Recent Trends and Advancements in the Diagnosis and Management of Gastric Cancer

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Simple Summary: Gastric cancer is the fifth most common tumor worldwide. In the past couple of decades, there have been many advancements toward earlier detection and better treatments for this aggressive disease. There are currently many serological tests and biomarkers being investigated to allow for the non-invasive early diagnosis of gastric cancer. The treatment options for this tumor are always rapidly evolving, and we will emphasize the medical treatment options available. We hope to outline and explain some of these latest advancements to allow clinicians and future researchers to have a better understanding of this rapidly changing field and allow them to make informed decisions for the care of their patients.

Abstract: Gastric cancer is an enigmatic malignancy that has recently been shown to be increasing in incidence globally. There has been recent progress in emerging technologies for the diagnosis and treatment of the disease. Improvements in non-invasive diagnostic techniques with serological tests and biomarkers have led to decreased use of invasive procedures such as endoscopy. A multidisciplinary approach is used to treat gastric cancer, with recent significant advancements in systemic therapies used in combination with cytotoxic chemotherapies. New therapeutic targets have been identified and clinical trials are taking place to assess their efficacy and safety. In this review, we provide an overview of the current and emerging treatment strategies and diagnostic techniques for gastric cancer.

Keywords: gastric cancer; diagnosis; management; biomarkers; immunotherapy; tyrosine kinase inhibitors; monoclonal antibodies

1. Introduction

As the fifth most common malignant neoplasm and the fourth most common cause of cancer-related death worldwide [1], there is no doubt that gastric cancer (GC) is a disease requiring further insight into how to better diagnose and manage it. Geographically, the incidence of gastric cancer is highest in East Asian and Eastern European regions, with around 60% of all GCs worldwide being seen in East Asia, of which 43.9% are accounted for by China alone [2]. One possible hypothesis for this pattern is that these regions are known to have a high prevalence of the established risk factors for GC, such as a different cytotoxic-associated gene A (cagA) strain of H. pylori and increased intake of salt-preserved or smoked foods [3]. Other risk factors for GC include smoking and heavy alcohol consumption [2].

Given its high incidence, it is imperative that further research is done to better understand this disease. In this review, we summarize the current status of diagnostic modalities and treatments for gastric cancer.
2. Diagnosis

In the United States, about one-third of patients diagnosed with gastric cancer have a distant metastasis at the time of diagnosis [4]. Upper GI series and endoscopy are the gold standard and mainstay in current clinical practice for early gastric cancer diagnosis. In fact, the use of endoscopy for screening is associated with lower gastric cancer-related mortality [5]. However, in the Western world, compared to Korea and Japan where there is a high prevalence of gastric cancer, the use of upper GI endoscopy for screening is cost-ineffective and invasive, and hence other non-invasive, cost-conscious diagnostic methods are being sought [6]. Liquid biopsies have emerged as a non-invasive way of using bodily fluids (i.e., blood, peritoneal lavage, gastric juice/lavage, etc.) to provide early tumor diagnosis, assess prognosis, identify druggable targets, and monitor tumor burden while undergoing treatment [7,8]. There are several advantages to using liquid biopsies as screening for GC, one of the most obvious being its relative non-invasiveness compared with the current gold standard of endoscopy. These blood tests can detect biomarkers which include a variety of molecules that are associated with carcinogenesis of gastric cancer, including proteins, DNA, various types of RNA, exosomes, etc. Figure 1 provides a schematic for some of the liquid biopsy markers currently being studied to diagnose gastric cancer.

![Figure 1. Liquid biopsy markers for gastric cancer. Primary gastric tumor sheds circulating tumor cells (CTCs) into the bloodstream. Some of the CTCs undergo apoptosis which allows for the release of the cell's genetic material, including circulating tumor DNA (ctDNA) and non-coding RNAs.](image)

2.1. Biomarkers

2.1.1. Proteins

Currently, the most widely used biomarkers for the diagnosis and monitoring of gastric cancer are carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9. Both CEA and CA19-9 have been shown to correlate with tumor burden and depth of tumor invasion [9]. However, both these markers have been proven to have low sensitivity and specificity by many studies and hence have poor diagnostic, prognostic, and monitoring values [9].

Pretreatment CA-125 is another classical prognostic marker for gastric cancer that has been associated with gastric cancer recurrence, rendering it a diagnostic tool to predict poor
prognosis. Furthermore, many studies have demonstrated that elevated levels of serum CA-125 correlate with peritoneal dissemination of the primary gastric tumor. Although the sensitivity of this biomarker is poor, ranging from 19.78% [10] in some studies up to 34.3% [11], it has still been shown to have clinical utility, especially in patients with unresectable advanced or recurrent gastric cancer [11].

Another tumor marker that has been gaining significant traction for the purpose of gastric cancer screening and monitoring is CA72-4 [12]. Although there are limited studies assessing its utility, it has been shown in one study to have a higher specificity in indicating the recurrence of gastric cancer compared to CEA and CA19-19 (97% vs. 79% and 74%, respectively) \((p < 0.05)\) [12]. However, despite its high specificity, it has been shown to have poor sensitivity and hence has limited clinical value.

Pepsinogen is another protein biomarker that can be used for the screening of gastric cancer. Pepsinogen, a precursor of pepsin, is secreted by the chief cells of the stomach and can be present in two forms, pepsinogen I (PG I), which is secreted from the fundus, and pepsinogen II (PGII), which is secreted from the pylorus and Brunner’s glands of the duodenum [13,14]. In normal conditions, the ratio between PG I and PG II is similar. In atrophic gastritis, which is a risk factor for gastric cancer since it can cause intestinal metaplasia, the destruction of fundic chief cells causes a remarkable reduction in PG I levels and hence causes a low PG I:PG II ratio [15,16]. Hence, a low PG I:PG II ratio is often used to screen for patients with atrophic gastritis which can possibly detect early gastric tumors. However, a major limitation of this biomarker is its poor sensitivity and specificity for detecting gastric tumors, which can be up to 77% and 73%, respectively, in the general population [17]. Furthermore, due to the vast variation in baseline pepsinogen levels based on ethnicity and gender, this practice has yet to be adopted into routine clinical practice [18].

Another promising biomarker is trefoil factor 3 (TFF3). This minute peptide is secreted from the goblet cells of the small and large intestine and can also be secreted from the gastric mucosa that has undergone intestinal metaplasia. Studies have shown high serum TFF3 levels to have a sensitivity of 80.9% and specificity of 81% for gastric cancer [19]. A meta-analysis of 17 studies evaluating the diagnostic value of TTF3 for GC showed that tissue TTF3 expression was associated with a higher risk of lymph node metastasis (OR 2.20, \(p < 0.001\)), muscularis propria invasion (OR 1.51, \(p = 0.006\)), and worse TNM stage (OR 2.26, \(p < 0.001\)) [20]. Furthermore, it has been shown that when combining the measurement of the PG I:PGII ratio with TFF3, there was a higher positive predictive value for detecting GC than when testing for each of the components separately [19,21]. Despite these promising results, currently there are no studies evaluating the utility of TFF3 for gastric cancer screening and diagnosis in clinical practice.

Alpha-fetoprotein (AFP) is another biomarker for gastric cancer that is most commonly seen in a rare subset of AFP-producing gastric carcinomas [22]. AFP is a glycoprotein synthesized from the embryonic yolk sac and liver during pregnancy; in clinical practice, it is most commonly used as a tumor marker for hepatocellular carcinoma [23]. Studies have found that AFP-positive GCs are characterized by a more aggressive behavior than AFP-negative GC tumors, with a higher chance of liver metastasis and venous invasion [23,24]. Hence, it is recommended that physicians routinely check AFP levels in gastric cancer patients, especially if there is concern about liver metastasis [25].

2.1.2. Circulating Tumor Cells

In 1869, a liquid biopsy was performed from the peripheral blood and provided the first known evidence for the presence of circulating tumor cells (CTCs) [26]. Liquid biopsies are samples of blood or other biological fluids that are used to detect and analyze cancer cells or cancer cell-derived molecules [27]. CTCs are cancer cells that have been released either from the primary tumor site or from the metastatic sites [28]. Several meta-analyses have demonstrated an association between the presence of GC CTCs and advanced tumor stage, lymphatic invasion, and poorer survival [29]. There are various markers for gastric cancer CTCs; for the epithelial subtype, they include EpCAM, cytokeratin (CK): CK8, CK18, and CK19.
and for the mesenchymal subtype, they include vimentin and twist [30,31]. Another interesting marker for gastric cancer CTCs is fluorescence in situ hybridization (FISH) detection of CTCs with chromosome 8 aneuploidy, a mutation commonly found in gastric tumor cells [32].

Studies have shown that the clinical utility of CTCs is mainly limited to monitoring gastric tumor treatment response and prognosis rather than the early diagnosis of the tumor [28]. For example, the PRODIGE 17 trial conducted in patients with advanced gastric and esophageal cancer demonstrated that the dynamic changes in CTC count between baseline and 4 weeks after treatment were significantly associated with progression-free survival (PFS) and overall survival (OS) [33,34]. However, since CTCs are generally quickly eliminated from the body through the immune system, only a few CTCs survive in the blood circulation (around 1 CTC/mL of blood) and hence this sparsity of CTCs leads to challenges in accurately detecting their presence from liquid biopsies [35]. Due to this phenomenon as well as the heterogeneous nature of CTCs, various CTC detection methods have yielded different detection rates.

2.1.3. Circulating Tumor DNA

Circulating tumor DNA (ctDNA) is another biomarker that can be extracted from liquid biopsies for the diagnosis and monitoring of gastric cancer. CtDNA can be produced from primary tumor cells, CTCs, or a distant metastasis and it can give a wide range of information on the malignancy, such as methylation status and other genetic alterations [28]. Fang et al. demonstrated a correlation in gastric cancer patients between ctDNA levels and vascular invasion, 5-year survival rate, and peritoneal recurrence [36]. Furthermore, a meta-analysis of 16 studies showed a significant association between the presence of ctDNA with worse OS \( (p < 0.001) \) and DFS \( (p < 0.001) \) [37]. The study also showed that ctDNA levels had a significant association with TNM stage, tumor depth, lymph node metastasis, and distant metastasis with a specificity of 95% and a sensitivity of 62%. However, due to the complex technology required to detect ctDNA within the plasma, it has yet to be of significant use in clinical practice [28].

2.1.4. Non-Coding RNA

Non-coding RNAs (ncRNAs) are types of RNA that do not encode protein and can be classified into two subgroups: small ncRNAs (sncRNAs) and long ncRNAs (lncRNAs). The sncRNAs can be further subclassified into microRNAs (miRNAs), small nuclear RNAs (snRNAs), and piwi-interacting RNAs (piRNAs). These various non-coding RNAs can also be used in the detection and monitoring of gastric cancer.

miRNAs play a crucial role in various cellular functions through regulating epigenetic mechanisms; these functions include cellular growth, apoptosis, differentiation, and even gastric tumor carcinogenesis. Wu et al. studied 50 GC patients and 50 patients without GC and found an increase in levels of miRNA-21 in patients with GC compared to those who did not have it \( (p < 0.01) \), with a sensitivity of 81.3% and a specificity of 73.4% [38]. Hung et al. demonstrated increased levels of miRNA-376c in the tissue, plasma, and urine of GC patients owing to the fact that miRNA-37c was found to increase the proliferation, migration, and anchorage-independent growth of carcinoma cells [39]. Other panels of miRNA that have also been shown to be upregulated include miRNA-196a [40], -200c [41], -375 [42], -940 [43], and many others [28]. Despite these promising results, the clinical utility of miRNA in routine practice has many current limitations. For example, there can be inaccuracies in miRNA quantification due to variations in processing, storage, RNA extraction, and reference gene choice during qRT-PCR since there is no unique protocol developed yet to control these parameters [32]. More details about the utility of miRNA in the diagnosis of GC are outlined in the next section on circulating extracellular vesicles.

Another sncRNA that is used as a biomarker in the diagnosis of gastric cancer is piRNAs. This newly discovered type of non-coding RNA has been shown to be a molecule that is not easily degraded and able to be detected in various human bodily fluids, including serum and gastric juice [44]. Cui et al. [45] performed a peripheral blood test in both healthy
and GC patients and showed that GC patients had lower levels of piRNA-651 and piRNA-823 compared to their healthy counterparts. These results also had relatively high sensitivity and specificity of 94.9% and 96.4%, respectively. Due to these promising results, further studies and clinical trials are being conducted to better understand the clinical utility of piRNAs as potential biomarkers for gastric cancer [46].

LncRNAs have also been proposed as biomarkers for GC. For example, a lncRNA called “high up-regulated in liver cancer” (HULC) has been shown to be increased in the serum of GC patients compared to normal controls [47]. Likewise, the lncRNA H19 also showed similar results [48]. Supporting this evidence, both serum HULC and H19 were shown to be significantly decreased in post-treatment GC patients compared to levels obtained prior to treatment. The sensitivity for HULC and H19 was 82% and 74%, respectively, while the specificity for both molecules was 83.6% and 58%, respectively. The clinical application limitations are similar to those of miRNA.

2.1.5. Circulating Extracellular Vesicles

Extracellular vesicles (EVs), also known as exosomes, are small spherical structures with an outer lipid bilayer that are secreted from cells into the extracellular space, and participate in inter-cellular communication through the transfer of functional molecules scavenged and secreted into EVs [8,49]. Exosomes are a type of EV measuring 40–120 nm that are produced in the endosomal compartment of the cell [50]. The contents of these exosomes include proteins, miRNAs, lncRNAs, etc. GC-derived exosomes can communicate with cells in the tumor microenvironment, allowing it to become more favorable in establishing metastatic niches. These exosomes also suppress host innate and adaptive immune responses by regulating host immunomodulatory mediators [8,51].

Some exosomal proteins are involved in the development of GC. TGF-β1 is an immunosuppressive cytokine that has been detected in exosomes of GC patients and was found to be correlated with lymphatic metastasis [52,53]. Tripartite motif 3 (TRIM3) is a protein that normally inhibits the proliferation of GC cells; it has been found that the levels of TRIM3 in serum exosomes of patients with GC are lower than those of healthy controls, making it a potential diagnostic biomarker for GC [54]. Gastrokine-1 (GKN-1) is another exosomal cargo protein involved in regulating the immune response and inhibiting proliferation of GC cells [54]. Yoon et al. found that healthy controls had significantly higher serum GKN1 levels than GC patients (6.34 ng/µL vs. 3.48 ng/µL, p < 0.0001), suggesting it to be another potential biomarker for GC. Heat shock proteins (HSP) 60 and 70 have been found in higher concentration within exosomes derived from malignant ascites in GC patients compared with exosomes derived from ascites derived from non-GC patients [55]. HSP-60 and 70 aid in the immune response against GC by promoting the maturation of dendritic cells, inducing a cytotoxic T-lymphocyte response against the tumor [54]. These exosomal proteins have yet to be studied in large cohort clinical trials and hence their applicability in the clinical setting is yet to be known.

The use of exosomal DNA for the diagnosis and prognosis of GC is an area of research rarely targeted in the literature. There have been only three studies investigating this up until now with only four exosomal genes identified in relation with GC so far: BARHL2, LINE1, SOX17, and miRNA-34b/c gene. Gastric juice-derived exosomal BARHL2 gene methylation was suggested to have promising potential as a biomarker with GC patients being more likely to have BARHL2 methylation compared to non-GC controls (90% sensitivity and 100% specificity) [56]. Another study also investigating the detection of methylated DNA in gastric juice-derived exosomes found that patients with GC had reduced LINE1 methylation whereas SOX17 gene methylation was detected in both early and advanced gastric cancer of both intestinal and diffuse type [57]. These findings suggest the promising potential of gastric juice-derived exosomal DNA for the early detection of GC in the clinical setting.

It has been proposed that exosomal miRNAs have promising potential as diagnostic molecules for GC tumors. Ren et al. extracted exosomes from GC cell lines and non-GC cell lines and found that the exosomes of GC cell lines contained higher levels of miRNA-21-5p
and miRNA-30-p compared to the non-GC cell lines [58]. Another study by Wang et al. found that exosomal miRNA-19b-3p and exosomal miRNA-106a-5p had 95% sensitivity and 90% specificity in detecting GC, suggesting them to be promising biomarkers for the diagnosis of GC [59]. Huang et al. identified six miRNAs that were significantly upregulated in the serum of GC patients, with four of them (miRNA-10b-5p, miRNA-195-5p, miRNA-20a-3p, and miRNA-296-5p) showing significant upregulation in serum exosomes [60]. Furthermore, Tokuhisa et al. found that miRNA-1225-5p and miRNA-21 from peritoneal lavage fluid were upregulated in the later stages of GC and correlated with serosal invasion, which could potentially predict peritoneal recurrence following curative GC resection [61]. Despite these extensive findings on the potential utility of exosomal miRNAs for the diagnosis and prognosis of GC, there have yet to be any clinical trials to investigate this further in the clinical setting and hence their applicability in the real world is yet to be determined [51,62].

3. Treatment

Although there is a wide range of therapies available for the management of gastric cancer, the molecular and clinical heterogeneity associated with the disease has led to newer classifications of GC patients which provide therapeutic approaches based on the genome and clinical evidence. Current guidelines recommend all patients eligible for systemic treatment undergo molecular profiling to determine the appropriate therapy and treatment strategy.

3.1. Epidermal Growth Factor Receptors

The human epidermal growth factor receptor (ErbB or EGFR) family is composed of four types of tyrosine kinase receptors (TKRs): EGFR (ErbB-1 or HER-1), HER-2 (ErbB-2), HER-3 (ErbB-3), and HER-4 (ErbB-4). These receptors play a critical role in cell growth, proliferation, and migration of tumors [63]. It has been known that gastric tumors express HER in a heterogeneous pattern, especially with HER-1 and HER-2. HER-1 is amplified in 27–64% of gastric tumors [64,65] whereas HER-2 is amplified in 30% of tumors [66]. Tables 1 and 2 list phase II and phase III clinical trials that studied the effects of targeting the HER-1 and HER-2 receptors in gastric cancer patients.

| Drug         | Trial                           | Phase | Method                              | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|--------------|---------------------------------|-------|-------------------------------------|---------------|----------------|---------------|
| Matuzumab    | MATRIX EG (first-line) [67]     | II    | Chemotherapy with or without matuzumab | 9.4 M vs. 12.2 M (p = 0.945) | 4.8 M vs. 7.1 M (p = 0.678) | 31.0% vs. 58.0% (p = 0.994) |
| Cetuximab    | DOCOX+C/second-line [68]        | II    | Chemotherapy (docetaxel + oxaliplatin) with or without cetuximab | 9.4 M vs. 8.5 M (p > 0.050) | 5.1 M vs. 4.7 M (p > 0.050) | 38.0% vs. 26.0% (p > 0.050) |
| Panitumumab  | ATTAX3/second-line [69]         | II    | Chemotherapy with or without panitumumab | 10.0 M vs. 11.7 M (p > 0.050) | 6.0 M vs. 6.9 M (p > 0.050) | 57.9% vs. 48.7% (p > 0.050) |
| Panitumumab  | first-line [70]                | II    | Single-arm: Chemotherapy with panitumumab | 11.3 M       | 6.9 M          | 35.0%         |
| Panitumumab  | MEGA/first-line [71]           | II    | Chemotherapy with or without panitumumab or rilotumumab | 8.3 M (P) vs. 11.3 M (R) (p = 0.43) | 4-month PFS rate: 57% (P) vs. 61% (R) (p = 0.31) | 43% (P) vs. 49% (R) (p = 0.52) |
| Nimotuzumab  | NCS/first-line [72]            | II    | Chemotherapy with or without nimotuzumab | 10.2 M vs. 14.3 M (p = 0.062) | 4.8 M vs. 7.2 M (p = 0.011) | 54.8% vs. 58.1% (p = 0.798) |
| Erlotinib    | first-line [73]                | II    | Single-arm: Chemotherapy with erlotinib | 11.0 M       | 5.5 M          | 51.5%         |
| Panitumumab  | REAL3/first-line [74]           | III   | Chemotherapy with or without Panitumumab | 8.8 M vs. 11.3 M (p = 0.013) | 6.0 M vs. 7.4 M (p = 0.068) | 46% vs. 42% (p = 0.42) |
| Cetuximab    | EXPAND/first-line [75]         | III   | Chemotherapy with or without cetuximab | 9.4 M vs. 10.7 M (p = 0.95) | 4.4 M vs. 5.6 M (p = 0.032) | 30% vs. 29% (p = 0.77) |
Table 2. Phase II and III trials of therapies targeting human epidermal receptor-2 (HER-2). mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; M, months; ADC, antibody–drug conjugate; TKI, tyrosine kinase inhibitor; CapeOx, capecitabine and oxaliplatin.

| Drug Class | Drug | Trial | Phase | Method | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|------------|------|-------|-------|--------|---------------|---------------|---------------|
| Trastuzumab | WJOG7112G (T-ACT)/second-line [74] | II | Chemotherapy (paclitaxel) with or without trastuzumab | 10.2 M vs. 9.95 M (p = 0.20) | 3.68 M vs. 3.19 M (p = 0.33) | 33.3% vs. 31.6% (p = 1.00) |
| Trastuzumab | first-line [77] | II | Single arm: chemotherapy (S-1 + cisplatin) with trastuzumab | 14.6 M | 7.4 M | 53.3% |
| Trastuzumab | first-line [78] | II | Single arm: chemotherapy (CapeOx) with trastuzumab | 21.0 M | 9.8 M | 67% |
| Trastuzumab | first-line [79] | II | Single arm: chemotherapy (docetaxel + capecitabine) | 20.9 M | 8.1 M | 67.8% |
| Trastuzumab | first-line [80] | II | Single arm: chemotherapy (S-1 + oxaliplatin) with trastuzumab | 18.1 M | 8.8 M | 70.7% |
| Margetuximab | second-line [81] | Ib/II | Margetuximab + pembrolizumab | 12.5 M | 2.73 M | 18.48% |
| Trastuzumab | ToGA/first-line [82] | III | Chemotherapy (cisplatin + 5-FU) with or without trastuzumab | 13.8 M vs. 11.1 M (p = 0.0046) | 6.7 M vs. 5.5 M (p = 0.0002) | 47% vs. 35% (p = 0.0017) |
| Trastuzumab | HELOISE/first-line [83] | IIIb | Chemotherapy (capecitabine + cisplatin) with standard-dose vs. high-dose trastuzumab | 12.5 M vs. 10.6 M (p = 0.2401) | 5.7 M vs. 5.6 M (p = 0.8222) | 58.9% vs. 56.9% (p = 0.76) |
| Trastuzumab/Pertuzumab | JACOB/first-line [84] | III | Trastuzumab + pertuzumab + chemotherapy (capecitabine, cisplatin, or S-FU) vs. trastuzumab + placebo + chemotherapy | 17.5 M vs. 14.2 M (p = 0.057) | 8.5 M vs. 7.0 M (p = 0.0001) | 56.7% vs. 48.3% (p = 0.026) |
| ADCs | Trastuzumab deruxtecan | DESTINY-Gastric01/second-line [85] | II | Chemotherapy or trastuzumab deruxtecan | 12.5 M vs. 8.4 M (p = 0.01) | 5.6 M vs. 3.5 M (p = N/A) | 51% vs. 14% (p = 0.001) |
| | RC48-ADC | second-line [86] | II | Single arm: RC48 | 7.9 M | 4.1 M | 18.1% |
| | Trastuzumab emtansine (T-DMI) | GATSBY/second-line [87] | III | T-DMI vs. taxane | 7.9 M vs. 8.6 M (p = 0.86) | 2.7 M vs. 2.9 M (p = 0.31) | 20.6% vs. 19.6% (p = 0.846) |
| TKIs | Dacomitinib | second-line [88] | II | Single arm: Dacomitinib | 7.1 M | 2.1 M | 7.4% |
| | Lapatinib | first-line [89] | II | Single arm: lapatinib | 4.8 M | 1.9 M | 11% |
| | Lapatinib | LoGIC/first-line [90] | III | Chemotherapy with or without lapatinib | 12.2 M vs. 10.5 M (p = 0.91) | 6.0 M vs. 5.4 M (p = 0.0381) | 53% vs. 39% (p = 0.0031) |
| | Lapatinib | TyTAN/second-line [91] | III | Paclitaxel with or without lapatinib | 11.0 M vs. 8.9 M (p = 0.1044) | 5.4 M vs. 4.4 M (p = 0.2441) | 27% vs. 9% (p < 0.001) |

3.1.1. HER-1

Normally, when a ligand (i.e., EGF, TGFα, amphiregulin, epiregulin, etc.) binds EGFR, it induces tyrosine phosphorylation, which stimulates multiple downstream signaling cascades that in turn promote cell proliferation, angiogenesis, migration, survival, and adhesion. Deregulation of EGFR signaling can occur through multiple mechanisms such as receptor overexpression, activating mutations, and gene copy numbers (GCNs) [92].

Although EGFR amplification has been shown to occur in a significant proportion of gastric cancers, there is no general consensus on its prognostic value. Some studies suggest that a higher overexpression is associated with poorer outcomes [93,94] while others suggest the complete opposite [95]. Since EGFR is a well-recognized mediator for the oncogenic phenotype of gastric cancer [96], many EGFR targeting agents have entered clinical practice, albeit with disappointing results. The first category of anti-EGFR therapeutic agents are tyrosine kinase inhibitors (TKIs) which have greater efficacy in tumors with activating EGFR mutations such as non-small cell lung cancer. The other category of anti-EGFR therapeutic agents are monoclonal antibodies which are effective in tumors that overexpress EGFR, regardless of whether the EGFR is actually mutated or not [92]. Anti-EGFR monoclonal antibodies have multiple mechanisms to induce anti-tumor activity, such as antibody-dependent cell-mediated cytotoxicity (ADCC), competitive inhibition of ligand binding, receptor endocytosis/internalization/degradation, and complement-mediated cytotoxicity [97].

Early phase II clinical trials have suggested a potential benefit for the use of EGFR inhibitors in patients with gastric cancer. For example, Richards et al. [68] demonstrated...
that the addition of cetuximab to combination chemotherapy of doxetaxel + oxaliplatin as a second-line therapy for the management of metastatic gastric cancer resulted in a higher mPFS of 5.1 months in the cetuximab therapy group, compared to 4.7 months in the combination chemotherapy alone group \((p > 0.05)\). However, two larger phase III randomized trials, REAL3 and EXPAND, demonstrated that there was no improvement in survival for patients with advanced gastric cancer treated with anti-EGFR therapy [74,75]. In fact, the REAL3 trial showed a statistically significant \((p = 0.013)\) worse mOS in the panitumumab subgroup and the EXPAND trial showed a statistically significant \((p = 0.032)\) worse mPFS in the cetuximab subgroup. Hence the evaluation of EGFR inhibition was abruptly abandoned for gastric cancer.

However, one caveat to the phase III trials was that there was no patient selection performed on the basis of EGFR amplification/overexpression which rendered the results as questionable due to the heterogeneity in the expression of EGFR in gastric cancer [98]. To address this, Smyth et al. [99] tested EGFR copy numbers in tissue and liquid biopsies taken from the patients evaluated in the REAL3 trial. The results showed that only 7% of patients in the trial were EGFR-amplified and that the use of anti-EGFR therapy (panitumumab) in these EGFR-amplified patients actually worsened the prognosis (although not statistically significant, likely due to the small number of EGFR-amplified cases). Furthermore, the data showed an antagonistic effect when anthracycline chemotherapy was combined with anti-EGFR therapy. These relatively consistent overall findings suggest that EGFR inhibition probably does not represent an important therapeutic target for most patients with advanced gastric cancer.

3.1.2. HER-2

HER-2 is a proto-oncogene that encodes the transmembrane receptor-like HER2 protein. When activated, it initiates signaling pathways that lead to cell proliferation, differentiation, and vascular and lymphatic angiogenesis [100]. HER-2 overexpression is determined through immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH). The IHC score has three categories depending on the degree of HER-2 amplification: negative (0+ or 1+), equivocal (2+), or positive (3+). Amplification of this proto-oncogene has been associated with poor prognosis and constitutes a predictive factor for poor response to chemotherapy [101]. Hence, targeting HER-2 in HER-2-positive gastric cancer is a plausible therapeutic approach. Similar to therapeutic agents targeting HER-1, the drugs targeting HER-2 can also be categorized as either anti-HER-2 monoclonal antibodies and HER-2 targeting TKIs.

The anti-HER-2 monoclonal antibody, Trastuzumab, has been the only well-established cornerstone management for many years for advanced HER-2 positive gastric cancer. The landmark phase III ToGA trial [82] conducted in 2010 compared the efficacy of trastuzumab in combination with the standard first-line chemotherapy regimen at the time (cisplatin + 5-FU) versus chemotherapy alone, and the trastuzumab with chemotherapy combination was shown to have a statistically significant improved OS, PFS, and ORR compared to chemotherapy alone. However, one limitation of the ToGA study was the fact that about one-third of the patients assigned to the trastuzumab arm were underdosed, which was theorized to have caused a worse survival. Hence, the phase III HELOISE trial [83] was conducted to assess whether there was any difference in efficacy when chemotherapy was combined with low-dose trastuzumab compared to high-dose trastuzumab. However, the authors found that the high-dose regimen did not result in improved OS or PFS. Following the ToGA study, another phase II trial studied the efficacy of combining trastuzumab with other chemotherapy regimens, such as replacing cisplatin with oxaliplatin and 5-FU with capecitabine. These results [76–80] showed similar results in terms of efficacy as the ToGA trial, and hence these chemotherapy combinations are also used along with trastuzumab for the first-line treatment of HER-2-positive advanced gastric cancer.
Another monoclonal antibody investigated for use in AGC is pertuzumab. It has a similar mechanism of action as trastuzumab except that pertuzumab binds to the dimerization domain of HER-2, which prevents HER-2 heterodimerization with other HER family receptors, whereas trastuzumab binds to the transmembrane domain, which prevents HER-2 dimerization [102]. The phase III JACOB trial evaluated the addition of pertuzumab vs. placebo to trastuzumab with chemotherapy in the first-line setting. However, although the mPFS and ORR showed statistically significant improvement, there was no statistically significant improvement in mOS, which was the primary endpoint [84]. These findings highlight the heterogeneity in HER-2 biology in gastric cancer vs. breast cancer and hence the varying efficacy of targeted therapy in both tumors.

Antibody–drug conjugates (ADC) are another therapeutic strategy currently being investigated for AGC. Trastuzumab emtansine (T-DM1) is an ADC consisting of the anti-HER-2 monoclonal antibody trastuzumab with the tubulin inhibitor emtansine. Emtansine is released into HER-2-positive tumor cells to cause mitotic arrest and apoptosis [100]. However, the phase III GATSBY trial demonstrated no statistically significant survival benefit of T-DM1 compared to standard taxane therapy [87]. Another ADC proposed for the management of AGC is trastuzumab deruxtecan (T-DXd) which combines trastuzumab with deruxtecan, a topoisomerase I inhibitor that when entering tumor cells leads to the inhibition of DNA replication resulting in cell cycle arrest and tumor cell apoptosis [103]. A phase II DESTINY trial [85] showed that T-DXd had a statistically significant improved OS (12.5 months vs. 8.4 months, \( p = 0.01 \)) and ORR (51% vs. 14%, \( p < 0.001 \)) compared to patients on chemotherapy alone, in patients with AGC as a third-line or later therapy. Following this study, the FDA approved T-DXd for use in AGC after failure with a trastuzumab-containing regimen. RC48 is another ADC that linked humanized anti-HER-2 IgG1, a valine–citrulline linker, and MMAE (a microtubule inhibitor) together, and a phase II study [86] found an ORR of 18.1% (95% CI: 11.8–25.9%) and a mOS of 7.6 months (95% CI: 6.6–9.2) in patients with HER-2 overexpressing AGC. RC48 is still currently being investigated in further clinical trials.

TKIs are another category of drugs used to target HER-2 in AGC. Lapatinib is a small molecule TKI that inhibits both EGFR and HER-2, which results in reduced intracellular signaling and hence suppressed tumor proliferation [104]. The phase III LOGiC trial examined the use of lapatinib as a first-line treatment when combined with CAPEOX compared to CAPEOX alone and found no statistically significant improvement in the primary endpoint, which was mOS (12.2 months vs. 10.5 months, \( p = 0.91 \)), although the PFS (6.0 months vs. 5.4 months, \( p = 0.038 \)) and ORR (53% vs. 39%, \( p = 0.0031 \)) were significant [90]. The TyTAN trial examined the efficacy of paclitaxel with or without lapatinib in the second-line setting; however, there was no statistically significant improvement in mOS (11.0 months vs. 8.9 months, \( p = 0.1044 \)) or mPFS (5.4 months vs. 4.4 months, \( p = 0.2441 \)), despite a significant ORR (27% vs. 9%, \( p < 0.001 \)) [91]. Dacomitinib is another TKI that had a phase II trial conducted, yet the results showed that there was no substantial therapeutic benefit for its use in HER-2-positive AGC [88].

3.2. Angiogenesis

The process of angiogenesis is modulated by the interaction of VEGF with its TKRs, known as VEGFRs. There are four types of VEGF (VEGF-A, VEGF-B, VEGF-C, and VEGF-D) that have been identified along with three types of VEGFRs (VEGFR-1, VEGFR-2, and VEGFR-3) [105].

Therapies targeting this pathway can be either monoclonal antibodies or TKIs. Even though there is no measurable predictive factor to determine which patients respond better to VEGF pathway inhibition, expression of VEGF has been seen to occur in almost 48% of gastric cancers and is associated with poorer prognosis [106]. Several clinical trials have shown that there is clinical benefit when targeting the VEGF/VEGFR pathway. Table 3 outlines the results of phase II and III trials against this molecular target.
Table 3. Phase II and III trials of therapies targeting angiogenesis. mOS, median overall survival; mPFS, median progression-free survival; HR, hazard ratio; M, months; ORR, objective response rate; 5-FU, 5-fluorouracil; FOLFOX, folinic acid, fluorouracil, oxaliplatin, oxaliplatin; FOLFIRI, folinic acid, fluorouracil, irinotecan; N/A, not available; TKI, tyrosine kinase inhibitor.

| Drug Class | Drug | Trial | Phase | Method | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|------------|------|-------|-------|--------|--------------|--------------|-------------|
| Bevacizumab | first-line [107] | II | Single arm: Bevacizumab + docetaxel + 5-FU | 16.8 M | 6-month PFS rate: 79% | 67% |
| Bevacizumab | first-line [108] | II | Single arm: Bevacizumab + docetaxel + cisplatin + irinotecan | N/A | N/A | 69% |
| Bevacizumab | first-line [109] | II | Single arm: Bevacizumab + docetaxel + oxaliplatin | 11.1 M | 6.6 M | 42% |
| Bevacizumab | first-line [110] | II | Single arm: Bevacizumab + irinotecan + cisplatin | 12.3 M | 8.3 M | 65% |
| Bevacizumab | first-line [111] | II | Single arm: Bevacizumab + capcitabine + oxaliplatin | 10.8 M | 7.2 M | 51.4% |
| Bevacizumab | first-line [112] | II | Single arm: Bevacizumab + carboplatin + capcitabine | 14.3 M | 8.5 M | 51% |
| Bevacizumab | first-line [113] | II | Single arm: bevacizumab + docetaxel + capcitabine + cisplatin | 13.9 M | 7.6 M | 54% |
| Bevacizumab | first-line [114] | II | Single arm: Bevacizumab + docetaxel + cisplatin + irinotecan | 17.9 M | 10.8 M | 74% |
| Bevacizumab | first-line [115] | II | Single arm: Bevacizumab + docetaxel + oxaliplatin + capcitabine | 12.0 M | 8.3 M | 70% |
| Bevacizumab | GASTRIC-3 / first-line [116] | II | Single arm: oxaliplatin + irinotecan + bevacizumab + docetaxel | 11.0 M | 7.0 M | 51.5% |
| Bevacizumab | first-line [117] | II | Single arm: mFOLFOX + Bevacizumab | 14.7 M | 7.8 M | 56.4% |
| Ramucirumab | first-line [118] | II | Chemotherapy (mFOLFOX6) with or without ramucirumab | 11.7 M vs. 11.5 M (p = 0.712) | 6.4 M vs. 6.7 M (HR = 0.98, p = 0.886) | 45.2% vs. 46.4% (p = 0.830) |
| Ramucirumab | RAINSTORM / first-line [119] | II | Chemotherapy (S-1 + oxaliplatin) with or without ramucirumab | N/A | 6.34 M vs. 6.74 M (p = 0.698) | 58% vs. 50% (p = 0.402) |
| Ramucirumab | REGARD / second-line [120] | II | Single arm: Ramucirumab | 8.6 M | 6.6 weeks | 0% |
| Bevacizumab | AVAGAST / first-line [121] | III | Chemotherapy (S-FU + cisplatin + capcitabine) with or without bevacizumab | 12.1 M vs. 10.1 M (p = 0.1002) | 6.7 M vs. 6.3 M (p = 0.0037) | 46.0% vs. 37.4% (p = 0.0315) |
| Bevacizumab | AVATAR / first-line [122] | III | Chemotherapy (capcitabine + cisplatin) with or without bevacizumab | 10.5 M vs. 11.4 M (p = 0.5567) | 6.3 M vs. 6.0 M (p = 0.4799) | 40.7% vs. 33.7% (p > 0.05) |
| Ramucirumab | RAINFALL / first-line [123] | III | Chemotherapy (cisplatin + 5-FU/capcitabine) with or without ramucirumab | 11.2 M vs. 10.7 M (p = 0.6787) | 5.7 M vs. 5.4 M (p = 0.0106) | 41% vs. 36% (p = 0.17) |
| Ramucirumab | REGARD / second-line [124] | III | Ramucirumab vs. placebo | 5.2 M vs. 3.8 M (p = 0.047) | 2.1 M vs. 1.3 M (p = 0.0001) | 3% vs. 3% (p > 0.05) |
| Ramucirumab | RAINBOW / second-line [125] | III | Chemotherapy (paclitaxel) with or without ramucirumab | 9.6 M vs. 7.4 M (p = 0.017) | 4.4 M vs. 2.9 M (p = 0.0001) | 28% vs. 16% (p = 0.0001) |
| Sorafenib | ECOG5203 / first-line [126] | II | Chemotherapy (docetaxel + cisplatin) with or without sorafenib | 13.6 M | 5.8 M | 41% |
| Sorafenib | first-line [127] | II | Chemotherapy (capcitabine + cisplatin) with or without sorafenib | 11.7 M vs. 10.8 M (p = 0.661) | 5.6 M vs. 5.3 M (p = 0.609) | 54% vs. 52% (p = 0.826) |
| Sorafenib | GEMCAD / second-line [128] | II | Single arm: Chemotherapy (oxaliplatin) with sorafenib | 6.5 M | 3 M | N/A |
| Sorafenib | ≥second-line [129] | II | Single arm: sorafenib | 9.7 M | 3.6 M | 3% |
| Sorafenib | second-line [130] | II | Single arm: sorafenib | 6.8 M | 2.3 M | 2.6% |
| Sorafenib | second-line [131] | II | Chemotherapy (docetaxel) with or without sorafenib | 8.0 M vs. 6.6 M (p = 0.802) | 3.9 M vs. 2.6 M (p = 0.206) | 41.1% vs. 14.3% (p = 0.002) |
| Sorafenib | ≥second-line [132] | II | Chemotherapy (Na-FOLFIRI) with or without sorafenib | 10.4 M vs. 8.9 M (p = 0.211) | 3.5 M vs. 3.3 M (p = 0.66) | 20% vs. 29% (p = N/A) |
| Sorafenib | ≥second-line [133] | II | Single arm: sorafenib | 5.81 M | 1.28 M | 3.9% |
| Telatinib | TEL0805 / first-line [134] | II | Single arm: chemotherapy (capcitabine + cisplatin) with telatinib | N/A | 4.7 M | 67% |
Table 3. Cont.

| Drug Class | Drug | Trial | Phase | Method | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|------------|------|-------|-------|--------|--------------|---------------|--------------|
| Orantinib  | first-line [135] | II    | with or without oratinib | 16.6 M vs. 15.5 M (p = 0.213) | 6.9 M vs. 7.1 M (p = 0.424) | 62.2% vs. 56.5% (p = 0.671) |
| Apatinib  | ≥third-line [136] | II | Placebo vs. apatinib (850 mg) vs. apatinib (425 mg bid) | 2.50 M vs. 4.83 M vs. 4.27 M (p < 0.05) | 1.40 M vs. 3.67 M vs. 3.20 M (p < 0.001) | 0% vs. 6.38% vs. 13.04% (p = N/A) |
| Pazopanib | first-line [137] | II | Single arm: chemotherapy (CapeOx) with pazopanib | 10.5 M | 6.5 M | 62.4% |
| Pazopanib | first-line [136] | II | Chemotherapy (5-FU + oxaliplatin) with or without pazopanib | 10.1 M vs. 7.0 M (p = N/A) | 5.1 M vs. 3.9 M (p = N/A) | N/A |
| Regorafenib | first-line [139] | II | Single arm: chemotherapy (mFOLFOX6) with regorafenib | 14.2 M | 7.1 M | 54% |
| Regorafenib | ≥second-line [140] | II | Regorafenib vs. placebo | 5.8 M vs. 4.5 M (p = 0.147) | 2.6 M vs. 0.9 M (p < 0.001) | N/A |
| Fruquintinib | second-line [141] | I/II | Single arm: fruquintinib with paclitaxel | 8.5 M | 4.0 M | 25.9% |
| Lenvatinib | ≥first-line [142] | II | Single arm: Lenvatinib + pembrolizumab | N/A | 6.9 M | 69% |
| Lenvatinib | ≥third-line [143] | II | Single arm: Lenvatinib + pembrolizumab | 5.9 M | 2.5 M | 10% |
| Apatinib | ≥third-line [144] | III | Apatinib vs. placebo | 6.5 M vs. 4.7 M (p = 0.0149) | 2.6 M vs. 1.8 M (p < 0.001) | 2.84% vs. 0.00% (p = 0.1695) |
| Recombinant fusion protein | Ziv-aflibercept | first-line [145] | II | Chemotherapy (mFOLFOX6) with or without ziv-aflibercept | 14.5 M vs. 18.8 M (p = 0.45) | 9.7 M vs. 7.4 M (p = 0.72) | 61.1% vs. 75.0% (p = 0.53) |

Bevacizumab is an anti-VEGF-A monoclonal antibody that inhibits circulating VEGF-A activity [146]. Although several phase II trials [107–117] have suggested that the combination of Bevacizumab with chemotherapy could possibly provide some clinical benefit for AGC patients, the phase III trials “AVAGAST” [121] and “AVATAR” [122] concluded that there was no significant difference in mOS between patients taking chemotherapy alone and patients taking chemotherapy along with bevacizumab. Interestingly, a sub-analysis of the AVAGAST trial [147] found that non-Asian patients who received bevacizumab in combination with chemotherapy had better outcomes than Asian patients. Ramucirumab is another human monoclonal antibody used for the management of AGC that works by blocking VEGFR-2 [148]. The phase III studies “REGARD” [124] and “RAINBOW” [125] demonstrated statistically significant improvements when ramucirumab was used as a second-line therapy, either alone or in combination with paclitaxel, respectively. However, there was no statistically significant difference seen in mOS when ramucirumab was combined with chemotherapy as a first-line therapy, as seen in the “RAINFALL” [123] trial. Many phase II trials [126–140] investigating the efficacy of VEGFR TKIs have shown a lack of survival benefit for AGC. However, the phase II trial investigating apatinib [136] showed promising results when used in the 850 mg dose, one daily in the third-line and beyond settings. This prompted a phase III study which showed statistically significant improvements in mOS and mPFS compared to placebo [144]. In 2014 and 2017, the Chinese and US FDA approved the use of apatinib for the treatment of AGC [149].

3.3. Immune Checkpoint Inhibitors

Evasion of the immune system is an established hallmark of cancer [150]. Programmed cell death protein-1 (PD-1) and cytotoxic T lymphocyte protein 4 (CTLA-4) are inhibitory pathways critical for maintaining self-tolerance. When PD-1, a negative co-stimulatory receptor expressed on activated T-cell surfaces, binds to its ligands, programmed cell death ligands 1 and 2 (PD-L1/L2), leading to an inhibition of cytotoxic T-cell response, which allows tumor cells to escape T-cell-induced anti-tumor activity. CTLA-4, another receptor found on T-cells, binds to B7 on antigen-presenting cell surfaces, which prevents the B7 from binding with the co-stimulatory CD28 receptor, preventing T-cell activation.

In the “era of revolution” in cancer management with immunotherapy, there have been attempts to integrate immune checkpoint inhibitors in the therapeutic algorithm for AGC.
Gastric tumors that are Epstein–Barr virus (EBV) positive and microsatellite-unstable (MSI) have been shown to be potentially most responsive to immunotherapy drugs [151]. EBV-positive GC (represents up to 9% of all GC tumors) is associated with programmed death ligand 1 (PD-L1 gene amplification, which suggests higher immunogenicity and hence is more likely to respond to immune checkpoint inhibition. MSI tumors (which represent up to 15–30% of all GC tumors) are characterized by a lymphocytic infiltrate which may reflect the activation of T-cells against tumor antigens and genomic changes in tumor cells linked to PD-L1 expression, hence indicating a potential role for immunotherapy [152,153]. Furthermore, both EBV and MSI-positive GC tumors have a high somatic mutational burden which is also a feature associated with response to immunotherapy. Table 4 outlines the results of phase II and III trials using immune checkpoint inhibitors in gastric cancer.

Table 4. Phase II and III trials of immune checkpoint inhibitors for gastric cancer. mOS, median overall survival; mPFS, median progression-free survival; HR, hazard ratio; M, months; ORR, objective response rate; 5-FU, 5-fluorouracil; FOLFOX, folinic acid, fluorouracil, oxaliplatin, oxaliplatin; FOLFIRI, folinic acid, fluorouracil, irinotecan; N/A, not available; TKI, tyrosine kinase inhibitor; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T lymphocyte protein 4; DKK1, Dickkopf-1; CPS, combined positive score.

| Drug Class | Drug | Trial | Phase | Method | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|------------|------|-------|-------|--------|---------------|---------------|--------------|
| Pembrolizumab | KEYNOTE-059/≥second-line [154] | II | Single arm: pembrolizumab | 2.0 M | 5.6 M | PD-L1-positive tumor: 15.9% PD-L1-negative tumor: 6.4% |
| Pembrolizumab | PANTHERA/first-line [155] | Ib/II | Single arm: Chemotherapy (capcitabine + cisplatin) + pembrolizumab + trastuzumab | 19.3 M | 8.6 M | 76.7% |
| Pembrolizumab | first-line [156] | II | Single arm: pembrolizumab + trastuzumab | 27.2 M | 13.0 M | 91% |
| Pembrolizumab | EFOC1706/≥first-line [142] | II | Single arm: lenvatinib + pembrolizumab | NR | 6.9 M | 69% |
| Pembrolizumab | ≥third-line [143] | II | Single arm: Lenvatinib + pembrolizumab | 5.9 M | 2.5 M | 10% |
| Pembrolizumab | second-line [81] | Ib/II | Margetuximab + pembrolizumab | 12.5 M | 2.73 M | 18.48% |
| Pembrolizumab | ≥second-line [157] | Ib/II | Single arm: DKN-01 + pembrolizumab | DKK1 high: 7.3 M DKK1 low: 4.0 M | DKK1 high: 5.1 M DKK1 low: 1.4 M | DKK1 high: 50% DKK1 low: 0% |
| Nivolumab | second-line [158] | Ib/II | Single arm: paclitaxel + nivolumab + ramucirumab | 13.1 M | 5.1 M | 37.2% |
| Nivolumab | NivoRAM/second-line [159] | I/II | Single arm: nivolumab + ramucirumab | 9.0 M | 2.9 M | 26.7% |
| Camrelizumab | first-line [160] | II | Single arm: CAPOX + camrelizumab + apatinib | 14.9 M | 6.8 M | 58.3% |
| Sintilimab | first-line [161] | II | Single arm: Chemotherapy (CAPOX) with sintilimab | N/A | N/A | N/A |
| Toripalimab | first-line [162] | Ib/II | Toripalimab alone vs. chemotherapy (CAPOX) with toripalimab | 4.8 M vs. NR | 1.9 M vs. 5.8 M | 12.1% vs. 66.7% |
| Tislelizumab | first-line [163] | II | Single arm: chemotherapy (CAPOX) + tislelizumab | N/A | 6.1 M | 46.7% |
| Pembrolizumab | KEYNOTE-061/second-line [164] | III | Pembrolizumab vs. paclitaxel | 9.1 M vs. 8.3 M (p = 0.0021) | 1.5 M vs. 4.1 M (p = N/A) | N/A |
| Pembrolizumab | KEYNOTE-062/first-line [165] | III | Pembrolizumab vs. chemotherapy (cisplatin + 5-FU/capcitabine) + pembrolizumab vs. chemotherapy with placebo | CPS ≥ 1: 10.6 M vs. 12.5 M vs. 11.1 M CPS ≥ 10: 17.4 M vs. 12.3 M vs. 10.8 M | CPS ≥ 1: 2.0 M vs. 6.9 M vs. 6.4 M CPS ≥ 10: 2.9 M vs. N/A vs. 6.1 M | CPS ≥ 1: 15% vs. 49% vs. 37% CPS ≥ 10: 25% vs. 53% vs. 38% |
| Pembrolizumab | KEYNOTE-081/first-line [166] | III | Trastuzumab + chemotherapy (CAPOX/5-FU + cisplatin) with or without pembrolizumab | N/A | N/A | 74.4% vs. 51.9% (p = 0.0008) |
| Pembrolizumab | LEAP-005/≥third-line [143] | II | Single arm: Lenvatinib + pembrolizumab | 5.9 M | 2.5 M | 10% |
| Nivolumab | ATTRACTION-2/≥second-line [167] | III | Nivolumab vs. placebo | 5.3 M vs. 4.1 M (p < 0.0001) | 1.61 M vs. 1.45 M (p < 0.0001) | 11.2% vs. 0% |
| Nivolumab | CheckMate-649/first-line [168] | III | Nivolumab + chemotherapy (CAPOX or FOLFOX) vs. chemotherapy alone | 13.8 M vs. 11.6 M (p < 0.0002) | 7.7 M vs. 6.9 M (p = N/A) | 60% vs. 45% |
| Nivolumab | CheckMate-577/adjuvant [169] | III | Nivolumab vs. placebo | DFS: 22.4 M vs. 11.0 M (p < 0.001) | N/A | N/A |
Blocking the PD-1/PD-L1 interaction can enhance the immune response against tumors. Pembrolizumab is a humanized IgG4 monoclonal anti-PD-1 antibody. The phase II KEYNOTE-059 [154] trial showed clinical benefit when using pembrolizumab monotherapy in the second-line setting and beyond for AGC. This led to it becoming FDA-approved in 2017 as a third-line treatment for patients with a PD-L1 combined positive score (CP) ≥ 1 AGC. However, the phase III KEYNOTE-061 [164] and KEYNOTE-062 [165] trials demonstrated that pembrolizumab was non-inferior to chemotherapy, both when used as a monotherapy and in combination with chemotherapy drugs, in the second- and first-line setting, respectively. In the phase III ATTRACTION-2 study [167], Nivolumab, another anti-PD-1 monoclonal antibody, was tested in Asian patients as a monotherapy in the second-line and beyond setting and showed statistically significant improvements in mOS and mPFS, which led to its approval in Japan as a third-line treatment for gastric cancer. Furthermore, the phase III trial CheckMate-649 [168] also showed significant improvements in mOS and mPFS when nivolumab was combined with standard first-line chemotherapy compared to the use of chemotherapy alone. Several other phase II trials have been conducted for other PD-1 inhibitors, such as camrelizumab [160], sintilimab [161], toripalimab [162], and tislelizumab [163]; however, none so far have produced results warranting further phase III trials.

Avelumab is an anti-PD-L1 monoclonal antibody that was investigated in the phase III JAVELIN Gastric 100 study [170] as a maintenance treatment after the first-line chemotherapy in AGC patients; however, it failed to show any significant improvement in mOS or mPFS. Ipilimumab is an anti-CTLA-4 antibody that has been shown to cause a statistically significant worse mPFS when combined with chemotherapy, compared to the use of chemotherapy alone. Immune checkpoint inhibitors have also been combined with other targeted therapies to produce promising results. For AGC, studies have mainly investigated the combination of anti-HER-2 monoclonal antibodies and VEGF/VEGFR inhibitors with immunotherapy. The phase II PANTHERA [155] study investigated the use of pembrolizumab combined with trastuzumab and chemotherapy to treat HER-2 AGC patients in the first-line setting and showed an ORR of 76.7%, with 56.6% of patients showing a reduction in over 50% of the tumor burden. These findings concurred with the ones seen in another phase II study assessing the efficacy of combining trastuzumab with pembrolizumab in AGC patients [156]. These promising results prompted the phase III KEYNOTE-811 [166] study assessing the use of pembrolizumab in the first-line setting combined with trastuzumab and chemotherapy, and showed to have an ORR of 74.4% in the intervention arm vs. 51.9% in the arm with trastuzumab and chemotherapy only (p = 0.00006). The results of the KEYNOTE-811 study led the FDA to grant accelerated approval on pembrolizumab plus trastuzumab and chemotherapy for first-line treatment of HER-2-positive gastric cancer in May 2021 [175].

### Table 4. Cont.

| Drug Class | Drug | Trial | Phase | Method | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|------------|------|-------|-------|--------|---------------|---------------|---------------|
| Anti-PD-L1 | Avelumab | JAVELIN Gastric 100/first-line [170] | III | Chemotherapy (5-FU + oxaliplatin) vs. nivolumab (3 mg/kg) with or without avelumab | 10.4 M vs. 10.9 M (p = 0.1779) | 3.2 M vs. 4.4 M (p = N/A) | 13.3% vs. 14.4% (p = N/A) |
| Anti-CTLA-4 | Ipilimumab | first-line [171] | II | Chemotherapy (5-FU + platinum) vs. nivolumab (3 mg/kg) with or without ipilimumab | 12.7 vs. 12.1 (p = N/A) | 2.7 M vs. 4.9 M (p = 0.034) | 1.8% vs. 7.0% (p = N/A) |
| Anti-PD-L/CTLA-4 | Nivolumab, ipilimumab | CheckMate-032/≥second-line [172] | I/II | Nivolumab (3 mg/kg) vs. nivolumab (1 mg/kg) with ipilimumab (3 mg/kg) vs. nivolumab (3 mg/kg) with ipilimumab (1 mg/kg) | 6.2 M vs. 6.9 M vs. 4.8 M | 1.4 M vs. 1.4 M vs. 1.6 M | 12% vs. 24% vs. 8% |
| Anti-PD-L1/CTLA-4 | Cadonilimab | AK104/first-line [173] | Ib/II | Single-arm: Chemotherapy (CAPOX) + cadonilimab | 17.41 M | 7.10 M | 65.9% |
| Anti-PD-L1/CTLA-4 | Durvalumab, tremelimumab | ≥second-line [174] | Ib/II | second-line durvalumab with tremelimumab vs. third-line durvalumab with tremelimumab vs. second-line durvalumab alone | 9.2 M vs. 10.6 M vs. 3.2 M | 1.8 M vs. 1.8 M vs. 1.6 M | 11.1% vs. 12.0% vs. 8.3% |
Margetuximab is a novel monoclonal antibody that binds to the same HER-2 dimerization domain as trastuzumab but, in contrast to trastuzumab, it has increased binding to the activating Fcy receptor IIIa and decreased binding to the Fcy receptor IIb, which results in enhanced anti-tumor activity compared to trastuzumab [176]. Furthermore, margetuximab has also been shown in in vitro studies to upregulate PD-L1 expression in tumor cells. This unique mechanism of action resulted in investigators conducting a phase Ib/II trial to assess the efficacy of combining margetuximab with pembrolizumab in HER-2-positive AGC [81], which showed promising results with an ORR of 18.5% and a DCR of 53%, in turn prompting investigators to conduct a phase II/III “MAHOGANY” trial [177] that is still ongoing.

NivoRAM was a phase I/II study that investigated the efficacy of combining nivolumab with paclitaxel and ramucirumab as a second-line treatment of AGC and the results showed patients to have an ORR of 26.7% [159]. The EPOC1706 study [142] was a phase II trial that examined the efficacy of combining lenvatinib with pembrolizumab in the first-line setting and beyond for AGC and the results showed promising results, with patients having an ORR of 69%, especially patients who had high PD-L1 expression (CPS ≥ 1 subgroup: 84%; CPS ≥ 10 subgroup 100%). The LEAP-005 phase II trial [143] which also studied the efficacy of combining lenvatinib with pembrolizumab concurred with the results of EPOC1706.

Combinations of different immune checkpoint inhibitor medications, mainly PD-1/PD-L1 inhibitors with CTLA-4 inhibitors, have also been explored for gastric cancer. The rationale behind this combination could be due to the fact that one of the causes of resistance to PD-1/PD-L1 blockade is the presence of immune suppression through other immune checkpoints, such as CTLA-4, which is a key negative regulator of anti-tumor T-cell response [178]. The phase I/II CheckMate-032 study [172] randomized patients to nivolumab monotherapy (3 mg/kg) and nivolumab with ipilimumab (in two different doses—1 mg/kg nivolumab + 3 mg/kg ipilimumab or 3 mg/kg nivolumab + 1 mg/kg ipilimumab) and found a higher ORR in the combination nivolumab (1 mg/kg) with ipilimumab (3 mg/kg) group compared to the other subgroups, hence supporting the hypothesis that the addition of CTLA-4 inhibitors could improve response to PD-1/PD-L1 inhibitors. Additionally, the promising phase Ib/II “AK104” study [173] examining the efficacy of caramellumab (a combined PD-1/CTLA-4 inhibitor drug) used in combination with first-line chemotherapy for AGC patients showed inspiring results, with an ORR of 65.9% (2.3% complete, 63.6% partial), disease control rate of 92.0%, mPFS of 7.10 months, and mOS of 17.4 months. This exciting study prompted another phase III study, which is still ongoing, to further examine these findings. In contrast to these studies, another phase Ib/II trial [174] examined the use of durvalumab (PD-L1 inhibitor) with tremelimumab (CTLA-4 inhibitor) combined and as monotherapies, but found no significant response rates in any subgroups.

3.4. Anti-DNA Synthesis

TAS-102 is an oral cytotoxic drug composed of trifluridine (TFD), an analog of the thymidine-based nucleoside which inhibits tumor cell growth by being incorporated into DNA during DNA synthesis, and tipiracil (TPI), a molecule which inhibits the metabolism of TFD, thereby prolonging its ability to exert effect [179]. Table 5 outlines the results of phase II and III trials against this molecular target. A phase III trial “TAGS” [180] demonstrated an impressively prolonged mOS in the TAS-102 subgroup vs. placebo in AGC patients in the second-line and beyond setting. Furthermore, a subgroup analysis of the TAGS study investigated the efficacy of this treatment in patients using it as a third-line and fourth-line treatment and found statistically significant improvements in mOS and mPFS compared to placebo [181]. These promising results led to the approval of TAS-102 (trifluridine/tipiracil) as a third-line treatment option in AGC [182]. A recently published phase II study [179] also investigated the combination of TAS-102 with ramucirumab and found modest activity in AGC patients, requiring further investigation.
### Table 5. Phase II and III trials of therapies targeting DNA synthesis. mOS, median overall survival; mPFS, median progression-free survival; HR, hazard ratio; M, months; ORR, objective response rate.

| Drug                  | Trial       | Phase          | Method                                      | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|-----------------------|-------------|----------------|---------------------------------------------|---------------|----------------|---------------|
| TAS-102 (Trifluridine/tipiracil) |           | ≥ second-line [183] | Single arm: TAS-102 (trifluridine/tipiracil) | 8.7 M          | 2.9 M          | 3.4%          |
|                       |            | ≥ second-line [179] | Single arm: TAS-102 + ramucirumab         | 6.2 M         | 4.9 M          | N/A           |
| TAGS/ ≥ second-line [180] | III        | Trifluridine/tipiracil vs. placebo | 5.7 M vs. 3.6 M (p = 0.00058) | 2.0 M vs. 1.8 M (p < 0.0001) | 4% vs. 2% (p = 0.28) |
| TAGS/third-line [181] | III         | Trifluridine/tipiracil vs. placebo | 6.8 M vs. 3.2 M (p = 0.0318) | 3.1 M vs. 1.9 M (p = 0.0004) | N/A |
| TAGS/ ≥ fourth-line [181] | III      | Trifluridine/tipiracil vs. placebo | 5.2 M vs. 3.7 M (p = 0.0192) | 1.9 M vs. 1.8 M (p < 0.0001) | N/A |

3.5. Anti-Hepatocyte Growth Factor Receptor (Anti-HGFR)

The mesenchymal-epithelial transition factor receptor (c-MET) is a proto-oncogenic receptor tyrosine kinase that is activated by hepatocyte growth factor (HGF). Activation of c-MET receptor promotes tumor formation through increased mitosis and inhibition of apoptosis. C-MET overexpression and gene amplification is a marker of poor prognosis in gastric cancer [184]. Rilotumumab is a humanized IgG2 monoclonal antibody that targets HGF, hence blocking the binding of HGF to c-MET [185]. Table 6 outlines the results of phase II and III trials against this molecular target.

### Table 6. Phase II and III trials of therapies targeting hepatocyte growth factor receptor-1. mOS, median overall survival; mPFS, median progression-free survival; HR, hazard ratio; M, months; ORR, objective response rate; FOLFOX, folinic acid, fluorouracil, oxaliplatin.

| Drug Class         | Drug                | Trial         | Phase          | Method                                      | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|--------------------|---------------------|---------------|----------------|---------------------------------------------|---------------|----------------|---------------|
| Monoclonal antibody| Rilotumumab         | first-line [186] | II             | Chemotherapy (epirubicin + cisplatin + capecitabine) with either rilotumumab 15 mg/kg, rilotumumab 7.5 mg/kg, or placebo | N/A           | 5.1 M vs. 6.8 M 4.2 M | N/A           |
| Rilotumumab        | MEGA/first-line [71] | II            | Chemotherapy with or without either panitumumab or rilotumumab | 8.3 M (P) vs. 11.5 M (R) vs. 13.1 M (C) | 4-month PFS rate: 57% (P) vs. 61% (R) vs. 71% (C) | 43% (P) vs. 49% (R) vs. 52% (C) |
| Onartuzumab        | YO28252/first-line [187] | II            | Chemotherapy (mFOLFOX6) with or without onartuzumab | 10.6 M vs. 11.3 M (p = 0.83) | 5.95 M vs. 6.80 M (p = 0.45) | 60.5% vs. 57.1% |
| Emibetuzumab       | ≥ third-line [188] | II            | Single arm: emibetuzumab | 3.9 M | 1.9 M | N/A |
| Emibetuzumab       | ≥ first-line [189] | Ib/II         | Single arm: ramucirumab + emibetuzumab | N/A | 1.6 M | 6% |
| Rilotumumab        | RILOMET-1/first-line [190] | III | Chemotherapy (epirubicin + cisplatin + capetcitabine) with or without rilotumumab | 8.8 M vs. 10.7 M (p = 0.003) | 5.6 M vs. 6.0 M (p = 0.016) | 29.8% vs. 44.6% (p = 0.0005) |
| Onartuzumab        | METGastric/first-line [191] | III | Chemotherapy (mFOLFOX6) with or without onartuzumab | 11.0 M vs. 11.3 M (p = 0.24) | 6.7 M vs. 6.8 M (p = 0.43) | 46.1% vs. 40.6% (p = 0.25) |
| TKIs               | Foretinib          | ≥ first-line [192] | II            | Single arm: foretinib intermittent dosing vs. daily dosing | Intermittent: 7.4 M Daily: 4.3 M | Intermittent: 1.6 M Daily: 1.8 M | 0% |
| Tivantinib         | first-line [193] | II            | Single arm: chemotherapy (FOLFOX) with tivantinib | 9.6 M | 6.1 M | 38% |

Although phase II studies [186] have suggested a possible benefit with the addition of rilotumumab to first-line chemotherapy, the phase III trial “RILOMET-1” [190] showed a statistically significant worse mOS, mPFS, and ORR in the group taking rilotumumab. The study was ultimately terminated early due to the increased number of deaths due to complications in patients treated with rilotumumab compared to placebo. Onartuzumab is a recombinant humanized anti-c-Met monoclonal antibody [185]. However, phase III trials [191] failed to show any clinical benefit with its addition to first-line chemotherapy. Emertuzumab is a humanized IgG4 monoclonal anti-Met antibody that prevents HGF from binding to c-Met and also degrades c-MET [185]. Phase II trials [188,189] have
demonstrated that it may have some anti-tumor activity, although further studies are needed to investigate this.

Some tyrosine kinase inhibitors of the c-Met/HGF pathway, such as foretinib [192] and tivantinib [193], have also been studied in phase II trials; however, none have produced any significant clinical benefit warranting further studies.

3.6. Anti-FGFR

The fibroblast growth factor receptor (FGFR) has four family members: FGFR-1, FGFR-2, FGFR-3, and FGFR-4. Of these, FGFR-2 has been shown to be the most frequently amplified and altered in gastric cancer, being overexpressed in around 2–30% of GCs [194]. Table 7 outlines the results of phase II and III trials against this molecular target. The FGFR1-2-3 TKI termed “AZD4547” was investigated in the phase II “SHINE” trial and failed to show any improvement in clinical outcomes. Following this, the phase II “FIGHT” trial [195] investigated the use of the anti-FGFR2b monoclonal antibody, bemarituzumab, in combination with first-line chemotherapy and found promising results with a statistically significant improvement in mPFS. The results of this study prompted a phase III trial for AGC which is still ongoing.

Table 7. Phase II and III trials of therapies targeting fibroblast growth factor receptor. mOS, median overall survival; mPFS, median progression-free survival; M, months; ORR, objective response rate; FOLFOX, folinic acid, fluorouracil, oxaliplatin.

| Drug Class         | Drug     | Trial Phase                  | Method                          | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|--------------------|----------|------------------------------|---------------------------------|---------------|----------------|---------------|
| Monoclonal antibody| Bemarituzumab | FIGHT/first-line [195]      | Chemotherapy (mFOLFOX6) with or without bemarituzumab | NR vs. 12.9 M (p = 0.03) | 9.5 M vs. 7.4 M (p = 0.07) | 53% vs. 40% |
| TKIs               | AZD4547  | SHINE/second-line [196]      | AZD4547 vs. chemotherapy (paclitaxel) | 5.5 M vs. 6.6 M (p = 0.82) | 1.8 M vs. 3.5 M (p = 0.96) | 2.6% vs. 23.3% (p = 0.99) |

3.7. PARP Inhibitors

Poly (ADP-ribose) polymerase (PARP) is important for DNA single-strand break re-pairs. In tumor cells that possess homologous recombination deficiency, inhibition of PARP can lead to the formation of single-strand breaks which are then transformed into DNA double-strand breaks (that are unable to be repaired through homologous recombination), ultimately leading to genomic instability and tumor cell death [197]. Table 8 outlines the results of phase II and III trials against this molecular target. Despite promising results in phase II trials [198], the phase III trials [199] investigating the use of olaparib with paclitaxel compared with paclitaxel failed to show any statistically significant clinical benefit.

Table 8. Phase II and III trials of therapies targeting poly (ADP-ribose) polymerase. mOS, median overall survival; mPFS, median progression-free survival; HR, hazard ratio; M, months; ORR, objective response rate.

| Drug     | Trial Phase                  | Method                          | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|----------|------------------------------|---------------------------------|---------------|----------------|---------------|
| Pamiparib | PARALLEL 303/ >first-line [200] | II Pamiparib vs. placebo       | 10.2 M vs. 12.0 M (p = N/A) | 3.7 M vs. 2.1 M (p = 0.14) | 7.7% vs. 6.3% |
| Olaparib | >first-line [198]            | II Chemotherapy (paclitaxel) with or without olaparib | 13.1 M vs. 8.3 M (p = 0.005) | 3.91 M vs. 3.35 M (p = 0.131) | 26.4% vs. 19.1% (p = 0.162) |
|          | GOLD/>first-line [199]       | III Chemotherapy (paclitaxel) with or without olaparib | 8.8 M vs. 6.9 M (p = 0.026) | 3.7 M vs. 3.2 M (p = 0.064) | 24% vs. 28% (p = 0.055) |

3.8. Anti-MMP-9

Matrix metalloproteinase-9 (MMP-9) is known to promote wound healing through collagen deposition as well as activation of cytokines and growth factors. MMP-9-mediated cleavage of cytokines such as interleukin (IL)-8 and IL-1β can induce tumor growth. MMP-9 also cleaves and activates growth factors such as VEGF and FGF-2. Inhibition of MMP-9
can suppress the tumor micro-environment and reduce tumor growth [201]. However, the phase III trial “GAMMA-1” [202] failed to show any statistically significant clinical benefit. A phase II trial [201] was also conducted to demonstrate the efficacy of PD-1 inhibitor nivolumab with andecaliximab compared to andecaliximab alone and also failed to show any clinical benefit with the addition of andecaliximab. Table 9 outlines the results of both of these phase II and III trials against MMP-9.

### Table 9. Phase II and III trials of therapies targeting matrix metalloproteinase-9. mOS, median overall survival; mPFS, median progression-free survival; HR, hazard ratio; M, months; ORR, objective response rate.

| Drug Class               | Drug               | Trial                | Phase | Method                                                                 | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|--------------------------|--------------------|----------------------|-------|------------------------------------------------------------------------|---------------|----------------|---------------|
| ICI + monoclonal antibody| Andecaliximab      | ≥first-line [201]    | II    | Andecaliximab + nivolumab vs. nivolumab alone                        | 7.1 M vs. 5.9 M (p = 0.23) | N/A            | 9.7% vs. 6.9% (p = 0.8) |
| Monoclonal antibody      | Andecaliximab      | GAMMA-1/first-line [202] | III   | Andecaliximab (mFOLFOX6) with or without andecaliximab                | 12.5 M vs. 11.8 M (p = 0.56) | 7.5 M vs. 7.1 M (p = 0.10) | 50.5% vs. 41.1% |

### 3.9. mTOR Inhibitors

The phosphatidylinositol 3-kinase (PI3K)/Akt and mammalian target of rapamycin (mTOR) is activated in 30% and 60% of GCs, respectively, and is associated with tumor progression [202]. Everolimus is an oral mTOR inhibitor that was evaluated for its efficacy in AGC, however, phase III clinical trials [203] failed to show any clinical benefit. Table 10 outlines the results of both of these trials.

### Table 10. Phase II and III trials of therapies targeting mammalian target of rapamycin mOS, median overall survival; mPFS, median progression-free survival; HR, hazard ratio; M, months; ORR, objective response rate.

| Drug            | Trial               | Phase | Method                  | mOS (p-Value) | mPFS (p-Value) | ORR (p-Value) |
|-----------------|---------------------|-------|-------------------------|---------------|----------------|---------------|
| Everolimus      | >first-line [204]   | II    | Single arm: everolimus  | 10.1 M        | 2.7 M          | N/A           |
| Everolimus      | GRANITE-1/>first-line [203] | III   | Everolimus vs. placebo  | 5.4 M vs. 4.3 M (p = 0.124) | 1.7 M vs. 1.4 M (p = N/A) | 4.5% vs. 2.1% (p = N/A) |

### 4. Conclusions

In conclusion, there have been significant recent developments in the detection and treatment of GC. Although there has been improvement, there are still numerous challenges. The amount of clinical data is growing every day but despite this, there are currently not enough high-quality, well-designed multi-center prospective trials available. Furthermore, the enormous inter-tumor and intra-tumor heterogeneity of GC across individuals and populations results in a lag in transitioning the current molecular research into clinical practice for patient benefit [205]. The diagnosis and treatment approaches used in the East and West also differ significantly [206]. The inconsistency between the approaches used globally limits the advancements toward earlier diagnosis and more effective therapy. Hence, in the future, more cross-disciplinary and international collaboration is needed.

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Conceptualization, methodology, E.H., A.E., M.A.; writing—original draft preparation, E.H., A.E.; writing—review and editing, data curation, visualization, A.E., I.M., H.S., M.A.; supervision, project administration, funding acquisition, M.A. All authors have read and agreed to the published version of the manuscript.

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References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2021, 71, 209–249. [CrossRef] [PubMed]

2. Morgan, E.; Arnold, M.; Camargo, M.C.; Gini, A.; Kunzmann, A.T.; Matsuda, T.; Meheus, F.; Verhoeven, R.H.A.; Vignat, J.; Laversanne, M.; et al. The current and future incidence and mortality of gastric cancer in 185 countries, 2020–40: A population-based modelling study. EClinicalMedicine 2022, 47, 101404. [CrossRef] [PubMed]

3. Tsugane, S.; Sasazuki, S. Diet and the risk of gastric cancer: Review of epidemiological evidence. Gastric Cancer 2007, 10, 75–83. [CrossRef] [PubMed]

4. Tang, C.T.; Zeng, L.; Yang, J.; Zeng, C.; Chen, Y. Analysis of the Incidence and Survival of Gastric Cancer Based on the Lauren Classification: A Large Population-Based Study Using SEER. Front. Oncol. 2020, 10, 1212. [CrossRef] [PubMed]

5. Noh, C.-K.; Lee, E.; Lee, G.H.; Kang, J.K.; Lim, S.G.; Park, B.; Park, J.B.; Shin, S.J.; Cheeong, J.Y.; Kim, J.H.; et al. Association of Intensive Endoscopic Screening Burden With Gastric Cancer Detection. JAMA Netw. Open 2021, 4, e2032542. [CrossRef] [PubMed]

6. Ebibgo, A.; Messmann, H.; Römmele, C. Endoscopic Upper GI Screening. Visc. Med. 2019, 35, 240–244. [CrossRef] [PubMed]

7. Lengyel, C.G.; Hussain, S.; Trapani, D.; El Bairi, K.; Odhiambo, A.; Habeeb, B.S.; Seid, F. The Emerging Role of Liquid Biopsy in Gastric Cancer. J. Clin. Med. 2021, 10, 2108. [CrossRef]

8. Virgilio, E.; Montali, F.; Annicchiario, A.; Salvemini, C.; Baldini, M.; Giarendero, E.; Montagnini, M.; Villani, S.; Proietti, A.; D’Urso, R.; et al. Exosomal Functional Cargoes from Liquid Biopsy of Gastric Cancer: A Systematic Review of Studies With Potential Clinical Relevance. Anticancer Res. 2022, 42, 2249–2259. [CrossRef]

9. Feng, F.; Tian, Y.; Xu, G.; Liu, Z.; Liu, S.; Zheng, G.; Guo, M.; Lian, X.; Fan, D.; Zhang, H. Diagnostic and prognostic value of CEA, CA19-9, AFP and CA125 for early gastric cancer. BMC Cancer 2017, 17, 737. [CrossRef]

10. Li, X.; Li, S.; Zhang, Z.; Huang, D. Association of multiple tumor markers with newly diagnosed gastric cancer patients: A retrospective study. PeerJ 2022, 10, e13488. [CrossRef]

11. Namikawa, T.; Kawanishi, Y.; Fujisawa, K.; Munekage, E.; Iwabu, J.; Munekage, M.; Maeda, H.; Kitagawa, H.; Kobayashi, M.; Hanazaki, K. Serum carbohydrate antigen 125 is a significant prognostic marker in patients with unrespectably advanced or recurrent gastric cancer. Surg. Today 2018, 48, 388–394. [CrossRef] [PubMed]

12. Marrelli, D.; Pinto, E.; De Stefano, A.; Farnetani, M.; Garosi, L.; Roviello, F. Clinical utility of CEA, CA 19-9, and CA 72-4 in the follow-up of patients with resectable gastric cancer. Am. J. Surg. 2001, 181, 16–19. [CrossRef]

13. Kim, N.; Jung, H.C. The Role of Serum Pepsinogen in the Detection of Gastric Cancer. Gut Liver 2010, 4, 307–319. [CrossRef] [PubMed]

14. Tong, Y.; Wu, Y.; Song, Z.; Yu, Y.; Yu, X. The potential value of serum pepsinogen for the diagnosis of atrophic gastritis among the health check-up populations in China: A diagnostic clinical research. BMC Gastroenterol. 2017, 17, 88. [CrossRef]

15. Lee, S.-Y. Endoscopic gastritis, serum pepsinogen assay, and Helicobacter pylori infection. Korean J. Intern. Med. 2016, 31, 835–844. [CrossRef]

16. Cha, J.H.; Jang, J.S. Clinical correlation using serum pepsinogen level and gastric atrophy in gastric neoplasm. Korean J. Intern. Med. 2020, 35, 550–558. [CrossRef]

17. Miki, K. Gastric cancer screening using the serum pepsinogen test method. Gastric Cancer 2006, 9, 245–253. [CrossRef]

18. Mitahussurur, M.; Waskito, L.A.; Aftab, H.; Vilaichone, R-K.; Subsompong, P.; Nusi, I.A.; Syam, A.F.; Ratanachu-Ek, T.; Doohan, D.; Siregar, G.; et al. Serum pepsinogens as a gastric cancer and gastritis biomarker in Southeast Asian populations. PLoS ONE 2015, 10, e0230064. [CrossRef]

19. Aikou, S.; Ohmoto, Y.; Gunji, T.; Matsusashi, N.; Ohtsu, H.; Miura, H.; Kubota, K.; Yamagata, Y.; Seto, Y.; Nakajima, A.; et al. Tests for Serum Levels of Trefoil Factor Family Proteins Can Improve Gastric Cancer Screening. Gastroenterology 2011, 141, 837–845. [CrossRef]

20. Zhang, C.-X.; Wu, C.-T.; Xiao, L.; Tang, S.-H. The diagnostic and clinicopathological value of trefoil factor 3 in patients with gastric cancer: A systematic review and meta-analysis. Biomarkers 2021, 26, 95–102. [CrossRef]

21. Kaise, M.; Miwa, J.; Tashiro, J.; Ohmoto, Y.; Morimoto, S.; Kato, M.; Urashima, M.; Ikegami, M.; Tajiri, H. The combination of serum trefoil factor 3 and pepsinogen testing is a valid non-endoscopic biomarker for predicting the presence of gastric cancer: A new marker for gastric cancer risk. J. Gastroenterol. 2011, 46, 736–745. [CrossRef] [PubMed]

22. Abdelwahab, H.; Tageldin, O.; Hasak, S.; Lee, H. AFP-producing gastric carcinoma. Hum. Pathol. Rep. 2022, 28, 300640. [CrossRef]

23. Xu, X.; Wang, Q.; Cao, H.; Gao, Z.; Qian, G.; Lu, Q.; Wu, Y. Prognostic value of serum alpha-fetoprotein levels in patients with gastric cancer: A meta-analysis. J. Int. Med. Res. 2020, 48, 030006051989978. [CrossRef]

24. Zhan, Z. Elevated serum alpha-fetoprotein is a significant prognostic factor for gastric cancer patients: Results based on a large-scale retrospective study. J. Clin. Oncol. 2022, 40 (Suppl. 16), e16059. [PubMed]

25. Gong, W.; Su, Y.; Liu, A.; Liu, J.; Sun, D.; Jiang, T.; Xiang, J.; Chi, C.; Sun, P. Clinical characteristics and treatments of patients with alpha-fetoprotein producing gastric carcinoma. Neoplasma 2018, 65, 326–330. [CrossRef] [PubMed]

26. Neumann, M.H.D.; Bender, S.; Krahn, T.; Schlange, T. ctDNA and CTCs in Liquid Biopsy—Current Status and Where We Need to Progress. Comput. Struct. Biotechnol. J. 2018, 16, 190–195. [CrossRef] [PubMed]

27. Leja, M.; Lině, A. Early detection of gastric cancer beyond endoscopy—new methods. Best Pract. Res. Clin. Gastroenterol. 2021, 50–51, 101731. [CrossRef]
Cancers 2022, 14, 5615

28. Necula, L.; Matei, L.; Dragu, D.; Neagu, A.I.; Mamet, C.; Nedelcuianu, S.; Bleotu, C.; Diaconu, C.C.; Chivu-Economescu, M. Recent advances in gastric cancer early diagnosis. *World J. Gastroenterol.* 2019, 25, 2029–2044. [CrossRef]

29. Nakamura, K.; Iwatsuki, M.; Kurashige, J.; Ishimoto, T.; Baba, Y.; Miyamoto, Y.; Yoshida, N.; Watanabe, M.; Baba, H. Circulating tumor cells in gastric cancer. *J. Cancer Metastasis Treat.* 2018, 4, 32. [CrossRef]

30. Lee, M.W.; Kim, G.H.; Jeon, H.K.; Park, S.J. Clinical Application of Circulating Tumor Cells in Gastric Cancer. *Gut Liver* 2019, 13, 394–401. [CrossRef]

31. Sudhakar, P.; Sanapala, P.; Naidu, B.P. Overview of Early Detection of Gastrointestinal Cancer. In *Recent Advancements in Biomarkers and Early Detection of Gastrointestinal Cancers*; Springer: Singapore, 2020; pp. 117–129.

32. Uchida, K.T.; Ferreira Martins, N.N.; Cristina Da Silva Oliveira, K.; Almeida, C.M.; Pinheiro, T.M.; Giger, C.O.; Roberto De Araujo Cavallero, S.; Assumpção, P.P.; Cardoso Smith, M.A.; Burbano, R.R.; et al. Liquid biopsy provides new insights into gastric cancer. *Onco target* 2018, 9, 15144–15156. [CrossRef] [PubMed]

33. Vasseur, A.; Kiavue, N.; Bidard, F.C.; Pierga, J.Y.; Cabel, L. Clinical utility of circulating tumor cells: An update. *Mol. Oncol.* 2021, 15, 1647–1666. [CrossRef] [PubMed]

34. Pernot, S.; Badoual, C.; Termre, M.; Castan, F.; Cazes, A.; Bouche, O.; Bennouna, J.; Francois, E.; Ghiringhelli, F.; De La Fouchardiere, C.; et al. Dynamic evaluation of circulating tumour cells in patients with advanced gastric and oesogastric junction adenocarcinoma: Prognostic value and early assessment of therapeutic effects. *Eur. J. Cancer* 2017, 79, 15–22. [CrossRef] [PubMed]

35. Klein, C.A. Parallel progression of primary tumours and metastases. *Nat. Rev. Cancer* 2009, 9, 302–312. [CrossRef]

36. Fang, W.-L.; Lan, Y.-T.; Huang, K.-H.; Liu, C.-A.; Hung, Y.-P.; Lin, C.-H.; Jiang, F.-Y.; Chang, S.-C.; Chen, M.-H.; Chao, Y.; et al. Clinical significance of circulating plasma DNA in gastric cancer. *Int. J. Cancer* 2016, 138, 2974–2983. [CrossRef]

37. Gao, Y.; Zhang, K.; Xi, H.; Cai, A.; Wu, X.; Cui, J.; Li, J.; Qiao, Z.; Wei, B.; Chen, L. Diagnostic and prognostic value of circulating tumor DNA in gastric cancer: A meta-analysis. *Onco target* 2017, 8, 6330–6340. [CrossRef]

38. Wu, J.; Li, G.; Wang, Z.; Yao, Y.; Chen, R.; Pu, X.; Wang, J. Circulating MicroRNA-21 Is a Potential Diagnostic Biomarker in Gastric Cancer. *Dis. Mkr.* 2015, 2015, 435656. [CrossRef]

39. Hung, P.-S.; Chen, C.-Y.; Chen, W.-T.; Kuo, C.-Y.; Fang, W.-L.; Huang, K.-H.; Chiu, P.-C.; Lo, S.-S. miR-376c promotes carcinogenesis and serves as a plasma marker for gastric cancer diagnosis. *PLoS ONE* 2017, 12, e0177346. [CrossRef]

40. Tsai, M.M.; Tsai, C.S.; Tsai, C.Y.; Huang, C.G.; Lee, K.F.; Huang, H.W.; Lin, Y.H.; Chi, H.C.; Kuo, L.M.; Lu, P.H.; et al. Circulating microRNA-196a/b are novel biomarkers associated with metastatic gastric cancer. *Eur. J. Cancer* 2016, 64, 137–148. [CrossRef]

41. Valladares-Ayerbes, M.; Reboredo, M.; Medina-Villaamil, V.; Iglesias-Diaz, P.; Lorenzo-Patiño, M.J.; Haz, M.; Santamarina, I.; Blanco, M.; Fernandez-Tajes, J.; Quindos, M.; et al. Circulating miR-200c as a diagnostic and prognostic biomarker for gastric cancer. *J. Transl. Med.* 2012, 10, 186. [CrossRef]

42. Ranjarb, R.; Hesari, A.; Ghasemi, F.; Sahebkar, A. Expression of microRNAs and IRAK1 pathway genes are altered in gastric cancer. *Mol. Cancer* 2016, 15, 41. [CrossRef] [PubMed]

43. Liu, X.; Kwong, A.; Sihoe, A.; Chu, K.M. Plasma miR-940 may serve as a novel biomarker for gastric cancer. *Oncotarget* 2016, 7, 2953. [CrossRef]

44. Qu, A.; Wang, W.; Yang, Y.; Zhang, X.; Dong, Y.; Zheng, G.; Wu, Q.; Zou, M.; Du, L.; Wang, Y.; et al. Serum piRNA signature as promising non-invasive diagnostic and prognostic biomarkers for colorectal cancer. *Cancer Manag. Res.* 2019, 11, 3703–3720. [CrossRef]

45. Cui, L.; Lou, Y.; Zhang, X.; Zhou, H.; Deng, H.; Song, H.; Yu, X.; Xiao, B.; Wang, W.; Guo, J. Detection of circulating tumor cells in peripheral blood from patients with gastric cancer using piRNAs as markers. *Clin. Biochem.* 2011, 44, 1050–1057. [CrossRef] [PubMed]

46. Riquelme, I.; Pérez-Moreno, P.; Letelier, P.; Brebi, P.; Roa, J.C. The Emerging Role of PIWI-Interacting RNAs (piRNAs) in Gastrointestinal Cancers: An Updated Perspective. *Cancers* 2021, 14, 202. [CrossRef]

47. Jin, C.; Shi, W.; Wang, F.; Shen, X.; Qi, J.; Cong, H.; Yuan, J.; Shi, L.; Zhu, B.; Luo, X.; et al. Long non-coding RNA HULC as a novel serum biomarker for diagnosis and prognosis prediction of gastric cancer. *Oncotarget* 2016, 7, 51763–51772. [CrossRef]

48. Arita, T.; Ichikawa, D.; Konishi, H.; Komatsu, S.; Shiozaki, A.; Shoda, K.; Kawaguchi, T.; Hirajima, S.; Nagata, H.; Kubota, T.; et al. Circulating long non-coding RNAs in plasma of patients with gastric cancer. *Anticancer Res.* 2013, 33, 3185–3193. [CrossRef]

49. Kalfon, T.; Loewenstein, S.; Gerstenhaber, S.; Leibou, S.; Geller, H.; Sher, O.; Nizri, E.; Lahat, G. Gastric Cancer-Derived Extracellular Vesicles (EVs) Promote Angiogenesis via Angiopoietin-2. *Cancers* 2022, 14, 2953. [CrossRef]

50. Nederveen, J.P.; Warnier, G.; Di Carlo, A.; Nilsson, M.I.; Tarnopolsky, M.A. Extracellular Vesicles and Exosomes: Insights From Exercise Science. *Front. Physiol.* 2020, 11, 604274. [CrossRef]

51. Fu, M.; Gu, J.; Jiang, P.; Qian, H.; Xu, W.; Zhang, X. Exosomes in gastric cancer: Roles, mechanisms, and applications. *Mol. Cancer* 2019, 18, 41. [CrossRef]

52. Im, K.; Baek, J.; Kwon, W.S.; Rha, S.Y.; Hwang, K.W.; Kim, U.; Min, H. The Comparison of Exosome and Exosomal Cytokines between Young and Old Individuals with or without Gastric Cancer. *Int. J. Gerontol.* 2018, 12, 233–238. [CrossRef]

53. Wang, X.; Huang, J.; Chen, W.; Li, G.; Li, Z.; Lei, J. The updated role of exosomal proteins in the diagnosis, prognosis, and treatment of cancer. *Exp. Mol. Med.* 2022, 54, 1390–1400. [CrossRef] [PubMed]

54. Su, H.; Ren, W.; Zhang, D. Research progress on exosomal proteins as diagnostic markers of gastric cancer (review article). *Clin. Exp. Med.* 2022, Online ahead of print. [CrossRef]
Cancers 2022, 14, 5615

55. Zhong, H.; Yang, Y.; Ma, S.; Xiu, F.; Cai, Z.; Zhao, H.; Du, L. Induction of a tumour-specific CTL response by exosomes isolated from heat-treated malignant ascites of gastric cancer patients. *Int. J. Hyperth.* 2011, 27, 604–611. [CrossRef]

56. Yamamoto, H.; Watanabe, Y.; Okawa, R.; Morita, R.; Yoshida, Y.; Maehata, T.; Yasuda, H.; Itoh, F. BARH2 Methylation Using Gastric Wash DNA or Gastric Juice Exosomal DNA is a Useful Marker For Early Detection of Gastric Cancer in an *H. pylori*-Independent Manner. *Clin. Transl. Gastroenterol.* 2016, 7, e184. [CrossRef] [PubMed]

57. Yamamoto, H. Detection of DNA methylation of gastric juice-derived exosomes in gastric cancer. *Integr. Mol. Med.* 2014, 1, 17–21. [CrossRef]

58. Ren, J.; Zhou, Q.; Li, H.; Li, J.; Pang, L.; Su, L.; Gu, Q.; Zhu, Z.; Liu, B. Characterization of exosomal RNAs derived from human gastric cancer cells by deep sequencing. *Tumor Biol.* 2017, 39, 101042831769501. [CrossRef]

59. Wang, N.; Wang, L.; Yang, G.; Xiao, B.; Liu, X. A serum exosomal microRNA panel as a potential biomarker test for gastric cancer. *Biochem. Biophys. Res. Commun.* 2017, 493, 1322–1328. [CrossRef]

60. Huang, Z.; Zhu, D.; Wu, L.; He, M.; Zhou, X.; Zhang, L.; Zhang, H.; Wang, W.; Zhu, J.; Cheng, W.; et al. Six Serum-Based miRNAs as Potential Diagnostic Biomarkers for Gastric Cancer. *Cancer Epidemiol. Biomark. Prev.* 2017, 26, 188–196. [CrossRef]

61. Tokuhisa, M.; Ichikawa, Y.; Kosaka, N.; Ochiya, T.; Yashiro, M.; Hirakawa, K.; Kosa, T.; Makino, H.; Akiyama, H.; Kunisaki, C.; et al. Exosomal miRNAs from Peritoneum Lavage Fluid as Potential Prognostic Biomarkers of Peritoneal Metastasis in Gastric Cancer. *PLoS ONE* 2015, 10, e0130472. [CrossRef]

62. Chen, K.B.; Chen, J.; Jin, X.L.; Huang, Y.; Su, Q.M.; Chen, L. Exosome-mediated peritoneal dissemination in gastric cancer and its clinical applications (Review). *Biomed. Rep.* 2018, 8, 503–509. [CrossRef]

63. Arienti, C.; Pignatta, S.; Tesei, A. Epidermal Growth Factor Receptor Family and its Role in Gastric Cancer. *Front. Oncol.* 2019, 9, 1308. [CrossRef] [PubMed]

64. Dulak, A.M.; Schumacher, S.E.; Van Lieshout, J.; Imamura, Y.; Fox, C.; Shim, B.; Ramos, A.H.; Saksena, G.; Baca, S.C.; Baselga, J. Gastrointestinal adenocarcinomas of the esophagus, stomach, and colon exhibit distinct patterns of genome instability and oncoc genesis. *Cancer Res.* 2012, 72, 4383–4393. [CrossRef] [PubMed]

65. Kim, M.A.; Lee, H.S.; Lee, H.E.; Jeon, Y.K.; Yang, H.K.; Kim, W.H. EGFR in gastric carcinomas: Prognostic significance of protein overexpression and high gene copy number. *Histopathology* 2008, 52, 738–746. [CrossRef] [PubMed]

66. Boku, N. HER2-positive gastric cancer. *Gastric Cancer* 2014, 17, 1–12. [CrossRef] [PubMed]

67. Rao, S.; Starling, N.; Cunningham, D.; Sumpter, K.; Gilligan, D.; Ruhstaller, T.; Valladares-Ayerbes, M.; Wilke, H.; Archer, C.; Kurek, R.; et al. Matuzumab plus epirubicin, cisplatin and capecitabine (ECX) compared with epirubicin, cisplatin and capecitabine alone as first-line treatment in patients with advanced oesophago-gastric cancer: A randomised, multicentre open-label phase II study. *Ann. Oncol.* 2010, 21, 2213–2219. [CrossRef]

68. Richards, D.; Kocs, D.M.; Spira, A.I.; David McCollum, A.; Diab, S.; Hecker, L.I.; Cohn, A.; Zhan, F.; Asmar, L. Results of docetaxel plus oxaliplatin (DOCOX) ± cetuximab in patients with metastatic gastric and/or gastroesophageal junction adenocarcinoma: Results of a randomised Phase 2 study. *Eur. J. Cancer* 2013, 49, 2823–2831. [CrossRef]

69. Tebbutt, N.C.; Price, T.J.; Ferraro, D.A.; Wong, N.; Veillard, A.-S.; Hall, M.; Sjoquist, K.M.; Pavlakis, N.; Strickland, A.; Varma, S.C.; et al. Panitumumab added to docetaxel, cisplatin and fluoropyrimidine in oesophago-gastric cancer: ATTAX3 phase II trial. *Br. J. Cancer* 2016, 114, 505–509. [CrossRef]

70. Kenteropoulos, N. Panitumumab in combination with modified docetaxel/cisplatin/5-fluorouracil as first-line treatment in gastric and gastroesophageal junction adenocarcinomas: A multicenter phase II study by the Hellenic Oncology Research Group. *Ann. Gastroenterol.* 2018, 31, 698–704. [CrossRef]

71. Malka, D.; François, E.; Penault-Llorca, F.; Castan, F.; Bouché, O.; Bennouna, J.; Ghiringhelli, F.; de la Foucaudière, C.; Borg, C.; Samalin, E.; et al. FOLFOX alone or combined with panitumumab or panitumumab as first-line treatment for patients with advanced gastroesophageal adenocarcinoma (PRODIGE 17-ACCORD 20-MEGA): A randomised, open-label, three-arm phase II trial. *Eur. J. Cancer* 2019, 115, 97–106. [CrossRef]

72. Du, F.; Zheng, Z.; Shi, S.; Jiang, Z.; Qu, T.; Yuan, X.; Sun, Y.; Song, Y.; Yang, L.; Zhao, J.; et al. S-1 and Cisplatin With or Without Nimotuzumab for Patients With Untreated Unresectable or Metastatic Gastric Cancer: A Randomized, Open-Label Phase 2 Trial. *Clin. Medicine* 2015, 14, e958. [CrossRef]

73. Wainberg, Z.A.; Lin, L.-S.; Dicarlo, B.; Dao, K.M.; Patel, R.; Park, D.J.; Wang, H.-J.; Elashoff, R.; Ryba, N.; Hecht, J.R. Phase II trial of modified FOLFOX6 and erlotinib in patients with metastatic or advanced adenocarcinoma of the oesophagus and gastro-oesophageal junction. *Br. J. Cancer* 2011, 105, 760–765. [CrossRef] [PubMed]

74. Waddell, T.; Chau, I.; Cunningham, D.; Gonzalez, D.; Okines, A.F.; Okines, C.; Wotherspoon, A.; Saffery, C.; Middleton, G.; Wadley, J.; et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophago-gastric cancer (REAL3): A randomised, open-label phase 3 trial. *Lancet Oncol.* 2013, 14, 481–489. [CrossRef]

75. Lordick, F.; Kang, Y.-K.; Chung, H.-C.; Salman, P.; Oh, S.C.; Bodoky, G.; Kurteva, G.; Volovat, C.; Moiseyenko, V.M.; Gorbunova, V.; et al. Cetuximab and cisplatin with or without panitumumab for patients with previously untreated advanced gastric cancer (EXPAND): A randomised, open-label phase 3 trial. *Lancet Oncol.* 2013, 14, 490–499. [CrossRef]

76. Makiyama, A.; Sagara, K.; Kawada, J.; Kashiwada, T.; Hosokawa, A.; Horie, Y.; Satake, H.; Yamamoto, Y.; Tanioka, H.; Shinozaki, K. A randomized phase II study of weekly paclitaxel±trastuzumab in patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum: WJOG7112G (T-ACT). *Am. Soc. Clin. Oncol.* 2018, 36, 4011. [CrossRef]
Cancers 2022, 14, 5615

77. Chua, C.; Tan, I.B.; Yamada, Y.; Rha, S.Y.; Yong, W.P.; Ong, W.S.; Tham, C.K.; Ng, M.; Tai, D.W.M.; Iwasa, S.; et al. Phase II study of trastuzumab in combination with S-1 and cisplatin in the first-line treatment of human epidermal growth factor receptor HER2-positive advanced gastric cancer. Cancer Chemother. Pharmacol. 2015, 76, 397–408. [CrossRef]

78. Ryu, M.H.; Yoo, C.; Kim, J.G.; Ryu, B.Y.; Park, Y.S.; Park, S.R.; Han, H.S.; Chung, I.J.; Song, E.K.; Lee, K.H.; et al. Multicenter phase II study of trastuzumab in combination with capecitabine and oxaliplatin for advanced gastric cancer. Eur. J. Cancer 2015, 51, 482–488. [CrossRef]

79. Wang, F.; Liu, T.S.; Yuan, X.L.; Luo, H.Y.; Gu, K.S.; Yuan, Y.; Deng, Y.H.; Xu, J.M.; Bai, Y.X.; Wang, Y.; et al. Trastuzumab plus docetaxel and capecitabine as a first-line treatment for HER2-positive advanced gastric or gastroesophageal junction cancer: A phase II, multicenter, open-label, single-arm study. Am. J. Cancer Res. 2020, 10, 3037–3046.

80. Takahari, D.; Chin, K.; Ishizuka, N.; Takashima, A.; Minashi, K.; Kadowaki, S.; Nishina, T.; Nakajima, T.E.; Amagai, K.; Machida, N.; et al. Multicenter phase II study of trastuzumab with S-1 plus oxaliplatin for chemotherapy-naive, HER2-positive advanced gastric cancer. Gastric Cancer 2019, 22, 1238–1246. [CrossRef]

81. Catenacci, D.V.T.; Kang, Y.K.; Park, H.; Uronics, H.E.; Lee, K.W.; Ng, M.C.H.; Enzinger, P.C.; Park, S.H.; Gold, P.J.; Lacy, J.; et al. Margetuximab plus pembrolizumab in patients with previously treated, HER2-positive gastro-oesophageal adenocarcinoma (CP-MGAH22-05): A single-arm, phase 1b-2 trial. Lancet Oncol. 2020, 21, 1066–1076. [CrossRef]

82. Bang, Y.J.; Van Cutsem, E.; Feyereislova, A.; Chung, H.C.; Shen, L.; Sawaki, A.; Lordick, F.; Ohtsu, A.; Oumuro, Y.; Satoh, T.; et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 2010, 376, 687–697. [CrossRef]

83. Shah, M.A.; Xu, R.-H.; Bang, Y.-J.; Hoff, P.M.; Liu, T.; Herráez-Baranda, L.A.; Xia, F.; Gang, A.; Shing, M.; Tabernero, J. HERLOISE: Phase IIIb Randomized Multicenter Study Comparing Standard-of-Care and Higher-Dose Trastuzumab Regimens Combined With Chemotherapy as First-Line Therapy in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Gastric or Gast. J. Clin. Oncol. 2017, 35, 2558–2567. [CrossRef] [PubMed]

84. Tabernero, J.; Hoff, P.M.; Shen, L.; Ohtsu, A.; Shah, M.A.; Cheng, K.; Song, C.; Wu, H.; Eng-Wong, J.; Kim, K.; et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): Final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018, 19, 1372–1384. [CrossRef]

85. Shitara, K.; Bang, Y.-J.; Iwasa, S.; Sugimoto, N.; Ryu, M.-H.; Sakai, D.; Chung, H.-C.; Kawakami, H.; Yabusaki, H.; Lee, J.; et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N. Engl. J. Med. 2020, 382, 2419–2430. [CrossRef] [PubMed]

86. Peng, Z.; Liu, T.; Wei, J.; Wang, A.; He, Y.; Yang, L.; Zhang, X.; Fan, N.; Luo, S.; Li, Z.; et al. Efficacy and safety of a novel anti-HER2 therapeutic antibody RC48 in patients with HER2-overexpressing, locally advanced or metastatic gastric or gastroesophageal junction cancer: A single-arm phase II study. Cancer Commun. 2021, 41, 1173–1182. [CrossRef]

87. Thuss-Patience, P.C.; Shah, M.A.; Ohtsu, A.; Van Cutsem, E.; Ajani, J.A.; Castro, H.; Mansoor, W.; Chung, H.C.; Bodeky, G.; Shitara, K.; et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positively advanced gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): An international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 2017, 18, 640–653. [CrossRef] [PubMed]

88. Oh, D.-Y.; Lee, K.-W.; Cho, J.Y.; Kang, W.K.; Im, S.-A.; Kim, J.W.; Bang, Y.-J. Phase II trial of dacomitinib in patients with HER2-positive gastric cancer. Gastric Cancer 2016, 19, 1095–1103. [CrossRef]

89. Iqbal, S.; Goldman, B.; Fenoglio-Preiser, C.M.; Lenz, H.J.; Zhang, W.; Danenberg, K.D.; Shibata, S.I.; Blanke, C.D. Southwest Oncology Group study S0413: A phase II trial of lapatinib (GW572016) as first-line therapy in patients with advanced or metastatic gastroesophageal junction cancer. Ann. Oncol. 2011, 22, 2610–2615. [CrossRef]

90. Hecht, J.R.; Bang, Y.-J.; Qin, S.K.; Chung, H.C.; Xu, J.M.; Park, J.O.; Jeziorski, K.; Shparyk, Y.; Hoff, P.M.; Sobroero, A.; et al. Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2–Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma: TRIO-013/LOGiC—A Randomized Phase III Trial. J. Clin. Oncol. 2016, 34, 443–451. [CrossRef]

91. Satoh, T.; Xu, R.-H.; Chung, H.C.; Sun, G.-P.; Doi, T.; Xu, J.-M.; Tsuji, A.; Oumuro, Y.; Li, J.; Wang, J.-W.; et al. Lapatinib Plus Paclitaxel Versus Paclitaxel Alone in the Second-Line Treatment of HER2-Amplified Advanced Gastric Cancer in Asian Populations: TyTAN—A Randomized, Phase III Study. J. Clin. Oncol. 2014, 32, 2039–2049. [CrossRef]

92. Strickler, J.H. EGFR Amplification as a Target in Gastroesophageal Adenocarcinoma: Do Anti-EGFR Therapies Deserve a Second Chance? Cancer Discov. 2018, 8, 679–681. [CrossRef]

93. Kandel, C.; Leclair, F.; Bou-Hanna, C.; Laboisse, C.L.; Mosnier, J.F. Association of HER1 amplification with poor prognosis in well differentiated gastric carcinomas. J. Clin. Pathol. 2014, 67, 307–312. [CrossRef] [PubMed]

94. Chen, C.; Yang, J.M.; Hu, T.T.; Xu, T.J.; Yan, G.; Hu, S.L.; Wei, W.; Xu, W.P. Prognostic role of human epidermal growth factor receptor in gastric cancer: A systematic review and meta-analysis. Arch. Med. Res. 2013, 44, 380–389. [CrossRef] [PubMed]

95. Aydin, K.; Okutur, S.K.; Bozkurt, M.; Turkmen, I.; Namal, E.; Pilanci, K.; Ozturk, A.; Akcali, Z.; Dogusoy, G.; Demir, O.G. Effect of epithelial growth factor receptor status on the outcomes of patients with metastatic gastric cancer: A pilot study. Oncol. Lett. 2014, 7, 255–259. [CrossRef] [PubMed]
96. Maron, S.B.; Alpert, L.; Kwak, H.A.; Lomnicki, S.; Chase, L.; Xu, D.; O’Day, E.; Nagy, R.J.; Lanman, R.B.; Cecchi, F.; et al. Targeted Therapies for Targeted Populations: Anti-EGFR Treatment for EGFR-Amplified Gastroesophageal Adenocarcinoma. Cancer Discov. 2018, 8, 696–713. [CrossRef]

97. Seshacharyulu, P.; Ponnusamy, M.P.; Haridas, D.; Jain, M.; Ganti, A.K.; Batra, S.K. Targeting the EGFR signaling pathway in cancer therapy. Expert Opin. Ther. Targets 2012, 16, 15–31. [CrossRef]

98. Apicella, M.; Corso, S.; Giordano, S. Targeted therapies for gastric cancer: Failures and hopes from clinical trials. Oncotarget 2017, 8, 57654–57669. [CrossRef]

99. Smyth, E.C.; Vlachogiannis, G.; Hedayat, S.; Harber, A.; Hulkkki-Wilson, S.; Salati, M.; Kouvelakis, K.; Fernandez-Mateos, J.; Cresswell, G.D.; Fontana, E.; et al. EGFR amplification and outcome in a randomised phase III trial of chemotherapy alone or chemotherapy plus panitumumab for advanced gastro-oesophageal cancers. Gut 2021, 70, 1632–1641. [CrossRef]

100. Kahraman, S.; Yalcin, S. Recent Advances in Systemic Treatments for HER-2 Positive Advanced Gastric Cancer. OncoTargets Ther. 2021, 14, 4149–4162. [CrossRef]

101. Park, D.I.; Yun, J.W.; Park, J.H.; Oh, S.J.; Kim, H.J.; Cho, Y.K.; Sohn, C.I.; Jeon, W.K.; Kim, B.I.; Yoo, C.H.; et al. HER-2/neu Amplification Is an Independent Prognostic Factor in Gastric Cancer. Dig. Dis. Sci. 2006, 51, 1371–1379. [CrossRef]

102. Von Minckwitz, G.; Procter, M.; De Azambuja, E.; Zardavas, D.; Benyunes, M.; Viale, G.; Suter, T.; Arahmani, A.; Rouchet, N.; Clark, E.; et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N. Engl. J. Med. 2017, 377, 122–131. [CrossRef]

103. Kotani, D.; Shitara, K. Trastuzumab deruxtecan for the treatment of patients with HER2-positive gastric cancer. Ther. Adv. Med. Oncol. 2021, 13, 175883592098651. [CrossRef] [PubMed]

104. Voigtlaender, M.; Schneider-Merck, T.; Trepel, M. Lapatinib. In Small Molecules in Oncology; Springer International Publishing: Cham, Switzerland, 2018; pp. 19–44.

105. Jung, Y.D.; Mansfield, P.F.; Akagi, M.; Takeda, A.; Liu, W.; Bucana, C.D.; Hicklin, D.J.; Ellis, L.M. Effects of combination anti-vascular endothelial growth factor receptor and anti-epidermal growth factor receptor therapies on the growth of gastric cancer in a nude mouse model. Eur. J. Cancer 2002, 38, 1133–1140. [CrossRef]

106. Lieto, E.; Ferraraccio, F.; Orditura, M.; Castellano, P.; Mura, A.L.; Pinto, M.; Zamboli, A.; De Vita, F.; Galizia, G. Expression of Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor Receptor (EGFR) is an Independent Prognostic Indicator of Worse Outcome in Gastric Cancer Patients. Ann. Surg. Oncol. 2008, 15, 69–79. [CrossRef] [PubMed]

107. Shah, M.A.; Jhaver, M.; Ilson, D.H.; Lefkovitz, R.A.; Robinson, E.; Capanu, M.; Kelsen, D.P. Phase II Study of Modified Docetaxel, Cisplatin, and Fluorouracil With Bevacizumab in Patients With Metastatic Gastroesophageal Adenocarcinoma. J. Clin. Oncol. 2011, 29, 868–874. [CrossRef]

108. Shah, M.A.; Jhaver, M.; Ilson, D.H.; Lefkovitz, R.A.; Robinson, E.; Capanu, M.; Kelsen, D.P. Phase II Study of Modified Docetaxel, Cisplatin, and Fluorouracil With Bevacizumab in Patients With Metastatic Gastroesophageal Adenocarcinoma. J. Clin. Oncol. 2011, 29, 868–874. [CrossRef]

109. Brenner, B.; Sarfaty, M.; Purim, O.; Kundel, Y.; Amit, L.; Abramovich, A.; Sadie Gonik, U.; Idelevich, E.; Gordon, N.; Medalia, G.; et al. A Phase Ib/II Study Evaluating the Combination of Weekly Docetaxel and Cisplatin Together with Bevacizumab and Cisplatin in Patients with Advanced Esophago-Gastric Carcinoma. PLoS ONE 2016, 11, e0157548. [CrossRef]

110. Meulendijks, D.; Beerepoot, L.V.; Boot, H.; de Groot, J.W.; Los, M.; Boers, J.E.; Vanhoutvin, S.A.; Polee, M.B.; Beeker, A.; Portielje, J.E.; et al. Trastuzumab and bevacizumab combined with docetaxel, oxaliplatin and capecitabine as first-line treatment of advanced HER2-positive gastric cancer. A multicenter phase II study. Invest. New Drugs 2016, 34, 119–128. [CrossRef] [PubMed]

111. Wöll, E.; Thaler, J.; Keil, F.; Gruenberger, B.; Hejna, M.; Eisterer, W.; Fridrik, M.A.; Ulmer, H.; Trommet, V.; Huemer, F.; et al. Oxaliplatin/Infusoplatin/Bevacizumab Followed by Docetaxel/Bevacizumab in Inoperable Locally Advanced or Metastatic Gastric Cancer Patients—AGMT_GASTRIC-3. Anticancer Res. 2017, 37, 5553–5558. [CrossRef] [PubMed]
117. Li, J.; Kortmansky, J.S.; Saif, M.; Fischbach, N.A.; Ravage-Mass, L.; Elligers, K.; Hahn, C.; Cohenuram, M.K.; Lacy, J. Phase II study of mFOLFOX6 with bevacizumab (Bev) in metastatic gastric and esophageal (GE) adenocarcinoma. *J. Clin. Oncol.* 2010, 28 (Suppl. 15), TPS203. [CrossRef]

118. Yoon, H.H.; Bendell, J.C.; Braiteh, F.S.; Firdaus, I.; Philip, P.A.; Cohn, A.L.; Lewis, N.; Anderson, D.M.; Arrowsmith, E.; Schwartz, J.D.; et al. Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: A randomized, double-blind, multicenter Phase II trial. *Ann. Oncol.* 2016, 27, 2196–2203. [CrossRef]

119. Muro, K.; Yoshikawa, T.; Shitara, K.; Oh, D.Y.; Kang, Y.K.; Chung, H.C.; Kudo, T.; Chin, K.; Kadowaki, S.; Hamamoto, Y.; et al. Randomized, double-blind, phase 2 study of S-1 plus oxaliplatin (SOX) with or without ramucirumab (RAM) as first-line therapy followed by paclitaxel plus RAM as second-line therapy in patients with advanced gastric or gastroesophageal junction adenocarcinoma (AGC). *J. Clin. Oncol.* 2018, 36 (Suppl. 15), 4036. [CrossRef]

120. Yamaguchi, K.; Fujitani, K.; Nagashima, F.; Omuoro, Y.; Machida, N.; Nishina, T.; Koue, T.; Tsujimoto, M.; Maeda, K.; Satoh, T. Ramucirumab for the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine-containing combination chemotherapy in Japanese patients: A phase 2, open-label study. *Gastric Cancer* 2018, 21, 1041–1049. [CrossRef] [PubMed]

121. Ohtsu, A.; Shah, M.A.; Van Cutsem, E.; Rha, S.Y.; Sawaki, A.; Park, S.R.; Lim, H.Y.; Yamada, Y.; Wu, J.; Langer, B.; et al. Phase II Trial of Sorafenib in Patients with Chemotherapy Refractory Metastatic Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study. *J. Clin. Oncol.* 2011, 29, 3968–3976. [CrossRef]

122. Shen, L.; Li, J.; Xu, J.; Pan, H.; Dai, G.; Qin, S.; Wang, L.; Wang, J.; Yang, Z.; Shu, Y.; et al. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: Randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer* 2015, 18, 168–176. [CrossRef]

123. Fuchs, C.S.; Shitara, K.; Di Bartolomeo, M.; Lonardi, S.; Al-Batran, S.E.; Van Cutsem, E.; Ilson, D.H.; Alsina, M.; Chau, I.; Lacy, J.; et al. Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFLA): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019, 20, 420–435. [CrossRef]

124. Fuchs, C.S.; Tomasek, J.; Yong, C.J.; Dumitru, F.; Passalacqua, R.; Goswami, C.; Safran, H.; Dos Santos, L.V.; Aprile, G.; Ferry, S.; et al. An open-label, multicentre biomarker-oriented AIO phase II trial of sunitinib for patients with chemotherapy refractory advanced gastric adenocarcinoma of the stomach or lower esophagus: A randomized, placebo-controlled study with serum biomarker analysis. *Br. J. Cancer* 2011, 106, 1511–1520. [CrossRef]

125. Fuchs, C.S.; Tomasek, J.; Yong, C.J.; Dumitru, F.; Passalacqua, R.; Goswami, C.; Safran, H.; Dos Santos, L.V.; Aprile, G.; Ferry, S.; et al. Multicenter phase II study of oxaliplatin and sunitinib in patients with metastatic gastric cancer after failure of cisplatin and fluoropyrimidine treatment. A gemcad study. *Investig. New Drugs* 2013, 31, 1573–1579. [CrossRef]

126. Martin-Richard, M.; Gallego, R.; Pericay, C.; Foncillas, J.G.; Queralt, B.; Casado, E.; Barriuso, J.; Iranzo, V.; Juez, I.; Visa, L.; et al. Phase II Trial of Sorafenib in Patients with Chemotherapy Refractory Metastatic Esophageal and Gastroesophageal (GE) Junction Adenocarcinoma. *PLoS ONE* 2015, 10, e0134731. [CrossRef]

127. Bang, Y-J.; Kang, Y-K.; Kang, W.K.; Boku, N.; Chung, H.C.; Chen, J-S.; Doi, T.; Sun, Y.; Shen, L.; Qin, S.; et al. Phase II study of sunitinib as second-line treatment for advanced gastric cancer. *Investig. New Drugs* 2011, 29, 1449–1458. [CrossRef]

128. Yi, J.H.; Lee, J.; Lee, J.; Park, S.H.; Park, J.O.; Kim, D.S.; Park, Y.S.; Lim, H.Y.; Kang, W.K.; et al. Randomised phase II trial of docetaxel and sunitinib in patients with metastatic gastric cancer who were previously treated with fluoropyrimidine and platinum. *Br. J. Cancer* 2012, 106, 1469–1474. [CrossRef]

129. Moeiller, M.; Gepfner-Tuma, I.; Maderer, A.; Thuss-Patience, P.C.; Ruessel, J.; Hegewisch-Becker, S.; Wilke, H.; Al-Batran, S-E.; Rafiyan, M.-R.; Weißinger, F.; et al. Sunitinib added to FOLFIRI versus FOLFI Ri in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: A randomized, placebo-controlled phase II AIO trial with serum biomarker program. *BMC Cancer* 2016, 16, 699. [CrossRef]

130. Moehler, M.; Mueller, A.; Hartmann, J.T.; Ebert, M.P.; Al-Batran, S.E.; Reimer, P.; Weihrauch, M.; Lordick, F.; Trarbach, T.; Biesterfeld, S.; et al. An open-label, multicentre biomarker-oriented AIO phase II trial of sunitinib for patients with chemorefractory advanced gastric cancer. *Eur. J. Cancer* 2011, 47, 1511–1520. [CrossRef]

131. Alsina, M.; Ko, A.H.; Garcia De Paredes, M.; Rivera, F.; Schwartzberg, L.S.; Fattaey, A.; Kunkel, L.A.; Tabernero, J.; Ajani, J.A. Clinical and pharmacodynamic (PD) results of TEL0805 trial: A phase II study of telatinib (TEL) in combination with capcitabine (X) and cisplatin (P) as first-line treatment in patients (pts) with advanced gastric or gastroesophageal junction (GE) cancer. *J. Clin. Oncol.* 2011, 29 (Suppl. 15), 4122. [CrossRef]
135. Koizumi, W.; Yamaguchi, K.; Hosaka, H.; Takinishi, Y.; Nakayama, N.; Hara, T.; Muro, K.; Baba, H.; Sasaki, Y.; Nishina, T.; et al. Randomised phase II study of S-1/cisplatin plus TSU-68 vs S-1/cisplatin in patients with advanced gastric cancer. Br. J. Cancer 2013, 109, 2079–2086. [CrossRef] [PubMed]

136. Li, J.; Qin, S.; Xu, J.; Guo, W.; Xiong, J.; Bai, Y.; Sun, G.; Yang, Y.; Wang, L.; Xu, N.; et al. Apatinib for Chemotherapy-Refractory Advanced Metastatic Gastric Cancer: Results From a Randomized, Placebo-Controlled, Parallel-Arm, Phase II Trial. J. Clin. Oncol. 2013, 31, 3219–3225. [CrossRef]

137. Kim, S.T.; Lee, J.; Lee, S.J.; Park, S.H.; Jung, S.-H.; Park, Y.S.; Lim, H.Y.; Kang, W.K.; Park, J.O. Prospective phase II trial of pazopanib plus CopeOx (capcitabine and oxaliplatin) in previously untreated patients with advanced gastric cancer. Oncotarget 2016, 7, 24088–24096. [CrossRef] [PubMed]

138. Thuss-Patience, P.C.; Al-Batran, S.-E.; Siveke, J.T.; Homann, N.; Malfertheiner, P.; Glaeser, D.; Stein, A.; Tamm, I.; Daum, S.; Potenberg, J.; et al. Pazopanib and 5-FU/oxaliplatin as first-line treatment in advanced gastric cancer: PaFLO, a randomized phase II study from the AIO (Arbeitsgemeinschaft Internistische Onkologie). J. Clin. Oncol. 2015, 33 (Suppl. 15), 4033. [CrossRef]

139. Moy, R.H.; Dos Santos Fernandes, G.; Jonsson, P.; Chou, J.F.; Basunia, A.; Ku, G.Y.; Chalasani, S.B.; Boyar, M.S.; Goldberg, Z.; Desai, A.M.; et al. Regorafenib in Combination with First-Line Chemotherapy for Metastatic Esophagogastric Cancer. Oncologist 2020, 25, 668–674. [CrossRef]

140. Pavlikis, N.; Sjoquist, K.M.; Martin, A.J.; Tsobanis, E.; Yip, S.; Kang, Y.-K.; Bang, Y.-J.; Alcindor, T.; O'Callaghan, C.J.; Burnell, M.J.; et al. Regorafenib for the Treatment of Advanced Gastric Cancer (INTERGEAT): A Multinational Placebo-Controlled Phase II Trial. J. Clin. Oncol. 2016, 34, 2728–2735. [CrossRef]

141. Zhang, Y.; Wang, Z.X.; Shen, L.; Li, J.; Huang, J.; Su, W.G.; Zhang, D.S.; Xu, R.H. A phase Ib/II study of fruquintinib in combination with paclitaxel as the second-line treatment for advanced gastric cancer. Cancer Commun. 2022; Online ahead of print. [CrossRef]

142. Kawazoe, A.; Fukuoka, S.; Nakamura, Y.; Kuboki, Y.; Mikamoto, Y.; Shima, H.; Fujishiro, N.; Higuchi, T.; Wakabayashi, M.; Nomura, S.; et al. An open-label phase II study of lenvatinib plus pembrolizumab in patients with advanced gastric cancer (EPC01706). J. Clin. Oncol. 2020, 38 (Suppl. 4), 374. [CrossRef]

143. Chung, H.C.; Iwin, Z.; Gomez-Roca, C.; Longo, F.; Yanez, E.; Castanon Alvarez, E.; Graham, D.; Doherty, M.; Cassier, P.; Lopez, J.S.; et al. LEAP-005: A phase II multicohort study of lenvatinib plus pembrolizumab in patients with previously treated solid tumors—Results from the gastric cancer cohort. J. Clin. Oncol. 2021, 39 (Suppl. 3), 230. [CrossRef]

144. Li, J.; Qin, S.; Xu, J.; Xiong, J.; Wu, C.; Bai, Y.; Liu, W.; Tong, J.; Liu, Y.; Xu, R.; et al. Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction. J. Clin. Oncol. 2016, 34 (Suppl. 3), 1448–1454. [CrossRef]

145. Cleary, J.M.; Horick, N.K.; Mccleary, N.J.; Abrams, T.A.; Yurgelun, M.B.; Azzoli, C.G.; Rubinson, D.A.; Brooks, G.A.; Chan, J.A.; Blaszkowsky, L.S.; et al. FOLFOX plus ziv-aflibercept or placebo in first-line metastatic esophagogastric adenocarcinoma: A double-blind, randomized, multicenter phase 2 trial. Cancer 2019, 125, 2223–2221. [CrossRef] [PubMed]

146. Presta, L.G.; Chen, H.; O’Connor, S.J.; Chisholm, V.; Meng, Y.G.; Krummen, L.; Winkler, M.; Ferrara, N. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res. 1997, 57, 4593–4599. [PubMed]

147. Shah, M.A.; Van Cutsen, E.; Kang, Y.-K.; Dakhil, S.R.; Satoh, T.; Chin, K.; Bang, Y.-J.; Bu, L.; Bilic, G.; Ohtsu, A. Survival analysis according to disease subtype in AVAGAST: First-line capecitabine and cisplatin plus bevacizumab (bev) or placebo in patients (pts) with advanced gastric cancer. J. Clin. Oncol. 2012, 30 (Suppl. 4), 5. [CrossRef]

148. Tada, Y.; Tosaki, Y.; Kotani, D.; Kuwata, T.; Satoh, A.; Kawazoe, A.; Doi, T.; Wada, H.; Nishikawa, H.; Shibata, K. Targeting VEGFR2 with Ramucirumab strongly impacts effector/activated regulatory T cells and CD8(+) T cells in the tumor microenvironment. J. Immunol. Cancer. 2018, 6, 106. [CrossRef]

149. Selim, J.H.; Shaheen, S.; Sheu, W.-C.; Hsueh, C.-T. Targeted and novel therapy in advanced gastric cancer. Exp. Hematol. Oncol. 2019, 8, 25. [CrossRef]

150. Hanahan, D.; Weinberg, R.A. Hallmarks of Cancer: The Next Generation. Cell 2011, 144, 646–674. [CrossRef]

151. Bass, A.J.; Thorsson, V.; Shmulevich, I.; Reynolds, S.M.; Miller, M.; Bernard, B.; Hinoue, T.; Laird, P.W.; Curtis, C.; Shen, H. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014, 513, 202. [PubMed]

152. Magalhães, H.; Fontes-Sousa, M.; Machado, M. Immunotherapy in Advanced Gastric Cancer: An Overview of the Emerging Strategies. Can. J. Gastroenterol. Hepatol. 2018, 2018, 2732408. [CrossRef]

153. Garattini, S.K.; Basile, D.; Cattaneo, M.; Fanotto, V.; Onzago, E.; Bonotto, M.; Negri, F.V.; Berenato, R.; Ermacora, P.; Cardellino, G.G. Molecular classifications of gastric cancers: Novel insights and possible future applications. World J. Gastrointest. Oncol. 2017, 9, 194. [CrossRef]

154. Fuchs, C.S.; Doi, T.; Jang, R.W.; Muro, K.; Satoh, T.; Machado, M.; Sun, W.; Jalal, S.I.; Shah, M.A.; Metges, J.-P.; et al. Safety and Efficacy of Pembroliuzumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer. JAMA Oncol. 2018, 4, e180013. [CrossRef]

155. Rha, S.Y.; Lee, C.-k.; Kim, H.S.; Kang, B.; Jung, M.; Kwon, W.S.; Bae, W.K.; Koo, D.-H.; Shin, S.-J.; Jeung, H.-C.; et al. A multi-institutional phase Ib/II trial of first-line triplet regimen (Pembroliuzumab, Trastuzumab, Chemotherapy) for HER2-positive advanced gastric and gastroesophageal junction cancer (PANTHERA Trial): Molecular profiling and clinical update. J. Clin. Oncol. 2021, 39 (Suppl. 3), 218. [CrossRef]
156. Janjigian, Y.Y.; Maron, S.B.; Chatila, W.K.; Millang, B.; Chavan, S.S.; Alterman, C.; Chou, J.F.; Segal, M.F.; Simmons, M.Z.; Mottaz, P.; et al. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: An open-label, single-arm, phase 2 trial. *Lancet Oncol.* 2020, 21, 821–831. [CrossRef]

157. Klempern, S.J.; Bendell, J.C.; Villaflor, V.M.; Tenner, L.L.; Stein, S.; Naik, G.S.; Sirard, C.A.; Kayge, M.; Chaney, M.F.; Strickler, J.H. DKN-01 in combination with pembrolizumab in patients with advanced gastroesophageal adenocarcinoma (GEA): Tumoral DKK1 expression as a predictor of response and survival. *J. Clin. Oncol.* 2020, 38 (Suppl. 4), 357. [CrossRef]

158. Nakajima, T.E.; Kadowaki, S.; Minashi, K.; Nishina, T.; Yamanaka, T.; Hayashi, Y.; Izawa, N.; Muro, K.; Hironaka, S.; Kawai, T.; et al. Multicenter Phase I/II Study of Nivolumab Combined With Paclitaxel Plus Ramucirumab as Second-line Treatment in Patients with Advanced Gastric Cancer. *Cancer Clin. Cancer Res.* 2021, 27, 1029–1036. [CrossRef]

159. Hara, H.; Shoji, H.; Takahari, D.; Esaki, T.; Machida, N.; Nagashima, K.; Aoki, K.; Honda, K.; Miyamoto, T.; Boku, N.; et al. Phase I/II study of ramucirumab plus nivolumab in patients in second-line treatment for advanced gastric adenocarcinoma (NivoRam study). *J. Clin. Oncol.* 2019, 37 (Suppl. 4), 129. [CrossRef]

160. Shen, L.; Peng, Z.; Zhang, Y.-Q.; Wei, J.; Wang, F.; Ying, J.; Deng, Y.; Gu, K.; Cheng, Y.; Yuan, X.; et al. Camrelizumab combined with capicitabine and oxaliplatin followed by camrelizumab and apatinib as first-line therapy for advanced or metastatic gastric or gastroesophageal junction cancer: Updated results from a multicenter, open label phase II trial. *J. Clin. Oncol.* 2019, 37 (Suppl. 15), 4031. [CrossRef]

161. Jiang, H.; Yu, X.; Kong, M.; Ma, Z.; Zhou, D.; Wang, W.; Li, N.; Wang, H.; He, K.; et al. Sintilimab plus oxaliplatin/capicitabine (CapeOx) as neoadjuvant therapy in patients with locally advanced, resectable gastric (G)/esophagogastric junction (GEJ) adenocarcinoma. *J. Clin. Oncol.* 2021, 39 (Suppl. 3), 211. [CrossRef]

162. Wang, F.; Wei, X.L.; Wang, F.H.; Xu, N.; Shen, L.; Dai, G.H.; Yuan, X.L.; Chen, Y.; Yang, S.J.; Shi, J.H.; et al. Safety, efficacy and tumor mutational burden as a biomarker of overall survival benefit in chemo-refractory gastric cancer treated with toripalimab, a PD-1 antibody in phase Ib/II clinical trial NCT02915432. *Ann. Oncol.* 2019, 30, 1479–1486. [CrossRef]

163. Xu, J.; Bai, Y.; Xu, N.; Li, E.; Wang, B.; Wang, J.; Li, X.; Wang, X.; Yuan, X. Tislelizumab Plus Chemotherapy as First-line Treatment for Advanced Esophageal Squamous Cell Carcinoma and Gastric/Gastroesophageal Junction Adenocarcinoma. *Clin. Cancer Res.* 2020, 26, 4542–4550. [CrossRef]

164. Fuchs, C.S.; Özgüroğlu, M.; Bang, Y.-J.; Di Bartolomeo, M.; Mandalà, M.; Ryu, M.-h.; Fornaro, L.; Olesinski, T.; Caglevic, C.; Chung, H.C.; et al. Pembrolizumab versus paclitaxel for previously treated patients with PD-L1–positive advanced gastric or gastroesophageal junction cancer (GC): Update from the phase III KEYNOTE-061 trial. *J. Clin. Oncol.* 2020, 38 (Suppl. 15), 4503. [CrossRef]

165. Shitara, K.; Van Cutsem, E.; Bang, Y.-J.; Fuchs, C.; Wyrwicz, L.; Lee, K.-W.; Kudaba, I.; Garrido, M.; Chung, H.C.; Lee, J.; et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer. *JAMA Oncol.* 2020, 6, 1571. [CrossRef] [PubMed]

166. Chung, H.C.; Bang, Y.-J.; S Fuchs, C.; Qin, S.-K.; Satoh, T.; Shitara, K.; Tabernero, J.; Van Cutsem, E.; Alsina, M.; Cao, Z.A.; et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. *Future Oncol.* 2021, 17, 491–501. [CrossRef] [PubMed]

167. Boku, N.; Satoh, T.; Ryu, M.-H.; Chao, Y.; Kado, K.; Chung, H.C.; Chen, J.-S.; Muro, K.; Kang, W.K.; Yeh, K.-H.; et al. Nivolumab in previously treated advanced gastric cancer (ATTRACTION-2): 3-year update and outcome of treatment beyond progression with nivolumab. *Gastric Cancer* 2021, 24, 946–958. [CrossRef] [PubMed]

168. Janjigian, Y.Y.; Shitara, K.; Moehler, M.; Garrido, M.; Salman, P.; Shen, L.; Wyrwicz, L.; Yamaguchi, K.; Skoczylas, T.; Campos Bragagnoli, A.; et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): A randomised, open-label, phase 3 trial. *Lancet* 2021, 398, 27–40. [CrossRef]

169. Kelly, R.J.; Ajani, J.A.; Kuzdzal, J.; Zander, T.; Van Cutsem, E.; Piessen, G.; Mendez, G.; Feliciano, J.; Motoyama, S.; Lièvre, A.; et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N. Engl. J. Med.* 2021, 384, 1191–1203. [CrossRef] [PubMed]

170. Moehler, M.; Dvorkin, M.; Boku, N.; Özgüroğlu, M.; Ryu, M.-H.; Muntean, A.S.; Lonardi, S.; Dehaene, M.; Bragagnoli, A.; Costa, H.S.; et al. Phase III Trial of Avelumab Maintenance After First-Line Induction Chemotherapy Versus Continuation of Chemotherapy in Patients With Gastric Cancers: Results From JAVELIN Gastric 100. *J. Clin. Oncol.* 2021, 39, 966–977. [CrossRef] [PubMed]

171. Janjigian, Y.Y.; Bendell, J.; Calvo, E.; Kim, J.W.; Ascierto, P.A.; Sharma, P.; Ott, P.A.; Peltola, K.; Jaeger, D.; Evans, J.; et al. CheckMate-032 Study: Efficacy and Safety of Nivolumab and Nivolumab Plus Ipilimumab in Patients With Metastatic Esophagogastric Cancer. *J. Clin. Oncol.* 2018, 36 (Suppl. 15), 2836–2844. [CrossRef]

172. Ji, J.; Shen, L.; Li, Z.; Xu, N.; Liu, T.; Chen, Y.; Li, C.; Gao, X.; Ji, K.; Mao, C.; et al. AK104 (PD-1/CTLA-4 bispecific) combined with chemotherapy as first-line therapy for advanced gastric (G) or gastroesophageal junction (GEJ) cancer: Updated results from a phase Ib study. *J. Clin. Oncol.* 2021, 39, 232. [CrossRef]
174. Kelly, R.J.; Lee, J.; Bang, Y.-J.; Almhanna, K.; Blum Murphy, M.A.; Catenacci, D.V.T.; Chung, H.C.; Wainberg, Z.A.; Gibson, M.; Lee, K.W.; et al. Safety and efficacy of durvalumab in combination with tremelimumab, durvalumab monotherapy, and tremelimumab monotherapy in patients with advanced gastric cancer. J. Clin. Oncol. 2018, 36, 4031. [CrossRef]

175. Takei, S.; Kawazoe, A.; Shiitara, K. The New Era of Immunotherapy in Gastric Cancer. Cancers 2022, 14, 1054. [CrossRef] [PubMed]

176. Markham, A. Margetuximab: First Approval. Drugs 2021, 81, 599–604. [CrossRef] [PubMed]

177. Catenacci, D.V.; Rosesale, M.; Chung, H.C.; Yoon, H.H.; Shen, L.; Moehler, M.; Kang, Y.K. MAHOGANY: Margetuximab combination in HER2+ unresectable/metastatic gastric/gastroesophageal junction adenocarcinoma. Future Oncol. 2021, 17, 1155–1164. [CrossRef]

178. Kawazoe, A.; Shiitara, K.; Boku, N.; Yoshikawa, T.; Terashima, M. Current status of immunotherapy for advanced gastric cancer. Jpn. J. Clin. Oncol. 2021, 51, 20–27. [CrossRef]

179. Mehta, R.; Kim, R.D.; Shah, N.; Carballido, E.M.; Kim, Y.; Imanirad, I.; Kim, D.W. A phase II study of TAS-102 in combination with ramucirumab in advanced, refractory gastric or gastroesophageal junction (GEJ) adenocarcinoma. J. Clin. Oncol. 2019, 37, TPS4149. [CrossRef]

180. Shitara, K.; Doi, T.; Prokharau, A.; Alsina, M.; Ghidini, M.; Faustino, C.; Gorbunova, V.; et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2018, 19 (Suppl. 15), 1437–1448. [CrossRef]

181. Taberner, J.; Shiitara, K.; Zaanan, A.; Doi, T.; Lorenzen, S.; Van Cutsen, E.; Fornaro, L.; Catenacci, D.V.T.; Fougeray, R.; Moreno, S.R.; et al. Trifluridine/tipiracil versus placebo for third or later lines of treatment in metastatic gastric cancer: An exploratory subgroup analysis from the TAGS study. ESMO Open 2021, 6, 100200. [CrossRef]

182. Fostea, R.M.; Arkenau, H.T. Trifluridine/tipiracil in the treatment of gastric cancer. Future Oncol. 2022, 18, 1511–1517. [CrossRef]

183. Bando, H.; Doi, T.; Muro, K.; Yasui, H.; Nishina, T.; Yamaguchi, K.; Takahashi, S.; Nomura, S.; Kuno, H.; Shiitara, K.; et al. A multicenter phase II study of TAS-102 monotherapy in patients with pre-treated advanced gastric cancer (EPOC1201). Eur. J. Cancer 2016, 62, 46–53. [CrossRef]

184. Thiel, A.; Ristimaki, A. Targeted therapy in gastric cancer. Apmit 2015, 123, 365–372. [CrossRef]

185. Shao, Z.; Pan, H.; Tu, S.; Zhang, J.; Yan, S.; Shao, A. HGF/c-Met Axis: The Advanced Development in Digestive System Cancer. Front. Cell Dev. Biol. 2020, 8, 801. [CrossRef] [PubMed]

186. Iveson, T.; Donehower, R.C.; Davidenko, I.; Tjulandin, S.; Depta, A.; Harrison, M.; Nirni, S.; Lakshmaiah, K.; Thomas, A.; Jiang, Y.; et al. Rilotumumab in combination with epirubicin, cisplatin, and capecitabine as first-line treatment for gastric or oesophagogastric junction adenocarcinoma: An open-label, dose-de-escalation phase 1b study and a double-blind, randomised phase 2 study. Lancet Oncol. 2014, 15, 1007–1018. [CrossRef]

187. Shah, M.A.; Cho, J.-Y.; Tan, I.B.; Tebbutt, N.C.; Yen, C.-J.; Kang, A.; Shames, D.S.; Bu, L.; Kang, Y.-K. A Randomized Phase II Study of FOLFOX With or Without the MET Inhibitor Onartuzumab in Advanced Adenocarcinoma of the Stomach and Gastroesophageal Junction. Oncologist 2016, 21, 1085–1090. [CrossRef] [PubMed]

188. Sakai, D.; Chung, H.C.; Oh, D.-Y.; Park, S.H.; Kadowaki, S.; Kim, Y.H.; Tsuji, A.; Komatsu, Y.; Kang, Y.-K.; Unaka, K.; et al. A non-randomized, open-label, single-arm, Phase II study of emibetuzumab in Asian patients with MET diagnostic positive, advanced gastric cancer. Cancer Chemother. Pharmacol. 2017, 80, 1197–1207. [CrossRef] [PubMed]

189. Harding, J.J.; Zhu, A.X.; Bauer, T.M.; Choueiri, T.K.; Drilon, A.; Voss, M.H.; Fuchs, C.S.; Abou-Alfa, G.K.; Wijayawardana, S.R.; Wang, X.A.; et al. A Phase Ib/II Study of Ramucirumab in Combination with Emibetuzumab in Patients with Advanced Cancer. J. Clin. Oncol. 2019, 37, 5202–5211. [CrossRef] [PubMed]

190. Catenacci, D.V.T.; Tebbutt, N.C.; Davidenko, I.; Murad, A.M.; Al-Batran, S.-E.; Ilson, D.H.; Tjulandin, S.; Gotovkin, E.; Karaszewska, B.; Bondarenko, I.; et al. Rilotumumab plus epirubicin, cisplatin, and capecitabine as first-line therapy in advanced MET-positive gastric or gastro-oesophageal junction cancer (RILOMET-1): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017, 18, 1467–1482. [CrossRef]

191. Shah, M.A.; Bang, Y.-J.; Lordick, F.; Alsina, M.; Chen, M.; Hack, S.P.; Bruey, J.; Smith, D.; Mccaffery, I.; Shames, D.S.; et al. Effect of Fluorouracil, Leucovorin, and Oxaliplatin With or Without Onartuzumab in HER2-Negative, MET-Positive Gastroesophageal Adenocarcinoma. JAMA Oncol. 2017, 3, 620. [CrossRef]

192. Shah, M.A.; Wainberg, Z.A.; Catenacci, D.V.T.; Hochster, H.S.; Ford, J.; Kunz, P.; Lee, F.-C.; Kallender, H.; Cecchi, F.; Rabe, D.C.; et al. Phase II Study Evaluating 2 Dosing Schedules of Oral Foretinib (GSK1363089), cMET/VEGFR2 Inhibitor, in Patients with Metastatic Gastric Cancer. PLoS ONE 2013, 8, e54014. [CrossRef]

193. Pant, S.; Patel, M.; Kurkjian, C.; Hemphill, B.; Flores, M.; Thompson, D.; Bendell, J. A Phase II Study of the c-Met Inhibitor Tivantinib in Combination with FOLFOX for the Treatment of Patients with Previously Untreated Metastatic Adenocarcinoma of the Distal Esophagus, Gastroesophageal Junction, or Stomach. Cancer Investig. 2017, 35, 463–472. [CrossRef]

194. Lengyel, C.G.; Hussain, S.; Seeber, A.; Jamil Nidhamalddin, S.; Trapani, D.; Habeeb, B.S.; Elkahaf, E.; Mazher, S.A.; Seid, F.; Khan, S.Z.; et al. FGFR Pathway Inhibition in Gastric Cancer: The Golden Era of an Old Target? Life 2022, 12, 81. [CrossRef]

195. Wainberg, Z.A.; Enzinger, P.C.; Kang, Y.-K.; Yamaguchi, K.; Qin, S.; Lee, K.-W.; Oh, S.C.; Li, J.; Turk, H.M.; Teixeira, A.C.; et al. Randomized double-blind placebo-controlled phase 2 study of bemarituzumab combined with modified FOLFOrX (mFOLFOrX) in first-line (1L) treatment of advanced gastro/oesophageal junction adenocarcinoma (FIGHT). J. Clin. Oncol. 2021, 39 (Suppl. 3), 160. [CrossRef]
196. Van Cutsem, E.; Bang, Y.J.; Mansoor, W.; Petty, R.D.; Chao, Y.; Cunningham, D.; Ferry, D.R.; Smith, N.R.; Frewer, P.; Ratnayake, J.; et al. A randomized, open-label study of the efficacy and safety of AZD4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with FGFR2 polysomy or gene amplification. *Ann. Oncol.* 2017, 28, 1316–1324. [CrossRef] [PubMed]

197. Wang, Y.; Zheng, K.; Huang, Y.; Xiong, H.; Su, J.; Chen, R.; Zou, Y. PARP inhibitors in gastric cancer: Beacon of hope. *J. Exp. Clin. Cancer Res.* 2021, 40, 211. [CrossRef] [PubMed]

198. Bang, Y.-J.; Im, S.-A.; Lee, K.-W.; Cho, J.Y.; Song, E.-K.; Lee, K.H.; Kim, Y.H.; Park, J.O.; Chun, H.G.; Zang, D.Y.; et al. Randomized, Double-Blind Phase II Trial With Prospective Classification by ATM Protein Level to Evaluate the Efficacy and Tolerability of Olaparib Plus Paclitaxel in Patients With Recurrent or Metastatic Gastric Cancer. *J. Clin. Oncol.* 2015, 33, 3858–3865. [CrossRef]

199. Bang, Y.J.; Xu, R.H.; Chin, K.; Lee, K.W.; Park, S.H.; Rha, S.Y.; Shen, L.; Qin, S.; Xu, N.; Im, S.A.; et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017, 18, 1637–1651. [CrossRef]

200. Ciardiello, F.; Bang, Y.-J.; Bendell, J.C.; Cervantes, A.; Dvorkin, M.; Lopez, C.D.; Metges, J.-P.; Sanchez, A.; Calvo, M.; Strickland, A.; et al. PARALLEL 303: Phase 2 randomized study of pamiparib vs placebo as maintenance therapy in patients (pts) with inoperable locally advanced or metastatic gastric cancer that responded to platinum-based first-line (1L) chemotherapy. *J. Clin. Oncol.* 2021, 39 (Suppl. 15), 3109. [CrossRef]

201. Shah, M.A.; Cunningham, D.; Metges, J.-P.; Van Cutsem, E.; Wainberg, Z.; Elboudwarej, E.; Lin, K.-W.; Turner, S.; Zavodovskaya, M.; Inzunza, D.; et al. Randomized, open-label, phase 2 study of anecaliximab plus nivolumab versus nivolumab alone in advanced gastric cancer identifies biomarkers associated with survival. *J. ImmunoTherapy Cancer* 2021, 9, e003580. [CrossRef]

202. Shah, M.A.; Bodoky, G.; Starodub, A.; Cunningham, D.; Yip, D.; Wainberg, Z.A.; Bendell, J.; Thai, D.; He, J.; Bhargava, P.; et al. Phase III Study to Evaluate Efficacy and Safety of Anecaliximab With mFOLFOX6 as First-Line Treatment in Patients With Advanced Gastric or GEJ Adenocarcinoma (GAMMA-1). *J. Clin. Oncol.* 2021, 39, 990–1000. [CrossRef]

203. Ohtsu, A.; Ajani, J.A.; Bai, Y.-X.; Bang, Y.-J.; Chung, H.-C.; Pan, H.-M.; Sahmoud, T.; Shen, L.; Yeh, K.-H.; Chin, K.; et al. Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study. *J. Clin. Oncol.* 2013, 31, 3935–3943. [CrossRef]

204. Doi, T.; Muro, K.; Boku, N.; Yamada, Y.; Nishina, T.; Takiuchi, H.; Komatsu, Y.; Hamamoto, Y.; Ohno, N.; Fujita, Y.; et al. Multicenter Phase II Study of Everolimus in Patients With Previously Treated Metastatic Gastric Cancer. *J. Clin. Oncol.* 2010, 28, 1904–1910. [CrossRef]

205. Hudler, P.; Komel, R. Clinical Implications of Molecular Heterogeneity of Gastric Cancer. In *Gastric Cancer*; InTech: London, UK, 2017. [CrossRef]

206. Miao, Z.-F.; Chen, H.; Wang, Z.-N.; Ji, J.-F.; Liang, H.; Xu, H.-M.; Wang, J. Progress and remaining challenges in comprehensive gastric cancer treatment. *Holist. Integr. Oncol.* 2022, 1, 4. [CrossRef]