

2016 Gastric Cancer: Global view

Recent updates of precision therapy for gastric cancer: Towards optimal tailored management

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Abstract

Signaling pathways of gastric carcinogenesis and gastric cancer progression are being avidly studied to seek optimal treatment of gastric cancer. Among them, hepatocyte growth factor (HGF)/c-MET, phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathways have been widely investigated. Their aberrant expression or mutation has been significantly associated with advanced stage or poor prognosis of gastric cancer. Recently, aberrations of immune checkpoints including programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) have been suggested as an important step in the formation of a microenvironment favorable for gastric cancer. Accomplishments in basic research have led to the development of novel agents targeting these signaling pathways. However, phase III studies of selective anti-HGF/c-MET antibodies and mTOR inhibitor failed to show significant benefits in terms of overall survival and progression-free survival. Few agents directly targeting STAT3 have been developed. However, this target is still critical issue in terms of chemoresistance, and SH2-containing protein tyrosine phosphatase 1 might be a significant link to effectively inhibit STAT3 activity. Inhibition of PD-1/PD-L1 showed durable efficacy in phase I studies, and phase III evaluation is warranted. Therapeutic strategy to concurrently inhibit multiple tyrosine kinases is a reasonable option, however, lapatinib needs to be further evaluated to identify good responders. Regorafenib has shown promising effectiveness in prolonging progression-free survival in a phase II study. In this topic highlight, we review the biologic roles and outcomes of clinical studies targeting these signaling pathways.

Key words: Gastric cancer; Hepatocyte growth factor; Mammalian target of rapamycin; Signal transducer and activator of transcription 3; Programmed cell death ligand-1

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Core tip: Among various cellular signaling pathways, hepatocyte growth factor/c-MET, phosphoinositide 3-kinase/Akt/mammalian target of rapamycin and janus kinase 2/signal transducer and activator of transcription 3 pathways are reportedly important in gastric carcinogenesis and metastasis. Aberrations of immune checkpoints have been vigorously investigated. However, clinical results of their target agents have not always matched the theoretical expectations of efficacy. In this review, we summarize the biologic impacts of the aforementioned signaling pathways, and their recent clinical outcomes including those of multiple kinase inhibitors in gastric cancer.

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INTRODUCTION

Gastric cancer is the fourth common malignant tumor worldwide, and the second most common cause of cancer-related mortality^[1]. The progress in therapeutic approaches has allowed complete remission of early gastric cancer by surgical or even endoscopic resection of tumors. However, if gastric cancer is advanced when diagnosed, the prognosis is generally poor and survival time is short even after surgical complete resection. Therefore, highly selective and effective chemotherapy remains an important issue for appropriate management of advanced gastric cancer.

A recent notable study provided a comprehensive molecular evaluation of primary gastric adenocarcinoma tissues as part of The Cancer Genome Atlas project^[2]. The authors proposed four subtypes of gastric cancer according to the molecular characteristics: Epstein-Barr virus positive tumors, microsatellite instability tumors, genomically stable tumors and chromosomal unstable tumors. This study is a prime example of efforts to develop optimal classification of gastric cancer by analyzing common dysregulated pathways and to provide distinct tailored therapy for individual patients. Since the report of significant clinical benefits of trastuzumab in human epidermal growth factor receptor 2 (HER2)-positive gastric and esophagogastric junction (EGJ) adenocarcinoma^[3], various targets have been investigated in the treatment of advanced gastric

cancer. These targets include epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), hepatocyte growth factor(HGF)/c-MET and mammalian target of rapamycin (mTOR)^[4]. However, we still have a long way to go before complete conquest of gastric cancer.

In this topic highlights, we aimed to review the biologic roles of several molecular signaling pathways on the basis of recent trials of targeted therapies in advanced gastric cancer. These include the HGF/c-MET, phosphoinositide 3-kinase (PI3K)/Akt/mTOR, janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) and programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) pathways. In the latter part, we focus on clinical outcomes of newly developed agents targeting the aforementioned pathways and summarize the findings of some clinical studies of multi-kinase inhibitors (MKIs), which can simultaneously multiple receptor tyrosine kinases (RTKs) in advanced gastric cancer.

CELLULAR SIGNALING PATHWAYS OF GASTRIC CANCER

HGF/c-MET pathway

c-MET is a heterodimeric subfamily of RTK. c-MET is composed of an α -chain, which possesses only an extracellular domain, and a β -chain composed of extracellular, transmembrane and intracellular domains^[5]. The ligand of c-MET, HGF, is converted into an active form that causes dimerization and activation of the c-MET receptor. The activated HGF/c-MET signal leads to autophosphorylation of multiple tyrosine residues of the intracellular region of c-MET, such as Y1230, Y1234, Y1235, Y1349 and Y1356, which form multi-functional docking sites to recruit several intracellular adaptor proteins^[6]. Among them, Grb2-associated binder 1 (GAB1) can directly bind to c-MET or forms a complex with growth factor-bound protein 2 (GRB2) to indirectly interact with c-MET. The c-MET association recruits several main adaptor proteins including STAT3 and PI3K, which in turn activate downstream biologic effects including cellular proliferation, migration/invasion and induction of epithelial-mesenchymal transition (EMT) (Figure 1)^[7].

Clinical impact of the HGF/c-MET pathway in gastric cancer has been well documented. High protein expression rate of c-MET in gastric carcinoma tissue has been demonstrated by immunohistochemistry (IHC; 43%-82%)^[8,9] and by gene amplification rate (2%-10%)^[9-12]. In both approaches, the elevated expression of c-MET has been positively associated with advanced tumor stage and poor survival rate. Consequently, multiple agents targeting the HGF/c-MET signaling pathway are being evaluated. Tivantinib, an anti-c-MET tyrosine kinase inhibitor (TKI), used in combination with the EGFR TKI, erlotinib, has extended progression-free survival (PFS) in patients

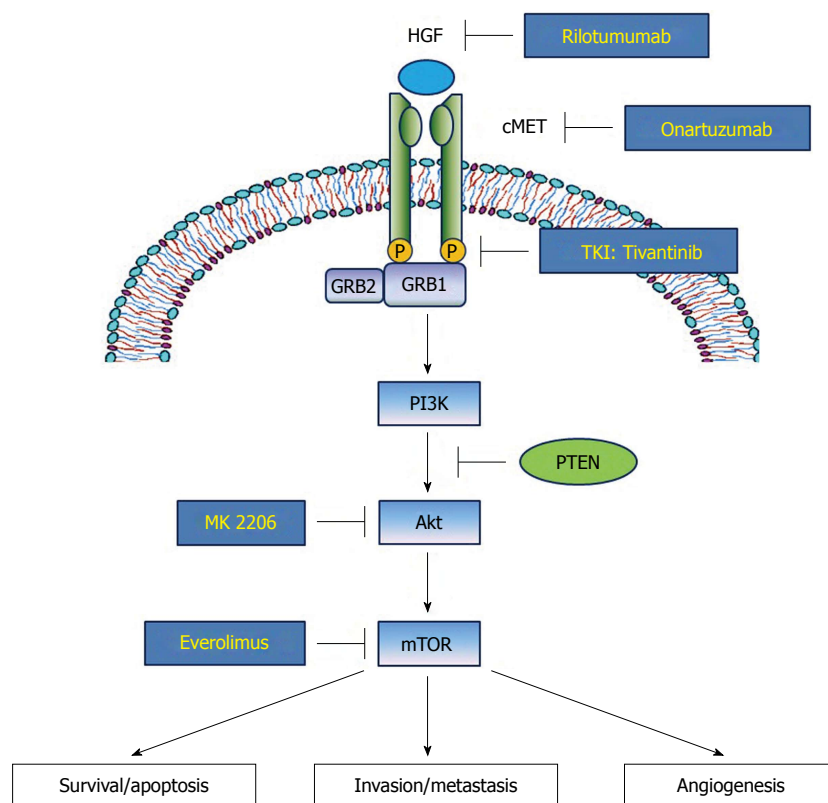


Figure 1 Hepatocyte growth factor/mesenchymal epithelial transition factor and phosphoinositide 3-kinase/Akt/mammalian target of rapamycin pathway, and their inhibitors evaluated in gastric cancer patients. HGF: Hepatocyte growth factor; cMET: Mesenchymal epithelial transition factor; GRB1: Grb2-associated binder 1; GRB2: Growth factor-bound protein 2; PI3K: Phosphoinositide 3-kinase; PTEN: Phosphatase and tensin homolog; mTOR: Mammalian target of rapamycin.

with locally advanced or metastatic non-squamous non-small-cell lung cancer in a phase III trial^[13]. In gastric cancer, phase III studies for rilotumumab, an anti-HGF monoclonal antibody, and onartuzumab, an anti-c-MET monoclonal antibody, have been completed, and clinical outcomes of tivantinib were recently reported^[14].

PI3K/Akt/mTOR pathway

The PI3K-Akt-mTOR pathway plays a pivotal role in oncogenesis and progression including cell growth, survival, invasion/metastasis and angiogenesis, and gastric cancer is no exception. PI3K is usually activated through binding and stimulation of various RTKs by growth factors including HGF and c-MET. Activated PI3K subsequently phosphorylates and activates phosphatidylinositol 3,4-bisphosphate (PIP₂), phosphatidylinositol 3,4,5-trisphosphate (PIP₃), phosphoinositide-dependent protein kinase 1 and Akt^[15]. Akt, which is also termed protein kinase B, is a major effector protein of the PI3K pathway. Phosphorylated Akt (p-Akt) modulates various biologic functions like cell survival, migration/invasion and angiogenesis through downstream adaptor molecules including mTOR (Figure 1)^[16].

Genetic alteration of biological signals involving the PI3K/Akt/mTOR pathway has been frequently detected in gastric carcinoma. For example, a point mutation of

PIK3CA encoding p110 (a class IA subunit of PI3K) is often observed in gastric carcinoma tissues, ranging from 4.3%-25%^[17-21], with the point mutation mostly seen in exon 9 and exon 20^[17]. Their mutation or gene amplification is positively associated with the T stage of gastric cancer^[20,22]. In contrast, *PTEN*, which encodes phosphatase and tensin homolog and inactivates Akt by converting PIP₃ to PIP₂, is deleted in 4%-23% of gastric cancers^[21,23,24] and loss of heterozygosity (LOH) is observed in 17%-47% cases of gastric cancer. LOH of *PTEN* is significantly associated with p-Akt level in gastric carcinoma tissues, TNM stage and poor prognosis of survival^[25-29]. Activated Akt signaling promotes mTOR protein complexes 1 and 2 (mTORC1 and mTORC2), which can play pivotal roles in cancer cell migration and metastasis. Prevalence of mTOR expression is reported as approximately 50% in gastric cancer tissues, and is negatively associated with *PTEN* expression^[30,31].

Clinical and laboratory evidence indicates the promising potential of targeting the PI3K-Akt-mTOR signaling pathway for efficacious treatment of gastric cancer, and various kinds of inhibitors or antibodies acting on this pathway have been developed and tried. These inhibitors are classified into several categories that include PI3K inhibitors, dual mTOR1/mTOR2 inhibitors, Akt inhibitors, mTOR1 inhibitors and dual PI3K/mTOR inhibitors^[15]. Among them, a phase I study

of isoform specific PI3K inhibitor (p110 α) BYL719 is ongoing (NCT01613950)^[32], and clinical outcomes of Akt inhibitor MK 2206 and mTOR1 inhibitor everolimus and rapamycin were previously reported, and are dealt with more fully in the latter part of this review.

JAK2/STAT3 pathway and inhibitory role of SH2-containing protein tyrosine phosphatase 1

The most established stimulator of STAT3 signaling pathway is the interleukin (IL)-6 family that includes IL-6, IL-11 and leukemia inhibitory factor, which bind to their receptors, and then phosphorylate and activate JAK2. Activated JAK2 recruits and activates STAT3 by phosphorylation, which can dimerize and translocate into the nucleus to act as a transcription factor and up-regulate various target genes involving cellular proliferation, migration/invasion and angiogenesis^[33]. Indeed, persistent constitutive activation of JAK2/STAT3 in cancer cells is closely associated with gastric carcinogenesis and poor prognosis^[34]. Besides this classic effect of JAK2/STAT3 pathway in cancer development, another pivotal role of STAT3 protein is the tumor microenvironment, where immune cells can be recruited and STAT3 can mediate various interactions with cancer cells to generate tumor progression. In gastric cancer, *Helicobacter pylori* (*H. pylori*)-induced cytotoxin-associated antigen (CagA) is closely associated with STAT3 activity in both gastric epithelial cells and mucosal immune cells. For example, *H. pylori* infection and CagA secretion can lead to IL-23 release from dendritic cells, which binds to their receptor and activates JAK2/STAT3 transmembrane signaling of naïve CD4⁺ T-cells, and causes differentiation of T-helper (Th)-17 specific lineages to release associated cytokines including IL-17^[35]. Up-regulated IL-17 can promote pro-inflammatory and oncogenic environment. Expression level of IL-17 is positively correlated with depth of tumor, lymphovascular invasion and lymph node involvement in gastric cancer tissues^[36,37], and IL-17 mediates angiogenesis *via* up-regulation of VEGF *in vivo* and *in vitro*^[38]. In gastric epithelial cells, CagA is translocated *via* the type-IV secretion system and releases IL-11. The released IL-11 bind to their receptor and activate the JAK2/STAT3 cascade^[39]. Activated STAT3 functions as a transcription factor to induce many target genes involved in proliferation, invasion/metastasis and angiogenesis including cyclin D1, surviving, matrix metalloproteinase-9, CD44v6 and VEGF^[34,40].

Thus, a therapeutic strategy to target the STAT3 signaling pathway appears to be reasonable. Routes of inhibition include blockade of JAK activation by dephosphorylation, inhibition of STAT3 phosphorylation, dimerization or gene transcription^[35]. In terms of dephosphorylation, several phosphatases have been reported to be associated with STAT3 activity. Among them, SH2-containing protein tyrosine phosphatase 1 (SHP1) may be crucial in the down-regulation of

the JAK2/STAT3 pathway by dephosphorylation^[41-43]. Several candidate agents including natural compounds were reported to induce SHP1 and inhibit STAT3 activity. Sorafenib and its synthetic analogues also can act as a SHP1 agonist to inhibit phosphor-STAT3 activity and show various anti-cancer effects, such as promotion of apoptosis, overcoming of radio- or chemo-resistance and inhibition of EMT or fibrosis on hepatocellular carcinoma cell lines^[44-51]. However, the exact inhibitory role of SHP1 in gastric cancer development and progress is unknown. We recently showed that expression of SHP1 is reduced or ameliorated in various gastric cancer cell lines due to epigenetic silencing, and that reinforced SHP1 expression significantly inhibits cellular proliferation, migration/invasion and induce apoptosis^[52]. SHP1 might be a promising target to effectively inhibit JAK2/STAT3 activity in gastric cancer cells (Figure 2).

Immune checkpoints

Immune checkpoints regarding tumor infiltrating lymphocytes and immune evasion mechanism associated with carcinogenesis have been studied in the search for alternative therapeutic targets. Among them, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-1, which are minimally expressed on the surface of resting T-lymphocytes but are widely expressed on activated T-lymphocytes, have been intensively studied for gastric carcinogenesis, and anti-PD-1 antibodies are already in clinical trials of gastric cancer chemotherapy^[53]. Ligands for PD-1 (PD-L1) and CTLA-4 (B7-1/B7-2), which are expressed on the surface of tumor cells, bind to PD-1 and CTLA-4 respectively, inhibit pivotal function of effector T-cells for immune surveillance and consequently promote the growth of gastric cancer cells (Figure 3)^[54].

PD-1 expression differs between gastric cancer tissues and non-cancerous tissues, with the significantly up-regulated PD-1 level in gastric cancer tissues being significantly correlated with poor clinical parameters including increased tumor size, advanced stage, metastasis and patient survival^[55-58]. Furthermore, PD-1 expression on CD4⁺ and CD8⁺ T cells from gastric cancer tissues is higher than non-cancer tissues or peripheral blood mononuclear cells from normal subjects, and is significantly associated with disease progression^[59]. However, a recent Korean study demonstrated that expression rate of PD-L1 on gastric cancer tissues was 43.6%, and was related to less advanced stage, intestinal type, well/moderately differentiated adenocarcinoma rather than poor differentiation and better overall survival (OS) and disease-free survival^[60]. A recent Chinese study investigated PD-L1 expression level using large number of gastric cancer tissues (almost 400 specimens); PD-L1 expression was significantly associated with TIL density, and moderate to high TIL density was closely correlated with better prognosis^[61]. Thus, the

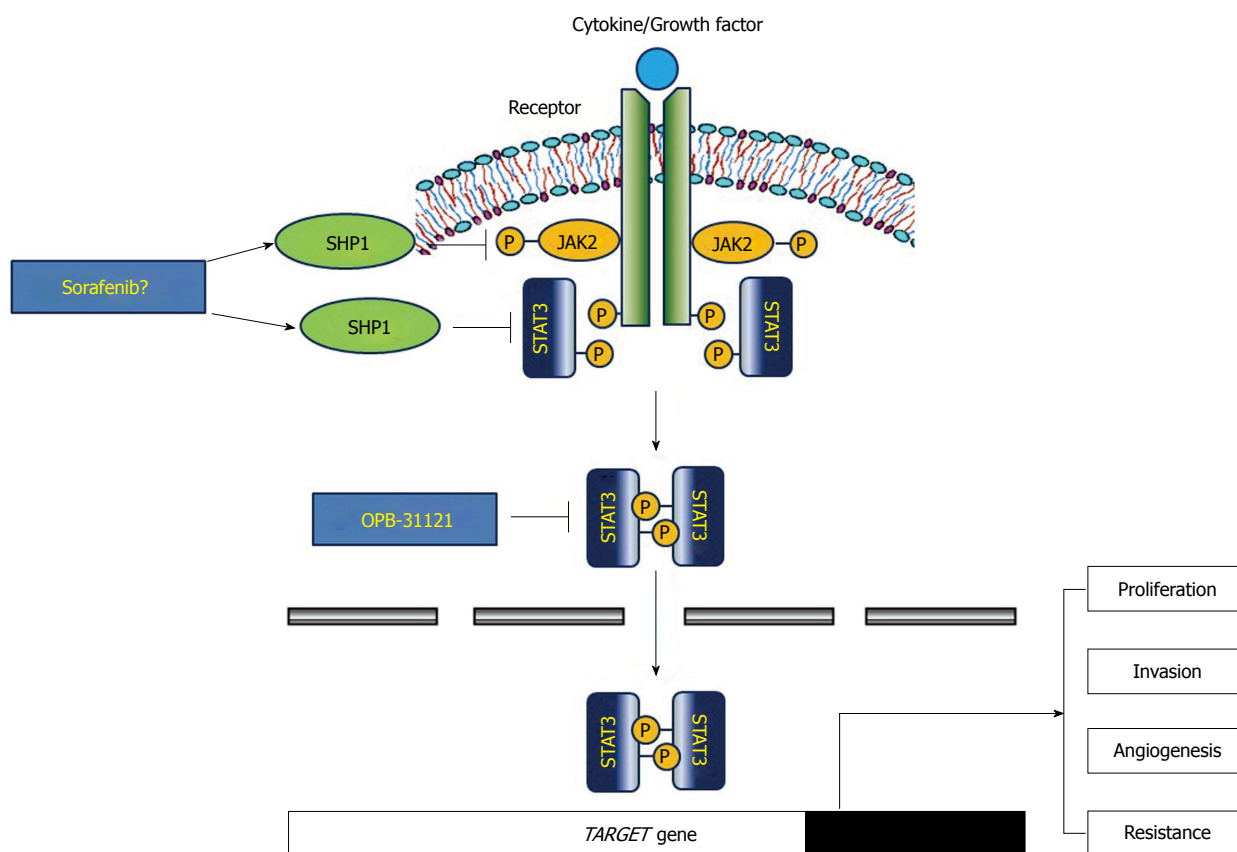


Figure 2 Janus kinase 2/signal transducer and activator of transcription 3 pathway and inhibitory role of SH2-containing protein tyrosine phosphatase 1. JAK2: Janus kinase 2; STAT3: Signal transducer and activator of transcription 3; SHP1: SH2-containing protein tyrosine phosphatase 1.

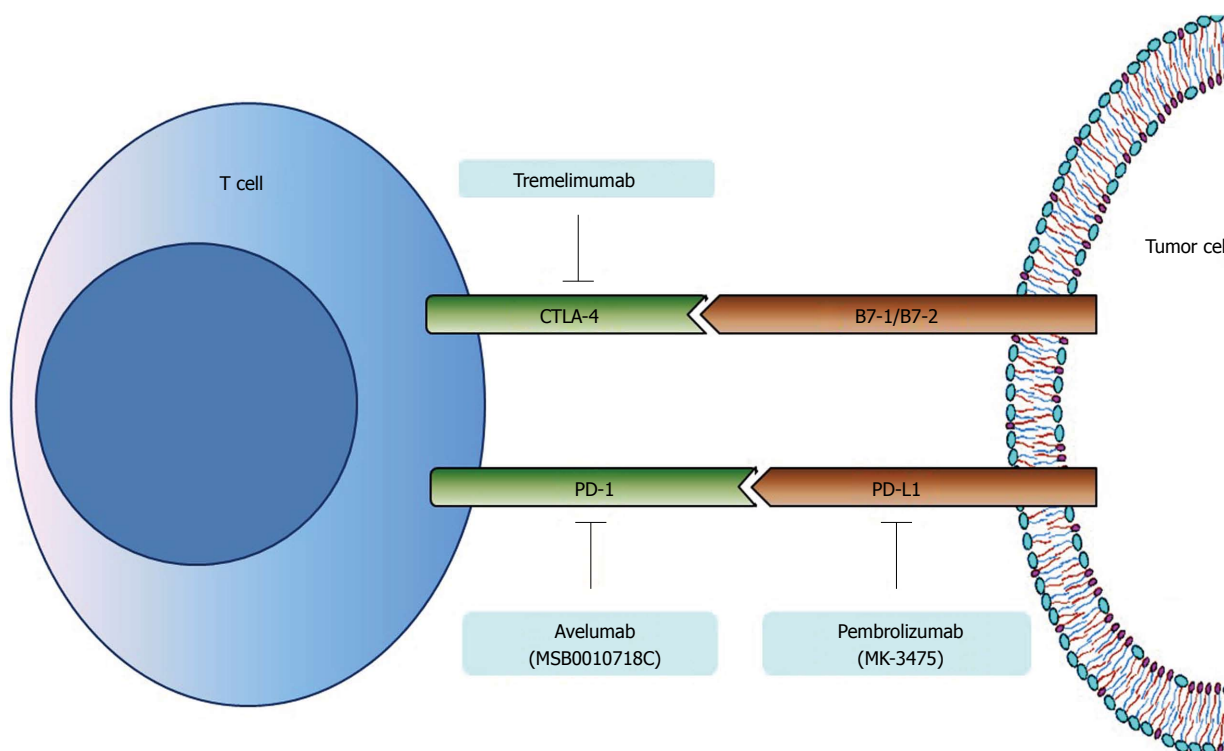


Figure 3 Immune checkpoints on tumor cell and T-cell, and their monoclonal antibodies evaluated in gastric cancer patients. CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PD-1: Programmed cell death-1; PD-L1: Programmed cell death ligand-1.

Table 1 Clinical outcomes of recent trials of targeted therapy in advanced gastric and esophagogastric junction adenocarcinoma

Author and trial	Line of treatment	Phase of study	n	Treatment arms	Outcomes
Anti-HGF/cMET antibodies					
Cunningham <i>et al</i> ^[63] , RILOMET-1 (2015)	First	III	609	ECX + rilotumumab <i>vs</i> ECX + placebo	OS: 9.6 mo <i>vs</i> 11.5 mo (HR = 1.37, <i>P</i> = 0.016) PFS: 5.7 mo <i>vs</i> 5.7 mo (HR = 1.30, <i>P</i> = 0.016) ORR: 30% <i>vs</i> 39.2% (OR 0.67, <i>P</i> = 0.027)
Shah <i>et al</i> ^[65] , METGastric (2015)	First	III	562	mFOLFOX + onartuzumab <i>vs</i> mFOLFOX + placebo	OS: 11.0 mo <i>vs</i> 11.3 mo (HR = 0.82, <i>P</i> = 0.244) PFS: 6.7 mo <i>vs</i> 6.8 mo (HR = 0.90, <i>P</i> = 0.429) ORR: 46% <i>vs</i> 41% (<i>P</i> = 0.253)
Malka <i>et al</i> ^[66] , PRODIGE 17 ACCORD 20 MEGA (2015)	First	II	162	mFOLFOX alone <i>vs</i> mFOLFOX + panitumumab <i>vs</i> mFOLFOX + rilotumumab	4-mo PFS rate: 71 <i>vs</i> 63 <i>vs</i> 63% PFS: 5.8 mo <i>vs</i> 5.2 mo <i>vs</i> 7.6 mo ORR: 54% <i>vs</i> 44% <i>vs</i> 50%
Akt/mTOR inhibitors					
Hudis <i>et al</i> ^[68] (2013)	Second/third	I	34	Trastuzumab + Akt inhibitor (MK-2206)	RR (including stable disease): 24% Time to progression: 72 d
Ohtsu <i>et al</i> ^[70] GRANITE (2013)	Second/third	III	646	Everolimus <i>vs</i> BSC	OS: 5.4 mo <i>vs</i> 4.3 mo (HR = 0.90, <i>P</i> = 0.124) PFS: 1.7 mo <i>vs</i> 1.4 mo (HR = 0.66, <i>P</i> < 0.001) ORR: 4.5% <i>vs</i> 2.1%; DCR: 43.3% <i>vs</i> 22.0%
Shen <i>et al</i> ^[71] (2014)	First	II	40	Everolimus + cisplatin + HDFL	OS: 10.5 mo (95%CI: 8.6-12.3) PFS: 6.9 mo (95%CI: 4.9-8.4)
STAT3 inhibitor					
Oh <i>et al</i> ^[74] (2015)	Second/third	I	25	STAT3 inhibitor (OPB-31121)	RR (including stable disease): 44.4%
Immune checkpoints inhibitors					
Ralph <i>et al</i> ^[89] (2010)	Second	II	18	Tremelimumab	OS: 4.8 mo (95%CI: 4.06-5.59) 12 mo OS rate: 33% (95%CI: 14-54) RR (including stable disease): 27.8%
Bang <i>et al</i> ^[90] , KEYNOTE-012 (2015)	Second/third	I	39	Pembrolizumab (MK-3475)	OS: 11.4 mo; PFS 1.9 mo ORR: 22% (95%CI: 10-39)
Yamada <i>et al</i> ^[93] (2015)	Second/third	I	20	Avelumab (MS0010718C)	PFS: 11.9 wk (95%CI: 6.0-12.3) ORR: 15.0% (95%CI: 3.2-37.9)
Multikinase inhibitors					
Sun <i>et al</i> ^[95] (2010)	First	II	44	Sorafenib + docetaxel + cisplatin	OS: 13.6 mo (90%CI: 8.6-16.1) PFS: 5.8 mo (90%CI: 5.4-7.4) PR: 41% (90%CI: 28-54)
Martin-Richard <i>et al</i> ^[96] , GERCAD (2013)	First	II	40	Sorafenib + oxaliplatin	OS: 6.5 mo (95%CI: 5.2-9.6) PFS: 3 mo (95%CI: 2.3-4.1) RR (including stable disease): 50.0%
Hecht <i>et al</i> ^[100] , LOGiC (2015)	First	III	487	CapeOx + lapatinib <i>vs</i> CapeOx + placebo	OS: 12.2 mo <i>vs</i> 10.5 mo (HR = 0.91, <i>P</i> = 0.349) PFS: 6.0 mo <i>vs</i> 5.4 mo (HR = 0.82, <i>P</i> = 0.0381) ORR: 53% <i>vs</i> 39% (<i>P</i> = 0.0031)
Satoh <i>et al</i> ^[101] , TyTAN (2014)	Second	III	261	Lapatinib + paclitaxel <i>vs</i> Paclitaxel alone	OS: 11.0 mo <i>vs</i> 8.9 mo (HR = 0.84, <i>P</i> = 0.1044) PFS: 5.4 mo <i>vs</i> 4.4 mo (HR = 0.85, <i>P</i> = 0.2441) ORR: 27% <i>vs</i> 9% (<i>P</i> < 0.001)
Pavakis <i>et al</i> ^[103] , INTEGRATE (2015)	Second/third	II	147	Regorafenib <i>vs</i> placebo	OS: 5.8 mo <i>vs</i> 4.5 mo (HR = 0.74, <i>P</i> = 0.11) PFS: 2.6 mo <i>vs</i> 0.9 mo (HR = 0.40, <i>P</i> < 0.0001) RR (including stable disease): 44% <i>vs</i> 16%
Lee <i>et al</i> ^[106] (2015)	First	II	66	CapeOx + pazopanib	PFS: 6.5 mo; OS: 10.5 mo; ORR: 57.6%

ECX: Epirubicin/Cisplatin/Capecitabine; mFOLFOX: 5-fluorouracil/leucovorin/oxaliplatin; OS: Overall survival; HR: Hazard ratio; PFS: Progression free survival; ORR: Objective response rate; BSC: Best supportive care; DCR: Disease control rate; HDFL: High-dose 5-fluorouracil/leucovorin; CapeOx: Capecitabine/oxaliplatin.

exact relationship between PD-1/PD-L1 expression and clinical parameters needs to be further evaluated.

RECENT TRIALS OF TARGET THERAPY FOR GASTRIC CANCER

The pivotal ToGA study of targeted therapy for the treatment of unresectable gastric/EGJ cancer investigated the synergistic effects of trastuzumab, a monoclonal anti-HER2 antibody, with capecitabine/cisplatin or fluorouracil/cisplatin regimen. OS and PFS were significantly prolonged^[3]. Since then, various target agents have been tried for the optimal

treatment of advanced gastric cancer. Among them, newly developed drugs targeting the HGF/c-MET, PI3K/Akt/mTOR, JAK2/STAT3 and PD-1/PD-L1 pathways are dealt with here, and MKIs that simultaneously target multiple tyrosine kinases is also introduced in this section. A portion of these studies were presented at the 2015 annual meeting of the American Society of Clinical Oncology (ASCO); their outcomes are summarized in Table 1.

Phase III studies of anti-HGF/c-MET antibodies

Rilotumumab, an anti-HGF monoclonal antibody, and onartuzumab, an anti-c-MET monoclonal antibody,

have been tried as first-line treatments for gastric or EGJ adenocarcinoma in phase III studies. Their clinical outcomes were presented at the ASCO 2015 meeting. Rilotumumab significantly increased PFS when combined with ECX (epirubicin/cisplatin/capecitabine) regimen in a phase I b/II study^[62]. From this background, the phase III RILOMET-1 study of first-line therapy of MET-positive, HER2-negative gastric/EGJ cancer compared rilotumumab (15 mg/kg) plus ECX with placebo plus ECX was performed. OS (9.6 mo vs 11.5 mo, HR = 1.37, $P = 0.021$) and objective response rate (ORR: 30.0% vs 39.2%, OR = 0.67, $P = 0.027$) were significantly inferior in the rilotumumab group, and subgroup analysis also showed that no subgroups appeared to be benefit with rilotumumab arm regardless of the degree of MET positivity^[63]. This result is contrary to that of a phase I/IIa study, which contained a larger number of Asian patients (18%) than the RILOMET-1 population (1%). The different racial distribution may have contributed to the opposite outcomes between the two studies. Thus, the phase III RILOMET-2 study has been performed to investigate the efficacy of rilotumumab in combination with cisplatin/capecitabine regimen as the first line chemotherapy among Asian patients with unresectable gastric/EGJ cancer^[64].

The METGastric study of onartuzumab (10 mg/kg) for the treatment of HER2-negative, MET-positive metastatic gastric or EGJ adenocarcinoma without prior treatment, used onartuzumab in combination with the 5-fluorouracil (5-FU)/leucovorin/oxaliplatin (FOLFOX) regimen and compared outcomes with FOLFOX alone^[65]. The addition of onartuzumab to FOLFOX was ineffective in the intention-to-treat analysis and OS, PFS and ORR were not significantly different between the two groups. However, addition of onartuzumab showed a marginal effect in OS for the moderate-to-strong MET positive subgroup (9.7 mo vs 11.0 mo, HR = 0.64, $P = 0.062$). Grade 3 or 4 adverse events were more common in the onartuzumab arm. Furthermore, a French phase II study that compared FOLFOX plus rilotumumab or panitumumab, an anti-EGFR antibody, with FOLFOX alone for first-line treatment of metastatic, HER2-negative gastric or EGJ adenocarcinoma showed that adding panitumumab or rilotumumab seemed more toxic and was not more effective than mFOLFOX6 alone^[66]. Considering recent outcomes of phase II/III studies of rilotumumab and onartuzumab, targeting HGF/c-MET in gastric cancer has little rationale for further evaluation. However, cMET still has potential for promising biomarkers considering that c-MET-positive gastric/EGJ cancers have strong association with shorter OS and poor prognosis^[67], and future research needs to search for other significant predictive factors for response to anti-HGF/c-MET therapy.

Akt and mTOR inhibitors

A phase I study evaluated the combinatory effect of

MK-2206, a potent pan-Akt inhibitor, with trastuzumab for treatment of HER2-positive, refractory gastric carcinoma. The rationale was that the PI3K/Akt pathway is a main downstream signaling pathway of HER2 and is closely related with trastuzumab resistance. Oral MKN-2206 was given either 135 mg every week or 60 mg every other day with trastuzumab 8 mg/kg intravenously on day 1 every 3 wk. Clinical benefit response rate including stable disease more than 4 mo was 24%, and median time to progression was 72 d^[68].

The PI3K/Akt pathway might be successfully inhibited by targeting mTORC1 kinase, and the development of rapamycin analogs (*e.g.*, everolimus, temsirolimus) have been promoted^[15]. A multicenter phase II study of everolimus, an oral inhibitor of mTOR, in patients with refractory metastatic gastric cancer showed a disease control rate of 56.0%, PFS of 2.7 mo (95%CI: 1.6-3.0 mo) and OS of 10.1 mo (95%CI: 6.5-12.1 mo), which warrant further phase III evaluation^[69]. However, results of the phase III GRANITE-1 study comparing everolimus with best supportive care for previously treated advanced gastric cancer were disappointing, and researchers failed to demonstrate significant benefit in OS (5.4 mo vs 4.3 mo, HR = 0.90, $P = 0.124$); indeed, PFS was significantly increased in the everolimus arm (1.7 mo vs 1.4 mo, HR = 0.66, $P < 0.001$)^[70]. A phase II multicenter study of low dose everolimus (10 mg on days 1, 8 and 15) plus cisplatin and a weekly 24-h infusion of high-dose 5-FU and leucovorin (cisplatin 35 mg/m² intravenous infusion for 24 h on days 1 and 8, 5-FU 2000 mg/m² and leucovorin 300 mg/m² intravenous infusion for 24 h on days 1, 8 and 15) for treatment-naïve gastric cancer was conducted but failed to increase ORR as in a preplanned statistical assumption (52.5%)^[71]. However, in one case everolimus was tried after failure of 1st and 2nd line chemotherapy for a young male metastatic gastric cancer patient with multiple liver metastases. A subsequent mutational analysis revealed a PIK3CA hotspot mutation and pS6 overexpression in the primary tumor. The patient achieved stable disease for 1 year and pS6 expression was nearly abolished after two cycles of everolimus treatment^[72]. Furthermore, a phase II study of everolimus for refractory metastatic gastric and EGJ adenocarcinoma showed that a subgroup with strong pS6 expression ($\geq 2 +$ IHC staining) was significantly correlated with better PFS and disease control rate^[73]. Therefore, subgroup analysis for finding of positive predictive biomarkers in patients treated with everolimus needs to be performed.

STAT3 inhibitors and effect of SHP1 inducers

Few agents capable of directly targeting STAT3 have been developed, and clinical trials of STAT3 inhibitors in the treatment of gastric cancer are lacking. A recent phase I study reported that OPB-31121, an oral STAT3 inhibitor, showed an overall response rate

Table 2 Ongoing clinical trials of target therapy in advanced gastric and esophagogastric junction adenocarcinoma

Trial identifier	Line of treatment	Phase of study	Treatment arms	Primary endpoint
Akt/mTOR inhibitors NCT01613950 ^[52]	Second/third	Ib	AUY922/BYL719	MTD
Immune checkpoints inhibitors NCT02335411 (KEYNOTE-059) ^[91]	Third	II	Cohort 1: pembrolizumab monotherapy Cohort 2: pembrolizumab + 5-FU/cisplatin or capecitabine/cisplatin	ORR
NCT02370498 (KEYNOTE-061) ^[92]	Second	III	Pembrolizumab <i>vs</i> paclitaxel	PFS, OS
Multikinase inhibitors NCT02015169 ^[107]	Neoadjuvant	II	XELOX + lapatinib	R0 resection rate
NCT01913639 ^[108]	First	II	FOLFOX + regorafenib	PFS

PFS: Progression free survival; OS: Overall survival; MTD: Maximum tolerated dose; 5-FU: 5-fluorouracil; ORR: Objective response rate; XELOX: Capecitabine/oxaliplatin; FOLFOX: 5-fluorouracil/leucovorin/oxaliplatin; mTOR: Mammalian target of rapamycin.

of 44.4% assessed as stable disease in advanced solid tumors including gastric cancer^[74]. However, STAT3 not only up-regulates various target oncogenes associated with gastric carcinogenesis and metastasis, but is closely related with drug resistance of standard chemotherapeutic agents including 5-FU, cisplatin and adriamycin in gastric cancer^[75-77]. In this regard, targeting of STAT3 remains a critical issue in the treatment of gastric cancer, and development of specific and effective inhibitors of STAT3 should be further investigated. Several natural compounds^[76,78-80] and pharmacologic medicines, such as proton pump inhibitors^[75,81], inhibit STAT3 activity in *in vitro* and *in vivo* studies of gastric cancer. These agents are expected to show a synergetic effect or enhance chemosensitivity when combined with standard chemotherapy agents.

Several natural compounds inhibit the STAT3 activation pathway through induction of SHP1 in hematopoietic cancer cell lines^[42,43,82-85] and hepatocellular carcinoma (HCC) cell lines^[86,87]. We recently showed that plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone), a quinonoid constituent extracted from the roots of the medical plant *Plumbago zeylanica* L, suppresses STAT3 activity and consequently targets gene expression *via* induction of SHP1 in gastric cancer cells^[88]. Because most gastric cancer cells showed reduced or lack of expression of SHP1, a therapeutic strategy to indirectly inhibit STAT3 pathway might be an alternative option in pharmacologic treatment of gastric cancer and SHP1 may play pivotal roles in this signaling pathway. As mentioned above, several MKIs, such as sorafenib and sunitinib, show a significant link between SHP1 and suppression of STAT3 activity in HCC cells.

Immune checkpoint inhibitors: anti-PD-1/PD-L1 antibodies

The anti-CTLA-4 monoclonal antibody tremelimumab was developed and a phase II study was performed to evaluate its use in second-line chemotherapy in advanced gastric and esophageal adenocarcinoma. However, the results were disappointing and only one patient achieved partial response among 18 enrolled

patients, and stable disease was observed only in four patients^[89]. Concerning the PD-1/PD-L1 pathway, pembrolizumab (MK-3475), an anti-PD-1 monoclonal antibody, and avelumab (MS0010718C), an anti-PD-L1 monoclonal antibody, have been developed. Pembrolizumab was tried for rescue therapy of recurrent or metastatic gastric or EGJ adenocarcinoma, which were positive for PD-L1, in the KEYNOTE-012 study^[90]. ORR by central review was 22.2%, PFS 1.9 mo and OS 11.4 mo, and pembrolizumab showed durable efficacy and manageable safety profile for the heavily pre-treated, PD-L1 positive population. Further studies to support the efficacy of pembrolizumab in advanced gastric cancer are now in progress. For example, KEYNOTE-059 (NCT02335411) is a phase II study of pembrolizumab monotherapy or in combination with standard chemotherapy^[91] and KEYNOTE-061 (NCT02370498) is a phase III study to compare pembrolizumab monotherapy with paclitaxel as the second-line therapy^[92] (Table 2).

In Japan, avelumab was tried for refractory stage IV gastric and EGJ adenocarcinoma. A dose of 10 mg/kg was administered intravenously every 2 wk until progression. Most of adverse events were grade 1 or 2, ORR was 15.0% and PFS was 11.9 wk. Additional studies to evaluate the efficacy of avelumab and biomarkers from tumor tissue and blood samples including PD-L1 expression need to be evaluated^[93].

MKIs

RTKs play crucial roles in the development of proliferation, differentiation, migration/invasion and apoptosis in gastric cancer. Currently, various inhibitors targeting the tyrosine kinase motif have been developed, and some display concurrent inhibitory effects of multiple tyrosine kinases. One of the first generation MKIs was sorafenib, which can inhibit BRAF, VEGF receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR)^[94]. A phase II study investigated the efficacy of sorafenib in combination with docetaxel and cisplatin as the first-line chemotherapy in metastatic gastric or EGJ adenocarcinoma. Partial response was achieved in

41% (90%CI: 28%-54%), and the median PFS was 5.8 mo (90%CI: 5.4-7.4 mo) and median OS was 13.6 mo (90%CI: 8.6-16.1 mo). No additional toxicities were observed by adding sorafenib to docetaxel/cisplatin regimen. The results of this study warranted further evaluation of sorafenib in chemotherapy of gastric cancer^[95]. However, another multicenter phase II study of oxaliplatin and sorafenib as the second-line chemotherapy after failure of cisplatin/fluoropyrimidine regimen in advanced gastric adenocarcinoma revealed a median PFS of 3.0 mo (95%CI: 2.3-4.1 mo) and median OS of 6.5 mo (95%CI: 5.2-9.7 mo), which failed to support the implementation of a phase III study^[96]. Sorafenib was also evaluated for combination therapy with oral fluoropyrimidine and cisplatin, such as S-1/cisplatin^[97] and capecitabine/cisplatin^[98], in phase I studies. Both studies showed tolerable safety profile and acceptable efficacy.

Lapatinib is a MKI that competitively inhibits ATP binding of tyrosine kinase in both HER2 and EGFR, and which is approved for the treatment of HER2-positive breast cancer^[99]. Two large-scale, randomized, phase III trials were recently reported. The researchers evaluated the efficacy and safety of lapatinib in HER2-positive, advanced or metastatic gastric and EGJ adenocarcinoma. The LOGiC study addressed lapatinib as the first-line chemotherapy in combination with capecitabine/oxaliplatin, and lapatinib arm was compared with capecitabine/oxaliplatin alone^[100]. Median OS was not significant between both arms (12.2 mo vs 10.5 mo, $P = 0.349$), while PFS was significantly longer (6.0 mo vs 5.3 mo, $P = 0.0381$) and ORR was higher (53% vs 39%, $P = 0.0031$) in the lapatinib arm. Subgroup analysis for OS revealed that Asians and younger patients (< 60 years) showed significant benefit. The TyTAN study compared lapatinib plus paclitaxel with paclitaxel alone in the second-line treatment of gastric cancer in an Asian population^[101]. This study showed no significant difference of median OS and PFS between both arms (11.0 mo vs 8.9 mo, $P = 0.1044$; 5.4 mo vs 4.4 mo, $P = 0.2441$; respectively). However, better efficacy was observed in the lapatinib arm in HER2-3+ subgroup. Further studies are warranted to examine the factors predicting good responders to lapatinib therapy.

Several novel MKIs have been investigated for the treatment of refractory gastric cancer. Findings were presented at the ASCO 2015 meeting. Among them, regorafenib, which inhibits multiple tyrosine kinases related to angiogenesis (VEGFR1-3), tumor microenvironment [PDGFR- β , fibroblast growth factor receptor (FGFR)] and oncogenesis (KIT), was previously developed and reported as effective in colon cancer and gastrointestinal stromal tumors (GISTs)^[102]. The phase II INTEGRATE study was designed and performed to investigate the efficacy of regorafenib in refractory, metastatic gastric and EGJ adenocarcinoma by comparing regorafenib 160 mg/d with placebo^[103]. PFS was significantly increased in regorafenib group (2.6

mo vs 0.9 mo, HR = 0.40, $P < 0.0001$), however, OS was not significantly different between two groups (5.8 mo vs 4.5 mo, HR = 0.74, $P = 0.11$). An interesting thing is that HR for PFS was significantly lower in Korean patients than in Western patients from Canada and Australia, which indicates that regorafenib might be more effective in Asian patients. Pazopanib is another potent MKI of VEGFR1-3, PDGFR α/β and FGFR1/3, and was previously approved by the United States Food and Drug Administration for the treatment of patients with advanced renal cell carcinoma^[104]. A phase II study was performed and reported the combinatory effect of pazopanib with capecitabine/oxaliplatin regimen as the first-line chemotherapy in metastatic gastric and EGJ cancer. ORR was 57.6% and adverse events of grade 3-4 were neutropenia (15.1%), anemia and thrombocytopenia (both 10.6%)^[105].

CONCLUSION

Many studies have focused on revealing biologic relevant mechanism of development and progression of gastric cancer, and many medical agents targeting these pathways have been validated in clinical trials. However, most of them failed to reach significant benefits in phase III trials, and novel therapeutic strategies are necessary in the future. To achieve this goal, individualized and precise target therapy should be planned on the basis of exploration of biologic characteristics of individual gastric cancer patients. In addition, targeting multiple RTKs rather than focusing on single pathway and attempts to overcome chemoresistance and enhance synergism with standard chemotherapeutic agents are expected to be prevalent. These approaches will hopefully lead to a more effective treatment, perhaps even conquest, of gastric cancer.

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