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REVIEW

Advances in molecular, genetic and immune signatures of gastric cancer: Are we ready to apply them in our patients' decision making?

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Abstract

In the last few years we have witnessed a vast expansion of our knowledge regarding the molecular and genetic profile of gastric cancer. The molecular subtypes described have shed light on the pathogenesis of the disease, thus prompting the development of new therapeutic strategies and favoring a more individualized approach for treatment. Most of the clinical trials for so called targeted therapies could be considered, at best, partially successful. In addition, checkpoint inhibitors have recently been added to our armamentarium in later stages of the disease, and combinations with chemotherapy and targeted agents are currently under development. In view of the rapid advances of molecular oncology, a new challenge for the clinical oncologist arises: The appropriate patient selection for each new therapy, which can be made possible only through the implementation of predictive biomarkers in our therapy decision making.

Key words: Gastric cancer; Cancer Genome Atlas; Asian Cancer Research Group; Targeted therapy

Core tip: Despite recent advances in cancer therapeutics, the survival of gastric cancer patients with metastatic disease is dismal due to the complexity of the disease, the constant evolution of tumors and our still limited understanding of its biology. It is evident that a wide spectrum of prognostic and predictive biomarkers is needed in order to rationalize our decisions when managing patients with this specific tumor type and tailor our treatment to suit better the individual patient's unique needs.

Gkolfinopoulos S, Papamichael D, Papadimitriou K, Papanastasopoulos P, Vassiliou V, Kountourakis P. Advances in molecular, genetic and immune signatures of gastric cancer: Are we ready to apply them in our patients' decision making? *World J Gastrointest Oncol* 2018; 10(7): 172-183 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i7/172.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i7.172

INTRODUCTION

Gastric cancer (GC) is the fifth most common type of cancer and the third most common cause of cancer-related mortality worldwide[1]. Despite recent advances in cancer therapeutics, driven by the application of the findings of basic science in cancer genetics and host-tumor immune interactions, the prognosis of most patients with metastatic disease is dismal[2]. Indeed, in GC we seem to lack clear molecular targets based on key regulatory genes or the aberrant expression of growth factor receptors. Furthermore, the universal rise of immunotherapeutic approaches in various tumor types has only recently been incorporated in GC. It is evident that a wide spectrum of prognostic and predictive biomarkers is needed in order to rationalize our decisions when managing patients with this specific tumor type and tailor our treatment to suit better the individual patient's unique needs.

Genetic heterogeneity of GC

Our understanding in GC genetics was greatly expanded in 2014, when four main molecular subtypes of the disease were recognized in the context of the Cancer Genome Atlas (TCGA) project[3]. Further efforts were undertaken in order to relate molecular subtypes with the known histological subtypes that Lauren had proposed roughly half a century ago as well as with the location of the primary tumor and prognosis[4]. These efforts were met with moderate success, since it is now widely accepted that there is an important degree of overlap. Various basic studies and clinical trials followed, aiming to discover a clinically meaningful way of utilizing the findings of the TCGA project[5]. Unfortunately, thus far, the results have fallen short of the initial high expectations, although some success has been noted in subgroups of patients across trials that exhibited unique molecular characteristics. In 2015, another major molecular classification was proposed, this time from the Asian Cancer Research Group (ACRG), which shares similarities with TCGA yet has enough differences to be considered completely distinct (Table 1). The novelty with the ACRG was that the molecular subtypes discovered were associated with clinical outcomes[6]. A short review and comparison of both classification systems will be presented, followed by a brief and non-exhaustive analysis of the most important clinical trials employing target or immunotherapeutic strategies in this expanding area of oncology.

MOLECULAR SUBTYPES OF GC ACCORDING TO TCGA

The first and most comprehensive molecular characterization of gastric adenocarcinoma was reported by the TCGA Network. In this study, 295 (therapy naive) primary gastric adenocarcinoma samples were characterized using six different molecular platforms, including array-based somatic copy number analysis, whole-exome sequencing, array-based DNA methylation profiling, messenger RNA sequencing, microRNA sequencing, and reverse-phase protein array. No survival or racial differences were found among patients from each subgroup[3]. As mentioned before, there were four main subtypes discovered, which can roughly be categorized in the following groups.

Subtypes not inherently immunogenic

The following two subtypes are less likely to respond to immunotherapeutic strategies *per se*. Rather, combination approaches are probably required in order to attain a response using immunotherapy, such as adding chemotherapy to checkpoint inhibition or dual checkpoint inhibition. However, in cases with marked T-cells infiltration, we might expect that the checkpoints are probably up-regulated, and thus immunotherapy might still work. Apart from immunotherapy, targeted therapy with tyrosine kinase inhibitors (TKI) may prove to be another option in select subgroups of patients that carry specific driver mutations.

Chromosomal instability (50% of samples): The majority of the tumors analyzed in the project have fallen in this category. This subtype is found more frequently in the gastroesophageal junction (GEJ)/cardia (65%), is of intestinal histology, and affects mainly older (> 70 yo) individuals[7]. Genetically, it is characterized by marked aneuploidy and high frequency of *TP53* mutations (73%). Consequently, it features a high number of focal amplification of receptor tyrosine kinases, most importantly *VEGFA*, *EGFR* (10%), *ERBB2* (24%), *ERBB3* (8%), and *c-Met* (8%) as well as amplification of genes encoding cell cycle mediators, such as *CCNE1*, *CCND1*,

Table 1 Molecular subtypes of gastric cancer according to the Cancer Genome Atlas and Asian Cancer Research Group

Molecular subtypes of gastric cancer	
TCGA	ACRG
CIN (50%)	MSS/TP53− (35.7%)
MSI-H (21%)	MSS/TP53+ (26.3%)
GS (20%)	MSI-H (22.7%)
EBV + (9%)	MSS-EMT (15.3%)

TCGA: Cancer Genome Atlas; ACRG: Asian Cancer Research Group; CIN: Chrosomal instability; MSI-H: Microsatellite-high; GS: Genomically stable; EBV: Epstein-Barr virus; MSS: Microsatellite stable; TP53: Tumor protein p53; EMT: Epithelial-mesenchymal transition.

and *CDK6*[8]. These genetic aberrations contribute to making it the ideal candidate for application of targeted treatment, especially TKI inhibitors and monoclonal antibodies[9].

Genomically stable (20% of samples): The trademark characteristics of this subtype are diploidy and somatic mutations in *CDH1* (37%), which is also the gene that is mutated in hereditary diffuse GC syndrome[10]. Further common genetic aberrations are either *RHOA* mutations or *CLDN18-ARHGAP* rearrangements, both discovered in approximately 30% of tumors and usually mutually exclusive. All those mutations lead to disrupted intercellular cohesion and enhanced invasiveness, thus it is no surprise that most (73%) of these tumors belong to the diffuse histological variant. Most patients are of younger age (median 59 years), and there is no gender predominance[3]. The inherent relative lack of immunogenicity and targetable driver mutations may lead to increased difficulty in applying individualized treatment in this subtype. Perhaps this is the single molecular subtype in TCGA classification where classic cytotoxic chemotherapy will continue to retain the primary role in treatment.

Highly immunogenic subtypes

The other two subtypes are characterized by extensive infiltration of PD-L1(+) immune cells, which are dispersed throughout the tumor instead of being located in the invasive margin, as is common with other malignancies[11]. It is speculated that the patients who exhibit response to checkpoint inhibitors will belong to this particular subgroup, although this has not yet been proven[12].

Microsatellite-high (21% of samples): The second most common subtype in the TCGA classification is characterized by extensive DNA methylation and multiple somatic mutations. These types of tumors are diagnosed at an older age (median age 72 years), with a slightly higher preponderance in female patients (56%). The various and dispersed mutations across the genome are mostly a consequence of *MLH1* promoter hypermethylation. Other important genes, with potentially targetable products, which are found mutated, are *PIK3CA, EGFR, ERBB2*, and *ERBB3*[3].

The extensively mutated genetic material of these tumors creates an opportunity for immune system-oriented strategies. Indeed, the high amount of neoantigens, often presented in MSI-high tumors, elicit an immune response, manifested through extensive PD-L1 expression, which in this subtype reaches 33% and 45% on tumor and immune cells, respectively[13,14].

Epstein-Barr virus-positive (9% of samples): This subtype, whose main characteristic is the high Epstein-Barr virus (EBV) burden, was found to occur predominantly in the gastric fundus or body (62%), and is more common in men (81%). In TCGA, a recurrent amplification of 9p24.1 genetic locus is described, which is the site of genes *JAK2, CD274*, and *PDCD1LG2.* The first accounts for the aberrant activation of the JAK-STAT pathway, while the latter two encode PD-L1 and PD-L2, respectively. The 9p amplifications are found in at least 15% of EBV (+) tumors and lead to enhanced neoepitope presentation. It is also characterized by extreme DNA hypermethylation, most notably of the *CDKN2A* promoter, which leads to complete lack of p16 (p16INK4A) protein. It also features recurrent *PIK3CA* (80%), *ARID1A* (55%), and BCOR (23%) mutations[3]. These molecular alterations characterizing this particular subtype hint at the therapeutic potential of *JAK* inhibition, *PI3K/MTOR* inhibition and immunotherapeutic approaches.

MOLECULAR SUBTYPES OF GC ACCORDING TO ACRG

The ACRG analyzed 300 GC samples using gene expression, genome-wide copy number microarray and targeted sequencing. Partially overlapping with the TCGA classification and sharing some similarities but also exhibiting enough differences to be categorized as a completely distinct classification, four molecular subtypes are described. In this case, the foundations of this molecular classification are based on the basis of MSI status, *TP53* function, and epithelial-mesenchymal transition (EMT). In this classification the subtypes were associated with relevant clinical outcomes and revealed survival differences that were validated in independent cohorts[6].

The basis on which the first division took place was the loss of function of genes involved in the mismatch repair (MMR) system, thus distinguishing the MSI subtype. Then, the remaining tumors were divided depending on alterations in cell adhesion, angiogenesis, and motility, thus forming the MSS/EMT subtype. The rest were divided in two subtypes, depending on the loss of function of TP53, namely the microsatellite stable/TP53 intact (MSS/TP53+) and microsatellite stable/TP53 loss (MSS/TP53-) subtypes. Among these subtypes, the MSI showed the best overall prognosis, followed by

MSS/TP53+, MSS/TP53-, and MSS/EMT[6]. More extensively, the molecular subtypes and their main specific characteristics are:

Microsatellite stable/TP53 loss (35.7% of samples)

This subtype is characterized by the highest rate of *TP53* mutations (60%). Also, it features a greater aneuploidy and recurrent focal amplifications in *MDM2, ROBO2, GATA6, MYC. ERBB2, EGFR, CCNE1*, and *CCND1*[6].

Microsatellite stable/TP53 intact (26.3% of samples)

Compared to the rest, this subtype is characterized by a higher prevalence of EBV infection. In addition to exhibiting an active TP53 pathway, it is associated with APC, *ARID1A, KRAS, PI3KCA*, and *SMAD4* mutations[6].

Microsatellite-high (22.7% of samples)

This subtype occurred frequently in the antrum (75%), was mostly (> 60%) of intestinal-type histology, and was diagnosed more frequently at early stages (Ⅰ or Ⅱ), thus exhibiting the best overall survival. Genetically, it was associated with the presence of hypermutation, especially in genes encoding KRAS (23.3%), the PI3K-PTEN-mTOR pathway (42%), ARID1A (44.2%), ERBB2 (16.3%), ERBB3 (14%), and ALK (16.3%)[6].

Microsatellite stable/epithelial-mesenchymal transition (15.3% of samples)

This subtype was associated with diffuse type histology, as it was expected considering that it features aberrations in genes responsible for cell adhesion and motility. It presents at a significantly younger age with most of the patients diagnosed at advanced stages (Ⅲ/Ⅳ). Consequently, it carries the worst overall prognosis and a higher chance of recurrence. It is also characterized by higher rates of peritoneal spread, which can also be attributed to the above mentioned genetic changes[6,15].

Comparison between TCGA and ACRG classifications

It is evident that, when comparing the two classifications, certain similarities exist between the different subtypes. Apart from the obvious association between the MSI subtypes in both classifications, it can be argued that roughly the equivalent of the genomically stable (GS) subtype in the ACRG classification is the microsatellite stable/epithelial-mesenchymal transition (MSS/EMT) subtype, while analogies exist between the EBV and chromosomal instability (CIN) subtypes on one hand, and MSS/TP53+ and MSS/TP53- on the other, respectively[14]. However, as has been stated previously, there are certain major differences. For instance, while in the TCGA classification, EBV is a distinct subtype; ACRG EBV-infected tumors represent a part of the spectrum of the wider MSS/TP53+ subtype, which, moreover, is not characterized by hypermethylation or hypermutation. Another important difference is that in ACRG classification, *CDH1* and *RHOA* mutations did not occur as frequently in the MSS/EMT as in its approximately equivalent GS subtype[14]. It can be argued that these differences, among others, point also to the genetic heterogeneity of GC between different populations of different ethnic backgrounds, suggesting potentially different pathogenetic mechanisms for this disease in different parts of the globe.

CLINICAL TRIALS FOCUSING ON MOLECULAR AND IMMUNE BIOMARKERS

Targeting molecular pathways

HER2 inhibition: HER2 protein in GC is overexpressed mainly as a result of gene amplification. Its overexpression results in increased cell proliferation *via* its main target pathways, namely PI3K/Akt/mTOR and the RAS/MAPK[16]. Consequently, its blockade may potentially halt tumor progression, at least temporarily, until an alternative pathway is switched-on driving resistance.

HER2 amplification is mainly a characteristic of GEJ tumors (15%-32%) rather than distal ones (10%-15%)[14]. Also, the exact location of the protein in the cell differs, depending on the level of differentiation of the tumor. Well-differentiated tumors express the protein in the cell surface, whereas it is located mainly in the cytoplasm in poorly differentiated cancer cells[17]. HER2 targeting has been implemented in various lines of therapy, with both monoclonal antibodies and TKIs with variable success (Table 2).

Trastuzumab, a chimeric monoclonal antibody targeting the domain Ⅳ of HER2, has gained approval in first-line therapy when combined with fluopyrimidine/cisplatin chemotherapy doublet, after the positive results of the phase Ⅲ ToGA trial. A subset analysis of this trial has indicated that the provided survival benefit is narrowed only to the group of patients where HER2 is clearly overexpressed, as manifested by combined immunohistochemistry (IHC) (+2) and fluorescent *in situ* hybridization (FISH) positivity, or IHC (+3) positivity. As a result, Trastuzumab should be administered to a specific subset of patients fulfilling the criteria mentioned above[18].

In an attempt to replicate the positive results of CLEOPATRA, where another HER2-targeting monoclonal antibody Pertuzumab gained approval in the treatment of advanced breast cancer, the phase Ⅲ JACOB trial was initiated. In this trial, Pertuzumab was combined with chemotherapy doublet and Trastuzumab in stage Ⅳ treatment-naive GC patients. Although the mOS was numerically superior in the Pertuzumab arm by 3.3 mo, with a 16% reduction in the risk of death, the trial missed statistical significance only just barely (P = 0.0565). Furthermore, as opposed to the ToGA trial, the majority of subgroups were consistent with the overall analysis. The combination therapy also resulted in more

Table 2 Main targeted agents evaluated in metastatic gastric cancer

Biologic target	Targeted agent	Name/type of trial	Line of therapy	Study arms	Results	Ref.
c-MET	Rilutumumab	RILOMET-1 Phase Ⅲ	1st	ECX + Ril	Negative effect	[58]
		EXPAND Phase Ⅲ	1st	XP ± Cet	No benefit	[48]
	Cetuximab	AIO Phase Ⅱ	1st	FOLFOX + Cet	> 4 *EGFR* gene copies: Increased OS (log-rank P = 0.011; HR = 0.2, 95%CI: 0-0.8; P = 0.022)	[50]
EGFR	Panitumumab	REAL-3 Phase Ⅲ	1st	EOX ± Pani	No benefit	[49]
	Trastuzumab	ToGA Phase Ⅲ	1st	XP/FP ± H	OS: 13.8 *vs* 11.1, P = 0.0046 OS (IHC+3, IHC+2/FISH+): 16 mo *vs* 11.8 mo, P = 0.0036	[18]
	Pertuzumab	JACOB Phase Ⅲ	1st	FP + H ± Pert	No benefit	[19]
HER-2	Lapatinib	Tytan Phase Ⅲ	2nd	Pac w ± Lap	No benefit (unselected population) OS (IHC: 3+): 14 mo *vs* 7.6 mo, P = 0.0176	[21]
	Trastuzumab emtansine	GATSBY Phase Ⅱ-Ⅲ	2nd	TDM-1 *vs* taxane	No superiority	[22]
mTOR	Everolimus	GRANITE-1 Phase Ⅲ	2nd, 3rd	Everolimus *vs* placebo	No benefit	[55]
	Bevacizumab	AVAGAST Phase Ⅲ	1st	XP ± Bev	Primary endpoint (OS) was not met PFS: 6.7 mo *vs* 5.3 mo, P = 0.0037 ORR: 46% *vs* 37.4%, P = 0.0315	[25]
		REGARD Phase Ⅲ	2nd	Ram *vs* placebo	OS: 5.2 mo *vs* 3.8 mo, P = 0.047	[26]
VEGF, VEGFR	Ramucirumab	RAINBOW Phase Ⅲ	2nd	Pac w ± Ram	OS: 9.6 mo *vs* 7.4 mo, P = 0.017	[27]
		Phase Ⅱ	1st	FOLFOX ± Ram	No benefit	[28]
	Apatinib	Phase Ⅲ	beyond 2nd line	Apa *vs* placebo	OS: 6.5 mo *vs* 4.7 mo, P = 0.0149 PFS: 2.6 mo *vs* 1.8, mo, P < 0.001	[30]

ECX: Epirubicin-Cisplatin-Capecitabine; Ril: Rilutumumab; XP: Cisplatin-Capecitabine; Cet: Cetuximab; EOX: Epirubicin - Oxaliplatin - Capecitabine; Pani: Panitumumab; FP: Cisplatin - 5Fu; H: Herceptin; Pert: Pertuzumab; Pac w: Paclitaxel weekly; Lap: Lapatinib; TDM-1: Trastuzumab emtansine; Bev: Bevacizumab; Ram: Ramucirumab; Apa: Apatinib; OS: Overall survival; PFS: Progression free survival; ORR: Overall response rate.

incidents of diarrhea and hypokalemia[19].

Another attempt at HER2 inhibition in first line was the phase Ⅲ TRIO-013/LOGIC trial, where, in a selected population of HER2 positive patients, the addition of Lapatinib, a small intracellular TKI of ERBB1 and ERBB2, was evaluated on whether it would improve the survival benefit derived by Oxaliplatin/Capecitabine doublet chemotherapy. Unfortunately, the trial failed to demonstrate a statistically significant survival benefit. However, it did raise the question of the accuracy of the current method of appreciating HER2 positivity, since the observed clinical benefit closely correlated with the degree of gene amplification as well as with HER2 protein levels, implying that implementing a different scoring system where HER2 over-expressing tumors are defined by an IHC score of more than 3 (IHC) or 2 (FISH) values, may be more precise[20].

Lapatinib was also evaluated in the second line in the phase Ⅲ Asian TyTAN trial, where it was added to weekly Paclitaxel. It is interesting to note that the trial was performed in an unselected population, with 31% demonstrating weak (IHC: 1+) or none at all HER2 positivity. No survival benefit was noted in the study population, although in the subgroup with strong HER2 positivity (IHC: 3+), median survival improved to 14 mo *vs* 7.6 mo (P = 0.0176)[21].

Another negative phase Ⅲ trial compared a monoclonal antibody used in HER2(+) breast cancer, Trastuzumab Emtansine (TDM-1), and taxane monotherapy in HER2(+) patients (GATSBY trial). However, as in the TyTAN trial, HER2 expression was evaluated in archived samples, not taking into account the clonal heterogeneity and the possibility of tumoral evolution that may have occurred from the first to second line chemotherapy setting[22].

An attractive hypothesis regarding the etiology of the negative results of the above mentioned trials, apart from using archival samples, is the downregulation of HER2(+) tumors as a result of our targeting the HER2 protein in the first line setting. It is possible that HER2-directed therapies should be implemented preferably in the beginning of the treatment algorithm, with continuation or switch to another HER2 targeting agent, beyond progression, remaining an option for the select few who retain HER2 positivity. However, this is currently hypothesis-generating and should be confir-

med within a clinical trial.

Inhibition of angiogenesis: Neoangiogenesis has an established role in GC pathogenesis, mainly through vascular endothelial growth factor (VEGF)/VEGFR2 signaling, as there is evidence that VEGF serum levels correlate with increased stage and worse prognosis[23]. In animal models, VEGFR2 inhibition led to angiogenesis impairment and tumor regression[24].

Based on these data, targeting this pathway, either the receptor or the ligand, with monoclonal antibodies and TKIs has been studied in various clinical trials. In this case, targeting VEGFA with Bevacizumab in combination with traditional chemotherapy in first line has not provided a substantial survival benefit in a phase Ⅲ trial, although results showed a significant improvement in progression free survival (PFS) (6.7 mo *vs* 5.3 mo) and overall response rate (46% *vs* 37.4%)[25].

On the contrary, targeting the receptor has been more effective. In the phase Ⅲ REGARD trial, Ramucirumab, a monoclonal antibody blocking VEGFR2 demonstrated superior survival over placebo in second line[26]. Also, the same drug, when combined with a taxane in second line, also led to a statistically significant survival benefit of 2.2 mo[27]. The attempt to expand the use of Ramucirumab in first line in combination with FOLFOX in a phase Ⅱ trial did not produce the required results[28]. However, there is another ongoing phase Ⅲ trial of Ramucirumab combined with Cisplatin and a fluoropyrimidine in HER2 negative patients in first line (RAINFALL; NCT02314117) that may clarify its efficacy in this setting[29].

Inhibiting angiogenesis with TKIs also has a role in the management of advanced GC. Apatinib, a multikinase inhibitor mainly targeting VEGFR2, significantly improved OS over placebo in a phase Ⅲ trial in patients with heavily pretreated advanced GC, which led to its regulatory approval as monotherapy beyond second line[30]. Also, Regorafenib, another multikinase inhibitor targeting, among others, VEGFR2, is currently being tested in the same setting in a phase Ⅲ trial after successfully achieving its primary endpoint of superior PFS in a relevant phase Ⅱ trial[31,32]. Sorafenib resulted in disease stabilization and moderately good PFS in chemo-refractory patients in first- and second-line, but its addition to chemotherapy did not provide adequately encouraging results to justify a phase Ⅲ trial[33-36]. Therefore, it appears that inhibition of angiogenesis has a definite role in advanced GC. Still, there are only hints regarding the potential predictive biomarkers that would help in individualizing its use. For instance, the two less immunogenic subtypes in the TCGA classification, namely the CIN and GS, were associated with *VEGFA* gene amplification and elevated expression of angiogenesis-related pathways, respectively, providing some clues regarding the importance of angiogenic pathways as a driving force of progression in tumors with these molecular signatures[14]. It must also be noted that the positive results with angiogenesis inhibition have been produced in the later lines of treatment, which may imply that in the early stages of GC progression, angiogenesis has a less substantial role, while it is more predominant in later stages of the natural course of the disease. Lastly, it is important to note that targeting the receptor rather than the ligand seems to be the appropriate strategy, a phenomenon for which we have not yet reached a clear and robust explanation but may prove crucial for future anti-angiogenic strategies.

EGFR inhibition: Epidermal growth factor receptor (EGFR) or Erb-B1 is a transmembrane receptor found overexpressed in 30% of GC, while the *EGFR* gene is amplified in nearly 5%[37]. Increased EGFR signaling has been correlated with higher stage, poorly differentiated tumors, and increased invasiveness[38-40]. In preclinical models, Cetuximab, a chimeric anti-EGFR antibody, induces antibody-dependent cell-mediated cytotoxicity (ADCC)[41]. Phase Ⅱ trials with Cetuximab, Panitumumab, or Erlotinib combined with cytotoxics have yielded responses ranging between 41% and 65%, while second line Gefitinib or Erlotinib monotherapy has provided less impressive results, with responses between 9% and 11%, limited mostly to proximal GC[42-47].

These data have prompted testing of anti-EGFR targeting in phase Ⅲ trials. However, both EXPAND and REAL3 phase Ⅲ trials testing Cetuximab and Panitumumab in combination with Cisplatin-Capecitabine and EOX, respectively, did not show any PFS or OS benefit. Again, this may be attributed to poor patient selection, since the study population was not evaluated for EGFR expression or gene amplification[48,49]. The potential importance of this parameter has been made clear in at least two studies: in the phase Ⅱ study combining FOLFOX with Cetuximab, where the patients that exhibited greater than four *EGFR* gene copies demonstrated increased OS, and also in the TRANS-COG, where the subset of EGFR-amplified patients derived a statistically significant survival benefit with the addition of Gefitinib (HR = 0.19; $P = 0.007$)[50,51].

This appears to have been taken into account in a phase Ⅲ trial of second-line Nimotuzumab with Irinotecan (NCT01813253), which is currently recruiting patients that harbor EGFR-overexpressing (IHC: +2/3) tumors[52].

PI3K/Akt/mTOR inhibition: Resistance to targeted therapies often appears as a result of activation of downstream effectors by alternative molecular pathways. The PI3K/Akt/mTOR pathway in GC may become constitutively activated either through mutations in the *PI3K* gene, which occurs most often in EBV(+) and MSI tumors, or through inactivation of *PTEN* gene, the main negative regulator of the pathway, which is mostly found in the MSI subtype[3,53].

Targeting this pathway with an mTOR inhibitor, Everolimus, has produced encouraging results in a phase Ⅱ trial, producing a median PFS of 2.7 mo and OS of 10.1 mo[54]. However, the phase Ⅲ GRANITE-1 trial

that compared Everolimus to placebo in an unselected patient population, as second- or third-line therapy, failed to demonstrate any survival benefit. Once again, the study population was unselected for PI3K pathway activation[55]. Impairment of *Akt* function *via* allosteric inhibition in a phase Ⅱ study of the small molecule MK-2206, in unselected patients, did not produce any positive results either[56].

The above findings, rather than just annulling the findings of basic science, may be viewed as a further indication for the need of appropriate patient selection. PI3k/Akt/mTOR inhibition may still have a role where activation of this pathway is indeed the driver of cancer progression.

MET inhibition: The *MET* proto-oncogene encodes the c-MET receptor tyrosine kinase that has a crucial role in cell proliferation, angiogenesis, and migration. Its canonical activation pathway is *via* binding of its ligand, hepatocyte growth factor (HGF), but the activation can result independently of the binding through gene amplification or somatic mutation. The MET gene has been found amplified in 4%-10% of GC, while its protein product has been found overexpressed by IHC in up to 70%[57]. The implications of this deviation between gene amplification and protein overexpression have been made evident in the MET-targeted clinical trials.

All phase Ⅱ and Ⅲ trials that included patients based on MET overexpression *via* IHC provided negative results. A probable explanation is the vague definition of MET positivity by IHC. In the phase Ⅲ RILOMET study, the addition of Rilutumumab, an HGF-targeting monoclonal antibody, to triplet chemotherapy (ECX) proved detrimental. The study was terminated prematurely because of increased risk of death in the investigational arm[58]. The main targeted agents evaluated in various clinical settings in GC are presented in Table 2.

Targeting cancer stemness

A possible way in which tumors survive complete elimination from cytotoxic chemotherapy is the presence of cancer stem cells. Cancer "stemness" is frequently manifested through the activation of the STAT3 pathway, which induces the transcription of *Nanog* and *Myc* genes. The rationale for investigating this pathway in GC after failure of previous therapies in a large phase Ⅲ trial (BRIGHTER) was provided by encouraging response and disease control data from phase Ⅰ and Ⅱ trials, where the small molecule BBI608 (Napabucasin) was combined with Paclitaxel This trial is ongoing, however, interim analysis indicated diminished possibility of achieving the primary endpoint of OS[59,60].

Targeting DNA damage repair pathway

Poly (ADP-ribose) polymerase (PARP) is essential in correcting single-strand DNA breaks induced by cytotoxic agents. Inhibition of PARP has provided significant benefit in the subgroup of patients with breast and ovarian cancer that already exhibit a certain level of defect in the DNA repair mechanism, such as loss of function of *BRCA1/2* genes. Since *BRCA1/2* mutations in GC are rare, this strategy was implemented in tumors that are characterized by other defects in the repair pathway, like in the *ATM* gene, a quality termed "BRCAness"[61,62]. Preclinical and early clinical trials on tumors with *ATM* deficiency and *TP53* mutations were completed with significant success[63]. However, the phase Ⅲ GOLD trial failed to reveal a statistically significant, according to predetermined criteria, survival benefit in patients treated with Olaparib and Paclitaxel. This failure might once again be attributed to poor patient selection, since the study population was not selected based on *TP53* mutations, while furthermore only 18% of patients were *ATM* negative[64].

Targeting the tumor microenvironment

Andecaliximab, previously known as GS-5745, is a monoclonal antibody that targets matrix metalloproteinase (MMP) 9, an extracellular enzyme involved in matrix remodeling, angiogenesis, tumor growth, and metastasis. Encouraging results from the phase Ⅰ study, where it was combined with FOLFOX in patients both treatment naive and pretreated, have secured its evaluation in a phase Ⅲ trial (NCT02545504), where it is tested in first line in the same combination. The trial has completed accrual, and results are awaited. It is important to note that this strategy, if successful, has the potential to be implemented in a wide spectrum of patients with GC, without the need for a predictive biomarker. Also, since MMP inhibition affects the collagenous stroma of the tumor, not only will it clear the path for the chemotherapy drugs to reach cancer cells, but also it will enhance tumor immunogenicity, with obvious implications for a potential combination with immunotherapy[65].

Manipulating immune responses

Immunotherapy, mainly through the form of checkpoint inhibitors, has over the last few years been added to the armamentarium of various cancer therapeutic approaches, with serial approvals for the treatment of a wide spectrum of solid and hematologic malignancies. Unfortunately, the only single predictive biomarker we currently have at our disposal is PD-L1, which is far from being the most efficient in the field. Indeed, patients without PD-L1 expression can still respond, while others who express the biomarker do not derive benefit. In GC, contrary to melanoma or lung cancer, PD-L1 is expressed mostly in myeloid-derived immune cells and not in tumor cells[61]. The presence of MSI, as manifested through IHC or polymerase chain reaction (PCR), is considered predictive for response to immunotherapy, while other approaches, such as IFN-γ signature and immunoscore, have not yet been incorporated to clinical practice.

There is adequate evidence supporting the implementation of immunotherapy in GC management, both

preclinical and clinical. Firstly, there seems to be an association between PD-L1 and disease burden and, consequently, to limited survival[66]. In addition, according to the data from TCGA, as previously mentioned, elevated PD-L1 expression has been noted in the EBV(+) GC subtype, which correlates with the significant amount of the neoantigens produced as an effect of viral infection, as well as of amplification of 9p24[3]. Furthermore, it is well established that MSI-high tumors also mount a robust immune response, which predicts for clinical outcome and benefit of immune checkpoint blockade[67-69]. Clinical trials thus far have focused on checkpoint inhibitors, especially anti-PD-1/anti-PD-L1 and anti-CTLA4 antibodies, with the best results having been produced by the former.

The first trial to test an anti-PD1 inhibitor in advanced disease was the Keynote-12, where the safety and activity of Pembrolizumab in this setting was assessed. Only patients with PD-L1 positive tumors were enrolled. PD-L1 positivity was deemed as membrane staining in ⩾ 1% of cells, or alternatively as the presence of a distinctive PD-L1 positive pattern at the interface between neoplastic cells and their adjacent stroma. In this trial, no association between PD-L1 levels and response was observed. The results were similar to other trials of anti-PD-1 in various solid malignancies, with a response rate of 22% (95%CI: 10-39) and manageable toxicity profile, prompting the initiation of two large phase Ⅲ trials[70]. The Keynote-061 is evaluating Pembrolizumab *vs* Paclitaxel in the second line[71]. In the first-line setting, Keynote-062 has three arms comparing pembrolizumab as monotherapy and platinum/5-FU combination with or without pembrolizumab[72]. Finally, following the most recent trend of combining immunotherapy with targeted therapies or chemotherapy, two multicenter phase IB/Ⅱ studies are ongoing, determining activity and safety of Pembrolizumab in combination with anti-HER2 agents in patients with HER2 positive GC (NCT02901301 and NCT02689284)[73,74]. Their results are eagerly awaited.

Continuing with PD-1/PD-L1 inhibition, Nivolumab, another anti-PD-1 agent, was the first to gain approval in the third line setting, following the positive results of the pivotal phase Ⅲ trial ONO-4538/BMS-936558 (ATTRACTION 2). This trial, which employed an all-Asian study population, showed a statistically significant, albeit numerically small, survival benefit for Nivolumab over placebo in heavily pretreated patients with advanced/metastatic GC or GEJC. Median OS was 5.3 mo *vs* 4.1 mo (HR = 0.63, $P < 0.0001$,) and mPFS was 1.61 mo *vs* 1.45 mo (HR = 0.60, $P < 0.0001$) in the Nivolumab ($n = 330$) and placebo arms ($n = 163$), respectively[75]. This resulted in the Food and Drug Administration (FDA) approval of Nivolumab for GC or GEJC, in third line or beyond, irrespective of PD-L1 expression.

Finally, in the field of PD-1/PD-L1 axis inhibition, another promising agent is the anti-PD-L1 Avelumab, which has provided promising clinical activity in unselected patients, treated as first-line maintenance or second-line after progression, in the phase Ib trial JAVELIN. In this trial, patients were randomized after treatment with a first-line chemotherapy-based regimen by progression status: patients achieving disease control received Avelumab as switch maintenance, while those with progressive disease received the drug as second line. An acceptable safety profile, which was the primary endpoint of the trial, was demonstrated. Overall response rate was 9.0% and 9.7% in the two subgroups, respectively[76]. Following these positive results, two randomized phase Ⅲ trials were developed: JAVELIN Gastric 100, testing Avelumab as switch maintenance in the first line setting, and JAVELIN Gastric 300, in the third line[77,78]. Unfortunately, it was recently announced that JAVELIN Gastric 300, comparing single-agent Avelumab with physician's choice of chemotherapy, did not meet its primary endpoint of superior overall survival. The other phase Ⅲ trial is still ongoing.

Less encouraging has been the use of anti-CTLA4 inhibitors. Firstly, regarding Ipilimumab, the Phase Ⅱ trial (NCT01585987) that compared the drug to placebo in the second line was stopped prematurely when it became evident that the final analysis would procure no PFS benefit[79]. Also, no responses were reported with Tremelimumab, another anti-CTLA-4 inhibitor in the same setting[80]. It should also be noted that higher toxicity was observed in these trials, as compared to anti-PD-1/PD-L1 blockade. These differences might be attributed to the different targeting of these two classes of checkpoint inhibitors. While those targeting the PD-1 axis have an immediate effect in the tumor microenvironment, the anti-CTLA-4 modulates the immune response mainly in the lymph nodes.

In an attempt to enhance the activity of anti-CTLA-4 agents, combination treatment with anti-PD-1 was tested. The CheckMate-32 was a phase Ⅰ/Ⅱ trial with three arms: 160 pretreated patients were randomized to receive either Nivolumab monotherapy in the dose of 3 mg/kg, or Nivolumab plus Ipilimumab in the doses of 3-1 mg/kg in the second arm or 1-3 mg/kg in the third arm of the study. In all three arms, notable responses were observed, with an overall disease-control rate of 38%. The responses differed between PD-L1-positive (⩾ 1%) and PD-L1-negative (< 1%) tumors, reaching 27% and 12%, respectively. The highest overall response rate (26%) and overall survival (6.9 mo) were observed in arm 3 (Nivolumab 1 mg/kg and Ipilimumab 3 mg/kg), which prompted the launch of a phase Ⅲ trial[81]. The ongoing CheckMate-649 investigates Nivolumab plus Ipilimumab *vs* FOLFOX/XELOX in the first line, and a subgroup analysis regarding PD-L1 expression has already been planned[82].

Conclusively, immunotherapy could have a role in GC management, although, as in the management of other cancers, better predictive biomarkers are required. Moreover, it remains to be seen whether there is rationale for combining immunotherapy with targeted therapies and/or chemotherapy.

CONCLUSION

Even though most clinical trials investigating targeted agents have not produced the desired results so far, their failures might be attributed mostly to erroneous study planning and unscrupulous patient selection. The value of recognizing distinct molecular cancerous pathways goes far beyond mere classification purposes, and shall be better appreciated when these results could be applied in everyday practice with the purpose of providing clinically meaningful outcomes for our patients. Unfortunately, it is still unclear whether the clinical benefits of implementing next-generation sequencing and targeted therapies in the clinic will outweigh the economic burden of such a practice. Perhaps a way to tackle this issue is to create a panel of the main molecular and immune signatures of implemented pathways in order to categorize appropriately the patients in distinct prognostic and predictive subgroups. The results of the TCGA and ACRG classifications, among others, may provide the basis of such a molecular/immune signature panel that remains to be validated prospectively in large clinical trials providing the basis for rational stratification and design.

Health economics concerns aside, if our goal is to optimize outcomes for our GC patients, we probably need to implement these new molecular signatures in our daily practice. Due to the complexity of the disease, the constant evolution of tumors, and our still limited understanding of its biology, our mission to provide the best therapy to our patients is extremely difficult and challenging. However, through targeting tumorigenic drivers and awakening the immune system through immune-oriented strategies, it might be possible that we will at least be able to achieve the goal of life prolongation, while, at the same time, effectively alleviate cancer-related symptoms. A potential, hopefully not overly idealized, glimpse to the future of managing this disease, entails its multidisciplinary management by a variety of experts from diverse scientific backgrounds, towards an individualized approach for each unique patient.

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