Gastrointestinal cancers: new therapies bring hope after much frustration

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Collectively representing numerous distinct cancers, gastrointestinal (GI) malignancies are a major health burden worldwide. Despite the development of numerous targeted therapies that have advanced the treatment of several GI cancer types, current treatment options have afforded only modest improvements in survival. Here, we discuss how valuable insights gained from both successes and failures are fostering hope for new therapies.

The challenge of GI cancers

Cancers that affect the GI tract include some of the most prevalent and lethal types of cancer, including gastric, colorectal, pancreatic, and hepatocellular cancers (Figure). Collectively, GI malignancies account for more than a quarter of all cancer diagnoses worldwide, and more deaths annually than breast and lung cancers combined.[1] If they are identified at an early stage they can often be effectively treated, but early diagnosis of these cancers can be extremely challenging and patients are often asymptomatic until more advanced stages of disease when significantly harder to treat.

The era of molecularly targeted therapies offered significant potential to improve treatment options for GI cancer. Gastrointestinal stromal tumors (GIST) were the first tumor types for which targeted therapy was approved by the US Food and Drug Administration (FDA); imatinib has since been joined by multiple other targeted drugs, approved for the treatment of various different GI cancers.

Despite these advances, only modest improvements in survival have been achieved. In many instances, GI cancers are not driven by a single common genetic alteration, meaning that targeted therapies are only effective in small subsets of patients, in other cases a lack of validated biomarkers to guide patient selection have limited their potential. The development of resistance has also posed a significant limitation. New therapies and a better understanding of the molecular underpinnings of GI cancers are highly sought after and the focus of ongoing frontline research.

Hit and miss with targeted therapies

Among the best studied targets for the most prevalent forms of GI cancer are members of the human epidermal growth factor receptor (HER) family, a group of 4 proteins that play vital roles in the activation of intracellular signaling pathways. Dysregulation of these pathways drives many of the hallmarks of cancer.

HER1/EGFR is overexpressed in a quarter to two-thirds of gastric cancers[2-4] and up to 85% of colorectal cancers (CRC)[5-7] and has been linked to increased aggressiveness and poorer prognosis. HER2, most renowned for its role in breast cancer, is also overexpressed in a significant number of patients with gastric cancer (estimates suggest between 7 and 34%, depending on histologic subtype and location[8-12]), though the relationship between HER2 status and prognosis is more controversial.[9] HER2 and EGFR represent promising therapeutic targets and have met with some success.

The HER2-targeting monoclonal antibody (mAb) trastuzumab was evaluated as first-line therapy in HER2-positive gastric cancer and ultimately approved by the FDA in 2010 for this indication, following the pivotal phase 3 TOGA trial, in which trastuzumab was added to cisplatin and fluoropyrimidine, a combination that has subsequently become standard of care.[8]

Trastuzumab continues to be evaluated in gastric cancer, including the phase 3 HELOISE trial in combination with cisplatin and capecitabine. Meanwhile, a number of other HER2-targeting agents are also being studied. There are several ongoing clinical trials of both pertuzumab, also a HER2-targeting mAb, and the antibody-drug conjugate (ADC) ado-trastuzumab emtansine, a HER2-targeting mAb conjugated to a cytotoxic agent, in gastric cancer patients (Table 1). Despite their success, HER2-targeting agents benefit only a small population of patients with gastric cancer, leaving a

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TABLE 1 Ongoing phase 3 trials in GI malignancies

Study drug	Mechanism of action	Manufacturer	Trial description (Trial name and/or clinicaltrials.gov identifier)
Trastuzumab(Herceptin)	HER2-targeted mAb	Genentech	■ In combination with cisplatin and capecitabine in patients with HER2-positive gastric or GEJ cancer (HELOISE; NCT01450696)
Pertuzumab(Perjeta)	HER2-targeted mAb	Roche	■ In combination with trastuzumab and chemotherapy in patients with advanced HER2-positive, metastatic gastric, or GEJ cancer (JACOB; NCT01774786)
Lapatinib (Tykerb)	HER2 inhibitor	GlaxoSmithKline	■ In combination with chemotherapy in patients with previously untreated, surgically resectable gastric or GEJ cancer (NCT00450203)
Ado-trastuzumab emtansine (Kadcyla)	HER2-targeted antibody-drug conjugate	Roche	■ Vs taxane chemotherapy in advanced gastric or GEJ cancer (GATSBY; NCT01641939)
Regorafenib (Stivarga)	Multikinase inhibitor	Bayer Healthcare	■ Vs placebo in patients with advanced HCC who have progressed on sorafenib treatment (RESORCE; NCT01774344) ■ In patients with metastatic CRC who have failed standard therapy (CONSIGN; NCT01538680)
Ramucirumab (Cyramza)	VEGFR2-targeted mAb	Eli Lilly	■ In combination with capecitabine and cisplatin in gastric or GEJ cancer (RAINFALL; NCT02314117) ■ Vs placebo in patients with HCC and elevated baseline AFP (REACH-2; NCT02435433)
Onartuzumab (MetMab)	MET-targeted mAb	Roche	■ In combination with mFOLFOX6 in patients with metastatic, HER2-negative, MET-positive GEJ cancer (MetGastric; NCT01662869)[a]
Nimotuzumab	EGFR-targeted mAb	YM Biosciences	■ In combination with irinotecan in the second-line setting in patients with gastric or GEJ cancer (ENRICH; NCT01813253) ■ In combination with CRT in locoregional esophageal squamous-cell carcinoma (NCT02409186) ■ In combination with gemcitabine in KRAS wildtype locally advanced or metastatic pancreatic cancer (NCT02395016)

AFP, alpha-fetoprotein; CRC, colorectal cancer; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; GEJ, gastroesophageal junction; GI, gastrointestinal; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; VEGFR2, vascular endothelial growth factor receptor 2

[a]Trial is ongoing, but not actively recruiting participants.

significant need for novel therapies to address those who are HER2-negative.

EGFR-targeting drugs have also been evaluated in a range of GI cancers. The EGFR-targeting small molecule tyrosine kinase inhibitor erlotinib is approved in combination with gemcitabine in patients with advanced pancreatic cancer,[13] while the mAbs panitumumab and cetuximab are both approved as monotherapy for second-line treatment in patients with metastatic CRC and more recently in combination with chemotherapy as front-line treatment.[14,15] Though initially hailed as an extremely promising advance for the treatment of GI malignancies, enthusiasm has been tempered over time as survival gains proved more modest than expected. The use of EGFR-targeting agents has been complicated by the fact that EGFR expression doesn't seem to correlate with clinical benefit, at least in CRC, and besides the identification of mutations in *KRAS* as an indication of probable failure, it has proven difficult to find biomarkers to identify patients that will most likely benefit from these drugs.[16]

EGFR-targeted agents have been less successful in the treatment of gastric cancer; none of the therapies tested to date have demonstrated a survival advantage and in some cases have proven potentially detrimental.[17] One of the few EGFR-targeting agents in ongoing clinical development in gastric cancer is nimotuzumab.

Another attractive tyrosine kinase target is MET or hepatocyte growth factor receptor (HGFR). The focus has been on gastric cancers in which MET overexpression is observed in 50%-60% of cases and is correlated with poor prognosis.[18] Despite significant promise in early clinical trials, their development has been plagued by a string of phase 3 failures. Most recently, Amgen halted development of its frontrunner rilotumumab after a planned safety review of the RILOMET-1 study in which rilotumumab was combined with epirubicin, cisplatin, and capecitabine, showed an increase in the number of deaths and probable attainment of the protocol-defined futility criteria.[19]

Roche's onartuzumab was also pursued in phase 3 clini-

TABLE 2 Key phase 3 trials of ramucirumab in GI malignancies

Trial Name (clinicaltrials.gov identifier)	Description (n)	Outcomes
REGARD (NCT00917384)	Ramucirumab vs placebo; metastatic gastric or GEJ adenocarcinoma; as second-line treatment following disease progression on platinum or fluoropyrimidine-containing combination therapy (355)	■ Basis of FDA approval for this indication in 2014 ■ Improved OS in ramucirumab arm (5.2 mo vs 3.8 mo for placebo; HR, 0.776; *P* = .047) ■ Survival benefit remained unchanged after multivariable adjustment for other prognostic factors ■ Higher rates of hypertension in the ramucirumab arm Similar rates between arms for other AEs[34]
RAINBOW (NCT01170663)	Ramucirumab + paclitaxel; metastatic gastric adenocarcinoma; second-line treatment after failure or progression after platinum or fluoropyrimidine therapy (665)	■ Basis of FDA approval for this indication in 2014 ■ Improved OS in ramucirumab + paclitaxel arm (9.6 mo vs 7.4 mo for fluoropyrimidine therapy; HR, 0.807; *P* = .017) ■ Manageable toxicity; most common ≥ grade 3 AEs included neutropenia, hypertension, anemia, and abdominal pain[35]
RAISE (NCT01183780)	Ramucirumab + FOLFIRI; metastatic CRC; as second-line treatment in patients whose disease progressed during or after therapy with bevacizumab, oxaliplatin, or fluoropyrimidine (1,072)	■ Basis of FDA approval for this indication in 2015 ■ Improved OS in ramucirumab + FOLFIRI arm (13.3 mo vs 11.7 mo for placebo; HR, 0.844; *P* = .0219) ■ Manageable toxicity – most common ≥ grade 3 AEs were neutropenia, hypertension, diarrhea, and fatigue[36]
REACH (NCT01140347)	Ramucirumab vs placebo; advanced HCC; as second-line treatment after failure of sorafenib (565)	■ No improvement in OS in overall population[37] ■ Prespecified subgroup analysis of 250 patients with baseline AFP levels ≥400 ng/mL demonstrated improved OS in ramucirumab-treated patients (7.8 mo vs 4.2 mo for placebo; HR, 0.67; *P* = .0059)[38]

AEs, adverse events; AFP, alpha-fetoprotein; CRC, colorectal carcinoma; FDA, United States Food and Drug Administration; FOLFIRI, leucovorin, fluorouracil (5-FU), and irinotecan; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival

cal trials, however a recent report on the MetGastric trial from the 2015 American Society of Clinical Oncology (ASCO) GI Cancers Symposium in San Francisco indicated that the addition of onartuzumab to mFOLFOX (modified leucovorin, fluorouracil [5-FU], oxaliplatin) did not improve progression-free survival (PFS) in the overall study population or in patients with MET-positive disease and produced more adverse events.[20]

One possible avenue of redemption for MET inhibitors in gastric cancer is the newer drug AMG-337. The results of 2 phase 1 dose-escalation studies were presented at the symposium, one involving daily administration of 25-400 mg and the other twice-daily dosing of 100-250 mg until disease progression. In a subgroup analysis of patients with advanced gastroesophageal junction (GEJ), gastric, and gastroesophageal cancer with MET overexpression, there were 8 objective responses, with ≥50% tumor shrinkage in 6 patients, including 1 in whom the tumor volume reduced by more than 90% after 33 weeks with response ongoing at 105 weeks of treatment.[21] Evaluation of AMG-337 is ongoing in a dose-expansion study that is limited to patients with MET-positive tumors.

New promise for anti-angiogenic strategy

Multiple tyrosine kinase pathways are often dysregulated in GI cancers, so a number of drugs that are multitargeted have been developed. The prime example is imatinib, one of the earliest targeted therapies to hit the market. Originally developed for the treatment of myeloid cancers that express the *BCR-ABL* oncogene, imatinib is a multikinase inhibitor that also targets stem-cell factor receptor (c-KIT) and platelet-derived growth factor receptor (PDGFR) A and B. More than 80% of GISTs express activated forms of c-KIT and those that don't are likely to harbor mutations in the *PDGFRA* gene, therefore imatinib and other drugs hitting these 2 targets have significant potential in the treatment of this type of GI malignancy.[22-24]

Imatinib was approved for the treatment of c-KIT-positive advanced or metastatic GIST in 2002 and has subsequently also been approved for adjuvant therapy in patients who have undergone surgical resection.[25] Resistance to imatinib is a common issue and a number of other multikinase inhibitors have been developed in an effort to treat patients when they inevitably progress, including sunitinib, which was approved for the treatment of c-KIT-positive GIST after failure of imatinib.

Sunitinib is also indicated for the treatment of pancreatic neuroendocrine tumors,[26] and differs from imatinib in that it also includes the vascular endothelial growth factor receptors (VEGFRs) among its targets. The development of multikinase inhibitors targeting VEGFRs were among the earliest attempts to harness anti-angiogenic

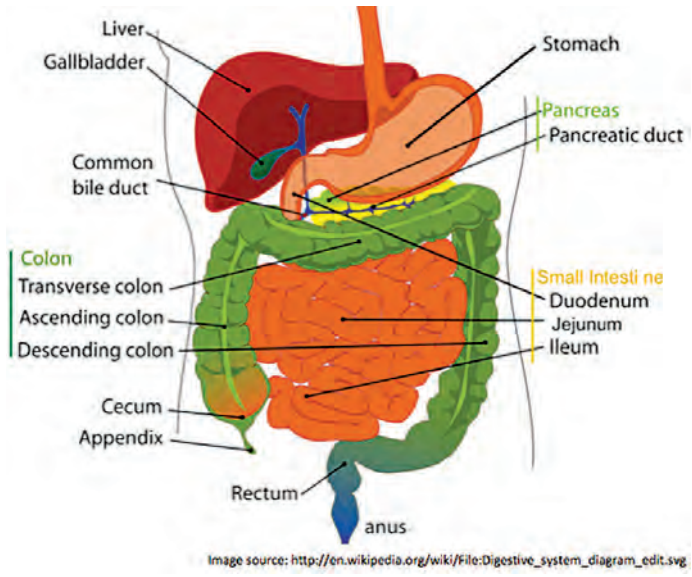

FIGURE 1 Gastrointestinal cancers are a group of at least 10 highly aggressive distinct malignancies that include cancers of the esophagus, stomach, rectum, colon, intestine, biliary tract, and pancreas. They are responsible for more than a quarter of worldwide annual cancer diagnoses. Reproduced with permission; http://en.wikipedia.org/wiki/File:Digestive_system_diagram_edit.svg.

therapy for the treatment of cancer. Angiogenesis is the process through which new blood vessels form from existing ones and hijacking the cellular pathways that control it, central among them the VEGFR pathway, is one of the hallmarks of cancer. It has long been suspected that targeting the VEGFR and other angiogenic pathways, could be a promising therapeutic avenue.[27]

More recently, a novel multikinase inhibitor, famitinib, has shown promise for the treatment of advanced CRC. In a phase 2 trial among patients who previously failed at least 2 lines of standard therapy, famitinib, which targets VEGFR, c-KIT, and PDGFR, improved PFS over placebo, although there was no difference in OS.[28]

As anti-angiogenic therapy evolved, drugs targeting various aspects of the VEGFR pathway have been developed. Most renowned is the mAb bevacizumab that targets the VEGF ligand, which has gained regulatory approval for the treatment of several solid tumors, including as first- and second-line treatment of metastatic CRC in combination with chemotherapy.[29] Bevacizumab has also been evaluated in gastric cancer, but the phase 3 AVAGAST and AVATAR trials failed to show improvements in OS, though there were significant improvements in several secondary endpoints in the AVAGAST trial, including PFS and overall response rate (ORR).[30,31]

The promise of anti-angiogenic therapy for GI cancer has been reinvigorated in recent years with the development of several agents that uniquely target VEGFR. Although bevacizumab remains the only anti-angiogenic agent approved in the first-line setting for CRC, 2 drugs – ziv-aflibercept and regorafenib – were recently approved as second-line treatment. Ziv-aflibercept is a recombinant fusion protein composed of the VEGF-binding portions of VEGFR1 and 2 fused to the Fc portion of human immunoglobulinG1. It acts as a decoy receptor that binds to VEGF with higher affinity than the naturally occurring receptors, effectively becoming a VEGF "trap" and preventing activation of the receptor.[29,32]

Regorafenib is a dual tyrosine kinase inhibitor that targets VEGFR and a second growth factor, the angiopoietin receptor (TIE-2), which is also required for angiogenesis. Regorafenib was approved for the treatment of metastatic CRC in 2012 and the indication was expanded to include advanced GIST that is refractory to both imatinib and sunitinib the following year. Regorafenib is the only anti-angiogenic drug to have demonstrated efficacy as monotherapy in CRC. The results of the phase 3 CONCUR study of regorafenib were recently presented at the 2015 European Society for Molecular Oncology (ESMO) World Congress on GI Cancer. A large expanded access program, this study confirmed the efficacy of regorafenib in previously treated, metastatic CRC, in a population of patients that more closely resembles clinical practice. Regorafenib is also gaining recognition as a potential third-line treatment option for metastatic CRC.[29,32,33]

Most promising among the new anti-angiogenic agents is ramucirumab, a mAb that targets VEGFR2. It has become the first FDA-approved anti-angiogenic therapy for gastric cancer, gaining approval as a single agent in April 2014 and in combination with paclitaxel later that year, on the basis of the phase 3 REGARD and RAINBOW trials (Table 2).[34,35] Exactly a year after the first approval for gastric cancer, ramucirumab received regulatory approval for the treatment of metastatic CRC in combination with FOLFIRI (leucovorin, fluorouracil [5-FU], and irinotecan) chemotherapy, based on the RAISE trial.[36]

Ramucirumab is also in late-stage clinical trials in HCC. Although the phase 3 REACH trial was unsuccessful in meeting its primary endpoint, it identified a potential predictive marker for ramucirumab efficacy – baseline alpha-fetoprotein (AFP) levels.[37,38] The phase 3 REACH-2 trial is ongoing, evaluating ramucirumab specifically in patients with elevated baseline AFP levels (NCT02435433).

Expanding reach of immune therapies

GI malignancies have traditionally been considered poorly immunogenic and thus not candidates for immunotherapies that aim to engage the antitumor immune response to fight cancer. The discovery of immune checkpoints, like programmed cell death-1 (PD-1) and its ligands PD-L1 and PD-L2, which regulate T-cell inhibitory pathways that can be hijacked by tumor cells to dampen the immune

TABLE 3 Clinical evaluation of immune checkpoint inhibitors in GI malignancies

Drug	Manufacturer	Trial description (trial name and/or clinicaltrials.gov identifier)
Pembrolizumab (Keytruda)	Merck	**Phase 3** ■ First-line mono- or combination therapy in advanced gastric or GEJ adenocarcinoma (KEYNOTE-062; NCT02494583) ■ Vs paclitaxel in advanced gastric or GEJ adenocarcinoma that progressed after therapy with platinum and fluoropyrimidine (KEYNOTE-061; NCT02370498) **Phase 2** ■ + RT or ablation in metastatic CRC (NCT02437071) ■ + chemotherapy in advanced CRC (NCT03475672) **Phase 1/2** In resectable/borderline resectable pancreatic cancer (NCT02305186)
Nivolumab (Opdivo)	Bristol-Myers Squibb	**Phase 3** ■ In unresectable advanced/recurrent gastric cancer (NCT02267343) **Phase 1/2** ■ As monotherapy or in combination with ipilimumab in recurrent/metastatic CRC (CheckMate142; NCT02060188) **Phase 1** ■ In advanced liver cancer (NCT01658878)
MEDI4736	Pfizer	**Phase 1/2** ■ + tremelimumab or as monotherapy in gastric or GEJ adenocarcinoma (NCT02340975) ■ + tremelimumab or as monotherapy in unresectable HCC (NCT02519348)

CRC, colorectal cancer; GEJ, gastroesophageal junction; GI; gastrointestinal; HCC, hepatocellular carcinoma; RT, radiation therapy

response against them, has emerged as an extremely promising anticancer strategy, even in the treatment of solid tumors. Immune checkpoint blockade is now being actively investigated in the management of GI malignancies also (Table 3).

Preliminary data from KEYNOTE-012, a phase 1 study of pembrolizumab, a PD-1-targeting mAb, were presented at the ESMO meeting in 2014. Further results were presented at the 2015 ASCO meeting. In a cohort of patients with previously treated, metastatic gastric cancer the ORR was 30%, disease control rate was 49%, and >40% of patients had a reduction in tumor burden. The median duration of response (DoR) was 24 weeks and 6-month PFS and OS were 24% and 69%, respectively. The level of PD-L1 expression was found to correlate with ORR. An interim analysis of the KEYNOTE-028 study was also presented and a similar ORR was observed among patients with squamous cell carcinoma or adenocarcinoma of the esophagus or GEJ, with a median DoR of 40 weeks. The drug was well-tolerated in both studies, with few grade 3 or higher adverse events.[39-42]

Pembrolizumab is also being evaluated in patients with previously treated, metastatic CRC. In a phase 2 study presented at the 2015 GI cancers symposium, pembrolizumab met the co-primary endpoints of immune-related ORR and PFS in mismatch repair (MMR)-deficient CRC, but not in MMR-proficient CRC, suggesting MMR status may predict clinical benefit from immune checkpoint inhibitors in advanced CRC.[43]

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