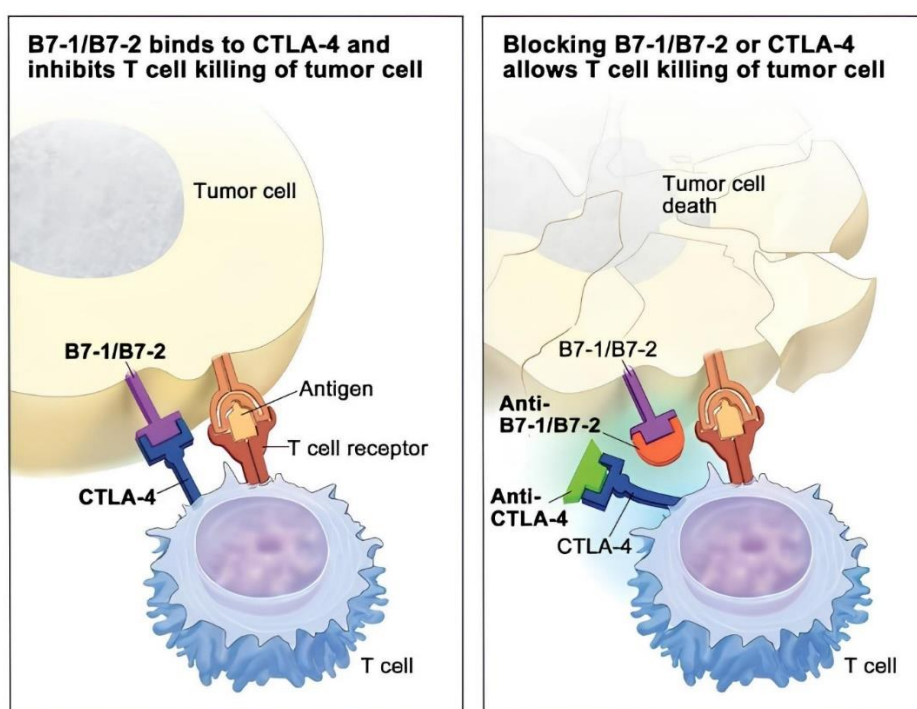
#### 4.1.1. CTLA-4 inhibitors

The use of anti-CTLA-4 agents, such as ipilimumab, is a major innovation in cancer immunotherapy and is focused mainly on reversing the immune suppression that tumors promote.



Blockade of CTLA-4, a coinhibitory receptor that negatively controls T-cell activation, improves antitumor T-cell activity, which is essential for obtaining lasting effects in various types of tumors [62]. In addition, it helps the immune system identify tumor cells and target them; moreover, it highlights the immunological setting of cancer therapy. Extending their scope, researchers have also discussed the impact of gut microbiomes on CTLA-4 inhibitors. For example, a particular class of *Bacteroides* has been shown to enhance antitumor effects; therefore, the authors contend that the microbiota heavily influences immune reactions during CTLA-4 blockade [63]. This discovery may open up avenues for microbiome-targeted treatments that would help make CTLA-4 inhibitors more effective while ushering in a new era of individual immunotherapy tailored to a patient's microbiome.

Furthermore, the effectiveness of CTLA-4 inhibitors is strongly associated with mutations in tumor-related genes. Thus, a greater mutational burden has been shown to be associated with positive outcomes after treatment with CTLA-4 blockade; thus, comprehensive molecular profiling of tumors is critical for understanding the mechanisms underlying patients' responses [64]. Figure 4: Illustration of the nature of the action of CTLA-4 inhibitors. Tumor cells express B7-1/B7-2, which bind to CTLA-4 on T cells, blocking their ability to kill tumor cells (left). By inhibiting the effective interaction of B7-1/B7-2 with a CTLA-4 inhibitor, T cells can no longer bind to free CTLA-4 receptors, enabling them to kill tumor cells (right). CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4.



**Figure 4.** Nature of the action of CTLA-4 inhibitors. Tumor cells express B7-1/B7-2 to bind with CTLA-4 in T cells so that the T cells are blocked from killing the tumor cells (left). By inhibiting the effective interaction of B7-1/B7-2 with a CTLA-4 inhibitor, it becomes impossible for T cells to bind to free CTLA-4 receptors, hence killing tumor cells (right). CTL-4 = cytotoxic T-lymphocyte-associated antigen 4. As a result of this process for the National Cancer Institute © 2015 Credit: © Terese Winslow, the United States Government has certain rights.

However, similar to other immunotherapy strategies, CTLA-4 inhibitors cannot be completely free from immune-related toxicity; for example, colitis can be potentially lethal. The timing and type of these side effects need to be understood so that patient safety can be addressed while achieving optimum therapeutic gain [65]. Special emphasis should be placed on assessing the first signs of toxicity in patients treated with combination therapies, including CTLA-4 blockade, as such combinations may increase toxicity. Another layer of complexity is the tumor microenvironment because factors such as myeloid-derived suppressor cells can also represent a target for overcoming resistance related to CTLA-4 therapies [66]. This resistance highlights the fact that a combined-state approach should be used to target both CTLA-4 and MDSCs, which may improve therapeutic efficacy and the antitumor immune response. Recent improvements in cancer immunotherapy using CTLA-4 inhibitors have led to the FDA approval of many monoclonal antibodies for the inhibition of CTLA-4, but issues concerning patient response remain. An urgent need has been reached for biomarkers that would help in predicting the therapeutic outcomes of these types of treatment, highlighting that the immune response to CTLA-4 blockade is nonlinear and that there is therefore a need for more research on probable factors that determine the immune response to therapies [67]. The use of CTLA-4 and PD-1 inhibitors has also received attention because these agents may have synergistic effects. Moreover, while CTLA-4 blockade promotes T-cell activation and proliferation, the add-on effect of PD-1 blockade may intensify antitumor immunity; therefore, combining these targets would result in improved immune effector function against tumors [67].

#### 4.1.2. PD-1 inhibitors

Pembrolizumab and nivolumab, PD-1 inhibitors, are at the forefront of immunotherapy for cancer and NSCLC. These agents, which are grouped according to their mechanism-label, exert effectiveness on the basis of genomic features, especially TMB. A positive correlation between TMB and the response to PD-1 blockade has been reported by Rizvi et al. (2015), who reported that the greater the number of mutations, the more responsive the tumor is likely to be to the inhibitor. This work entailed the application of genomic markers in the development of effective slug management plans for the treatment of oncology patients with reference to the peculiarities of the tumor. Moreover, the neoantigen and T-cell responses detected in PD-1-treated patients suggest that these inhibitors act not only on tumor cells but also on the immune system to eliminate cancer [68].

The findings of genomic determination are further supported in subsequent studies and depict the molecular smoking index as well as DNA repair pathway mutations as important factors that predict the efficacy of PD-1 inhibitors (Rizvi et al., 2015). This finding supports the view that an understanding of a patient's polygenic profile is necessary when administering PD-1 therapy in the clinical setting [68]. In addition to genomic inputs, the gut microbiome has been identified as a key area of interest in terms of PD-1 inhibitors. Routy et al. (2018) explained how, through the destruction of immune regulatory microbiota in the gut, the use of antibiotics is capable of worsening treatment results. Some bacterial species, such as *Akkermansia muciniphila*, are known to be strongly correlated with PD-1 therapy outcome. Thus, these results suggest that a healthy gut microbiome may be necessary to achieve optimal results from PD-1 inhibitors and hence opens a new direction for influencing treatment responses via microbiota modulation [69].

The action of PD-1 inhibitors continues to be discussed in the literature, with an emphasis on the functions of PD-1 and CTLA-4 as immune checkpoints according to Buchbinder and Desai (2016).

This blockade can strongly promote specific antitumor immunity, which represents a major shift in cancer therapy strategies. The fact that the early and late phases of immune response regulation are distinct and modulated by CTLA-4 and PD-1 offers important lessons in harnessing these agents for immunotherapies and combinations that yield maximum benefit to patients [70]. However, only a few questions arise related to the restrictions on the use of PD-1 therapy and the problems with its effectiveness. Some aspects have been found to be linked to hyperprogressive disease (HPD) related to PD-1 inhibitors, and important questions arise for choosing patients and screening analysis during treatment. HPD is proof of the need for further investigation and the constant development of effective treatment methods as well as the prevention of essential adverse effects responsible for the decrease in therapeutic outcomes [71]. However, knowledge of the safety profiles of PD-1 inhibitors is crucial for patient management. The side effects of these therapies may differ, meaning that the treatment plans used in their management and treatment should be made to fit everyone. A systematic review of adverse events focused on comparisons of the therapeutic effectiveness of PD-1 inhibitors with possible side effects [71].

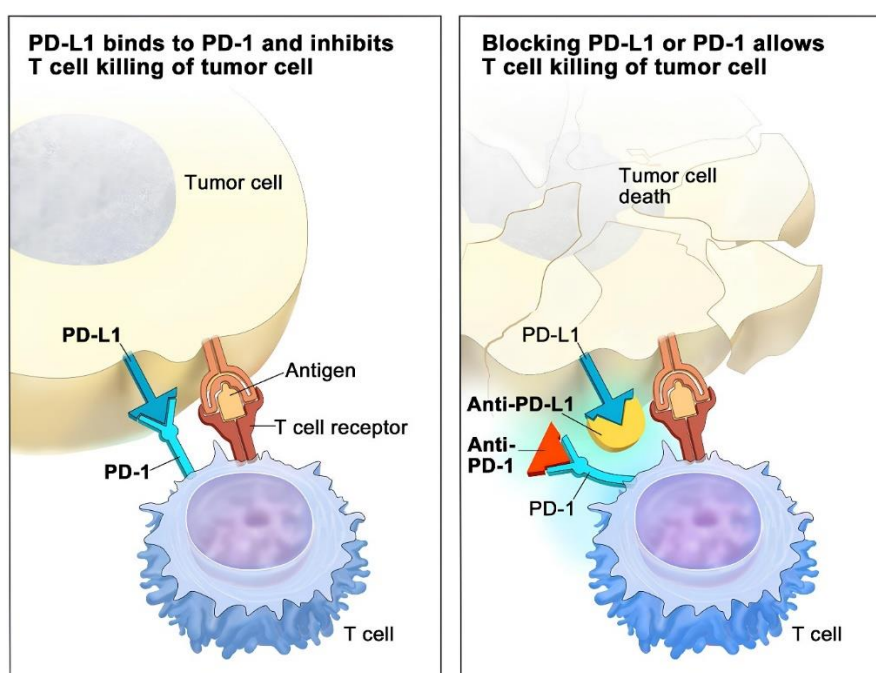
#### 4.1.3. PD-L1 inhibitors

PD-L1 inhibitors are the major subtype of ICPs that significantly contribute to cancer immunotherapy, especially through immune checkpoint blockade, which is targeted at improving recognition of tumor cells by the immune system. The exact mode of action of these inhibitors, including both anti-PD-1 and anti-PD-L1 antibodies, is related to the regulation of the relationship between immune and cancer cells toward reversal of the immunosuppressive effects elicited by tumors. In this context, clinical trials have established that although these inhibitors induce substantial antitumor outcomes, they are usually associated with subtype specificity. This could be because PD-L1 is expressed in a variable way within the tumoral microenvironment, implying that there is much to learn about the actual role of PD-L1 in immune escape [71]. Subsequent analyses focused on the role of predictive biomarkers such as the TMB and the extent of PD-L1 expression in defining patient outcomes in response to PD-L1 inhibitors, especially in advanced NSCLC. The TMB increases, and the clinical benefit increases; therefore, the TMB should be added to PD-L1-based models for selecting patients who will benefit from immunotherapy [59]. The requirement for such case-based approaches is further compounded by a newly identified worst-case scenario called hyperprogressive disease (HPD), where some patients experience an increased rate of tumor growth after receiving PD-L1 inhibitors. This raises the need for proper selection of patients, especially elderly patients, for this treatment and close follow-up of any patient's condition [72].

Figure 5 shows the types of immune-limiting proteins: PD-L1, which is present on tumor cells, and PD-1, which is present on T cells. PD-L1 forms a complex with PD-1, which inhibits the ability of T cells to kill tumor cells within the body (left panel). When this interaction is impaired by immune checkpoint inhibitors (anti-PD-L1 or anti-PD-1), T cells can once again kill tumor cells.

Furthermore, concerns exist regarding the safety of PD-L1 inhibitors for their therapeutic use in the clinic. Compared with other PD-L1 inhibitors, systematic reviews have revealed that there is inconsistency in the distributions of treatment-related AEs; thus, there is a need to conduct safety analyses continually to assist clinicians in choosing suitable drugs [73]. These results indicate that most PD-L1 inhibitors have favorable risk profiles for major types of adverse effects; thus, more studies related to individual cancers and agents associated with efficacy and safety are needed.

Subsequent meta-analysis studies have also supported the use of PD-L1 inhibitors irrespective of the PD-L1 expression level, which contradicts the prior belief that PD-L1 levels should be the basis for treatment choice. The body of knowledge indicates that these therapies could offer significant survival gains; therefore, there should be increased utilization in practice not based on this biomarker [74]. This inevitably raises questions about the interaction of PD-L1 inhibitors with other therapeutic schemes, including combination treatment regimens that can potentially improve overall outcomes. In our view, one exciting area of investigation concerns the use of PD-L1 inhibitors in conjunction with other modalities of treatment, such as IL-6 blockade, especially in difficult-to-treat cancers, including PDAC. Previous research has shown that such combinations may enhance antitumor responses; therefore, the optimization of multiple modality treatment approaches may augment the efficacy features of PD-L1 inhibitors [75].



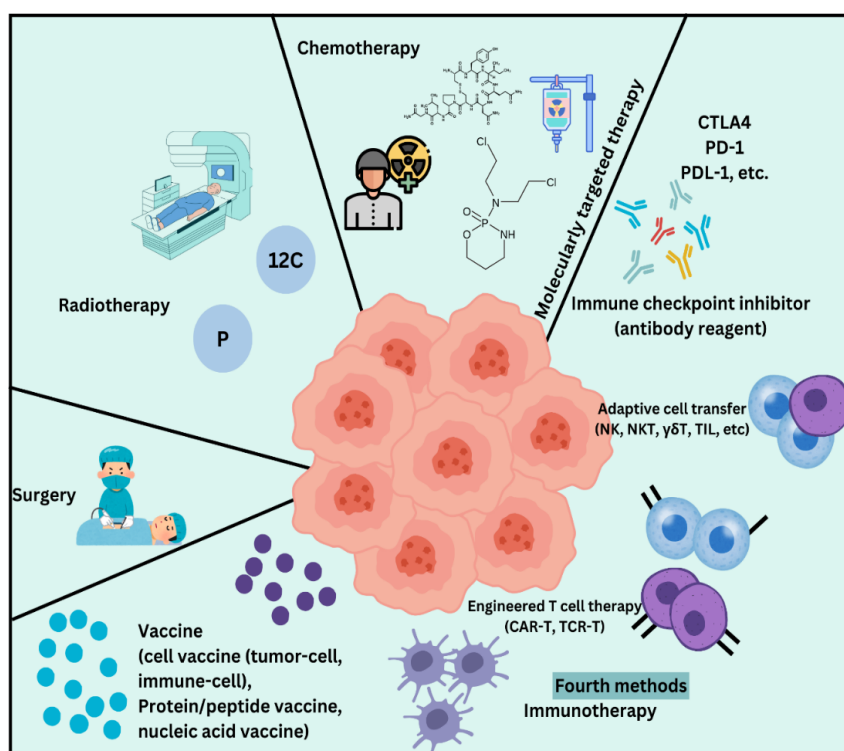
**Figure 5.** Immune-limiting proteins include PD-L1, which is expressed on tumor cells, and PD-1, which is expressed on T cells. PD-L1 binds to PD-1, preventing T cells from killing tumor cells in the body (left panel). The ligand PD-L1 binds to the immune checkpoint PD-1 and dampens the ability of T cells to kill tumor cells, but when the interaction is blocked with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1), T cells kill tumor cells (right panel). Credit: © Terese Winslow.

#### 4.2. Conventional therapy

Conventional cancer treatment primarily encompasses three main modalities: Surgery, chemotherapy, and radiation therapy. These approaches have been standard for oncology therapy for many years and are typically used concurrently to improve effectiveness against tumors [76]. Surgery is often the initial approach, assuming that the tumors are localized and that they are mostly initially located. Surgery for cancer aims at eradicating all the tumor mass while also taking a thin margin of

healthy tissues to remove all cancer cells. Surgery is especially beneficial in stage I cancers where tumor removal is likely to remove the disease completely [77]. However, while chemotherapy relies on agents that are toxic to cancerous tissues and cells, the drugs used in chemotherapy are those that selectively target and destroy rapidly dividing cells. This treatment can be performed orally or through injection and is performed either as a primary treatment or an additional treatment after surgery to eradicate cancer cells not captured by surgery [78].

However, chemotherapy is effective in reducing the size of a tumor and increasing the prognosis and survival time and it often has complications that affect normal cells in the body, such as nausea, fatigue and infections. In addition, challenges associated with treatment, such as drug resistance, can be quite definitive [79,80]. Radiation therapy uses ionizing energy, in the form of rays or particles, including X-rays, to destroy cancer cells. Some types of cancer are confined, and the rays can be accurately aimed at the affected area. Radiation can be used as an initial modality in combination with surgery and/or chemotherapy. However, like chemotherapy, it can also impact other parts of the body and healthy cells, which can cause various side effects [81,82]. Figure 6 shows an overview of conventional and recent advancements in cancer treatment methods, highlighting surgery, chemotherapy, radiation therapy, and immunotherapy as key approaches in combating cancer. Over the past few years, there has been an increased focus on combinations of focused therapies along with immunotherapies along with conventional treatment plans. These modern methods attempt to pinpoint cancer cells or improve the body's ability to fight tumors, thereby causing less damage to healthy cells than conventional treatments do. However, conventional therapies continue to be important parts of cancer management because they form a solid foundation on which more recent approaches are based [83].



**Figure 6.** An overview of conventional and recent advancements in cancer treatment methods, highlighting surgery, chemotherapy, radiation therapy, and immunotherapy as key approaches in combating cancer.

## 5. Cancer vaccines

The invention of vaccines has given a vast chance for the eradication or control of infectious diseases; the first known vaccine was created by Edward Jenner in 1796 on the basis of cowpox and protection against smallpox. In time, vaccines have been used to treat other illnesses, including cancer [84]. The first type of cancer vaccine, which is based on tumor cells and lysates, was developed in 1980 and targeted colorectal cancer via autologous tumor cells. The turning point was the discovery of a new melanoma-associated antigen in the early 1990s, which focused on the development of tumor antigens for vaccines [85]. A major breakthrough was achieved in 2010 when a Sipuleucel-T dendritic cell-based cancer vaccine was successfully used to manage prostate cancer, and there is hope in the field of cancer vaccines. The current COVID-19 vaccination has also advanced great progress in the development of novel cancer vaccines [86]. These vaccines mainly use the concepts of tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs) to work on the immune system and consider both cellular immunity and humoral immunity to prevent tumor formation and eliminate cancer cells. This approach is mostly used for cancer vaccines, which are at the preclinical and clinical levels and therefore require further definitions of more specific antigens and more effective development platforms [87]. Cancer vaccines differ from conventional vaccines in that their major purpose is to elicit selective immune reactions against cancer cells without the need to target usually foreign organisms. There are only two virus-associated preventive cancer vaccines approved by the FDA: The hepatitis B vaccine and the HPV vaccine [88]. In contrast to most typical immunogens where the antigens are exogenous, tumor antigens are endogenous and thus usually weak self-antigens that present low immunogenicity, thereby complicating efforts to elicit immune responses. All these vaccines, particularly cancer vaccines, mainly elicit affinity for CD8<sup>+</sup> cytotoxic T lymphocytes and not the more familiar antibodies that are evoked by traditional vaccines [89].

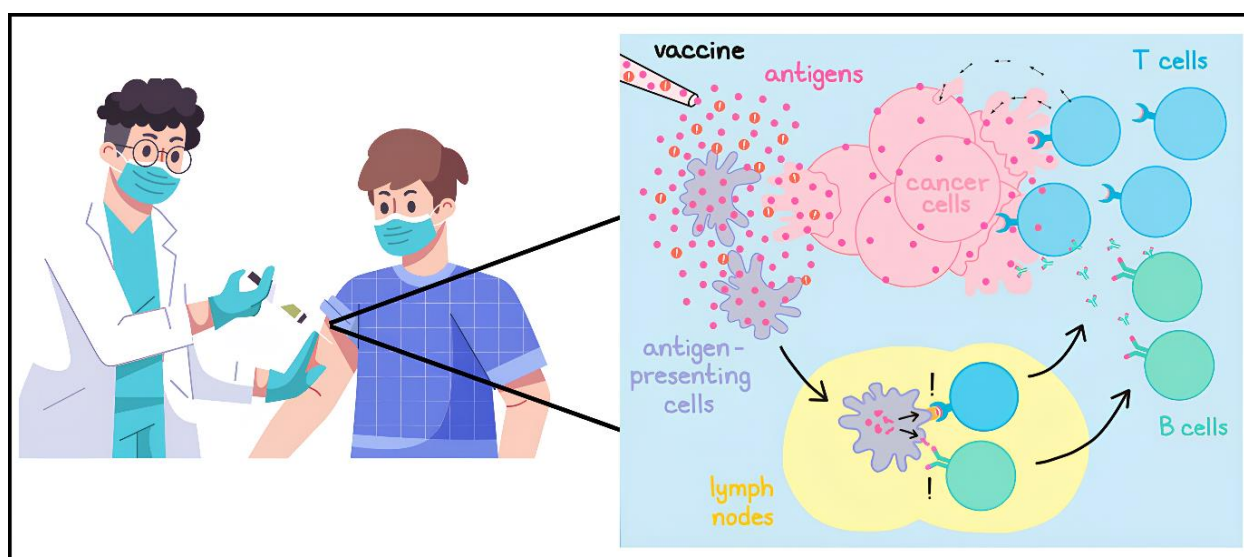
### 5.1. Mechanism of cancer vaccines

The adaptation of the current approaches and effectiveness of cancer vaccines involves increasing immune system recognition of cancer. New developments have led to the development of approaches that can help eradicate prevailing difficulties, especially those of the tumor stroma and the attributes of cancer stem cells.

Cancer vaccines work on a very strategic basis on the premise of eliciting an immune response against tumor cells using tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs). These antigens are first transported to antigen-presenting cells (APCs), such as dendritic cells, via peptides, proteins, or whole tumor cells. After the APCs capture the antigens, they break them down into fragments and display them on their surface via the MHC [90]. This presentation is important for T-cell activation because T cells express their TCRs on their surface to identify MHC-antigen overload. Illustrated above are the interactions between T cells and APCCs for the effective activation of T cells; T cells need to recognize the MHC-antigen complex and receive costimulatory signals [91]. Once fully activated, CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs) are prepared to recognize and kill cancer cells harboring the same antigens [92]. Similarly, helper CD4<sup>+</sup> T cells efficiently induce a stronger antitumor immune response via the stimulation of cytokines that support the growth and differentiation of CTLs and assist B cells in producing antibodies against tumor antigens [92]. To improve this response, numerous cancer vaccines contain adjuvants—molecules that can increase the immunoresponse by



engaging additional APCs and by increasing costimulative signals. For example, certain vaccines organize Toll-like receptor (TLR) agonists to stimulate innate immune signaling and overproduction of proinflammatory cytokines, which reinforce adaptive immunity [93]. However, the immunosuppressive tumor microenvironment (TME) might obstruct cancer vaccines; this may include situations where regulatory T cells and myeloid-derived suppressor cells recapitulate T cells [94]. To overcome these challenges, scientists are considering the use of cancer vaccines together with immune checkpoint inhibitors, which are molecules that block negative signals on T cells (PD-1/PD-L1 or CTLA-4) [95]. Some of these new advancements in PM have also been spurred by the development of neoantigen vaccines that are designed and developed for a particular tumor type identified in a patient to provoke a strong immune response and subsequently high clinical effectiveness [96]. In aggregate, cancer vaccines are designed to produce enduring antitumor immunity that can manage or eradicate tumors over a period of time, which demonstrates a shift in the immunotherapy of cancer [97]. Figure 7 shows that cancer vaccines utilize antigens and adjuvants to activate the immune system, teaching it to identify and eliminate harmful cells.



**Figure 7.** Cancer vaccines utilize antigens and adjuvants to activate the immune system, teaching it to identify and eliminate harmful cells.

## 6. Biomarkers and patient selection

Circulating biomarkers are vital in oncology, mainly for the enrichment in patient selection and treatment strategies [98]. These are quantitative expressions of biological states or conditions, which may be present in blood or tissue and can provide useful information on cancer in an individual. Two of the prominent biomarkers identified are PD-L1 and MSI, the latter of which have become highly important predictors for guiding therapies for several cancers, such as stomach cancers [99].

Another typical biomarker is PD-L1 expression, and the value of such biomarkers relies on the use of such characteristics of the tumor to guide clinicians. PD-L1 is a protein that can be overexpressed on the surface of tumor cells, indicating how cancer cells may communicate with the immune system [100]. When PD-L1 proteins are overexpressed, immunostimulatory drugs, generally

known as checkpoint inhibitors, are used to enhance immunity against such tumors [101]. For example, the sensitivity of the antitumor immune response in stomach cancer patients with high PD-L1 expression may indicate better results from therapies such as pembrolizumab or nivolumab, which target the PD-1/PD-L1 pathway. This understanding enables oncologists to customize treatment regimens according to the chances of response to immunotherapy and hence enhances the quality of their results while reducing adverse effects from other unproductive therapies [102].

Second, the MSI status is another important prognostic biomarker for patient selection during treatment. MSI refers to the Mutator phenotype associated with defects in the DNA mismatch repair system, which is a state of genetic hypermutability [103]. Cancers that are classified as MSI-high for their high level of MSI are predicted to undergo better immunotherapy because of the high mutation loads, which create neoantigens capable of triggering immune activity. In stomach cancer, the MSI status can be used to inform treatment directions that prioritize immunotherapy as more effective than usual chemotherapy. For example, MSI-high tumors should be treated with pembrolizumab or other checkpoint inhibitors, but MSS tumors should be treated differently [104].

A biomarker test can be performed on different tumor samples through different techniques, including immunohistochemistry, next-generation sequencing, or polymerase chain reaction, among others. These tests can be used to identify targetable mutations or protein expression that can inform therapy [105]. For example, having a biomarker of HER2 amplification following surgery for stomach cancer may mean that this patient may require treatment, such as trastuzumab, which completely changes the treatment options for this patient [106]. In addition, biomarkers also help in choosing the right treatment but also in anticipating the patient's response and assessing the impact of the treatment. With the help of biomarkers that include PD-L1 and MSI status, clinicians have learned how well a particular patient is likely to respond to the treatments recommended [107]. This is a promising feature, as it provides the opportunity to modify the therapy via real-time evaluations of treatment efficacy. The development of biomarker research has also given rise to worldwide tumor-agnostic treatment—medical treatments for various cancer types on the basis of molecular markers regardless of their origin [108]. This change in thinking focuses on biomarkers over traditional dichotomies and offers new possibilities for patients with fewer choices previously. For example, drugs developed to act on certain mutations in BRAF or NTRK can be used in many forms of cancer if these mutations exist in the cancer's origin [109]. However, several issues related to the practical application of biomarker testing in clinical practice remain. Contamination and novel testing suggest that oncologists should be not only well informed of new biomarkers but also that tests are relevant to treatment protocols. Finally, further differences between primary tumors and metastases with respect to biomarkers exist, which can make therapy planning more challenging; for this reason, rebiopsies may sometimes be required for proper evaluation [110].

Table 2 presents various biomarkers relevant to stomach cancer, which are categorized into four main groups. Blood and protein biomarkers include classical tumor markers, circulating biomarkers, genetic and epigenetic biomarkers, and other novel biomarkers. Every row provides information about biomarkers, their usage in the clinic, and their impact on stomach cancer.



**Table 2.** Overview of biomarkers relevant to stomach cancer.

Biomarker Type	Biomarker	Clinical Application	Action on Stomach Cancer	Ref
Classical Tumor Markers	CEA	Diagnosis, monitoring, and predicting recurrence	Higher cancer levels suggest higher stages and possibility of liver metastasis	[111,112]
	CA19-9	Diagnosis and monitoring	Linked to other clinicopathological characteristics and employed for predicting relapse	[113,114]
	CA72-4	Follow-up after treatment	Good specificity for gastric cancer; used to identify relapses	[113,115]
	Alpha-fetoprotein (AFP)	Diagnosis and prognosis	Indicates aggressive disease and higher metastatic potential	[116,117]
Circulating Biomarkers	Circulating free miRNAs	Early diagnosis and prognosis	Several miRNAs observed in the study are potential players in clinical prognosis: total survival, lymph node metastasis	[118,119]
	Circulating tumor cells	Monitoring treatment response	Noninvasive method to assess tumor dynamics in real-time	[120]
	Exosomal lncRNAs	Diagnostic and prognostic indicators	Some lncRNAs could express greatly significant difference in cancer tissues compared with that in healthy individuals	[121,122]
Genetic and Epigenetic Markers	Microsatellite Instability (MSI)	Predictive for immunotherapy response	High mutational load correlates with better survival outcomes	[123,124]
	EBV status	Prognostic indicator	Connected with a particular type of gastric cancer that defines the therapy approaches	[125,126]
Emerging Biomarkers	Long noncoding RNAs (lncRNAs)	Early detection and prognosis	These lncRNAs have potential for use as stable diagnostic indicators of gastric cancer	[127]
	Circular RNAs (circRNAs)	Diagnostic potential	Some of the circRNA panels have been shown to distinguish gastric cancer tissues from normal ones	[128]

## 7. The impact of helicobacter pylori infection on gastric cancer immunotherapy

Findings suggest that *Helicobacter pylori* infection may be beneficial for gastric cancer immunotherapy, although findings have been mixed across studies. The relationship between *H. pylori* infection and immunotherapy is complex, with some studies having shown that this enhances the efficacy of drugs like PD-1/PD-L1 therapy by modifying the microenvironment of the tumor [129,130]. However,

other researchers have found that *H. pylori* infection can negatively impact the outcomes of immunotherapy, particularly in terms of survival rates [131,132].

The presence of *H. pylori* can cause chronic inflammation, which may influence immune responses in a way that would promote immunotherapeutic interventions in certain situations. Incorporation of further elaboration of *H. pylori* infection in scientific journals may be of utmost importance to explain its role in cancer treatment. The role of *H. pylori* in gut microbiota and different tumor molecular subtypes is equally crucial in assessing the effectiveness of immunotherapy [130,132]. Further research is needed to fully understand how *H. pylori* infection influences immunotherapy outcomes across cancer types. The study highlights the importance of testing for *H. pylori* infection in cancer patients undergoing immunotherapy to tailor treatment strategies effectively. Overall, the interaction between *H. pylori* and immunotherapy offers promising avenues for improving cancer treatment outcomes. More comprehensive analysis of *H. pylori*'s effects could lead to better personalized treatment approaches for gastric cancer patients.

## 8. Challenges in immunotherapy for gastric cancer

### 8.1. Variability in patient response to immunotherapies

We identified several limitations in immunotherapy for gastric cancer; however, one of the greatest concerns is the heterogeneity of patient responses. Such variability could be due to genetic factors, tumor-related factors, or the tumor microenvironment. For example, van der Laak et al. reported that the TMB can vary among individual patients and is generally predictive of the response to ICIs [133]. It has been assumed that high TMB is associated with better outcomes because the likelihood of neo-antigen generation is high; however, the relationship is not as direct. Research has revealed that the proportion of high ITH in tumor samples implies that even a high TMB can lead to a poor response because other factors, such as ITH and immune-suppressive cells, can exist in the TME [134].

Furthermore, molecules, including programmed death-1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), can regulate immune responses. These molecules can be upregulated or downregulated and can have quite different levels between patients and, sometimes, between different parts of the same tumor [135]. This variability also threatens the ability to predict which patients will benefit from ICIs. Moreover, the identification of definite molecular profiles that can be used accurately to predict responses to treatments remains a challenge [136]. Although many companies and scientists have been looking for such predictive biomarkers for years, none have been validated as ready-to-use means of choosing appropriate participants in immunotherapy; as a result, many patients receive immunotherapy that is suitable only partially or even not suitable at all [137].

### 8.2. Immune evasion and tumor heterogeneity

The second fundamental challenge involves aspects of immune escape strategies deployed by tumors. Tumor cells have developed mechanisms by which they can avoid being recognized and killed by the immune system. The gastric cancer TME not only progresses over time but also changes in tumor immunosuppressive properties and resistance to therapy [138].

Tumor heterogeneity exacerbates this scenario. Preclinical data highlight that gastric tumors are highly diverse within a tumor mass with genetic and immune cell subpopulations. This is why some

tumor regions may have more immune cells and vice versa, as well as why there may be different reactions to a particular treatment [139]. For example, while some subclones that arise from the same tumor mass may produce immune checkpoint ligands at high density, others may produce few to no immune ligands, leaving an immune presence in the tumor piecemeal. Furthermore, the process of clonal evolution can lead to outcome-determining clones with a genetically ingrained capacity for immune escape and therefore constitute a genuine threat to immunotherapeutic efficacy.

The interactions between ITH and TMB are also determinants of treatment outcomes. Although a high TMB implies that more likely neo-antigens are produced that could be targeted by an immune response, heterogeneous cancer subclones may be represented by clones dominating tumors that are poorly recognized by the immune system due to various mechanisms, including the loss of antigen-processing machinery or the downregulation of neoantigens. This complexity means that it is necessary to gain deeper insight into how these factors jointly and severally impinge on patients [140].

### 8.3. *Management of immune-related adverse events*

Another relevant factor in immunotherapy is immune-related adverse events or irAEs. As immunotherapies can inspire vigorous reactions against tumors, they can also react to normal tissues with broad-range dangerous outcomes ranging from mild manifestations to life-threatening conditions [141]. The common organ-specific irAEs are dermatological reactions, colitis, hepatitis, and endocrinopathies. These events may occur randomly and with varying severity in some patients, depending, inter alia, on genetic factors and the presence of other diseases. The management of irAEs is crucial to avoid hazardous conditions for the patient while offering the highest chance of benefit from treatment. The perceived consequences of immunotherapeutic agents commonly act as barriers to early recognition and intervention; however, increased knowledge concerning the side effects of such agents is vital. Furthermore, the ability to achieve a good cancer outcome while avoiding or at least limiting irAEs presents a unique challenge to oncologists. At per protocol doses, some severe adverse events may require dose modification or temporary withdrawal of the therapy, but this does not necessarily imply the abandonment of the protocol treatment [142].

## 9. **Conclusions**

Gastric cancer remains a formidable global health challenge, demanding innovative therapeutic strategies to improve patient outcomes. In this review, we explored the landscape of immunotherapeutic approaches, including immune checkpoint inhibitors, CAR-T cell therapy, and therapeutic vaccines, highlighting their mechanisms and potential. The complex interplay within the tumor microenvironment, involving immune cells, fibroblasts, and the extracellular matrix, significantly influences therapeutic responses and necessitates a deeper understanding. Emerging trends in gastric cancer epidemiology, such as the rise of cardia gastric cancer and shifts in risk factor profiles, underscore the need for targeted prevention and personalized treatment strategies. While immunotherapy offers promising avenues for combating gastric cancer, challenges such as therapeutic resistance and the need for tailored approaches persist. Continued research focused on elucidating the intricacies of the tumor microenvironment, refining immunotherapeutic techniques, and addressing emerging epidemiological trends is crucial for advancing the field, improving the lives of gastric cancer patients.

## Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Author contributions

Mujibullah Sheikh: Conceptualization, literature search, methodology, data collection, data analysis, writing-original draft, writing-review & editing, supervision. Pranita S. Jirvankar: Data collection, data analysis, writing-original draft, writing-review & editing.

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