New agents on the horizon in gastric cancer

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Background: Conventional cytotoxic chemotherapy has been the backbone of advanced gastric cancer treatment for decades and still represents a key element of the therapeutic armamentarium. However, only small increments in survival outcomes have been reached. A better understanding of genetic alterations and molecular signatures of gastric cancer has been reached in the last years. It will serve as a roadmap for better treatment stratification and future drug development.

Materials and methods: We reviewed preclinical and clinical studies that assessed novel treatment targets and emerging drug therapies in gastric cancer. We performed research via PubMed, and the congress webpages of the American Society of Clinical Oncology, European Society of Medical Oncology and the Japanese Society of Medical Oncology.

Results: HER2-targeting with trastuzumab is effective in HER2-positive metastatic gastric cancer; combined HER2 targeting strategies are being investigated. Studies assessing the role of HER2 targeting in the perioperative setting are ongoing. Novel treatment targets include inhibition of cancer stemness-related signaling pathways like STAT3. DNA damage repair and Claudin 18.2, a tight junction protein with high expression in gastric cancers are also novel molecular drug targets. Modification of the tumor microenvironment, including activation of immune response by PD-1/PD-L1 checkpoint inhibitors and stroma modification by matrix metalloproteinase-9 inhibition, led to first promising treatment results.

Conclusion: Novel treatment options for gastric cancer patients are emerging. They involve novel mechanisms of action, and are based on our constantly increasing understanding of tumor biology and better molecular stratification of gastric cancer patients.

Key words: gastric cancer, HER2, immunotherapy, stem cell inhibition, Claudin 18.2, STAT3

Introduction

Gastric Cancer (GC) is one of the most common cancers worldwide. The incidence of GC in Central Europe and North America ranges ~10 newly diagnosed patients/100 000 inhabitants/year. Higher incidence rates are found in East Asia, East Europe and parts of South America [1]. GC has a poor prognosis. In Europe and USA, only 10–25% of GC patients achieve long-term survival [2]. Stage for stage GC patients have better outcomes in East Asia due to earlier diagnosis and likely related to differences in the tumor biology and host immunity [3].

Chemotherapy is the mainstay of treatment of GC. For locally advanced GC perioperative chemotherapy in the West and adjuvant chemotherapy in the East are standard. In stage IV chemotherapy prolongs survival and controls cancer-related symptoms [4]. Oxaliplatin or cisplatin plus a fluoropyrimidine (5-fluorouracil, capecitabine or S-1) are standard in a first-line setting. The addition of a third drug increases response rates and survival outcomes, but leads to significant increases in toxicity [5]. Patients for triplet chemotherapy should therefore be selected carefully. Responses to chemotherapy are often of short duration and median overall survival (OS) in advanced GC is no longer than 8–11 months median in the West and 13–17 months in East Asia/Japan. GC has numerous somatic genetic alterations, some of them contributing to CTx resistance [6].

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The molecular characterization of GC is rapidly evolving. A recent study identified 22 recurrent genomic alterations in GC, comprising both known GC targets (FGFR2, ERBB2) and genes not previously reported to be amplified in GC (KLF5, GATA6). Genes related to RTK/RAS signaling, in particular FGFR2, KRAS, ERBB2, EGFR and MET can be amplified in GC. These amplifications are frequently but not universally mutually exclusive [7, 8]. The Cancer Genome Atlas (TCGA) network has refined the disease into four distinct subclasses based on mutations, gene copy-number changes, gene expression, and DNA methylation [9]. (i) Tumors positive for Epstein–Barr-Virus (EBV), (ii) microsatellite instability-high (MSI) tumors, (iii) genomically stable (GS) tumors, and (iv) tumors with chromosomal instability (CIN) (Table 1). TCGA reported a different distribution of the four subtypes among the different locations of the stomach with an enrichment of the CIN subtype at the gastro-esophageal junction (GEJ). Among the different locations of the stomach with an enrichment of the CIN subtype at the gastro-esophageal junction (GEJ). Another study investigated >1600 GCs and found that immunity signatures differ significantly between GC in Asian and non-Asian patients. GC in non-Asians is associated with enrichment of tumor-infiltrating T cells, as well as T-cell gene-expression signatures [3].

The design of future GC trials, particularly in molecularly targeted and immune therapy, should consider genetic and immune differences, as they may impact treatment response and clinical outcomes.

### Table 1. The new molecularly-based classification of GC according to The Cancer Genome Atlas (TCGA) 2014 [1]

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Epstein–Barr virus–infected tumors (EBV)</th>
<th>Microsatellite instability tumors (MSI)</th>
<th>Genomically stable tumors (GS)</th>
<th>Tumors with chromosomal instability (CIN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical molecular features</td>
<td>EBV positive</td>
<td>DNA hyper-methylation</td>
<td>Tumors lacking aneuploidy and elevated rates of mutation or hyper-methylation</td>
<td>Marked aneuploidy</td>
</tr>
<tr>
<td></td>
<td>Profound hyper-methylation</td>
<td>Silencing of MLH1</td>
<td>(PIK3CA 42%, and ERBB3 26%)</td>
<td>TP53 mutations</td>
</tr>
<tr>
<td></td>
<td>CDKN2A silencing</td>
<td>Elevated somatic mutations</td>
<td>Somatic RHOA and CDH1 mutations</td>
<td>Recurrent amplifications of receptor tyrosine kinases (HER2 24%)</td>
</tr>
<tr>
<td></td>
<td>80% PIK3CA mutation</td>
<td></td>
<td>CLDN18-AKGAP6 or ARIKGAP26 fusions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PD-L1/2 overexpression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association with anatomy or traditional subtypes</td>
<td>Fundus and body</td>
<td>Fundus, body, and antrum</td>
<td>Mostly diffuse subtype</td>
<td>Majority of tumors at the esophago-gastric junction</td>
</tr>
</tbody>
</table>

The molecular characterization of GC is rapidly evolving. A recent study identified 22 recurrent genomic alterations in GC, comprising both known GC targets (FGFR2, ERBB2) and genes not previously reported to be amplified in GC (KLF5, GATA6). Genes related to RTK/RAS signaling, in particular FGFR2, KRAS, ERBB2, EGFR and MET can be amplified in GC. These amplifications are frequently but not universally mutually exclusive [7, 8]. The Cancer Genome Atlas (TCGA) network has refined the disease into four distinct subclasses based on mutations, gene copy-number changes, gene expression, and DNA methylation [9]. (i) Tumors positive for Epstein–Barr-Virus (EBV), (ii) microsatellite instability-high (MSI-H) tumors, (iii) genomically stable (GS) tumors, and (iv) tumors with chromosomal instability (CIN) (Table 1). TCGA reported a different distribution of the four subtypes among the different locations of the stomach with an enrichment of the CIN subtype at the gastro-esophageal junction (GEJ). The Asian Cancer Research Group (ACRG) taxonomy complements the TCGA classification by incorporating two key molecular mechanisms related to TP53 activity and mesenchymal-like features, linking subtypes to clinical outcomes [10]. Another study investigated >1600 GCs and found that immunity signatures differ significantly between GC in Asian and non-Asian patients. GC in non-Asians is associated with enrichment of tumor-infiltrating T cells, as well as T-cell gene-expression signatures [3].

The design of future GC trials, particularly in molecularly targeted and immune therapy, should consider genetic and immune differences, as they may impact treatment response and clinical outcomes.

### Receptor tyrosine kinase inhibitors

Up to 60% of GCs belong to the CIN subtype and depend on receptor tyrosine kinase (RTK) signaling for growth and development [9–12]. Human epidermal growth factor receptor-2 (HER2) is a therapeutically relevant RTK in 10–20% of the overall GC population and up to 30% of GEJ adenocarcinomas harboring HER2 gene amplification or protein overexpression. In the Trastuzumab for Gastric Cancer (ToGA) trial patients treated with trastuzumab (a HER2-directed monoclonal antibody) and CTx had a significant improvement in OS (13.8 versus 11.1 months, hazard ratio [HR] 0.74, P = 0.0046), progression-free survival (PFS) (6.7 versus 5.5 months, HR 0.71, P = 0.0002), and overall response rate (ORR) (47% versus 35%, P = 0.0017.) The OS benefit was the highest in the subset of tumors defined as HER2 immunohistochemistry (IHC) 3+ or IHC2+/fluorescence in situ hybridization (FISH)+ with unprecedented OS of 16 in the trastuzumab group versus 11.8 months with CTx alone (HR 0.68, 95% CI 0.5–0.83) [13]. The phase-3 JACOB study of trastuzumab/chemotherapy±pertuzumab (which binds to HER2 at a different subdomain than trastuzumab and inhibits the dimerization of HER2 with other RTK) in first-line HER2-positive advanced GC (NCT01774786) recently completed patient accrual (Table 2).

Although trastuzumab is the standard of care for HER2-positive advanced GC the other HER2 directed therapies thus far have been unsuccessful. Phase-3 studies exploring lapatinib (EGFR/HER2 reversible tyrosine kinase inhibitor [TKI]) or trastuzumab-emtansine (T-DM1, an antibody-drug conjugate consisting of trastuzumab linked to the cytotoxic agent DM1) failed in the second line setting and no standard HER2 directed options are currently available beyond trastuzumab [14–16]. The phase-2/3 GATSBY study examined T-DM1 in second-line advanced GC and failed to show a primary endpoint efficacy benefit of T-DM1 over paclitaxel or docetaxel (median OS 7.9 versus 8.6 months; HR 1.13 P = 0.31) [16]. Failure of T-DM1 does not eliminate HER2 as a target in second line GC. For achieving therapeutic success, assessment of the true HER-2 status in this setting may have required HER2 staining in newly obtained tissue biopsies. Also, other HER2-antibody drug conjugates such as DS-8201a are in early clinical development [17, 18].

Phase-3 studies testing lapatinib in combination with paclitaxel (TyTan) in the second-line setting and of lapatinib with capetitabine/oxaliplatin in treatment-naïve patients with advanced HER2 amplified GC (LOGiC) were both negative [14, 19]. Although lapatinib prolonged median OS by almost 2 months in both studies, this improvement did not reach statistical significance and lapatinib therefore is not indicated in treatment of HER2-positive GC. In LOGiC, first-line lapatinib demonstrated OS 12.2 versus 10.5 months, HR 0.91; P = 0.3492), the ORR was significantly higher in the lapatinib arm (53% versus 39%; P = 0.0031) and a preplanned exploratory analysis demonstrated robust OS benefit in Asians (16.5 versus 10.9 months,
paclitaxel was 11.0 versus 8.9 months (TyTAN trial, OS with the addition of lapatinib to second-line 

tation levels correlated with PFS in the lapatinib arm [20]. In the 

9.0 months, HR 0.69; 

P

HR: 0.68; 

P

¼0.0261) and younger patients OS (12.9 versus 

9.0 months, HR 0.69; P = 0.0141). In addition, HER2 amplification 

levels correlated with PFS in the lapatinib arm [20]. In the 

TyTAN trial, OS with the addition of lapatinib to second-line 

paclitaxel was 11.0 versus 8.9 months (P = 0.1044) and patients 

with IHC score 3+ tumor HER2-expression appeared to benefit 

from lapatinib with improved OS (HR 0.59; P = 0.0176) [14], 

supporting the rationale to further explore dual EGFR/HER2 

inhibitors in this disease.

Much remains to be learned about HER2 and other RTKs as 

drivers in GC. As our understanding of the genomic subtypes 

of GC deepens, it is becoming clear that co-occurring genomic 

aberrations impact the efficacy of HER2 targeted agents. 

Trastuzumab refractory GCs up-regulate RTK signaling through 

cytokine signaling [21]. Although the majority of 

HER2-positive tumors continue to depend on HER2 for signal-

ing, up-regulation of alternative signaling and the complex biol-

ogy of gastric cancer challenge the paradigm of the ‘one target, 

one drug’ therapeutic approach. In addition, the known hetero-

geneity of HER2 expression in GC may impact on the efficacy 

of anti-HER2-directed therapy.

Unfortunately, the attempt to target other RTKs like EGFR, 

MET or FGFR by monoclonal antibodies or TKIs, did not improve 

OS in GC thus far [22–26]. Appropriate patient selection and mo-

lecular stratification have not been done in many trials. However,

retrospective analyses of these studies and small studies of TKIs for 

gene amplified GC suggest a potential benefit from RTK-directed 

therapies in molecularly defined subgroups [27–31].

### Immunotherapy

The subtype of EBV-positive GCs according to TCGA [9] is char-

acterized by recurrent PIK3CA and ARID1A mutations, high 

amplification of 9p chromosomes with increased expression of 

programmed cell death-ligand-1 and -2 (PD-L1/L2), and extreme 

DNA hypermethylation; in contrast, the MSI-H subtype shows 

frequent mutations in multiple genes including frameshifts or 

missense mutations, which contribute to increased expression of 

neoantigens. From the immunological viewpoint, Asian GCs 

showed significantly lower expression of T-cell markers (CD3, 

CD45RO, CD8), and higher expression of the immunosuppres-

sive transcription factor FOXP3 was reported in Japanese GCs 

[3]. On the other hand, PD-L1 expression was reported in both 

Western and Asian patient cohorts [32, 33]. Both studies showed 

PD-L1 expression was more frequently observed in immune cells 

rather than tumor cells. The influence of these immunological 

factors on the efficacy of immune checkpoint inhibitors warrants 

further evaluation in clinical studies.

PD-L1 is a negative co-stimulatory receptor expressed primarily 

on the surface of activated T cells. The binding of PD-L1 to its
Pembrolizumab is a humanized IgG4 monoclonal PD-1 antibody. In a phase 1b clinical study (KEYNOTE-012), 39 patients (19 Asians and 20 non-Asians) with PD-L1-positive advanced GC received pembrolizumab [35]. IHC of PD-L1 (22C3 antibody) was applied as screening test, and those with 1% or more staining in cancer cells or any staining of stromal cells were considered as PD-L1 positive (65 of 162 patients [40%] in total). The ORR by central assessment was 22.2%. A reduction in the size of the target lesions was observed in 53% of patients. Although the median PFS was only 1.9 months, the 6-month survival rate was 69% with an interesting median OS of 11.4 months despite the fact that 67% of the patients had received two or more of lines of prior therapy. No significant difference in clinical outcomes was observed between Asians and non-Asians in terms of response, PFS and OS [35]. Treatment-related adverse events were quite similar to those of previous immunotherapy studies for other solid tumors. Clinical trials of pembrolizumab are currently underway in each line of therapy, including a large phase 2 trial (KEYNOTE-059; NCT02335411), a phase 3 trial (KEYNOTE-060; NCT02370498) comparing pembrolizumab with paclitaxel in second-line, and a phase-3 trial (KEYNOTE-062; NCT02494583) comparing single agent pembrolizumab or a combination therapy of fluoropyrimidine + cisplatin + pembrolizumab or placebo in first-line for patients with PD-L1+/HER2− advanced GC (Table 2).

Nivolumab is a humanized IgG4 recombinant anti-PD-1 monoclonal antibody. In a phase 1/2 trial (CheckMate-032), 59 patients were treated with nivolumab monotherapy, and 83% of the patients had received two or more prior regimens [36]. The ORR was 14%, median PFS was 1.4 months, and median OS was 5.0 months. The 6- and 12-month OS rates were 49% and 36%, respectively. In contrast to pembrolizumab trials, nivolumab GC trials enrolled patients with PD-L1 positive and negative tumors with responses seen in both cohorts. Nivolumab single agent activity in GC in patients with PD-L1 positive tumors is similar to pembrolizumab, with higher response rates with dual anti-PD-1 and anti-CTLA-4 therapy. In the GC cohort of CheckMate-032 [37] ORR was the highest with nivolumab 1 mg/kg with ipilimumab 3 mg/kg (26%, 12 of 46 patients), relative to the nivolumab 3 mg/kg (14%, 8 of 59 patients) or nivolumab 3 mg/kg with ipilimumab 1 mg/kg (10%, 5 of 49 patients) cohorts. In the nivolumab monotherapy cohort, response rates were higher in PD-L1-positive tumors (27%), but patients with PD-L1 negative tumors also benefited from study therapy with 12% ORR. The cohort on combination of nivolumab 1 mg/kg with ipilimumab 3 mg/kg had the highest ORR—44% of patients with PD-L1 positive and 21% patients with PD-L1 negative tumors. Nivolumab 1 mg/kg with ipilimumab 3 mg/kg resulted in an encouraging median OS of 6.9 months and a 12-month OS rate of 34% in chemotherapy-refractory patients with PD-L1-positive and PD-L1-negative tumors. Treatment related adverse events in the nivolumab monotherapy and in combination with ipilimumab were consistent with those previously reported. A phase 3 trial of nivolumab 1 mg/kg with ipilimumab 3 mg/kg in patients with metastatic gastric cancer (Checkmate649; NCT02872116) is underway (Table 2).

A phase-3 study of nivolumab in advanced GC patients refractory to two or more lines of treatments (ONO-4538-12) has finished its recruitment and has met its primary endpoint, which is OS. As of the data cut-off on 13 August 2016, 5.6 months after last patient randomized, median OS was 5.32 months with nivolumab versus 4.14 months with placebo (HR 0.63; 95% CI 0.50–0.78; P < 0.0001), and OS rates at 6 and 12 months were 46.4% versus 34.7% and 26.6% versus 10.9%, respectively. The ORR was 11.2% (95% CI, 7.7–15.6) with nivolumab versus 0% (95% CI, 0.0–2.8) with placebo (P < 0.0001). Median PFS was 1.61 months with nivolumab versus 1.45 months with placebo (HR, 0.60; 95% CI, 0.49–0.75; P < 0.0001) [38].

Further, in a phase-1 trial with an expansion cohort of Japanese patients with gastric cancer not preselected for PD-L1 expression, the anti-PD-L1 antibody avelumab demonstrated an ORR of 15% with a median PFS of 11.9 weeks in 3rd-line or later line [39]. Phase 1b in Korea and Western countries also showed response rate of 9.0% in 1st-line maintenance and 9.7% in a 2nd-line cohort [40]. Currently, two phase 3 studies in maintenance therapy after 1st-line (JAVELIN Gastric 100; NCT02625610) and third line (JAVELIN Gastric 300; NCT02625623) are ongoing (Table 2).

Although there have been no established biomarkers of immune checkpoint inhibitors to date, an association has been suggested, in several different types of cancers, between therapeutic effects and PD-L1 expression, types of tumor infiltrating lymphocytes, the number of somatic mutations (mainly passenger mutations), and immune-related gene expression (RNA signature). At the time being, the impact of PD-L1 expression or RNA signatures as biomarkers in advanced GC is not clear [35], and should be further analysed in a cohort of larger sample size from ongoing phase 3 trials. MSI-H tumors harbor hundreds to thousands of mutations that may produce neoantigens that can be recognized by T cells. Actually, MSI-H noncolorectal cancers including advanced GC seem to be very sensitive to immune checkpoint inhibitors with objective response rate of ~50% [41].

Response rates of immune checkpoint inhibitor monotherapy are still not impressively high, ~10–30%. Therefore, it is important to develop combined treatment approaches to improve outcomes. These strategies include combination of PD-1 or PD-L1 inhibitors with chemotherapy, molecular targeted agents, radiotherapy or injection of oncolytic viruses to enhance the local immunity. Combination with other immune checkpoint inhibitors directed against CTLA-4, LAG-3, or Tim-3 is also being assessed. Regarding the combination of anti-angiogenesis and immune checkpoint inhibitors, a phase 1 study of ramucirumab and pembrolizumab is ongoing [42]. Prolonged exposure to VEGF-A was reported to induce the expression of inhibitory molecules and to exhaust CD8-positive T cells in a mouse model, indicating the possibility of the combined use of immune checkpoint inhibitors with VEGF inhibitors [43].
(REGARD and RAINBOW) assessing the anti-VEGFR2-directed fully human monoclonal IgG1 antibody ramucirumab improved OS in the second-line setting. Ramucirumab targets VEGFR2, inhibits VEGF-A, -C, -D binding and endothelial cell proliferation. Patients treated with ramucirumab monotherapy in REGARD had better OS compared with patients treated with placebo, and, additionally, ramucirumab plus paclitaxel in RAINBOW was more effective than paclitaxel alone. This was also associated with longer maintaining patient quality of life and with delayed symptom worsening and functional status deterioration [46–48]. It is unclear whether the inconsistent study results indicate that ramucirumab compared with bevacizumab is the more powerful antibody for treating advanced GC. Ramucirumab has potential advantages over bevacizumab as it is selective for VEGFR2, whereas bevacizumab by targeting VEGF-A affects VEGF-R1, -R2, and the noncatalytic coreceptors neuropilin-1 and -2. Ramucirumab thus leaves the VEGF-R1 receptor unmodified, which behaves like a decoy receptor, providing additional potency to the VEGF-R2 inhibitory effect. An additional benefit may result from VEGF-R2 expression on macrophages, which get suppressed by ramucirumab [49]. An alternative, although hypothetical explanation is that following progression on first-line platinum-containing chemotherapy GC biology changes and allows for better treatment efficacy of anti-angiogenic agents in second-line. Considering this it is interesting to note that a randomized first-line phase-2 study involving 168 randomized patients failed to show any benefit when ramucirumab was combined with FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin). This study did not meet the primary end point of PFS (6.4 versus 6.7 months, HR 0.98) or the secondary end point of OS (11.7 versus 11.5 months). ORRs (45.2% versus 46.4%) were also similar between arms [50]. One can also speculate if platinum-fluoropyrimidine CTx is not an optimal combination partner for anti-angiogenic therapy in GC. The RAINFALL phase-3 study (NCT02314117) will eventually show if patients with metastatic GC who receive cisplatin/fluoropyrimidine first-line chemotherapy benefit from the addition of ramucirumab (Table 2).

Anti-angiogenic treatment with bevacizumab has yielded disappointing results not only in first-line metastatic GC, but also in the curative setting, where the addition of bevacizumab to perioperative epirubicine, cisplatin and capecitabine did not improve survival outcomes compared to chemotherapy alone [51].

Unfortunately, a biomarker-based selection of patients for anti-angiogenic treatment is still lacking. A recently published retrospective exploratory analysis from the REGARD study showed that none of the tested biomarkers (tumor HER2 or VEGFR2 and serum VEGF-C and -D, and soluble VEGFR1 and 3) identified a strong predictive biomarker of ramucirumab efficacy [52]. In contrast, a recently published biomarker analysis from the AVAGAST study revealed that baseline plasma Ang-2 is a prognostic marker for OS in advanced GC and strongly associated with liver metastases. Differences in Ang-2 mediated vascular response and may, in part, account for outcome differences between Asian and non-Asian patients [53]. Predictive biomarkers are urgently needed to identify patients who have a clinically significant benefit. For the selection of second-line treatment in patients with HER2-positive GC, it is important to note that the benefit associated with ramucirumab did not appear to differ by tumoral HER2 expression [52].

As tumor biology and outcomes between Asian and non-Asian patients differ [3, 44], the safety and efficacy of ramucirumab plus paclitaxel was evaluated in Japanese and Western subgroups from the RAINBOW trial [54]. In conclusion, safety profiles of the ramucirumab plus paclitaxel arm were similar between populations, though there was a higher incidence of neutropenia in Japanese patients. PFS and ORR improvements were observed for ramucirumab plus paclitaxel in both populations while significant OS improvements were limited to the Western population [54].

Apatinib, a novel VEGFR2 tyrosine kinase inhibitor, was investigated in China and improved OS with an acceptable safety profile in patients with advanced GC refractory to two or more lines of prior CTx [55]. Treatment with apatinib was estimated to provide an incremental 0.09 quality-adjusted life years (QALYs) at an incremental cost of $8114 compared with placebo, which resulted in an incremental cost-effectiveness ratio of $90 154 per QALY. Therefore, apatinib has been considered not a cost-effective option for patients with advanced GC who experienced failure of at least two lines chemotherapy in China [56]. Studies conducted in and outside of China are planned to validate the trial results obtained with apatinib (Table 2).

Regorafenib is a multiple TKI directed against VEGFR, TIE2, KIT, RET, RAF-1, BRAF, BRAFV600E, PDGFR, and FGFR. Beyond its anti-tumoral activity it has an anti-angiogenic mode of action [57]. INTEGRATE was an international (Australia and New Zealand, South Korea, and Canada) placebo-controlled phase-2 trial. Patients were randomly assigned at a 2:1 ratio and stratified by lines of prior chemotherapy for advanced disease and region to receive regorafenib 160 mg or matching placebo orally on days 1–21 of each 28-day cycle. Among 147 evaluable patients, regorafenib was effective in prolonging the primary endpoint PFS (regorafenib, 2.6 months and placebo 0.9 months; HR 0.40; P< 0.001). Regional differences were found with a greater effect in in South Korea [58]. Before regorafenib may be considered for patients with advanced GC, these findings should be validated in INTEGRATE II (NCT02773524), a randomized phase-3 double-blind placebo-controlled study of regorafenib in refractory advanced gastro-esophageal cancer (Table 2).

**Stem cell inhibition**

Cancer stem cells (CSCs) are considered to be associated with resistance to conventional therapeutic interventions based on several molecular profiles. STAT3 activation is one of the hallmark associated to cancer ‘stemness’. It acts as a transcription factor located downstream of a variety of pro-oncogenic cytokines and JAK. It is reported that phosphorylated STAT3 activates the transcription of Nanog and Myc, genes [59]. BBI608 (Napabucasin) specifically inhibits cancer stem-like cells that are highly positive for the glycoprotein CD44, and for STAT3, and possess the capability to form spheres [59]. Although a randomized study to compare BBI608 and placebo for refractory colorectal cancers was terminated prematurely due to futility in the general study population, it showed a trend for improved OS and PFS among patients with phosphorylated-STAT3-high colorectal cancer [60]. Also, encouraging anticancer activity of BBI608 and paclitaxel in refractory AGC was observed in a phase-1b and subsequent phase-2 study with an ORR of 31% and disease control rate of 75% [61]. Currently, the
results of the phase III Randomized, Double-Blind, Placebo-Controlled Clinical Trial of BBI608 plus Weekly Paclitaxel vs. Placebo plus Weekly Paclitaxel in Adult Patients with Advanced, Previously Treated Gastric and Gastro-Esophageal Junction Adenocarcinoma (BRIGHTER, NCT02178956) are awaited (Table 2).

Sulfasalazine is an inhibitor of the cystine-glutamate exchange transporter, a variant form of CD44 (CD44v). Sulfasalazine induces a reduction of CD44v-positive cells and intracellular reduced glutathione levels in patients with advanced GC [62]. Currently, combination of SSZ with cisplatin in patients with CD44v-expressing advanced GC is investigated in an early clinical trial (UMIN00001595).

DNA damage repair

The pathogenesis of GC is linked to DNA damage and chronic inflammation from Helicobacter pylori [63, 64] and EBV infections [65], to lifestyle factors including obesity and chronic gastric acid reflux. Large-scale genome sequencing of GC indicate that somatic mutations in genes involved in homologous recombination DNA repair are common features [9–12]. Defining a biomarker that identifies the subset of GCs deficient in DNA repair is critical for the rational design of clinical trials using DNA mismatch repair targeting agents. BRCA mutation-associated GC may potentially benefit from therapies synthetically lethal to a deficiency in homologous recombination. Since BRCA 1/2 mutations are relatively rare, further identification of somatic gene signatures that impart BRCA-like sensitivity in GC to DNA damaging agents is needed. The oral poly(ADP-ribose)-polymerase (PARP) inhibitors trap inactivated PARP onto single-strand DNA breaks, preventing repair and generating a potential DNA replication block, leading to double-strand DNA breaks. Ataxia telangiectasia mutated (ATM) is a gene essential to the cellular double strand DNA breaks response necessary to maintain genome stability levels. Preclinical and clinical data have shown that PARP inhibition is effective, particularly in ATM-deficient cells with co-occurring TP53 mutations [66]. Second-line randomized phase-2 data in metastatic GC looked very promising, demonstrating OS of 13.1 months in patients treated with olaparib and paclitaxel, with remarkable benefit in a ATM-negative cohort which comprised 50% of the study population (median OS, not reached versus 8.2 months, HR 0.35; \( P = 0.002 \)) [67]. Unfortunately, in the follow up phase-3 Gold study the magnitude of OS benefit was not as dramatic in the overall study population (HR 0.79; \( P = 0.0262 \), required \( P < 0.025 \) for significance), partly due to inappropriate patient selection and formally also because of the statistical correction performed for multiple primary endpoints [68]. In GOLD, the study population was not selected based on TP53 mutations and only 18% of patients were ATM negative. Therefore, the study was underpowered to show a statistically significant survival benefit. At present, there is no role for olaparib in standard practice in GC patients and further studies of PARP inhibition in GC should be restricted to ATM-/TP53 mutant tumors.

Matrix metalloproteinase-9

Matrix metalloproteinases (MMPs) have long been heralded as promising targets for cancer therapy on the basis of their massive up-regulation in malignant tissues and their unique ability to degrade all components of the extracellular matrix. MMP-9 is an extracellular enzyme involved in matrix remodeling, angiogenesis, tumor growth, and metastasis [71]. Preclinical studies demonstrate that MMP-9 inhibition alters the tumor microenvironment, which is associated with greater chemotherapy penetration and improved antitumor immunity. GS-5745 is a monoclonal antibody that inhibits MMP-9 and has been combined with various chemotherapy regimens. Results from the expanded cohort of GC evaluating modified FOLFOX with GS-5745 were recently reported [72]. Median PFS in 40 patients was 7.4 months, with a median duration of response of 9.4 months and an ORR of 50%. Of those 40 patients, 30 were chemotherapy naive and demonstrated a median PFS of 12 months, with a median duration of response of 11 months and an ORR of 57%. Collagen decreased with continued treatment, demonstrating on-target effects. GS-5745 is now being examined in a phase-3 study in the first-line treatment of GC with FOLFOX (NCT02545504) (Table 2).

Novel cytotoxic drugs

Nab-paclitaxel (Nab-PTX) is nanoparticle albumin bound PTX which does not contain cremophor or ethanol as a formulation vehicle used for poorly-water soluble drugs. As a result, nab-PTX has a smaller risk of hypersensitivity reactions and high doses can be administered over a short infusion time. ABSOLUTE is a Japanese
phase-3 trial that showed noninferiority of weekly nab-PTX to soluble-based PTX as second-line chemotherapy for advanced GC in terms of OS [73]. In contrast, noninferiority of nab-PTX every 3 weeks to soluble-based PTX in OS was not confirmed with lower QoL scores. DHPI07 is a novel oral lipid formulation of paclitaxel. DREAM is a randomized phase III study for advanced GC after failure of first-line therapy to compare DHPI07 and paclitaxel [74]. Noninferiority regarding PFS was confirmed, although higher gastrointestinal toxicities are reported.

A randomized phase 2 trial of S-1 plus capecitabine (TAS-118) versus S-1 plus capecitabine and oxaliplatin (SOL) versus S-1 plus cisplatin in advanced GC patients showed a higher response rate of SOL with a longer OS [75]. Currently, the phase III SOLAR study comparing TAS-118 plus oxaliplatin with S1 plus cisplatin is ongoing in Asian countries (NCT02322593). TAS-102 is a novel oral nucleoside antitumor agent containing trifluridine and tipiracil hydrochloride, which prevents the degradation of trifluridine. Based on a phase 2 trial of TAS-102 for pretreated advanced GC with a disease control rate of 65.5% [76], the ongoing global phase III trial is investigating the efficacy and safety of TAS-102 in patients with advanced GC refractory to standard treatments (NCT02500043) (Table 2).

Conclusions and future prospects

After years of stagnation in the medical treatment of GC, including numerous negative phase-3 trials investigating molecularly targeted drugs, eventually, some progress is emerging. This development, although still in its adolescence, is linked to our increasing knowledge of genetic alterations and molecular signatures in GC, as elaborated by The Cancer Genome Atlas consortium and other networks. A major limitation, however, is the biological heterogeneity, which is inherent to GC [77].

A major step forward is expected from immunotherapy. Anti-PD-1 and anti-PD-L1 directed agents, alone or in combination with anti-CTLA-4 show promising activity. The first positive trial for nivolumab in GC progressive on standard chemotherapy has just been presented and many trials in all lines of treatment are underway. It remains to be elucidated, which subgroup of GC patients has the greatest benefit.

Appropriate molecular stratification of the population for targeted treatment remains challenging. Screening platforms for detection of specific molecular alterations may be linked with umbrella and basket trials for specific investigational agents.

Progress achieved with anti-angiogenic agents, namely with the VEGFR2-directed antibody ramucirumab in second-line treatment of advanced GC, was rather small. Now, first-line data are awaited and the integration of ramucirumab in multimodal treatment concepts as well as combination with novel targeted agents like immune checkpoint inhibitors remains interesting.

Other emerging therapeutic options comprise targeting of the tight-junction protein Claudin 18.2, STAT-3 dependent gene expression as a cancer stemness related pathway, and tumor stroma modification via inhibition of MMP-9.

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