



WJG 20th Anniversary Special Issues (8): Gastric cancer

Treatment options in patients with metastatic gastric cancer: Current status and future perspectives

Ahmet Bilici

Ahmet Bilici, Department of Medical Oncology, Medical Faculty, Istanbul Medipol University, Bagcilar, 34214 Istanbul, Turkey
Author contributions: Bilici A solely contributed to this paper.
Correspondence to: Ahmet Bilici, MD, Department of Medical Oncology, Medical Faculty, Istanbul Medipol University, TEM Avrupa Otoyolu Goztepe Cikisi No: 1, Bagcilar, 34214 Istanbul, Turkey. ahmetknower@yahoo.com
Telephone: +90-532-5280486 Fax: +90-216-4422947
Received: October 7, 2013 Revised: December 27, 2013
Accepted: January 20, 2014
Published online: April 14, 2014

Abstract

Despite advances in the treatment of gastric cancer, it remains the world's second highest cause of cancer death. As gastric cancer is often diagnosed at an advanced stage, systemic chemotherapy is the mainstay of treatment for these patients. However, no standard palliative chemotherapy regimen has been accepted for patients with metastatic gastric cancer. Palliative chemotherapy including fluoropyrimidine, platin compounds, docetaxel and epirubicin prolongs survival, and improves a high quality of life to a greater extent than best supportive care. The number of clinical investigations associated with targeted agents has recently increased. Agents targeting the epidermal growth factor receptor 1 and human epidermal growth factor receptor 2 (HER2) have been widely tested. Trastuzumab was the first target drug developed, and pivotal phase III trials showed improved survival when trastuzumab was integrated into cisplatin/fluoropyrimidine-based chemotherapy in patients with metastatic gastric cancer. Trastuzumab in combination with chemotherapy was thus approved to be a new standard of care for patients with HER2-positive advanced esophagogastric adenocarcinoma. Thus, the evaluation of HER2 status in all patients with metastatic gas-

troesophageal adenocarcinoma should be considered. Other agents targeting vascular endothelial growth factor, mammalian target of rapamycin, and other biological pathways have also been investigated in clinical trials, but showed little impact on the survival of patients. In this review, systemic chemotherapy and targeted therapies for metastatic gastric cancer in the first- and second-line setting are summarized in the light of recent advances.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Gastric cancer; Chemotherapy; Targeted therapy; Metastasis; Advanced-stage

Core tip: Although palliative chemotherapy have been demonstrated to improve survival and quality of life, the prognosis of patients with metastatic gastric cancer remains poor and responses to first-line chemotherapy are partial and heterogeneous. In order to improve the results of currently available treatments, remarkable advancements in new targeted agents have recently been obtained. The addition of trastuzumab to cisplatin/fluoropyrimidine-based chemotherapy significantly improved survival in patients with human epidermal growth factor receptor 2-positive metastatic gastric cancer, which is now the new standard of care. Our manuscript will elucidate current systemic chemotherapy and promising targeted therapies for metastatic gastric cancer in the first- and second-line setting in the light of recent advances.

Bilici A. Treatment options in patients with metastatic gastric cancer: Current status and future perspectives. *World J Gastroenterol* 2014; 20(14): 3905-3915 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i14/3905.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i14.3905>

INTRODUCTION

Gastric cancer is the second most common cause of cancer death worldwide. Although the overall incidence and mortality of this disease have dramatically declined over the last few decades, it remains a major health problem^[1,2]. Radical gastrectomy is the only curative treatment of gastric cancer, but recurrences are common, being detected in approximately 60% of patients^[3]. In addition, gastric cancer is often diagnosed at an advanced stage, other than in Japan and Korea, where screening is widely performed. For these patients, systemic chemotherapy is the mainstay of treatment^[4,5]. Although recent phase III studies showed some benefit from chemotherapy regimens including docetaxel, capecitabine, irinotecan, cisplatin and oxaliplatin^[5], there is no internationally accepted standard of care.

Treatment responses and prognosis are highly variable even within the same stage. Therefore, a thorough understanding of cancer biology is essential for better management of gastric cancer in the future. To date, molecular targets such as epidermal growth factor (EGFR) receptor, vascular endothelial growth factor (VEGF) receptor and human epidermal growth factor receptor 2 (HER2) have been tested by clinical trials in metastatic gastric cancer^[6,7]. A recent phase III trial proved the benefit of trastuzumab (anti-HER2 antibody) in combination with chemotherapy in advanced HER2-positive gastric cancer or esophagogastric junction^[8]. Despite these marked advances, the prognosis of patients with advanced gastric cancer remains poor. Therefore, new therapeutic molecular targets are required to improve the survival of patients^[7].

In this article, we review the currently available treatments in light of the most recent publications and guidelines, along with promising therapeutic options that are still under development for patients with advanced gastric cancer.

CURRENT TREATMENT OPTIONS FOR ADVANCED GASTRIC CANCER

First-line chemotherapy

Palliative chemotherapy versus best supportive care (BSC) for patients with metastatic gastric cancer has been evaluated in several clinical trials, which showed that palliative chemotherapy improved overall survival (OS) for several months longer on average than supportive care^[9-12]. A meta-analysis performed by Wagner *et al*^[12] demonstrated an overall HR of 0.39 (95%CI: 0.28-0.52) for OS in favor of chemotherapy compared with BSC, which translates to a benefit in weighted mean average survival of about 6 months. Moreover, chemotherapy also provided relief of symptoms, and improved and prolonged a high quality of life more than BSC^[9].

In the last 20 years, multiple randomized trials testing different combination regimens in patients with metastatic gastric cancer have indicated that there is no

international consensus regarding the best management approach^[13-16], and meta-analysis of these studies^[12] has demonstrated that combination chemotherapy is superior to monotherapy, with a HR of 0.83 for OS (95%CI: 0.74-0.93) in favor of combination chemotherapy.

In the early 1980s, the FAM chemotherapy regimen (fluorouracil, doxorubicin mitomycin) was accepted as the gold standard regimen for patients with metastatic gastric cancer^[17]. Subsequently, in a study carried out by Webb *et al*^[18], 274 patients with metastatic esophagogastric cancer were randomly assigned to receive either epirubicin, cisplatin and fluorouracil (ECF) or fluorouracil, doxorubicin, and methotrexate (FAMTX). The patients treated with ECF had a significantly longer median OS (8.9 months *vs* 5.7 months, $P = 0.0009$) than the FAMTX group. Multiple randomized studies have compared various fluorouracil-based regimens and of all the combination regimens, ECF has been considered to be the reference standard regimen in the United States and Europe based on OS and quality of life benefits^[19].

The REAL-2 trial reported that oxaliplatin and capecitabine were found to be noninferior to cisplatin and fluorouracil, with manageable toxicity profiles^[20]. This trial compared capecitabine with fluorouracil and oxaliplatin with cisplatin in 1002 patients with advanced esophageal, gastroesophageal junction, or gastric cancer. In a two-by-two design, patients with histologically confirmed advanced esophagogastric cancer were randomized to receive one of four epirubicin-based regimens [ECF, epirubicin, oxaliplatin and fluorouracil (EOF), epirubicin, cisplatin and capecitabine (ECX) and epirubicin, oxaliplatin and capecitabine (EOX)]. The median OS times in the ECF, EOF, ECX and EOX groups were 9.9, 9.3, 9.9 and 11.2 months, respectively. For the capecitabine-fluorouracil and oxaliplatin-cisplatin comparisons, the results indicated a noninferior median OS in patients treated with capecitabine rather than 5-FU (HR_{death}: 0.86; 95%CI: 0.82-0.99) and in patients treated with oxaliplatin in place of cisplatin (HR_{death}: 0.92; 95%CI: 0.80-1.10)^[20]. Since REAL-2, oxaliplatin and capecitabine have often been substituted for cisplatin and 5-FU within the ECF regimen in many cancer centers.

Another phase III randomized noninferiority trial, ML17032, performed by Kang *et al*^[21], compared the combination capecitabine and cisplatin (XP) with the combination of fluorouracil and cisplatin (FP) in patients with previously untreated advanced gastric cancer in the first-line setting. Both overall response rates (ORR) and median OS times were superior for patients treated with the XP regimen (ORR; 41% *vs* 29% and OS; 10.5 months *vs* 9.3 months, respectively), although the median progression-free survival (PFS) time was found to be similar for both regimens (5.6 months for XP and 5.0 months for FP). The authors concluded that capecitabine is as effective as fluorouracil in the treatment of patients with advanced esophagogastric cancer. Thereafter, a meta-analysis of the REAL-2 and ML17032 trials demonstrated that OS was superior in the 654 patients who received capecitabine-based

regimens compared with the 664 patients treated with fluorouracil-based combinations, but there was no significant difference with respect to PFS between treatment groups^[22].

An incremental improvement in OS was also suggested in the V325 trial^[23]. This randomized multinational phase III trial evaluated the combination of docetaxel, cisplatin and fluorouracil (DCF) in patients with untreated advanced gastric cancer. Four hundred and forty-five patients were randomized to receive either DCF every 3 wk or cisplatin and fluorouracil (CF). Time-to-progression (TTP) for patients who received DCF was significantly longer than that of patients treated with CF (5.6 mo *vs* 3.7 mo; HR = 1.47; 95%CI: 1.19-1.82; $P < 0.001$; risk reduction 32%). Moreover, the median OS time was significantly worse for patients who received DCF compared with patients who received CF (9.2 mo *vs* 8.6 mo; HR = 1.29; 95%CI: 1.0-1.6; $P = 0.02$; risk reduction 23%)^[23]. High toxicity rates were reported in this trial, especially involving febrile neutropenia, which was more common in patients who received DCF (29% *vs* 12%); the death rate in the study was 10.4% for patients who received the DCF regimen and 9.4% for patients treated with the CF arm.

As the DCF regimen resulted in high toxicity profiles, several clinical trials have tested modifications of the DCF regimen with the aim of reducing toxicity and improving tolerability^[24-26]. The recent GATE phase II study carried out by Van Cutsem *et al*^[27] showed that the combination of docetaxel, oxaliplatin and fluorouracil (DOF) had a better RR, TTP and median OS time (47%, 7.7 and 15 mo, respectively) compared with the combination docetaxel and oxaliplatin (23%, 4.5 and 9 mo, respectively) and docetaxel, oxaliplatin and capecitabine (26%, 5.6 and 11 mo, respectively) in patients with previously untreated advanced gastric cancer. Furthermore, the DOF regimen produced a better safety profile compared to other regimens.

Al-Batran *et al*^[28], in their phase III trial, reported that median PFS showed a tendency to be better in patients who received a combination of fluorouracil, leucovorin and oxaliplatin (FLO) than that of patients who received a combination of fluorouracil, leucovorin and cisplatin (FLP) (5.8 mo *vs* 3.9 mo, $P = 0.077$). On the other hand, the median OS time did not differ significantly (10.7 mo *vs* 8.8 mo, $P > 0.05$) between the two groups. Thereafter, the authors performed a post hoc subgroup analysis in patients older than 65 years, and the FLO regimen produced a significantly superior RR (41.3% *vs* 16.7%), median PFS (6.0 mo *vs* 3.1 mo, $P = 0.029$) and time-to-treatment failure (5.4 mo *vs* 2.4 mo, $P < 0.001$), and an improved median OS (13.9 mo *vs* 7.2 mo, $P = 0.08$) compared with the FLP regimen. In addition, there was significantly less toxicity with FLO in this trial.

The comparison of irinotecan-containing versus non-irinotecan-containing regimens (mainly fluorouracil-cisplatin) showed a nonstatistically significant trend toward better survival with irinotecan (HR for death:

0.86, 95%CI: 0.73-1.02) in the previous meta-analysis^[5]. Furthermore, irinotecan-based regimens have also been tested comprehensively and found to be active in single arm and randomized clinical trials^[29-34]. In a phase III randomized trial performed by Dank *et al*^[32], irinotecan in combination with fluorouracil and folinic acid (IF) was compared with the combination of cisplatin and infusional fluorouracil (CF) in patients with advanced adenocarcinoma of esophagogastric cancer. The results of this trial showed that the IF regimen resulted in improved TTP, but not OS, compared with CF. However, IF was better with respect to toxic deaths, discontinuation for toxicity, severe neutropenia, thrombocytopenia and stomatitis. The authors concluded that IF may provide an acceptable, platinum-free front-line treatment alternative for metastatic gastric cancer. Another phase II trial revealed that the combination of capecitabine and irinotecan had a similar ORR (37.7% *vs* 42%, respectively) and median PFS (4.2 mo *vs* 4.8 mo, respectively), but a trend towards better median OS (10.2 mo *vs* 7.9 mo, respectively) than the capecitabine-cisplatin regimen^[34].

S-1 is an oral fluoropyrimidine that includes three different agents: tegafur, gimeracil (5-chloro-2,4 dihydropyridine) and oteracil (potassium oxonate). This novel oral agent has shown promising results in patients with advanced gastric cancer, but the majority of data supporting the use of S-1 for advanced gastric cancer are from studies including Asian patients^[5,35]. The randomized phase III SPIRITS trial in 298 patients with advanced gastric cancer showed that both the median PFS (6.0 mo *vs* 4.0 mo) and median OS (13 mo *vs* 11 mo, $P = 0.04$) for patients who received combined S1 plus cisplatin were significantly better than those of patients who received S-1 alone in an Asian population. On the other hand, the grade 3 and 4 toxicity rates were significantly higher^[36].

Tegafur is metabolized differently in Western and Asian populations, and as a result, the maximally tolerated dose also differs. Therefore, Western experience with combined S-1 plus cisplatin for advanced gastric cancer is limited, but also promising^[37,38]. In their phase III FLAGS trial including 1053 patients with advanced esophagogastric adenocarcinoma, Ajani *et al*^[39] randomized patients to cisplatin plus either 5-FU or S-1. They showed that the median OS was not significantly inferior with S-1/cisplatin compared to the CF regimen (8.6 mo *vs* 7.9 mo). In addition, S-1/cisplatin was associated with a more favorable side effect profile and fewer treatment-related deaths^[39]. It is thought that the lower cisplatin dose intensity in the S-1/cisplatin arm (75 mg/m² *vs* 100 mg/m²) may have contributed to the survival and toxicity results. Despite the results of the FLAGS trial, future studies are needed to confirm the activity of S-1 in Western populations. Recently, updated results of the phase III START trial presented at the 2012 ESMO meeting showed that among the 635 patients with metastatic gastric cancer analysed, the median OS time was 12.48 mo when S-1 was combined with docetaxel compared to 10.78 mo in patients who received S-1 alone. Neutropenia was the most

Table 1 Selected phase III clinical trials of current chemotherapy regimens for patients with advanced gastric cancer in the first-line setting

Ref.	Regimen	No. of patients	Response rate	Median PFS/TTP and OS (mo)
Van Cutsem <i>et al</i> ^[23]	DCF <i>vs</i> CF	445	37% <i>vs</i> 25%	TTP, 5.6 <i>vs</i> 3.7; OS, 9.2 <i>vs</i> 8.6
Cunningham <i>et al</i> ^[20]	EOF <i>vs</i> EOX <i>vs</i> ECX <i>vs</i> ECF	1002	42.4% <i>vs</i> 47.9% <i>vs</i> 46.4% <i>vs</i> 40.7%	PFS, 6.5 <i>vs</i> 7.0 <i>vs</i> 6.7 <i>vs</i> 6.2; OS, 9.3 <i>vs</i> 11.2 <i>vs</i> 9.9 <i>vs</i> 9.9
Kang <i>et al</i> ^[21]	CX <i>vs</i> CF	316	41% <i>vs</i> 29%	PFS, 5.6 <i>vs</i> 5.0; OS, 10.5 <i>vs</i> 9.3
Al-Batran <i>et al</i> ^[24]	FLC <i>vs</i> FLO	220	34.8% <i>vs</i> 24.5%	PFS, 5.8 <i>vs</i> 3.9; OS, 10.7 <i>vs</i> 8.8
Dank <i>et al</i> ^[32]	IF <i>vs</i> CF	333	31.8% <i>vs</i> 25.8%	TTP, 5.0 <i>vs</i> 4.2; OS, 9.0 <i>vs</i> 8.7
Koizumi <i>et al</i> ^[36]	CS <i>vs</i> S	305	54% <i>vs</i> 31%	PFS, 6.0 <i>vs</i> 4.0; OS, 13 <i>vs</i> 11
Ajani <i>et al</i> ^[39]	CS <i>vs</i> CF	1053	29.1% <i>vs</i> 31.9%	PFS, 4.8 <i>vs</i> 5.5; OS, 8.6 <i>vs</i> 7.9
Yoshida <i>et al</i> ^[40]	DS <i>vs</i> S	635	38.8% <i>vs</i> 26.8%	PFS, 5.29 <i>vs</i> 4.17; OS, 12.48 <i>vs</i> 10.78

DCF: Docetaxel, cisplatin and fluorouracil; CF: Cisplatin and fluorouracil; EOF: Epirubicin, oxaliplatin and fluorouracil; EOX: Epirubicin, oxaliplatin and capecitabine; ECX: Epirubicin, cisplatin and capecitabine; ECF: Epirubicin, cisplatin and fluorouracil; CX: Cisplatin and capecitabine; FLO: Fluorouracil, leucovorin and oxaliplatin; FLC: Fluorouracil, leucovorin and cisplatin; IF: Irinotecan and cisplatin; CS: Cisplatin and S-1; S: S-1; DS: Docetaxel and S-1; PFS: Progression-free survival; OS: Overall survival; TTP: Time-to progression.

frequent adverse event in the docetaxel/S-1 arm, with one death occurring from grade 4 thrombocytopenia^[40]. Selected phase III clinical trials of current chemotherapy regimens for patients with advanced gastric cancer in the first-line setting are summarized in Table 1.

Targeted therapy

Anti-HER2 agents: EGFR overexpression has been found in different cancer types including gastric cancer and is believed to be associated with tumor invasion, high grade histology, and poor prognosis^[41]. The EGFR family comprises four members, of which epidermal growth factor receptor 1 (EGFR1) and HER2 (EGFR- II) have been comprehensively investigated as targets for drugs in patients with metastatic gastric cancer. HER2 amplification and HER2 overexpression increase from 12% to 27% and 9% to 23%, respectively, in esophagogastric cancer, a similar percentage to that seen in breast cancer^[42-46]. HER2 positivity is reported to be more frequent in patients with intestinal histology (34%) than in those with diffuse-type histology (6%), as well as in gastro-esophageal junction (32%) compared to gastric cancer (18%)^[46].

The trastuzumab for gastric cancer (ToGA) trial, a pivotal randomized, prospective, multicenter, phase III clinical trial, evaluated the efficacy of anti-HER2 trastuzumab in combination with chemotherapy in patients with HER-2-positive advanced, mostly metastatic, gastric cancer^[8]. After screening 3807 patients, 584 eligible HER2-positive patients according to immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH), were randomized to trastuzumab plus chemotherapy (fluorouracil or capecitabine and cisplatin) or chemotherapy alone. The study treatment was administered every 3 wk for six cycles, and trastuzumab was continued every 3 wk until disease progression, unacceptable toxicity, or withdrawal of consent. Crossover to trastuzumab at disease progression was not permitted. The ORR was significantly higher in the trastuzumab-containing arm (47% *vs* 35%). At a median follow-up of 17.1 to 18.6 mo, the median OS was significantly longer in the trastuzumab-containing arm (13.8 mo *vs* 11.1 mo, HR = 0.74,

95%CI: 0.60-0.91, *P* = 0.0046). There was no significant difference in rates of any adverse event, and cardiotoxicity was equally rare in both arms (an asymptomatic decrease in the left ventricular ejection fraction, 5% *vs* 1%). Grade 3 to 4 heart failure was reported in one and two patients, respectively. In subgroup analysis, trastuzumab was most effective in prolonging survival in the subgroup of patients with IHC 3+ tumors (HR = 0.66, 95%CI: 0.50-0.87), less effective in patients with IHC 2+ tumors (HR = 0.78, 95%CI: 0.55-1.10), and ineffective in those with *HER2* gene-amplified, but non protein-expressing (IHC 0 or 1+) tumors^[8]. In the light of these findings, trastuzumab in combination with chemotherapy was approved to be a new standard of care for patients with HER2-positive advanced esophagogastric adenocarcinoma. Therefore, all patients with metastatic gastro-esophageal adenocarcinoma should be evaluated in terms of HER2 status.

Lapatinib, an orally active tyrosine kinase inhibitor, has double targeted inhibition of both EGFR1 and HER2. The results of the randomized, phase III TyTAN trial were presented at the 2013 ASCO Gastrointestinal Cancer Symposium^[47]. The addition of lapatinib produced no significant benefit with respect to PFS (5.4 mo *vs* 4.4 mo) or OS (11.0 mo *vs* 8.9 mo) in the intent to treat population of advanced gastric cancer. On the other hand, there was significant benefit in both PFS (5.6 mo *vs* 4.2 mo) and OS (14.0 mo *vs* 7.6 mo) for patients with IHC 3+. The preliminary results of the TRIO-013/LOGiC trial were presented at the 2013 ASCO annual meeting^[48]. In 545 patients with advanced gastroesophageal cancer, the benefit derived from the addition of lapatinib to chemotherapy was tested in first-line treatment. The combination of lapatinib and capecitabine/oxaliplatin did not significantly improve the median OS (12.2 mo *vs* 10.5 mo, HR = 0.91, 95%CI: 0.73-1.12) compared with chemotherapy alone. No correlation between intensity of staining for HER2 by IHC and outcomes was found. However, in subgroup analysis, Asian patients (median OS, 16.5 mo *vs* 10.9 mo, HR 0.68) and those under age 60 (median OS, 12.9 mo *vs* 9 mo, HR 0.69) seemed to benefit from lapatinib. The addition of lapatinib was as-

sociated with increased toxicity.

Anti-EGFR1 agents: EGFR is a transmembrane tyrosine kinase receptor involved in the proliferation and survival of cancer cells. EGFR overexpression is associated with advanced stages and poor prognosis in gastric cancer patients^[49], and EGFR expression has been reported in 60% of gastric cancer patients^[50,51]. Anti-EGFR monoclonal antibodies bind to the extracellular domain of EGFR in its inactive state; they compete for receptor binding by occluding the ligand-binding region, and thereby block ligand-induced EGFR tyrosine kinase activation. Cetuximab is a chimeric monoclonal antibody targeting EGFR and its inhibition prevents tumor cell growth, angiogenesis, invasion, and metastasis, and induces apoptosis. The efficacy of this anti-EGFR monoclonal antibody in combination with chemotherapy has been reported in several phase II clinical trials^[52-54]. On the other hand, the benefit derived from the addition of cetuximab to chemotherapy could not be confirmed in a phase III trial comparing chemotherapy alone in the first-line setting. In a recent phase III (EXPAND) trial, 904 patients with advanced gastroesophageal adenocarcinoma were randomized to capecitabine and cisplatin with or without cetuximab^[55]. The median PFS for patients who received the cetuximab-chemotherapy regimen was 4.4 mo compared with 5.6 mo for patients treated with chemotherapy alone (HR = 1.09, 95%CI: 0.92-1.29, $P = 0.32$). Moreover, the cetuximab arm resulted in more grade 3-4 adverse events (88% *vs* 77%). Similar results were reported in another phase III trial of panitumumab. The REAL3 trial evaluated the benefit of the addition of panitumumab to chemotherapy in 553 patients with previously untreated advanced unselected esophagogastric cancer^[56]. Patients were randomly allocated (1:1) to receive up to eight 21-day cycles of EOX or modified EOX (with a reduction in oxaliplatin to 100 mg/m² and capecitabine to 1000 mg/m² per day) plus panitumumab. The authors indicated that the addition of panitumumab was associated with a similar response rate but a significantly worse OS (median 8.8 mo *vs* 11.3 mo). In the light of these results, the addition of an anti-EGFR antibody to chemotherapy cannot be considered a standard approach for patients with advanced esophagogastric adenocarcinoma.

Small molecule tyrosine kinase inhibitors (TKI) have also been tested for advanced esophagogastric cancer in phase II trials. The activity of erlotinib was suggested in patients with unresectable or metastatic adenocarcinoma originating in the EGJ or stomach in first-line treatment in the SWOG trial^[57]. Six of the 70 patients obtained an ORR (9%, one complete), all of whom had EGJ tumors. The predictive significance of EGFR expression with respect to clinical outcome was not shown.

Anti-VEGF/VEGFR agents: VEGF is overexpressed by up to 60% and its overexpression correlates with an advanced stage, higher risk of recurrence and tumor aggressiveness and is an indicator for poor prognosis^[58-60].

Anti-VEGF agents have recently been developed and comprise monoclonal antibodies and TKIs.

Bevacizumab is a humanized monoclonal antibody against VEGF, which is an endothelial cell-specific mitogen and the most potent driver of angiogenesis in tumorigenesis as it increases microvascular permeability. The inhibition of VEGF-A prevents pathological angiogenesis by inhibiting its interaction with VEGFR-2. This inhibition by bevacizumab has had a positive impact on patient outcomes in several malignancies including colorectal, lung, and renal cell carcinoma, as well as recurrent glioblastoma^[50]. Several phase II trials produced promising results when using bevacizumab in combination with different chemotherapeutic agents in treatment-naïve patients with locally advanced or metastatic gastric cancer^[61-63].

The recently published AVAGAST, phase III trial evaluated the benefit of bevacizumab in combination with cisplatin and capecitabine as a first-line therapy in 774 patients with advanced gastric carcinoma^[64]. Patients received capecitabine and cisplatin (XP) in combination with either bevacizumab or a placebo. AVAGAST did not reach its primary endpoint with no significant difference in OS (12.1 mo in bevacizumab-arm *vs* 10.1 mo in placebo-chemotherapy arm; HR = 0.87, $P = 0.1002$); however, both PFS (6.7 mo *vs* 5.3 mo, HR = 0.80, $P = 0.0037$) and ORR (46.0% *vs* 37.4%, $P = 0.0315$) improved significantly in the bevacizumab arm. In an unplanned subgroup analysis, OS for the pan-American subgroup was 6.8 mo for placebo *vs* 11.5 mo for bevacizumab (HR = 0.63). For European and Asian-Pacific subgroups, the OS was 8.6 *vs* 11.1 mo (HR = 0.85), and 12.1 mo *vs* 13.9 mo (HR = 0.97), respectively, with all results favoring bevacizumab. It was not clear whether the discrepancy came from genetic differences in ethnicity or from differences in treatment patterns, but Asian patients had fewer EGJ primaries, a lower frequency of liver metastases, and received second-line chemotherapy more often than did pan-American patients. Similar negative results for the addition of bevacizumab to XP in Asian patients with advanced gastric cancer were also presented at the 2012 ASCO Gastrointestinal Cancers Symposium in a preliminary report of the AVATAR study^[65].

Ramucirumab (IMC-1121B) is a fully humanized monoclonal antibody against VEGFR-2^[66]. Several phase II and phase III trials are currently underway or planned including ramucirumab plus chemotherapy *vs* chemotherapy plus placebo or best supportive care in both the first- and second-line setting (NCT00917384, NCT01170663, NCT01246960).

Apatinib is a TKI agent targeting VEGFR-2 (VEGFR), and its anti-angiogenesis effect has been demonstrated in preclinical tests. A recently published phase II trial tested apatinib in patients with chemotherapy-refractory advanced metastatic gastric cancer. The median OS times were 2.50, 4.83 and 4.27 mo, in the placebo, apatinib 850 mg, once and apatinib 450 mg, twice daily arms respectively, and the median PFS times were 1.40, 3.67, and 3.20

Table 2 Phase-III trials regarding targeted therapies in advanced gastric cancer

Ref.	Study/setting	Treatment	No. of patients	Response rate	Median PFS/TTP and OS (mo)
Anti-HER2 agents					
Bang <i>et al</i> ^[61]	ToGA/first-line	Trastuzumab + CX/CF <i>vs</i> CX/CF	584	47% <i>vs</i> 35%	PFS, 6.7 <i>vs</i> 5.5; OS, 13.8 <i>vs</i> 11.1
Bang <i>et al</i> ^[47]	TyTAN/second-line	Lapatinib + P <i>vs</i> P	430	NA	PFS, 5.4 <i>vs</i> 4.4; OS, 11.0 <i>vs</i> 8.9
Hecht <i>et al</i> ^[48]	TRIO-013/LOGiC/first-line	Lapatinib + CAPOX <i>vs</i> CAPOX	545	53% <i>vs</i> 40%	PFS, 6.0 <i>vs</i> 5.4; OS, 12.2 <i>vs</i> 10.5
Anti EGFR1 agents					
Lordick <i>et al</i> ^[55]	EXPAND/first-line	Cetuximab + CX <i>vs</i> CX	904	29% <i>vs</i> 30%	PFS, 4.4 <i>vs</i> 5.6; OS, 9.4 <i>vs</i> 10.7
Waddell <i>et al</i> ^[56]	REAL-3/first-line	Panitumumab + mEOX <i>vs</i> EOX	553	42% <i>vs</i> 46%	PFS, 6.0 <i>vs</i> 7.4; OS, 8.8 <i>vs</i> 11.3
Anti-VEGF agents					
Ohtsu <i>et al</i> ^[64]	AVAGAST/first-line	Bevacizumab + CX <i>vs</i> placebo + CX	774	46% <i>vs</i> 37.4%	PFS, 6.7 <i>vs</i> 5.3; OS, 12.1 <i>vs</i> 10.1
mTOR inhibitors					
Ohtsu <i>et al</i> ^[76]	GRANITE-1/first-line	Everolimus + BSC <i>vs</i> placebo + BSC	656	4.5% <i>vs</i> 2.1%	PFS, 1.7 <i>vs</i> 1.4; OS, 5.4 <i>vs</i> 4.3

HER2: Human epidermal growth factor receptor 2; EGFR1: Epidermal growth factor receptor 1; VEGF: Vascular endothelial growth factor; mTOR: Mammalian target of rapamycin; CX: Cisplatin and capecitabine; CF: Cisplatin and fluorouracil; P: Paclitaxel; CAPOX: Capecitabine and oxaliplatin; EOX: Epirubicin, oxaliplatin and capecitabine; mEOX: Modified EOX; BSC: Best supportive care; PFS: Progression-free survival; TTP: Time-to progression; OS: Overall survival; NA: Not applicable.

mo respectively. The differences between the apatinib and placebo groups were statistically significant for both PFS ($P < 0.001$) and OS ($P < 0.001$ and 0.0017)^[67]. Toxicities were tolerable or manageable. A phase III trial evaluating apatinib *vs* placebo for patients with advanced gastric cancer in the third-line setting is ongoing (NCT01512745).

Sunitinib and sorafenib are multi-target TKIs that also inhibit the VEGF receptor, as well as other TKs. Early reported phase II trials have indicated mixed results. In a phase II trial of sunitinib monotherapy for second-line treatment of metastatic gastric cancer, a partial response was obtained in only two of 78 patients, while another 25 showed a best response of stable disease ≥ 6 wk. Median PFS and OS were 2.3 and 6.8 mo, respectively^[68]. Another open-label randomized phase II trial for the second-line treatment of 107 patients with unresectable or metastatic gastric cancer evaluated the combination of sunitinib plus docetaxel *vs* docetaxel monotherapy^[69]. Although the sunitinib arm was associated with a significantly higher ORR, there was no significant difference in either TTP or OS. The combination of sorafenib plus docetaxel and cisplatin was tested in a phase II trial in the first-line setting for patients with locally advanced or metastatic esophagogastric adenocarcinoma^[70]. This trial demonstrated that the ORR was 41% and the median OS was 13.6 mo; the major grade 3 or 4 toxicity was neutropenia. However, these results will need to be further evaluated in a randomized trial in comparison with historical data on docetaxel plus cisplatin alone. There are a number of studies of locally advanced or metastatic gastroesophageal adenocarcinoma patients currently underway or planned for sunitinib and sorafenib combined with capecitabine-cisplatin or oxaliplatin-capecitabine, S-1-cisplatin, the FOLFIRI regimen, and new agents (NCT00555620, NCT00524186, NCT01020630). Table 2 shows selected phase III clinical trials of targeted therapies in patients with advanced gastric cancer.

Other targeted agents: Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that integrates mul-

tipule signals from growth factors and hormones and plays a central role in the control of cell survival, hyperplasia, apoptosis, and other important physiological functions critical to tumorigenesis and cancer development, and is thus a potential target of anti-cancer therapy^[71]. The first mTOR targeting agent was everolimus, an oral mTOR serine/threonine kinase inhibitor approved for the treatment of renal cell carcinoma, breast cancer, and progressive neuroendocrine tumors of pancreatic origin^[72-74]. A phase II study performed by Doi *et al*^[75], in 53 patients with previously treated metastatic gastric cancer, reported that the median PFS and OS times were 2.7 and 10.1 mo, respectively, with good tolerability. A subsequent phase III GRANITE-1 trial evaluated everolimus or BSC plus placebo in 656 previously treated advanced gastric cancer patients and the results of this trial showed insignificant benefit for the median OS (5.39 mo) in the everolimus arm when compared to the placebo arm (4.3 mo, $P = 0.1244$). On the other hand, promising results regarding PFS with everolimus treatment were reported in this study. The median PFS time was 1.68 mo in patients who received everolimus compared with patients treated with placebo (1.41 mo, HR = 0.68, $P < 0.0001$)^[76]. There are currently several ongoing phase II and III studies in metastatic gastroesophageal adenocarcinoma patients comparing everolimus combined with paclitaxel, 5-FU, cisplatin, leucovorin and capecitabine (NCT01248403, NCT00632268, NCT01099527).

c-MET (mesenchymal-epithelial transition factor) is an oncogene encoding membrane TK receptor, and binding of hepatocyte growth factor (HGF), its ligand, to the receptor TK MET is implicated in the malignant process of multiple cancers, making disruption of this interaction a promising therapeutic strategy. MET expression or amplification has been found to be associated with poor prognosis in gastric cancer^[77,78]. Onartuzumab is a humanized, monovalent (one-armed) monoclonal antibody against the MET receptor and blocks HGF binding to MET. The efficacy and safety of onartuzumab in combination with mFOLFOX6 in pa-

tients with metastatic HER2-negative gastroesophageal adenocarcinoma is currently being evaluated in phase II and III trials (NCT01590719, NCT01662869). Rilotumumab is another human monoclonal antibody (IgG2) against HGF that blocks binding of HGF to its receptor MET, inhibiting HGF/MET-driven activities in cells. A phase II, double-blind, randomized study evaluated the efficacy and safety of rilotumumab with ECX regimen in patients with previously untreated metastatic gastroesophageal adenocarcinoma. The primary results of this study showed that the primary endpoint of PFS showed a tendency for a better outcome with rilotumumab plus ECX. The addition of rilotumumab to chemotherapy improved the median PFS from 4.2 to 5.6 mo (HR = 0.64). The secondary endpoint of OS also trended in favor of rilotumumab, with an improved median OS from 8.9 to 11.1 mo (HR = 0.73). The most common adverse events seen in the rilotumumab plus ECX arms were peripheral edema, neutropenia, anemia, thrombocytopenia and deep vein thrombosis. An exploratory analysis according to the MET protein expression level was presented at the 2012 ASCO annual meeting^[79]. The addition of rilotumumab to ECX chemotherapy in patients with gastric tumors with high MET expression improved the median OS from 5.7 to 11.1 mo (HR = 0.29, $P = 0.012$). Conversely, in patients with gastric tumors with low MET expression, the addition of rilotumumab to chemotherapy was associated with a trend towards unfavorable OS (HR = 1.84). These results have led to a phase III study to confirm the efficacy of rilotumumab in advanced esophagogastric cancer with high MET expression. This study is currently ongoing (RILOMET-1 trial, NCT01697072).

According to pre-clinical studies, histone deacetylase inhibitors (HDAC) have been found to be potential therapeutic targets in gastric cancer^[80]. Vorinostat is a novel targeted agent that prevents tumor cell proliferation, survival and angiogenesis through histone deacetylase inhibition. Phase I / II studies comparing the effect of vorinostat with that of standard chemotherapy regimens in patients with advanced gastric cancer are underway (NCT01045538 and NCT00537121).

Second-line chemotherapy

Despite the improvement in survival of patients with metastatic gastric cancer, most patients develop progression of disease after first-line chemotherapy. Some patients with gastric cancer after failure of the first-line regimen are treated with second-line chemotherapy, but there was no standard second-line option until the positive results of recent phase III trials^[81]. In a Korean trial 202 patients with advanced gastric cancer who had received one or two prior chemotherapy regimens involving both a fluoropyrimidine and a platinum agent, and with a performance status (PS) of 0 or 1, were randomly assigned to either salvage chemotherapy (docetaxel 60 mg/m² every 3 wk or irinotecan 150 mg/m² every 2 wk) or best supportive care in a 2:1 fashion^[82]. The authors showed that second-line chemotherapy was associated with a sig-

nificant improvement in median OS (5.3 mo) versus BSC (3.8 mo) (HR = 0.657, $P = 0.007$), and patients were also significantly more likely to receive further salvage chemotherapy. There was no difference in median OS between docetaxel and irinotecan (5.2 mo *vs* 6.5 mo, $P = 0.116$).

In a smaller randomized, AIO trial carried out by Thuss-Patience *et al*^[83], 40 patients with tumor progression after first-line chemotherapy and a PS of 0-2 were randomized to BSC or single-agent irinotecan. The median OS was significantly longer for patients treated with irinotecan chemotherapy than that of patients who received BSC (4 mo *vs* 2.4 mo, HR = 0.48, $P = 0.012$).

Similarly, the phase III COUGAR-02 trial showed a modest survival benefit for single-agent docetaxel (75 mg/m² every 3 wk) in 168 patients who progressed within 6 mo of a platinum/fluoropyrimidine chemotherapy regimen. A preliminary report of this trial was presented at the 2013 ASCO annual meeting and the addition of docetaxel to BSC was associated with few ORR (7%), stable disease in 46% and a modest but statistically significant prolongation of median OS (5.2 mo *vs* 3.6 mo)^[84]. A high rate of grade 4 toxicity was noted in the docetaxel arm, but symptom scores for pain were significantly better.

A meta-analysis of these trials was recently published^[81]. The authors indicated that a significant reduction in the risk of death (HR = 0.64, $P < 0.0001$) was found with second-line chemotherapy. In addition, subgroup analysis showed a significant reduction in the risk of death with both irinotecan (HR = 0.55, $P = 0.0004$) and docetaxel (HR = 0.71, $P = 0.004$). In conclusion, the authors reported evidence to support the efficacy of second-line chemotherapy in the treatment of metastatic gastric cancer. In the light of these findings, although not all patients may be eligible for second-line therapy, it should be considered an option in appropriate patients.

A results of randomized, phase III, TCOG GI-0801 trial was presented at the 2013 ASCO Gastrointestinal Cancers Symposium and median PFS for irinotecan plus cisplatin (4.17 mo) was significantly better than irinotecan alone (3.03 mo; $P = 0.0324$) in patients with previously treated with S-1-based chemotherapy for advanced gastric cancer^[85]. No significant differences were detected in the TTF and RR (TTF, 3.4 mo *vs* 2.9 mo; RR; 21.9% *vs* 16.4% with irinotecan plus cisplatin and irinotecan alone, respectively). OS was immature. Related adverse events were comparable with irinotecan plus cisplatin and irinotecan. The authors concluded that irinotecan in combination with cisplatin has promising efficacy for the second-line chemotherapy compared with single agent irinotecan for metastatic gastric cancer. Recent phase III clinical trials of second-line chemotherapy regimens for patients with advanced gastric cancer after failure of the first-line regimen are described in Table 3.

CONCLUSION

Recent trials of multiple agent chemotherapy regimens have demonstrated positive results in terms of improved survival; however, the prognosis of patients with meta-

Table 3 Second-line chemotherapy trials in patients with advanced gastric cancer

Ref.	Regimen	No. of patients	Response rate	Median PFS/TTP and OS (mo)
Kang <i>et al</i> ^[82]	Docetaxel or irinotecan + BSC <i>vs</i> BSC	202	-	TTP, NA; OS, 5.3 <i>vs</i> 3.8
Thuss-Patience <i>et al</i> ^[83]	Irinotecan <i>vs</i> BSC	40	44% <i>vs</i> 5%	PFS, 2.6 <i>vs</i> NA; OS, 4.0 <i>vs</i> 2.4
Ford <i>et al</i> ^[84]	Docetaxel + BSC <i>vs</i> BSC	168	7% <i>vs</i> NA	PFS, 5.6 <i>vs</i> 5.0; OS, 5.2 <i>vs</i> 3.6
Shimada <i>et al</i> ^[85]	Irinotecan + cisplatin <i>vs</i> irinotecan	130	21.9% <i>vs</i> 16.4%	PFS, 4.17 <i>vs</i> 3.03; OS, NA

BSC: Best supportive care; NA: Not applicable; PFS: Progression-free survival; OS: Overall survival; TTP: Time-to progression.

static gastric cancer remains poor and responses to first-line chemotherapy are modest and heterogeneous. Therefore, in patients with refractory gastric cancer, although not all patients may be eligible, second-line chemotherapy should be considered an option in appropriate patients in the light of recent phase III trials and meta-analyses. In order to improve the results of currently available treatments, clinical investigations of targeted agents have recently been conducted. Agents targeting EGFR1 and HER2 have been widely tested. The addition of trastuzumab to cisplatin/fluoropyrimidine-based chemotherapy significantly improved survival in patients with HER2-positive metastatic gastric cancer, which is now the new standard of care by recent ToGA trial. However, this benefit is limited to only approximately 20% of patients with metastatic gastric cancer. Therefore, there remains a critical need for both the development of more effective agents. Other clinical trials of agents targeting VEGF, mTOR, and other biological pathways, have shown marginally positive results. However, future studies are needed to confirm the benefit of adding these targeted agents to chemotherapy and for the detection of novel, molecular, predictive factors and therapeutic targets in order to identify better and optimal treatment modalities for metastatic gastric cancer.

REFERENCES

- 1 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 23335087 DOI: 10.3322/caac.21166]
- 2 Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; **12**: 354-362 [PMID: 16489633]
- 3 Buzzoni R, Bajetta E, Di Bartolomeo M, Miceli R, Beretta E, Ferrario E, Mariani L. Pathological features as predictors of recurrence after radical resection of gastric cancer. *Br J Surg* 2006; **93**: 205-209 [PMID: 16363019 DOI: 10.1002/bjs.52259]
- 4 Field K, Michael M, Leong T. Locally advanced and metastatic gastric cancer: current management and new treatment developments. *Drugs* 2008; **68**: 299-317 [PMID: 18257608]
- 5 Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, Fleig WE. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010; (3): CD004064 [PMID: 20238327 DOI: 10.1002/14651858]
- 6 Ku GY, Ilson DH. Esophagogastric cancer: targeted agents. *Cancer Treat Rev* 2010; **36**: 235-248 [PMID: 20122806 DOI: 10.1016/j.ctrv.2009.12.009]
- 7 Wagner AD, Moehler M. Development of targeted therapies in advanced gastric cancer: promising exploratory steps in a new era. *Curr Opin Oncol* 2009; **21**: 381-385 [PMID: 19412098 DOI: 10.1097/CCO.0b013e32832c42e0]
- 8 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G,

- 9 Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121-X]
- 10 Glimelius B, Ekström K, Hoffman K, Graf W, Sjöden PO, Haglund U, Svensson C, Enander LK, Linné T, Sellström H, Heuman R. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997; **8**: 163-168 [PMID: 9093725]
- 10 Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993; **72**: 37-41 [PMID: 8508427]
- 11 Pyrhönen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995; **71**: 587-591 [PMID: 7533517]
- 12 Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006; **24**: 2903-2909 [PMID: 16782930 DOI: 10.1200/JCO.2005.05.0245]
- 13 Loehrer PJ, Harry D, Chlebowski RT. 5-fluorouracil vs. epirubicin vs. 5-fluorouracil plus epirubicin in advanced gastric carcinoma. *Invest New Drugs* 1994; **12**: 57-63 [PMID: 7960608]
- 14 Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, Yamamichi N, Miyata Y, Ikeda N, Yamamoto S, Fukuda H, Yoshida S. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003; **21**: 54-59 [PMID: 12506170 DOI: 10.1200/JCO.2003.04.130]
- 15 Barone C, Corsi DC, Pozzo C, Cassano A, Fontana T, Noviello MR, Landriscina M, Colloca G, Astone A. Treatment of patients with advanced gastric carcinoma with a 5-fluorouracil-based or a cisplatin-based regimen: two parallel randomized phase II studies. *Cancer* 1998; **82**: 1460-1467 [PMID: 9554521]
- 16 De Lisi V, Cocconi G, Tonato M, Di Costanzo F, Leonardi F, Soldani M. Randomized comparison of 5-FU alone or combined with carmustine, doxorubicin, and mitomycin (BAFMi) in the treatment of advanced gastric cancer: a phase III trial of the Italian Clinical Research Oncology Group (GOIRC). *Cancer Treat Rep* 1986; **70**: 481-485 [PMID: 3516397]
- 17 MacDonald JS, Schein PS, Woolley PV, Smythe T, Ueno W, Hoth D, Smith F, Boiron M, Gisselbrecht C, Brunet R, Lagarde C. 5-Fluorouracil, doxorubicin, and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. *Ann Intern Med* 1980; **93**: 533-536 [PMID: 7436184]
- 18 Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil,

- doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997; **15**: 261-267 [PMID: 8996151]
- 19 **Ross P**, Nicolson M, Cunningham D, Valle J, Seymour M, Harper P, Price T, Anderson H, Iveson T, Hickish T, Lofts F, Norman A. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) With epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002; **20**: 1996-2004 [PMID: 11956258 DOI: 10.1200/JCO.2002.08.105]
 - 20 **Cunningham D**, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358**: 36-46 [PMID: 18172173 DOI: 10.1056/NEJMoa073149]
 - 21 **Kang YK**, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Guan Z, Khasanov R, Zheng L, Philco-Salas M, Suarez T, Santamaria J, Forster G, McCloud PI. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009; **20**: 666-673 [PMID: 19153121 DOI: 10.1093/annonc/mdn717]
 - 22 **Okines AF**, Norman AR, McCloud P, Kang YK, Cunningham D. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. *Ann Oncol* 2009; **20**: 1529-1534 [PMID: 19474114 DOI: 10.1093/annonc/mdp047]
 - 23 **Van Cutsem E**, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**: 4991-4997 [PMID: 17075117 DOI: 10.1200/JCO.2006.06.8429]
 - 24 **Al-Batran SE**, Hartmann JT, Hofheinz R, Homann N, Rethwisch V, Probst S, Stoehlmacher J, Clemens MR, Mahlberg R, Fritz M, Seipelt G, Sievert M, Pauligk C, Atmaca A, Jäger E. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol* 2008; **19**: 1882-1887 [PMID: 18669868 DOI: 10.1093/annonc/mdn403]
 - 25 **Shah MA**, Shibata S, Stoller RG, Kemeny M, Ritch PS, Krishnamurthi SS, Su YB, Janjigian YY, Capanu M, Kelsen DP. Random assignment multicenter phase II study of modified docetaxel, cisplatin, fluorouracil (mDCF) versus DCF with growth factor support (GCSF) in metastatic gastroesophageal adenocarcinoma (GE). *J Clin Oncol* 2010; **28** (Suppl 15): Abstract 4014
 - 26 **Inal A**, Kaplan MA, Kucukoner M, Isikdogan A. Docetaxel and Cisplatin Plus Fluorouracil compared with Modified Docetaxel, Cisplatin, and 5-Fluorouracil as first-line therapy for advanced gastric cancer: a retrospective analysis of single institution. *Neoplasma* 2012; **59**: 233-236 [PMID: 22248282 DOI:10.4149/neo_2012_030]
 - 27 **Van Cutsem E**, Boni C, Tabernero J, Massuti B, Richards DA, Prenen H, Steinberg I, Rougier P. Randomized phase II study (GATE study) of docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer. *J Clin Oncol* 2011; **29** (Suppl 15): Abstract 4018
 - 28 **Al-Batran SE**, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, Rethwisch V, Seipelt G, Homann N, Wilhelm G, Schuch G, Stoehlmacher J, Derigs HG, Hegewisch-Becker S, Grossmann J, Pauligk C, Atmaca A, Bokenmeyer C, Knuth A, Jäger E. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008; **26**: 1435-1442 [PMID: 18349393 DOI: 10.1200/JCO.2007.13.9378]
 - 29 **Ajani JA**, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, Charnsangavej C. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. *Cancer* 2002; **94**: 641-646 [PMID: 11857295 DOI: 10.1002/cncr.10279]
 - 30 **Moehler M**, Haas U, Siebler J, Schimanski C, Hertkorn C, Hoehler T, Galle PR, Heike M. Weekly treatment with irinotecan, folinic acid and infusional 5-fluorouracil (ILF) in patients with advanced gastric cancer. *Anticancer Drugs* 2003; **14**: 645-650 [PMID: 14501387]
 - 31 **Bouché O**, Raoul JL, Bonnetain F, Giovannini M, Etienne PL, Lledo G, Arsène D, Paitel JF, Guérin-Meyer V, Mitry E, Buecher B, Kaminsky MC, Seitz JF, Rougier P, Bedenne L, Milan C. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study--FFCD 9803. *J Clin Oncol* 2004; **22**: 4319-4328 [PMID: 15514373 DOI: 10.1200/JCO.2004.01.140]
 - 32 **Dank M**, Zaluski J, Barone C, Valvere V, Yalcin S, Peschel C, Wenzl M, Goker E, Cisar L, Wang K, Bugat R. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 2008; **19**: 1450-1457 [PMID: 18558665 DOI: 10.1093/annonc/mdn166]
 - 33 **Enzinger PC**, Ryan DP, Clark JW, Muzikansky A, Earle CC, Kulke MH, Meyerhardt JA, Blaszkowsky LS, Zhu AX, Fidias P, Vincitore MM, Mayer RJ, Fuchs CS. Weekly docetaxel, cisplatin, and irinotecan (TPC): results of a multicenter phase II trial in patients with metastatic esophagogastric cancer. *Ann Oncol* 2009; **20**: 475-480 [PMID: 19139178]
 - 34 **Moehler M**, Kanzler S, Geissler M, Raedle J, Ebert MP, Däum S, Flieger D, Seufferlein T, Galle PR, Hoehler T. A randomized multicenter phase II study comparing capecitabine with irinotecan or cisplatin in metastatic adenocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 2010; **21**: 71-77 [PMID: 19605504 DOI: 10.1093/annonc/mdp269]
 - 35 **Ajani JA**, Faust J, Ikeda K, Yao JC, Anbe H, Carr KL, Houghton M, Urrea P. Phase I pharmacokinetic study of S-1 plus cisplatin in patients with advanced gastric carcinoma. *J Clin Oncol* 2005; **23**: 6957-6965 [PMID: 16145066 DOI: 10.1200/JCO.2005.01.917]
 - 36 **Koizumi W**, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215-221 [PMID: 18282805 DOI: 10.1016/S1470-2045(08)70035-4]
 - 37 **Ajani JA**, Lee FC, Singh DA, Haller DG, Lenz HJ, Benson AB, Yanagihara R, Phan AT, Yao JC, Strumberg D. Multicenter phase II trial of S-1 plus cisplatin in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol* 2006; **24**: 663-667 [PMID: 16446338 DOI: 10.1200/JCO.2005.04.2994]
 - 38 **Lenz HJ**, Lee FC, Haller DG, Singh D, Benson AB, Strumberg D, Yanagihara R, Yao JC, Phan AT, Ajani JA. Extended safety and efficacy data on S-1 plus cisplatin in patients with untreated, advanced gastric carcinoma in a multicenter phase II study. *Cancer* 2007; **109**: 33-40 [PMID: 17133415 DOI: 10.1002/cncr.22329]
 - 39 **Ajani JA**, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, Vynnychenko I, Garin A, Lang I, Falcon S. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric

- or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol* 2010; **28**: 1547-1553 [PMID: 20159816 DOI: 10.1200/JCO.2009.25.4706]
- 40 **Yoshida K**, Fujii M, Koizumi W, Kim H, Kim Y, Takeuchi M, Nakajima T. S-1 plus Docetaxel versus S-1 for Advanced Gastric Cancer (START Trial) Update 2012 (JACCRO and KCSG study Group). *Ann Oncol* 2012; **23** (Suppl 9): LBA19_PR
- 41 **Arteaga C**. Targeting HER1/EGFR: a molecular approach to cancer therapy. *Semin Oncol* 2003; **30**: 3-14 [PMID: 12840796]
- 42 **Park YS**, Hwang HS, Park HJ, Ryu MH, Chang HM, Yook JH, Kim BS, Jang SJ, Kang YK. Comprehensive analysis of HER2 expression and gene amplification in gastric cancers using immunohistochemistry and in situ hybridization: which scoring system should we use? *Hum Pathol* 2012; **43**: 413-422 [PMID: 21855114 DOI: 10.1016/j.humpath.2011.05.019]
- 43 **Barros-Silva JD**, Leitão D, Afonso L, Vieira J, Dinis-Ribeiro M, Fragoso M, Bento MJ, Santos L, Ferreira P, Rêgo S, Brandão C, Carneiro F, Lopes C, Schmitt F, Teixeira MR. Association of ERBB2 gene status with histopathological parameters and disease-specific survival in gastric carcinoma patients. *Br J Cancer* 2009; **100**: 487-493 [PMID: 19156142 DOI: 10.1038/sj.bjc.6604885]
- 44 **Yan B**, Yau EX, Bte Omar SS, Ong CW, Pang B, Yeoh KG, Salto-Tellez M. A study of HER2 gene amplification and protein expression in gastric cancer. *J Clin Pathol* 2010; **63**: 839-842 [PMID: 20696687 DOI: 10.1136/jcp.2010.076570]
- 45 **Gómez-Martin C**, Garralda E, Echarri MJ, Ballesteros A, Arcediano A, Rodríguez-Peralto JL, Hidalgo M, López-Ríos F. HER2/neu testing for anti-HER2-based therapies in patients with unresectable and/or metastatic gastric cancer. *J Clin Pathol* 2012; **65**: 751-757 [PMID: 22569536 DOI: 10.1136/jclinpath-2012-200774]
- 46 **Gravalos C**, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008; **19**: 1523-1529 [PMID: 18441328 DOI: 10.1093/annonc/mdn169]
- 47 **Bang YJ**. A randomized, open-label, phase III study of lapatinib in combination with weekly paclitaxel versus weekly paclitaxel alone in the second-line treatment of HER2 amplified advanced gastric cancer (AGC) in Asian population: Tytan study. *J Clin Oncol* 2013; **31**: (Suppl 4), abstract 11
- 48 **Hecht JR**, Bang YJ, Qin S, Chung HC, Xu JM, Park JO, Jeziorski K, Shparyk Y, Hoff PM, Sobrero AF, Salman P, Li J, Protzenko S, Buyse ME, Afenjar K, Kaneko T, Kemner A, Santillana S, Press MF, Slamon DJ. Lapatinib in combination with capecitabine plus oxaliplatin (CAPOX) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: the TRIO-013/LOGiC trial. *J Clin Oncol* 2013; **31**: (Suppl 4), LBA4001
- 49 **Kopp R**, Ruge M, Rothbauer E, Cramer C, Kraemling HJ, Wiebeck B, Schildberg FW, Pfeiffer A. Impact of epidermal growth factor (EGF) radioreceptor analysis on long-term survival of gastric cancer patients. *Anticancer Res* 2002; **22**: 1161-1167 [PMID: 12168918]
- 50 **Moehler M**, Schwarz S, Wagner AD. Esophagogastric cancer: integration of targeted therapies into systemic chemotherapy. *Curr Cancer Drug Targets* 2011; **11**: 681-687 [PMID: 21651462 DOI: 10.2174/156800911796191006]
- 51 **Drescher D**, Moehler M, Gockel I, Frerichs K, Müller A, Dünschede F, Borschitz T, Biesterfeld S, Holtmann M, Wehler T, Teufel A, Herzer K, Fischer T, Berger MR, Junginger T, Galle PR, Schimanski CC. Coexpression of receptor-tyrosine-kinases in gastric adenocarcinoma--a rationale for a molecular targeting strategy? *World J Gastroenterol* 2007; **13**: 3605-3609 [PMID: 17659711]
- 52 **Pinto C**, Di Fabio F, Siena S, Cascinu S, Rojas Llimpe FL, Ceccarelli C, Mutri V, Giannetta L, Giaquinta S, Funaioli C, Berardi R, Longobardi C, Piana E, Martoni AA. Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). *Ann Oncol* 2007; **18**: 510-517 [PMID: 17164226 DOI: 10.1093/annonc/mdl459]
- 53 **Pinto C**, Di Fabio F, Barone C, Siena S, Falcone A, Cascinu S, Rojas Llimpe FL, Stella G, Schinzari G, Artale S, Mutri V, Giaquinta S, Giannetta L, Bardelli A, Martoni AA. Phase II study of cetuximab in combination with cisplatin and docetaxel in patients with untreated advanced gastric or gastro-oesophageal junction adenocarcinoma (DOCETUX study). *Br J Cancer* 2009; **101**: 1261-1268 [PMID: 19773760 DOI: 10.1038/sj.bjc.6605319]
- 54 **Lordick F**, Lubber B, Lorenzen S, Hegewisch-Becker S, Folprecht G, Wöll E, Decker T, Endlicher E, Röthling N, Schuster T, Keller G, Fend F, Peschel C. Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Br J Cancer* 2010; **102**: 500-505 [PMID: 20068568 DOI: 10.1038/sj.bjc.6605521]
- 55 **Lordick F**, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, Kurteva G, Volovat C, Moiseyenko VM, Gorbunova V, Park JO, Sawaki A, Celik I, Götte H, Melezínková H, Moehler M. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14**: 490-499 [PMID: 23594786 DOI: 10.1016/S1470-2045(13)70102-5]
- 56 **Waddell T**, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, Wotherspoon A, Saffery C, Middleton G, Wadley J, Ferry D, Mansoor W, Crosby T, Coxon F, Smith D, Waters J, Iveson T, Falk S, Slater S, Peckitt C, Barbachano Y. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14**: 481-489 [PMID: 23594787 DOI: 10.1016/S1470-2045(13)70096-2]
- 57 **Dragovich T**, McCoy S, Fenoglio-Preiser CM, Wang J, Benedetti JK, Baker AF, Hackett CB, Urba SG, Zaner KS, Blanke CD, Abbruzzese JL. Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. *J Clin Oncol* 2006; **24**: 4922-4927 [PMID: 17050876 DOI: 10.1200/JCO.2006.07.1316]
- 58 **Shi H**, Xu JM, Hu NZ, Xie HJ. Prognostic significance of expression of cyclooxygenase-2 and vascular endothelial growth factor in human gastric carcinoma. *World J Gastroenterol* 2003; **9**: 1421-1426 [PMID: 12854133]
- 59 **Maeda K**, Chung YS, Ogawa Y, Takatsuka S, Kang SM, Ogawa M, Sawada T, Sowa M. Prognostic value of vascular endothelial growth factor expression in gastric carcinoma. *Cancer* 1996; **77**: 858-863 [PMID: 8608475]
- 60 **Song ZJ**, Gong P, Wu YE. Relationship between the expression of iNOS, VEGF, tumor angiogenesis and gastric cancer. *World J Gastroenterol* 2002; **8**: 591-595 [PMID: 12174362]
- 61 **Shah MA**, Ramanathan RK, Ilson DH, Levnor A, D'Adamo D, O'Reilly E, Tse A, Trocola R, Schwartz L, Capanu M, Schwartz GK, Kelsen DP. Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol* 2006; **24**: 5201-5206 [PMID: 17114652 DOI: 10.1200/JCO.2006.08.0887]
- 62 **Shah MA**, Jhawer M, Ilson DH, Lefkowitz RA, Robinson E, Capanu M, Kelsen DP. Phase II study of modified docetaxel, cisplatin, and fluorouracil with bevacizumab in patients with metastatic gastroesophageal adenocarcinoma. *J Clin Oncol* 2011; **29**: 868-874 [PMID: 21189380 DOI: 10.1200/JCO.2010.32.0770]
- 63 **El-Rayes BF**, Zalupski M, Bekai-Saab T, Heilbrun LK, Hammad N, Patel B, Urba S, Shields AF, Vaishampayan U, Dawson S, Almhanna K, Smith D, Philip PA. A phase II study of bevacizumab, oxaliplatin, and docetaxel in locally advanced and metastatic gastric and gastroesophageal junction cancers. *Ann Oncol* 2010; **21**: 1999-2004 [PMID: 20332133 DOI: 10.1093/annonc/mdq065]
- 64 **Ohtsu A**, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J, Langer B, Starnawski M,

- Kang YK. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; **29**: 3968-3976 [PMID: 21844504 DOI: 10.1200/JCO.2011.36.2236]
- 65 **Shen L**, Jin L, Xu JM, Pan HM, Dai G, Qin S, Wang L, Wang J, Yang Z, Yongqian S. Efficacy and tolerability of bevacizumab plus capecitabine and cisplatin in Chinese patients with locally advanced or metastatic gastric/gastroesophageal junction cancer (AGC): Results from the AVATAR study. *J Clin Oncol* 2012; **30** (suppl 4): abstract 73
- 66 **Wadhwa R**, Taketa T, Sudo K, Blum-Murphy M, Ajani JA. Ramucirumab: a novel antiangiogenic agent. *Future Oncol* 2013; **9**: 789-795 [PMID: 23718298 DOI: 10.2217/fo.13.68]
- 67 **Li J**, Qin S, Xu J, Guo W, Xiong J, Bai Y, Sun G, Yang Y, Wang L, Xu N, Cheng Y, Wang Z, Zheng L, Tao M, Zhu X, Ji D, Liu X, Yu H. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol* 2013; **31**: 3219-3225 [PMID: 23918952 DOI: 10.1200/JCO.2013.48.8585]
- 68 **Bang YJ**, Kang YK, Kang WK, Boku N, Chung HC, Chen JS, Doi T, Sun Y, Shen L, Qin S, Ng WT, Tursi JM, Lechuga MJ, Lu DR, Ruiz-Garcia A, Sobrero A. Phase II study of sunitinib as second-line treatment for advanced gastric cancer. *Invest New Drugs* 2011; **29**: 1449-1458 [PMID: 20461441 DOI: 10.1007/s10637-010-9438-y]
- 69 **Yi JH**, Lee J, Lee J, Park SH, Park JO, Yim DS, Park YS, Lim HY, Kang WK. Randomised phase II trial of docetaxel and sunitinib in patients with metastatic gastric cancer who were previously treated with fluoropyrimidine and platinum. *Br J Cancer* 2012; **106**: 1469-1474 [PMID: 22460270 DOI: 10.1038/bjc.2012.100]
- 70 **Sun W**, Powell M, O'Dwyer PJ, Catalano P, Ansari RH, Benson AB. Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203. *J Clin Oncol* 2010; **28**: 2947-2951 [PMID: 20458043 DOI: 10.1200/JCO.2009.27.7988]
- 71 **Guertin DA**, Sabatini DM. Defining the role of mTOR in cancer. *Cancer Cell* 2007; **12**: 9-22 [PMID: 17613433 DOI: 10.1016/j.ccr.2007.05.008]
- 72 **Motzer RJ**, Escudier B, Oudard S, Hutson TE, Porta C, Braccarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; **372**: 449-456 [PMID: 18653228 DOI: 10.1016/S0140-6736(08)61039-9]
- 73 **Ciruelos E**, Cortes-Funes H, Ghanem I, Manso L, Arteaga C. Role of inhibitors of mammalian target of rapamycin in the treatment of luminal breast cancer. *Anticancer Drugs* 2013; **24**: 769-780 [PMID: 23838677 DOI: 10.1097/CAD.0b013e328363adc5]
- 74 **Sadaria MR**, Hruban RH, Edil BH. Advancements in pancreatic neuroendocrine tumors. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 477-490 [PMID: 23899286 DOI: 10.1586/17474124.2013.811058]
- 75 **Doi T**, Muro K, Boku N, Yamada Y, Nishina T, Takiuchi H, Komatsu Y, Hamamoto Y, Ohno N, Fujita Y, Robson M, Ohtsu A. Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer. *J Clin Oncol* 2010; **28**: 1904-1910 [PMID: 20231677 DOI: 10.1200/JCO.2009.26.2923]
- 76 **Ohtsu A**, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, Sahnoud T, Shen L, Yeh KH, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Lebwohl D, Van Cutsem E. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol* 2013; **31**: 3935-3943 [PMID: 24043745 DOI: 10.1200/JCO.2012.48.3552]
- 77 **Appleman LJ**. MET signaling pathway: a rational target for cancer therapy. *J Clin Oncol* 2011; **29**: 4837-4838 [PMID: 22042966 DOI: 10.1200/JCO.2011.37.7929]
- 78 **Lee J**, Seo JW, Jun HJ, Ki CS, Park SH, Park YS, Lim HY, Choi MG, Bae JM, Sohn TS, Noh JH, Kim S, Jang HL, Kim JY, Kim KM, Kang WK, Park JO. Impact of MET amplification on gastric cancer: possible roles as a novel prognostic marker and a potential therapeutic target. *Oncol Rep* 2011; **25**: 1517-1524 [PMID: 21424128 DOI: 10.3892/or.2011.1219]
- 79 **Kelly SO**, Rui T, Abraham A, Yun L, Timothy I, Ross CD, Yizhou J, Sarita D, Elwyn L. Evaluation of MET pathway biomarkers in a phase II study of rilotumumab (R, AMG 102) or placebo (P) in combination with epirubicin, cisplatin, and capecitabine (ECX) in patients (pts) with locally advanced or metastatic gastric (G) or esophagogastric junction (EGJ) cancer. *J Clin Oncol* 2012; **30** (suppl 15); abstract 4005
- 80 **Claerhout S**, Lim JY, Choi W, Park YY, Kim K, Kim SB, Lee JS, Mills GB, Cho JY. Gene expression signature analysis identifies vorinostat as a candidate therapy for gastric cancer. *PLoS One* 2011; **6**: e24662 [PMID: 21931799 DOI: 10.1371/journal.pone.0024662]
- 81 **Kim HS**, Kim HJ, Kim SY, Kim TY, Lee KW, Baek SK, Kim TY, Ryu MH, Nam BH, Zang DY. Second-line chemotherapy versus supportive cancer treatment in advanced gastric cancer: a meta-analysis. *Ann Oncol* 2013; **24**: 2850-2854 [PMID: 23942775 DOI: 10.1093/annonc/mdt351]
- 82 **Kang JH**, Lee SI, Lim do H, Park KW, Oh SY, Kwon HC, Hwang IG, Lee SC, Nam E, Shin DB, Lee J, Park JO, Park YS, Lim HY, Kang WK, Park SH. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012; **30**: 1513-1518 [PMID: 22412140 DOI: 10.1200/JCO.2011.39.4585]
- 83 **Thuss-Patience PC**, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, Dogan Y, Gebauer B, Schumacher G, Reichardt P. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011; **47**: 2306-2314 [PMID: 21742485 DOI: 10.1016/j.ejca.2011.06.002]
- 84 **Ford H**, Marshall A, Wadsley J, Coxon FY, Mansoor W, Bridgewater JA, Madhusudan S, Falk S, Middleton GW, Swinson D, Chau I, Thompson J, Blazeby JM, Cunningham D, Kareclas P, Dunn JA. COUGAR-02: a randomized phase III study of docetaxel versus active symptom control in patients with relapsed esophago-gastric adenocarcinoma. *J Clin Oncol* 2013; **31** (suppl 4): abstract: LBA4
- 85 **Shimada K**, Higuchi K, Hosaka N, Sasaki E, Nakayama N, Amagai K, Takeda Y, Moriwaki T, Sekikawa T, Sakuyama T, Yajima K, Tanabe S, Saito Y, Maeda Y, Nishimura K, Sasaki T, Kobayashi K, Shimoyama T, Hyodo I, Koizumi W. Randomized phase III trial of irinotecan plus cisplatin versus irinotecan alone after S-1 based chemotherapy failure for patients with advanced and recurrent gastric cancer (AGC) (TCOG GI-0801). *J Clin Oncol* 2013; **31** (suppl 4): abstract: 61

P- Reviewers: Al-Wadei HAN, Bi F S- Editor: Wen LL
L- Editor: A E- Editor: Wang CH





百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**

Flat C, 23/F., Lucky Plaza,

315-321 Lockhart Road, Wan Chai, Hong Kong, China

Fax: +852-65557188

Telephone: +852-31779906

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045