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Review Article

Targeted therapy in gastrointestinal malignancies

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Abstract

Increased understanding of cancer pathogenesis has identified several pathways that serve as potential targets for novel targeted agents in development. The selection of targeted cancer therapy based on biomarkers has instigated a new era of personalized medicine and changed the way we practice oncology. Many targeted agents are approved for treatment of gastrointestinal malignancies most targeting tumor angiogenesis, and many more are in different phases of development. Here we briefly summarize nine different targeted agents that are approved currently in the U.S. and several other agents currently being studied in various gastrointestinal cancers.

Keywords: Gastrointestinal cancers, monoclonal antibodies, targeted drugs, tyrosine kinase inhibitors

INTRODUCTION

With improved understanding of cancer genomics, proteomics and molecular events associated with cell growth, proliferation, angiogenesis, apoptosis and signal transduction, along with biotechnological advancements such as immunohistochemical and hybridization techniques, our knowledge of cancer pathogenesis has increased exponentially. Though incomplete, we have identified several key molecular events involved in carcinogenesis and targeting them offers survival benefit in several cancers such as breast cancer, colon cancer and leukemia. The concept of targeted therapy was born more than a century ago but its practical application in cancer therapy took several decades. Today we have developed several agents designed to target specific molecule such as cell receptors, enzymes various cytokines and signaling pathways. The National Cancer Institute defines targeted therapy as "a type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells".[1] Over the last 2 decades, the development of drugs targeted at specific molecular pathway/receptor has led us one step closer to individualized cancer therapy. Many targeted therapies have been approved by the United States Food and Drug Administration (FDA) for clinical use in humans while as many are in various phases of development as well. For the scope of this review article, we will discuss only the relevant trials in gastrointestinal cancers with regard to each targeted agent. Figure 1 shows the conceptual diagram of several molecular targets and signaling pathways involved in carcinogenesis and Table 1 describes targeted agents studied in gastrointestinal (GI) cancers and their FDA approval status.

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MONOCLONAL ANTIBODIES

Cetuximab (Erbitux®)

Cetuximab, a partially humanized murine IgG1 monoclonal antibody, has been approved in combination with the chemotherapy regimen 5-fluorouracil (5-FU), leucovorin

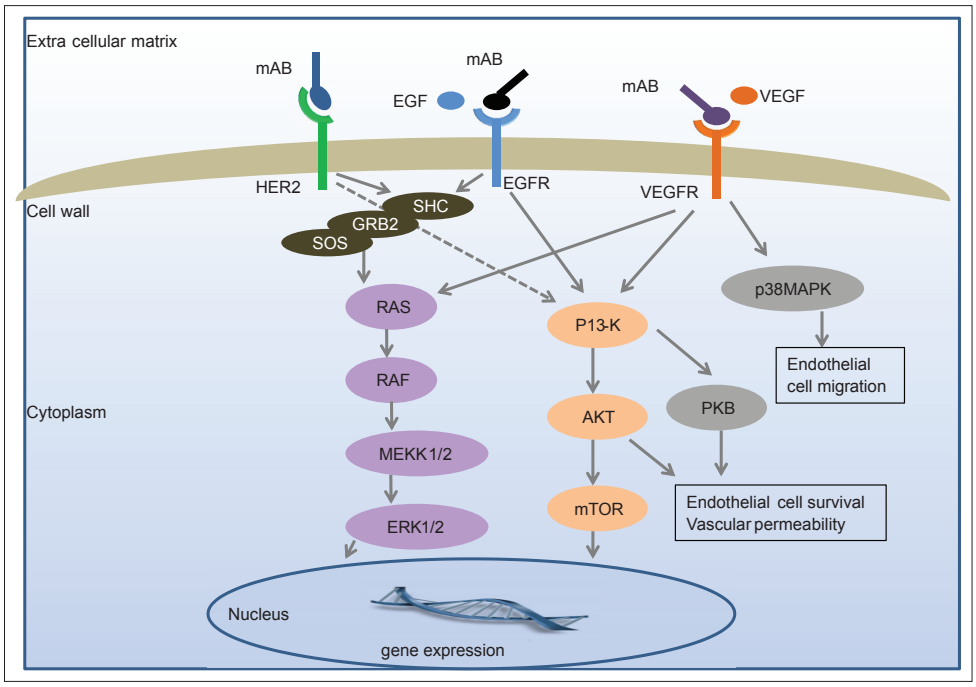

Figure 1: Molecular targets and signaling pathways of various targeted therapies used in the treatment of gastrointestinal cancers

and irinotecan (FOLFIRI) as the first line treatment for *KRAS* mutation negative and anti-epidermal growth factor receptor (EGFR) expressing metastatic colorectal cancer based on a randomized, multicenter, open-label, phase III trial (CRYSTAL trial) where each group had 599 patients (cetuximab + FOLFIRI vs. FOLFIRI alone).[2] The addition of cetuximab to FOLFIRI reduced the risk of progression by 15%, increased the median progression free survival (PFS) from 8 to 8.9 months (mo) (hazard ratio [HR]: 0.85, 95% confidence interval [CI]: 0.72-0.99, $P = 0.048$), increased the median overall survival (OS) from 18.6 to 19.9 mo (HR: 0.93, 95% CI: 0.81-1.07, $P = 0.31$). The adjusted odds ratio for a tumor response to cetuximab group was 1.40 (95% CI: 1.12-1.77, $P = 0.004$). Median OS in cetuximab + FOLFIRI and FOLFIRI groups were respectively 24.9 and 21.0 mo in the wild type-KRAS population as well as 17.5 and 17.7 mo, in the mutant-KRAS population.

Cetuximab has been studied in the gastroesophageal cancer with limited success. Cetuximab in combination with chemoradiation containing different regimen has shown up to 40% objective response rate in locally advanced disease and up to 16.6 mo of OS in metastatic disease.[3,4] The Southwest Oncology Group directed (S0205) phase III trial evaluated the role of cetuximab in metastatic or locally advanced unresectable pancreatic adenocarcinoma, where 371 patients were treated with gemcitabine alone versus 372 patients with gemcitabine + cetuximab.[5] The addition of cetuximab to gemcitabine failed to improve median OS and PFS significantly (one-sided $P = 0.19$ for OS and $P = 0.18$ for PFS). Moreover, EGFR expression had no impact on median survival (HR: 0.98, 95% CI: 0.83-1.17, $P = 0.42$). The efficacy of gemcitabine + oxaliplatin + cetuximab was assessed in 45 unresectable or advanced hepatocellular carcinoma (HCC) patients in a multicenter phase II trial. Median PFS of 4.7 mo (95% CI: 2.6-9.5) and median OS of 9.5 mo (95% CI: 7.8-11) were observed. The 1-year survival rate was 40%.[6] An interim analysis of the BINGO trial, an open label phase II study comparing gemcitabine + oxaliplatin with or without cetuximab was presented at the 2009 American Society of Clinical Oncology meeting. At 4 mo, PFS rate was 61% (95% CI: 36-83) in cetuximab group compared to 44% (95% CI: 20-70) in the other group.[7]

Panitumumab (Vectibix®)

Panitumumab is the first fully human IgG2 kappa monoclonal antibody directed to EGFR. Panitumumab is approved for the treatment of EGFR expressing, metastatic colorectal cancer with disease progression on or following fluoropyrimidine, oxaliplatin and irinotecan containing chemotherapy regimen. The approval was based on an open label phase III trial where 231 patients were assigned to panitumumab + best supportive care and 232 patients received only best supportive care. Panitumumab significantly prolonged median PFS (8 weeks vs. 7.3 week, HR: 0.54; 95% CI: 0.44-0.66, $P < 0.0001$).[8] Panitumumab lacks activity in mutant *KRAS* expressing metastatic colorectal cancer.[9] *Post hoc* analysis of the original phase III trial found other clinically important findings as well such as (1) median OS of 6.4 mo in all *KRAS*-evaluable patients randomized to panitumumab versus 4.4 mo in patients with mutant-*KRAS* tumors randomized to

supportive care (HR: 0.76, 95% CI: 0.60-0.98); (2) median OS of 8.1 mo in wild-*KRAS* tumors randomized to panitumumab versus 4.4 mo in patients with mutant-*KRAS* tumors randomized to supportive care (HR: 0.56, 95% CI: 0.49-0.87); (3) median OS of 7.9 mo in wild-*KRAS* group versus 4.7 mo in all patients with mutant-*KRAS* tumors, regardless of treatment group assignment.[10] Panitumumab as a first line agent in metastatic colorectal cancer was evaluated in a phase III randomized

Table 1: Various targeted agents, their molecular targets, FDA approval status and common toxicities

Targeted agents	Mechanism of action	FDA approval status in GI cancers	Common grade 3-4 adverse reactions
Monoclonal antibodies			
Cetuximab	EGFR inhibitor	Yes-colorectal cancer	Rash, fatigue, headache, infection, dyspnea, hypomagnesemia, neuropathy, nausea, abdominal pain
Panitumumab	EGFR inhibitor	Yes-colorectal cancer	Skin toxicity, fatigue, edema, abdominal pain, nausea, diarrhea, hypomagnesemia, ocular toxicities
Trastuzumab	HER 2 inhibitor	Yes-gastric cancer, gastroesophageal cancer	Cardiac dysfunction, cough, nausea, diarrhea, vomiting, headache, nasopharyngitis, pyrexia, rash
Bevacizumab	VEGF inhibitor	Yes-colorectal cancer	Hypertension, headache, fatigue, infection, proteinuria, alopecia, anorexia, vomiting, hemorrhage, upper respiratory infection
Ziv-aflibercept	Binds VEGF-A, VEGF-B, PIGF	Yes-colorectal cancer	Fatigue, abnormal LFT, neutropenia, leucopenia, thrombocytopenia, diarrhea, anorexia, hypertension, proteinuria
Nimotuzumab	EGFR inhibitor	No	
Conatumumab	Activates death receptor 5	No	
Ganitumab	IGF 1 inhibitor	No	
Tyrosine Kinase inhibitors			
Erlotinib	EGFR associated TK inhibitor	Yes-pancreatic cancer	Rash, fatigue, diarrhea, nausea, anorexia, vomiting, cough, dyspnea, chest pain
Sorafenib	Multi kinase inhibitor	Yes-hepatocellular cancer	Leucopenia, rash, hand-foot syndrome, hypertension, fatigue, diarrhea, hypoalbuminemia, hypophosphatemia
Imatinib	PDGF and SCF TK inhibitor	Yes-GIST	Fatigue, cramping, edema, anemia, neutropenia, fever, abnormal, cough, nasopharyngitis, LFT, periorbital edema, rash, hyponatremia
Sunitinib	Multi kinase inhibitor	Yes-GIST, PNET	Rash, hand-foot syndrome, hair and skin discoloration, pancytopenia, hypertension, decrease ejection fraction, myalgia, arthralgia, nausea, anorexia, diarrhea, stomatitis, electrolytes abnormality, renal failure, abnormal LFT
Regorafenib	Multi kinase inhibitor	Yes-colorectal cancer, GIST	Electrolytes disturbance, pancytopenia, anorexia, diarrhea, hypertension, infection, abnormal LFT, fatigue, proteinuria, hand-foot syndrome, rash
Gefitinib	EGFR associated TK inhibitor	No	Rash, acne, diarrhea, nausea
Cediranib	VEGF associated TK inhibitor	No	
Lapatinib	EGFR and HER 2 associated TK inhibitor	No	Fatigue, hand-foot syndrome, diarrhea, fatigue, pancytopenia, abnormal LFT, nausea
Vandetanib	Multi kinase inhibitor	No	Corneal abnormality, rash, hypertension, QT prolongation, leucopenia, nausea, diarrhea, hypocalcemia, headache
Linifanib	Multi kinase inhibitor	No	
Vatalanib	VEGF 1 and 2 associated TK inhibitor	No	
Brivanib	VEGFR 2 and FGFR 1 and 2 associated TK inhibitor	No	
Nilotinib	c-KIT, PDGF associated TK inhibitor	No	Rash, headache, fatigue, neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, abdominal pain, hypertension, edema, arthralgia, musculoskeletal pain, night sweat, cough
Non-TK target inhibitor			
Everolimus	mTOR, VEGF, HIF 1 inhibitor	Yes-PNET	Fatigue, headache, seizure, abnormal LFT, skin toxicity, hypertension, edema, electrolytes and lipid abnormalities, pancytopenia, arthralgia, weakness
Selumetinib	MAPK 1 and 2 inhibitor	No	
Trametinib	MEK 1 and 2 inhibitor	No	
Yttrium clivatuzumab tetraxetan		No	

FDA: Food and drug administration, GI: Gastrointestinal; EGFR: Epidermal growth factor receptor; HER 2: Human epidermal growth factor receptor 2; VEGF: Vascular endothelial growth factor; PIGF: Placental growth factor; LFT: Liver function tests; IGF: Insulin like growth factor; TK: Tyrosine kinase; SCF: Stem cell factor; GIST: Gastrointestinal stromal tumor; PNET: Pancreatic neuroendocrine tumor; c-KIT: v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; mTOR: Mammalian target of rapamycin; HIF: Hypoxia inducible factor; MAPK: Mitogen activated protein kinase inhibitor; MEK: Mitogen activated extracellular kinase; PDGF: Platelet derived growth factor; VEGFR: Vascular endothelial growth factor receptor; FGFR: Fibroblast growth factor receptor; EGFR: Epidermal growth factor receptor

trial (PRIME) in combination with 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX4). In wild-*KRAS* tumors, the addition of panitumumab to FOLFOX4 significantly improved PFS compared with FOLFOX4 alone (9.6 mo vs. 8.0 mo, respectively; HR: 0.80, 95% CI: 0.66-0.97, $P = 0.02$). However, overall response rate was not significantly different (55% vs. 48% respectively, $P = 0.068$).[11] Adding panitumumab to irinotecan alone does not improve OS in wild-*KRAS* tumors.[12] Combination of panitumumab and FOLFIRI as a second line agent showed significant improvement in PFS compared to FOLFIRI alone (HR: 0.73, 95% CI: 0.59-0.9, $P = 0.004$).[13] Combination targeted therapies (panitumumab + bevacizumab) when combined with standard chemotherapy (oxaliplatin and irinotecan based) as a first line agent in metastatic colorectal cancer decreases PFS and increases toxicity.[14]

Panitumumab, when studied with chemotherapy (gemcitabine + oxaliplatin + capecitabine) as a first line therapy for wild-*KRAS* expressing unresectable biliary cancer, median PFS of 8.3 mo (95% CI: 6.7-8.7) and median OS of 10 mo (95% CI: 7.4-12.7) were observed.

Trastuzumab (Herceptin®)

Trastuzumab, a humanized IgG1 kappa monoclonal antibody, selectively binds with extracellular domain of *EGFR2* (HER2) receptor preventing ligand binding which otherwise would initiate signal transduction pathways involved in cell proliferation, differentiation, migration, adhesion and apoptosis.[15] It is approved in combination with cisplatin + capecitabine or 5-FU, for the treatment of patients with HER2 over expressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease based on results of the ToGA trial.[16] The ToGA trial recruited 594 HER2 positive gastric or gastroesophageal junction cancer patients, randomized to trastuzumab + chemotherapy ($n = 294$); orchemotherapy (cisplatin + capacitabine or 5-FU) alone ($n = 290$). Median OS was 13.8 mo (95% CI: 12-16) in trastuzumab group versus 11.1 mo (95% CI: 10-13) in chemotherapy alone group (HR: 0.74, 95% CI: 0.60-0.91, $P = 0.0046$). The addition of trastuzumab improved median survival by 2.5 mo. Median PFS was 6.7 mo in trastuzumab group versus 5.5 mo in chemotherapy alone group ($P = 0.0002$). The overall response rate was favorable for trastuzumab (47.3% vs. 34.5%, $P = 0.0017$). In HER-2 over expressing metastatic pancreatic cancer, addition of trastuzumab to capecitabine does not offer added benefit compared with standard chemotherapy.[17]

Bevacizumab (Avastin®)

Bevacizumab, an angiogenesis inhibitor, is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). Bevacizumab is approved as the first or second line treatment for metastatic colorectal cancer in combination with 5-FU based on a phase III, randomized, placebo controlled trial.[18] The trial included 411 and 402 patients suffering from metastatic colon cancer to irinotecan + 5-FU + leucovorin + placebo group and irinotecan + 5-FU + leucovorin + bevacizumab group, respectively. Median OS as well as PFS were significantly longer in bevacizumab group (20.3 mo vs. 15.6 mo for OS, HR: 0.66, $P < 0.001$ and 10.6 mo vs. 6.2 mo for PFS, HR: 0.54, $P < 0.001$). Median survival in bevacizumab group was 74.3% versus 63.4% in the other group ($P < 0.001$). Recently, a systematic review of all trials comprising infusional bolus of 5-FU based chemotherapy was performed. Median PFS and OS were 10.8 mo (95% CI, 8.9-12.8) and 23.7 mo (95% CI, 18.1-31.6), respectively.[19] Bevacizumab is also studied in the adjuvant setting in an open label, randomized phase III trial of stage II and III colon cancer. The FOLFOX group and FOLFOX + bevacizumab groups had respectively 1338 and 1334 evaluable subjects. Addition of bevacizumab to FOLFOX did not increase disease free survival significantly (HR: 0.89, CI: 0.76-1.04, $P = 0.15$). The lack of benefit persist even when analysis was performed in stage II and III disease separately. However, time dependent favorable effect was observed when exploratory analysis was performed at 15 mo landmark. The HR before the 15 mo landmark strongly favored bevacizumab (HR: 0.61, CI: 0.48-0.78, $P < 0.001$), whereas this benefit was lost subsequently (HR: 1.22, CI: 0.98-1.52, $P = 0.076$).[20] In a phase II study, bevacizumab was studied in metastatic colorectal cancer as first line agent in combination with capecitabine + oxaliplatin ($n = 127$) and capecitabine + irinotecan ($n = 120$). Median PFS and OS were respectively 10.4 mo (95% CI: 9.0-12.0) and 24.4 mo (95% CI: 19.3-30.7) in capecitabine + oxaliplatin + bevacizumab group and 12.1 mo (95% CI: 10.8-13.2) and 25.5 mo (95% CI: 21.0-31.0) incapacitabine + irinotecan + bevacizumab.[21]

The AVAGAST trial was a large multinational, randomized trial designed to evaluate the efficacy of adding bevacizumab to capecitabine + cisplatin as a first-line treatment of advanced gastric cancer. Each arm had 387 patients. Median OS was 12.1 mo in bevacizumab arm versus 10.1 mo in placebo arm (HR: 0.87, 95% CI: 0.73-1.03, $P = 0.1002$). Both median PFS (6.7 mo vs. 5.3 mo; HR: 0.80, 95% CI: 0.68-0.93, $P = 0.0037$) and overall response rate (46.0% vs. 37.4%, $P = 0.0315$) were significantly improved with bevacizumab. Bevacizumab in combination with capecitabine + oxaliplatin showed median PFS of 7.2 mo, median OS of 10.8 mo, and 51.4% response rate in a phase II trial of metastatic gastroesophageal cancer.[22] In another trial, bevacizumab when administered with cisplatin + irinotecan in 47 patients with metastatic/

unresectable gastric or gastroesophageal junction tumor, 65% overall response rate (95% CI: 46-80) and median survival of 12.3 mo (95% CI: 11.3-17.2) were observed.[23] A systematic review of phase II trials of bevacizumab in advanced HCC as a monotherapy or combination chemotherapy reported median PFS and OS ranging 5.3-9.0 mo and 5.9-13.7 mo, respectively. The disease control rate was 51.1-76.9%.[24] GI perforation is a serious adverse event associated with bevacizumab. A systematic review and meta-analysis of published randomized controlled trial found that bevacizumab had a significantly increased risk of GI perforation compared with patients treated with control medication, with a relative risk of 2.14 (95% CI: 1.19-3.85, $P = 0.011$). Risk varied with bevacizumab dose and tumor type. Relative risks for patients receiving bevacizumab at 5 and 2.5 mg/kg/week were 2.67 (95% CI: 1.14-6.26) and 1.61 (95% CI: 0.76-3.38), respectively. Higher risks were observed in patients with colorectal cancer (relative risk 3.10, 95% CI: 1.26-7.63).[25]

Ziv-aflibercept (Zaltrap®)

Ziv-aflibercept, a fusion protein directed towards VEGF-A, VEGF-B and a placental growth factor. Ziv-aflibercept is approved in combination with FOLFIRI for metastatic colorectal cancer that is resistant to or has progressed following oxaliplatin based regimen. A randomized, phase III trial of FOLFIRI + Ziv-aflibercept ($n = 612$) versus FOLFIRI + placebo ($n = 614$) was conducted in metastatic colorectal cancer patients who were previously treated with oxaliplatin including those who were treated with bevacizumab.[26] Median OS and PFS were significantly longer in Ziv-aflibercept group compared with the placebo group (13.5 mo. vs. 12.06 mo for OS, HR: 0.817, 95% CI: 0.713-0.913, $P = 0.0032$ and 6.9 mo. vs. 4.67 mo for PFS, HR: 0.758, 95% CI: 0.661-0.869; $P < 0.0001$). This survival benefit of Ziv-aflibercept persisted even when subgroup analysis was performed for bevacizumab pretreated patients. Response rate was 19.8% (95% CI: 16.4-23.2) in Ziv-aflibercept group compared with 11.1% (95% CI: 8.5-13.8) in placebo group ($P = 0.0001$).

A randomized, double-blind, placebo controlled, phase III trial evaluated the addition of aflibercept to gemcitabine in patients with advanced pancreatic cancer. The study was stopped for futility following a planned interim analysis.[27]

Nimotuzumab (Theracim®, h-R3®)

Nimotuzumab, a humanized monoclonal antibody, binds to extracellular domain of EGFR, and inhibits downstream signal conduction. It is approved in more than 20 countries but not U.S. for various indications (i.e., gliomas, head and neck cancer, esophageal cancer, etc.) with very favorable side-effect profile. A retrospective study evaluated 66 esophageal squamous cell cancer patients treated with Nimotuzumab and radiation/chemoradiation. Median OS and PFS were 26.0 mo and 16.7 mo, respectively. OS, PFS and locoregional control at 2 years were 54%, 37% and 80%, respectively.[28] A phase II trial evaluated nimotuzumab 200 mg weekly as a second line agent in advanced pancreatic cancer patients. For 36 evaluable patients, median PFS of patients with stable disease was 19.2 weeks and 6.7 weeks for all patients (95% CI: 6.43-7.14). PFS after 1 year was 10.3% with median OS of 18.1 weeks.[29]

Yttrium clivatuzumab tetraxetan (hPAM4-Cide®)

A monoclonal antibody, clivatuzumab, combined with yttrium (a radioisotope) where tetraxetan acts as a chelator (YCT). YCT is directed to mucin antigen found in 85% pancreatic adenocarcinoma but absent in normal pancreatic tissue.[30] This unique combo was studied along with gemcitabine, a radio sensitizer, in advanced pancreatic cancer based on preclinical data. Previously untreated 38 patients ($n = 33$, stage IV; $n = 6$, stage III) where 19 patients received escalating dose of YCT in repeat cycles. Grade III/IV toxicities were observed in all patients after second cycle. The median OS was 7.7 mo for all 38 patients, including 11.8 mo for those who received repeated cycles (46% [6 of 13 patients] ≥1 year), with improved efficacy at higher doses.[31]

Conatumumab (AMG 655)

Conatumumab, an agonist monoclonal antibody directed towards the death receptor 5, causing the activation of capcase and subsequent apoptosis. Patients with mutant *KRAS* metastatic colorectal cancer refractory to fluoropyrimidine-and oxaliplatin-based chemotherapy were randomized to FOLFIRI plus conatumumab, ganitumab, or placebo. Median PFS in conatumumab, ganitumab, and placebo group were 6.5 mo (HR: 0.69; $P = 0.147$), 4.5 mo (HR: 1.01; $P = 0.998$) and 4.6 mo, respectively. median OS were 12.3 mo (HR: 0.89; $P = 0.650$), 12.4 mo (HR: 1.27; $P = 0.357$) and 12.0 mo, respectively.[32] In metastatic pancreatic adenocarcinoma, addition of conatumumab to gemcitabine showed trend towards improved 6 mo survival rate compared to gemcitabine alone (59% vs. 50%).[33]

Ganitumab (AMG 479)

Ganitumab, a monoclonal antibody directed against insulin-like growth factor-1. In a multicenter, phase II, open-label trial, ganitumab was studied in metastatic progressive carcinoid or pancreatic neuroendocrine tumor (PNET) but failed to show any significant tumor response.[34] However, in metastatic pancreatic adenocarcinoma, addition of ganitumab to gemcitabine showed trend toward improved 6 mo survival rate compared to gemcitabine alone (57% vs. 50%).[33] As mentioned earlier,

ganitumab + FOLFIRI in metastatic colorectal cancer failed to show any significant tumor response.

TYROSINE KINASE INHIBITORS

Erlotinib (Tarceva®)

Erlotinib is a reversible human HER1 and EGFR tyrosine kinase inhibitor. Erlotinib is approved in combination with gemcitabine for unresectable locally advanced or metastatic pancreatic adenocarcinoma based on a double-blind, placebo controlled, phase III trial.[35] Though modest, median OS was significantly greater in erlotinib + gemcitabine group compared with gemcitabine alone group (OS 6.24 mo. vs. 5.91 mo, HR: 0.82, 95% CI: 0.69-0.99, $P = 0.038$). One year survival (23% vs. 17%; $P = 0.023$) and PFS (3.75 mo vs. 3.55 mo, HR: 0.77, 95% CI: 0.64-0.92, $P = 0.004$) were also greater in erlotinib arm. Though well-tolerated, erlotinib arm had higher incidence of rash, diarrhea, infection and stomatitis. Erlotinib in combination with radiotherapy for locally advanced unresectable esophageal cancer was studied in 16 patients where median OS of 7.3 mo (95% CI: 3.8-22.3), estimated PFS of 4.5 mo (95% CI: 2.4-7.3) and estimated 1-year survival of 29% (95% CI: 11-51) were observed.[36] The addition of bevacizumab and erlotinib to neoadjuvant concurrent chemoradiation therapy for localized esophageal/gastroesophagel cancer did not demonstrate survival benefit but targeted agent specific toxicities were evident.[37] Erlotinib monotherapy when studied as a second line agent in a phase II trial in metastatic esophageal cancer, showed some benefit in squamous cell tumors but not in adenocarcinoma (3.3 mo vs. 1.6 mo, $P = 0.026$).[38] A phase II trial (SWOG 0127) evaluated erlotinib as a monotherapy in unresectable/metastatic gastroesophagel junction and gastric adenocarcinoma and found its activity in gastroesophageal junction tumors but not in gastric adenocarcinoma.[39] A phase III, randomized, double blind, placebo controlled trial compared sorafenib + erlotinib ($n = 362$) and sorafenib + placebo ($n = 358$) in advanced HCC. There was no significant advantage of adding erlotinib to sorafenib (median OS 9.5 mo vs. 8.5 mo, HR: 0.929, 95% CI: 0.781-1.106, $P = 0.204$ and time to progression [TTP] was 3.2 mo vs. 4.0 mo, HR: 1.135, 95% CI: 0.944-1.366, $P = 0.91$).[40] The combination of erlotinib + bevacizumab in unresectable/metastatic HCC did not show any improvement in PFS compared to sorafenib alone.[41] Erlotinib has also been studied in a phase III trial in biliary tract cancer where it did not show any benefit when added to gemcitabine and platinum based chemotherapy.[42] The addition of erlotinib to bevacizumab as maintenance treatment after first-line chemotherapy in metastatic colorectal cancer did not improve PFS significantly.[43] In a phase II trial, combination of FOLFOX, bevacizumab and erlotinib could not be tolerated as a first line agent in previously untreated metastatic colorectal cancer due to toxicity profile resulting in high withdrawal rates.[44]

Sorafenib (Nexavar®)

Sorafenib, a small molecule multi kinase inhibitor, is approved for unresectable primary HCC. In a phase III, double-blind, placebo controlled trial, 297 and 302 evaluable patients received sorafenib and placebo respectively. Median OS in sorafenib group was 10.7 mo versus 7.9 mo in placebo group (HR: 0.69; 95% CI: 0.55-0.87, $P < 0.001$). Though no difference in symptomatic progression between two groups, median time to radiologic progression was 5.5 mo in sorafenib group versus 2.8 mo in placebo group ($P < 0.001$).[45] In a phase II trial of advanced or metastatic gastric and gastroesophageal junction adenocarcinoma, sorafenib with docetaxel + cisplatin showed 41% partial response (95% CI: 28-54). Median PFS was 5.8 mo (90% CI: 5.4-7.4) and median OS was 13.6 mo (90% CI: 8.6-16.1).[46] Addition of sorafenib to gemcitabine for advanced pancreatic cancer has not shown any added benefit in a phase III trial.[47] Sorafenib sensitizes the colon cancer cells to radiation induced cytotoxicity in xenograft models.[48-50] and helps to overcome irinotecan resistance by inhibiting drug efflux pump.[51]

Imatinib (Gleevec®)

Imatinib, a multi kinase inhibitor, is approved for unresectable/metastatic gastrointestinal stromal tumor (GIST). In two phase III trials, comparing 400 mg daily dose (conventional dose) versus 400 mg twice a day dose (higher dose), objective response rate (45% in both groups) and median OS (55 mo [CI: 47-62] in conventional dose vs. 51 mo [CI: 46-60] in higher dose, $P = 0.83$) were similar in both groups. However, the results of PFS were conflicting in both trials. Dose reduction and treatment interruption were more frequent with twice a day regimen.[52,53] When different *c-KIT* (stem cell factor receptor) mutations and treatment response were analyzed in these patients, exon-9 *c-KIT* mutation was the strongest adverse prognostic factor for response to imatinib and higher dose regimen resulted in significant superior median PFS ($P = 0.0013$).[54] Possibly, indefinite treatment in imatinib responders may be required in GIST as its discontinuation after successful use for 3 years resulted in rapid progression in a phase III, open label trial (2-year PFS was 80% [95% CI: 58-91] in continuation arm vs. 16% [95% CI: 5-33] in the interruption group, $P < 0{\cdot}0001$).[55]

Sunitinib (Sutent®)

Sunitinib, a multikinase inhibitor, is approved for GIST after imatinib failure. In a randomized, double blind, placebo controlled, phase III study, 228 patients received 6 week cycles of sunitinib (50 mg daily for 4 weeks followed by 2 weeks break) and 114 patients received placebo.[56] Blinding was

terminated after the interim analysis showed significantly prolonged survival in sunitinib arm and respectively 63% in sunitinib and 87% in placebo arm, received open label sunitinib afterward. Median follow-up of 41.7 mo (95% CI: 40.3-43.8), median OS for sunitinib and placebo arms were respectively 72.7 weeks (95% CI: 61.3-83.0) and 64.9 weeks (95% CI: 45.7-96.0) when calculated for the entire study period (blind and open label phase). Sunitinib nearly doubled median OS and halved the hazard of death compare to placebo (HR: 0.505; 95% CI: 0.262-1.134, $P = 0.306$). Disease progression was 3 fold greater in placebo arm (HR: 0.339; 95% CI: 0.244-0.472, $P \leq 0.001$). The median TTP among all patients in the final intent to treat population was 26.6 weeks (95% CI: 16.0-32.1) in sunitinib and 6.4 weeks (95% CI: 4.4-10.0) in placebo arm, respectively. In a maintenance therapy in metastatic pancreatic adenocarcinoma, PFS at 6 mo was 3.6% (95% CI: 0-10.6) and 22.2% (95% CI: 6.2-38.2; $P < 0.01$); 2 year OS was 7.1% (95% CI: 0-16.8) and 22.9% (95% CI: 5.8-40.0%; $P = 0.11$) and stable disease was 21.4% and 51.9% ($P = 0.02$) in placebo and sunitinib groups, respectively.[57] Addition of sunitinib to FOLFIRI or as a single agent in metastatic colorectal cancer refractory to standard chemotherapy did not offer any advantage.[58,59] A phase III, open-label trial (SUN 1170) comparing sunitinib with sorafenib in patients with advanced HCC was discontinued due to increased sunitinib related serious adverse events and the improbability of achieving noninferior or superior efficacy.

Regorafenib (Stivarga®)

Regorafenib is a small molecule multikinase inhibitor. It is approved for patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-and irinotecan-based chemotherapy, an anti-VEGF therapy and if *KRAS* wild type, an anti-EGFR therapy based on the results of a placebo controlled, randomized, phase III trial (CORRECT trial).[60] In this study, median OS was 6·4 mo in regorafenib group ($n = 500$) versus 5·0 mo in placebo group ($n = 253$) (HR: 0·77, 95% CI: 0·64-0·94, one-sided $P = 0·0052$). Regorafenib is also approved for patients with locally advanced, unresectable or metastatic GIST who have been previously treated with imatinib and sunitinib. Efficacy was confirmed in a phase III trial in which 199 patients were randomly assigned to best supportive care with either regorafenib (160 mg daily for 3 of every 4 weeks) or placebo. Median PFS was 4·8 mo (range 1·4-9·2) for regorafenib and 0·9 mo (range 0·9-1·8) for placebo (HR: 0·27, 95% CI: 0·19-0·39, $P < 0·0001$).[61] In a phase II trial of regorafenib in HCC after failure of first line sorafenib, 36 patients were included. Median TTP and OS were 4.3 mo and 13.8 mo respectively, but 89% patients had treatment interruption due to adverse drug reaction.[62]

Gefitinib (Iressa®)

Gefitinib, an EGFR tyrosine kinase inhibitor, when studied in phase II trials in metastatic or recurrent esophageal/gastroesophageal junction adenocarcinoma and squamous cell cancers, has been well tolerated. Gefitinib increases the radiosensitivity of gastric cancer cell lines.[63] In pancreatic cell lines, gefitinib has shown to reverse multidrug resistance via *RAF1/ERK* signaling pathway.[64] Moreover, gefitinib has shown antiproliferative effect on pancreatic cancer cell lines as well as on cholangiocarcinoma cells and gallbladder carcinoma when combined with gemcitabine. In a phase II trial of gefitinib combined with gemcitabine, 6 mo PFS was 30%. Median PFS and OS were 4.1 and 7.3 mo, respectively.[65] In human and murine HCC cells, gefitinib induced cell cycle arrest, apoptosis and cell growth inhibition.[66,67] In phase II trials, FOLFOX4 + gefitinib showed median OS of 12 mo and median event free survival of 5.4 mo in previously treated metastatic colorectal cancer,[68] as well as median OS of 20.5 mo and median TTP of 9.3 mo in previously untreated metastatic cases.[69] These results discourage the addition of gefitinib to FOLFOX-4 in metastatic colorectal cancer. In chemotherapy naïve metastatic colorectal cancer, addition of gefitinib to capecitabine + oxaliplatin showed 80% disease control rate, median TTP was 7.3 mo (95% CI: 4.76-9.2) and median OS was 21.9 mo (95% CI: 15.1-not reached).[70] EGFR phosphorylation status in colon cancer is predictive of response to gefitinib, even synergistic when used with platinum based chemotherapy.[71] Expression of p21 gene in combination with p53 gene mutation is a predictor of resistance to combination of chemotherapy + gefitinib.[72] The combination of gefitinib + cetuximab has synergistic effect on cell proliferation and apoptosis when studied in colon cancer cell lines.[73]

Cediranib (AZD 2171)

Cediranib, a vascular EGFR tyrosine kinase inhibitor, inhibits tumor cell migration and invasion, with no effects on cell proliferation when studied in colorectal, pancreatic and HCC cell lines.[74] Cediranib, when studied in advanced HCC, median OS of 5.8 mo (95% CI: 3.4-7.3) and median TTP of 2.8 mo (95% CI: 2.3-4.4) were observed. Grade ≥ 3 adverse events were observed in 93%.[75] In a phase III, randomized, double blind trial (HORIZON II), previously untreated metastatic colorectal cancer patients received either cediranib ($n = 502$) or placebo ($n = 358$) in addition to FOLFOX or capecitabine + oxaliplatin. The addition of cediranib to FOLFOX or capecitabine + oxaliplatin resulted in median PFS prolongation from 8.3 mo in placebo arm to 8.6 mo in cediranib arm (HR: 0.84, 95% CI: 0.73-0.98, $P = 0.0121$) but had no impact on OS (median OS, 19.7 mo for cediranib vs. 18.9 mo for placebo, HR: 0.94; 95% CI: 0.79-1.12, $P = 0.5707$). There were no significant differences in objective response rate, duration of response, or liver

resection rate.[76] In a phase II, randomized trial of cediranib in metastatic colorectal cancer, 20 mg daily dose reached primary objective, median PFS increased from 8.3 mo to 10.2 mo (HR: 0.70, 95% CI: 0.44-1.11, $P = 0.167$).[77] Cediranib was comparable to bevacizumab when combined with modified FOLFOX6 regimen (HORIZON III trial).[78]

Lapatinib (Tykerb®)

Lapatinib, a dual tyrosine kinase inhibitor associated with HER2/*neu* and EGFR receptor. The combination of lapatinib with cisplatin or 5-FU or trastuzumab synergistically inhibits cell proliferation and exhibits an enhanced pro-apoptotic effect on esophageal cancer cells. Lapatinib has not proved to be beneficial in HCC, pancreatic, biliary or refractory colorectal cancers when studied in small preclinical or phase II studies.

Vandetanib (Caprelsa®)

Vandetanib inhibits tyrosine kinase activity of EGFR, vascular EGFR families, *RET, BRK* and *TIE2*. In a preclinical trial, vandetanib synergistically enhanced the sunitinib-associated inhibition of gastric cancer cell growth.[79] Preclinical trial has shown beneficial effect of vandetanib in liver and early intestinal cancer in mice. In several phase I trials, vandetanib is being studied with different chemotherapy combination in advanced colorectal cancer.

Linifanib (ABT 869)

Linifanib is a selective inhibitor of vascular EGFR and platelet-derived growth factor receptor (GFR) tyrosine kinases. In a phase II trial of unresectable or metastatic HCC, linifanib showed median time to disease progression of 3.7 mo and median OS of 9.7 mo and thus raised hopes for another effective targeted agent in HCC beyond sorafenib.[80]

Vatalanib (PTK787)

Vatalanib is an oral antiangiogenic agent that acts as a vascular EGFR inhibitor. In a phase III, randomized, placebo controlled trial of previously untreated metastatic colorectal cancer, patients were randomly assigned to FOLFOX4 + vatalanib (evaluable $n = 581$) or FOLFOX4 + placebo (evaluable $n = 575$) arm.[81] Median PFS in vatalanib arm was 7.7 mo versus 7.6 mo in placebo arm (HR: 0.88, 95% CI: 0.74-1.03, $P = 0.118$); median OS in vatalanib and placebo arms were respectively 21.4 mo and 20.5 mo (HR: 1.08, 95% CI: 0.94-1.24, $P = 0.260$). In *post hoc* analysis of PFS in patients ($n = 158$/arm) with high serum lactate dehydrogenase, a potential marker of hypoxia, PFS was longer with vatalanib versus placebo (7.7 vs. 5.8 mo, respectively; HR: 0.67, 95% CI: 0.49-0.91, $P = 0.009$). Similar results were observed in another phase III, randomized trial when FOLFOX4 + vatalanib or placebo combination was studied in previously treated metastatic colorectal cancer.[82] Subsequently, vascular density analysis was performed in biopsy specimens of 141 colorectal cancer patients (placebo arm [$n = 70$] and vatalanib [$n = 71$]) in above phase III trials. The vascular density correlated with response to therapy, PFS and OS. The response rate increased from 15% (3/20) to 50% (11/22) in tumors with high vascular density, when vatalanib was added to chemotherapy ($P = 0.02$).[83]

Brivanib (BMS 582664)

Brivanib is an inhibitor of vascular EGFR and fibroblast GFR. The results of large phase III trials are disappointing despite encouraging phase II trials, where brivanib was used as a first and second line agent in advanced HCC. In a phase III, multicenter, double blind, placebo controlled, randomized trial of advanced HCC (BRISK-PS), patients failed/intolerant to sorafenib, were randomly assigned to receive brivanib and best supportive care ($n = 263$) versus placebo and best supportive care ($n = 132$).[84] Median OS was 9.4 mo for brivanib and 8.2 mo for placebo (HR: 0.89, 95.8% CI: 0.69-1.15, $P = 0.3307$) and median TTP was 4.2 mo for brivanib and 2.7 mo for placebo (HR: 0.56, 95% CI: 0.42-0.76, $P < 0.001$). Moreover, brivanib related side-effect caused discontinuation in 23%. In another, phase III, randomized, double blind trial, brivanib ($n = 577$) and sorafenib ($n = 578$) were compared head to head in untreated advanced HCC (BRISK-FL). The primary end point of OS non-inferiority for brivanib versus sorafenib in the per-protocol population ($n = 1150$) did not meet (HR: 1.06, 95.8% CI: 0.93-1.22). Median OS was 9.9 mo for sorafenib and 9.5 mo for brivanib. TTP, objective response rate and disease control rate were similar between two arms.[85] The combination of cetuximab and brivanib has been studied in metastatic, chemotherapy refractory, wild type-*KRAS* colorectal cancer in a phase III, randomized, placebo controlled trial (AGITG CO.20). Median OS in the intent-to-treat population was 8.8 mo in brivanib arm ($n = 376$) and 8.1 mo in placebo arm ($n = 374$) (HR: 0.88; 95% CI: 0.74-1.03, $P = 0.12$). Median PFS was 5.0 mo in brivanib and 3.4 mo in placebo arm (HR: 0.72, 95% CI: 0.62-0.84; $P < 0.001$). Any grade ≥ 3 adverse events were 78% in brivanib and 53% in placebo arms.[86]

Nilotinib (Tasigna®)

Nilotinib, a second generation tyrosine kinase inhibitor, prevents autophosphorylation of *c-KIT* and platelet GFR. In a phase III, open label trial, nilotinib was studied in advanced GIST resistant to imatinib and sunitinib.[87] Patients ($n = 248$) were randomized to nilotinib or best supportive care with imatinib/sunitinib/placbo. Median PFS was similar in both arms (nilotinib 109 days vs. best supportive care 111 days; $P = 0.56$) based on central radiology review. However, intent-to-treat analysis favored nilotinib over best supportive care (119 days vs. 70 days, $P = 0.0007$). A nonsignificant but positive trend was noted for OS in nilotinib group. *Post*

hoc subset analyses in patients with progression and only one prior regimen each of imatinib and sunitinib revealed a significant difference in median OS of > 4 months in favor of nilotinib (405 vs. 280 days; $P = 0.02$).

NON TYROSINE KINASE TARGET INHIBITORS

Everolimus (Afinitor®)

Everolimus is a mammalian target of rapamycin inhibitor. Everolimus causes dose dependent decrease in cell proliferation, cell cycle arrest in G1/S phase and damages cell shape.[88] Everolimus with capecitabine showed favorable toxicity profile and modest benefit (median PFS 1.8 months [95% CI: 0.8-2.8] in previously treated metastatic gastric cancer).[89] Everolimus monotherapy in previously chemotherapy treated advanced gastric cancer was studied in a phase II trial where no complete or partial response were observed. However, a decrease in tumor size from baseline was observed in 45%, disease control rate was 56.0% (95% CI: 41.3-70.0), median PFS was 2.7 mo (95% CI: 1.6-3.0) and median OS was 10.1 mo (95% CI: 6.5-12.1).[90] Everolimus augments the effects of sorafenib synergistically in orthotopic HCC model.[91] In a phase II trial of everolimus in advanced HCC with 0-2 previous regimens, median PFS and OS were 3.8 mo (95% CI: 2.1-4.6) and 8.4 mo (95% CI: 3.9-21.1), respectively. The estimated PFS rate at 24 weeks was 28.6% (95% CI: 7.9-49.3).[92] In a phase III, randomized trial, low-grade or intermediate-grade PNETs with radiologic progression within the previous 12 mo to receive everolimus ($n = 207$), or placebo ($n = 203$). Median PFS was 11.0 mo in everolimus versus 4.6 mo in placebo (HR: 0.35, 95% CI: 0.27-0.45, $P < 0.001$), representing a 65% reduction in the estimated risk of progression or death.[93] Everolimus and octreotide are effective independently in PNETs. However, this combination was recently studied in a phase II trial in treatment naïve 50 patients with well differentiated metastatic neuroendocrine tumors. Disease control rate was 92% and median TTP was 16.3 mo (95% CI: 10.7-20.1).[94] Everolimus is ineffective in metastatic colorectal cancer resistant to multiple chemotherapy agents.[95]

Selumetinib (AZD 6244)

Selumetinib inhibits mitogen-activated protein kinase (*MEK* or *MAPK/ERK* kinase) 1 and 2. Single agent (selumetinib or capecitabine) trial in colorectal cancer patients who previously failed one or two chemotherapeutic agent showed similar median PFS (81 days in selumetinib vs. 88 days in capecitabine arm).[96] In a phase II trial, erlotinib + selumetinib combination was studied in pancreatic adenocarcinoma ($n = 46$) treated with one prior chemotherapy. Estimated median PFS and OS by Kaplan-Meier were 2.6 and 7.5 mo, respectively and disease control rate was 51% in 41 evaluable patients.[97] Combination of selumetinib and vorinostat synergistically inhibits cell proliferation in two colorectal cancer cell lines with *KRAS* mutation.[98] Another phase II trial compared selumetinib or capecitabine as a single agent in advanced or metastatic pancreatic cancer patients ($n = 70$) who failed gemcitabine. Median OS was 5.4 mo in selumetinib arm and 5.0 mo in capecitabine arm (HR: 1.03, two-sided 80% CI: 0.68-1.57, $P = 0.92$).[99] In a phase II study of selumetinib in metastatic biliary cancer, median PFS and OS were 3.7 (95% CI: 3.5-4.9) and 9.8 (95% CI: 5.97-not available) mo, respectively.[100]

Trametinib (Mekinist®)

Trametinib is a reversible *MEK* 1 and 2 inhibitor. In a pre-clinical study of pancreatic cancer cell lines treated with trametinib, cancer cell proliferation was inhibited and addition of EGFR/HER2 inhibitor, lapatinib enhanced the inhibition elicited by trametinib in three of eight cell lines.[101] Trametinib when combined with 5-FU markedly decreased colony numbers of colon cancer cell lines.[102]

CLINICALLY USED BIOMARKERS FOR TARGETED THERAPY SELECTION IN GI CANCERS

In GI cancers, tumor receptor tyrosine kinase-targeted therapies (i.e., trastuzumab, imatinib) and antibodies (cetuximab, panitumumab) demonstrate a robust clinical response in patients that exhibit overexpression of their intended targets or certain genetic alterations. Trastuzumab is used only in gastric or gastroesophageal junction cancers that overexpress HER2. Imatinib is used for GIST expressing *c-KIT* and further studies of *KIT* mutation and platelet derived growth factor mutations have also been shown to correlate with response/resistance to imatinib. Although initially approved for all metastatic colon cancers, the label was changed to indicate cetuximab should only be used for the treatment of *KRAS* mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer (in combination with FOLFIRI as first-line treatment, in combination with irinotecan [in patients refractory to irinotecan-based chemotherapy], or as a single agent in patients who have failed oxaliplatin and irinotecan based chemotherapy or who are intolerant to irinotecan). Similarly, monotherapy with panitumumab in treatment of EGFR-expressing refractory metastatic colorectal cancer with disease progression on or following fluoropyrimidine-, oxaliplatin- and irinotecan-based regimens. Currently, no biomarkers for antiangiogenic therapies have been shown to correlate with survival.

Pharmacokinetic/pharmacodynamic markers: Erlotinib is cleared rapidly by smokers with 25-40% lower exposure and hence cautiously increasing the dose in active smokers

is recommended in the package insert. Exposure to imatinib was assessed in a study of 73 patients who were randomly assigned to 400 or 600 mg of imatinib daily for advanced GIST, there was a 10-fold variance in trough levels with either dose (from 414 to 4182 ng/mL).[103] Clinical outcomes were correlated with trough levels at steady state. Trough values below 1100 ng/mL correlated strongly with a significantly shorter time to tumor progression and a lower rate of clinical benefit as compared to higher trough levels and authors have suggested lower exposure may contribute to drug resistance.

CONCLUSION

The "one size fits all' approach for cancer therapy has long gone. With integration of optimum technology and better understanding of how cancers evolve at the molecular level, newer potential therapeutic targets are discovered faster than ever before. This understanding has helped us to embrace personalized approaches to treat cancer. Since the approval of bevacizumab in 2004 for colon cancer, there are now nine approved targeted drugs for treatment of GI cancers (five for colon, two for PNET, one for gastric/gastroesophageal, one for HCC, one for pancreas) and small incremental benefits have been seen in survival in each of these cancers. The era of personalized medicine is here, identifying validated assays and targets and doing studies in selected populations where the effect size is large as the population is preselected with patients who are most likely to benefit, has set a new standard for developing novel targeted agents in GI cancers. As their survival is generally poor and cost of drugs and toxicity is high, reducing sample size of trials and focusing on clinically meaningful rather than merely statistically significant benefit has become our driving principle for the future.

The results of ongoing and planned trials in colon cancer seek to expand the current approved indications for these agents, since the successful approval of bevacizumab as second line after failure of bevacizumab containing first line regimen. Notable phase 3 trials that are ongoing or planned include using ziv-aflibercept in the first line setting and adjuvant trials post metastatectomy that include regorafenib. Other studies plan to evaluate integration of targeted therapies with liver directed therapies, e.g. FOXFIRE global study evaluating incorporation of sirspheres with FOLFOX bevacizumab versus FOLFOX bevacizumab alone in advanced colon cancer and sorafenib with or without chemoembolization. The RADIANT-4 trial that seeks to re-examine the role of everolimus in carcinoids has completed accrual and is expected to be analyzed at the end of 2014. Given the success of trastuzumab in gastric cancer, the analysis of the LOGIC trial that has completed accrual and examines the role of adding lapatinib to standard chemotherapy in HER-2 positive gastric cancer is eagerly awaited. With the exception of erlotinib, all tyrosine kinase inhibitors approved for treatment of GI malignancies have been approved as single agents. More trials evaluating the benefits of targeted therapy in the adjuvant setting for GI cancers are needed, with better risk assessment to aid decision making as is used now for imatinib in the adjuvant setting for GIST tumors. The STORM study evaluating the value of adjuvant sorafenib 400 mg BID in delaying/preventing recurrence after radio frequency ablation or surgery for potentially curable HCC has completed accrual and results are awaited. Several ongoing trials of chemotherapy plus a tyrosine kinase inhibitor are ongoing or planned and despite many notable failures of this approach especially in pancreatic cancer, many investigators remain optimistic that the preclinical success with this approach may translate into clinical benefit. Biomarker driven approaches are ideal, but limited availability of tissue for such studies and lack of validated assays has been a major challenge. As a class of agents combined VEGF and FGFR inhibitors appear promising, but as yet have not received approval for any malignancy. In addition, many trials of vaccines and immune modulatory agents are planned or ongoing and integration with chemo and targeted therapies is also of great interest.

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