Chapter 9
Gastric Cancer: Role of Phytochemicals and Tyrosine Kinase Inhibitors

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Abstract Cancer is one of the prominent causes of mortality in the world while carcinoma of stomach happens to be the seventh most prevalent reason for carcinoma-related mortality worldwide. The development of chemotherapeutic drugs has certainly improved cancer patients' outcomes; however, metastasized cancer remains largely untreatable. Hence, the innovation and research for the effective and safer chemoprevention and treatment of cancers are needed. Cancer chemoprevention and treatments with natural phytochemical compounds is an emerging strategy to potentially cure cancer. For a long time, the study of phytochemicals has shown very encouraging results in clinical trials against cancer cells. Hence, it is recommended that consuming fruits and vegetables by modifying/improving lifestyle can result in the prevention of different gastrointestinal cancers, including gastric carcinoma. In this chapter, we discuss some of the key natural phytochemicals that exercise their antioxidant properties and also act as inhibitors of inflammation and cancer-causing agents by aiming certain pathways and molecules

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in gastric carcinoma along with newer targeted therapies of gastric cancer. We also highlight the role of inhibitors of receptor tyrosine kinases in the carcinoma of stomach.

Keywords Gastric carcinoma · Phytochemicals · Tyrosine kinase inhibitors · Anticancer mechanisms · Clinical trials

Abbreviations

DNA	Deoxyribonucleic acid
EGFR	Epidermal growth factor receptor
FGFR	Fibroblast growth factor receptor
GEJ	Gastroesophageal junction
GST	Glutathione S transferase
H Pylori	*Helicobacter pylori*
IHC	Immunohistochemistry
IL	Interleukin
ITC	Isothiocyanates
NADPH	Nicotinamide adenine dinucleotide phosphate
OS	Overall survival
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinases
SFN	Sulforaphane
TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
UDP	Uridine 5′-diphosphate
UGT	UDP-glucuronosyltransferase
VEGFR	Vascular endothelial growth factor receptor

1 Introduction

Cancer remains one of the leading sources of morbidity and death worldwide, and an upsurge in cancer incidence is witnessed in the recent years as well. It is second behind cardiovascular diseases as the leading source of mortality in developed nations [1]. The development of malignancy is marked by uncontrolled and sustained proliferation, notwithstanding apoptosis, which can invade tissues and angiogenesis. Genetic alterations in the cell can produce unstable genetic makeover resulting in normal cells transforming into a malignant cell. These changes consist of alterations in tumor-suppressor genes, oncogenes, and DNA repair genes, which are involved in cell growth and differentiation. Some extrinsic elements (smoking,

infectious agents, and radiation) as well as intrinsic causes (immune conditions, and hormones) are responsible for these mutations.

Carcinoma of the stomach stands as the top ten leading sources of carcinoma-related deaths. Studies have shown that factors such as exposure to cancer causing chemical agents and bacteria such as *Helicobacter pylori* are the two main causative factors resulting in the initiation of several events causing gastric carcinoma [2]. Infection by *H. pylori* can result in gastric mucosal infiltration with macrophages and neutrophil cells which further results in the production of harmful free radicals called reactive oxygen species (ROS) including superoxide and nitric oxide, which go on to cause gastric mucosal injury, ulcer, and eventually carcinoma [3]. Phytochemicals with antioxidant properties may help in protecting against carcinoma.

Consumption of fruits and herbal medicine is the most suitable and productive method of taking phytochemicals on a daily basis and in a cost-effective manner. In this chapter, we review the natural phytochemicals that possess antioxidant, anti-oncogenic, or anti-inflammatory properties that function via altering the course of action of different molecules involved in gastric carcinogenesis. We also discuss the newer targeted therapies extensively being studied for gastric cancer with special reference to tyrosine inhibitors that play critical roles in gastric cancer outcomes.

2 Curcumin

Turmeric plants (*Curcuma longa*) contain a bright yellow pigment called curcumin. Curcumin also happens to be the major curcuminoid present in turmeric. There is vast evidence about the numerous advantages of curcumin such as anti-inflammatory, antioxidant, and antitumor properties [4, 5]. The mode of action of curcumin is mainly mediated by targeting multiple intracellular pathways [6]. Over the years, inability to clear *H. pylori* infection has been implicated as the main cause of gastritis, ulcers, and eventually gastric carcinoma. Recently, it has been shown that curcumin is effective in arresting the growth of *H. pylori* [7]. The prospective therapeutic capabilities of curcumin have been assessed through several in vitro studies. The main reason for tumors being resistant to chemotherapy is the overexpression of nuclear transcription factor NF-κB. Curcumin can suppress the NF-κB effects, thereby augmenting chemotherapeutic drug effects. Yu et al. [8] in their studies showed enhanced activity of chemotherapeutic drugs (doxorubicin and etoposide) in combination with curcumin as compared to either of the drugs alone. Studies on the gastric cancer cell cultures (SGC 7901) in humans have shown that curcumin causes downregulation of NF-κB, which further results in the downregulation cell death inhibitor genes such as Bcl-2 and Bcl-xl via inhibition of NF-κB activity [8].

It has been shown previously that curcumin inhibits the receptor tyrosine kinase, EGFR, as well as downstream regulation of EGFR tyrosine kinase, p21-activated tyrosine kinase 1 (PAK1), without affecting its expression. In addition, curcumin causes mRNA suppression, which results in decreased production of cyclin-D1

protein and eventually results in the arrest of cell cycle progression in G1 phase. Consequently, curcumin can inhibit not only the cell proliferation but also the invasion of gastric carcinoma cells [9].

3 Isothiocyanates

Isothiocyanates (ITCs) are plant phytochemicals that are abundantly present in vegetables belonging to the family Cruciferae such as broccoli, Brussels sprouts, wasabi, radish, and turnips [3]. These occur in their inactive form, glucosinolates, and become reactive after coming in contact with an enzyme called myrosinase present in the oral cavity and small intestine. Some of the ITCs consist of aliphatic ITC (AITC) and sulforaphane (SFN) which are aliphatic compounds, and phenethyl ITC (pEITC) and benzyl ITC (BITC) which are aromatic.

Isothiocyanates have been shown to decrease the activity of enzymes that are responsible for the biotransformation of xenobiotics. The oxidative enzyme that facilitates phase one reactions is nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome P450 reductase while glutathione S transferase (GST) and uridine 5′-diphospho (UDP)-glucuronosyltransferase (UGT) enzymes are responsible for second-phase reactions. It is believed that ITCs such as sulforaphane exert its antioxidant effects by stimulating Nrf-2-dependent enzymes, such as GST, thus guarding against the free radicals [10–12]. Sulforaphane can maintain the effect of enzymes such as NADPH, quinone oxidoreductase NQOI, and GST in Nrf-2-deficient mice when injected with foods containing large quantities of salt and *H. pylori* [3]. These results demonstrate the antioxidant potential of sulforaphane on the gastric mucosa.

SFN can also increase the Nrf-2-dependent antioxidant effect. A study by Fahey et al. [10] has shown that sulforaphane can inhibit the development of gastric cancer in the Institute of Cancer Research (ICR) mice which were treated with benzo[a] pyrene. These effects are thought to be facilitated by stimulation of phase two reactions of GST and NQOI, and also by an increase in the production of antioxidant enzymes, which are abolished by the deletion of Nrf-2 gene in the mice [10]. In patients with gastritis due to *H. pylori*, eradication of the bacteria augmented or reinstated the GST enzyme levels, which further reinforces the significance of antioxidants in preventing *H. pylori*-associated gastric tumors [13].

Sulforaphane also possesses chemopreventive activities against *H. pylori* infection [3]. During a study on people infected with *H. pylori*, 48 subjects were followed who ingested 70 g/d of broccoli (precursor of 420 μmol/L sulforaphane) for 8 weeks and were compared with placebo. The study reported a decline in *H. pylori* markers such as stool antigen and urease enzyme when compared to placebo. A decline in gastric inflammation markers such as pepsinogen 1 and 2 was noticed in broccoli group as well compared to placebo [14]. A study in C57BL/6 female mice that were infected with *H. pylori* and were kept on excessive salt regime also established the potential of sulforaphane in bacterial inhibition [14]. Consumption of

sulforaphane-enriched broccoli in mice resulted in low levels of interleukin (IL)-1β and tumor necrosis factor (TNF)-α adding to the improvement of inflammation, decrease of bacterial colonization, and thus prevention of gastric corpus atrophy via high-salt diet. Interestingly, there were no effects of sulforaphane on Nrf-2 gene-depleted mice, suggesting that its mechanism of action is Nrf-2 dependent [14].

4 Resveratrol

Resveratrol belongs to the family of a polyphenol commonly found in red wine and red grapes. There has been a widely reported benefit of red wine with the inverse relation of cardiovascular diseases [15]. Studies have also shown beneficial effects of resveratrol on the neuronal cell death [16]. It is also believed that resveratrol is responsible for the benefits of red wine on cardiovascular diseases [17]. This prompted for extensive research on resveratrol in malignancies during the last 20 years focusing on its anti-inflammatory, antioxidant, and anticancer potential [18]. Exposure of gastric cells to *H. pylori* results in elevated IL-8 production and free radical production. Furthermore, *H. pylori* infection resulted in stimulation of gastric motility and phenotype alterations observed in cell lines through humming-bird effect [19]. It was also established that resveratrol possesses antibacterial activity against *H. pylori* infection, resulting in hampering of the *H. pylori* proliferation [20–22]. Treatment with resveratrol significantly reduced IL-8 expression, decreased free radical production, and suppressed the phenotype alterations in *H. pylori*-infected cells. These positive results explain the potential of resveratrol in gastric cancer treatment.

In vitro studies have shown that resveratrol can cause cell cycle arrest in the G0/G1 phase via inhibition of the kinase C-mediated processes and further stimulation of cell apoptosis. This cell cycle inhibition hampers the formation of RF-1 and KATO-III cells [23, 24]. Another critical mechanism by which resveratrol regulates the growth and expansion of gastric adenocarcinoma cells happens to be the MEK1/2-ERK1/2-c-Jun cascade. Studies have postulated that resveratrol causes MEK1/2-ERK1/2 phosphorylation downregulation, thereby further inhibiting c-Jun translocation into the nucleus, ultimately resulting in cell growth inhibition [25]. Furthermore, resveratrol (50–200 μmol/L) can also stimulate cell death by producing ROS in human gastric cancer SGC7901 cells. These effects of resveratrol could be overturned when tumor cells are treated with substances such as superoxide dismutase and catalase, which dilute the apoptotic process [26]. Resveratrol can cause cell death of transplanted tumor cells, most likely mediated by suppression of Bcl2 anti-apoptotic genes and cell death activation via Bax gene in an implanted gastric tumor cells in nude mice [27] (Fig. 9.1).

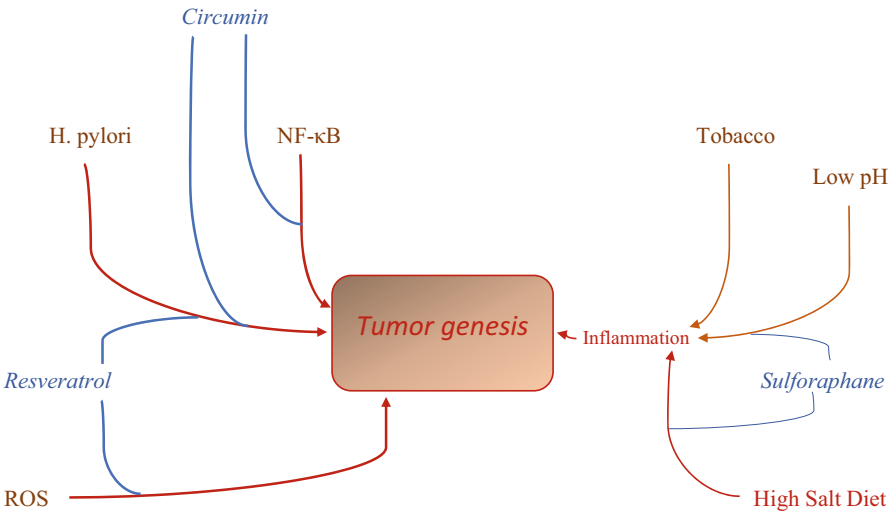

Fig. 9.1 Schematic representation of the mechanisms of action of phytochemicals and pro-cancer/tumor formation agents

5 Receptor Tyrosine Kinases (RTKs) and Tyrosine Kinase Inhibitors (TKIs)

Studies have shown that in gastric cancer, several receptor tyrosine kinases get stimulated and amplified. So, drugs aimed at controlling the RTKs can be beneficial in advanced gastric carcinoma people. RTKs occur as transmembrane glycoproteins that comprise a domain for ligand attachment extracellular, a motif for the tyrosine kinase, and another domain across the membrane [28–30]. The extracellular domain of the RTK helps in the identification of various subfamilies of the kinases. Binding of the corresponding ligands to the RTKs results in their activation via tyrosine molecule phosphorylation and further activation of cellular proteins [31]. Activated RTKs play a major regulatory role in a variety of cellular processes including proliferation, differentiation, migration, and survival [32]. When some of the bivalent ligands bind to two receptor molecules, it forms a dimer, which results in the activation of the kinases [33]. The activation of kinases is dependent on two key steps; the first step is augmentation of catalysis intrinsically while the second step consists of formation of protein attachment sites intracellularly, both of which are dependent on tyrosine autophosphorylation. While phosphorylation of tyrosine molecules near the enzyme's activation loop upregulates kinase actions, phosphorylation of the enzyme adjacent to the membrane helps in the formation of anchors for the attachment of modules, which identify the phosphotyrosine molecules in precise patterns [34] (Fig. 9.2).

Tyrosine kinase receptors are classified into 21 groups, such as the epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor

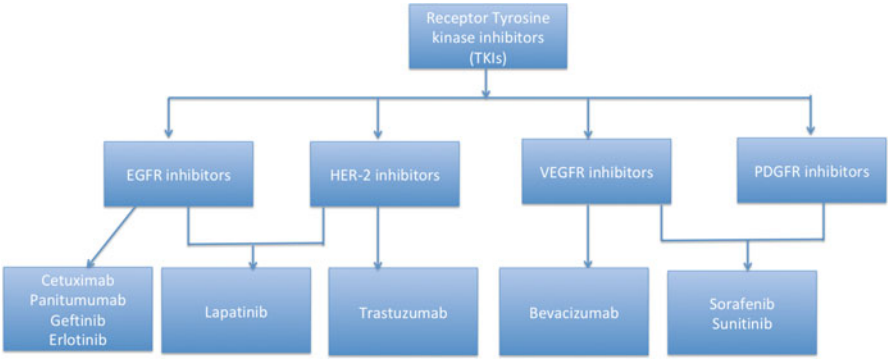

Fig. 9.2 Selected tyrosine kinase inhibitors and their relationship with gastric cancer

(VEGFR), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR) families [35]. In cancer cells, RTKs play a major role in various cellular processes such as growth, differentiation, and metabolism. Studies have also shown that monoclonal antibodies can inhibit the activation and overexpression of kinases in cancer cells. Some of the RTK inhibitors that became standard treatment options in various malignancies include trastuzumab in carcinoma of breast [36], gefitinib in lung cancer [37], and cetuximab in advanced colorectal carcinoma [38].

Studies have shown that RTKs exhibit various mutations and changes in gastric cancer patients. Mutations and overexpression of RTKs were observed in 37% of people diagnosed with gastric carcinoma [39]. The study has also reported the family of kinases that were amplified including KRAS in 8.8% of people with gastric cancer, FGFR2 in 9.3%, EGFR in 7.7%, and ErbB2 in 7.2% of the diagnosed patients. Moreover, upregulation of RTKs was found to be associated with patient prognosis; higher RTK levels correlated with inferior patient outcomes. Later, in a study by Morishita et al. [31], the levels of various RTKs (EGFR, FGFR1/2, ErbB2) were amplified in tumor cells in contrast with healthy gastric cells. The findings of these studies propose that drugs targeting kinase receptors can be beneficial in patients with gastric malignancies.

There are many monoclonal antibodies under various phases of clinical trials such as trastuzumab, cetuximab, and lapatinib, which are classified based on their ability of inhibition of various families of RTKs (Table 9.1). Below we summarize the biological and clinical applications of these monoclonal antibodies in gastric cancer.

Table 9.1 An updated summary of the current clinical trials studying tyrosine kinase inhibitors in gastric cancer

Sl. No.	Name of the study	Drug evaluated	Country, trial is conducted	Status of the trial	Condition treated
1.	Study Evaluating Pyrotinib/ Pyrotinib in Combination with Docetaxel in Patients with HER2+ Advanced Gastric Cancer	Pyrotinib/pyrotinib with docetaxel	• Beijing Cancer Hospital, Peking University, Beijing, China • Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China • Chinese PLA General Hospital, Beijing, China • Cancer Center, Sun Yet-Sen University, Guangzhou, Guangdong, China	Unknown	HER2-positive gastric cancer
2.	FLO +/− Pazopanib as First-line Treatment in Advanced Gastric Cancer	• Pazopanib • 5-FU, oxaliplatin, leucovorin (FLO)	Charite University Medicine, Berlin, Germany	Completed	Advanced gastric cancer
3.	Exploratory Clinical Study of Apatinib and SHR-1210 in Treating Advanced Hepatocellular Carcinoma or Gastric Cancer	• Apatinib • SHR-1210	The Affiliated Hospital of the Chinese Academy of Military Medical Sciences, Beijing, China	Unknown	• Gastric cancer • Hepatocellular carcinoma
4.	A Study to Evaluate the Clinical Efficacy of JNJ-42756493 (Erdafitinib), A Pan-Fibroblast Growth Factor Receptor (FGFR) Tyrosine Kinase Inhibitor, in Asian Participants with Advanced Non-small-Cell Lung Cancer, Urothelial Cancer, Esophageal Cancer or Cholangiocarcinoma	Erdafitinib	• Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China • Beijing Cancer Hospital of Peking University, Beijing, China • Beijing Cancer Hospital of Peking University, Beijing, China • (and 33 more …)	Recruiting	Neoplasm
5.					

	Study of GSK1363089 in Metastatic Gastric Cancer	GSK1363089 (formerly XL880)	• GSK Investigational Site, Birmingham, Alabama, USA • GSK Investigational Site, Scottsdale, Arizona, USA • GSK Investigational Site, Los Angeles, California, USA • (and 14 more . . .)	Completed. Has results	Neoplasms, gastrointestinal tract
6.	Apatinib Combined with Capecitabine Second-line Treatment of Advanced Gastric Cancer: A Single-Arm Exploratory Clinical Pilot Trial	Apatinib/capecitabine	First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China	Not yet recruiting	Progression-free survival; disease control rate; safety
7.	Conversion Therapy of Sintilimab in Combination with Apatinib and Chemotherapy in Unresectable Gastric Cancer	• Sintilimab • Apatinib • S1 • Nab paclitaxel	Department of Gastrointestinal Medical Oncology, Tianjin Medical University Cancer Hospital, Tianjin, China	Recruiting	Gastric cancer stage
8.	Cabozantinib in Combination with Durvalumab in Patients with Gastroesophageal Cancer and Other Gastrointestinal Malignancies (CAMILLA)	• Cabozantinib • Durvalumab	The University of Kansas Cancer Center, Fairway, Kansas, USA	Recruiting	• Gastric cancer • Esophageal adenocarcinoma • Hepatocellular carcinoma • Colorectal cancer
9.	Prognostic Value and Clinical Pathology of c-MET Expression and Amplification in Gastric Carcinoma	Prognostic markers/values	Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China	Unknown	Gastric cancer
10.	Cabozantinib S-malate in Treating Patients with Neuroendocrine Tumors Previously Treated with Everolimus That Are Locally Advanced,	• Cabozantinib S-malate • Laboratory biomarker analysis • Placebo administration • Quality-of-life assessment	• Katmai Oncology Group, Anchorage, Alaska, USA • Kingman Regional Medical Center, Kingman, Arizona, USA • University of Arkansas for Medical Sciences, Little	Recruiting	• Atypical carcinoid tumor • Carcinoid tumor • Digestive system neuroendocrine neoplasm • (and 13 more...)

(continued)

Table 9.1 (continued)

Sl. No.	Name of the study	Drug evaluated	Country, trial is conducted	Status of the trial	Condition treated
	Metastatic, or Cannot Be Removed by Surgery		Rock, Arkansas, USA • (and 347 more . . .)		
11.	Capecitabine and Cisplatin (XP) + Sorafenib in Advanced Gastric Cancer (AGC): Sorafenib + XP	Capecitabine, cisplatin, sorafenib	Asan Medical Center, Seoul, Korea	Completed. Has results	Advanced gastric cancer
12.	Patterns of Care and Outcomes of Patients with METAstatic Gastrointestinal Stromal Tumors (METAGIST)	Oral tyrosine-kinase inhibitors (TKI) of KIT and PDGFR as per recommendations	Institut Bergonié, Comprehensive Cancer Center, Bordeaux, France	Recruiting	Gastrointestinal stromal tumor
13.	Efficacy and Safety of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) in Previously Treated Participants with Select Solid Tumors (MK-7902-005/E7080-G000–224/LEAP-005)	• Pembrolizumab • Lenvatinib	• City of Hope (Site 0002), Duarte, California, USA • Cedars Sinai Medical Center (Site 0003), Los Angeles, California, USA • University of California, Davis Comprehensive Cancer Center (Site 0005), Sacramento, California, USA • (and 45 more . . .)	Active, not recruiting	• Advanced solid tumors • Triple-negative breast cancer • Ovarian cancer • (and 4 more . . .)
14.	Targeted Therapy Directed by Genetic Testing in Treating Patients with Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (the MATCH Screening Trial)	• Adavosertib • Afatinib • Afatinib Dimaleate • (and 30 more . . .)	• University of Alabama at Birmingham Cancer CenterBirmingham, Alabama, USA • Mobile Infirmary Medical Center, Mobile, Alabama, USA • University of South Alabama Mitchell Cancer Institute, Mobile, Alabama, USA • (and 1312 more . . .)	Recruiting	• Advanced malignant solid neoplasm • Bladder carcinoma • Breast carcinoma • (and 47 more . . .)

15.	GIST: Assessment of Tumor Mutations and TKI Plasma Exposure	• Vena puncture for blood collection • Tumor biopsy	• Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands • University Medical Center Groningen, The Netherlands • Leiden University Medical Center, Leiden, The Netherlands • (and 2 more . . .)	Recruiting	Gastrointestinal stromal tumor
16.	Multi-center Placebo-Controlled Double-blinded Phase II Study of Lenvatinib Efficacy in Patients with Locally Advanced or Metastatic GIST (Gastrointestinal Stromal Tumor) After Imatinib/Sunitinib Failure	Lenvatinib	• Centre Léon BérardLyon, France • Institut Gustave Roussy, Villejuif, France	Not yet recruiting	Gastrointestinal stromal tumor
17	A Phase 1 Study of KBP-5209 in Patients with Advanced Solid Tumors	KBP-5209	• Indiana University, Melvin and Bren Simon Cancer Center, Indianapolis, Indiana, USA • University of Texas, MD Anderson Cancer CenterHouston, Texas, USA • University of Utah Huntsman Cancer Institute, Salt Lake City, Utah, USA	Unknown	Advanced solid tumors

5.1 HER-2 Inhibitors

5.1.1 Trastuzumab

Trastuzumab is a monoclonal antibody which targets HER-2 and causes inhibition of its downward signaling. ErbB2/HER cluster comprises four different receptors and HER-2 (ErbB2) is one among them. Studies have demonstrated that 10–38% of people with gastric malignancies present with amplification of HER-2; inhibition of HER-2 has demonstrated successful results in metastatic gastric carcinoma cases [40–42]. Nevertheless, the study was unable to show clear results regarding the relationship between HER-2 amplification and clinical outcome in advanced gastric cancer [43, 44].

Bang et al. [45] in the ToGA trial reported that patients who were HER-2 positive had a greater benefit [based on the immunohistochemistry (IHC) scoring system] when managed with trastuzumab. In 2006, the results of clinical trials on the effects of trastuzumab in late stages of gastric cancer got published. In the first phase II clinical trials, the combination of trastuzumab with cisplatin and docetaxel showed improved response on radiological findings in four out of five patients with advanced gastric carcinoma and cancer of gastroesophageal junction (GEJ) who are HER-2 positive [46]. Another phase II study was conducted in people who presented with metastatic gastric cancer or GEJ cancer and are HER-2 positive. During the study, the patients were put on a combination therapy consisting of trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) and cisplatin (75 mg/m^2) every 3 weeks until relapse. The study reported positive results in terms of patient response (35% out of 17 people) at the end of an average of two treatment cycles [47].

An open-label, global, phase III, clinical trial (the ToGA study) was conducted including many countries where the people with gastric cancer were randomly given either combination therapy with trastuzumab + chemotherapy or chemotherapy monotherapy. The study demonstrated positive results in terms of median overall survival (OS) in the combination therapy arm which was 13.8 months, whereas in the second group the median OS was only 11.1 months. The combination arm also showed an improved OS and progression-free survival (PFS); an increase in median survival by almost 2.7 months was witnessed in the trastuzumab group [45]. However, it was worth noting that trastuzumab was associated with an elevated probability of type 2 chemotherapy-related cardiac issues, which were managed by the removal of the antibody [48]. Nevertheless, the patients in the trastuzumab group did not report any positive results in terms of quality of life [49].

5.2 EGFR Inhibitors

EGFR amplification and activation happened in significant number of patients (27–64%) with gastric carcinoma, more predominantly for proximally located

cancers. The EGFR amplification was correlated with poor prognosis as well [50, 51]. Other factors that were associated with EGFR overexpression were elderly people, infiltrative pathologies, and advanced cancers. Drugs that are aimed against EGFR include the following:

5.2.1 Cetuximab

Cetuximab is a monoclonal antibody (mAb) that inhibits EGFR. It also remains the most frequently studied EGFR inhibitor in people with gastric carcinoma. In gastric cancer patients, several studies were conducted to understand the impact of cetuximab. A total of six clinical studies reported that the combination therapy of cetuximab and chemotherapy resulted in positive results in terms of response rate (41–63%) and median OS (9–16.6 months) [52–55]. Contrary to this, the initial results from a phase II study in 2011 [56] showed that the combination therapy consisting of cetuximab and docetaxel + oxaliplatin failed to produce positive results. Later, a phase III clinical study (NCT00678535) [57] that examined the effects of cetuximab in combination with cisplatin + capecitabine also reported similar results in 2013. The combination therapy reported no benefit in terms of PFS (4.4 months in combination therapy vs. 5.6 months in chemotherapy alone). Furthermore, majority of the patients in the study (83% in combination therapy group and 77% in chemotherapy alone) suffered from adverse events including diarrhea, dermatitis, low potassium and magnesium levels, and hand-foot syndrome.

5.2.2 Gefitinib and Erlotinib

EGFR inhibitors, gefitinib and erlotinib, are frontline drugs used in the management of GEJ cancer. However, in patients with advanced gastric cancer, both the drugs failed to produce positive results when used as monotherapy during the phase II clinical trials [58].

5.2.3 Panitumumab

There are very few study results regarding the effect of panitumumab in advanced gastric carcinoma therapy. REAL3, a phase III clinical study [59], classified and studied esophagogastric carcinoma patients based on the treatment received; the first group received combination therapy consisting of chemotherapeutic agents epirubicin, oxaliplatin, and capecitabine (EOC) and panitumumab whereas the second set of patients received chemotherapy alone. The median overall survival in the chemotherapy-alone (EOC) group was 11.3 months whereas the median OS was 8.8 months in the combination (mEOC plus P) group. The patients in the combination therapy arm also suffered from drug side effects such as diarrhea, rash, mucositis, and neutropenia.

Matuzumab and nimotuzumab are other EGFR inhibitors that were tested in combination with chemotherapy during phase II clinical studies. Unfortunately, both the drugs produced unsatisfactory clinical outcomes in terms of PFS [60, 61].

5.3 Combined EGFR and HER-2 Inhibitor

Lapatinib is a dual inhibitor of RTKs acting on HER-2 and EGFR. The efficacy of lapatinib in gastric carcinoma patients was tested in a phase II trial where the drug demonstrated positive clinical outcomes in terms of overall reduction rate (ORR), which was 7%, and disease stabilization rate of 20%. Adverse effects included grade 4 fatigue (two patients) and vomiting [62]. In patients with metastatic gastric cancer, the efficacy of lapatinib is being tested in two current phase III clinical studies. In the first study (LoG-IC trial) [63], lapatinib is being tested as a frontline drug in combination with chemotherapeutic agents oxaliplatin and capecitabine. The second clinical trial (TYTAN) [64] is being conducted on Asian population who are diagnosed with HER-2-positive gastric cancer. In this trial, paclitaxel is tested as a second-line drug with/without lapatinib combination. The results of both these studies are expected to help establish lapatinib as an option for metastatic gastric carcinoma treatment.

5.4 VEGFR Inhibitor

Bevacizumab (Avastin) is a monoclonal antibody, which suppresses angiogenesis via inhibition of vascular endothelial growth factor-A (VEGF-A). In advanced gastric cancer patients, bevacizumab has shown an ORR of 42–67% and an OS of 8.9–16.2 months, during the phase II clinical trials. Adverse events consisted of grade 3–4 thromboembolic disease (25%) and gastric perforation (8%) [65–67]. The phase III clinical trial (AVAGAST) [68] focused on assessing the effectiveness of bevacizumab as second-line therapy in metastatic gastric cancer patients. Patients were classified into two groups; the first set of patients were put on bevacizumab in addition to frontline therapy with capecitabine-cisplatin whereas the second group received chemotherapy alone. The overall survival drastically enhanced after bevacizumab incorporation (46% vs. 37%) and the median PFS got notably prolonged as well (6.7 vs. 5.3 months). Moreover, the results varied based on the geographical location.

An increase in the OS was also seen in all the patients of American origin whereas no significant survival benefits were observed in the Asian and European patients. However, the authors reported a prognostic benefit with bevacizumab. These results could be due to alterations in patient selection, genetic variations within populations, and intake of second-line drugs in those patients. During the AVAGAST study, Ohtsu et al. stated that the prognosis of patients with metastatic gastric cancer could

be associated with the levels of angiogenic factors, such as tumor neuropilin-1 and plasma VEGF-A [68, 69]. Unfortunately, patients in both the study arms experienced side effects such as anemia, neutropenia, and anorexia [68].

5.5 Dual Inhibitors of VEGFR and PDGFR

Sorafenib suppresses a variety of RTKs such as VEGF, PDGFR, and BRAF. Sunitinib causes inhibition of VEGFR, PDGFR, c-Kit, and Flt-3. Both the antibodies did not show any significant survival benefits in phase II studies [70–72] (Table 9.1).

6 Conclusion

Phytochemicals are abundantly found in fruits and vegetables and have been valuable in gastric cancer. While the combination of phytochemicals could augment antitumor effects on gastric cancer through multiple prevention mechanisms, additional translational and clinical outcome researches are necessary to greatly understand their potential benefits in cancer prevention and prognosis. In addition, several receptor tyrosine kinases are stimulated in gastric malignancies; therefore identification of kinase inhibitors can be potentially beneficial in providing tailored treatment to the patients. Several clinical trials are in development and are anticipated to provide benefits in clinical practice.

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References

1. Siegel, R. L., Miller, K. D., & Jemal, A. (2020). Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians, 70*(1), 7–30.
2. Kuipers, E. J. (1999). Exploring the link between Helicobacter pylori and gastric cancer. *Alimentary Pharmacology & Therapeutics, 13*, 3–11.
3. Yanaka, A. (2011). Sulforaphane enhances protection and repair of gastric mucosa against oxidative stress in vitro, and demonstrates anti-inflammatory effects on helicobacter pylori infected gastric mucosae in mice and human subjects. *Current Pharmaceutical Design, 17*(16), 1532–1540.

4. Esatbeyoglu, T., Huebbe, P., Ernst, I. M., Chin, D., Wagner, A. E., & Rimbach, G. (2012). Curcumin—From molecule to biological function. *Angewandte Chemie International Edition, 51*(22), 5308–5332.
5. Goel, A., & Aggarwal, B. B. (2010). Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs. *Nutrition and Cancer, 62*(7), 919–930.
6. Lee, K. W., Bode, A. M., & Dong, Z. (2011). Molecular targets of phytochemicals for cancer prevention. *Nature Reviews Cancer, 11*(3), 211.
7. De, R., Kundu, P., Swarnakar, S., Ramamurthy, T., Chowdhury, A., Nair, G. B., & Mukhopadhyay, A. K. (2009). Antimicrobial activity of curcumin against Helicobacter pylori isolates from India and during infections in mice. *Antimicrobial Agents and Chemotherapy, 53* (4), 1592–1597.
8. Yu, L. L., Wu, J. G., Dai, N., Yu, H. G., & Si, J. M. (2011). Curcumin reverses chemoresistance of human gastric cancer cells by downregulating the NF-κB transcription factor. *Oncology Reports, 26*(5), 1197–1203.
9. Cai, X. Z., Wang, J., Xiao-Dong, L., Wang, G. L., Liu, F. N., Cheng, M. S., & Li, F. (2009). Curcumin suppresses proliferation and invasion in human gastric cancer cells by down-regulation of PAK1 activity and cyclin D1 expression. *Cancer Biology & Therapy, 8*(14), 1360–1368.
10. Fahey, J. W., Haristoy, X., Dolan, P. M., Kensler, T. W., Scholtus, I., Stephenson, K. K., Talalay, P., & Lozniewski, A. (2002). Sulforaphane inhibits extracellular, intracellular, and antibiotic-resistant strains of Helicobacter pylori and prevents benzo [a] pyrene-induced stomach tumors. *Proceedings of the National Academy of Sciences USA, 99*(11), 7610–7615.
11. Fahey, J. W., Zhang, Y., & Talalay, P. (1997). Broccoli sprouts: An exceptionally rich source of inducers of enzymes that protect against chemical carcinogens. *Proceedings of the National Academy of Sciences USA, 94*(19), 10367–10372.
12. Ramos-Gomez, M., Kwak, M. K., Dolan, P. M., Itoh, K., Yamamoto, M., Talalay, P., & Kensler, T. W. (2001). Sensitivity to carcinogenesis is increased and chemoprotective efficacy of enzyme inducers is lost in nrf2 transcription factor-deficient mice. *Proceedings of the National Academy of Sciences US, 98*(6), 3410–3415.
13. van Oijen, A. H., Verhulst, M. L., Roelofs, H. M., Peters, W. H., de Boer, W. A., & Jansen, J. B. (2001). Eradication of Helicobacter pylori restores glutathione S-transferase activity and glutathione levels in antral mucosa. *Japanese Journal of Cancer Researc, 92*(12), 1329–1334.
14. Yanaka, A., Fahey, J. W., Fukumoto, A., Nakayama, M., Inoue, S., Zhang, S., Tauchi, M., Suzuki, H., Hyodo, I., & Yamamoto, M. (2009). Dietary sulforaphane-rich broccoli sprouts reduce colonization and attenuate gastritis in Helicobacter pylori-infected mice and humans. *Cancer Prevention Research, 2*(4), 353–360.
15. Kopp, P. (1998). Resveratrol, a phytoestrogen found in red wine. A possible explanation for the conundrum of the 'French paradox'? *European Journal of Endocrinology, 138*(6), 619–620.
16. Sun, A. Y., Simonyi, A., & Sun, G. Y. (2002). The "French paradox" and beyond: Neuroprotective effects of polyphenols. *Free Radical Biology and Medicine, 32*(4), 314–318.
17. Hung, L. M., Chen, J. K., Huang, S. S., Lee, R. S., & Su, M. J. (2000). Cardioprotective effect of resveratrol, a natural antioxidant derived from grapes. *Cardiovascular Research, 47*(3), 549–555.
18. Catalgol, B., Batirel, S., Taga, Y., & Ozer, N. K. (2012). Resveratrol: French paradox revisited. *Frontiers in Pharmacology, 3*, 141.
19. Zaidi, S. F., Ahmed, K., Yamamoto, T., Kondo, T., Usmanghani, K., Kadowaki, M., & Sugiyama, T. (2009). Effect of resveratrol on Helicobacter pylori-induced interleukin-8 secretion, reactive oxygen species generation and morphological changes in human gastric epithelial cells. *Biological and Pharmaceutical Bulletin, 32*(11), 1931–1935.
20. Daroch, F., Hoeneisen, M., González, C. L., Kawaguchi, F., Salgado, F., Solar, H., & García, A. (2001). In vitro antibacterial activity of Chilean red wines against Helicobacter pylori. *Microbios, 104*(408), 79–85.

21. Mahady, G. B., Pendland, S. L., & Chadwick, L. R. (2003). Resveratrol and red wine extracts inhibit the growth of CagA+ strains of Helicobacter pylori in vitro. *The American Journal of Gastroenterology, 98*(6), 1440.
22. Mahady, G. B., & Pendland, S. L. (2000). Resveratrol inhibits the growth of Helicobacter pylori in vitro. *The American Journal of Gastroenterology, 95*(7), 1849.
23. Atten, M. J., Attar, B. M., Milson, T., & Holian, O. (2001). Resveratrol-induced inactivation of human gastric adenocarcinoma cells through a protein kinase C-mediated mechanism. *Biochemical Pharmacology, 62*(10), 1423–1432.
24. Atten, M. J., Godoy-Romero, E., Attar, B. M., Milson, T., Zopel, M., & Holian, O. (2005). Resveratrol regulates cellular PKC α and δ to inhibit growth and induce apoptosis in gastric cancer cells. *Investigational New Drugs, 23*(2), 111–119.
25. Aquilano, K., Baldelli, S., Rotilio, G., & Ciriolo, M. R. (2009). Trans-resveratrol inhibits H_2O_2-induced adenocarcinoma gastric cells proliferation via inactivation of MEK1/2-ERK1/2-c-Jun signalling axis. *Biochemical Pharmacology, 77*(3), 337–347.
26. Wang, Z., Li, W., Meng, X., & Jia, B. (2012). Resveratrol induces gastric cancer cell apoptosis via reactive oxygen species, but independent of sirtuin1. *Clinical and Experimental Pharmacology and Physiology, 39*(3), 227–232.
27. Zhou, H. B., Chen, J. J., Wang, W. X., Cai, J. T., & Du, Q. (2005). Anticancer activity of resveratrol on implanted human primary gastric carcinoma cells in nude mice. *World Journal of Gastroenterology, 11*(2), 280.
28. Robinson, D. R., Wu, Y. M., & Lin, S. F. (2000). The protein tyrosine kinase family of the human genome. *Oncogene, 19*(49), 5548–5557. https://doi.org/10.1038/sj.onc.1203957.
29. Schlessinger, J. (2000). Cell signaling by receptor tyrosine kinases. *Cell, 103*(2), 211–225.
30. Olayioye, M. A., Neve, R. M., Lane, H. A., & Hynes, N. E. (2000). The ErbB signaling network: Receptor heterodimerization in development and cancer. *The EMBO Journal, 19*(13), 3159–3167.
31. Morishita, A., Gong, J., & Masaki, T. (2014). Targeting receptor tyrosine kinases in gastric cancer. *World Journal of Gastroenterology, 20*(16), 4536.
32. Hubbard, S. R., & Till, J. H. (2000). Protein tyrosine kinase structure and function. *Annual Review of Biochemistry, 69*(1), 373–398.
33. Lemmon, M. A., & Schlessinger, J. (2010). Cell signaling by receptor tyrosine kinases. *Cell, 141*(7), 1117–1134.
34. Kuriyan, J., & Cowburn, D. (1997). Modular peptide recognition domains in eukaryotic signaling. *Annual Review of Biophysics and Biomolecular Structure, 26*(1), 259–288.
35. Becker, J. C., Müller-Tidow, C., Serve, H., Domschke, W., & Pohle, T. (2006). Role of receptor tyrosine kinases in gastric cancer: New targets for a selective therapy. *World Journal of Gastroenterology, 12*(21), 3297–3305.
36. Shawver, L. K., Slamon, D., & Ullrich, A. (2002). Smart drugs: Tyrosine kinase inhibitors in cancer therapy. *Cancer Cell, 1*(2), 117–123.
37. Cohen, M. H., Williams, G. A., Sridhara, R., Chen, G., & Pazdur, R. (2003). FDA drug approval summary: Gefitinib (ZD1839) (Iressa) tablets. *The Oncologist, 8*(4), 303–306.
38. (2004). New treatments for colorectal cancer. *FDA Consumer, 38*(3), 17.
39. Deng, N., Goh, L. K., Wang, H., Das, K., Tao, J., Tan, I. B., Zhang, S., Lee, M., Wu, J., Lim, K. H., & Lei, Z. (2012). A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. *Gut, 61*(5), 673–684.
40. Yano, T., Ohtsu, A., Boku, N., Hashizume, K., Nakanishi, M., & Ochiai, A. (2006). Comparison of HER2 gene amplification assessed by fluorescence in situ hybridization and HER2 protein expression assessed by immunohistochemistry in gastric cancer. *Oncology Reports, 15*(1), 65–71.
41. Koeppen, H. K., Wright, B. D., Burt, A. D., Quirke, P., McNicol, A. M., Dybdal, N. O., Sliwkowski, M. X., & Hillan, K. J. (2001). Overexpression of HER2/neu in solid tumours: An immunohistochemical survey. *Histopathology, 38*(2), 96–104.

42. Jaehne, J., Urmacher, C., Thaler, H. T., Friedlander-Klar, H., Cordon-Cardo, C., & Meyer, H. J. (1992). Expression of Her2/neu oncogene product p185 in correlation to clinicopathological and prognostic factors of gastric carcinoma. *Journal of Cancer Research and Clinical Oncology, 118*(6), 474–479.
43. Im, S. A., Lee, K. E., Nam, E., Kim, D. Y., Lee, J. H., Han, H. S., Seoh, J. Y., Park, H. Y., Cho, M. S., Han, W. S., & Lee, S. N. (2005). Potential prognostic significance of p185HER2 overexpression with loss of PTEN expression in gastric carcinomas. *Tumori Journal, 91*(6), 513–521.
44. Chua, T. C., & Merrett, N. D. (2012). Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes—A systematic review. *International Journal of Cancer, 130*(12), 2845–2856.
45. Bang, Y. J., Van Cutsem, E., Feyereislova, A., Chung, H. C., Shen, L., Sawaki, A., Lordick, F., Ohtsu, A., Omuro, Y., Satoh, T., & Aprile, G. (2010). 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. *The Lancet, 376*(9742), 687–697.
46. Moelans, C. B., van Diest, P. J., Milne, A. N., & Offerhaus, G. J. (2011). Her-2/neu testing and therapy in gastroesophageal adenocarcinoma. *Pathology Research International, 2011*, 674182.
47. Nicholas, G., Cripps, C., Au, H. J., Jonker, D., Salim, M., Bjarnason, G., Chiritescu, G., & Gallant, V. (2006). Early results of a trial of trastuzumab, cisplatin, and docetaxel (TCD) for the treatment of metastatic gastric cancer overexpressing HER-2. *Annals of Oncology, 17*, 316–316.
48. Ewer, S., & Lippman, S. M. (2005). Type II chemotherapy-related cardiac dysfunction: Time to recognize a new entity by Michael. *Journal of Clinical Oncology, 23*, 2900–2902.
49. Tanaka, Y., Yonetani, Y., Shiozaki, Y., Kitaguchi, T., Sato, N., Takeshita, S., & Horibe, S. (2010). Retear of anterior cruciate ligament grafts in female basketball players: A case series. *BMC Sports Science, Medicine and Rehabilitation, 2*(1), 7.
50. Kim, M. A., Lee, H. S., Lee, H. E., Jeon, Y. K., Yang, H. K., & Kim, W. H. (2008). EGFR in gastric carcinomas: Prognostic significance of protein overexpression and high gene copy number. *Histopathology, 52*(6), 738–746.
51. Ilson, D. H., Kelsen, D., Shah, M., Schwartz, G., Levine, D. A., Boyd, J., Capanu, M., Miron, B., & Klimstra, D. (2011). A phase 2 trial of erlotinib in patients with previously treated squamous cell and adenocarcinoma of the esophagus. *Cancer, 117*(7), 1409–1414.
52. Pinto, C., Di Fabio, F., Barone, C., Siena, S., Falcone, A., Cascinu, S., Llimpe, F. R., Stella, G., Schinzari, G., Artale, S., & Mutri, V. (2009). Phase II study of cetuximab in combination with cisplatin and docetaxel in patients with untreated advanced gastric or gastro-oesophageal junction adenocarcinoma (DOCETUX study). *British Journal of Cancer, 101*(8), 1261–1268.
53. Pinto, C., Di Fabio, F., Siena, S., Cascinu, S., Rojas Llimpe, F. L., Ceccarelli, C., Mutri, V., Giannetta, L., Giaquinta, S., Funaioli, C., & Berardi, R. (2007). Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). *Annals of Oncology, 18*(3), 510–517.
54. Kim, C., Lee, J. L., Ryu, M. H., Chang, H. M., Kim, T. W., Lim, H. Y., Kang, H. J., Park, Y. S., Ryoo, B. Y., & Kang, Y. K. (2011). A prospective phase II study of cetuximab in combination with XELOX (capecitabine and oxaliplatin) in patients with metastatic and/or recurrent advanced gastric cancer. *Investigational New Drugs, 29*(2), 366–373.
55. Han, S. W., Oh, D. Y., Im, S. A., Park, S. R., Lee, K. W., Song, H. S., Lee, N. S., Lee, K. H., Choi, I. S., Lee, M. H., & Kim, M. A. (2009). Phase II study and biomarker analysis of cetuximab combined with modified FOLFOX6 in advanced gastric cancer. *British Journal of Cancer, 100*(2), 298–304.
56. Richards, D., Kocs, D. M., Spira, A. I., McCollum, A. D., Diab, S., Hecker, L. I., Cohn, A., Zhan, F., & Asmar, L. (2013). Results of docetaxel plus oxaliplatin (DOCOX) ± cetuximab in

patients with metastatic gastric and/or gastroesophageal junction adenocarcinoma: Results of a randomised phase 2 study. *European Journal of Cancer, 49*(13), 2823–2831.

57. Lordick, F., Kang, Y. K., Chung, H. C., Salman, P., Oh, S. C., Bodoky, G., Kurteva, G., Volovat, C., Moiseyenko, V. M., Gorbunova, V., & Park, J. O. (2013). 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, 14*(6), 490–499.
58. Dragovich, T., McCoy, S., Fenoglio-Preiser, C. M., Wang, J., Benedetti, J. K., Baker, A. F., Hackett, C. B., Urba, S. G., Zaner, K. S., Blanke, C. D., & Abbruzzese, J. L. (2006). Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. *Journal of Clinical Oncology, 24*(30), 4922–4927.
59. Waddell, T., Chau, I., Cunningham, D., Gonzalez, D., Okines, A. F., Wotherspoon, A., Saffery, C., Middleton, G., Wadsley, J., Ferry, D., & Mansoor, W. (2013). 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, 14*(6), 481–489.
60. Rao, S., Starling, N., Cunningham, D., Sumpter, K., Gilligan, D., Ruhstaller, T., Valladares-Ayerbes, M., Wilke, H., Archer, C., Kurek, R., & Beadman, C. (2010). Matuzumab plus epirubicin, cisplatin and capecitabine (ECX) compared with epirubicin, cisplatin and capecitabine alone as first-line treatment in patients with advanced oesophago-gastric cancer: A randomised, multicentre open-label phase II study. *Annals of Oncology, 21*(11), 2213–2219.
61. Smolen, G. A., Sordella, R., Muir, B., Mohapatra, G., Barmettler, A., Archibald, H., Kim, W. J., Okimoto, R. A., Bell, D. W., Sgroi, D. C., & Christensen, J. G. (2006). Amplification of MET may identify a subset of cancers with extreme sensitivity to the selective tyrosine kinase inhibitor PHA-665752. *Proceedings of the National Academy of Sciences USA, 103*(7), 2316–2321.
62. Iqbal, S., Goldman, B., Fenoglio-Preiser, C. M., Lenz, H. J., Zhang, W., Danenberg, K. D., Shibata, S. I., & Blanke, C. D. (2011). Southwest Oncology Group study S0413: A phase II trial of lapatinib (GW572016) as first-line therapy in patients with advanced or metastatic gastric cancer. *Annals of Oncology, 22*(12), 2610–2615.
63. LOGiC-Lapatinib Optimization Study in ErbB2 (HER2) Positive Gastric Cancer: A Phase III Global, Blinded Study Designed to Evaluate Clinical Endpoints and Safety of Chemotherapy Plus Lapatinib. ClinicalTrials.gov. accessed January 27, 2020 from https://clinicaltrials.gov/ct2/show/results/NCT00680901.
64. Satoh, T., Bang, Y., Wang, J., Xu, J., Chung, H. C., Yeh, K., Chen, J., Mukaiyama, A., Yoshida, P., & Ohtsu, A. (2010). Interim safety analysis from TYTAN: A phase III Asian study of lapatinib in combination with paclitaxel as second-line therapy in gastric cancer. *Journal of Clinical Oncology, 28*(15_suppl), 4057.
65. Shah, M. A., Ilson, D. H., D'Adamo, D. O., Tse, A. T., Schwartz, L. C., & Schwartz, G. K. (2006). Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. *Journal of Clinical Oncology, 24*(33), 5201–5206.
66. Shah, M. A., Jhawer, M., Ilson, D. H., Lefkowitz, R. A., Robinson, E., Capanu, M., & Kelsen, D. P. (2011). Phase II study of modified docetaxel, cisplatin, and fluorouracil with bevacizumab in patients with metastatic gastroesophageal adenocarcinoma. *Journal of Clinical Oncology, 29*(7), 868–874.
67. Cohenuram, M. K., Lacy, J. FOLFOX6 and bevacizumab (FOLFOX6/B) for metastatic esophageal (E), gastroesophageal (GE), and gastric (G) adenocarcinoma: A single institution's initial clinical experience. In: Proceedings of the American Society of Clinical Oncology Gastrointestinal Cancers Symposium. 2008.
68. Ohtsu, A., Shah, M. A., Van Cutsem, E., Rha, S. Y., Sawaki, A., Park, S. R., Lim, H. Y., Yamada, Y., Wu, J., Langer, B., & Starnawski, M. (2011). Bevacizumab in combination with

chemotherapy as first-line therapy in advanced gastric cancer: A randomized, double-blind, placebo-controlled phase III study. *Journal of Clinical Oncology, 29*(30), 3968–3976.
69. Van Cutsem, E., de Haas, S., Kang, Y. K., Ohtsu, A., Tebbutt, N. C., Xu, J. M., Yong, W. P., Langer, B., Delmar, P., Scherer, S. J., & Shah, M. A. (2012). Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: A biomarker evaluation from the AVAGAST randomized phase III trial. *Journal of Clinical Oncology, 30*(17), 2119–2127.
70. Martin-Richard, M., Gallego, R., Pericay, C., Foncillas, J. G., Queralt, B., Casado, E., Barriuso, J., Iranzo, V., Juez, I., Visa, L., & Saigi, E. (2013). Multicenter phase II study of oxaliplatin and sorafenib in advanced gastric adenocarcinoma after failure of cisplatin and fluoropyrimidine treatment. *A GEMCAD study. Investigational New Drugs, 31*(6), 1573–1579.
71. Bang, Y. J., Kang, Y. K., Kang, W. K., Boku, N., Chung, H. C., Chen, J. S., Doi, T., Sun, Y., Shen, L., Qin, S., & Ng, W. T. (2011). Phase II study of sunitinib as second-line treatment for advanced gastric cancer. *Investigational New Drugs, 29*(6), 1449–1458.
72. Moehler, M. H., Hartmann, J. T., Lordick, F., Al-Batran, S., Reimer, P., Trarbach, T., Ebert, M. P., Daum, S., Weihrauch, M., Galle, P. R., & Upper GI Group of German AIO. (2010). An open-label, multicenter phase II trial of sunitinib for patients with chemorefractory metastatic gastric cancer. *Journal of Clinical Oncology, 28*(15_suppl), e14503.