The Development of Bevacizumab in Noncolorectal Gastrointestinal Malignancies: Gastroesophageal, Pancreatic, and Hepatocellular Carcinoma

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Abstract: Bevacizumab (Avastin, Genentech) is a potent inhibitor of vascular endothelial growth factor A that has demonstrated modest antitumor activity across a broad range of malignancies when combined with chemotherapy. In colorectal cancer, bevacizumab in combination with chemotherapy is a standard of care for first-line therapy, and is used as second-line therapy in both bevacizumab-naive patients and those who have progressed on first-line therapy containing bevacizumab. Bevacizumab has been examined in nongastrointestinal malignancies as well. Across these multiple studies, virtually all of which demonstrate some improvement in progression-free survival, the combination of chemotherapy and bevacizumab has not led to a significant improvement in overall survival. Unfortunately, the addition of bevacizumab to chemotherapy translates into only slight improvement in overall survival in a few malignancies, including colorectal cancer. In this review, we highlight the development of bevacizumab in noncolorectal gastrointestinal malignancies, and potential future directions in antiangiogenic drug development.

Introduction

Angiogenesis, the formation of blood vessels, is a complex process that involves numerous pathways and receptors essential for growth of solid tumor malignancies, including tumor proliferation and the development of vascular metastases. Proangiogenic cytokines, driven primarily by hypoxia, are released by a variety of malignancies. The critical role in tumor angiogenesis played by vascular endothelial growth factor (VEGF) has led to the development of specific antibody inhibitors, such as the monoclonal anti-VEGF antibody bevacizumab (Avastin, Genentech).[1,2]

The VEGF family consists of VEGF-A through VEGF-E, and placental growth factors 1 and 2. The molecular target of bevacizumab is VEGF-A. The gene that encodes for VEGF is located at 6p21.1 (the short arm of chromosome 6), and comprises 8 exons separated by 7 introns. Owing to differential pre-mRNA splicing, the single *VEGF* gene gives rise to several isoforms of VEGF-A.[3]

The most well studied isoforms are $VEGF_{121}$, $VEGF_{165}$, and $VEGF_{189}$. These isoforms differ chiefly according to the presence or absence of a heparin sulfate (HS)-binding domain at the N-terminus. In larger isoforms (eg, $VEGF_{165}$ and $VEGF_{189}$), the HS-binding domain engages HS in the extracellular matrix.[4,5] Lower-molecular-weight isoforms, however, such as $VEGF_{110}$ and $VEGF_{121}$, lack this motif and are freely soluble. Extracellular matrix–bound and soluble VEGF-A isoforms have differing effects on vascular morphogenesis.[6] Specifically, soluble VEGF-A isoforms (ie, only the small isoforms) are associated with large, tortuous, unbranched vessels, whereas matrix-bound VEGF-A isoforms (ie, the large isoforms) are associated with thinner, more branched blood vessels.

VEGF-A is a major regulator of angiogenesis that binds to and activates both of the VEGF receptor (VEGFR) tyrosine kinases, VEGFR-1 (Flt-1), and VEGFR-2 (KDR/Flk-1). VEGFR-1 is expressed on endothelial cells as well as on myeloid cells. It promotes tumor growth and the formation of metastases, as well as inflammation. VEGFR-2 is responsible for neoangiogenesis, particularly in relation to cancer.[7] Inhibition of VEGF-A in preclinical models has demonstrated antitumor activity, particularly with regard to development of metastases and neoangiogenesis.[8]

Based on these data, and the emerging understanding of the role of angiogenesis in solid tumor growth and proliferation, along with the formation of metastases, bevacizumab has emerged as the leading antiangiogenic therapy. Over the past decade, bevacizumab has proven beneficial in a variety of malignancies. Multiple randomized phase 3 trials have demonstrated improved survival (either progression-free survival [PFS] or overall survival [OS]) with bevacizumab and chemotherapy compared with chemotherapy alone across a range of cancer types, namely colorectal,[9-11] breast,[12-15] non–small cell lung,[16,17] renal,[18,19] gastric,[20,21] pancreatic,[22,23] and ovarian cancers.[24,25] Among gastrointestinal malignancies, bevacizumab is approved for both first- and second-line therapy for colorectal cancer, and has been examined in noncolorectal gastrointestinal malignancies as well. I herein review the data examining the efficacy of bevacizumab in gastrointestinal malignancies exclusive of colorectal cancer, with an emphasis on gastroesophageal malignancies, pancreatic cancer, and hepatocellular cancer.

Gastroesophageal Cancer

Worldwide, gastric cancer is diagnosed in nearly 1 million individuals each year and is the second most common cause of cancer-related death.[26,27] Gastroesophageal adenocarcinoma is increasing in incidence, and metastatic disease is commonly treated in the same way as gastric cancer. Most patients with gastroesophageal malignancies present with stage IV disease. Despite this late presentation, systemic chemotherapy can lead to an improvement in cancer-related symptoms and prolong survival.[28-31] However, even with treatment, most patients with advanced gastroesophageal cancer have a median survival of less than 1 year.

Bevacizumab has been examined in gastric and gastroesophageal junction (GEJ) adenocarcinoma. Bevacizumab has not been examined in squamous cell carcinoma of the esophagus owing to concerns about an increased risk of bleeding and perforation, as extrapolated from a random-assignment phase 2 study of bevacizumab and chemotherapy in non–small cell lung cancer.[32] In this study, the rate of fatal bleeding was 9%, and seemed to cluster in patients with large central lung cancers with squamous cell carcinoma histology. Since that time, bevacizumab has been approved[33] and examined exclusively in nonsquamous carcinoma histologies.

Three Types of Gastric Cancer

Gastric adenocarcinoma is a diverse disease. Using cancer epidemiology, pathologic characteristics, tumor location, and emerging molecular signatures,[34,35] gastric adenocarcinoma can now be segregated into 3 distinct disease subtypes, as summarized by Shah and Kelsen.[30] These subtypes are: (1) diffuse gastric cancer (ie, signet ring cells) by Lauren classification,[36] caused in some patients by a mutation in the *CDH1* gene[37] encoding for E-cadherin; (2) nondiffuse gastric cancer of the gastric body or antrum that is linked to atrophic gastritis and chronic inflammation, usually secondary to infection with *Helicobacter pylori*[38-40]; and (3) nondiffuse cancers of the stomach cardia and GEJ, which are rapidly increasing in incidence in Western and industrialized countries[41] and are related to obesity and to chronic gastric acid reflux, which causes a different type of inflammation than that related to *H pylori*.[42,43] Lauren's diffuse gastric cancers have a higher propensity for lepidic growth and intraperitoneal metastasis,[44] whereas cardia and GEJ tumors have a worse prognosis, stage for stage,[45] compared with noncardia tumors. Proximal nondiffuse tumors (GEJ/cardia) are characterized by the highest incidence of human epidermal growth factor receptor 2 overexpression or amplification of all the gastric cancer subtypes.[46-48] With the improved classification of gastric cancer subtypes, our understanding of biologic drivers of each distinct disease (diffuse/signet ring cell type, noncardia/nondiffuse, and nondiffuse cardia/GEJ cancer) will improve, thereby refining our ability to apply targeted therapies to this disease.

Angiogenesis Inhibition in Gastroesophageal Malignancies

VEGF functions as a potent mitogen for vascular endothelial cells, promoting their migration and organization for the neovascularization of micrometastases. VEGF is expressed in gastric cancer, and its expression increases with

Table 1. Summary of Studies on Bevacizumab Plus Chemotherapy in Gastroesophageal Malignancies

Author/Study	Regimen	n	ORR	Median TTP, mo	Median OS, mo
First-line (phase 2)					
Shah,[53] 2006	Bevacizumab + cisplatin/irinotecan	47	65%	8.3	12.3
Shah,[55] 2011	Bevacizumab + mDCF	44	GC 1,[a] 85% GC 2,[a] 38% GC 3,[a] 56%	12.0	16.8
Enzinger,[57] 2008	Bevacizumab + docetaxel/cisplatin/irinotecan		63%	NR	NR
El-Rayes,[58] 2010	Bevacizumab + docetaxel/oxaliplatin	23	59%	NR	NR
Uronis,[59] 2013	Bevacizumab + oxaliplatin/capecitabine	35	51.4%	7.2	10.8
First-line (phase 3)					
Ohtsu,[20] 2011 (AVAGAST)	Bevacizumab + cisplatin/capecitabine vs	387	46%	6.7	12.1
	placebo + cisplatin/capecitabine	387	37% P=.03	5.3 P=.004	10.1 P=.1
Second-line (phase 2)					
Enzinger,[85] 2006	Bevacizumab + docetaxel	26	24%	NS	NS

mDCF, modified docetaxel/cisplatin/fluorouracil; mo, months; NR, not reported; NS, not significant; ORR, overall response rate; OS, overall survival; TTP, time to progression.

[a] GC 1-3 designates gastric cancer subtypes. GC 1 refers to subtype 1, gastroesophageal junction/cardia nondiffuse gastric cancer; GC 2 refers to diffuse gastric cancer; and GC 3 refers to subtype 3, distal and body, nondiffuse gastric cancer.

increasing stage and tumor burden.[49,50] VEGF expression is a negative prognostic factor for survival in patients with gastroesophageal cancer.[51,52] These data suggest that VEGF and angiogenesis appear to play an important role in the pathogenesis and progression of this disease and its inhibition may be of therapeutic value.

Use of the Anti-VEGF Monoclonal Antibody Bevacizumab

A number of encouraging studies have been reported with bevacizumab in metastatic gastric and GEJ cancer. The safety and efficacy of bevacizumab with irinotecan and cisplatin in gastric and GEJ cancers was initially demonstrated in a phase 2 study. The addition of bevacizumab to chemotherapy resulted in encouraging time to disease progression (TTP) (8.3 months; 95% CI, 5.5-9.9 months) and OS (12.3 months; 95% CI, 11.3-17.2 months), which were improved compared with a historical control (TTP of 5 months and OS of approximately 8 or 9 months).[53] There was no difference in the TTP between patients with gastric vs GEJ adenocarcinoma. This study demonstrated that bevacizumab can be administered with primary gastric tumors in place. A relatively low percentage of patients experienced significant bleeding (2%), although 6% had gastric perforations. However, 25% of patients experienced serious thromboembolic events during the study. This was similar to the 30% incidence of thromboembolism observed in patients with locally advanced gastric cancer receiving preoperative cisplatin/irinotecan therapy (without bevacizumab).[54]

To explore the utility of bevacizumab in combination with modern 3-drug combination therapy, bevacizumab was examined in combination with a modified regimen of docetaxel/cisplatin/fluorouracil (mDCF).[55] Therapy appeared to be more tolerable than the parent DCF regimen.[56] Median PFS was 12.0 months (95% CI, 8.8-18.2 months), and median OS was 16.8 months (95% CI, 12.1-26.1 months). In subset analysis, Lauren's diffuse/signet ring cell type had significantly worse PFS, OS, and response rate compared with the other gastric cancer subtypes.[55] Studies of bevacizumab with docetaxel/cisplatin/irinotecan[57] and docetaxel/oxaliplatin[58] have yielded similarly encouraging results. Most recently, investigators from Duke University completed a phase 2 study of capecitabine/oxaliplatin with bevacizumab that produced similar results, with median PFS of 7.2 months and median OS of 10.8 months.[59] Table 1 summarizes these studies, and includes one phase 2 evaluation of bevacizumab and docetaxel in the second-line setting. Based on the phase 2 study results, a registration phase 3 study on the addition of bevacizumab to chemotherapy was performed.[60] The AVAGAST (Avastin in Gastric Cancer) study was a global, random-assignment, double-blind, placebo-controlled phase 3 study of capecitabine and cisplatin in combination with either bevacizumab or placebo as first-line treatment for patients with advanced gastric cancer. Although treatment with bevacizumab was associated with a longer PFS vs placebo that was statistically significant (6.7 vs 5.3 months; hazard ratio [HR], 0.80; P=.0037), the difference in OS did not reach statistical

significance (12.1 vs 10.1 months; HR, 0.87; P=.1002).[60] The authors concluded that the heterogeneity of gastric cancer was possibly responsible for the negative primary outcome of the AVAGAST study when compared with the previous phase 2 studies. Specifically, preplanned sensitivity analyses suggest regional differences in the extent of benefit with bevacizumab in combination with chemotherapy, with the greatest benefit appearing to be in North America, South America, and Europe (vs Asia).[60]

Biomarker analyses may contribute to the identification of patients who derive a more substantial benefit from anti-VEGF therapy. VEGF and related pathways are directly influenced by VEGF inhibition and therefore represent valid biomarker candidates. The other biomarker that was suggestive of predictive ability was plasma VEGF-A levels.[21] For both tissue neuropilin 1 and plasma VEGF-A, subgroup analysis demonstrated a significant improvement in survival. However, this benefit appeared to be more pronounced when limiting the analysis to non-Asian patients. Thus, the distinction of gastric/GEJ cancers across the globe remains an enigma, particularly when it comes to anti–VEGF-A therapy. At this time, bevacizumab is not approved for advanced gastric or GEJ adenocarcinoma.

Pancreatic Cancer

Pancreatic cancer is a dismal disease, and carries the highest case-to-mortality ratio of any solid tumor. More than 90% of patients with pancreatic cancer will develop metastases. The survival for these patients is particularly poor, at a median of 2 to 4 months without treatment.[61] Pancreatic cancer can be characterized by tumor hypoxia and overexpression of hypoxia-inducible factor 1 alpha, and the consequent induction of the target genes, VEGFA and IL8.[62] Pancreatic tumors also often express the VEGF receptors, VEGFR-1 and VEGFR-2,[63] suggesting the potential for an autocrine loop for growth stimulation and proliferation. Based on these and additional preclinical studies, bevacizumab has been examined in pancreatic cancer, both in locally advanced unresectable disease and in patients with pancreatic metastases.

Bevacizumab has been examined with chemotherapy and radiation in a Radiation Therapy Oncology Group (RTOG) phase 2 study of patients with locally advanced pancreatic cancer.[64] Eighty-two patients with locally advanced pancreatic cancer without invasion of the duodenum received capecitabine 825 mg/m^2 twice daily (Monday through Friday) and bevacizumab 5 mg/kg on days 11, 15, and 29, with radiotherapy (50.4 Gy over 28 fractions). Patients received maintenance gemcitabine and bevacizumab following chemoradiotherapy until disease progression.[64] The addition of bevacizumab did not significantly increase the acute toxicity of the chemoradiation regimen. Acute gastrointestinal toxicity (grade 3 or higher) occurred in 22.0% of patients, and was even lower (at 18%) among patients who did not have a protocol deviation related to the radiotherapy treatment field. Notably, unacceptable radiation therapy protocol deviations (ie, volume of radiation inappropriately large) did correlate with grade 3 or higher gastrointestinal toxicity during chemoradiotherapy (45% vs 18%; adjusted odds ratio [OR], 3.7; 95% CI, 0.98-14.1; P=.05). The gastrointestinal bleeding rate was 6.1%. None of the gastrointestinal bleeding occurred at the tumor site, and most occurred more than 3 months following chemoradiation. The primary endpoint of this study was to improve 1-year survival from the historical rate of 43% to 58% with the addition of bevacizumab. Unfortunately, this endpoint was not met.

Bevacizumab has also been examined in the metastatic setting, in several phase 2 studies and 2 random-assignment phase 3 studies[22,23] (summarized in Table 2). Although several phase 2 studies had suggested a benefit with bevacizumab,[65-67] this was not validated in phase 3 studies,[22,23] similar to the experience with gastroesophageal cancer. Bevacizumab combinations in phase 2 trials have shown response rates ranging from 20% to 30%, and median OS of 7.4 to 8.8 months. Importantly, in two phase 2 studies, a moderate incidence of perforation was observed: 5.7% when bevacizumab was administered with gemcitabine at a fixed dose rate with low-dose cisplatin,[66] and 8% when bevacizumab was combined with gemcitabine alone.[65] These initial concerns were not corroborated in phase 3 evaluations, when the visceral perforation rate was 0.4% and 1.0% in the two phase 3 studies.[22,23] Unfortunately, neither study demonstrated an improvement in survival when chemotherapy was combined with bevacizumab. When bevacizumab was combined with gemcitabine, the HR for OS was 1.04 (95% CI, 0.88-1.24),[22] and when combined with gemcitabine plus erlotinib, the HR for OS was 0.89 (95% CI, 0.74-1.07).[23] Both studies suggested a benefit of antiangiogenic therapy in improving the PFS vs chemotherapy alone, however: 4.6 months for bevacizumab/gemcitabine/erlotinib vs 3.6 months for gemcitabine/erlotinib (HR, 0.73; 95% CI, 0.61-0.86; P=.0002), and 3.8 months for bevacizumab/gemcitabine vs 2.9 months for gemcitabine alone (P=.075). Based on these negative phase 3 studies, bevacizumab is not approved or indicated for the treatment of advanced pancreatic cancer.

A potential biomarker of bevacizumab efficacy was reported in patient blood samples from both of these studies. In the study of gemcitabine/erlotinib with or without bevacizumab, a single nucleotide polymorphism (SNP) in the VEGFR-1 receptor (rs9582036) was associated with OS in the bevacizumab group (P=.00014).[68] Carriers of

Table 2. Summary Results of Phase 2 and 3 Studies Examining Bevacizumab in Metastatic Pancreatic Cancer

Author/Study	Regimen	n	ORR	Median TTP, mo	Median OS, mo
First-line (phase 2)					
Kindler,[65] 2005	Bevacizumab + gemcitabine	52	21%	5.4	8.8
Ko,[66] 2008	Bevacizumab + fixed-dose-rate gemcitabine	52	NR	6.6	8.2
Martin,[67] 2012	Bevacizumab + gemcitabine/5-FU (24 h)	42	30%	5.9	7.4
First-line (phase 3)					
Van Cutsem,[23] 2009	Bevacizumab + gemcitabine/erlotinib vs gemcitabine/erlotinib	306 301	13.5% 8.6% P=.057	4.6 3.6 P=.0002	7.1 6.0 P=.21
Kindler,[22] 2010	Bevacizumab + gemcitabine vs gemcitabine	302 301	13% 10%	3.8 2.9 P=.075	5.8 5.9 P=.95

5-FU, fluorouracil; h, hours; mo, months; NR, not reported; ORR, overall response rate; OS, overall survival; TTP, time to progression.

the AC and CC alleles exhibited a significant improvement in survival compared with carriers of the AA allele among patients who received bevacizumab, with no effect of allele type on survival in the placebo group. Similarly, a nonsynonymous SNP in interleukin 17F (IL-17F) was associated with worse OS in the Cancer and Leukemia Group B (CALGB) 80303 study.[69] Median survival was significantly shorter in patients who were heterozygous for this SNP (rs763780) compared with patients who did not have this SNP (3.1 months vs 6.8 months; P=10^{-7}).[69] Investigators postulated that the angiogenesis-driven induction of metastases was greater for individuals who carried the variant IL-17F allele than for those with the wild type, conferring a considerably worse prognosis. Both of these findings will need further evaluation and prospective validation.

Hepatocellular Cancer

Hepatocellular carcinoma (HCC) is a prevalent worldwide malignancy. Worldwide, it is the fifth most frequent cancer among men, the seventh most common cancer among women, and the third most common cause of cancer-related mortality.[70] HCC is a vascular malignancy, and is characterized by increased tumor angiogenesis as a result of increased VEGF signaling. High VEGF expression is associated with more aggressive disease,[71] and serum VEGF is an adverse prognostic marker in this disease.[72]

To date, several phase 2 clinical studies have examined bevacizumab as an antiangiogenic therapy in the treatment of HCC (summarized in Table 3). In the first-line setting, the studies—apart from the study from Hsu and colleagues[73]—consistently demonstrated a median PFS of approximately 7 months and an OS of approximately 10 to 14 months, with response rates in the 10% to 20%

range.[74-76] Bevacizumab-specific toxicity included hypertension (10%) and bleeding (8%). The few deaths that were reported (n=5) occurred in patients with significant liver disease and consequences thereof, including portal hypertension, esophageal varices, and cirrhosis.[73-80] Bevacizumab was generally well tolerated and was possibly associated with improved activity in HCC. There is no current phase 3 study of bevacizumab in HCC and, as such, bevacizumab therapy in HCC remains investigational.

Additional Antiangiogenic Agents

Sunitinib (Sutent, Pfizer) and sorafenib (Nexavar, Bayer/Onyx) are oral multitarget tyrosine kinase inhibitors with activity against VEGFR. Initial evaluation in advanced gastric and GEJ cancer as monotherapy or in combination with chemotherapy has shown only limited response in unselected patient populations with gastroesophageal adenocarcinomas.[81,82] A phase 2 study by the Eastern Cooperative Oncology Group (ECOG) evaluated sorafenib with docetaxel/cisplatin as first-line therapy in 53 patients with metastatic or unresectable gastric and GEJ adenocarcinoma.[82] The overall response rate was 39%, including 1 complete response. While median OS was 15 months, the extent to which sorafenib was responsible for this encouraging survival is not clear, as PFS was 5.8 months and apparently was incongruent with the reported OS.[82] In a refractory setting, the addition of sunitinib to docetaxel did not appear to improve efficacy compared with docetaxel alone in a random-assignment phase 2 study.[81]

On the other hand, the novel antibody ramucirumab demonstrated a positive result in refractory gastric cancer. Ramucirumab (IMC-1121B) is a fully human immunoglobulin G1 monoclonal antibody targeting VEGFR-2.

Table 3. Summary of Bevacizumab-Based Studies in Hepatocellular Carcinoma

Author/Study	Regimen	n	Cirrhosis Status	Response Rate	Median TTP, mo	Median OS, mo
First-line (phase 2)						
Siegel,[76] 2008 (1st or 2nd line)	Bevacizumab	46	CLIP ≤2, 80% 3-4, 20%	13%	6.9	12.4
Hsu,[73] 2010	Bevacizumab + capecitabine	45	CLIP ≤2, 40% 3-4, 60%	8.9%	2.7	5.9
Sun,[75] 2011	Bevacizumab + oxaliplatin/capecitabine	40	Child-Pugh A, 57.5% B, 37.5%	20%	6.8	9.8
Kaseb,[74,80] 2012 (1st or 2nd line)	Bevacizumab + erlotinib	59	CLIP ≤2, 51% 3-4, 49%	23.7%	7.2	13.7
Second-line or greater (phase 2)						
Yau,[79] 2012 (≥2nd line)	Bevacizumab + erlotinib	10	Child-Pugh A, 100%	0%	1.5	4.4
Philip,[78] 2012 (2nd line)	Bevacizumab + erlotinib	27	Child-Pugh A, 74% B, 26%	2.1%	3.0	9.5
Zhu,[77] 2006 (≤3rd line)	Bevacizumab + gemcitabine/oxaliplatin	33	CLIP Median, 2 (range, 0-3)	18.0%	5.3	9.6

CLIP, Cancer of the Liver Italian Program score; mo, months; OS, overall survival; TTP, time to progression.

The REGARD (Ramucirumab Monotherapy for Previously Treated Advanced Gastric or Gastro-oesophageal Junction Adenocarcinoma) study, a placebo-controlled, double-blind, phase 3 international trial, was conducted in the second-line setting in patients with metastatic gastric or GEJ adenocarcinoma.[83] Median OS was 5.2 months for ramucirumab and 3.8 months for placebo (HR, 0.776; 95% CI, 0.603-0.998; P=.0473). The significance of this study is that it provides a proof of principle that antiangiogenic therapy does have activity in gastroesophageal malignancies. The REGARD study supports the concept that subtypes of gastric cancer exist, and may be differentially sensitive to antiangiogenic therapy. Our task, then, is to identify a biomarker that would predict bevacizumab efficacy.

The RAINBOW (A Study of Paclitaxel With or Without Ramucirumab in Metastatic Gastric Adenocarcinoma) study, a randomized phase 3 trial of ramucirumab in combination with paclitaxel vs paclitaxel monotherapy in the second-line treatment of metastatic gastric cancer, completed patient enrollment in September 2012 (NCT01170663). This study was recently reported in abstract form only, and did demonstrate an advantage of ramucirumab when combined with weekly paclitaxel vs paclitaxel alone (HR, 0.807; 95% CI, 0.678-0.962, P=.017).[84] Upcoming important trials in antiangiogenic therapies include the ST-03, or MAGIC-B study, which will examine the impact of perioperative bevacizumab when added to epirubicin, cisplatin, and capecitabine chemotherapy in a phase 3 setting (NCT00450203). However, the results of the REGARD and RAINBOW studies are both supportive of ongoing development of antiangiogenic therapies in gastroesophageal malignancies.

Summary and Future Directions

Antiangiogenic therapy has become commonplace in a variety of malignancies over the past 10 to 15 years. Bevacizumab, as the prototypical antiangiogenic agent, has demonstrated antitumor activity across a wide variety of malignancies, and is approved in combination with chemotherapy for numerous solid tumor malignancies, including colorectal cancer. Bevacizumab has been examined in noncolorectal cancer gastrointestinal malignancies as well. Unfortunately, random-assignment studies have disappointingly failed to demonstrate an OS benefit. Certainly, the impact of antiangiogenic therapy across gastrointestinal malignancies has been somewhat less than revolutionary. A key aspect of drug development is to identify, or enrich, the treatment population that may benefit most from targeted therapy: in this case, antiangiogenic therapy. As our

understanding of the cellular mechanisms of carcinogenesis in subtypes of gastric, pancreatic, and hepatocellular cancer improves, so will our ability to design rational therapies to specifically target these aberrancies. The success of future trials examining novel molecular targets will depend on biomarker-driven patient selection and tissue correlative components to further our understanding of the biology of noncolorectal gastrointestinal malignancies.

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