

Trends in clinical use of targeted therapy for gastrointestinal cancers

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ABSTRACT

Targeted drugs therapies that block the molecular pathways involved in the development and progression of gastro-intestinal (GI) cancers have recently gained considerable attention. In addition to agents targeting vascular endothelial growth factor (VEGF), epidermal growth factor receptor, the multi-kinase inhibitor, and regorafenib have also become available for the treatment of metastatic colorectal cancer patients. Currently, trastuzumab, an antibody targeting human epidermal growth factor receptor-2 (HER-2), in combination with cytotoxic drugs is considered as the standard treatment for patients with HER-2 positive gastric cancer (GC). The efficacy of ramucirumab, a human monoclonal antibody that inhibits VEGF from binding to its receptor in GC, has also been recently demonstrated. At present, a great number of novel targeted drugs are in pre-clinical or clinical studies. In this review, we summarize trends in the use of molecularly targeted drugs that have proven to be effective for treating GI cancers, with a focus on emerging strategies for personalized treatment.

Key words: Gastro-intestinal tumors, molecular pathways, molecular targeted drug

Introduction

Many targeted drugs have been studied to target the molecular pathways involved in the development of gastro-intestinal (GI) cancers. Targeted drugs therapies that block the molecular pathways involved in the development and progression of GI cancers have recently gained considerable attention. Several molecular pathways were reported. Vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR), the multi-kinase inhibitor, regorafenib, have also become available for the treatment of metastatic colorectal cancer (mCRC) patients. Currently, trastuzumab, an antibody targeting human epidermal growth factor receptor-2 (HER-2), in combination with cytotoxic drugs is considered to be the standard treatment for patients with HER-2 positive gastric cancer (GC). The efficacy of ramucirumab, a human monoclonal antibody (mAb) that inhibits VEGF from binding to its receptor in GC, has also been recently demonstrated.

Although the above improvements have reduced GI cancers mortality in the past few decades, there is sufficient evidence suggesting that the majority of patients undergoing drug therapy will not benefit and will instead experience severe and even lethal adverse drug events. Therefore, new and better molecular targeted

therapies are needed. At present, a great number of novel targeted drugs are in pre-clinical or clinical studies.

The aim of this review is to provide a comprehensive overview of the state of art, focusing on the new emerging strategies in the personalized treatment of GI cancers and discussing about the possible implications for GI cancers therapy.

The Main Pathways Targeted in Gastro-intestinal Tumors

Many targeted drugs that block the molecular pathways involved in the development and progression of GI tumors have been studied. Some of these agents are most efficacious in combination with conventional chemotherapy regimens. The molecular targeted drugs that have been approved for the treatment of GI cancers are summarized in Table 1. We have reviewed representative pathways that serve as targets in GI cancers.

Vascular endothelial growth factor pathway

Angiogenesis is the process of new capillary formation from pre-existing blood vessels, and it

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Table 1: Approved molecular targeted drugs in advanced gastro-intestinal tumors

Primary cancer site	Targets	Drugs	OS (month)	Reference
GC	HER-2	Trastuzumab	13.8 (first-line)	[51]
	VEGFR-2	Ramucirumab	9.6 (second-line)	[53]
CRC	VEGF	Bevacizumab	20.3 (first-line)	[63]
		Aflibercept	13.5 (second-line)	[84]
	VEGFR, BRAF, KIT, RET, PDGFR	Regorafenib	6.4 (third-line)	[81]
	EGFR	Cetuximab	24.9 (first-line)	[75]
		Panitumumab	26.0 (first-line)	[78]

HER2: Human epidermal growth factor receptor 2; VEGFR-2: Vascular endothelial growth factor receptor-2; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; BRAF: V-Raf murine sarcoma viral oncogene homolog B1; KIT: Mast/stem cell growth factor receptor; RET: Rearranged during transfection; PDGFR: Platelet-derived growth factor receptor; OS: Overall survival; EGFR: Epidermal growth factor receptor; CRC: Colorectal cancer; GC: Gastric cancer

plays an important role in the growth and spread of cancers.^[1] Neovascularization promotes tumor growth by supplying nutrients, oxygen and growth factors that promote tumor cell proliferation.^[2,3] VEGF was first isolated in 1983 as a factor that increases vascular permeability in tumors.^[4] The VEGF family of proteins comprises VEGF-A, -B, -C, -D and -E, and structurally resembles the platelet-derived growth factor (PDGF) and placenta growth factor (PLGF) families of proteins. These growth factors bind selectively, but with different affinity, to at least five distinct receptors.^[5-7] Many cytokines and growth factors, including PDGF, tumor necrosis factor, transforming growth factor (TGF)- α , TGF- β , fibroblast growth factor (FGF)-4, keratinocyte growth factor/FGF-7, EGF, interleukin (IL)-1 α , IL-1 β , IL-6 and insulin-like growth factor (IGF)-1, are involved in upregulating *VEGF* gene expression.^[8] Overexpression of VEGF has been associated with increased microvessel density, tumor invasion, metastasis and thus with poor prognosis in many types of cancers.^[9]

Epidermal growth factor receptor pathway

The EGFR family consists of four homologous receptors: The EGFR (ErbB1/EGFR/HER-1), ErbB2 (HER-2/neu), ErbB3 (HER-3) and ErbB4 (HER-4).^[10] EGFR is a 170 kDa cell surface tyrosine kinase (TK) transmembrane receptor that initiates signaling cascades leading to cell proliferation, motility, adhesion, invasion, cell survival and angiogenesis.^[11] Mutation in the TK domain of the *EGFR* gene has been found in several types of cancers and has become a therapeutic target in non-small cell lung cancer.^[12] Overexpression and/or amplification of HER-2 has been observed in various cancers,^[13-15] including breast, esophageal and GCs at 7-34% frequency,^[16,17] and several studies have shown that HER-2 is an important biomarker and a key driver of tumorigenesis.^[18] Therefore, blockade of the EGFR family should lead to the inhibition of cell growth, thereby constituting an effective anti-cancer therapy.^[19] However, cross-talk between the various ErbB receptors that may induce drug resistance has been demonstrated.^[20] Because the intra-cellular space is vastly complex, targeting more

than one signaling pathway or blocking multiple targets within a single pathway may be necessary to effectively suppress cancer growth.

Phosphatase and tensin homolog-phosphoinositide 3-kinase-AKT-mammalian target of rapamycin pathway

Phosphoinositide 3-kinases (PI3Ks) are a family of lipid kinases that phosphorylate the 3'-hydroxyl group of phosphoinositides with the conversion of phosphatidylinositol-4, 5-bisphosphate to phosphatidylinositol-3, -4, 5-trisphosphate (PIP3). PIP3 is a critical second messenger that activates protein kinase B (AKT) through phosphorylation. Once activated, phospho-AKT phosphorylates up to 100 other proteins, including the mammalian target of rapamycin (mTOR), which is part of the mTOR complex (mTORC) 1 and mTORC 2.^[21,22] The activation of mTOR increases cellular proliferation and survival and decreases apoptosis. In normal tissue, this pathway is negatively regulated by the tumor suppressor phosphatase on chromosome 10 (phosphatase and tensin homolog), which targets the lipid products of PI3K for dephosphorylation.^[23]

Ras-Raf-MEK-extra-cellular-signal-regulated kinase pathway (MAPK pathway)

The Raf/mitogen-activated protein kinase (MAPK)/extra-cellular-signal-regulated kinase (ERK) pathway is an important pro-survival signaling pathway, that is, primarily involved in cell growth and survival and regulation of cellular differentiation. This pathway transduces extra-cellular signals from membrane-bound TK receptors, such as EGFR, VEGF receptor (VEGFR), IGF receptor (IGFR), hepatocyte growth factor receptor (c-MET) and PDGF receptor (PDGFR), to the nucleus. Binding of growth factors results in receptor phosphorylation, which activates an adapter molecule complex. This sequence in turn activates the Raf/mitogen-extra-cellular protein kinase (MEK)/ERK pathway, which triggering a cascade of specific phosphorylation events.^[24] Within this pathway, the small GTPase Ras and the serine/threonine kinase Raf are the key signal regulators.^[25] Intermediate

signaling is regulated by MEK1 and MEK2, which are responsible for phosphorylating and activating the final downstream signaling molecules ERK1 and 2.^[23] ERK1/2 regulates cellular activity by acting on more than 100 substrates, both in the cytoplasm and nucleus. Ras also regulates the PI3K/AKT/mTOR, the phospholipase C/protein kinase C, and the Ral guanine nucleotide dissociation stimulator pathways.^[26,27]

Wnt pathway

Extensive descriptions of the roles of Wnt signaling in development and disease can be found in recent reviews.^[28,29] The canonical Wnt/ β -catenin signaling pathway involves the sequestration of β -catenin from a destruction complex, which consists of adenomatous polyposis coli glycogen synthase kinase 3- α , casein kinase 1 and axin. The activation of Wnt/ β -catenin signaling is important for both the initiation and progression of cancers in various tissues.^[30] Therefore, the disruption of Wnt/ β -catenin signaling represents an opportunity for rational cancer chemoprevention and therapy.^[30] In CRC, 90% of all tumors have a mutation in a key regulatory factor of the Wnt/ β -catenin signaling pathway that results in pathway activation, and up to 80% of tumors exhibit nuclear accumulation of β -catenin.^[31-33]

Nuclear factor- κ B pathway

In recent years, several studies have revealed the connection between inflammation and carcinogenesis.^[34,35] In chronic inflammation, cytokines and chemokines produced by inflammatory cells propagate a localized inflammatory response and enhance the survival of pre-malignant cells by activating the nuclear factor- κ B (NF- κ B) pathway. NF- κ B is aberrantly activated in 50% of CRC patients and those with colitis-associated tumors, and mouse studies have established that NF- κ B plays a role in the development of colitis-associated cancer.^[36,37] As the NF- κ B pathway plays a pivotal role in apoptosis, tumor promotion and maintenance, inhibitors of this signaling pathway would be useful in CRC therapy. Non-steroidal anti-inflammatory drugs (NSAIDs) exhibit anti-neoplastic activities in the colon.^[38] Stimulation of NF- κ B expression is inhibited by various NSAIDs, indicating that NSAIDs may act as chemopreventive agents. Several studies, including randomized trials, have shown that regular use of NSAIDs is associated with decreased CRC incidence and mortality.^[39,40]

Clinical Application of Targeted Drugs

Esophageal cancer

Esophageal cancer is the eighth most frequent cause of cancer death and is increasing worldwide.^[41] This malignancy comprises two major histologic types, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC and EAC

differ substantially in their underlying etiology and tumorigenesis. A tri-modal treatment strategy consisting of radiotherapy, chemotherapy and surgery is standard for patients with local and/or advanced cancer of the esophagus.^[42,43] Unfortunately, as the 5-year survival rate remains < 15% the majority of patients at advanced stages of the disease fails to benefit from these treatments,^[44] and more effective therapies are eagerly awaited. Therefore, clinical trials of targeted drugs as monotherapy or in combination with conventional chemotherapy have been recently conducted for patients with esophageal cancer. However, a recent randomized Phase III trial demonstrated that the addition of cetuximab, a humanized mouse EGFR mAb, to capecitabine-cisplatin provided no additional benefit to chemotherapy alone in the first-line treatment of advanced esophagogastric AC.^[45] Similarly, the addition of panitumumab; another EGFR mAb to epirubicin; oxaliplatin and capecitabine did not increase overall survival (OS) of patients with advanced esophagogastric AC.^[46] However, nimotuzumab, a humanized EGFR mAb, in combination with standard chemotherapy (cisplatin plus 5-fluorouracil [5-FU]), has shown a good therapeutic response in a pilot study of patients with ESCC.^[47]

VEGF is up-regulated in EAC, and overexpression of VEGF protein has been reported as a negative prognostic marker in ESCC.^[9] Therefore, VEGF may be a potential therapeutic target in esophageal cancers. Although Phase II trials demonstrated that the addition of bevacizumab to conventional chemotherapy improved response rates (RRs) in patients with esophagogastric AC,^[48] no Phase III trial has demonstrated a survival benefit of bevacizumab.^[49]

The efficacy of molecular targeted drugs for esophageal cancer is still controversial. Further investigations to elucidate molecular mechanisms of esophageal cancer are needed to establish effective targeted treatment strategies.

Gastric cancer

GC is the fourth most commonly diagnosed cancer and the second leading cause of cancer mortality worldwide.^[50] Despite the recent progress in cancer treatment, the prognosis of patients with advanced GC remains poor. The understanding of molecular pathways involved in gastric carcinogenesis offers novel treatment options. When compared with chemotherapy alone, the HER-2-targeting antibody trastuzumab in combination with capecitabine/cisplatin was shown to improve the survival of advanced GC patients harboring HER-2 overexpression caused by gene amplification.^[51] Another agent with promising results in clinical trials is ramucirumab, an antibody targeting VEGFR-2.^[52,53] However, clinical trials have failed to demonstrate the benefit of agents targeting EGFR (cetuximab, panitumumab),^[45,46] VEGF-A (bevacizumab)^[54] or mTOR (everolimus).^[55] The results of Phase III trials to

evaluate the efficacy of molecular targeted drugs in GC are summarized in Table 2.

Trastuzumab

Trastuzumab is a recombinant humanized mAb directed against the extra-cellular domain of HER-2. Amplification or overexpression of HER-2 has been observed in 7-34% of GC.^[16,17,56] A recent large-scale Phase III study (the ToGA trial) demonstrated that trastuzumab combined with cisplatin and capecitabine provided a significant survival advantage over chemotherapy alone in patients with HER-2-positive GC and confirming that HER-2 is a crucial therapeutic GC target.^[51] The median OS was 13.8 months in the trastuzumab plus chemotherapy group ($n = 294$) and 11.1 months in the chemotherapy alone group ($n = 290$; hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.60-0.91; $P = 0.0046$). In the subgroup with high HER-2 expression (defined as immunohistochemistry 2+ and fluorescence *in situ* hybridization positive, immunohistochemistry 3+), the median OS was 16.0 months in the trastuzumab plus chemotherapy group and 11.8 months in the chemotherapy alone group (HR: 0.65; 95% CI: 0.51-0.83). Trastuzumab is the first molecularly targeted drug that has been proven efficacious against GC.

Ramucirumab

Ramucirumab is a human mAb that binds to VEGFR-2 and works as a receptor antagonist blocking the binding of VEGF to the receptor. A Phase I trial demonstrated its anti-tumor activity and anti-angiogenic effect over a wide range of doses, suggesting clinical efficacy.^[57] In the REGARD Phase III randomized trial, 355 patients were treated with best supportive care plus ramucirumab or placebo in a second-line setting. Both the median OS (5.2 vs. 3.8 months; HR: 0.776; 95% CI: 0.603-0.998) and the median progression-free survival (PFS) (2.1 vs. 1.3 months; HR: 0.483; 95% CI: 0.376-0.620) were significantly longer in the ramucirumab than the placebo group, and the safety profile of the drug was acceptable.^[52] In the RAINBOW Phase III trial, ramucirumab was used as a second-line treatment in addition to paclitaxel (665 patients).^[53] The

addition of ramucirumab resulted in a significant survival benefit; the median OS increased from 7.4 to 9.6 months (HR: 0.807; 95% CI: 0.678-0.962), and the median PFS increased from 2.9 to 4.4 months (HR: 0.635; 95% CI: 0.536-0.752).^[53] Currently, a randomized Phase II trial investigating the efficacy of ramucirumab as a first-line treatment in GC is ongoing.^[58]

Colorectal cancer

Estimated new cases of CRC exceed 1.2 million/year worldwide, with more than 600,000 deaths/year.^[59] Liver metastases are observed in 25% of CRC patients at the time of diagnosis and recurrence after surgery is often encountered. The 5-year survival rate of patients with distant metastases diseases is only 10-20%, although that of patients without lymph node metastasis is more than 80%.^[60] The majority of CRC occurrences are sporadic, without the existence of family history or genetic pre-disposition, and the etiological factors for CRC tumorigenesis appear to be complex and heterogeneous. There has been significant progress in identifying distinct molecular pathways leading to CRC that include either increased function of oncogenes or loss of tumor suppressor genes.^[61] Currently, the recent introduction of molecular targeted drugs has improved the treatment of advanced CRC. Cetuximab and panitumumab (EGFR mAbs) and bevacizumab (VEGF, mAb) have ushered in a new era of targeted therapy for CRC.^[62-65] Table 3 summarizes molecular targeted drugs used to treat CRC.

Bevacizumab

Bevacizumab, developed in the early 1990s, is a recombinant, humanized immunoglobulin G1 (IgG1) mAb that effectively disrupts the interactions of all isoforms of VEGF-A with VEGFRs.^[66] Pre-clinical studies have demonstrated that bevacizumab exhibits a broad range of anti-tumor activity.^[67] The AVF2107 study, a trial to investigate the efficacy of bevacizumab combined with irinotecan, bolus 5-FU and leucovorin (LV) (IFL) for patients with previously untreated mCRC,^[63] demonstrated that the addition of bevacizumab to IFL improved the RR and prolonged OS. In another

Table 2: Results of completed Phase III trials with molecular targeted therapy in advanced GC

Target	Trial	Regimen	Patients (n)	OS (month)	P
HER2	ToGA	Cisplatin, capecitabine or FU ± trastuzumab	584	13.8 versus 11.1 (first-line)	0.0046
HER2	LOGIC	Capecitabine, oxaliplatin ± trastuzumab	545	12.2 versus 10.5 (first-line)	0.35
HER2	TyTAN	Paclitaxel ± lapatinib	261	11.0 versus 8.9 (first-line)	0.21
EGFR	EXPAND	Cisplatin, capecitabine ± cetuximab	679	9.4 versus 10.7 (first-line)	0.95
EGFR	REAL3	Oxaliplatin, capecitabine, epirubicin ± panitumumab	553	8.8 versus 11.3 (first-line)	0.013
VEGFR-2	REGARD	BSC ± ramucirumab	355	5.2 versus 3.8 (second-line)	0.047
VEGFR-2	RAINBOW	Paclitaxel ± ramucirumab	665	9.6 versus 7.4 (second-line)	0.017
VEGFR-A	AVAGAST	Cisplatin, capecitabine or FU ± bevacizumab	774	12.1 versus 10.1 (first-line)	0.10
mTOR	GRANITE-1	BSC ± everolimus	633	5.4 versus 4.3 (second- or third-line)	0.12

HER2: Human epidermal growth factor receptor 2; EGFR: Epidermal growth factor receptor; VEGFR-2: Vascular endothelial growth factor receptor-2; VEGFR-A: Vascular endothelial growth factor receptor-A; mTOR: Mammalian target of rapamycin; OS: Overall survival; FU: Fluorouracil; BSC: Best supportive care; GC: Gastric cancer

Table 3: Results of completed Phase III trials with molecular targeted therapy in advanced CRC

Target	Trial	Regimen	Patients (n)	OS (month)	P
VEGF	AVF2107	IFL ± bevacizumab	402	20.3 vs. 15.5 (first-line)	< 0.001
VEGF	NO16966	FOLFOX4 or XELOX ± bevacizumab	701	21.3 vs. 19.9 (first-line)	0.077
VEGF	TREE1/2	mFOLFOX6 or XELOX ± bevacizumab	260	26.1 vs. 19.2 (mFOLFOX6 first-line) 24.6 vs. 17.2 (XELOX first-line)	
VEGF	VELOUR	FOLFIRI ± aflibercept	1,226	13.5 vs. 12.1 (second-line)	0.0032
VEGFR, BRAF, KIT, RET, PDGFR	CORRECT	Regorafenib or placebo	760	6.4 vs. 5.0	0.0052
EGFR	CRYSTAL	K-Ras WT FOLFIRI ± cetuximab	348	23.5 vs. 20.0 (first-line)	0.0093
EGFR	FIRE-3	FOLFIRI ± cetuximab	592	28.7 vs. 25.0 (first-line)	0.017
VEGF	PRIME	FOLFIRI ± bevacizumab	656	23.9 vs. 19.7 (first-line)	0.17
EGFR		K-Ras WT FOLFOX4 ± panitumumab			
EGFR	Update PRIME	K-Ras WT/MT other Ras FOLFOX4 ± panitumumab	108	17.1 vs. 18.3 (first-line)	0.31

VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; BRAF: V-Raf murine sarcoma viral oncogene homolog B1; KIT: Mast/stem cell growth factor receptor; RET: Rearranged during transfection; PDGFR: Platelet-derived growth factor receptor; EGFR: Epidermal growth factor receptor; OS: Overall survival; CRC: Colorectal cancer; IFL: 5-fluorouracil and leucovorin

Phase III clinical trial performed,^[68] patients with mCRC were randomly assigned to receive one of three different irinotecan-containing regimens: irinotecan plus infusional 5-FU and LV (FOLFIRI), modified IFL and irinotecan plus oral capecitabine and FOLFIRI plus bevacizumab. This latter group showed a higher RR and a longer PFS and median OS than patients receiving FOLFIRI without bevacizumab. Subsequent trials with oxaliplatin-based regimens produced less robust differences.^[69-71] In the Phase III trial NO16966,^[71] the effect of capecitabine and oxaliplatin was compared with that of infused 5-FU, LV and oxaliplatin (FOLFOX), with or without bevacizumab. As compared to chemotherapy alone, treatment with bevacizumab in addition to oxaliplatin-based therapy significantly improved OS and PFS. Another Phase III trial, the TREE study^[70] investigated the tolerability of oxaliplatin in combination with three different 5-FU regimens (continuous infusion, bolus and oral) with or without bevacizumab as a first-line therapy. The study showed that as compared to patients who received chemotherapy alone, patients treated with FOLFOX6 plus bevacizumab experienced improvements in overall response, OS and PFS.

However, there is a controversy regarding the use of adjuvant treatments in CRC. The NSABP PROTOCOL C-08 trial showed that the addition of bevacizumab for 1-year to a modified FOLFOX6 adjuvant regimen did not significantly prolong disease-free survival (DFS) in Stage II and III CRC.^[72] Similarly, the AVANT trial showed that bevacizumab did not prolong DFS when added to adjuvant chemotherapy in resected Stage III CRC, and OS data suggested a potential adverse effect with bevacizumab plus oxaliplatin-based adjuvant therapy.^[73]

Cetuximab

Cetuximab is a recombinant, chimeric, human/murine IgG1 mAb that binds specifically to the extra-cellular domain of EGFR in normal and tumor cells, promoting receptor internalization and degradation without receptor phosphorylation and activation.^[74] In the pivotal Phase II study, the BOND trial, patients with mCRC were randomized to various treatment groups.^[62] As compared to cetuximab alone, the combination of irinotecan and cetuximab significantly improved overall patient response, median OS and PFS. Retrospective analysis of *KRAS* status in the CRYSTAL trial has recently shown statistically significant differences in PFS and overall response between patients with wild-type *KRAS* and those with mutant *KRAS* treated with FOLFIRI plus cetuximab.^[75] In the Phase III study, the FIRE-3, by Heinemann *et al.*^[76] patients with mCRC were randomly assigned to FOLFIRI plus either cetuximab or bevacizumab. Patients in the cetuximab and bevacizumab arms had similar times to disease progression, but those treated with cetuximab had a significantly improved OS. One of the problems of cetuximab treatment is an increased risk of severe adverse events. A meta-analysis to investigate severe adverse events in CRC patients, reported the most common severe adverse events to be neutropenia, diarrhea and rash. However, cetuximab was not associated with an increased risk of fatal adverse events.^[77]

Panitumumab

Panitumumab is a fully human, recombinant IgG2 mAb that binds specifically and with high affinity to the extra-cellular domain of EGFR in normal and tumor

cells. Through competitive binding to EGFR ligands, panitumumab prevents EGFR dimerization, auto-phosphorylation and signaling, thereby inhibiting proliferation and promoting apoptosis.^[78] A Phase III study, the PRIME trial, evaluated the combination of FOLFOX4 with panitumumab or FOLFOX4 alone as first-line treatment.^[79] As compared to chemotherapy alone, the combination therapy significantly improved PFS and increased RR in patients with wild-type *KRAS*. A non-significant increase in OS was also observed. In order to assess the efficacy and safety of FOLFOX4 with panitumumab as compared to FOLFOX4 alone according to *KRAS* (exon 2-4) and *NRAS* (exon 2-4) mutation status, data from the PRIME trial were analyzed.^[80] Patients without any Ras mutation who were treated with panitumumab had a significantly longer OS and PFS than those treated with chemotherapy alone.

Regorafenib

Regorafenib is an inhibitor of PDGFRs, c-KIT, FGF receptor and VEGF1-3.^[81] In the pivotal Phase III study, the CORRECT trial, patients with mCRC who had progressed after undergoing treatment with approved drugs were randomly assigned to regorafenib or placebo.^[82] As compared to placebo, treatment with regorafenib significantly prolonged OS and PFS, suggesting a potential new line of therapy with survival benefits for patients who have progressed after all standard therapies.

Aflibercept

Aflibercept is a recently developed, multiple angiogenic factors trap that inhibits not only VEGF-A, VEGF-B and PLGF, from activating their native receptor (VEGFR-1).^[83,84] Aflibercept has a higher VEGF-A binding affinity than bevacizumab. The velour trial evaluated FOLFIRI plus aflibercept or FOLFIRI alone after progression on an oxaliplatin-based chemotherapy.^[85] As compared to chemotherapy alone, the addition of bevacizumab significantly improved OS.

Conclusion

The clinical application of molecular targeted drugs has improved the survival of patients with GI cancers. We believe that both the identification of novel targets and the development of new drugs targeting several important pathways such as c-MET, rearranged during transfection, MEK and IGF/IGFR will contribute to further improvements in treatment results and the realization of personalized treatments for GI cancer.

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Conflicts of interest

There are no conflicts of interest.

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