

Overview on Gastric Cancer

Chapter 1

Targeted Therapy and Immunotherapy

*Daniel da Motta Girardi**

Department of oncology, Hospital Sirio-Libanês, Brasília, Brazil.

**Correspondence to: Daniel da Motta Girardi, Department of oncology, Hospital Sirio-Libanês, Brasília, Brazil.*

Email: danielmgirardi@gmail.com

1. Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third most common cause of cancer-related death globally [1]. The prognosis of GC is poor, especially for patients with metastatic disease, for whom the 5-year overall survival (OS) rate is approximately 5% [2]. For these patients, systemic therapy is the mainstay of treatment, and the goals of this therapy include palliation of symptoms and prolongation of survival.

Systemic treatment with chemotherapy was the first to show a survival benefit over best supportive care (BSC) [3]. Despite some benefit from chemotherapy regimens, including docetaxel, fluoropyrimidines, irinotecan, cisplatin and oxaliplatin, metastatic disease has a dismal prognosis, with a median OS of approximately 11 months for patients not harboring human epidermal growth factor receptor 2 (HER2) overexpression [4].

Over the past several decades, we have witnessed the advent of precision medicine, and remarkable advancements in the fields of targeted therapy and immunotherapy have recently been achieved. Precision medicine involves characterizing the molecular pathways of carcinogenesis and pharmaceutical development of monoclonal antibodies and small-molecule inhibitors that interfere with crucial molecular targets. Successful examples include imatinib for patients with chronic myeloid leukemia [5] and trastuzumab for HER2-overexpressing breast tumors [6].

2. Molecular Characterization of GC

Recent molecular profiling studies have enabled better comprehension of molecular

pathways in GC. The Cancer Genome Atlas (TCGA) Project performed a comprehensive molecular evaluation of 295 gastric adenocarcinomas and has proposed a molecular classification scheme by which GC is categorized into four subtypes: Epstein–Barr virus (EBV)-positive tumors, microsatellite unstable (MSI) tumors, genomically stable (GS) tumors and tumors with chromosomal instability (CIN) [7]. EBV-positive tumors represent 9% of gastric adenocarcinomas and display recurrent phosphatidylinositol 3-kinase CA (PIK3CA) mutations and amplification of HER2, JAK2 and programmed cell death-ligands 1 and 2 (PD-L1 and PD-L2). The MSI subtype represents 22% of GCs and is prevalent in women and older adults. These tumors are strongly associated with MLH1 promoter hypermethylation, show elevated mutation rates, elevated levels of microsatellite instability and recurrent mutations in PIK3CA, HER3 and HER2. GS tumors are observed in 20% of GC patients, are enriched for the diffuse-type adenocarcinoma and have frequent mutations in RHOA and CDH1. Fusions involving RHO-family GTPase-activating proteins (CLDN18 and ARHGAP26) are also enriched in this subtype, and their fusion products impact RHOA function, which is involved in cell contractility and cellular motility. Finally, the CIN subtype accounts for 50% of gastric adenocarcinomas, is enriched by intestinal histology and shows frequent TP53 mutations and receptor tyrosine kinase (RTK)/RAS amplifications [7,8].

Another notable study sought to identify the most prevalent molecular alterations in GC. The authors identified 22 recurrent focal somatic copy number alterations including known targets such as Fibroblast growth factor receptors 2 (FGFR2) and HER2 but also novel genes such as KLF5 and GATA6. Interestingly, RTK/RAS amplifications were frequent and occurred in approximately 37% of GCs, and KRAS amplifications were also frequent and associated with an adverse prognosis [9].

3. Targeted Agents

Data from systematic profiling studies has revealed numerous molecular alterations in GC. This increased knowledge has significantly improved pharmaceutical development to design and clinically test selective inhibitors against proteins and lipid kinases that play crucial roles in carcinogenesis.

3.1. Anti-HER2 agents

HER2 is a tyrosine kinase member of the epidermal growth factor receptor (EGFR) family. HER2 is involved in the carcinogenesis of many types of cancer and its overexpression can be identified in up to 30% of GCs with some differences regarding histological and location characteristics. The overexpression is more common in the intestinal type (34%) than in the diffuse type (6%) and more prevalent in esophagogastric junction (GEJ) tumors (32%) than other locations of stomach (18%) [10,11].

Trastuzumab, a recombinant humanized monoclonal antibody against HER2, was the first targeted agent to be approved for GC in 2010. The approval was based on a phase III trial (ToGA) that evaluated 594 patients with HER2-positive advanced gastric or EGJ cancer. Trastuzumab (8 mg/kg loading dose, then 6 mg/kg every three weeks) was investigated as a first-line treatment in association with chemotherapy consisting of capecitabine plus cisplatin or fluorouracil plus cisplatin administered every 3 weeks for six cycles. The median OS was 13.8 months for the trastuzumab-plus-chemotherapy arm and 11.1 months for patients in the chemotherapy-alone arm (hazard ratio (HR) 0.74; 95% CI 0.60–0.91; P=0.0046). The response rate (RR) was also higher in the experimental arm (47% versus 35%), as was the median progression-free survival (PFS) (6.7 months versus 5.5 months; HR 0.71; P=0.0002) [11].

Other HER2 blockade drugs were not as successful as trastuzumab. The phase 3 LOGIC trial evaluated the efficacy of lapatinib, a tyrosine kinase inhibitor of EGFR and HER2, as a first-line treatment in combination with chemotherapy (capecitabine plus oxaliplatin). The median OS of the experimental arm was not significantly different from that of the control arm of chemotherapy alone (12.2 versus 10.5 months; HR 0.91; P=0.3492) (check **Table 1** for details) [12]. The TYTAN trial evaluated lapatinib in the second-line setting with paclitaxel. Similar to the LOGIC trial, the median OS was not significantly different (11.0 months for lapatinib and paclitaxel versus 8.9 months for paclitaxel alone; P=0.1044) [13] (**Table 1**). Trastuzumabemtansine (T-DM1) also failed to show survival advantage over standard chemotherapy. The phase III GATSBY trial investigated the efficacy of T-DM1 in patients previously treated for HER2-positive GCs. The median OS was 7.9 months with T-DM1 and 8.6 months with taxane (HR 1.15; one-sided P=0.86) [14] (**Table 1**). Currently, the phase III JACOB trial (NCT01774786) is on going and will evaluate the efficacy and safety of pertuzumab in combination with trastuzumab, fluoropyrimidine and cisplatin as a first-line treatment in participants with HER2-positive metastatic GCs.

3.2. Anti-vascular endothelial growth factor receptor (VEGF) agents

Ramucirumab, a recombinant monoclonal antibody that binds to VEGFR-2, is approved alone and in combination with paclitaxel as a second-line treatment based on two randomized phase 3 trials. The REGARD trial randomized 355 patients, who showed disease progression during first-line platinum-containing or fluoropyrimidine-containing treatment, to ramucirumab-alone (8 mg/kg IV every two weeks) or placebo. The median OS was 5.2 months for the ramucirumab arm and 3.8 months for the placebo arm (HR 0.776; P=0.047). Median progression-free survival was 2.1 months in patients receiving ramucirumab and 1.3 months in those receiving placebo (HR 0.483; P<0.0001). The RR was 3% in both arms [15]. The RAINBOW study compared weekly paclitaxel (80 mg/m² on days 1, 8, and 15 of each 28-day cycle) plus ramucirumab (8 mg/kg IV every two weeks) to a placebo arm using 665 patients

with metastatic GC or EGJ cancer after first-line platinum and fluoropyrimidine-based combination therapy. The median OS was significantly longer in the ramucirumab arm versus that in the placebo arm (9.6 months versus 7.4 months; HR 0.807; P=0.017) as well as the median PFS (4.4 months versus 2.9 months; HR 0.635; P<0.0001). The RR was also greater in the ramucirumab plus paclitaxel arm (28% versus 16%; P=0.0001) [16].

The benefit of bevacizumab, a monoclonal antibody that binds to soluble VEGF and prevents binding to VEGFR, is uncertain. The AVAGAST trial investigated bevacizumab as a first-line treatment with capecitabine plus cisplatin every 21 days for a maximum of six cycles. Thereafter, capecitabine plus either bevacizumab or placebo was continued until disease progression. There was no significant survival benefit for the experimental arm over the control arm (median OS of 12.1 versus 10.1 months, HR 0.87; P=0.1002), but the median PFS (6.7 versus 5.3 months; HR 0.80; P=0.0037) and overall RR (46.0% versus 37.4%; P=0.0315) were significantly improved [17] (**Table 1**). The AVATAR trial was a phase 3 study, similar to the AVAGAST trial, which was conducted only in Chinese patients. Similar to AVAGAST, the AVATAR trial showed that, compared with the placebo plus chemotherapy, addition of bevacizumab to capecitabine-cisplatin chemotherapy did not improve the median OS (10.5 versus 11.4 months, HR 1.11; P=0.56) [18] (**Table 1**).

Apatinib, an orally active VEGFR-2 inhibitor, was evaluated in a phase 3 Chinese trial that randomized 267 patients with advanced GC or EGJ adenocarcinoma who had progressed through two or more prior lines of chemotherapy. Patients received 850 mg oral apatinib or placebo once daily. The median OS was modestly, but significantly, prolonged (6.5 versus 4.7 months; HR 0.709; P=0.0156), and the median PFS was also improved (2.6 versus 1.8 months; HR 0.444; P<0.001) [19]. Apatinib is approved in China for treatment of advanced GC but is not available in the United States or Europe.

Sunitinib and sorafenib are tyrosine kinase inhibitors (TKIs) that inhibit VEGFR-1, VEGFR-2, and VEGFR-3, as well as other tyrosine kinases. Sunitinib was investigated in a randomized phase 2 trial as a second-line therapy in combination with docetaxel. The primary time-to-progression endpoint was not significantly prolonged with the combination therapy compared with docetaxel alone (3.9 months versus 2.6 months, HR 0.77; P=0.206) [20] (**Table 1**). Sorafenib was evaluated in a phase 2 trial in combination with docetaxel and cisplatin as a first-line treatment for metastatic GC or EGJ adenocarcinoma. The median OS was 13.6 months, the median PFS was 5.8 months and the objective RR was noted in 41% of patients [21].

3.3. Anti-EGFR agents

EGFR overexpression occurs in 2.3%-40% of GCs, depending on the study and the methodology used to investigate the overexpression (immunohistochemistry or fluorescence

in situ hybridization) [10]. However, targeted agents against EGFR have had disappointing clinical outcomes. The phase 3 EXPAND trial evaluated cetuximab, a chimeric monoclonal antibody against EGFR, in a first-line setting with chemotherapy (capecitabine and cisplatin). The median PFS (primary endpoint) was 4.4 months for chemotherapy plus cetuximab and 5.6 months for patients in the chemotherapy-alone arm (HR 1.09; P=0.32) [22] (**Table 1**). Similarly, the REAL3 trial enrolled patients in a first-line setting for chemotherapy (epirubicin, oxaliplatin, and capecitabine) with or without panitumumab (a fully human monoclonal antibody against EGFR). The median OS, which was primary endpoint, was 8.8 months for chemotherapy plus panitumumab versus 11.3 months for the chemotherapy-alone arm (HR 1.37; 95%; P=0.013) [23] (**Table 1**).

3.4. PI3K/AKT/mTOR pathway inhibition

PI3K/AKT/mTOR is one of the most frequently activated pathways in human cancer and is activated in up to 60% of GCs [24]. Everolimus, a mechanistic (formerly known as mammalian) target of rapamycin (mTOR) inhibitor, was investigated in a phase 3 trial (GRANITE-1) in which 656 patients were randomized to the everolimus (10 mg daily) or placebo group after progression to one or two lines of systemic chemotherapy. The median OS was not significantly different (5.4 months for the everolimus arm versus 4.3 months for the placebo arm, HR 0.90; P=0.124), and the median PFS was modestly improved (1.7 months for the everolimus arm versus 1.4 months for the placebo arm, HR 0.66; P<0.001) [25] (**Table 1**). Currently, another phase 3 trial is investigating everolimus in a second-line setting in association with paclitaxel (NCT01248403).

Several other drugs that target the PI3K/AKT/mTOR pathway are under investigation. AZD5363, an AKT inhibitor, is being investigated in two phase 2 trials in combination with paclitaxel as a second-line treatment for patients with GC harboring a PIK3CA mutation (NCT02451956) and in biomarker-negative (PIK3CA/MEK/RAS/TP53/MET) patients (NCT02449655). Another randomized phase 2 trial is investigating the efficacy of GDC-0068, another AKT inhibitor, in combination with modified FOLFOX6 in a first-line scenario (NCT01896531). Finally, a phase IB, dose escalation study, is evaluating the PI3K inhibitor BYL719 in patients with GCs harboring a PIK3CA mutation or HER2 amplification (NCT01613950).

3.5. c-MET inhibitors

Mesenchymal-epithelial transition (MET) receptor amplification or overexpression occurs in 0-23% of GCs [21]. c-MET inhibitors have been tested in GC patients with disappointing results. Two phase 3 trials investigated the safety and efficacy of rilotumumab, a monoclonal antibody against c-Met. RILOMET-1 and RILOMET-2 were designed to test rilotumumab in combination with chemotherapy as a first-line treatment. Both trials were closed in Novem-

ber 2014 based on an increase in the number of deaths in the rilotumumab and chemotherapy arms [26]. MET Gastric was another phase 3 trial that evaluated onartuzumab, a monovalent anti-MET antibody; enrollment was halted early due to the negative results in a phase 2 trial. The analysis of the 592 patients enrolled failed to show the benefit of onartuzumab associated with mFOLFOX6 in the first-line scenario [8]. Foretinib and tivantinib, TKIs against c-MET, also failed to show sustained activity in GC patients in phase 2 trials [8].

3.6. Fibroblast growth factor receptor blockade

Fibroblast growth factor receptors (FGFR1-4) are transmembrane tyrosine kinase receptors that play important roles in carcinogenesis by regulating angiogenesis, cell proliferation, migration and differentiation. FGFR2 amplification is evident in approximately 5% to 10% of GC tumors and is associated with a poor prognosis [27,28].

AZD4547 is a selective FGFR1-3 inhibitor that has been evaluated in comparison with paclitaxel in a randomized phase 2 trial (the SHINE study) as a second-line treatment for GC patients with FGFR2 polysomy or gene amplification. The PFS analysis did not show any statistically significant differences between the two arms [29]. Dovitinib is an oral multi-targeted TKI that targets FGFR1-3. A phase 2 trial is ongoing and evaluating dovitinib monotherapy as a salvage treatment in patients with metastatic GC harboring FGFR2 amplifications (NCT01719549). Another phase I/II study is evaluating dovitinib in association with docetaxel as a second-line treatment (NCT01921673).

3.7. Poly-ADP ribose polymerase (PARP) inhibition

PARP, together with the ataxia telangiectasia (ATM) protein, plays an essential role in the DNA damage response [30]. Low ATM protein expression is evident in approximately 13% to 22% of tumors from patients with GC and is correlated with sensitivity to PARP inhibition [30,31]. Olaparib is a PARP inhibitor that was investigated in a randomized phase 2 trial in which olaparib plus paclitaxel was compared with paclitaxel alone in a population of recurrent or metastatic GC patients whose disease had progressed after first-line chemotherapy; the population was enriched with patients with low or undetectable ATM levels. A total of 124 patients were enrolled and the median PFS (primary endpoint) was not significantly different between the two arms (3.91 months for olaparib and paclitaxel arm and 3.55 months for paclitaxel alone arm; $P=0.131$). However, the median OS was significantly improved in the overall population of the study in favor of the combination arm (13.1 versus 8.3 months, HR 0.56; $P=0.005$), and the results were even more pronounced in the population with low ATM levels (not reached versus 8.2 months, HR 0.35; $P=0.002$) [32]. A phase 3 trial is ongoing to evaluate this combination in the second-line setting (NCT01924533).

3.8. Claudin 18.2

Claudins constitute a family of proteins that participate in controlling the flow of molecules between cellular tight junctions. Isoform 2 of the tight junction molecule claudin-18 (CLDN18.2) is frequently expressed in GCs and is involved in carcinogenesis [33]. Claudiximab is a chimeric monoclonal antibody against CLDN18.2 [34]. The FAST trial, a phase IIb trial, evaluated the role of claudiximab in association with chemotherapy in the first-line scenario. A total of 161 patients with GC and EGJ tumors who were claudin-18.2 positive by immunohistochemistry were randomized to receive the EOX regimen (epirubicin 50 mg/m², oxaliplatin 130 mg/m² d1, and capecitabine 625 mg/m² bid, d1–21, every 21 days) with or without claudiximab (loading dose 800 mg/m², then 600 mg/m² d1, every 21 days). The study met its primary endpoint with a median PFS of 7.9 months for the experimental arm versus 4.8 months for the chemotherapy-alone arm (HR 0.47; P=0.0001). The median OS was also significantly higher for the claudiximab arm (13.3 versus 8.4 months; HR 0.51; P<0.001) [34]. Future phase 3 trials evaluating the role claudiximab for GC patients are expected.

Table 1: Gastric cancer targeted therapy - Negative trials

Study	Phase	Line	N	Investigational arm	Control arm	RR	PFS	OS
LOGIC	3	First	545	Lapatinib + capecitabine and oxaliplatin	capecitabine + oxaliplatin	53% vs 39%; P=0.0031	6.0 vs 5.4 months; P=0.0381	12.2 vs 10.5 months; P=0.3492
TYTAN	3	Second	261	Lapatinib + paclitaxel	Paclitaxel	27% vs 9%; P<0.001	5.5 vs 4.4 months; P=0.244	11.0 vs 8.9 months; P=0.1044
GATSBY	3	Second	345	T-DM1	Taxane	20.6% vs 19.6%; P=0.8406	2.7 vs 2.9 months; P=0.31	7.9 vs 8.6 months; p=0.86
AVAGAST	3	First	774	Bevacizumab + capecitabine+ cisplatin	capecitabine+ cisplatin	46.0% vs 37.4%; P=0.0315	6.7 vs 5.3 months; P=0.0037	12.1 vs 10.1 months; P=0.1002
AVATAR	3	First	202	Bevacizumab + capecitabine+ cisplatin	capecitabine+ cisplatin	41% vs 34%; P=0.35	6.3 vs 6.0 months; P=0.47	10.5 vs 11.4 months; P=0.56
Lee, et al	2	Second	107	Sunitinib + docetaxel	Docetaxel	41.1% vs 14.3%; P=0.002	3.9 vs 2.6 months; P=0.206	8.0 vs 6.6 months; P=0.802
EXPAND	3	First	904	Cetuximab + capecitabine + cisplatin	capecitabine + cisplatin	30% vs 29%; P=0.77	4.4 vs 5.6 months; P=0.32	9.4 vs 10.7 months; P=0.95
REAL3	3	First	553	Panitumumab + epirubicin, oxaliplatin, and capecitabine	epirubicin, oxaliplatin, and capecitabine	46% vs 42%; P=0.42	6.0 vs 7.4 months; P=0.068	8.8 vs 11.3 months; P=0.013

GRAN-ITE-1	3	Second or third	656	Everolimus	Placebo	4.5% vs 2.1%	1.7 vs 1.4 months; P< 0.001	5.4 vs 4.3 months; P=0.124
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Abbreviations: RR = response rate; PFS = progression-free survival; OS = overall survival

4. Immunotherapy agents

Immunotherapy is already a reality in oncology and has achieved outstanding results in many cancer types [35-37]. The mechanisms involved in the immune suppression by the tumor are complex. The programmed cell death 1 protein (PD-1) and its ligands (PD-L1 and PD-L2) are key factors that control the ability of tumors to evade the immune surveillance [38]. Similarly, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) negatively regulates T-cell effector responses and is implicated in tumor immunological evasion signature [39]. Currently, several immunotherapy agents that address this mechanism are being tested as treatments for GC patients.

4.1. Pembrolizumab

Pembrolizumab is an anti-PD1 monoclonal antibody. The phase 1b KEYNOTE 012 trial has evaluated 39 patients with PD-L1-positive gastric or EGJ tumors who received pembrolizumab (10 mg/kg every two weeks). This trial has shown manageable toxicities and promising results with 22% of patients achieving an overall response [40]. Early results of the KEYNOTE-059 trial were presented at the 2017 annual meeting of the American Society of Clinical Oncology (ASCO). Cohort 1 comprised 259 patients (not selected by PD-L1 status) who had progressed on ≥ 2 prior chemotherapy regimens and received pembrolizumab 200 mg every three weeks. The RR was 11.2% in the entire cohort and 15.5% for patients with PD-L1-positive tumors. Grade 3-5 treatment-related adverse events (AEs) occurred in 17% of patients [41]. In cohort 2, the safety and efficacy of pembrolizumab (200 mg every three weeks) plus chemotherapy (cisplatin 80 mg/m² + 5-FU 800 mg/m² or capecitabine 1000 mg/m² every three weeks) as a first-line treatment was evaluated. A total of 25 patients were enrolled with an RR of 60%, a median PFS of 6.6 months and a median OS of 13.8 months. Grade 3-4 treatment-related AEs occurred in 76% of patients in this cohort [42].

Future trials will further clarify the role of pembrolizumab in the treatment of metastatic GC patients. The ongoing phase 3 KEYNOTE-061 trial is evaluating pembrolizumab versus paclitaxel as a second-line treatment (NCT02370498), and the phase 3 KEYNOTE-062 is evaluating pembrolizumab associated with cisplatin plus 5-FU as a first-line treatment (NCT02494583).

4.2. Nivolumab

Nivolumab is another anti-PD1 monoclonal antibody with promising results in GC. The phase 1/2 CheckMate 032 study evaluated nivolumab with or without ipilimumab in heavily pretreated patients with gastric, esophageal or EGJ cancers. Updated results were presented at the 2017 ASCO Annual Meeting. The study evaluated three cohorts: 59 patients received 3 mg/kg nivolumab every two weeks, 49 patients received 1 mg/kg nivolumab plus 3 mg/kg ipilimumab every three weeks (N1 + I3) and 52 patients received 3 mg/kg nivolumab plus 1 mg/kg ipilimumab (N3 + I1). In the nivolumab-alone cohort, the RR was 12%, and the median OS was 6.2 months [43].

The results from a phase 3 trial that evaluated nivolumab as a salvage treatment in 493 patients with gastric and EGJ cancers were presented at the 2017 ASCO Gastrointestinal Cancer Symposium. All patients had failed two or more previous chemotherapy regimens and were randomized to receive nivolumab 3 mg/kg or placebo every two weeks. The median OS was 5.32 months for the nivolumab arm versus 4.14 months for the placebo arm (HR 0.63; $P < 0.0001$). The RR was also significantly better for the nivolumab arm (11.2% versus 0%; $P < 0.0001$), as was the median PFS (1.61 months versus 1.45 months, HR 0.60; $P < 0.0001$). Grade 3 or higher treatment-related AEs occurred in 11.5% of patients in the nivolumab arm [44].

4.3. Ipilimumab

Ipilimumab is a monoclonal antibody that targets CTLA-4. A phase 2 study evaluated the safety and efficacy of ipilimumab versus BSC for patients with advanced gastric or EGJ cancers as a second-line treatment. Fifty-seven patients were randomized to 10 mg/kg ipilimumab every 3 weeks for four doses versus BSC. Immune-related PFS, the primary endpoint, was not improved (2.92 months for ipilimumab versus 4.90 months for BSC, HR 1.44; $P = 0.09$) [45].

As described above, the CheckMate 032 trial investigated the efficacy of nivolumab plus ipilimumab. The RR was 24% in the N1 + I3 cohort and 8% in the N3 + I1 cohort. The median OS was 6.9 months for the N1 + I3 patients and 4.8 months for the N3 + I1 patients. Grade 3–4 treatment-related AEs were higher for the N1 + I3 cohort than those for the nivolumab-alone patients and N3 + I1 patients. For example, grade 3-4 diarrhea was observed in 14% of patients in the N1 + I3 cohort and in only 2% of patients in the other two cohorts [43]. The phase 3 CheckMate 649 trial is currently recruiting metastatic gastric or EGJ cancer patients with or without PD-L1 expression to evaluate the efficacy of nivolumab plus ipilimumab versus oxaliplatin plus fluoropyrimidine as a first-line treatment (NCT02872116).

4.4. Avelumab

Avelumab is a monoclonal antibody against PD-L1. The phase 1b JAVELIN trial analyzed a cohort of patients with gastric and EGJ tumors. Patients received avelumab as first-line maintenance or a second-line treatment. A total of 151 patients received avelumab (10 mg/kg IV every two weeks). An unconfirmed response was observed in 9.0% of patients in the maintenance group and in 9.7% of patients who received the medication as a second-line treatment. The disease control rate was 57.3% and 29.0%, and the median PFS was 12 weeks and 6 weeks for the first-line maintenance and second-line treatment groups, respectively. Grade 3 or higher treatment-related AEs were observed in 9.7% of patients [46]. These results led to the development of phase 3 trials addressing avelumab as a first-line maintenance therapy (NCT02625610) and as a third-line treatment (NCT02625623) for metastatic gastric and EGJ cancers.

5. Abbreviations

GC: Gastric Cancer; OS: Overall Survival; BSC: Best supportive care; HER2: Human Epidermal growth factor Receptor 2; TCGA: The Cancer Genome Atlas; EBV: Epstein–Barr virus; MS: Microsatellite unstable; GS: Genomically stable; CIN: Chromosomal instability; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; JAK2: Janus kinase 2; PD-L1: Programmed death-ligand 1; PD-L2: Programmed death-ligand 2; RHOA: Ras homolog gene family, member A; CDH-1: Cadherin-1; RTK: Receptor tyrosine kinase; FGFR2: Fibroblast growth factor receptor 2; KLF5: Krueppel-like factor 5; GATA6: GATA Binding Protein 6; KRAS: Kirsten rat sarcoma viral oncogene homolog; HR: Hazard ratio; RR: Response rate; PFS: Progression-free survival; EGFR: Epidermal growth factor receptor; T-DM1: Trastuzumabemtansine; VEGFR: Vascular endothelial growth factor receptor; EGJ: Esophagogastric junction; mTOR: Mechanistic target of rapamycin; ERK: Extracellular signal-regulated kinases; MET: Mesenchymal-epithelial transition; TKI: Tyrosine kinase inhibitors; PARP: Poly-ADP ribose polymerase; ATM: Ataxia telangiectasia; PD-1: The programmed cell death 1 protein; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; ASCO: American Society of Clinical Oncology

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