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TOPIC HIGHLIGHT

2015 Advances in Gastric Cancer

Gastric cancer: The times they are a-changin'

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Abstract

Gastric cancer is the third leading cause of cancer death worldwide. Even though during these last decades gastric cancer incidence decreased in Western countries, it remains endemic and with a high incidence in Eastern countries. The survival in advanced and metastatic stage of gastric cancer is still very poor. Recently the Cancer Genoma Atlas Research Network identified four subtypes with different molecular profiles to classify gastric cancer in order to offer the optimal targeted therapies for pre-selected patients. Indeed, the key point is still the selection of patients for the right treatment, on basis of molecular tumor characterization. Since chemotherapy reached a plateau of efficacy for gastric cancer, the combination between cytotoxic therapy and biological agents gets a better prognosis and decreases chemotherapeutic toxicity. Currently, Trastuzumab in combination with platinum and fluorouracil is the only approved targeted therapy in the first line for c-erbB2 positive patients, whereas Ramucirumab is the only approved targeted agent for patients with metastatic gastric cancer. New perspectives for an effective treatment derived from the immunotherapeutic strategies. Here, we report an overview on gastric cancer treatments, with particular attention to recent advances in targeted therapies and in immunotherapeutic approach.

Key words: Targeted therapy; Chemotherapy; Gastric cancer; Immunotherapy

Core tip: Gastric cancer, despite its decrease in West Countries, remains one of the most common malignancies worldwide. The prognosis in the advanced setting is often poor even with a multidisciplinary approach, which aims to increase the patients' survival. The molecular classification of four subtypes of gastric adenocarcinomas (The Cancer Genome Atlas project) allowed a better stratification of patients in clinical trials for targeted

therapies. Biologic agents, modulating the immune checkpoints, seem to be the best promising therapeutic approach, opening new perspective for advanced gastric cancer treatment.

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INTRODUCTION

During these last decades gastric cancer incidence decreased, but it still remains he third most frequent cause of cancer-related mortality worldwide[1,2]. At diagnosis, about half of gastric cancer patients show an advanced disease, with a 5-year survival rate lower than 30%[3,4]. Even though gastric cancer incidence decreased in Western countries, it remains endemic and with a high incidence in Eastern countries. The incidence in Eastern Asia was 24.2/100000; in Latin America and Caribben was 15.8-23.7/100000; in Africa and Northern America there was the lowest incidence (http://globocan.iarc.fr, accessed on 16/01/2015). In the United States the estimated number of new cases of gastric cancer in 2014 overtook 22000 cases[2], with differences among several ethnic groups. In Europe gastric cancer holds the 5th place for male sex and the 6th place for female sex for incidence[5,6].

Gastric cancer can be hereditary and associated to specific mutations[7]. Often Gastric cancer are sporadic and depends on progressive accumulations of genotypic and phenotypic modifications due to different etiological factors such as wrong diets, presence of gastritis, infection by *H. pylori*, smoking, obesity, elevated body mass index (BMI) and reflux[8,9]. Indeed, combinations of smoking, elevated BMI, and reflux may account for almost 70% of total cases[10,11]. Untreated gastritis induces a chronic mucosal inflammation, that causes structural changes of gastric mucosa, leading to metaplastic transformation and structural changes of the glandular tissue, that can undergo to a neoplastic differentiation[9,12].

Many efforts have been done in order to prevent gastric cancer: recognition and treatment of *Helicobacter pylori* (*H. pylori)* infections; diet changes like lower use of salted foods, and the use of refrigerators are factors which contributed to reduce the incidence of gastric cancer[13]. Nonetheless, the incidence of the cancers of gastro-esophageal junction (GEJ) and gastric cardia increased in western country[14]. To explain these epidemiological data there are several interpretations, such as problems related to a correct subdivision among esophageal, junctional and cardia adenocarcinomas, that may have cloud the issue leading to a misclassification[14,15].

MOLECULAR CLASSIFICATION: "THERE'S A BATTLE OUTSIDE AND IT IS RAGING"

The most common classification systems, such as the Laurén and the World Health Organization classifications, are essential for therapeutic decision, but are unable to predict response to targeted therapies. Recent studies on molecular profiling of upper gastrointestinal (GI) tumors increased our knowledge on the biology of gastric cancer and developed a molecular classification, identifying dysregulated pathways in different subgroups of gastric cancer.

The Cancer Genoma Atlas (TCGA) analysis uncovered four main genotypes of gastric cancer based on the molecular characterization of 295 primary adenocarcinomas[16]: Epstein-Barr virus (EBV) positive; microsatellite unstable (MSI); genomically stable (GS); and tumors with chromosomal instability (CIN). The EBV-associated tumors are about 10% of the cancers; they display CDKN2A promoter hypermethylation and in 80% of the cases they have PIK3CA mutations and amplification of JAK2 and CD274 and PDCD1LG2. This subset of gastric cancer can benefit of targeted immunotherapy. MSI tumors represent approximately the 20% of the cases and show mutations in PIK3CA, HER2, HER3, and EGFR. GS gastric tumors represent about 20% of the adenocarcinomas, they show newly described mutations in RHOA, which are relevant to control actin-myosin-dependent cell contractility and motility. Almost 50% of gastric tumors showed CIN, with a marked aneuploidy and focal amplification of receptor tyrosine kinases, such as VEGFA. This subtype is frequently found in GEJ cancer. This study provides a guide to test new agents against new molecular targets specific for a gastric cancer subtype, enabling clinicians to make a better selection of patients for future trials with targeted therapy and immunotherapy in gastric cancer.

SURGICAL TREATMENT

Radical surgery is still the only one curative treatment, but gastric cancer is mostly diagnosed in local advanced or metastatic stage, when the survival still remains poor[17]. Surgical resection for gastric or GEJ cancer combined with D1/D2 lymph node dissection should be performed by experienced team to reduce mortality and morbidity[18]. Surgery with curative intent has to provide free-margin and at least D1 resection combined with removal at minimum of 15 lymph nodes[19]. The extent of lymph node dissection is a significant surgical procedure that specifies the lymph node involvement, because preoperative lymph node staging is considered highly unreliable. The results of many randomized studies have not agreed to demonstrate superiority of D2 resection *vs* the D1 resection; to conclude the standard recommended surgery could be at least D1 resection, while D2 resection could be indicated in some

particular young patients[20-22].

A combine approach of surgery and chemotherapy can improve outcomes of gastric cancer patients, with potentially resectable tumors. The Magic trial conducted in United Kingdom[23] and the ACCORD trial conducted in France[24] showed a statistically significant longer 5-year survival for patients treated with perioperative chemotherapy. Decisions were less clear for adjuvant setting: chemotherapy alone or with radiotherapy should be recommended for patients underwent to a less than optimal lymph node resection, R1 or with lymph node involvement[25].

CYTOTOXIC CHEMOTHERAPY: "YOUR OLD ROAD IS RAPIDLY AGING"

The only treatment for patients with metastatic disease is the systemic chemotherapy. Currently there is no first-line standard single chemotherapeutic regimen but cisplatin based regimens, which able to improve the overall survival (OS) because a cytotoxic combination is superior to a single-agent regimen[26]. The physician's choice of platinum-based doublets or triplets is taken after careful assessment of the patients' performance status. Currently, standard first-line options include FOLFOX [5-fluorouracil (5-FU, oxaliplatin)], S1/cisplatin or 5-FU/cisplatin, DCF (docetaxel, cisplatin, and 5-FU), ECF/EOX (epirubicin, cisplatin/oxaliplatin, and 5-FU/capecitabine). In the platinum-based doublets oxaliplatin could substitute cisplatin, while capecitabine and S1 are equivalent in terms of effectiveness to 5-FU[27,28].

A third drug, usually epirubicin or taxotere, can be added with the aim to obtain a high response rate (RR) and a better control of the disease[29,30].

Although most patients receive a first-line chemotherapy, in clinical practice only less than half of patients progressing after treatment receive a salvage treatment, mostly in western countries. Only recently a second-line chemotherapy has shown to be superior to the best supportive care in advanced disease: Two distinct trials proved that irinotecan and docetaxel, in monochemotherapy, control the metastatic disease[31,32].

It's evident that chemotherapy reached a plateau of efficacy for gastric cancer, thus in an attempt to improve it, getting a better prognosis and decreasing chemotherapeutic toxicity, the combination between cytotoxic therapy and biological agents is useful. Indeed, results of ToGA trial allow to approve the first biologic drug for stomach cancer. Today, trastuzumab is indicated for first-line in patients HER2-positive in combination with 5-FU or capecitabine and cisplatinum[33].

Even more recently, two randomized trials demonstrated that Ramucirumab, a monoclonal antibody directed against VEGFR-2, is effective both alone or in combination with a second line chemotherapy with paclitaxel, in patients with metastatic gastric cancer[34,35].

BIOMARKERS FOR GASTRIC CANCER

Since chemotherapy is not effective in all patients, who are resistant to cytotoxic treatment, it's mandatory to develop new anticancer regimens and to identify biomarkers able to predict the patients' responses to different citotoxic drugs in gastric cancer. One of the molecules currently under investigation is the alpha-1 Microglobulin/Bikunin Precursor (AMBP), because its high level in serum could predict poor response to paclitaxel- capecitabine regimen[36]. Thus AMBP could be a potential biomarker to identify patients who would benefit from this specific chemotherapeutic regimen.

Forkhead box transcription factor 1 (FoxM1) could be an other potential biomarker and target for gastric cancer. Indeed, FoxM1 overexpression is correlated with the pathogenesis of a variety of human malignancies such as breast cancer, non-small-cell lung cancer and ovarian cancer, and it is a critical molecule for chemoresistance to a microtubule-stabilizing anticancer agent as docetaxel[37-42]. FoxM1 overexpression was significantly associated with resistance in chemotherapy of docetaxel in addition to 5-FU, S-1 and cisplatin (CDDP) for patients with advanced gastric cancer[43,44]. Taken together, these results suggest that FoxM1 is involved in the mechanisms of resistance to cytotoxic drugs and its inhibition might be a promising therapeutic strategy for is a pleiotropic protein affecting a wide range of molecular and cellular processes.

Accumulating data, derived by different studies on the role of ANXA2 in tumorigenesis, suggest that ANXA2 is aberrantly expressed in a wide spectrum of tumors, affecting tumor cell adhesion, proliferation, apoptosis, invasion, metastasis and the interaction between immune cells and cancer cells in the microenvironment[45,46]. The expression of ANXA2 in gastric cancer tissue is associated to a poor prognosis[47,48]. A recent study reported that ANXA2 might be a good diagnostic and predictive marker for response to chemotherapy, indeed the chemotherapy-unresponsive patients show higher serum ANXA2 levels than the chemotherapy-responsive ones[49].

Several studies have consistently demonstrated that miRNAs, short noncoding RNA molecules involved in post-translational regulation of gene expression, contribute significantly to human carcinogenesis by modulating the expression of both proto-oncogenes and tumor suppressor genes[50]. Studies on gastric cancer allowed to identify up- and down-regulated miRNAs, which can be associated to clinical-pathological features of gastric cancer[51,52]. Moreover, many data report that the expression of different miRNA patterns is also associated with premalignant stages or even risk conditions to develop gastric cancer, such as *H. pylori* infection[53,54].

TARGETED THERAPY: "FOR THE LOSER NOW, WILL BE LATER TO WIN"

Advances in knowledge of the cancer biology led to the

discover of specific oncogenic signalling pathways of different driver mutations, resulting in the development of many new target agents. The prevalence of genomic alterations in gastric cancer patients has been recently assessed. Indeed, five distinct gastric cancer patient subgroups have been identified, according to the genomic alterations: FGFR2 (9% of tumours), KRAS (9%), epidermal growth factor receptor (EGFR) (8%), ERBB2 (7%) and MET (4%). Therefore, about 37% gastric cancer patients could be treated with anti-RTK/RAS agents[55]. Many new target therapies were tested in clinical trials in gastric cancer patients, but without great results, thus we need further molecular studies to identify right patients for the right drugs.

EGFR1 inhibitors

EGFR is a trans-membrane glycoprotein receptor expressed in about 60% of gastric cancer patients. A meta-analysis on 1600 gastric cancer patients evaluated the survival according to the EGFR expression, showing that positive EGFR expression does not significantly predict the poor survival of gastric cancer[56].

Cetuximab is an immunoglobulin G1 type chimeric monoclonal antibody targeting EGFR. Thanks to the successes achieved by the cetuximab in colorectal cancer, it was also tested in gastric cancer in combination with chemotherapy in phase Ⅱ studies: FOLFIRI[57]; cisplatin plus docetaxel[58]; oxaliplatin plus 5-FU[59,60] with encouraging results regarding ORR in all trials. However, the expected results from the combination of chemotherapy and cetuximab were not confirmed by the phase Ⅲ EXPAND study (cetuximab in combination with capecitabin and cisplatin), that failed both in terms of OS and of progression-free survival (PFS)[61]. The analysis of potential biomarkers such as KRAS mutations, EGFR expression, HER2 expression, did not identify the patients group responsive to cetuximab.

The REAL3 randomised study tested the efficacy of panitumumab in combination with EOX (epirubicin, oxaliplatin, capecitabine). In October 2011, trial recruitment was halted and panitumumab withdrawn because did not show any benefit at interim analysis. In multivariate OS analysis with performance status and disease stage, both *KRAS* mutation and *PIK3CA* mutation were negatively prognostic. No prognostic effect was associated with *HER2* or *PTEN* status, and no *BRAF* mutations were identified[62].

The phase Ⅲ COG trial evaluated Gefitinib *vs* placebo in patients with metastatic esophageal or types Ⅰ/Ⅱ junctional adeno or squamous cell carcinoma, progressing after prior chemotherapy. This study did not improve OS; however, there was significant improvement in PFS, quality of life and palliation of symptoms[63].

Some trials of several novel EGFR agents are still ongoing. The phase Ⅲ ENRICH trial of nimotuzumab in combination with irinotecan in the second-line setting is pre-selecting patients with high EGFR expression (NCT01813253). Finally, before defining EGFR inhibitors as ineffective in gastric cancer, we absolutely identify predictive biomarker for response, in order to avoid repeating the mistakes done with gefitinib in lung cancer[64,65].

HER2 inhibitors

All members of the HER family of receptor tyrosine kinases, whose members include HER1 (or EGFR), HER2, HER3, and HER4, are expressed in gastric cancer. HER2 is a protoncogene encoded by ERBB2 found on chromosome 17. The percentage of gastric cancer patients positive to HER2 ranges from 7% to 42% due to tumor heterogeneity and the different methods and scoring systems used for evaluating HER2[66]. HER2-positivity also depends on histologic type: It is frequent in patients with intestinal histology (34%), rare in those with diffuse-type histology (6%); it also depends on disease site: It's frequent in GEJ (32%) and rare in gastric cancer (18%)[67]. It remains unclear whether HER2 positivity is a negative prognostic factor because there are studies both for and against this hypothesis[68,69]. The ToGA trial is a randomized Phase Ⅲ study which brought to the approval of Herceptin as the only targeted agent for patients with HER2 positive metastatic gastric and GEJ cancer. Three thousand six hundred patients were assessed for HER2 positivity, and the 594 patients HER2-positive were recruited in the clinical trial[33], which evaluated efficacy of anti-HER2 trastuzumab in combination with 5-FU or capecitabine and cisplatin *vs* chemotherapy alone in HER2 patient. Median OS in control arm was 11.1 mo compared with 13.8 mo in experimental arm with a statistically significant increase in RR. Every 3 wk for six cycles, the treatment was administered, whereas trastuzumab was continued every 3 wk until disease progression, or unacceptable toxicity, or withdrawal of consent. One of the most interesting result of this study was that the survival advantage was greatest in patients with IHC 3+ tumors (HR = 0.66, 95%CI: 0.50-0.87), less effective in patients with IHC 2+ tumors (HR = 0.78, 95%CI: 0.55-1.10), and ineffective in those with HER2 gene-amplified, but not protein expressing (IHC 0 or 1+) tumors. Grade 3 or 4 adverse events (AEs) occurred in similar percentages in both arms. Now all patients with advanced or metastatic gastric or GEJ cancer, and suitable for combination chemotherapy with fluoropyrimidine and cisplatin, should be assessed for the expression of HER2 and therefore can be treated with additional trastuzumab.

The phase Ⅲ HELOISE trial, combining trastuzumab with cisplatin and capecitabine (NCT01450696), and the TEX regimen, combining trastuzumab with Taxotere, Eloxatin and Xeloda as treatment for HER2 positive non-resectable cancer (NCT01295086) are ongoing to improve the efficacy of combination chemotherapy. Heloise trial aims to assess whether trastuzumab maintenance is able to increase the gastric cancer patients' survival. The second trial evaluates the safety

and efficacy of three drugs combination in addition to trastuzumab.

Development of resistance to trastuzumab urged investigators to test new drugs target HER2, but not all HER2-targeting agents have had such an unequivocal success.

The dual HER2/EGFR inhibitor lapatinib (Tykerb) is an orally drug. Lapatinib is a very interesting TK1 inhibitor, able to interfere with cell proliferation, to sensitize gastric cancer cells to the irinotecan metabolite SN-38[70] and to have a synergic effect combined with chemotherapy[71].

Lapatinib was evaluated in the first setting in combination with capecitabine/oxaliplatin (LOGiC trial). 545 patients were randomized and 487 had HER2+ centrally confirmed, but combination treatment failed to improve the median OS (12.2 mo *vs* 10.5 mo, HR = 0.91, 95%CI: 0.73-1.12) compared with chemotherapy alone. No correlation was found between intensity of staining for HER2 by IHC and outcomes**.** However, the LOGiC trial did suggest that Asian patients and those under age 60 years might benefit of this combination[72].

The TyTAN trial is a phase Ⅲ study second-line therapy of paclitaxel. Investigators enrolled 261 HER2-amplified Asian patients and they observed statistically significant improvements in OS and PFS among a pre-specified subgroup of patients with strong HER2 positivity. However, addition of lapatinib did not produce any significant benefit on PFS (5.4 mo *vs* 4.4 mo) or OS (11.0 mo *vs* 8.9 mo) with significant gastrointestinal (diarrhoea 20%) and bone marrow toxicity (febrile neutropenia, 7%)[73]. Several other HER2-targeting agents were also evaluated in clinical trials, including trastuzumab emtansine (T-DM1; Kadcyla) and pertuzumab (Perjeta).

T-DM1 is a conjugate molecule that combine a cytotoxic agent with an antibody targeted specific tumor cells. Due to positive results in breast cancer (EMILIA trial)[74], is now ongoing a randomized, multicenter, adaptive phase Ⅱ/Ⅲ study to study the efficacy and safety of trastuzumab emtansine (T-DM1) *vs* taxane (docetaxel or paclitaxel), in patients with previously treated locally advanced or metastatic HER2-positive gastric cancer, including adenocarcinoma of the GEJ (GATSBY trial, NCT01641939). Another phase Ⅰ/Ⅱ study was designed to assess T-DM1 in combination with capecitabine in patients with metastatic gastric cancer (NCT01702558). The ongoing phase Ⅲ JACOB trial is evaluating the combination of pertuzumab, trastuzumab, and chemotherapy (NCT01774786). The combination of two antibodies aims to amplify the trastuzumab antitumor efficacy in HER2-positive patients. Again with the aim of overcoming resistance to trastuzumab, it is also ongoing a phase Ⅱ trial with afatinib, an irreversible panHER TK1 (NCT01522768). A better and more accurate knowledge of the mechanisms of cellular resistance to trastuzumab is essential for the future. Certainly, the intra-tumor heterogeneity in HER2 expression/amplification is very important, but other mechanisms have been implicated as PI3K/Akt pathway, m-TOR inhibitors, MET-inhibitors (when c-MET is overexpressed), overexpression of IGF-1 receptor (IGF-1R), SRC inhibitors. From these pre-clinical studies will emerge the right molecules to be tested in the next clinical trials.

Another HER2-directed strategy is represented by vaccines. Despite the great success of HER2 vaccine strategies in animal models, effective clinical results have not yet been obtained[75].

HER2 vaccines, DNA or peptide-based, are studied mainly for breast cancer, often in combination with other HER2 targeted therapies[76]. Regional treatments are another possible application. Radio-immunotherapy is now evaluating 212Pb immunoconjugates with trastuzumab in intraperitoneal treatment[77].

Angiogenesis inhibitors

Angiogenesis is crucial for tumor growth, thus anti-angiogenic drugs are now a standard of care for many solid tumors of the adult. In gastric cancer VEGF is overexpressed in 40% and VEGFR in 36% of cases. Some studied reported that VEGF overexpression correlates with advanced and aggressive disease[78-80]. We recently showed that even though VEGF serum levels were higher in gastric patients than in controls, they were not correlated to the OS[81].

Bevacizumab is a recombinant humanized monoclonal antibody anti-VEGF-A, a strong driver of angiogenesis in tumorigenesis. Phase Ⅱ studies conducted with bevacizumab in chemotherapy combination, showed encouraging RR, time to disease progression (TTP), and OS[82,83], but not confirmed by phase Ⅲ trials. The phase Ⅲ trial AVAGAST evaluated effects of bevacizumab in combination with cisplatin and capecitabine as a first-line therapy in 774 patients with advanced gastric carcinoma[84]. Addition of bevacizumab failed to improve OS, with median OS 12.1 mo *vs* 10.1 mo, even though it achieved a significant increase in PFS (6.7 mo *vs* 5.3 mo) and overall RR (46.0% *vs* 37.4%). To evaluate the hypothesis that angiogenic markers may be predictive for bevacizumab efficacy, correlations between pre-specified biomarkers (VEGF-A, protein expression of neuropilin-1, and VEGFR-1 and VEGFR-2) and clinical outcomes were assessed too. High plasma VEGF-A levels and low expression of neuropilin-1 showed a trend toward improved OS. These are strong biomarker candidates that aim to predict the response to bevacizumab in gastric cancer patients from non-Asian regions[85]. Moreover, the sub-group analysis by geographical regions, tumor site and histology concluded that the highest survival benefits are for non-Asian patients with distal gastric non-diffuse type cancer (OS 11.4 mo *vs* 7.3 mo).

MAGIC-B trial with bevacizumab in combination with chemotherapy (ECX regimen) in perioperative setting is ongoing[86]. The study results could provide relevant information on antiangiogenic efficacy in the early stages of disease.

In this complex and rather disappointing background,

results of ramucirumab in the treatment of advanced gastric cancer have been published. Ramucirumab (IMC-1121B) is a fully human IgG1 monoclonal antibody direct aganist VEGFR-2. The phase Ⅲ REGARD trial was conducted to assess efficacy and safety of ramucirumab as second-line treatment *vs* supportive care in advanced gastric cancer. Three hundred and fifty-five patients were enrolled. Ramucirumab significantly improved OS (OS 5.2 mo *vs* 3.8 mo) and PFS (2.1 mo *vs* 1.3 mo), with good tolerability. Most frequent grade 3-4 AEs were hypertension (7.3% in experimental arm *vs* 2.6% in placebo arm), anemia (6.4% *vs* 7.8%), abdominal pain (51.% *vs* 2.6%), ascites effusion (4.2% *vs* 4.3%), asthenia (42.% *vs* 3.5%), hyponatremia (3.4% *vs* 0.9%) and anorexia (3.4% *vs* 3.5%). No grade 4 hypertension has been observed[34].

The phase Ⅲ RAINBOW was conducted in 665 patients with the aim to evaluate efficacy and safety of ramucirumab plus paclitaxel combination in second-line treatment in advanced gastric cancer patients. The study reached its primary objective of increasing OS, indeed the combination resulted superior in median OS (9.7 mo *vs* 7.3 mo), median PFS (4.4 mo *vs* 2.8 mo) and RR (28% *vs* 16%). Hypertension, fatigue and neutropenia were the most frequent toxicities in experimental arm, whereas febrile neutropenia had comparable incidence.

Gaining the results of ramucirumab in second-line, we would have expected a good success also in first-line. However, the study combination of FOLFOX6 plus ramucirumab has not demonstrated to increase OS and PFS in patients with metastatic gastric cancer (23%), GEJ (31%) and esophageal (46%). 168 patients were enrolled, median PFS 6.4 mo *vs* 6.7 mo, OS 11.7 mo *vs* 11.5 mo. Addition of RAM to FOLFOX6 showed PFS difference at 3 mo and improved disease control rate (DCR); longer PFS in RAM *vs* placebo was observed in gastric/GEJ cancer patients[87].

Apatinib is a tyrosine kinase inhibitor (TKI) agent targeting VEGFR-2 (VEGFR). A phase Ⅱ randomised trial tested apatinib *vs* placebo in 144 pre-treated gastric cancer patients. Apatinib was taken orally in two different ways: 850 mg once and 450 mg twice a day. Median OS times were 2.50 mo (in the placebo arm), 4.83 mo (apatinib 850 mg once a day arm) and 4.27 mo (apatinib 450 mg twice a day arm). Median PFS times were 1.40 mo, 3.67 mo, and 3.20 mo, respectively. The differences between apatinib and placebo groups were statistically significant for both PFS ($P < 0.001$) and OS ($P < 0.001$ and 0.0017).Toxicities were tolerable and manageable[88]. The multicenter, randomized, double-blind, placebo-controlled phase 3 trial tested Apatinib 850 mg, po, qd, 28 d as one cycle or matching placebo. The study was planned to enroll 270 cases, stratified to the number of metastatic sites ($\leqslant 2$ or > 2). Median overall survival (mOS) was significantly prolonger in the apatinib group compare with in the placebo group. The results confirmed the efficacy and safety of apatinib in the patients with advanced gastric cancer[89].

Sunitinib and sorafenib are multi-target TKIs also studied in order to suppress angiogenesis in gastric cancer. Phase Ⅱ open-label randomized trial evaluated the combination of sunitinib plus docetaxel *vs* docetaxel monotherapy in second-line treatment in 107 patients with metastatic gastric cancer. Sunitinib arm was associated with a significantly higher ORR (41.1% *vs* 14.3%), but there was no significant difference in TTP (3.9 mo *vs* 2.6 mo) [90].

Sorafenib targets BRAF, VEGF, and PDGFR[91]. Combination of sorafenib plus chemotherapy (docetaxel and cisplatin) was assessed in a phase Ⅱ trial, first-line setting, in 44 patients with metastatic gastric cancer. The combination demonstrated a PFS of 5.8 mo, median OS of 13.6 mo, and ORR 41%; grade 3-4 EAs toxicity was neutropenia[92].

Pazopanib is an oral second-generation multitargeted TKI, which showed antiangiogenic and antitumor activity. There are two phase Ⅱ trials now ongoing in order to evaluate efficacy and safety of pazopanib as first-line treatment in metastatic gastric cancer. The first one, a phase Ⅱ PaFLO trial, wants to examine FLO (5-FU, leukovorin and oxaliplatin) + pazopanib used in combination for advanced gastric cancer (ClinicalTrials.gov Identifier: NCT01503372). The second one, a phase Ⅱ non-randomized open label trial, evaluates Pazopanib in combination with Capecitabine and Oxaliplatin in patients with advanced gastric cancer. The primary end-point is RR, the second end-points are PFS, OS and metabolic response rate by PET-CT (ClinicalTrials.gov Identifier: NCT01130805).

Hepatocyte growth factor-mesenchymal-epithelial transition factor axis

Mesenchymal-epithelial transition factor (c-MET) is the TK receptor of hepatocyte growth factor (HGF)[93]. c-MET expression or amplification was documented in many solid tumors and was correlated with poor prognosis in gastric cancer too. IHC analysis in gastric cancer specimens showed c-MET expression in 65% of cases with high-intensity staining in about 20% of cases[94]. However, the real activation of c-MET mutations and its resulting amplification, is a rare event: c-MET amplification occurs in 5%-10% of cases[95]. This discrepancy between expression and amplification of c-MET has important consequences when we design clinical trials with HGF-c-MET pathway inhibitors.

Rilotumumab (AMG 102) is human monoclonal antibody (IgG2) against HGF. A phase Ⅱ double-blind randomized study, evaluated the efficacy and safety of rilotumumab with ECX regimen in gastric cancer patients in first-line treatment. Rilotumumab associated to chemotherapy improved the median PFS from 4.2 to 5.6 mo, and the OS from 8.9 to 11.1 mo. In the rilotumumab plus ECX arms, the most common adverse observed eventswere: neutropenia, anemia, peripheral edema, thrombocytopenia, and deep vein thrombosis[96]. MET protein levels and gene copy

numbers were measured in archival tumor samples by immunohistochemistry (IHC) and fluorescence *in situ* hybridization, respectively. Rilotumumab in combination with ECX improved the median OS from 5.7 to 11.1 mo in patients with gastric tumors with high MET expression.

The RILOMET-01 phase Ⅲ trial evaluated the efficacy and safety of Rilotumumab + ECX in MET-pos by IHC, previously untreated G/GEJ cancer. Primary endpoint was OS. 609 patients were randomized, but the study was stopped early bacause an imbalance in deaths (data cutoff: Nov 2014). OS, PFS and ORR were statistically worse in the exsperimental arm. The subgroup with higher percentages of cells with ⩾ 1+ MET expression does not seem to benefit with ramucirumab. PK and MET biomarker analyses are pending, thus we don't know whether they will offer any answers to this failure[97].

Onartuzumab is a humanized, monovalent (one-armed) monoclonal antibody against MET. One phase Ⅲ trial (randomized multicenter double-blind placebo-controlled studies), currently ongoing (but it's not recruiting participants) is evaluating the efficacy and safety of onartuzumab (MetMAb) in combination with mFOLFOX6 in patients with metastatic HER2-negative and Met-positive adenocarcinoma of the stomach or GEJ (NCT01662869).

Crizotinib is a small MET kinase inhibitor. Phase Ⅰ study showed promising activity in c-MET amplified gastric cancer patients[98].

Tivatinib is a selective non-ATP competitive small-molecule inhibitor of c-MET. Phase Ⅱ single-arm study evaluated the efficacy of tivantinib monotherapy in Asian patients with previous treatment for MGC (ARQ-197). Tivantinib was administered orally daily. The primary end-point was the DCR. Thirty patients were enrolled and no objective responses were observed, and DCR was 36.7%. There was not relationship between efficacy and gene amplification of c-MET, expression of c-MET, p-MET and HGF[99]. New clinical trials with c-MET inhibitors were restricted to patients defined as a "MET positive" to identify selected patients for a special genetic/molecular profile. However, the HGF/c-MET axis is involved in multiple pathways that operate at different levels[100]. The anti-HGF compounds may not be sufficient to complitely inhibit HGF/c-MET axis[101]. Hereafter it will be necessary to define with much more precision what "MET positive" gastric cancer means.

m-TOR inhibitors - PI3K pathway inhibition

m-TOR regulates angiogenesis, cellular metabolism, proliferation, and cell growth. Its activation is done through the PI3K pathway (*via* Akt/protein kinase B and tuberous sclerosis complex). In gastric cancer, mTOR and p-mTOR (its activated form) overexpression were respectively 50.8% and 46.5%. Overexpression of total mTOR protein significantly correlated with tumor differentiation, T1/T2 tumors, and stage Ⅰ/Ⅱ/Ⅲ disease. p-mTOR overexpression significantly correlated with lymph node metastasis and all stage disease[102].

Everolimus is an oral m-TOR inhibitor, approved for the treatment of renal cell carcinoma, breast cancer, and progressive NET of pancreatic origin. A phase Ⅱ study, in 53 patients with previously treated metastatic gastric cancer, reported a median PFS of 2.7 mo and OS of 10.1 mo. Common grade 3/4 AEs included anemia, hyponatremia, increased gamma-glutamyltransferase, and lymphopenia. Grade 1/2 pneumonitis was reported in 15.1% of patients[103]. Another phase Ⅱ trial assessed the efficacy and safety of combination regimen of capecitabine plus everolimus in patients with refractory gastric cancer who have failed at least two cytotoxic regimens. Forty seven patients were enrolled in this trial. Everolimus in combination with capecitabine achieved an ORR of 10.6% and a DCR of 48.9%, with respectively a median PFS and OS of 2.3 mo and 5.1 mo[104]. The phase Ⅲ GRANITE-1 evaluated everolimus or BSC plus placebo in 656 previously treated advanced gastric cancer patients. The results of this trial showed median OS of 5.39 mo in the everolimus arm and an OS of 4.3 mo in the placebo arm, with an advantage in PFS statistically significant but clinically irrelevant (1.7 mo *vs* 1.4 mo)[105]. Phase Ⅲ study in advanced gastroesophageal adenocarcinoma patients comparing everolimus combined with paclitaxel *vs* paclitaxel alone (NCT01248403) is ongoing.

IGF family

The IGF family plays an important role in growth and metabolism. Deregulation of IGFs/IGF-1R system promotes metastases diffusion, proliferation and invasion in gastric cancer. A number of antibodies targeting IGF-1R have been studied. Ganitumab (AMG 479) and figitumumab (CP 751) have been evaluated in phase Ⅰ study in patients with solid tumors, including gastric cancer. They showed promising results[106].

PARP inhibitors

PARP inhibitors (Poly-ADP-Ribose-Polymerase) have been studied in breast cancer with a know history of deficient BRCA1/2. The activity of PARPS inhibitors is improved in presence of drugs that cause double-strand breaks in DNA such as platinum compounds.

Olaparib activity has been proven in a phase Ⅱ trial with paclitaxel (Bang YJ Im SA J ClinOncol 2013 31(sup). The study failed to increase the PFS, but it improved OS. A randomized phase Ⅲ with paclitaxel in gastric cancer patient second-line is ongoing (NCT019245337).

IMMUNOTHERAPY: "…AND KEEP YOUR EYES WIDE"

Until few years ago, the more validated hypothesis was that epithelial tumors originate from tissue stem cells. A large intra-tumoral heterogeneity exists and cancer stem cells are part of it, indeed they are in the primary tumors, but they also disseminate to different

organs, remaining dormant or originating metastases and often are responsible to chemo-resistance[107,108]. To date, it's evident that tumor growth depends on the interactions among cancer cells, microenvironment and immune system cells. Tumor and cancer stem cells express receptors for antigens on specific cell type, thus determining the capability of one tumor to metastasize to a specific organ, such as for breast, lung and prostate cancer which commonly metastasize to bone[109-112]. The importance of tumor microenvironment in promoting cancer progression is even more recognized, because its cellular components release a series of factors which constitute a favourable soil for cancer cell homing and growth[113,114]. Looking at the immune system, a variable number of immune cells infiltrate tumors: mast cells, lymphocytes, macrophages and myeloid derived suppressor cells (MDSCs), with a deep impact on tumor progression[115]. For instance, MDSCs are a heterogeneous population of immature myeloid cells driving the progression of cancer disease by suppressing both the innate and adaptive immune response. Indeed they suppress CD4 and CD8 T cell populations, and promote the activation and expansion of regulatory T cells, which mediate immunosuppression[116-118].

A strong rationale exists to adopt the immunotherapy for gastric cancer, because inflammation has been recognised as an hallmark of cancer[119] and gastric cancer, particularly the upper GI tumors are an inflammatory-mediated disease[120]. Here we will describe the last frontiers of immunotherapy in gastric cancer treatment, but a comprehensive overview of immunotherapy in gastric cancer has been recently published my Murphy *et al*[121].

Encouraging results derive from the combination of cellular immunotherapy and chemotherapy, that improves the quality of life and might prevent the recurrence in patients with advanced gastric carcinoma[122]. The TCGA network identified elevated programmed death ligand-1 (PD-L1) expression in the EBV subtype in gastric cancer[16]. PD-1 is an immune checkpoint, involved in tumor suppression and in tumor microenvironment, because it regulates T cell pathways. New frontiers of immunotherapy are focalized on targeting the immune checkpoints, in order to remove inhibitory pathways that block an effective T cell response against the tumor[123]. Two antibodies against PD-1 (Pembrolizumab and Nivolumab) have been approved in 2014 form United States Food and Drug Administration. The checkpoint therapy could be useful for gastroesophageal cancer, which express PD-L1 in 18% to 42 % of cases[124]. Phase Ⅱ and phase Ⅲ clinical trials involving either single agent PD-1/PD-L1 inhibition or combined with CTLA-4 inhibitors (ipilimumab) are ongoing. In KEYNOTE-012 trial 39 patients PD-L1-positive with advanced gastric cancer received pembrolizumab, which showed a positive anti-cancer activity with an objective response of 22.2%, the median time to response was 8 wk (range 7-16 wk), with a median duration of response of 24 wk (range 8+ to 33+ wk). At 6 mo, 24% of patients showed no signs of disease progression, and 69% remained alive; the median PFS reached 1.9 mo. The most common AEs included fatigue (17.9%), decreased appetite (12.8%), hypothyroidism (12.8%), and arthralgia (10.3%). Four patients showed severe AEs associated with pembrolizumab, particularly, one of these patients died for treatment-associated hypoxia[125]. The OS data were presented at 2015 ASCO Annual meeting: The 6-mo OS rate was 69%. These results support the ongoing development of pembrolizumab for gastric cancer[126]. The phase Ⅱ KEYNOTE-059 study will soon be initiated to evaluate pembrolizumab as monotherapy or in combination with cisplatin and 5-FU in patients with advanced gastric or GEJ adenocarcinoma[127].

On May 2015 the phase Ⅲ KEYNOTE-061 study started. This is a Randomized trial of Pembrolizumab *vs* Paclitaxel in Advanced Gastric or GEJ adenocarcinoma patients who progressed after first-line therapy with platinum and fluoropyrimidine (NCT02370498).

In the near future, ipilimumab and nivolumab, two immunostimulatory monoclonal antibodies with antineoplastic effects, might offer new therapeutic options for patients with advanced gastric cancer[128]. In particular, Nivolumab, a fully human IgG4 anti-PD-1 monoclonal antibody, resulted active and generally well tolerated in patients with advanced solid tumors in a phase Ⅰ trial[129,130]. A Japanese randomized phase Ⅲ study started in october 2014 to evaluate Nivolumab (ONO-4538) *vs* BSC in patients with unresectable advanced or recurrent GC patients (NCT02267343).

CONCLUSION: "...AS THE PRESENT NOW, WILL LATER BE PAST"

Gastric cancer is one of the most common causes of cancer death in the world. Healing can only be guaranteed by an optimal surgery and still in the early stages of the disease. However, especially in Western countries, diagnosis is too late and the survival of patients with metastatic disease rarely exceeds 12 mo of diagnosis.

The multidisciplinary approach is always mandatory: The perioperative treatment, when indicated, has shown to be effective in increasing the survival of these patients and, in advanced disease, the total care by nutritionist, surgeon and oncologist has positive impact on the quality of life of these patients.

Chemotherapy in metastatic disease is the only chance of cure, but brings with it side effects also important and poor response rates. "... Your old road is rapidly aging" sang Bob Dylan (www.bobdylan.com), but it is true that at the moment that is the way we know best. Perhaps times are changing. As for lung and colorectal cancer, the targeted therapies are revolutionizing the clinical practice, but we also learned that to achieve maximum efficacy of these new molecules we have to change tumors classification.

New drugs and new classification: the genomic and molecular classification given by TCGA network will help

us to characterize with greater precision our patients. "... There's a battle outside and it is raging" but we will be armed with new knowledge.

Some clinical trials have led to the registration of drugs such as trastuzumab and ramucirumab. For EGFR inhibitors, lapatinib or everolius, the phase Ⅲ studies represented a setback.

However, the key is still patients selection on basis of molecular tumor characterization. Gefitinib in lung cancer reminds us "... for the loser now, will be later to win".

Which is the best cytotoxic combination for target therapies? Which is the best setting for using the new molecules? We do not know yet. In deed, it's possible that gastric cancer during progression disease and under evolutionary pressure of cytotoxic treatment can transform molecularly into a different phenotype.

Moreover, ethnic differences may cause different responses to the same molecules. Even this finding will lead to a personalized cancer medicine.

Finally, immunotherapy opens a vast and fascinating scenery for gastric cancer treatment. Some etiological factors such as viral and bacterial infections *via* EBV and *H. pylori* suggests that gastric cancer can be treated with new drugs such as immunotherapy checkpoint inhibitors.... And keep your eyes wide.

REFERENCES

1 **Parkin DM**. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006; **118**: 3030-3044 [PMID: 16404738 DOI: 10.1002/ijc.21731]

2 **Siegel R**, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014; **64**: 9-29 [PMID: 24399786 DOI: 10.3322/caac.21208]

3 **Suzuki R**, Yamamoto E, Nojima M, Maruyama R, Yamano HO, Yoshikawa K, Kimura T, Harada T, Ashida M, Niinuma T, Sato A, Nosho K, Yamamoto H, Kai M, Sugai T, Imai K, Suzuki H, Shinomura Y. Aberrant methylation of microRNA-34b/c is a predictive marker of metachronous gastric cancer risk. *J Gastroenterol* 2014; **49**: 1135-1144 [PMID: 23942619 DOI: 10.1007/s00535-013-0861-7]

4 **Bria E**, De Manzoni G, Beghelli S, Tomezzoli A, Barbi S, Di Gregorio C, Scardoni M, Amato E, Frizziero M, Sperduti I, Corbo V, Brunelli M, Bersani S, Tortora G, Scarpa A. A clinical-biological risk stratification model for resected gastric cancer: prognostic impact of Her2, Fhit, and APC expression status. *Ann Oncol* 2013; **24**: 693-701 [PMID: 23131390]

5 **Ferlay J**, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; **49**: 1374-1403 [PMID: 23485231]

6 **Botterweck AA**, Schouten LJ, Volovics A, Dorant E, van Den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol* 2000; **29**: 645-654 [PMID: 10922340]

7 **Wang K**, Yuen ST, Xu J, Lee SP, Yan HH, Shi ST, Siu HC, Deng S, Chu KM, Law S, Chan KH, Chan AS, Tsui WY, Ho SL, Chan AK, Man JL, Foglizzo V, Ng MK, Chan AS, Ching YP, Cheng GH, Xie T, Fernandez J, Li VS, Clevers H, Rejto PA, Mao M, Leung SY. Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. *Nat Genet* 2014; **46**: 573-582 [PMID: 24816253]

8 **Pizzi M**, Saraggi D, Fassan M, Megraud F, Di Mario F, Rugge M. Secondary prevention of epidemic gastric cancer in the model of Helicobacter pylori-associated gastritis. *Dig Dis* 2014; **32**: 265-274 [PMID: 24732192]

9 **Rugge M**, Capelle LG, Cappellesso R, Nitti D, Kuipers EJ. Precancerous lesions in the stomach: from biology to clinical patient management. *Best Pract Res Clin Gastroenterol* 2013; **27**: 205-223 [PMID: 23809241]

10 **Engel LS**, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, Schoenberg JB, Mayne ST, Dubrow R, Rotterdam H, West AB, Blaser M, Blot WJ, Gail MH, Fraumeni JF. Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst* 2003; **95**: 1404-1413 [PMID: 13130116]

11 **Olsen CM**, Pandeya N, Green AC, Webb PM, Whiteman DC. Population attributable fractions of adenocarcinoma of the esophagus and gastroesophageal junction. *Am J Epidemiol* 2011; **174**: 582-590 [PMID: 21719746]

12 **Rugge M**, Fassan M, Pizzi M, Farinati F, Sturniolo GC, Plebani M, Graham DY. Operative link for gastritis assessment vs operative link on intestinal metaplasia assessment. *World J Gastroenterol* 2011; **17**: 4596-4601 [PMID: 22147965 DOI: 10.3748/wjg.v17.i41.4596]

13 **Bagnardi V**, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, Scotti L, Jenab M, Turati F, Pasquali E, Pelucchi C, Galeone C, Bellocco R, Negri E, Corrao G, Boffetta P, La Vecchia C. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer* 2015; **112**: 580-593 [PMID: 25422909]

14 **Corley DA**, Kubo A. Influence of site classification on cancer incidence rates: an analysis of gastric cardia carcinomas. *J Natl Cancer Inst* 2004; **96**: 1383-1387 [PMID: 15367571 DOI: 10.1093/jnci/djh265]

15 **Ekström AM**, Signorello LB, Hansson LE, Bergström R, Lindgren A, Nyrén O. Evaluating gastric cancer misclassification: a potential explanation for the rise in cardia cancer incidence. *J Natl Cancer Inst* 1999; **91**: 786-790 [PMID: 10328109]

16 Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202-209 [PMID: 25079317]

17 **Crew KD**, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; **12**: 354-362 [PMID: 16489633]

18 **Rausei S**, Dionigi G, Sano T, Sasako M, Biondi A, Morgagni P, Garofalo A, Boni L, Frattini F, D'Ugo D, Preston S, Marrelli D, Degiuli M, Capella C, Sacco R, Ruspi L, De Manzoni G, Roviello F, Pinotti G, Rovera F, Noh SH, Coit D, Dionigi R. Updates on surgical management of advanced gastric cancer: new evidence and trends. Insights from the First International Course on Upper Gastrointestinal Surgery--Varese (Italy), December 2, 2011. *Ann Surg Oncol* 2013; **20**: 3942-3947 [PMID: 23838909 DOI: 10.1245/s10434-013-3082-7]

19 **Maruyama K**, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg* 1987; **11**: 418-425 [PMID: 3630186]

20 **Hartgrink HH**, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, Welvaart K, van Krieken JH, Meijer S, Plukker JT, van Elk PJ, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H, Sasako M. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol* 2004; **22**: 2069-2077 [PMID: 15082726 DOI: 10.1200/JCO.2004.08.026]

21 **McCulloch P**, Niita ME, Kazi H, Gama-Rodrigues JJ. Gastrectomy with extended lymphadenectomy for primary treatment of gastric cancer. *Br J Surg* 2005; **92**: 5-13 [PMID: 15635680 DOI: 10.1002/bjs.4839]

22 **Degiuli M**, Sasako M, Ponti A, Vendrame A, Tomatis M, Mazza C, Borasi A, Capussotti L, Fronda G, Morino M. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. *Br J Surg* 2014; **101**: 23-31 [PMID: 24375296 DOI: 10.1002/bjs.9345]

23 **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]

24 **Boige V**, Pignon J, Saint-Aubert B, Lasser P, Conroy T, Bouché O, Segol P, Bedenne L, Rougier P, Ychou M. Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial. *J Clin Oncol* 2007; **25** (18 Suppl)

25 **Lutz MP**, Zalcberg JR, Ducreux M, Ajani JA, Allum W, Aust D, Bang YJ, Cascinu S, Hölscher A, Jankowski J, Jansen EP, Kisslich R, Lordick F, Mariette C, Moehler M, Oyama T, Roth A, Rueschoff J, Ruhstaller T, Seruca R, Stahl M, Sterzing F, van Cutsem E, van der Gaast A, van Lanschot J, Ychou M, Otto F. Highlights of the EORTC St. Gallen International Expert Consensus on the primary therapy of gastric, gastroesophageal and oesophageal cancer - differential treatment strategies for subtypes of early gastroesophageal cancer. *Eur J Cancer* 2012; **48**: 2941-2953 [PMID: 22921186]

26 **Wagner AD**, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006; **24**: 2903-2909 [PMID: 16782930]

27 **Lordick F**, Lorenzen S, Yamada Y, Ilson D. Optimal chemotherapy for advanced gastric cancer: is there a global consensus? *Gastric Cancer* 2014; **17**: 213-225 [PMID: 24048758 DOI: 10.1007/s10120-013-0297-z]

28 **Ajani JA**, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, Vynnychenko I, Garin A, Lang I, Falcon S. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol* 2010; **28**: 1547-1553 [PMID: 20159816]

29 **Ross PJ**, Hill ME, Norman A, Cunningham D. ECF in gastric cancer. *J Clin Oncol* 2000; **18**: 3874-3875 [PMID: 11078502]

30 **Van Cutsem E**, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**: 4991-4997 [PMID: 17075117]

31 **Thuss-Patience PC**, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, Dogan Y, Gebauer B, Schumacher G, Reichardt P. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011; **47**: 2306-2314 [PMID: 21742485]

32 **Ford HE**, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, Mansoor W, Fyfe D, Madhusudan S, Middleton GW, Swinson D, Falk S, Chau I, Cunningham D, Kareclas P, Cook N, Blazeby JM, Dunn JA. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014; **15**: 78-86 [PMID: 24332238]

33 **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. 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]

34 **Fuchs CS**, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalcberg JR, Chau I, Campbell W, Sivanandan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Tabernero J. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; **383**: 31-39 [PMID: 24094768]

35 **Wilke H**, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 1224-1235 [PMID: 25240821]

36 **Huang H**, Han Y, Gao J, Feng J, Zhu L, Qu L, Shen L, Shou C. High level of serum AMBP is associated with poor response to paclitaxel-capecitabine chemotherapy in advanced gastric cancer patients. *Med Oncol* 2013; **30**: 748 [PMID: 24135868 DOI: 10.1007/s12032-013-0748-8]

37 **Gormally MV**, Dexheimer TS, Marsico G, Sanders DA, Lowe C, Matak-Vinković D, Michael S, Jadhav A, Rai G, Maloney DJ, Simeonov A, Balasubramanian S. Suppression of the FOXM1 transcriptional programme via novel small molecule inhibition. *Nat Commun* 2014; **5**: 5165 [PMID: 25387393]

38 **Yu G**, Zhou A, Xue J, Huang C, Zhang X, Kang SH, Chiu WT, Tan C, Xie K, Wang J, Huang S. FoxM1 promotes breast tumorigenesis by activating PDGF-A and forming a positive feedback loop with the PDGF/AKT signaling pathway. *Oncotarget* 2015; **6**: 11281-11294 [PMID: 25869208]

39 **Bergamaschi A**, Madak-Erdogan Z, Kim YJ, Choi YL, Lu H, Katzenellenbogen BS. The forkhead transcription factor FOXM1 promotes endocrine resistance and invasiveness in estrogen receptor-positive breast cancer by expansion of stem-like cancer cells. *Breast Cancer Res* 2014; **16**: 436 [PMID: 25213081]

40 **Peake BF**, Nahta R. Resistance to HER2-targeted therapies: a potential role for FOXM1. *Breast Cancer Manag* 2014; **3**: 423-431 [PMID: 25598845 DOI: 10.2217/bmt.14.33]

41 **Kong FF**, Qu ZQ, Yuan HH, Wang JY, Zhao M, Guo YH, Shi J, Gong XD, Zhu YL, Liu F, Zhang WY, Jiang B. Overexpression of FOXM1 is associated with EMT and is a predictor of poor prognosis in non-small cell lung cancer. *Oncol Rep* 2014; **31**: 2660-2668 [PMID: 24715097 DOI: 10.3892/or.2014.3129]

42 **Chiu WT**, Huang YF, Tsai HY, Chen CC, Chang CH, Huang SC, Hsu KF, Chou CY. FOXM1 confers to epithelial-mesenchymal transition, stemness and chemoresistance in epithelial ovarian carcinoma cells. *Oncotarget* 2015; **6**: 2349-2365 [PMID: 25537512]

43 **Li X**, Yao R, Yue L, Qiu W, Qi W, Liu S, Yao Y, Liang J. FOXM1 mediates resistance to docetaxel in gastric cancer via up-regulating Stathmin. *J Cell Mol Med* 2014; **18**: 811-823 [PMID: 24628949 DOI: 10.1111/jcmm.12216]

44 **Okada K**, Fujiwara Y, Takahashi T, Nakamura Y, Takiguchi S, Nakajima K, Miyata H, Yamasaki M, Kurokawa Y, Mori M, Doki Y. Overexpression of forkhead box M1 transcription factor (FOXM1) is a potential prognostic marker and enhances chemoresistance for docetaxel in gastric cancer. *Ann Surg Oncol* 2013; **20**: 1035-1043 [PMID: 23054116 DOI: 10.1245/s10434-012-2680-0]

45 **Xu XH**, Pan W, Kang LH, Feng H, Song YQ. Association of annexin A2 with cancer development (Review). *Oncol Rep* 2015; **33**: 2121-2128 [PMID: 25760910 DOI: 10.3892/or.2015.3837]

46 **Zhang F**, Liu Y, Wang Z, Sun X, Yuan J, Wang T, Tian R, Ji W, Yu M, Zhao Y, Niu R. A novel Anxa2-interacting protein Ebp1 inhibits cancer proliferation and invasion by suppressing Anxa2 protein level. *Mol Cell Endocrinol* 2015; **411**: 75-85 [PMID: 25917452]

47 **Emoto K**, Sawada H, Yamada Y, Fujimoto H, Takahama Y, Ueno M, Takayama T, Uchida H, Kamada K, Naito A, Hirao S, Nakajima Y. Annexin II overexpression is correlated with poor prognosis in human gastric carcinoma. *Anticancer Res* 2001; **21**: 1339-1345 [PMID: 11396210]

48 **Zhang Q**, Ye Z, Yang Q, He X, Wang H, Zhao Z. Upregulated expression of annexin II is a prognostic marker for patients with gastric cancer. *World J Surg Oncol* 2012; **10**: 103 [PMID: 22681645]

49 **Tas F**, Tilgen Yasasever C, Karabulut S, Tastekin D, Duranyildiz D. Circulating annexin A2 as a biomarker in gastric cancer patients:

correlation with clinical variables. *Biomed Pharmacother* 2015; **69**: 237-241 [PMID: 25661364]
50 **Fassan M**, Croce CM, Rugge M. miRNAs in precancerous lesions of the gastrointestinal tract. *World J Gastroenterol* 2011; **17**: 5231-5239 [PMID: 22219591 DOI: 10.3748/wjg.v17.i48.5231]
51 **Wang JL**, Hu Y, Kong X, Wang ZH, Chen HY, Xu J, Fang JY. Candidate microRNA biomarkers in human gastric cancer: a systematic review and validation study. *PLoS One* 2013; **8**: e73683 [PMID: 24040025 DOI: 10.1371/journal.pone.0073683]
52 **Ueda T**, Volinia S, Okumura H, Shimizu M, Taccioli C, Rossi S, Alder H, Liu CG, Oue N, Yasui W, Yoshida K, Sasaki H, Nomura S, Seto Y, Kaminishi M, Calin GA, Croce CM. Relation between microRNA expression and progression and prognosis of gastric cancer: a microRNA expression analysis. *Lancet Oncol* 2010; **11**: 136-146 [PMID: 20022810]
53 **Petrocca F**, Visone R, Onelli MR, Shah MH, Nicoloso MS, de Martino I, Iliopoulos D, Pilozzi E, Liu CG, Negrini M, Cavazzini L, Volinia S, Alder H, Ruco LP, Baldassarre G, Croce CM, Vecchione A. E2F1-regulated microRNAs impair TGFbeta-dependent cell-cycle arrest and apoptosis in gastric cancer. *Cancer Cell* 2008; **13**: 272-286 [PMID: 18328430]
54 **Shrestha S**, Hsu SD, Huang WY, Huang HY, Chen W, Weng SL, Huang HD. A systematic review of microRNA expression profiling studies in human gastric cancer. *Cancer Med* 2014; **3**: 878-888 [PMID: 24902858 DOI: 10.1002/cam4.246]
55 **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]
56 **Hong L**, Han Y, Yang J, Zhang H, Jin Y, Brain L, Li M, Zhao Q. Prognostic value of epidermal growth factor receptor in patients with gastric cancer: a meta-analysis. *Gene* 2013; **529**: 69-72 [PMID: 23954221]
57 **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]
58 **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]
59 **Han SW**, Oh DY, Im SA, Park SR, Lee KW, Song HS, Lee NS, Lee KH, Choi IS, Lee MH, Kim MA, Kim WH, Bang YJ, Kim TY. Phase II study and biomarker analysis of cetuximab combined with modified FOLFOX6 in advanced gastric cancer. *Br J Cancer* 2009; **100**: 298-304 [PMID: 19127259]
60 **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]
61 **Lordick F**, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, Kurteva G, Volovat C, Moiseyenko VM, Gorbunova V, Park JO, Sawaki A, Celik I, Götte H, Melezínková H, Moehler M. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14**: 490-499 [PMID: 23594786]
62 **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]
63 **Dutton SJ**, Ferry DR, Blazeby JM, Abbas H, Dahle-Smith A, Mansoor W, Thompson J, Harrison M, Chatterjee A, Falk S, Garcia-Alonso A, Fyfe DW, Hubner RA, Gamble T, Peachey L, Davoudianfar M, Pearson SR, Julier P, Jankowski J, Kerr R, Petty RD. Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *Lancet Oncol* 2014; **15**: 894-904 [PMID: 24950987]
64 **Giaccone G**, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, Natale RB, Schiller JH, Von Pawel J, Pluzanska A, Gatzemeier U, Grous J, Ochs JS, Averbuch SD, Wolf MK, Rennie P, Fandi A, Johnson DH. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 1. *J Clin Oncol* 2004; **22**: 777-784 [PMID: 14990632 DOI: 10.1200/JCO.2004.08.001]
65 **Herbst RS**, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, Scagliotti G, Rosell R, Oliff I, Reeves JA, Wolf MK, Krebs AD, Averbuch SD, Ochs JS, Grous J, Fandi A, Johnson DH. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 2. *J Clin Oncol* 2004; **22**: 785-794 [PMID: 14990633 DOI: 10.1200/JCO.2004.07.215]
66 **Asioli S**, Maletta F, Verdun di Cantogno L, Satolli MA, Schena M, Pecchioni C, Botta C, Chiusa L, Molinaro L, Conti L, Viale G, Ingravallo G, Maiorano E, Sapino A. Approaching heterogeneity of human epidermal growth factor receptor 2 in surgical specimens of gastric cancer. *Hum Pathol* 2012; **43**: 2070-2079 [PMID: 22658277]
67 **Gravalos C**, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008; **19**: 1523-1529 [PMID: 18441328]
68 **Fisher SB**, Fisher KE, Squires MH, Patel SH, Kooby DA, El-Rayes BF, Cardona K, Russell MC, Staley CA, Farris AB, Maithel SK. HER2 in resected gastric cancer: Is there prognostic value? *J Surg Oncol* 2014; **109**: 61-66 [PMID: 24122802 DOI: 10.1002/jso.23456]
69 **Jørgensen JT**, Hersom M. HER2 as a Prognostic Marker in Gastric Cancer - A Systematic Analysis of Data from the Literature. *J Cancer* 2012; **3**: 137-144 [PMID: 22481979 DOI: 10.7150/jca.4090]
70 **LaBonte MJ**, Manegold PC, Wilson PM, Fazzone W, Louie SG, Lenz HJ, Ladner RD. The dual EGFR/HER-2 tyrosine kinase inhibitor lapatinib sensitizes colon and gastric cancer cells to the irinotecan active metabolite SN-38. *Int J Cancer* 2009; **125**: 2957-2969 [PMID: 19536776 DOI: 10.1002/ijc.24658]
71 **Kim JW**, Kim HP, Im SA, Kang S, Hur HS, Yoon YK, Oh DY, Kim JH, Lee DS, Kim TY, Bang YJ. The growth inhibitory effect of lapatinib, a dual inhibitor of EGFR and HER2 tyrosine kinase, in gastric cancer cell lines. *Cancer Lett* 2008; **272**: 296-306 [PMID: 18774637]
72 **Hecht JR**, Bang YJ, Shukui Q, Chung HC, Xu JM, Park JO, Jeziorski K, Shparyk Y, Hoff PM, Sobrero AF, Salman P, Li J, Protsenko S, Buyse ME, Afenjar K, Kaneko T, Kemner A, Santillana S, Press MF, Slamon DJ. Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): The TRIO-013/LOGiC Trial. *J Clin Oncol* 2013; **31** (suppl; abstr LBA4001)
73 **Satoh T**, Bang YJ. 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** (suppl; abstr 4057)
74 **Verma S**, Miles D, Gianni L, Krop IE, Welslau M, Baselga J,

Pegram M, Oh DY, Diéras V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; **367**: 1783-1791 [PMID: 23020162 DOI: 10.1056/NEJMoa1209124]

75 **Occhipinti S**, Sponton L, Rolla S, Caorsi C, Novarino A, Donadio M, Bustreo S, Satolli MA, Pecchioni C, Marchini C, Amici A, Cavallo F, Cappello P, Pierobon D, Novelli F, Giovarelli M. Chimeric rat/human HER2 efficiently circumvents HER2 tolerance in cancer patients. *Clin Cancer Res* 2014; **20**: 2910-2921 [PMID: 24668647]

76 **Hamilton E**, Blackwell K, Hobeika AC, Clay TM, Broadwater G, Ren XR, Chen W, Castro H, Lehmann F, Spector N, Wei J, Osada T, Lyerly HK, Morse MA. Phase 1 clinical trial of HER2-specific immunotherapy with concomitant HER2 kinase inhibition [corrected]. *J Transl Med* 2012; **10**: 28 [PMID: 22325452]

77 **Yong KJ**, Milenic DE, Baidoo KE, Brechbiel MW. (212)Pb-radioimmunotherapy induces G(2) cell-cycle arrest and delays DNA damage repair in tumor xenografts in a model for disseminated intraperitoneal disease. *Mol Cancer Ther* 2012; **11**: 639-648 [PMID: 22238365]

78 **Fondevila C**, Metges JP, Fuster J, Grau JJ, Palacín A, Castells A, Volant A, Pera M. p53 and VEGF expression are independent predictors of tumour recurrence and survival following curative resection of gastric cancer. *Br J Cancer* 2004; **90**: 206-215 [PMID: 14710231 DOI: 10.1038/sj.bjc.6601455]

79 **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 DOI: 10.1002/(SICI)1097-0142(19960301)77:5<858: : AID-CNCR8>3.0.CO; 2-A]

80 **Vidal O**, Metges JP, Elizalde I, Valentíni M, Volant A, Molina R, Castells A, Pera M. High preoperative serum vascular endothelial growth factor levels predict poor clinical outcome after curative resection of gastric cancer. *Br J Surg* 2009; **96**: 1443-1451 [PMID: 19918848 DOI: 10.1002/bjs.6780]

81 **D'Amico L**, Satolli MA, Mecca C, Castiglione A, Ceccarelli M, D' Amelio P, Garino M, De Giuli M, Sandrucci S, Ferracini R, Roato I. Bone metastases in gastric cancer follow a RANKL-independent mechanism. *Oncol Rep* 2013; **29**: 1453-1458 [PMID: 23404437 DOI: 10.3892/or.2013.2280]

82 **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]

83 **Shah MA**, Jhawer M, Ilson DH, Lefkowitz RA, Robinson E, Capanu M, Kelsen DP. Phase II study of modified docetaxel, cisplatin, and fluorouracil with bevacizumab in patients with metastatic gastroesophageal adenocarcinoma. *J Clin Oncol* 2011; **29**: 868-874 [PMID: 21189380]

84 **Ohtsu A**, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J, Langer B, Starnawski M, Kang YK. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; **29**: 3968-3976 [PMID: 21844504]

85 **Van Cutsem E**, de Haas S, Kang YK, Ohtsu A, Tebbutt NC, Ming Xu J, Peng Yong W, Langer B, Delmar P, Scherer SJ, Shah MA. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol* 2012; **30**: 2119-2127 [PMID: 22565005]

86 **Okines AF**, Langley RE, Thompson LC, Stenning SP, Stevenson L, Falk S, Seymour M, Coxon F, Middleton GW, Smith D, Evans L, Slater S, Waters J, Ford D, Hall M, Iveson TJ, Petty RD, Plummer C, Allum WH, Blazeby JM, Griffin M, Cunningham D. Bevacizumab with peri-operative epirubicin, cisplatin and capecitabine (ECX) in localised gastro-oesophageal adenocarcinoma: a safety report. *Ann Oncol* 2013; **24**: 702-709 [PMID: 23108952]

87 **Yoon JH**, Bendell JC, Braiteh FS, Firdaus I, Philip PA, Lee Cohn AL, Lewis N, Anderson DM, Arrowsmith E, Schwartz JD, Xu Y, Koshiji M, Alberts SR, Wainberg ZA. Ramucirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial. *J Clin Oncol* 2014; **32** (5 suppl; abstr 4004)

88 **Li J**, Qin S, Xu J, Guo W, Xiong J, Bai Y, Sun G, Yang Y, Wang L, Xu N, Cheng Y, Wang Z, Zheng L, Tao M, Zhu X, Ji D, Liu X, Yu H. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol* 2013; **31**: 3219-3225 [PMID: 23918952]

89 **Qin S**. Phase III study of apatinib in advanced gastric cancer: A randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2014; **32** (5 suppl; abstr 4003)

90 **Yi JH**, Lee J, Lee J, Park SH, Park JO, Yim DS, Park YS, Lim HY, Kang WK. Randomised phase II trial of docetaxel and sunitinib in patients with metastatic gastric cancer who were previously treated with fluoropyrimidine and platinum. *Br J Cancer* 2012; **106**: 1469-1474 [PMID: 22460270]

91 **Moggio A**, Pittatore G, Cassoni P, Marchino GL, Revelli A, Bussolati B. Sorafenib inhibits growth, migration, and angiogenic potential of ectopic endometrial mesenchymal stem cells derived from patients with endometriosis. *Fertil Steril* 2012; **98**: 1521-30.e2 [PMID: 22981172]

92 **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]

93 **Trusolino L**, Bertotti A, Comoglio PM. MET signalling: principles and functions in development, organ regeneration and cancer. *Nat Rev Mol Cell Biol* 2010; **11**: 834-848 [PMID: 21102609]

94 **Ha SY**, Lee J, Kang SY, Do IG, Ahn S, Park JO, Kang WK, Choi MG, Sohn TS, Bae JM, Kim S, Kim M, Kim S, Park CK, Ignatius Ou SH, Kim KM. MET overexpression assessed by new interpretation method predicts gene amplification and poor survival in advanced gastric carcinomas. *Mod Pathol* 2013; **26**: 1632-1641 [PMID: 23807774]

95 **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]

96 **Oliner KS**, Tang R, Anderson A, Lan Y, Iveson T, Donehower RC, Jiang Y, Dubey D, Loh E. Evaluation of MET pathway biomarkers in a phase II study of rilotumumab (R, AMG 102) or placebo (P) in combination with epirubicin, cisplatin, and capecitabine (ECX) in patients (pts) with locally advanced or metastatic gastric (G) or esophagogastric junction (EGJ) cancer. *J Clin Oncol* 2012; **30** (suppl; abstr 4005)

97 **Cunningham D**, Tebbutt NC, Davidenko I, Murad AM, Al-Batran S, Ilson DH, Tjulandin S, Gotovkin E, Karaszewska B, Bondarenko I, Tejani MA, Udrea AA, Tehfe MA, Baker N, Smith Oliner KM, Zhang Y, Hoang T, Sidhu R, Catenacci DVT. Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study. *J Clin Oncol* 2015; **33** (suppl; abstr 4000)

98 **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]

99 **Kang YK**, Muro K, Ryu MH, Yasui H, Nishina T, Ryoo BY,

Kamiya Y, Akinaga S, Boku N. A phase II trial of a selective c-Met inhibitor tivantinib (ARQ 197) monotherapy as a second- or third-line therapy in the patients with metastatic gastric cancer. *Invest New Drugs* 2014; **32**: 355-361 [PMID: 24337769 DOI: 10.1007/s10637-013-0057-2]

100 **Lai AZ**, Abella JV, Park M. Crosstalk in Met receptor oncogenesis. *Trends Cell Biol* 2009; **19**: 542-551 [PMID: 19758803]

101 **Olwill SA**, Joffroy C, Gille H, Vigna E, Matschiner G, Allersdorfer A, Lunde BM, Jaworski J, Burrows JF, Chiriaco C, Christian HJ, Hülsmeyer M, Trentmann S, Jensen K, Hohlbaum AM, Audoly L. A highly potent and specific MET therapeutic protein antagonist with both ligand-dependent and ligand-independent activity. *Mol Cancer Ther* 2013; **12**: 2459-2471 [PMID: 24002935]

102 **Yu G**, Wang J, Chen Y, Wang X, Pan J, Li G, Jia Z, Li Q, Yao JC, Xie K. Overexpression of phosphorylated mammalian target of rapamycin predicts lymph node metastasis and prognosis of chinese patients with gastric cancer. *Clin Cancer Res* 2009; **15**: 1821-1829 [PMID: 19223493]

103 **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]

104 **Lee SJ**, Lee J, Lee J, Park SH, Park JO, Park YS, Lim HY, Kim KM, Do IG, Jung SH, Yim DS, Kang WK. Phase II trial of capecitabine and everolimus (RAD001) combination in refractory gastric cancer patients. *Invest New Drugs* 2013; **31**: 1580-1586 [PMID: 24013904 DOI: 10.1007/s10637-013-0022-0]

105 **Ohtsu A**, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, Sahmoud T, Shen L, Yeh KH, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Lebwohl D, Van Cutsem E. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol* 2013; **31**: 3935-3943 [PMID: 24043745]

106 **Molife LR**, Fong PC, Paccagnella L, Reid AH, Shaw HM, Vidal L, Arkenau HT, Karavasilis V, Yap TA, Olmos D, Spicer J, Postel-Vinay S, Yin D, Lipton A, Demers L, Leitzel K, Gualberto A, de Bono JS. The insulin-like growth factor-I receptor inhibitor figitumumab (CP-751,871) in combination with docetaxel in patients with advanced solid tumours: results of a phase Ib dose-escalation, open-label study. *Br J Cancer* 2010; **103**: 332-339 [PMID: 20628389]

107 **Marusyk A**, Almendro V, Polyak K. Intra-tumour heterogeneity: a looking glass for cancer? *Nat Rev Cancer* 2012; **12**: 323-334 [PMID: 22513401]

108 **Chen J**, Li Y, Yu TS, McKay RM, Burns DK, Kernie SG, Parada LF. A restricted cell population propagates glioblastoma growth after chemotherapy. *Nature* 2012; **488**: 522-526 [PMID: 22854781]

109 **Mundy GR**. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer* 2002; **2**: 584-593 [PMID: 12154351 DOI: 10.1038/nrc867]

110 **D'Amico L**, Patanè S, Grange C, Bussolati B, Isella C, Fontani L, Godio L, Cilli M, D'Amelio P, Isaia G, Medico E, Ferracini R, Roato I. Primary breast cancer stem-like cells metastasise to bone, switch phenotype and acquire a bone tropism signature. *Br J Cancer* 2013; **108**: 2525-2536 [PMID: 23801032]

111 **Keller ET**, Zhang J, Cooper CR, Smith PC, McCauley LK, Pienta KJ, Taichman RS. Prostate carcinoma skeletal metastases: cross-talk between tumor and bone. *Cancer Metastasis Rev* 2001; **20**: 333-349 [PMID: 12085970]

112 **Roato I**. Bone metastases: When and how lung cancer interacts with bone. *World J Clin Oncol* 2014; **5**: 149-155 [PMID: 24829862 DOI: 10.5306/wjco.v5.i2.149]

113 **Casey SC**, Amedei A, Aquilano K, Azmi AS, Benencia F, Bhakta D, Bilsland AE, Boosani CS, Chen S, Ciriolo MR, Crawford S, Fujii H, Georgakilas AG, Guha G, Halicka D, Helferich WG, Heneberg P, Honoki K, Keith WN, Kerkar SP, Mohammed SI, Niccolai E, Nowsheen S, Vasantha Rupasinghe HP, Samadi A, Singh N, Talib WH, Venkateswaran V, Whelan RL, Yang X, Felsher DW. Cancer prevention and therapy through the modulation of the tumor microenvironment. *Semin Cancer Biol* 2015; **pii**: S1044-579X(15)00015-2 [PMID: 25865775 DOI: 10.1016/j.semcancer.2015.02.007]

114 **Joyce JA**, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. *Science* 2015; **348**: 74-80 [PMID: 25838376 DOI: 10.1126/science.aaa6204]

115 **Fridman WH**, Pagès F, Sautès-Fridman C, Galon J. The immune contexture in human tumours: impact on clinical outcome. *Nat Rev Cancer* 2012; **12**: 298-306 [PMID: 22419253 DOI: 10.1038/nrc3245]

116 **Kusmartsev S**, Nefedova Y, Yoder D, Gabrilovich DI. Antigen-specific inhibition of CD8+ T cell response by immature myeloid cells in cancer is mediated by reactive oxygen species. *J Immunol* 2004; **172**: 989-999 [PMID: 14707072]

117 **Liu Y**, Van Ginderachter JA, Brys L, De Baetselier P, Raes G, Geldhof AB. Nitric oxide-independent CTL suppression during tumor progression: association with arginase-producing (M2) myeloid cells. *J Immunol* 2003; **170**: 5064-5074 [PMID: 12734351]

118 **Mazzoni A**, Bronte V, Visintin A, Spitzer JH, Apolloni E, Serafini P, Zanovello P, Segal DM. Myeloid suppressor lines inhibit T cell responses by an NO-dependent mechanism. *J Immunol* 2002; **168**: 689-695 [PMID: 11777962]

119 **Hanahan D**, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57-70 [PMID: 10647931]

120 **Houghton J**, Wang TC. Helicobacter pylori and gastric cancer: a new paradigm for inflammation-associated epithelial cancers. *Gastroenterology* 2005; **128**: 1567-1578 [PMID: 15887152]

121 **Murphy A**, Kelly RJ. Immunotherapy in upper GI malignancies. *Curr Treat Options Oncol* 2015; **16**: 20 [PMID: 25859830 DOI: 10.1007/s11864-015-0336-6]

122 **Cui J**, Li L, Wang C, Jin H, Yao C, Wang Y, Li D, Tian H, Niu C, Wang G, Han W, Xu J, Chen J, Li W. Combined cellular immunotherapy and chemotherapy improves clinical outcome in patients with gastric carcinoma. *Cytotherapy* 2015; **17**: 979-988 [PMID: 25890480]

123 **Sharma P**, Allison JP. The future of immune checkpoint therapy. *Science* 2015; **348**: 56-61 [PMID: 25838373]

124 **Sun J**, Xu K, Wu C, Wang Y, Hu Y, Zhu Y, Chen Y, Shi Q, Yu G, Zhang X. PD-L1 expression analysis in gastric carcinoma tissue and blocking of tumor-associated PD-L1 signaling by two functional monoclonal antibodies. *Tissue Antigens* 2007; **69**: 19-27 [PMID: 17212704]

125 **Muro K**, Bang Y, Shankaran V, Geva R, Catenacci DVT, Gupta S, Eder JP, Berger R, Gonzalez EJ, Ray A, Dolled-Filhart M, Emancipator K, Pathiraja K, Lunceford JK, Cheng DJ, Koshiji M, Chung H. Relationship between PD-L1 expression and clinical outcomes in patients (Pts) with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (Pembro; MK-3475) in KEYNOTE-012. *J Clin Oncol* 2015; **33** (suppl 3; abstr 3)

126 **Bang Y**, Chung H, Shankaran V, Geva R, Catenacci DVT, Gupta S, Eder JP, Berger R, Gonzalez EJ, Ray A, Dolled-Filhart M, Emancipator K, Pathiraja K, Lunceford JK, Cheng DJ, Koshiji M, Muro K. Relationship between PD-L1 expression and clinical outcomes in patients with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) in KEYNOTE-012. *J Clin Oncol* 2015; **33** (Suppl; abstr 4001)(15)

127 **Muro K**, Bang Y-J, Shankaran V, Ravit G, Catenacci DVT, Gupta S, Eder JP, Berger R, Gonzalez EJ, Ray A, Dolled-Filhart M, Emancipator K, Pathiraja K, Lunceford JK, Cheng JD, Koshiji M, Chung HC. Relationship between PD-L1 expression and clinical outcomes in patients (Pts) with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (Pembro; MK-3475) in KEYNOTE-012. *J Clin Oncol* 2015; **33** (3 suppl; abstr 3)

128 **Venerito M**, Nardone G, Selgrad M, Rokkas T, Malfertheiner P. Gastric cancer--epidemiologic and clinical aspects. *Helicobacter*

2014; **19** Suppl 1: 32-37 [PMID: 25167943 DOI: 10.1111/hel.12164]

129 **Gettinger SN**, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, Powderly JD, Heist RS, Carvajal RD, Jackman DM, Sequist LV, Smith DC, Leming P, Carbone DP, Pinder-Schenck MC, Topalian SL, Hodi FS, Sosman JA, Sznol M, McDermott DF, Pardoll DM, Sankar V, Ahlers CM, Salvati M, Wigginton JM, Hellmann MD, Kollia GD, Gupta AK, Brahmer JR. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2015; **33**: 2004-2012 [PMID: 25897158]

130 **Galluzzi L**, Kroemer G, Eggermont A. Novel immune checkpoint blocker approved for the treatment of advanced melanoma. *Oncoimmunology* 2014; **3**: e967147 [PMID: 25941597 DOI: 10.4161/21624011.2014.967147]

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