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Targeted Therapies in Metastatic Gastric Cancer: Challenges and Perspectives

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Abstract

Gastric cancer is one of the most commonly diagnosed cancers worldwide. Metastatic gastric cancer is correlated with a poor prognosis. Despite the large progress in cancer's treatment strategies, metastatic gastric cancer still a provider of bad outcomes. The importance of targeted therapy became clear over the last few years. This paper summarized comprehensive and current overview of the latest translational and clinical research articles and congress presentations, for a pragmatic use of targeted therapies in advanced gastric cancer.

Keywords: Gastric cancer; Metastases; Targeted therapies

Introduction

Gastric cancer has been declared by the World Health Organization (WHO) to be a global public health problem. Almost 1 million cases have been identified worldwide, making it the fifth most common malignancy and despite a steady decline remains the third leading cause of cancer mortality [1]. The highest estimated mortality rates are in eastern Asia, the lowest in northern America. High mortality rates are also present in both sexes in Central and Eastern Europe, and in Central and South America [1]. Only 27% of newly diagnosed gastric cancers are localized with disappointing 5-years Overall Survival (OS) rate of 30.4% [2]. Multimodal strategies have been developed last years to improve the prognosis of localized disease. Advanced disease remains aggressive with a poor median survival of 11 months despite all therapeutic progress. Chemotherapy combinations based on platinum compounds and fluoropyrimidines are effective by improving survival rates, symptoms and Quality of Life (QOL) [3]. Combinations with targeted therapies have given additional hope, particularly with anti-HER2 therapies [4]. HER2 and VEGFR2 are clinically validated molecular targets in the treatment of metastatic gastric cancer [4]. Trastuzumab, a HER2-directed monoclonal antibody, and ramucirumab, a VEGFR2-directed antibody, are now considered the standard of care for the treatment of metastatic gastric cancer [5]. Revolutionary progress has been made in the understanding of gastric cancer as a heterogeneous disease with many molecular subtypes [6]. With the improved understanding of molecular characteristization of gastric cancer, we hope that these improvements may lead to better targeted approaches to the treatment of various forms of gastric cancer. In this review, we provide a comprehensive and current overview of the latest translational and clinical research articles and congress presentations, for a pragmatic use of targeted therapies in advanced gastric cancer.

Axes of Development in the Treatment for Metastatic Gastric Cancer

Molecular alterations in gastric cancer

In several neoplasms, molecular alterations have permitted the introduction of targeted therapies which modified the prognosis of these diseases [7]. Some cancers (breast cancer, lung cancer, colorectal cancer and melanoma) dispose currently of a molecular classification which dictates the choice of the best treatment for each patient [7]. In gastric cancer, classification was traditionally based on clinical and histological characteristics until recent years. In last years, we identified a couple of molecular anomalies, not yet clearly organized into a validated classification, but allowing to hope some therapeutic approaches [7]. Growth factor receptors other than HER2 or Receptor Tyrosine Kinases (RTKs), such as Epidermal Growth Factor Receptor (EGFR), Mesenchymal-Epithelial Transition factor (MET; a receptor for Hepatocyte Growth Factor Receptor [HGFR]), and Fibroblast Growth Factor Receptor (FGFR), have been described as implicated in the cancerogenesis of gastric cancer [8]. Detailed molecular profiles of gastric cancer have also been recently reported in large-scale international cancer genome studies. Analysis from the Cancer Genome Atlas (TCGA) project has recently redefined the disease into four distinct subclasses based on mutations, gene copy number changes, gene expression, and DNA methylation data across 295 patients. It is not clear if these genotypes will ultimately guide patient therapy [9]. The four major genomic subtypes of gastric cancer with histological and etiological heterogeneity are detailed in Table 1. This classification can be used supplementary to histopathology to provide patient stratification as a guide to targeted agents. The TCGA genotypes have now been validated as prognostic [9].

Subtype	Epstein–Barr virus infected tumors	Microsatellite instability tumors	Tumors with chromosomal instability Genomically	Stable tumors
Typical molecular features	+EBV positive+Profound Hypermethylation +CDKN2A silencing+80% PIK3CA Mutation+Amplification of JAK2+PD-L1/2 overexpression	+DNA hypermethylation silencing of MLH 1+Elevated somatic mutations (PIK3CA 42%, and ERBB3 26%)	+Marked aneuploidy+TP53 mutations+ Recurrent amplifications of receptor tyrosine kinases (HER2 24%)	+Tumors lacking aneuploidy and elevated rates of mutation or hypermethylation+Somatic RHOA and CDH1mutations +CLDN18–ARHGAP6 or ARHGAP26 fusions
Association with anatomy or traditional subtypes	Fundus and body	Fundus, body, and antrum	Majority of tumors at the esophagogastric junction	Mostly diffuse subtype

Table 1: Molecularly based classification of gastric cancer according to The TCGA 2014 [6]. EBV: Epstein-Barr virus; PD-L1: Programmed Death receptor Ligand-1; RHOA: Ras Homolog gene family member A.

Another prognostic classification is available, made by the Asian Cancer Research Group (ACRG) and based on the analysis of 300 primary gastric cancers using targeted sequencing, genome-wide copy-number data and gene expression data to describe four molecular subtypes linked to distinct clinical outcomes and prognosis [6]. In few words, the Asian Cancer Research Group stratification complements the TCGA classification, adds prognostic information and supplements it by incorporating two key molecular mechanisms related to TP53 activity and mesenchymal like features to further stratify gastric cancer patients [6,9]. Recurrence rates, according to the ACRG classification are resumed in Table 2. The worst prognosis stands for mesenchymal-like tumors, followed by TP53 inactive, TP53-active, and the best for microsatellite-instability tumors [6,9].

Characteristics	MSI	MSS/TP53+	MSS/TP53-	MSS/EMT
Reccurence rates	23.5%	39.2%	43.9%	67.4%

Table 2: Rates of recurrence linked to molecular characterization according to the ACRG [6]. EMT: Epithelial-Mesenchymal Transition; MSI: MicroSatellite Instable; MSS: MicroSatellite Stable; TP53: Tumor Protein 53.

Targeted therapies in gatsric cancer

Chemotherapy was for a long time the single standard of care in metastatic gastric cancer [4,5]. Several associations have demonstrated a huge increasing in median survival [6]. The adjonction of targeted therapies have allowed an interesting additional effect on median survival and QOL [6].

Her2 positive disease: +Trastuzumab: As HER2 positive breast cancer, trastuzumab is actually an indispensable molecule since first line treatment in association with active chemotherapy in metastatic gastric cancer [6]. Trastuzumab is a monoclonal antibody which binds to the extracellular domain of the HER2 [10]. It mediates cellular cytotoxicity by inhibiting proliferation of cells that overexpress HER2 protein, resulting in the blockade of receptor dimerization [10]. In the ToGA trial (phase III prospective multicentric study), trastuzumab has been a success as the first biologic agent with documented clinical activity in the first-line advanced and metastatic gastric and GEJ cancer setting [11]. Through 594 patients with HER2-overexpressing tumors either by Immunohistochemistry (IHC) or Fluorescence in situ Hybridization (FISH), randomized to receive cisplatin plus a fluoropyrimidine with or without trastuzumab. Patients assigned to receive trastuzumab with chemotherapy had a significant improvement in all measures of efficacy including OS (13.8 *vs.* 11.1 months, HR 0.74, 95% CI 0.60-0.91, p=0.0046), Progression-Free-Survival (PFS, 6.7 *vs.* 5.5 months, HR 0.71, 95% CI 0.59-0.85, p=0.0002), and Overall Response Rate (ORR, 47 *vs.* 35%, p=0.0017) [11]. The safety profile was acceptable according to the authors, since the most common grade 3 or 4 toxicities in patients treated with trastuzumab plus chemotherapy were neutropenia, anemia, diarrhea, nausea, anorexia, and vomiting. Cardiac adverse reactions were rare, with no difference between the two groups. Cardiac failure occurred in less than 1% of patients [11]. Molecular stratification according to HER2 status must be an essential step before first line treatment in metastatic disease [10]. In the subgroup analysis of the ToGA trial, patients with strongly HER2-positive tumors (IHC 2+/FISH+or IHC 3+) derived the greatest OS benefit with the addition of trastuzumab to chemotherapy (16.0 *vs.* 11.8 months, HR 0.68, 95% CI 0.5-0.83) [11].

+Reversible EGFR/HER2 TKIs: Lapatinib: Small molecules which inhibit tyrosine kinase protein of the EGFR and HER2 can represent therapeutic opportunity after trastuzumab failure [10]. Lapatinib is a reversible TKI of EGFR and Her2 that blocks by binding to intracellular Adenosine Triphosphate (ATP) binding site of these kinases [10]. Lapatinib has shown activity in HER2 positive breast cancer refractory to trastuzumab, suggesting that anti HER2 pressure continues to be useful in this population [12,13]. The TyTAN phase III randomized study have explored Lapatinib plus Paclitaxel *vs.* Paclitaxel alone in the second-Line treatment of HER2-Amplified advanced gastric cancer in Asian populations [12]. 261 patients enrolled with a primary end-point of OS. Median OS was 11.0 months with lapatinib plus paclitaxel *vs.* 8.9 months with paclitaxel alone (p=0.1044), with no significant difference in median PFS (5.4 *vs.* 4.4 months) or TTP (5.5 *vs.* 4.4 months). ORR was higher with lapatinib plus paclitaxel *vs.* paclitaxel alone (odds ratio, 3.85; p=0.001). Lapatinib plus paclitaxel demonstrated activity in the second-line treatment of patients with HER2 FISH-positive IHC3_ advanced gastric cancer but did not significantly improve OS [12]. The randomized Phase III trial

« TRIO-013/LOGiC » was made to evaluate the efficacy of adding lapatinib to capecitabine and oxaliplatin (CapeOx) in patients with previously untreated human epidermal growth factor receptor 2 (HER2)-amplified advanced gastro esophageal adenocarcinoma [13]. 487 patients were randomized, and the OS was the principal end-point of this study. The addition of lapatinib to CapeOx did not increase OS in patients with HER2-amplified gastric cancer [13].

+TDM-1 (Trastuzumab-Emtansine): In preclinical gastric cancer models, trastuzumab-Emtansine (TDM-1), an anti-HER2-directed antibody-drug conjugate, has shown more effective tumor activity than trastuzumab [14]. A recently presented phase 2/3 study investigating TDM1, failed to meet its primary end point. TDM-1 in second-line HER2-postive gastric cancer did not improve OS compared with taxane standard therapy (8.6 months with taxane *vs.* 7.9 months with T-DM1, HR: 1.15, p=0.8589) [14]

Anti EGFR therapies

+Cetuximab: It's a monoclonal anti-body, directed against the extracellular domain of the EGFR [10]. Its activity was experimented on the randomized open-label phase III trial *« EXPAND »,* exploring Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer. The primary end-point (PFS) wasn't met, and the addition of cetuximab to capecitabine-cisplatin provided no additional benefit to chemotherapy alone in the first-line treatment of advanced gastric cancer [15].

+Panitumumab: The « *REAL3* » randomized open label phase III trial, aimed to assess addition of the anti-EGFR humanized antibody Panitumumab to Epirubicin, Oxaliplatin, and Capecitabine (EOC) in patients with advanced oesophagogastric adenocarcinoma. This trial was negative, and panitumumab was neither efficient nor safe to be used in metastatic gastric cancer [16]. The addition of panitumumab didn't provide any survival benefit and was associated with increased incidence of grade 3-4 digestive and cutaneous side effects [16].

Anti-angiogenesis

Anti-angiogenic therapy has been proved that it might be one of the two clinically effective targeted therapies, besides anti HER2 therapy [10]. Despite the initial failures, targeting angiogenesis has become an unavoidable approach thanks to some optimistic results.

+Bevacizumab: Is a monoclonal antibody inhibiting VEGF-mediated angiogenesis by binding and inactivating VEGFA ligand [10]. Two randomized phase III trials failed to obtain OS benefit by adding bevacizumab to active chemotherapy. The AVAGAST trial, have enrolled 774 patients to receive capecitabine and cisplatin with or without bevacizumab [17]. The analyses demonstrated an increase in ORR (46.0% *vs.* 37.4%, p=0.0315) and PFS (median, 6.7 *vs.* 5.3 months; HR=0.80 [95% Confidence Interval [CI], 0.68-0.93], p=0.0037) with the addition of bevacizumab to chemotherapy, but with no significant improvement in OS (median, 12.1 *vs.* 10.1 months; HR=0.87 [95% CI, 0.73-1.03], p=0.1002) which was the principal end-point [17]. Preplanned subgroup analyses in AVAGAST suggest regional differences in the efficacy of bevacizumab [17]. Patients enrolled in North America and Latin America appeared to have a survival benefit with the addition of bevacizumab (median, 11.5 *vs.* 6.8 months for placebo-chemotherapy; HR=0.63 [95% CI, 0.43-0.94]), whereas patients enrolled in Asia (90% from Japan and Korea) appeared to have no benefit (HR=0.97 [95% CI, 0.75 to 1.25]), and European patients had intermediate results (HR=0.85; [95% CI, 0.63-1.14]) [17]. The second phase III trial is AVATAR. The study design was similar to AVAGAST, conducted in Chinese patients with advanced gastric cancer, also shows that the addition of bevacizumab to capecitabine-cisplatin does not improve PFS (median, 6.3 *vs.* 6.0 months; HR=0.89 [95% CI, 0.66-1.21], p=0.4709) and OS (median, 10.5 *vs.* 11.4 months; HR=1.11 [95% CI, 0.79-1.56], p=0.5567) [18]. Unfortunately, the subsequent biological marker analysis of the AVAGAST study does not figure out the underlying reasons of the survival differences. In addition, no specific surogate marker has been found to predict the efficacy of Bevacizumab [17,18].

+Ramucirumab: Is an anti-VEGFR2-directed fully human monoclonal IgG1 antibody who managed to put the anti on the road of success [10]. Two phase III randomized trials demonstrated its efficacy [6]. The « REGARD » study included 355 patients to explore the efficacy of ramucirumab as second line treatment in metastatic gastric cancer [19]. The analyses of outcomes demonstrate the improvements in PFS (median, 2.1 *vs.* 1.3 months; HR=0.483 [95% CI, 0.376-0.620], p<0.0001) and OS (median, 5.2 *vs.* 3.8 months; HR=0.776 [95% CI, 0.603-0.998], p=0.047), and no improvement in ORR was found [19]. The particularity of this study is that patients with refractory gastric cancer can be treated henceforth without neither a fluoropyrimidine- nor a taxane-based regimen. Another larger international randomized, double blind, placebo-controlled trial « RAINBOW trial », combining ramucirumab with paclitaxel as the second-line treatment for patients with metastatic Gastro Esophageal Junction (GEJ) and gastric adenocarcinoma [20]. This study randomized 665 patients and demonstrate that the improvements in ORR (28.0% *vs.* 16.0%, p=0.0001), PFS (median, 4.40 *vs.* 2.86 months; HR=0.635 [95% CI, 0.536-0.752], p<0.0001) and OS (median, 9.63 *vs.* 7.36 months; HR=0.807 [95% CI, 0.678-0.962], p<0.0001) are observed in the ramucirumab plus paclitaxel group [20]. Once again preplanned subgroup analyses suggest regional differences in the efficacy of anti-angiogenic therapy. Patients enrolled in non-Asia appear to have a survival benefit (8.6 *vs.* 5.9 months for placebo-chemotherapy; HR=0.73 [95% CI, 0.58-0.91]) with the addition of ramucirumab, whereas patients enrolled in Asia appear to have no benefit (median, 11.4 *vs.* 11.5 months for placebo chemotherapy; HR=0.88 [95% CI, 0.60-1.28]) [20]. The positive results of the REGARD trial and RAINBOW trial in survival allow us to conclude that ramucirumab is now the first biologic strategy in an unselected patient population to impact survival benefit in chemotherapy-refractory gastric cancer. Among the currently available treatment options for second-line advanced gastric cancer, the combination of ramucirumab and paclitaxel seems to be the most effective one. Ramucirumab is now explored as first-line therapy for HER2 negative metastatic gastric cancer, in the large RAINFALL phase III study.

+Apatinib: Is a small-molecule VEGFR tyrosine kinase inhibitor, administrated to inhibit the intracellular catalytic function of VEGFR family by blocking the receptors of tyrosine kinases expressed by endothelial cells [21]. This Tyrosine Kinase Inhibitor (TKI) was evaluated in randomized phase III study to assess the efficacy and safety of apatinib, in patients with advanced gastric or GEJ adenocarcinoma for whom at least two lines of prior chemotherapy had failed [21]. This Chinese trial has enrolled 267 patients to receive apatinib or placebo. The Median OS was significantly improved in the apatinib group compared with the placebo group (6.5 months; 95% CI, 4.8 to 7.6 *vs.* 4.7 months; 95% CI, 3.6 to 5.4; p=0.0149; hazard ratio, 0.709; 95% CI, 0.537 to 0.937; p=0.0156). Similarly, apatinib significantly prolonged median PFS compared with placebo (2.6 months; 95% CI, 2.0 to 2.9 *vs.* 1.8 months; 95% CI, 1.4 to 1.9; P=0.001;

hazard ratio, 0.444; 95% CI, 0.331 to 0.595; p=0.001) [21]. Larger studies are necessary including non-Asiatic patients to conclude into the efficacy of apatinib as treatment in advanced gastric cancer.

Anti-MET/HGF: c-MET is a receptor tyrosine kinase that, after binding with its ligand, Hepatocyte Growth Factor (HGF), activates a wide range of different cellular signaling pathways, including those involved in proliferation, motility, migration and invasion [6].

+Onartuzumab: A monovalent anti-MET antibody inhibits the MET/HGF pathway [22]. It was investigated in first-line with active chemotherapy in metastatic, HER2 negative, MET positive metastatic gastric cancer [22]. The MET Gastric phase III randomized study enrolled 562 patients to receive either chemotherapy alone based on the mFOLFOX6 regimen or chemotherapy associated to onartuzumab [22]. The addition of onartuzumab to mFOLFOX6 doesn't meet the co-primary end-points represented by OS in Intent-to-Treat (ITT) and MET 2+/3+ patients [22]. The safety profile of onartuzumab was dominated by hematologic toxicity as neutropenia or thrombocytopenia which was well managed according to the authors [22]. We need further studies and stronger data to introduce onartuzumab as effective treatment in metastatic gastric cancer.

+Rilotumumab: Is a fully human monoclonal antibody that selectively targets the ligand of the MET receptor, HGF [6,7]. The RILOMET-1 phase III trial aimed to assess the efficacy, safety, and pharmacokinetics of rilotumumab combined with epirubicin, cisplatin, and capecitabine, and to assess potential biomarkers, in patients with advanced MET-positive gastric or GEJ adenocarcinoma [23]. This study has recruited 609 patients, who were randomly assigned epirubicin, cisplatin, and capecitabine with Rilotumumab or placebo [23]. Study treatment was stopped early after an independent data monitoring committee found a higher number of deaths in the rilotumumab group than in the placebo group [6]. These results suggest that inhibition of the MET pathway in MET-expressing tumors with onartuzumab or rilotumumab is not effective in improving clinical outcomes in patients with gastro-esophageal cancer [6]. These agents are unlikely to play a major role in the treatment of gastric cancer in the near future given the current limited understanding of the contribution of the MET pathway to tumor development [6].

Anti-mammalian target of rapamycin (mTor)

Phosphatidylinositol 3-kinase (PI3K)/Akt and mammalian target of rapamycin (mTOR) is activated in 30% and 60% of human gastric carcinomas, respectively [6]. PI3K/Akt/mTOR pathway dysregulation is also implicated in some complicated mechanisms of chemotherapy resistance [6,7,10]. The oral mTOR inhibitor everolimus has demonstrated clinical benefit in several human cancers (clear cell renal cancer, breast cancer…) associated to a tolerable safety profile [24]. The randomized, double-blind, phase III GRANITE-1 study has evaluated everolimus in patients with advanced gastric cancer that progressed after one or two lines of systemic chemotherapy [24]. 656 patients were enrolled and randomized between Best Supportive Care (BSC) or everolimus 10 mg per day. Everolimus didn't improve the median OS 5.4 months with everolimus and 4.3 months with placebo (HR, 0.90; 95% CI, 0.75 to 1.08; p=0.124) [24]. The everolimus safety profile observed was generally consistent with that previously observed for everolimus in cancer, with no new safety signals identified [24].

Perspective

As we can see above, many disappointments have marked the development of targeted therapies in gastric cancer. Except for trastuzumab and ramucirumab, targeted therapies have failed to establish themselves as unavoidable therapeutic options. Tumor heterogenity seems to be the main cause of all these failures [6,7]. In this context a pragmatic look seems to be wise to move towards the future through molecular stratification with therapeutic implications. Many studies are currently ongoing to validate a molecular classification that will allow personalized treatment strategies [6]. On the other hand, the genomic instability that characterizes the heterogeneity of gastric cancer can be put to good use, making it a good candidate for immune therapy, owing to neoepitope presentation on cancer cell surfaces that enhances tumor immunogenicity [6,7]. A Recent study assessed the clinical significance of Programmed-cell-death protein-Ligand 1 (PD-L1) mRNA expression in blood specimens obtained from patients with gastric cancer [25]. PD-L1 mRNA expression was significantly higher in patients with advanced gastric cancer than in patients with early gastric cancer (p=0.002) [25]. In addition, PD-L1 expression correlated significantly with depth of tumor invasion, distant metastasis, and stage (p=0.001, p<0.001, and p<0.001, respectively). Patients with high PD-L1 expression displayed significantly poorer prognosis than those with low PD-L1 expression (p<0.0001). Multivariate analysis demonstrated PD-L1 expression as an independent prognostic factor [25].

Immune checkpoint inhibitors

+Pembrolizumab: Is a humanized IgG4 monoclonal antibody without Antibody-Dependent Cytotoxicity (ADCC) activity. It competitively inhibits the binding of PD-1 to PD-L1 and PD-L2 [26]. Currently used in many cancers (Lung, melanoma…), it has been evaluated in phase Ib study (KEYNOTE-012) [26]. 39 patients were enrolled. 36 were evaluable for response by central assessment. In this population of patients with recurrent or metastatic PD-L1-positive gastric cancer, pembrolizumab had a promising antitumor activity as a quarter of patients (22%, 95% CI 10-39) were judged to have had an overall response at central review [26]. The safety profile was manageable warranting further study in phase 2 and 3 trials (Table 3).

+Nivolumab: Is a humanized IgG4 recombinant anti-PD-1 monoclonal antibody [27]. The CheckMate-032 study have enrolled 59 patients with metastatic heavily pretreated gastric cancer to receive nivolumab alone (3 mg/kg IV Q2W) and treated until Disease Progression (PD) or intolerable toxicity. The primary endpoint was ORR. 12% have observed objective response (n=7/58; 1 complete response, 6 partial responses) and 12 patients (21%) had stable disease. Median OS (secondary end-point) was 6.8 mo (95% CI, 3.3-12.4); 12-mo OS rate was 38% (95% CI, 23.2-52.7) [27]. In Asiatic population, ATTRACTION-2 phase III study has demonstrated superiority of nivolumab in heavily treated metastatic gastric cancer. 493 patients were assigned to receive either Nivolumab or placebo [28]. Median overall survival was 5, 26 months (95% CI 4·60-6·37) in the nivolumab group and 4, 14 months (3·42-4·86) in the placebo group (hazard ratio 0·63, 95% CI 0·51-0·78; p<0·0001) [28].This absolute benefit of 1 month and half plus an acceptable safety profile help us to conclude that nivolumab might be a new treatment option for heavily pretreated patients with advanced gastric or GEJ cancer. Ongoing trials that include non-Asian patients are investigating nivolumab for advanced gastric or GEJ cancer in various settings and earlier treatment lines (Table 3) [6]. Immune therapy seems to be a serious therapeutic

modality in the near future. In a phase I trial with an expansion cohort of Japanese patients with gastric cancer, the anti–PD-L1 antibody, Avelumab demonstrated an ORR of 15% with median PFS of 11.9 weeks [29]. Currently, 2 phase III studies of maintenance therapy after first-line (JAVELIN Gastric 100) and third-line (JAVELIN Gastric 300) treatment are ongoing table 3. In another hand combination strategies will allow to generate an additional therapeutic effect, with amelioration outcomes of metastatic gastric cancer patients [6,7,10]. These strategies include combinations of systemic chemotherapy; molecular targeting agents; radiotherapy; immune checkpoint inhibitors, such as Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), Lymphocyte Activation Gene-3 (LAG-3), and T-cell immunoglobulin domain, mucin domain (Tim-3); inhibitors of suppressive factors, such as Indoleamine 2,3-Dioxygenase (IDO) or Transforming Growth Factor β (TGF-β); and depletors of suppressive lymphocytes, such as Chemokine Receptor 4 (CCR4) anti-body, as well as local injection of oncolytic viruses to enhance the local immune response [7,8,10]. Many combination possibilities are under exploration (table 3) and may offer a hopeful insight since these strategies have significantly improved the prognosis of several tumor sites, considered fatal for a long time.

Trial (Clinical Trials.gov Identifier)	Line	Control Arm	Agents (Experimental)	Target
Immune therapy				
KEYNOTE-062 (NCT02494583)	First	XP/FP	+Pembrolizumab	PD-1
JAVELIN Gastric 100 (NCT02625610)	First (maintenance)	Continuation of first line	Avelumab	PD L1
KETNOTE-061 (NCT02370498)	Second	Paclitaxel	Pembrolizumab	PD-1
JAVELIN Gastric 300 (NCT02625623)	Third	Paclitaxel/Irinoteca/BSC	Avelumab	PD-L1
Anti HER2 combination therapies				
JACOB (NCT01774786)	First	XP or FP/trastuzumab	+Pertuzumab	HER2
Antiangiogenic therapy				
RAINFALL (NCT02314117)	First	XP	+Ramucirumab	VEGFR2
INTEGRATE-2 (planned) (NCT02773524	Third or fourth	Placebo	Regorafenib	VEGFR, RET, RAF
Other therapies				
ENRICH (NCT01813253)	Second	Irinotecan	+Nimotuzumab	EGFR
GOLD (NCT01924533)	Second	Paclitaxel	+Olaparib	PARP
BRIGHTER (NCT02178956)	Second	Paclitaxel	0	STAT3

Table 3: Ongoing Phase III Trials for Advanced Gastric Cancer [6]. BSC: Best Supportive Care; EGFR: Epidermal Growth Factor Receptor; FP: 5-FU Plus cisplatin; PARP: Poly (ADP-Ribose) Polymerase; PD-1: Programmed cell Death 1; PD-L1: Programmed cell Death Ligand 1; STAT3: Signal Transducer and Activator of Transcription-3; VEGFR: Vascular Endothelial Growth Factor Receptor; XP: Capecitabine plus Cisplatin

Conclusion

Metastatic gastric cancer is heterogeneous disease. Many targeted therapies are already standard of care in metastatic gastric cancer, and allow a huge amelioration in survival outcomes. Personalized medicine, based on molecular setting may be integrated in future strategies to have more benefit and to define stratified attitude.

Acknowledgements

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