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Molecular Targeting Therapy for Gastric Cancer: Current Advances and Obstacles

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Abstract

Although the incidence of gastric cancer (GC) has declined steadily in recent years, GC remains a major cancer burden. Multimodal therapies have been developed and first-line chemotherapy for advanced GC patients, even they have good performance status, could provide only modest efficacy. Furthermore, treatment outcomes after failure of first-line chemotherapy remain poor. In order to provide a solution to this unmet clinical need, since the management of various types of cancer has progressed rapidly into the molecular era, biomarker-targeted therapy for GC has received enormous attention in recent years. This review focuses on the current treatment achievement of molecular targeting agents for GC, such as trastuzumab, pertuzumab, trastuzumab emtansine, lapatinib, cetuximab, panitumumab, nimotuzumab, mammalian target of rapamycin, bevacizumab, ramucirumab, sunitinib, sorafenib, apatinib, rilotumumab, and onartuzumab. However, problems are also emerged with regard to resistance and refractoriness. This chapter also focuses on the current obstacles concerning resistance and refractoriness, as well as provides discussions concerning future directions with regard to molecular categorization to predict response and toxicities leading to select patients most likely to benefit.

Keywords: gastric cancer, molecular targeting therapy, human epidermal growth factor receptors, angiogenesis, resistance

1. Introduction

Although the incidence of gastric cancer (GC) has declined steadily in recent years, GC remains a major cancer burden. GC is still the fifth most common malignancy and third leading cause of cancer death in both sexes worldwide, comprising 8.8% of total cancer deaths [1]. Radical resection is the only potentially curative approach for GC; however, approximately 40–70% of GC recurs even after curative resection [2]. When the disease reaches an

advanced state, chemotherapy becomes a mainstay of the treatment [3]. The most frequently used first-line chemotherapy regimens worldwide are platinum derivatives plus fluoropyrimidine doublet or a triplet regimen with the addition of epirubicin or docetaxel. The reality is that chemotherapy has reached a plateau of efficacy for GC with a median overall survival (mOS) of around or less than 12 months [4, 5]. Furthermore, although second-line treatment is recommended for the patients with failure after first-line chemotherapy because it prolongs survival as compared with the best supportive care [6–8], the global standard regimens of second-line chemotherapy have not yet been determined [4].

These somewhat painfully slow rates of advances in treatment have been impetus to develop new concepts of strategies. As an example, receptor tyrosine kinases (RTKs) consist of the ligand binding of extracellular domains, a transmembrane domain, and a tyrosine kinase motif, which is involved in a subsequent downstream signal cascade. Since this cascade leads to cell growth, differentiation, adhesion, migration, and apoptosis [9], each step is theoretically a therapeutic target. This review focuses on advances in molecular targeted therapy for GC in recent years, as well as problems to be resolved.

2. Focus on human epidermal growth factor receptors (HERs)

Membrane-bound human epidermal growth factor receptors (HERs) consist of a ligand-binding domain at the extracellular surface, a single transmembrane segment, and a cytoplasmic portion harboring the protein kinase activity. The HER family includes four structurally related members, namely the epidermal growth factor receptor (EGFR, also known as HER1), HER2, HER3, and HER4. Ligand binding to the extracellular domain triggers conformational changes of receptors that form HER-dimerization, and subsequently, activates downstream a signaling cascade and ultimately stimulates tumor cell proliferation. Therefore, HERs are the most innovative targets for GC treatment.

2.1. Trastuzumab

HER2 is responsible for GC cell growth when overexpressed [10]. A literature review demonstrates that the mean incidence of HER2-positive gastric cancer is 18%, ranging from 4 to 53% [11], and the most recent research confirmed that the HER2 positivity rate to be 21% among Japanese patients [12]. A systematic analysis demonstrated the potential role for HER2 as a negative prognostic factor [11]; thus, it has become a rational therapeutic target. Trastuzumab, a humanized monoclonal antibody that targets the extracellular domain IV of the HER2, was evaluated by the first landmark randomized controlled trial (RCT) (ToGA trial) [M]. The ToGA trial provided evidence of a significant improvement by the addition of trastuzumab to chemotherapy as compared with chemotherapy alone as a first-line setting. In patients with HER2-positive GC, while trastuzumab could achieve longer mOS, a higher response rate (RR), and a longer median progression free survival (mPFS) (**Table 1**), toxicity did not differ between groups. A post-hoc analysis revealed that the survival differences between groups were more evident in patients with immunohistochemistry (IHC) 2+

Reference	Publication year	Design	Phase	Experimental arm		Control arm		RR			mPFS			mOS			Study name
				Agents	<i>n</i>	Agents	<i>n</i>	Experi- mental arm	Control arm	<i>p</i>	Experi- mental arm	Control arm	<i>p</i>	Experi- mental arm	Control arm	<i>p</i>	
[13]	2010	1st	III	F, Cis, T	294	F, Cis	290	47%	35%	0.0017	6.7	5.5	0.0002	13.8	11.1	0.0046	ToGA
[36]	Ongoing	1st	III	T, F, Cis, Per	NA	T, F, Cis	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	JACOB (NCT01774786)
[37]	2016	2nd	II/III	T-DM1	228	TAX	117	21%	20%	ND	2.7	2.9	NS	7.9	8.6	NS	GATSBY (NCT01641939)
[39]	2015	1st	III	Cape, Ox, L	249	Cape, Ox	238	53%	39%	0.0031	6	5.4	0.04	12.2	10.5	NS	LoGiC
[40]	2014	2nd	III	PTX, L	132	PTX	129	27%	9%	<0.001	5.4	4.4	NS	11	8.9	NS	TyTAN
[41]	2013	1st	III	Cape, Cis, Cet	455	Cape, Cis	449	30%	29%	NS	4.4	5.6	NS	9.4	10.7	NS	EXPAND
[42]	2010	1st	III	EOC, Pani	278	EOC	275	42%	46%	NS	7.4	6	NS	8.8	11.3	0.013	REAL-3
[43]	2015	1st	rII	S1, Cis, Nimo	31	S1, Cis	31	55%	58%	NS	7.2	4.8	0.011	14.2	10.2	0.06	
[44]	2015	2nd	rII	Iri, Nimo	40	Iri	43	18%	10%	NS	73d	85d	NS	251d	232d	NS	
[50]	2013	2nd or further	III	Eve	439	–	217	4	2	ND	1.7	1.4	<0.001	5.3	4.3	NS	GRANITE-1
[56]	2011	1st	III	Cape, Cis, Bev	387	Cape, Cis	387	46%	37%	0.03	6.7	5.3	0.0037	12.1	10.1	NS	AVAGAST
[57]	2015	1st	III	Cape, Cis, Bev	102	Cape, Cis	100	41%	34%	NS	6.3	6	NS	10.5	11.4	NS	AVATAR
[62]	2014	2nd	III	Ram	238	–	117	3%	3%	NS	2.1	1.3	<0.0001	5.2	3.8	0.047	REGARD
[63]	2014	2nd	III	PTX, Ram	330	PTX	335	28%	16%	0.0001	4.4	2.9	<0.0001	9.6	7.4	0.017	RAINBOW

Reference	Publication year	Design	Phase	Experimental arm		Control arm		RR			mPFS			mOS			Study name
				Agents	n	Agents	n	Experimental arm	Control arm	p	Experimental arm	Control arm	p	Experimental arm	Control arm	p	
[65]	Ongoing	1st	III	F, Cis, Ram	NA	F, Cis	NA	ND	ND	ND	ND	ND	ND	ND	ND	ND	RAINFALL (NCT02314177)
[66]	2014	1st	rII	FOLFOX, Ram	84	FOLFOX	84	45	46	ND	6.4	6.7	ND	11.7	11.5	ND	
[67]	2014	3rd	III	Apatinib	176	–	91	2.8	0	NS	2.6	1.8	<0.001	6.5	4.7	0.0149	
[73]	2016	2nd or further	rII	FOLFILL, sunitinib	45	FOLFILI	45	20	29	ND	3.5	3.3	NS	10.4	8.9	NS	RILOMET-1 (NCT01697072)
[87]	2015	1st	III	E, Cis, Cape, rilotumumab	304	E, Cis, Cape	305	30	39	0.027	5.7	5.7	0.016	9.6	11.5	0.016	
[88]	Ongoing	1st	III	Cis, Cape, rilotumumab	NA	Cis, Cape	NA	ND	ND	ND	ND	ND	ND	ND	ND	ND	
[92]	2017	1st	III	FOLFOX6, Ona	279	FOLFOX6	283	46	41	NS	6.7	6.8	NS	11	11.3	NS	

RR—response rate; mPFS—median progression free survival; mOS—median overall survival; rII—randomized phase II; NA—not described; NS—not significant; Bev—bevacizumab; Cape—capecitabine; Cet—cetuximab; Cis—cisplatin; E—epirubicin; EOC—epirubicin, oxaliplatin, capecitabine; Eve—everolimus; F—fluoropyrimidines; FOLFIRI—leucovorin + 5-fluorouracil + irinotecan; FOLFOX—leucovorin + 5-fluorouracil + oxaliplatin; Iri—irinotecan; L—lapatinib; Nimo—nimotuzumab; Ona—onartuzumab; Ox—oxaliplatin; Pani—panitumumab; Per—pertuzumab; PTX—paclitaxel; Ram—ramucirumab; T—trastuzumab; T-DM1—trastuzumab emtansine.

Table 1. Results of phase III or randomized phase II trials of molecular targeting therapy for gastric cancer.

and fluorescence *in situ* hybridization (FISH) positive tumors or IHC3+ tumors [13]. The ToGA trial also provided evidence of a prolongation of time to the deterioration of health-related quality of life [14]. Furthermore, the subgroup analyses of the ToGA trial restricted to Japanese patients [15] and a subsequent similar phase III study recruiting only Chinese patients [16] have confirmed again such promising results, suggesting the efficacy of trastuzumab irrespective of country of origin. The results of the ToGA study have changed the treatment paradigm for GC harboring HER2 overexpression. Subsequently, a HELOISE study has been conducted to investigate the efficacy of different doses of trastuzumab with cisplatin and capecitabine [17], resulting in no differences between 6 and 10 mg of trastuzumab in terms of mOS and mPFS.

However, targeting HER2 raises important issues that must be discussed, namely, heterogeneity and resistance. Heterogeneity should be considered because of a different HER2 positivity rate according to cancer histology, the location of GC, and geographic area, making for various prevalence rates of HER2-positive GC from study to study or from country to country. In the ToGA trial discussed above, the HER2 positivity rate was higher in the intestinal type (31.8%) than in the diffuse type (6.1%), in specimens from the gastroesophageal junction (32.2%) than in those from the stomach (21.4%), and in patients from Asia-Pacific (23.9%) or Europe (23.6%) than in patients from Central/South America (16.1%) [18]. In addition, one-third of IHC3+ patients had <30% of stained cells, suggesting staining variability within the same tumor. Furthermore, variations of scoring criteria between studies may be another explanation for heterogeneity [11]. Since these variations may undoubtedly complicate the interpretation of the results of the clinical trials, there is a need for establishing a unique scoring system specific for GC [19], which could help identify and select HER2-positive patients who benefit from trastuzumab. Another important issue is a trastuzumab resistance, which has begun to arise along with the accumulation of experience of trastuzumab use. Not all HER2-positive patients immediately benefit from trastuzumab, and even those who initially respond to trastuzumab will eventually experience progress, suggesting refractoriness and resistance. In breast cancer, the majority of those who initially responded to trastuzumab ultimately became resistant during prolonged treatment [20, 21]. In looking at the ToGA trial, mPFS was 6.7 months in the trastuzumab arm or the absolute increase in the RR was only 12%, suggesting that half of the GC patients—even though they were HER2 positive—exhibit acquired resistance within 7 months or do not necessarily respond to trastuzumab.

When considering the onset of nonresponsiveness to trastuzumab, two statuses should be distinguished, namely, resistance and refractoriness. Resistance is a condition of disease progression at first evaluation even under trastuzumab use, whereas refractoriness is a condition of disease progression at second or later evaluations after an initial clinical response [22]. The resistance may be ascribed to intrinsic mechanisms, while refractoriness may be related to acquired properties. The precise mechanisms of these phenomena are unclear; several pathways may be involved, including phosphatidylinositol-3-kinase (PI3K) [23], a mammalian target of rapamycin (mTOR) [23], insulin-like growth factor-1 (IGF-1) [24], and a phosphatase and tensin homolog (PTEN) [25]. This encourages the development of second-generation agents of targeting HER2 to overcome HER2 resistance.

2.2. Pertuzumab

Pertuzumab is a humanized monoclonal antibody that binds to the HER2 domain II—the interface of the dimer formation of HER. As discussed earlier, since trastuzumab binds to the HER2 domain IV—a region not involved in receptor dimerization [26, 27], trastuzumab inhibits ligand-independent dimerization of HER2 while it is not effective for the inhibition of ligand-dependent heterodimerization. These biological properties could imply one mechanism of trastuzumab resistance. For example, HER ligands are able to induce the formation of HER2-containing heterodimers such as the ligand-dependent HER2/HER3 heterodimer even in the presence of trastuzumab; thus HER3 plays some roles in trastuzumab resistance. Notably, HER3 is overexpressed in 14–62% of GC [28–30], and HER3 *per se* is associated with poor survival rates. Considering that pertuzumab binds to the HER2 domain II and subsequently blocks the heterodimerization of HER2 with other members of the HER family, pertuzumab is expected to overcome trastuzumab resistance.

In *in vitro* studies and animal models, pertuzumab and trastuzumab showed synergistic anti-tumor effects [31–33]. Subsequent RCT in HER2-positive metastatic breast cancer demonstrated that pertuzumab, trastuzumab, and docetaxel significantly improved overall survival rates for HER2-positive metastatic breast cancer when compared with placebos, trastuzumab, and docetaxel [34]. Such positive results were maintained when the follow-up period was extended [35]. Motivated by the promising results, a phase III study is ongoing which randomizes HER2-positive advanced GC patients to first-line trastuzumab, cisplatin, and fluoropyrimidine with or without pertuzumab [36].

2.3. T-DM1

T-DM1 is an antibody drug conjugate of trastuzumab and emtansine (DM1), a microtubule inhibitor. TDM-1 is expected to deliver a cytotoxic agent directly to cancer cells. Unfortunately, however, the efficacy of T-DM1 as compared to taxane as a second-line setting failed to meet its primary endpoint (GATSBY trial). The mOS, mPFS, and RR were not different between the two arms [37].

2.4. Lapatinib

Lapatinib is a small molecule inhibitor of the intracellular domain of tyrosine kinase of EGFR and HER2, thus interrupting EGFR- and HER2-associated downstream signaling cascades. Theoretically, lapatinib and trastuzumab synergistically act even on the status of trastuzumab resistance. Indeed, a meta-analysis has revealed [38] the efficacy of lapatinib on HER2-positive breast cancer patients. Accordingly in GC, lapatinib in combination with chemotherapy has been evaluated by two randomized trials as first-line [39] and second-line [40] settings. Unfortunately, the addition of lapatinib to capecitabine plus oxaliplatin (LoGiC trial) [39] or the addition of lapatinib to paclitaxel (TyTAN trial) [40] failed to demonstrate any significant improvement of mOS when compared with chemotherapy without lapatinib.

However, some confusion may exist when considering clinicopathological subsets that receive benefit from agents against HER2. A LoGiC study revealed that Asian or younger

(age <60 years old) patients may benefit from lapatinib [39], while a ToGA trial proved trastuzumab efficacy to be more effective in patients from Central/South America or from Europe, or in older patients [13]. In addition, the TyTAN study, which was conducted only in Asia, failed to identify any clear subgroup benefit from lapatinib except for patients from mainland China. Therefore, it is important to clarify biomarkers that may predict which patients may benefit from dual EGFR/HER2 inhibition.

2.5. Cetuximab, panitumumab, and nimotuzumab

Cetuximab is a recombinant human-mouse chimeric anti-EGFR antibody. A randomized EXPAND study as a first-line setting revealed that the addition of cetuximab to capecitabine plus cisplatin provided no additional benefit to chemotherapy [41]. Panitumumab is a fully humanized anti-HER1 antibody. A REAL-3 study randomized advanced GC patients to first-line epirubicin, oxaliplatin, and capecitabine with or without panitumumab [42]. Again, pertuzumab provided no additional survival benefit to chemotherapy or seemed to be even harmful.

Following by the negative results of the two RCTs (EXPAND and REAL-3), another anti-EGFR antibody, nimotuzumab, a recombinant humanized monoclonal antibody against EGFR [43, 44] has been developed. Regrettably, however, a randomized phase II study adding first-line nimotuzumab to S-1 plus cisplatin failed to improve mOS when compared to S-1 plus cisplatin. In this study, even among the EGFR2+/3+ subgroup, adding nimotuzumab did not provide any additional benefit to the S-1 plus cisplatin combination [43]. However, nimotuzumab and irinotecan could improve survival rates in the EGFR2+/3+ subgroup [44]. The exact reasons underlying these different results according to the chemotherapy agents combined with nimotuzumab are unclear, but putative mechanisms responsible for the confusing results may be negative synergistic effects between the anti-EGFR antibody and capecitabine.

Unlike in colorectal cancer, KRAS mutations have not been a negative predictive marker for EGFR-targeting therapy in GC [45], and prespecified KRAS mutations have limited clinical value. Therefore, the significance of KRAS gene mutations, which is a predictive factor for a lack of efficacy in colorectal cancer, may not be extrapolated to GC, and KRAS mutations are not validated at this time. It is possible that alternative mechanisms other than KRAS mutations to escape from cetuximab action may exist. In this regard, attempts to find predictors of the efficacy of EGFR-targeting therapies have been reported in Refs. [46–48]; however, a small number of patients investigated in such biomarker analyses and a retrospective study design may preclude drawing a meaningful conclusion. Furthermore, the very low rate of KRAS mutation in GC (3–9%) [46–48] also hinders further application in clinical practice. The identification of reliable predictive markers is of paramount importance for selecting the most appropriate agents to the patients benefiting most.

2.6. Mammalian target of rapamycin (mTOR)

The mammalian target of rapamycin (mTOR) is one of the key protein kinases that regulate cell growth, proliferation, and angiogenesis [49] and is integrated in the downstream cascade of HER. The inhibition of mTOR is thus an intriguing new therapeutic approach. Everolimus, an oral mTOR inhibitor, did not significantly improve mOS but could reduce the risk of disease progression ($p < 0.001$) when compared with the best supportive care (GRANITE-1 trial) [50].

3. Anti-antigenic

Angiogenesis was postulated 40 years ago as an essential event for tumors to grow beyond a critical size of few millimeters. Except for physiological conditions requiring angiogenesis such as embryogenesis and wound healing, inhibiting neovascularization may contribute to tumor growth arrest with minimal toxicities to normal tissues. Therefore, targeting molecules involved in neovascularization has gained recognition as a rational therapeutic option.

3.1. Bevacizumab

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF)-A, which is effective in combination with chemotherapy in several kinds of malignancies including the colon [51], breast [52], and lung [53]. Against the background that the overexpression of VEGF was correlated with tumor aggressiveness and poor prognosis in GC [54, 55], a randomized AVAGAST study was conducted to evaluate the efficacy of adding bevacizumab to capecitabine plus cisplatin in the first-line treatment of advanced GC [56]. The results did not meet the primary outcome; however, adding bevacizumab to chemotherapy resulted in a significant prolongation of mPFS and a significant increase in RR. In the subgroup analysis of AVAGAST study, geographical differences in efficacy were suggested, it being effective in Pan-America whereas not so in Asia and Europe. Subsequently, an AVATAR trial in which the trial design is similar with that of AVAGAST has been conducted for 202 Chinese patients with the results recently published [57]. Again, neither mOS nor mPFS were improved by the addition of bevacizumab to chemotherapy. Based on the negative results of the two RCTs, research should be continued to seek the biomarker predictive for bevacizumab efficacy in order to determine the bevacizumab rational position in the treatment of advanced GC [58]. Candidates for potential predictive biomarkers include plasma VEGF-A level and tissue neuropilin-1 expression [58]. However, other cancers had potential other predictive markers for bevacizumab efficacy, being VEGF-A and VEGFR-2 in breast cancer [59] or VEGFR-1 single-nucleotide polymorphism in pancreatic and renal cell cancer [60].

3.2. Ramucirumab

Ramucirumab is a fully humanized monoclonal antibody that blocks the binding of VEGF-A, C, and D to the extracellular domain of VEGF receptor-2 (VEGFR-2); thus, ramucirumab inhibits the ligand activation of a downstream signal transduction of VEGF-R [61]. The REGARD trial is the first RCT demonstrating survival benefits for second-line ramucirumab when compared with the best supportive care [62]. Subsequently, the RAINBOW trial was conducted to evaluate the second-line efficacy of weekly paclitaxel with or without ramucirumab [63]. The subgroup analysis demonstrated that ramucirumab was not effective in Asian patients when compared with those from Europe and the USA; however, this geographical difference was ascribed partly to the high proportion of patients receiving postdiscontinuation therapy—at least for Japanese patients [64]. Currently, ramucirumab has been evaluated as a first-line setting in combination with fluoropyrimidines and cisplatin (RAINFALL trial) [65] or in combination with FOLFOX [66].

3.3. VEGFR tyrosine kinase inhibitors—sunitinib, sorafenib, and apatinib

VEGFR-1, -2, and -3 are RTKs by which a downstream signaling cascade is stimulated to induce angiogenesis when corresponding ligands VEGF-A, -B, -C, and -D bind to the receptors. Several small molecules, which block some steps of this cascade, have been developed. Apatinib is a small molecule of VEGFR-2 tyrosine kinase inhibitor that has been compared with placebos for the second-line treatment of advanced GC. One RCT revealed that apatinib achieved significantly prolonged mOS and mPFS when compared with placebos [67]. These positive findings by inhibiting VEGFR-2 and its related tyrosine kinases have promoted interest in VEGFR inhibition as a therapeutic strategy.

However, pathways of other growth factors, such as platelet-derived growth factor (PDGF), may be responsible for alternative escape mechanisms to the VEGF-VEGFR blockade [68, 69] and may be one reason for resistance to antiangiogenic therapy. These findings have prompted the development of several small molecules targeting multiple RTKs with expectations to overcome an escape from the VEGF-VEGFR blockade. Sorafenib is a multikinase inhibitor that targets multiple RTKs such as VEGFR-2, -3, PDGF-receptor (PDGF-R), c-Kit, and Raf [70, 71]. Sunitinib is another oral multitarget kinase inhibitor of VEGFR, PDGFR, and the Kit receptor [72]. A randomized phase II trial demonstrated a trend toward better mOS in sunitinib plus FORFIRI arm as compared with a FOLFIRI arm, whereas PFS and RR were similar between both arms [73]. Regorafenib is another oral multikinase inhibitor of receptor tyrosine kinases of VEGFR, B-RAF, and PDGFR [74]. A PFS was significantly improved by regorafenib as compared with a placebo in patients with gastrointestinal stromal tumor (GIST) refractory to standard therapy [75]. Encouraged by these results, a phase II INTEGRATE study was conducted and revealed a significant prolongation of mPFS in favor of regorafenib as compared with a placebo [76].

3.4. Resistance to antiangiogenic therapy

In consideration of targeting molecules to suppress angiogenesis, the caveats lie in a paradoxical increase in tumor growth or in a rebound phenomenon that is greater tumor aggressiveness followed by the cessation of antiangiogenic therapy. An animal xenograft model exhibited the worrying observation of a higher incidence of metastasis and/or shorter survival time by antiangiogenic therapy [77], suggesting angiogenesis inhibition as a driving force in tumor progression to stages of greater malignancy. It is plausible for cancer cells exposed to hypoxic conditions to acquire properties that allow them to overcome the lack of energy and oxygen supply. This acquisition means a transformation to a threatening form of tumor adaptation against starving strategy, leading to assume a malignant behavior. In addition, the rebound phenomenon should be mentioned because the withdrawal of antiVEGF TKI resulted in a rapid regrowth of the tumor vasculature that was suppressed during the therapy [78]. For example, renal cell cancer patients showing complete response by sunitinib and sorafenib experienced a relapse on discontinuation of the therapy, but all responded again to a reintroduction of the drug [79]. These findings have confirmed several current limitations to antiangiogenic therapy, posing future challenges for their expanded use.

The precise mechanisms for this phenomenon are unclear. In addition to the multiple pathways to escape from the VEGF-VEGFR blockade as described earlier, it is possible that tumor hypoxia induced by antiangiogenic therapy triggers another angiogenic switch for cancer cells to survive or forces cancer cells to migrate to their nonhypoxic lesion. At present, there is no clinical evidence that the rebound phenomenon is a result of anti-angiogenic therapy or any adverse effects of the inherent nature of anti-angiogenic therapy. A recent review has proposed putative mechanisms of resistance to antiangiogenic therapy [80], which could uncover evasive or intrinsic changes within the tumor as resistance mechanisms of antiangiogenic therapy.

A key molecule involved in another angiogenic switch under conditions of antiangiogenic therapy is the hypoxia inducible factor (HIF) [81]. HIF induces a hepatocyte growth factor (HGF) [82] that subsequently activates a mesenchymal-epidermal transition factor receptor (MET). Activation of this HGF/MET pathway leads to GC cell proliferation, survival, and migration [83]; thus, the HIF and HGF/MET axis is another rational therapeutic target for overcoming the resistance to antiangiogenic therapy. Furthermore, a strategy of HGF/MET inhibition is important because MET solely [84] or its interaction with EGFR [85] or HER3 [86] may mediate resistance to anti-HER therapy.

3.5. HGF/MET inhibitors—rilotumumab and onartuzumab

A number of inhibitors of the HGF/MET pathway have been developed, including monoclonal antibodies, such as rilotumumab and onartuzumab, or small molecule RTK inhibitor such as foretinib.

Rilotumumab, a humanized monoclonal antibody against HGF, has been investigated by two first-line RCTs. RILOMET-1 is a comparison between rilotumumab plus ECX (epirubicin, cisplatin and capecitabine) and a placebo plus ECX [87], and RILOMET-2 aims to evaluate cisplatin plus capecitabine with or without rilotumumab [88]. A rilotumumab benefit was seen in MET-positive patients [89] or was rilotumumab concentration dependent [90]. A very recent pharmacokinetic study revealed a lack of drug-drug interaction between rilotumumab and ECX [91]; however, the results were negative, thereby recommending the early cessation of the RILOMET-1 study [87]. Onartuzumab is a recombinant, fully humanized, monoclonal anti-MET antibody. A randomized phase II study of FOLFOX with or without onartuzumab failed to gain positive results with regard to mPFS and mOS [92]. Foretinib, an oral small molecule multikinase inhibitor that targets MET and VEGFR-2, has been evaluated by a phase II study; however, the results are discouraging [93].

4. Future perspectives

GC and breast cancer have similarities with regard to HER2 positivity rate and molecularly targeted agents first used, such as trastuzumab. However, differences are apparent with regard to tumor response to another HER-inhibitor between the two tumors. The evidence obtained by the current clinical trials suggests that GC and breast cancer do not necessarily show the same response to the HER-2 targeted therapies even if both tumors are HER2 positive. Such similarities

and differences also exist between GC and colorectal cancer. This is partly ascribed to the absence of a validated biomarker specific for GC, for which we are currently unable to select patients who may benefit most or those who may most likely suffer toxicities. The recruitment of molecularly unselected patients may be one reason why many clinical trials did not add benefits or show any superiority over the conventional chemotherapy. The molecular categorization according to which pathways are most activated and which molecules are predominantly involved, as well as which factors or genes are most predictive to response and toxicities highlights the most responsible therapeutic target(s) and the opportunity to explore the most cost-effective agents. These challenges could enable only molecularly selected patients to be treated and the benefit-to-toxicity ratio will likely improve as well. This will ultimately allow clinicians to administer the right treatment to the right patients. Clinical trials with unselected patients are nearing their end, and welcome to those recruiting only correctly selected patients. The innovation of new therapeutic agents designed under this concept will certainly emerge in the future to help oncologists improve the clinical management of GC.

5. Conclusions

Chemotherapy has reached a plateau of efficacy for GC, with an mOS of around 12 months. Unfortunately, progress in treating this disease with chemotherapy over the last years has lagged behind other malignancies such as breast and colorectal cancer. During this time, molecular targeting therapies for colorectal cancer have evolved and their clinical efficacy has been evaluated by various phase III trials, resulting in the mOS being at least doubled. In GC, the use of molecularly targeted therapies is still in the early stages, but more and more targeted drugs have begun to be developed to target each step of the signaling pathways. Disappointingly, however, both monoclonal antibodies and RTK inhibitors targeting signal transduction pathways failed to meet expectations or their efficacy was modest at best.

Such a painful slow advance is partly ascribed to either the lack of validated biomarkers to predict a therapeutic response or adverse events to molecular targeting therapy or to escape or resistance phenomena. Better therapeutic responses could sometimes be obtained at the expense of adverse events; however, drug-related severe adverse events might depress patient QOL. In addition, the blockade of a single signal transduction axis does not provide long-term efficacy due to escape or resistance phenomena. Research should be continued to bridge these adverse events and efficacy gaps or to circumvent resistance, but we are still far from any major breakthrough. Such a reality is challenging, but thanks to the accumulation of the knowledge of the mechanisms of RTK action and its downstream signal transduction cascade, there are several candidate surrogate biomarkers of response and adverse events, or multiple blockade strategies or kinases are being developed. New predictive biomarkers and the clarification of resistance mechanisms may hopefully lead to the selection of a potentially drug-sensitive cohort, to intensify drug efficacy, and to predict more accurately adverse events, holding promise for more tailored therapies. In this respect, both challenges and progress engender optimism as they unveil biological mechanisms underlying GC, ultimately identifying those patients most likely to benefit.

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References

- [1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer*. 2015;**136**:E359-E386. DOI: 10.1002/ijc.29210
- [2] D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. *Annals of Surgery*. 2004;**240**:808-816
- [3] Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: A systematic review and meta-analysis based on aggregate data. *Journal of Clinical Oncology*. 2006;**24**:2903-2909
- [4] Shimoyama S. Chemotherapy for gastric cancer. What comes next? In: Rangel LBA, Silva V, editors. *Updates on Cancer Treatment*. In Tech, Croatia; 2015. pp. 103-117
- [5] GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Oba K, Paoletti X, Bang YJ, Bleiberg H, Burzykowski T, Fuse N, Michiels S, Morita S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, Sasako M, Shitara K, Tsuburaya A, Van Cutsem E, Buyse M. Role of chemotherapy for advanced/recurrent gastric cancer: An individual-patient-data meta-analysis. *European Journal of Cancer*. 2013;**49**:1565-1577. DOI: 10.1016/j.ejca.2012.12.016
- [6] Badiani B, Maratea D, Messori A. Second-line treatments for advanced gastric cancer: Interpreting outcomes by network meta-analysis. *World Journal of Clinical Oncology*. 2015;**6**:73-79. DOI: 10.5306/wjco.v6.i4.73
- [7] Thuss-Patience PC, Kretschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, Dogan Y, Gebauer B, Schumacher G, Reichardt P. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *European Journal of Cancer*. 2011;**47**:2306-2314. DOI: 10.1016/j.ejca.2011.06.002
- [8] Kang JH, Lee SI, Lim DH, Park KW, Oh SY, Kwon HC, Hwang IG, Lee SC, Nam E, Shin DB, Lee J, Park JO, Park YS, Lim HY, Kang WK, Park SH. Salvage chemotherapy for pretreated gastric cancer: A randomized phase III trial comparing chemotherapy

plus best supportive care with best supportive care alone. *Journal of Clinical Oncology*. 2012;**30**:1513-1518. DOI: 10.1200/JCO.2011.39.4585

- [9] Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell*. 2010; **141**:1117-1134. DOI: 10.1016/j.cell.2010.06.011
- [10] Gravalos C, Jimeno A. HER2 in gastric cancer: A new prognostic factor and a novel therapeutic target. *Annals of Oncology*. 2008;**19**:1523-1529. DOI: 10.1093/annonc/mdn169
- [11] Jorgensen JT, Hersom M. HER2 as a prognostic marker in gastric cancer—A systematic analysis of data from the literature. *Journal of Cancer*. 2012;**3**:137-144. DOI: 10.7150/jca.4090
- [12] Matsusaka S, Nashimoto A, Nishikawa K, Miki A, Miwa H, Yamaguchi K, Yoshikawa T, Ochiai A, Morita S, Sano T, Kodera Y, Kakeji Y, Sakamoto J, Saji S, Yoshida K. Clinicopathological factors associated with HER2 status in gastric cancer: Results from a prospective multicenter observational cohort study in a Japanese population (JFMC44-1101). *Gastric Cancer*. 2016;**19**:839-851. DOI: 10.1007/s10120-015-0518-8
- [13] Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. *Lancet*. 2010;**376**:687-697. DOI: 10.1016/S0140-6736(10)61121-X
- [14] Satoh T, Bang YJ, Gotovkin EA, Hamamoto Y, Kang YK, Moiseyenko VM, Ohtsu A, Van Cutsem E, Al-Sakaff N, Urspruch A, Hill J, Weber HA, Chung HC; ToGA Trial Investigators. Quality of life in the trastuzumab for gastric cancer trial. *The Oncologist*. 2014;**19**:712-719. DOI: 10.1634/theoncologist.2014-0058
- [15] Sawaki A, Ohashi Y, Omuro Y, Satoh T, Hamamoto Y, Boku N, Miyata Y, Takiuchi H, Yamaguchi K, Sasaki Y, Nishina T, Satoh A, Baba E, Tamura T, Abe T, Hatake K, Ohtsu A. Efficacy of trastuzumab in Japanese patients with HER2-positive advanced gastric or gastroesophageal junction cancer: A subgroup analysis of the Trastuzumab for Gastric Cancer (ToGA) study. *Gastric Cancer*. 2012;**15**:313-322. DOI: 10.1007/s10120-011-0118-1
- [16] Shen L, Xu JM, Feng FY, Jiao SC, Wang LW, Li J, Guan ZZ, Qin SK, Wang JJ, Yu SY, Wang YJ, Jin YN, Tao M, Zheng LZ, Pan LX. Trastuzumab in combination with chemotherapy versus chemotherapy alone for first-line treatment of HER2-positive advanced gastric or gastroesophageal junction cancer: A Phase III, multi-center, randomized controlled trial, Chinese subreport. (In Chinese with English abstract) *Zhonghua Zhong Liu Za Zhi*. 2013;**35**:295-300. DOI: 10.3760/cma.j.issn.0253-3766.2013.04.012
- [17] A Study of Herceptin (Trastuzumab) in Combination With Cisplatin/Capecitabine Chemotherapy in Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Metastatic Gastric or Gastro-Esophageal Junction Cancer (HELOISE). <https://clinicaltrials.gov> [NCT 01450696]

- [18] Van Cutsem E, Bang YJ, Feng-Yi F, Xu JM, Lee KW, Jiao SC, Chong JL, López-Sánchez RI, Price T, Gladkov O, Stoss O, Hill J, Ng V, Lehle M, Thomas M, Kiermaier A, Rüschoff J. HER2 screening data from ToGA: Targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer*. 2015;**18**:476-484. DOI: 10.1007/s10120-014-0402-y
- [19] Hofmann M, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, Ochiai A, Rüschoff J, Henkel T. Assessment of a HER2 scoring system for gastric cancer: Results from a validation study. *Histopathology*. 2008;**52**:797-805. DOI: 10.1111/j.1365-2559.2008.03028.x
- [20] Shimoyama S. Unraveling trastuzumab and lapatinib in gastric cancer. *Molecular and Clinical Oncology*. 2014;**2**:175-181. DOI: 10.3892/mco.2013.218
- [21] Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *The New England Journal of Medicine*. 2001;**344**:783-792
- [22] Wong H, Leung R, Kwong A, Chiu J, Liang R, Swanton C, Yau T. Integrating molecular mechanisms and clinical evidence in the management of trastuzumab resistant or refractory HER-2⁺ metastatic breast cancer. *The Oncologist*. 2011;**16**:1535-1546. DOI: 10.1634/theoncologist.2011-0165
- [23] Serra V, Markman B, Scaltriti M, Eichhorn PJ, Valero V, Guzman M, Botero ML, Lluch E, Atzori F, Di Cosimo S, Maira M, Garcia-Echeverria C, Parra JL, Arribas J, Baselga J. NVP-BEZ235, a dual PI3K/mTOR inhibitor, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations. *Cancer Research*. 2008;**68**:8022-8030. DOI: 10.1158/0008-5472.CAN-08-1385
- [24] Nahta R, Yuan LX, Zhang B, Kobayashi R, Esteva FJ. Insulin-like growth factor-I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. *Cancer Research*. 2005;**65**:11118-11128
- [25] Nagata Y, Lan KH, Zhou X, Tan M, Esteva FJ, Sahin AA, Klos KS, Li P, Monia BP, Nguyen NT, Hortobagyi GN, Hung MC, Yu D. PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. *Cancer Cell*. 2004;**6**:117-127
- [26] Cho HS, Mason K, Ramyar KX, Stanley AM, Gabelli SB, Denney DW Jr, Leahy DJ. Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab. *Nature*. 2003;**421**:756-760
- [27] Baselga J, Swain SM. Novel anticancer targets: Revisiting ERBB2 and discovering ERBB3. *Nature Reviews Cancer*. 2009;**9**:463-475. DOI: 10.1038/nrc2656
- [28] Zhang XL, Yang YS, Xu DP, Qu JH, Guo MZ, Gong Y, Huang J. Comparative study on overexpression of HER2/neu and HER3 in gastric cancer. *World Journal of Surgery*. 2009;**33**:2112-2118. DOI: 10.1007/s00268-009-0142-z

- [29] Tang D, Liu CY, Shen D, Fan S, Su X, Ye P, Gavine PR, Yin X. Assessment and prognostic analysis of EGFR, HER2, and HER3 protein expression in surgically resected gastric adenocarcinomas. *OncoTargets and Therapy*. 2014;**8**:7-14. DOI: 10.2147/OTT.S70922
- [30] Ema A, Yamashita K, Ushiku H, Kojo K, Minatani N, Kikuchi M, Mieno H, Moriya H, Hosoda K, Katada N, Kikuchi S, Watanabe M. Immunohistochemical analysis of RTKs expression identified HER3 as a prognostic indicator of gastric cancer. *Cancer Science*. 2014;**105**:1591-1600. DOI: 10.1111/cas.12556
- [31] Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Cancer Research*. 2004;**64**:2343-2366
- [32] Lee-Hoeflich ST, Crocker L, Yao E, Pham T, Munroe X, Hoeflich KP, Sliwkowski MX, Stern HM. A central role for HER3 in HER2-amplified breast cancer: Implications for targeted therapy. *Cancer Research*. 2008;**68**:5878-5887. DOI: 10.1158/0008-5472.CAN-08-0380
- [33] Scheuer W, Friess T, Burtscher H, Bossenmaier B, Endl J, Hasmann M. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Research*. 2009;**69**:9330-9336. DOI: 10.1158/0008-5472.CAN-08-4597
- [34] Swain SM, Kim SB, Cortés J, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Knott A, Clark E, Ross G, Benyunes MC, Baselga J. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *The Lancet Oncology*. 2013;**14**:461-471. DOI: 10.1016/S1470-2045(13)70130-X
- [35] Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Heeson S, Clark E, Ross G, Benyunes MC, Cortés J; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *The New England Journal of Medicine*. 2015;**372**:724-734. DOI: 10.1056/NEJMoa1413513
- [36] Tabernero J, Hoff PM, Shen L, Ohtsu A, Yu R, Eng-Wong J, Kang Y-K. Pertuzumab (P) with trastuzumab (T) and chemotherapy (CTX) in patients (pts) with HER2-positive metastatic gastric or gastroesophageal junction (GEJ) cancer: An international phase III study (JACOB). *Journal of Clinical Oncology*. 2013;**31**:TPS 4150
- [37] Kang Y-K, Shah MA, Ohtsu A, Van Cutsem E, Ajani JA, van der Horst T, Harle-Yge M-L, Piao Y, Betsy Althaus B, Thuss-Patience PC. A randomized, open-label, multicenter, adaptive phase 2/3 study of trastuzumab emtansine (T-DM1) versus a taxane (TAX) in patients (pts) with previously treated HER2-positive locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma (LA/MGC/GEJC). *Journal of Clinical Oncology*. 2016;**34**:abs5
- [38] Amir E, Ocaña A, Seruga B, Freedman O, Clemons M. Lapatinib and HER2 status: Results of a meta-analysis of randomized phase III trials in metastatic breast cancer. *Cancer Treatment Reviews*. 2010;**36**:410-415. DOI: 10.1016/j.ctrv.2009.12.012

- [39] Hecht JR, Bang YJ, Qin SK, Chung HC, Xu JM, Park JO, Jeziorski K, Shparyk Y, Hoff PM, Sobrero A, Salman P, Li J, Protsenko SA, Wainberg ZA, Buyse M, Afenjar K, Houé V, Garcia A, Kaneko T, Huang Y, Khan-Wasti S, Santillana S, Press MF, Slamon D. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC—A randomized phase III trial. *Journal of Clinical Oncology*. 2016;**34**:443-451. DOI: 10.1200/JCO.2015.62.6598
- [40] Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, Tsuji A, Omuro Y, Li J, Wang JW, Miwa H, Qin SK, Chung IJ, Yeh KH, Feng JF, Mukaiyama A, Kobayashi M, Ohtsu A, Bang YJ. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN—A randomized, phase III study. *Journal of Clinical Oncology*. 2014;**32**:2039-2049. DOI: 10.1200/JCO.2013.53.6136
- [41] Lordick F, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, Kurteva G, Volovat C, Moiseyenko VM, Gorbunova V, Park JO, Sawaki A, Celik I, Götte H, Melezínková H, Moehler M; Arbeitsgemeinschaft Internistische Onkologie and EXPAND Investigators. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): A randomised, open-label phase 3 trial. *The Lancet Oncology*. 2013;**14**:490-499. DOI: 10.1016/S1470-2045(13)70102-5
- [42] Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, Wotherspoon A, Saffery C, Middleton G, Wadsley J, Ferry D, Mansoor W, Crosby T, Coxon F, Smith D, Waters J, Iveson T, Falk S, Slater S, Peckitt C, Barbachano Y. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): A randomised, open-label phase 3 trial. *The Lancet Oncology*. 2013;**14**: 481-489. DOI: 10.1016/S1470-2045(13)70096-2
- [43] [43]. Du F, Zheng Z, Shi S, Jiang Z, Qu T, Yuan X, Sun Y, Song Y, Yang L, Zhao J, Wang J, Chi Y. S-1 and cisplatin with or without nimotuzumab for patients with untreated unresectable or metastatic gastric cancer: A randomized, open-label phase 2 trial. *Medicine (Baltimore)*. 2015;**94**:e958. DOI: 10.1097/MD.0000000000000958
- [44] Satoh T, Lee KH, Rha SY, Sasaki Y, Park SH, Komatsu Y, Yasui H, Kim TY, Yamaguchi K, Fuse N, Yamada Y, Ura T, Kim SY, Munakata M, Saitoh S, Nishio K, Morita S, Yamamoto E, Zhang Q, Kim JM, Kim YH, Sakata Y. Randomized phase II trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer. *Gastric Cancer*. 2015;**18**:824-832. DOI: 10.1007/s10120-014-0420-9
- [45] Park SR, Kook MC, Choi IJ, Kim CG, Lee JY, Cho SJ, Kim YW, Ryu KW, Lee JH, Lee JS, Park YI, Kim NK. Predictive factors for the efficacy of cetuximab plus chemotherapy as salvage therapy in metastatic gastric cancer patients. *Cancer Chemotherapy and Pharmacology*. 2010;**65**:579-587. DOI: 10.1007/s00280-009-1067-9
- [46] Lordick F, Lubber P, Lorenzen S, Hegewisch-Becker S, Folprecht G, Wöll E, Decker T, Endlicher E, Röthling N, Schuster T, Keller G, Fend F, Peschel C. Cetuximab plus

- oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: A phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *British Journal of Cancer*. 2010;**102**:500-505. DOI: 10.1038/sj.bjc.6605521
- [47] Moehler M, Mueller A, Trarbach T, Lordick F, Seufferlein T, Kubicka S, Geissler M, Schwarz S, Galle PR, Kanzler S; German Arbeitsgemeinschaft Internistische Onkologie. Cetuximab with irinotecan, folinic acid and 5-fluorouracil as first-line treatment in advanced gastroesophageal cancer: A prospective multi-center biomarker-oriented phase II study. *Annals of Oncology*. 2011;**22**:1358-1366. DOI: 10.1093/annonc/mdq591
- [48] Stella G, Llimpe FR, Barone C, Falcone A, Di Fabio F, Martoni A, Lamba S, Ceccarelli C, Siena S, Bardelli A, Pinto C. KRAS and BRAF mutational status as response biomarkers to cetuximab combination therapy in advanced gastric cancer patients. *Journal of Clinical Oncology*. 2009;**27**:abs e15503
- [49] Bjornsti MA, Houghton PJ. The TOR pathway: A target for cancer therapy. *Nature Reviews Cancer*. 2004;**4**:335-348
- [50] Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, Sahmoud T, Shen L, Yeh KH, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Lebwohl D, Van Cutsem E. Everolimus for previously treated advanced gastric cancer: Results of the randomized, double-blind, phase III GRANITE-1 study. *Journal of Clinical Oncology*. 2013;**31**:3935-3943. DOI: 10.1200/JCO.2012.48.3552
- [51] Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *The New England Journal of Medicine*. 2004;**350**:2335-2342
- [52] Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *The New England Journal of Medicine*. 2007;**357**:2666-2676
- [53] Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, Manegold C. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. *AVAil. Journal of Clinical Oncology*. 2009;**27**:1227-1234. DOI: 10.1200/JCO.2007.14.5466
- [54] Kim SE, Shim KN, Jung SA, Yoo K, Lee JH. The clinicopathological significance of tissue levels of hypoxia-inducible factor-1alpha and vascular endothelial growth factor in gastric cancer. *Gut Liver*. 2009;**3**:88-94. DOI: 10.5009/gnl.2009.3.2.88
- [55] Lieto E, Ferraraccio F, Orditura M, Castellano P, Mura AL, Pinto M, Zamboli A, De Vita F, Galizia G. Expression of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) is an independent prognostic indicator of worse outcome in gastric cancer patients. *Annals of Surgical Oncology*. 2008;**15**:69-79

- [56] Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J, Langer B, Starnawski M, Kang YK. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: A randomized, double-blind, placebo-controlled phase III study. *Journal of Clinical Oncology*. 2011;**29**:3968-3976. DOI: 10.1200/JCO.2011.36.2236
- [57] Shen L, Li J, Xu J, Pan H, Dai G, Qin S, Wang L, Wang J, Yang Z, Shu Y, Xu R, Chen L, Liu Y, Yu S, Bu L, Piao Y. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: Randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer*. 2015;**18**:168-176. DOI: 10.1007/s10120-014-0351-5
- [58] Van Cutsem E, de Haas S, Kang YK, Ohtsu A, Tebbutt NC, Ming Xu J, Peng Yong W, Langer B, Delmar P, Scherer SJ, Shah MA. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: A biomarker evaluation from the AVAGAST randomized phase III trial. *Journal of Clinical Oncology*. 2012;**30**:2119-2127. DOI: 10.1200/JCO.2011.39.9824
- [59] Miles DW, de Haas SL, Dirix LY, Romieu G, Chan A, Pivot X, Tomczak P, Provencher L, Cortés J, Delmar PR, Scherer SJ. Biomarker results from the AVADO phase 3 trial of first-line bevacizumab plus docetaxel for HER2-negative metastatic breast cancer. *British Journal of Cancer*. 2013;**108**:1052-1060. DOI: 10.1038/bjc.2013.69
- [60] Lambrechts D, Claes B, Delmar P, Reumers J, Mazzone M, Yesilyurt BT, Devlieger R, Verslype C, Tejpar S, Wildiers H, de Haas S, Carmeliet P, Scherer SJ, Van Cutsem E. VEGF pathway genetic variants as biomarkers of treatment outcome with bevacizumab: An analysis of data from the AViTA and AVOREN randomised trials. *The Lancet Oncology*. 2012;**13**:724-733. DOI: 10.1016/S1470-2045(12)70231-0
- [61] Bronte G, Galvano A, Cicero G, Passiglia F, Rolfo C, Bazan V, Russo A. Ramucirumab and its use in gastric cancer treatment. *Drugs of Today (Barcelona, Spain)*. 2014;**50**:613-621. DOI: 10.1358/dot.2014.50.9.2207198
- [62] Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalcberg JR, Chau I, Campbell W, Sivanandan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Tabernero J; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2014;**383**:31-39. DOI: 10.1016/S0140-6736(13)61719-5
- [63] Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. *The Lancet Oncology*. 2014;**15**:1224-1235. DOI: 10.1016/S1470-2045(14)70420-6

- [64] Shitara K, Muro K, Shimada Y, Hironaka S, Sugimoto N, Komatsu Y, Nishina T, Yamaguchi K, Segawa Y, Omuro Y, Tamura T, Doi T, Yukisawa S, Yasui H, Nagashima F, Gotoh M, Esaki T, Emig M, Chandrawansa K, Liepa AM, Wilke H, Ichimiya Y, Ohtsu A. Subgroup analyses of the safety and efficacy of ramucirumab in Japanese and Western patients in RAINBOW: A randomized clinical trial in second-line treatment of gastric cancer. *Gastric Cancer*. 2016;**19**:927-938. DOI: 10.1007/s10120-015-0559-z
- [65] Hofheinz RD, Lorenzen S. Ramucirumab as second-line treatment for patients with metastatic esophagogastric adenocarcinoma. *Expert Review of Anticancer Therapy*. 2015;**15**:607-614. DOI: 10.1586/14737140.2015.1052412
- [66] Yoon HH, Bendell JC, Braithen FS, Firdaus I, Philip PA, Cohn AL, Lewis N, Anderson DM, Arrowsmith E, Schwartz JD, Gao L, Hsu Y, Xu Y, Ferry D, Alberts SR, Wainberg ZA. Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: A randomized, double-blind, multicenter Phase II trial. *Annals of Oncology*. 2016;**27**: 2196-2203. DOI: 10.1093/annonc/mdw423
- [67] Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, Liu W, Tong J, Liu Y, Xu R, Wang Z, Wang Q, Ouyang X, Yang Y, Ba Y, Liang J, Lin X, Luo D, Zheng R, Wang X, Sun G, Wang L, Zheng L, Guo H, Wu J, Xu N, Yang J, Zhang H, Cheng Y, Wang N, Chen L, Fan Z, Sun P, Yu H. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. *Journal of Clinical Oncology*. 2016;**34**: 1448-1454. DOI: 10.1200/JCO.2015.63.5995
- [68] Erber R, Thurnher A, Katsen AD, Groth G, Kerger H, Hammes HP, Menger MD, Ullrich A, Vajkoczy P. Combined inhibition of VEGF and PDGF signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms. *FASEB Journal*. 2004;**18**:338-340. DOI: 10.1096/fj.03-0271fje
- [69] Fischer C, Jonckx B, Mazzone M, Zacchigna S, Loges S, Pattarini L, Chorianopoulos E, Liesenborghs L, Koch M, De Mol M, Autiero M, Wyns S, Plaisance S, Moons L, van Rooijen N, Giacca M, Stassen JM, Dewerchin M, Collen D, Carmeliet P. Anti-PlGF inhibits growth of VEGF(R)-inhibitor-resistant tumors without affecting healthy vessels. *Cell*. 2007;**131**:463-475. DOI: 10.1016/j.cell.2007.08.038
- [70] Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. *Molecular Cancer Therapeutics*. 2008;**7**:3129-3140. DOI: 10.1158/1535-7163.MCT-08-0013
- [71] Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, Schwartz B, Simantov R, Kelley S. Discovery and development of sorafenib: A multikinase inhibitor for treating cancer. *Nature Reviews Drug Discovery*. 2006;**5**:835-844
- [72] Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, Schreck RE, Abrams TJ, Ngai TJ, Lee LB, Murray LJ, Carver J, Chan E, Moss KG, Haznedar JO, Sukbuntherng J, Blake

- RA, Sun L, Tang C, Miller T, Shirazian S, McMahon G, Cherrington JM. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: Determination of a pharmacokinetic/pharmacodynamic relationship. *Clinical Cancer Research*. 2003;**9**:327-337
- [73] Moehler M, Gepfner-Tuma I, Maderer A, Thuss-Patience PC, Ruessel J, Hegewisch-Becker S, Wilke H, Al-Batran SE, Rafiyan MR, Weißinger F, Schmoll HJ, Kullmann F, von Weikersthal LF, Siveke JT, Weusmann J, Kanzler S, Schimanski CC, Otte M, Schollenberger L, Koenig J, Galle PR. Sunitinib added to FOLFIRI versus FOLFIRI in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: A randomized, placebo-controlled phase II AIO trial with serum biomarker program. *BMC Cancer*. 2016;**16**:699. DOI: 10.1186/s12885-016-2736-9
- [74] Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, Thierauch KH, Zopf D. Regorafenib (BAY 73-4506): A new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *International Journal of Cancer*. 2011;**129**:245-255. DOI: 10.1002/ijc.25864
- [75] Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG; GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;**381**:295-302. DOI: 10.1016/S0140-6736(12)61857-1
- [76] Pavlakakis N, Sjoquist KM, Martin AJ, Tsobanis E, Yip S, Kang YK, Bang YJ, Alcindor T, O'Callaghan CJ, Burnell MJ, Tebbutt NC, Rha SY, Lee J, Cho JY, Lipton LR, Wong M, Strickland A, Kim JW, Zalcberg JR, Simes J, Goldstein D. Regorafenib for the Treatment of Advanced Gastric Cancer (INTEGRATE): A multinational placebo-controlled phase II trial. *Journal of Clinical Oncology*. 2016;**34**:2728-2735. DOI: 10.1200/JCO.2015.65.1901
- [77] Ebos JM, Lee CR, Cruz-Munoz W, Bjarnason GA, Christensen JG, Kerbel RS. Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. *Cancer Cell*. 2009;**15**:232-239. DOI: 10.1016/j.ccr.2009.01.021
- [78] Mancuso MR, Davis R, Norberg SM, O'Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hu-Lowe DD, McDonald DM. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. *The Journal of Clinical Investigation*. 2006;**116**:2610-2621
- [79] Johannsen M, Flörcken A, Bex A, Roigas J, Cosentino M, Ficarra V, Kloeters C, Rief M, Rogalla P, Miller K, Grünwald V. Can tyrosine kinase inhibitors be discontinued in patients with metastatic renal cell carcinoma and a complete response to treatment? A multicentre, retrospective analysis. *European Urology*. 2009;**55**:1430-1438. DOI: 10.1016/j.eururo.2008.10.021

- [80] Sennino B, McDonald DM. Controlling escape from angiogenesis inhibitors. *Nature Reviews Cancer*. 2012;**12**:699-709. DOI: 10.1038/nrc3366
- [81] Salceda S, Caro J. Hypoxia-inducible factor 1alpha (HIF-1alpha) protein is rapidly degraded by the ubiquitin-proteasome system under normoxic conditions. Its stabilization by hypoxia depends on redox-induced changes. *Journal of Biological Chemistry*. 1997;**272**:22642-22647
- [82] Yu F, Lin Y, Zhan T, Chen L, Guo S. HGF expression induced by HIF-1 α promote the proliferation and tube formation of endothelial progenitor cells. *Cell Biology International*. 2015;**39**:310-317. DOI: 10.1002/cbin.10397
- [83] Lordick F. Targeting the HGF/MET pathway in gastric cancer. *The Lancet Oncology*. 2014;**15**:914-916. DOI: 10.1016/S1470-2045(14)70273-6
- [84] Bardelli A, Corso S, Bertotti A, Hobor S, Valtorta E, Siravegna G, Sartore-Bianchi A, Scala E, Cassingena A, Zecchin D, Apicella M, Migliardi G, Galimi F, Lauricella C, Zanon C, Perera T, Veronese S, Corti G, Amatu A, Gambacorta M, Diaz LA Jr, Sausen M, Velculescu VE, Comoglio P, Trusolino L, Di Nicolantonio F, Giordano S, Siena S. Amplification of the MET receptor drives resistance to anti-EGFR therapies in colorectal cancer. *Cancer Discovery*. 2013;**3**:658-673. DOI: 10.1158/2159-8290.CD-12-0558
- [85] Troiani T, Martinelli E, Napolitano S, Vitagliano D, Ciuffreda LP, Costantino S, Morgillo F, Capasso A, Sforza V, Nappi A, De Palma R, D'Aiuto E, Berrino L, Bianco R, Ciardiello F. Increased TGF- α as a mechanism of acquired resistance to the anti-EGFR inhibitor cetuximab through EGFR-MET interaction and activation of MET signaling in colon cancer cells. *Clinical Cancer Research*. 2013;**19**:6751-6765. DOI: 10.1158/1078-0432.CCR-13-0423
- [86] Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, Lindeman N, Gale CM, Zhao X, Christensen J, Kosaka T, Holmes AJ, Rogers AM, Cappuzzo F, Mok T, Lee C, Johnson BE, Cantley LC, Jänne PA. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science*. 2007;**316**:1039-1043
- [87] Cunningham D, Tebbutt NC, Davidenko I, Murad AM, Al-Batran SE, Ilson DH, Tjulandin S, Gotovkin E, Karaszewska B, Bondarenko I, Tejani MA, Udre AA, Tehfe MA, Baker N, Oliner KS, Zhang Y, Hoang T, Sidhu R, Catenacci DVT. Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study. *Journal of Clinical Oncology*. 2015;**33**:abs4000
- [88] A Phase 3 Study of Rilotumumab (AMG 102) With Cisplatin and Capecitabine (CX) as First-line Therapy in Gastric Cancer. <https://clinicaltrials.gov> [NCT 02137343]
- [89] Zhu M, Tang R, Doshi S, Oliner KS, Dubey S, Jiang Y, Donehower RC, Iveson T, Loh EY, Zhang Y. Exposure-response analysis of rilotumumab in gastric cancer: The role of tumour MET expression. *British Journal of Cancer*. 2015;**112**:429-437. DOI: 10.1038/bjc.2014.649

- [90] Doshi S, Gisleskog PO, Zhang Y, Zhu M, Oliner KS, Loh E, Perez Ruixo JJ. Rilotumumab exposure-response relationship in patients with advanced or metastatic gastric cancer. *Clinical Cancer Research*. 2015;**21**:2453-2461. DOI: 10.1158/1078-0432.CCR-14-1661
- [91] Zhang Y, Kuchimanchi M, Zhu M, Doshi S, Hoang T, Kasichayanula S. Assessment of pharmacokinetic interaction between rilotumumab and epirubicin, cisplatin and capecitabine (ECX) in a Phase 3 study in gastric cancer. *British Journal of Clinical Pharmacology*. 2017;**83**:1048-1055. DOI: 10.1111/bcp.13179
- [92] Shah MA, Bang YJ, Lordick F, Alsina M, Chen M, Hack SP, Bruey JM, Smith D, McCaffery I, Shames DS, Phan S, Cunningham D. Effect of fluorouracil, leucovorin, and oxaliplatin with or without onartuzumab in HER2-negative, MET-positive gastroesophageal adenocarcinoma: The METGastric randomized clinical trial. *JAMA Oncology*. 2017;**3**: 620-627. DOI: 10.1001/jamaoncol.2016.5580
- [93] Shah MA, Wainberg ZA, Catenacci DV, Hochster HS, Ford J, Kunz P, Lee FC, Kallender H, Cecchi F, Rabe DC, Keer H, Martin AM, Liu Y, Gagnon R, Bonate P, Liu L, Gilmer T, Bottaro DP. Phase II study evaluating 2 dosing schedules of oral foretinib (GSK1363089), cMET/VEGFR2 inhibitor, in patients with metastatic gastric cancer. *PLoS One*. 2013; **8**:e54014. DOI: 10.1371/journal.pone.0054014