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Tumour Review

Unmet needs and challenges in gastric cancer: The way forward

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ABSTRACT

Although the incidence of gastric cancer has fallen steadily in developed countries over the past 50 years, outcomes in Western countries remain poor, primarily due to the advanced stage of the disease at presentation. While earlier diagnosis would help to improve outcomes for patients with gastric cancer, better understanding of the biology of the disease is also needed, along with advances in therapy. Indeed, progress in the treatment of gastric cancer has been limited, mainly because of its genetic complexity and heterogeneity. As a result, there is an urgent need to apply precision medicine to the management of the disease in order to ensure that individuals receive the most appropriate treatment. This article suggests a number of strategies that may help to accelerate progress in treating patients with gastric cancer. Incorporation of some of these approaches could help to improve the quality of life and survival for patients diagnosed with the disease. Standardisation of care across Europe through expansion of the European Registration of Cancer Care (EURECCA) registry – a European cancer audit that aims to improve quality and decrease variation in care across the region – may also be expected to lead to improved outcomes for those suffering from this common malignancy.

Introduction

Gastric cancer (GC) is the fourth most common cancer worldwide, with 980,000 cases being diagnosed in 2008, 83,000 of which were in the European Union [1]. While dietary improvements and reduction in chronic *Helicobacter pylori* infection due to the use of antibiotics have resulted in a steady fall in incidence and mortality rates in developed countries over the past 50 years [2], outcomes in Western countries remain poor. In Europe, overall 5-year survival from GC is around 25%, contrasting with a 70% survival rate in Japan [3,4]. These differences reflect the fact that the disease is often diagnosed at an early stage in Japan due to screening, while in the West the disease is frequently at an advanced stage at presentation [2]. While earlier diagnosis would help to improve outcomes for patients with GC, a better understanding of the biology of the disease is also needed, along with advances in therapy.

Pathogenesis of GC

Most GCs are gastric adenocarcinomas, which are malignant epithelial neoplasms. However, GC is a highly heterogeneous entity with respect to patterns of architecture and growth, cell differentiation, histogenesis and molecular pathogenesis. Currently, five

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major types are recognised by the World Health Organization (WHO) classification: papillary, tubular and mucinous adenocarcinoma, poorly cohesive carcinoma (with or without signet ring cells) and mixed carcinoma [5]. Two major types of GC were described by Laurén – intestinal and diffuse [6]. These display different clinicopathological profiles and molecular pathogenesis, and often occur in distinct epidemiological settings [7]. Intestinal type carcinomas generally occur in older patients and are thought to arise through a background of chronic gastritis with progression to intestinal metaplasia, dysplasia and gastric carcinoma [7,8]. Progression of chronic atrophic gastritis has been shown to be associated with *H. pylori* infection, with risk of developing GC being dependent on strain virulence and host susceptibility [9–12]. The diffuse type is more common in younger individuals and its pathogenesis is less well understood [13]. Tubular and papillary carcinomas (WHO classification) roughly correspond to the intestinal type described by Laurén, and poorly cohesive carcinomas (encompassing cases constituted partially or totally by signet ring cells) correspond to the diffuse type. Rare variants account for about 10% of gastric carcinomas and a further 10% are thought to be caused by Epstein–Barr virus [14].

Most GCs (90%) are sporadic. Familial clustering is observed in 10% of cases and only 1–3% of GCs are hereditary, comprising hereditary diffuse gastric cancer (HDGC) [15–17] and the recently described gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) [18]. The molecular pathogenesis of GC is complex. One of the key molecular features in sporadic cancers is the amplification of human epidermal growth factor receptor 2 (*HER2*). Around 15% of patients have HER2-positive (HER2+) GC in clinical practice, though the proportion is higher in those with intestinal GC (33%) and lower for individuals with diffuse disease (6%) [19]. HER2 may also have a prognostic role in GC, though the association remains controversial [20]. Epidermal growth factor receptor (EGFR) is also over-expressed in around 40% of GCs [21]; however, its role in the pathogenesis of the disease is unclear. Most HDGCs are caused by alterations of the E-cadherin gene (*CDH1*) [22–24], with a minority thought to be due to α-E-catenin [25]. E-cadherin mutations may also influence the sporadic form of the disease and may present a target for novel cancer therapies. The gene responsible for the recently described GAPPS syndrome has not been identified to date [18].

The timescale of the progression of normal gastric mucosa to gastric carcinoma is 10–20 years, yet most cases present at an advanced stage due to the asymptomatic nature of early-stage disease, emphasising the need for earlier diagnosis to improve the possibility of cure. However, current Western guidelines recommend gastroscopy only for symptomatic patients or those with a family history of GC, with prophylactic gastrectomy being recommended for individuals with a genetic predisposition for HDGC [23,26,27]. National screening for *H. pylori* to reduce GC risk has the potential to reduce mortality, but is only likely to be cost-effective in countries with the highest incidence of the disease (e.g. Japan).

Genomic approaches to GC heterogeneity

A range of therapies are available for the treatment of GC, though the molecular and clinical heterogeneity associated with the disease creates an urgent need to apply precision medicine to management to ensure that individuals receive the most appropriate drugs. In recent years, efforts have concentrated on translational research in order to identify key alterations in GC that may represent important targets for novel therapies. These studies have revealed a number of commonly mutated genes, of which tumour protein 53 (*TP53*) is the most frequently found, though active mutations can also be identified in phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) (which governs mammalian target of rapamycin [mTOR] signalling) and *CTNNB1* (Wnt signalling) [28]. Mutations in chromatin remodelling genes (*ARID1A, MLL3* and *MLL*) are also common, occurring in more than 40% of GCs. In particular, *ARID1A* mutations have been found in up to 10% of tumours, often concurrent with microsatellite instability and *PIK3CA*-activating mutations. *ARID1A* may also be a novel tumour suppressor gene, presenting possible therapeutic opportunities [28]. Receptor tyrosine kinase (RTK)/*RAS* amplifications (e.g. fibroblast growth factor receptor 2 [*FGFR2*], *ERBB2/HER2*, *EGFR* and *MET*) are further frequent alterations in GC, and around 37% of patients may be potentially treatable with RTK/RAS-directed therapies (Fig. 1) [29]. Additionally, DNA methylation alterations are present in around 40% of GC tumours [30], suggesting a role for epigenetic agents in the treatment of the disease. Activating mutations in *KRAS* are rare in GC, though gene amplification of wild-type *KRAS* is frequent and confers a poor prognosis [29].

Recently, gene expression profiling using mRNA consensus clustering has revealed three distinct GC subtypes – mesenchymal, proliferative and metabolic (Table 1) [31]. It is hoped that the distinct molecular and genetic features displayed by these newly-identified subtypes and the differences in their responses to treatment may help in the quest to develop more personalised therapy for patients with GC. For example, the results of preclinical studies suggest that mesenchymal-subtype GCs may be more sensitive to PIK3CA/mTOR/AKT pathway targeting drugs compared with GCs of other subtypes.

Current treatment of localised GC

Surgery is the only means of cure for patients with GC and is the treatment of choice for early-stage disease. Endoscopic resection may be used as an alternative to surgery for early-stage tumours if they are well differentiated (⩽2 cm), confined to the mucosa and not ulcerated (Fig. 2) [32]. The primary goal of surgery for localised GC is a complete resection with negative margins (R0) [33–36]. The value of surgical expertise in GC is highlighted by the considerable variations in GC cure rates reported in different regions. In particular, surgery for patients with locally advanced GC is curative in around 80% of patients in Japan, though the percentage is much lower in the West (up to 55%). Indeed, experience from Japan has underlined the efficacy of more extensive lymph node dissection (D2 rather than D1) coupled with longer-term

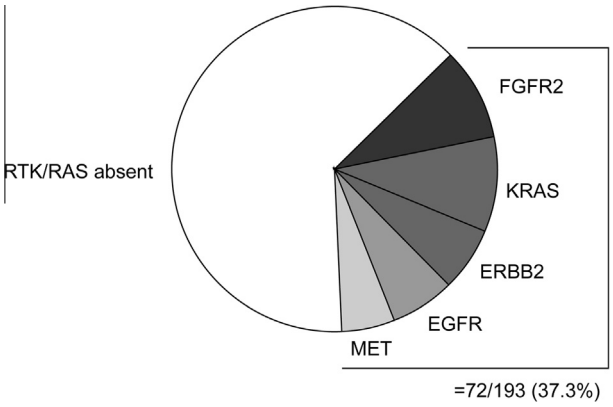

Fig. 1. Frequency of receptor tyrosine kinase (RTK)/RAS genomic alterations in gastric cancer. Reproduced from Deng et al. [29]. Different gastric cancer subgroups exhibiting RTK/RAS amplification. Gastric cancers exhibiting at least one RTK/RAS amplification event comprise a collective 37% of the cohort analysed. EGFR, epidermal growth factor receptor; FGFR2, fibroblast growth factor receptor 2.

Table 1
Biological properties and drug sensitivities of molecular subtypes of gastric cancer identified by mRNA consensus clustering [31].

Subtype	Histological features	Associated genes	Drug sensitivity
Mesenchymal	Diffuse subtype	• EMT pathways • CSC pathways • *TGFβ* • mTOR signalling	Sensitive to PI3K/AKT/mTOR inhibitors
Proliferative	Intestinal subtype	• Genomic instability • *TP53* mutations • Cell cycle • DNA replication • Mitosis • Copy number alterations (*ERBB2/HER2* and *KRAS*)	Unresponsive to 5-FU
Metabolic	Gastric phenotype	• Metabolic processes • Digestion • Secretion • SPEM	Increased sensitivity to 5-FU

CSC, cancer stem cell; EMT, epithelial mesenchymal transition; 5-FU, 5-fluorouracil; mTOR, mammalian target of rapamycin; SPEM, spasmolytic polypeptide-expressing metaplasia; TGFβ, transforming growth factor beta.

follow-up [37]. In particular, the Japanese rules have defined the relationship between the extent of gastrectomy and the nodal dissection: in a D1 total gastrectomy, stations 1, 2, 3, 4, 5, 6 and 7 should be resected while in a D2 procedure 8a, 9, 10, 11 and 12 are added. Furthermore, in a D1 subtotal gastrectomy, stations 1, 3, 4, 5, 6 and 7 are removed, with 8a, 9, 11p and 12a being added in a D2 procedure. It is now accepted in the West that D2 dissection, performed in specialist centres, should be standard in medically fit patients with resectable GC [32]. This approach has led to an improvement in cure rates from 30% to up to 55% in the last decade [38–41]. Minimally invasive approaches for gastric resection are being increasingly used, though it is important to ensure that the same oncological outcome can be achieved as that possible in open surgery, and the results of current trials comparing the two techniques will be very informative [42,43].

For patients with localised disease, better predictions of nodal disease and prognosis are needed in order to select the most appropriate treatment (surgery alone or multi-modal therapy). Endoscopic ultrasound and computed tomography of the chest and abdomen are currently the primary means of staging for locally advanced GC, with laparoscopy to exclude small volume peritoneal metastatic disease in most cases [32,36]. The accuracy of these techniques in determining preoperative stage varies from 60% to 80%. Surgery alone may be sufficient for individuals with stage II GC, though trials suggest a benefit for neoadjuvant chemotherapy in such patients and even more convincingly in stage III, improving the ability to perform an R0 resection and reducing tumour size and tumour burden [44–46]. In particular, perioperative epirubicin, cisplatin and 5-fluorouracil (5-FU) (ECF) has been shown to significantly improve 5-year survival versus surgery alone (36.3% versus 23%, respectively) in patients with resectable GC [44], resulting in this approach being adopted as the standard of care in many European countries [32]. Nevertheless, there were limitations to the design of this trial [47], and more detailed preoperative local staging, better identification of the patients who might benefit and improved trial designs are needed for future neoadjuvant studies. Many centres now substitute 5-FU with capecitabine (ECX), since this drug avoids the need for central line access and has been shown to be non-inferior to 5-FU in the advanced disease setting [48].

Adjuvant chemo(radio)therapy may also result in a survival benefit for patients with localised disease, though there is no consensus as to the best approach. While the US INT-0116 trial reported an improvement in median overall survival (OS) for adjuvant chemoradiotherapy (36 months versus 27 months for surgery alone) [49], inadequate surgical radicality may have led to an overestimation of the benefit [50]. However, the results of the ongoing Chemoradiotherapy after Induction Chemotherapy in Cancer of the Stomach (CRITICS) trial may help to confirm the benefit of combination adjuvant chemoradiotherapy for localised disease. Although individual trials failed to show a survival benefit for adjuvant therapy in Western patients, a recent large meta-analysis demonstrated a survival benefit for adjuvant chemotherapy in patients

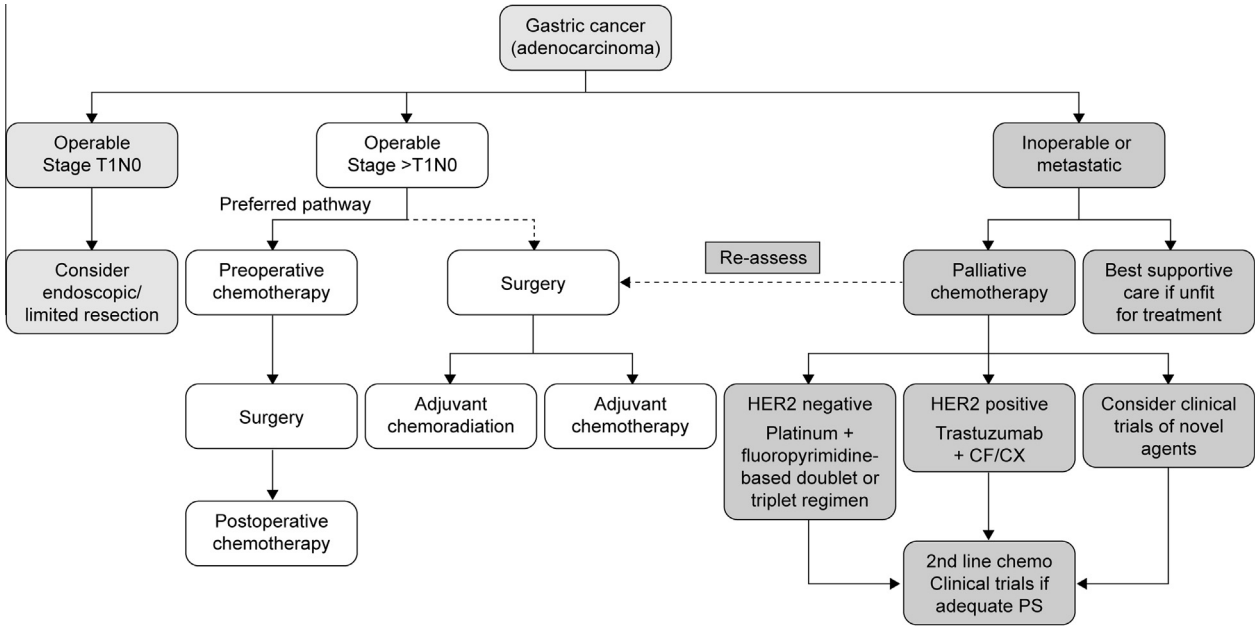

Fig. 2. Algorithm for the management of patients with gastric cancer recommended by the European Society for Medical Oncology (ESMO), the European Society of Surgical Oncology (ESSO) and the European Society of Radiotherapy and Oncology (ESTRO). Reproduced from Waddell et al. [32]. CF, cisplatin/5-fluorouracil; CX, cisplatin/capecitabine; PS, performance status.

with resectable GC [51]. Furthermore, postoperative adjuvant chemotherapy has become a standard option in Asia [52,53].

In order to improve outcomes for patients with resectable GC, improved methods of staging incorporating prognosis and nodal risk are needed.

Current treatment options and unmet needs in advanced GC

The standard treatment for advanced GC is chemotherapy since it provides a survival benefit and improved quality of life compared with best supportive care (BSC) alone [26,32,36,54]. Five classes of cytotoxic agents are currently used in GC (fluoropyrimidines, platinums, taxanes, topoisomerase inhibitors and anthracyclines), though the optimal combination is not well defined. Nevertheless, selection of an appropriate regimen must take into consideration comorbidities, performance status (PS) and organ function, with palliation being the main aim of treatment [55,56].

A number of validated doublet and triplet chemotherapy options are available as first-line therapy for advanced GC, though recommended regimens vary between guidelines. Doublets are superior to cytotoxic monotherapy and limited data suggest that triplets may be more active than doublets, but with increased toxicity [57,58]. Consequently, triplets may only be an option for younger, fit patients with normal organ functions who are more able to tolerate increased toxicity. Guidelines issued by the European Society of Medical Oncology (ESMO) advocate the use of combination regimens incorporating a platinum agent and a fluoropyrimidine based on the results of the Randomised ECF for Advanced and Locally Advanced Esophagogastric Cancer-2 (REAL-2) study, with capecitabine being preferred to 5-FU [58–61]. Other first-line options include irinotecan plus 5-FU and taxane-based regimens [32,62].

For HER2+ patients with advanced GC, guidelines recommend the use of trastuzumab combined with a fluoropyrimidine (5-FU or capecitabine) plus cisplatin, based on the improved disease-free survival (DFS) and OS demonstrated in the Trastuzumab for Gastric Cancer (ToGA) trial [19,32,36]. These findings led to the approval of trastuzumab by the European Medicines Agency for HER2+ patients based on an immunohistochemistry (IHC) score of 3+ or 2+ confirmed by fluorescence in situ hybridisation (FISH) and the regimen is now the standard of care for this population. However, quality control of molecular testing for HER2 is an important issue and standardised protocols are needed to ensure precise identification of eligible patients [63]. The activity of trastuzumab beyond disease progression is not well established and no data are available in the second-line, neoadjuvant or adjuvant settings, though studies investigating neoadjuvant trastuzumab are ongoing. Trastuzumab is currently the only validated anti-receptor tyrosine kinase-directed agent in GC, and the role of other targeted agents is not well defined. Novel agents under phase III investigation include panitumumab, cetuximab, lapatinib, onartuzumab and rilotumumab, though findings with these agents to date have been disappointing [56,64–66]. Consequently, they should only be used within a clinical trial at present [36]. Inhibition of tumour angiogenesis has proved to be an effective treatment approach in many cancers and a number of anti-angiogenic therapies are under investigation in GC, including bevacizumab [67] and ramucirumab [68,69].

Available data suggest that patients with good PS should be offered second-line therapy, preferably within the setting of a clinical trial [32,36], though data on the optimal regimen in this setting are limited [70–73]. Irinotecan or docetaxel monotherapy are possible options and confer a small survival benefit over BSC [74–76], with further treatment possibilities including paclitaxel, FOLFIRI (folinic acid, 5-FU and irinotecan) or ECX [77]. Monotherapy with the anti-vascular endothelial growth factor receptor-2 (VEGFR-2) monoclonal antibody, ramucirumab, revealed a comparable survival benefit [69]. The combination of ramucirumab plus paclitaxel has also been shown recently to confer a survival benefit over paclitaxel alone (median OS 9.63 months versus 7.36 months, respectively) [78]. It should be noted, however, that this agent is not yet available in many countries. Patients can also be re-challenged with the first-line treatment if they relapse more than 3 months after the end of treatment [32]. However, further trials are needed to establish the best combination and sequence of cytotoxic agents for first- and second-line therapy, and to define the benefit of third-line treatment in GC. Additional challenges in advanced GC include the lack of data on prognostic and predictive factors. However, retrospective analysis of the cohorts from existing studies may help to identify biomarkers of response for different targeted therapies. Consideration should also be given to the collection of repeat biopsies in future early-phase studies for biomarker detection. Since patients with advanced GC are often frail with symptoms resulting from a high tumour burden [55,56], the toxicity of chemotherapeutic regimens must also be taken into account, with patient-reported outcomes and quality of life endpoints being incorporated into future clinical trials.

New cellular targets for drug treatment in GC

The molecular diversity of GC means that personalised therapy with targeted agents is likely to play an important role in the coming years. While only one targeted agent (trastuzumab) is approved in GC at present, advances in molecular biology have identified a number of promising new targets, including EGFR, HER3, vascular endothelial growth factor (VEGF), PI3K/mTOR, FGFR2 and MET (Table 2) [19,29,64–66,68,69,78–80]. For example, the EGFR and HER2 inhibitor, lapatinib, plus paclitaxel has shown significant efficacy in HER2 3+ patients as second-line therapy in the TyTAN study, though the trial failed to reach its primary endpoint of prolonging OS in the intent-to-treat population [66]. Other HER2-targeted agents under investigation in the first- and second-line settings, respectively, include pertuzumab and trastuzumab-DM1 (TDM1), with the anti HER2/HER4 agent neratinib also being examined in patients with GC. In addition, HER3 may be an important target in GC and has been associated with tumour resistance to EGFR- and HER2-targeted agents [81,82]. A number of phase I/II trials with HER3 monoclonal antibodies, including LJM716 and MM-12, are underway in GC. EGFR over-expression occurs in more than 50% of tumours, suggesting that EGFR may be a promising target in GC. However, the REAL-3 (panitumumab) and Erbitux in Combination with Xeloda and Cisplatin in Advanced Esophagic-gastric Cancer (EXPAND) (cetuximab) studies failed to demonstrate a benefit for either of the EGFR-targeted agents currently under investigation in an unselected population of patients with GC [64,65].

VEGF is a key mediator in angiogenesis and its expression is associated with more aggressive disease and poor prognosis in GC [83,84]. A number of anti-VEGF-directed drugs are in development, including the monoclonal antibody bevacizumab [68]. Although the phase III Avastin in Gastric Cancer Study (AVAGAST) with bevacizumab in advanced GC did not meet the primary endpoint of extending OS, the results of a subset analysis suggest that the agent may be of benefit in certain GC subtypes (e.g. non-Asiatic patients with diffuse or distal GC), warranting further prospective evaluation [67,85]. These data may be explained by differences in certain biomarkers (e.g. VEGF-A, neuropilin-1), though further studies are needed to confirm this finding [86]. The anti- VEGFR-2 monoclonal antibody, ramucirumab, is also under investigation, with phase II and III studies demonstrating a survival benefit in the second-line treatment of GC [69,78] A further pathway of

Table 2
Randomised phase III trials with selected targeted therapies in gastric cancer.

Therapy	Study	Target	*N*	Primary endpoint	Regimen	Median OS (months)	ORR (%)	Primary endpoint met
First line	ToGA	HER2	594	OS	CX	11.1	34.5	Yes
	(Bang et al., 2010) [19]				CX + trastuzumab	13.8	47.3	
	AVAGAST	VEGF	774	OS	CX	10.1	37	No
	(Ohtsu et al., 2011) [68]				CX + bevacizumab	12.1	46	
	REAL-3	EGFR	553	OS	EOC	11.3	42	No
	(Waddell et al., 2013) [64]				mEOC + panitumumab	8.8	46	
	EXPAND	EGFR	904	PFS	CX	10.7	29	No
	(Lordick et al., 2013) [65]				CX + cetuximab	9.4	30	
Second line	GRANITE-1	mTOR	656	PFS	Placebo	4.34	2.1	No
	(Ohtsu et al., 2013) [80]				Everolimus	5.39	4.5	
	REGARD	VEGFR-2	355	OS	Placebo	3.8	2.6	Yes
					Ramucirumab	5.2	3.4	
	(Fuchs et al., 2014) [69]							
	TyTAN	HER2	430	OS	Paclitaxel	11	27	No
	(Bang et al., 2012) [66]				Paclitaxel + lapatinib	8.9	9	
	RAINBOW	VEGFR-2	665	OS	Paclitaxel	7.36	16	Yes
	(Wilke et al., 2014) [78]				Paclitaxel + ramucirumab	9.63	28	

AVAGAST, Avastin in Gastric Cancer Study; CX, cisplatin/capecitabine; EGFR, epidermal growth factor receptor; EOC, epirubicin/oxaliplatin/capecitabine; EXPAND, Erbitux in Combination with Xeloda and Cisplatin in Advanced Esophagic-gastric Cancer; HER2, human epidermal growth factor receptor 2; mEOC, modified dose EOC; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; REAL-3, Randomised ECF for Advanced and Locally Advanced Esophagogastric Cancer-3; ToGA, Trastuzumab for Gastric Cancer; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

interest in GC is the PI3K/mTOR pathway since it is dysregulated in 50–60% of tumours [87,88]. The mTOR inhibitor, everolimus, has shown preclinical and early clinical efficacy in GC [87,89,90], though the phase III GRANITE-1 study assessing second-line everolimus in advanced GC was negative [80], most likely because the population was not selected according to dysregulation of the PI3K pathway.

Inhibition of cMET is being investigated as it is over-expressed in 75–90% and amplified in 1.5–20% of GCs [29,91,92]. Approaches being investigated include antibodies directed at kinase ligands, HGF (e.g. rilotumumab) or MET (e.g. onartuzumab) [93,94]. Although large phase III trials are underway to investigate these strategies, it is unclear at present whether only patients with amplification will benefit from cMET inhibition or whether those with cMET protein over-expression would also benefit. Since the cMET receptor can dimerise with almost any receptor and may be an escape mechanism for other targeted therapies, cMET inhibitors may also be studied in the refractory setting or in combination with other targeted agents. Further therapeutic approaches being investigated in GC include strategies targeting the immune system, the Wnt/β-catenin pathway and other stem cell-associated pathways.

Selection of the right patients for targeted therapy is a key challenge in GC in order to improve response to treatment, along with linkage of preclinical research on the molecular patterns in the disease to clinical practice. A further issue is that the molecular profile of tumours is likely to change under the stress of treatment suggesting that biopsies should be repeated following relapse and/or between first- and second-line therapies. However, advances in liquid biopsies are needed in this regard as repeat tumour biopsies can be hampered by difficult localisation (e.g. peritoneal metastases) and other obstacles in many patients. Furthermore, blood must be treated within 20 min for analysis of circulating DNA at present due to the presence of degrading enzymes. Further research is needed, therefore, to determine the optimal methods for stabilising, freezing and thawing blood.

Issues and new approaches in drug development for GC

Although effective perioperative chemotherapy is available for GC, locoregional control remains an issue, with 20–25% of resected tumours developing locoregional relapse. For this reason, a number of studies have investigated the efficacy of combining chemotherapy and radiotherapy, either perioperatively or postoperatively [49,95–97]. While such approaches may improve response rates, the results of ongoing phase III studies such as the Trial Of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR) and CRITICS are needed to determine whether they can improve survival. Further improvements in perioperative treatment require strategies to improve the efficacy of chemotherapy, including its combination with targeted therapy. For example, the combination of trastuzumab and pertuzumab with chemotherapy may be an option for patients with HER2+ GC, though recruitment may be an issue for such a trial as HER2+ is relatively uncommon (<15% of GCs). The combination of chemotherapy with the anti-angiogenic drug, bevacizumab, is also being studied in the STO3 trial, with initial findings suggesting that the agent was well tolerated, though cardiac events were increased by around 10% [67].

A further challenge in the treatment of GC is the need for research into the optimal management for those with limited metastatic disease as current strategies are not well established. Nevertheless, the results of the ongoing 5-FU, oxaliplatin, leucovorin and docetaxel (FLOT)-3 study, which aims to determine whether prognosis for such patients may be improved by combining chemotherapy and surgical approaches, may help to resolve this issue [98]. Treatment of patients with diffuse-type GC is also difficult and further studies are needed. It should be noted, however, that trials in this population will require reliable and validated histopathological diagnosis along with good collaborative networks in order to recruit sufficient numbers of patients. The development of collaborative networks must also be considered for screening patients for rare alterations in GC (e.g. amplification of *cMET*, *FGFR* and others) in order to accelerate progress in drug development. Further measures to speed up drug development include adoption of novel endpoints such as histopathological tumour regression [99], though its assessment requires good quality assurance and centralised pathology. The efficiency of future trials in GC may also be improved by the inclusion of metabolic imaging with fluorodeoxyglucose-positron emission tomography (FDG-PET) to detect early response to treatment [98,100,101].

Towards provision of better GC healthcare services in Europe

Surgery for GC is complex and requires training to ensure standardisation, along with multidisciplinary team effort. The

importance of specialist care for patients with GC has been highlighted by the Dutch Gastric Cancer Trial, which demonstrated that outcomes can be improved by training surgeons more effectively [41,102]. In this study, surgical quality control was enhanced by ensuring that all surgeons received expert training, with all D1 and D2 resections being supervised. After a 15-year follow-up, mortality was significantly lower for D2 versus D1 resection, leading to D2 being recommended as the standard approach for resectable GC in the Netherlands. Outcomes can also be improved by centralisation of care, selecting centres with the best results and the highest patient volumes ($\geqslant$20 cases/year), as well as by auditing the performance of hospitals and surgeons. Audits undertaken to date within a number of European countries (e.g. UK, Denmark, Sweden and the Netherlands) have identified a significant inverse relationship between patient volume and 30-day mortality. However, considerable variation was seen between both countries and hospitals, underlining the need for a uniform European registry [103].

The European Registration of Cancer Care (EURECCA), initiated through collaboration between seven European countries (Denmark, France, Ireland, the Netherlands, Poland, Sweden and the UK), is designed to meet this need and aims to compare surgical outcomes, resection rates and patterns of care for patients with GC in Europe [104,105]. The registry will employ a European cancer audit to improve quality and decrease variation in care across the region by identifying and spreading best practices, monitoring outcomes and developing guidelines. It is hoped that centralisation and auditing of services through EURECCA will go some way to improve long-term outcomes for patients with GC throughout the region.

Summary

Although the incidence of GC has fallen in developed countries in recent years, advances in the treatment of the disease have been limited, primarily due to its genetic complexity and heterogeneity. This group of authors has suggested a number of strategies that may help to accelerate progress in treating patients with the condition, as summarised in Table 3. Incorporation of some of the approaches described in this article could help to improve quality of life and survival for patients with GC. Standardisation of care across Europe through expansion of the EURECCA registry may also be expected to lead to improved outcomes for those suffering from this common malignancy.

Table 3
Summary of the challenges in gastric cancer and proposals for addressing them.

Challenge	Proposal for addressing
Only one targeted agent has been approved for first-line treatment in GC to date (trastuzumab) and only one agent has been successful as second-line treatment (ramucirumab) primarily due to the genetic complexity and heterogeneity of the disease	• Strategies aimed at applying precision medicine to management to ensure that individuals receive the most appropriate drugs • Use of translational research to identify key mutations may reveal important targets for novel therapies • Standardised protocols for HER2 testing to ensure precise identification of eligible patients and improve response rates • Repeat biopsies to examine changes in the molecular profile of tumours taking place under the stress of treatment
Cure rates following surgery for resectable GC in the West (up to 55%) lag behind those in Japan (80%)	• Surgery for GC performed in specialist centres by experienced surgeons • Adoption of D2 dissection as the standard of care for medically fit patients with resectable GC • Standardisation of D2 dissection • Auditing of the performance of hospitals and individual surgeons, with monitoring being performed by the medical profession to avoid surgeons only undertaking lower-risk cases • Expansion of the EURECCA registry, which seeks to improve quality and decrease variation in care across Europe by identifying and spreading best practices and monitoring outcomes
The optimal treatment (surgery alone or multi-modal therapy) for early-stage disease has not been established and the neoadjuvant approach is not universally accepted as standard	• Future neoadjuvant studies require more detailed preoperative local staging, better identification of the patients who might benefit and improved trial design • Results from ongoing ST03 and CRITICS trials to confirm the benefit of additional anti-angiogenic therapy or radiotherapy for localised disease • Improved methods of staging are needed, incorporating prognosis and nodal risk to improve outcomes
Treatment for advanced GC is challenging and the optimal combination of chemotherapy (doublets, triplets or sequence) is not well defined	• Triplets should be considered only for younger, fit patients with normal organ functions who are more able to tolerate increased toxicity • Further trials are needed to establish the best combination and sequence of cytotoxic agents in first- and second-line, and to define the benefit of third-line treatment in GC • Retrospective analysis of the cohorts from existing studies, prospective data and biomaterial collection to identify biomarkers of response for different targeted therapies • Collection of repeat biopsies in future early-phase studies for biomarkers detection • Incorporation of patient-reported outcomes and quality of life endpoints into future clinical trials
Locoregional control after resection remains an issue, with 20–25% of resected GC tumours developing locoregional relapse	• Results of ongoing phase III studies (e.g. TOPGEAR and CRITICS) to determine whether combining chemotherapy and radiotherapy (perioperatively or postoperatively) can improve survival • Strategies designed to improve the efficacy of chemotherapy, including its combination with targeted therapy

EURECCA, European Registration of Cancer Care; CRITICS, Chemoradiotherapy after Induction Chemotherapy In Cancer of the Stomach; GC, gastric cancer; HER2, human epidermal growth factor receptor 2.

Conflict of interest statement

Florian Lordick has received research grants from Merck Serono and GSK, and acts as a consultant for Ganymed, Amgen, Merck, Roche, Taiho, Lilly and Astellas. William Allum has acted as a consultant for Lilly, Nestlé and Astellas. Fátima Carneiro has received a research grant from Roche. Josep Tabernero has acted as a consultant for Amgen, Astellas, Chugai, Genentech, Lilly, Merck Serono, Novartis, Roche, Sanofi and Taiho. Eric Van Cutsem has received research funding from Amgen, Roche, Sanofi and Merck Serono. Andrés Cervantes has received research grants from Roche and has acted as a consultant for Amgen, Merck Serono, Shinogi and Genentech.

Emmanuel Mitry, Patrick Tan and Cornelis van de Velde report no conflicts of interest.

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