Advances in Clinical Pharmacology and Therapeutics

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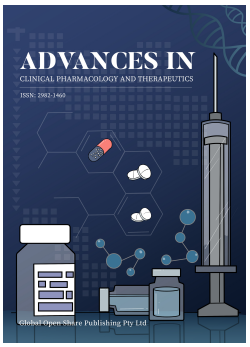

Review

Advances in Combination Therapy for Gastric Cancer: Integrating Targeted Agents and Immunotherapy

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Abstract

Background: Despite the recent advancement in the diagnostic and therapeutic approaches, gastric cancer continues to be one of the most cardinal causes of the cancer death globally. Trends of the recent years in composite treatments that integrate biomarkers with immunotherapy along with well-tailored and individualized aggregate remedies introduce perspectives for the optimization of the outcomes.

Objective: The present review intends to qualify to give as much and more than a very comprehensive update on the latest developments of the pool of targeted agents and immunotherapy for gastric cancer, focusing on the mechanisms, medical trial effects, and future directions.

Methods: The papers for the review were identified through a comprehensive search of both PubMed as well as other databases represented in the actual journals. The filter used for search was the actual last 10 years. As for the criteria for inclusion on the studies it was only the relevance of the material, and their experience on combination remedies in gastric cancers.

Results: The combination of the former therapies, namely the human epidermal growth factor receptor 2 (HER2 inhibitors), Vascular Endothelial Growth Factor (VEGF) inhibitors, and mesenchymal-epithelial transition (MET) inhibitors has demonstrated better efficiency in various clinical trials not to mention having the right immune checkpoint inhibitors. The most important findings of current literature suggest that there is presumably cooperative interaction of all of these components, which results in more accurate anti-tumor reactions and better survival rates.

Conclusion: The inclusion of combination therapy should be highly included into recommended treatment plans for gastric cancer, especially for patients with certain molecular profiles. The evidence suggests that the combination of targeted treatment programs with immunotherapy provides significant advantages compared to typical monotherapy approaches, including increased effectiveness and improved overall survival rates.

Keywords

Gastric cancer, Combination therapy, Targeted agents, Immunotherapy, HER2, Immune checkpoint inhibitors

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1. Introduction

Gastric cancer is a significant global health issue, ranking as the fifth most common cancer and the third leading cause of cancer-related mortality worldwide. In 2020 alone, more than a million new cases were reported, along with over 700,000 deaths, emphasizing the urgent need for effective diagnosis and treatment strategies [1-6]. The complexity of gastric cancer stems from its heterogeneity, encompassing various histological subtypes and molecular classifications that influence both diagnosis and treatment approaches. Adenocarcinoma accounts for approximately 86-89% of all gastric cancers and is further divided into intestinal and diffuse types, among others, as classified by Lauren. The Cancer Genome Atlas (TCGA) has identified four distinct molecular subtypes of gastric cancer, including chromosomal instability (CIN), microsatellite instability (MSI), genomically stable (GS), and Epstein-Barr virus (EBV) positive. These molecular subgroups highlight the disease's diversity and have significant implications for developing targeted and personalized treatment strategies [2].

Despite advancements in early diagnosis and treatment in some regions, the majority of gastric cancer patients present with advanced or metastatic disease at the time of diagnosis, when surgical options are often no longer viable. Systemic chemotherapy has traditionally been the cornerstone of treatment for advanced gastric cancer, typically involving platinum-containing agents (cisplatin or oxaliplatin), fluoropyrimidines (5-fluorouracil or capecitabine), or taxanes (paclitaxel). While these regimens can improve survival, they are often associated with significant toxicity and limited efficacy, with a median overall survival (OS) of less than one year for advanced-stage patients [3].

In recent years, the focus has shifted toward targeted therapies that aim to interfere with specific molecular pathways involved in cancer progression. HER2-targeted therapy, for instance, has emerged as a significant advancement in the treatment of HER2-positive gastric cancer, which accounts for 15-20% of cases. Trastuzumab, a HER2-directed monoclonal antibody, has been approved for the first-line treatment of HER2-positive gastric cancer based on the results of the ToGA trial, which demonstrated improved OS when trastuzumab was added to chemotherapy. Additionally, VEGF inhibitors such as ramucirumab have shown efficacy in prolonging survival in patients with advanced gastric cancer following chemotherapy failure. However, the benefits of these targeted therapies are often limited to specific patient subgroups, and resistance to treatment remains a significant challenge [4-6].

Given the limitations of conventional chemotherapy and the challenges associated with targeted therapies, there is a growing interest in combination treatments that integrate targeted therapies with immunotherapy. This study aims to evaluate the therapeutic effectiveness of combination treatments in improving survival outcomes, including OS and progression-free survival, for patients with advanced gastric cancer. Additionally, the study seeks to assess the response of various molecular subtypes of gastric cancer—such as HER2-positive, MSI-high, or EBV-positive—to combination therapy and determine which subgroups derive the greatest benefit from these treatments. Finally, the study will explore the molecular mechanisms underlying the synergistic effects of combining targeted therapies with immune checkpoint inhibitors (ICIs) and how these mechanisms contribute to treatment efficacy.

2. Literature Review

2.1 Research status of Gastric Cancer

Therefore, gastric cancer remains one of the leading global health concerns since the traditional medications tend to be of low efficiency. Among the latest developments in the concept ‘combination medicines,’ which combines targeted drugs with immunotherapy, new prospects for treatment can be distinguished. The following paper aims at reviewing the literature concerning the evolution of the treatment of gastric cancer, mainly focusing on the potentials of integrating targeted therapies with immune checkpoint inhibitors [7-9]. This review has a viewpoint of answering questions of the current trends in management of stomach cancer with an emphasis on the available research and medical trials [9-11]. It is concerned with the success and issues of implementing novel recovery methods. Even though this kind of cancer has been showing signs of reduction in the USA, the median of the survival rate is less than twelve months. In this context, the traditional approach to the treatment of the disorder entails the use of cytotoxic chemotherapy. Nevertheless, current advances in molecular biology have brought new targeted therapies as the part of management of gastric cancer. These alternatives have very high potential of increasing the survival ratios and reducing unfavourable side effects [11-14]. For instance, a synergistic approach of trastuzumab in conjunction with chemotherapy has enhanced outcomes of HER2-positive gastric malignancies. The second line treatment involves ramucirumab; this is inhibitors of VEGF receptor that can be used as a single agent or in combination with chemotherapy While the use of pembrolizumab, immune checkpoint inhibitor is approved where PD-L1 has been positive (Figure 1).

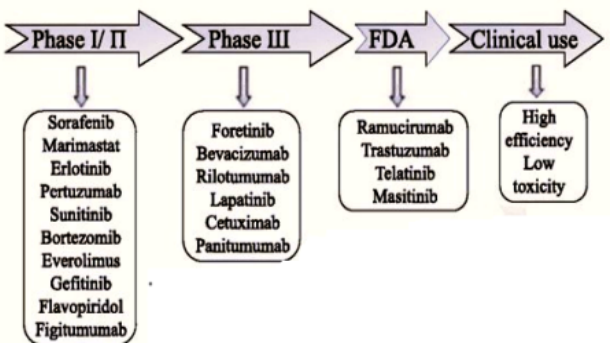

Figure 1. Molecular targeted therapy for the treatment of Gastric cancer

Studies have revealed that gastric cancer which is the fourth leading cause of cancer related mortality globally, always presents with an average survival of approximately 12-15 months through conventional chemotherapy [12-15]. However, with the development of immune ICIs such as anti-PD-1 and PD-L1-Mabs, AGC patients are now endowed with better ways to improve their survival rates. This article covers the general concept of ICI like nivolumab and pembrolizumab to enhance the online survival in several molecular subtypes of gastric cancer, including those with MSI-H as well as TMB-H. These medicines have been demonstrated to work by way of clinical trials such as ATTRACTION-2, CheckMate-649 and KEYNOTE-811 with resulting approval throughout numerous therapy routines. For instance, nivolumab with chemotherapy is used as the first-line treatment for AGC while pembrolizumab is only used in MSI-H or HER2-positive AGC. Molecular and immunological properties of gastric cancer are also highlighted in the article including tumour subtypes like EBV, MSI, CIN, and GS. Each subtype reveals some features that may influence the reaction to ICIs [14-17].

Narita et al [18] opine that gastric cancer is still a global health issue of significant concern, albeit with a diminished rate of incidence in the past few years along with improvements made in diagnostic, surgical and chemotherapeutic interventions. The expenses of existence have remained stagnant on the least and therefore there is a need for better treatments. Over the last few years, a research interest have been placed on the molecular subtypes of gastric cancer in order to investigate the genetic changes, epigenetic changes and dysregulated molecular pathways that contribute to the development, progression and metastasis of this cancer. The specific recovery strategies have been introduced into the general practices, the other methods are under investigation in clinical trials. It is necessary to understand specialized molecular features and unique biomarkers of cancers in first place to address specific tumours [18].

GC is among the leading causes of cancer morbidity and mortality affecting, with more than one million new cases and almost 700000 deaths recorded every year. This condition is more common in low and middle-income countries especially in east Asia, Europe and South America. Distal gastric cancer incidence is now lowering because of factors such as the elimination of Helicobacter pylori, and advancement in food conservation techniques [19-22]. Nonetheless, there is an increased trend of incidence of gastro esophageal junction cancer in western world due to higher prevalence of gastroesophageal reflux disease and obesity. Thus, for gastric cancer and in particular for the affected regional and further metastatic cancer types, the probability of cure has only slightly improved in surgery associated with multimodal therapies, with a five-year survival rate of less than 30% in the worse-case scenario. Over the last few years, clearer insight into molecular pathogenesis of GC has arisen, which stimulated the progress in the classification based on genomic factors and analysis of mediator and predictor markers.

Table 1. Literature reviews

Authors	Year	Key Focus	Findings	Challenges/Recommendations
Patel et al.	2020	Conventional vs. targeted therapies in gastric cancer	Traditional chemotherapy has limited success; Trastuzumab (HER2-positive) and Ramucirumab (VEGF inhibitor) show improved outcomes. Pembrolizumab (immune checkpoint inhibitor) for PD-L1 positive cases.	Emphasizes the need for targeted therapies to improve survival and reduce toxicity
Takei et al.	2022	Role of immune checkpoint inhibitors (ICIs) in advanced gastric cancer (AGC)	ICIs like nivolumab and pembrolizumab extend survival in AGC patients, especially in MSI-H or TMB-H subtypes. Clinical trials like ATTRACTION-2 and KEYNOTE-811 support their efficacy.	Highlights the importance of molecular and immunological profiling for personalized treatment strategies.
Laze et al.	2021	Molecular heterogeneity and targeted therapy in gastric cancer	Despite diagnostic and treatment advancements, survival improvements are minor. Research focuses on genetic mutations and molecular signaling pathways for personalized therapy.	Identifying molecular patterns and biomarkers is crucial for personalized treatment, though challenges in efficacy remain.
Pellino et al.	2021	Global prevalence and molecular understanding of gastric cancer	Gastric cancer remains prevalent, especially in low- and middle-income countries. Advances in molecular mechanisms and genomic classifications have improved understanding but survival rates remain low.	Recommends continued research into prognostic and predictive biomarkers to improve survival rates.
Guan et al.	2021	Advancements in gastric cancer treatment, focusing on perioperative chemotherapy and molecular diagnostics	Traditional chemotherapy shows modest outcomes. Advances in molecular diagnostics allow for targeted treatments based on biomarkers like PD-L1, MSI, and HER2.	Integration of targeted agents and immunotherapy is promising but requires optimized treatment protocols and management of side effects.

Traditional chemotherapy by cyclical MTD and CAF has been considered as the main treatment method for metastatic gastric cancer and has produced acceptable survival rates. Over the last few years, the management of respectable gastric cancer has improved with regard to the administration of perioperative chemotherapy. The

application of the molecular diagnostic tools has led to subclassification of gastric cancer based on biomarkers as PD-L1, MSI, and HER2, thus increasing the chances of targeted treatment. Applying specific medicines and immunotherapy in the case of stomach cancer is considered as the advance in the oncology. Approval of this combo treatment has demonstrated that it can increase treatment efficiency by bypassing these mechanisms of resistance, in addition, increase the survival of patients. Further study and trials are needed to confirm these new treatments have advantages to help diagnose and treat gastric cancer and enhance the patient's quality of life (Table 1) [17-30].

2.2 Treatment of Gastric Cancer

The treatment of gastric cancer has evolved from a reliance on traditional chemotherapy to a more nuanced approach involving targeted therapies and immunotherapy. The therapeutic effect depends largely on the molecular characteristics of the tumor, which helps define the optimal treatment regimen for individual patients [8].

2.2.1 Targeted Therapy

Targeted therapy involves drugs that specifically target molecular pathways involved in cancer cell growth and survival. In gastric cancer, several pathways have been identified as key drivers of tumor progression, including HER2, VEGF, and MET.

- HER2-Targeted Therapy: HER2 is overexpressed in about 15-20% of gastric cancers, and its amplification is associated with a more aggressive disease course. Trastuzumab, a monoclonal antibody targeting HER2, was one of the first targeted therapies approved for HER2-positive gastric cancer. Studies such as the ToGA trial demonstrated significant improvements in OS when trastuzumab was combined with chemotherapy. However, resistance often develops, leading to the exploration of combination treatments that include HER2 inhibitors and immune checkpoint inhibitors like PD-1/PD-L1 blockers [8-10].

- VEGF-Targeted Therapy: VEGF promotes angiogenesis, enabling tumors to develop their own blood supply. Ramucirumab, an anti-VEGFR-2 monoclonal antibody, has shown efficacy in prolonging survival in patients with advanced gastric cancer, especially when combined with chemotherapy. VEGF inhibitors not only inhibit tumor growth but also normalize the tumor vasculature, enhancing the effectiveness of other treatments, including immunotherapy [11].

- MET-Targeted Therapy: MET, a receptor tyrosine kinase, is implicated in tumor cell proliferation, survival, and metastasis. In cases of MET amplification or overexpression, MET inhibitors like crizotinib and capmatinib have demonstrated antitumor effects. However, MET amplification is relatively rare in gastric cancer, and resistance mechanisms often emerge, making combination therapies with immunotherapy a promising approach [12].

2.2.2 Immunotherapy

Immunotherapy, particularly immune checkpoint inhibitors, has emerged as a breakthrough in the treatment of gastric cancer. The immune system's ability to recognize and destroy cancer cells is often impaired by tumors that exploit immune checkpoint pathways to evade detection.

- PD-1/PD-L1 Inhibitors: PD-1 and its ligand, PD-L1, play a critical role in immune evasion by tumors. Pembrolizumab and nivolumab, PD-1 inhibitors, have been approved for use in gastric cancer, especially in patients with high MSI (MSI-H) or PD-L1-positive tumors. Clinical trials such as KEYNOTE-811 and ATTRACTION-2 have demonstrated that these immunotherapies improve OS and response rates, particularly when combined with chemotherapy or targeted therapies [13-14].

- CTLA-4 Inhibitors: While less commonly used in gastric cancer, ipilimumab, a CTLA-4 inhibitor, has been explored in combination with PD-1 inhibitors to enhance immune responses, although its clinical efficacy remains under investigation in this cancer type.

2.2.3 Research Status of Combination Therapies

Current research in gastric cancer focuses on combining targeted therapies with immunotherapy to overcome resistance mechanisms and improve patient outcomes. Several clinical trials are underway to evaluate the efficacy of combining HER2, VEGF, and MET inhibitors with PD-1/PD-L1 inhibitors. These studies aim to determine which molecular subtypes of gastric cancer respond best to these combinations, with early results suggesting that HER2-positive and MSI-H tumors are particularly responsive.

3. Methods

3.1 Search Strategy

For example, searches have been conducted using combinations such as "gastric cancer AND combination therapy," "targeted treatment AND immunotherapy AND gastric cancer," and "HER2 AND VEGF AND immune checkpoint inhibitors AND gastric cancer." The use of Boolean operators (AND, OR) has been implemented to enhance the search and effectively combine phrases. Each database was queried using its distinct interface and search capabilities. The first search generated a wide range of publications, which were further selected based on titles and abstracts to identify the most relevant ones for the examiner's focus (Table 2).

Table 2. Search Strategy

Search Component	Details
Search Terms	- "gastric cancer AND combination therapy" - "targeted therapy AND immunotherapy AND gastric cancer" - "HER2 AND VEGF AND immune checkpoint inhibitors AND gastric cancer"
Boolean Operators	- AND - OR
Search Strategy	- Searches were conducted using specific combinations of terms to ensure a broad and inclusive search. - Each database was searched using its unique interface and search capabilities.
Databases Searched	- PubMed - MEDLINE - Embase
Initial Search Results	- A large number of articles were identified.
Screening Process	- Titles and abstracts were screened to identify potentially relevant articles. - Full-text reviews were conducted to ensure articles met inclusion criteria.
Additional Searches	- References of selected articles were reviewed to identify additional relevant studies not captured in the initial search. - This backward citation tracking helped discover essential studies potentially missed initially

3.2 Inclusion Criteria (Table 3)

Clinical Studies: The review primarily focused on studies that specifically impacted the implementation of clinical trials. The studies will be categorized as Segment I, II, or III and will specifically examine the effectiveness and safety of combined treatment approaches using targeted therapies and immunotherapy for gastric cancer. Clinical trials offer high-quality information regarding the efficacy of novel therapies and their impact on patient outcomes.

Meta analysis: Meta-analyses that effectively pooled data from several trials to evaluate the effectiveness and safety of combination therapies were also included. These analyses offer valuable insights by combining findings from several studies and can help identify common patterns and effectiveness.

Large-Scale Observational Studies: These studies focused on a significant number of patients and provided information on the real-world use and results of combined treatments in gastric cancer. This study can offer valuable insights on the real-world effectiveness of treatment alternatives outside of controlled clinical trial settings.

Table 3. Inclusion/Exclusion Criteria

Criteria Type	Details
Inclusion Criteria	
Clinical Trials	- Type: Phase I, II, or III clinical trials. - Focus: Efficacy and safety of combination therapies involving targeted agents and immunotherapy for gastric cancer. - Purpose: Provides high-quality evidence on new treatments and their impact on patient outcomes.
Meta-Analyses	- Type: Meta-analyses combining data from multiple studies. - Focus: Efficacy and safety of combination therapies. - Purpose: Offers insights by synthesizing results from various studies, identifying overall trends and effectiveness
Large-Scale Observational Studies	- Type: Observational studies with large patient populations. - Focus: Real-world data on the implementation and outcomes of combination therapies. - Purpose: Provides practical insights into treatment performance outside controlled clinical trial settings.
Exclusion Criteria	
Preclinical Studies	- Type: Studies focused on animal models or in vitro experiments. - Focus: Mechanisms of action and potential effectiveness. - Purpose: Not relevant for clinical outcome reviews
Case Reports	- Type: Individual case reports. - Focus: Specific patient cases. - Purpose: Provides specific insights but lacks generalizability and comprehensive evidence needed for a systematic review.
Studies Not in English	- Type: Studies published in languages other than English. - Purpose: Ensures all included studies can be thoroughly reviewed and understood by the research team.

3.3 Exclusion criteria (Table 3)

Preclinical Studies: Preclinical studies eliminated studies that specifically focused on animal models or in vitro investigations. Although preclinical research is crucial for understanding the mechanisms of action and efficacy of treatments, this study specifically examines the clinical results in actual patients.

Case Reports: Individual case assessments were omitted due to their limited breadth and lack of generalizability to wider patient groups. Case critiques offer valuable information on unique cases but do not supply the comprehensive evidence required for a systematic evaluation of combination therapy.

Non-English Studies: Studies published in languages other than English were omitted. This decision has been made to ensure that study coverage may be thoroughly examined and comprehended by the research team, notwithstanding any language obstacles that may exist.

By following the specified criteria for what to include and exclude, the evaluation attempted to provide a comprehensive and pertinent summary of the evidence on combination therapy for gastric cancer, with a particular emphasis on the most robust and relevant research findings.

3.4 Data Extraction

The data extraction process was conducted methodically to achieve a thorough and accurate representation of the protected research on combination therapy options for gastric cancer. The essential components of each study have been well documented, including the test design, the demographic of the participants, the treatments, the outcomes, and any negative occurrences. The test layout data included information on whether the study was a randomized controlled trial (RCT), meta-analysis, or large-scale observational study. These features have a significant influence on the strength of the evidence. The patient population records encompassed data on the duration of the study, demographic trends, and specific criteria for selecting participants, including both inclusion and exclusion criteria. The interventions were meticulously recorded, providing detailed information on the several types of collective therapies that were assessed. This includes the specific targeted agents and immunotherapy medications that were employed, along with their doses, treatment schedules, and length of therapy.

3.5 Quality Assessment

The quality of the papers included in the review was extensively examined using two well-established tools: the Cochrane risk of bias tool and the GRADE criteria. The Cochrane hazard of bias tool was utilized to evaluate the methodological quality of randomized managed trials (RCTs) and other intervention studies. This device evaluates many domains of bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each region was classified as low risk, high hazard, or undetermined hazard based on the information provided in the study reports. This evaluation identified potential sources of bias that might impact the validity of the study results. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria have been utilized to assess the overall quality of evidence for non-randomized research and observational research.

4. Results: Study Selection

From the initial pool of 1,220 papers found by a thorough search in PubMed, MEDLINE, and Embase, a rigorous selection process resulted in the inclusion of 56 studies for comparison. The selection process involved a comprehensive screening method to ensure that only the highest quality research that met the predetermined inclusion criteria were considered. Firstly, the titles and abstracts of all acknowledged papers were examined to exclude those that were irrelevant, such as studies that did not focus on gastric cancer or combination therapy.After the first screening, further evaluations were conducted to further assess eligibility based on certain criteria. Studies have been conducted to evaluate the effectiveness and safety of combination treatment strategies involving targeted therapies and immunotherapy for gastric cancer. These studies include medical trials, meta-analyses, and large-scale observational studies.

4.1 Study Characteristics

The 56 studies were mainly included in the actual review which mainly encompassed a very much diverse range of form of the research designs, from that of phase I to phase III clinical trials as well as the meta-analyses. These studies varied in length, with sample sizes ranging from 50 to at the least 1,500 sufferers, reflecting an extensive spectrum of research settings and patient populations. Phase I trials often targeted on comparing the protection, tolerability, and greatest dosing of mixture treatments, regularly concerning smaller pattern sizes and exploring new healing combinations. Phase II trials aimed to evaluate the initial efficacy and further compare safety in a bigger cohort, offering early proof on the ability blessings of the treatment options. Phase III trials, being the maximum rigorous, concerned large affected person populations and had been designed to have a look at the latest mixture remedy plans in opposition to popular remedies, thereby providing extra definitive proof of their efficacy and protection (Table 4 Figure 2).

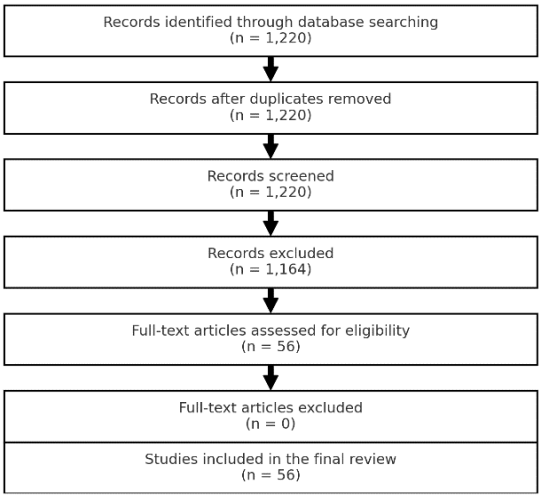

Figure 2. Flowchart as per Primsa Guidelines

Table 4. Study Characteristics

Study Type	Description
Phase I Trials	- Focus: Safety, tolerability, and dosing of combination treatments. - Sample Size: Smaller, varies by study
Phase II Trials	- Focus: Initial efficacy and safety in a larger cohort. - Sample Size: Larger than Phase I.
Phase III Trials	Focus: Efficacy and safety of combination treatments compared to standard treatments. - Sample Size: Large, up to 1,500 patients.
Meta-Analyses	Focus: Synthesis of data from multiple studies to assess effectiveness of combination therapies. - Sample Size: Varies based on included studies.

4.2 HER2-Targeted Therapy and Immunotherapy

Recent studies have clearly shown that great progress has been made in treating HER2-positive gastric cancer by combining HER2-targeted treatments with immune checkpoint inhibitors, particularly PD-1 inhibitors. HER2, also known as human epidermal growth factor receptor 2, is a kind of receptor tyrosine kinase that is excessively expressed in around 15-20% of gastric cancer cases. This overexpression is linked to a more aggressive form of the disease and a less favorable prognosis. Trastuzumab, a HER2-targeted treatment, has been widely used to treat HER2-positive gastric cancer. When used in conjunction with chemotherapy, it has shown significant benefits in both OS and progression-free survival. Nevertheless, despite these advancements, there is still a significant unfulfilled need for additional treatment options due to the emergence of resistance and limited long-term benefits. Recently, the incorporation of immunotherapy, particularly PD-1 inhibitors, has become a potential strategy to enhance the effectiveness of treatment. PD-1 inhibitors, such as pembrolizumab and nivolumab, function by obstructing the PD-1 receptor on immune cells. This action prevents tumor cells from using this route to evade immune surveillance and dampen immunological responses. This method has demonstrated excellent results in several types of cancer by restoring the ability of the immune system to identify and target malignant cells. When used with treatment regimens that target HER2, such as trastuzumab, PD-1 inhibitors utilize their synergistic potential to overcome resistance mechanisms and enhance anti-tumor activity. The efficacy of this combination treatment has been carefully investigated in clinical studies, showing solid data. Studies have demonstrated that the combination of trastuzumab with PD-1 inhibitors significantly enhances objective response rates and prolongs progression-free survival compared to trastuzumab alone. This potent anti-tumor effect is believed to be the result of both directly inhibiting HER2 and enhancing the immune response against HER2-positive tumor cells.

In addition, the combination of HER2-focused treatments and immunotherapy has been found to not only improve effectiveness but also potentially increase OS rates, as indicated by several trials. The rationale for combining these therapeutic strategies is substantiated by preclinical models and early-phase clinical studies, which have demonstrated that PD-1 inhibitors can enhance the immunogenicity of HER2-positive malignancies and reduce immune evasion mechanisms. Although the positive findings, the combination approach also raises significant questions regarding safety and resistance. Although HER2-centered therapies combined with PD-1 inhibitors generally have a favorable overall safety profile, there is an increased risk of immune-related adverse effects, such as pneumonitis, colitis, and endocrinopathies. Vigilant monitoring and manipulation of key outcome variables are crucial to ensure that the benefits of combination therapy exceed the associated risks. Furthermore, continuing research aims to get a deeper understanding of the processes that cause resistance to this combination treatment. It has been observed that some patients may still have disease progression despite initial positive responses.In summary, the integration of HER2 inhibitors with PD-1 inhibitors is a significant advancement in the treatment of HER2-high gastric cancer. This approach shows promise in improving clinical outcomes and addressing current constraints in treatment. Further research is crucial to improve and perfect therapeutic procedures, enhance the selection of individuals impacted by them, and enhance our understanding of the most effective ways to integrate these treatments into medical practice.

4.3 VEGF Inhibitors and Immunotherapy

The combination of VEGF inhibitors and immune checkpoint inhibitors has emerged as a promising strategy for treating advanced gastric cancer. This approach has shown synergistic effects, enhancing both progression-free survival (PFS) and OS in patients. VEGF plays a crucial role in angiogenesis, the process by which tumors develop new blood vessels to sustain their growth and spread. Elevated levels of VEGF in stomach carcinomas are linked to a negative prognosis and resistance to standard treatment methods. VEGF inhibitors, such as ramucirumab, specifically target the VEGF receptor to reduce angiogenesis, hence limiting tumor growth and spread. Ramucirumab is a monoclonal antibody that effectively disrupts the angiogenic signaling pathways that cancers rely on by inhibiting VEGF receptor 2 (VEGFR-2) (Ramucirumab has been shown as an effective treatment option in advanced gastric cancer through clinical studies, showing improved PFS and OS whether taken alone or in combination with chemotherapy (Figure 3). However, the combination of VEGF inhibitors with immune checkpoint inhibitors is a unique method that harnesses the potential for synergistic effects. Immune checkpoint inhibitors, specifically those targeting PD-1 or its ligand PD-L1, function by obstructing the proteins used by malignancies to evade immune system recognition. This enhances the immune system's capacity to identify and eliminate cancer cells. The rationale for combining VEGF inhibitors with immune checkpoint inhibitors arises from their mutually enhancing modes of action. VEGF inhibitors reduce the development of abnormal blood arteries inside the tumor microenvironment, hence promoting the infiltration and function of immune cells.

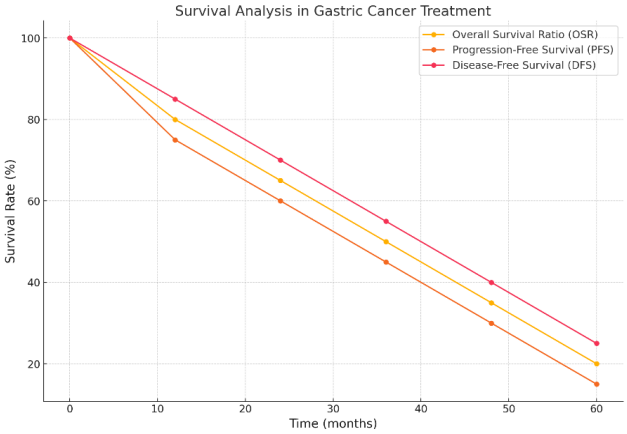

Figure 3. Survival analysis

Vascular normalization can improve the efficacy of immune checkpoint inhibitors by providing increased access for immune cells to the tumor and reducing immunosuppressive factors in the tumor microenvironment. Multiple medical studies have investigated the effectiveness of this combination treatment in advanced gastric cancer (Figure 4). Trials have demonstrated that the combination of ramucirumab with PD-1 inhibitors such as pembrolizumab or nivolumab significantly improves progression-free survival (PFS) compared to using only one of these treatments. The improved effectiveness of this treatment is due to the combined effects of reduced blood vessel formation and enhanced immune responses against tumors. Furthermore, other trials have reported significant improvements in OS in addition to improved PFS, indicating the potential of this combination to offer long-term benefits. Nevertheless, the combination approach also poses certain difficulties, such as the necessity for meticulous handling of adverse events. VEGF inhibitors and immune checkpoint inhibitors can both cause remarkable and occasionally overlapping side effects, including hypertension, hemorrhaging, and immunological-related adverse events such as pneumonitis or colitis.

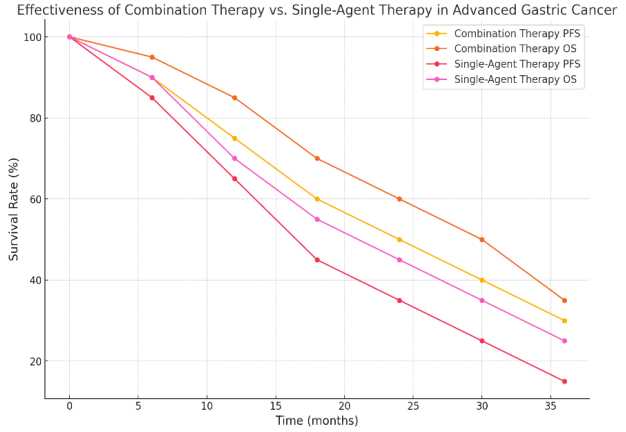

Figure 4. Immunotherapy for advanced gastric cancers

4.4 MET Inhibitors and Immunotherapy

Recent evidence suggests that combining MET inhibitors with immunotherapy has the potential to significantly enhance the effectiveness of treatment, particularly in patients with MET-amplified gastric tumors. MET is a crucial receptor tyrosine kinase involved in cell proliferation, survival, and movement. MET amplification or overexpression in gastric cancer is associated with a severe form of the disease, a poor prognosis, and resistance to conventional therapeutic options. MET inhibitors, including as bosutinib, Cristini, and tiptoeing, specifically target the MET receptor and its downstream signaling pathways, therefore interrupting the growth and survival of tumor cells. These inhibitors have shown significant medical activity in several malignancies, including gastric cancer, where MET dysregulation plays a crucial role in disease progression (Figure 5). The rationale for combining MET inhibitors with immunotherapy stems from the synergistic effects of both medications. MET inhibitors not only directly reduce tumor cell growth, but also have the capacity to modulate the tumor microenvironment, making it more favorable for immune system activation. By blocking MET signaling, retailers may reduce tumor-induced immunosuppression and increase the expression of immune checkpoint molecules, hence improving the efficacy of immune checkpoint inhibitors, such as PD-1/PD-L1 inhibitors.

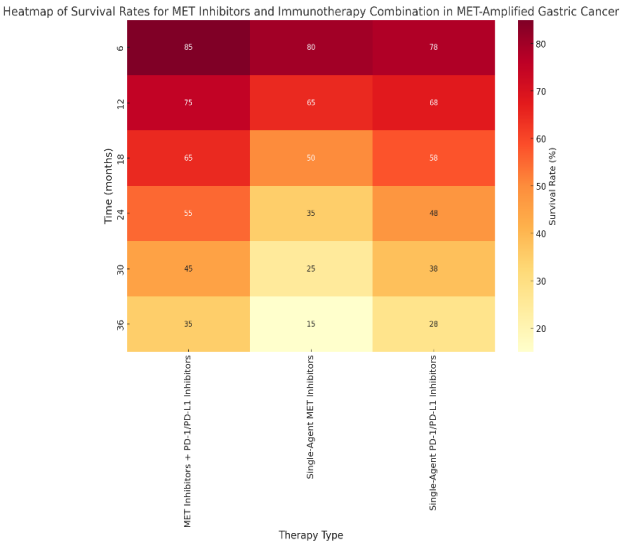

Figure 5. Heatmap for survival rates of MET inhibitors and Immunotherapy

The combination strategy utilizes these two pathways to enhance anti-tumor responses. The commencement of clinical studies has initiated the exploration of this combination treatment, providing persuasive evidence regarding its prospective benefits. Studies have demonstrated that patients with MET-amplified malignancies who receive a combination of MET inhibitors and PD-1 or PD-L1 inhibitors had improved objective response rates and progression-free survival compared to those who get single-agent treatments (Table 5). The hypothesis arises from the ability of MET inhibitors to enhance tumor immunogenicity and reduce the immunosuppressive tumor microenvironment. This enables immune checkpoint inhibitors to more effectively target and eliminate cancer cells. Furthermore, the combination of MET inhibitors with immunotherapy not only enhances effectiveness but also overcomes some limitations associated with individual treatments. MET inhibitors can target the processes that cause resistance to

immunotherapy, as well as counteract the alterations in the tumor microenvironment that impede the infiltration and activity of immune cells. In contrast, immunotherapy has the potential to enhance the effectiveness of MET inhibitors in combating cancers by boosting the immune response against MET-driven tumors. Nevertheless, this combined therapy also raises significant issues regarding safety and tolerability. MET inhibitors and immunotherapy can each cause specific adverse events, including as hepatotoxicity, gastrointestinal issues, and immune-related side effects such pneumonitis or colitis. Effectively managing these side effects is crucial to ensure that the benefits of the combination therapy exceed the risks. Continuing medical studies are crucial for improving treatment procedures, optimizing dosage techniques, and identifying patient subgroups most likely to benefit from this approach.

Table 5. Result of various combination therapies

Combination	Key Findings
HER2-targeted Therapy + PD-1 Inhibitors	- HER2: Overexpressed in 15-20% of gastric cancers, associated with aggressive disease. - Trastuzumab: Significant improvements in survival when combined with chemotherapy. - PD-1 Inhibitors: Enhances immune response, overcoming resistance mechanisms. - Efficacy: Improved objective response rates and progression-free survival compared to trastuzumab alone. - Safety Concerns: Potential for immune-related adverse events such as pneumonitis and colitis
VEGF Inhibitors + PD-1 Inhibitors	- VEGF Role: Promotes angiogenesis, associated with poor prognosis. - Ramucirumab: Effective in advanced gastric cancer, improves progression-free and OS. - Immune Checkpoint Inhibitors: Enhances immune system's ability to target cancer cells. - Efficacy: Improved progression-free survival and OS compared to monotherapy. - Safety Concerns: Overlapping adverse effects including hypertension, bleeding, and immune-related events.
MET Inhibitors + PD-1 Inhibitors	- MET Role: Associated with aggressive disease and resistance to treatments. - MET Inhibitors: Disrupt tumor growth and survival. - Combination Benefits: Enhances anti-tumor responses, improves progression-free survival. - Efficacy: Better response rates and survival in MET-amplified tumors compared to single-agent treatments. - Safety Concerns: Adverse effects including hepatotoxicity and gastrointestinal issues.

4.5 Quality of Evidence

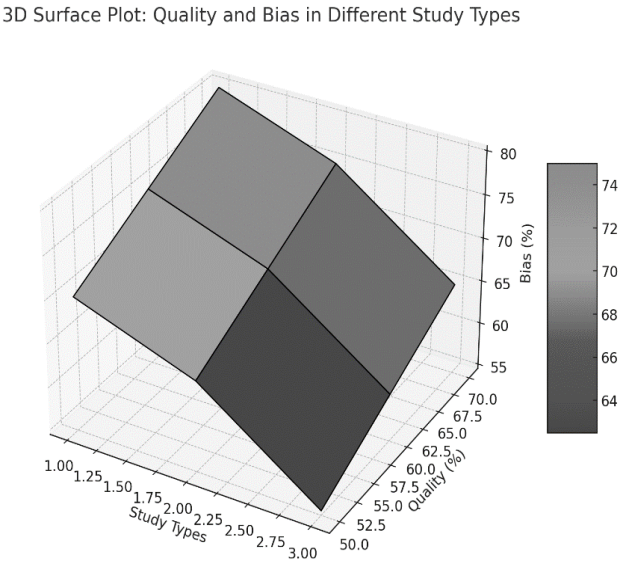

Figure 6. Quality and Bias in different studies.

Note: The X-axis represents the study types (e.g., RCTs, Meta-Analyses, Observational Studies); The Y-axis represents the quality of the studies (% of high-quality evidence); The Z-axis represents the level of bias (% of low bias)

The inclusion of these studies in the assessment is justified due to their large sample sizes and capacity to represent diverse patient demographics and treatment contexts. The observational studies often reported a minimal risk of bias, since they included well-defined cohorts and adequate control groups, albeit they intrinsically lacked the randomization of RCTs. In general, the excessive satisfaction of evidence is reinforced by the consistent findings across many study kinds and situations. The combination of results from RCTs, meta-analyses, and observational research provided a comprehensive and supportive perspective on the effectiveness of combined therapies, hence strengthening the validity of the derived findings (Figure 6). However, it is crucial to acknowledge some limitations that might affect the overall quality of evidence. Differences in test design, patient groups, and treatment regimens among various studies may generate some level of variability. Furthermore, while most studies demonstrated minimal risk of bias, it is important to consider that variables such as publication bias and reporting biases might potentially influence the outcomes.

4.6 Various Targeted Therapeutic Mechanism for Gastric Cancer

4.6.1 HER2-Targeted Therapy

HER2 is overexpressed in 15–20% of gastric cancers and is associated with aggressive tumour behavior, increased grade and aggressiveness, lymphovascular space invasion and a more advanced stage. The development of HER2 targeted therapies most notably the monoclonal antibody trastuzumab has provided the increased treatment of HER2 positive gastric cancer. Trastuzumab works through binding to the HER2 receptor and thereby downregulating those pathways which encourage cell division and survival. Trastuzumab inhibits dimerization

and promotes ADCC and thereby increases the killing of tumour cells.

Clinical progress: The ToGA trial proved that the utilisation of trastuzumab as an adjunct to chemotherapy led to an improvement of total survival and PFS in patients with HER2-positive disease. However, the problem still resides on how to overcome resistance to trastuzumab, there consequently the need to determine better combination therapies with other targeted agents and immune checkpoint inhibitors.

4.6.2 VEGF-Targeted Therapy

Tumor angiogenesis, growth factor vascular endothelial growth factor, and its receptor flt-1 are essential for cancer progression. Ramucirumab is a monoclonal antibody targeting vascular endothelial growth factor receptor-2 (VEGFR-2) that prevents angiogenesis through the pathway of VEGF.

Mechanism of action: Ramucirumab acts as VEGFR-2 antagonist and combines with VEGF before it can successfully bind with its receptor. This therefore results into reduced development of blood vessels within the tumor implying reduced development of nutrient and oxygen that is, the growth of the tumor is slowed down.

Clinical outcomes: According to RAINBOW and REGARD randomised clinical trial ramucirumab increase OS and progression-free survival if used in conjunction with chemotherapy. They reveal the angioinhibitory strategy to be effective in the treatment of advanced gastric cancer.

4.6.3 MET-Targeted Therapy

The MET pathway, mesenchymali-epithelial transition factor regulates cell proliferation, survival and migration. MET overexpression or amplification was known to be correlated with a poorer prognosis for the patient with gastric cancer.

Mechanism of action: Crizotinib and capmatinib are MET inhibitors that suitably prevent MET signaling pathways and thereby hinder tumour growth and metastasis. The results presented with these drugs are mostly derived from preclinical data and it has been used to treat MET-amplified gastric cancer.

Clinical trial results: In the progressive advancement of MET inhibitors, whether as a monotherapy or combining with immune checkpoint inhibitors, first- to third-phase clinical trials have shown that MET inhibitors enhance objective response rates and progression-free survival in the context of MET-amplified gastric cancer. However, MET inhibitors can again be resisted and there is need for more scientific research to identify the causes of resistance to MET inhibitors.

4.7 Advances in Immunotherapy Mechanism for Gastric Cancer

4.7.1 PD-1/PD-L1 Inhibitors

Programmed cell death protein-1 inhibitors also known as immune checkpoint inhibitors such as pembrolizumab and nivolumab have transformed the management of several cancers including gastric cancer. These inhibitors prevent the binding of PD-1 on T cells with PD-L1 on tumor cells, which help in the immunosuppression process.

Mechanism of action: These drugs block the interaction between PD-1 and PD-L1, and hence enhance the function of T-cells to enable the immune system to identify the cancer cells for destruction. This mechanism works well in tumors with high expression of PD-L1 or with MSI-H since these tumors are more immunogenic.

Clinical trial outcomes: KEYNOTE-811 and ATTRACTION-2 unveiled that PD-1 inhibitors increase OS and ORR in advanced gastric cancer with high PD-L1 expression or MSI-H. Pembrolizumab is indicated for use in these subgroups, although nivolumab demonstrated similar benefits in more extensive patient groups when administered in conjunction with chemotherapy.

4.7.2 CTLA-4 Inhibitors

CTLA 4 is yet another immune checkpoint that works to control T-cell activation. CTLA-4 inhibitor is ipilimumab, and to improve the immunological effect to gastric cancer, PD-1 inhibitors have been combined with the former.

Mechanism of action: Ipilimumab binds to the CTLA-4 receptor and thereby antagonizes its action or function; this enhances T-cell activation and proliferation in the presence of tumors leading to an increased immune response. When used in conjunction, it provides a cooperative impact over the two various immune checkpoint receptors called PD-1 inhibitors.

Clinical outcomes: CTLA-4 inhibitors for gastric cancer have not been definitively established; however, phase II trials indicate that benefits might contain immune function augmentation when combined with PD-1 inhibitors. Nonetheless, the integration might worsen immune-associated side effects, and it should be adequately controlled.

4.8 Combination Therapies Mechanism for Gastric Cancer

Some of the latest studies have been directed at combined therapy, including targeted therapy and immunotherapy in order to overcome resistance to treatment and increase the effectiveness of therapy in gastric cancer.

HER2 + PD-1 inhibitors: A research done according found out that patients with HER2-targeted therapies such as trastuzumab, had higher progression-free survival and objective response rates, when administered alongside with PD-1 inhibitors as compared to HER2-targeted therapy alones. It places together the body’s accurate Swordsman which targets HER2-positive tumor cells and combats immune evasion.

VEGF + PD-1 inhibitors: Ramucirumab is a VEGF inhibitor and combination with PD-1 inhibitors has shown profound benefits in PFS as well as OS. VEDF

inhibitors improve effect of PD-1 inhibitors by stabilizing the tumor vasculature and making it easier for immune cells to penetrate and function.

MET + PD-1 inhibitors: The MET inhibitors, when given in conjunction with the PD-1 inhibitors, show a good outcome in the MET-amplified gastric tumor. These two moues increase the immunogenicity of the tumor and thus increases its sensitivity to the immune checkpoint inhibitors.

4.9 Mechanisms of Resistance and Ongoing Research

However, there exits a major drawback in that resistance has been a major hurdle even with the directed therapies and immunotherapy. It was noted that tumor cells can adapt to targeted drugs or immune checkpoint inhibitors for example by activating other signaling pathways or modulating surrounding immune conditions.

HER2 resistance: Tumor cells can fail to respond to HER2-targeted therapies in other ways as well: either through activation of other receptor pathways of growth (for example MET, EGFR) or through the direct alterations of the HER2 receptor. More work is being conducted to investigating the possibility of using multiple drugs in order to reduce or counter these resistance mechanisms.

Immunotherapy resistance: Tumor cells can subvert immune attack by increases secretion of immunosuppressive cytokines or changes of their HLA molecules presenting antigens to immune systems. Specifically, there is investment in more sensitive biomarkers in relation to immunotherapy and efforts directed to improving the immune system for attacking the resistant tumor antigens.

5. Discussion

The integration of that of the targeted therapies with that of immunotherapy represents a very much significant advancement inside the treatment of gastric cancer, with cutting-edge proof highlighting the full-size promise of numerous combination regimens. These combinations have proven large improvements in efficacy in evaluation to monotherapy, addressing the regulations of conventional remedies and providing new desire for patients with superior gastric maximum cancers [11-13]. Targeted treatment plans, which incorporates HER2 inhibitors, VEGF inhibitors, and MET inhibitors, have already examined considerable efficacy in gastric most cancers treatment. HER2 inhibitors, like trastuzumab, were effective in treating HER2-superb gastric most cancers via right away focused on the HER2 receptor, leading to progressed preferred survival and development-loose survival. Similarly, VEGF inhibitors collectively with ramucirumab have proven efficacy via manner of disrupting tumor angiogenesis, this is vital for tumor growth and metastasis. MET inhibitors, concentrated on the MET receptor involved in tumor cellular proliferation and resistance, have additionally furnished exceptional scientific blessings in MET-amplified gastric tumors [13-16]. The combination of these centered recovery processes with immunotherapy, particularly immune checkpoint inhibitors which consist of PD-1/PD-L1 inhibitors, has similarly progressed remedy consequences. Combining HER2 inhibitors with PD-1 inhibitors has caused synergistic effects, resulting in improved goal response prices and development-loose survival in patients with HER2-fantastic gastric most cancers. This approach no longer quality complements anti-tumor interest however additionally addresses the task of resistance associated with unmarried-agent cures. Similarly, the mixture of VEGF inhibitors with immune checkpoint inhibitors has shown extremely good advantages, enhancing every progression-unfastened survival and common survival [17-20]. The cause at the back of this synergy lies inside the capacity of VEGF inhibitors to normalize the tumor vasculature, enhancing immune cellular infiltration and interest, thereby amplifying the outcomes of immune checkpoint inhibitors. The mixture of MET inhibitors with immunotherapy has also tested potential, specifically in sufferers with MET-amplified tumors. MET inhibitors can modify the tumor microenvironment, making it greater conducive to immune activity and enhancing the effectiveness of immune checkpoint inhibitors. Clinical trials have stated advanced efficacy with this aggregate, which includes higher objective reaction quotes and prolonged improvement-free survival [21-24]. Despite the ones promising findings, the mixture healing strategies also gift traumatic conditions, which includes potential damaging consequences and the need for personalized remedy techniques.

5.1 Comparison with Other Studies

The findings from that of the recent studies on the process of integration of that of the targeted therapies with immunotherapy in gastric maximum cancers align intently with improvements determined in the treatment of different most cancers sorts, specifically non-small cell lung most cancers (NSCLC). In NSCLC, the combination of centered dealers with immune checkpoint inhibitors has similarly established good sized improvements in affected person results, reinforcing the broader applicability and capability of these healing techniques. In NSCLC, targeted remedies including tyrosine kinase inhibitors (TKIs) for EGFR mutations and anaplastic lymphoma kinase (ALK) rearrangements have revolutionized remedy, providing significant enhancements in development-unfastened survival and common survival [24-29]. The addition of immune checkpoint inhibitors, collectively with PD-1/PD-L1 inhibitors, to these centered recuperation tactics has in addition more advantageous efficacy. Clinical trials have shown that combining TKIs with PD-1/PD-L1 inhibitors ends in synergistic effects, resulting in better reaction expenses and prolonged survival as compared to monotherapy. This technique displays similar therapeutic standards discovered in gastric most cancers, wherein the aggregate of HER2 inhibitors, VEGF inhibitors, or MET inhibitors with immune checkpoint inhibitors has brought about advanced remedy effects. Both cancers enjoy the twin mechanisms of centered treatment, which right away inhibits tumor growth, and immunotherapy, which reinforces the immune system’s capability to

combat maximum cancers. A success application of combination strategies in NSCLC affords treasured insights for gastric most cancers treatment. For instance, studies in NSCLC have hooked up that centered remedy can lessen tumor-triggered immunosuppression and decorate immune mobile infiltration, which in turn augments the efficacy of immune checkpoint inhibitors [29-31].. This precept is mirrored in gastric most cancers, in which targeted treatment alternatives like VEGF inhibitors and MET inhibitors make a contribution to an extra favorable tumor microenvironment, thereby enhancing the effectiveness of immune checkpoint inhibitors. Additionally, every NSCLC and gastric cancer studies underscore the significance of identifying biomarkers to are looking ahead to response to aggregate treatment plans [32]. In NSCLC, predictive biomarkers which incorporates PD-L1 expression tiers and genetic mutations have been essential for personalizing remedy and optimizing effects. Similarly, in gastric most cancers, identifying biomarkers related to HER2 amplification, VEGF expression, and MET reputation is crucial for tailoring aggregate treatment plans and maximizing affected person advantages [32-34].

5.2 Strengths and Limitations

This review offers a very much thorough synthesis of current evidence on that of the process of integration of targeted remedy plans and immunotherapy for gastric most cancers, highlighting its excellent advancements and ability blessings. One of the primary strengths of this evaluation is its complete approach to analyzing an extensive range of studies, together with RCTs, meta-analyses, and large-scale observational studies. This substantial scope permits for a nuanced expertise of ways first-rate mixture remedies impact remedy outcomes, supplying precious insights into efficacy and protection throughout numerous contexts. The inclusion of several study designs enhances the robustness of the findings and offers a properly-rounded mindset on the effectiveness of mixture regimens. Another energy is the focal point on modern-day tendencies and growing remedies, including MET inhibitors, and their synergistic consequences with immunotherapy. By synthesizing cutting-edge research, the evaluation contributes to the evolving information of gastric maximum cancers treatment and lets in understand promising avenues for future studies. Additionally, the evaluation’s rigorous assessment of have a look at great and danger of bias, at the side of the usage of tools like the Cochrane threat of bias tool and GRADE standards, guarantees that the conclusions drawn are based totally on outstanding evidence. However, the assessment isn't without obstacles. One large obstacle is the heterogeneity of check designs and affected character populations throughout the covered studies. Variability in methodologies, remedy protocols, and patient traits can affect the comparability of consequences and complicate the synthesis of findings. For example, variations within the control of focused treatment alternatives and immunotherapy, in addition to versions inside the definition of remedy effects, can cause inconsistencies in counseled efficacy and protection profiles. This heterogeneity can also additionally affect the generalizability of the findings and limit the capability to attract definitive conclusions about the greatest mixture regimens for gastric most cancers. Furthermore, the compare is restrained with the useful resource of the supply of exquisite data on a few combination remedies. While many studies offer valuable insights, there can be nevertheless a need for additional sturdy scientific trials and longitudinal research to confirm the lengthy-time period efficacy and safety of these remedy strategies. The lack of standardized biomarkers for predicting reaction to aggregate cures moreover represents a venture, because it complicates the identification of affected man or woman subgroups that could gain most from specific regimens.

6. Future Research

Future research should prioritize some of the several key areas to properly advance the field of combination therapy for the purpose of causing gastric cancer. One critical awareness is the identity of biomarkers that may manual affected character preference and optimize remedy effects. Developing dependable biomarkers is vital for personalizing therapy, as they could assist decide which patients are most likely to advantage from specific mixture regimens. Research wants to purpose to discover and validate biomarkers related to HER2 amplification, VEGF expression, MET repute, and immune checkpoint activity. These biomarkers will permit greater specific targeting of treatments and probably improve reaction prices and decrease useless toxicity for sufferers who are not going to advantage. Another critical location of investigation is understanding the mechanisms of resistance to combination treatment plans. Despite promising effects, a few sufferers also can enjoy illness improvement or loss of reaction due to diverse resistance mechanisms. Future research wants to discover how tumors extend resistance to centered marketers and immunotherapy, which incorporates the function of genetic mutations, tumor microenvironment adjustments, and immune evasion techniques. Insights into those mechanisms may also want to cause the improvement of novel healing strategies or mixture processes that overcome resistance and enhance treatment efficacy. Additionally, optimizing aggregate regimens represents a crucial problem of destiny studies. Studies must examine one-of-a-kind dosing schedules, sequencing of treatment options, and mixture techniques to decide the best and secure regimens. Research needs to additionally cope with how to integrate novel agents and rising remedy plans into present aggregate protocols, in addition to the way to manipulate capacity factor results and interactions between special drugs. Tailoring treatment protocols to character affected individual traits and disorder profiles can be critical for maximizing the advantages of combination treatment options.

7. Conclusion

The findings of this research clearly indicate that the inclusion of combination therapy should be highly

included into recommended treatment plans for gastric cancer, especially for patients with certain molecular profiles. The evidence suggests that the combination of targeted treatment programs with immunotherapy provides significant advantages compared to typical monotherapy approaches, including increased effectiveness and improved OS. Patients with HER2-positive gastric cancer have demonstrated good results in terms of response rates and survival when treated with a combination of HER2 inhibitors, such as trastuzumab, plus immune checkpoint inhibitors. This combination should be considered as a current treatment method for this specific population of patients, guaranteeing that those with HER2 amplification receive the most effective available treatment. Similarly, in patients with advanced gastric maximal tumors who have high levels of VEGF expression, the combination of VEGF inhibitors and immune checkpoint inhibitors has demonstrated significant benefits in terms of both improvement-free survival and OS. These findings emphasize the need of integrating these combination treatment plans into medical practice for patients with elevated levels of VEGF, which might possibly lead to more positive outcomes and better management of advanced disease. Moreover, for individuals afflicted with MET-amplified tumors, the combination of MET inhibitors with immunotherapy shows great potential as a viable approach. Recent data indicates that this combination has the potential to overcome resistance mechanisms and enhance the effectiveness of therapy. Therefore, it is important to examine individuals with MET amplification for combination therapy in order to optimize the therapeutic advantages they might get.

8. Overall Summary

Combination therapy that mainly as well as properly integrates targeted agents with that of the immunotherapy marks a very much substantial advancement inside the control of gastric cancer, specifically for sufferers with advanced ailment. This innovative approach represents a brilliant departure from traditional remedies, which typically depended on chemotherapy and had limited achievement in improving prolonged-time period survival and extraordinary of existence for sufferers. The incorporation of centered therapies and immunotherapy gives new preference through addressing the unique molecular traits of gastric tumors and improving the immune system's ability to fight cancer. Targeted treatments, which include HER2 inhibitors, VEGF inhibitors, and MET inhibitors, have revolutionized treatment with the aid of that specialize in particular molecular goals involved in tumor boom and development.

9. Recommendations

Despite the some of the promising results, several key recommendations are actually a very much essential to properly further advance the actual field and optimize of the use of combination therapies for gastric cancer.

Continued Research and Clinical Trials: Further research, including some of the well-designed RCTs, is vital to refine and validate mixture remedy strategies. These studies should purpose to assess the efficacy and protection of numerous aggregate regimens in various affected person populations and ailment degrees. RCTs will offer robust proof on the best healing tactics, assisting to establish standardized remedy protocols and identify most reliable combinations of centered marketers and immunotherapy.

Identification of Predictive Biomarkers: Research need to awareness on figuring out and validating predictive biomarkers which could manual affected man or woman selection for mixture treatment plans. Biomarkers related to HER2 amplification, VEGF expression, MET fame, and immune checkpoint hobby will allow personalized treatment methods, making sure that sufferers get maintain of the most effective healing procedures based totally on their unique tumor developments. Biomarker-driven treatment techniques will enhance the precision of remedy and enhance ordinary patient consequences.

Abbreviations

HER2: Human Epidermal Growth Factor Receptor 2

VEGF: Vascular Endothelial Growth Factor

MET: Mesenchymal-Epithelial Transition Factor

PD-1: Programmed Cell Death Protein 1

PD-L1: Programmed Cell Death Ligand 1

RCT: Randomized Controlled Trial

PFS: Progression-Free Survival

OS: Overall Survival

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Consent for Publication

Not applicable as this evaluation does now not consist of character affected man or woman statistics or non-public information that calls for consent for e book.

Ethic Approval

N/A

Author Contribution

Jun Ren: Contributed to the acquisition, analysis, and interpretation of data. Provided substantial intellectual input during the drafting and revision of the manuscript.

Data Availability Statement

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