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Molecular Prognostic Factors in Gastric Cancer

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Abstract

Gastric cancer represents a major health problem worldwide. Literature data have demonstrated that gastric tumors present a high molecular heterogeneity, responsible for the process of carcinogenesis and dissemination. By revealing the molecular subtype of the tumor, it is possible to assess its behavior, the outcome of the patient, and the treatment approach, according to its genetic and epigenetic profile. This chapter aims to highlight some of the many different genetic mutations, epigenetic alterations, as well as aberrant signaling pathways involved in the pathogenesis of stomach cancers, each of these molecular abnormalities acting in a specific stage of the disease. Moreover, the manuscript describes the novel therapeutic agents that target some of these aberrant molecular signaling pathways. Unfortunately, only a few agents are currently part of the standard treatment of gastric cancer, while most of the others remain to prove their therapeutic efficacy in the setting of clinical trials. By discovering the different molecular subtypes of gastric cancer, as well as numerous classes of targeted molecular agents, in the future, we would be able to perform an individualized treatment, associated with maximum efficiency and less costs.

Keywords: gastric cancer, molecular classification, gene expressions-based prognostic scoring system, molecular biomarkers, molecular targeted treatment

1. Introduction

Despite a decline in the incidence in past decades, gastric cancer remains a major health problem globally [1, 2], being the fifth most common type of cancer worldwide, with almost one million new cases estimated to have occurred in 2012, according to Globocan [3]. Furthermore, stomach cancer represents the third leading cause of cancer death in both sexes worldwide (723,000 deaths) [3].

According to the World Health Organization classification, the vast majority of gastric cancers are adenocarcinomas, divided into papillary, tubular, mucinous (colloid), and poorly cohesive carcinomas (including signet-ring cell carcinoma and other variants) [4]. Although it was proposed a long time ago (1965), the Lauren classification is still widely used in clinical practice and subdivides gastric carcinomas into intestinal and diffuse types, associated with different pathogenesis, ways of spreading, and outcome [5]. Unfortunately, these two classification systems have little clinical impact, making the development of classifiers that can define prognosis and guide patient's treatment as an urgent need.

Literature data have demonstrated that the development of gastric cancer is associated in the majority of cases with infectious agents such as the Gram-negative spiral bacterium *Helicobacter pylori* (most often) [6] and Epstein-Barr virus (EBV) (about 9% of all cases of gastric cancer) [7]. Only a small percentage of gastric cancer patients (hereditary cases) are associated with germline mutation in E-cadherin (CDH1) [8] or mismatch repair genes (Lynch syndrome) [9]. In contrast to the familial clustering of gastric cancer, sporadic mismatch repair-deficient gastric tumors present epigenetic silencing of hMLH1 and p16 in the context of a CpG island methylator phenotype (CIMP) [10].

Due to a lack of early specific clinical features, most patients with gastric cancer are diagnosed in advanced stages, resulting in poor 5-year survival rates [11], with a median survival of less than 1 year in case of metastatic stage IV patients [12–14]. Nowadays, survival has gained only minor improvement despite the advances in diagnostic techniques, the multidisciplinary therapeutic management, and the development of novel molecular targeted treatment agents.

Unfortunately, despite modern treatments, less than a quarter of gastric cancer patients survive longer than 5 years after surgery. Gastric cancer represents a complex disease, showing major differences in their tumor cell behavior and responses to chemotherapy.

Recent data have demonstrated that gastric tumors present a high molecular heterogeneity involved both in the process of carcinogenesis and cancer spread. By identifying the specific molecular patterns of the tumor, it is possible to assess its behavior, the prognosis of the patient, and also to decide the most appropriate treatment, a much more personalized one. It is well known that in the pathogenesis of stomach cancers many different genetic mutations, epigenetic alterations, as well as dysregulated signaling pathways are involved, each of these molecular abnormalities acting in a different stage of the disease.

Currently, novel therapeutic agents that target some of these aberrant molecular signaling pathways are already part of the standard treatment of gastric cancer, while others remain to prove their therapeutic efficacy in the setting of clinical trials [15].

2. Oncogenic pathway combinations predict outcome of gastric cancer patients

Gastric cancers are molecularly heterogeneous tumors, showing different dysregulated oncogenic pathways such as E2F, K-RAS, p53, and Wnt/ β -catenin signaling that occur with varying

frequencies in these types of tumors [16, 17]. In contrast to the previous studies that have focused on single pathways [18–20], experimental evidence indicates that, in most cases, carcinogenesis is dictated by complex interactions between multiple pro- and anti-oncogenic signaling pathways [21].

Unlike previous gastric tumor microarray researches relating different gene expression patterns to specific histological features or anatomical location [22], Ooi et al. [23] have succeeded in subdividing gastric cancers into molecularly homogenous subgroups that enable personalizing patient treatments and improving prognosis. It was for the first time when, by using multiple patterns of oncogenic pathway activation, a novel cancer classification approach has been developed, namely a genomic taxonomy of gastric cancer. They developed an *in silico* technique to define activation levels of different oncogenic pathways implemented in context of complex tumor profiles and validated this classification approach using proof-of-concept examples from breast cancer. Afterward, they have applied this method to gastric tumors and evaluated 11 oncogenic pathways previously known to be involved in gastric tumorigenesis [16–20, 24–27]. They have assessed over 300 primary stomach cancers coming from three independent patient cohorts. The researchers have discovered three oncogenic pathways, nuclear factor- κ B (NF- κ B), Wnt/ β -catenin, and proliferation/stem cell, which were dysregulated in over 70% of gastric cancers and validated the patient stratification *in vitro* using gastric cancer cell lines. Patient classification by oncogenic pathway combinations revealed significant survival differences, suggesting a major role for pathway combinations in determining gastric cancer behavior. Therefore, gastric cancer can be taxonomized into biologically, molecularly, and clinically significant subtypes.

The authors defined concomitant activation of different oncogenic pathways, such as of E2F, MYC, p21 (repression), and the “proliferation/stem cell” pathway, most likely due to increased cellular proliferation in tumor cells [28], and in stem cells (embryonic stem cells (ESCs)) [29]. Co-activation of different pathways demonstrates the ability of the cancer cell to dictate the activity of multiple pathways.

The study showed that NF- κ B signaling may be elevated in a significant proportion of gastric cancers probably due to *H. pylori* infection [30]; therefore, targeted NF- κ B inhibitors may represent an appropriate treatment for gastric tumors. Pathway-based taxonomies may be useful in developing potential pathway inhibitors and novel targeted therapies that would be studied on prestratifying patients using molecular or pathologic criteria.

3. Molecular classification of gastric cancers by “The Cancer Genome Atlas (TCGA)” project

The goals of “The Cancer Genome Atlas (TCGA)” project were to develop a molecular classification of gastric cancer with clinical impact and to detect the major dysregulated pathways of distinct subtypes of gastric cancer [31].

The researchers have analyzed fresh frozen gastric adenocarcinoma primary tumor tissue from 295 patients with no prior chemo- or radiotherapy, using six genomic and molecular platforms

including genome/exome/methylome DNA sequencing, RNA sequencing, and protein arrays. Germline DNA from blood/nonmalignant gastric mucosa was used as a control for detecting somatic alterations. Nonmalignant gastric samples were also collected for DNA methylation ($n = 527$) and expression ($n = 529$) assessment.

Tumors were first subgrouped by EBV-positivity (9%), then by MSI-high status (named MSI; 22%), and the remaining tumors were classified by degree of aneuploidy into genomically stable cancers (20%) or those exhibiting chromosomal instability (CIN; 50%).

This project revealed that the vast majority of the diffuse histological subtype belongs to the genomically stable group. CIN tumors were mostly located in the gastroesophageal junction/cardia, whereas most of the EBV-positive tumors were located in the gastric fundus or body. Genomically, stable tumors were diagnosed at an earlier age compared to MSI tumors; most EBV-positive cases were male (81%), in concordance with previous results [32].

As previously reported [33], all EBV-positive tumors exhibited extreme CIMP, distinct from that in the MSI subtype [10] (CDKN2A promoter hypermethylation versus MLH1 hypermethylation) [34]. Furthermore, in concordance with prior data [35, 36], the study revealed a strong predilection for PIK3CA mutation in EBV positive tumors, with nonsilent PIK3CA mutations found in 80% of this subgroup ($P < 0.001$), that could be targeted using PI(3)-kinase inhibition.

By assessing 63 hypermutated tumors, there were identified 37 significantly mutated genes including TP53, KRAS, ARID1A, PIK3CA, ERBB3, PTEN, and HLA-B. The analysis of genes mutated within MSI subgroup of gastric cancers revealed alterations in major histocompatibility complex class I genes, a beneficial event for hypermutated tumors by dysregulating antigen presentation to the immune system.

Through the analysis of the 215 nonhypermutated cancers, there were identified 25 significantly mutated genes, including TP53, ARID1A, KRAS, PIK3CA, and RNF43, genes involved in the β -catenin pathway, the TGF- β pathway, RASA1, and ERBB2 (therapeutic target).

In addition to PIK3CA mutations, EBV-positive tumors had frequent ARID1A and BCOR (encoding an anti-apoptotic protein) gene mutations. TP53 mutations were detected in 71% of CIN tumors. The genomically stable subtype presented a high frequency of CDH1 somatic mutations and inactivating ARID1A mutations. RHOA mutations were detected almost exclusively in genomically stable tumors. In its activated form, RHOA controls cellular motility [37, 38] and activates STAT3 to initiate tumorigenesis [39, 40]. It seems that the activation of RHOA-driven pathways contribute to the invasive phenotype of diffuse gastric cancer.

Oncogenic signaling pathways, including candidate therapeutic targets such as receptor tyrosine kinases (RTKs), RAS, and PI(3)-kinase signaling were characterized. EBV-positive tumors contained PIK3CA mutations and recurrent JAK2 and ERBB2 amplifications. MSI cases presented some mutations in PIK3CA, ERBB3, ERBB2, and EGFR [41]. The genomically stable subtype expressed recurrent RHOA and CLDN 18 events. CIN tumors showed genomic amplifications of RTKs that may be therapeutically blocked. Recurrent amplification of the gene encoding ligand VEGFA and frequent amplifications of cell cycle mediators highlight the role of the VEGFR2 targeting antibody (the already approved agent ramucirumab) [42] and suggest the possible efficacy of cyclin-dependent kinases.

All the subtypes (to a lesser degree the genomically stable tumors) showed increased expression of components involved in the mitotic process, such as AURKA/B and E2F, DNA damage response pathways, targets of MYC activation, and FOXM1 and PLK1 signaling pathways. In addition, the genomically stable subtype exhibited elevated expression of cell adhesion pathways, the B1/B3 integrins, syndecan-1 mediated signaling, and angiogenesis-related pathways, suggesting more potential therapeutic targets, including the aurora kinases (AURKA/B) and polo-like (PLK) family members. The elevated IL-12-mediated signaling expression, along with evidence of PD-L1/2 overexpression in EBV-positive tumors, suggests the importance of immune checkpoint inhibitors evaluation in this subtype of gastric cancer [31].

Therefore, the four major genomic subtypes defined by “The Cancer Genome Atlas (TCGA)” may provide a guide to molecular targeted agents that should be assessed in clinical trials for distinct populations of gastric cancer patients.

4. Gene-expression signatures as markers for cancer grades and stages

Cui et al. [43] developed for the first time a computational study aimed to identify a set of genes whose expression patterns can distinguish among gastric cancers of different grades, with the aim of developing a gene expression-based grading system for gastric cancer.

A total of 452 genes were found to be differentially expressed in the 54 gastric cancer specimens studied. It was revealed that genes whose expression changes correlated with the degree of differentiation are highly enriched among secreted/membrane proteins, involved in signaling pathways (ErbB, FAS, NOD-like receptor, PPAR and Wnt signaling), as well as cell adhesion molecules (CAMs) and tight junctions.

The researchers identified a 19-gene group that can distinguish between well versus poorly differentiated tumors (overall agreement at 79.2%), based on the expression fold change in cancer versus control tissues. The protein products of these 19 genes mentioned above are involved in cell growth, differentiation (IL17RB, SMYD1, SHCBP1), and motility (ACTG2), angiogenesis (ADIPOQ), tumorigenesis (ECRG4), matrix protein synthesis (COL3A1, COL6A3), and extracellular communication.

Moreover, there is a 198-gene group which can distinguish among the four different cancer grades (well-, moderate-, poorly-, and un-differentiated) and the control group according to their gene expression (74.2% accuracy). In addition, the functions of the 198-gene group involve cell division, immune response control, signal transduction, and transcription.

There were also analyzed grade-specific gene signatures. LAPTM4B gene has demonstrated a high classification accuracy for tumor and control samples in the well-differentiated group (AUC = 0.97), a gene known to be essential for cell growth and survival; its up-regulation has been previously found to be correlated with the degree of differentiation of hepatocellular carcinoma [15]. Similarly, they have also identified single gene discriminators for each grade group.

Cui et al. have identified two multigene signatures that can distinguish early stage (stages I and II) and advanced stage gastric cancer (stages III and IV), namely a 10-gene group (CPS

1+DEFA5+DES+DMN+GFRA3+MUC17+OR9G1+REEP3+TMED6+TTN) and a 9-gene group (DPT+EIF1AX+FAM26D+IFITM2+ LOC401498+OR2AE1+PRRG1+REEP3+RTKN2). The overall classification accuracy obtained on the three groups, early, advanced stomach cancer, and control, was 71.4%. Among the early-stage signature genes, there are signaling and immune-related genes that may represent the early changes of tissue cells during carcinogenesis. A few genes were found to be in both the cancer grading and staging signatures (e.g., CPS1, DES, GFRA3, TMED6, and DPT), indicating some functional connection between cancer differentiation and progression. LANCL3, MFAP2, and PPA1 were genes highly correlated with different pathological stages, showing consistent upregulation or downregulation along with tumor progression.

There were found 62 genes with consistent differential expression in gastric cancer versus control tissues, related to extracellular processes such as CAMs, tight junction, cytokine-cytokine receptor interaction, and ECM receptor interaction, the plasminogen activation cascade, as well as signaling pathways (Wnt and Integrin signaling) related to the control of cell growth and proliferation.

The study revealed that the differential expression patterns of 15 genes are highly specific to gastric cancer (e.g., GKN2, CLDN7, THY1, GIF, and PGA4), while most others are general to numerous cancer types, including a few members of the collagen gene family, the carcinoembryonic antigen-related cell adhesion molecule, matrix metalloproteinases, topoisomerase, and secreted phosphoprotein. Only three genes, CLDN7, CLDN1, and DPT, were significantly differentiated in all grades and stages of gastric neoplasia; the consistent expression of dysregulation across all the cancer subgroups may indicate their involvement in major biological pathways leading to cancer development and progression. Dermatotontin (DPT) represents an extracellular matrix protein that creates a link between the dermal fibroblast cell surface and its extracellular matrix, previously found to be downregulated in both uterine leiomyomas and keloids [44].

5. Gene expression-based prognostic scoring systems

Data from literature revealed the important role of the molecular biological characteristics of gastric cancer in the prognosis of the patients and determination of a most suitable clinical therapy for these patients. There are some dysregulated gene expressions found to be associated with the prognosis, such as the overexpressions of HER2 [45] and p53 genes [46]. Also, the hypoxia inducible factor-1 alpha (HIF-1 α) seems to be related to the early development of gastric tumor [47].

Takeno et al. [48] elaborated a gastric cancer regulatory network with CDKN1A as the node and examined the expression levels of seven genes in different stages of gastric cancer (iMMP7, SPARC, SOD2, INHBA, IGFBP7, NEK6, and LUM). Their results showed that these seven genes were activated as the disease progressed, suggesting the association of these genes with cancer development.

Wang et al. [49] proposed the hypothesis that molecular features are determining the tumor behavior and can be used to establish prognostic scoring system. Based on the Cancer Genome Atlas (TCGA) data and using different multivariate clustering techniques to identify the key

genes for prognostic classification of these analyses, they created a 53-gene expression prognostic scoring system and successfully implemented it to predict overall survival (OS) in the TCGA and the GSE15459 data (Gastric Cancer Project 2008).

These prognostic scores are able to distinguish between patients with good prognosis and bad prognosis, respectively. These genes include TNFAIP2 [50], FGFR4 [51, 52], CXCL10 [53], CEP55 [54], CXCL1 [55], LIMK1 [56], LAMC2 [57], APOE [58], INHBA [59], OSMR [60], APOC1 [61], KLF4 [62], MMP14 [63], ADH1C [64], COL6A3 [65], CCT2 [66], NOL8 [67], EPHB4 [68], and MCM2 [69]. The high expression of FGFR4 protein was previously reported to be associated with a poor prognosis in patients with advanced gastric tumors [51], while the FGFR4 Gly388Arg polymorphism proved to be a useful prognostic marker for early gastric cancer patients [52]. CEP55 functions in cell cycle regulation; knockdown of CEP55 led to diminished proliferation in gastric cancer cell lines acting on the PI3K/AKT signaling pathway and the expression of cyclin-related proteins, suggesting a potential role of CEP55 as a target used in gastric cancer treatment [54]. Some studies show that MCM2 expression levels are a useful tool for the diagnosis and prognosis of gastric tumors [69] and that SNPs in miRNA-binding sites may represent susceptibility markers for gastric cancer [50]. Chemokine (C-X-C motif) ligand (CXCL1) seems to play a major role in tumor metastasis; it has been previously reported that its expression is associated with hepatocellular carcinoma survival [55]. The study of Wang showed that CXCL1 is also involved in gastric cancer overall survival. ATP-binding cassette E1 (ABCE1) known to play a crucial role in the metastasis of lung cancers, and therefore, a potential therapeutic target in this setting [70], was also elevated in gastric tumors and predicted the prognosis of patients.

6. The role of molecular biomarkers in the treatment of gastric cancer

Besides the few standard chemotherapeutic agents having efficiency in the treatment of gastric cancer, molecular targeted therapy for gastric cancer is limited, including mainly agents acting on the HER2 and vascular endothelial growth factor (VEGF) pathways [71].

On the other hand, until present, the only used markers for gastric cancer in clinical practice are carcinoembryonic antigens, CA 19-9 [72] and CA-72 [73], with questionable efficacy. Nowadays, there are multiple molecular biomarkers that had shown their accuracy as diagnostic or prognostic tools but still need further validation for implementing in the routine clinical practice, predicting the response to chemotherapy, posttreatment survival, or disease recurrence.

6.1. Molecular biomarkers predicting the treatment response

The future of cancer treatment aims for a personalized medicine, treating the patient according to his genetic and epigenetic profile, and identifying the occurrence of chemoresistance using specific markers in order to obtain maximum treatment efficiency with lower costs [74]. Heretofore, the vast majority of data regarding predictive biomarkers derive from small retrospective studies; therefore, these biomarkers cannot be used for the moment in clinical practice, outside the setting of clinical trials.

6.1.1. Genetic markers

Lin et al. [75] described the link between integrated genomic signatures, the biological functions, and the background molecular pathways [76]. There were developed prediction models of activity for eight anticancer drugs [76], along with clinical responses to 5-FU (cDNA microarray analysis) [77] and resistance-related genes such as dihydropyrimidine dehydrogenase (DPD) and HB-EGF-like growth factor genes [78]. Also, it was reported that metallothionein-IG and heparin-binding epidermal growth factor-like growth factor (HB-EGF), glutathione-S-transferase, and cyclooxygenase-2 genes were cisplatin-resistance-related and genes such as ADAM22, CYR61, FN1, SPHK1, and GNAI1 were linked to doxorubicin response [79]. Furthermore, in some studies, the genetic polymorphism was linked to the response of 5-FU, cisplatin [80], and paclitaxel [81].

Cristescu et al. described four molecular subtypes of gastric tumors related to disease progression and prognosis: the mesenchymal-like type with highest recurrence frequency, microsatellite-unstable tumors that are hyper-mutated and are associated with the best overall prognosis, tumor protein 53 (TP53)-active and TP53-inactive types that have intermediate prognosis and recurrence [82].

As already mentioned, researchers from “The Cancer Genome Atlas (TCGA)” project proposed a molecular classification dividing gastric tumors into four subtypes, useful for stratifying patients and choosing the appropriate targeted treatment: (1) Epstein-Barr virus positive tumors: PIK3CA mutations, DNA hypermethylation, and amplification of JAK2, CD274, and PDCD1LG2; (2) microsatellite unstable tumors: increased mutation rates, including genes encoding targetable proteins involved in oncogenic signaling pathways; (3) genomically stable tumors: mutations of RHO-family GTPase-activating proteins; (4) tumors with chromosomal instability: marked aneuploidy and amplification of receptor tyrosine kinases [41].

6.1.2. Epigenetic markers

MicroRNA was linked by some studies to the resistance to trastuzumab [83], the pathologic response to neoadjuvant chemotherapy [81], and the chemotherapeutic response of cisplatin/fluorouracil [84].

Long noncoding RNAs (lncRNAs) are potential biomarkers for gastric cancer especially using minimally invasive routes (blood, gastric secretions) [85]. The lncRNA MRUL (Multidrug resistance (MDR)-related and upregulated lncRNA) originated from tissue samples was associated with multidrug chemotherapeutic resistance [86].

Methylation-related biomarkers: methylation of Bcl-2/adenovirus E1B 19 kDa-interacting protein 3 and death-associated protein kinase (DAPK) correlate with poor response to fluoropyrimidine-based chemotherapy [87]; decreased methylation of the bone morphogenetic protein 4 (BMP4) correlates with cisplatin resistance, and the regain of treatment response may be achieved using targeted inhibition of BMP4 [88]. Also, the increased expression of Reprimo (a highly glycosylated cellular protein) due to methylation was associated with a lower response to cisplatin/5-FU chemotherapy [89].

6.1.3. Protein markers

Cellular enzymatic activity: Cellular enzymatic activity was correlated with the chemotherapeutic resistance, thymidylate synthetase (TS) and DPD being associated with tumor sensitivity to 5-FU-based regimens [90].

Cellular proteins: Serum level of alpha-1-microglobulin/bikunin precursor (AMBP) protein, as well as increased expression of β -tubulin III protein, was demonstrated to predict lower chemotherapeutic response to paclitaxel-capecitabine schemes [91, 92]; regenerating gene family member 4 (Reg IV or REG4) predicted resistance to 5-FU-based regimens [93]; fork-head box M1 (FOXM1) transcription factor seems to predict resistance to docetaxel [94]; and dysregulated ribosomal proteins were found to enhance vincristine, adriamycin, and 5-FU resistance [95].

6.2. Molecular aberrations as potential therapeutic targets

Although a great number of targeted therapies belonging to different classes of drugs have been investigated in both preclinical and clinical trials for the treatment of gastric cancer, their use in clinical practice is still limited for the moment.

6.2.1. Anti-HER2 therapies

The HER2 receptor belongs to the EGFR/HER family, having an important role in signal transduction, cell growth, and differentiation [96]. Recent data have revealed HER2 overexpression in 7-34% of patients with gastroesophageal adenocarcinomas and an efficiency of anti-HER2 therapies for both in vitro and in vivo gastric cancer models [97].

6.2.1.1. Monoclonal antibodies targeting HER-2

Trastuzumab (Herceptin) is a humanized anti-HER2 monoclonal antibody; its efficacy for gastric cancer being demonstrated in a phase III trial (ToGA) that randomized naive patients with metastatic or locally advanced unresectable gastric adenocarcinoma with overexpressed HER2 to chemotherapy associated with trastuzumab versus classic chemotherapy [98]. The results of this study demonstrated that adding trastuzumab to standard chemotherapy could increase the OS of these patients to more than 1 year. Currently, the combination of trastuzumab with capecitabine/5-fluorouracil and cisplatin is recommended for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach, defined as an immunohistochemical (IHC) 3 positive result or an IHC 2 and fluorescence in situ hybridization (FISH) double positive result.

There are several other ongoing studies of trastuzumab treatment in advanced gastric cancer, such as the HELOISE trial, the phase II study NCT01130337, the TOXAG study, the HERFLOT study, and the phase III trial RTOG 1010. Two phase II clinical trials confirmed the efficacy of trastuzumab combined with XELOX (capecitabine/oxaliplatin) or SP (S-1/cisplatin), respectively, for advanced gastric cancer treatment [99, 100].

The second generation of anti-HER2 agents includes Pertuzumab, which binds to a distinct site on the HER2 receptor. This drug is currently being investigated in the phase III JACOB study in patients with HER2-positive metastatic or locally advanced gastric cancer. [101]. Trastuzumab emtansine (TDM-1) is another second-generation agent currently assessed in a second-line phase II/III trial in advanced gastric cancer [102].

6.2.1.2. Tyrosine kinase inhibitors (TKIs) of HER2

Lapatinib is an oral TKI of EGFR and HER2, which was studied in combination with standard chemotherapy in patients with HER2-positive advanced gastric adenocarcinomas in the phase III LOGIC study [45] and in the phase III Asian TyTAN trial without demonstrating an improvement in OS. Currently, the MAGIC-B study is evaluating the addition of lapatinib to perioperative epirubicin, cisplatin, and capecitabine (ECX) chemotherapy in patients with HER2 (+) gastric cancers [103].

6.2.2. EGFR inhibition

EGFR overexpression is found in 30-50% of gastroesophageal tumors, associated with a more aggressive behavior [104].

6.2.2.1. Anti-EGFR monoclonal antibodies

Cetuximab (Erbix) is a chimeric monoclonal anti-EGFR antibody. Unfortunately, clinical trials, including the phase III EXPAND trial did not demonstrate a PFS or OS benefit for cetuximab as first-line chemotherapy in the treatment of gastric cancer [105, 106].

Panitumumab is a fully human monoclonal anti-EGFR antibody without a demonstrated efficacy in naive patients with advanced esophagogastric cancer according to the results of clinical trials including the REAL-3 study [107, 108].

Nimotuzumab is a recombinant humanized monoclonal antibody that was evaluated in a double-blind phase II trial [109] including patients with advanced gastric cancer who received nimotuzumab plus irinotecan versus irinotecan alone, showing no difference in PFS or OS between these two groups. Nevertheless, the EGFR2+/3+ subgroups presented a significant benefit when treated with nimotuzumab.

6.2.2.2. TKIs of EGFR

Gefitinib is an oral EGFR TKI currently assessed in a phase I/II study, in combination with chemoradiation, in subjects with resectable gastric cancer [110], in a phase II study in patients with unresectable and/or metastatic gastric carcinomas, and also in a phase III trial in patients with advanced gastro-esophageal junction cancers after progression on chemotherapy [111]. The results of these studies could define the role of this agent in gastric cancer treatment.

Erlotinib (Tarceva) is an oral EGFR TKI, shown to be active in a phase II trial only in patients with gastro-esophageal cancer, but not in those with gastric cancer [112].

6.2.3. VEGF/VEGF receptor inhibition

Angiogenesis is an essential event in tumor growth and spread. VEGF has demonstrated a major role in tumor angiogenesis, growth, and metastasis in numerous tumors, including gastric cancer [113], therefore, being considered an essential therapeutic target. Data revealed that VEGF expression correlates with the clinical stage and prognosis of gastric cancer [114].

6.2.3.1. Anti-VEGF monoclonal antibodies

Bevacizumab (Avastin) efficacy as a first-line treatment in combination with cisplatin-based chemotherapy for advanced gastric cancer was evaluated in the phase III AVAGAST trial (Avastin in gastric cancer) [115], which demonstrated a median PFS and overall response rate significantly improved in the bevacizumab group, but without a significant benefit in OS. Another phase III study, AVATAR, also found that bevacizumab combined with capecitabine/cisplatin chemotherapy did not significantly improve OS in patients with advanced gastric cancer [116]. Possibly, the negative results of these studies might have resulted from not having selected the most molecularly suitable gastric cancer patients.

The MAGIC-B study is currently assessing the role of bevacizumab for perioperative chemotherapy in resectable adenocarcinoma of the stomach, [117]. Hopefully, this trial will allow for the detection of predictive biomarkers that could identify the subset of patients with the greatest potential benefit from the use of perioperative VEGF-A inhibitory monoclonal antibody [118].

Currently, the safety and efficacy of adding bevacizumab to taxane-based chemotherapeutic regimens irinotecan [119] or anti-Her2-targeted treatment in advanced/metastatic gastric cancer is being evaluated in several clinical trials with pending results [120].

6.2.3.2. Anti-VEGF receptor monoclonal antibodies

Ramucirumab is a human monoclonal antibody that inhibits VEGFR-2. It was approved by the FDA as a single agent in gastric cancer after progression on a platinum- or fluoropyrimidine-containing regimen, based on the phase III REGARD study (second-line ramucirumab monotherapy for advanced gastric adenocarcinoma), which found significantly longer OS for ramucirumab versus best supportive care (BSC) [42]. Furthermore, the results of a phase III clinical trial of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the second-line treatment of metastatic gastric adenocarcinoma (RAINBOW trial) revealed significantly longer PFS and OS for the ramucirumab group [121], also leading to approval by the FDA of ramucirumab in combination with paclitaxel as a second-line therapy. Therefore, ramucirumab is for the moment, the only antiangiogenic agent that has been approved for the treatment of gastric carcinoma [122].

Endostar is a novel recombinant human endostatin, which was investigated [123] combined with SOX (S-1/oxaliplatin) for the first-line treatment of patients with advanced gastric cancer; the results showed significantly better PFS for the group including Endostar. More studies for the efficacy of Endostatin in stomach cancer settings are needed.

6.2.3.3. TKIs of VEGF

Apatinib is an anti-VEGF-2 small molecule TKI evaluated in China [124]. Phase II and III studies have shown that apatinib was the first discovered anti-VEGF-2 molecule TKI with benefits for Asian patients with advanced gastric cancer [125], representing a significant progress for third-line treatment, although it prolonged OS by less than 2 months. Further studies are needed to assess the efficacy and safety of this agent in Caucasians. Based on these positive results, apatinib was approved by the Chinese Food and Drug Administration (CFDA) for metastatic adenocarcinoma of the stomach after second-line chemotherapy progression [126].

Sunitinib represents an oral multitargeted TKI of VEGFR, PDGFR, c-KIT (stem cell factor receptor), rearranged during transfection, and FMS-like tyrosine kinase-3 receptor; when administrated in a phase III trial as second-line monotherapy in patients with advanced gastric cancer, it showed a median OS of 6.8 months [127]. The efficacy of sunitinib in advanced gastric cancer was also confirmed by other studies [128].

Sorafenib (Nexavar) is a multitargeted TKI. A phase II study using sorafenib combined with docetaxel and cisplatin as a second-line treatment for gastric cancer patients obtained very long median PFS and median OS [129], although other clinical trials have been terminated early because of low response rates [130].

Pazopanib is an oral agent that inhibits angiogenesis through multiple pathways (VEGFR, PDGFR, and c-KIT), which is currently under investigation in two phase II trials in patients with advanced gastric tumors: the PaFLO trial (FLO ± pazopanib as first-line treatment) [131] and another trial associating pazopanib with capecitabine and oxaliplatin [132].

Regorafenib is an oral multikinase; a phase II trial investigating the efficacy of regorafenib in the treatment of refractory advanced esophagogastric cancer demonstrated a significantly longer median PFS (11 wk versus 3.9 wk) and OS (25 wk versus 19.4 wk) for the regorafenib group versus the placebo group [133] but with serious drug-related toxicity. The role of regorafenib in advanced gastric cancer will be better assessed by the ongoing phase I and II trials.

6.2.4. IGF-1 inhibition

IGF-1 receptor (IGF-1R) is a transmembrane tyrosine kinase receptor promoting tumor angiogenesis, growth, and metastasis in several cancers, including gastroesophageal tumors [134].

Figitumumab is a humanized IgG2 monoclonal antibody against IGF-1R. Some phase I clinical trials have assessed the overall safety and pharmacokinetic profile of figitumumab administered in patients with advanced solid tumors [135]. Its role in gastric cancer treatment requires further studies.

6.2.5. Fibroblast growth factor TKIs

Fibroblast growth factor (FGF) and its signaling receptors have a major role in cell proliferation, differentiation, and transformation [136].

Although AZD2171 (AZD), a potent oral FGF TKIs, led to tumor inhibition in animal models of gastric cancer, unfortunately, the results of a phase II study [137] showed no statistically significant difference in PFS for FGFR2 amplified gastric cancer patients treated with AZD.

A phase I, first in-human study of JNJ-42756493 (a pan-FGFR TKI) was initiated in advanced solid tumor patients, including gastric cancer, showing that this agent had excellent pharmaceutical properties and safety profile [138].

Ki23057 is an oral TKI broad-range FGF TKI that inhibits the proliferation of gastric scirrhou cancer cells presenting FGFR2 gene amplification. The study of Qiu et al. found that the FGFR2 inhibitor Ki23057 might be therapeutically promising for treating drug-resistant gastric cancer cells, especially when used in combination with other chemotherapeutic drugs. [139].

We expect the results of the ongoing phase I and II clinical trials using TKI such as dovitinib, brivanib, and INCB054828 (FGF inhibitors) in patients with advanced gastric cancer to add new informations regarding the role of FGF inhibitors in this type of tumor [140].

6.2.6. Hepatocyte growth factor/c-MET (mesenchymal-epithelial transition factor receptor) inhibitors

C-MET and its signal pathway activation determine gastric cancer cell proliferation, survival, and migration [141].

6.2.6.1. Anti-HGF/c-MET monoclonal antibodies

Rilotumumab is a human monoclonal antibody directed against HGF, demonstrated to show efficacy in locally advanced/metastatic gastric cancer patients with MET overexpression by immunohistochemistry (phase II study). Unfortunately, due to the increased toxicity of the agent and treatment-related deaths in the RILOMET-1 trial, all of the clinical trials investigating the role of rilotumumab in gastric tumors, including the phase III RILOMET-1 (with ECX) and RILOMET-2 (with cisplatin and capecitabine) studies, were interrupted.

Onartuzumab is a humanized antibody directed against MET that is also being investigated in a first-line, phase III trial in MET-positive, HER2-negative gastroesophageal patients in combination with mFOLFOX6. The results of this study revealed unfortunately that this treatment could not prolong OS [142].

6.2.6.2. Anti-HGF/c-MET tyrosine kinase

Foretonib is an oral molecule inhibitor of c-MET and VEGFR-2A, which was investigated in a phase II study as a single agent in patients with metastatic gastric cancer, demonstrating good tolerability but only minimal antitumor efficacy [143].

6.2.7. PI3 kinase/mammalian target of the rapamycin pathway inhibition

Upregulation of the PI3k/Akt/mTOR pathway was associated with poor prognosis and could be implicated in the chemoresistance of gastric cancer [144].

Everolimus is an oral mTOR inhibitor demonstrated to have efficiency in both phase I and phase II studies, which have shown that everolimus monotherapy had a good response rate for advanced gastric cancer patients in the second-line setting [145, 146]. Unfortunately, the phase III GRANITE-1 trial investigating the everolimus monotherapy as a second-/third-line in patients with advanced gastric cancer did not show OS benefit, only the association of severe adverse reactions [147]. Therefore, the use of this agent in the treatment of gastric cancer needs further investigations.

Rapamycin has shown efficiency in preclinical studies and animal models against gastric cancer, increasing also the effectiveness of chemotherapeutic drugs [148]; nevertheless, its use in gastric cancer does not have enough support yet.

6.2.8. PARP inhibitors

These agents were demonstrated to prevent the cancer cell's single stranded break repair mechanism, leading to tumor cell death [149].

A phase II trial in metastatic/recurrent gastroesophageal cancer studied the effectiveness of administering the PARP inhibitor olaparib as a second-line treatment [150], demonstrating improved OS. There is also an ongoing phase III study of second-line treatment using paclitaxel with or without olaparib in advanced gastric cancer patients [151].

Veliparib was developed to increase the effectiveness of DNA-damaging therapies, such as chemo- or radiotherapy. A study of the efficacy of veliparib associated with the FOLFIRI regimen in gastric cancer is pending results [152].

6.2.9. Immunotherapy/immuno-checkpoint blockade

Because it was revealed that tumors evade host immune recognition [153], immunotherapy has emerged as a novel field of antitumor treatment, which acts by using the blockage mechanism of the inhibitory immune regulatory pathways. New agents targeting immune checkpoints, programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1), have been recently investigated.

Ipilimumab blocks the inhibitory receptor called cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Unfortunately, a phase II trial assessing the efficacy of ipilimumab after first-line chemotherapy in unresectable locally advanced or metastatic gastric cancer patients revealed no statistically significant improvement in OS [154].

Nivolumab blocks the interactions between PD-1 and PD-L1 stimulated immune function *in vitro*, showing antitumor activity in preclinical models. A phase I/II study of nivolumab monotherapy versus nivolumab combined with ipilimumab in patients with advanced or metastatic solid tumors, including gastric cancer, is still ongoing [155]. Interim results revealed that nivolumab monotherapy demonstrated encouraging antitumor activity in heavily pretreated gastric cancer patients [156]. Furthermore, a phase III trial is currently assessing the tolerability and efficacy of nivolumab in patients with unresectable advanced or recurrent gastric cancer refractory to standard chemotherapy [157].

Pembrolizumab is an agent that blocks the binding of PD-1 to PDL-1, demonstrated to have good tolerability, as well as anti-tumor activity in a phase 1 study including recurrent and metastatic gastric adenocarcinoma patients with PD-L1 (+) tumors [158]. Other phase I-III trials are investigating this agent in advanced gastric cancer [159, 160], with the aim of investigating the molecular subtypes of gastric tumors through integrative genomic analysis [161]. Some phase I/II studies are assessing its efficacy in combination with other classes of agents (anti-HER2 or anti-VEGFR monoclonal antibodies, multitargeted TKIs) [162–165].

Durvalumab, an anti-PDL-1 drug, has shown some activity in gastric cancer treatment [166]. The combination of durvalumab and tremelimumab (anti-CTLA-4) plus first-line chemotherapy is currently being investigated in advanced solid tumors (including gastric cancers) [167, 168].

6.2.10. *Guanylyl cyclase C inhibitors*

Guanylyl cyclase C (GCC) is a transmembrane cell surface receptor, expressed both on normal intestinal tissue and on the tumor cells of gastrointestinal neoplasias. MLN0264 consists of a human monoclonal antibody targeting GCC, demonstrating good tolerability of the drug and promising results in a phase I trial in patients with gastrointestinal malignancies expressing GCC [169, 170]. Phase I-II studies of MLN 0264 in previously treated patients with metastatic/recurrent gastric GCC (+) cancers are currently recruiting patients [171, 172].

6.2.11. *Inhibitors of the tumor cell cycle*

In gastric tumors, there is an alteration of cell cycle regulatory mechanisms [173]. Flavopiridol is a cyclin-dependent kinase inhibitor, unfortunately demonstrated to have low efficacy and serious adverse effects in gastric cancer [174]. Because of its low activity as a single agent, it must be investigated in combination with other chemotherapeutics.

6.2.12. *Agents inducing tumor cell apoptosis*

The induction of tumor cell apoptosis seems to be a promising target in cancer treatment. NF- κ B expression showed to be positively correlated with the degree of the tumor and is negatively correlated with cancer prognosis.

Bortezomib is a highly potent proteasome inhibitor that acts by inhibiting activation of the NF- κ B signaling pathway. Preclinical studies have demonstrated an effect of growth inhibition of this agent in combination with standard chemotherapy for gastric cancer [175, 176]. However, phase II studies assessing the efficacy of bortezomib either alone or in combination with irinotecan or paclitaxel plus carboplatin showed no positive results [177–179].

6.2.13. *Matrix metalloproteinase inhibitors*

The aberrant synthesis of matrix metalloproteinase (MMPs) leads to local tumor invasion by destroying the extracellular matrix and the basement membrane. Literature data have previously associated the high expression of some MMPs with a poor prognosis of gastric cancer [180, 181].

Marimastat is a broad-spectrum MMP. There was a study in patients with nonresectable gastric adenocarcinoma that revealed the first indication of a survival benefit for an MMP

inhibitor, supporting a possible role for this agent as a maintenance treatment following chemotherapy [182].

7. Conclusion

Gastric cancer represents a major health problem worldwide, with most of the patients being diagnosed in advanced stages of the disease, associated with poor prognosis. Gastric tumors are molecularly heterogeneous; therefore, it is of major importance to identify the molecular subtype of the tumor and specific molecular biomarkers in order to assess the prognosis of the patient.

Furthermore, it is essential to identify molecular biomarkers that could predict treatment response according to the genetic and epigenetic profile of the patients and also to identify the occurrence of chemoresistance using specific markers, in order to obtain maximum response. The discovery of the molecular background of gastric cancer leads to the development of novel molecular targeted treatments. Heretofore, among the multitude of classes of agents targeting different signaling pathways, such as VEGF, EGFR, HER-2, IGF, immunotherapy, and mTOR pathways, only anti-HER2 monoclonal antibody trastuzumab and anti-VEGFR antibody ramucirumab have been approved for the treatment of advanced gastric cancer. Also, Apatinib, an anti-VEGFR2 TKI demonstrated efficiency in Chinese gastric cancer patients, receiving approval for treatment in this setting. Moreover, there are other classes of agents such as immunotherapy drugs (e.g., Pembrolizumab) that showed encouraging results in clinical trials, but we have still to wait for the final results until implementing them in clinical practice.

Therefore, further clinical studies are needed to demonstrate the effectiveness of molecular targeted treatments in order to have a personalized treatment approach and to improve the outcome of gastric cancer patients.

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References

- [1] Ferro A, Peleteiro B, Malvezzi M, Bosetti C, Bertuccio P, Levi F, Negri E, La Vecchia C, Lunet N. Worldwide trends in gastric cancer mortality (1980-2011), with predictions to 2015, and incidence by subtype. *European Journal of Cancer* 2014;**50**:1330-1344. PMID: 24650579 DOI: 10.1016/j.ejca.2014.01.029
- [2] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: A Cancer Journal for Clinicians* 2011;**61**:69-90. PMID: 21296855 DOI: 10.3322/caac.20107
- [3] Globocan 2012. Estimated cancer incidence, mortality and prevalence worldwide in 2012. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
- [4] WHO Classification of Tumours of the Digestive System. 4th ed. International Agency for Research on Cancer; 2010
- [5] Lauren, P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. *Acta Pathologica et Microbiologica Scandinavica* 1965;**64**:31-49. PMID:14320675
- [6] 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. *New England Journal of Medicine*. 2001;**345**:784-789. DOI: 10.1056/NEJMoa001999
- [7] Fuentes-Pananá EM, Morales-Sánchez A. Epstein-Barr Virus-associated Gastric Cancer and Potential Mechanisms of Oncogenesis. *Current Cancer Drug Targets*. 2016 Sep 26. [Epub ahead of print] PMID: 27677953
- [8] Richards FM, McKee SA, Rajpar MH, Cole TR, Evans DG, Jankowski JA, McKeown C, Sanders DS, Maher ER. Germline E-cadherin gene (CDH1) mutations predispose to familial gastric cancer and colorectal cancer. *Human Molecular Genetics*. 1999;**8**:607-610. PMID:10072428
- [9] Keller G, Grimm V, Vogelsang H, Bischoff P, Mueller J, Siewert JR, Hofler H. Analysis for microsatellite instability and mutations of the DNA mismatch repair gene MLH1 in familial gastric cancer. *International Journal of Cancer*. 1996;**68**:571-576. DOI: 10.1002/(SICI)1097-0215(19961127)68:5<571::AID-IJC3>3.0.CO;2-W
- [10] Toyota M, Ahuja N, Suzuki H, Itoh F, Ohe-Toyota M, Imai K, Baylin SB, Issa J-PJ. Aberrant methylation in gastric cancer associated with the CpG island methylator phenotype. *Cancer Research*. 1999;**59**:5438-5442. PMID: 10554013
- [11] Correa P. Is gastric cancer preventable? *Gut*. 2004;**53**:1217-1219. PMID: 15306570 DOI: 10.1136/gut.2004.039834
- [12] Cervantes A, Roda D, Tarazona N, Roselló S, Pérez-Fidalgo JA. Current questions for the treatment of advanced gastric cancer. *Cancer Treatment Reviews*. 2013;**39**:60-67. PMID: 23102520 DOI: 10.1016/j.ctrv.2012.09.007

- [13] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA: A Cancer Journal for Clinicians*. 2014;**64**:9-29. PMID: 24399786 DOI: 10.3322/caac.21208
- [14] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA: A Cancer Journal for Clinicians*. 2009;**59**:225-249. PMID: 19474385
- [15] Kothari N, Almhanna K. Current status of novel agents in advanced gastroesophageal adenocarcinoma. *Journal of Gastrointestinal Oncology*. 2015;**6**:60-74. PMID: 25642339 DOI: 10.3978/j.issn.2078-6891.2014.098
- [16] Suzuki T, Yasui W, Yokozaki H, Naka K, Ishikawa T, Tahara E. Expression of the E2F family in human gastrointestinal carcinomas. *International Journal of Cancer*. 1999;**81**:535-538. DOI: 10.1002/(SICI)1097-0215(19990517)81:4<535::AID-IJC5>3.0.CO;2-4
- [17] Zheng H, Takahashi H, Murai Y, Cui Z, Nomoto K, Miwa S, Tsuneyama K, Takano Y. Pathobiological characteristics of intestinal and diffuse-type gastric carcinoma in Japan: An immunostaining study on the tissue microarray. *Journal of Clinical Pathology*. 2007;**60**:273-277. PMCID: PMC1860577 DOI: 10.1136/jcp.2006.038778
- [18] Hiyama T, Haruma K, Kitadai Y, Masuda H, Miyamoto M, Tanaka S, Yoshihara M, Shimamoto F, Chayama K. K-ras mutation in helicobacter pylori-associated chronic gastritis in patients with and without gastric cancer. *International Journal of Cancer*. 2002;**97**:562-566. PMID: 11807778
- [19] Cheng X, Wang Z, Chen X, Sun Y, Kong Q, Liu J, Li H. Correlation of Wnt-2 expression and β -catenin intracellular accumulation in Chinese gastric cancers: Relevance with tumour dissemination. *Cancer Letters*. 2005;**223**:339-347. PMID: 15896469 DOI: 10.1016/j.canlet.2004.11.013
- [20] Sasaki N, Morisaki T, Hashizume K, Yao T, Tsuneyoshi M, Noshiro H, Nakamura K, Yamanaka T, Uchiyama A, Tanaka M, Katano M. Nuclear factor-kappaB p65 (RelA) transcription factor is constitutively activated in human gastric carcinoma tissue. *Clinical Cancer Research*. 2001;**7**:4136-4142. PMID: 11751513
- [21] Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;**100**:57-70. PMID: 10647931 DOI: 10.1016/S0092-8674(00)81683-9
- [22] Tay ST, Leong SH, Yu K, Aggarwal A, Tan SY, Lee CH, Wong K, Visvanathan J, Lim D, Wong WK, Soo KC, Kon OL, Tan P. A combined comparative genomic hybridization and expression microarray analysis of gastric cancer reveals novel molecular subtypes. *Cancer Research*. 2003;**63**: 3309-3316. PMID: 12810664
- [23] Ooi CH, Ivanova T, Wu J, Lee M, Tan IB, Tao J, Ward L, Koo JH, Gopalakrishnan V, Zhu Y, Cheng LL, Lee J, Rha SY, Chung HC, Ganesan K, So J, Soo KC, Lim D, Chan WH, Wong WK, Bowtell D, Yeoh KG, Grabsch H, Boussioutas A, Tan P. Oncogenic pathway combinations predict clinical prognosis in gastric cancer. *PLoS Genetics*. 2009;**5**(10):e1000676. PMID: 19798449 PMCID: PMC2748685 DOI: 10.1371/journal.pgen.1000676

- [24] Xie HL, Su Q, He XS, Liang XQ, Zhou JG, Yin Song Y, Li YQ. Expression of p21(WAF1) and p53 and polymorphism of p21(WAF1) gene in gastric carcinoma. *World Journal of Gastroenterology*. 2004;**10**:1125-1131. PMCID: PMC4656346 DOI: 10.3748/wjg.v10.i8.1125
- [25] Humar B, Fukuzawa R, Blair V, Dunbier A, More H, Charlton A, Yang HK, Kim WH, Reeve AE, Martin I, Guilford P. Destabilized adhesion in the gastric proliferative zone and c-SRC kinase activation mark the development of early diffuse gastric cancer. *Cancer Research*. 2007;**67**:2480-2489. DOI: 10.1158/0008-5472.CAN-06-3021
- [26] Choi JH, Kwon HJ, Yoon BI, Kim JH, Han SU, Joo HJ, Kim DY. Expression profile of histone deacetylase 1 in gastric cancer tissues. *Japanese Journal of Cancer Research*. 2001;**92**:1300-1304. PMID:11749695
- [27] Katoh M. Dysregulation of stem cell signaling network due to germline mutation, SNP, *Helicobacter pylori* infection, epigenetic change and genetic alteration in gastric cancer. *Cancer Biology & Therapy*. 2007;**6**:832-839. DOI:10.4161/cbt.6.6.4196
- [28] Collier HA, Grandori C, Tamayo P, Colbert T, Lander ES, Eisenman RN, Golub TR. Expression analysis with oligonucleotide microarrays reveals that MYC regulates genes involved in growth, cell cycle, signaling, and adhesion. *Proceedings of the National Academy of Sciences of the United States of America*. 2000;**97**:3260-3265. PMID:10737792 PMCID: PMC16226
- [29] Orford KW, Scadden DT. Deconstructing stem cell self-renewal: Genetic insights into cell-cycle regulation. *Nature Reviews. Genetics*. 2008;**9**:115-128. PMID:18202695 DOI:10.1038/nrg2269
- [30] Hirata Y, Maeda S, Ohmae T, Shibata W, Yanai A, Ogura K, Yoshida H, Kawabe T, Omata M. *Helicobacter pylori* induces I κ B kinase α nuclear translocation and chemokine production in gastric epithelial cells. *Infection and Immunity*. 2006;**74**(3):1452-1461. DOI: 10.1128/IAI.74.3.1452-1461.2006
- [31] Bass AJ, Thorsson V, Shmulevich I, Reynolds SM, Miller M, Bernard B, Hinoue T, from The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014 Sep 11;**513**(7517):202-209. PMID:25079317 PMCID: PMC4170219 DOI: 10.1038/nature13480
- [32] Murphy G, Pfeiffer R, Camargo MC, Rabkin CS. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. *Gastroenterology*. 2009;**137**:824-833. PMID: 19445939 PMCID: PMC3513767 DOI:10.1053/j.gastro.2009.05.001
- [33] Matsusaka K, Kaneda A, Nagae G, Ushiku T, Kikuchi Y, Hino R, Uozaki H, Seto Y, Takada K, Aburatani H, Fukayama M. Classification of Epstein-Barr virus-positive gastric cancers by definition of DNA methylation epigenotypes. *Cancer Research*. 2011;**71**:7187-7197. PMID:21990320 DOI:10.1158/0008-5472.CAN-11-1349

- [34] Geddert H, Zur Hausen A, Gabbert HE, Sarbia M. EBV-infection in cardiac and non-cardiac gastric adenocarcinomas is associated with promoter methylation of p16, p14 and APC, but not hMLH1. *Analytical Cellular Pathology*. 2010;**33**:143-149. PMCID: PMC4605817 DOI: 10.3233/ACP-CLO-2010-0540
- [35] Lee J, van Hummelen P, Go C, Palescandolo E, Jang J, Park HY, Kang SY, Park JO, Kang WK, MacConaill L, Kim KM. High-throughput mutation profiling identifies frequent somatic mutations in advanced gastric adenocarcinoma. *PLoS One*. 2012;**7**:e38892. DOI: <http://dx.doi.org/10.1371/journal.pone.0038892>
- [36] Sukawa Y, Yamamoto H, Nosho K, Kunitomo H, Suzuki H, Yasushi A, Nakazawa M, Nobuoka T, Kawayama M, Mikami M, Matsuno T, Sasagawa T, Hirata K, Imai K, Shinomura Y. Alterations in the human epidermal growth factor receptor 2-phosphatidylinositol 3-kinase-v-Akt pathway in gastric cancer. *World Journal of Gastroenterology*. 2012;**18**:6577-6586. PMCID: PMC3516204 DOI: 10.3748/wjg.v18.i45.6577
- [37] Ridley AJ, Schwartz MA, Burridge K, Firtel RA, Ginsberg MH, Borisy G, Parsons JT, Horwitz AR. Cell migration: Integrating signals from front to back. *Science*. 2003;**302**:1704-1709. PMID:14657486 DOI: 10.1126/science.1092053
- [38] Thumkeo D, Watanabe S, Narumiya S. Physiological roles of Rho and Rho effectors in mammals. *European Journal of Cell Biology*. 2013;**92**:303-315. DOI: <http://dx.doi.org/10.1016/j.ejcb.2013.09.002>
- [39] Aznar S. et al. Simultaneous tyrosine and serine phosphorylation of STAT3 transcription factor is involved in Rho A GTPase oncogenic transformation. *Molecular Biology of Cell*. 2001;**12**:3282-3294. PMCID: PMC60173
- [40] Yu H, Jove R. The STATs of cancer—New molecular targets come of age. *Nature Reviews Cancer*. 2004;**4**:97-105. PMID:14964307 DOI:10.1038/nrc1275
- [41] The Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012;**487**:330-337. <http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path%5B%5D=1781&path%5B%5D=2086>
- [42] 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, Zalberg 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 DOI: 10.1016/S0140-6736(13)61719-5
- [43] Cui J, Li F, Wang G, Fang X, Puett JD, Xu Y. Gene-expression signatures can distinguish gastric cancer grades and stages. *PLoS One*. 2011;**6**(3):e17819. PMID: 21445269 PMCID: PMC3060867 DOI:10.1371/journal.pone.0017819

- [44] Catherino WH, Leppert PC, Stenmark MH, Payson M, Potlog-Nahari C, Nieman LK, Segars JH. Reduced dermatopontin expression is a molecular link between uterine leiomyomas and keloids. *Genes Chromosomes Cancer*. 2004;**40**:204-217. PMID: 15139000 PMCID: PMC4152899 DOI: 10.1002/gcc.20035
- [45] Hecht JR, Bang YJ, Qin SK, Chung HC, Xu JM, Park JO, Jeziorski K, Shparyk Y, Hoff PM, Sobrero A, Salman P, Li J, Protsenko SA, Wainberg ZA, Buyse M, Afenjar K, Houé V, Garcia A, Kaneko T, Huang Y, Khan-Wasti S, Santillana S, Press MF, Slamon D. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC-a randomized Phase III trial. *Journal of Clinical Oncology*. 2016;**34**:443-451. PMID:26628478 DOI: 10.1200/JCO.2015.62.6598
- [46] Mattioni M, Soddu S, Porrello A, D'Alessandro R, Spila A, Guadagni F. Serum anti-p53 antibodies as a useful marker for prognosis of gastric carcinoma. *The International Journal of Biological Markers*. 2006;**22**:302-306. PMID:18161662
- [47] Cabuk D, Basaran G, Celikel C, Dane F, Yumuk PF, Iyikesici MS, Ekenel M, Turhal NS. Vascular endothelial growth factor, hypoxia-inducible factor 1 alpha and CD34 expressions in early-stage gastric tumors: Relationship with pathological factors and prognostic impact on survival. *Oncology*. 2007;**72**:111-117. PMID:18025805 DOI: 10.1159/111118
- [48] Takeno A, Takemasa I, Doki Y, Yamasaki M, Miyata H, Takiguchi S, Fujiwara Y, Matsubara K, Monden M. Integrative approach for differentially overexpressed genes in gastric cancer by combining large-scale gene expression profiling and network analysis. *British Journal of Cancer*. 2008;**99**:1307-1315. DOI:10.1038/sj.bjc.6604682
- [49] Wang P, Wang Y, Hang B, Zou X, Mao JH. A novel gene expression-based prognostic scoring system to predict survival in gastric cancer. *Oncotarget*. 2016;**7**(34):55343-55351. DOI: 10.18632/oncotarget.10533
- [50] Xu Y, Ma H, Yu H, Liu Z, Wang L-E, Tan D, Muddasani R, Lu V, Ajani JA, Wang Y, Wei Q. The miR-184 binding site rs8126 T> C polymorphism in TNFAIP2 is associated with risk of gastric cancer. *PLoS One*. 2013;**8**:e64973. PMID: 23724109 PMCID: PMC3665554 DOI: 10.1371/journal.pone.0064973
- [51] Ye YW, Zhang X, Zhou Y, Wu J, Zhao C, Yuan L, Wang G, Du C, Wang C, Shi Y. The correlations between the expression of FGFR4 protein and clinicopathological parameters as well as prognosis of gastric cancer patients. *Journal of Surgical Oncology*. 2012;**106**:872-879. PMID: 22585711 DOI:10.1002/jso.23153
- [52] Shen YY, Lu YC, Shen DP, Liu YJ, Su XY, Zhu GS, Yin XL, Ni XZ. Fibroblast growth factor receptor 4 Gly388Arg polymorphism in Chinese gastric cancer patients. *World Journal of Gastroenterology*. 2013;**19**:4568-4575. PMCID: PMC3725383 DOI: 10.3748/wjg.v19.i28.4568

- [53] Rajkumar T, Vijayalakshmi N, Gopal G, Sabitha K, Shirley S, Raja UM, Ramakrishnan SA. Identification and validation of genes involved in gastric tumorigenesis. *Cancer Cell International*. 2010;**10**:45. PMID:21092330 PMCID:PMC3004887 DOI:10.1186/1475-2867-10-45
- [54] Tao J, Zhi X, Tian Y, Li Z, Zhu Y, Wang W, et al. CEP55 contributes to human gastric carcinoma by regulating cell proliferation. *Tumor Biology*. 2014;**35**:4389-4399. PMID:24390615 DOI:10.1007/s13277-013-1578-1
- [55] Xiang Z, Jiang DP, Xia GG, Wei ZW, Chen W, He Y, Zhang CH. CXCL1 expression is correlated with Snail expression and affects the prognosis of patients with gastric cancer. *Oncology Letters*. 2015;**10**:2458-2464. DOI: 10.3892/ol.2015.3614
- [56] You T, Gao W, Wei J, Jin X, Zhao Z, Wang C, Li Y. Overexpression of LIMK1 promotes tumor growth and metastasis in gastric cancer. *Biomedicine & Pharmacotherapy*. 2015;**69**:96-101. PMID: 25661344 DOI: 10.1016/j.biopha.2014.11.011
- [57] Yamamoto H, Kitadai Y, Yamamoto H, Oue N, Ohdan H, Yasui W, Kikuchi A. Laminin gamma2 mediates Wnt5a induced invasion of gastric cancer cells. *Gastroenterology*. 2009;**137**:242. PMID:19582886
- [58] Sakashita K, Tanaka F, Zhang X, Mimori K, Kamohara Y, Inoue H, Sawada T, Hirakawa K, Mori M. Clinical significance of ApoE expression in human gastric cancer. *Oncology Reports*. 2008;**20**:1313-1319. DOI: 10.3892/or_00000146
- [59] Oshima T, Yoshihara K, Aoyama T, Hasegawa S, Sato T, Yamamoto N, Akito N, Shiozawa M, Yoshikawa T, Numata K, Rino Y, Kunisaki C, Tanaka K, Akaike M, Imada T, Masuda M. Relation of INHBA gene expression to outcomes in gastric cancer after curative surgery. *Anticancer Research*. 2014;**34**:2303-2309
- [60] Junnila S, Kokkola A, Karjalainen-Lindsberg ML, Puolakkainen P, Monni O. Genome-wide gene copy number and expression analysis of primary gastric tumors and gastric cancer cell lines. *BMC Cancer*. 2010;**10**:73. PMID:20187983 PMCID:PMC2837868 DOI:10.1186/1471-2407-10-73
- [61] Oue N, Hamai Y, Mitani Y, Matsumura S, Oshimo Y, Aung PP, Kuraoka K, Nakayama H, Yasui W. Gene expression profile of gastric carcinoma identification of genes and tags potentially involved in invasion, metastasis, and carcinogenesis by serial analysis of gene expression. *Cancer Research*. 2004;**64**:2397-2405. PMID:15059891
- [62] Zhang L, Kim S, Ding W, Tong Y, Zhang X, Pan M, Chen S. Arsenic sulfide inhibits cell migration and invasion of gastric cancer in vitro and in vivo. *Drug Design, Development and Therapy*. 2015;**9**:5579-5590. PMID:26487802 PMCID:PMC4607060 DOI:10.2147/DDDT.S89805
- [63] Dong Y, Chen G, Gao M, Tian X. Increased expression of MMP14 correlates with the poor prognosis of Chinese patients with gastric cancer. *Gene*. 2015;**563**:29-34. PMID:25748728 DOI: 10.1016/j.gene.2015.03.003

- [64] Duell EJ, Sala N, Travier N, Muñoz X, Boutron-Ruault MC, Clavel-Chapelon F, Barricarte A, Arriola L, Navarro C, Sánchez-Cantalejo E, Quirós JR, Krogh V, Vineis P, et al. Genetic variation in alcohol dehydrogenase (ADH1A, ADH1B, ADH1C, ADH7) and aldehyde dehydrogenase (ALDH2), alcohol consumption and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Carcinogenesis*. 2012;**33**:361-367. PMID:22144473 DOI: 10.1093/carcin/bgr285
- [65] Xie X, Liu X, Zhang Q, Yu J. Overexpression of collagen VI $\alpha 3$ in gastric cancer. *Oncology Letters* 2014;**7**:1537-1543. DOI: 10.3892/ol.2014.1910
- [66] Malta-Vacas J, Nolasco S, Monteiro C, Soares H, Brito M. Translation termination and protein folding pathway genes are not correlated in gastric cancer. *Clinical Chemistry and Laboratory Medicine*. 2009;**47**:427-431. DOI:10.1515/CCLM.2009.091
- [67] Jinawath N, Furukawa Y, Nakamura Y. Identification of NOL8, a nucleolar protein containing an RNA recognition motif (RRM), which was overexpressed in diffuse-type gastric cancer. *Cancer Science*. 2004;**95**:430-435. PMID:15132771
- [68] Liersch-Löhn B, Slavova N, Buhr HJ, Bennani-Baiti IM. Differential protein expression and oncogenic gene network link tyrosine kinase ephrin B4 receptor to aggressive gastric and gastroesophageal junction cancers. *International Journal of Cancer*. 2016;**138**:1220-31. DOI: 10.1002/ijc.29865
- [69] Yang C, Wen Y, Li H, Zhang D, Zhang N, Shi X, Jiang B, Ma X, Yang P, Tang H, Peng Z, Yang Y. Overexpression of minichromosome maintenance 2 predicts poor prognosis in patients with gastric cancer. *Oncology Reports*. 2012;**27**:135-142. PMID:21947329 DOI: 10.3892/or.2011.1473
- [70] Tian Y, Tian X, Han X, Chen Y, Song CY, Jiang WJ, Tian DL. ABCE1 plays an essential role in lung cancer progression and metastasis. *Tumor Biology*. 2016;**37**(6):8375-82. [Epub ahead of print].
- [71] Matboli M, El-Nakeep S, Hossam N, Habieb A, Azazy AEM, Ebrahim AE, Nagy Z, Abdel-Rahman O. Exploring the role of molecular biomarkers as a potential weapon against gastric cancer: A review of the literature. *World Journal of Gastroenterology*. 2016;**22**(26):5896-5908. DOI: 10.3748/wjg.v22.i26.5896
- [72] Pectasides D, Mylonakis A, Kostopoulou M, Papadopoulou M, Triantafillis D, Varthalitis J, Dimitriades M, Athanassiou A. CEA, CA 19-9, and CA-50 in monitoring gastric carcinoma. *American Journal of Clinical Oncology*. 1997;**20**:348-353. PMID: 9256887
- [73] Aloe S, D'Alessandro R, Spila A, Ferroni P, Basili S, Palmirota R, Carlini M, Graziano F, Mancini R, Mariotti S, Cosimelli M, Roselli M, Guadagni F. Prognostic value of serum and tumor tissue CA 72-4 content in gastric cancer. *International Journal of Biological Markers*. 2003;**18**:21-27. PMID: 12699059
- [74] Cho JY. Molecular diagnosis for personalized target therapy in gastric cancer. *Journal of Gastric Cancer*. 2013;**13**:129-135. PMID: 24156032 DOI: 10.5230/jgc.2013.13.3.129

- [75] Lin X, Zhao Y, Song WM, Zhang B. Molecular classification and prediction in gastric cancer. *Computational and Structural Biotechnology Journal*. 2015;**13**:448-458. PMID: 26380657 DOI: 10.1016/j.csbj.2015.08.001
- [76] Tanaka T, Tanimoto K, Otani K, Satoh K, Ohtaki M, Yoshida K, Toge T, Yahata H, Tanaka S, Chayama K, Okazaki Y, Hayashizaki Y, Hiyama K, Nishiyama M. Concise prediction models of anticancer efficacy of 8 drugs using expression data from 12 selected genes. *International Journal of Cancer*. 2004;**111**:617-626. PMID: 15239142 DOI: 10.1002/ijc.20289
- [77] Sève P, Mackey J, Isaac S, Trédan O, Souquet PJ, Pérol M, Lai R, Voloch A, Dumontet C. Class III beta-tubulin expression in tumor cells predicts response and outcome in patients with nonsmall cell lung cancer receiving paclitaxel. *Molecular Cancer Therapeutics*. 2005;**4**:2001-2007. PMID: 16373715 DOI: 10.1158/1535-7163.MCT-05-0244
- [78] Suganuma K, Kubota T, Saikawa Y, Abe S, Otani Y, Furukawa T, Kumai K, Hasegawa H, Watanabe M, Kitajima M, Nakayama H, Okabe H. Possible chemoresistance-related genes for gastric cancer detected by cDNA microarray. *Cancer Science*. 2003;**94**:355-359. PMID: 12824904
- [79] Liu H, Li N, Yao L, Jiang L, Bao G, Li J, Ma Q, Liu Z. Prediction of doxorubicin sensitivity in gastric cancers based on a set of novel markers. *Oncology Reports*. 2008;**20**:963-969. PMID: 18813841
- [80] Bashash M, Shah A, Hislop G, Trembl M, Bretherick K, Janoo Gilani R, Leach S, Le N, Bajdik C, Brooks-Wilson A. Genetic polymorphisms at TIMP3 are associated with survival of adenocarcinoma of the gastroesophageal junction. *PLoS One*. 2013;**8**:e59157. PMID: 23527119 DOI: 10.1371/journal.pone.0059157
- [81] Liu K, Qian T, Tang L, Wang J, Yang H, Ren J. Decreased expression of microRNA let-7i and its association with chemotherapeutic response in human gastric cancer. *World Journal of Surgical Oncology*. 2012;**10**:225. PMID: 23107361 DOI: 10.1186/1477-7819-10-225
- [82] Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, Liu J, Yue YG, Wang J, Yu K, Ye XS, Do IG, Liu S, Gong L, Fu J, Jin JG, Choi MG, Sohn TS, Lee JH, Bae JM, Kim ST, Park SH, Sohn I, Jung SH, Tan P, Chen R, Hardwick J, Kang WK, Ayers M, Hongyue D, Reinhard C, Loboda A, Kim S, Aggarwal A. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nature Medicine*. 2015;**21**:449-456. PMID: 25894828 DOI: 10.1038/nm.3850
- [83] 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. *Annals of Surgical Oncology*. 2014;**21**:343-350. PMID: 24154840 DOI: 10.1245/s10434-013-3325-7
- [84] Huang D, Wang H, Liu R, Li H, Ge S, Bai M, Deng T, Yao G, Ba Y. miRNA27a is a biomarker for predicting chemosensitivity and prognosis in metastatic or recurrent gastric cancer. *Journal of Cellular Biochemistry*. 2014;**115**:549-556. PMID: 24122958 DOI: 10.1002/jcb.24689

- [85] Yang Z, Guo X, Li G, Shi Y, Li L. Long noncoding RNAs as potential biomarkers in gastric cancer: Opportunities and challenges. *Cancer Letters*. 2016;**371**:62-70. PMID: 26577810 DOI: 10.1016/j.canlet.2015.11.011
- [86] Wang Y, Zhang D, Wu K, Zhao Q, Nie Y, Fan D. Long noncoding RNA MRUL promotes ABCB1 expression in multidrug-resistant gastric cancer cell sublines. *Molecular and Cellular Biology*. 2014;**34**:3182-3193. PMID: 24958102 DOI: 10.1128/MCB.01580-13
- [87] Sugita H, Iida S, Inokuchi M, Kato K, Ishiguro M, Ishikawa T, Takagi Y, Enjoji M, Yamada H, Uetake H, Kojima K, Sugihara K. Methylation of BNIP3 and DAPK indicates lower response to chemotherapy and poor prognosis in gastric cancer. *Oncology Reports*. 2011;**25**:513-518. PMID: 21152877 DOI: 10.3892/or.2010.1085
- [88] Ivanova T, Zouridis H, Wu Y, Cheng LL, Tan IB, Gopalakrishnan V, Ooi CH, Lee J, Qin L, Wu J, Lee M, Rha SY, Huang D, Liem N, Yeoh KG, Yong WP, Teh BT, Tan P. Integrated epigenomics identifies BMP4 as a modulator of cisplatin sensitivity in gastric cancer. *Gut*. 2013;**62**:22-33. PMID: 22535375 DOI: 10.1136/gutjnl-2011-301113
- [89] Ooki A, Yamashita K, Yamaguchi K, Mondal A, Nishimiya H, Watanabe M. DNA damage-inducible gene, reprimofin, functions as a tumor suppressor and is suppressed by promoter methylation in gastric cancer. *Molecular Cancer Research*. 2013;**11**:1362-1374. PMID: 23982217 DOI: 10.1158/1541-7786.MCR-13-0091
- [90] Ishikawa Y, Kubota T, Otani Y, Watanabe M, Teramoto T, Kumai K, Takechi T, Okabe H, Fukushima M, Kitajima M. Dihydropyrimidine dehydrogenase and messenger RNA levels in gastric cancer: Possible predictor for sensitivity to 5-fluorouracil. *Japanese Journal of Cancer Research*. 2000;**91**:105-112. PMID: 10744051
- [91] 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. *Medical Oncology*. 2013;**30**:748. PMID: 24135868 DOI: 10.1007/s12032-013-0748-8
- [92] Yu J, Gao J, Lu Z, Li Y, Shen L. Serum levels of TUBB3 correlate with clinical outcome in Chinese patients with advanced gastric cancer receiving first-line paclitaxel plus capecitabine. *Medical Oncology*. 2012;**29**:3029-3034. PMID: 22766748 DOI: 10.1007/s12032-012-0292-y
- [93] Mitani Y, Oue N, Matsumura S, Yoshida K, Noguchi T, Ito M, Tanaka S, Kuniyasu H, Kamata N, Yasui W. Reg IV is a serum biomarker for gastric cancer patients and predicts response to 5-fluorouracil-based chemotherapy. *Oncogene* 2007;**26**:4383-4393. PMID: 17237819 DOI: 10.1038/sj.onc.1210215
- [94] 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. *Annals of Surgical Oncology*. 2013;**20**:1035-1043. PMID: 23054116 DOI: 10.1245/s10434-012-2680-0

- [95] Shi Y, Zhai H, Wang X, Han Z, Liu C, Lan M, Du J, Guo C, Zhang Y, Wu K, Fan D. Ribosomal proteins S13 and L23 promote multidrug resistance in gastric cancer cells by suppressing drug-induced apoptosis. *Experimental Cell Research*. 2004;**296**:337-346. PMID: 15149863 DOI: 10.1016/j.yexcr.2004.02.009
- [96] Coussens L, Yang-Feng TL, Liao YC, Chen E, Gray A, McGrath J, Seeburg PH, Libermann TA, Schlessinger J, Francke U. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science*. 1985;**230**:1132-1139. PMID: 2999974 DOI: 10.1126/science.2999974
- [97] Stintzing S, Jung A, Rossius L, Modest DP, von Weikersthal LF, Decker T, Kiani A, Al-Batran SE, Vehling-Kaiser U, Heintges T, Moehler M, Scheithauer W, Kirchner T, Heinemann V. Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3-A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. *Journal of Clinical Oncology*. 2014;**32**(Suppl 3):abstr 445
- [98] 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 DOI: 10.1016/S0140-6736(10)61121-X
- [99] Clinical trials.gov. A Study of the Combination of Oxaliplatin, Capecitabine and Herceptin (Trastuzumab) and Chemoradiotherapy in the Adjuvant Setting in Operated Patients with HER2 Gastric or Gastro-esophageal Junction Cancer (TOXAG Study). Available from: <http://www.clinicaltrials.gov/show/NCT01748773>
- [100] Ryu MH, Yoo C, Kim JG, Ryoo BY, Park YS, Park SR, Han HS, Chung IJ, Song EK, Lee KH, Kang SY, Kang YK. Multicenter phase II study of trastuzumab in combination with capecitabine and oxaliplatin for advanced gastric cancer. *European Journal of Cancer*. 2015;**51**:482-488. PMID: 25661103 DOI: 10.1016/j.ejca.2014.12.015
- [101] Hoff P, Tabernero J, Shen L. P-0111 pertuzumab, trastuzumab and chemotherapy in HER2-positive metastatic gastric or gastrooesophageal junction cancer: An international phase III study (JACOB). *Annals of Oncology*. 2013;**24**:iv67. DOI: 10.1093/annonc/mdt203.109
- [102] Clinical trials.gov. A Study of Trastuzumab Emtansine versus Taxane in Patients with Advanced Gastric Cancer. Available from: <http://clinicaltrials.gov/show/NCT01641939>
- [103] Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, Tsuji A, Omuro Y, Li J, Wang JW, Miwa H, Qin SK, Chung IJ, Yeh KH, Feng JF, Mukaiyama A, Kobayashi M, Ohtsu A, Bang YJ. Lapatinib plus paclitaxel versus paclitaxel alone in the secondline treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN—A randomized, phase III study. *Journal of Clinical Oncology*. 2014;**32**:2039-2049. PMID: 24868024 DOI: 10.1200/JCO.2013.53.6136

- [104] 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. *Annals of Surgical Oncology*. 2008;**15**:69-79. PMID: 17896140
- [105] 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. *The Lancet Oncology*. 2013;**14**:490-499. PMID: 23594786 DOI: 10.1016/S1470-2045(13)70102-5
- [106] Clinical trials.gov. Cetuximab, Cisplatin, and Irinotecan in Treating Patients With Metastatic Esophageal Cancer, Gastroesophageal Junction Cancer, or Gastric Cancer That Did Not Respond to Previous Irinotecan and Cisplatin. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT00397904>
- [107] 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. *The Lancet Oncology*. 2013;**14**:481-489. PMID: 23594787 DOI: 10.1016/S1470-2045(13)70096-2
- [108] Clinical trials.gov. Panitumumab, Paclitaxel, Carboplatin and 5FU in the Treatment of Potentially Resectable Gastroesophageal Adenocarcinoma. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01182610>
- [109] Satoh T, Lee KH, Rha SY, Sasaki Y, Park SH, Komatsu Y, Yasui H, Kim TY, Yamaguchi K, Fuse N, Yamada Y, Ura T, Kim SY, Munakata M, Saitoh S, Nishio K, Morita S, Yamamoto E, Zhang Q, Kim JM, Kim YH, Sakata Y. Randomized phase II trial of nimo-tuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer. *Gastric Cancer*. 2015;**18**:824-832. PMID: 25185971 DOI: 10.1007/s10120-014-0420-9
- [110] Clinical trials.gov. Gefitinib in Combination with Chemoradiation in Resectable Gastric Cancer. Available from: <https://www.clinicaltrials.gov/ct2/show?term=gefitinib, gastric cancer&rank=2>
- [111] Clinical trials.gov. Cisplatin and Irinotecan Chemotherapy, Followed by ZD 1839 (Iressa) in Patients With Esophageal or Gastric Carcinomas. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT00215995>
- [112] 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. *Journal of Clinical Oncology*. 2006;**24**:4922-4927. PMID: 17050876 DOI: 10.1200/JCO.2006.07.1316

- [113] Carmeliet P. Angiogenesis in health and disease. *Nature Medicine*. 2003;**9**:653-660. PMID: 12778163
- [114] Grigore D, Simionescu CE, Stepan A, Mărgăritescu C, Bălăsoiu M, Georgescu CC, Cernea D, Dumitrescu D. Assessment of CD105, α -SMA and VEGF expression in gastric carcinomas. *Romanian Journal of Morphology and Embryology*. 2013;**54**:701-707. PMID: 24322015
- [115] 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 firstline therapy in advanced gastric cancer: A randomized, doubleblind, placebo-controlled phase III study. *Journal of Clinical Oncology*. 2011;**29**:3968-3976. PMID: 21844504 DOI: 10.1200/JCO.2011.36.2236
- [116] Shen L, Li J, Xu J, Pan H, Dai G, Qin S, Wang L, Wang J, Yang Z, Shu Y, Xu R, Chen L, Liu Y, Yu S, Bu L, Piao Y. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: Randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer*. 2015;**18**:168-176. PMID: 24557418 DOI: 10.1007/s10120-014-0351-5
- [117] Clinical trials.gov, Cunningham D. Chemotherapy With or Without Bevacizumab or Lapatinib to Treat Operable Oesophagogastric Cancer (ST03). Available from: <https://clinicaltrials.gov/ct2/show/NCT00450203>
- [118] Choi AH, Kim J, Chao J. Perioperative chemotherapy for resectable gastric cancer: MAGIC and beyond. *World Journal of Gastroenterology*. 2015;**21**:7343-7348. PMID: 26139980 DOI: 10.3748/wjg.v21.i24.7343
- [119] Clinical trials.gov. Docetaxel, Cisplatin, Irinotecan and Bevacizumab (TPCA) in Metastatic Esophageal and Gastric Cancer. Available from: <https://clinicaltrials.gov/ct2/show/NCT00394433>
- [120] Clinical trials.gov. Docetaxel, Oxaliplatin, Capecitabine, Bevacizumab and Trastuzumab in Patients with Locally Advanced or Metastatic Gastric Cancer (B-DOCT). Available from: <https://clinicaltrials.gov/ct2/show/NCT01359397>
- [121] Wilke H, Van Cutsem E, Oh SC. RAINBOW: A global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine containing combination therapy: Results of a multiple Cox regression analysis adjusting for prognostic factors. *Journal of Clinical Oncology*. 2014;**32**:abstr 4076
- [122] Casak SJ, Fashoyin-Aje I, Lemery SJ, Zhang L, Jin R, Li H, Zhao L, Zhao H, Zhang H, Chen H, He K, Dougherty M, Novak R, Kennett S, Khasar S, Helms W, Keegan P, Pazdur R. FDA approval summary: Ramucirumab for gastric cancer. *Clinical Cancer Research*. 2015;**21**:3372-3376. PMID: 26048277 DOI: 10.1158/1078-0432

- [123] Xu R, Ma N, Wang F, Ma L, Chen R, Chen R, Kebinu M, Ma L, Han Z, Ayixiamu M, Su P, Naman Y, Jieensi H, Yang H, Adili A, Aili S, Liu J. Results of a randomized and controlled clinical trial evaluating the efficacy and safety of combination therapy with Endostar and S-1 combined with oxaliplatin in advanced gastric cancer. *OncoTargets and Therapy*. 2013;**6**:925-929. PMID: 23926435 DOI: 10.2147/OTT.S46487
- [124] Geng R, Li J. Apatinib for the treatment of gastric cancer. *Expert Opinion on Pharmacotherapy*. 2015;**16**:117-122. PMID: 25420417 DOI: 10.1517/14656566.2015.981526
- [125] 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. *Journal of Clinical Oncology*. 2013;**31**:3219-3225. PMID:23918952 DOI: 10.1200/JCO.2013.48.8585
- [126] Apatinib got CFDA approval. Available from: <http://www.inyaohui.com/news/201502/05/5059.html>
- [127] 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. *Investigational New Drugs*. 2011;**29**:1449-1458. PMID: 20461441 DOI: 10.1007/s10637-010-9438-y
- [128] Lee KW, Park SR, Oh DY, Park YI, Khosravan R, Lin X, Lee SY, Roh EJ, Valota O, Lechuga MJ, Bang YJ. Phase I study of sunitinib plus capecitabine/cisplatin or capecitabine/oxaliplatin in advanced gastric cancer. *Investigational New Drugs*. 2013;**31**:1547-1558. PMID: 24091982 DOI: 10.1007/s10637-013-0032-y
- [129] Clinical trials.gov. Sorafenib. ICORG 06-41, V4. Available from: <https://clinicaltrials.gov/ct2/show/NCT01158287>
- [130] Clinical trials.gov. Sorafenib as a second line treatment in patients with advanced or metastatic gastric cancer. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT00595985>
- [131] Clinical trials.gov. FLO/- pazopanib as first-line treatment in advanced gastric cancer (PaFLO). Available from: <http://clinicaltrials.gov/ct2/show/NCT01503372>
- [132] Clinical trials.gov. A Study of Pazopanib with CAPEOX in AGC Patients. Available from: <http://clinicaltrials.gov/ct2/show/NCT01130805>
- [133] Pavlakakis N, Sjoquist KM, Tsobanis E. INTEGRATE: A randomized phase II double-blind placebo-controlled study of regorafenib (REG) in refractory advanced esophagogastric cancer (AOGC)—A study by the Australasian Gastrointestinal Trials Group (AGITG): Final overall and subgroup results. *Annals of Oncology*. 2015;**26**(Suppl t4):119
- [134] Foulstone E, Prince S, Zaccheo O, Burns JL, Harper J, Jacobs C, Church D, Hassan AB. Insulin-like growth factor ligands, receptors, and binding proteins in cancer. *Journal of Pathology* 2005;**205**:145-153. PMID: 15641016 DOI: 10.1002/path.1712

- [135] Clinical trials.gov. Study of CP-751,871 in Combination with Sunitinib in Patients with Advanced Solid Tumors. Available from: <https://www.clinicaltrials.gov/ct2/show/study/NCT00729833>
- [136] Grose R, Dickson C. Fibroblast growth factor signaling in tumorigenesis. *Cytokine and Growth Factor Reviews*. 2005;**16**:179-186. PMID: 15863033 DOI: 10.1016/j.cytogfr.2005.01.003
- [137] Bang YJ, Van Cutsem E, Mansoor W. A randomized, open label phase II study of AZD4547 (AZD) versus Paclitaxel (P) in previously treated patients with advanced gastric cancer (AGC) with Fibroblast Growth Factor Receptor 2 (FGFR2) polysomy or gene amplification (amp): SHINE study. *Journal of Clinical Oncology*. 2015;**33**(Suppl):abstr 4014
- [138] Dienstmann R, Bahleda R, Adamo B, Rodon J, Varga A, Gazzah A, Platero S, Smit H, Perera T, Zhong B, Stuyckens K, Elsayed Y, Takimoto C, Peddareddigari V, Tabernero J, Luo FR, Soria JR. Abstract CT325: First in human study of JNJ-42756493, a potent pan fibroblast growth factor receptor (FGFR) inhibitor in patients with advanced solid tumors. *Proceedings: AACR Annual Meeting*. 2014; April 5-9, San Diego, CA. *Cancer Research*. 2014;**74**:CT325. DOI: 10.1158/1538-7445.AM2014-CT325
- [139] Qiu H, Yashiro M, Zhang X, Miwa A, Hirakawa K. A FGFR2 inhibitor, Ki23057, enhances the chemosensitivity of drug resistant gastric cancer cells. *Cancer Letters* 2011;**307**:47-52. PMID: 21482024 DOI: 10.1016/j.canlet.2011.03.015
- [140] Clinical trials.gov. Combination of Brivanib With 5-Fluorouracil/Leucovorin (5 FU/LV) and 5-Fluorouracil/Leucovorin/Irinotecan(FOLFIRI). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01046864>
- [141] Lordick F. Targeting the HGF/MET pathway in gastric cancer. *The Lancet Oncology*. 2014;**15**:914-916. PMID: 24965570
- [142] Shah MA, Bang YJ, Lordick F. MET Gastric: A phase III study of onartuzumab plus mFOLFOX6 in patients with metastatic HER2-negative (HER2-) and MET-positive (MET) adenocarcinoma of the stomach or gastroesophageal junction (GEC). *Journal of Clinical Oncology*. 2015;**33**(Suppl):abstr 4012
- [143] Jhaver 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. *Journal of Clinical Oncology*. 2009;**27**:abstr 4502
- [144] Yu HG, Ai YW, Yu LL, Zhou XD, Liu J, Li JH, Xu XM, Liu S, Chen J, Liu F, Qi YL, Deng Q, Cao J, Liu SQ, Luo HS, Yu JP. Phosphoinositide 3-kinase/Akt pathway plays an important role in chemoresistance of gastric cancer cells against etoposide and doxorubicin induced cell death. *International Journal of Cancer*. 2008;**122**:433-443. PMID: 17935137 DOI: 10.1002/ijc.23049
- [145] Okamoto I, Doi T, Ohtsu A, Miyazaki M, Tsuya A, Kurei K, Kobayashi K, Nakagawa K. Phase I clinical and pharmacokinetic study of RAD001 (everolimus) administered

daily to Japanese patients with advanced solid tumors. *Japanese Journal of Clinical Oncology*. 2010;**40**:17-23. PMID: 19783551 DOI: 10.1093/jjco/hyp120

- [146] 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. *Journal of Clinical Oncology*. 2010;**28**:1904-1910. PMID: 20231677 DOI: 10.1200/JCO.2009.26.2923
- [147] 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. *Journal of Clinical Oncology*. 2013;**31**:3935-3943. PMID: 24043745 DOI: 10.1200/JCO.2012.48.3552
- [148] 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. *Modern Pathology*. 2013;**26**:1632-1641. PMID: 23807774 DOI: 10.1038/modpathol.2013.108
- [149] Underhill C, Toulmonde M, Bonnefoi H. A review of PARP inhibitors: From bench to bedside. *Annals of Oncology*. 2011;**22**:268-279. PMID: 20643861 DOI: 10.1093/annonc/mdq322
- [150] Bang YJ, Im SA, Lee KW, Cho JY, Song EK, Lee KH, Kim YH, Park JO, Chun HG, Zhang DY, Fielding A, Rowbottom J, Hodgson D, O'Connor MJ, Yin X, Kim WH. Olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer: A randomized, double-blind phase II study. *Journal of Clinical Oncology*. 2013;**31**:abstr 4013
- [151] Clinical trials.gov. Efficacy and Safety Study of Olaparib in Combination With Paclitaxel to Treat Advanced Gastric Cancer. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01924533>
- [152] Clinical trials.gov. Evaluating the Safety and Tolerability of the Poly-ADP Ribose (PARP) Inhibitor with FOLFIRI in subjects with solid tumor. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01123876>
- [153] Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, Wolchok JD, Hersey P, Joseph RW, Weber JS, Dronca R, Gangadhar TC, Patnaik A, Zarour H, Joshua AM, Gergich K, Ellassaiss-Schaap J, Algazi A, Mateus C, Boasberg P, Tumei PC, Chmielowski B, Ebbinghaus SW, Li XN, Kang SP, Ribas A. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *New England Journal of Medicine*. 2013;**369**:134-144. PMID: 23724846 DOI: 10.1056/NEJMoa1305133
- [154] Clinical trials.gov. An Efficacy Study in Gastric and Gastroesophageal Junction Cancer Comparing Ipilimumab Versus Standard of Care immediately Following First Line Chemotherapy. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01585987>

- [155] Clinical trials.gov. A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01928394>
- [156] Le DT, Bendell JC, Calvo E, Kim JW, Ascierto PA, Sharma P, Ott PA, Bono P, Jaeger D, Evans TRJ, De Braud FG, Chau I, Christensen O, Harbison C, Lin CS, Janjigian YY. Safety and activity of nivolumab monotherapy in advanced and metastatic (A/M) gastric or gastroesophageal junction cancer (GC/GEC): Results from the CheckMate-032 study. 2016 Gastrointestinal Cancers Symposium. Journal of Clinical Oncology. 2016;**34**(Suppl4S):abstr 6
- [157] Clinical trials.gov. Study of ONO-4538 in Unresectable Advanced or Recurrent Gastric Cancer. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02267343>
- [158] Muro K, Bang Y, Shankaran V. LBA15 A phase 1b study of pembrolizumab (PEMBRO; MK-3475) in patients (PTS) with advanced gastric cancer. Annals of Oncology. 2014;**25**:1-41. DOI: 10.1093/annonc/mdu438.15
- [159] Clinical trials.gov. Study of Pembrolizumab (MK-3475) as FirstLine Monotherapy and Combination Therapy for Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (MK-3475-062/KEYNOTE-062). Available from: <https://clinicaltrials.gov/ct2/show/NCT02494583>
- [160] Clinical trials.gov. A Study of Pembrolizumab (MK-3475) in Participants with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (MK-3475-059/KEYNOTE-059). Available from: <https://clinicaltrials.gov/ct2/show/NCT02335411>
- [161] Clinical trials.gov. Study of Pembrolizumab in Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma Who Progressed after First-Line Therapy with Platinum and Fluoropyrimidine: Integration of Molecular Subtypes through Integrative Genomic Analysis. Available from: <https://clinicaltrials.gov/ct2/show/NCT02589496>
- [162] Clinical trials.gov. Combination Margetuximab and Pembrolizumab for Advanced, Metastatic HER2(+) Gastric or Gastroesophageal Junction Cancer. Available from: <https://clinicaltrials.gov/ct2/show/NCT02689284>
- [163] Clinical trials.gov. Pembrolizumab and Monoclonal Antibody Therapy in Advanced Cancer (PembroMab). Available from: <https://clinicaltrials.gov/ct2/show/NCT02318901>
- [164] Clinical trials.gov. A Study of Ramucirumab Plus Pembrolizumab in Participants With Gastric or GEJ Adenocarcinoma, NSCLC or Transitional Cell Carcinoma of the Urothelium. Available from: <https://clinicaltrials.gov/ct2/show/NCT02443324>
- [165] Clinical trials.gov. A Combination Clinical Study of PLX3397 and Pembrolizumab to Treat Advanced Melanoma and Other Solid Tumors. Available from: <https://clinicaltrials.gov/ct2/show/NCT02452424>

- [166] Lutzky J, Antonia SJ, Blake-Haskins A, Li X, Robbins PB, Shalabi AM, Vasselli J, Ibrahim RA, Khleif S, Segal NH. A phase 1 study of MEDI4736, an anti-PD-L1 antibody, in patients with advanced solid tumors. *J Clin Oncol*. 2014;**32**:abstr 3001
- [167] Clinical trials.gov. Durvalumab and Tremelimumab in Combination With First-Line Chemotherapy in Advanced Solid Tumors. Available from: <https://clinicaltrials.gov/ct2/show/NCT02658214>
- [168] Clinical trials.gov. A Phase 1b/2 Study of MEDI4736 With Tremelimumab, MEDI4736 or Tremelimumab Monotherapy in Gastric or GEJ Adenocarcinoma. Available from: <https://clinicaltrials.gov/ct2/show/NCT02340975>
- [169] Clinical trials.gov. Phase 1 Study of MLN0264 in Adult Patients With Advanced Gastrointestinal Malignancies Expressing Guanylyl Cyclase C. Available from: <https://clinicaltrials.gov/show/NCT01577758>
- [170] Messersmith W, Almhanna K, Rodon J, Cruz C, Ryan D, Jung JA, Fasanmade A, Wyant T, Kalebic T. PD-0032MLN0264, an investigational, first-in-class antibody drug conjugate targeting guanylyl cyclase C (GCC): First in-human study in patients with advanced gastrointestinal malignancies. *Annals of Oncology*. 2013;**24**:piv36
- [171] Clinical trials.gov. A Study of MLN0264 in Patients with Cancer of the Stomach or Gastroesophageal Junction. Available from: <https://clinicaltrials.gov/ct2/show/NCT02202759>
- [172] Clinical trials.gov. MLN0264 in Previously Treated Asian Patients with Advanced Gastrointestinal Carcinoma or Metastatic or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma Expressing Guanylyl Cyclase C. Available from: <https://clinicaltrials.gov/ct2/show/NCT02391038>
- [173] Lim S, Kaldis P. Cdks, cyclins and CKIs: Roles beyond cell cycle regulation. *Development*. 2013;**140**:3079-3093. PMID: 23861057 DOI: 10.1242/dev.091744
- [174] Schwartz GK, Ilson D, Saltz L, O'Reilly E, Tong W, Maslak P, Werner J, Perkins P, Stoltz M, Kelsen D. Phase II study of the cyclin-dependent kinase inhibitor flavopiridol administered to patients with advanced gastric carcinoma. *Journal of Clinical Oncology*. 2001;**19**:1985-1992. PMID: 11283131
- [175] Fujita T, Doihara H, Washio K, Ino H, Murakami M, Naito M, Shimizu N. Antitumor effects and drug interactions of the proteasome inhibitor bortezomib (PS341) in gastric cancer cells. *Anti-Cancer Drugs*. 2007;**18**:677-686. PMID: 17762396
- [176] Bae SH, Ryoo HM, Kim MK, Lee KH, Sin JI, Hyun MS. Effects of the proteasome inhibitor bortezomib alone and in combination with chemotherapeutic agents in gastric cancer cell lines. *Oncology Reports*. 2008;**19**:1027-1032. PMID: 18357392 DOI: 10.3892/or.19.4.1027

- [177] Ocean AJ, Christos P, Sparano JA, Shah MA, Yantiss RK, Cheng J, Lin J, Papetti M, Matulich D, Schnoll-Sussman F, BesanceneyWebler C, Xiang J, Ward M, Dilts KT, Keresztes R, Holloway S, Chen EX, Wright JJ, Lane ME. Phase II trial of bortezomib alone or in combination with irinotecan in patients with adenocarcinoma of the gastro-esophageal junction or stomach. *Investigational New Drugs*. 2014;**32**:542-548. PMID: 24526575 DOI: 10.1007/s10637-014-0070-0
- [178] Jatoi A, Dakhil SR, Foster NR, Ma C, Rowland KM, Moore DF, Jaslowksi AJ, Thomas SP, Hauge MD, Flynn PJ, Stella PJ, Alberts SR. Bortezomib, paclitaxel, and carboplatin as a firstline regimen for patients with metastatic esophageal, gastric, and gastro-esophageal cancer: Phase II results from the North Central Cancer Treatment Group (N044B). *Journal of Thoracic Oncology*. 2008;**3**:516-520. PMID: 18449005 DOI: 10.1097/JTO.0b013e31816de276
- [179] Shah MA, Power DG, Kindler HL, Holen KD, Kemeny MM, Ilson DH, Tang L, Capanu M, Wright JJ, Kelsen DP. A multicenter, phase II study of bortezomib (PS-341) in patients with unresectable or metastatic gastric and gastroesophageal junction adenocarcinoma. *Investigational New Drugs*. 2011;**29**:1475-1481. PMID: 20574790
- [180] Zhang QW, Liu L, Chen R, Wei YQ, Li P, Shi HS, Zhao YW. Matrix metalloproteinase-9 as a prognostic factor in gastric cancer: A meta-analysis. *Asian Pacific Journal of Cancer Prevention*. 2012;**13**:2903-2908. PMID: 22938481
- [181] He L, Chu D, Li X, Zheng J, Liu S, Li J, Zhao Q, Ji G. Matrix metalloproteinase-14 is a negative prognostic marker for patients with gastric cancer. *Digestive Diseases and Sciences*. 2013;**58**:1264-1270. PMID: 23314917 DOI: 10.1007/s10620-012-2513-9
- [182] Bramhall SR, Hallissey MT, Whiting J, Scholefield J, Tierney G, Stuart RC, Hawkins RE, McCulloch P, Maughan T, Brown PD, Baillet M, Fielding JW. Marimastat as maintenance therapy for patients with advanced gastric cancer: A randomised trial. *British Journal of Cancer*. 2002;**86**:1864-1870. PMID: 12085177

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