J Cancer Res Clin Oncol (2009) 135:855–866
DOI 10.1007/s00432-009-0583-7

REVIEW

Gastric cancer in the era of molecularly targeted agents: current drug development strategies

Hendrik-Tobias Arkenau

Received: 21 October 2008 / Accepted: 26 March 2009 / Published online: 11 April 2009

Abstract Gastric cancer is the second most common cause of cancer death worldwide with approximately one million cases diagnosed annually. Despite considerable improvements in surgical techniques, innovations in clinical diagnostics and the development of new chemotherapy regimens, the clinical outcome for patients with advanced gastric cancer and cancer of the GEJ is generally poor with 5-year survival rates ranging between 5 and 15%. The understanding of cancer relevant events has resulted in new therapeutic strategies, particularly in developing of new molecular targeted agents. These agents have the ability to target a variety of cancer relevant receptors and down-stream pathways including the epidermal growth factor receptor (EGFR), the vascular endothelial growth factor receptor (VEGFR), the insulin-like growth factor receptor (IGFR), the c-Met pathway, cell-cycle pathways, and down-stream signalling pathways such as the Akt-PI3k-mTOR pathway. In the era of new molecularly targeted agents this review focuses on recent developments of targeting relevant pathways involved in gastric cancer and cancer of the GEJ.

Keywords Molecularly targeted agents · Gastric cancer · Gastroesophageal cancer · GEJ

H.-T. Arkenau (✉)
The Medical Professorial Unit,
Prince of Wales Medical School,
University of New South Wales, Level 1,
South Wing, Edmund Blacket Building,
Avoca Street, Sydney, NSW 2031, Australia
e-mail: ht.arkenau@unsw.edu.au; htarkenau@aol.com

Introduction

Gastric cancer is the second most common cause of cancer death worldwide with approximately one million cases diagnosed annually. Histopathologically and genetically, gastric cancer and cancer of the gastro-esophageal junction (GEJ) are heterogeneous diseases influenced by gene-environment interactions resulting in activation of various molecular pathways. A number of specific molecular and genetic changes have been associated with histopathological features and biological behaviour (Tahara 2004). Based on the current knowledge of gastric cancer biology new targeted agents have been developed and are currently investigated in clinical trials.

Cell surface receptor inhibitors

EGFR inhibitors

The most extensively explored approach is the inhibition of the epidermal growth factor receptor (EGFR) using two different mechanisms: inhibition of the EGFR via monoclonal antibodies (i.e. cetuximab, matuzumab and panitumumab) or tyrosine kinase inhibitors (i.e. gefitinib, erlotinib).

The epidermal growth factor receptor is a cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands. Ligand binding to the extracellular domain leads to EGFR activation, which then homodimerizes, resulting in the phosphorylation of the intracellular tyrosine kinase initiating a series of intracellular signals including the central Ras/Raf/mitogen activated protein kinase (MAPK) or the Akt/mTOR pathway (Carpenter and Cohen 1990).

Cetuximab is a recombinant, human/mouse chimeric IgG1 monoclonal antibody that binds specifically to the extracellular domain of the human EGFR on both normal and tumour cells, and competitively inhibits the binding of epidermal growth factor and other ligands, such as transforming growth factor-alpha. Additionally, cetuximab has also been shown to mediate antibody-dependent cell cytotoxicity (ADCC). The current approval status is for patients with advanced colorectal cancer (ACRC) and squamous cell head and neck cancer (Saltz et al. 2004).

Cetuximab has been investigated in multiple phase II studies in patients with advanced gastric cancer alone or in combination with various chemotherapy regimens including irinotecan, cisplatin/docetaxel, FUFOX/FOLFOX (5-fluorouracil, oxaliplatin, folinic acid) and FOLIFIRI (5-fluorouracil, irinotecan, folinic acid). In heavily pre-treated patients single agent cetuximab resulted in low response rates of 5%; however, in combination with irinotecan a tumour control rate of 62% was achieved (Woell et al. 2008; Stein et al. 2007; Tebbutt et al. 2008). In untreated patients with advanced gastric cancer and cancer of the GEJ the combination of cetuximab with different chemotherapy backbones such as FUFOX/FOLFOX, cisplatin/docetaxel or FOLFIRI achieved tumour response rates between 44 and 62.5%. With these combinations time-to-progression (TTP) ranged between 5.5 and 8.0 months with an overall survival (OS) between 9.5 and 16 months. Serious cetuximab-related adverse events observed in all clinical trials were infusion reactions, skin toxicity, and diarrhea (Lordick et al. 2007; Han et al. 2009; Pinto et al. 2008; Pinto et al. 2007). Currently, there are phase III trials ongoing evaluating cetuximab in combination with various chemotherapy backbones (Tables 1, 2, 3).

Matuzumab, a humanized monoclonal antibody (IgG1) targeting EGFR with high affinity, has been investigated with epirubicin, cisplatin and capecitabine in patients with advanced gastric and cancer of the GEJ. In a dose finding phase I study in 17 EGFR expressing patients disease control was achieved in 57% (4PR/2SD) at a dose level of 400 mg and 43% (3PR/2SD) at 800 mg matuzumab (Rao et al. 2008). Further exploration of this agent in phase II trials is planned.

Panitumumab is the first fully human monoclonal antibody (IgG2) specific to the EGFR. Clinical activity has been demonstrated in patients with EGFR positive advanced colorectal cancer (ACRC) who failed standard therapies (Van Cutsem et al. 2007). A phase III trial (REAL III) is due to start investigating the role of panitumumab in combination with epirubicin, cisplatin and capecitabine (ECX) in patients with locally advanced or metastatic gastric cancer or adenocarcinoma of the GEJ.

Interestingly, clinical trials of EGFR tyrosine kinase inhibitors in gastric carcinoma have provided minimal evidence of efficacy in the first-line setting. A phase II study of gefitinib (250 mg/day or 500 mg/day) which included 75 patients demonstrated that only 18% with advanced gastric cancer achieved disease control (Rojo et al. 2006). Another trial investigated the role of erlotinib in 70 patients with advanced gastric cancer or cancer of the GEJ. In this trial the overall response rate was 9%, all occurring in GEJ cancer patients. In this trial the median OS was 6.7 months in GEJ patients and 3.5 months in patients with advanced gastric cancer (Dragovich et al.

Table 1 Cell surface receptor inhibitors in gastric cancer and cancer of the GEJ

Cell surface receptor inhibitors in gastric cancer		Clinical trials, Phase
EGF-R		
Antibody	Cetuximab	III
	Panitumumab	III
	Matuzumab	I–II
Receptor tyrosine kinase	Gefinitib	II
	Erlotinib	II
HER2-R		
Antibody	Antibody	III
VEGF-R		
Antibodies	Bevacizumab (VEGF only)	III
Receptor tyrosine kinase	Vatalanib	III
	Semaxinib (SU5416)	Preclinical
IGF-R		
Antibody	CP-751,871	I–II
Receptor tyrosine kinase	OSI 906	I
HGF/Met-R		
Antibody	AMG 102	I–II
Receptor tyrosine kinase	GSK1363089 (XL880)	II
	Arqule	I–II
FGF-R		
Receptor tyrosine kinase	Brivanib	II
	Ki23057	Preclinical
Dual tyrosine kinase inhibitor		
EGF/HER2-R		
Receptor tyrosine kinase	Lapatinib	II
	BIBW 2992	II
EGF/VEGF-R		
Receptor tyrosine kinase	Vadatenib	I–II
Multi tyrosine kinase inhibitor		
Raf, VEGFR-2, VEGFR-3, PDGFR-β		
Receptor tyrosine kinase	Sorafenib	II
RET, VEGFR, PDGFR, Flt3, c-KIT		
Receptor tyrosine kinase	Sunitinib	II

Table 2 Cell cycle associated inhibitors and inhibitors of downstream signalling pathways in gastric cancer and cancer of the GEJ

Cell cycle associated drug target inhibitors in gastric cancer	Clinical trials, Phase
Cyclin dependent Kinase (CDK)	
Flavopiridol	III
Matrix Metallo Proteinase (MMP)	
Marimastat	III
HSP 90	
17-AAG	Preclinical, I
HDAC	
Belinostat (PXD101)	Preclinical, I
Polo-like Kinase	
BI 2536	Preclinical, I
Downstream Signalling pathways	
Ubiquitine-Proteasome	
Bortezomib	II
PI3 K-Akt-mTOR	
Everolismus (RA001)	II

2006). The authors concluded that erlotinib was active in patients with GEJ adenocarcinoma, but appeared inactive in gastric cancers.

Over-expression and amplification of HER2/ErbB2 has been described in 15–45% of gastric cancers and cancers of the GEJ resulting in a potential target for monoclonal antibodies (Trastuzumab) and tyrosine kinase inhibitors (Lapatinib) (Tanner et al. 2005; Kim et al. 2008). Lapatinib, a dual tyrosine kinase inhibitor of EGFR and HER2/ErbB2, was administered to 47 untreated advanced gastric cancer patients at a dose of 1,500 mg per os daily. Although lapatinib was well tolerated it had modest single-agent activity with a 12% response rate and 20% disease stabilization. The median time to treatment failure (TTF) was 2 months, and the OS was 5 months, respectively (Iqbal et al. 2007). Moreover, in previously treated patients with gastric or GEJ cancers lapatinib had limited single-agent activity with only two patients who experienced durable SD (Hecht et al. 2008). Another dual EGFR/HER2 tyrosine kinase is BIBW 2992 which has shown clinical activity in phase I trials in various cancers including cancer of the gastrointestinal tract. This compound is currently investigated in a phase II trial in patients harbouring tumours with EGFR and/or HER2 gene amplifications or EGFR activating mutations (Eskens et al. 2008).

Trastuzumab is a humanized monoclonal antibody, which was approved by the United States Food and Drug

Table 3 EGFR Antibody trials in combination with chemotherapy

EGFR Antibody trials in combination with chemotherapy								
Reference	Line	*N*	Chemo	EGFR-AB	ORR (%)	TTP months	OS months	Toxicity Grade 3/4
Woell et al. (2008)	1st	40	Oxaliplatin/irinotecan	Cetuximab	NA	NA	NA	Neutropenia 17.5% Diarrhea 12.5% Rash 8%
Lordick et al. (2007)	1st	52	FUFOX	Cetuximab	62.5	7.6	9.5	Diarrhea 33% Skin 24% Fatigue 10%
Han et al. (2009)	1st	38	mFOLFOX6	Cetuximab	50	5.5	9.9	Neutropenia (NA) Diarrhea (NA) Rash (NA)
Pinto et al. (2008)	1st	48	Cisplatin/docetaxel	Cetuximab	40.5	At 3 months 80% no TTP	NA	Neutropenia 46% Rash $\geq$ 231% Asthenia 23%
Pinto et al. (2007)	1st	38	FOLFIRI	Cetuximab	44	8	16	Neutropenia 44% Rash 21% Diarrhea 8%
Stein et al. (2007)	Refractory	13	Irinotecan	Cetuximab	23	2.5	3.2	Neutropenia 23% Rash 23% Diarrhea 15%
Tebbutt et al. (2008)	Refractory	38	Docetaxel	Cetuximab	6	2.1	5.3	Anorexia 16% Diarrhea 11% Nausea 8%

NA not assessed, *ORR* overall response rate, *TTP* median time to tumour progression; *OS* median overall survival, *FUFOX* 5-FU/leucovorin/oxaliplatin, *mFOLFOX* modified 5-FU/leucovorin/oxaliplatin, *FOLFIRI* 5-FU/leucovorin/irinotecan

Administration (FDA) in 1998 for the treatment of advanced breast cancer and later for early breast cancer (Hinoda et al. 2004). Preclinical data demonstrated that trastuzumab has activity in human gastric cancer cells lines that over-express HER2/ErbB2 (Gong et al. 2004). A small phase II trial investigated trastuzumab in 21 untreated patients with HER2/ErbB2 overexpressing/amplifying advanced gastric cancers. In this trial the overall response rate was 35% (1/5 CR/PR) and disease stabilization was 17%, amounting for 52% disease control (Cortés-Funes et al. 2007). Based on these promising results a phase III trial (TOGA-trial) is currently evaluating the role of trastuzumab +/− chemotherapy in patients with HER2/ErbB2 over-expressing/amplifying advanced gastric cancer. Of the 2,484 gastric cancer samples screened to date, 544 were HER2 positive and 1,940 HER2 negative, giving an overall HER2-positivity rate of 21.9%. Clinical results of this trial are awaited (Bang et al. 2008).

Antiangiogenic agents

Blood vessel formation via angiogenesis is one of the most crucial steps in progression of cancer from localized to metastatic disease. During tumourigenesis, the process of angiogenesis is markedly disordered and requires the continued production of stimulators by tumour and stromal cells in excess of inhibitors. Among pro-angiogenic stimulators, vascular endothelial growths factors (VEGF-family A-D) play a key role in both vasculogenesis and angiogenesis. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis (Carmeliet 2003). And indeed, in patients with gastric cancer and cancer of the GEJ the serum concentrations of VEG factors have shown a relationship between the serum concentration of VEGF and metastasis and/or poor outcome (Karayiannakis et al. 2002).

There are various strategies to inhibit tumour angiogenesis, and one of the most commonly studied targets is the vascular endothelial growth factor (VEGF) and its receptors (VEFG receptors) via monoclonal antibodies or tyrosine kinase inhibitors. A number of antiangiogenic agents have been investigated or are currently in clinical trials.

Bevacizumab, a chimeric monoclonal antibody, binds the vascular endothelial growth factor (VEGF) and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. Bevacizumab was the first FDA-approved therapy designed to inhibit angiogenesis in patients with advanced colorectal cancer (ACRC) and later non small cell lung cancer (NSCLC), renal and breast cancer (Presta et al. 1997).

Clinical data of bevacizumab in patients with advanced gastric cancer or cancer of the GEJ are currently based on phase II experiences and therefore limited. The fact that there are various accepted standard first-line chemotherapy regimens for advanced gastric cancer and cancer of the GEJ bevacizumab has been investigated with different chemotherapies in untreated patients.

In a small phase II trial 47 patients were treated with a combination of cisplatin, irinotecan and bevacizumab. This trial achieved a promising response rate of 67%, and after a median follow up of 9.0 months the TTP was 9.9 months with a median OS of 12.6 months. Despite those encouraging findings, there was concern about the incidence of thromboembolic events, which occurred in 25% of the patients (Shah et al. 2006). Additionally, another phase II study treated eight patients with a combination of oxaliplatin, docetaxel and bevacizumab. This regimen resulted in four partial responses and disease stabilization was observed in four patients. However, of concern were two gastrointestinal perforations (Hammad et al. 2008). Another phase II study investigated the role of the commonly used DCF (docetaxel, cisplatin, 5-FU) chemotherapy in combination with bevacizumab. Out of 21 patients with gastric, GEJ or esophageal cancer (patients: 15:5:1) 71% achieved a partial response and 21% stable disease. After a 6-month median follow-up the median survival has not been reached yet. In this trial side effects included asymptomatic venous thromboembolism (29%) and one patient developed a grade 3 upper gastrointestinal bleeding (Jhawer et al. 2008). Less toxicity and also promising response rates were observed combining bevacizumab with 5-FU, leucovorin and oxaliplatin (FOLFOX). Out of 16 patients (esophageal and GEJ/gastric cancer: 9/7) ten patients (63%) achieved a partial response and six patients (37%) achieved minor response or disease stabilization. The median TTP and OS were 7 and 8.9 months, respectively (Cohenuram and Lacy 2008). Unlike the above-mentioned studies there was no observed bevacizumab associated toxicity, such as arterial/venous thrombotic events (ATE, VTE), gastrointestinal bleeding or perforation.

Despite these promising results from phase II studies, all authors stated that bevacizumab should only be used in the context of clinical trials at this current stage until mature data from phase III trials become available.

A different approach in inhibiting the VEGF pathway includes tyrosine kinase inhibitors which are directed against the receptors of the VEGF, Flt-1 and Flk-1/KDR. This drug class comprises a variety of compounds, some of them specific to the VEGF receptors such as PTK787/ZK222584 (Vatalanib) or SU5416, and others that inhibit not only the VEGF receptor but also other tyrosine kinase receptors such as ZD6474 (vandetanib), sunitinib and sorafenib.

These compounds have been investigated in different cell lines and animal models including gastric cancer and

carcinoma of the GEJ, but clinical data are currently limited. For example, the dual VEGFR and EGFR tyrosine kinase inhibitor ZD6474 showed in an orthotopic gastric cancer model inhibition of tumour growth, decrease in microvessel density and slow down in tumour cell proliferation. This compound is currently being investigated in a phase I/II trial in combination with oxaliplatin and docetaxel (McCarty et al. 2004). Sunitinib, an oral multitargeted tyrosine kinase inhibitor of VEGFR, platelet derived growth factor (PDGFR), Kit, RET and Flt3 has been approved by the FDA for the treatment of metastatic renal cell carcinoma (RCC) and resistant or imatinib intolerant gastrointestinal stromal tumours (GIST) (Motzer et al. 2007). Preliminary results of a phase II study of 72 previously chemotherapy-treated patients with advanced gastric were promising. Of patients who received sunitinib, partial responses were achieved in two patients, and stable disease (SD) was achieved in 17 patients (12 with SD for >3 months and 3 for >6 months). Median progression-free survival was 2.8 months, with overall survival of 11.9 months (Bang et al. 2007). A recent preliminary report of a phase II study in 52 patients with chemo refractory metastatic gastric cancer reported good tolerability of sunitinib (50 mg/day for 4 weeks and 2 weeks rest) and disease control rates in 5 of 14 patients were encouraging (Moehler et al. 2009).

Sorafenib is a potent inhibitor of the Raf tyrosine kinase and of several other receptor tyrosine kinases including VEGFR-2, VEGFR-3, PDGFR-β. A phase II study including 44 patients with advanced gastric cancer or cancer of the GEJ investigated the combination of sorafenib with docetaxel and cisplatin. In this trial the objective response rate was 38.6%, including one complete response (CR 2.3%). The median PFS was 5.8 months, and the median OS 14.9 months. The authors are planning to test this combination in a phase III trial (Sun et al. 2008).

Dual inhibitors of the VEGF and EGFR pathway

There is a strong body of evidence that the combination of anti-EGFR and anti-VEGF treatment strategies have additive effects in preclinical tumour models. EGFR, HER2 and VEGF share common pathways, and EGFR activation induces VEGF expression in cancer cells and tumour associated tumour cells expressing EGFR (Tortora et al. 2008). Pro-angiogenic effects by EGFR activation might also occur in conditions of chronic inflammation through intermediates such as cyclo-oxygenase 2 (COX2) (Mann et al. 2005). Studies conducted with anti-EGFR drugs have shown a link between EGFR blockage and tumour induced anti-angiogenesis resulting in decreased microvessel density and reduced production of pro-angiogenic factors (Hirata et al. 2002). Since both pathways play an important role in patients with gastric cancer and cancer of the GEJ the strategy of dual targeting is currently investigated in various trials.

Clinically, the anti EGFR-VEGF strategy has been investigated in patients with advanced colorectal cancer (ACRC). In these patients who failed standard chemotherapy treatments including oxaliplatin and irinotecan containing regimens the combination of irinotecan, cetuximab and bevaziumab resulted in significant superior outcome compared to irinotecan and cetuximab alone (Saltz et al. 2007). Despite promising preclinical and small clinical studies the results of two phase III trials in advanced CRC (PACCE and the CAIRO 2) were surprising, resulting in inferior outcome by using the double-targeting strategy in combination with firstline chemotherapy (Hecht et al. 2009; Tol et al. 2009). Whether these results were based on poor patient selection, drug administration schedules or drug interactions remains speculative and is currently under investigation.

Insulin-like growth factor-I (IGF-IR) inhibitors

The receptor of the type I insulin-like growth factor (IGF-IR) is a cell membrane receptor which is activated by its ligands, IGF-1 and IGF-2. IGF-IR has been identified to play a critical role in malignant transformation, angiogenesis, metastasis and resistance to apoptosis. Increased expression of IGF-I or the IGF-IR has been documented in several malignancies including lung, breast, colon, prostate and cancer of the upper gastrointestinal tract (Grimber and Cohen 2000).

A study of 87 patients with advanced gastric cancer who underwent gastrectomy demonstrated that 77% were expressing IGF-IR and this was correlated with poor clinical outcome. Additionally, this study showed a link between IGF-IR expression and co-expression (immunohistochemistry staining, IHC) of EGFR and HER2: 55% of tumours co-expressed IGF-IR and EGFR and all tumours which were HER2 positive (18%) expressed IGF-IR. Interestingly, for patients who showed a low expression of both, IGF-IR and EGFR, the OS was significantly longer compared to patients with a high expression rate (Matsubara et al. 2008). Despite the small number of patients in this trial, these findings are of interest and could indicate a potential role in co-targeting both receptors. Moreover, strong evidence is accumulating about cross-talk mechanisms between IGF-IR and EGFR. For example, one of the known mechanisms to promote resistance to anti-EGFR treatment is switching to the IGF-IR downstream pathway (Jones et al. 2006). Strategies of targeting the IGF-IR pathway include the use of neutralizing antibodies, IGF-IR antisense/siRNA and receptor tyrosine kinases. Clinically several phase I studies of monoclonal antibodies against

IGF-IR and receptor tyrosine kinase inhibitors are indicating clinical activity in various tumour types and good tolerability (Haluska et al. 2007).

A phase I trial combining docetaxcel and the IGF-IR antibody CP-751,871 showed promising results in patients with advanced gastroesophageal cancers (Attard et al. 2006).

Fibroblast growth factor (FGF) inhibitors

The subgroup of scirrhous gastric cancer has the worst prognosis of all gastric cancers. Common features include invasive progression, fibrosis, high frequency of metastasis to the peritoneum or lymph nodes and clinically chemoresistance. The poor prognosis is associated with amplification of K-sam-II which encodes for the fibroblast growth factor receptor 2 (FGF-R2) (Hattori et al. 1996).

Ki23057 is a new tyrosine kinase inhibitor of the K-sam-II/FGF-R2 which competes with the adenosine triphosphate (ATP) binding site. KI23057 was investigated in five human gastric cell lines (mouse models) and mice injected with the scirrhous cancer cell lines (OCUM-2MD3) had significantly prolonged survival compared to non-scirrhous cancer cells (Nakamura et al. 2006). A recently published preclinical study investigated another tyrosine kinase inhibitor, ZD2171, with a broad inhibitory spectrum including VEGFR-1, VEGFR-3, and c-Kit. In cancers dependent on FGF-R signalling, like scirrhous gastric carcinoma, ZD2171 showed also inhibitory properties and therefore may provide clinical benefit for patients with this subgroup of gastric cancer. Ongoing phase II studies investigate the role of FGF-inhibition in gastric cancer patients.

c-Met inhibitors

The c-Met signalling pathway is implicated in a variety of human malignancies, such as colon, gastric, lung, head & neck, thyroid, and prostate cancers as well as sarcomas, haematological malignancies, melanoma, and central nervous system tumours. The proto-oncogene, c-Met, encodes the high-affinity receptor for hepatocyte growth factor (HGF) or scatter factor (SF). c-Met and HGF are each required for normal mammalian development and have been shown to be particularly important in cell migration, morphogenic differentiation, and organization of three-dimensional tubular structures as well as cell growth and angiogenesis (Maulik et al. 2002). Both are deregulated in various human cancers including gastric cancers and correlate with poor prognosis. The most common cause of activation of the c-met pathway in gastric and GEJ cancers is via amplification of the MET gene, with subsequent protein over-expression and kinase activation (Inoue et al. 2004). A study including 121 patients with advanced gastric cancer demonstrated that HGF and c-Met were significantly over-expressed in patients with liver metastases compared to patients without liver metastasis (Amemiya et al. 2002). Additionally, for patients with advanced gastric cancer, co-expression of c-Met and HER2 proteins have been associated with poorer survival compared with over-expression of either one (Nakajima et al. 2000).

There are several strategies by inhibiting this pathway including HGF/MET antibodies (e.g. AMG 102) and small molecules; however, clinical data for patients with gastric or GEJ cancers are currently limited.

Based on phase I trial results, GSK1363089 (XL880) a potent oral tyrosine kinase inhibitor of c-Met and VEGFR2/KDR, is currently studied in a phase II study including patients with advanced poorly differentiated gastric cancer. Interim results of 12 evaluable patients showed a 20% decrease in tumour size at the first 8-week evaluation. Of these 12 patients, six remain on study (2 for >12 weeks, 4 for >8 weeks) and six had disease progression at <8 weeks (Jhawer et al. 2008). Another c-Met inhibitor is, ARQ197, which is currently trialled in phase I and II studies in upper gastrointestinal cancers. ARQ197 is a non ATP competitive drug and results of a phase I trial showed disease stabilization in 7 of 11 patients with prolonged stabilization for >32 weeks in five tumour types including gastric cancer (Yap et al. 2008).

Cell cycle associated drug targets

Aurora Kinase inhibitors

Aurora Kinases (A, B, and C) are serine/threonine kinases which regulate mitotic progression in various organisms and control centromere maturation, separation, mitotic entry, spindle formation and chromosome alignment. In normal cells the aurora kinase protein levels increase from G2 to M phase and are enriched at the centromere and mitotic spindle (Marumoto et al. 2002). Over-expression of aurora kinases A result in chromosomal instability in a variety of tumours including gastric carcinoma. A recent study could demonstrate that aurora kinase A over-expression in upper gastrointestinal cancers resulted in activation of the aurora A/Akt/hdm2 pathway demonstrating a potential role for regulating p53 and cancer cell survival (Dar et al. 2008). Additionally, aurora kinase A over-expression had an effect on inhibition of drug-induced apoptosis in various gastrointestinal cell lines providing these cells with a drug-resistant phenotype and survival properties (Kamada et al. 2004). Cells which over-express aurora kinase A prevent the release of cytochrome C from mitochondria and increased levels of cytochrome C lead to inactivation of caspases and thus protecting cells from apoptosis. Over-expression of

aurora kinase A could therefore be a factor contributing to poor clinical outcome in patients with gastric and GEJ cancers (Macarulla et al. 2008). Currently various aurora tyrosine kinase inhibitors are under investigation in phase I-II trials and results are awaited.

Polo-like kinase inhibitors

Polo-like kinases are a family of four serine/threonine kinases which are involved in signal transduction pathways essential for various mitotic processes such as centrosome maturation and chromosome segregation.

PLK-1 is the most common isoform which has been studied so far and its over-expression is seen in various malignancies including gastric cancer (Takai et al. 2005). A recent study in patients with gastric cancer showed that PLK-1 over-expression was associated with lymph node metastasis and diffuse growth pattern. This study demonstrated that inhibition of PLK-1 expression results in mitotic arrest, induction of apoptosis and suppression of tumour growth (Weichert et al. 2006). Additionally, the inhibition of PLK-1 via small interferences RNA (siRNA) resulted in PLK-1 depletion, cdc2 activity, increased cyclin B expression and accumulation of gastric cancer cells at G2/M, improper mitotic spindle formation, and delayed chromosome separation. Moreover, PLK-1 depletion was associated with decreased proliferation, attenuated procaspase 3 levels and increased apoptosis (Jang et al. 2006). Currently different phase I trials evaluate the role of PLK inhibitors in various tumours including gastric and GEJ and esophageal cancer.

Cyclin dependent kinase (cdk) inhibitors

Cyclin dependent kinases comprise a group of protein kinases (cdk1–cdk9) which are involved in cell cycle regulation via the retinoblastoma product (Rb, tumour suppressor gene). Inactivation of the Rb-pathway is a result of either over-expression or amplification of cdk's or down-regulation of negative factors such as endogenous cdk-inhibitors or mutations in the Rb gene product. In various malignancies, this pathway is deregulated resulting in a disturbed G1 to S phase of the cell cycle (Senderowicz 2000).

Flavopiridol is a synthetic flavonoid with strong inhibitory properties of cdks including cdk-1, cdk-2, cdk-4, cdk-7 and hypophosphorylation of Rb. In multiple cell lines flavopiridol induced apoptosis, inhibited angiogenesis, and increased the effects of chemotherapy by arresting the cell cycle in the G1 or G2/M transition phase (Wang 2001). In a phase I study comprising 38 advanced cancer patients flavopiridol was administered as a 72-h infusion and at the maximum tolerated dose (MTD) level of 40 mg/m² one patient with gastric cancer achieved a complete response lasting more than 48 months (Thomas et al. 2002). However, results of a phase II study in 16 patients with advanced gastric cancer showed no activity but increased toxicity (Schwartz et al. 2001). The authors recommended further development of this drug by using different schedules and in combination with cytotoxic agents.

Inhibitor of epigenetic changes

Histone deacetylase (HDAC) inhibitors

Over the past years there is an increasing body of evidence that epigenetic silencing of tumour suppressor genes induced by over-expression of histone deacetylases (HDAC) plays a crucial role in carcinogenesis and recent developments in understanding the cancer cell cycle are providing large opportunities for developing new anti-cancer agents (Miremadi et al. 2007). In humans, 18 HDAC enzymes have been identified and categorized in three classes based on homology to yeast HDAC's (Class I includes HDAC 1, 2, 3, and 8; Class II includes HDAC's 4, 5, 6, and 9; Class III HDAC's include the so called Sir2 family of deacetylases, which are not inhibited by compounds that inhibit class I and II HDAC's) (Bolden et al. 2006).

In gastric cancer moderate to strong expression of HDAC2 was found in 44 (62%) out of a total of 71 tumours. Interestingly, HDAC2 expression appeared to be associated with tumour aggressiveness (Song et al. 2005). Another study revealed that high HDAC expression in gastric cancer was significantly associated with nodal spread and was additionally an independent prognostic marker for gastric cancer (Weichert et al. 2008).

HDAC inhibitors (HDACI) are under considerable exploration due to their potential role in reversing the silenced genes in transformed tumour cells by modulating transcriptional processes. HDACIs are known to induce cell-cycle arrest in G1 and/or G2, apoptosis in cancer cells, and to be relatively non-toxic to non-transformed cells (Marks and Jiang 2005). One of the most studied HDACIs is trichostatin A (TSA). In a trial using the gastric cancer cell lines BGC-823 and SGC-7901 TSA induced apoptosis in a dose- and time-dependent manner (Zou et al. 2008). Furthermore, administration of SK-7068, a novel hybrid synthetic HDAC inhibitor, in HDACI-sensitive gastric cancer cell lines induced cell cycle arrest predominantly in the G2/M phase. In these cells HDAC inhibition induced mitotic arrest and abnormal positioning of metaphasic gamma-tubulin followed by high levels of apoptotic cell death (Park et al. 2004). Another HDAC inhibitor is SAHA (Suberoylanilide Hydroxamic Acid) which induces prolongation or hyper-acetylation of various histones leading to induction of both p21 and p27, resulting in both G1 and

G2/M cell cycle arrest. The increase in the G2/M population of cells treated with SAHA has been attributed to an increase in the percentage of G2 cells (Cheema et al. 2004). In patients with oesophago-gastric cancer a phase II trial is currently investigating the combination of FOLFIRI ± vorinostat (HDACI).

Down stream signalling inhibitors

Heat shock protein 90 (HSP 90) inhibitors

Heat shock protein (Hsp) 90 is a highly expressed molecular chaperone protein capable of sensing cellular stress. In cells, Hsp90 mediates the maturation and stability of a set of cancer-associated proteins, collectively referred to as "clients" including steroid receptors, epidermal growth factor receptor family members, IGFR, MET, Raf-1, AKT, Bcr-abl, mutant p53, cyclin-dependent kinase 4, and many other oncogenic molecules. These client proteins are involved in signal-transduction pathways, cell-cycle regulation, and apoptosis pathways commonly deregulated in cancer (Tsutsumi and Neckers 2007).

In gastric cancer HSP90 expression is increased and has a close relationship with occurrence and lymph node metastasis (Zuo et al. 2003). Down-regulation of Hsp90 could change cell cycle distribution and increase the drug sensitivity of tumour cells. A study in gastric cancer cell lines using the HSP 90 inhibitor geldanamycin, a derivate of 17-allylamino-17-demethoxygeldanamycin (17-AAG), showed a reduction in constitutive and inducible activation of extracellular signal-regulated kinase 1/2, Akt, and signal transducer and activator of transcription 3 and decreased nuclear HIF-1α protein (Lang et al. 2007). Additionally, EGFR, HER-2 and EGF-mediated VEGF secretion were down-regulated after Hsp90 inhibition. Currently there are several phase I/II studies ongoing which evaluate the use the HSP 90 inhibitors in various cancer entities.

Ubiquitin-proteasome pathway inhibitors

The ubiquitin-proteasome pathway plays an important role in the degradation of cellular proteins and cell cycle control. Disturbance in the degradation of such proteins has profound effects on tumour growth, cell proliferation, and apoptosis (Mani and Gelmann 2005).

Bortezomib, a boronic acid dipeptide derivative, is a potent inhibitor of the proteasome and has prominent effects in vitro and in vivo against several solid tumours. In three gastric cancer cell lines (AZ521, MUGC-3 and MKN-45), bortezomib induced the suppression of tumour cell growth and apoptosis (Fujita et al. 2007). Furthermore, the combination of bortezomib with cisplatin and docetaxel displayed dramatically increased tumour cell growth suppression compared to single drug treatment alone (Bae et al. 2008).

In a phase II trial including 44 patients with advanced gastric cancer, 28 chemo-naive patients (Arm A) received irinotecan in combination with bortezomib and 12 patients who were pre-treated received bortezomib alone (Arm B). Preliminary results of this trial showed response rates of 44% in arm A and 9% in arm B. The PFS and OS were 1.9 months and 5.4 months in arm A and 1.4 months and 4.1 months in arm B, respectively (Ocean et al. 2007). Further evaluation of this agent in combination with other chemotherapy backbones is ongoing.

PI3k/Akt/mTOR pathway inhibitors

Another important pathway involved in gastric carcinogenesis is the intracellular signalling machinery of the PI3 Kinase/Akt/mammalian target of rapamycin (PI3 K/Akt/mTOR) downstream pathway. Events resulting in mTOR activation involve loss of PTEN function, mutation or amplification of the PI3 K, amplification of Akt, and inactivation or mutations of Akt-associated mTOR-regulatory proteins (Morgensztern and McLeod 2005).

A reduction or abnormal PTEN expression indirectly stimulates PI3K activity thereby contributing to oncogenesis. Abnormal expression of the PTEN protein is found to be infrequent in gastric cancer (11%) and is related to tumour differentiation, infiltrating depth, lymph node metastasis, pTMN staging and chemo-resistance (Oki et al. 2005).

In gastric cancer activated Akt (29%) promotes cell proliferation, growth and survival and other processes involved in cancer development by phosphorylating various intracellular proteins. Preclinical models showed that phospho-Akt1 was over-expressed in human gastric cancers and its levels correlated with tumour differentiation and pTNM (Han et al. 2008). Of particular interest among the Akt targets is the downstream effector mTOR. With the involvement of the PI3K-Akt pathway, mTOR releases signals to translational regulators, specifically enhancing the translation of mRNAs encoding proteins essential for cell growth and cell cycle progression through G1 to S phase. As a result of its central position within this downstream pathway, mTOR has been considered an important target for new anticancer drug development (Lang et al. 2007).

RAD001 (everolimus) is an oral mTOR inhibitor and has shown anti-cancer activity in in vitro and in vivo models of gastric cancer (Cejka et al. 2008). To evaluate the activity and safety of single agent RAD001, a multi-centre phase II study for pre-treated patients with advanced gastric cancer and cancer of the GEJ is currently ongoing and preliminary results showed that out of 17 evaluable patients 10 patients

achieved SD lasting more than 8 weeks. Generally this treatment was well tolerated with manageable side effects (Muro et al. 2008).

There are currently several phase I trials ongoing that investigate the role of PI3-kinase and AKT-inhibitors in various tumour types.

Other mechanisms

COX inhibitors

Cyclooxygenase is the most important regulator of prostaglandin synthesis which catalyzes the conversion of arachidonic acid into prostaglandin H2 (PGH2) a precursor of prostaglandins, prostacyclins, and thromboxanes (Kuwano et al. 2004).

There is epidemiologic evidence that helicobacter pylori (H. pylori) infection plays an important role in gastric and GEJ carcinogenesis. Chronic infection by H. pylori leads to increased cyclooxygenase 2 (COX2), inducible nitric oxide synthetase (iNOS) and cytokines expression (Lax and Thomas 2002). Additionally, over-expression of COX2 increases the production of prostaglandin E2 (PGE2), BCL2 and reduces the tumour growth factor 2 (TGF2) receptor expression and E-cadherin protein. Furthermore, COX2 can induce angiogenesis via VEGF and b fibroblast growth factor (bFGF) expression, and increases the metastatic potential by up-regulation of uPA and matrix-metallo-proteinase 2 (MMP2). These changes result in an increased tumourigenic potential and supports the hypothesis that COX2 over-expression plays a key role in the cancer transformation process (Iwamoto et al. 2008).

Numerous preclinical studies have indicated that the inhibition of COX2 by non steroidal anti-inflammatory drugs (NSAID) results in inhibition of gastric cancer cell formation and growth. A meta-analysis of observational studies showed an association between long term NSAID use and the reduced risk of gastric cancer (Wang et al. 2003). Despite these findings there remain various unanswered questions by using cyclooxygenase inhibitors in clinical practice including the optimal dosing and timing, e.g. chemoprevention and the duration of treatment.

Matrix metalloproteinase (MMP) inhibitors

Matrix metalloproteinases are a family of zinc-dependent enzymes involved in degradation of extracellular matrix (gelatinases, collagenases, stromelysins) and play a key role for metastasis and angiogenesis. The enzymatic activity contributes to the degradation of the basal membrane and extracellular matrix, and therefore enables local tumour growth and angio-invasion (Cauwe et al. 2007). In patients with gastric cancer several MMPs are over-expressed (MMP2, MMP 7, MMP 9 and MMP14) and associated with poor clinical survival. Recently, plasma levels of MMP 9 were found to be a prognostic marker for the clinical outcome for patients with gastric cancer (de Mingo et al. 2007). Despite intensive research in the field of MMP inhibition most clinical trials of MMP inhibitors (MMPIs) resulted in negative results.

The oral MMPI, Marimastat (BB 2516, TA 2516), demonstrated in a mouse xenograft model shrinkage of peritoneal disease using the human gastric cancer cell line TMK-1. Furthermore, marimastat decreased the tumour growth in mice injected with MGLVA1 human gastric tumours (Wada et al. 2003). In the clinical setting a phase I study of marimastat showed an acceptable safety profile in 35 patients with advanced GC or carcinoma of the GEJ. Despite any radiological responses a significant number of patients where control endoscopies were performed showed increased fibrotic cover of the tumour (32%) and a reduction in tumour haemhorrage was seen in 26% of patients (Tierney et al. 1999). Based on these results a phase III trial investigated the role of marimastat versus placebo in patients with advanced gastric cancer and carcinoma of the GEJ. 396 patients who had received no more than a single regimen of 5-FU based chemotherapy were randomized to receive either marimastat or placebo. This trial showed significant improvement in the 2-year OS (9% vs. 3%) in the marimastat cohort; however, this study did not meet its endpoint to show an OS difference ($P = 0.07$). Interestingly, the subgroup of pre-treated patients had a significantly prolonged survival compared to patients who were treatment naïve (8.4 months vs. 5.8 months, $P = 0.045$). Due to a poor tolerability (musculoskeletal toxicity) this drug was not further developed in this setting (Bramhall et al. 2002). The clinical development of another oral MMP-inhibitor, Prinomastat (reversible, selective inhibitor of MMP-2, MMP-3, MMP-9, MMP-13 and MMP-14), was omitted due to an unfavourable toxicity profile (Zucker et al. 2000).

Future perspectives

Despite advances in clinical diagnostics, surgical techniques, improvement of chemo- and radiotherapy regimens the prognosis of gastric cancer remains poor and the need for novel treatment options is urgent.

In recent years the understanding of cancer biology has improved and resulted in the development of new molecular targeted agents with the potential to suppress key pathways involved in carcinogenesis. These findings open new possibilities to apply ‘targeted therapy’ for patients with gastric cancer. And indeed, there are currently several promising examples and future studies will incorporate

these agents either as single, multi-targeted approach or in combination with accepted chemotherapy backbones.

However, to avoid unnecessary drug development failure and immense costs associated with it we have to re-think our current drug development strategies.

Given the diversity of molecular changes acquired during malignant transformation there is often no single neoplastic pathway responsible. Molecular profiling will therefore play a crucial role to test for the relevant target or pathway, and moreover to validate whether the target is inhibited or functionally of importance. Also, to identify the right patient population molecular-based population enrichment will play a crucial role, especially in early clinical trials.

Additionally, the fact that molecularly targeted agents often result only in prolonged disease stabilization rather than tumour shrinkage is a great challenge. The way clinical trials for targeted agents are designed will therefore change, especially in the phase II setting, where 'randomized phase II' and 'randomized discontinuation trials' will become more apparent. These new trial designs may help to identify relevant tumour subgroups benefiting from treatment.

Conflict of interest statement Dr Hendrik-Tobias Arkenau has no conflict of interest.

References

Amemiya H, Kono K, Itakura J et al (2002) C-Met expression in gastric cancer with liver metastasis. Oncology 63(3):286–296. doi:10.1159/000065477

Attard G, Fong PC, Molife R et al (2006) Phase I trial involving the pharmacodynamic (PD) study of circulating tumour cells, of CP-751, 871 (C), a monoclonal antibody against the insulin-like growth factor 1 receptor (IGF-1R), with docetaxel (D) in patients (p) with advanced cancer. J Clin Oncol 24:3023

Bae SH, Ryoo HM, Kim MK et al (2008) Effects of the proteasome inhibitor bortezomib alone and in combination with chemotherapeutic agents in gastric cancer cell lines. Oncol Rep 19(4):1027–1032

Bang Y, Kang Y, Kang W et al (2007) Sunitinib as second-line treatment for advanced gastric cancer: preliminary results from a phase II study. J Clin Oncol 25:4603. doi:10.1200/JCO.2007.10.8688

Bang Y, Chung H, Sawaki A et al (2008) HER2-positivity rates in advanced gastric cancer (GC): results from a large international phase III trial. J Clin Oncol 26:4526

Bolden JE, Peart MJ, Johnston RW (2006) Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov 5(9):769–784. doi:10.1038/nrd2133

Bramhall SR, Hallissey MT, Whiting J et al (2002) Marimastat as maintenance therapy for patients with advanced gastric cancer: a randomised trial. Br J Cancer 86(12):1864–1870. doi:10.1038/sj.bjc.6600310

Carmeliet P (2003) Angiogenesis in health and disease. Nat Med 9:653–660. doi:10.1038/nm0603-653

Carpenter G, Cohen S (1990) Epidermal growth factor. J Biol Chem 265:7709–7712

Cauwe B, Van den Steen PE, Opdenakker G (2007) The biochemical, biological, and pathological kaleidoscope of cell surface substrates processed by matrix metalloproteinases. Crit Rev Biochem Mol Biol 42(3):113–185. doi:10.1080/10409230701340019

Cejka D, Preusser M, Woehrer A et al. (2008) Everolimus (RAD001) and anti-angiogenic cyclophosphamide show long-term control of gastric cancer growth in vivo. Cancer Biol Ther 7(9) (epub ahead of print)

Cheema HS, Motwani MV et al. (2004) Suberoylanilide Hydroxamic Acid (SAHA), a histone deacetylase (HDAC) inhibitor, induces a unique mitotic effect and potentiates flavopiridol (F) induced apoptosis. Proc Am Assoc Cancer Res 45: 2443

Cohenuram MK, Lacy J (2008) FOLFOX6 and bevacizumab (FOLFOX6/B) for metastatic esophageal (E), gastroesophageal (GE), and gastric (G) adenocarcinoma: a single institution's initial clinical experience. Proc GI ASCO: 74

Cortés-Funes H, Rivera F, Alés I et al (2007) Phase II of trastuzumab and cisplatin in patients (pts) with advanced gastric cancer (AGC) with HER2/neu overexpression/amplification. J Clin Oncol 25:4613

Dar AA, Zaika A, Piazuela MB et al (2008) Frequent overexpression of aurora kinase A in upper gastrointestinal adenocarcinomas correlates with potent antiapoptotic functions. Cancer 112(8):1688–1698. doi:10.1002/cncr.23371

de Mingo M, Morán A, Sánchez-Pernaute A et al (2007) Expression of MMP-9 and TIMP-1 as prognostic markers in gastric carcinoma. Hepatogastroenterology 54(73):315–319

Dragovich T, McCoy S, Fenoglio-Preiser CM et al (2006) Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. J Clin Oncol 24(30):4922–4927. doi:10.1200/JCO.2006.07.1316

Eskens FA, Mom CH, Planting AS et al (2008) A phase I dose escalation study of BIBW 2992, an irreversible dual inhibitor of epidermal growth factor receptor 1 (EGFR) and 2 (HER2) tyrosine kinase in a 2-week on, 2-week off schedule in patients with advanced solid tumours. Br J Cancer 98(1):80–85. doi:10.1038/sj.bjc.6604108

Fujita T, Doihara H, Washio K et al (2007) Antitumor effects and drug interactions of the proteasome inhibitor bortezomib (PS341) in gastric cancer cells. Anticancer Drugs 18(6):677–686. doi:10.1097/CAD.0b013e32808bf9d8

Gong SJ, Jin CJ, Rha SY et al (2004) Growth inhibitory effects of trastuzumab and chemotherapeutic drugs in gastric cancer cell lines. Cancer Lett 214(2):215–224. doi:10.1016/j.canlet.2004.04.029

Grimber A, Cohen P (2000) Role of insulin-like growth factor and their binding proteins in growth control and carcinogenesis. J Cell Physiol 183:1–9. doi:10.1002/(SICI)1097-4652(200004)183:1<1::AID-JCP1>3.0.CO;2-J

Haluska P, Shaw H, Batzel GN et al (2007) Phase I dose escalation study of the anti-IGF-1R monoclonal antibody CP-751, 871 in patients with refractory solid tumors. J Clin Oncol 25:3586

Hammad N, Philip PA, Shields AF et al. (2008) A phase II study of bevacizumab, docetaxel, and oxaliplatin in gastric and gastroesophageal junction (GEJ) cancer. Proc GI ASCO: 30

Han Z, Wu K, Shen H et al (2008) Akt1/protein kinase B alpha is involved in gastric cancer progression and cell proliferation. Dig Dis Sci 53(7):1801–1810. doi:10.1007/s10620-007-9824-2

Han SW, Oh DY, Im SA et al (2009) Phase II study and biomarker analysis of cetuximab in combination with modified FOLFOX6 in advanced gastric cancer. Br J Cancer 100(2):298–304. doi:10.1038/sj.bjc.6604861

Hattori Y, Itoh H, Uchino S et al (1996) Immunohistochemical detection of K-sam protein in stomach cancer. Clin Cancer Res 2(8):1373–1381

Hecht JR, Urba SG, Koehler M et al. (2008) Lapatinib monotherapy in recurrent upper gastrointestinal malignancy: phase II efficacy and biomarker analyses. Proc GI ASCO: 43

Hecht JR, Mitchell E, Chidiac T et al (2009) A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 27(5):672–680. doi:10.1200/JCO.2008.19.8135

Hinoda Y, Sasaki S, Ishida T et al (2004) Monoclonal antibodies as effective therapeutic agents for solid tumors. Cancer Sci 96:443–446

Hirata A, Ogawa S, Kometani T et al (2002) ZD1839 (Iressa) induces antiangiogenic effects through inhibition of epidermal growth factor receptor tyrosine kinase. Cancer Res 62(9):2554–2560

Inoue T, Kataoka H, Goto K et al (2004) Activation of c-Met (hepatocyte growth factor receptor) in human gastric cancer tissue. Cancer Sci 95(10):803–808. doi:10.1111/j.1349-7006.2004.tb02185.x

Iqbal S, Goldman B, Lenz HJ et al (2007) S0413: a phase II SWOG study of GW572016 (lapatinib) as first line therapy in patients (pts) with advanced or metastatic gastric cancer. J Clin Oncol 25:4621

Iwamoto J, Mizokami Y, Takahashi K et al (2008) The effects of cyclooxygenase2-prostaglandinE2 pathway on Helicobacter pylori-induced urokinase-type plasminogen activator system in the gastric cancer cells. Helicobacter 13(3):174–182. doi:10.1111/j.1523-5378.2008.00597.x

Jang YJ, Kim YS, Kim WH et al (2006) Oncogenic effect of Polo-like kinase 1 expression in human gastric carcinomas. Int J Cancer 29(3):589–594

Jhawer MP, Ilson D, Robinson E et al. (2008) Interim results of a phase II study of modified docetaxel, cisplatin, fluorouracil (mDCF), and bevacizumab (BEV) in patients with metastatic gastroesophageal (GE) adenocarcinoma. Proc GI ASCO: 109

Jhawer MP, Kindler HL, Wainberg ZA et al (2008b) Preliminary activity of XL880, a dual MET/VEGFR2 inhibitor, in MET amplified poorly differentiated gastric cancer (PDGC): interim results of a multicenter phase II study. J Clin Oncol 26:4572. doi:10.1200/JCO.2007.15.5655

Jones HE, Gee JMW, Hutcheson IR et al (2006) Growth factor receptor interplay and resistance in cancer. Endocr Relat Cancer 13(Suppl 1):S45–S51. doi:10.1677/erc.1.01275

Kamada K, Yamada Y, Hirao T et al (2004) Amplification/overexpression of Aurora-A in human gastric carcinoma: potential role in differentiated type gastric carcinogenesis. Oncol Rep 12(3):593–599

Karayiannakis AJ, Syrigos KN, Polychronidis A et al (2002) Circulating VEGF levels in the serum of gastric cancer patients: correlation with pathological variables, patient survival, and tumor surgery. Ann Surg 236(1):37–42. doi:10.1097/00000658-200207000-00007

Kim JW, Kim HP, Im SA et al. (2008) The growth inhibitory effect of lapatinib, a dual inhibitor of EGFR and HER2 tyrosine kinase, in gastric cancer cell lines. Cancer Lett (e-pub ahead of print)

Kuwano T, Nakao S, Yamamoto H (2004) Cyclooxygenase 2 is a key enzyme for inflammatory cytokine-induced angiogenesis. FASEB J 18(2):300–310. doi:10.1096/fj.03-0473com

Lang SA, Klein D, Moser C et al (2007a) Inhibition of heat shock protein 90 impairs epidermal growth factor-mediated signaling in gastric cancer cells and reduces tumor growth and vascularization in vivo. Mol Cancer Ther 6(3):1123–1132. doi:10.1158/1535-7163.MCT-06-0628

Lang SA, Gaumann A, Koehl GE et al (2007b) Mammalian target of rapamycin is activated in human gastric cancer and serves as a target for therapy in an experimental model. Int J Cancer 120(8):1803–1810. doi:10.1002/ijc.22442

Lax AJ, Thomas W (2002) How bacteria could cause cancer: one step at a time. Trends Microbiol 10(6):293–299. doi:10.1016/S0966-842X(02)02360-0

Lordick F, Lorenzen S, Hegewisch-Becker S et al (2007) Cetuximab plus weekly oxaliplatin/5FU/FA (FUFOX) in 1st line metastatic gastric cancer. Final results from a multicenter phase II study of the AIO upper GI study group. J Clin Oncol 26:4526

Macarulla T, Ramos FJ, Tabernero J (2008) Aurora kinase family: a new target for anticancer drug. Recent Patents Anticancer Drug Discov 3(2):114–122

Mani A, Gelmann EP (2005) The Ubiquitin-Proteasome pathway and its role in cancer. J Clin Oncol 23(21):4776–4789. doi:10.1200/JCO.2005.05.081

Mann JR, Backlund MG, DuBois RN (2005) Mechanisms of disease: inflammatory mediators and cancer prevention. Nat Clin Pract Oncol 2(4):202–210. doi:10.1038/ncponc0140

Marks PA, Jiang X (2005) Histone deacetylase inhibitors in programmed cell death and cancer therapy. Cell Cycle 4(4):549–551

Marumoto T, Hirota T, Morisaki T et al (2002) Roles of aurora-A kinase in mitotic entry and G2 checkpoint in mammalian cells. Genes Cells 7:1173–1182. doi:10.1046/j.1365-2443.2002.00592.x

Matsubara J, Yamada Y, Hirashima Y et al (2008) Impact of insulin-like growth factor type 1 receptor, epidermal growth factor receptor, and HER2 expressions on outcomes of patients with gastric cancer. Clin Cancer Res 14(10):3022–3029. doi:10.1158/1078-0432.CCR-07-1898

Maulik G, Shrikhande A, Kijima T et al (2002) Role of the hepatocyte growth factor receptor, c-Met, in oncogenesis and potential for therapeutic inhibition. Cytokine Growth Factor Rev 13(1):41–59. doi:10.1016/S1359-6101(01)00029-6

McCarty MF, Wey J, Stoeltzing O et al (2004) ZD6474, a vascular endothelial growth factor receptor tyrosine kinase inhibitor with additional activity against epidermal growth factor receptor tyrosine kinase, inhibits orthotopic growth and angiogenesis of gastric cancer. Mol Cancer Ther 3(9):1041–1048

Miremadi A, Oestergaard MZ, Pharoah PD et al (2007) Cancer genetics of epigenetic genes. Hum Mol Genet 16(1):R28–R49. doi:10.1093/hmg/ddm021

Moehler M, Hartmann JT, Lordick F et al. (2009) Sunitinib in patients with chemorefractory metastatic gastric cancer: preliminary results of an open-label, prospective non-randomised multicentre AIO Phase II trial. Proc GI ASCO: 61

Morgensztern D, McLeod HL (2005) PI3K/Akt/mTOR pathway as a target for cancer therapy. Anticancer Drugs 16(8):797–803. doi:10.1097/01.cad.0000173476.67239.3b

Motzer RJ, Hutson TE, Tomczak P et al (2007) Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356(2):115–124. doi:10.1056/NEJMoa065044

Muro K, Boku N, Yamada Y et al (2008) Multicenter phase II study of RAD001 for previously treated metastatic gastric cancer (MGC): preliminary results. J Clin Oncol 26:4541

Nakajima M, Sawada H, Yamada Y et al (2000) The prognostic significance of amplification and overexpression of c-met and c-erb B-2 in human gastric carcinomas. Cancer 85:1894–1902

Nakamura K, Yashiro M, Matsuoka T et al (2006) A novel molecular targeting compound as K-samII/FGF-R2 phosphorylation inhibitor, Ki23057, for Scirrhous gastric cancer. Gastroenterology 131(5):1530–1541. doi:10.1053/j.gastro.2006.08.030

Ocean AJ, Schnoll-Sussman F, Chen X et al. (2007) Phase II study of PS-341 (VELCADE, bortezomib) with or without irinotecan in patients (pts) with advanced gastric adenocarcinomas (AGA). Proc GI ASCO: 45

Oki E, Baba H, Tokunaga E et al (2005) Akt phosphorylation associates with LOH of PTEN and leads to chemoresistance for gastric cancer. Int J Cancer 117(3):376–380. doi:10.1002/ijc.21170

Park JH, Jung Y, Kim TY et al (2004) Class I histone deacetylase-selective novel synthetic inhibitors potently inhibit human tumor proliferation. Clin Cancer Res 10(15):5271–5281. doi:10.1158/1078-0432.CCR-03-0709

Pinto C, Di Fabio F, Siena S et al (2007) Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). Ann Oncol 18(3):510–517. doi:10.1093/annonc/mdl459

Pinto C, Di Fabio F, Barone C et al. (2008) Phase II study of cetuximab in combination with cisplatin/docetaxel as first-line treatment in patients with unresectable/metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma (DOCETUX Study): preliminary results. Proc GI ASCO: 34

Presta LG, Chen H, O'Connor SJ et al (1997) Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 57:4593–4599

Rao S, Starling N, Cunningham D et al. (2008) Phase I study of epirubicin, cisplatin and capecitabine plus matuzumab in previously untreated patients with advanced oesophagogastric cancer. Br J Cancer (epub ahead of print)

Rojo F, Tabernero J, Albanell J et al (2006) Pharmacodynamic studies of gefitinib in tumor biopsy specimens from patients with advanced gastric carcinoma. J Clin Oncol 24(26):4309–4316. doi:10.1200/JCO.2005.04.2424

Saltz LB, Meropol NJ, Loehrer PJ et al (2004) Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 22:1201–1208. doi:10.1200/JCO.2004.10.182

Saltz LB, Lenz HJ, Kindler HL et al (2007) Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 Study. J Clin Oncol 25:4557–4561. doi:10.1200/JCO.2007.12.0949

Schwartz GK, Ilson D, Saltz L et al (2001) Phase II study of the cyclin-dependent kinase inhibitor flavopiridol administered to patients with advanced gastric carcinoma. J Clin Oncol 19(7):1985–1992

Senderowicz AM (2000) Small molecule modulators of cyclin-dependent kinases for cancer therapy. Oncogene 19(56):6600–6606. doi:10.1038/sj.onc.1204085

Shah MA, Ramanathan RK, Ilson DH et al (2006) Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 24(33):5201–5206. doi:10.1200/JCO.2006.08.0887

Song J, Noh JH, Lee JH et al (2005) Increased expression of histone deacetylase 2 is found in human gastric cancer. APMIS 113(4):264–268. doi:10.1111/j.1600-0463.2005.apm_04.x

Stein A, Al-Batran SE, Arnold D et al. (2007) Cetuximab with irinotecan as salvage therapy in heavily pretreated patients with metastatic gastric cancer. Proc GI ASCO: 47

Sun W, Powell ME, O'Dwyer P et al (2008) A phase II study: combination of sorafenib with docetaxel and cisplatin in the treatment of metastatic or advanced unresectable gastric and gastroesophageal junction (GEJ) adenocarcinoma (ECOG 5203). J Clin Oncol 26:4535

Tahara E (2004) Genetic pathways of two types of gastric cancer. IARC Sci Publ 157:327–349

Takai N, Hamanaka R, Yoshimatsu J et al (2005) Polo-like kinases (Plks) and cancer. Oncogene 24(2):287–291. doi:10.1038/sj.onc.1208272

Tanner M, Hollmen M, Junttila TT et al (2005) Amplification of HER-2 in gastric carcinoma: association with topoisomerase II alpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol 16:273–278. doi:10.1093/annonc/mdi064

Tebbutt NC, Sourjina T, Strickland AH et al (2008) ATTAX2: docetaxel plus cetuximab as second-line treatment for docetaxel-refractory oesophago-gastric cancer—final results of a multicentre phase II trial by the AGITG. J Clin Oncol 26:15554

Thomas JP, Tutsch KD, Cleary JF et al (2002) Phase I clinical and pharmacokinetic trial of the cyclin-dependent kinase inhibitor flavopiridol. Cancer Chemother Pharmacol 50(6):465–472. doi:10.1007/s00280-002-0527-2

Tierney GM, Griffin NR, Stuart RC et al (1999) A pilot study of the safety and effects of the matrix metalloproteinase inhibitor marimastat in gastric cancer. Eur J Cancer 35(4):563–568. doi:10.1016/S0959-8049(99)00007-6

Tol J, Koopman M, Cats A et al. (2009) Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 360(6):563–572

Tortora G, Ciardiello F, Gasparini G (2008) Combined targeting of EGFR-dependent and VEGF-dependent pathways: rationale, preclinical studies and clinical applications. Nat Clin Pract Oncol 5(9):521–530. doi:10.1038/ncponc1161

Tsutsumi S, Neckers L (2007) Extracellular heat shock protein 90: a role for a molecular chaperone in cell motility and cancer metastasis. Cancer Sci 98(10):1536–1539. doi:10.1111/j.1349-7006.2007.00561.x

Van Cutsem E, Peeters M, Siena S et al (2007) Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 25(13):1658–1664. doi:10.1200/JCO.2006.08.1620

Wada N, Otani Y, Kubota T et al (2003) Reduced angiogenesis in peritoneal dissemination of gastric cancer through gelatinase inhibition. Clin Exp Metastasis 20(5):431–435. doi:10.1023/A:1025453500148

Wang HK (2001) Flavopiridol. National Cancer Institute. Curr Opin Invest Drugs 2(8):1149–1155

Wang WH, Huang JQ, Zheng GF et al (2003) Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. J Natl Cancer Inst 95(23):1784–1791

Weichert W, Ullrich A, Schmidt M et al (2006) Expression patterns of polo-like kinase 1 in human gastric cancer. Cancer Sci 97(4):271–276. doi:10.1111/j.1349-7006.2006.00170.x

Weichert W, Röske A, Gekeler V et al (2008) Association of patterns of class I histone deacetylase expression with patient prognosis in gastric cancer: a retrospective analysis. Lancet Oncol 9(2):139–148. doi:10.1016/S1470-2045(08)70004-4

Woell E, Greil R, Eisterer W et al (2008) Oxaliplatin, irinotecan and cetuximab in advanced gastric cancer: first results of a multicenter phase II trial (AGMT Gastric-2). J Clin Oncol 26:15587

Yap TA, Harris D, Barriuso J et al (2008) Phase I trial to determine the dose range for the c-Met inhibitor ARQ 197 that inhibits c-Met and FAK phosphorylation, when administered by an oral twice-a-day schedule. J Clin Oncol 26:3584

Zou XM, Li YL, Wang H et al (2008) Gastric cancer cell lines induced by trichostatin A. World J Gastroenterol 14(30):4810–4815. doi:10.3748/wjg.14.4810

Zucker S, Cao J, Chen WT (2000) Critical appraisal of the use of matrix metalloproteinase inhibitors in cancer treatment. Oncogene 19(56):6642–6650. doi:10.1038/sj.onc.1204097

Zuo DS, Dai J, Bo AH et al (2003) Significance of expression of heat shock protein90alpha in human gastric cancer. World J Gastroenterol 9(11):2616–2618