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TOPIC HIGHLIGHT

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Clinical management of advanced gastric cancer: The role of new molecular drugs

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Abstract

Gastric cancer is the fourth most common malignant neoplasm and the second leading cause of death for cancer in Western countries with more than 20000 new cases yearly diagnosed in the United States. Surgery represents the main approach for this disease but, notwithstanding the advances in surgical techniques, we observed a minimal improvement in terms of overall survival with a significant increasing of relapsing disease rates. Despite the development of new drugs has significantly improved the effectiveness of chemotherapy, the prognosis of patients with unresectable or metastatic gastric adenocarcinoma remains poor. Recently, several molecular target agents have been investigated; in particular, trastuzumab represents the first target molecule showing improvements in overall survival in human epithelial growth factor 2-positive gastric cancer patients. New molecules targeting vascular epithelial growth factor, mammalian target of rapamycin, and anti hepatocyte growth factor-c-Met pathway are also under investigation, with interesting results. Anyway, it seems necessary to select more accurately the population to treat with new agents by the identification of new biomarkers in order to optimize the results. In this paper we review the actual "scenario" of targeted treatments, also focusing on the new agents in development for gastric cancer and gastro-esophageal carcinoma, discussing their efficacy and potential applications in clinical practice.

Key words: Advanced gastric cancer; Gastrointestinal cancer; Targeted therapy; Monoclonal antibodies; Tyrosine-kinase inhibitor; Gastric cancer

Core tip: In this article we review the actual "scenario" of targeted treatments in advanced gastric cancer, also focusing on the new agents in development,discussing their efficacy and potential applications in clinical practice.

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INTRODUCTION

Despite the worldwide incidence of gastric cancer (GC) decreased in the last decades, it represents the fourth most common malignant neoplasm and the second leading cause of death for cancer[1]. In the United States approximately 21600 patients are diagnosed every year, and about 50% of them are expected to die[2]. Surgery is considered as the only option for cure and multidisciplinary treatment has improved the prognosis in radically resectable disease[3-6]. However, most of patients shows an advanced disease at diagnosis or relapses after a prior curative surgical approach. For these sub-group of patients the prognosis is very poor and chemotherapy represents the reference treatment determining a significantly higher survival compared to supportive care alone[7]. Nevertheless, despite the use of last generation chemotherapy schedules, the median survival in these cases remains low, reaching about 9-10 mo[7]. These results can be also explained by the consideration that GC, such as other solid tumors, is an heterogeneous disease that can be divided into subgroups according to histological, anatomical, epidemiological and molecular classifications[8-13]. For instance, the breakdown of gastric cancer in three subgroups represented by proximal non diffuse, diffuse, and distal non diffuse, is associated not only to epidemiological and histological differences, but also to different genetic patterns[14]. Proximal non diffuse GC corresponds to a lesion located in the cardia and gastro-esophageal junction where carcinogenic inflammation is often related to gastric acid reflux[13]. The overexpression of human epidermal growth factor receptor 2 (HER2) is more prevalent in proximal GC[15-17] similarly to epidermal growth factor receptor (EGFR) expression that is reported in 30%-60% of proximal tumors[18-20]. Such as HER2 and EGFR, also MET amplification occurs more frequently in gastroesophageal cancer[21,22]. Distal non diffuse tumors, that are located between the gastric body and pylorus, are often the consequence of a chronic *Helicobacter pylori* (*H. pylori*) infection[11]. This subtype significantly expresses high vascular-endothelial growth factor (VEGF), interleukin-8 and nitric oxide levels: these molecules are implicated in *H. pylori*-related gastric carcinogenesis, at least in part due to the stimulation of angiogenesis, suggesting the critical role of this pathway in the form[23-25]. Finally, diffuse GC appears as a poorly differentiated signet ring cell type without apparent gastritis, associated with a downregulation of CDH1, a tumor suppressor gene encoding for E-cadherin, a protein playing a key-role in cellular adhesion, forming junctions to bind cells within tissues together[26-29]. Further molecular aberrations include fibroblastic growth factor receptor 2 (FGFR2) signaling and phosphoinositide 3 kinase-AKT-mammalian target of rapamycin (PI3K-AKT-mTOR) pathway activation[30-32]. Furthermore, human epitelial growth factor receptor 3 (HER3) signalling, selectively activated in undifferentiated GC cells, is highly expressed in diffuse subtype compared with the intestinal subtype[17,33]. Finally, matrix metalloproteinases are enzymes involved in degradation of extracellular matrix with an important role in metastasization. Their expression is significantly higher in diffuse than in intestinal GC subtypes contributing to tumor aggressiveness[29]. The distinction of different subtypes of GC is related to a different outcome in terms of survival and response to chemotherapy[34]. Therefore, it seems clear that there are multiple molecular alterations related to signaling pathways associated with cell proliferation, apoptosis and angiogenesis that can be considered as potential targets for specific biomolecular treatments. Recent data based on GC primary tumors, suggest the existence of five distinct gastric cancer patients subgroups, defined by specific genomic amplifications that occur in a mutually exclusive way: FGFR2 (9% of tumors), KRAS (9%), EGFR (8%), ERBB2 (7%) and MET (4%). Collectively, these subgroups suggest that at least 37% of GC patients may be potentially treatable by RTK/RAS directed therapies[22]. These results have been confirmed by a further analysis showing that amplified genes were noted in 37% of gastro-esophageal tumors, including in therapeutically targetable kinases such as ERBB2, FGFR1, FGFR2, EGFR, and MET[35]. Moving from these results, several agents such as monoclonal antibodies (mAbs) and receptor tyrosine kinase inhibitors targeting these pathways, have been developed.

ANTI-VEGF/VEGFR AGENTS

Angiogenesis is one of the main mechanisms for the development and progression of cancer and the VEGF plays a crucial role in the growth of most primary tumors and the subsequent process of metastasis[36]. The family of VEGF consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PGF). Each component of this family links several VEGF receptors (VEGFR): in particular, VEGF-A binds to VEGFR-1 and VEGFR-2, VEGF-B and PGF to VEGFR-1, and VEGF-C and D to VEGFR-2 and 3[37]. VEGFR2 has critical functions in physiological and pathological angiogenesisis and it is widely considered the main receptor driving angiogenesis[38]. The expression of VEGFR2 in intestinal-type GC was found to correlate with the vessel count and the stage of disease[39]. Furthermore, there is evidence that VEGFR2 plays a key-role in regulation of proliferation of GC cells[40]. The overexpression of VEGF is usually associated to the increase of the microvascular density and advanced stage, representing, therefore, an indicator of poor prognosis[41-46]. Many anti-VEGF agents have been developed; among these, monoclonal antibodies and multi-target tyrosine kinase inhibitors (TKIs) have found more clinical applications.

Bevacizumab

Bevacizumab is a monoclonal antibody targeting VEGF-A that showed activity in several solid tumors such as colorectal, breast, ovarian and non-small cell lung cancer. It binds to VEGF, preventing its interaction to VEGFR-1 and VEGFR-2 on the surface of endothelial

Table 1 Phase Ⅱ/Ⅲ trials with anti vascular-endothelial growth factor agents for advanced gastric cancer and gastro-esophageal junction cancers

Trial	Phase	Setting	Regimen	Patients (*n*)	RR	OS (mo)	TTP/PFS (mo)
NCT00084604[49], 2006	Ⅱ	1st line	Iri + C + Bev	47	65%	12.3	8.3
NCT00217581[50], 2010	Ⅱ	1st line	DOCOX + Bev	38	59%	11.1	6.6[1]
AVAGAST[51,54], 2010	Ⅲ	1st line	XC + Bev	387	46%	12.1	6.7
			XC + Placebo	387	37.4%	10.1	5.3
ST03[55], 2012	Ⅱ/Ⅲ	Perioperative	ECX-B	200	-	-	-
REGARD[58], 2012	Ⅲ	2nd line	Ram + BSC	235	-	5.2	2.1[1]
			BSC	117		3.8	1.7[1]
RAINBOW[60], 2014	Ⅲ	2nd line	PTX + Ram	665	28%	9.6	4.4
			PTX + placebo				
ECOG 5203[63], 2010	Ⅱ	1st line	TXT + C + Sor	44	39%	13.6	5.8
NCT01262482[64], 2012	Ⅱ	2nd line	Sor + O	40	-	6.5	3.0[1]
NCT00411151[67], 2011	Ⅱ	2nd line	Sun	52	3.9%	5.81	1.28[1]
NCT00226811[68], 2011	Ⅱ	2nd line	Sun	78	2.6%	6.8	2.3
NCT00970138[73], 2011	Ⅱ	3rd line	A: Placebo		-	2.5	1.4[1]
			B: Apa (850 mg)		-	4.83	3.67[1]
			C: Apa (425 mg *bid*)	144		4.27	3.2[1]
NCT01512745[74], 2012	Ⅲ	3rd line	Apa	-	-	-	-
			Placebo				
TEL0805 trial[75], 2011	Ⅱ	1st line	XC + Tel	39	6.7%	-	-

[1]Progression free survival (PFS). Iri: Irinotecan; Cis: Cisplatin; Bev: Bevacizumab; X: Capecitabine; C: Cisplatin; E: Epirubicin; Ram: Ramucirumab; PTX: Paclitaxel; Sor: Sorafenib; Sun: Sunitinib; Apa: Apatinib; Tel: Telantinib; DOCOX: Docetaxel plus oxaliplatin; O: Oxaliplatin; TXT: Docetaxel; BSC: Best supportive care; RR: Response rate; OS: Overall survival; TTP/PFS: Time to progression/progression free survival.

cells. The biological activity of VEGF interferes with the formation of new tumor blood vessels thus preventing tumor growth[47,48].

Several phase Ⅱ and phase Ⅲ trials investigate the efficacy of first-line Bevacizumab combined with chemotherapy (CT), in patients with advanced GC and gastro-esophageal junction (GEJ) tumors (Table 1).

In a multicenter phase Ⅱ study, conducted by Shah *et al*[49], the efficacy and safety of the addition of bevacizumab (15 mg/kg on day 1) to CT with CPT11 (65 mg/m^2 on days 1 and 8, every 21 d) and CDDP (30 mg/m^2 on days 1 and 8, every 21 d) in 47 patient with GC and GEJ tumors were evaluated. The response rate (RR) was 65% (95%CI: 46-80) and the median overall survival (mOS) was 12.3 mo (95%CI: 11.3-17.2). No increase in chemotherapy-related toxicity was registered. Bevacizumab-related toxicity included a 28% incidence of grade 3 hypertension, 25% of grade 3 to 4 thromboembolic events, 4.2% of gastric perforation and a 2.1 of cardiovascular events. Although the primary cancer was not resected in 40 patients, in only two cases an upper gastrointestinal bleeding has been detected (one patient was treated with anticoagulants for a pulmonary embolism).

In a second phase Ⅱ trial, bevacizumab (7.5 mg/kg) in addition to the chemotherapy regimen with docetaxel (70 mg/mq) and oxaliplatin (75 mg/mq) was administered in 38 patients. A 79% disease control rate (DCR), a 6.6 mo median progression free survival (PFS) and a 11.1 mo OS was observed. In 2 cases, a complete response was achieved. Grade 3-4 neutropenia was observed in 34% of patients and intestinal perforation occurred in 3 patients[50].

Basing on the results of these phase Ⅱ trials, it was conducted a double blind international randomized phase Ⅲ trial (AVAGAST). This study included 774 patients with previously untreated locally advanced or metastatic GC or GEJ cancer. Patients were treated with capecitabine (1000 mg/mq twice daily for 14 d every 3 wk) and cisplatin (80 mg/mq) in combination with either bevacizumab (7.5 mg/kg) or a placebo. Although bevacizumab-arm was associated with a significantly longer PFS (38.0 mo *vs* 29.5 mo, $P = 0.0121$) *vs* placebo, the mOS did not obtain a statistical significance advantage (10.1 mo with placebo and 12.1 mo with bevacizumab, HR = 0.87, $P = 0.1002$). Grade 3 and grade 4 toxicities were observed in 0.5% in the placebo group and in 6.2% in the B group. Arterial or venous thrombois and gastrointestinal perforation were observed in 15.2% and 2.1% of patients in the placebo group *vs* 9.6% and 1.3% of patients in the bevacizumab arm[51,52]. In a subgroup analysis, OS for the pan-American cohort was 6.8 mo for placebo *vs* 11.5 mo for bevacizumab (HR = 0.63). For European and Asian-Pacific subgroups, OS was 8.6 mo *vs* 11.1 mo (HR = 0.85), and 12.1 mo *vs* 13.9 mo (HR = 0.97), respectively. These results indicate that the patients enrolled in Asian-Pacific trial showed a better survival, regardless other prognostic factors. European and American patients with one or more bad prognostic factors seems to have an ad-

vantage in terms of overall survival from bevacizumab[52]. Diversity of patient selection, clinical practice, population genetics, and second-line chemotherapy may explain these results. An update of biomarker analysis performed in AVAGAST trial evidenced that patients with increased plasmatic levels of VEGF-A and a low tumour neuropilin-1 (NRP-1) expression, showed better outcomes; moreover, these markers were more diffused in distal and diffuse GC, and were identified as potential predictors of efficacy for bevacizumab[53,54].

ST03 is a multicenter, randomized, phase Ⅱ/Ⅲ study aiming to assess in 200 patients enrolled between October 2007 and April 2010, the safety, the feasibility and the efficacy of the addition of bevacizumab (7.5 mg/kg) to perioperative epirubicin (50 mg/m^2), cisplatin (60 mg/m^2), capecitabine (dose banded as based on patient BSA) CT. The incidence of cardiac complications was similar in both arms except for arterial thromboembolic events and more asymptomatic left ventricular ejection fraction falls that were more frequent with ECX plus bevacizumab. OS was the primary end-point while response rate, resection rate, DFS, safety of treatment, and quality of life were the secondary end-points. The preliminary data are expected in 2014[55].

Ramucirumab

Ramucirumab (IMC-1121B) is a fully human IgG1 monoclonal antibody specifically blocking with high affinity the extracellular VEGF-binding domain of VEGFR-2 and inhibiting downstream signaling involved in the formation and maintenance of aberrant blood vessels that supply blood to tumor[56]. The specific targeting of VEGFR2 by anti-angiogenetic agents is more effective since their principal targets are endothelial cells, which are genetically stable and, therefore, less likely to develop resistance to these agents. Ramucirumab is administered intravenously. Pharmacokinetic data support dosing every 1, 2, or 3 wk with a maximum tolerated dose (MTD) weekly identified as 13 mg/kg; dose-limiting toxicities (DLT) observed in Cycle 1 weekly dosing were hypertension (at 10 mg/kg per week and 16 mg/kg per week): deep vein thrombosis (at 16 mg/kg per week). No DLT and no MTD were identified in every 2 wk and every 3 wk study. Phase I clinical trials demonstrated its safety and efficacy also in patients with advanced cancer refractory to standard chemotherapy[57]. REGARD, an international, randomised, double-blind, placebo-controlled, phase Ⅲ trial is the first positive study with a biological monotherapy in patients with advanced GC progressing after first line chemotherapy. Patients were randomly assigned with a 2:1 ratio to receive best supportive care plus ramucirumab 8 mg/kg or placebo, intravenously once every 2 wk. Ramucirumab improved significantly OS (5.2 mo *vs* 3.8 mo with placebo, HR = 0.776, $P = 0.047$) and PFS (2.1 mo *vs* 1.3 mo with placebo, HR 0.483, $P < 0.0001$); the rate of disease control was significantly higher in patients given ramucirumab than in those given placebo. Finally, the duration of disease control was significantly longer in the ramucirumab group than in the placebo one (median 4.2 mo *vs* 2.9 mo, $P = 0.036$)[58]. Ramucirumab was well tolerated. Rates of serious adverse events were similar between arms; for ramucirumab, the incidence of any individual severe toxicity was low and supportive care requirements were modest. The patients who received at least 4 cycles of therapy with ramucirumab, maintained their quality of life. Performance status (PS) was maintained for a significantly longer time with ramucirumab[59].

The RAINBOW trial is a randomized, multicenter, double-blind, placebo controlled phase Ⅲ study testing paclitaxel (80 mg/kg on days 1, 8, 15, every 4 wk) with or without ramucirumab (8 mg/kg inta-venous infusion on days 1 and 15 every 4 wk) in patients with metastatic GC refractory or progressive after first-line therapy with platinum and fluoropyrimidine. The study, which randomized a total of 665 patients, had as primary endpoint OS while secondary endpoints included: PFS, time to progression (TTP), objective response, quality of life and safety[60]. This study has met its primary endpoint of improved OS and secondary endpoint of improved PFS. In fact, median overall survival was 9.6 mo for the combination and 7.4 mo for paclitaxel alone with a 19% reduction in the risk of death ($P = 0.0169$) with ramucirumab. Median progression-free survival was 4.4 mo and 2.9 mo, respectively, a 27% reduction in risk ($P < 0.0001$). The objective response rate associated with the combination was 28% *vs* 16% with paclitaxel alone ($P = 0.0001$). At 6 mo, the progression-free survival rate was 36% *vs* 17%, and at 9 mo was 22% *vs* 10%, respectively. In addition, the disease control rate was much better with ramucirumab, 80% *vs* 64%, respectively ($P < 0.0001$). Ramucirumab was relatively well tolerated, although adverse events of grade ⩾ 3 were somewhat greater with combination treatment and included neutropenia (40.7% *vs* 18.8%) - but the incidence of febrile neutropenia was comparable (3.1% *vs* 2.4%) - leukopenia (17.4% *vs* 6.7%), hypertension (14.1% *vs* 2.4%) and fatigue (7.0% *vs* 4.0%). These adverse events did not lead to increased treatment discontinuation in the ramucirumab arm, nor were rates of treatment-related deaths different between the two arms (4.0% with ramucirumab/paclitaxel *vs* 4.6% with paclitaxel alone). Other adverse events were anaemia (9.2% *vs* 10.3%), abdominal pain (5.5% *vs* 3.3%) and asthenia (5.5% *vs* 3.3%). Ramuricumab is an effective new drug for patients with metastatic or locally advanced gastric cancer for whom first-line combination chemotherapy has failed. It also shows that an effective second-line therapy improves overall survival. It is the only study to show a two-month improvement in survival in this setting[60]. A randomized ongoing phase Ⅱ study (NCT01246960) for patients with untreated advanced esophageal, GC and GEJ carcinoma is evaluating FOLFOX-6 ± ramucirumab; it will enroll a total of 166 patients with PFS as primary endpoint[61] (Table 1).

Sorafenib

Sorafenib is an oral multi-target TKI inhibitor, linking

to VEGFR-1, VEGFR-2, VEGFR-3, platelet derived growth factor receptor (PDGFR), B-Raf, Raf-1 and c-Kit. It plays its antineoplastic role through two pathways: firstly, it acts directly through the inhibition of tumor proliferation by blocking the RAF/MEK/ERK-mediated cell signaling pathway; on the other hand it indirectly inhibits angiogenesis by blocking VEGFR and PDGFR[62]. The ECOG 5203 phase Ⅱ trial[63] tested sorafenib (400 mg orally twice a day for 21 d) in combination with cisplatin (75 mg/m^2) and docetaxel (75 mg/m^2) in 44 patient with advanced GC and GEJ carcinoma. They achieved an overall response rate (ORR) of 41% (primary end point), an OS of 13.6 mo and a PFS of 5.8 mo. This result is lower than the PFS obtained in a phase Ⅲ trial of chemotherapy alone. The results of this study suggest that sorafenib may confer an additional antitumor effect to the combination of docetaxel and cisplatin in the treatment of metastatic and advanced unresectable GC and GEJ adenocarcinoma but there is no significant superiority over historical data from the docetaxel and cisplatin combination CT, thereby prompting no further clinical development of sorafenib in GC. In a phase Ⅱ trial presented by a Spanish group at 2012 ASCO annual meeting, evaluated the combination of oxaliplatin (130 mg/m^2) and sorafenib (400 mg orally) in previously treated with cisplatin and fluoropyrimidine advanced GC patients. In this trial 40 patients (36 evaluable for response) in second line setting were enrolled: 47.2% of patients obtained a SD and in one case a CR, while The median PFS and OS was 3 mo and 6.5 mo respectively. However for patients who obtained a PFS to first line > 6 mo, was recorded an OS of 9.7 mo; on the other hand the OS was only 5.6 mo for patients with and PFS was lower than 6 mo (P = 0.04). The association of sorafenib and oxliplatin resulted in a good safety profile and suggested that PFS after a first line treatment based on cisplatin plus fluoropyrimidine identifies more subgroups of patients with different clinical features[64] (Table 1).

A randomized phase Ⅱ trial comparing the addition of sorafenib to cisplatin and capecitabine as first line treatment with PFS as primary endpoint, has completed the accrual and the results are waited[65].

Sunitinib

Sunitinib is an oral TKI targeting RET, VEGFR-1, VEGFR-2, VEGFR-3, PDGFRα, PDGFRβ, Flt3, c-KIT, and colony-stimulating factor receptor 1 (CSFR-1). In advanced GC, Sunitinib showed a low activity as single agent in second-line setting[66]. In a phase Ⅱ study, 52 patients with chemo-resistant advanced GC, received sunitinib as single agent obtaining a mOS of 5.8 mo. Tumoral VEGF-C expression was linked to a shorter median PFS if compared with no expression (1.2 mo *vs* 2.8 mo, P = 0.0119) even if no differences in RR were observed[67]. In a further phase Ⅱ study, sunitinib was tested in 78 patients as 2nd-line therapy. The primary endpoint was the ORR, defined as the percentage of all patients who experienced a confirmed complete response (CR) or partial response (PR), as defined by RECIST criteria. Two patients (2.6%) had partial responses and 25 patients (32.1%) had as best response a stable disease for ⩾ 6 wk. Between the secondary end-points, the median PFS was 2.3 mo and median OS was 6.8 mo. Thought the low toxicity profile, no further clinical trials in GC are actually scheduled[68] (Table 1).

Cediranib

Cediranib (AZD2171) is a powerful VEGFR-1 and VEGFR-2, c-Kit and PDGFR-β inhibitor[69]. Its efficacy in association with cisplatin plus S-1 or capecitabine has been evaluated in a phase I trial in 14 untreated advanced GC patients. It emerged a good tolerability prifile (anorexia, fatigue and nausea were the most commonly observed toxicities). Anyway, preliminary efficacy results evidenced only one CR and three PR. Therefore, more confirmatory studies are needed[69,70].

Apatinib

Apatinib is a TKI selectively targeting VEGFR-2, similar to vatalanib (PTK787), but with a binding affinity higher than that of vatalanib or sorafenib[71,72]. A randomized, three-arm phase Ⅱ trial investigated apatinib (850 mg/d) as third-line therapy in 141 patients with advanced GC. DCR of 51%, 34.7% and 10.4% respectively and median PFS of 3.4, 3.4 and 1.4 mo respectively were observed. The median OS was 4.8, 4.3 and 2.5 mo, respectively. Most common adverse effects included hypertension and hand-foot syndrome. Patients given apatinib as a once-daily regimen had fewer grade 3 to 4 adverse events than those given apatinib at a dose of 425 mg twice daily. Also, the incidence of hypertension, hand-foot syndrome, thrombocytopenia, and diarrhea was reduced among patients treated with apatinib 850 mg once daily. Therefore, the dosing regimen of 850 mg once daily was recommended for following studies[73]. A third line setting randomized phase Ⅲ trial is actually comparing apatinib (850 mg/daily) to placebo. The enrollment target is 270 patients. PFS and OS are the primary endpoints; DCR, ORR, quality of life, safety profile are the secondary endpoints[74] (Table 1).

Telatinib

Telatinib is an oral selective inhibitor of VEGFR, PDGFR and KIT tyrosine kinases. It is well tolerated at high doses and shows no overlapping toxicities with CT. Telatinib associated with standard chemotherapy has been tested in in 39 untreated patients in a phase Ⅱ trial. The objective of this study was evaluating the antitumor activity, safety and tolerability of telatinib. The primary outcome was PFS, and secondary outcomes were OS, ORR, safety and tolerability, pharmacokinetic (PK) and biomarkers. Sixty four percent of patients showed a PR and 1 patient (2.6%) had a CR. A 92% DCR and 140 d PFS were detected; the association was well tolerated at standard dose, In fact hypertension and fatigue, the most represented toxicities, were manageable and reversible[75].

On the basis of these data, a phase Ⅲ multicenter, double-blind, randomized trial testing telatinib plus cisplatin and capecitabine is planned (Table 1).

ANTI-EGFR THERAPIES

EGFR-HER1 is one of four receptors involved in the pathway of epidermal growth factor transfer (HER, human epidermal growth factor receptor). It is a transmembrane receptor composed of an extracellular binding domain, a transmembrane portion, and an intracellular cytoplasmic domain with a tyrosine kinase functionality[76]. It is activated by specific ligands, such as epidermal growth factor (EGF), transforming growth factor-α, amphiregulin, heparin-binding EGF, betacelulin, epiregulin, and neuregulin 2-α; the ligand binding can induce homodimerization or heterodimerization with a consequent tyrosine kinase autophosphorylation and activation[77]. This process leads to several intracellular signals cascades, including the Ras/Raf/mitogen activated protein kinase (MAPK) or the Akt/mTOR pathway determining cell proliferation and growth, prevention of apoptosis, tumor-induced angiogenesis, and activation of invasion and metastatic growth[77,78]. In a large study of EGFR expression in GC using immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH), it has been evidenced that the samples were positive for IHC (2+ and 3+) in 27.4% of cases, while an amplification of EGFR was found only in 2.3% of the samples. EGFR IHC expression correlated with lymph node metastasis, lymphatic invasion and higher stage. Furthermore, differently from FISH amplification, EGFR expression was a poor prognostic factor[79].

In preclinical models it has been shown that the EGFR inhibition leads to an anti-tumour activity with synergy with chemotherapy as well as radiotherapy[80,81].

In colorectal cancer models, the presence of a KRAS mutation is usually associated with a downstream activation of the Ras/MAPK pathway, leading to cell proliferation that can't be blocked by anti EGFR-antibodies. Therefore, KRAS mutational status represents an important predictor of response to cetuximab and panitumumab and a wild type status is usually associated with a higher RR, OS and PFS[82]. However, differently from colon cancer, only in a low percentage of GC can be detected a KRAS mutation[81]. In one of the largest international multicenter database on 710 GC patients, KRAS mutations were detected in 4.1% of samples; the frequency was 5.8% among United Kingdom patients, 4% among Japanese patients and 2.8% among Chinese patients[83]. Therefore, at present, none of trials with anti-EGFR mAbs was restricted to patients with wild-type KRAS and no data suggesting that *KRAS* gene mutation is predictive of lack of efficacy of EGFR-targeted MAb therapy in this tumor type are currently available.

TKIs inhibitors: Gefitinib and erlotinib

Gefitinib is an oral EGFR quinazoline tyrosine kinases inhibitor, and its antitumor activity on GC cell cultures (GLM-1, GLM-2, GLM-4, NCI-N87) lead the research of its clinical efficacy[84]. It has been firstly tested in GC in a phase Ⅱ trial where 75 previously treated unselected patients with locally advanced or metastatic GC (77%) and GEJ carcinoma (21%) received the drug at the dose of 250 or 500 mg/die in order to assess its biologic activity in tumor samples. Although gefitinib reached enough tumor concentrations to inhibit EGFR activation with some evidences of biological effect on EGFR pathway, these results were not translated in a clinical benefit, obtaining a low DCR (18.3%)[85]. In a second phase Ⅱ trial, gefitinib in combination with cisplatin (20 mg/m^2 daily) and fluorouracil (1000 mg/m^2 daily) with concomitant radiotherapy (30 and 1.5 Gy bis in die) was compared to chemoradiotherapy alone as neo-adjuvant treatment in 80 patients with locally advanced esophageal cancer and GEJ cancer. ORR was not increased but it was observed a benefit in 3-year OS if compared with historical controls (42% *vs* 28%, $P = 0.06$)[86].

Gefitinib showed anticancer properties in HER2 overexpressed GC cells inducing apoptosis, and a low antitumor effect in EGFR positive ones. This controversial activity of drug is still unclear but it could be explained by the studies that hypothesized gefitinib to prevent the formation of HER2/HER3 heterodimers by taking part in the sequestration of HER2 and HER3 with inactive EGFR/HER2 and EGFR/HER3 heterodimers[87]. Furthermore, it seems to be able to selectively arrest the phosphorylation of Akt in cells with HER2 overexpression, although cells with low HER2 expression also displayed constitutive activation of P13K/Akt pathway[84] (Table 2).

Erlotinib hydrochloride is an oral reversible inhibitor of the adenosine triphosphate binding site of EGFR receptor tyrosine kinase[88]. Its efficacy in GC was tested in a large phase Ⅱ trial conduced by Southwestern Oncology Group (SWOG 0127)[89] where 70 patients with unresectable or metastatic GC (37%) or GEJ carcinoma (63%) were treated. The GC group ($n = 26$) was closed after the first phase due to lack of activity of the drug, while esophageal/GEJ group ($n = 46$) completed the accrual. In this group were observed all of the objective responses (1 CR and 4 PR) with an ORR of 9%, (95%CI: 3-22). Most common toxicities were skin rash (86% and 72%), fatigue (51% and 44%) and AST/ALT elevation (28% and 28%), respectively for GEJ and gastric localizations. Therefore, erlotinib seems to be a moderately active drug in clinical management of patients with GEJ adenocarcinoma, but appears inactive in GC. Considering all these data, it emerges a low efficacy of EGFR TKIs in GC: this evidence could be also explained because EGFR mutations, in particular L858R or delE746-A750 mutations that are related to the activity of EGFR TKIs, are very rare in this tumor[90] (Table 3).

Monoclonal antibodies: Cetuximab, panitumumab, matuzumab and nimotuzumab

Anti-EGFR monoclonal antibodies cetuximab and panitumumab (MAbs) compete with ligand-receptor interac-

Table 2 Phase Ⅱ trials of epidermal growth factor receptor tyrosine kinase inhibitors for advanced gastric cancer and gastro-esophageal junction cancers

Author/trial	Phase	Setting	Regimen	Patients (*n*)	RR	OS (mo)	TTP (mo)
NCT00237900[86], 2010	Ⅱ	Neoadjuvant	CF + G + RT	80	-	42% (3-yr)	-
SWOG 0127[89], 2006	Ⅱ	1st line	Erlotinib 150 mg/d	44 (GEJ)	9% (GEJ)	6.7 (GEJ)	-
				26 (stomach)	0% (stomach)	3.5 (stomach)	-

C: Cisplatin; F: 5 fluorouracil; G: Gefitinib; RT: Radiotherapy; RR: Response rate; OS: Overall survival; TTP: Time to progression; GEJ: Gastro-esophageal junction.

Table 3 Phase Ⅱ/Ⅲ trials of anti-epidermal growth factor receptor agents for advanced gastric cancer and gastro-esophageal junction cancer

Trial	Phase	Setting	Regimen	Patients (*n*)	RR	OS (mo)	TTP (mo)
FOLCETUX[187], 2007	Ⅱ	1st line	FOLFIRI + Cet	38	44.1%	16.0	8.0
NCT00477711[188], 2008	Ⅱ	1st line	CX + Cet	54	48.1%	-	5.23
DOCETUX[95], 2009	Ⅱ	1st line	C + TXT + Cet	72	41.2%	9.0	5.0
AIO[93], 2010	Ⅱ	1st line	FUFOX + Cet	52	65.0%	9.5	7.6
NCT01123811[94], 2011	Ⅱ	1st line	FOLFIRI + Cet	49	46.0%	16.5	90.0
NCT00398398[189], 2011	Ⅱ	1st line	XELOX + Cet	44	52.3%	11.8	6.5
NCT00517829[96], 2013	Ⅱ	1st line	DOCOX	75	26.5%	8.5	-
			DOCOX + Cet	75	38.0%	9.4	-
EXPAND[97], 2013	Ⅲ	1st line	CX + Cet	455	29.0%	9.4	4.4
			CX	449	30.0%	10.7	5.6
REAL-Ⅲ[103], 2013	Ⅱ-Ⅲ	1st line	EOX + P	278	42.0%	8.8	6.0
			EOX	275	46.0%	11.3	7.4
NCT00113581[107], 2008	Ⅰ	1st line	ECX + M	21	65.0%	-	5.2
MATRIX[190], 2010	Ⅱ	1st line	ECX + M	35	58.0%	12.2	7.1
			ECX		31.0%	9.4	4.8
NCT01813253[111], 2011	Ⅱ	2nd line	Iri	82	18.4%	7.5%	85 d
			Iri + N		10.3%	9.7%	73 d

Cet: Cetuximab; C: Cisplatin; TXT: Docetaxel; X: Capecitabine; E: Epirubicin; O: Oxaliplatin; P: Panituimumab; E: Epirubicin; Iri: Irinotecan; M: Matuzumab; N: Nimotuzumab; FOLFIRI: 5 fluorouracil plus folinic acid plus irinotecan; FUFOX: 5 fluorouracil plus oxaliplatin; DOCOX: Docetaxel plus oxaliplatin; XELOX: Capecitabine plus oxaliplatin; RR: Response rate; OS: Overall survival; TTP: Time to progression.

tion and downstream tyrosine kinase activity through the binding to the extracellular EGFR domain, occluding in this way the ligand-binding region. It results in a receptor internalization and degradation. Another mechanism of activity is represented by an indirect antitumor effect by antibody-dependent cell-mediated cytotoxicity activity[76,91].

Cetuximab is a chimeric (mouse/human) IgG1 antibody, able to initiate an immune-mediated antitumor response (*i.e.*, antibody-dependent cell-mediated cytotoxicity) through natural killer cell binding[76].

The employment of cetuximab as single agent in metastatic or unresectable GC did not seem effective[92]. On the other side, the addition of the monoclonal antibody to fluoropyrimidine-based regimens showed interesting results. In a small phase Ⅱ trial conduced by Lordick *et al*[93], 52 patients received cetuximab (400 mg/m^2 at first infusion followed by weekly infusions of 250 mg/m^2) with FUFOX (oxaliplatin 50 mg/m^2, 5-FU 2000 mg/m^2, and folinic acid 200 mg/m^2 on days 1, 8, 15 and 22 qd36). Among 46 patients assessable for response, ORR was 65% (95%CI: 50-79) with a median TTP of 7.6 mo (95%CI: 5.0-10.1) and a median OS of 9.5 mo (95%CI: 9.7-11.1). The treatment was well tolerated: the most common grade 3/4 toxicities were diarrhoea (33%), and skin toxicity (24%). Furthermore, no clear association between the detection of EGFR and the response rate was found. Moehler *et al*[94] published in 2010 the results of a phase Ⅱ trial testing the efficacy of the addition of cetuximab to irinotecan (80 mg/m^2) and a 24-h continuous infusion of folinic acid (200 mg/m^2) and 5-FU (1500 mg/m^2). After a median follow-up of 31.2 mo, results showed an ORR of 46% (95%CI: 31-61) with a DCR of 79%. Median PFS and OS times were 9.0 mo (95%CI: 7.1-15.6) and 16.5 mo (95%CI: 11.7-30.1) respectively. The biomarkers analysis evidenced that tumor response was more frequent in EGFR-expressing tumors (P = 0.041); furthermore, PTEN overexpression was associated with a longer PFS (P = 0.035) and OS (P = 0.0127). In a phase Ⅱ Italian study[95], 72 patients with metastatic or unresectable disease (stomach 81.9% and GEJ 18.1%) were enrolled to receive a first-line CT with cetuximab (initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2), cisplatin (75 mg/m^2 on day 1), docetaxel (75 mg/m^2 on day 1), every 3 wk. The assessed ORR was 41.2% (95%CI: 29.5-52.9), with a DCR of 76.5%, a median TTP of 5 mo (95%CI: 3.7-5.4) and a median OS time of 9 mo (95%CI: 7-11). Most common G3-G4 tox-

icity observed was neutropenia (44.4%). Recently it has been published a phase Ⅱ trial evaluating the addition of cetuximab (400 mg/m^2 first dose then 250 mg/m^2 weekly) to DOCOX (docetaxel 60 mg/m^2 plus oxaliplatin 130 mg/m^2 on day 1 of each 21-d cycle) in 150 patients with previously untreated advanced GC. Results evidenced in two arms of treatment (DOCOX *vs* DOCOX + cetuximab) a RR of 26.5% and 38.0% respectively, with a median PFS of 4.7 and 5.1 mo respectively (95%CI: 3.0-5.6/4.3-5.9) and a median OS of 8.5 and 9.4 mo respectively. Grade 3-4 treatment-related adverse events included neutropenia (50% *vs* 44%), febrile neutropenia (13% *vs* 19%), diarrhoea (12% *vs* 17%), fatigue (12% *vs* 17%) and leukopenia (7% *vs* 14%)[96].

Moving from these promising data, the EXPAND trial has been designed in order to assess the real impact of addition of cetuximab to standard chemotherapy in advanced GC[97]. In this phase Ⅲ trial, 904 patients with locally advanced or metastatic disease were randomly assigned to receive capecitabine (1000 mg/m^2 twice daily, on days 1 to 15) and cisplatin (80 mg/m^2) with or without cetuximab (400 mg/m^2 followed by 250 mg/m^2 per week) every 3 wk. The median PFS (primary endpoint of this trial) was 4.4 mo (95%CI: 4.2-5.5) in the cetuximab arm, a not statistically significant data if compared with 5.6 mo (95%CI: 5.1-5.7) obtained in the XP alone arm (HR = 1.091, 95%CI: 0.920-1.292, P = 0.3158). The addition of monoclonal antibody to chemotherapy resulted even detrimental in terms of median OS: 9.4 mo (95%CI: 8.3-10.6) in the cetuximab arm and 10.7 mo (9.4-11.3) in the XP arm (HR = 1.004, 95%CI: 0.866-1.165, P = 0.9547). The RR was similar in cetuximab and chemotherapy arm (30% and 29% respectively). Fifty four percent of 446 patients in the cetuximab group and 44% of 436 in the control group had any grade of serious adverse event. In particular, 83% of patients in the chemotherapy plus cetuximab group and 77% in the chemotherapy group experienced grade 3-4 toxicities; the most common G3-4 toxic events were: diarrhoea, hypokalaemia, hypomagnesaemia, rash, and hand-foot syndrome. Grade 3-4 neutropenia was more common in controls than in patients who received cetuximab. Incidence of grade 3-4 skin reactions and acne-like rash was higher in the cetuximab arm than in the control arm. These results suggest that cetuximab in addition to standard chemotherapy is not an effective choice in patients with advanced GC[97].

Panitumumab is a fully human IgG2 monoclonal antibody targeting the epithelial growth factor receptor. Its immunogenicity is minimal or non-existent, therefore it avoids the problem of generating human murine antibodies, minimizing the risk of hypersensitivity reactions and compromising treatment efficacy[98].

In metastatic wild-type KRAS colorectal cancer, panitumumab showed activity in combination with chemotherapy in chemo-refractory patients improving PFS both in the first[98] and in second-line settings[99,100]. Its efficacy in addition to standard treatment in advanced settings of esophageal-gastic cancer has been tested in a large phase Ⅲ trial, also known as REAL-3 study[101-103]. Five hundred fifty-three patients were randomised to receive EOC [epirubicin (50 mg/m^2), oxaliplatin (130 mg/m^2), and capecitabine (1250 mg/m^2/d)], or mEOC [epirubicin (50 mg/m^2), oxaliplatin (100 mg/m^2), capecitabine (1000 mg/m^2 per day)], and panitumumab 9 mg/kg. The primary endpoint was OS, the secondary endpoints were PFS, RR, and safety. The median survival time was 11.3 mo with EOC compared to 8.8 mo with mEOC plus panitumumab (HR = 1.37, 95%CI: 1.07-1.76, P = 0.013). The median PFS was 7.4 and 6.0 mo, respectively (HR = 1.22, 95%CI: 0.98-1.52, P = 0.068), with a RR of 42% and 46% respectively. Multivariate analysis demonstrated that KRAS mutation (HR = 2.1, 95%CI: 1.10-4.05, P = 0.025) and PIK3CA mutation (HR = 3.2, 95%CI: 1.01-10.40, P = 0.048) had a negative prognostic value. According to these results, the addiction of a monoclonal antibody targeting EGFR does not seem to be a valid therapeutic option for advanced GC. A phase Ⅱ trial assessing the efficacy and safety of panitumumab in combination with docetaxel and cisplatin in patients with untreated GC or GEJ carcinoma (SPIGA trial) is actually ongoing[104] (Table 3).

Matuzumab (EMD 72000) is a humanized IgG1 monoclonal antibody against human EGFR. It has approximately a 10% murine origin, therefore it is characterized by a limited immunogenicity, and being IgG1, it is able to induce antibody dependent cell cytotoxicity[105]. Matuzumab showed an anti-tumoural activity in preclinical studies of xenograft models of different human tumours in mice[106]. Its efficacy in advanced GC has been tested in a small phase I trial where 21 EGFR-positive patients received matuzumab (400 and 800 mg weekly and 1200 mg every 3 wk) plus ECX (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 daily) until disease progression or unacceptable toxicities. Even if this study was designed in order to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of the drug, efficacy results were very interesting: ORR was 65% (95%CI: 43-82) with 25% of SD (95%CI: 11-47) and 10% of PD; the overall median TTP was 5.2 mo (95%CI: 3.0-16.0). The treatment resulted well tolerated, and fatigue was the major dose-limiting toxicity[107].

Nimotuzumab (h-R3) is a humanized IgG1 monoclonal antibody targeting human EGFR showing efficacy in malignant gliomas and head and neck squamous cells cancer[108-110]. Its activity and tolerance in advanced GC has been recently studied with interesting results: in a randomized phase Ⅱ trial[111], patients received nimotuzumab plus irinotecan or irinotecan alone as a second-line therapy. The primary endpoint was PFS. Median PFS was 73 and 85 d, respectively (HR = 0.860, 95%CI: 0.516-1.435, P = 0.5668). The median OS was 250.5 and 232 d in the nimotuzumab and irinotecan monotherapy groups, respectively (HR = 0.994, 95%CI: 0.618-1.599, P = 0.9778). The RR was 18.4% and 10.3%, respectively. In a subgroup analysis of EGFR 2+ or 3+ patients (assessed

Table 4 Clinical trials with anti-human epidermal growth factor receptor 2 agents for advanced gastric cancer and gastro-esophageal junction cancer

Trial	Phase	Setting	Regimen	Patients (*n*)	OS (mo)	TTP/PFS (mo)
ToGa Trial[122], 2010	Ⅲ	1st line	CF/X + T	594	13.8	6.7
			CF/X		11.1	5.5
NCT00680901[129], 2013	Ⅲ	1st line	OX + Lap	487	12.2	6.0
			OX		10.5	5.4
NCT00486954[130], 2010	Ⅲ	2nd line	PTX + Lap	430	11.0	5.6
			PTX		8.9	4.2

C: Cisplatin; F: 5-fluorouracil; X: Capecitabine; T: Trastuzumab; O: Oxaliplatin; Lap: Lapatinib; PTX: Paclitaxel; OS: Overall survival; TTP/PFS: Time to progression/progression free survival.

by IHC) a median PFS of 118.5 and 59.0 d in the nimotuzumab and irinotecan monotherapy groups respectively was assessed. On the other hand, a shorter median PFS was observed in EGFR 0 or 1+ patients (58.5 and 87.5 d). Therefore, these results, even if preliminary, did not show a clear benefit by the addition of nimotuzumab to standard chemotherapy but it might show some activity in EGFR 2+, 3+ patients. In a recent phase Ⅱ trial presented at the 2012 ASCO annual meeting, 62 patients with advanced GC were randomized to receive cisplatin and S-1 chemotherapy with or without nimotuzumab. Median TTP was 5 and 3 mo respectively with a good tolerability of association[112] (Table 3).

HER2 TARGETING AGENTS

HER2 is a transmembrane receptor belonging to the family of epidermal growth factor receptors (HER1, HER2, HER3 and HER4). Its structure is composed by an extracellular ligand-binding domain, a short hydrophobic transmembrane region, and an intracellular domain with a tyrosine kinase activity (except for HER3). The activation of HER2 does not require a ligand[113] and induces a receptor homo- or hetero-dimerization that initiates phosphorylation cascades and subsequent activation of the PI3K-Akt-mTOR and Ras-Raf-ERK pathways[114]. Among different dimers the HER2-HER3 heterodimer is considered the most active; moreover, HER3 has a critical function in HER2-mediated transformation and plays a central role in the tumor cell growth and proliferation in HER2 overexpressed tumors. In GC HER2 and HER3 co-expression was found in 15% of cases[115].

Recent studies show a main role of HER2 in the development of several types of human cancer including GC and GEJ cancers. HER2 overexpression is observed in 10%-38% of GC tumor samples, with a higher prevalence in intestinal-type and GEJ tumors than in diffuse type and GC[116]. Hofmann *et al*[117] examined the HER2 status in 178 GC samples with immune-histo-chemistry (IHC) and fluorescence *in situ* hybridization (FISH) analysis and reported that IHC and FISH differences occurred mainly for non-uniformity of staining between the basement membrane side (positive) and granular lumen side (negative) of fundic gland cells, and heterogeneous GC cells. Basing on these considerations, a modified HercepTest has been developed, taking more into account the characteristics of GC. Differently from breast cancer, the prognostic value of HER-2 overexpression in GC remains controversial. A recent trial investigating the prognostic significance of HER-2 evaluated in 382 patients with metastatic GC and GEJ adenocarcinoma, found that approximately 20% of patients were HER2 positive, but HER2 positivity wasn't an independent prognostic factor[118].

Anti-HER2 drugs include trastuzumab, lapatinib and pertuzumab[119] (Table 4).

Trastuzumab

Trastuzumab is a humanized recombinant monoclonal antibody selectively binding to the extracellular domain of HER2, blocking its downstream signaling, down-modulation of the HER2 protein, and activation of apoptotic signals of the tumor cells. Another mechanism of activity is represented by an indirect antitumor effect by antibody-dependent cell-mediated cytotoxicity activity[120]. These therapeutic effects are enhanced when trastuzumab is associated with chemotherapeutic agents such as cisplatin, capecitabine, irinotecan, doxorubicin and taxanes achieving an ORR ranging from 35% to 44% in clinical phase Ⅱ trials[121].

ToGA trial was the first randomized phase Ⅲ controlled study to be conduced in order to verify trastuzumab efficacy and safety in combination with chemotherapy for patients with HER2-positive advanced GC and GEJ cancers. In this study, 594 patients were randomized to receive 5-fluorouracil (800 mg/m^2 per day on days 1-5 continuous infusion) or capecitabine (1000 mg/m^2/d on days 1-14) and cisplatin (80 mg/m^2 on day 1) with trastuzumab (8 mg/kg loading dose on day 1 followed by 6 mg/kg) every 3 wk for 6 cycles, or CT alone. The primary aim was to compare OS in both arms, and the secondary ones were PFS, TTP, ORR, control disease, duration of response, and quality of life. Tumor specimens from 3807 patients were centrally tested to determine the HER2 status: 22.1% were HER2-positive with a higher rate of HER2 positivity for the intestinal type than diffuse one (34% *vs* 6%) and for adenocarcinoma of GEJ compared to GC (33.2% *vs* 20.9%). Five hundred eighty-four patients included in primary analysis were allocated to either the FC arm or the FC + trastuzumab arm and at randomization, patients were stratified ac-

cording to ECOG PS, chemotherapy regimen, extent of disease, primary cancer site, and measurability of disease. The addition of trastuzumab to chemotherapy led to a significantly higher ORR (47% *vs* 35%, $P = 0.0017$), significantly longer PFS, (6.7 mo *vs* 5.5 mo, $P = 0.0002$), and significantly longer OS duration (13.8 mo *vs* 11.1 mo, $P = 0.0046$). The greatest benefit was seen in patients with higher levels of HER2 expression (IHC score of 3 or 2 with FISH positivity) in which the OS time reached 16 mo. The safety profiles in the two groups were similar, and there were no unexpected adverse events in the trastuzumab arm. There was no difference in terms of heart failure between the two arms. Decreases in asymptomatic left ventricular ejection fraction were reported in 4.6% of patients in the trastuzumab combined arm and in 1.1% of those in the chemotherapy arm[122]. The ToGA trial is a milestone of a targeted therapy in GC and GEJ cancer and, the first study to demonstrate a significant improvement in OS for a preselected patient population. Therefore, trastuzumab with chemotherapy is the new standard treatment of HER2-positive GC and GEJ cancer in the first line setting.

In the second-line setting, a trial studied single-agent trastuzumab after failure of platinum or 5-FU-based regimens, but it was limited by poor accrual[123].

A randomized, open-label, multicenter, international phase Ⅲb study will compare the efficacy and safety of two trastuzumab dosing regimens in combination with cisplatin/capecitabine chemotherapy in patients with metastatic gastric or gastro-esophageal junction adenocarcinoma. Patients who have not received prior treatment for metastatic disease will be randomized to receive trastuzumab either an 8 mg/kg loading dose followed by 6 mg/kg every 3 wk or an 8 mg/kg loading dose followed by 10 mg/kg every 3 wk. Capecitabine will be administered for 6 cycles at a dose of 800 mg/m^2 orally twice on days 1-14 of each 3-wk cycle, cisplatin will be administered intravenously for 6 cycles at a dose of 80 mg/m^2 on day 1 of each 3-wk cycle. Anticipated time on study treatment is until disease progression occurs[124].

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate currently in clinical development combining the humanized antibody trastuzumab and the potent cytotoxic antimicrotubule DM1 (derivative of maytansine). When T-DM1 binds to HER2, a proportion of the receptors are thought to be internalized by the process of receptor endocytosis, with a consequent intracellular release of an active form of DM1, causing cell death. Trastuzumab-DM1 showed highly effective in preclinical models of HER2-positive GC and so it has investigated in phase Ⅱ/Ⅲ studies[125].

An ongoing multicenter, randomized, phase Ⅱ/Ⅲ study will evaluate the efficacy and safety of T-DM1 compared to standard taxane in patients with previously treated locally advanced or metastatic HER2-positive GC, including adenocarcinoma of the GEJ. About 100 patients will be randomized to receive trastuzumab emtansine 3.6 mg/kg every 3 wk or 2.4 mg/kg every week and standard taxane therapy (docetaxel or paclitaxel) with primary endpoint OS[126].

Lapatinib

Lapatinib is an oral TKI inhibiting both EGFR and HER2 kinases that can be employed in subjects with trastuzumab-resistant tumors. Many phase Ⅱ studies investigated lapatinib in monotherapy in GC.

A phase Ⅱ trial tested single agent lapatinib as first-line therapy in 47 patients with advanced GC demonstrating an excellent tolerability and moderate activity with a median time to treatment failure of 1.9 mo and OS of 4.8 mo. Only 7% of patients showed a partial response (PR) and 20% a stable disease (SD)[127].

Furthermore, out of 21 previously treated patients in another phase Ⅱ study, only 2 cases of SD were observed with lapatinib, although these two trials did not limit patients to HER2-positive[128]. In another phase Ⅱ trial of capecitabine in combination to lapatinib as first-line treatment in 58 patients with GC (76%) or GEJ cancer (24%), 24% of patients showed PR (17% confirmed), 36 % a SD and 26% a progression disease (PD)[125].

Two phase Ⅲ studies are currently conducted to investigate the efficacy of lapatinib in combination with chemotherapy in second-line and first-line setting for patients with HER2-positive GC. The LOGiC study (Lapatinib Optimization Study in HER2 Positive Gastric Cancer) is a phase Ⅲ global study, designed to evaluate clinical endpoints and safety of chemotherapy (capecitabine and oxaliplatin with or without lapatinib) plus lapatinib in a first line setting. Patients were randomized in a 1:1 ratio to receive CapeOx (oxaliplatin 130 mg/m^2 day 1; capecitabine 850 mg/m^2 *bid* days 1-14, every 3 wk) plus daily lapatinib (1250 mg) or placebo. The primary endpoint was OS and secondary endpoints included PFS, ORR and safety. Five hundred forty-five patients were randomized and 487 had HER2 positivity centrally confirmed. The primary endpoint was not reached with a hazard ratio for OS of CapeOx plus lapatinib compared to CapeOx plus placebo of 0.91 (95%CI: 0.73-1.12, $P = 0.35$); median PFS was 12.2 mo *vs* 10.5 mo, respectively. HR for uncensored PFS was 0.86 (95%CI: 0.71-1.04, $P = 0.10$); median 6.0 mo *vs* 5.4 mo. The analysis of PFS showed a HR of 0.82 (95%CI: 0.68-1.00, $P = 0.04$). ORR was 53% in the CapeOx + lapatinib arm and 40% in the CapeOx + placebo arm. Pre-specified subgroup analysis showed significant improvements in OS in Asian patients (HR = 0.68) and those under 60 years (HR = 0.69). There was no association between IHC and OS. Toxicity profiles were similar except for increased overall diarrhea, and skin toxicity and grade 3+ diarrhea (12% *vs* 3%) with CapeOx + lapatinib[129]. The addition of lapatinib to CapeOx did not reach its primary endpoint, though certain subgroups showed improvement (Table 4).

The TYTAN trial is a randomized, phase Ⅲ study comparing paclitaxel with and without lapatinib as second-line treatment in advanced HER2-positive GC. The study included 430 patients with advanced GC who

had progressed on first-line fluoropyrimidine and/or cisplatin-containing therapy and who showed HER2 amplification by FISH. Prior to randomization, patients were stratified by previous trastuzumab treatment and gastrectomy status.

mOS of the entire study population was 11.0 mo with the addition of lapatinib to paclitaxel compared with 8.9 mo with paclitaxel alone. Despite the 2.1 mo improvement in survival, the difference between arms did not reach statistical significance (HR = 0.84, P = 0.2088). However, the findings of a preplanned subgroup analysis revealed that median OS among patients in the HER2 IHC 3+ subgroup was 14.0 mo with lapatinib and paclitaxel compared with 7.6 mo with paclitaxel alone, a striking and significant 6.4 mo difference (HR = 0.59, P = 0.0176). PFS (5.6 mo *vs* 4.2 mo, HR 0.54, P = 0.0101) and the ORR (27% *vs* 9%) were also better than population treated without lapatinib among patients in the IHC 3+ subgroup[130].

Pertuzumab

Pertuzumab is a new humanized anti-HER2 antibody exercising its antitumor activity through the binding to HER2 domain Ⅱ, the region of dimer formation, inhibiting the dimerization of HER2 with other HER family proteins and preventing ligand-dependent HER2 signalling. It induces the suppression of several HER signaling pathways. As it can be supposed by the different mechanisms of HER2 inhibition, pertuzumab and trastuzumab in combination might provide more effective antitumor activity than either single agent for HER2-positive tumors including GC. In fact, the combination of pertuzumab and trastuzumab dramatically increases the antitumor activity compared with pertuzumab or trastuzumab alone in HER2-positive human GC xenograft models[131].

In order to identify pertuzumab dose for clinical studies in HER2 positive GC and GEJ cancer, the JOSHUA phase Ⅱ trial was conducted, evaluating the pharmacokinetics (PK) of two different dose of pertuzumab in the fisrt metastatic setting. Patients will be randomized to receive pertuzumab 840 mg q3w for cycle 1 and 420 mg for cycles 2-6 (ARM A) or pertuzumab 840 mg (ARM B) intravenously every 3 wk in combination with trastuzumab (initial dose of 8 mg/kg *iv* followed by 6 mg/kg *iv* every 3 wk) and cisplatin and fluoropyrimidine (capecitabine or 5-fluorouracil) for the first 6 treatment cycles. Patients will continue to receive pertuzumab or placebo and trastuzumab until disease progression or unacceptable toxicities. Primary endpoints were pertuzumab trough concentration at day 43 and safety. Of 15 patients randomized to each arm, 15 and 13 were evaluable for pertuzumab at day 43 in Arm A e B respectively[132].

The mean concentration was higher in patients in arm B than arm A at day 43 (57.9 μg/mL *vs* 40.0 μg/mL) and so a dose of 840 mg 3 weekly was selected for an ongoing phase Ⅲ trial JACOB, a double-blind, placebo-controlled, randomized, multicenter, international, parallel arm study that will evaluate the efficacy and safety of pertuzumab in combination with trastuzumab, fluoropyrimidine and cisplatin as first-line treatment in patients with HER2-positive metastatic GEJ or GC. Patients will be randomized to receive pertuzumab 840 mg or placebo intravenously every 3 wk in combination with trastuzumab (initial dose of 8 mg/kg *iv* followed by 6 mg/kg *iv* every 3 wk) and cisplatin and fluoropyrimidine (capecitabine or 5-fluorouracil) for the first 6 treatment cycles. Patients will continue to receive pertuzumab or placebo and trastuzumab until disease progression or unacceptable toxicity occurs[133].

PI3K-AKT-MTOR TARGETED THERAPY

PI3K/AKT pathway is an intracellular signaling pathway transducing signals from cell membrane receptors (*i.e.*, VEGF, HER2, IGF) to the cytoplasm and playing an important role in cell proliferation by acting on the anti-apoptosis and cell cycle, in protein translation and synthesis via mTOR and angiogenesis[134]. PI3K/AKT/mTOR activation was observed in 30%-60% of tumors including GC due to PIK3CA mutations and gene amplification, AKT gene amplification and loss of PTEN[135].

Everolimus (RAD001) is an oral inhibitor of the mammalian target of rapamycin serine-threonine kinase (mTOR) inhibiting the PI3K/Akt/ mTOR pathway; it showed efficacy in preclinical and phase Ⅰ/Ⅱ studies in patients with GC[136].

The activity of the drug has been tested in a phase Ⅱ study in which 53 patients with previously treated metastatic GC received everolimus (10 mg orally daily) until disease progression or unacceptable toxicity. The results showed a DCR of 56.0% (95%CI: 41.3-70.0) and median PFS of 2.7 mo (95%CI: 1.6-3.0). After a median follow-up of 9.6 mo, the median OS was 10.1 mo (95%CI: 6.5-12.1) and good tolerability was noted[137]. According to these results, a global phase Ⅲ trial (GRANITE-1) was conducted to compare everolimus *vs* placebo in a total of 656 patients with advanced GC who showed disease progression after prior treatment with first or second-line CT. Data released from the 2012 ASCO Gastrointestinal Cancers Symposium showed no significant OS advantages in subjects receiving everolimus compared to best supportive care (BSC) (5.4 mo *vs* 4.3 mo, P = 0.1244). However, everolimus showed a reduction of the progression risk by 34% with a PFS of 1.7 mo *vs* 1.4 mo respectively (P = 0.0001)[138]. The most common everolimus-related toxicities observed were: anemia (everolimus 16.0% *vs* placebo 12.6%), anorexia (11.0% *vs* 5.6%) and fatigue (7.8% *vs* 5.1%), and were almost similar to those observed in other carcinomas. GRANITE-1 represents one of the larger randomised trials in this population with results anticipated, anyway the primary endpoint was not achieved. The results of PFS and disease stabilization provided, however, some evidence that they have antitumor effect for GC.

The ongoing randomized, double blind phase Ⅲ two-arm multi-center study (AIO-STO-0111/RADPAC) is

Table 5 Clinical trials with everolimus in previously treated patients with advance gastric cancer and gastro-esophageal junction cancer

Trial	Phase	Setting	Regimen	Patients (*n*)	OS (mo)	PFS (mo)
NCT00985192[137], 2010	Ⅱ	Advanced	Eve	53	10.1	2.7
NCT00879333[138], 2013	Ⅲ	Advanced	Eve + BSC	656	5.4	1.7
			BSC		4.3	1.4
NCT01248403[139], Ongoing	Ⅲ	Advanced	Eve + PTX	480	-	-
			PTX			

Eve: Everolimus; PTX: Paclitaxel; OS: Overall survival; PFS: Progression free survival.

actually evaluating the efficacy of the combination of RAD001 (10 mg 2 × 5 mg tablets/d d1-d28) and paclitaxel *vs* paclitaxel alone (80 mg/m^2 on day 1, day 8 and day 15 of every 28-d cycle) in patients with advanced GC and GEJ carcinoma relapsed after up to two prior treatment regimen containing a fluoropyrimidine (*e.g.*, 5-FU, S-1, capecitabine and other 5-FU prodrugs or derivatives) with OS as primary endpoint. A total of 480 patients (240 patients per treatment arm) will be enrolled in the study[139]. Both of these studies (GRANITE-1 and RADPAC) include an exploratory biomarker research program that will examine the predictive role of phosphorylated S6K1, HER2, phosphorylated Akt, HIF-2a, PTEN, cyclin D1, Ki-67 frequency, p53 and CC3, as well as the mutational status of PI3K catalytic subunit and PTEN, with efficacy endpoints. Therefore, it will be possible to identify potential markers of response to everolimus and validate their role in future studies (Table 5).

Recently a phase I trial of everolimus in combination with mitomycin C (MMC) was conducted in 16 metastatic pretreated GC patients to assess the recommended dose and the dose-limiting toxicity (DLT) of everolimus in association with MMC. In this trial, patients received escalated doses of oral everolimus (5, 7.5, and 10 mg/d) in combination with intravenous MMC (5 mg/m^2 every 3 wk). Endpoints were the DLT, safety, and response rates. HER2-status, mutations in the PTEN, PIK3CA, AKT1, CTNNB1, and E-cadherin type 1 genes were tested on tumor tissue. Most frequent grade 3 toxicities were leukopenia (18.8%) and neutropenia (18.8%). Other grade 3 toxicities were lower than 10%. No grade 4 toxicities occurred. 18.8% of patients experienced PR and four patients achieved a SD. Antitumor activity, according to RECIST-criteria, was highest in the 10 mg/d cohort. According to these results, recommended dose of everolimus combined with MMC is 10 mg/d[140] (Table 5).

HGF-C-MET PATHWAY

The receptor tyrosine kinase mesenchymal-epithelial transition factor (c-Met) is the cell surface receptor for hepatocyte growth factor (HGF) and leads to activation of different signalling pathway regulating the cancer cell metastasization, proliferation, motility, invasion and angiogenesis[141,142]. High c-Met expression is associated with poor prognosis in several cancer types, including upper gastrointestinal malignancies[143,144]. MET amplification was described in approximately 4%-10% of gastric tumors[145,146] and MET protein overexpression assessed by IHC in approximately 50% of advanced gastric cancers[147-149]. MET amplification and overexpression correlate with a worse clinical outcome, in particular with increased invasiveness and increased potential of metastasization[147-149]. Recently, a MET amplification was confirmed in 10% of resected GC patients (21 out of 216) who showed a significantly worse prognosis in terms of DFS and OS[143].

The c-Met expression and activation in GC was studied in preclinical trial in cell lines and tumor tissue evidencing that c-Met activation was strongly related to invasion and liver metastasis[150,151].

Therefore, several drugs playing an inhibitory role against c-Met activity have been developed in recent years.

Foretinib

Foretinib is an oral multikinase inhibitor targeting MET, RON, AXL, TIE-2, and VEGFR2 receptors. A phase Ⅱ study evaluated safety, tolerability and ORR of 2 dosing schedules (240 mg/d, for 5 d every 2 wk or 80 mg/d) of oral foretinib (GSK1363089), in 74 patients with metastatic GC (93% previously treated). Best response was SD in 23% of patients receiving intermittent dosing and 20% receiving daily dosing; SD duration was 1.9-7.2 mo (median 3.2 mo). Of 67 patients with tumor samples, 3 showed a MET amplification, one of whom achieved a SD. Treatment-related adverse events occurred in 91% of patients. Rates of hypertension (35% *vs* 15%) and elevated aspartate aminotransferase (23% *vs* 8%) were higher with intermittent dosing. In both patients with high baseline tumor phospho-Met (pMET), the pMet/total Met protein ratio decreased with foretinib treatment. These results indicate that single-agent foretinib lacked efficacy in unselected patients with metastatic GC[152].

Tivantinib

Tivantinib is a selective, non-ATP competitive, small-molecule c-Met inhibitor. In a phase Ⅱ trial the activity of single agent tivantinib was tested in 30 previously treated metastatic GC subjects. Primary outcome was DCR and secondary efficacy endpoints include antitumor effect (tumor response), PFS and OS. Also PK and safety were evaluated. The results showed no objective

responses, a DCR of 36.7% with a median PFS of 43 d (95%CI: 29.0-92.0). Grade 3 or 4 toxicities were observed in 43.3% of patients[153].

Crizotinib

Crizotinib (PF-02341066) was recently approved for the treatment of non small-cell lung cancer positive for fusion of the echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase genes. This agent is also a potent MET inhibitor, playing at the ATP-binding sites of the MET kinase domain: therefore, it represents a potential drug for the treatment of patients with GC with MET amplification. In GC cellular lines, the inhibition of MET activity with crizotinib resulted in an inhibition of AKT and ERK signaling pathways as well as in the induction of apoptosis by the upregulation of BIM, a member of the Bcl-2 family with a proapoptotic activity[154].

It has been recently found that crizotinib has an antitumor activity in 2 of 4 patients with MET-amplified gastroesophageal cancer, suggesting further analysis of the molecular mechanism underlying its anticancer action in this type of tumors[155].

Rilotumumab

Rilotumumab (AMG102) is a human IgG2 targeting human hepatocyte growth factor/scatter factor (SF) that blocks the binding of HGF/SF to its receptor MET; it results in inhibition of the MET signaling pathways as shown in preclinical models[156,157]. In clinical trials, rilotumumab administered biweekly as single agent or in combination with CT showed manageable toxicities and a maximum tolerated dose was not reached[158]. The effectiveness of this agent was reported in a randomised phase Ⅱ trial presented at 2011 ESMO congress. The results showed an advantage in PFS for the arm treated with rilotumumab plus chemotherapy compared to chemotherapy alone (PFS median 5.6 mo *vs* 4.2 mo, HR = 0.58) and more remarkable for c-Met overexpression patients established by IHC. Recently, in 2012 ASCO annual meeting, the results of study were updated according to c-Met expression analysis. Patients with c-Met overexpression who received rilotumumab plus chemotherapy, had an OS of 11.1 mo with an absolute benefit of 5.4 mo over patients who received chemotherapy alone (HR = 0.29, 95%CI: 0.11-0.76)[159]. Moving from these results, a phase Ⅲ, randomized double-blind placebo controlled study (RILOMET-1) is actually ongoing. This trial is evaluating epirubicin (50 mg/mq), cisplatin (60 mg/mq), capecitabine (625 mg/mq *bid*) with rilotumumab (15 mg/kg) or placebo for untreated advanced MET-positive gastric or GEJ adenocarcinoma. OS is the primary outcome while secondary outcomes are represented by PFS, TTP, ORR, DCR, TTR and safety[160].

Onartuzumab

Onartuzumab is a monovalent, humanized anti-MET antibody, that binds the extracellular domain of c-Met, preventing the link of HGF; the activation of the c-Met signaling pathway results thus inhibited, inducing the death of the cell in c-Met-expressing tumors. A randomized, multicenter, double-blind, placebo-controlled phase Ⅲ study, evaluating the efficacy and safety of onartuzumab in combination with mFOLFOX6 in patients with metastatic HER2-negative and MET positive adenocarcinoma of the stomach or gastroesophageal junction is now ongoing. Patients are being randomized in a 1:1 ratio to receive onartuzumab or placebo in combination with mFOLFOX6[161]; the primary endpoint is OS and secondary endpoints include: PFS, TTP, ORR, and safety.

TARGETING FIBROBLAST GROWTH FACTOR RECEPTOR AGENTS

The fibroblast growth factor receptors (FGFR) bind fibroblast growth factor (FGF), belonging to the largest family of growth factor ligands. Each receptor consists of a cellular ligand domain, composed of three immunoglobulin-like domains, a single transmembrane helix domain and an intracellular domain with tyrosine kinase activity. The FGFR family comprises four different tyrosine kinase receptors: FGFR1, FGFR2, FGFR3 and FGFR4[162]. Recently it was discovered another receptor known as FGFR5 or FGFRL1, lacking the tyrosine kinase domain and thus it can not signal by transautophosphorylation as other FGFRs, but it probably acts as a decoy receptor that binds FGF ligands and sequesters them away from the conventional FGFRs[163].

FGFR signaling starts by the binding of the receptors to different FGFs ligands and the formation of various complexes which lead to the signal transduction[164,165].

FGFRs are involved in many physiological processes, including development, cellular proliferation, differentiation, motility, transforming activities, regulation of angiogenesis and wound repair[166-169]. Furthermore, they play leading roles in many types of neoplasms, because mutations or gene amplification induce aberrant FGFR activation, leading to carcinogenesis[170]. The most known FGFR mutations related to tumors are: the gain of function mutation of FGFR1 kinase domain in glioblastoma; chromosomal translocation of FGFR1 in the 8p11 myeloproliferative syndrome and alveolar rhabdomyosarcoma[171,172]; gene amplification of FGFR1 in lung cancer, in oral squamous carcinoma and in about 10% of breast cancer[173]; the FGFR2 mutations in 12% of endometrial cancer[174]; the *FGFR3* mutation in about 50% of bladder cancer[165,169,175]. In a recent study, FGFR2 amplification was evaluated by FISH in 313 resected GC samples and correlated to clinicopathologic parameters and survival. FGFR2 amplification was found in 4.5% (14 out of 313) of samples and was associated with a higher T stage, a higher N stage, and distant metastasis; furthermore it was significantly associated with a worse survival, confirming the correlation among FGFR2 amplification, advanced disease and poor prognosis[176]. On the other hand, FGFR2 amplification was observed in 4.1% (11

out of 267) of patients who underwent surgery for a GC in another retrospective study[166]. These data suggest that FGFR2 may be a promising therapeutic target in GC. Different small molecules such as PD173074, KI23057, SU5402, cediranib (AZD2171), dovitinib (TKI258) and ponatinib (AP24534) inhibit FGFR2 phosphorylation and cell growth in FGFR2-amplified GC cell lines in preclinical trials[22,177-179].

Ponatinib (AP24534) is an oral multitarget tyrosine kinase inhibitor with a pan-FGFR activity: exposure of GC cell lines with high levels of FGFR2 activity due to genomic amplification results in a potent inhibition of cell growth[180]. Dovitinib is a multitarget tyrosine kinase receptors inhibitor, including FGFR1, FGFR2, FGFR3, VEGFR-1, VEGFR-2, VEGFR-3, PDGFRβ and c-kit[181,182]. In preclinical model, a potent growth inhibitory activity of dovitinib was observed in FGFR2-amplified GC cell lines. AZD4547 is an oral, highly selective, and potent ATP-competitive small-molecule TKI of FGFR1-3. GC cell lines with FGFR2 amplification, were extremely sensitive to AZD4547 which effectively inhibited phosphorylation of FGFR2 and its downstream signaling molecules. Furthermore, an enhancement of *in vivo* antitumor efficacy was seen combining AZD4547 with chemotherapy[183]. Actually the SHINE phase Ⅱ study (NCT01457846) is evaluating the efficacy and safety of FGFR2 inhibitor AZD4547 in GC patients with FGFR2 polysomy or gene amplification and one prior chemotherapy. In this trial 160 patients will be randomized between paclitaxel or AZD4547 with PFS as primary endpoint[184].

CONCLUSION

The understanding of different molecular alterations that could play a pivotal role in the pathogenesis of GC, albeit still incomplete, is undoubtedly the main progress recorded in recent years in the treatment of this disease. In fact, if the outcome of patients with metastatic disease under chemotherapy continues to remain particularly disappointing, studies such as ToGA have indicated the route to be followed over the coming years, providing for the first time an algorithm of first-line treatment selection of GC based on a key molecular driver such as HER-2. Based on this trial the addition of trastuzumab to combination chemotherapy is now considered the standard first-line treatment for HER2 positive advanced GC patients. However, beside the need to improve our biological knowledge concerning GC, several points remain to be elucidate. First of all, the selection of patients based on the identification of specific predictive biomarkers appears as a very crucial point. A paradigmatic example of this statement lies in the results of the two randomized phase Ⅲ trials REAL-3 and EXPAND with panitumumab and cetuximab that have recruited over 1450 unselected patients with negative and inferior results when compared to control arm with chemotherapy alone. Not different appear the considerations for GRANITE-1 study that enrolled more than 600 patients without achieving its primary endpoint. However at this time various markers, including EGFR and VEGF overexpression, have not been validated to be predictive in advanced GC patients, and HER-2 overexpression and HER-2 amplification remain the only predictive biomarkers. Moreover, because the expression of different and potential targets depends on the tumor site, histology and ethnics differences, it seems important to design clinical trials stratified according to these factors. The onset of resistance to targeted therapy is an issue particularly relevant which involves mechanisms rather complex. A costitutive activation of the PI3K pathway through PIK3CA mutation or PTEN loss may play a role in resistance to receptor monoclonal antibodies, including trastuzumab. In preclinical studies carried with the aim to identify pathway regulating the sensitivity of HER2-positive GC cells to trastuzumab, the overexpression of micro-RNA gene 21 down-regulated PTEN expression and increased AKT phosphorylation, significantly suppressing trastuzumab-induced apoptosis and finally decreasing the sensitivity of GC cells to trastuzumab[185]. Taken together, these data provide a support to evaluate the combination of mTOR inhibitors with trastuzumab in HER2-positive GC. Several studies have shown that also activation of alternative receptor tyrosine kinases may promote resistance to anti-HER-2 therapy. For instance, activation of MET RTK substantially reduces growth inhibition of HER2 positive GC cell lines induced by lapatinib and is an example of acquired resistance mediated by activation of secondary RTK restoring downstream signaling pathways[186]. Although only few studies (ToGA, REGARD) with targeted agents have obtained positive results at this time, it is unquestionable that this is the only way that has shown promising results in this setting. Nevertheless given that only a small number of GC patients carries specific molecular alterations, it is paramount to identify emerging molecular pathways that characterize cell growth, cell cycle, apoptosis, angiogenesis and invasion so providing rationally designed therapies aimed at specific novel molecular targets in selected patients to improve advanced GC outcome.

REFERENCES

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

2 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 23335087 DOI: 10.3322/caac.21166]

3 **Macdonald JS**, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725-730 [PMID: 11547741]

4 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;

355: 11-20 [PMID: 16822992]
5 **Stahl M**, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, Langer P, Engenhart-Cabillic R, Bitzer M, Königsrainer A, Budach W, Wilke H. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009; **27**: 851-856 [PMID: 19139439 DOI: 10.1200/JCO.2008.17.0506]
6 **Ychou M**, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; **29**: 1715-1721 [PMID: 21444866 DOI: 10.1200/JCO.2010.33.0597]
7 **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.CD004064.pub3]
8 **Lauren P**. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49 [PMID: 14320675]
9 **You WC**, Blot WJ, Li JY, Chang YS, Jin ML, Kneller R, Zhang L, Han ZX, Zeng XR, Liu WD. Precancerous gastric lesions in a population at high risk of stomach cancer. *Cancer Res* 1993; **53**: 1317-1321 [PMID: 8443811]
10 **Correa P**, Haenszel W, Cuello C, Zavala D, Fontham E, Zarama G, Tannenbaum S, Collazos T, Ruiz B. Gastric precancerous process in a high risk population: cross-sectional studies. *Cancer Res* 1990; **50**: 4731-4736 [PMID: 2369747]
11 **Peek RM**, Blaser MJ. Helicobacter pylori and gastrointestinal tract adenocarcinomas. *Nat Rev Cancer* 2002; **2**: 28-37 [PMID: 11902583]
12 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297]
13 **Crew KD**, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; **12**: 354-362 [PMID: 16489633]
14 **Shah MA**, Khanin R, Tang L, Janjigian YY, Klimstra DS, Gerdes H, Kelsen DP. Molecular classification of gastric cancer: a new paradigm. *Clin Cancer Res* 2011; **17**: 2693-2701 [PMID: 21430069 DOI: 10.1158/1078-0432.CCR-10-2203]
15 **Gravalos C**, Márquez A, García-Carbonero R, Rivera F, Colomer R, Sastre J. Correlation between Her2/neu overexpression/amplification and clinicopathological parameters in advanced gastric cancer patients: a prospective study 2007. *Gastrointestinal Cancers Symposium* 2007; **130**: Abstract 89
16 **Leon-Chong J**, Lordick F, Kang YK, Park SR, Bang YJ, Sawaki A, Van Cutsem E, Stoss O, Jordan BW, Feyereislova A. HER2 positivity in advanced gastric cancer is comparable to breast cancer - ASCO Annual Meeting Proceedings, Part I. *J Clin Oncol* 2007; **25** (18S): Abstract 15057. Available from: URL: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/15057
17 **Zhang XL**, Yang YS, Xu DP, Qu JH, Guo MZ, Gong Y, Huang J. Comparative study on overexpression of HER2/neu and HER3 in gastric cancer. *World J Surg* 2009; **33**: 2112-2118 [PMID: 19636613 DOI: 10.1007/s00268-009-0142-z]
18 **Lieto E**, Ferraraccio F, Orditura M, Castellano P, Mura AL, Pinto M, Zamboli A, De Vita F, Galizia G. Expression of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) is an independent prognostic indicator of worse outcome in gastric cancer patients. *Ann Surg Oncol* 2008; **15**: 69-79 [PMID: 17896140]
19 **Matsubara J**, Nishina T, Yamada Y, Moriwaki T, Shimoda T, Kajiwara T, Nakajima TE, Kato K, Hamaguchi T, Shimada Y, Okayama Y, Oka T, Shirao K. Impacts of excision repair cross-complementing gene 1 (ERCC1), dihydropyrimidine dehydrogenase, and epidermal growth factor receptor on the outcomes of patients with advanced gastric cancer. *Br J Cancer* 2008; **98**: 832-839 [PMID: 18231104 DOI: 10.1038/sj.bjc.6604211]
20 **Isinger-Ekstrand A**, Johansson J, Ohlsson M, Francis P, Staaf J, Jönsson M, Borg A, Nilbert M. Genetic profiles of gastroesophageal cancer: combined analysis using expression array and tiling array--comparative genomic hybridization. *Cancer Genet Cytogenet* 2010; **200**: 120-126 [PMID: 20620594 DOI: 10.1016/j.cancergencyto.2010.03.01]
21 **Janjigian YY**, Tang LH, Coit DG, Kelsen DP, Francone TD, Weiser MR, Jhanwar SC, Shah MA. MET expression and amplification in patients with localized gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2011; **20**: 1021-1027 [PMID: 21393565 DOI: 10.1158/1055-9965.EPI-10-1080]
22 **Deng N**, Goh LK, Wang H, Das K, Tao J, Tan IB, Zhang S, Lee M, Wu J, Lim KH, Lei Z, Goh G, Lim QY, Tan AL, Sin Poh DY, Riahi S, Bell S, Shi MM, Linnartz R, Zhu F, Yeoh KG, Toh HC, Yong WP, Cheong HC, Rha SY, Boussioutas A, Grabsch H, Rozen S, Tan P. A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. *Gut* 2012; **61**: 673-684 [PMID: 22315472 DOI: 10.1136/gutjnl-2011-301839]
23 **Kitadai Y**, Sasaki A, Ito M, Tanaka S, Oue N, Yasui W, Aihara M, Imagawa K, Haruma K, Chayama K. Helicobacter pylori infection influences expression of genes related to angiogenesis and invasion in human gastric carcinoma cells. *Biochem Biophys Res Commun* 2003; **311**: 809-814 [PMID: 14623253]
24 **Wu CY**, Wang CJ, Tseng CC, Chen HP, Wu MS, Lin JT, Inoue H, Chen GH. Helicobacter pylori promote gastric cancer cells invasion through a NF-kappaB and COX-2-mediated pathway. *World J Gastroenterol* 2005; **11**: 3197-3203 [PMID: 15929167]
25 **Tuccillo C**, Cuomo A, Rocco A, Martinelli E, Staibano S, Mascolo M, Gravina AG, Nardone G, Ricci V, Ciardiello F, Del Vecchio Blanco C, Romano M. Vascular endothelial growth factor and neo-angiogenesis in H. pylori gastritis in humans. *J Pathol* 2005; **207**: 277-284 [PMID: 16184519]
26 **Carneiro F**, Huntsman DG, Smyrk TC, Owen DA, Seruca R, Pharoah P, Caldas C, Sobrinho-Simões M. Model of the early development of diffuse gastric cancer in E-cadherin mutation carriers and its implications for patient screening. *J Pathol* 2004; **203**: 681-687 [PMID: 15141383]
27 **Tamura G**, Yin J, Wang S, Fleisher AS, Zou T, Abraham JM, Kong D, Smolinski KN, Wilson KT, James SP, Silverberg SG, Nishizuka S, Terashima M, Motoyama T, Meltzer SJ. E-Cadherin gene promoter hypermethylation in primary human gastric carcinomas. *J Natl Cancer Inst* 2000; **92**: 569-573 [PMID: 10749913]
28 **Liu YC**, Shen CY, Wu HS, Hsieh TY, Chan DC, Chen CJ, Yu JC, Yu CP, Harn HJ, Chen PJ, Hsieh CB, Chen TW, Hsu HM. Mechanisms inactivating the gene for E-cadherin in sporadic gastric carcinomas. *World J Gastroenterol* 2006; **12**: 2168-2173 [PMID: 16610016]
29 **Zhou Y**, Li G, Wu J, Zhang Z, Wu Z, Fan P, Hao T, Zhang X, Li M, Zhang F, Li Q, Lu B, Qiao L. Clinicopathological significance of E-cadherin, VEGF, and MMPs in gastric cancer. *Tumour Biol* 2010; **31**: 549-558 [PMID: 20563765 DOI: 10.1007/s13277-010-0068-y]
30 **Hattori Y**, Itoh H, Uchino S, Hosokawa K, Ochiai A, Ino Y, Ishii H, Sakamoto H, Yamaguchi N, Yanagihara K, Hirohashi S, Sugimura T, Terada M. Immunohistochemical detection of K-sam protein in stomach cancer. *Clin Cancer Res* 1996; **2**: 1373-1381 [PMID: 9816310]
31 **Kobayashi M**, Nagata S, Iwasaki T, Yanagihara K, Saitoh I, Karouji Y, Ihara S, Fukui Y. Dedifferentiation of adenocarcinomas by activation of phosphatidylinositol 3-kinase. *Proc Natl Acad Sci USA* 1999; **96**: 4874-4879 [PMID: 10220386]

32 **Murayama T**, Inokuchi M, Takagi Y, Yamada H, Kojima K, Kumagai J, Kawano T, Sugihara K. Relation between outcomes and localisation of p-mTOR expression in gastric cancer. *Br J Cancer* 2009; **100**: 782-788 [PMID: 19223902 DOI: 10.1038/sj.bjc.6604915]

33 **Kobayashi M**, Iwamatsu A, Shinohara-Kanda A, Ihara S, Fukui Y. Activation of ErbB3-PI3-kinase pathway is correlated with malignant phenotypes of adenocarcinomas. *Oncogene* 2003; **22**: 1294-1301 [PMID: 12618754]

34 **Tan IB**, Ivanova T, Lim KH, Ong CW, Deng N, Lee J, Tan SH, Wu J, Lee MH, Ooi CH, Rha SY, Wong WK, Boussioutas A, Yeoh KG, So J, Yong WP, Tsuburaya A, Grabsch H, Toh HC, Rozen S, Cheong JH, Noh SH, Wan WK, Ajani JA, Lee JS, Tellez MS, Tan P. Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. *Gastroenterology* 2011; **141**: 476-85, 485.e1-11 [PMID: 21684283 DOI: 10.1053/j.gastro.2011.04.042]

35 **Dulak AM**, Schumacher SE, van Lieshout J, Imamura Y, Fox C, Shim B, Ramos AH, Saksena G, Baca SC, Baselga J, Tabernero J, Barretina J, Enzinger PC, Corso G, Roviello F, Lin L, Bandla S, Luketich JD, Pennathur A, Meyerson M, Ogino S, Shivdasani RA, Beer DG, Godfrey TE, Beroukhim R, Bass AJ. Gastrointestinal adenocarcinomas of the esophagus, stomach, and colon exhibit distinct patterns of genome instability and oncogenesis. *Cancer Res* 2012; **72**: 4383-4393 [PMID: 22751462]

36 **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]

37 **Ferrara N**, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med* 2003; **9**: 669-676 [PMID: 12778165]

38 **Shibuya M**, Claesson-Welsh L. Signal transduction by VEGF receptors in regulation of angiogenesis and lymphangiogenesis. *Exp Cell Res* 2006; **312**: 549-560 [PMID: 16336962]

39 **Takahashi Y**, Cleary KR, Mai M, Kitadai Y, Bucana CD, Ellis LM. Significance of vessel count and vascular endothelial growth factor and its receptor (KDR) in intestinal-type gastric cancer. *Clin Cancer Res* 1996; **2**: 1679-1684 [PMID: 9816116]

40 **Ren J**, Dong L, Xu CB, Pan BR. The role of KDR in the interactions between human gastric carcinoma cell and vascular endothelial cell. *World J Gastroenterol* 2002; **8**: 596-601 [PMID: 12174363]

41 **Kolev Y**, Uetake H, Iida S, Ishikawa T, Kawano T, Sugihara K. Prognostic significance of VEGF expression in correlation with COX-2, microvessel density, and clinicopathological characteristics in human gastric carcinoma. *Ann Surg Oncol* 2007; **14**: 2738-2747 [PMID: 17687613]

42 **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]

43 **Kim SE**, Shim KN, Jung SA, Yoo K, Lee JH. The clinicopathological significance of tissue levels of hypoxia-inducible factor-1alpha and vascular endothelial growth factor in gastric cancer. *Gut Liver* 2009; **3**: 88-94 [PMID: 20431729 DOI: 10.5009/gnl.2009.3.2.88]

44 **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]

45 **Yoshikawa T**, Tsuburaya A, Kobayashi O, Sairenji M, Motohashi H, Yanoma S, Noguchi Y. Plasma concentrations of VEGF and bFGF in patients with gastric carcinoma. *Cancer Lett* 2000; **153**: 7-12 [PMID: 10779624]

46 **Karayiannakis AJ**, Syrigos KN, Polychronidis A, Zbar A, Kouraklis G, Simopoulos C, Karatzas G. Circulating VEGF levels in the serum of gastric cancer patients: correlation with pathological variables, patient survival, and tumor surgery. *Ann Surg* 2002; **236**: 37-42 [PMID: 12131083]

47 **Wang Y**, Fei D, Vanderlaan M, Song A. Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. *Angiogenesis* 2004; **7**: 335-345 [PMID: 15886877]

48 **De Vita F**, Giuliani F, Silvestris N, Rossetti S, Pizzolorusso A, Santabarbara G, Galizia G, Colucci G, Ciardiello F, Orditura M. Current status of targeted therapies in advanced gastric cancer. *Expert Opin Ther Targets* 2012; **16** Suppl 2: S29-S34 [PMID: 22443228 DOI: 10.1517/14728222.2011.652616]

49 **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]

50 **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]

51 **Kang Y**, Ohtsu A, van Cutsem E, Rha SY, Sawaki A, Park S, Lim H, Wu J, Langer B, Shah MA. AVAGAST: A randomized, double-blind, placebo-controlled, phase III study of first-line capecitabine and cis plus bevacizumab or placebo in patients with advanced gastric cancer (AGC). *J Clin Oncol* 2010; **28** (18s): Abstract LBA4007

52 **Shah MA**, Van Cutsem E, Kang YK, Dakhil SR, Satoh T, Chin K, Bang YJ, Bu L, Bilic G, Ohtsu A. Survival analysis according to disease subtype in AVAGAST: First-line capecitabine and cisplatin plus bevacizumab (bev) or placebo in patients (pts) with advanced gastric cancer. *J Clin Oncol* 2012; **30**: Abstract 05

53 **Kang Y**, Ohtsu, A, van Cutsem E, Roman L, Nunes J, Li C, Otero D, Rivera F, Aprile G, Pimentel Alvarez PR, Moehler MH, Wu J, Langer B, Shah MA. Survival analysis by pooling risk factors in AVAGAST: First-line capecitabine plus bevacizumab or placebo in patients with advanced gastric cancer. *J Clin Oncol* 2011; **29**: Abstract 4119

54 **Shah M**, Kang YK, Ohtsu A, Delmar P, Foernzler D, Langer B, Scherer S, van Cutsem E. Tumor and blood plasma biomarker analyses in the AVAGAST phase III randomized study of first-line bevacizumab capecitabine/cis in patients with advanced gastric cancer. *ESMO* 2010; Abstract 4675

55 **Smyth EC**, Langley RE, Stenning SP, Stevenson L, Allum WH, Grabsch H, Alderson D, Riddell AM, Crosby T, Mason R. ST03: A randomized trial of perioperative epirubicin, cis plus capecitabine (ECX) with or without bevacizumab (B) in patients (pts) with operable gastric, oesophagogastric junction (OGJ) or lower oesophageal adenocarcinoma. *J Clin Oncol* 2012; **30**: Abstract TPS4143

56 **Krupitskaya Y**, Wakelee HA. Ramucirumab, a fully human mAb to the transmembrane signaling tyrosine kinase VEGFR-2 for the potential treatment of cancer. *Curr Opin Investig Drugs* 2009; **10**: 597-605 [PMID: 19513949]

57 **Spratlin JL**, Cohen RB, Eadens M, Gore L, Camidge DR, Diab S, Leong S, O'Bryant C, Chow LQ, Serkova NJ, Meropol NJ, Lewis NL, Chiorean EG, Fox F, Youssoufian H, Rowinsky EK, Eckhardt SG. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol* 2010; **28**: 780-787 [PMID: 20048182 DOI: 10.1200/JCO.2009.23.7537]

58 **Fuchs CS**, Tomasek J, Cho JY, Dumitru F, Passalacqua R, Goswami C, Safran H, Vieira dos Santos L, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Tabernero J, Zalcberg JR, Chau I, Koshiji M, Hsu Y, Schwartz JD, Ajani JA. REGARD: A phase III, randomized, double blind trial of ramucirumab and best supportive care (BSC) versus placebo and

BSC in the treatment of metastatic gastric or GEJ adenocarcinoma following disease progression on first-line platinum and/or fluoropyrimidine containing combination therapy. GICS 2013. *J Clin Oncol* 2012; **30**: Abstract LBA5

59 **Chau I**, Passalacqua R. Tolerability and quality-of-life (QoL) results from the phase III REGARD study: Ramucirumab versus placebo in patients with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma. *Eur J Cancer* 2011; **47** (Supplement 1): Abstract 2588

60 **Wilke H**, Van Cutsem E. RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy. *J Clin Oncol* 2014; **32** (suppl 3): abstr LBA7

61 ClinicalTrials.gov. A study of ramucirumab in patients with gastric, esophageal and gastroesophageal cancer. Available from: URL: http://clinicaltrials.gov/ct2/show/record/NCT01246960

62 **Wilhelm SM**, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. *Mol Cancer Ther* 2008; **7**: 3129-3140 [PMID: 18852116 DOI: 10.1158/1535-7163.MCT-08-0013]

63 **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]

64 **Gallego R**, Martin-Richard M, Pericay C, Garcia-Foncillas J, Queralt B, Casado E, Feliu J, Vega I, Juez I, Visa L. Phase II study of oxaliplatin and sorafenib in advanced gastric cancer after failure of cis-fluoropyrimidine-based (PF) treatment. *J Clin Oncol* 2012; **30**: Abstract 4079

65 NCT00565370: Capecitabine and Cisplatin (XP) Sorafenib in Advanced Gastric Cancer (AGC) (XP Sorafenib). Available from: URL: http://clinicaltrial.gov/ct2/show/NCT00565370?term = NCT00565370 HYPERLINK

66 **Chow LQ**, Eckhardt SG. Sunitinib: from rational design to clinical efficacy. *J Clin Oncol* 2007; **25**: 884-896 [PMID: 17327610]

67 **Moehler M**, Mueller A, Hartmann JT, Ebert MP, Al-Batran SE, Reimer P, Weihrauch M, Lordick F, Trarbach T, Biesterfeld S, Kabisch M, Wachtlin D, Galle PR; German Arbeitsgemeinschaft Internistische Onkologie (AIO). An open-label, multicentre biomarker-oriented AIO phase II trial of sunitinib for patients with chemo-refractory advanced gastric cancer. *Eur J Cancer* 2011; **47**: 1511-1520 [PMID: 21561763 DOI: 10.1016/j.ejca.2011.04.006]

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 **Lindsay CR**, MacPherson IR, Cassidy J. Current status of cediranib: the rapid development of a novel anti-angiogenic therapy. *Future Oncol* 2009; **5**: 421-432 [PMID: 19450171 DOI: 10.2217/fon.09.18]

70 **Satoh T**, Yamada Y, Muro K, Hayashi H, Shimada Y, Takahari D, Taku K, Nakajima TE, Shi X, Brown KH, Boku N. Phase I study of cediranib in combination with cisplatin plus fluoropyrimidine (S-1 or capecitabine) in Japanese patients with previously untreated advanced gastric cancer. *Cancer Chemother Pharmacol* 2012; **69**: 439-446 [PMID: 21853311 DOI: 10.1007/s00280-011-1723-8]

71 **Tian S**, Quan H, Xie C, Guo H, Lü F, Xu Y, Li J, Lou L. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. *Cancer Sci* 2011; **102**: 1374-1380 [PMID: 21443688 DOI: 10.1111/j.1349-7006.2011.01939.x]

72 **Wilhelm SM**, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujath J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auclair D, Taylor I, Gedrich R, Voznesensky A, Riedl B, Post LE, Bollag G, Trail PA. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004; **64**: 7099-7109 [PMID: 15466206]

73 **Li J**, Qin S, Xu J, Guo WJ, Xiong JP, Bai Y, Sun G, Yang Y, Wang L, Xu N, Cheng Y, Zhe-Hai W, Zheng L, Tao M. A randomized, double-blind, multicenter, phase II, three-arm, placebo-control study of apatinib as third-line treatment in patients with metastatic gastric carcinoma. *J Clin Oncol* 2011; **29** (supplement): Abstract 4019

74 Phase III Study of Apatinib Tablets in the Treatment of Advanced or Metastatic Gastric Cancer. Accessed on 20 November 2012. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01512745/

75 TEL0805 trial: A phase 2 study of telatinib (TEL) in combination with capecitabine (X) and cis (P) as first-line treatment in patients (pts) with advanced gastric or gastro-esophageal junction (GEJ) cancer. A Study of Telatinib in Combination with Chemotherapy in Subjects With Advanced Gastric Cancer. Available from: URL: http://clinicaltrials.gov/show/NCT00952497/

76 **Ciardiello F**, Tortora G. EGFR antagonists in cancer treatment. *N Engl J Med* 2008; **358**: 1160-1174 [PMID: 18337605 DOI: 10.1056/NEJMra0707704]

77 **Hynes NE**, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. *Nat Rev Cancer* 2005; **5**: 341-354 [PMID: 15864276]

78 **Oda K**, Matsuoka Y, Funahashi A, Kitano H. A comprehensive pathway map of epidermal growth factor receptor signaling. *Mol Syst Biol* 2005; **1**: 2005.0010 [PMID: 16729045]

79 **Kim MA**, Lee HS, Lee HE, Jeon YK, Yang HK, Kim WH. EGFR in gastric carcinomas: prognostic significance of protein overexpression and high gene copy number. *Histopathology* 2008; **52**: 738-746 [PMID: 18397279 DOI: 10.1111/j.1365-2559.2008.03021.x]

80 **Baselga J**. Targeting the epidermal growth factor receptor: a clinical reality. *J Clin Oncol* 2001; **19**: 41S-44S [PMID: 11560970]

81 **Nyati MK**, Morgan MA, Feng FY, Lawrence TS. Integration of EGFR inhibitors with radiochemotherapy. *Nat Rev Cancer* 2006; **6**: 876-885 [PMID: 17036041]

82 **Lee SH**, Lee JW, Soung YH, Kim HS, Park WS, Kim SY, Lee JH, Park JY, Cho YG, Kim CJ, Nam SW, Kim SH, Lee JY, Yoo NJ. BRAF and KRAS mutations in stomach cancer. *Oncogene* 2003; **22**: 6942-6945 [PMID: 14534542]

83 **van Grieken NC**, Aoyama T, Chambers PA, Bottomley D, Ward LC, Inam I, Buffart TE, Das K, Lim T, Pang B, Zhang SL, Tan IB, Carvalho B, Heideman DA, Miyagi Y, Kameda Y, Arai T, Meijer GA, Tsuburaya A, Tan P, Yoshikawa T, Grabsch HI. KRAS and BRAF mutations are rare and related to DNA mismatch repair deficiency in gastric cancer from the East and the West: results from a large international multicentre study. *Br J Cancer* 2013; **108**: 1495-1501 [PMID: 23511561 DOI: 10.1038/bjc.2013.109]

84 **Yokoyama H**, Ikehara Y, Kodera Y, Ikehara S, Yatabe Y, Mochizuki Y, Koike M, Fujiwara M, Nakao A, Tatematsu M, Nakanishi H. Molecular basis for sensitivity and acquired resistance to gefitinib in HER2-overexpressing human gastric cancer cell lines derived from liver metastasis. *Br J Cancer* 2006; **95**: 1504-1513 [PMID: 17088902]

85 **Rojo F**, Tabernero J, Albanell J, Van Cutsem E, Ohtsu A, Doi T, Koizumi W, Shirao K, Takiuchi H, Ramon y Cajal S,

Baselga J. Pharmacodynamic studies of gefitinib in tumor biopsy specimens from patients with advanced gastric carcinoma. *J Clin Oncol* 2006; **24**: 4309-4316 [PMID: 16963731]

86 **Rodriguez CP**, Adelstein DJ, Rice TW, Rybicki LA, Videtic GM, Saxton JP, Murthy SC, Mason DP, Ives DI. A phase II study of perioperative concurrent chemotherapy, gefitinib, and hyperfractionated radiation followed by maintenance gefitinib in locoregionally advanced esophagus and gastroesophageal junction cancer. *J Thorac Oncol* 2010; **5**: 229-235 [PMID: 20009775 DOI: 10.1097/JTO.0b013e3181c5e334]

87 **Anido J**, Matar P, Albanell J, Guzmán M, Rojo F, Arribas J, Averbuch S, Baselga J. ZD1839, a specific epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, induces the formation of inactive EGFR/HER2 and EGFR/HER3 heterodimers and prevents heregulin signaling in HER2-overexpressing breast cancer cells. *Clin Cancer Res* 2003; **9**: 1274-1283 [PMID: 12684395]

88 **Moyer JD**, Barbacci EG, Iwata KK, Arnold L, Boman B, Cunningham A, DiOrio C, Doty J, Morin MJ, Moyer MP, Neveu M, Pollack VA, Pustilnik LR, Reynolds MM, Sloan D, Theleman A, Miller P. Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. *Cancer Res* 1997; **57**: 4838-4848 [PMID: 9354447]

89 **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]

90 **Moutinho C**, Mateus AR, Milanezi F, Carneiro F, Seruca R, Suriano G. Epidermal growth factor receptor structural alterations in gastric cancer. *BMC Cancer* 2008; **8**: 10 [PMID: 18199332 DOI: 10.1186/1471-2407-8-10]

91 **De Vita F**, Orditura M, Martinelli E, Vecchione L, Innocenti R, Sileni VC, Pinto C, Di Maio M, Farella A, Troiani T, Morgillo F, Napolitano V, Ancona E, Di Martino N, Ruol A, Galizia G, Del Genio A, Ciardiello F. A multicenter phase II study of induction chemotherapy with FOLFOX-4 and cetuximab followed by radiation and cetuximab in locally advanced oesophageal cancer. *Br J Cancer* 2011; **104**: 427-432 [PMID: 21245865 DOI: 10.1038/sj.bjc.6606093]

92 **Gold PJ**, Goldman B, Iqbal S, Leichman LP, Zhang W, Lenz HJ, Blanke CD. Cetuximab as second-line therapy in patients with metastatic esophageal adenocarcinoma: a phase II Southwest Oncology Group Study (S0415). *J Thorac Oncol* 2010; **5**: 1472-1476 [PMID: 20631636 DOI: 10.1097/JTO.0b013e3181e77a92]

93 **Lordick F**, Luber 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]

94 **Moehler M**, Mueller A, Trarbach T, Lordick F, Seufferlein T, Kubicka S, Geissler M, Schwarz S, Galle PR, Kanzler S; German Arbeitsgemeinschaft Internistische Onkologie. Cetuximab with irinotecan, folinic acid and 5-fluorouracil as first-line treatment in advanced gastroesophageal cancer: a prospective multi-center biomarker-oriented phase II study. *Ann Oncol* 2011; **22**: 1358-1366 [PMID: 21119032 DOI: 10.1093/annonc/mdq591]

95 **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]

96 **Richards D**, Kocs DM, Spira AI, David McCollum A, Diab S, Hecker LI, Cohn A, Zhan F, Asmar L. Results of docetaxel plus oxaliplatin (DOCOX) ± cetuximab in patients with metastatic gastric and/or gastroesophageal junction adenocarcinoma: results of a randomised Phase 2 study. *Eur J Cancer* 2013; **49**: 2823-2831 [PMID: 23747051 DOI: 10.1016/j.ejca.2013.04.022]

97 **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; Arbeitsgemeinschaft Internistische Onkologie and EXPAND Investigators. 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]

98 **Douillard JY**, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Oliner KS, Wolf M, Gansert J. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010; **28**: 4697-4705 [PMID: 20921465 DOI: 10.1200/JCO.2009.27]

99 **Peeters M**, Hotko YS, Cervantes-Ruiperez A, Ducreux M, Andre T, Strickland A, Wilson G, Tian Y, Gansert JL. Randomized phase III study of panitumumab (pmab) with FOLFIRI versus FOLFIRI alone as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC): Patient reported outcomes (PRO). Orlando, FL: Presented at 2010 Gastrointestinal Cancers Symposium, 2010: Abstract 282

100 **Amado RG**, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, Juan T, Sikorski R, Suggs S, Radinsky R, Patterson SD, Chang DD. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 1626-1634 [PMID: 18316791 DOI: 10.1200/JCO.2007.14.7116]

101 **Okines AF**, Ashley SE, Cunningham D, Oates J, Turner A, Webb J, Saffery C, Chua YJ, Chau I. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for advanced esophagogastric cancer: dose-finding study for the prospective multicenter, randomized, phase II/III REAL-3 trial. *J Clin Oncol* 2010; **28**: 3945-3950 [PMID: 20679619 DOI: 10.1200/JCO.2010.29.2847]

102 **Chau I**, Okines AFC, González de Castro D, Saffery C, Barbachano Y, Wotherspoon L, Puckey L, Hulkki Wilson S, Coxon FY, Middleton GW. REAL3: A multicentre randomized phase II/III trial of epirubicin, oxaliplatin, and capecitabine (EOC) versus modified (m) EOC plus panitumumab (P) in advanced oesophagogastric (OG) cancer. Response rate (RR), toxicity, and molecular analysis from phase II. *J Clin Oncol* 2011; **29**: Abstract 4131

103 **Waddell T**, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, Wotherspoon A, Saffery C, Middleton G, Wadsley 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]

104 NCT01379807. Efficacy and Safety of Panitumumab Combined With Docetaxel and Cisplatin as a First-line Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (SPIGA). Available from: URL: http://clinicaltrial.gov/ct2/show/study/NCT01379807?term = panitumumab gastric cancer HYPERLINK

105 **Lo KM**, Lan Y, Zhang X. The role of ADCC effector func-

tion in the anti-tumor efficacy of anti-EGFR antibodies in a mouse xenograft model. AACR-NCI-EORTC. *Int Conf Mol Targets Cancer Ther* 2003; Abstract A123
106 **Burger AM**, Heiss NS, Kreysch HG. The humanized monoclonal anti-EGFR antibody EMD72000 potently inhibits the growth of EGFR-expressing human tumor xenografts insensitive to chemotherapeutic drugs. *Proc Am Assoc Cancer Res* 2003; **44**: Abstract 5719
107 **Rao S**, Starling N, Cunningham D, Benson M, Wotherspoon A, Lüpfert C, Kurek R, Oates J, Baselga J, Hill A. Phase I study of epirubicin, cisplatin and capecitabine plus matuzumab in previously untreated patients with advanced oesophagogastric cancer. *Br J Cancer* 2008; **99**: 868-874 [PMID: 19238629 DOI: 10.1038/sj.bjc.6604622]
108 **Spicer J**. Technology evaluation: nimotuzumab, the Center of Molecular Immunology/YM BioSciences/Oncoscience. *Curr Opin Mol Ther* 2005; **7**: 182-191 [PMID: 15844627]
109 **Crombet T**, Torres L, Neninger E, Catalá M, Solano ME, Perera A, Torres O, Iznaga N, Torres F, Pérez R, Lage A. Pharmacological evaluation of humanized anti-epidermal growth factor receptor, monoclonal antibody h-R3, in patients with advanced epithelial-derived cancer. *J Immunother* 2003; **26**: 139-148 [PMID: 12616105]
110 **Brade AM**, Magalhaes J, Siu L, Oza A, Lovell S, de Borja M, Pond G, Sherman I, Hedley D, Chen E. A single agent, phase I pharmacodynamic study of nimotuzumab (TheraCIM-h-R3) in patients with advanced refractory solid tumors. 2007 ASCO Annual Meeting Proceedings Part I. *J Clin Oncol* 2007; **25** (18S): Abstract 14030
111 **Kim YH**, Sasaki Y, Lee KH, Rha SY, Park S, Boku N, Komatsu Y, Kim T, Kim S, Sakata Y. Randomized phase II study of nimotuzumab, an anti-EGFR antibody, plus iri in patients with 5-fluorouracil-based regimen-refractory advanced or recurrent gastric cancer in Korea and Japan: Preliminary results. *J Clin Oncol* 2011; **29**: Abstract 87
112 **Wang JW**, Chi Y, Zheng Z, Qu T, Zhou A, Yang L, Jiang W, Shi S, Sun Y, Song Y, Kang S. Randomized, single-centered, phase II clinical trial of nimotuzumab plus cis and S-1 as first-line therapy in patients with advanced gastric cancer. *J Clin Oncol* 2012; **30**: Abstract e14668
113 **Slamon DJ**, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344**: 783-792 [PMID: 11248153]
114 **Cidon EU**, Centeno RG, Lagarto EG, Peral JI. HER-2 Evaluation in a Specific Gastric Cancer Population with the Highest Rate of Mortality in Spain. *J Oncol* 2011; **2011**: 391564 [PMID: 22131990 DOI: 10.1155/2011/391564]
115 **Begnami MD**, Fukuda E, Fregnani JH, Nonogaki S, Montagnini AL, da Costa WL, Soares FA. Prognostic implications of altered human epidermal growth factor receptors (HERs) in gastric carcinomas: HER2 and HER3 are predictors of poor outcome. *J Clin Oncol* 2011; **29**: 3030-3036 [PMID: 21709195 DOI: 10.1200/JCO.2010.33.6313]
116 **Grabsch H**, Sivakumar S, Gray S, Gabbert HE, Müller W. HER2 expression in gastric cancer: Rare, heterogeneous and of no prognostic value - conclusions from 924 cases of two independent series. *Cell Oncol* 2010; **32**: 57-65 [PMID: 20208134 DOI: 10.3233/CLO-2009-0497]
117 **Hofmann M**, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, Ochiai A, Rüschoff J, Henkel T. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology* 2008; **52**: 797-805 [PMID: 18422971 DOI: 10.1111/j.1365-2559.2008.03028.x]
118 **Janjigian YY**, Werner D, Pauligk C, Steinmetz K, Kelsen DP, Jäger E, Altmannsberger HM, Robinson E, Tafe LJ, Tang LH, Shah MA, Al-Batran SE. Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA International collaborative analysis. *Ann Oncol* 2012; **23**: 2656-2662 [PMID: 22689179]
119 **De Vita F**, Giuliani F, Silvestris N, Catalano G, Ciardiello F, Orditura M. Human epidermal growth factor receptor 2 (HER2) in gastric cancer: a new therapeutic target. *Cancer Treat Rev* 2010; **36** Suppl 3: S11-S15 [PMID: 21129604 DOI: 10.1016/S0305-7372(10)70014-1]
120 **Sliwkowski MX**, Lofgren JA, Lewis GD, Hotaling TE, Fendly BM, Fox JA. Nonclinical studies addressing the mechanism of action of trastuzumab (Herceptin). *Semin Oncol* 1999; **26**: 60-70 [PMID: 10482195]
121 **Cortés-Funes H**, Rivera F, Alés I, Márquez A, Velasco A, Colomer R, García-Carbonero R, Sastre J, Guerra J, Grávalos C. Phase II of T and cis in patients (pts) with advanced gastric cancer (AGC) with HER2/neu overexpression/amplification. *J Clin Oncol* 2007; **25**: Abstract 4613
122 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. 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]
123 **Rech J**, Arnold D, Folprecht G. A pilot study of trastuzumab monotherapy in patients whoprogressed while on chemotherapy for metastatic or locally advanced HER-2 positive gastric cancer. *ESMO* 2006; **17**: 314 (Abstract 1096)
124 NCT01450696. HELOISE Study: A Study of Herceptin (Trastuzumab) in Combination With Cisplatin/Capecitabine Chemotherapy in Patients With HER2-Positive Metastatic Gastric or Gastro-Esophageal Junction Cancer. Available from: URL: http://clinicaltrials.gov/show/NCT01450696
125 **Lewis Phillips GD**, Li G, Dugger DL, Crocker LM, Parsons KL, Mai E, Blättler WA, Lambert JM, Chari RV, Lutz RJ, Wong WL, Jacobson FS, Koeppen H, Schwall RH, Kenkare-Mitra SR, Spencer SD, Sliwkowski MX. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Res* 2008; **68**: 9280-9290 [PMID: 19010901 DOI: 10.1158/0008-5472.CAN-08-1776]
126 NCT01641939. A Study of Trastuzumab Emtansine Versus Taxane in Patients With Advanced Gastric. Available from: URL: http://clinicaltrials.gov/show/NCT01641939
127 **Iqbal S**, Goldman B, Lenz HJ, Fenoglio-Preiser CM, Blanke CD. S0413: A phase II SWOG study of GW572016 (lapatinib) as first line therapy in patients (pts) with advanced or metastatic gastric cancer. *J Clin Oncol* 2007; **25**: Abstract 4621
128 **Galsky MD**, Von Hoff DD, Neubauer M, Anderson T, Fleming M, Nagarwala Y, Mahoney JM, Midwinter D, Vocila L, Zaks TZ. Target-specific, histology-independent, randomized discontinuation study of lapatinib in patients with HER2-amplified solid tumors. *Invest New Drugs* 2012; **30**: 695-701 [PMID: 20857170 DOI: 10.1007/s10637-010-9541-0]
129 NCT00680901, LOGiC-Lapatinib Optimization Study in ErbB2 (HER2) Positive Gastric Cancer: A Phase III Global, Blinded Study Designed to Evaluate Clinical Endpoints and Safety of Chemotherapy Plus Lapatinib. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT00680901?term = LOGiC &rank = 8/
130 **Satoh T**, Bang Y, Wang J, Xu J, Chung HC, Yeh K, Chen J, Mukaiyama A, Yoshida P, Ohtsu A. Interim safety analysis from TYTAN: A phase III Asian study of lapatinib in combination with paclitaxel as second-line therapy in gastric cancer. *J Clin Oncol* 2010; **28**: Abstract 4057
131 **Yamashita-Kashima Y**, Iijima S, Yorozu K, Furugaki K, Kurasawa M, Ohta M, Fujimoto-Ouchi K. Pertuzumab in combination with trastuzumab shows significantly enhanced antitumor activity in HER2-positive human gastric cancer xenograft models. *Clin Cancer Res* 2011; **17**: 5060-5070

[PMID: 21700765 DOI: 10.1158/1078-0432.CCR-10-2927]
132 **Kang YK**, Rha SY, Tassone P, Barriuso J, Yu R, Szado T, Garg A, Bang Y. Pertuzumab Pharmacokinetics And Safety In Combination With Trastuzumab And Chemotherapy In Patients With Her2-Positive Advanced Gastric Cancer (Agc). *Ann Oncol* 2013; **24** (suppl 4): Iv19
133 NCT01774786. A Study of Perjeta (Pertuzumab) in Combination With Herceptin (Trastuzumab) and Chemotherapy in Patients With HER2-Positive Metastatic Gastroesophageal Junction or Gastric Cancer. Available from: URL: http://clinicaltrials.gov/show/NCT01774786
134 **Shitara K**, Doi T, Ohtsu A. Molecular Targeting Therapy and Biomarker for Advanced Gastric Cancer. *J Phys Chem Biophys* 2012; **2**: 1-6 [DOI: 10.4172/2161-0398.100010]
135 **Markman B**, Atzori F, Pérez-García J, Tabernero J, Baselga J. Status of PI3K inhibition and biomarker development in cancer therapeutics. *Ann Oncol* 2010; **21**: 683-691 [PMID: 19713247 DOI: 10.1093/annonc/mdp347]
136 **Cidon EU**, Ellis SG, Inam Y, Adeleke S, Zarif S, Geldart T. Molecular targeted agents for gastric cancer: a step forward towards personalized therapy. *Cancers* (Basel) 2013; **5**: 64-91 [PMID: 24216699 DOI: 10.3390/cancers5010064]
137 **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]
138 **Van Cutsem E**, Yeh KH, Bang YJ, Shen L, Ajani JA , Bai YX, Chung HC, Pan HM, Chin K, Muro K, Kim YH, Smith H, Costantini C, Musalli S, Rizvi S, Sahmoud T, Ohtsu A. Phase III trial of everolimus (EVE) in previously treated patients with advanced gastric cancer (AGC): GRANITE-1. *J Clin Oncol* 2012; **30** (suppl 4): Abstract LBA3
139 NCT01248403. A Randomized, Double Blind Study Evaluating Paclitaxel With and Without RAD001 in Patients With Gastric Carcinoma After Prior Chemotherapy (AIO-STO-0111). Available from: URL: http://clinicaltrials.gov/show/NCT01248403
140 **Werner D**, Atmaca A, Pauligk C, Pustowka A, Jäger E, Al-Batran SE. Phase I study of everolimus and mitomycin C for patients with metastatic esophagogastric adenocarcinoma. *Cancer Med* 2013; **2**: 325-333 [PMID: 23930209 DOI: 10.1002/cam4.77]
141 **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]
142 **Sierra JR**, Tsao MS. c-MET as a potential therapeutic target and biomarker in cancer. *Ther Adv Med Oncol* 2011; **3**: S21-S35 [PMID: 22128285 DOI: 10.1177/1758834011422557]
143 **Graziano F**, Galluccio N, Lorenzini P, Ruzzo A, Canestrari E, D'Emidio S, Catalano V, Sisti V, Ligorio C, Andreoni F, Rulli E, Di Oto E, Fiorentini G, Zingaretti C, De Nictolis M, Cappuzzo F, Magnani M. Genetic activation of the MET pathway and prognosis of patients with high-risk, radically resected gastric cancer. *J Clin Oncol* 2011; **29**: 4789-4795 [PMID: 22042954 DOI: 10.1200/JCO.2011.36.7706]
144 **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]
145 **Hara T**, Ooi A, Kobayashi M, Mai M, Yanagihara K, Nakanishi I. Amplification of c-myc, K-sam, and c-met in gastric cancers: detection by fluorescence in situ hybridization. *Lab Invest* 1998; **78**: 1143-1153 [PMID: 9759658]
146 **Tsugawa K**, Yonemura Y, Hirono Y, Fushida S, Kaji M, Miwa K, Miyazaki I, Yamamoto H. Amplification of the c-met, c-erbB-2 and epidermal growth factor receptor gene in human gastric cancers: correlation to clinical features. *Oncology* 1998; **55**: 475-481 [PMID: 9732228]
147 **Nakajima M**, Sawada H, Yamada Y, Watanabe A, Tatsumi M, Yamashita J, Matsuda M, Sakaguchi T, Hirao T, Nakano H. The prognostic significance of amplification and overexpression of c-met and c-erb B-2 in human gastric carcinomas. *Cancer* 1999; **85**: 1894-1902 [PMID: 10223227]
148 **Huang TJ**, Wang JY, Lin SR, Lian ST, Hsieh JS. Overexpression of the c-met protooncogene in human gastric carcinoma--correlation to clinical features. *Acta Oncol* 2001; **40**: 638-643 [PMID: 11669338]
149 **Amemiya H**, Kono K, Itakura J, Tang RF, Takahashi A, An FQ, Kamei S, Iizuka H, Fujii H, Matsumoto Y. c-Met expression in gastric cancer with liver metastasis. *Oncology* 2002; **63**: 286-296 [PMID: 12381909]
150 **Zhao J**, Zhang X, Xin Y. Up-regulated expression of Ezrin and c-Met proteins are related to the metastasis and prognosis of gastric carcinomas. *Histol Histopathol* 2011; **26**: 1111-1120 [PMID: 21751142]
151 **Cho H**, Zhang X, Jung M, Kwon W, Jung J, Jeung H, Roh JH, Chung HC, Rha SH. C-met as a therapeutic target for metastatic potential of gastric cancer. *J Clin Oncol* 2010; **28**: Abstract e14568
152 **Jhawer M**, Kindler HL, Wainberg Z, Ford J, Kunz P, Tang L, McCallum S, Kallender H, Shah MA. Assessment of two dosing schedules of GSK1363089 (GSK089), a dual MET/VEGFR2 inhibitor, in metastatic gastric cancer (GC): Interim results of a multicenter phase II study. *J Clin Oncol* 2009; **27**: Abstract 14502
153 **Muro K**, Ryu MH, Yasui H, Nishina T, Ryoo BY, Boku N, Kang YK. A phase II study of tivantinib monotherapy in patients with previously treated advanced or recurrent gastric cancer. *J Clin Oncol* 2012; **30**: Abstract 4082
154 **Okamoto W**, Okamoto I, Arao T, Kuwata K, Hatashita E, Yamaguchi H, Sakai K, Yanagihara K, Nishio K, Nakagawa K. Antitumor action of the MET tyrosine kinase inhibitor crizotinib (PF-02341066) in gastric cancer positive for MET amplification. *Mol Cancer Ther* 2012; **11**: 1557-1564 [PMID: 22729845 DOI: 10.1158/1535-7163.MCT-11-0934]
155 **Lennerz JK**, Kwak EL, Ackerman A, Michael M, Fox SB, Bergethon K, Lauwers GY, Christensen JG, Wilner KD, Haber DA, Salgia R, Bang YJ, Clark JW, Solomon BJ, Iafrate AJ. MET amplification identifies a small and aggressive subgroup of esophagogastric adenocarcinoma with evidence of responsiveness to crizotinib. *J Clin Oncol* 2011; **29**: 4803-4810 [PMID: 22042947 DOI: 10.1200/JCO.2011.35.4928]
156 **Cao B**, Su Y, Oskarsson M, Zhao P, Kort EJ, Fisher RJ, Wang LM, Vande Woude GF. Neutralizing monoclonal antibodies to hepatocyte growth factor/scatter factor (HGF/SF) display antitumor activity in animal models. *Proc Natl Acad Sci USA* 2001; **98**: 7443-7448 [PMID: 11416216]
157 **Gao CF**, Xie Q, Zhang YW, Su Y, Zhao P, Cao B, Furge K, Sun J, Rex K, Osgood T, Coxon A, Burgess TL, Vande Woude GF. Therapeutic potential of hepatocyte growth factor/scatter factor neutralizing antibodies: inhibition of tumor growth in both autocrine and paracrine hepatocyte growth factor/scatter factor: c-Met-driven models of leiomyosarcoma. *Mol Cancer Ther* 2009; **8**: 2803-2810 [PMID: 19825800 DOI: 10.1158/1535-7163.MCT-09-0125]
158 **Gordon MS**, Sweeney CS, Mendelson DS, Eckhardt SG, Anderson A, Beaupre DM, Branstetter D, Burgess TL, Coxon A, Deng H, Kaplan-Lefko P, Leitch IM, Oliner KS, Yan L, Zhu M, Gore L. Safety, pharmacokinetics, and pharmacodynamics of AMG 102, a fully human hepatocyte growth factor-neutralizing monoclonal antibody, in a first-in-human study of patients with advanced solid tumors. *Clin Cancer Res* 2010; **16**: 699-710 [PMID: 20068101 DOI: 10.1158/1078-0432.CCR-09-1365]
159 **Iveson T**, Donehower RC, Davidenko I, Tjulandin S, Deptala A, Harrison M, Loh E, Jiang Y, Oliner K, Dubey S. Safety

and Efficacy of Epirubicin, Cis, and Capecitabine (ECX) Plus Rilotumumab (R) as First-line Treatment for Unresectable Locally Advanced (LA) or Metastatic (M) Gastric or Esophagogastric Junction (EGJ) Adenocarcinoma. *ESMO* 2011; Abstract 6504

160 NCT01697072. First-Line Treatment for Locally Advanced or Metastatic Mesenchymal Epithelial Transition Factor (MET) - Positive Gastric, Lower Esophageal, or Gastroesophageal Junction (GEJ) Adenocarcinoma (RILOMET-1). Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01697072?term=RILOMET&rank=1

161 A study of Onartuzumab (MetMab) in combination with mFOLFOX6 in patients with metastatic HER2-negative and MET-positive gastroesophageal cancer (NCT01662869). Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01662869?term = NCT01662869 HYPERLINK

162 **Itoh N**, Ornitz DM. Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease. *J Biochem* 2011; **149**: 121-130 [PMID: 20940169 DOI: 10.1093/jb/mvq121]

163 **Trueb B**. Biology of FGFRL1, the fifth fibroblast growth factor receptor. *Cell Mol Life Sci* 2011; **68**: 951-964 [PMID: 21080029 DOI: 10.1007/s00018-010-0576-3]

164 **Tiong KH**, Mah LY, Leong CO. Functional roles of fibroblast growth factor receptors (FGFRs) signaling in human cancers. *Apoptosis* 2013; **18**: 1447-1468 [PMID: 23900974]

165 **Turner N**, Grose R. Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer* 2010; **10**: 116-129 [PMID: 20094046 DOI: 10.1038/nrc2780]

166 **Matsumoto K**, Arao T, Hamaguchi T, Shimada Y, Kato K, Oda I, Taniguchi H, Koizumi F, Yanagihara K, Sasaki H, Nishio K, Yamada Y. FGFR2 gene amplification and clinicopathological features in gastric cancer. *Br J Cancer* 2012; **106**: 727-732 [PMID: 22240789 DOI: 10.1038/bjc.2011.603]

167 **Itoh H**, Hattori Y, Sakamoto H, Ishii H, Kishi T, Sasaki H, Yoshida T, Koono M, Sugimura T, Terada M. Preferential alternative splicing in cancer generates a K-sam messenger RNA with higher transforming activity. *Cancer Res* 1994; **54**: 3237-3241 [PMID: 8205545]

168 **Moffa AB**, Tannheimer SL, Ethier SP. Transforming potential of alternatively spliced variants of fibroblast growth factor receptor 2 in human mammary epithelial cells. *Mol Cancer Res* 2004; **2**: 643-652 [PMID: 15561780]

169 **Grose R**, Dickson C. Fibroblast growth factor signaling in tumorigenesis. *Cytokine Growth Factor Rev* 2005; **16**: 179-186 [PMID: 15863033]

170 **Zhang X**, Ibrahimi OA, Olsen SK, Umemori H, Mohammadi M, Ornitz DM. Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. *J Biol Chem* 2006; **281**: 15694-15700 [PMID: 16597617]

171 **Rand V**, Huang J, Stockwell T, Ferriera S, Buzko O, Levy S, Busam D, Li K, Edwards JB, Eberhart C, Murphy KM, Tsiamouri A, Beeson K, Simpson AJ, Venter JC, Riggins GJ, Strausberg RL. Sequence survey of receptor tyrosine kinases reveals mutations in glioblastomas. *Proc Natl Acad Sci USA* 2005; **102**: 14344-14349 [PMID: 16186508]

172 **Beenken A**, Mohammadi M. The FGF family: biology, pathophysiology and therapy. *Nat Rev Drug Discov* 2009; **8**: 235-253 [PMID: 19247306 DOI: 10.1038/nrd2792]

173 **Courjal F**, Cuny M, Simony-Lafontaine J, Louason G, Speiser P, Zeillinger R, Rodriguez C, Theillet C. Mapping of DNA amplifications at 15 chromosomal localizations in 1875 breast tumors: definition of phenotypic groups. *Cancer Res* 1997; **57**: 4360-4367 [PMID: 9331099]

174 **Dutt A**, Salvesen HB, Chen TH, Ramos AH, Onofrio RC, Hatton C, Nicoletti R, Winckler W, Grewal R, Hanna M, Wyhs N, Ziaugra L, Richter DJ, Trovik J, Engelsen IB, Stefansson IM, Fennell T, Cibulskis K, Zody MC, Akslen LA, Gabriel S, Wong KK, Sellers WR, Meyerson M, Greulich H. Drug-sensitive FGFR2 mutations in endometrial carcinoma. *Proc Natl Acad Sci USA* 2008; **105**: 8713-8717 [PMID: 18552176 DOI: 10.1073/pnas.0803379105]

175 **Cappellen D**, De Oliveira C, Ricol D, de Medina S, Bourdin J, Sastre-Garau X, Chopin D, Thiery JP, Radvanyi F. Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas. *Nat Genet* 1999; **23**: 18-20 [PMID: 10471491]

176 **Jung EJ**, Jung EJ, Min SY, Kim MA, Kim WH. Fibroblast growth factor receptor 2 gene amplification status and its clinicopathologic significance in gastric carcinoma. *Hum Pathol* 2012; **43**: 1559-1566 [PMID: 22440694 DOI: 10.1016/j.humpath.2011.12.002]

177 **Takeda M**, Arao T, Yokote H, Komatsu T, Yanagihara K, Sasaki H, Yamada Y, Tamura T, Fukuoka K, Kimura H, Saijo N, Nishio K. AZD2171 shows potent antitumor activity against gastric cancer over-expressing fibroblast growth factor receptor 2/keratinocyte growth factor receptor. *Clin Cancer Res* 2007; **13**: 3051-3057 [PMID: 17505008 DOI: 10.1158/1078-0432.CCR-06-2743]

178 **Kunii K**, Davis L, Gorenstein J, Hatch H, Yashiro M, Di Bacco A, Elbi C, Lutterbach B. FGFR2-amplified gastric cancer cell lines require FGFR2 and Erbb3 signaling for growth and survival. *Cancer Res* 2008; **68**: 2340-2348 [PMID: 18381441 DOI: 10.1158/0008-5472.CAN-07-5229]

179 **Nakamura K**, Yashiro M, Matsuoka T, Tendo M, Shimizu T, Miwa A, Hirakawa K. A novel molecular targeting compound as K-samII/FGF-R2 phosphorylation inhibitor, Ki23057, for Scirrhous gastric cancer. *Gastroenterology* 2006; **131**: 1530-1541 [PMID: 17101326]

180 **Gozgit JM**, Wong MJ, Moran L, Wardwell S, Mohemmad QK, Narasimhan NI, Shakespeare WC, Wang F, Clackson T, Rivera VM. Ponatinib (AP24534), a multitargeted pan-FGFR inhibitor with activity in multiple FGFR-amplified or mutated cancer models. *Mol Cancer Ther* 2012; **11**: 690-699 [PMID: 22238366 DOI: 10.1158/1535-7163.MCT-11-0450]

181 **Trudel S**, Li ZH, Wei E, Wiesmann M, Chang H, Chen C, Reece D, Heise C, Stewart AK. CHIR-258, a novel, multitargeted tyrosine kinase inhibitor for the potential treatment of t(4; 14) multiple myeloma. *Blood* 2005; **105**: 2941-2948 [PMID: 15598814]

182 **Lee SH**, Lopes de Menezes D, Vora J, Harris A, Ye H, Nordahl L, Garrett E, Samara E, Aukerman SL, Gelb AB, Heise C. In vivo target modulation and biological activity of CHIR-258, a multitargeted growth factor receptor kinase inhibitor, in colon cancer models. *Clin Cancer Res* 2005; **11**: 3633-3641 [PMID: 15897558]

183 **Xie L**, Su X, Zhang L, Yin X, Tang L, Zhang X, Xu Y, Gao Z, Liu K, Zhou M, Gao B, Shen D, Zhang L, Ji J, Gavine PR, Zhang J, Kilgour E, Zhang X, Ji Q. FGFR2 gene amplification in gastric cancer predicts sensitivity to the selective FGFR inhibitor AZD4547. *Clin Cancer Res* 2013; **19**: 2572-2583 [PMID: 23493349 DOI: 10.1158/1078-0432.CCR-12-3898]

184 Clinicaltrials.gov NCT01457846: "Efficacy and Safety of AZD4547 Versus Paclitaxel in Advanced Gastric or Gastro-oesophageal Junction Cancer Patients (SHINE). Available from: URL: http://clinicaltrials.gov/ct2/results?term = NCT01457846 HYPERLINK

185 **Eto K**, Iwatsuki M, Watanabe M, Ida S, Ishimoto T, Iwagami S, Baba Y, Sakamoto Y, Miyamoto Y, Yoshida N, Baba H. The microRNA-21/PTEN pathway regulates the sensitivity of HER2-positive gastric cancer cells to trastuzumab. *Ann Surg Oncol* 2014; **21**: 343-350 [PMID: 24154840]

186 **Chen CT**, Kim H, Liska D, Gao S, Christensen JG, Weiser MR. MET activation mediates resistance to lapatinib inhibition of HER2-amplified gastric cancer cells. *Mol Cancer Ther* 2012; **11**: 660-669 [PMID: 22238368 DOI: 10.1158/1535-7163.MCT-11-0754]

187 **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]

188 **Zhang X**, Xu J, Shen L, Wang J, Liang J, Xu N, Bai Y, Wang J. A phase II study of cetuximab with cis and capecitabine as first-line treatment in advanced gastric cancer. *J Clin Oncol* 2008; **26**: Abstract 15663

189 **Kim C**, Lee JL, Ryu MH, Chang HM, Kim TW, Lim HY, Kang HJ, Park YS, Ryoo BY, Kang YK. A prospective phase II study of cetuximab in combination with XELOX (capecitabine and oxaliplatin) in patients with metastatic and/or recurrent advanced gastric cancer. *Invest New Drugs* 2011; **29**: 366-373 [PMID: 19997960 DOI: 10.1007/s10637-009-9363-0]

190 **Rao S**, Starling N, Cunningham D, Sumpter K, Gilligan D, Ruhstaller T, Valladares-Ayerbes M, Wilke H, Archer C, Kurek R, Beadman C, Oates J. Matuzumab plus epirubicin, cisplatin and capecitabine (ECX) compared with epirubicin, cisplatin and capecitabine alone as first-line treatment in patients with advanced oesophago-gastric cancer: a randomised, multicentre open-label phase II study. *Ann Oncol* 2010; **21**: 2213-2219 [PMID: 20497967 DOI: 10.1093/annonc/mdq247]

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