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Review article

Harnessing Immune Checkpoint Inhibitors Against Gastric Cancer: Charting the Course to Expanded Therapeutic Benefit

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ABSTRACT

Cancer immunotherapy has become a groundbreaking approach in treatment, with immune checkpoint inhibitors (ICIs) showing exceptional success in blocking the pathways that tumors use to escape immune detection. This review delves into the clinical significance and predictive power of ICIs in the treatment of gastric cancer. It introduces ICIs, explaining their mechanisms of action, reviews key findings from critical trials, and discusses the role of programmed death ligand-1 (PD-L1) testing as a potential biomarker for selecting suitable patients. The review also addresses the limitations of PD-L1 testing, while highlighting emerging predictive markers and ongoing research aimed at discovering novel biomarkers, optimizing therapeutic combinations, characterizing the tumor microenvironment, and understanding mechanisms of resistance to therapy. This effort to optimize ICIs aims to extend their significant clinical benefits to a larger group of patients with gastric cancer. In summary, this review provides specialists with an updated overview of the advancements in employing immunotherapy against gastric cancer and outlines the path towards enhancing patient outcomes through continuous research and the refinement of biomarkers.

Key words: Gastric cancer, immunotherapy, immune checkpoint inhibitors, PD-L1, biomarkers, tumor microenvironment

INTRODUCTION

Cancer immunotherapy represents a revolutionary method for treating cancer, leveraging the patient's immune system to target and destroy malignant cells [1,2]. Notably, immune checkpoint inhibitors (ICIs) have emerged as a significant breakthrough in immunotherapies, showing profound efficacy in treating a wide array of cancers. This is achieved by inhibiting specific pathways that tumors exploit to evade immune detection and destruction [3–5]. This review focuses specifically on the role and predictive value of ICIs in the context of gastric cancer, addressing several crucial questions: 1. What are the current uses and effectiveness of ICIs in the treatment of gastric cancer? 2. How does the expression of PD-L1 influence the selection of patients for ICI therapy? 3. What challenges and limitations exist concerning PD-L1 testing as a predictive biomarker? 4. Which new biomarkers and approaches are being explored to enhance the selection process and outcomes for patients receiving ICIs?

In this review, we discuss the immune checkpoint pathways, including CTLA-4 and PD-1/PD-L1, and how ICIs boost anti-tumor immunity. We delve into the findings from pivotal trials, emphasizing the clinical advantages when ICIs are combined with chemotherapy for patients with advanced gastric cancer. The role of programmed death ligand-1 (PD-L1) as a potential biomarker for guiding patient selection is examined, alongside a discussion of its limitations and the exploration of other promising predictors.

One of the significant challenges in identifying suitable candidates for ICI therapy is the variability in PD-L1 assays, the heterogeneity of the disease, and mechanisms of resistance that can reduce the durability of the response. The review also covers emerging research directions, including the investigation of new biomarkers, strategic therapeutic combinations, in-depth studies of the tumor microenvironment, and understanding resistance mechanisms. These areas of research aim to broaden the group of gastric cancer patients who achieve substantial disease control through immunotherapy.

Recent advances in immunotherapy, especially with the advent of ICIs, have dramatically altered the landscape of cancer treatment. While ICIs have shown remarkable success in various cancers, including gastric cancer, their efficacy is not universal among all patients [6,7]. This underscores the urgent need for reliable predictive biomarkers that can guide patient selection and optimize treatment outcomes. This review offers a timely, in-depth examination of the state of ICI therapy in gastric cancer, with a particular focus

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on PD-L1 expression as a predictive biomarker and on the exploration of new strategies to improve the effectiveness of patient selection and treatment.

In summary, this review serves both as an introduction to ICIs for those new to the field of cancer immunotherapy and as an update for specialists on the latest developments in gastric cancer treatment. It highlights the path toward improved patient outcomes through the ongoing optimization of predictive markers and therapeutic combinations, pushing the boundaries of immunotherapy to realize its full potential.

MECHANISMS OF IMMUNE CHECKPOINT BLOCKADE

Immune checkpoint inhibitors (ICIs) are at the forefront of cancer immunotherapy, designed to amplify anti-tumor immunity by unlocking T cell potential. These checkpoints, integral for preserving self-tolerance and modulating immune response, can be hijacked by tumors to avoid detection and destruction. By inhibiting these regulatory pathways, ICIs enhance the T cell-driven attack on cancer cells.

Overview of Key Immune Checkpoints

At the heart of immune regulation lie immune checkpoints, which provide either co-stimulatory or co-inhibitory signals to control immune responses[8,9]. Cancers often evade the immune system by manipulating these inhibitory pathways[8]. For instance, CTLA-4, located on Tregs, binds to CD80/CD86 on APCs outcompeting stimulatory signals and thus dampening T cell activation early in the immune response[8]. Similarly, PD-1, found on activated T cells, engages with PD-L1/PD-L2 on tumor cells or APCs, curtailing T cell effector functions and facilitating immune escape[8]. Although ICIs targeting CTLA-4 and PD-1/PD-L1 pathways have shown promise, not all patients respond favorably, and some experience significant side effects[8].

The search for new therapeutic targets has identified additional immune checkpoints, including VISTA, ectonucleotidases (CD39/CD73/CD38), and ARG1, all utilized by tumors to undermine anti-tumor immunity[8,10,11]. VISTA, an inhibitory receptor on T cells and APCs, interacts with an unidentified ligand to inhibit T cell activation[12]. Ectonucleotidases CD39 and CD73 convert extracellular ATP into adenosine, a potent immunosuppressant, while CD38 influences adenosine signaling[13]. ARG1, meanwhile, reduces available arginine, essential for T cell function[14]. Targeting these mechanisms opens new avenues for immunotherapy, potentially enhancing outcomes for more patients.

In essence, while immune checkpoints are critical for immune regulation, their exploitation by cancers allows for immune evasion. The strategic blockade of these checkpoints by ICIs aims to counteract this. Yet, the challenge of non-responsiveness and adverse effects persists. Future research focusing on novel checkpoints, biomarker identification, therapeutic combinations, and fine-tuning checkpoint modulation holds promise for broadening the beneficiary pool of immune-based cancer treatments.

Harnessing Immunity Against Cancer

Immune surveillance is a natural defense mechanism against cancer, which, however, can be circumvented by tumors through checkpoint manipulation[15]. ICIs boost anti-tumor T cell activity by inhibiting checkpoint controls[15,16].

Ipilimumab, targeting CTLA-4, marked the advent of FDA-approved ICIs for advanced melanoma in 2011, enhancing T cell activation[16]. This success led to the development of PD-1 inhibitors, pembrolizumab and nivolumab, and PD-L1 blockers, atezolizumab, avelumab, and durvalumab, now utilized across multiple cancer types16. These agents disrupt the interactions that deactivate T cells, enabling an efficient immune assault on tumor cells.

Emerging strategies targeting other aspects of the tumor microenvironment, such as Siglec-15, tumor-associated macrophages, or employing CAR-macrophage cell therapy, promise to further extend the repertoire of immunotherapeutic weapons against cancer[15,17].

PD-1/PD-L1 Signaling in Gastric Cancer

The PD-1/PD-L1 pathway plays a critical role in the immune evasion mechanisms of gastric cancer, with PD-1 located on T cells and PD-L1/PD-L2 found on both tumor cells and antigen-presenting cells (APCs). This interaction between ligands and receptors inhibits T cell activity, facilitating cancer cell escape[18]. Preclinical studies have highlighted that the expression levels of PD-L1 within the gastric tumor microenvironment significantly affect the success of anti-PD-1/PD-L1 therapies[19]. Notably, both the reduction and increase of PD-L1 expression have been associated with improved therapeutic outcomes, which indicates the complexity of PD-1/PD-L1 signaling and its impact on anti-tumor immunity in gastric cancer[19].

In summary, the development of immune checkpoint inhibitors (ICIs) has significantly advanced cancer

treatment by blocking the immune checkpoint pathways that cancer cells exploit to avoid immune destruction. However, challenges such as suboptimal response rates and immune-related adverse effects limit their efficacy. Ongoing research into predictive biomarkers for better patient selection, exploration of new checkpoint targets, innovative combination strategies, and optimization of checkpoint expression patterns is vital. These research directions aim to enable more patients to achieve lasting benefits from immuno-oncology treatments, which leverage the power of the patient's own immune system to combat cancer.

THE EVOLVING CLINICAL ROLE OF ICIS IN GASTRIC CANCER

Several pivotal clinical trials have critically assessed the use of immune checkpoint inhibitors (ICIs) in the treatment of advanced gastric cancer, significantly influencing the current clinical approach.

Current ICI Applications

As of now, Pembrolizumab (Keytruda) stands as the sole FDA-approved immune checkpoint inhibitor for treating gastric cancer, granted accelerated approval in 2017. This approval was for patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1, informed by the outcomes of the KEYNOTE-059 trial[10,20,21]. Pembrolizumab serves as a third-line treatment following the failure of two or more chemotherapy lines[10,20].

This initial endorsement was based on the condition of proving further clinical benefit in the confirmatory KEYNOTE-061 trial[22]. Although this Phase 3 trial did not achieve its primary goal of demonstrating enhanced overall survival compared to chemotherapy in the second-line setting, subset analyses based on the PD-L1 combined positive score (CPS) favored pembrolizumab for treating PD-L1 positive tumors[23], subsequently leading to the FDA converting pembrolizumab's accelerated approval[24].

Nivolumab (Opdivo), in combination with chemotherapy, received approval too for first-line treatment of inoperable advanced or recurrent gastric cancer[25], following evidence of survival benefits from the CheckMate-649 trial[26].

In considering ICI therapy, clinicians must evaluate the patient's broader clinical picture, including performance status[27], comorbid conditions such as autoimmune disorders that could heighten the risk of exacerbating underlying issues, prior treatment regimes received, and an overall clinical risk assessment[28]. Evidence suggests that specific prior treatments, including radiation or certain chemotherapy protocols, could improve the subsequent ICI therapy benefits by optimally priming the immune response[29]. Therefore, an individualized assessment to balance potential risks and benefits is crucial when selecting immunotherapy candidates[30].

Efficacy and Safety

ICIs, particularly PD-1/PD-L1 antibodies, are designed to boost anti-tumor immunity by hindering cancer cells' ability to exploit inhibitory pathways. This section digest the salient clinical trial outcomes regarding ICIs for gastric cancer.

The phase 3 CheckMate-649 trial demonstrated that combining nivolumab with chemotherapy significantly bettered overall survival against chemotherapy alone as a first-line treatment for advanced gastric, GEJ, and esophageal adenocarcinoma[26,31–35]. The ATTRACTION-4 trial echoed these survival benefits with nivolumab plus chemotherapy as a first-line treatment for advanced gastric cancer when compared to chemotherapy alone[36].

ICIs are generally well-tolerated in gastric cancer trials, exhibiting a lower incidence of adverse events relative to chemotherapy[37]. Nonetheless, immune-related adverse events (irAEs) such as rash, colitis, pneumonitis, and thyroid disorders do occur, necessitating vigilant monitoring and management[38,39]. Strategies include regular monitoring, prompt engagement of specialists for severe toxicities, and, if necessary, pausing ICI treatment and initiating corticosteroids or anti-TNF therapy based on the severity and grade of irAEs[40]. A collaborative approach, adhering to toxicity management protocols, is essential for ensuring safe and effective ICI administration[41].

Limitations and Real-World Application

Challenges such as the small cohort size in early-phase trials like KEYNOTE-059[42], limited follow-up durations[43], the predominance of Asian patient populations in trials[44–46], and the complex landscape of PD-L1 biomarker testing in clinical settings[47,48], highlight the need for cautious interpretation of these trials' generalizability. Addressing the variability and costs associated with PD-L1 testing remains crucial for integrating ICIs effectively into treatment paradigms[49].

In conclusion, ICIs, in combination with chemotherapy, have shown marked effectiveness in key gastric cancer trials, leading to their approved use. However, recognizing the constraints of existing studies,

including sample sizes, follow-up lengths, patient diversity, and biomarker testing challenges, is vital for real-world applicability. Ongoing research aims to fill these gaps, enhancing the utility of ICI-based treatments.

Comparative Analysis with Traditional Therapies

Compared to conventional chemotherapy, ICIs, when used in chemotherapy combination regimens, have demonstrated superior efficacy in treating advanced gastric cancer, offering significant survival advantages [50–52]. Moreover, ICIs facilitate a more personalized therapy approach through predictive biomarker profiling, potentially leading to better patient outcomes [53,54].

To summarize, targeting immune checkpoints with ICIs has significantly advanced the treatment landscape for gastric cancer, unlocking new and promising therapeutic approaches. Further studies are expected to continue this trajectory, improving patient care.

PD-L1 as a Putative Biomarker in Gastric Cancer

PD-L1 Testing as a Predictive Biomarker

Programmed death ligand 1 (PD-L1) expression on tumor and immune cells has emerged as a potential predictive biomarker for selecting patients who may benefit from anti-PD-1/PD-L1 immunotherapy [55,56]. PD-L1 expression is typically detected by immunohistochemistry and has been associated with clinical outcomes with immune checkpoint inhibitors across various cancer types [55,56].

In gastric cancer, the assessment of PD-L1 expression could enable more personalized therapeutic decisions regarding the application of immune checkpoint inhibitors, although its clinical utility is still being defined [55,56].

PD-L1 expression quantified by immunohistochemistry is currently the most widely used biomarker to guide patient selection for anti-PD-1/PD-L1 antibodies [56]. However, challenges remain, including the use of different diagnostic assays, variability in performance and cutoff points, and the lack of prospective comparisons [56].

Moreover, recent preclinical studies have shown that regulating PD-L1 expression in the tumor microenvironment can improve the efficacy of immunotherapy. For instance, both downregulation and upregulation of PD-L1 have been found to enhance the response to anti-PD-1/PD-L1 treatment [56].

Associations Between PD-L1 Expression and Clinicopathological Features

The relationship between PD-L1 expression and clinicopathological characteristics in gastric cancer has been examined in several studies, with inconsistent results reported across different cohorts.

Some analyses have found positive associations between PD-L1 status and indicators of advanced disease. A study in a Vietnamese cohort reported that higher PD-L1 expression correlated with a more advanced TNM stage, the presence of lymph node metastasis, and poorer tumor differentiation [57]. Similarly, another study found that PD-L1 positivity was associated with advanced TNM stage, lymph node involvement, and poor differentiation grade [58]. These findings suggest that PD-L1 overexpression may be linked to more aggressive tumor phenotypes and later-stage disease in certain gastric cancer patients.

However, other studies have failed to demonstrate significant correlations between PD-L1 expression and clinicopathological features. No associations were found between PD-L1 status and depth of invasion, nodal metastasis, or TNM stage in several reports [59,60]. Heterogeneous results have also been noted for histological subtype, tumor size, age, gender, and other characteristics across different analyses. In a recent study of 87 Vietnamese gastric cancer patients, higher PD-L1 expression by tumor proportion score (TPS) was associated with lymphatic invasion, while a higher combined positive score (CPS) correlated with the intestinal subtype [61].

The variable results across studies highlight the complex biology underlying PD-L1 expression in gastric cancer. The reasons for the discordant clinicopathological associations remain unclear. Potential factors contributing to the inconsistent findings include differences in study cohorts, testing methodologies, PD-L1 antibody clones, scoring cutoffs, and statistical approaches.

Standardization of PD-L1 testing protocols and positivity criteria will be important moving forward to better elucidate the relationships with clinicopathological features. Larger multi-center analyses using harmonized methodologies will also help clarify the true associations. Continued research is still required to fully characterize the clinical and biological significance of PD-L1 overexpression in gastric cancer.

Prognostic Value of PD-L1 Expression Patterns

Although correlations with clinicopathological features remain unclear, multiple studies have demonstrated an association between PD-L1 expression and

worse prognosis in gastric cancer. In a Vietnamese cohort, PD-L1 positive patients had significantly shorter overall survival compared to PD-L1 negative patients57. PD-L1 emerged as an independent prognostic factor linked to poorer survival outcomes.

Similarly, a meta-analysis in gastric cancer found PD-L1 positivity was associated with worse overall survival[62]. Another meta-analysis also reported that PD-L1 overexpression correlated with significantly poorer overall survival[63].

These findings indicate that PD-L1 expression patterns may have prognostic value in predicting more aggressive clinical behavior and poorer long-term outcomes in gastric cancer. The association with reduced survival is consistent across multiple large-scale analyses.

This highlights the potential clinical utility of PD-L1 as a prognostic biomarker to guide expectations of prognosis and clinical outcomes. Testing for PD-L1 status could help stratify gastric cancer patients into favorable and unfavorable prognostic groups.

Patients with PD-L1 positive tumors may warrant more aggressive treatment and intensive follow-up, as they are at higher risk of disease progression and mortality. Further validation is still needed, but PD-L1 testing shows promise as a clinically actionable prognostic tool in gastric cancer management.

PREDICTIVE BIOMARKERS FOR GASTRIC CANCER IMMUNOTHERAPY

Immune checkpoint inhibitors (ICIs) offer a promising treatment path for gastric cancer. However, the challenge of identifying the patients who are most likely to benefit from these therapies has sparked extensive research into predictive biomarkers for more targeted patient selection.

Emerging Biomarkers Beyond PD-L1 Testing

The programmed death ligand-1 (PD-L1) assay is currently the cornerstone biomarker for clinical application of ICIs[53,54,56,64]. Studies such as KEYNOTE-059 and ATTRACTION-2 have shown enhanced efficacy of PD-1 inhibitors in PD-L1-positive gastric tumors[65,66]. Although PD-L1 testing is at the forefront of ICI biomarker research, the quest to discover additional genetic and molecular predictors of response is relentless.

Tumor Mutational Burden (TMB) has been recognized as a promising indicator of ICI response. It measures the number of mutations within tumor cells, expressed in mutations per megabase (muts/Mb). A higher TMB correlates with an increased production of neoantigens, leading to greater immune system activation and improved response to PD-1 inhibitors across several cancer types[67–69]. Combining TMB assessment with PD-L1 levels may yield a more precise prediction of ICI therapy success.

Microsatellite Instability (MSI) indicative of a defect in DNA repair, has similarly emerged as a significant biomarker. Like TMB, MSI-high tumors generate more neoantigens, potentially improving patient response to immunotherapy[70]. Employing MSI alongside PD-L1 testing could widen the pool of patients eligible for immunotherapeutic approaches.

Inflammatory Gene Signatures reflecting the levels of T-cell inflammation and interferon-gamma (IFN-γ) activity, have been linked to favorable ICI treatment outcomes[71–73]. IFN-γ plays a pivotal role in enhancing the effectiveness of cytotoxic T cells and natural killer cells. Integrating analysis of these gene signatures with PD-L1 expression can refine patient stratification methods.

Current models, such as the FDA-approved FoundationOne CDx assay, amalgamate PD-L1, TMB, and MSI to direct immunotherapy choices in a range of cancers, offering a holistic view of a tumor's immune profile[74,75].

The reliance on PD-L1 expression as a standalone marker is problematic due to assay variability and differing scoring methodologies. This has led to an increased interest in composite biomarkers. A study involving 87 Vietnamese gastric cancer patients utilized the combined positive score (CPS), incorporating both tumor and immune cell PD-L1 expression, revealing a link between higher CPS and the intestinal cancer subtype[61].

The pursuit of integrated predictive models is crucial for enhancing patient selection and optimizing immunotherapy effectiveness. Advanced bioinformatics approaches that leverage multi-omics data are paving the way for novel biomarkers and a deeper understanding of the molecular dynamics influencing ICI sensitivity.

Emerging Molecular Predictors

While PD-L1 testing leads ICI biomarker development, there is intense interest in identifying additional genetic/molecular markers that predict outcomes. Early findings link certain somatic mutations, infectious agents, and genomic instability markers to increased immune activity or ICI response, though validation is still needed.

Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations occur frequently in gastric cancer[76,77]. These mutations, particularly those causing loss of function, are associated with factors suggesting enhanced ICI sensitivity—increased T-cell infiltration and PD-L1 expression[78,79].

Epstein-Barr virus (EBV) characterizes a subset of gastric cancer that exhibits high PD-L1 expression and distinct immune signatures[80]. Studies indicate superior ICI outcomes in EBV-positive disease, making EBV status a potential predictor[80].

AT-rich interaction domain 1A (ARID1A) is frequently mutated in gastric cancer[81,82]. ARID1A mutations are linked to heightened immune activity[83], potentially predicting sensitivity. However, the mechanisms remain unclear.

A high neoantigen load, derived from tumor-specific mutations, may enhance immune attack, associating with improved ICI outcomes[84]. Quantifying neoantigen load could thus inform strategies for gastric cancer biomarkers[84].

Multi-omics analysis, integrating genomics, transcriptomics, and proteomics, provides a comprehensive landscape revealing molecular alterations and co-occurring features that predict ICI response[85].

Ongoing research to identify and validate predictive biomarkers is critical for the optimization of gastric cancer immunotherapies.

Illuminating the Tumor Microenvironment (TME)

The TME, comprising a mix of cellular and acellular elements, plays a critical role in modulating responses to ICIs. It includes tumor cells, immune cells, stromal cells, and the extracellular matrix, with their interactions significantly affecting tumor behavior and treatment outcomes[86].

Key to the TME's influence on ICI response is the presence and characteristics of $CD8^+$ T cell infiltrates. These immune cells are essential for anti-tumor immunity, and their abundance, diversity, and proximity to tumor cells enhance ICI sensitivity[87–89]. Analyzing the presence and patterns of $CD8^+$ T cells within the TME can offer predictive insights regarding ICI treatment success[90].

Other TME constituents, like myeloid-derived suppressor cells and regulatory T cells (Tregs), contribute to the immunosuppressive microenvironment, potentially hindering ICI therapy[91]. Cancer-associated fibroblasts (CAFs), another prevalent TME component, can influence tumor growth and ICI responsiveness by interacting with immune cells[92]. Addressing the suppressive nature of these TME elements may improve ICI treatment outcomes.

Advancements in technology, such as multiplex immunofluorescence and single-cell transcriptomics, have enriched our understanding of the TME's complexity, allowing for more precise patient selection and predictions regarding ICI therapy[93].

The full potential of ICIs in treating gastric cancer can only be realized through a comprehensive approach that combines the strengths of various biomarkers, from genetic and molecular indicators to an in-depth analysis of the TME. Continuing to enhance our understanding and application of these biomarkers will pave the way for personalized immunotherapeutic strategies, tailored to the unique characteristics of each patient's cancer.

Challenges Predicting ICI Response

The integration of Immune Checkpoint Inhibitors (ICIs) into gastric cancer treatment has been associated with several challenges in predicting clinical responses.

Addressing PD-L1 Testing Limitations

PD-L1 expression testing by Immunohistochemistry (IHC) is a critical component of cancer management but faces several technical challenges that can impact its utility as a predictive biomarker. There is variability across different assay platforms[48] and antibodies[94] in terms of sensitivity and specificity. Heterogeneous scoring approaches[95] and positivity cut-offs[95] also contribute to discordant results between tests. Limited and non-representative tumor sampling can provide an inaccurate PD-L1 assessment, given temporal and spatial heterogeneity in expression over time and between tumor sites[48,96].

One key source of variability is the use of different diagnostic assays and antibody clones. Comparing clones 22C3, 28-8, SP263, and SP142, inter-assay concordance for defining PD-L1 tumor proportion score (TPS) was only moderate[97,98]. This indicates PD-L1 status can differ based on the test platform. Differing sensitivities/specificities of antibody clones also impact results. For instance, a study found that 22C3 is the most sensitive PD-L1 IHC assay for tumor cell expression, followed by 28-8 and then SP142[97]. Another study observed that the PD-L1 clones, 22C3 and 28-8, are comparable, and if PD-L1 expression using 22C3 is negative, considering the use of 28-8 for evaluating expression may be beneficial[99].

Pre-analytical factors such as sample fixation and storage conditions can significantly influence the stability and detectability of PD-L1 protein. Prolonged

fixation or improper storage may lead to antigen degradation and false-negative results[100]. Standardizing pre-analytical protocols is crucial for a reliable PD-L1 assessment[94].

Heterogeneity of PD-L1 expression within a tumor, both spatially and temporally, poses another challenge[101]. Sampling bias and the use of archival tissues may not accurately reflect the current PD-L1 status of the tumor[102], leading to misclassification of patients. Scoring approaches and positivity cutoffs also differ. While some tests use tumor cell staining alone, others incorporate immune cell staining with tumor cell positivity[49,103]. Variable cutoffs to determine PD-L1 positive status contribute to discordant classification. For instance, KEYNOTE-061 used CPS $\geq$1[104] while KEYNOTE-059 used CPS $\geq$10[105] to assess pembrolizumab efficacy.

Obtaining a representative tumor sample is another challenge. Heterogeneity in PD-L1 expression can lead to under- or over-estimation if limited sections are tested[102,106,107]. Moreover, there can be discordance in PD-L1 status between primary and metastatic lesions[96,108]. One study found an inconsistency rate of 33.0% in PD-L1 expression between primary and recurrent/metastatic lesions[109]. Another study found that the concordance of PD-L1 positivity between primary and metastatic tumors was moderate with one assay (22C3), but poor with another (SP142)[110]. This discordance can pose significant issues in determining the appropriate therapeutic approach.

Overall, variability in assays, antibodies, scoring, sampling, and cutoffs impacts reliable PD-L1 assessment. Standardizing techniques and interpretation is critical to improve the utility of guiding immunotherapy decisions[94,111].

Overcoming Disease Heterogeneity

Gastric cancer (GC) is a highly complex and heterogeneous disease, characterized by diverse molecular subtypes driven by unique genomic aberrations[112]. These molecular subtypes harbor differential immunogenic, inflammatory, and immunosuppressive profiles that can modulate sensitivity to Immune Checkpoint Inhibitors (ICIs)[112].

The molecular subtypes of GC include Epstein-Barr virus (EBV)-positive, microsatellite unstable (MSI), genetically stable (GS), and Chromosomal Instability (CIN) cancers[112]. Each subtype exhibits distinct genomic and immune characteristics that influence their response to ICIs[112].

EBV-positive and MSI gastric cancers are known for their high immune signatures and ICI response rates[112]. EBV-positive gastric cancers are associated with high levels of DNA hypermethylation, recurrent PIK3CA mutations, and amplification of JAK2, PD-L1, and PD-L2[112]. MSI gastric cancers, on the other hand, are characterized by high mutation rates due to defects in the DNA mismatch repair system[112]. These genomic features contribute to the high immunogenicity of these subtypes, leading to increased ICI response rates[112].

In contrast, GS and CIN gastric cancers generally exhibit lower immune signatures and ICI response rates[112]. GS gastric cancers are often associated with diffuse histology and mutations in CDH1 and RHOA[112]. CIN gastric cancers, the most common subtype, are characterized by marked aneuploidy and receptor tyrosine kinase amplifications[112]. The genomic stability of these subtypes may contribute to their lower immunogenicity and ICI response rates[112].

Given the heterogeneity of GC, there is an ongoing need to develop tailored ICI-based regimens matched to specific genomic and immune-based subtypes[112]. Recent advancements in GC diagnosis, staging, treatment, and prognosis have paved the way for the development of such personalized treatment strategies[113]. In conclusion, understanding the heterogeneity of GC at the molecular level is crucial for the development of effective ICI-based therapies. As research in this field continues to advance, it is hoped that more personalized and effective treatment strategies for GC will be developed.

Mitigating Therapeutic Resistance

Immune Checkpoint Inhibitors (ICIs) have revolutionized the treatment landscape for various malignancies, including advanced gastric cancer[114,115]. These therapies work by blocking inhibitory pathways, known as immune checkpoints, that are often hijacked by cancer cells to evade immune destruction[115]. Despite the promising therapeutic potential of ICIs, a significant proportion of patients eventually develop resistance, limiting the long-term efficacy of these treatments[114,115].

One mechanism of resistance involves the upregulation of alternative immune checkpoints[114]. Cancer cells can express a variety of immune checkpoint molecules that can inhibit T cell function and promote immune evasion[116]. When one immune checkpoint pathway is blocked, others may be upregulated to compensate, leading to resistance[116].

Loss of antigenicity is another mechanism that can contribute to resistance[114]. This can occur due to mu-

tations in the genes encoding tumor antigens or alterations in the machinery involved in antigen processing and presentation [114]. As a result, the immune system may fail to recognize and target the cancer cells [117].

Deficiencies in the antigen presentation machinery can also lead to resistance [114]. This can occur due to mutations in the genes encoding the components of the antigen presentation machinery or due to the downregulation of these components [118]. As a result, the immune system may fail to recognize and target the cancer cells [118].

The exclusion of T cells from the tumor microenvironment is another mechanism that can contribute to resistance [114]. This can occur due to the presence of physical barriers, such as a dense extracellular matrix, or due to the secretion of immunosuppressive factors by cancer cells or other cells within the tumor microenvironment [119]. As a result, T cells may be unable to infiltrate the tumor and exert their anti-tumor effects [119].

While resistance to ICIs poses a significant challenge in the treatment of advanced gastric cancer, ongoing research into the underlying mechanisms and potential strategies for overcoming resistance offers hope for improving long-term treatment outcomes. However, further studies focused specifically on elucidating resistance mechanisms and testing approaches to mitigate or reverse resistance in gastric cancer are warranted.

In summary, significant challenges persist in accurately identifying gastric cancer patients likely to achieve optimal clinical benefit with Immune Checkpoint Inhibitors. Advancing biomarker development, unraveling genomic and immune heterogeneity in gastric cancer, and understanding resistance mechanisms represent critical unmet needs to further enhance the predictive potential of immunotherapeutic approaches.

FUTURE OUTLOOK: BIOMARKER RESEARCH DIRECTIONS

Biomarkers have become indispensable in precision oncology, offering the potential to significantly enhance the success of cancer drug development and treatment [120]. The aim is to accelerate the approval of more effective cancer therapies while adeptly navigating the inherent high risks within this arena [120].

The future trajectory of biomarker research points towards an increased reliance on liquid biopsy and serial sampling. These methodologies aim to unravel tumor heterogeneity and drug resistance mechanisms more effectively [121]. Liquid biopsies, such as circulating tumor DNA (ctDNA) analyses, represent a promising, minimally invasive technique for the ongoing monitoring of treatment responses and the identification of resistance mechanisms [122]. By delivering instantaneous insights into the changing molecular composition of tumors, liquid biopsies facilitate the early detection of resistance to therapy, thereby enabling the prompt adjustment of treatment protocols [123].

Ongoing monitoring of biomarkers through liquid biopsies could also shine a light on the dynamics of immune response and the initial signs of immune evasion [122]. This insight is crucial for devising strategies aimed at either circumventing or overcoming immunotherapy resistance. When integrated with other molecular and clinical data, the insights from liquid biopsies could lead to a more nuanced understanding of treatment response and resistance dynamics. This knowledge, in turn, could foster the development of tailored immunotherapy strategies [124]. However, validating the clinical utility of liquid biopsies, particularly in the context of gastric cancer immunotherapy, and standardizing their implementation remain critical needs.

Genomic sequencing technologies are at the forefront of identifying cancer biomarkers, gene signatures, and aberrant expressions that influence cancer development and progression, alongside identifying molecular therapy targets [125]. Immunogenomic profiling has deepened our understanding of cancer, revealing potential therapeutic targets, new subtypes, and more effective treatment modalities [126]. The surge in available high-throughput molecular data — including genomics, transcriptomics, and proteomics — presents vast opportunities for discovering novel, predictive biomarkers [127]. Utilizing integrative bioinformatics to analyze multi-omics data could yield groundbreaking biomarkers and reveal the interplay between molecular alterations and immunotherapy response [128,129].

Advanced bioinformatics, employing techniques such as machine learning and data mining, is instrumental in sifting through these large datasets to uncover patterns linked to treatment outcomes or resistance. The fusion of bioinformatic pipelines and multi-omics data promises a comprehensive understanding of the tumor microenvironment's complex interactions. This approach could identify primary factors driving immune responses and potential immunotherapy targets.

Moreover, the precision of statistical methodologies in analyzing these intricate datasets cannot be emphasized enough. Sophisticated statistical modeling is crucial for extracting meaningful insights from

the wealth of multi-dimensional data [130]. The growing adoption of predictive modeling, harnessing machine learning, and artificial intelligence, is propelling us towards more accurately predicting patient outcomes following immune checkpoint inhibitor therapy [54,131].

Emerging research highlights the importance of not just the presence and makeup of tumor-infiltrating immune cells but also their spatial distribution in influencing tumor behavior and treatment response [132,133]. Holistic analyses combining genomic, transcriptomic, proteomic, and multiplex immunohistochemistry (IHC) techniques are paving the way for precision oncology. These include next-generation sequencing for therapy-guiding DNA/RNA variant detection [134], transcriptomic analyses to profile proteins [135], proteomics for identifying protein expression modifications [136], and multiplex IHC for the assessment of various immune markers simultaneously [137].

Personalized immunotherapy, particularly using patient-specific tumor neoantigens for vaccine development, presents a promising avenue [138,139]. These vaccines aim to elicit strong anti-tumor T-cell responses by presenting the immune system with unique tumor-specific antigens [138,139]. Clinical trials exploring personalized neoantigen vaccine platforms, often in combination with immune checkpoint inhibitors, suggest a potential for improved patient outcomes [140,141].

Additionally, the gut microbiome's role in modulating anti-tumor immunity and enhancing immunotherapy effectiveness is gaining attention [142]. Studies indicating specific bacterial species' enrichment in treatment responders suggest that microbiome modulation could be a novel strategy to augment immunotherapy success [143]. Exploring metabolic pathway targeting within the tumor microenvironment emerges as another strategy to boost immunotherapy efficacy by fostering conditions that support anti-tumor immunity [144–146].

Collaborative efforts across research, clinical, and bioinformatics disciplines are crucial for harnessing big data's full potential in advancing predictive biomarker research toward clinical application. Ongoing endeavors to refine predictive biomarkers beyond PD-L1, aiming to pin down patients who would benefit most from immune checkpoint inhibitors, hold promise. However, realizing these advancements in routine clinical practice necessitates further research, validation, and multi-disciplinary cooperation.

Emergence of Combination Strategies To enhance efficacy, immunotherapies are being explored in combination strategies to address tumor heterogeneity [147]. One well-studied approach combines immune checkpoint inhibitors (ICIs) with chemotherapy. Several trials have demonstrated improved survival compared to chemotherapy alone when used as a first-line treatment, including in triple-negative breast cancer [148,149]. Beyond chemotherapy, studies are investigating the combination of ICIs with other modalities including anti-angiogenics, epigenetic agents, targeted therapies, immunomodulators, radiation, and cancer vaccines [29,150]. Each offers distinct mechanisms that potentially enhance ICIs. For example, anti-angiogenics inhibit blood vessel formation, starving tumors [29], while epigenetic agents alter cancer cell gene expression, potentially increasing their susceptibility to immune attack [151,152]. Targeted therapies act on specific cancer-related molecular targets; immunomodulators enhance anti-cancer immunity [150,153]. Overcoming the immunosuppressive tumor microenvironment is key. Determining the optimal treatment sequences/partnerships to address this barrier is an active area of immuno-oncology research [147]. In summary, combination strategies are promising, but optimization, along with strategies that counter tumor-mediated immune suppression, warrant further study.

Evolution of Precision Medicine Approaches Precision, or personalized medicine, aims to tailor cancer treatment based on the molecular profile of an individual's tumor [154], with the potential to improve outcomes by targeting genomic drivers while minimizing unnecessary toxicity [154]. Comprehensive genomic profiling initiatives are shifting management toward precision immuno-oncology [155,156]. These initiatives utilize advanced genomic sequencing to guide the selection of therapies most likely to benefit an individual patient [155]. Immunotherapies, specifically immune checkpoint inhibitors (ICIs), have transformed cancer treatment [156], but not all patients respond [53]. Defining alterations linked to ICI response represents a focus area [53]—identifying genetic/molecular changes associated with sensitivity to guide patient selection and limit unnecessary treatment [53]. Tailoring combination regimens based on the genomic profile of individual tumors epitomizes precision medicine [154]. This approach employs multiple targeted therapies to maximize benefit within molecularly defined cohorts [154]. Recent advances have seen the development of combinations joining ICIs and targeted therapies, demonstrating the potential to enhance immunotherapy efficacy and overcome resistance [157]. Single-arm

basket trials represent a novel approach, testing a single intervention across multiple molecularly defined tumor types/subtypes[155]. Enrichment strategies facilitate the delivery of personalized therapy matched to tumor genomic profiles[155], a promising advancement. In summary, precision medicine is rapidly progressing through genomic profiling initiatives, alterations predicting ICI response, tailored combinations, and basket trial enrichment strategies that promise to improve patient outcomes.

Overcoming Therapeutic Resistance Immune checkpoint inhibitors (ICIs) have shown promising efficacy in advanced gastric cancer. However, many patients eventually develop resistance, limiting long-term benefits[114]. Understanding resistance mechanisms is key to improving outcomes. One mechanism of resistance involves the upregulation of alternative checkpoints like VISTA or LAG-3 when initial pathways are blocked[158,159]. This enables ongoing immune evasion, allowing cancer cells to continue growing despite the presence of ICIs. Approaches that simultaneously target multiple checkpoints could potentially help overcome this redundancy[160]. For instance, combination therapies that target both PD-1 and LAG-3 have shown promise in preclinical models[160]. Moreover, a number of clinical trials are currently exploring more effective combination therapy programs[160]. Loss of antigenicity, due to mutations in genes encoding tumor antigens, can also drive resistance[161,162]. This mechanism allows cancer cells to evade the immune system and continue to proliferate. Strategies focused on enhancing antigen presentation may help reactivate anti-tumor immunity[163]. Presenting new neoantigens, which are unique to individual tumors, is another potential approach to improve the efficacy of gastric cancer treatment[163]. Neoantigens can stimulate a stronger immune response as they are not present in normal cells, making them ideal targets for immunotherapy[163]. Research is ongoing to develop strategies for identifying and targeting these neoantigens in gastric cancer[163]. Deficiencies in antigen processing and presentation contribute to resistance to immune checkpoint inhibitors (ICIs) in gastric cancer[163,164]. This is because the antigen processing and presentation machinery (APM) plays a crucial role in the immune response to tumors[163,164]. When this machinery is deficient, it can lead to a decrease in the presentation of tumor antigens to the immune system, thereby allowing tumor cells to evade immune surveillance[163,164]. Stimulating the APM is a promising strategy to counter such resistance[163,164]. For instance, a study proposed a signature based on genes associated with antigen processing and presentation (APscore) to predict prognosis and response to ICIs in advanced gastric cancer[163]. The APscore was found to be an effective predictive biomarker of the response to ICIs[163]. Additionally, the physical exclusion of T cells from tumor sites can enable immune evasion. This is often mediated by the tumor microenvironment, which can create a physical barrier to T cell entry[165–167]. Modulating barriers that inhibit infiltration could help overcome this exclusion and improve T cell activity at tumor sites. For instance, a study showed that cancer-associated fibroblasts, along with the extracellular matrix within the tumor microenvironment, create a physical barrier to T cell entry[165]. Targeting these fibroblasts effectively reversed this exclusion, promoting T cell infiltration into tumors and potentiating the response to immunotherapy[165]. Another study highlighted the role of cytokines and chemokines in modulating the recruitment of T cells and the overall cellular compositions of the tumor microenvironment[166]. Manipulating the cytokine or chemokine environment has shown success in preclinical models and early-stage clinical trials[166,167]. While resistance limits efficacy, ongoing research into underlying mechanisms and strategies like combination therapies, improving antigenicity, and modulation of immunosuppression shows promise in prolonging patient benefit with immunotherapies.

CONCLUSIONS

This review explores the predictive value and emerging role of immune checkpoint inhibitors (ICIs) in the treatment of gastric cancer. Key themes include:

- ICIs, such as anti-PD-1/PD-L1 antibodies, demonstrate promising efficacy in advanced gastric cancer, especially when combined with chemotherapy. Pivotal trials have shown survival benefits of adding ICIs to chemotherapy versus chemotherapy alone.
- ICIs exhibit an acceptable safety profile, with lower rates of adverse events compared to those associated with chemotherapy. However, immune-related side effects do occur but are generally manageable.
- PD-L1 expression testing on tumor cells is currently the main biomarker guiding patient selection for ICIs. This approach, however, faces limitations regarding assay inconsistencies and score cutoffs, highlighting the need for better standardization.
- Beyond PD-L1 testing, emerging supplemental predictive biomarkers being assessed include tumor mutational burden, microsatellite instability, and immune gene expression signatures related to T-cell inflammation and interferon signaling.

- Accurately identifying patients likely to benefit from ICIs remains challenging due to issues around PD-L1 testing, disease heterogeneity, and resistance mechanisms that limit the durability of response.

Key research directions focus on overcoming these obstacles by developing novel biomarkers, optimizing combination immunotherapies, further elucidating the immune microenvironment, and unraveling mechanisms of therapeutic resistance. Based on the findings of this review, several actionable insights for clinicians and researchers can be derived. In clinical practice, it is essential to adopt standardized PD-L1 testing protocols and interpretation criteria to ensure reliable patient selection for ICI therapy. Furthermore, a multidisciplinary approach involving collaboration between oncologists, pathologists, and bioinformaticians is recommended to optimize the implementation of predictive biomarkers and personalized treatment strategies. In terms of research priorities, further validation of emerging biomarkers beyond PD-L1, such as tumor mutational burden, microsatellite instability, and immune gene signatures, should be pursued to refine patient stratification. Additionally, investigating rational combination approaches, particularly those targeting the immunosuppressive tumor microenvironment, holds promise for enhancing ICI efficacy and overcoming resistance. Continued efforts to elucidate the complex interplay between tumor genomics, immune landscape, and therapeutic response will be essential to advance the field.

Looking ahead, the future of ICI treatment in gastric cancer is promising, with ongoing research and technological advancements poised to revolutionize patient care. The integration of multi-omics profiling, liquid biopsy techniques, and artificial intelligence-based predictive models holds immense potential to enable real-time monitoring of treatment response, early detection of resistance, and dynamic adaptation of therapeutic strategies. Furthermore, the development of personalized neoantigen vaccines and microbiome-modulating approaches represents exciting avenues for enhancing ICI efficacy. Importantly, fostering interdisciplinary collaborations among clinicians, researchers, bioinformaticians, and industry partners will be crucial to accelerate progress and translate discoveries into tangible benefits for patients. By leveraging collective expertise and resources, the gastric cancer community can work towards a future where precision immunotherapy becomes a reality, offering hope for improved outcomes and quality of life for those affected by this challenging disease. In conclusion, ICIs represent a promising new therapeutic avenue in gastric cancer but require further optimization of predictive markers, rational combinations, and strategies to counter resistance to expand meaningful clinical benefit to more patients. Continued research progress in these areas is critical to fully harness the potential of immunotherapy for this disease.

ABBREVIATIONS

APCs: Antigen presenting cells, APM: Antigen processing and presentation machinery, APscore: Antigen processing and presentation, ARG1: Enzyme arginase-1, ARID1A: AT-rich interaction domain 1A, ATP: Adenosin Triphosphat, CAFs: Cancer-associated fibroblasts, CAR: Engineered chimeric antigen receptor, CD: Cluster of Differentiation, CDH1: Cadherin-1, CIN: Chromosomal Instability, ctDNA: circulating tumor DNA, CTLA-4: Cytotoxic T lymphocyte antigen-4, CPS: Combined positive score, DNA: Deoxyribonucleic Acid, EBV: Epstein-Barr virus, FDA: Food and Drug Administration, GC: Gastric cancer, GEJ: Gastroesophageal junction, GS: Genetically stable, ICIs: Immune checkpoint inhibitors, IFN-γ: Interferon-gamma, IHC: Immunohistochemistry, irAEs: immune-related adverse events, JAK2: Janus Kinase 2, MSI: Microsatellite instability, Muts/Mb: Mutations per megabase, PD-1: Programmed cell death protein-1, PD-L1: Programmed death ligand-1, PIK3CA: 3-kinase catalytic subunit alpha, RHOA: Ras Homolog Family Member A, RNA: Ribonucleic Acid, TMB: Tumor Mutational Burden, TME: The tumor microenvironment, TNF: Tumor Necrosis Factor, TNM: Tumor, Node, and Metastasis, TPS: Tumor proportion score

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The authors declare that they have no competing interests.

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