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Contents

ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

MINIREVIEWS

Molecular-targeted therapy toward precision medicine for gastrointestinal cancer: Current progress and challenges

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Abstract

Gastrointestinal (GI) cancer remains the deadliest cancer in the world. The current standard treatment for GI cancer focuses on 5-fluorouracil-based chemotherapeutic regimens and surgery, and molecular-targeted therapy is expected to be a more effective and less toxic therapeutic strategy for GI cancer. There is well-established evidence for the use of epidermal growth factor receptor-targeted and vascular endothelial growth factor-targeted antibodies, which should routinely be incorporated into treatment strategies for GI cancer. Other potential therapeutic targets involve the PI3K/AKT pathway, tumor growth factor-β pathway, mesenchymal-epithelial transition pathway, WNT pathway, poly (ADP-ribose) polymerase, and immune checkpoints. Many clinical trials assessing the agents of targeted therapy are underway and have presented promising and thought-provoking results. With the development of molecular biology techniques, we can identify more targetable molecular alterations in larger patient populations with GI cancer. Targeting these molecules will allow us to reach the goal of precision medicine and improve the outcomes of patients with GI cancer.

Key Words: Gastrointestinal cancer; Esophageal cancer; Gastric cancer; Colorectal cancer; Targeted therapy; Precision medicine

Core Tip: Outcomes in metastatic gastrointestinal (GI) cancer are improving with the better understanding and use of targeted therapies. Herein, a review of the literature and recent conference presentations was conducted regarding the topic of targeted therapies for precision medicine in GI cancer. This article clarifies the current evidence for targeted therapies in GI cancer by evaluating the latest data regarding anti-epidermal growth factor receptor, human epidermal growth factor receptor 2, vascular

endothelial growth factor, phosphatidylinositol-3-hydroxykinase/protein kinase B, tumor growth factor-β, mesenchymal-epithelial transition, wireless network technology, poly (ADP-ribose) polymerase, and immunotherapies.

INTRODUCTION

In recent years, molecular-targeted agents that inhibit tyrosine kinase have been approved and have become a standard therapy for various cancers. Many of these drugs exert an antitumor effect by inhibiting the activity of the abnormal tyrosine kinase resulting from a genetic aberration. The use of agents against actionable gene mutations has shown a significantly higher response rate as well as longer survival compared to conventional chemotherapy in certain cancers[1]. For example, precision therapeutic attempts have markedly altered the management of advanced non-small-cell lung cancer (NSCLC). NSCLC harboring epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) fusion can be treated with anticancer drugs that target the aberrant gene products[2]. Today, patients with NSCLC survive for 3-4 years with a sequential use of effective targeted therapies, compared to 1-year survival for those without targetable mutations. There is relatively fewer evidence supporting the use of matched molecular-targeted agents as a treatment for gastrointestinal (GI) cancer[3].

For patients with gastric cancer (GC), anti-human epidermal growth factor receptor 2 (HER2) and anti-vascular endothelial growth factor (VEGF)-targeted therapies have become a standard therapeutic regimen. HER2-targeted therapy for patients with HER2-positive GC has been shown to provide better therapeutic survival than conventional chemotherapy, demonstrating that HER2-targeted therapy is a meaningful step forward to achieve precision therapy[1]. Similarly, United States National Comprehensive Cancer network guidelines recommend investigating the *RAS* [karst and national regulatory authorities (KRAS and NRAS)] mutation status in colorectal cancer (CRC) patients for the potential use of inhibitors for epidermal growth factor receptor mutations. Due to the ineffectiveness of anti-EGFR therapy for CRC patients with BRAF mutations, the identification of the BRAF mutation status was also recommended[4].

In this section, we outline the current advances of molecular-targeted drugs which are required for the advancement of precision medicine in GI cancer.

LITERATURE SEARCH

We first conducted a search of the PubMed database for English articles using the medical subject heading terms in combination with "gastrointestinal cancer," "esophageal cancer," "gastric cancer," "colorectal cancer," "molecular targeted therapy," and "precision medicine." Relevant articles from experimental studies and clinical trials since 1989 were selected, as well as articles related to the disease processes. Articles that did not deal with the precision medicine of GI cancer were excluded from this review. Liver and pancreatic cancer and GI stromal tumors were not covered in this review due to the limited scope of the topic.

TARGETING EGFR

EGFR, also known as ErbB1/HER1, belongs to the ErbB family that also includes ErbB2/HER2/Neu, ErbB3/HER3, and ErbB4/HER4[5]. Driven largely by its role in promoting cell proliferation and opposing apoptosis, the EGFR has been vilified as a

proto-oncogene. These EGFR mutation and/or overexpression activate downstream pro-oncogenic signaling pathways, including the RAS-RAF-MEK- extracellular signal-regulated kinase (ERK) pathways. These pathways then activate many biological outputs that are beneficial to cancer cell proliferation, and is the target of multiple cancer therapies currently adopted in the clinical practice[5]. Panitumumab and cetuximab are major EGFR monoclonal antibodies (mAbs) approved for the treatment of *RAS* wild-type metastatic (m) CRC. Because of the clinical significance of hot-spot KRAS mutations (codons 12 and 13) in patients with advanced CRC to anti-EGFR therapy resistance, KRAS mutation testing has become obligatory testing before managing anti-EGFR therapy[6,7]. To date, trifluridine/tipiracil (TAS-102) and regorafenib are the only last-line treatment options for mCRC, based on an improvement in median overall survival (OS) in randomized clinical trials. Nimotuzumab, a recombinant humanized mAb against human EGFR, demonstrated blocking ability against the binding of epidermal growth factor and tumor growth factor-alpha (TGF-α) to EGFR. Currently, a Phase III trial comparing paclitaxel plus cisplatin in combination with either nimotuzumab or placebo as the first-line treatment for patients with metastatic esophageal squamous cell cancer (ESCC) is under investigation in China (NCT02611700).

Simultaneous blocking of the entire EGFR family might improve therapeutic efficacy. Three phase II clinical trials are evaluating the combination of afatinib with chemotherapy. One study analyzes afatinib in combination with cisplatin and 5-fluorouracil (5-FU) as a first-line treatment for advanced GC (NCT01743365). The combination of afatinib and paclitaxel has been launched in patients with EGFR-positive GC as a second-line treatment (NCT02501603), and another phase II study compared afatinib in combination with paclitaxel *vs* paclitaxel alone in refractory esophagogastric cancer (EC) (NCT01522768). Poziotinib, formerly known as HM781-36B, is an irreversible pan-HER tyrosine kinase inhibitor (TKI) that targets EGFR, HER2, and HER4. Poziotinib is currently being investigated in a global phase II clinical trial which is expected to evaluate the efficacy of poziotinib in patients with EC, GC, or CRC who have failed two or three lines of treatment (NCT03770988, NCT01746771, and NCT04172597).

However, despite appropriate patient selection based on molecular testing, secondary resistance to anti-EGFR antibodies will occur in several patients[8]. Multiple studies have thus focused on exploring resistance mechanisms. One of the most familiar mechanisms of acquired resistance to EGFR blockade in mCRC are mutations in the extracellular domain (ECD) of the *EGFR* gene[9]. Sym004, a mixture of two anti-EGFR mAbs, *i.e.*, futuximab and modotuximab, binds to nonoverlapping epitopes in *EGFR* ECD III, leading to more completely and durable pathway inhibition. The most significant information obtained from the analysis of the circulating free deoxyribo-nucleic acid (DNA) in mCRC patients treated with anti-EGFR agents is that resistance to these drugs is likely to be multiclonal rather than monoclonal in the majority of cases.

Several studies have presented some concomitant genomic alterations in patients who show progressing disease while they are being treated with anti-EGFR drugs. Patients were found to carry mutations in *KRAS, NRAS, BRAF, EGRF,* and *MEK1* but also amplification of *ERBB2, MET, FLT3,* and *KRAS*[10-14]. These aberrant alterations result in resistance to anti-EGFR therapy mainly through a constitutive activation of EGFR downstream signaling pathways in spite of EGFR blockade.

BRAF mutation in CRC patients results in poor prognosis and resistance to treatment, leading to the need for a combination of multimolecular strategies. Mutations in BRAF, which are detected in approx. 10% of CRC patients overall, are mutually exclusive of KRAS mutations and occur more frequently in patients with mismatch repair (MMR) deficiency[15]. The most common BRAF mutation is valine (V) 600 glutamic acid (E), which results in an amino acid change from V to E, leading to a constitutive activation of BRAF by mimicking tyrosine kinase phosphoryl-ation [16]. The results of several experiments implied that anti-EGFR therapy is not effective for mCRC patients with BRAF V600E-mutation[17,18]. Unfortunately, the BRAF inhibitor vemurafenib failed to reveal efficacy as a single agent in BRAF-mutated mCRC[19].

Based on the evidence that BRAF inhibition disrupts a negative feedback loop through EGFR and facilitates cellular proliferation, combined therapy consisting of both a BRAF inhibitor and an EGFR inhibitor would provide complemental benefit in patients with BRAF V600E-mutated mCRC[20]. A clinical study investigating the combined inhibition of BRAF V600E with vemurafenib and EGFR with cetuximab + irinotecan in BRAF V600E-mutated mCRC patients is underway (NCT02164916).

The serine/tyrosine/threonine kinase MEK plays an important role in the RAS/RAF/MEK/ERK cell signaling pathway, which is frequently dysregulated in human cancers. A phase II study of selumetinib (AZD6244; ARRY-142866) (a tyrosine kinase inhibitor of MEK) + docetaxel as second-line chemotherapy for patients with GC is underway. Selumetinib + docetaxel revealed useful efficacy and tolerable safety in GC patients with a MEK signature or RAS gene alterations. Novel treatment combinations of BRAF and MEK inhibitors have started to demonstrate activity in early-phase trials of BRAF V600E mutant CRC.

DNA MMR deficiency is recognized as being predictive of benefit from immune checkpoint inhibitors, which have now been approved for use in later lines of treatment in this molecular subgroup of CRC. The triple inhibition of EGFR, BRAF, and MEK was evaluated by using panitumumab, dabrafenib, and trametinib, respectively, and the treatment proved to be a tolerable and promising therapeutic strategy for BRAF V600E-mutant CRC, resulting in the overall response rate (ORR) of 21%, and median progression-free survival (PFS) of 4.2 mo[21].

TARGETING HER2

The overexpression of HER2 has been implicated in resistance to anti-EGFR therapy *via* aberrant MEK-AKT pathway activation[22]. Dual HER2 inhibition with trastuzumab and lapatinib in patients with HER2-amplified, KRAS wild-type metastatic CRC who are resistant to standard therapies, including EGFR-targeted agents, demonstrated that dual HER2 blockade can produce objective responses[23]. These findings suggested a need for continued exploration to find viable treatment options for HER2-positive CRC[23]. Similarly, trastuzumab and pertuzumab demonstrated a 23% response rate and 69% disease control rate in the colorectal arm of a basket study[24].

HER2-targeted therapy for patients with HER2-positive GC who progressed on trastuzumab-based therapy is still challenging. Fam-trastuzumab deruxtecan (DS-8201a), a HER2-directed antibody and DNA topoisomerase I inhibitor conjugate, showed an acceptable safety profile and promising antitumor activity in salvage-line subjects with HER2-positive GC patients who previously received trastuzumab[25]. The randomized, phase II, multicenter, open-label, destiny-Gastric01 study is ongoing (NCT03329690). The primary purpose of this trial is to compare the efficacy and safety of DS-8201a and physician's choice treatment in HER2-positive GC. Similarly, the destiny-CRC01 trial is under evaluation; its main objective is to test the safety and effectiveness of DS-8201a for patients with HER2-positive CRC (NCT03384940). Ongoing studies are evaluating trastuzumab + pertuzumab *vs* cetuximab and irinotecan (NCT03365882), and tucatinib (ONT-380; a highly selective small molecule inhibitor of Her-kinase) and trastuzumab in patients with HER2-positive, previously treated advanced CRC (NCT03043313).

TARGETING ANGIOGENESIS

Angiogenesis plays a pivotal role in the growth, metastasis, and ascites formation of malignancies. The overexpression of angiogenic factors such as VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) was reported to be correlated with the tumor development and poor survival of GI cancer patients[26]. The OS for GI cancer increased to 3 years with the application of anti-VEGF monoclonal antibodies[27]. Three clinical trials comparing patients treated with fluorouracil/ Leucovorin alone or in combination with bevacizumab showed improved response rates and OS[28]; however, the therapeutic effect of anti-VEGF therapy in mCRC patients was reduced for several months due to acquired resistance. During bevacizumab exposure, VEGF-A is decreased, instead of increased levels of vascular endothelial growth factor receptor 1 (VEGFR1) which result in drug resistance. Hepatocyte growth factor (HGF)-ligand inhibition and silencing HOXB9 is expected to be a promising approach to regulate this resistance[29,30].

Similarly, the anti-VEGF drug ramucirumab in combination with chemotherapy in the treatment of advanced GC significantly improved the ORR and prolonged the PFS and OS compared to chemotherapy alone[31]. The rainbow subgroup analysis of patients who received prior trastuzumab therapy showed that the OS was prolonged in the second-line ramucirumab + paclitaxel combination group (11.4 mo; 95%CI: 7.0-17.9) *vs* the placebo + paclitaxel group (7.0 mo; 95%CI: 3.4-14.6)[32]. In 2012,

regorafenib, a multikinase inhibitor, was approved by the United States food and drug administration (FDA) for the treatment of patients with mCRC who have progressed on standard chemotherapies[33]. Significant improvement in the OS of chemo-refractory KRAS wild-type mCRC patients was observed when regorafenib was administered before cetuximab +/− irinotecan, compared to the reverse treatment sequence (HR: 0.61, *P* = 0.0293)[34]. Regorafenib has shown promising activity in GC patients in the integrate phase II trial[35]. Thus, blockage of the interaction of multiple growth factors with their receptors might improve therapeutic efficacy.

Vandetanib (ZD6474) is an oral tyrosine kinase inhibitor of VEGFR-2, VEGFR-3, RET, and EGFR. A Phase I trial demonstrated that the administration of vandetanib with a chemotherapy regimen as well as concurrent radiation therapy is feasible in the neoadjuvant setting for the treatment of locally advanced esophageal cancer[36]. Apatinib is an orally bioavailable TKI that selectively inhibits VEGFR-2, c-Kit and Src, which has been approved by China's national medical products administration (formerly the China food and drug administration) for third-line treatment of patients with GC[37]. The phase II clinical trial of apatinib monotherapy for chemotherapy-refractory mCRC revealed improved survival outcomes over the historical control expected from a placebo or best supportive care[38].

In contrast, apatinib may be an option to improve the chemosensitivity of paclitaxel and 5-FU in the treatment of GC[39]. Axitinib, a first-generation anti-VEGFR TKI with high potency against VEGFRs, platelet-derived growth factor receptor (PDGFR) and c-KIT, has been approved by the FDA for the treatment of renal cell carcinoma[40]. In phase II trials, the median PFS was significantly increased in the axitinib group compared to the placebo group (4.9 mo *vs* 3.1 mo; *P* = 0.0116) for patients with first-line mCRC, suggesting that axitinib is a promising candidate for the maintenance treatment of mCRC[41]. Fruquintinib, a novel oral TKI of VEGFR-1, -2 and -3, afforded significantly superior median OS (HR: 0.65, *P* < 0.001) and median PFS (HR: 0.26, *P* < 0.001) compared to placebo in patients with chemo-refractory mCRC, and it demonstrated the benefit of VEGFR inhibition in the latter lines of mCRC treatment [42].

Bemarituzumab (FPA144), a fucosylated mAb directed against FGFR2b, can be safely administered to patients with advanced gastroesophageal adenocarcinoma. In a phase I study of bemarituzumab (FPA144) treatment for patients with advanced FGFR2b-selected gastroesophageal adenocarcinoma, stable disease was the best observed response in 13 additional patients, leading to an overall disease control rate [*i.e.*, partial response (PR) + stable disease] of 64.3% (95%CI: 44.1%-81.4%) in the subgroup with high FGFR2b overexpression[43]. A randomized double-blinded phase II study with a primary endpoint of overall survival with or without bemarituzumab in addition to mFOLFOX6 for GC is now underway (NCT03694522).

To date, erdafitinib was developed for treating patients with advanced or metastatic urothelial cancer with FGFR3 or FGFR2 alterations, accounting for 15%-20% of patients [44]. Erdafitinib is now being evaluated in a multicenter phase II clinical trial which is expected to determine the efficiency of erdafitinib in ECC and GC patients with FGFR translocation or mutation (NCT02699606).

TARGETING THE PI3K/ AKT/MTOR PATHWAY

The PI3K pathway, discovered over 20 years ago, plays an important role in a variety of cellular activities. Emerging data show that the PI3K/AKT/mechanistic target of rapamycin (mTOR) cascade is involved in the development of GI cancer[45]. Despite extensive efforts evaluating the value of PI3K/AKT/mTOR inhibitors in GI cancer (*e.g.*, BEZ235, NVP-BEZ235, OSI-027, MK-2206, KRX-0401, BYL719, and BKM120), several significant problems remain to be clarified regarding the molecular mechanisms underlying the targeting of the PI3K/AKT pathway in GI cancer and overcoming resistance. The selection of patients who could obtain the greatest advantage from treatment as well as combination therapies with agents targeting another pathway would be important. Interestingly, a phase I/II trial examined the efficacy of everolimus, an inhibitor of mTOR, in combination with mFOLFOX6 + bevacizumab as a first-line treatment for mCRC patients; the response rate was assessed based on the expression of phosphatase and tensin homolog (PTEN)[46].

A phase Ib clinical trial evaluating triple-drug combinations of cetuximab, encorafenib (BRAF inhibitors), and a PI3Kα inhibitor, alpelisib, demonstrated more convincing efficacies than "targeted doublets"[47]. The ORR was 53% in the whole population, and it was superior (86%) in the patients with PTEN expression below the

threshold (*P* = 0.03). A phase III randomized, double-blind study of paclitaxel with and without everolimus failed to show improved outcomes with the addition of everolimus. However, everolimus significantly prolonged the PFS of the patients pretreated with taxane (*P* = 0.03)[48]. BYL719 is a selective PI3Kα inhibitor that was reported to be equipotent against the wild-type and the most common somatic mutations of PI3Kα[49]. BYL719 has shown markedly selective efficacy in *PIK3CA* mutants. A multi-center, open-label phase II biomarker-driven umbrella trial is in progress in Korea, investigating ECC (NCT03292250): BYL719 is selectively applied for the patients with relevant genetic alterations including a PI3K pathway alteration revealed by next-generation sequencing.

AZD5363 is a novel AKT kinase inhibitor that has potential based on the genetic status of PIK3CA, PTEN[50]. A phase II study of AZD5363 in combination with paclitaxel in patients with GC harboring a PIK3CA mutation or amplification as a second-line chemotherapy was launched in 2015 (NCT02451956). ABI-009 (nab-rapamycin) is a nanoparticle form of human albumin-bound rapamycin with a mean particle size of approx. 100 nm, developed with a proprietary nanoparticle albumin-bound technology[51]. In CRC, a multicenter open-label phase I/II trial to investigate the efficacy of ABI-009 in combination with mFOLFOX6 and bevacizumab as first-line therapy is underway (NCT03439462).

TARGETING THE TGF-B PATHWAY

TGF-β is a cytokine involved in both physiological and pathological processes including tumorigenesis and cancer spreading[52]. TGF-β signaling mediates immune/inflammatory responses and tumor microenvironments throughout the development of a tumor. It also regulates tumor growth, the epithelial-mesenchymal transition, and cancer cell stemness[52]. In the majority of CRC and GC patients with microsatellite instability (MSI), inactivating mutations in the *TGFBR2* gene were shown[53]. Mutations in Smad4, which have been identified in > 30% of CRC patients, have been said to disrupt TGF-β signaling[54].

Thus, participates in the development of GI cancers, and management targeting the TGF-β signaling pathway may be effective for the treatment of GI cancers. M7824 (MSB0011359C) is a first-in-class bifunctional fusion protein composed of the extracellular domain of two TGF-β receptor 2 (TGF-βR2) molecules that serve as a TGF-β sequestering or trap molecule fused to a fully humanized mAb against PD-L1 [55]. M7824 simultaneously blocks the PD-L1 and TGF-β pathways of immune evasion. A phase 1 trial of M7824 with 19 patients with heavily pretreated advanced solid tumors, including CRC, revealed a manageable safety profile comparable to other anti-PD-1/PD-L1 antibodies[56] (NCT02517398).

Even though few drugs targeting TGF-β have exhibited efficiency in clinical trials, the future of TGF-β pathway-based strategies against GI cancers is encouraging from these inspiring clinical trials[57]. Vactosertib (EW-7197) is a potent, orally active and ATP-competitive TGFBR1 and ALK inhibitor. A phase 1b/2a multicenter study to assess the safety, tolerability, pharmacokinetics, and antitumor activity of vactosertib in combination with pembrolizumab in patients with mCRC or GC is currently underway (NCT03724851).

TARGETING HGF/ C-MET

C-MET, a kinase receptor for HGF, is well known for its roles in driving tumori-genesis. HGF/ mesenchymal-epithelial transition (c-MET) is also thought to promote the progression of tumorigenesis[58]. In GC, elevated c-MET expression is also a predictor of poor OS compared to c-MET negative tumors[59]. Several c-MET inhibitors have been developed as anticancer drugs in GC therapy. A phase I study of the c-Met tyrosine kinase inhibitor SAR125844 in Asian patients with MET-amplified solid tumors, including GC, demonstrated that among 19 patients with MET-amplified solid tumors, with the administration of 570 mg/m^2 of SAR125844, two GC patients had partial responses, seven patients had stable disease (six GC and one renal cancer), and 10 patients had progressive disease[60].

An ongoing phase Ib clinical trial is currently evaluating the efficacy and safety of INC280, an orally administered c-Met inhibitor, in combination with cetuximab in patients with c-Met-positive metastatic CRC whose disease progressed on cetuximab or panitumumab treatment (NCT02205398). A potent and selective MET inhibitor,

savolitinib, is being investigated in a phase II trial in patients with MET-amplified CRC (NCT03593641). More and more c-MET inhibitors have been found to have antitumor activity in GI cancer, but many drug studies have remained at a nonclinical stage.

TARGETING THE WNT PATHWAY

Wnt proteins are cysteine-rich glycoproteins that bind to the extracellular domain of frizzled receptor and lipoprotein receptor-related protein 5/6. Wnt signaling mediates diverse cellular processes, including cell fate, movement, polarity, and organoge-nesis [61]. In recent years, the understanding of the role of Wnt secretion in tumor initiation has developed and revealed novel therapeutic targets. Mutations of RNF43 and R-spondin fusion proteins, which mutually exclusively occur with APC mutations in CRC, were subsequently identified as a predictor of effective therapy targeting Wnt secretion[62]. Based on these results, a phase I/II trial of LGK974 was initiated for patients with mCRC harboring mutations of RNF43 or R-spondin fusions. In addition, a novel orally available porcupine inhibitor (*i.e.*, ETC-1922159) that was found to prevent the growth of R-spondin-fusion-positive CRC is being assessed in a clinical trial (NCT02521844). A current phase I/II study is evaluating the orally bioavailable and specific porcupine inhibitor WNT974 in patients with mCRC with BRAF V600 and ring finger protein 43 mutations or RSPO fusions, in combination with a BRAF inhibitor and anti-EGFR agent to mitigate acquired resistance through the Wnt-β-catenin pathway (NCT02278133).

Foxy-5, a Wnt-5a agonist, is a mimicking peptide of Wnt-5a and a non-canonical member of the Wnt family which impairs the migration and invasion of epithelial cancer cells[63]. Foxy-5 is currently being tested in a resected CRC setting in the Neo Fox trial, in which standard therapy (surgery + FOLFOX 6-month regimen) + neo-adjuvant administration of Foxy-5 prior to and following surgery is being compared to standard therapy alone in patients with Wnt-5a low CRC (NCT03883802). Dickkopf-1 was identified as a secretory protein that can inhibit the Wnt signaling pathway by competitively binding to Wnt ligand-receptor LRP5/6. An ongoing phase IIa study is evaluating the use of DKN-01 in combination with tislelizumab and chemotherapy as first-line or second-line therapy in patients with GC (NCT04363801).

TARGETING POLY (ADP-RIBOSE) POLYMERASE

Chromosomal instability is the hallmark of the chromosomal instability subtype of GC according to the cancer genome atlas classification. The poly (ADP-ribose) polymerases are a family of enzymes that are activated by DNA damage and facilitate DNA repair[64]. A defect in DNA repair may lead to the loss of chromosomes associated with sensitivity to PARP inhibitors[65]. In preclinical studies, the PARP inhibitor olaparib was active against GC cell lines with low levels of ataxia telangiectasia mutated (ATM) kinase, which is an activator of the DNA damage response[65]. Although the advantage of combining olaparib with paclitaxel therapy for metastatic GC was not shown in a phase III trial[66], these trials involved only a few patients with low levels of ATM. A trial evaluating the safety and activity of olaparib combined with durvalumab in patients with advanced-stage GC is underway (NCT02734004). A phase I/II pilot study was prepared to analyze the efficacy of olaparib in combination with ramucirumab in patients with metastatic, recurrent or unresectable GC (NCT03008278), and a phase II trial designed to assess the efficacy and safety/tolerability of olaparib in patients with advanced EC is currently ongoing (NCT03829345).

As well, a phase II non-randomized open-label study to evaluate temozolomide in combination with olaparib in patients with MGMT promoter hypermethylated advanced CRC is now recruiting (NCT04166435). Rucaparib (Rubraca®) is a small-molecule PARP inhibitor with potent activity against PARP-1, -2 and -3. It is approved in the United States and the EU for the treatment of patients with BRCA-mutated ovarian cancer who have failed upfront standard chemotherapy[67]. A phase I/II trial of rucaparib in combination with ramucirumab with or without nivolumab in patients with advanced GC who have been treated with two or more lines of chemotherapy is in progress (NCT03995017).

TARGETING ANAPLASTIC LYMPHOMA KINASE

ALK, which is also known as ALK tyrosine kinase receptor, is a tyrosine kinase encoded by the ALK gene. ALK is constitutively activated by fusion events, which leads to cellular transformation and the facilitation of survival and growth through downstream signaling[68]. Gene fusion is the most frequent molecular alteration occurring in this gene across different tumor types including GI cancer. ALK, ROS1, and NTRK fusions occur in 0.2%-2.4% of cases of CRC. Entrectinib is an oral inhibitor of TRK A/B/C, ROS1, and ALK. The results of two phase I studies with 119 patients have been published; 18 of these patients had GI cancer[69]. The ORR was 57% in the ALK-rearranged solid tumors, which included CRC. Thus, targeted agents may provide clinical benefit to patients with rare fusions. A*l*though their incidences are minor, the presence of gene fusions is easily detectable by a liquid biopsy, and further research is thus worthwhile.

OTHER CANDIDATES

Claudin (CLDN) 18.2 is an isoform of claudin proteins, which play a role in maintaining tight cell junctions. The identification of CLDN 18.2 in GC became a potential target with the ensuing development of a mAb against CLDN 18.2, *i.e.*, zolbetuximab (formerly known as IMAB362). More recently, the results of the randomized phase II fast study demonstrated that the combination of claudiximab + EOX significantly increased the response rate and improved the PFS and OS of patients with higher CLDN 18.2 expression. Monotherapy with zolbetuximab, a chimeric IgG1 mAb that binds to CLDN 18.2, showed superior antitumor activity in patients with CLDN18.2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinomas[70].

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors are orally bioavailable drugs that have been explored as anticancer agents. These agents directly block the activity of the cyclin D-CDK4/6 holoenzyme, which leads to the inhibition of the growth of sensitive tumor cells. The CDK4/6 inhibitors specifically block cell-cycle progression from the G1 to the S phase of the cell cycle. There is an ongoing phase II trial comparing palbociclib, an oral inhibitor of CDK4/6 + binimetinib *vs* TAS-102 for the treatment of patients with KRAS and NRAS mutation-positive CRC (NCT03981614). Regarding GC, alvocidib, a flavonoid alkaloid CDK9 kinase inhibitor under clinical development for the treatment of acute myeloid leukemia, has been investigated in phase I and II trials. In patients with GC, the efficacy of alvocidib in combination with nivolumab or pembrolizumab is being tested (NCT03311334).

Histone deacetylases (HDACs) have a key impact on chromatin remodeling and epigenetics, which makes their inhibitors a very attractive area of investigation. In hepatocellular carcinoma, epigenetic therapy with belinostat, a potent HDAC inhibitor, demonstrated that a 58% disease stabilization rate (*i.e.*, CR + PR + SD) in tumors with high and low HR23B histoscores[71]. However, although the objective PR was 42%, the combination of vorinostat with capecitabine + cisplatin is not likely to show enhanced efficacy in comparison with standard fluoropyrimidine-platinum doublet regimens in patients with GC[72].

Napabucasin is a cancer stemness inhibitor that targets a number of oncogenic pathways, including the signal transducer and activator of transcription 3 pathway. Phase I/II studies have indicated the tolerability and antitumor activity of napabucasin in various types of cancer, including CRC. For example, a multicenter randomized phase II study (modulate) is in progress to assess the efficacy of the combination of nivolumab and BNC105 (a microtubule/tubulin inhibitor) and the combination of nivolumab and napabucasin to modulate the tumor microenvironment in patients with microsatellite-stable refractory CRC. A phase III study of napabucasin + standard therapy in GC and CRC is ongoing (NCT02178956, NCT3522649).

Notch pathway signaling is associated with several human cancers[73]. A role for Notch signaling in the maintenance of cancer stem cells has been presented in preclinical experiments and recently in clinical trials. CB-103, an orally active small-molecule inhibitor of the Notch transcription activation complex, is being investigated in a phase I/II trial in patients with refractory solid tumors, including CRC (NCT03422679). *Th*e ubiquitin proteasome system plays an important role in the degradation of intracellular proteins involved in multiple cellular processes, including cell-cycle division, DNA repair, and the regulation of membrane receptors[74]. Bortezomib is one of the major components of proteasome inhibitors, with activity in

multiple myeloma. Bortezomib/paclitaxel/carboplatin is currently being tested in patients with metastatic esophageal cancer and gastroesophageal adenocarcinoma (NCT02912559).

Heat shock protein (Hsp) 90 serves as a chaperone protein that promotes the proper folding of proteins involved in a variety of signal transduction processes[75]. HSP90 has been demonstrated to play pivotal roles in tumor development and resistance to recently applied therapies. However, recent clinical trials using established inhibitors against HSP90 demonstrated limited clinical efficacy when the inhibitors were used as a monotherapy. These results suggest that combinations of the inhibitors with standard chemotherapeutic agents might improve the antitumor efficacy of the HSP90-inhibitors.

Luminespib is a representative HSP90 inhibitor that shows anticancer effects *via* binding to the ATPase domain of HSP90, causing a loss of chaperone functions. Luminespib is currently being investigated in a phase II clinical trial, which is expected to enroll 21 patients to evaluate the efficacy of luminespib + trastuzumab in patients with HER2-positive advanced GC who have received trastuzumab + chemotherapy as the first-line treatment (NCT 01402401).

The hedgehog signaling pathway is an evolutionarily conserved pathway of signal transmission from the cell membrane to the cell nucleus[76]. The hedgehog signaling pathway plays a significant role in the normal embryonic development of invertebrates and vertebrates. Vismodegib, a first-in-class small molecule inhibitor of Hedgehog pathway signaling was approved by the FDA and the European Medicines Agency for the treatment of adults with basal cell carcinoma. The phase II trial to investigate the efficacy of vismodegib in GC patients with SMO overexpression is ongoing (NCT03052478).

THE DEVELOPMENT OF IMMUNOLOGY

One of the fundamental avoidant mechanisms of cancer cells is the alteration of the host immune system. Immunotherapy has been shown to be aggressive in tumors containing a high mutation as confirmed in melanoma and lung cancer[77,78]. An increased amount of mutations is responsible for the production of neoantigens, which leads to enhanced tumor immunogenicity. In MSI, frameshift mutations in protein-coding sequences retain the ability to produce a variety of peptides with potential neoepitopes acknowledged as foreign substances by the immune system[79]. The immune checkpoint receptor programmed death-1 (PD-1) is a co-inhibitory molecule that is physiologically expressed on immune cells such as T and B lymphocytes and myeloid cells providing the signal for the termination of immune system activity. PD-1 receptor has two natural ligands, programmed death-ligand 1 (PD-L1) and PD-L2, which can be expressed in immune cells as well as tumor cells; this represents a potential mechanism of immune surveillance escape[79].

In GC, subtypes such as MSI-H tumors harboring multiple neoantigens resulting from MMR gene deficiency as well as Epstein-Barr virus (EBV)-positive tumors expressing PD-L1/L2 may serve as candidates for immunotherapy. It is suspected that roughly one-third of all GC cases are potentially immunogenic. A recent randomized phase III trial, attraction-2 (ONO-4538-12), investigated treatment with nivolumab, a mAb targeting PD-1, after two or more previous chemotherapy regimens in advanced GC patients; the results demonstrated extended median overall survival compared to that associated with a placebo[80]. Based on that trial, nivolumab gained approval in Japan. The clinical effectiveness of using nivolumab alone or in combination with ipilimumab (a fully human IgG1 monoclonal antibody inhibitor of cytotoxic T-lymphocyte associated protein-4) in patients with chemotherapy-refractory advanced GC/GEJC was shown in the GC cohort of the phase I/II CheckMate-032 trial[81]. A previous study reported that a patient with EBV-infected GC achieved a robust response to treatment with the anti-PD-L1 antibody avelumab[82].

ARID1A alterations are significantly associated with EBV infection, which in turn leads to longer PFS after anti-PD-1/PD-L1 immunotherapy, regardless of the microsatellite and tumor mutational burden status[82]. Another PD-1 antibody, pembrolizumab, also showed encouraging antitumor activity for PD-L1-positive advanced GC in phase II and III trials[83,84]. The ATTRACTION-3 trial, which was a phase III trial of the efficiency of nivolumab, revealed that nivolumab treatment resulted in significantly higher OS relative to chemotherapy (docetaxel or paclitaxel) in a PDL1-unselected population with EC[85]. Camrelizumab + apatinib in combination with liposomal paclitaxel and nedaplatin could be a new treatment option for patients

with unresectable locally advanced or metastatic ESCC (NCT03603756). Thus far, CRC has been a poor candidate for immunotherapy. Early studies are deficient in objective clinical responses to nivolumab among patients with unresectable mCRC. However, and increasing amount of evidence suggests the effectiveness of the application of a check-point inhibitor (CPI) in patients with MSI-H CRC[86].

Clinical trials investigating the combination of nivolumab + ipilimumab for patients with MSI-H demonstrated high response rates and encouraging PFS and OS at 12 mo, manageable safety, and meaningful improvements in key patient-reported outcomes [87]. Subsequently, there is growing attention regarding the use of a combination of CPI with chemotherapies or targeted therapies. The combined therapy of bevacizumab + atezolizumab revealed a clear significant effect for MSI-H patients in a phase III clinical trial (NCT02997228). An ongoing trial is evaluating the safety and efficacy of the combination of regorafenib + nivolumab in patients with previously treated advanced gastric cancer or CRC (NCT32085012).

A better understanding of cancer immunotherapy agents that can provide prolonged survival in the microsatellite-stable (MSS) subgroup of GI cancer will contribute to the outcomes of this patient subset, which accounts for the majority of GI cancer patients. One approach to further improving GI cancer therapy is a vaccination with peptides alone, peptide-expressing viruses, peptide-loaded antigen-presenting cells, or the application of peptide-specific T cells. Traditionally, the advancement of such cancer vaccines started with peptides derived from tumor-associated antigens (TAAs), tumor-specific antigens, and cancer testis antigens. Several lines of evidence support neoantigens as important targets for immune responses. A phase I/II open-label study exploring the immune response to TAA CEA of a dendritic cell vaccination in patients with Lynch syndrome or CRC with MSI is ongoing (NCT01885702).

Similarly, chimeric antigen receptor (CAR)-T cell immunotherapy enhances the immune cells' ability to eradicate cancer cells by reprogramming them to express CAR protein and selectively binding to the cancer cells. The efficacy of CAR-T cell therapy has been demonstrated in mouse models of mCRC and GC[88]. A phase I prospective nonrandomized controlled trial to investigate the safety and efficacy of the infusion of intraperitoneal EpCAM CAR-T cells for the treatment of advanced GC with peritoneal metastasis is now underway (NCT03563326).

CLOSING REMARKS AND FUTURE PERSPECTIVE

This review has briefly summarized the current evidence and ongoing clinical trials regarding the application of targeted therapy in GI cancer in various settings. The goal of treating GI cancer is to provide the most effective approach across multiple lines of therapy for individual patients, using the tumor characteristics to inform the selection and sequencing of agents. In addition to EGFR and VEGF signaling, new molecular targets are being continuously detected, *e.g.*, MET, FGFR, ALK, TGF-β, WNT, PAPP, CDK, Hedgehog, CLDN18.2, and immune checkpoint inhibitors, which has prompted the development of new therapies. In the past few decades, evolving sequencing technologies have uncovered genomic, transcriptional, proteomic, and epigenetic details as never before. Numerous investigations of new GI cancer-targeted agents have been conducted with the goals of achieving better patient compliance, lower rates of adverse events, and more personalized treatment options.

Genomic profiling for optimum patient selection has great promise to guide future precision medicine applications for GI cancer. The specific use of TKIs should be planned based on the patients' genetic backgrounds, and the precise signaling pathway that induces the carcinogenic properties of the cells for a given cancer type should be identified. The targeted agents for GI cancer now being investigated in clinical trials are summarized in Tables 1-3 and Figure 1.

Cancer cell growth, differentiation, and angiogenesis are thought to be mediated by multiple intracellular and cell-surface protein kinases with their downstream pathways. Multi-kinase inhibitors, which are agents that target several kinases or pathways simultaneously, have recently been developed for malignancies. Regorafenib and sorafenib are currently approved by the United States FDA for treating patients with CRC and renal cancer, respectively. Sorafenib, a broad-spectrum TKI targeting VEGFR2 and PDGFR as well as RET and RAF1, has been investigated in phase II trials, and the results have led to disease stabilization and encouraging PFS in patients with refractory EC[89].

In addition, as noted above, vandetanib, apatinib, axitinib and fruquintinib are currently being tested in GI cancer settings in clinical trial. Pazopanib is another TKI

Table 1 Clinic al trials of esophageal cancer classified on molecular targets

Signaling	Agents	Type of trial	Line of treatment	Phase	Results	Comments
EGFR						
NCT00100945	Gefitinib	Single group, open-label	Second	II	Completed	Gefitinib
NCT01249352	Nimotuzumab	Randmized, open-label	First	II/III	Completed	Chemoradiation + nimotuzumab
NCT02591784	Nimotuzumab	Single group, open-label	First	II	Completed	Radiotherapy+ nimotuzumab
NCT01855854	Icotinib	Single group, open-label	Second	II	Completed	Icotinib in EGFR-positive EC
NCT02353936	Afatinib (target EGFR/HER2)	Single group, open-label	Second	II	Active, not-recruiting	Afatinib
NCT01522768	Afatinib (target EGFR/HER2)	Single group, open-label	Second	II	Active, not-recruiting	Afatinib ± paclitaxel
NCT01608022	Dacomitib	Single group, open-label	Third	II	Completed	Dacomitib
NCT03817567	SCT200	Single group, open-label	Third	I/II	Recruiting	SCT200
NCT03770988	Poziotinib (target EGFR/HER2/HER4)	Single group, open-label	Third	II	Not yet recruiting	Poziotinib
RAF						
NCT00917462	Sorafenib (target VEGFR2/PDGFR/RET/RAF1)	Single group, open-label	Third	II	Completed26275293	Sorafenib
HER2						
NCT01608022	Vizimpro	Single group, open-label	First	II	Completed	Vizimpro
NCT02120911	Pertuzumab	Single group, open-label	First	I/II	Completed	Chemoradation + Ttastumab + pertuzumab
FGFR						
NCT03292250	Nintedanib	Non-randmized, open-label	Second	II	Recruiting	Nintedanib
NCT02699606	Erdafitinib	Single group, open label	Second	II	Recruiting	Erdafitinib
VEGFR						
NCT02773524	Regorafenib	Randomized, triple	Third	III	Recruiting	Regorafenib
NCT03762534	Ramucirumab	Randomized, open label	Second	II	Recruiting	Ramucirumab + paclitaxel
NCT03542422	Apatinib (target VEGFR2/c-Kit/Src)	Single group, open label	First	II	Not yet recruiting	Apatinib
NCT03787251	Apatinib	Randomized, open label	Second	II	Not yet recruiting	Apatinib + chemotherapeutic drug
NCT04063638	Anlotinib (target VEGFR/FGFR/PDGFR)	Single group, open label	First	II	Recruiting	Anlotinib
PI3K						
NCT03544905	CYH33	Single group, open label	Second	I	Recruting	CYH33
NCT03292250	BYL719	Non-randmized, open-label	Second	II	Recruting	BYL719
mTOR						

NCT01490749	Everolimus	Single group, open label	First	I	Completed	Everolimus + FXELOX followed by radiation
PARP						
NCT03995017	Rucaparib	Non-randomized, open label	Second	I/II	Recruting	Rucaparib + Ramucirumab
NCT03829345	Olaparib	Single group, open-label	Third	II	Recruting	Olaparib
ALK						
NCT03917043	APG-2449 (target ALK/FAK/ROS1)	Sequential Assignment	Second	I	Recruting	APG-2449
Hedgehog						
NCT02138929	Sonidegib	Single group, open label	Third	I	Active, not recruiting	Sonidegib + everolimus
DKK1						
NCT02013154	DKN-01	Non-randomized, open label	Third	I	Active, not recruiting	DKN-01 + paclitaxel or pembrolizumab + chemotherapy
SHP2						
NCT04000529	TNO155	Non-randomized, open label	Third	I	Recuruiting	TNO155 + spartalizumab + ribociclib
Cadherin						
NCT02375958	PCA062 (target P-cadherin)	Single group, open label	Third	I	Completed	PCA062 in p-cadherin positive tumors

EC: Esophageal cancer; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; also known as PKB, mTOR: Mammalian target of rapamycin; MEK: Mitogen-activated protein kinase; EGFR: Epidermal growth factor receptor; HER2/3/4: Human epidermal growth factor 2/3/4; MAPK: Mitogenactivated protein kinase; STAT3: Signal transducer and activator of transcription 3; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet-derived growth factor receptor; FGFR: Eibroblast growth factor receptor; HGF: Hepatocyte growth factor; MET: Mesenchymal-epithelial transition factor; TEK: Tunica interna endothelial cell kinase; DDR: Discoidin domain receptor tyrosine kinase; MKNK/MAP: Kinase-interacting serine/Threonine protein kinase; FLT3: Fms-related tyrosine kinase 3; N.A.: Not applicable; MSS: Microsatellite stable; DKK1: Dickkopf-1; ALK: Anaplastic lymphoma kinase; PARP: Poly (ADP-ribose) polymerases.

that targets VEGFR, PDGFR, FGFR, and C-kit; it emerged almost a decade after sorafenib. Pazopanib is being investigated in ongoing phase I/II studies in combination with chemotherapy in GC and CRC as first-line treatments (NCT01716546 and NCT00387387). A large-scale phase III randomized trial was launched in 2008 with the primary endpoint of OS; it compared brivanib alaninate with or without cetuximab in patients with K-RAS wild-type tumors following failure of treatment with chemotherapy for mCRC (NCT00640471). Similarly, there are several ongoing clinical trials in GI cancer evaluating the use of inhibitors targeting multi-kinases including VEGFR (sunitinib, lenvatinib, nintedanib, dasatinib, carbozantinib, surufatinib, sitravatinib, vorolanib, dovitinib, and telatinib) with or without cytotoxic agents.

Crizotinib, an oral ALK/MET/ROS1 inhibitor, prompted the development of ALK target therapy[90]. It became the first ALK inhibitor to be approved by the FDA for standard first-line therapy in patients with ALK-positive NSCLC. Crizotinib is also currently being investigated in a clinical trial evaluating the efficacy of poziotinib in patients with mCRC and ALK mutation who have failed two or three lines of therapy (NCT03792568).

Multi-kinase inhibitors, which broadly inhibit cancer-related kinases, also carry the risk of inhibiting kinases whose function is unknown. Thus, along with their efficacy, multi-kinase inhibitors have been found to cause several unfavorite side effects such as proteinuria, stomatitis, diarrhea and hypertension, the latter of which were observed in more than half of the treated patients[91]. Future studies should continue to examine multi-kinase inhibitors toward the goal of achieving synergistic activity while minimizing toxicity.

In principle, combinatorial therapies that target a wide range of tumor biological functions (including cell proliferation, motility, apoptosis, and others) are considered an attractive option. The concurrent administration of several drugs that target

Table 2 Clinic al trials for gastric cancer classified on molecular targets

Clinical Trials gov idntifier	Agents	Type of trial	Line of treatment	Phase	Results	Comments
EGFR						
NCT01813253	Nimotuzumab	Randomized, open label	Second	III	Terminated	Nimotuzumab + irinotecan
NCT02370849	Nimotuzumab	Randomized, open label	First	II	Completed	Nimotuzumab + cisplatin + S-1
NCT03130790	Varlitinib	Randomized, double	First	II/III	Active, not recruiting	Varlitinib; mFOLFOX6
NCT01743365	Afatinib	Nonr-andomized, open-label	First	II	Completed	Afatinib ± 5-FU/cisplatin
NCT02501603	Afatinib	Single group, open label	Second	II	Recruiting	Afatinib + paclitaxel
NCT01746771	Poziotinib (target EGFR/HER2/HER4)	Single group, open label	First	I/II	Completed	Poziotinib + Paclitaxel + Trastuzumab in HER2-positive GC
HER2(3)						
NCT01152853	Vizimpro	Single group, open label	Second	II	Completed	Vizimpro
NCT01602406	LJM716	Single group, open label	Second	I	Completed	LJM716 + Trastuzumab
NCT03329690(DESTINY-Gastric01)	DS-8201a	Randomized, open label	Third	II	Active, not recuriiting	DS-8201a + physician's choice treatment
NCT03619681	KN026	Single group, open label	N.A.	I	Recruiting	KN026 in HER2-positive GC
NCT02689284	Margetuximab	Single group, open-label	Third	I/II	Active, not-recruiting	Margetuximab + pembrolizumab
FGFR						
NCT04071184	Alofanib	Single group, open label	Third	I	Recruiting	Alofanib
NCT02699606	Erdafitinib	Single group, open label	Second	II	Recruiting	Erdafitinib
NCT03694522	Bemarituzumab (FPA144)	Randomized, double blinded	First	II	Active, not recuiting	Bemarituzumab + mFOLFOX6
NCT04149691	CPL304110	Single group, open label	Third	I	Recruiting	CPL304110
VEGFR						
NCT03817411	Telatinib (target VEGFR/PDGFα/c-Kit)	Randomized, quadruple	First	II	Recruting	Telatinib + capecitabine/oxaliplatin
NCT01238055	Sunitinib (target VEGFR/PDGFR)	Randomized, open label	Second	II	Completed	Sunitinib + docetaxel
NCT01719549	Dovitinib (target FLT3/c-Kit/ FGFR1/3/VEGFR1/2/3/PDGFR/CFS-1R)	Single group, open label	Third	II	Completed	Dovitinib as a salvage chemotherapy
NCT01921673	Dovitinib	Single group, open label	Second	I/II	Completed	Dovitinib + docetaxel
NCT04286711	Apatinib (target VEGFR2/c-Kit/Src)	Single group, open label	Second	I/II	Not yet recruiting	Apatinib + Camrelizumab + Albumin-paclitaxel
NCT03286244	Vorolanib (target VEGFR/PDGFR/CSF1R)	Single group, open label	Second	I	Recruiting	Vorolanib + paclitaxel
NCT01716546	Pazopanib (target VEGFR/PDGFR/FGFR/c-Kit)	Single group, open label	First	I/II	Terminated	Pazopanib + DCF

NCT03609359	Lenvatinib (target VEGFR2/3)	Single group, open label	N.A.	II	Active, not recruiting	Lenvatinib + pembrolizumab
NCT03941873	Sitravatinib (target VEGFR1/2/3, Axl, MER, KIT, FLT3, DDR2, RET)	Nonr-andomized, open-label	Third	I/II	Recruiting	Sitravatinib + Tislelizumab
AKT						
NCT02451956	AZD5363	Single group, open label	Second	II	Completed	AZD5363 + paclitaxel in PIK3CA mutation or/and amplification GC
NCT02240212	Afuresertib	Non-Randomized, open-label	Second	I	Completed	Afuresertib + paclitaxel
PI3KCA						
NCT01613950	Alpelisib	Single group, open label	Second/third	I	Completed	Alpelisib + AUY922 in GC mutated PI3KCA
MET						
NCT02096666	AMG337	Single group, open label	Third	I/II	Completed	AMG337
NCT03542877	Cabozantinib (target MET/RET/VEGFR-2)	Single group, open label	Third	I	Recruiting	Cabozantinib + durvalumab
TGF-β						
NCT03724851	Vactosertib (target TGFBR1/ALK4/5)	Single group, open label	Second	I/II	Recuriuting	Vactosertib + pembrolizumab
PARP						
NCT01063517(Study 39)	Olaparib	Multicenter, randomized, double	Second	II	Active, not recruiting	Olaparib + paclitaxel *vs* paclitaxel
NCT01924533(GOLD)	Olaparib	Multicenter, randomized, double	Second	III	Active, not recruiting	Olaparib + paclitaxel *vs* placebo + paclitaxel
NCT03008278	Olaparib	Randomized, open-label	First	I/II	Recruiting	Olaparib + ramucirumab
NCT03427814	Pamiparib	Randomized, double	Second	II	Active, not recruiting	Pamiparib
NCT04178460	Niraparib	Single group, open label	Second	I	Recruiting	Niraparib + MGDO013
NCT03995017	Rucaparib	Non-randomized, open-label	Third	I/II	Recruiting	Rucaparib + ramucirumab + nivolumab
STAT						
NCT02178956	Napabucasin	Randomized, quadruple	Second	III	Completed	Napabucasin + paclitaxel
ALK						
NCT02435108	Crizotinib (target ALK/ROS1/MET)	Single group, open label	Third	II	Completed	Crizotinib for c-MET positive GC
NCT03698825	Vactosertib (target ALK4/5)	Single group, open label	Thurd	I/II	Recruiting	Vactosertib+paclitaxel
CDK						
NCT03480256	SHR6390 (target CDK 4/6)	Sequential Assigment, open label	Second	I	Recruiting	SHR6390 + pyrotinib in HRE2 positive GC
NCT03311334	Alvocidib (target CDK9)	Non-randomized, open-label	Third	I/II	Recruiting	Alvocidib+nivolumab or pembrolizumab
HSP90						
NCT01402401	Luminespib	Single group,	Second	II	Terminated	Luminespib +

		open label				trastuzumab
Hedgehog						
NCT03052478	Vismodegib	Single group, open label	Second	II	Active, not recruiting	Vismodegib
NCT04007744	Sonidegib	Single group, open label	Second	I	Recruiting	Sonidegib + pembrolizumab
DKK1						
NCT04363801(DisTinGuish)	DKN-01	Non-randomized, open label	First or Second	II	Not yet recruiting	DKN-01 + ttsleizumab + chemotherapy
CLDN18.2						
NCT03528629	Zolbetuximab	Non-randomized, open label	Third	I	Completed	Zolbetuximab
NCT03504397	Zolbetuximab	Randomized, double	First	III	Recruiting	Zolbetuxima + mFOLFOX6
NCT03653507	Zolbetuximab	Randomized, double	First	III	Recruiting	Zolbetuximab + CAPOX in CLDN-positive, HER2-negative GC
NCT01671774	IMAB362	Non-randomized, open label	First	I	Completed	IMAB362 + zoledronicacid + interleukin-2

GC: Gastric cancer; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; also known as PKB; mTOR: Mammalian target of rapamycin; MEK: Mitogen-activated protein kinase, EGFR: Epidermal growth factor receptor; HER2/3/4: Human epidermal growth factor 2/3/4; MAPK: Mitogenactivated protein kinase; STAT3: Signal transducer and activator of transcription 3; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; EGFR Epidermal growth factor receptor; PDGFR: Platelet-derived growth factor receptor; FGFR: Fibroblast growth factor receptor; HGF: Hepatocyte growth factor; MET: Mesenchymal-epithelial transition factor; TEK: Tunica interna endothelial cell kinase; DDR: Discoidin domain receptor tyrosine kinase; MKNK/MAP: Kinase-interacting serine/threonine protein kinase; FLT3: Fms-related tyrosine kinase 3, MEK: Mitogen-activated protein kinase; N.A.: Not applicable; MSS: Microsatellite stable; HDAC: Histone deacetylases; CLDN: Claudin.

different cellular drivers of tumor cells has been reported to be frequently beneficial over monotherapeutic approaches, due to their synergistic effect[92]. Moreover, combinatorial therapies can reduce the doses of the individual drugs and therefore prevent primary and secondary therapeutic resistance by down-regulating different metabolic factors[93,94]. Theoretically, a combination of TKIs that could doubly inhibit similar signaling pathways is thought to be ideal because it may prevent primary and secondary therapeutic resistance. For example, as noted above, dual HER2 inhibition is active in patients with CRC[23].

There are several ongoing studies including LJM716 + trastuzumab treatment for GC (NCT01602406) and tucatinib + trastuzumab treatment for CRC. The triple inhibition of *EGFR, BRAF* and *MEK* demonstrated synergistic activity for *BRAF* V600E-mutant CRC[21]. Another strategy under development consists of a crosstalk inhibition of another class of drug. In melanoma, many successful new combinations use mAbs that inhibit immune checkpoints such as CTLA-4 or PD-1 receptors and MEK and BRAF inhibitors[95]. These combined therapies have shown enhanced anti-metastatic effects and enhanced antitumor immunity in clinical trials[96]. In mCRC, a phase III multicenter open-label three-arm randomized study (COTEZO IMblaze370) is underway to investigate the efficacy of cobimetinib + atezolizumab and atezol-izumab monotherapy *vs* regorafenib.

The synergistic effects of immune checkpoint blockade and anti-angiogenesis approaches in cancer treatment are now attracting attention. Based on the interaction between tumor immunity and angiogenesis, it is speculated that anti-angiogenesis approaches might enhance the efficacy of immune checkpoint inhibitors. In the case of GI cancer, lenvatinib (a TKI that acts on a range of receptors including VEGFR, PDGFR, FGFR and RET) is currently being investigated in a global phase II clinical trial that will evaluate the efficacy of lenvatinib + pembrolizumab in patients with advanced GC or CRC who have failed two or three lines of therapy (NCT03797326). As mentioned above, the combination of TKIs is ideal from a theoretical point of view. However, the achievement of its clinical application is not easy in light of the toxicity; RTKIs have specific toxicities that are related to the primary target kinases or an off-target effect or are caused by a specific metabolite of the kinase inhibitor. This may be

Clinical Trials gov idntifier	Agents	Type of trial	Line of treatment	Phase	Results	Comments
EGFR						
NCT01862003	AZD-8931 (target EGFR/HER2/3)	Single group, open label	First	II	Completed	AZD-8931 + FOLFILI
NCT03457896	Neratinib (target EGFR/HER2/4)	Non-Randomized, open label	Third	II	Recruiting	Neratinib + trastuzumab or neratinib + cetuximab in KRAS/NRAS/BRAF/PI3CA wild-type mCRC
NCT04172597	Poziotinib (target EGFR/HER2/HER4)	Single group, open label	Second	II	Recruiting	Poziotinib in EGFR or HER2 activating mutations
MEK						
NCT03428126	Trametinib	Single group, open label	Third	II	Active, not recruiting	Trametinib + durvalumab in MSS mCRC
NCT03905148	PD-0325901	Non-Randomized, open label	Second	II	Recruiting	PD-0325901 + lifirafenib
NCT02788279(COTEZO IMblaze370)	Cobimetinib	Randomized, open label	Third	III	Completed	Cobimetinib + atezolizumab and atezolizumab Monotherapy *vs* regorafenib
Raf						
NCT00869570	Sorafenib (target VEGFR/PDGFR/B-Raf/c-Kit)	Single group, open label	Neoadjuvant	I/II	Completed29241084	Sorafenib + capecitabine + radiation therapy
NCT00826540(Alliance)	Sorafenib	Single group, open label	Third	II	Completed	Sorafenib + Bevacizumab as salvage therapy
NCT01715441	Sorafenib	Randomized, open-label	Second	II	Completed	Sorafenib + irinotecan in K-Ras wild type mCRC
NCT01086267	BMS-908662	Randomized, open label	Second	I/II	Completed	BMS-908662 + Cetuximab
NCT03668431	Debrafenib	Single group, open label	Third	II	Recruiting	Debrafenib + trametinib + PDR001 in BRAF V600E mCRC
HER2						
NCT03418558	Trastuzumab-emtansine	Single group, open label	Third	II	Recruiting	Trastuzumab-emtansine
NCT03384940(DESTINY-CRC01)	DS-8201a	Non-randomized, open-label	Third	II	Active, not recruting	DS-8201a in HER2 positive CRC
NCT03043313	Tucatinib	Randomized, open-label	Third	II	Recruiting	Tucatinib + trastuzumab in HER2 positive mCRC
VEGFR						
NCT00387387	Pazopanib (target VEGFR/PDGFR/FGFR/c-Kit)	Non-randomized, open-label	First	I	Completed	Pazopanib + FOLFOX6 or CapeOx
NCT03170960	Cabozantinib (target MET/RET/VEGFR-2)	Non-randomized, open-label	First	I/II	Recruiting	Cabozantinib + atezolizumab
NCT03797326	Lenvatinib (target VEGFR/PDGFR/FGFR/RET)	Single group, open label	Second	II	Active, not recruiting	Lenvatinib + pembrolizumab
NCT 02549937	Surufatinib (target VEGFR1-3 /FGFR1/CSF-1α)	Non-randomized, open-label	Second	I/II	Recruiting	Surufatinib
NCT03190616	Apatinib (target VEGFR-2/c-Kit/Src)	Single group, open label	Third	II	Completed	Apatinib
NCT03271255	Apatinib (target VEGFR-2/c-Kit/Src)	Randomized, open-label	Second	II	Recruiting	Apatinib *vs* bevacizumab with FOLFIRI

NCT00640471	Brivanib (VEGFR-2/FGFR)	Randomized, triple blind	Second	III	Completed	Cetuximab + brivanib in K-Ras wild type mCRC
Akt						
NCT01802320	MK-2206	Single group, open label	Second	II	Completed	MK-2206
mTOR						
NCT03439462	ABI-009 (Nab-rapamycin)	Non-randomized, open-label	First	I/II	Recruiting	ABI009 + mFOLFOX6 + bevacizumab
MET						
NCT02205398	INC280	Non-randomized, open-label	Third	I	Terminated	INC280 + cetuximab in c-MET positivemCRC
NCT02745769	Merestinib (MET/TEK/ROS1/DDR/MKNK)	Non-randomized, open-label	Third	I	Completed	Merestinib + ramucirumab
NCT002008383	Cabozantinib (target MET/RET/VEGFR-2)	Non-randomized, open-label	Second	I	Completed	Cabozantinib + panitumumab
NCT03542877	Cabozantinib (target MET/RET/VEGFR-2)	Non-randomized, open-label	Third	II	Active, not recruiting	Cabozantinib with refractory mCRC
NCT03592641	Savolitinib	Single group, open label	Second	II	Recruiting	Savolitinib in MET amplified CRC
WNT						
NCT02521844	ETC-1922159	Non-randomized, open-label	First	I	Active, not recruiting	ETC-1922159
NCT02278133	WNT974	Single group, open label	Second	I/II	Completed	WNT974 + LGX818 + cetuximab in BRAF V600-mutanta mCRC
NCT03883802(Neo Fox)	Foxy-5	Randomized, open-label	Neoadjuvant	II	Recruiting	Foxy-5 in Wnt-5a low CRC
STAT						
NCT02687009	Niclosamide (target STAT3)	Single group, open label	Neoadjuvant	I	Terminated	Niclosamide
NCT02983578	Danvatirsen (target STAT3)	Single group, open label	Second	II	Recruiting	Danvatirsen + durvalumab
NCT03522649	Napabucasin (target STAT3)	Randomized, open label	Second	III	Recruiting	napabucasin + FOLFIRI
NCT03647839(MODULATE)	Napabucasin (target STAT3)	Randomized, open label	Third	II	Recruiting	Nivolumab + napabucasin *vs* nivolumab + BNC105
Notch						
NCT03422679	CB-103	Single group, open label	Second	I/II	Recruiting	CB-103 in patients with solid tumors including CRC
TGF-β						
NCT04031872	LY3200882	Single group, open label	Third	I/II	Yet not recuriuting	LY3200882 + Capecitabine
PARP						
NCT04166435	Olaparib	Single group, rnonrandomized, open-label	Third	II	active	Olaparib + temozolomide in patients with MGMT promoter hypermathylated CRC
BTK						
NCT03332498	Ibrutinib	Single group, open label	Second	I/II	active	Ibrutinib + Pembrolizumab

ALK						
NCT03792568	Crizotinib (target ALK/ROS1/MET)	Single group, open label	First	N.A.	Recruting	mCRC with ALK mutation
CDK						
NCT03981614	Palbociclib	Randomized, open-label	Third	II	Recruting	Palbociclib + binimetinib in patients with KRAS and NRAS mutation

CRC: Colorectal cancer; mCRC: Metastatic colorectal cancer; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; also known as PKB; mTOR: Mammalian target of rapamycin; MEK: Mitogen-activated protein kinase; EGFR: Epidermal growth factor receptor; HER2/3/4: Human epidermal growth factor 2/3/4; MAPK: Mitogenactivated protein kinase; STAT3: Signal transducer and activator of transcription 3; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; EGFR: Epidermal growth factor receptor; PDGFR: Platelet-derived growth factor receptor; FGFR: Fibroblast growth factor receptor; HGF: Hepatocyte growth factor; MET: Mesenchymal-epithelial transition factor; TEK: Tunica interna endothelial cell kinase; DDR: Discoidin domain receptor tyrosine kinase; MKNK/MAP: Kinase-interacting serine/Threonine protein kinase; FLT3: Fms-related tyrosine kinase 3; N.A.: Not applicable; MSS: Microsatellite stable; ALK: Anaplastic lymphoma kinase.

prevented by a better determination of toxicity profiles of each drug before they are used in combination, in order to select the most specific TKIs[97]. Investigations of the synergistic properties of TKIs with other agents (such as a monoclonal antibody targeting PD-1) will likely contribute to the advancement of effective therapeutics with low toxicity, including tolerance for drug combinations, toward the achievement of better cancer therapy.

Collectively, the findings presented above are encouraging. Patients with GI cancer are living longer with the best treatment strategies, several of which could eventually be quite beneficial. Selected mutant gene profiles are eligible for target therapy. GI cancer is a heterogeneous disease with many diverse sets of alterations in tumor suppressor genes and oncogenes. The profiling of the entire spectrum of genetic changes based on advances in next-generation sequencing and whole-genome sequencing will provide a foundation that can be used to stratify patients in distinct molecular subclasses that suggest prognostic relevance and possible treatment advantages. However, many questions remain to be answered such as treatment scheduling, optimized dosages, and combinations with other agents. The identification of potential biomarkers that can predict the patients' clinical responses and the toxicities of these targeted therapies is challenging. Adverse events which may be caused by combined targeted agents and acquired resistance are additional research focuses for targeted drug advancement. Feasibility studies are necessary to develop well-designed randomized clinical trials that can evaluate the appropriate biomarkers, synergic effects, and degrees of toxicity.

CONCLUSION

Together, the above-described findings indicate that clinical trials designed based on patients' molecular profiles will lead to more personalized precision treatments for patients and better outcomes. Improved algorithms for the selection of immune checkpoint inhibitors or combination therapy should be established. These developments could facilitate precision medicine for patients with gastric cancer in the near future.
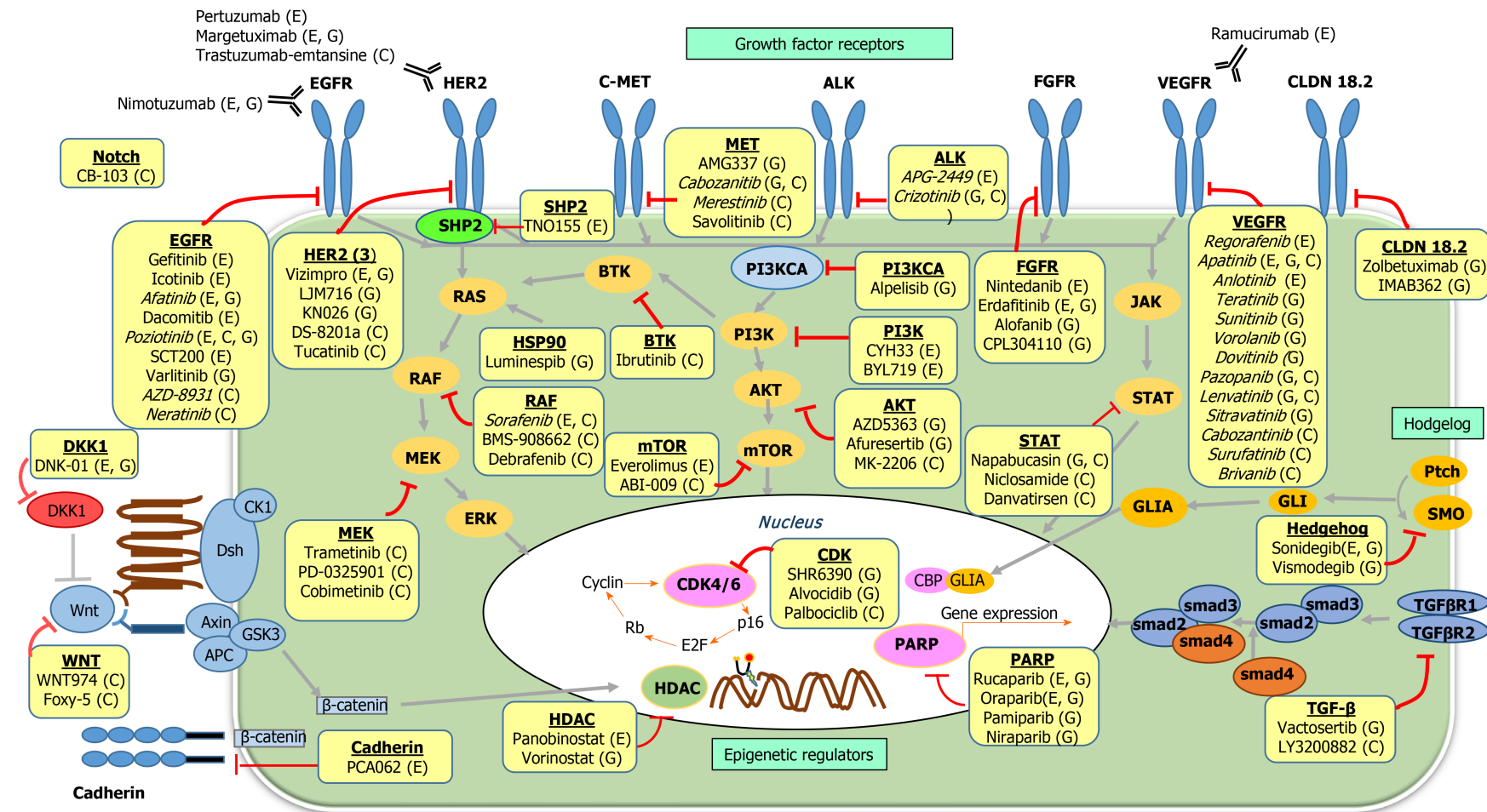
Figure 1 Ongoing gastrointestinal cancer clinical trials. A schematic representation of the therapies targeting the key oncogenic signaling pathways in gastrointestinal cancer. These therapies include agents that specifically inhibit components and antibodies of the growth factor receptors such as Epidermal growth factor receptor, RAS/BRAF/mitogen-activated protein kinase, Human epidermal growth factor 2, mesenchymal-epithelial transition, SHP2, Bruton tyrosine kinase, anaplastic lymphoma kinase, fibroblast growth factor recepto, janus kinase - signal transducer and activator of transcription, vascular endothelial growth factor receptor, phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin, and tumor growth factor-β pathway; epigenetic regulators such as poly (ADP-ribose) polymerases, cyclin-dependent kinase, and histone deacetylases, and other family members such as WNT, dickkopf-1, hedgehog, CLDN 18.2, and cadherin. EGFR: Epidermal growth factor receptor; HER2/3/4: Human epidermal growth factor 2/3/4; MET: Mesenchymal-epithelial transition; ALK: Anaplastic lymphoma kinase; FGFR: Fbroblast growth factor receptor; VEGFR: Vascular endothelial growth factor receptor; MEK: Mitogen-activated protein kinase; DKK1: Dickkopf-1; ERK: Extracellular signal-regulated kinase; CKD4/6: Cyclin-dependent kinase 4/6; HDAC: Histone deacetylases; PARP: Poly (ADP-ribose) polymerases; mTOR: Mammalian target of rapamycin ; AKT: Protein kinase B; PI3K Phosphoinositide 3-kinase; STAT: Signal transducer and activator of transcription; JAK Janus kinase; BKT: Bruton tyrosine kinase; TGF-β: Tumor growth factor-β; CLDN: Claudin.

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