



## Current and emerging therapies in unresectable and recurrent gastric cancer

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### Abstract

Gastric cancer is one of the most lethal cancers worldwide despite many advances and options in therapy. As it is often diagnosed at an advanced stage, prognosis is poor with a median overall survival of less than twelve months. Chemotherapy remains the mainstay of treatment for these patients but it confers

only a moderate survival advantage. There remains a need for new targeted treatment options and a way to better define patient populations who will benefit from these agents. In the past few years, there has been a better understanding of the biology, molecular profiling, and heterogeneity of gastric cancer. Our increased knowledge has led to the identification of gastric cancer subtypes and to the development of new targeted therapeutic agents. There are now two new targeted agents, trastuzumab and ramucirumab, that have recently been approved for the treatment of advanced and metastatic gastric cancer. There are also many other actively investigated targets, including epidermal growth factor receptor, the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin pathway, c-Met, poly ADP-ribose polymerase, and immune checkpoint inhibition. In this review, we discuss the current management of advanced gastric cancer as well as emerging targeted therapies and immunotherapy.

**Key words:** Advanced gastric cancer; Immunotherapy; Human epidermal growth factor receptor type 2; Targeted therapy; Vascular endothelial growth factor receptor

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**Core tip:** Despite many advances in medical and surgical treatments, gastric cancer remains the second leading cause of cancer deaths. There is a greater understanding of the molecular heterogeneity of gastric cancer in recent years, resulting in the development and clinical investigation of different targeted agents. This review will discuss current treatment strategies and highlight targeted therapies and emerging drugs for advanced gastric cancer.

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## INTRODUCTION

Gastric cancer is the fourth most common cancer and second leading cause of cancer deaths worldwide<sup>[1-3]</sup>. Gastric cancer is commonly diagnosed at an advanced stage and those patients with advanced disease have a median survival of less than 1 year<sup>[4]</sup>. Incidence rates and location of the tumor vary considerably between geographic regions. The highest incidence is in East Asia, Eastern Europe and parts of South and Central America where adenocarcinomas of the distal stomach are more prevalent. Cancers located in the proximal stomach or at the gastroesophageal junction (GEJ) are more prevalent in Western Europe and North America<sup>[5]</sup>.

For patients with locally advanced and metastatic disease, chemotherapy remains the mainstay of treatment. Treatment options include platinum, irinotecan, epirubicin, fluoropyrimidines, and taxanes. The addition of a third drug to a two agent regimen increases the response rate with a modest survival improvement but at the expense of increased toxicity<sup>[6]</sup>.

In recent years, advances in the understanding of the biology and molecular profiling of gastric cancer have led to the development of targeted treatments and to a better survival in select patients with advanced disease. There are now two new targeted agents, trastuzumab and ramucirumab, that have been approved in the last 5 years for the treatment of advanced or metastatic gastric cancer. Many more targeted therapies are currently being actively investigated.

In this review, we discuss the management of advanced gastric cancer and the progress in recent years in targeted therapy and immunotherapy.

## CHEMOTHERAPY

Gastric cancer is a chemotherapy-sensitive disease with multiple active agents, including fluoropyrimidines, anthracyclines, platinum agents, taxanes, and irinotecan. Treatment of advanced gastric cancer with chemotherapy confers a moderate survival advantage and is primarily palliative. Combination therapy is associated with a higher response rate and increased survival when compared to single agents. The combination of cisplatin and fluorouracil (CF), or with epirubicin in a triple-drug regimen (ECF), has been the most commonly used doublet and triplet regimens. Newer agents were added to these regimens to try to improve response rate (RR), time to progression (TTP) and overall survival (OS). These trials are listed in Table 1.

The addition of docetaxel to cisplatin and fluorouracil (DCF) was shown to be associated with improvement of RR (37% vs 25%,  $P = 0.01$ ), TTP (5.6 mo vs 3.7 mo,  $P < 0.001$ ), and OS (9.2 mo vs 8.6 mo,  $P = 0.02$ ); however there were significant grade 3 to 4 toxicities, including a high rate of febrile neutropenia<sup>[7]</sup>. These toxicities limited the adoption of this regimen into clinical practice.

Oxaliplatin (O) and oral fluoropyrimidines - capecitabine (X) and S-1 - have been substituted for cisplatin and fluorouracil (5-FU) respectively, and found to be noninferior and less toxic<sup>[8-10]</sup>. The phase III REAL-2 study evaluated the efficacy of oxaliplatin and capecitabine in a 2 × 2 noninferiority trial with four regimens: ECF (control arm), ECX, EOF, and EOX. The median survival times were 9.9 mo, 9.9 mo, 9.3 mo and 11.2 mo respectively<sup>[9]</sup>. Progression free survival (PFS) and RR did not differ significantly between the different regimens. This study has led to the widespread use of oxaliplatin-based regimens in the frontline treatment of advanced gastric and GEJ cancer.

In Japan, the SPIRITS trial showed that the combination of cisplatin and S-1 (CS) significantly improved OS when compared to S-1 monotherapy (13 mo vs 11 mo), leading to this doublet being considered standard first-line in Japan<sup>[11]</sup>. However, in the United States and Europe, the FLAGS study showed no improvement in outcome when substituting S-1 for 5-FU in combination with cisplatin, so S-1 remains unlicensed in these areas<sup>[12]</sup>.

Irinotecan has also been evaluated in combination with fluorouracil in patients with advanced gastric cancer with no significant differences in response rate, progression free and overall survival compared to the standard care<sup>[13,14]</sup>. This regimen was found to be less toxic so irinotecan has now been incorporated into the treatment approach.

Although most patients receive first-line chemotherapy, patients who progress after treatment usually have a worsened performance status, which limits treatment options. However, recent studies assessed the administration of irinotecan or docetaxel monotherapy as second-line therapy compared to best supportive care and demonstrated a survival advantage with chemotherapy<sup>[15-17]</sup>. Therefore, it is now considered standard of care for appropriate patients with a preserved performance status to receive second-line chemotherapy although no standard regimen has been established. A recent trial reported that irinotecan and taxanes have similar survival outcomes<sup>[18]</sup>.

Despite all these treatments, however, the median survival is less than 1 year. There remains a need for new treatment options with targeted therapy and a way to identify which patients would benefit from these new agents.

**Table 1 First line chemotherapy completed trials**

Ref.	Arms	n	TTP/PFS (mo)	OS (mo)
Van Cutsem <i>et al</i> <sup>[7]</sup>	DCF vs CF	445	TTP: 5.6 vs 3.7 P < 0.001	9.2 vs 8.6 P = 0.02
Al-Batran <i>et al</i> <sup>[8]</sup>	FLO vs FLP	220	PFS: 5.8 vs 3.9 P = 0.077	10.7 vs 8.8
REAL-2 <sup>[9]</sup>	ECF vs ECX vs EOF vs EOX	1002	PFS: 6.2 vs 6.7 vs 6.5 vs 7.0	9.9 vs 9.9 vs 9.3 vs 11.2
Kang <i>et al</i> <sup>[10]</sup>	XP vs FP	316	PFS: 5.6 vs 5.0	10.5 vs 9.3
SPIRITS <sup>[11]</sup>	CS vs S-1	298	PFS: 6.0 vs 4.0 P < 0.0001	13.0 vs 11.0 P = 0.04
FLAGS <sup>[12]</sup>	CS vs CF	1053	PFS: 4.8 vs 5.5 P = 0.920	8.6 vs 7.9 P = 0.20
Dank <i>et al</i> <sup>[13]</sup>	IF vs CF	333	TTP: 5.0 vs 4.2 P = 0.088	9.0 vs 8.7
Guimbaud <i>et al</i> <sup>[14]</sup>	FOLFIRI vs ECX	416	PFS: 5.3 vs 5.8 P = 0.960	9.5 vs 9.7 P = 0.95

DCF: Docetaxel/cisplatin/fluorouracil; CF: Cisplatin/fluorouracil; FLO: Fluorouracil/leucovorin/oxaliplatin; FLP: Fluorouracil/leucovorin/cisplatin; ECF: Epirubicin/cisplatin/fluorouracil; ECX: Epirubicin/cisplatin/capecitabine; EOF: Epirubicin/oxaliplatin/fluorouracil; EOX: Epirubicin/oxaliplatin/capecitabine; XP: Cisplatin/capecitabine; FP: Cisplatin/fluorouracil; CS: Cisplatin/S-1; SOX: S-1/oxaliplatin; IF: Irinotecan/fluorouracil; FOLFIRI: Fluorouracil/leucovorin/irinotecan.

**MOLECULAR CLASSIFICATION**

Gastric cancer is a heterogeneous disease; however, it wasn't until recently that we developed a better understanding of the molecular and genomic basis of gastric cancer. The Cancer Genome Atlas proposed four molecularly unique subtypes of gastric cancer: tumors positive for Epstein-Barr virus (EBV), microsatellite unstable (MSI) tumors, genomically stable tumors and tumors with chromosomal instability<sup>[19]</sup>.

Tumors associated with EBV were predominantly in the fundus or body and were shown to have a higher prevalence of mutations in *PIK3CA* (approximately 80%), extensive DNA hypermethylation, overexpression of PD-L1 and PD-L2, and EBV-CpG island methylator phenotype (CIMP) expression. MSI tumors were diagnosed at a relatively older age (median age 72 years) and showed elevated mutation rates, gastric CIMP and *MLH1* silencing but generally lacked targetable amplifications. Unlike in colorectal cancer, BRAF mutations were not seen in gastric MSI tumors. Genomically stable tumors tended to be diagnosed at an earlier age (median age 59 years) and were enriched for diffuse histology, associated with *CDH1* and *RHOA* mutations and *CLDN18-ARHGAP* fusion, which is implicated in cell motility. Almost half of gastric tumors demonstrated chromosomal instability, which was predominantly intestinal histology with an elevated frequency in the GEJ and cardia and showed marked aneuploidy. They were associated with *TP53* mutation with RTK-RAS activation.

This study showed distinct genomic features in the different molecular subtypes that provide a guide to targeted therapy and allow for development of clinical trials to explore therapies in defined sets of patients.

**TARGETED THERAPIES**

**Human epidermal growth factor receptor 2 inhibitors**

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor belonging to the epidermal growth factor receptor (EGFR) family. Activation of the HER2 receptor activates downstream signals in the Ras/Raf/mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathways that are responsible for regulating a variety of tumor biology, such as cell growth, differentiation, and survival<sup>[20-22]</sup>. The reported HER2 positivity in patients with gastric cancer ranges widely from 6% to 34% depending on the histologic subtype and location with the highest rates of expression observed in intestinal type tumors and in cancers located in the GEJ<sup>[23-25]</sup>. Unlike in breast cancer where overexpression of HER2 associates with a more aggressive tumor<sup>[26]</sup>, the prognostic role of HER2 in gastric cancer is less clear. Also HER2 testing in gastric cancer differs from that in breast cancer because of inherent differences in tumor biology - gastric cancer more frequently shows tumor heterogeneity and incomplete membrane staining due to its high frequency of glandular formation<sup>[27]</sup>. There are several different strategies for targeting HER2: anti-HER2 monoclonal antibodies or small-molecule tyrosine kinase inhibitors (TKIs). Table 2 summarizes the completed trials with targeted agents in advanced gastric cancer and Table 3 outlines the ongoing trials.

The first targeted agent approved in gastric cancer was trastuzumab, which acts on the extracellular domain of the HER2 receptor and inhibits HER2-mediated signaling. Trastuzumab for gastric cancer (ToGA) was a phase III, randomized controlled trial

**Table 2 Targeted therapy completed trials**

Ref.	Name Phase	Indication	Line	Arms	n	PFS (mo)	OS (mo)
HER2 [28]	ToGA Phase III	HER2(+) Adv/Met GC and GEJ	1 <sup>st</sup>	Fluoropyrimidine/cisplatin ± trastuzumab	594	6.7 vs 5.5 P = 0.0002	13.8 vs 11.1 P = 0.0050
[29]	LOGiC Phase III	HER2(+) Adv/Met GC and GEJ	1 <sup>st</sup>	CapeOx ± lapatinib	545	6.4 vs 5.4 p = 0.1000	12.2 vs 10.5 P = 0.3492
[30]	TyTAN Phase III	HER2(+) Adv/Met GC and GEJ	2 <sup>nd</sup>	Paclitaxel ± lapatinib	261	5.4 vs 4.4 P = 0.2441	11.0 vs 8.9 P = 0.2088
EGFR [36]	EXPAND Phase III	Adv/Met GC and GEJ	1 <sup>st</sup>	Capecitabine/cisplatin ± cetuximab	904	4.4 vs 5.9 P = 0.3200	9.4 vs 10.7 P = 0.9500
[37]	REAL3 Phase III	Adv/Met GC and GEJ	1 <sup>st</sup>	EOX vs modified EOX + panitumumab	553	6.0 vs 7.4 P = 0.0680	8.8 vs 11.3 P = 0.013
VEGFR [48]	Sunitinib Phase II	Adv GC and GEJ	2 <sup>nd</sup>	Sunitinib	78	2.3	6.8
[49]	Sunitinib Phase II	Adv GC and GEJ	2 <sup>nd</sup> or 3 <sup>rd</sup>	FOLFIRI ± sunitinib	91	3.6 vs 3.3 P = 0.6600	10.5 vs 9.0 P = 0.2100
[50]	Sorafenib Phase II	Adv/Met GC and GEJ	1 <sup>st</sup>	Docetaxel/cisplatin + sorafenib	44	5.8	13.6
[51]	Sorafenib Phase II	Adv GC and GEJ	2 <sup>nd</sup>	Oxaliplatin + sorafenib	40	3	6.5
[53]	Regorafenib Phase II	Adv GC and GEJ	2 <sup>nd</sup> or 3 <sup>rd</sup>	Regorafenib vs placebo	152	11.1 wk vs 3.9 wk P < 0.0001	25 wk vs 19.4 wk P = 0.1100
[41]	AVAGAST Phase III	Adv GC and GEJ	1 <sup>st</sup>	Capecitabine/cisplatin ± bevacizumab	774	6.7 vs 5.3 P = 0.0037	12.1 vs 10.1 P = 0.1002
[43]	REGARD Phase III	Met GC and GEJ	2 <sup>nd</sup>	BSC ± ramucirumab	355	2.1 vs 1.3 P < 0.0001	5.2 vs 3.8 P = 0.0473
[44,45]	RAINBOW Phase III	Met GC and GEJ	2 <sup>nd</sup>	Paclitaxel ± ramucirumab	665	4.4 vs 2.86 P < 0.0001	9.63 vs 7.36 P = 0.0169
[47]	Apatinib Phase III	Adv GC and GEJ	3 <sup>rd</sup>	Apatinib vs placebo	270	78 d vs 53 d P < 0.0001	195 d vs 140 d P < 0.016
mTOR [58]	GRANITE-1 Phase III	Adv GC and GEJ	2 <sup>nd</sup> or 3 <sup>rd</sup>	BSC ± everolimus	656	1.7 vs 1.4 P = 0.0010	5.4 vs 4.3 P = 0.124

Adv: Advanced; Met: Metastatic; GC: Gastric cancer; GEJ: Gastroesophageal junction; CapeOx: Capecitabine/oxaliplatin; EOX: Epirubicin/oxaliplatin/capecitabine; FOLFIRI: Fluorouracil/leucovorin/irinotecan; BSC: Best supportive care; HER2: Human epidermal growth factor receptor 2; EGFR: Epidermal growth factor receptor; VEGFR: Vascular endothelial growth factor receptor; mTOR: Mammalian target of rapamycin.

involving 584 treatment naïve patients with metastatic or locally advanced unresectable HER2-overexpressing (defined as IHC3+ or FISH positive) gastric or GEJ adenocarcinoma<sup>[28]</sup>. The addition of trastuzumab to standard chemotherapy demonstrated a significant clinical benefit with higher response rate (47% vs 35%), improved progression-free survival (PFS) (6.7 mo vs 5.5 mo) and improved OS (13.8 mo vs 11.1 mo) compared to the chemotherapy alone arm. In an exploratory analysis, trastuzumab had the greatest survival benefit in patients with IHC3+ tumors, and with FISH+/IHC2+ tumors and ineffective in those with FISH positive but IHC 0 or 1+ tumors. Based on this data, trastuzumab was approved in combination with chemotherapy for the treatment of patients with metastatic HER2-overexpressing gastric or GEJ adenocarcinoma who have not received prior treatment. The ongoing HELOISE trial is evaluating whether a higher dose of trastuzumab in patients with a high tumor burden will have improved OS compared to the standard dosing [NCT01450696].

Given these significant results from the ToGA study,

other strategies to target HER2 have been evaluated. Lapatinib is a tyrosine kinase inhibitor of EGFR and HER2 that binds to the intracellular ATP binding site of these kinases and interferes with their activation. However, unlike with trastuzumab, the trials with lapatinib failed to meet their primary endpoints. The phase III LOGiC trial evaluated the addition of lapatinib to capecitabine and oxaliplatin as first line therapy in 545 patients with HER2 positive advanced gastric and GEJ adenocarcinomas<sup>[29]</sup>. Median OS was 12.2 vs 10.5 mo in the lapatinib arm compared to the placebo arm with a hazard ratio (HR) of 0.91 (95%CI: 0.73-1.12, P = 0.35). However, subgroup analysis showed that certain subgroups - Asian patients (median OS 16.5 mo vs 10.9 mo, HR = 0.91) and those under 60 years (median OS 12.9 mo vs 9 mo, HR = 0.69) - had significant improvements in OS. Similar negative results were seen in the second line setting: the TyTAN trial compared weekly paclitaxel with or without lapatinib and although the median OS was prolonged by two months (11.0 mo vs 8.9 mo, HR = 0.84), it was not statistically significant<sup>[30]</sup>. The subgroup of

**Table 3 Ongoing trials**

Name	Indication	Line	Agent	ClinicalTrials.gov Identifier
<b>HER2</b>				
HELOISE Phase III	HER2(+) Met GC and GEJ	1 <sup>st</sup>	Trastuzumab	NCT01450696
JACOB Phase III	HER2(+) Met GC and GEJ	1 <sup>st</sup>	Pertuzumab	NCT01774786
<b>VEGFR</b>				
RAINFALL Phase III	HER2(-) Met GC and GEJ	1 <sup>st</sup>	Ramucirumab	NCT02314117
<b>PARP</b>				
Olaparib Phase III	Adv GC and GEJ	2 <sup>nd</sup>	Olaparib	NCT01924533
<b>Immune checkpoints</b>				
KEYNOTE-059 Phase II	Adv GC and GEJ		Pembrolizumab	NCT02335411
KEYNOTE-061 Phase III	Adv GC and GEJ	2 <sup>nd</sup>	Pembrolizumab	NCT02370498
KEYNOTE-062 Phase III	Adv GC and GEJ	1 <sup>st</sup>	Pembrolizumab	NCT02494583
MEDI4736 Phase I/ II	Advanced solid tumors		MEDI4736	NCT01693562
JAVELIN Gastric 100 Phase III	Adv/Met GC and GEJ	1 <sup>st</sup>	Avelumab	NCT02625610
JAVELIN Gastric 300 Phase III	Met/recurrent GC and GEJ	3 <sup>rd</sup>	Avelumab	NCT02625623
Phase I/ II	Met/recurrent GC and GEJ		MEDI4736 + Tremelimumab vs Tremelimumab	NCT02340975
Phase I/ II	Advanced solid tumors		Nivolumab +/- Ipilimumab	NCT01928394

Adv: Advanced; Met: Metastatic; GC: Gastric cancer; GEJ: Gastroesophageal junction; HER2: Human epidermal growth factor receptor 2; VEGFR: Vascular endothelial growth factor receptor; PARP: Poly ADP-ribose polymerase.

patients with IHC3+, however, did have a significant benefit in both PFS (5.6 mo vs 4.2 mo) and OS (14 mo vs 7.6 mo).

Two other drugs that have been FDA approved for the treatment of patients with metastatic HER2 positive breast cancer are being investigated in HER2 positive gastric cancer. Pertuzumab is an antibody that binds to a different site on HER2 than trastuzumab and inhibits the dimerization of HER2. The phase III JACOB trial will evaluate the efficacy and safety of pertuzumab in combination with trastuzumab, fluoropyrimidine and cisplatin [NCT01774786]. TDM-1 is an antibody-drug conjugate of trastuzumab and a potent microtubule inhibitor DM1. The multicenter phase II/III GATSBY trial to evaluate TDM-1 vs a taxane in advanced gastric cancer as second line did not show an efficacy benefit of TDM-1 over taxane<sup>[31]</sup>.

**EGFR inhibitors**

EGFR (HER1) is a member of the same family of tyrosine kinase receptors as HER2 and it activates the same intracellular signaling pathways that are responsible for regulating cell growth, differentiation, and survival<sup>[32,33]</sup>. EGFR overexpression occurs in 30%-60% of gastric cancer and is associated with a worse prognosis<sup>[34,35]</sup>. However, studies evaluating antibody inhibitors of EGFR have failed to demonstrate a survival advantage.

Cetuximab is a chimeric monoclonal IgG1 antibody that binds to the extracellular domain of EGFR and competitively inhibits the binding of EGF and other ligands. The phase III trial EXPAND randomized 904 patients to capecitabine and cisplatin with or without cetuximab and did not find progression free or overall survival benefit for the cetuximab group (4.4 mo vs 5.6 mo and 9.4 mo vs 10.7 mo, respectively)<sup>[36]</sup>. Response rates were comparable between the two arms (30% vs 29%) but the cetuximab arm resulted in a higher rate of grade 3 and 4 toxicity (88% vs 77%).

Panitumumab is a fully humanized monoclonal IgG2 antibody targeting EGFR. The phase II/III REAL3 trial evaluated the efficacy of epirubicin, oxaliplatin, and capecitabine with or without panitumumab as first line therapy<sup>[37]</sup>. The phase III study did not show any benefit and actually showed a lower survival in the experimental arm at a preplanned interim analysis (median OS 8.8 mo vs 11.3 mo) so it was discontinued prematurely.

**Vascular endothelial growth factor receptor inhibitors**

Pathological angiogenesis is crucial for tumor growth, survival and metastases. VEGF is an important regulator of angiogenesis and acts on its vascular endothelial growth factor receptor (VEGFR) to stimulate endothelial cells to divide and migrate to form new blood vessels or sprout from existing ones and to help newly formed



blood vessels survive<sup>[38]</sup>. VEGFR is overexpressed in 30%–60% of gastric cancer and is a predictor of poor prognosis<sup>[39,40]</sup>. Trials evaluating anti-VEGF agents are listed in Table 2.

Bevacizumab is a recombinant humanized IgG1 monoclonal antibody against VEGF. AVAGAST was a large randomized phase III study evaluating the addition of bevacizumab to capecitabine and cisplatin<sup>[41]</sup>. Median PFS (6.7 mo vs 5.3 mo) and overall response rate (ORR) (46% vs 37.4%) was significantly improved in the bevacizumab arm but the primary endpoint of OS was not met (12.1 mo vs 10.1 mo,  $P = 0.1002$ ). In subgroup analysis, patients from North and South America showed survival benefit from the addition of bevacizumab (11.5 mo vs 6.8 mo, HR = 0.63, 95%CI: 0.43–0.94), patients from Europe showed a trend toward benefit (HR = 0.85, 95%CI: 0.63–1.14), and patients from Asia had no benefit (HR = 0.97, 95%CI: 0.75–1.25), further suggesting heterogeneity of this disease worldwide. Similar negative results were seen in the AVATAR study where bevacizumab was added to capecitabine and cisplatin in Asian patients with advanced gastric cancer<sup>[42]</sup>.

Ramucirumab is a fully humanized monoclonal antibody against VEGFR-2. The phase III REGARD trial compared ramucirumab monotherapy with best supportive care in the second line<sup>[43]</sup>. The study showed improved median PFS (2.1 mo vs 1.3 mo,  $P < 0.001$ ) and median OS (5.2 mo vs 3.8 mo,  $P = 0.047$ ). In the phase III RAINBOW study, advanced gastric or GEJ adenocarcinoma patients were randomized to paclitaxel with or without ramucirumab in the second line setting<sup>[44,45]</sup>. The addition of ramucirumab showed improved OS of 9.6 mo vs 7.4 mo compared to paclitaxel alone ( $P = 0.0169$ ) and improved PFS (4.4 mo vs 2.9 mo). Based on these trial results, ramucirumab was approved as a single agent for treatment of patients with advanced gastric or GEJ cancer after progressing on prior treatment, as well as in combination with paclitaxel. This is the first approval of a biologic agent in an unselected population with gastric and GEJ cancers. Ramucirumab was also tested in the first line setting in combination with FOLFOX, but it did not show an improvement in the primary endpoint of PFS or median<sup>[46]</sup>. It is also being studied in the phase III RAINFALL trial comparing PFS in patients with HER2-negative, metastatic gastric or GEJ adenocarcinoma receiving ramucirumab with cisplatin and fluoropyrimidine vs cisplatin and fluoropyrimidine as first line treatment [NCT02314117].

A phase III trial assessing a TKI against VEGFR, apatinib, with a two-to-one randomization to apatinib vs placebo in the third line setting in advanced gastric cancer showed that median OS was significantly prolonged in the apatinib group of 195 d vs 140 d ( $P < 0.016$ ), as was median PFS of 78 d vs 53 d ( $P < 0.0001$ )<sup>[47]</sup>.

Sunitinib and sorafenib are multitargeted TKIs

that inhibit VEGFR as well as other kinases. Phase II trials have been conducted both as monotherapy and in combination with chemotherapy and have shown mixed results<sup>[48–51]</sup>. These results are summarized in Table 2. Pazopanib, another multitargeted TKI that inhibits angiogenesis, showed marginal efficacy in a phase II trial as first line with 5-FU/oxaliplatin<sup>[52]</sup>. Data on a phase II trial of regorafenib, a multi-kinase inhibitor, following progression after 1<sup>st</sup> or 2<sup>nd</sup> line chemotherapy demonstrated significantly improved PFS in the regorafenib arm<sup>[53]</sup>. Pre-specified analyses found the effect of regorafenib to be greater in South Korea than in Australia, New Zealand and Canada.

### **mTOR inhibitors**

PI3K/Akt/mTOR pathway is a major downstream cascade of tyrosine kinase signaling and one of the most frequently altered pathways in malignancies. mTOR, an intracellular key serine/threonine protein kinase, regulates cell growth, motility, cellular metabolism and angiogenesis<sup>[54,55]</sup>. Dysregulation of this pathway is associated with poor survival and may contribute to resistance to chemotherapy<sup>[56,57]</sup>.

Everolimus, an oral mTOR inhibitor, was evaluated in the phase III GRANITE-1 trial where it was compared to best supportive care in advanced gastric cancer that progressed after previous chemotherapy<sup>[58]</sup>. The trial randomly assigned 656 patients in a 2:1 ratio to everolimus or placebo. Although median PFS was improved (1.68 mo vs 1.41 mo,  $P < 0.001$ ), the trial did not meet its primary endpoint of improved OS (5.39 vs 4.3 mo,  $P = 0.124$ ). Everolimus is currently being evaluated in combination with paclitaxel as second line treatment in a phase III trial [NCT01248403].

### **c-MET inhibitors**

MET is a tyrosine kinase receptor and signals through RAS-MAPK and PI3K-AKT pathways to mediate cell migration, survival, invasion and angiogenesis. Aberrant HGF/MET signaling triggers multiple intracellular signals that lead to tumor growth, proliferation and metastasis<sup>[59]</sup>. In addition to oncogenesis, aberrant MET signaling has been associated with *in vitro* resistance to cytotoxic agents<sup>[60]</sup>. c-MET amplification is associated with a higher tumor stage, a more aggressive phenotype and a significantly diminished survival<sup>[61,62]</sup>.

Crizotinib is a small molecule inhibitor of anaplastic lymphoma kinase and MET tyrosine kinase that is approved in non-small cell lung cancer. In a study of patients with gastroesophageal cancer, of the 489 tumors screened, 10 patients (2%) harbored MET amplification (> 5 copies)<sup>[63]</sup>. These tumors were more likely to be high-grade and present at advanced stages. Two out of these four patients had a clinical response with a delay in tumor progression. However the responses were transient and time to progression in these two patients was 3.7 mo and 3.5 mo.

Rilotumumab is a fully humanized monoclonal IgG2

against HGF that inhibits the binding of HGF to the MET receptor. A phase II trial evaluating rilotumumab in combination with ECX in patients with untreated advanced gastroesophageal cancer showed minimally improved median PFS and median OS but an exploratory analysis showed that patients with high MET expression appeared to experience marked clinical benefit from addition of rilotumumab to ECX with improvement in median OS from 5.7 to 11.1 mo (HR = 0.29)<sup>[64,65]</sup>. These results led to 2 phase III studies: RILOMET-1 (rilotumumab in combination with ECX as first-line treatment for advanced MET-positive gastroesophageal cancer) and RILOMET-2 (rilotumumab with cisplatin and capecitabine as first-line therapy in gastric cancer). However, data from RILOMET-1 showed that OS, PFS and ORR were statistically worse in the rilotumumab arm<sup>[66]</sup>. No subgroups seemed to benefit with rilotumumab, including those with higher percentages of cells with  $\geq 1+$  MET expression.

Onartuzumab is a monovalent humanized monoclonal antibody against the MET receptor and prevents HGF binding to MET. Onartuzumab in combination with mFOLFOX6 was evaluated in patients with untreated metastatic gastroesophageal cancer that were HER2-negative and MET-positive (III 50% of tumor with moderate-strong intensity staining by IHC based on central review) in a phase III trial, MetGastric. The trial showed that the addition of onartuzumab to mFOLFOX6 did not improve PFS in the unselected population or in the MET-positive subgroup<sup>[67,68]</sup>. Monoclonal antibodies that target c-MET have limited activity as seen in the phase III trials with rilotumumab and onartuzumab, and better biomarkers are needed to select patients for trials with c-MET inhibitors.

### **Poly ADP-ribose polymerase inhibitors**

Poly ADP-ribose polymerase (PARP) is a family of proteins that are critical for the function of base excision repair (BER). BER repairs single strand DNA breaks. If these single strand breaks are not repaired, they become double strand breaks which leads to cell death<sup>[69]</sup>. PARP inhibitors interfere with BER and prevent this repair mechanism which may ultimately lead to death of tumor cells<sup>[70]</sup>.

Olaparib was studied in a second line phase II trial for metastatic or recurrent gastric cancer in combination with paclitaxel vs paclitaxel alone<sup>[71]</sup>. The trial found a statistically significant improvement in OS, but not PFS. Initial preclinical data suggested that responsiveness of gastric cancer cell lines to olaparib was associated with low ataxia telangiectasia mutated (ATM) protein levels, so the study performed a subset analysis and found that patients with low ATM showed a larger improvement in OS with olaparib. These results led to a phase III trial of olaparib in combination with paclitaxel compared with paclitaxel monotherapy in patients with advanced gastric cancer who have progressed following first line therapy [NCT01924533].

Another PARP inhibitor, veliparib, is currently being studied in a phase I trial with FOLFIRI in patients with advanced gastric cancer [NCT01123876].

## **IMMUNOTHERAPY**

Tumor cells have developed mechanisms in which they modulate the immune system, allowing them to escape the immune cells and provide a shield for which the tumor is able to invade, migrate, and grow<sup>[72,73]</sup>. Immune checkpoints are inhibitory pathways that maintain self-tolerance and protect tissues from damage when the immune system is active. The expression of immune-checkpoint proteins can be dysregulated by tumors, making this an important immune resistance mechanism<sup>[74]</sup>. This has led to increasing interest in immunotherapy as a treatment option in multiple solid malignancies.

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) was the first immune checkpoint receptor to be clinically targeted. It is expressed exclusively on T cells and is a negative regulator of T-cell activation. There are two fully humanized CTLA4 antibodies, ipilimumab and tremelimumab. After ipilimumab became the first therapy to improve overall survival in patients with advanced melanoma<sup>[75]</sup>, it is now being evaluated in other advanced cancers including gastric cancer. A phase II trial to evaluate the efficacy of ipilimumab after first-line chemotherapy in the treatment of unresectable or metastatic gastric or GEJ adenocarcinomas was just completed and awaiting results [NCT01585987]. Tremelimumab was investigated in a phase II trial as second-line treatment for patients with metastatic gastric cancer but had an ORR of only 5% and median OS similar to that of second-line chemotherapy<sup>[76]</sup>.

Another immune-checkpoint protein which is expressed on T cells, programmed cell death protein 1 (PD-1), inhibits the activity of the T cell when bound to its ligands PD-L1 and PD-L2 on the surface of a cell. Tumor cells often overexpress PD-L1 or PD-L2 resulting in T cell anergy and escape from immunosurveillance. The KEYNOTE-012 phase Ib study of pembrolizumab, a monoclonal antibody that blocks PD-1 interaction with its ligands, in patients with recurrent and metastatic gastric cancer with PD-L1 tumor positivity based on a prototype IHC assay showed an ORR of 31.6% in Asia Pacific and 30% in the rest of world<sup>[77]</sup>. These results present an exciting novel strategy in the treatment of advanced gastric cancer. The phase II KEYNOTE-059 of pembrolizumab with cisplatin and 5-FU as first-line is currently enrolling [NCT02335411]. Also, two phase III trials, KEYNOTE-061 [NCT02370498] of pembrolizumab vs paclitaxel as second line therapy and KEYNOTE-062 [NCT02494583] of pembrolizumab alone or in combination with cisplatin and fluoropyrimidine vs chemotherapy as first line therapy, are currently ongoing.

There was preliminary evidence of an association

between PD-L1 expression and PFS ( $P = 0.032$ ) and ORR ( $P = 0.071$ ) in the KEYNOTE-012 study. This relationship between PD-L1 expression and clinical outcomes was further explored and found that PD-L1 expression level was associated with ORR (1-sided  $P = 0.10$ ) and ORR was 22% (95%CI: 10-39) by central review and 33% (95%CI: 19-50) by investigator review<sup>[78]</sup>. The 6-mo PFS rate was 24% and the 6-mo OS rate was 69%. Another biomarker that may be predictive of anti-PD-1 therapy is mismatch repair-deficiency. A phase II trial of pembrolizumab for the treatment of colorectal and other GI tumors, including gastric cancer, with mismatch repair-deficiency, or high microsatellite instability (MSI-H), demonstrated high ORR and prolonged PFS [immune-related ORR 71% (5 of 7 patients); immune-related PFS 67% (4 of 6 patients)] when treated with pembrolizumab, supporting the hypothesis that mismatch repair-deficient tumors are more responsive to PD-1 blockade than are mismatch repair-proficient tumors<sup>[79]</sup>.

MEDI4736, a PD-L1 IgG1 antibody, is being studied in a phase I/II trial in patients with advanced solid tumors including gastric cancer and the results of the phase I showed good clinical activity with tumor shrinkage and durable responses<sup>[80]</sup>. Expansion in multiple cancers is ongoing [NCT01693562]. Another PD-L1 inhibitor, Avelumab (MSB0010718C), is being investigated in phase I trials in advanced cancers [NCT01943461, NCT01772004] and in phase III trials in the first line [NCT02625610] and third line [NCT02625623] settings. The combination of CTLA-4 and PDL-1 inhibitors is also being evaluated [NCT01975831, NCT02340975, NCT01928394]. These ongoing trials are outlined in Table 3.

## CONCLUSION

Chemotherapy has long been the standard treatment for advanced gastric cancer. Current combination cytotoxic regimens are associated with response rates of  $\geq 40\%$  but median survival is still less than one year. To improve on this outcome, we have made many advances in our knowledge of the molecular etiology and heterogeneity of gastric cancer, which has led to the development of different targeted therapies. The ToGA trial has established trastuzumab as a new standard of care for patients with HER2 positive (IHC3+ or IHC2+/FISH positive) advanced or metastatic gastric cancer, but this benefit is limited to only approximately 20% of patients with advanced disease. Ramucirumab has also been approved recently for treatment in the second line setting and offers a valuable alternative or addition to chemotherapy. Despite these advances, standard therapy for advanced gastric cancer in the first line setting for patients who are not HER2 positive is still combination chemotherapy with either a doublet or triplet of a platinum and a fluoropyrimidine. Second line options are still limited and include irinotecan, docetaxel, paclitaxel with or without ramucirumab or

ramucirumab monotherapy.

There remains a need to better define patient populations who will benefit from targeted therapy and predict the response to drugs. The Cancer Genome Atlas Research Network has recently classified four molecular subtypes of gastric cancer and identified other possible targets for future clinical research. This will allow for the development of clinical trials in the future to explore therapies in defined sets of patients. Better use of biomarkers to select these sets of patients to improve outcomes will be crucial. Also, as our understanding of the complex interplay between the tumor, the tumor microenvironment and the immune system expand, use of immunotherapy will continue to grow. Although the optimal use of these agents is not yet defined, they may provide an unmet need for patients who did not benefit or unable to tolerate traditional chemotherapy. Further work is necessary to determine the role of targeted therapy and the combination of targeted agents with cytotoxic agents that will translate into improved survival but the future looks optimistic.

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