World Journal of Gastrointestinal Oncology

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DOI: 10.4251/wjgo.v7.i11.263

World J Gastrointest Oncol 2015 November 15; 7(11): 263-270
ISSN 1948-5204 (online)

EDITORIAL

Novel therapy for advanced gastric cancer

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Author contributions: Zhang Y and Wu S contributed the same to this paper.

Conflict-of-interest statement: None to declare.

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Received: June 18, 2015
Peer-review started: June 20, 2015
First decision: July 27, 2015
Revised: August 14, 2015
Accepted: September 16, 2015
Article in press: September 18, 2015
Published online: November 15, 2015

Abstract

Gastric cancer (GC) is a common lethal malignancy. Gastroesophageal junction and gastric cardia tumors are the fastest rising malignancies due to increasing prevalence of obesity and acid reflex in the United States. Traditional chemotherapy remains the main treatment with trastuzumab targeting human epidermal growth factor receptor 2 positive disease. The median overall survival (OS) is less than one year for advanced GC patients; thus, there is an urgent unmet need to develop novel therapy for GC. Although multiple targeted agents were studied, only the vascular endothelial growth factor receptor inhibitor ramucirumab was approved recently by the United States Food and Drug Administration because of its 1.4 mo OS benefit (5.2 mo *vs* 3.8 mo, $P = 0.047$) as a single agent; 2.2 mo improvement of survival (9.6 mo *vs* 7.4 mo, $P = 0.017$) when combined with paclitaxel in previously treated advanced GC patients. It is the first single agent approved for previously treated GC and the second biologic agent after trastuzumab. Even with limited success, targeted therapy may be improved by developing new biomarkers. Immune therapy is changing the paradigm of cancer treatment and is presently under active investigation for GC in clinical trials. More evidence supports GC stem cells existence and early stage studies are looking for its potential therapeutic possibilities.

Key words: Gastric cancer; Novel therapy; Targeted therapy; Immune therapy; Gastric cancer stem cell

Core tip: Advanced gastric cancer (GC) has very poor outcome with chemotherapy remains the main treatment. There is an urgent unmet need to develop novel therapy for GC. Limited success is achieved for targeted therapy after trastuzumab for human epidermal growth factor receptor 2 positive disease. Ramucirumab was recently approved by Food and Drug Administration as a single agent or combined with paclitaxel in refractory advanced GC patients. Immune therapy and GC stem cell research are on the horizon.

Zhang Y, Wu S. Novel therapy for advanced gastric cancer. *World J Gastrointest Oncol* 2015; 7(11): 263-270 Available from: URL: http://www.wjgnet.com/1948-5204/full/v7/i11/263.htm
DOI: http://dx.doi.org/10.4251/wjgo.v7.i11.263

INTRODUCTION

Gastric cancer (GC) is a common malignancy and the second leading cause of cancer death worldwide[1]. In the United States, there were approximately 22220 new cases and 10990 death in 2014[2]. With overweight and obesity being a more serious epidemiologic issue in the United States, gastroesophageal junction and gastric cardia adenocarcinoma have been the fastest rising cancer. Majority of GCs are present at advanced stages with either metastatic or extensive local/regional disease. It is a group of heterogeneous diseases with different anatomy, epidemiology, etiology, pathogenesis, and behavior. Chemotherapy using fluoropyrimidine or platinum as backbone is the main treatment for advanced GCs. The median survival is limited to 7 to 12 mo in clinical trial setting[3,4]. There is an urgent demand for new therapy to improve its treatment and outcome.

DIFFICULTY AND PROGRESS IN TARGETED THERAPY

Targeted therapy has been the main focus in clinical trials, even though majority of the targeted agents were tested in an unselected "off target" patient population and there was a lacking of biomarkers. It has led to the failure of multiple large phase Ⅲ clinical trials in different pathways. Trastuzumab is approved for human epidermal growth factor receptor 2 (HER2) positive GCs. Ramucirumab has recently gained its label as a single agent or in combination with paclitaxel for refractory GCs patients following fluoropyrimidine or platinum containing chemotherapy.

Epidermal growth factor receptor targeting therapy

Epidermal growth factor receptor (EGFR) has been studied extensively. EXPAND and REAL 3 are the two recent phase Ⅲ clinical trials with EGFR antibodies: cetuximab and panitumumab. Both of them failed to show survival benefit and were concerning for worse toxicity in the EGFR inhibitor study arms. In the EXPAND trial, median progression-free survival (PFS) (4.4 mo *vs* 5.6 mo, $P = 0.32$) and overall survival (OS) (9.4 mo *vs* 10.7 mo, $P = 0.95$) favored the chemotherapy only group, overall response rates (RR) were similar 30% *vs* 29%[5]. Grade 3-4 toxicities were substantially higher in the cetuximab-containing regimen than in the control regimen[5]. REAL 3 trial demonstrated inferior OS in the panitumumab study group when compared to control group (11.3 mo *vs* 8.8 mo, $P = 0.013$) with more toxicities[6]. Biomarker was not used to select patient in both studies. Only 6% screened patients were positive for Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation, a potential association of benefit was found in KRAS mutated group although not significant[6]. This result is contrary to KRAS mutated colon cancer[7].

Phosphatidylinositol 3-kinase /Akt/ mammalian target of rapamycin targeting therapy

The phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin signaling pathway was studied with everolimus in 656 previous treated advanced GC patients in a phase Ⅲ trial: GRANITE-1. Primary endpoint was not reached (OS: 5.4 mo *vs* 4.3 mo, $P = 0.12$), even though PFS was improved (1.7 mo *vs* 1.4 mo, $P < 0.001$)[8]. No biomarker was required for this study entry.

HER2 targeting therapy

HER2 overexpression by immunohistochemistry or gene amplification by fluoresecnence *in situ* hybridization was required for patients' recruitment for the phase Ⅲ ToGA trial. This pivotal trial led to trastuzumab approval with all the outcomes better in the study group (median OS: 13.8 mo *vs* 11.1 mo, $P = 0.0046$; PFS: 6.7 mo *vs* 5.5 mo, $P = 0.0002$; RR: 47% *vs* 35%, $P = 0.0017$)[9]. A post-hoc analysis grouped HER2 status and suggested that larger survival benefit in patients with tumor HER 2 IHC 3+ or 2+ and FISH positive group (OS: 16.0 mo *vs* 11.8 mo, $P = 0.036$)[9]. Lapatinib is a dual tyrosine kinase inhibitor (TIK) inhibitor of HER2 and EGFR. It failed to meet OS benefit in two large phase Ⅲ trials: TRIO-013/Logic in the first line and TyTan in the second line settings (TRIO-013/Logic: 12.2 mo *vs* 10.5 mo, $P = 0.35$; TyTan: 11.0 mo *vs* 8.9 mo, $P = 0.1044$)[10,11]. Lapatinib failure in GC trials might partially relate to its EGFR inhibition effect. Pertuzumab is another humanized monoclonal antibody that binds HER2. Its combination with trastuzumab and chemotherapy is established as first line treatment for metastatic HER2 positive breast cancer[12]. This combination is being evaluated in a phase Ⅲ clinical trial for HER 2 positive advanced GCs (NCT01774786). Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate with monoclonal antibody trastuzumab lined to cytotoxic agent emtansine. A randomized phase Ⅲ trial is ongoing with T-DM1 *vs* taxane for previously treated advanced GCs (NCT01641939).

Antiangiogenic pathway targeting therapy

Vascular endothelial growth factor (VEGF) pathway (angiogenesis) is of great interest in advanced GCs with recent success in ramucirumab, although VEGF-A neutralizing antibody bevacizumab did not reach its primary endpoint in phase Ⅲ AVAGAST trial (OS: 12.1 mo *vs* 10.1 mo, $P = 0.1002$; PFS: 6.7 mo *vs* 5.3 mo, $P = 0.0037$; RR: 46% *vs* 37.4%, $P = 0.0315$)[13]. Ramucirumab is a vascular endothelial growth factor receptor 2 (VEGFR2) monoclonal antibody inhibiting VEGF binding. Two pivotal phase Ⅲ clinical trials REGARD and RAINBOW have led to the approval of ramucirumab in 2014 for advanced GCs after progression on fluropyrimidine or platinum containing chemotherapy. In REGARD trial, ramucirumab was compared to placebo in previously treated advanced GC patients. Survival was significant better as a single agent (OS: 5.2 mo *vs* 3.8 mo, $P = 0.047$)[14]. Ramucirumab was investigated in combination with paclitaxel compared to paclitaxel alone in RAINBOW trial. It demonstrated survival benefit again (OS: 9.6 mo *vs* 7.4 mo, $P = 0.017$)[15]. Advanced GC patients in both trials have been treated previously

and the OS benefits were impressive. Ramucirumab has become the standard second line treatment for advanced GC. In the first line setting, ramucirumab was studied together with FOLFOX in a phase Ⅱ trial. It did not add much improvement (PFS: 6.4 mo *vs* 6.7 mo, *P* = 0.89; OS: 11.7 mo *vs* 11.5 mo)[16]. No biomarker has been established for ramucirumab either. A global phase Ⅲ trial RAINFALL (NCT 02314117) is ongoing comparing fluropyrimidine/Cisplatin with or without ramucirumab in HER2 negative advanced GC patients as first line treatment[17]. Apatinib is an oral small molecular TKI of VEGFR-2. In a phase Ⅲ clinical trial of advanced GC patients who failed second-line chemotherapy, the OS was significantly prolonged in the apatinib group when compared to the placebo group (6.5 mo *vs* 4.7 mo, *P* < 0.016; PFS: 2.6 mo *vs* 1.8 mo, *P* < 0.0001; RR 2.84% and 0.00%)[18]. This study further confirmed the efficacy of VEGFR-2 inhibitor for the patients with advanced GC[18]. Regorafenib, an oral multi kinase inhibitor with antiangiogenic effect by VEGFR-2 inhibition, showed PFS benefit over placebo for refractory advanced GC patients in a global phase Ⅱ trial (INTEGRATE, PFS: 11.1 wk *vs* 3.9 wk, *P* < 0.0001; OS: 25 wk *vs* 19.4 wk, *P* = 0.11)[19]. Another phase Ⅱ PaFLO trial (NCT 01503372) examined chemotherapy with or without the antiangiogenic TKI pazopanib as first line in HER2 negative patients. The study did not meet its predefined PFS rate of minimum of 40% at 6 mo (PFS rate: 31.4% *vs* 25.9%). Marginal efficacy in the pazopanib group was observed with median PFS 5.1 mo compared to 3.9 mo in the control group (HR: 0.93, 95%CI: 0.56-1.54)[20].

Mesenchymal-epithelial transition factor receptor/ hepatocyte growth factor targeting therapy

Mesenchymal-epithelial transition factor receptor (c-MET) and its ligand hepatocyte growth factor (HGF) were also evaluated. Rilotumumab is an antibody to HGF, and it was tested in the frontline with chemotherapy in MET-positive advanced GC patients in two phase Ⅲ clinical trials RILOMET-1 (NCT01697072) and RILOMET-2 (NCT02137343) based on the positive phase Ⅱ study[21]. Chemotherapies with or without the drug were examined. These studies have to stop early due to increased fatal adverse events for advanced GC patients. RILOMET-1 study recently reports significantly worse OS in the study group (OS: 9.6 mo *vs* 11.5 mo, HR: 1.37, *P* = 0.016)[22]. Onartuzumab is an antibody against c-MET being studied in combination chemotherapy in advanced GC patients with HER2-negative, MET-positive disease (MetGastric) in the frontline setting (NCT01662869). The study was negative with the addition of onartuzumab to chemotherapy favored placebo group (OS ITT: 11.3 mo *vs* 11.0 mo, *P* = 0.24; OS: MET 2+/3+ 9.7 mo *vs* 11.0 mo, *P* = 0.062)[23].

Poly (ADP-ribose) polymerase targeting therapy

Poly (ADP-ribose) polymerase (PARP) inhibitor in combination with paclitaxel was studied in a second line phase Ⅱ advanced GC study (NCT01063517). The study was enriched for patients with low ATM tumors by IHC based on preclinical data of responsiveness of GC cell lines to olaparib association with low ATM protein level. Of the 124 randomized patients, olaparib plus paclitaxel was well tolerated. Although the primary endpoint of PFS was not met (All patients: 3.9 mo *vs* 3.6 mo, *P* = 0.261; ATM patients: 5.3 mo *vs* 3.7 mo, *P* = 0.35), the OS was statistically significant improved in the study for both all patients and ATM patients (All patients: 13.1 mo *vs* 8.3 mo, *P* = 0.010; ATM patients: NC *vs* 8.2 mo, *P* = 0.003)[24]. A large phase Ⅲ study is ongoing in Asian patients (NCT01924533).

Hedgehog pathway targeting therapy

Hedgehog pathway inhibitor vismodegib combined with FOLFOX was examined in a phase Ⅱ study for advanced GC patients. Hedgehog pathway is over-expressed in GE tumors and pre-clinical data suggested hedgehog inhibitors control tumor growth, cell motility and invasiveness. Median PFS was 11.5 mo *vs* 9.3 mo (*P* = 0.34) and median OS was 12.2 mo *vs* 13.9 mo (*P* = 0.48)[25]. It is another negative trial in an unselected advanced GC population.

Fibroblast growth factor receptor targeting therapy

Fibroblast growth factor receptor (FGFR) pathway is required for driving growth and survival of GC carrying *FGFR2* gene amplification. Dovitinib (TKI258) and AZD4547 are evaluated in this pathway for GCs. Dovitinib is currently being studied as monotherapy or combined with docetaxel in the second or third line setting. One trial (NCT01719549) required patients to have FGFR2 gene amplification and the other two trials (NCT01576380, NCT01921673) were performed in the unselected patient population. The SHINE study (NCT01457846) of AZD4547 monotherapy *vs* paclitaxel for patients with FGFR2 polysomy or gene amplification recently reported to be negative. The PFS was 1.8 mo in the AZD group compared to 3.5 mo in the paclitaxel group[26].

No biomarkers except HER2 are available for clinical practice. The difficulty to identify predictive biomarkers for targeted therapy remains, and warrants further investigation. Majority of the above mentioned large phase Ⅱ or Ⅲ trials were done in unselected patient populations with negative results. The cancer genome atlas project recently proposed to divide GC into four subtypes: Epstein–Barr virus positive tumor, microsatellite unstable tumors, genomically stable tumor, and chromosomally unstable tumor[27]. This classification is based on comprehensive molecular characterization. The advance in technology and understanding of its heterogeneity will potentially lead to identify key targets and pathways for treatments. The laboratory testing to establish positive markers need to be standardized. Future clinical trial design should consider both predictive and prognostic biomarkers to direct targeted therapies.

ERA OF IMMUNE THERAPY

Immune therapy has gained tremendous interest in cancer research and starts a new era for cancer treatment in recent years. Immune checkpoint pathway has made significant progress with several new agents approved for clinical use recently. Suppressing this pathway allows T cell activation and use human immune system to attack tumor cells. High RR and possible durable response have been seen in melanoma and lung cancer with relative low toxicities[28-31]. There are two classes of agents which are under evaluation including inhibitors for cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) and program cell death 1 (PD-1) or its ligand (PD-L1) inhibitors. Multiple agents are in early development and some have been tested in clinical trials. CTLA-4 inhibitors such as ipilimumab (MDX-010) and tremelimumab (CP-675,206) regulate the amplitude of early stage T cell activation. PD-1 and PD-L1 inhibitors such as nivolumab (ONO-4538), pembrolimumab (MK-3475), MEDI4736 and MPDL3280A act on the T cell activity in the peripheral tissues. Seven GC patients were included in a safety study for anti-PD-L1 antibody BMS 936559[32]. Multiple early phase clinical trials are presently ongoing to evaluate their safety and efficacy in advanced solid tumors including GC (for example: NCT01375842, NCT01693562).

CTLA-4 inhibitor tremelimumab was studied in 18 advanced GC patients as a second line treatment. One patient achieved partial response (PR) and four patients had stable disease (SD). Improved survival was observed in patients experiencing a post treatment carcinoembryonic antigen proliferative response (OS: 17.1 mo *vs* 4.7 mo, $P = 0.004$) despite the objective RR was low[33]. Another phase Ⅱ trial of sequential ipilimumab *vs* best supportive care as a second line therapy has completed with results pending (NCT01585987).

PD-1 inhibitor pembrolizumab (MK-3475) demonstrated encouraging results in the phase 1b KEYNOTE-012 study for GC with 67% patients received ⩾ 2 prior therapies. PD-L1+ was used as the biomarker with 65 out of 162 (40%) screened patient being positive, and 39 patients enrolled eventually. ORR was 22% by central review and 33% by investigator review[34]. Median time to response was 8 wk with a median response duration of 24 wk. The 6-mo PFS and OS rate were 24% and 69%[34]. Four patients experienced high-grade drug-related adverse events: peripheral sensory neuropathy, fatigue, decreased appetite, hypoxia, and pneumonitis[34]. This promising result has led to further investigation. A phase Ⅱ KEYNOTE-059 (NCT02335411) study has been launched with pembrolizumab monotherapy or in combination with cisplatin plus 5-fluorouracil for advanced GC. Phase Ⅲ KEYNOTE-061 (NCT02370498) is planned with pembrolizumab *vs* paclitaxel after the first line therapy with platinum and fluropyrimidine. Another phase Ⅲ study with nivolumab (ONO-4538) is recruiting patients with advanced GC (NCT02267343) in Asian countries and PD-L1 positivity was not required.

Combining checkpoint pathway inhibitors are studied in advanced solid tumors with the hope to generate stronger immunogenicity. A phase Ⅰb/Ⅱ study is ongoing to assess the safety and efficacy of PD-L1 inhibitor MEDI4736 in combination with CTLA-4 inhibitor tremelimumab *vs* monotherapy for patients with advanced GC (NCT02340975). Another Phase Ⅰb/Ⅱ study of advanced solid tumor included GC is evaluating nivolumab monotherapy *vs* nivolumab combined with ipilimumab (NCT01928394).

Immune therapy is currently opening a new page for cancer treatment. Harness human immune system to fight for GC may become a reality very soon. Many obstacles and challenges warrant further investigation such as standardization of laboratory testing, biomarkers, tumor immune response criteria, management of immune related adverse events, safety and efficacy of re-exposure.

GC STEM CELL

Hematopoietic stem cell transplant has been well established and widely used in clinical practice to save lives. With more accumulative evidence in recent years, the questionable solid tumor stem cells hypothesis becomes more believable. GC stem cells are thought to be responsible for tumor self-renewal, metastasis, chemotherapy resistance and tumor recurrence[35]. *In vitro* sphere-forming assays and *in vivo* tumor formation in immune-deficient mice have been employed for solid tumor stem cell research. The gastric stem cell was thought to be existed in gastric epithelium initially. Bone marrow derived cells were also identified in mouse models of Helicobacter-induced GC[36,37]. However majority of the studies are still *in vitro* or using mice model[38]. One oral first in class cancer stemness inhibitor called BBI608 was studied plus weekly paclitaxel in a phase Ⅰb trial in refractory solid tumors. Two out of the five refractory GC patients had a partial response (48% and 45% regressions), one had stable disease (25% regression) and two had prolonged stable disease ⩾ 24 wk[39]. A phase Ⅲ clinical trial is ongoing (BRIGHTER: NCT02178956) with this cancer cell stemness inhibitor for previously treated advanced GC patients[40]. One GC patient demonstrated minor regression or SD ⩾ 16 wk in another phase Ⅰ cancer stem cell inhibitor BBI503 trial (NCT01781455)[41].

FUTURE PERSPECTIVE

GC is a common malignancy with poor outcomes. There is an urgent unmet need to improve treatment and outcome for this lethal disease. Understanding the heterogeneous nature of this cancer and incorporate genomic atlas to develop biomarkers as well as newer target agents are important. Develop precision medicine and tailor optimal therapies to individual patient based on

Table 1 Summary of selected targeted agents for advanced gastric cancer

Target	Study agent	Trial	Treatments	Phase	Biomarker	Results primary end point
EGFR	Cetuximab	EXPAND NCT00678535	Arm1: CX + cetuximab Arm 2: CX	Ⅲ	No	Negative PFS: 4.4 mo *vs* 5.6 mo (P = 0.32)
EGFR	Panitumumab	REAL3 NCT00824785	Arm1: EOC+ Panitumumab Arm2: EOC	Ⅱ / Ⅲ	No	Negative OS: 8.8 mo *vs* 11.3 mo (P = 0.013)
mTOR	Everolimus	GRANITE-1 NCT00879333	Arm1: Everolimus Arm2: Placebo	Ⅲ	No	Negative OS: 5.4 mo *vs* 4.3 mo (P = 0.124)
HER2	Trastuzumab	ToGA NCT01041404	Arm1: CF + Trastuzumab Arm2: CF	Ⅲ	Yes HER2	Positive OS: 13.8 mo *vs* 11.1 mo (P = 0.0046)
HER2/EGFR	Lapatinib	TRIO-013/Logic NCT00680901	Arm1: CX + Lapatinib Arm2: CX	Ⅲ	Yes HER2	Negative OS: 12.2 mo *vs* 10.5 mo (P = 0.35)
HER2/EGFR	Lapatinib	TyTAN NCT00486954	Arm1: Paclitaxel + Lapatinib Arm2: Paclitaxel	Ⅲ	Yes HER2	Negative OS: 11.1 mo *vs* 8.9 mo (P = 0.1044)
HER2	Pertuzumab	JACOB NCT0177486	Arm1: CF + Trasuzumab + Pertuzumab Arm2: CF + Trastuzumab	Ⅲ	Yes HER2	Ongoing
HER2	T-DM1	GATSBY NCT01641939	Arm1: Taxane Arm2: T-DM1 2.4 mg/kg once a week Arm3: T-DM1 3.6 mg/kg every 3 wk	Ⅱ / Ⅲ	Yes HER2	Ongoing
VEGF	Bevacizumab	AVAGAST NCT00548548	Arm1: CF + Bevacizumab Arm2: CF	Ⅲ	No	Negative OS: 12.1 mo *vs* 10.1 mo (P = 0.1002)
VEGFR	Ramucirumab	REGARD NCT00917384	Arm1: Ramucirumab Arm2: Placebo	Ⅲ	No	Positive OS: 5.2 mo *vs* 3.8 mo (P = -0.047)
VEGFR	Ramucirumab	RAINBOW NCT01170663	Arm1: Paclitaxel + Ramucirumab Arm2: Paclitaxel	Ⅲ	No	Positive OS: 9.6 mo *vs* 7.4 mo (P = 0.017)
VEGFR	Ramucirumab	RAINFALL NCT02314117	Arm1: CF + Ramucirumab Arm2: CF	Ⅲ	Yes HER2 negative	Ongoing
VEGFR	Apatinib	NCT0152745	Arm1: Apatinib Arm2: Placebo	Ⅲ	No	Positive OS: 6.5 mo *vs* 4.7 mo (P < 0.016), PFS: 2.6 mo *vs* 1.8 mo (P < 0.0001)
VEGFR (multi-kinase)	Regorafenib	INTEGRATE	Arm1: Regorafenib Arm2: Placebo	Ⅱ	No	Positive PFS: 11.1 wk *vs* 3.9 wk (P < 0.0001)
VEGFR, PDGFR c-Kit	Pazopanib	PaFLO	Arm1: FLO + Pazopanib Arm2: FLO	Ⅱ	Yes HER2 negative	Negative PFS rate at 6 mo 31.4% *vs* 25.9% (Did not meet predefined 40%)
MET/HGF	Rilotumumab	RILOMET-1 NCT01697072	Arm1: ECX + Rilotumumab Arm2:	Ⅲ	Yes MET	Terminated due to increased death signal Negative (Detrimental) OS: 9.6 *vs* 11.5 mo (HR 1.37, P = 0.016)
MET/HGF	Rilotumumab	RILOMET-2 NCT02137343	Arm1: CX + Rilotumumab Arm2: CX	Ⅲ	Yes MET	Terminated due to increased death signal
MET	Onartuzumab	METGastric NCT01662869	Arm1: FOLFOX Arm2: FOLFOX + Onartuzumab	Ⅲ	Yes MET+, HER2-	Negative ITT OS: 11.3 mo *vs* 11.0 mo (P = 0.24) MET2+/3+ OS: 9.7 mo *vs* 11.0 mo (P = 0.06)
PARP	Olaparib	NCT01063517	Arm1: Paclitaxel + Olaparib Arm2: Paclitaxel	Ⅱ	Yes ATM	Negative PFS: 3.9 mo *vs* 2.6 mo (P = 0.261) All patients PFS: 5.3 mo *vs* 3.7 mo (P = 0.315) ATM- patients Positive for secondary endpoints OS: 13.1 mo *vs* 8.3 mo (P = 0.010) All Patients OS: NR mo *vs* 8.2 mo (P = 0.003) ATM- patients
PARP	Olaparib	NCT01924533	Arm1: Paclitaxel + Olaparib Arm2: Paclitaxel	Ⅲ	No	Ongoing
Hedgehog	Vismodegib	NCT00982592	Arm1: FOLFOX + Vismodegib Arm2: FOLFOX	Ⅱ	No	Negative PFS: 7.3 mo *vs* 9.0 mo (P = 0.64)
FGFR	Dovitinib	NCT01719549	Dovitinib monotherapy	Ⅱ	Yes FGFR	Ongoing
FGFR	Dovitinib	NCT01576380	Dovitinib monotherapy	Ⅱ	No	Completed, waiting for result
FGFR	Dovitinib	NCT01921673	Docetaxel + Dovitinib	Ⅰ / Ⅱ	No	Ongoing
FGFR/VEGFR	AZD4547	SHINE NCT1457846	Arm1: AZD4547 Arm2: Paclitaxel	Ⅱ	Yes FGFR	Negative PFS: 1.8 (AZD) *vs* 3.5 mo

EOC: Epirubicin, oxalilatin, capecitabine; CF: Fluoropyrimidine, cisplatin; T-DM1: Trastuzumab emtansine; ECX: Epirubicin, csiplatin, capecitabine; CX: Cisplatin, capecitabine; FOLFOX: 5-Fluorouracil, folinic acid, oxaliplatin; NR: Not reached; FLO: 5-FU, leucovorine, oxaliplatin; EGFR: Epidermal growth factor receptor; mTOR: Mammalian target of rapamycin; HER2: Human epidermal growth factor receptor 2; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet-derived growth factor receptor; MET: Mesenchymal-epithelial transition factor; HGF: Hepatocyte growth factor; PARP: Poly ADP-ribose polymerase; FGFR: Fibroblast growth factor receptor.

information including molecular study results will be the future focus. With the recent breakthrough in immune therapy in other solid tumors and promising early phase clinical trial results in GC, immune checkpoint pathway inhibitors are undergoing evaluation. In order to generate stronger immunogenicity, combining different checkpoint pathway inhibitors or chemotherapy or targeted therapy might be needed. GC stem cell research was initially cluttered with skepticism until more evidence accumulated recently. It is an exciting field warrants further evaluation.

CONCLUSION

Ramucirumab is the second biologic agent after trastuzumab approved with statistically significant but marginal survival benefit for GC patients in spite of multiple negative phase Ⅲ clinical trials of other targeted agents (as summarized in Table 1). Better understanding and use of genomic atlas/biomarkers will potentially lead to development of targeted agents with better efficacy. Immune therapy especially checkpoint pathway inhibition is a promising field and being studied in multiple clinical trials. GC stem cell therapy is finally moving from bench work to early phase clinical investigation. Targeted therapy, immune therapy and cancer stem cell therapy are promising fields and may meet the urgent demand for novel therapy to treat GC in near future.

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P- Reviewer: Kim Y, Tuosto L
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