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The Therapeutic Ability of Cluster of Differentiation Cd279 and Cd274 with B7 Homolog 1 Antibodies for Most Cancers Prevention: An Innovative Approaches in Immunotherapy

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Abstract
Therapy aimed at CD279 or programmed cell death protein 1, along with its ligand B7 homolog 1 or PD-L1 has taken oncology to a significantly higher level and has introduced many promising avenues for enhanced responses of the immune system against tumors. This work studies the possibility of antibodies in preventive and therapeutic approaches against these molecules for different cancers. The cells involved in cancer evade this response by causing T-cell exhaustion through the CD279/B7 homolog 1 pathway. Monoclonal antibodies such as atezolizumab, durvalumab, and nivolumab disrupt this interaction, reactivating T cells and enabling the immune system to recognize and eliminate cancer cells effectively. Although clinical studies have established efficacy in managing cancers like renal cell carcinoma and non-small cell lung cancer, among others, challenges in the development of these molecules include toxicity, resistance, and patient-to-patient variability in their response. Apart from this, other biomarkers that have been studied for predicting therapeutic outcomes are tumor mutation burden and PD-L1 expression, which have demonstrated inconsistent clinical utility. Integration of CD279/B7 homolog 1 inhibitors with other treatments, such as chemotherapy and radiotherapy, along with molecular agents, has shown that this enhances efficacy. Still, mechanisms of resistance include alteration in the tumor microenvironment and dysregulation of the immune system, among others. Despite these challenges, the development of immunotherapy has provided new opportunities for the fine-tuning of therapeutic strategies, the expansion of application scope, and possibly the prevention of cancer in at-risk populations. The optimization of these treatments and ensuring greater clinical benefit will require further research into biological mechanisms, predictive biomarkers, and therapeutic combinations.
Key words: Automated death ligand 1 (B7 homolog 1), Automated cell death protein 1 (CD279 (Cluster of differentiation 279), Cancer prevention, Immune system, T cell proliferation.

Introduction

The global burden of cancer continues to be a massive health challenge that requires perpetual innovation to further improve the outcome for all affected. Traditionally, chemotherapy and radiation therapy have been the main treatments for cancer for many years. Although these can be successful, they often do have very harmful side effects and are not universally curative in the case of all cancer types or at all stages[1, 2]. This calls for other ways, which can really help with the fight against cancer and even reduce the pain associated with it. One of the promising methods for overcoming these issues has become using the immune system against the disease[3, 4]. Immunotherapy employs natural body defenses to recognize and destroy malignant cells without causing damage to the healthy tissues.

The targeted therapy provides many benefits over the conventional treatments as they reduce systemic toxicity and make the patients safer. The immune checkpoint inhibitors primarily programmed cell death protein 1 (CD279), along with its ligand B7 homolog 1, have transformed oncology into a landmark in terms of the advancement in cancer treatment[5, 6].

Immune checkpoints ensure proper self-tolerance by balancing immune responses, therefore acting to prevent autoimmunity. Cancer cells exploit these pathways to avoid immune surveillance, which contributes to the growth and development of the tumor. Inhibition of the CD279/B7 homolog 1 pathway by checkpoint inhibitors can reactivate exhausted T cells to fight against the tumor once more with full strength[7, 8]. Although these inhibitors are promising enough to alter the course of the disease, the clinical drug effectiveness varies widely between patients and cancer types. Variability in outcomes is caused by factors such as tumor microenvironment, immune system heterogeneity, and mechanisms of resistance[9].

For example, pancreatic and gastric cancers suppress the function of T-cell priming and activation through immunosuppressive microenvironments[10]. Again, hypoxic conditions in a tumor also compromise the immune responses and, therefore, need a change in the tumor microenvironment and potentiation of immunity. Combining therapies, like the concomitant administration of immune checkpoint inhibitors with chemotherapy, radiotherapy, or targeted therapy have been developed to overcome such limitations[11, 12]. These strategies aim at putting together the effects of a single treatment and, therefore, amplifying the therapeutic efficacy and power of immunotherapy. However, there are still several challenges. Immune checkpoint inhibitors face primary or acquired resistance as one of the major challenges. Primary resistance is when the tumors are inherently non-responsive to immunotherapy, and acquired resistance develops after initial treatment success[13, 14].

Deeper insights into molecular and genetic mechanisms underpinning resistance and identification of predictive biomarkers will be used to individualize treatment decisions. There are many biomarkers that have been studied in detail for potential use in predicting therapeutic responses: tumor mutation burden and expression of B7 homolog 1, among others, which have not yet shown clinical utility[15, 16]. Furthermore, the immune system and tumor microenvironment are very active areas of study. Tregs, MDSCs, and other factors of immunosuppression within the tumor environment create problems for treatment. Advances like SNA liposomal nanoparticle conjugates and novel delivery systems could be promising approaches to increase the penetration and efficacy of immune checkpoint inhibitors[17, 18].

Revealing the pathway for CD279 (Cluster of differentiation 279)/B7 homolog 1: Comprehending t cell regulation and cancer immune evasion

A vital aspect of the immune system is that it governs T-cell function and secures peripheral T-lymphocyte tolerance. Nevertheless, through the creation of B7 homolog 1, which binds to CD279 on T cells, leading to T cell exhaustion and diminished immune response, malignant cells can take advantage of this route. Similarly, it has been revealed that non-coding RNAs (ncRNAs) control cancer[10], offering new insights into potential curative strategies. As a result, this pathway is critical for T cell activity and is often utilized by cancer cells to elude the immune system. By delaying T-cell depletion, obstructing this pathway with proteins such as immune-mediated checkpoint proteins may improve the immune response.

Blockers of CD279 (Cluster of differentiation 279) and B7 homolog 1 in Cancer Immunotherapy

Tumors utilize essential aspects of the immune system, including programmed cell death protein 1 and its ligand, B7 homolog 1, to thwart the immune system. Reactivation of T cells to combat cancer is an intriguing method for inhibitors targeting CD279/B7 homolog 1 to protect against cancer[11]. It is recommended that patients receive this vaccine as either monotherapy or combination therapy because it has shown efficacy against a variety of malignancies, such as renal cell carcinoma, non-small cell lung cancer, and breast cancer. These inhibitors are infrequently used in hospitals as monotherapy for breast cancer; rather, integrated strategies are required to optimize their safety and efficacy[12,13]. Furthermore, problems and therapeutic potential arise from interactions in the tumor microenvironment (TME), which comprises regulatory T cells (Tregs) and T helper 17 (Th17) cells. Blocking this signaling using new techniques, such as spherical nucleic acid (SNA) liposomal nanoparticle conjugates, has been proven to mitigate cancer progression and enhance survival in preclinical models[14,15]. In conclusion, accomplishments in the battle against cancer and research into overcoming resistance and improving care are still progressing. The complexity of the TMJ and the necessity for an integrated treatment approach rely on the merits of this field. To fully utilize these inhibitors in the treatment of cancer, exploration of their mechanisms of action and the development of novel therapeutic modalities are required[16,17].

Mechanism by which antibodies prevent CD279 and B7 homolog 1 from functioning

The biological process by which antibodies hinder these functions is impeding the interactions between the CD279 receptor and its ligand, PD-ligand 1 (B7 homolog 1), which is often overexpressed on the surface of cancer cells. Typically, this interaction causes T-cell fatigue or anemia, which effectively prevents the immune system from fighting the tumor. blocking antibodies reactivate T-cells by impeding this interaction, which amplifies the immune response towards tumors[18]. Remarkably, because of the complicated functional pathways and cross-connectivity within the immune checkpoint system, despite being considered part of the same immunotherapy subclass, may display distinct properties and procedures. The CD279: B7 homolog 1/PD-L2 and B7 homolog 1/CD28/CTLA-4: B7-1 axes overlap and regulate each other's epitopes, interfaces, and signaling pathways, indicating that the specific agents in these categories could differ by virtue of their pharmacokinetics, pharmacodynamics, and mechanisms of action[19].

In summary, antibodies mitigate immunosuppressive signals that cancer cells employ to avoid recognition by the immune system. By blocking these interactions, these antibodies enable the immune system to identify and target tumor cells once again. To completely comprehend the clinical efficacy and safety profiles of CD279 (Cluster of differentiation 279) and B7 homolog 1 inhibitors, further head-to-head comparative studies are necessary to determine the specific mechanisms of action and potential differences between them[20,21].

CD279 /B7 homolog 1 inhibitors' effectiveness against various cancer types

More than 20 types of cancer have displayed exceptional clinical efficacy, constituting an enormous advancement in the fight against cancer. These types of inhibitors provide long-lasting curative benefits and significant benefits by prompting the immune system to identify and eradicate carcinomas[22]. However, not all patients recover consistently from these treatments; only a small minority of patients show noticeable improvements in progression-free survival and overall survival. It is important to consider that while CD279/B7 homolog 1 inhibitors are considered to be the gold standard for monotherapy or combination therapy in advanced cancer, their effectiveness differs depending on the type of cancer[23], and drug resistance continues to be an obstacle. For instance, metastatic prostate cancer has been modestly treated with these inhibitors, highlighting the importance of a combination of therapies for better outcomes[24]. In contrast, obstruction has been found to be a successful strategy for malignant breast tumors with high immunogenicity, such as triple-negative and HER-2 negative breast cancer. This medicine has recently been authorized by the FDA and is now an accepted therapy for solid tumors[25]. Inhibitors are a staple in modern cancer immunotherapy, illustrating their potency across a range of cancer subgroups. However, not all malignancies respond in precisely the same way to these inhibitors; thus, to maximize their therapeutic potential while offering benefits to a broader patient population, fundamental level predictive biomarkers and combination medication are needed[26,27].

A prolonged response is one of the benefits of CD279 (cluster of differentiation 279)/B7 homolog 1 inhibitors

Immune-regulating drugs that target the CD279/B7 homolog 1 axis can cause persistent side effects in some cancer patients. By reactivating T cell-mediated cancer prevention immune defenses, these inhibitors improve survival rates and lengthen tumor regression for cancers. The FDA's swift authorization of medications, such as pembrolizumab and nivolumab, for an array of tumors, including melanoma and non-small cell lung cancer, because of their impressive antitumor responses, is proof of the clinical efficacy of these inhibitors[28]. Despite these responses being constant, it is essential to remember that they are not always the case. Blockade is not beneficial for a substantial number of patients, and resistance, both primary and acquired, continues to be troublesome[29]. While therapies carry a higher risk of immune-related side effects, combination procedures, such as CD279 plus CTLA-4 obstructions, are showing interest in augmenting response rates, especially in those with an immune system that is less likely to respond to single-agent hindering. In conclusion, the clinical excellence of these inhibitors is that they offer the added advantage of relentless response in a particular subset of cancer patients[30].

To optimize the use of these medications while extending their positive effects to a broader patient population, additional research is required because of the differences in response and the presence of resistance mechanisms[31]. To boost both the efficacy and predictability of congestion, several techniques are being investigated, notably, combination therapies and the acquisition of predictive biomarkers, which can have lasting effects in a significant number of cancers patients[32]. By suppressing a link between these medications effectively lift the "brakes" on the immune system and empower it to target cancer cells with greater force[33]. In cancers such as non-small cell lung cancer (NSCLC), where they have been licensed for second-line treatment and have exhibited essential potency and long-lasting effects in select patient subgroups, clinical effectiveness is particularly noteworthy[34]. However, the

development of primary or acquired resistance and the lack of consistent biomarkers to predict response may restrict the beneficial effects of these inhibitors, which have shown promise in treating a variety of cancers[35].

Table 1: Clinical Applications of CD279 and B7 Homolog 1 Inhibitors.

Cancer Type	CD279 Inhibitor	B7 Homolog 1 Inhibitor	References
Non-small cell lung cancer (NSCLC)	Pembrolizumab, Nivolumab	Atezolizumab, Durvalumab	[97, 98]
Melanoma	Pembrolizumab, Nivolumab	-	[99, 100]
Renal cell carcinoma (RCC)	Nivolumab	Atezolizumab	[101, 102]
Triple-negative breast cancer (TNBC)	-	Atezolizumab	[103, 104]
Head and neck cancer	Nivolumab	Avelumab	[105, 106]
Hepatocellular carcinoma (HCC)	Pembrolizumab, Nivolumab	Atezolizumab, Durvalumab	[107, 108]

Their use in treating brain metastases is complicated by the unusual immune environment of the brain and the paucity of clinical data resulting from the exclusion of patients with active brain metastases from most clinical trials[36]. Let's sum up by saying that the inhibitors provide the benefit of long-lasting effects in the treatment of cancer, which is a huge advancement in the handling of some cancers, including NSCLC. After prior treatments fail, patients now have new hope because of these inhibitors, despite obstacles such as resistance and the requirement for predictive biomarkers[37]. To maximize the use of these inhibitors and extend their advantages to a larger patient group, it is imperative that combination therapy and biomarker research be continued[38,39].

Assessing Reaction with CD279 (Cluster of differentiation 279)/B7 homolog 1 Inhibitors

Given that CD279/B7 homolog 1 inhibitors have demonstrated efficacy in treating various malignancies, including non-small cell lung cancer (NSCLC), a significant area of research is the evaluation of the response of individuals to these inhibitors[40]. To maximize treatment outcomes, treatment response rates vary and establishing accurate biomarkers is vital. Although tumor mutational demand and B7 homolog 1 expression are two of the most effective prognostic biomarkers, further biomarkers are currently being studied because their predictive value has not yet been confirmed. Although B7 homolog 1 expression has already been thoroughly studied, research has presented varying outcomes that address its association with therapy outcomes[41]. Further refinement is needed to assess the significance of B7 homolog 1 in choosing recipients for combined treatments such as chemotherapy and immunotherapy, regardless of whether this combination has been established as a notable advancement. Further biomarkers evaluated for their forecasting ability included immune-related adverse events, neutrophil-to-lymphocyte ratio, and microbiota[42]. Although tumor mutational take and B7 homolog 1 expression constitute essential biomarkers for predicting the response to CD279/B7 homolog 1 inhibitors, their capacity for forecasting is limited, and research on additional biomarkers is still in progress[43]. Optimizing patient selection for immune checkpoint inhibitor-based counseling requires the establishment of new biomarkers and the enhancement of existing biomarkers. Utilizing several biomarkers can enhance the reliability of therapeutic outcome prediction and, in turn, maximize the success of cancer immunotherapy[44,45].

Response-related biomarkers, include B7 homolog 1 expression and tumor mutational burden. Two identified markers associated with the response to immune checkpoint inhibitor (ICI) therapy were tumor mutational burden (TMB) and B7 homolog 1 expression. The receptivity of various types of cancer to immune checkpoint blockers (ICIs) has been predicted through B7 homolog 1 expression[46]; nevertheless, this predictive value is not absolute and may fluctuate based on the cancer subtype and other variables. In contrast, TMB has been found to be associated with an increased likelihood of response to immune checkpoint antagonists (ICIs), particularly for malignant tumors with high mutation rates, such as melanoma and non-small cell lung cancer (NSCLC), reflecting a greater probability of neoantigen creation[47]. Interestingly, there was an elaborate connection between TMB and the expression of B7 homolog 1. Contrary to previous studies, these biomarkers could direct the use of ICIs on their own because they do not significantly correlate with a wide range of cancer subtypes.

For instance, pembrolizumab was successful in treating a case of jejunal adenocarcinoma with low B7 homolog 1 expression but high TMB and microsatellite instability (MSI)[48]. This underlines the importance of considering genetic markers, in addition to B7 homolog 1 expression, such as TMB and MSI. In addition, it has been found that the capacity to forecast TMB varies depending on the age

group of lung cancer patients, with female patients demonstrating a stronger predictive performance. In the final analysis, TMB and B7 homolog 1 expression were significant biomarkers for predicting response to immune-mediated checkpoint blocker therapy; however, not all cancer types or patient demographics reacted similarly to both biomarkers[49]. They may function alone or in conjunction with additional indicators to help steer treatment decisions. Further research is required to enhance the utilization of these indicators in medical settings while understanding the deeper causes of their predictive abilities[50].

The limitations of existing biomarkers and the necessity for more research

Recently, accessible biomarkers related to the CD279 (Cluster of differentiation 279)/B7 homolog 1 axis have shown potential in diagnosing an extensive spectrum of malignancies and in anticipating the therapeutic efficacy of immunotherapies. However, these are specific constraints that make further investigation necessary[51]. Additional complicated biomarkers need to be developed, as exemplified by the finding that, whereas high CD279+ lymphocyte density has been associated with worse clinical failure-free survival in prostate cancer, this finding was not highly significant across all patient classes. Conversely, squamous cell carcinoma and lung adenocarcinoma exhibit distinct predictive performance for B7 homolog 1, showing that the function of the pathway might vary according to the context and requires additional research[52]. When the broader application of these biomarkers is brought into consideration, there are inconsistencies and intriguing details of the surface. Another investigation that threw suspicion on the assumption that primary tumor biopsies are reflective of the disease position was the detection of B7 homolog 1 in circulating tumor cells, which was not consistent with the immunohistochemical findings in the initially diagnosed tumors of patients with clear cell renal cell carcinoma[53].

Distinct manifestation patterns have been observed in immune cell subsets in comparison with controls, raising concerns regarding the function of this protein in illnesses such as multiple sclerosis[54]. In summary, the limits to the currently available biomarkers are clear, despite the fact that they are a crucial component of the immune response to cancer and have been successfully targeted with immunotherapies[55]. These involve discrepancies in the predictive value between cancer types, contradictions between circulating and primary tumor biomarkers, and unclear functions in non-cancerous ailments. For the purpose of further developing these biomarkers, understanding how they operate under a variety of conditions, and to develop more accurate forecasting and prognostic tools, further study is vita[56,57].

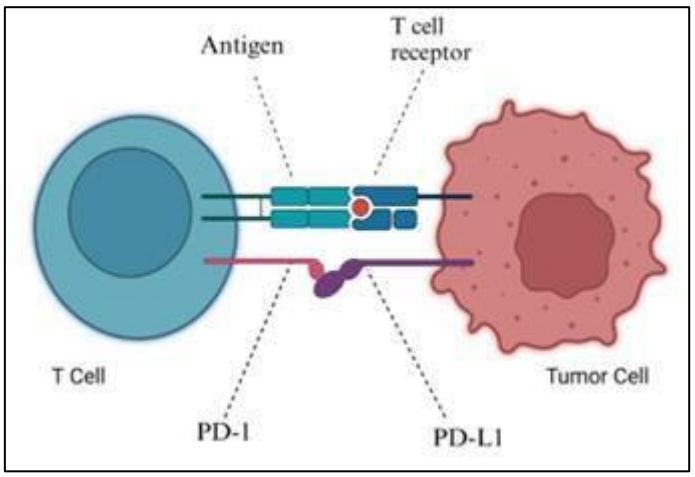

Figure 1. The interaction between PD-1 and PD-L1 plays a significant role in determining T lymphocyte survival. PD-1, a protein found on the surface of T lymphocytes, prevents apoptosis or programmed cell death by binding to its ligand PD-L1. This process helps maintain immunological homeostasis by limiting T cell depletion. Checkpoint inhibitors, which block the PD-1/PD-L1 connection, are used in cancer treatment to improve anti-tumor immunity and restore T-cell function, offering promising prospects for combating malignant cells by enhancing the immune system response.

Combination Treatments Using CD279 (Cluster of differentiation 279)/B7 homolog 1 Inhibitors

The combination of inhibitors is increasingly recognized as a means to enhance the therapeutic efficacy of cancer medications. When combined with other types of medicines, these inhibitors, which serve as immune checkpoint inhibitors (ICIs), show promise for improving patient outcomes[58]. The rationale behind combination therapy is to focus on multiple pathways in the immune system or cancer, potentially overcoming the limitations of monotherapy and addressing drug resistance. Although they

have been successful in treating many cancers, their effectiveness can be significantly increased by combining them with other treatments[59]. For example, in metastatic colorectal cancer (CRC), patients with disease-specific features, such as high microsatellite instability (MSI-H) or poor treatment response (dMMR), show increased sensitivity to inhibitors, suggesting that the focus in the combination could be better. to be[60]. practical. Similarly, in bladder cancer, combining DNA damage inhibitors with CD279 /B7 homolog 1 inhibitors may improve outcomes, especially in patients with mutations that result in greater or lesser changes in DNA repair genes. In addition, new combination strategies, such as the use of histone deacetylase 2 inhibitors and ICIs in hepatocellular carcinoma (HCC), are potentially effective[61]. In conclusion, a combination of inhibitors represents a promising strategy for improving the effectiveness of cancer treatment. The success of these combinations depends on many factors, including the type of cancer, the patient's genetic makeup, and the specific medications used[62]. Clinical studies and ongoing research are important to identify the most effective combinations and develop appropriate biomarkers for patient selection. The future of combination therapies based on inhibitors appears promising, with the potential to provide more personalized and effective treatments for patients with cancer[63].

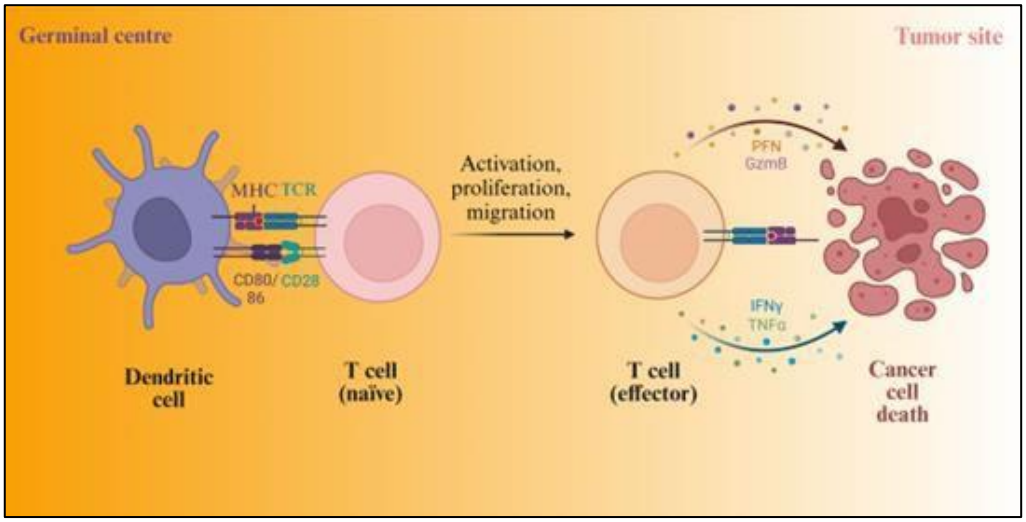

Figure 2. T cells play a crucial role in the eradication of tumor cells by employing various methods, such as producing interferon alpha and activating dendritic cells. These actions enhance the immune system's overall ability to combat tumors by eliciting immune responses against cancer cells and promoting their demise.

The rationale for integrating CD279 (Cluster of differentiation 279)/B7 homolog 1 inhibitors with different treatments

The rationale for combining CD279 (Cluster of differentiation 279)D-L1 inhibitors with other treatments is multifactorial. which have revolutionized anticancer drugs; however, their benefits are limited to a small number of patients, and drug resistance is common[64]. Combining these drugs with other treatments, such as oncolytic drugs, anti-tumor drugs, molecular drugs, chemotherapy, and radiation therapy, may improve outcomes through joint interventions[65]. Additionally, PARP inhibitors have been shown to stimulate the expression of the B7 homolog 1 and induce tumorigenesis, which may increase their effectiveness[66]. Many challenges remain, such as hyper progressive disease (HPD), which can completely reduce overall survival, highlighting the need for further research to develop these connections. Combination strategies are not universally effective; therefore, there is a need to identify appropriate biomarkers to predict responses to these treatments[67]. In summary, other treatments rely on the potential for synergism and may overcome the limitations of monotherapy, such as low response and drug resistance[68]. However, the development of combination therapies must be carefully evaluated in clinical trials to confirm their effectiveness and safety and to identify target pain groups that will be frequently rewarded[69]. There is significant clinical interest in this area, as evidenced by several clinical studies investigating these strategies. A comprehensive report showed that 81% of clinical trials in solid tumors, including NSCLC, SCLC, mesothelioma, and thymic epithelial tumors, were evaluated as combination therapies[70]. These models reflect the medical community's knowledge of the benefits of combining PD-(L)1 blockade with other treatments, such as chemotherapy or immunotherapy, to increase efficiency and overcome the defense mechanism[71]. Interestingly, although some anti-PD-(L)1 agents have been approved by the FDA for certain indications, some studies continue to assign patients to treatments that are not suitable for optimal treatment, demonstrating

ethical issues and inefficiencies in clinical trials. Additionally, other treatments are not limited to intrathoracic tumors[72]. For example, hepatocellular carcinoma has been combined with other therapies, indicating its widespread use in different types of cancer. Together, these combination trials are an important part of oncology immunotherapy research and aim to improve patient outcomes by addressing the limitations of monotherapy and PD-(L)1 blockade[73].

Challenges and prospects for CD279 and pdl-1

inhibitors have been shown to be effective for the treatment of many malignancies. Despite this success, challenges such as major and minor resistance to these drugs remain, and new strategies must be developed to improve their outcomes[74]. Additionally, poor immune status is an important issue that must be addressed to improve patient outcomes. Interestingly, although these are effective against some cancers, their efficacy is limited to other cancers such as breast cancer[75]. This suggests the need for further research into the combination of tumor immunogenicity and tumor microenvironment interactions. Additionally, B7 homolog 1 expression in tumor cells has emerged as a potential biomarker to predict the response to treatment, providing a noninvasive approach for monitoring treatment pain[76]. In summary, this research includes overcoming resistance mechanisms through combination therapies and identifying biomarkers for response prediction. Efforts to reduce the incidence of immune-mediated diseases and to treat patients are also important. Ongoing research and clinical trials are necessary to explore their potential for cancer treatment[77].

Table 2: Challenges in CD279/B7 Homolog 1 Therapy.

Challenge	Description	References
Resistance Development	Primary or acquired resistance reduces therapeutic efficacy.	[106]
Biomarker Validation	Lack of reliable biomarkers for predicting patient response.	[107]
Immune-Related Adverse Events (irAEs)	Severe side effects such as autoimmune reactions limit widespread application.	[108]
High Treatment Costs	Financial burden restricts accessibility and affordability for patients.	[109]
Tumor Microenvironment (TME)	Suppressive microenvironments diminish immune system activation.	[110]

Overcoming CD279 (Cluster of differentiation 279)/B7 homolog 1 Inhibitor Resistance

The effectiveness of CD279/B7 homolog 1 inhibitors in cancer treatment is well documented; however, resistance to these treatments remains a problem. Resistance mechanisms are multifactorial, include primary or acquired resistance, and may be influenced by factors such as the gut microbiota or the tumor microenvironment[78]. Strategies to address drug resistance include the development of new drugs, combination therapies, and the use of smart drug delivery systems (SDDS). Interestingly, although the target is usually the pathway, resistance can also arise due to changes in other immune cells or pathways. Additionally, the gut microbiota appears to modulate the ICI response, and traditional Chinese medicine may play a role in this response. In addition, the design was reviewed to improve its efficacy[79]. Overcoming resistance is a complex problem requiring multiple approaches. Current research suggests that a combination of new drugs, clinical treatments, and an understanding of the tumor microenvironment and gut microbiota may provide ways to improve the response to this disease. The development of SDDS and identification of appropriate biomarkers will be important to improve the effectiveness of CD279 (Cluster of differentiation 279)/B7 homolog 1 inhibitors and related drugs[80].

Table 3. Provide a detailed overview of the utilization of cluster of differentiation 279 (cd279) inhibitors in various cancer types in the field of targeted immunotherapy in oncology.

Cancer Type	PD-1 Inhibitor	References
Melanoma	Pembrolizumab, Nivolumab	[97]
Non-small cell lung cancer (NSCLC)	Pembrolizumab, Nivolumab	[98]
Renal cell carcinoma (RCC)	Nivolumab	[99]

Cancer Type	PD-1 Inhibitor	References
Bladder cancer	Atezolizumab, Pembrolizumab	[100]
Head and neck squamous cell carcinoma (HNSCC)	Nivolumab	[101]
Hodgkin lymphoma	Nivolumab	[102]
Urothelial carcinoma	Pembrolizumab	[103]
Merkel cell carcinoma	Avelumab	[104]
Liver cancer	Pembrolizumab, Nivolumab	[105]

Expanding the utility of CD279/B7 homolog 1 inhibitors for cancer prevention

CD279/B7 homolog 1 inhibitors have been widely used in cancer therapy for the treatment of various malignancies, particularly non-small cell lung cancer (NSCLC), gastrointestinal (GI) cancer, and hepatocellular carcinoma. (HCC), and endometrial cancer (EC). These inhibitors block the CD279/B7 homolog 1 pathway, which tumor cells often use to fight disease, thus enhancing T cell- mediated antitumor protection[81]. However, there are issues in its clinical use, such as the emergence of primary or acquired resistance, poor immune response, and lack of biomarkers to predict performance. Additionally, the high costs associated with these treatments have a significant impact on the medical budget, necessitating the development of cost-effective strategies. The publication does not directly address the potential of CD279/B7 homolog 1 inhibitors in preventing cancer, but their role in treatment suggests that they may be useful if standards for early intervention can be determined, and the problems mentioned can prevent cancer formation[82]. application. In summary, although the cluster of differentiation 279/B7 homolog 1 inhibitors have revolutionized cancer treatment and show promise in improving patient outcomes, their widespread use in cancer prevention requires further investigation. This will include understanding early interactions in the tumor microenvironment, identifying high-risk populations that may benefit from such interventions, and addressing issues regarding vaccines, adverse events, and costs. Available data indicate the need for a deeper understanding of biomarkers of response and molecular mechanisms of resistance to inhibitors, which will be important to support their use in treatment and prevention[83].

Table 4. Reviewing the Use of ligand B7 homolog 1 Inhibitor Therapy for Different Cancer Types.

Cancer Type	PD-L1 Inhibitor	References
Non-small cell lung cancer (NSCLC)	Atezolizumab, Pembrolizumab, Durvalumab	[98]
Bladder cancer	Atezolizumab, Durvalumab	[106]
Triple-negative breast cancer (TNBC)	Atezolizumab	[107]
Head and neck squamous cell carcinoma (HNSCC)	Avelumab	[101]
Urothelial carcinoma	Atezolizumab, Durvalumab	[108]

Cancer Type	PD-L1 Inhibitor	References
Renal cell carcinoma (RCC)	Atezolizumab	[109]
Merkel cell carcinoma	Avelumab	[104]
Cervical cancer	Avelumab, Pembrolizumab	[110]
Gastric cancer	Avelumab, Pembrolizumab	[111]

Discussion

Programmed cell death protein 1 (CD279) and its ligand B7 homolog 1 are key components of the immune system that cancer cells use to evade the immune system. CD279/B7 homolog 1 inhibitors are monoclonal antibodies that block this effect, thereby increasing the ability of the immune system to attack tumor cell[84,85]s. This vaccine has been shown to be effective both as monotherapy and in combination with other treatments in the treatment of a variety of cancers, including non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), melanoma, and breast cancer. . Get official approval. Despite progress, challenges remain, such as lack of awareness or access to disease prevention and control[86]. To address these issues, experimental combinations and new therapeutic strategies, such as spherical nucleic acid (SNA) liposomal nanoparticle conjugates, are being explored to improve clinical outcomes and control immune system inhibition[87,88]. In addition, B7 homolog 1 expression is associated with the outcome of HCC, and other immune factors, such as lymphocyte activation gene 3 (LAG3), have also been reported to be associated with CD279/B7 homolog 1 activity and may affect small-cell tumors[89]. (SCLC) Survival outcomes (small cell lung cancer) As a result, CD279/B7 homolog 1 inhibitors have become the mainstay of cancer prevention because they can reactivate the immune system against tumors. Continuing research aims to improve the efficacy and overcome resistance, including combination therapy and new drugs targeting the tumor microenvironment[90].

Potential for further optimizing these therapies to improve cancer outcomes

The ability to improve cancer treatment outcomes is a multifaceted endeavor, as evidenced by the many strategies discussed in the literature review[91]. Treatment plans have advanced by focusing on the molecular and genetic basis of cancer, providing personalized treatments, and combining these with existing conventional treatments to improve performance[92,93]. However, the problems of resistance mechanisms and tumor heterogeneity require continued development of new-generation drugs and combination therapy. Interestingly, repurposing approved non-oncological drugs represents a cost-effective strategy with the potential to prevent cancer[94]. This approach can accelerate treatment, particularly in limited areas. Nanotechnology, especially NE-PDT, can target cancer cells and show synergy with other treatments; however, its clinical translation needs to be improved. Antibiotic resistance is a concern, and strategies to reduce these effects are important for improving patient outcomes. Nursing plays an important role in patient compliance with oral cancer treatment and is critical for the success of these treatments.

Bioengineering techniques and future directions in treatment planning to improve drug delivery and specificity involve the use of a combined process to improve the plan and treatment outcomes. Chronopharmacology provides new insights by integrating therapeutics with circadian rhythms to reduce side effects and increase their effectiveness[95]. With the development of precision medicine, the psychology of cancer treatment must be carefully considered to ensure effective patient care. Finally, as BAQ SNN shows, new applications of nanotechnology in drug development are opening new avenues in cancer therapy by improving drug delivery and targeting autophagy. In summary, cancer treatment can be improved by combining advanced treatments, repurposing existing drugs, using nanotechnology, reducing side effects, and enabling patients to pursue health and wellness. Research and clinical trials must continue to address issues of resistance, heterogeneity, and immunosuppression and understand the benefits of these new strategies to improve outcomes for cancer patients[96].

Conclusion

The therapeutic targeting of CD279 and B7 homolog 1 is revolutionizing oncology, addressing some critical challenges in treatment and prevention. By disturbing the pathways involved in tumor immune evasion, it restores T-cell function and restores antitumor immunity, their therapeutic efficacy in curing

melanomas, non-small cell lung carcinoma, and renal cell carcinoma underlines potential transformation in cancer treatment. However, clinical application challenges, including variability in patient responses and development of resistance, as well as toxicity issues, plague these therapies. Overcoming these issues, research will focus more on optimizing the administration of combination therapies and integrating predictive biomarkers to personalize treatment. The study of new delivery systems, especially nanotechnology, also is expected to improve precision therapy and reduce adverse effects. Beyond therapy, prevention may be the future of these inhibitors in high-risk populations: one promising frontier in cancer control. Future studies shall be needed to elucidate the molecular intricacies that are involved in resistance mechanisms, refine biomarker validations, and assess cost effectiveness for widespread adoption. Advances in immunotherapy represent a step change in oncology, thereby providing hope for improved survival with better quality of life from cancer for patients worldwide. The innovation will be continuous, so it is bound to redefine the landscape of cancer care. It is likely to bring in a gap between treatment and prevention and pave the way for a new era in precision oncology.

Authors Contribution

All authors are contributing their efforts to compile the manuscript including text editing, table and figure creating and involved in the final preparation and given approval of manuscript for publication.

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Conflict of interest statement

Authors declare they do not have any conflict of interest.

Ethical Approval

Not Applicable

References

1. Mokhtari RB, Sambi M, Qorri B, Baluch N, Ashayeri N, Kumar S, Cheng HL, Yeger H, Das B, Szewczuk MR. The next generation of combination cancer immunotherapy: Epigenetic immunomodulators transmogrify immune training to enhance immunotherapy. Cancers. 2021 Jul 18;13(14):3596.
2. Subhash VV, Yeo MS, Tan WL, Yong WP. Strategies and advancements in harnessing the immune system for gastric cancer immunotherapy. Journal of immunology research. 2015 Oct 22;2015.
3. Li Y, Liu X, Zhang X, Pan W, Li N, Tang B. Immune Cycle-Based Strategies for Cancer Immunotherapy. Advanced Functional Materials. 2021 Dec;31(50):2107540.
4. Panda AK, Bose S, Sarkar T, Roy D, Chakraborty D, Chakraborty S, Sarkar I, Sa G. Cancer-immune therapy: restoration of immune response in cancer by immune cell modulation. The Nucleus. 2017 Aug;60:93-109.
5. DePillis LG, Eladdadi A, Radunskaya AE. Modeling cancer-immune responses to therapy. Journal of pharmacokinetics and pharmacodynamics. 2014 Oct;41:461-78.
6. Kumar AR, Devan AR, Nair B, Vinod BS, Nath LR. Harnessing the immune system against cancer: current immunotherapy approaches and therapeutic targets. Molecular biology reports. 2021 Dec 1:1-21.
7. Kim SI, Cassella CR, Byrne KT. Tumor burden and immunotherapy: impact on immune infiltration and therapeutic outcomes. Frontiers in immunology. 2021 Feb 1;11:629722.
8. Kitahara S, Suzuki Y, Ezaki T. How immunotherapy and targeted therapy are changing gastrointestinal cancer treatment. Medical Research Archives. 2018 Nov 15;6(11).
9. Kim SI, Cassella CR, Byrne KT. Tumor burden and immunotherapy: impact on immune infiltration and therapeutic outcomes. Frontiers in immunology. 2021 Feb 1;11:629722.
10. Schütz F, Stefanovic S, Mayer L, von Au A, Domschke C, Sohn C. PD-1/PD-L1 pathway in breast cancer. Oncology research and treatment. 2017 May 27;40(5):294-7.
11. Klyuchagina Y, Sokolova Z, Baryshnikova M. Role of PD-1 receptor and its ligands PDL1 and PD-L2 in cancer immunotherapy. Oncopediatry. 2017;4(1):49-55.
12. Zatloukalová P, Pjechová M, Babčanová S, Hupp TR, Vojtěšek B. The role of PD-1/PD-L1 signaling pathway in antitumor immune response. Klinicka Onkologie: Casopis Ceske a Slovenske Onkologicke Spolecnosti. 2016 Jan 1;29(Suppl 4):72-7.
13. Andrieu GP, Shafran JS, Smith CL, Belkina AC, Casey AN, Jafari N, Denis GV. BET protein targeting suppresses the PD-1/PD-L1 pathway in triple-negative breast cancer and elicits anti-tumor immune response. Cancer letters. 2019 Nov 28;465:45-58.

14. Andrieu GP, Shafran JS, Denis GV. BET bromodomain targeting suppresses the PD-1/PD-L1 pathway in triple-negative breast cancer and elicits anti-tumor immune response. Available at SSRN 3260754. 2018 Oct 1.
15. Ding L, Lu S, Li Y. Regulation of PD-1/PD-L1 pathway in cancer by noncoding RNAs. Pathology & Oncology Research. 2020 Apr;26(2):651-63.
16. Zhao J, Huang J. Breast cancer immunology and immunotherapy: targeting the programmed cell death protein-1/programmed cell death protein ligand-1. Chinese Medical Journal. 2020 Apr 5;133(7):853-62.
17. Zhang L, Zhang M, Xu J, Li S, Chen Y, Wang W, Yang J, Li S, Gu M. The role of the programmed cell death protein-1/programmed death-ligand 1 pathway, regulatory T cells and T helper 17 cells in tumor immunity: a narrative review. Annals of Translational Medicine. 2020 Nov;8(22).
18. Pezeshki PS, Mahdavi Sharif P, Rezaei N. Resistance mechanisms to programmed cell death protein 1 and programmed death ligand 1 inhibitors. Expert Opinion on Biological Therapy. 2021 Dec 2;21(12):1575-90.
19. Zhang N, Tu J, Wang X, Chu Q. Programmed cell death-1/programmed cell death ligand-1 checkpoint inhibitors: differences in mechanism of action. Immunotherapy. 2019 Apr;11(5):429-41.
20. Tsaktanis T, Linnerbauer M, Lößlein L, Farrenkopf D, Vandrey O, Peter A, Cirac A, Beyer T, Nirschl L, Grummel V, Mühlau M. Regulation of the programmed cell death protein 1/programmed cell death ligand 1 axis in relapsing–remitting multiple sclerosis. Brain Communications. 2023;5(4):fcad206.
21. Ao Y, Gao M, Sun B, Hao H, Yan H, Li C, Sun D, Yang X, Ju Y, Zhang X, Ma J. Programmed Cell Death Protein 1 Inhibitor-Mediated Peripheral Neuropathy. JTO Clinical and Research Reports. 2023 Apr 1;4(4):100495.
22. Liu R, He X, Li Z. Positive clinical outcomes following therapy with programmed cell death protein 1/programmed cell death ligand 1 inhibitors in neuroendocrine carcinoma of the cervix. Frontiers in Pharmacology. 2022 Nov 17;13:1029598.
23. Santarpia M, González-Cao M, Viteri S, Karachaliou N, Altavilla G, Rosell R. Programmed cell death protein-1/programmed cell death ligand-1 pathway inhibition and predictive biomarkers: understanding transforming growth factor-beta role. Translational lung cancer research. 2015 Dec;4(6):728.
24. Mital R, Cartron AM, Trinidad JC, Spaccarelli N, Gibbons-Fideler IS, Kaffenberger BH, Chung CG. Novel cutaneous eruptions in the setting of programmed cell death protein 1 inhibitor therapy. JAAD Case Reports. 2023 Jan 1;31:124-7.
25. Abaza A, Idris FS, Shaikh HA, Vahora I, Moparthi KP, Al Rushaidi MT, Muddam MR, Obajeun OA, Jaramillo AP, Khan S, Muddam M. Programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) immunotherapy: a promising breakthrough in cancer therapeutics. Cureus. 2023 Sep 2;15(9).
26. Villaruz LC, Blumenschein Jr GR, Otterson GA, Leal TA. Emerging therapeutic strategies for enhancing sensitivity and countering resistance to programmed cell death protein 1 or programmed death-ligand 1 inhibitors in non–small cell lung cancer. Cancer. 2023 May 1;129(9):1319-50.
27. Geng Q, Jiao P, Jin P, Su G, Dong J, Yan B. PD-1/PD-L1 inhibitors for immuno-oncology: from antibodies to small molecules. Current Pharmaceutical Design. 2017 Nov 1;23(39):6033-41.
28. Gristina V, Iacono F, Lisanti C, La Mantia M, Galvano A. Available Immunotherapy Drugs in Oncology. InCardio-Oncology: Management of Toxicities in the Era of Immunotherapy 2022 Aug 10 (pp. 5-23). Cham: Springer International Publishing.
29. Venkatachalam S, McFarland TR, Agarwal N, Swami U. Immune checkpoint inhibitors in prostate cancer. Cancers. 2021 May 2;13(9):2187.
30. Bu X, Yao Y, Li X. Immune checkpoint blockade in breast cancer therapy. Translational Research in Breast Cancer: Biomarker Diagnosis, Targeted Therapies and Approaches to Precision Medicine. 2017:383-402.
31. Inthagard J, Edwards J, Roseweir AK. Immunotherapy: enhancing the efficacy of this promising therapeutic in multiple cancers. Clinical Science. 2019 Jan;133(2):181-93.
32. Chang X, Lu X, Guo J, Teng GJ. Interventional therapy combined with immune checkpoint inhibitors: emerging opportunities for cancer treatment in the era of immunotherapy. Cancer Treatment Reviews. 2019 Mar 1;74:49-60.
33. Verma J, Verma D, Maria A. Pcn154 efficacy and safety of pd-1/pd-l1 inhibitors used in the treatment of patients with advanced and metastatic melanoma–a systematic review and network meta-analysis. Value in Health. 2020 May 1;23:S50.

34. Rausch MP, Hastings KT. Immune checkpoint inhibitors in the treatment of melanoma: from basic science to clinical application. Exon Publications. 2017 Nov 30:121-42.
35. Mahoney KM, Freeman GJ, McDermott DF. The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. Clinical therapeutics. 2015 Apr 1;37(4):764-82.
36. Keenan TE, Burke KP, Van Allen EM. Genomic correlates of response to immune checkpoint blockade. Nature medicine. 2019 Mar;25(3):389-402.
37. Zhang N, Wei L, Ye M, Kang C, You H. Treatment progress of immune checkpoint blockade therapy for glioblastoma. Frontiers in Immunology. 2020 Nov 30;11:592612.
38. Li Y, Liu J, Gao L, Liu Y, Meng F, Li X, Qin FX. Targeting the tumor microenvironment to overcome immune checkpoint blockade therapy resistance. Immunology letters. 2020 Apr 1;220:88-96.
39. Cremolini C, Vitale E, Rastaldo R, Giachino C. Advanced nanotechnology for enhancing immune checkpoint blockade therapy. Nanomaterials. 2021 Mar 8;11(3):661.
40. Hu ZI, Ho AY, McArthur HL. Combined radiation therapy and immune checkpoint blockade therapy for breast cancer. International Journal of Radiation Oncology* Biology* Physics. 2017 Sep 1;99(1):153-64.
41. Care P. S019 Laboratory Investigation of Trace Element Deficiencies. Ind J Clin Biochem. 2019;34(1):S1-233.
42. Chen YM. Immune checkpoint inhibitors for nonsmall cell lung cancer treatment. Journal of the Chinese Medical Association. 2017 Jan 1;80(1):7-14.
43. Pembrolizumab, a PD-1 inhibitor, is also approved for first-line treatment of NSCLC, highlighting its role as a significant advancement in cancer immunotherapy (Qu et al., 2020).
44. Qiao M, Jiang T, Zhou C. Shining light on advanced NSCLC in 2017: combining immune checkpoint inhibitors. Journal of Thoracic Disease. 2018 May;10(Suppl 13):S1534.
However, the efficacy of these inhibitors can be limited by factors such as the lack of effective biomarkers to predict response and the development of primary or acquired resistance (Qiao et al., 2018).
45. Qu J, Jiang M, Wang L, Zhao D, Qin K, Wang Y, Tao J, Zhang X. Mechanism and potential predictive biomarkers of immune checkpoint inhibitors in NSCLC. Biomedicine & Pharmacotherapy. 2020 Jul 1;127:109996.
46. Berghoff AS, Venur VA, Preusser M, Ahluwalia MS. Immune checkpoint inhibitors in brain metastases: from biology to treatment. American Society of Clinical Oncology Educational Book. 2016 Jan 1;36:e116-22.
47. Powles T, Albiges L, Bex A, Grünwald V, Porta C, Procopio G, Schmidinger M, Suárez C, De Velasco G, ESMO Guidelines Committee. ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. Annals of Oncology. 2021 Dec 1;32(12):1511-9.
48. Kelly WJ, Gilbert MR. Glucocorticoids and immune checkpoint inhibitors in glioblastoma. Journal of neuro-oncology. 2021 Jan;151:13-20.
49. Shien K, Papadimitrakopoulou VA, Wistuba II. Predictive biomarkers of response to PD-1/PD-L1 immune checkpoint inhibitors in non–small cell lung cancer. Lung Cancer. 2016 Sep 1;99:79-87.
50. Miura S. SY10-4 Clinical biomarkers to predict the efficacy of immune checkpoint inhibitors. Annals of Oncology. 2021 Jul 1;32:S255.
51. Shi WJ, Zhao W. Biomarkers or factors for predicting the efficacy and adverse effects of immune checkpoint inhibitors in lung cancer: achievements and prospective. Chinese Medical Journal. 2020 Oct 20;133(20):2466-75.
52. Pirker R. Biomarkers for immune checkpoint inhibitors in advanced nonsmall cell lung cancer. Current Opinion in Oncology. 2019 Jan 1;31(1):24-8.
53. Wang C, Wang HN, Wang L. Biomarkers for predicting the efficacy of immune checkpoint inhibitors. Journal of Cancer. 2022;13(2):481.
54. Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: recent progress and potential biomarkers. Experimental & molecular medicine. 2018 Dec;50(12):1-1.
55. Lapuente-Santana Ó, van Genderen M, Hilbers PA, Finotello F, Eduati F. Interpretable systems biomarkers predict response to immune-checkpoint inhibitors. Patterns. 2021 Aug 13;2(8).
56. Hendriks LE, Rouleau E, Besse B. Clinical utility of tumor mutational burden in patients with non-small cell lung cancer treated with immunotherapy. Translational lung cancer research. 2018 Dec;7(6):647.
57. Yarchoan M, Albacker LA, Hopkins AC, Montesion M, Murugesan K, Vithayathil TT, Zaidi N, Azad NS, Laheru DA, Frampton GM, Jaffee EM. PD-L1 expression and tumor mutational burden are independent biomarkers in most cancers. JCI insight. 2019 Mar 3;4(6).

58. Kim SR, Chun SH, Kim JH, Kim SY, Lee BI, Jung CK, Kang JH. Clinical experience of immune checkpoint inhibitor for a metastatic jejunal cancer patient with a high tumor mutational burden and low expression of programmed death-ligand 1. Korean Journal of Clinical Oncology. 2020 Jun;16(1):57.
59. Wang S, Zhang J, He Z, Wu K, Liu XS. The predictive power of tumor mutational burden in lung cancer immunotherapy response is influenced by patients' sex. International journal of cancer. 2019 Nov 15;145(10):2840-9.
60. Xu X, Yang Y, Liu X, Cao N, Zhang P, Zhao S, Chen D, Li L, He Y, Dong X, Wang K. NFE2L2/KEAP1 mutations correlate with higher tumor mutational burden value/PD-L1 expression and potentiate improved clinical outcome with immunotherapy. The oncologist. 2020 Jun 1;25(6):e955-63.
61. Yang H, Ma W, Sun B, Fan L, Xu K, Hall SR, Al-Hurani MF, Schmid RA, Peng RW, Hida T, Wang Z. Smoking signature is superior to programmed death-ligand 1 expression in predicting pathological response to neoadjuvant immunotherapy in lung cancer patients. Translational lung cancer research. 2021 Sep;10(9):3807.
62. Wang S, Qu X, Li Z, Che X, Cao L, Yang X, Hu X, Xu L, Hou K, Fan Y, Wen T. Distinct prognostic values of programmed death-ligand 1 and programmed cell death protein 1 in lung adenocarcinoma and squamous cell carcinoma patients. Annals of Translational Medicine. 2021 Mar;9(5).
63. Chen BH, Kao CC, Xu T, Yang YN, Cha TL, Tsai YT, Liu SY, Wu ST, Meng E, Tsao CW, Chen CL. Determining programmed cell death ligand 1 expression in circulating tumor cells of patients with clear cell renal cell carcinoma and its correlation with response to programmed cell death protein 1 inhibitors. International Journal of Urology. 2022 Sep;29(9):947-54.
64. Yamane H, Isozaki H, Ochi N, Kudo K, Honda Y, Yamagishi T, Kubo T, Kiura K, Takigawa N. Both programmed cell death protein 1 and programmed death-ligand 1 molecules can be expressed on the cell surface of small-cell lung cancer. Cancer Research. 2015 Aug 1;75(15_Supplement):1323-.
65. Ao Y, Gao M, Sun B, Hao H, Yan H, Li C, Sun D, Yang X, Ju Y, Zhang X, Ma J. Programmed Cell Death Protein 1 Inhibitor-Mediated Peripheral Neuropathy. JTO Clinical and Research Reports. 2023 Apr 1;4(4):100495.
66. Pillai RN, Behera M, Owonikoko TK, Kamphorst AO, Pakkala S, Belani CP, Khuri FR, Ahmed R, Ramalingam SS. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non–small cell lung cancer: A systematic analysis of the literature. Cancer. 2018 Jan 15;124(2):271-7.
67. Chan SL. Hyperprogression in hepatocellular carcinoma: Illusion or reality?. Journal of hepatology. 2021 Feb;74(2):269-71.
68. Oliveira AF, Bretes L, Furtado I. Review of PD-1/PD-L1 inhibitors in metastatic dMMR/MSI-H colorectal cancer. Frontiers in oncology. 2019 May 14;9:396.
69. Qiao M, Jiang T, Ren S, Zhou C. Combination strategies on the basis of immune checkpoint inhibitors in non–small-cell lung cancer: where do we stand?. Clinical lung cancer. 2018 Jan 1;19(1):1-1.
70. Kong X, Lu P, Liu C, Guo Y, Yang Y, Peng Y, Wang F, Bo Z, Dou X, Shi H, Meng J. A combination of PD-1/PD-L1 inhibitors: The prospect of overcoming the weakness of tumor immunotherapy. Molecular Medicine Reports. 2021 May 1;23(5):1-6.
71. Goncalves A, Mezni E, Bertucci F. Combining poly (ADP-ribose) polymerase inhibitors and immune checkpoint inhibitors in breast cancer: Rationale and preliminary clinical results. Current Opinion in Oncology. 2020 Nov 1;32(6):585-93.
72. Zhao LP, Hu JH, Hu D, Wang HJ, Huang CG, Luo RH, Zhou ZH, Huang XY, Xie T, Lou JS. Hyperprogression, a challenge of PD-1/PD-L1 inhibitors treatments: potential mechanisms and coping strategies. Biomedicine & Pharmacotherapy. 2022 Jun 1;150:112949.
73. Schmidt EV. Developing combination strategies using PD-1 checkpoint inhibitors to treat cancer. InSeminars in immunopathology 2019 Jan 11 (Vol. 41, No. 1, pp. 21-30). Berlin/Heidelberg: Springer Berlin Heidelberg.
74. Xie D, Jiang B, Wang S, Wang Q, Wu G. The mechanism and clinical application of DNA damage repair inhibitors combined with immune checkpoint inhibitors in the treatment of urologic cancer. Frontiers in Cell and Developmental Biology. 2023 May 25;11:1200466.

75. Setordzi P, Chang X, Liu Z, Wu Y, Zuo D. The recent advances of PD-1 and PD-L1 checkpoint signaling inhibition for breast cancer immunotherapy. European journal of pharmacology. 2021 Mar 15;895:173867.
76. Ren Y, Song J, Li X, Luo N. Rationale and clinical research progress on PD-1/PD-L1-based immunotherapy for metastatic triple-negative breast cancer. International Journal of Molecular Sciences. 2022 Aug 10;23(16):8878.

77. Kareff SA, Samtani S, Burotto M, Prasad V, Kim C. Current landscape of immunotherapy trials involving the programmed cell death protein 1/programmed death-ligand 1 axis in intrathoracic tumors. JTO Clinical and Research Reports. 2021 Apr 1;2(4):100149.
78. Mocan T, Sparchez Z, Craciun R, Bora CN, Leucuta DC. Programmed cell death protein-1 (PD-1)/programmed death-ligand-1 (PD-L1) axis in hepatocellular carcinoma: prognostic and therapeutic perspectives. Clinical and Translational Oncology. 2019 Jun 14;21(6):702-12.
79. Pezeshki PS, Mahdavi Sharif P, Rezaei N. Resistance mechanisms to programmed cell death protein 1 and programmed death ligand 1 inhibitors. Expert Opinion on Biological Therapy. 2021 Dec 2;21(12):1575-90.
80. Li D, Chen R, Wang YW, Fornace Jr AJ, Li HH. Prior irradiation results in elevated programmed cell death protein 1 (PD-1) in T cells. International Journal of Radiation Biology. 2018 Apr 2;94(5):488-94.
81. Huang J, Jiang Z, Wang Y, Fan X, Cai J, Yao X, Liu L, Huang J, He J, Xie C, Wu Q. Modulation of gut microbiota to overcome resistance to immune checkpoint blockade in cancer immunotherapy. Current Opinion in Pharmacology. 2020 Oct 1;54:1-0.
82. Trojaniello C, Vitale MG, Scarpato L, Esposito A, Ascierto PA. Melanoma immunotherapy: strategies to overcome pharmacological resistance. Expert Review of Anticancer Therapy. 2020 Apr 2;20(4):289-304.
83. Qadri H, Shah AH, Mir M. Novel strategies to combat the emerging drug resistance in human pathogenic microbes. Current Drug Targets. 2021 Sep 1;22(12):1424-36.
84. Morganti S, Curigliano G. Combinations using checkpoint blockade to overcome resistance. Ecancermedicalscience. 2020;14.
85. AmeliMojarad M, AmeliMojarad M, Cui X. Prospective role of PD-1/PD-L1 immune checkpoint inhibitors in GI cancer. Pathology-Research and Practice. 2023 Apr 1;244:154338.
86. Li Y, Wang S, Lin M, Hou C, Li C, Li G. Analysis of interactions of immune checkpoint inhibitors with antibiotics in cancer therapy. Frontiers of Medicine. 2022 Jun;16(3):307-21.
87. Bai J, Liang P, Li Q, Feng R, Liu J. Cancer immunotherapy-immune checkpoint inhibitors in hepatocellular carcinoma. Recent Patents on Anti-cancer Drug Discovery. 2021 May 1;16(2):239-48.
88. Mutlu L, Harold J, Tymon-Rosario J, Santin AD. Immune checkpoint inhibitors for recurrent endometrial cancer. Expert Review of Anticancer Therapy. 2022 Mar 4;22(3):249-58.
89. Cheng AL, Hsu C, Chan SL, Choo SP, Kudo M. Challenges of combination therapy with immune checkpoint inhibitors for hepatocellular carcinoma. Journal of hepatology. 2020 Feb 1;72(2):307-19.
90. Sun H, Dai J, Zhao L, Zhu J, Wang H, Chen P, Lu H, Chen Q, Zhang Z. Lymphocyte activation gene-3 is associated with programmed death-ligand 1 and programmed cell death protein 1 in small cell lung cancer. Annals of Translational Medicine. 2021 Sep;9(18).
91. Zhu S, Liu C, Dong Y, Shao J, Liu B, Shen J. A retrospective study of lenvatinib monotherapy or combined with programmed cell death protein 1 antibody in the treatment of patients with hepatocellular carcinoma or intrahepatic cholangiocarcinoma in China. Frontiers in Oncology. 2021 Dec 17;11:788635.
92. Kudo M. Scientific rationale for combined immunotherapy with PD-1/PD-L1 antibodies and VEGF inhibitors in advanced hepatocellular carcinoma. Cancers. 2020 Apr 27;12(5):1089.
93. Sharma A, Jasrotia S, Kumar A. Effects of Chemotherapy on the Immune System: Implications for Cancer Treatment and Patient Outcomes. Naunyn-Schmiedeberg's Archives of Pharmacology. 2023 Oct 31:1-6.
94. Debra Winkeljohn RN. Adherence to oral cancer therapies: nursing interventions. Clinical Journal of Oncology Nursing. 2010 Aug 1;14(4):461.
34. Alexander-Bryant AA, Berg-Foels WS, Wen X. Bioengineering strategies for designing targeted cancer therapies. Advances in cancer research. 2013 Jan 1;118:1-59.
95. McFarland DC, Sharma M, Alici Y. Psychiatric Toxicities of Cancer Therapies. Psycho-Oncology. 2021 Jan 22:374.
96. Li Y, Ma Z, Zhang D, Ramachandran M, Lin TY. Novel strategies to target autophagy to improve cancer therapy. Cancer Research. 2020 Aug 15;80(16_Supplement):1221-.
97. Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). The Lancet. 2017 Oct 21;390(10105):1853-62.
98. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-

small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. The Lancet. 2016 Apr 9;387(10027):1540-50.
99. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D. Nivolumab versus everolimus in advanced renal-cell carcinoma. New England Journal of Medicine. 2015 Nov 5;373(19):1803-13.
100. Rosenberg JE, Hoffman-Censits J, Powles T, Van Der Heijden MS, Balar AV, Necchi A, Dawson N, O'Donnell PH, Balmanoukian A, Loriot Y, Srinivas S. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. The Lancet. 2016 May 7;387(10031):1909-20.
101. Ferris RL, Blumenschein Jr G, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. New England Journal of Medicine. 2016 Nov 10;375(19):1856-67.
102. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, Schuster SJ, Millenson MM, Cattry D, Freeman GJ, Rodig SJ. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. New England Journal of Medicine. 2015 Jan 22;372(4):311-9.
103. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, Plimack ER, Hahn NM, de Wit R, Pang L, Savage MJ. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. The Lancet Oncology. 2017 Nov 1;18(11):1483-92.
104. D'Angelo SP, Russell J, Lebbé C, Chmielowski B, Gambichler T, Grob JJ, Kiecker F, Rabinowits G, Terheyden P, Zwiener I, Bajars M. Efficacy and safety of first-line avelumab treatment in patients with stage IV metastatic Merkel cell carcinoma: a preplanned interim analysis of a clinical trial. JAMA oncology. 2018 Sep 1;4(9):e180077-.
105. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, Sarker D. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. The Lancet Oncology. 2018 Jul 1;19(7):940-52.
106. Powles T, Durán I, Van der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, Oudard S, Retz MM, Castellano D, Bamias A, Fléchon A. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. The Lancet. 2018 Feb 24;391(10122):748-57.
107. Emens LA, Cruz C, Eder JP, Braiteh F, Chung C, Tolaney SM, Kuter I, Nanda R, Cassier PA, Delord JP, Gordon MS. Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study. JAMA oncology. 2019 Jan 1;5(1):74-82.
108. Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, Lee JL, Ong M, Sridhar SS, Vogelzang NJ, Fishman MN. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA oncology. 2017 Sep 1;3(9):e172411-.
109. Atkins MB, Plimack ER, Puzanov I, Fishman MN, McDermott DF, Cho DC, Vaishampayan U, George S, Olencki TE, Tarazi JC, Rosbrook B. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. The Lancet Oncology. 2018 Mar 1;19(3):405-15.
110. Frenel JS, Le Tourneau C, O'Neil B, Ott PA, Piha-Paul SA, Gomez-Roca C, Van Brummelen EM, Rugo HS, Thomas S, Saraf S, Rangwala R. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1–positive cervical cancer: results from the phase Ib KEYNOTE-028 trial. Journal of Clinical Oncology. 2017 Dec 20;35(36):4035-41.
111. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, Sun W, Jalal SI, Shah MA, Metges JP, Garrido M. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA oncology. 2018 May 1;4(5):e180013-.