Review Article

Advanced Gastric Cancer: Current Treatment Landscape and a Future Outlook for Sequential and Personalized Guide: Swiss Expert Statement Article

Alexander R. Siebenhüner[a, b]   Sara De Dosso[c, d]   Daniel Helbling[e]

Christoforos Astaras[f]   Petr Szturz[g]   Peter Moosmann[h]   Stefanie Pederiva[i]

Thomas Winder[e]   Philippe Von Burg[j]   Markus Borner[k]

[a]Clinic for Medical Oncology and Hematology, University Hospital Zurich and University of Zurich, Zurich, Switzerland; [b]Cantonal Hospital Schaffhausen, Schaffhausen, Switzerland; [c]Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland; [d]Università della Svizzera Italiana, Lugano, Switzerland; [e]OnkoZentrum Zurich, Zurich, Switzerland; [f]University Hospital of Geneva (HUG), Geneva, Switzerland; [g]Lausanne University Hospital (CHUV), Lausanne, Switzerland; [h]Cantonal Hospital Aarau, Aarau, Switzerland; [i]Cantonal Hospital Baden, Baden, Switzerland; [j]Buergerspital Solothurn, Solothurn, Switzerland; [k]ONCOCARE AG Oncology Centre in the Klinik Engeried, Bern, Switzerland

Abstract

Background: Gastric cancer is a leading cause of cancer-related deaths worldwide. Several treatment possibilities have been investigated, but only a few show clinically meaningful results. ***Summary:*** Systemic treatment options for advanced gastric cancer (aGC) have evolved over the recent years, implementing the growing molecular knowledge of this heterogeneous disease. Molecular profiling (at least for HER-2-expression, microsatellite instability status, *Epstein-Barr virus* expression, and programmed death ligand-1 expression/combined positive score [CPS]) is recommended for all therapy-fit patients prior to the start of a systemic treatment and is crucial for decisions on treatment strategy and drug selection. Various examples like the application of trastuzumab in the HER-2-positive subgroup underline the benefits of this approach starting from the first-line setting. A combination of platinum and fluoropyrimidine remains the first-line chemotherapy backbone in the treatment of advanced gastric cancer. Triplet combinations adding taxanes to the doublet regimen are reserved for certain scenarios. Unfortunately, almost all patients who receive first-line treatment (with or without anti-HER-2 blockade) progress and <70% are eligible for a second-line therapy. The addition of monoclonal antibodies has substantially improved outcomes in this setting. As such, ramucirumab has led to significant and clinically meaningful advancements in the second-line treatment. Furthermore, immuno-oncology with checkpoint inhibition and immune stimulation has evolved in the field of aGC. Recent first-line data show a significant survival benefit in aGC patients with a CPS ≥ 5 under immunochemotherapy. Nonetheless, the impact of immunotherapy combinations and immunochemotherapy remains an area of investigation. ***Key Message:*** In this review, we highlight recent improvements in the treatment landscape of advanced gastric cancer, the heterogeneity of this disease, and possible personalized targets.

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Introduction

Gastric cancer (GC), including adenocarcinoma of the gastroesophageal junction (GEJ) and stomach, is the fifth most common cancer and the third leading cause

Correspondence to:
Alexander R. Siebenhüner, alexander.siebenhuener @ spitaeler-sh.ch

Table 1. TCGA subtypes

Subtypes	EBV-positive	MSI	GS	CIN
Frequency, %	8.8	21.7	19.7	49.8
Demographic	Male patients (81%)	Old age (median 72 years)	Young age (median 59 years)	No special
Histology			Diffuse histology	Intestinal histology
Main location	Fundus or body (62%)			GEJ/cardia (65%)
Molecular alterations	EBV-CIMP *PD-L1/2*, *JAK2* overexpression Mutation in *PIK3CA*, *ARID1A*, and *BCOR* *CDKN2A* silencing Immune cell signaling Rare *TP53* mutations	Gastric-CIMP Hypermutation in *TP53*, *PIK3CA*, *ERBB3*, and *ARID1A* *MLH1* silencing Mitotic pathways activation Commune changes in the genes of CMHI	*CDH1* and *RHOA* mutation *CLDN18-ARHGAP* fusion Cell adhesion, angiogenesis pathways enriched Rare *TP53* mutations	*TP53* mutation RTK-RAS activation Mutations of *SMAD4* and *APC*
Potential targets	PIK3CA, JAK2, and PD-L1/PD-L2	PIK3CA, ERBB2/3, EGFR, PD-L1, and MLH1 silencing	RHOA and CLDN18	RTKS, EGFR, VEGFA, CCNE1, CCND1, and CDK6
Treatment reaction		No respond to adjuvant chemotherapy		
Predictive	Yes	Yes	No	No
Prognostic	Yes	Yes	Yes	Yes

ARID1A, AT-rich interactive domain-containing protein 1A; BCOR, B-cell lymphoma 6 corepressor; CIN, chromosomal instability; GS, genomically stable; GC, gastric cancer; CIMP, CpG island methylator phenotype; DNMT3b, DNA methyltransferase 3b; EBV, Epstein-Barr virus; EGFR, epithelial growth factor receptor; ERBB2, Erb-B2 receptor tyrosine kinase 2; JAK2, Janus-associated kinase 2; LMP2A, latent membrane protein 2A; LELC, lymphoepithelioma-like carcinoma; MSI, microsatellite instability; PI3K, phosphatidylinositol-3-kinase; RHOA, Ras homolog family member A; TCGA, The Cancer Genome Atlas; PD-L1/2, programmed death ligand-1/2; CDK6, cell division protein kinase 6; GEJ, gastroesophageal junction.

of cancer-related death [1]. The incidence of GC is highest in eastern Europe, Eastern Asia, and South America and is greatly dependent on diet and *Helicobacter pylori* infection [2]. In Western countries, the majority of patients are diagnosed at an advanced stage, which is characterized by inoperable metastatic spread. Although new agents have emerged, long-lasting disease control has not been achieved to this date. Thus, the prognosis of advanced GC remains poor with a 5-year survival rate of <10% [3].

Molecular and histopathological classifications as well as risk factor analyses provide a comprehensive evaluation of gastric adenocarcinoma. On the basis of the Lauren classification, GC is histologically divided into the 2 subtypes: diffuse or intestinal. However, the molecular heterogeneity of GC results in limited utility of traditional morphology-based classification systems, including the World Health Organization (WHO) and Lauren classifications, in guiding clinical treatment [4]. Therefore, patient risk factors must be analyzed in addition to tumor classifications.

The incidence of noncardia GC has decreased due to changes in diet and treatment of chronic *Helicobacter pylori* infections, accounting for nearly 90% of new noncardia GC cases [5]. In contrast, GC of the cardia has become more frequent in the Western Hemisphere. Risk factors for GC include obesity, coinfection by *Epstein-Barr virus* (EBV) or *H. pylori* and gastroesophageal reflux disease [6, 7]. Based on these risk factors and the growing knowledge of the tumor microenvironment, subgroups of patients can be identified, making more precise and personalized treatment approaches possible. This is an important step toward the implementation of targeted molecular drugs and immune checkpoint inhibitors in the management of specific patient subgroups.

Environmental and hereditary factors, including germ line alterations of the cadherin-1 gene, result in the development of hereditary diffuse GC [8]. Patients affected by inherited conditions, such as the Lynch syndrome, familial adenomatous polyps, and Peutz-Jeghers syndrome have a substantially higher risk of developing gastric carcinoma [9]. However, classifications based on molecular features are important for risk evaluation in all advanced gastric cancer (aGC) patients. They facilitate the development of sequential systemic treatment pathways for defined subgroups. In this article, we outline the most important aspects regarding molecular marker testing in aGC and recent recommendations concerning related treatments.

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Current Classification Systems and Progress of Molecular Understanding with Clinically Meaningful Impact

Adenocarcinoma represents the vast majority of GC. Within this group, considerable heterogeneity exists among patients [10]. The traditional morphology-based classification systems include the WHO classification (papillary, tubular, mucinous, signet cell, and poorly cohesive) [11] and the Lauren classification (intestinal, diffuse, and mixed) [12]. A modified WHO classification (differentiated and undifferentiated) has proven helpful in the prediction of the risk of lymph node metastasis in early tumors considered for endoscopic resection, but not in advanced tumors [13]. Given the heterogeneity of GC, molecular analyses were implemented to further improve categorization. This has resulted in several molecular classifications of GC, including intrinsic subtypes, Lei subtypes, the Cancer Genome Atlas (TCGA) subtypes, and Asian Cancer Research Group (ACRG) subtypes, among others [14].

Although the TCGA classification [4] (shown in Table 1) is comprehensive and contains relevant information for clinical use, no classification system comprises all clinically meaningful markers. This would be necessary to optimally guide a personalized approach. Interestingly, the TCGA subtypes differ significantly among Caucasians when compared to the former data, with a lower frequency of microsatellite instability (MSI)-h and EBV-positive aGC [4, 15]. Many markers can be tested, but only a few are of predictive value, allowing for targeted treatment options. The remaining markers result in various subclassifications and are currently mostly used for prognostication. According to TCGA, GC molecular subtypes include chromosomal instability as the most frequent type represents up to 50% of the samples, EBV-positive accounting for 9%, MSI-h making up to 21%, and genomically stable accounting for 20% of the cases.

At the time point of treatment evaluation for aGC, molecular testing of the HER-2 status (expression and amplification) should be performed, initially by immunohistochemistry and then FISH in case of a 2 + score. For the evaluation of immunotherapy, predictive markers, such as MSI-h/mismatch-repair deficiency (MMR-d) using immunohistochemistry (IHC) or polymerase chain reaction (PCR)-based methods and EBV status should be analyzed using in situ hybridization [16]. Regarding EBV status, the definitive role as a biomarker is not yet fully determined. Evidence exists that EBV-positive GC is potentially associated with immunogenicity and may hence exhibit a greater vulnerability to checkpoint-blockade therapy. To this date, clinical trials have used EBV status as a stratification marker, but not as a definitive biomarker. Therefore, EBV status can be considered a biomarker

when evaluating salvage therapy, but not for every aGC patient upfront.

Interestingly, programmed death ligand-1 (PD-L1) status does not only function as a predictive marker for immunotherapy-driven concepts but is also associated with prognosis [17]. However, the prognostic relevance of PD-L1 protein expression in aGC remains controversial and must be interpreted in a differentiated manner [18, 19].

This leads directly to the development and use of immunoscores in order to enable a comprehensive evaluation of the tumor as well as environmental factors in terms of immunogenicity. As such, PD-L1 CPS is defined as the ratio of the number of all PD-L1-expressing cells (tumor cells, lymphocytes, and macrophages) to the number of all tumor cells [20]. CPS functions as a predictive marker for checkpoint inhibition and has been used in large clinically relevant trials in aGC. In summary, to select patients for individualized treatment in the first-line setting, we recommend to determine HER-2 status, CPS, and mismatch-repair status.

Clinical Biomarkers with Therapeutic Relevance

Tyrosine Kinase Inhibition
Anti-HER-2 Drugs and HER-2 Testing
More than 20% of GCs show an overexpression and/or amplification of HER-2. This rate increases to 33% in GEJ tumors. Importantly, HER-2 testing criteria differ significantly from those routinely applied in breast cancer. Concerning the pattern of reactivity in HER-2-overexpressing cells, the completeness of membrane staining and the number of stained cells necessary to consider a case as positive vary between the 2 entities. Additionally, heterogeneity of HER-2 positivity is more frequent in GC than breast cancer, and a less stringent correlation exists between HER-2 amplification and protein overexpression [17]. In the ToGA trial, adding trastuzumab to chemotherapy showed no benefit in patients with HER-2 amplification and no HER-2 expression (about 20% of cases) [21]. For this reason, the European Medicines Agency primarily suggests an evaluation of HER-2 status by immunohistochemistry, followed by fluorescence in situ hybridization in case of a 2 + score [22].

Treatment of HER-2-Positive aGC Patients
The ToGA trial showed a clear benefit of the addition of trastuzumab to the chemotherapy backbone of cisplatin/5-fluorouracil. Therefore, it is the standard of care in this setting today [18]. Adding trastuzumab to the backbone chemotherapy improved overall survival (OS) significantly from 11.1 months to 13.8 months (HR = 0.74) [21]. Attempts to further improve this standard

have failed; although the addition of pembrolizumab to cisplatin/5-fluorouracil/trastuzumab seems promising based on phase II trial results [23] and is currently being investigated in a phase III trial (NCT03615626). According to the T-ACT study, continuation of anti-HER-2-directed therapy beyond progression showed no advantage [24]. Moreover, several anti-HER-2 agents, such as pertuzumab (JACOB trial), T-DM1 (GATSBY trial), MM-111 (a novel molecule inhibiting heregulin-activated HER-3 signaling in HER-2+ tumors), and tyrosine kinase inhibitors, including lapatinib (LOGIC trial) failed to demonstrate survival benefits in randomized trials in the advanced setting [25–27]. The disappearance of HER-2 positivity after trastuzumab therapy is common [28] and represents the most likely cause of treatment failure in these negative trials. Treatment selection leads to the loss of HER-2 expression and hence promotes the emergence of HER-2 resistance mechanisms [29]. If affected patients progress further, therapy lines follow the recommendations for HER-2-negative aGC. For example, the combination of paclitaxel and ramucirumab represents a second-line option.

In the refractory setting (after 2 or more treatment lines), the randomized phase II DESTINY trial offers a new treatment option for patients who remain clearly HER-2-positive. In this trial, trastuzumab deruxtecan (an antibody-drug-conjugate consisting of an anti-HER-2 antibody and a topoisomerase-I inhibitor) showed a prolongation of the median OS from 8.4 months to 12.5 months (HR = 0.59, $p = 0.01$) when compared to the physician's choice of therapy [30]. FDA approval for this novel treatment option was granted in January 2021. Limiting factors included that the study was exclusively conducted in Japan and Korea.

Further interesting data concerning HER-2-positive GC were presented during ASCO 2020. The phase I/II PANTHERA trial investigated the combination of trastuzumab, pembrolizumab, cisplatin, and capecitabine and met its primary end point, objective response rate (ORR) benefit. With an ORR of 76.7%, progression-free survival (PFS) of 8.4 months (95% CI 7.2–22) as well as OS of 18.4 months (95% CI 17.9-NA), regardless of PD-L1 status, promising observations could be made. This led directly to the phase III trial KN-811 (NCT03615326), which aims to validate the combination in a larger population [31].

Anti-EGFR and Anti-FGFR without Therapeutic Consequences

Anti-epithelial growth factor receptor (E1GFR) treatment with cetuximab (EXPAND trial) [32] or panitumumab (REAL trial) [33] showed no additional benefit to chemotherapy alone in the first-line treatment of aGC. However, these trials were not biomarker selected for EGFR overexpression. A former retrospective analysis indicated that EGFR overexpression might be of predictive value for the susceptibility to anti-EGFR drugs [34]. However, EGFR amplification more likely correlates with the activity of EGFR inhibitors than EGFR overexpression.

Compared with the promising results of fibroblast growth factor receptor-2 (FGFR-2) inhibition in intrahepatic cholangiocellular carcinoma, this target is more complex in GC as FGFR-2 amplification is very heterogeneous within this entity, even in the same patient. This was shown in the SHINE trial using the FGFR-2 inhibitor AZD4547 [35]. Further studies concerning FGFR inhibitors are currently recruiting. During ASCO GI 2021, bemarituzumab, a first-in-class, humanized IgG1 monoclonal antibody that selectively binds to FGFR-2b, showed promising results with a median PFS of 9.4 months compared to 7.4 months in the placebo group. However, the secondary end point was not reached in the phase II FIGHT study [36]. In conclusion, targeting FGFR or members of the EGFR family apart from HER-2 is not of clinical relevance compared to other first-line options in HER-2-negative aGC.

Rare Targets

To date, no favorable results of MET receptor targeting in aGC have been obtained and neither MET positivity as determined by IHC nor MET gene amplification are of prognostic or predictive value [37, 38]. BRCA mutations are rare in GC. However, they have clinically relevant implications. These tumor types with a greater amount of DNA damage are sensitive to platinum-based chemotherapy and to poly-ADP-ribose polymerase (PARP) inhibition. Clinical trials investigating PARP maintenance strategies after platinum-based therapy in aGC (NCT03427814) and the use of PARP inhibition in combination with immune checkpoint blockade (NCT02734004) are currently ongoing. The rationale for the combination of PARP inhibition and immune checkpoint blockade is the stimulation of tumor antigen presentation by PARP inhibitors, potentially amplifying the effect of immunotherapy. More DNA damage increases the exposure of tumor antigens, which are targeted by immune-modulating drugs. Furthermore, the combination of PARP inhibitors and anti-VEGF antibodies seems promising and is undergoing investigation (NCT03008278).

Early Insights into Possible New Targets

Anti-Claudin 18.2
Targeting the tight junction protein claudin seems auspicious. The randomized phase II FAST trial was significantly positive regarding PFS and OS for the combi-

nation of epirubicin, oxaliplatin, and capecitabine with the first-in-class anti-claudin 18.2 antibody IMAB362 (zolbetuximab, previously known as claudiximab) [39]. However, trials like SPOTLIGHT, investigating the efficacy of zolbetuximab in this setting, are still ongoing (NCT 03504397).

MMP

The inhibition of matrix metalloproteinases with the aim to induce tumor stroma modifications constitutes another therapeutic option currently under investigation. Unfortunately, results of the phase III GAMMA-1 study, presented at the ASCO GI Cancer Symposium 2019, demonstrated no significant difference in outcome for the antibody GS-5745 (andecaliximab) in combination with FOLFOX compared to FOLFOX alone [40].

Era of Immunotherapy and Hints for Predictive Marker Testing

Mismatch Repair Deficiency

Several markers are used to predict the efficacy of immunotherapy with immune checkpoint blockade. MSI-h or MMR-d represents the most important and best-established exponent of this group of biomarkers with a reported incidence in GC of 10–22% in the Western population [4, 41]. In general, microsatellite instable GC is associated with older age (>65-year-old patients), female gender, onset in the distal stomach, and intestinal histological type according to the Lauren classification. It is more common in patients suffering from multiple synchronous GCs than in those with a solitary tumor [42]. PCR and IHC are the main methods used to detect MSI-h. Molecular testing with PCR allows for a direct detection of MSI-h as a consequence of MMR-d. In the 5–11% of microsatellite instable malignancies not exhibiting MMR protein loss, usually due to retained antigenicity in an otherwise nonfunctional protein, IHC may underestimate MSI-h cases. In this situation, a PCR-based test is applied to establish the correct diagnosis. Some laboratories use next-generation sequencing (NGS) to determine microsatellite status. In most cases, NGS-based MSI-h analysis requires both tumor and normal tissue. An advantage of this method is the broader range of microsatellite loci included. While the PCR-based method focuses on 5 microsatellite sites, NGS is not limited to these. However, the investment costs per sample are high and the time needed to perform the test is significantly longer than PCR [43].

Epstein-Barr Virus

According to the literature, approximately 9% of GCs are EBV-positive [44]. Nonetheless, we observe fewer cases in our clinical experience. Testing is performed using in situ hybridization targeting EBV-encoded small RNA 1 [45]. Although EBV is a strong predictive marker for immunotherapy [46], it is not applied in patient selection for front-line immunotherapy. It is however used as a biomarker in treatment refractory cases. Interestingly, EBV-positive aGC was found to express high levels of PD-L1 in cancer cells and infiltrating immune cells [47]. Moreover, a strong correlation between PD-L1-positive and EBV-positive/MSI-h GC was observed, bringing up the hypothesis that immunotherapy may be as effective in EBV-positive GC patients as it is in MSI-h patients [46]. To this date, some clinical data showing a high efficacy of immunotherapy in EBV-positive aGC could be obtained. However, this concept remains to be proven in clinical trials [46].

Tumor Mutational Burden

Tumor mutational burden (TMB) is correlated with enhanced clinical response to immunotherapy in melanoma and non-small-cell lung cancer patients [48, 49]. Furthermore, there is evidence that a high TMB could be of predictive value for OS in aGC [48]. As observed in non-small-cell lung cancer, little overlap exists between the TMB-high and PD-L1-positive subgroups [50, 51]. Of note, pembrolizumab has been approved by the FDA for all tumors with a TMB >10 Mt/mb based on the results of the KN-158 study.

Programmed Death, Programmed Death Ligand-1, and Combined Positive Score

PD-L1 expression is commonly used as a predictive marker in aGC, but there are many caveats to be considered. First, PD-L1 does not represent a strong predictive marker for immune checkpoint inhibition and its predictive value varies depending on the immune checkpoint inhibitor used. There are heterogeneous data between responses to nivolumab and pembrolizumab, but this might be more due the different scores used and not of intrinsic different mechanism of both checkpoint inhibitors. In addition, different antibodies are used to measure PD-L1 positivity and poor inter-reader concordance in identifying positive tests is reported in the literature [55]. CPS is an attempt to strengthen the predictive value of PD-L1 and is defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. Concerning nivolumab, PD-L1 positivity measured by CPS, correlates with the efficacy of the substance as shown in the Checkmate-649 trial [52] as well as in a post hoc analysis of Checkmate-032 [53]. Additionally, CPS correlated with avelumab activity in the JAVELIN gastric 100 trial [54]. In summary, data supporting CPS as a predictive marker for the activity of different PD-1/PD-L1 inhibitors in GC are thus becoming more robust.

Treatment of the Immunogenic aGC

To date, MSI seems to be the strongest predictive marker for immunotherapy with checkpoint inhibition in GC. In the Keynote-062 trial, an exploratory analysis showed substantial benefit of pembrolizumab monotherapy (arm A) as first-line treatment in patients with MSI tumors. Median OS was not reached for pembrolizumab (95% CI, 10.7-NR) versus 8.5 months for chemotherapy alone (arm C) (95% CI, 5.3–20.8), HR = 0.29 [56]. The combination of chemotherapy and pembrolizumab in arm B of the Keynote-062 trial resulted in slightly lower ORR in MSI tumors, favoring pembrolizumab monotherapy. This finding was true for both subgroups of CPS ≥ 1 and CPS ≥ 10. The impressive OS difference observed makes pembrolizumab an option for front-line therapy in the MSI patient group. However, the results for the MSI subgroup should be interpreted with caution, taking into account its small size ($n = 14$).

Comparable OS benefits (HR = 0.33) for MSI tumors were observed in the CheckMate-649 trial. Similarly to Keynote-062, this trial was not conducted specifically in a MSI population. The combination of checkpoint blockade and chemotherapy as first-line treatment of aGC was reserved for the CPS ≥ 5 population (see below) [52]. Consistent with findings regarding upfront treatment, pembrolizumab (vs. paclitaxel) has also demonstrated a clear benefit in MSI patients in the second-line setting (Keynote-061) [57]. In summary, we recommend the earliest possible use of checkpoint inhibitors in the treatment of metastatic MSI gastric cancer.

PD-L1 expression/CPS is not as strong of a predictive marker as MSI. Nevertheless, it is widely used in the clinical trial landscape. Recently, the CheckMate-649 trial demonstrated a statistically significant survival benefit with the addition of nivolumab to FOLFOX or CAPOX in the first-line setting of aGC. Clinically meaningful effects were noted especially in the subgroup exhibiting CPS ≥ 5 [52]. In this population, a median PFS of 7.7 months versus 6.0 months (HR 0.68; $p < 0.0001$) and an mOS of 14.4 months versus 11.1 months (HR 0.71; $p < 0.0001$) could be observed. The study had practice changing impacts, leading the FDA to grant priority review to 1L nivolumab combinations in gastric/GEJ/esophageal cancers in January 2021.

Currently, checkpoint inhibition plays no role in the second-line treatment of aGC, regardless of PD-L1 expression/CPS [57, 58]. In the third-line setting, pembrolizumab was approved by the FDA in 2017 (but not EMA or Swissmedic) based on results of the cohort 1 of the Keynote 059 trial. In this single-arm, phase II trial, gastric or GEJ tumors expressing PD-L1 showed a 16% ORR with responses lasting for 16 months [59]. An alternative checkpoint inhibitor for third-line treatment is nivolumab, which is approved for this indication by Swissmedic based on the placebo-controlled ATTRACTION-02 trial [60]. Although nivolumab was active independently of PD-L1 expression, the results of this trial were not widely adopted in Western countries mainly because of the purely Asian study population.

The concept of combinatorial strategies, ranging from immune-immune combinations to immunochemotherapy combinations, is currently under investigation. The phase I/II CheckMate-032 trial showed a higher efficacy of the combination of anti-PD-1 and anti-CTLA-4 than single-agent anti-PD-1 therapy, but higher toxicity levels were observed in the combination group, undermining the clinical relevance of this study [61]. In Keynote-590 [62], the combination of pembrolizumab and a platinum/5FU-based chemotherapy resulted in a clear survival benefit in squamous cell esophageal cancer patients with PD-L1 CPS ≥ 10 as well as Siewert type 1 GEJ adenocarcinoma patients with PD-L1 CPS ≥ 10. Median OS of all patients in the intervention group was 13.5 months compared to 9.4 months in the control group (HR 0.64; $p < 0.0001$). In the squamous cell esophageal cancer subgroup mOS was prolonged from 8.8 months to 13.9 months (HR 0.57; $p < 0.0001$). A limiting factor of this study is the fact that regarding adenocarcinomas, only GEJ Sievert type I tumors were included. CM-649, on the other hand, provided data favoring this regimen for first-line treatment of aGC including all adenocarcinoma locations of the stomach. Further combination trials investigating immunochemotherapy (NCT03382600 and NCT03675737) or therapeutic combinations with VEGFR-2 blockade (NCT02999295) and immunotherapy are ongoing.

Treatment of aGC Patients in Absence of Molecular Targets and Immunogenic Profile (HER-2-Negative, Microsatellite Stable), Relevance of Anti-VEGF Targeting

Although triplet therapy with FLOT has become the new standard in the perioperative setting, we do not recommend the routine use of this regimen as first-line therapy in aGC. The V325 study group reported superiority of docetaxel, cisplatin, and fluorouracil (DCF) in the first-line setting over cisplatin/fluorouracil. In their phase III study, DCF prolonged time to progression (32% risk reduction) as well as OS (21% risk reduction) [63]. However, triplet therapy also resulted in higher toxicity with a significantly greater amount of grade 3 and 4 side effects, even in the era prior to immunotherapy-chemotherapy combinations. Therefore, we do not see a clear benefit of this triplet chemotherapy in the first-line treatment of aGC. Consistently, a recently published Japanese study
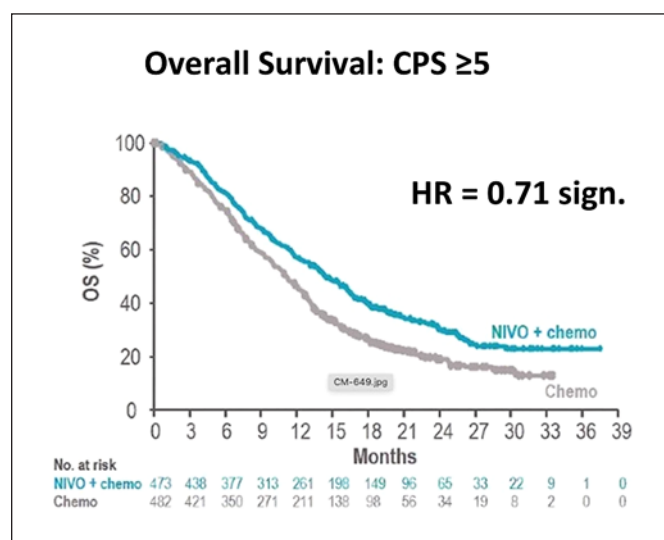
investigated the addition of a taxane to a cisplatin/S1 backbone. Results showed no survival advantage and toxicity was increased [64]. A smaller randomized AIO phase II trial also failed to demonstrate a PFS benefit of FLOT compared to FLO in patients aged 65 years or older [65]. To conclude, triplet combinations (e.g., DCF or FLOT) should be reserved for carefully selected cases. For example, the phase II FLOT-3 trial [66] tested a valuable concept of surgical removal of primary and metastatic sites after neoadjuvant chemotherapy in highly selected patients with limited metastatic disease with the addition of postoperative FLOT. This study showed favorable survival rates for the included patients, setting up a rationale for future randomized trials.

Furthermore, second-line and consecutive regimens remain a challenge. Evidence regarding checkpoint inhibitor monotherapy and alternative chemotherapeutic approaches like irinotecan is limited. Concerning the second-line use of FOLFIRI, some data are available and can be considered [67]. The RAINBOW trial showed superiority of the combination of ramucirumab/paclitaxel over paclitaxel/placebo after previous platinum-based chemotherapy. The absolute benefit amounted to an OS prolongation of 2.2 months. Ramucirumab/paclitaxel can be considered the standard of care in the second-line setting [68], especially in patients with a good performance status. Other options include monotherapy with ramucirumab, a taxane or irinotecan. Effects of monotherapy are limited in efficacy and duration of response compared to drug combinations. Therefore, this option should be reserved for patients with reduced performance status, whereas drug combinations will not be possible. Moreover, particularly with the upcoming availabilities of first-line combination therapies and second-line immunotherapy options, alternative compounds to VEGF antibodies or mono-agent chemotherapy should be debated (shown in Fig. 1).

In refractory disease, TAS-102 showed a clear survival benefit compared with placebo in the phase III TAGS trial [69]. Since toxicity was manageable and quality of life could be maintained [70], it represents the standard of care in this setting. As mentioned previously, nivolumab is another option demonstrating superiority over placebo in a phase III trial (ATTRACTION-2) [60]. The population of this study comprised exclusively Asian patients, resulting in a rather reluctant use of nivolumab in this setting in the Western world.

Conclusion

The comprehensive analysis of subgroups, such as defined by the TCGA, adds substantial value to the understanding of GC and provides clinically relevant information. Upfront testing for MSI, HER-2, and PD-L1 CPS is recommended in the aGC setting. If these targets are identified among the tumor characteristics, immune checkpoint blockade or anti-HER-2 antibodies should be added to the treatment regimen according to Checkmate-649 and the ToGa trial, respectively. In case of a reimbursement of the FOLFOX/CAPOX combination with nivolumab, we recommend this therapeutic option as first-line treatment for the PD-L1 CPS > 5 population. It should be considered as the new standard of care in this subgroup. For the majority of aGC patients, doublet chemotherapy will remain the standard treatment in the first-line setting.

Concerning the second line of therapy, VEGF blockade with or without taxanes is the adequate choice for most patients. However, alternative chemotherapy regimens have been tested and proven to be effective.

Since second-line options have led to an improvement of prognosis, a growing proportion of aGC patients become candidates for third-line therapies. In this situation, TAS-102 and nivolumab have demonstrated significant survival benefits compared with placebo in phase III trials. Nivolumab however is not widely accepted in this setting in the Western world due to an exclusively Asian study population. In some cases, rare targetable mutations are found in aGC, justifying a comprehensive panel analysis early in the treatment history. Hopefully, additional biomarkers will be discovered in the near future, making more personalized treatment choices possible.

To date (March 2021), EMA and Swissmedic approved medications for aGC in the first-, second-, and refractory-line settings comprise platin derivates, 5FU, taxanes, irinotecan, ramucirumab and TAS-102 (only EMA). The approval of pembrolizumab based on the Keynote-590

Fig. 1. Second-line therapy: overview. OS, overall survival.

trial is pending; Keytruda® monotherapy in MSI-h or TMB-high tumors is neither approved by EMA nor Swissmedic. In order to apply pembrolizumab in this setting, the communication with the insurance company has to be made using the FDA approval statement. EMA approval for nivolumab monotherapy in second- or further-line therapy was recently withdrawn and, to date, there is no Swissmedic approval for this indication. However, with the expected EMA approval based on the CM-649 trial, the combination of chemotherapy plus nivolumab will be clearly indicated in the first-line treatment of CPS-positive tumors.

Conflict of Interest Statement

A.R.S has received honoraria due to his scientific consultancy role from AdvancedAcceleratorApp, Amgen, Bayer, BMS, Eisai, Lilly, MSD, Novartis, Pfizer Servier, and Sanofi and has received research grants from Ipsen and Roche. S.D.D. has received consulting honoraria from Amgen, Bayer, BMS, IPSEN, Lilly, Merck, BMS, Novartis, Pfizer, Roche, Sanofi, and Servier, and travel grants from Amgen, BMS, IPSEN, Roche, and Servier. D.H. has received travel grants and congress fees from Servier and Janssen Pharmaceutica and consulting honoraria from Medtalks Switzerland (Play-ToKnow AG). C.A. has received honoraria from Merck and Servier for participation in Educational Advisory Board-meetings. P.S. has had in the last 3 years or has advisory relationships with: Merck-Serono, Servier, and BMS. P.M. has received consultation honoraria from Servier and Bayer, travel support from Bayer. S.P. has received travel grants from Amgen, Celgene, Roche, and Servier. T.W. has nothing to disclose. P.V.B. has received honoraria due to his scientific consultancy role from Astellas, Bayer, BMS, Janssen, MSD, Novartis, Sanofi, and Servier. M.B. has nothing to disclose.

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Author Contributions

A.R.S. and D.H. designed this review and drafted the initial manuscript. C.A., T.W., S.D.D., P.S., P.M., S.P., and P.V.B. analyzed the data and made substantial contributions to the drafted manuscript. M.B. verified the analytical methods and made final adjustments. All of the authors provided critical feedback, wrote this manuscript, and gave final approval of the submitted version.

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