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Antiangiogenesis: Implications for the Treatment of Solid Tumor Malignancies

Part 1 of a 3-Part Series:

Targeting VEGF—Current and Future Research Directions

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Abstract

Angiogenesis produces new blood vessel growth in tumors. Vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) play a major role in tumor angiogenesis, prompting the development of biologic therapies against these factors. Antiangiogenic therapies, whether monoclonal antibodies or small molecule inhibitors, appear to act via multiple mechanisms to regulate tumor vasculature as well as to act upon tumor cells directly. These agents have been tested in a variety of cancers with good results. A monoclonal antibody against VEGF, bevacizumab, has been shown to increase the efficacy of several chemotherapeutic regimens in metastatic colorectal cancer, and has been approved for first-line use in combination with 5-fluorouracil-based chemotherapy. In addition, bevacizumab has shown promise in phase II trials in renal cell carcinoma and phase III trials in non-small cell lung cancer, and it is being tested in breast cancer. Small molecule inhibitors of VEGFRs have also been extensively studied in colorectal cancer and renal cell carcinoma. Phase III studies of the VEGFR antagonist PTK787/ZK222584 in colorectal cancer are ongoing but initial analysis did not demonstrate a benefit of the addition of this agent to FOLFOX. BAY 43-9006, a dual-action Raf kinase and VEGFR inhibitor, as well as SU11248 and AG-013736, which are VEGFR and platelet-derived growth factor receptor inhibitors, have been tested in renal cell carcinoma with encouraging results. Future studies will clarify the role of the biologics in these diseases and will focus on the best dose, schedule, and therapeutic combinations.

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Statement of Need

Recent advances in understanding the biologic mechanisms responsible for tumor growth and proliferation have led to significant breakthroughs in the treatment of several cancer types. Among these, antiangiogenic therapy has been particularly promising, with efficacy seen in colorectal cancer, non-small cell lung cancer, renal cell carcinoma, and other cancer types. Novel agents targeting the vascular endothelial growth factor (VEGF) and its receptors have been approved by the US Food and Drug Administration (FDA) for the treatment of colorectal cancer in combination with chemotherapy, and phase III trials in other disease settings have demonstrated similar efficacy with reasonable toxicity. Current studies are focusing on elucidating the mechanisms of action responsible for the effectiveness of anti-VEGF agents in combination with chemotherapeutics, and on the continued evaluation of several such agents in numerous disease settings in order to identify the best dose, schedule, and combinations.

Target Audience

This publication is specifically designed for practicing clinicians, medical oncologists, and radiation oncologists who wish to review and update their knowledge of antiangiogenesis therapy.

Educational Objectives

1. Discuss the potential mechanisms of action of anti-VEGF therapy plus chemotherapy combinations.
2. Discuss the results of clinical trials evaluating antiangiogenic therapy in the treatment of colorectal cancer.
3. Discuss the results of clinical trials evaluating antiangiogenic therapy in the treatment of renal cell carcinoma.

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Keywords

Angiogenesis, antiangiogenesis, vascular endothelial growth factor receptor, colorectal cancer, non-small cell lung cancer

Pre-Test

1. What hypotheses to explain the antitumor effects of anti-VEGF therapy plus chemotherapy are currently being explored?
2. What combinations of chemotherapy plus antiangiogenic agents have shown efficacy in the treatment of colorectal cancer?
3. What therapeutic regimens involving antiangiogenic agents have shown efficacy in the treatment of renal cell carcinoma?

Mechanisms of Action of Anti-VEGF Therapy



Lee M. Ellis, MD

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Angiogenesis in tumors is accomplished by a complex process whereby tumor cells create angiogenic factors that prompt new blood vessel growth. The most potent angiogenic factor known to date is vascular endothelial growth factor (VEGF). VEGF triggers a number of signaling pathways within tumor endothelial cells, leading to endothelial cell proliferation, migration, and differentiation, as well as increased permeability and survival.

Several proteins with similar homology comprise the VEGF family (Slide 1). VEGF-A is the protein typically referred to as VEGF, as this was the prototypical family member first described by Hal Dvorak and colleagues in the late 1970s and cloned simultaneously by Napoleon Ferrara in 1989. Other VEGF family members include VEGF-B, C and D and placental growth factor. These ligands bind to specific tyrosine kinase (TK) receptors, such as VEGF receptors (VEGFRs) 1, 2, and 3. Once bound, these TK receptors dimerize and transmit downstream signals that mediate dif-

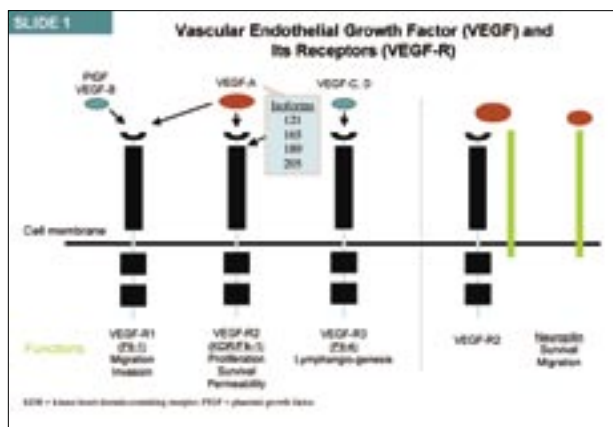
Studies of malignant ascites from patients with carcinomatosis have shown that VEGF levels are significantly higher in malignant ascites than in the nonmalignant ascites seen in cirrhotic patients. Very high levels of VEGF have also been found in malignant pleural effusions. VEGF has been validated as a therapeutic target in many tumor systems, as it is overexpressed in the malignant tissue relative to corresponding normal tissues.

Slide 2 shows several approaches to targeting the VEGF pathway. The first evidence that inhibiting VEGF activity could inhibit tumor growth came from the use of bevacizumab, a humanized monoclonal antibody against VEGF. The US Food and Drug Administration (FDA) has approved bevacizumab for first-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil (5-FU)-based chemotherapy.

Single-agent bevacizumab therapy does not lead to a significant number of responses, as was recently seen in the Eastern Cooperative Oncology Group (ECOG) 3200 trial.¹ In this trial, 829 patients who had not responded to first-line fluoropyrimidine- and irinotecan-based chemotherapy received either bevacizumab alone, bevacizumab plus FOLFOX4 (oxaliplatin plus 5-FU/leucovorin [LV]) or FOLFOX4 alone. The response rate (RR) in the bevacizumab-alone arm was only 3%, and the overall survival (OS) was 10.2 months, not significantly different from the FOLFOX4-alone arm.

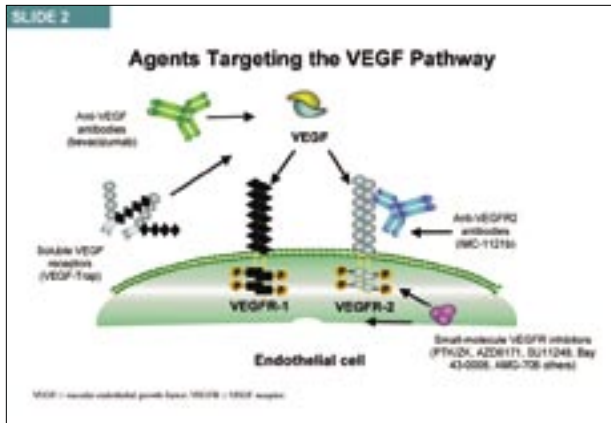
While bevacizumab monotherapy does not appear particularly effective, it is very effective when used in combination with chemotherapy. In the above-mentioned ECOG 3200 trial, the RR with FOLFOX4 alone was 9.2%, but increased to 21.8% among patients treated with FOLFOX4 plus bevacizumab ($P < .0001$). Similarly, OS was 10.8 months and 12.9 months, respectively ($P = .0018$). A number of other phase II and III trials in patients with colorectal cancer, lung carcinoma, and breast carcinoma have also found increases in RR among patients receiving bevacizumab in combination with chemotherapy.²⁻⁴

That bevacizumab can increase RR when combined with chemotherapy is quite surprising, as it was initially hypothesized that antiangiogenic therapy would simply limit further tumor growth. Some investigators have therefore questioned the mechanism of action of anti-VEGF therapy. The fact that anti-VEGF therapy does produce prolonged stabilization of multiple tumor sites demonstrates that it is



ferent pathways within endothelial cells. Another family of VEGFRs, the neuropilins, also mediate cell migration and survival signals.

VEGF has a number of functions in the body. It activates endothelial cells and enhances their survival, migration, and proliferation. Arguably the most important function of VEGF, however, is its ability to induce vascular permeability. In fact, the molecule was initially termed vascular permeability factor because of its ability to induce permeability that was 50,000-fold that of histamine, the gold standard for permeability induction.



antiangiogenic. However, there must be other mechanisms of action leading to the increase in RR with chemotherapy.

One possible explanation is the normalization hypothesis pioneered by Jain,⁵ suggesting that anti-VEGF agents can cause a transient relative vasoconstriction of the large aberrant blood vessels present in tumors. This normalization of tumor vasculature may actually improve blood flow and decrease hypoxia in the tumor because abnormal blood vessels have erratic and chaotic blood flow. Improved blood flow then allows for improved delivery of chemotherapeutic agents. This hypothesis has been supported by evidence from preclinical trials^{6,7} and from a small clinical trial in patients with locally advanced rectal cancer.⁸ However, the window of normalization in these trials appears to be relatively short, and in mice it occurs 4–6 days after anti-VEGF treatment. Therefore, the normalization hypothesis probably applies early in treatment with anti-VEGF therapy, but likely plays little role after patients have been exposed to anti-VEGF therapy for a period of time.

A second hypothesis for the improvement in RR seen with anti-VEGF therapy plus chemotherapy is that the molecule directly effects tumor cells. Previously, it was thought that VEGFRs were present only on endothelial cells, but recent in vitro evidence shows that they are also present on tumor cells. VEGFR-1 has been found on colon cancer and pancreatic cancer cell lines,^{9,10} and other TK receptors for VEGF have been detected on melanoma cells and lung and breast carcinoma cells.^{11–13} Interestingly, the addition of anti-VEGF therapy to chemotherapy appears to have efficacy against several of these tumor types.

The last hypothesis for the mechanism of anti-VEGF therapy is vascular constriction. Binding of VEGF to its receptor leads to a release of nitric oxide (NO), a vasodilator, from endothelial cells. Inhibition of VEGF activity prevents the release of NO and results in a relative constriction of the vasculature. Several clinical studies have shown that anti-VEGF therapy can diminish the perfusion permeability of vessels in tumors as measured by either dynamic contrast-enhanced

magnetic resonance imaging or computerized tomography perfusion,^{14,15} suggesting that the immediate effect of anti-VEGF therapy is not the eradication of blood vessels, but rather tumor vasoconstriction which limits blood flow and permeability.

In summary, the proposed mechanisms of action of anti-VEGF therapy include normalization of tumor vasculature shortly after the initiation of treatment, direct action upon tumor cells, and inhibition of NO and the resulting tumor vasoconstriction. While the exact mechanism(s) have yet to be determined, the clinical relevance of anti-VEGF therapy has been proven in studies showing significant improvements in RR, and in some cases OS, when anti-VEGF therapy is added to chemotherapy.

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Anti-VEGF Therapy and Metastatic Colon Cancer



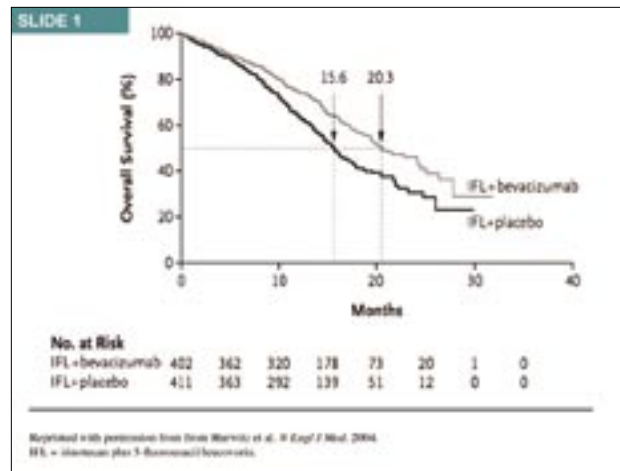
Joel Randolph Hecht, MD

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First-line Bevacizumab in Metastatic Colorectal Cancer

Bevacizumab was the first antiangiogenic agent approved by the FDA, with the first successful studies in colorectal cancer. In addition to ECOG 3200, discussed by Dr. Ellis, several other trials have been conducted. Kabbinavar et al¹ conducted a randomized phase II study comparing 5-FU/LV with or without bevacizumab in patients with metastatic colorectal cancer. A total of 104 patients received 5-FU/LV, 5-FU/LV plus bevacizumab 5 mg/kg every 2 weeks, or 5-FU/LV plus bevacizumab 10 mg/kg every 2 weeks. The RR in the 5-FU/LV-alone arm was 17%, increasing to 40% in the low-dose bevacizumab arm and to 24% in the high-dose bevacizumab arm. The median time to progression (TTP) was 5.2, 9.0, and 7.2 months in the 5-FU/LV, low-dose bevacizumab, and high-dose bevacizumab arms, respectively, although these differences did not reach statistical significance. Bevacizumab also produced a longer median survival: 13.8, 21.5, and 16.1 months, respectively. Most clinical studies to follow used the 5 mg/kg every 2 weeks dose of bevacizumab because of these data. In general, bevacizumab seemed to be well tolerated. Increased thrombosis was the most significant adverse event (AE) in this trial, resulting in 1 patient death. Other AEs included hypertension, proteinuria, and epistaxis.

These findings led to a large phase III trial in patients with previously untreated metastatic colorectal cancer.² In the time between the trials the standard of care in colorectal cancer had changed to a regimen of bolus 5-FU and irinotecan. Therefore, Hurwitz et al randomized 813 patients to receive irinotecan, bolus 5-FU, and LV (IFL regimen) plus either bevacizumab 5 mg/kg or placebo. The addition of bevacizumab to IFL resulted in an improvement in all clinical parameters. The median duration of survival was 20.3 months in the combination group and 15.6 months in the IFL group ($P<.001$; Slide 1). Median progression-free survival (PFS) was 10.6 and 6.2 months, respectively, and the RRs were 44.8% and 34.8%, respectively. Again, hypertension was more common among patients receiving bevacizumab (11% vs 2.3%), and gastrointestinal perforation was seen in approximately 1.5% of patients receiving bevacizumab. An increase in arterial thrombosis and decreased wound healing were also seen in patients receiving bevacizumab.



At the same time, Kabbinavar et al³ conducted a large randomized phase II trial in patients who were not candidates for first-line irinotecan. Here, 209 patients with metastatic disease were randomized to receive 5-FU/LV plus either bevacizumab 5 mg/kg or placebo. Patients receiving bevacizumab had an improved RR (26.0% vs 15.2%) and median survival (16.6 vs 12.9 months) when compared with placebo, but neither were statistically significant. The median PFS did differ significantly between the 2 groups: 9.2 and 5.5 months, respectively ($P=.0002$). Bevacizumab was well tolerated, although grade 3 hypertension was more common with bevacizumab than with placebo (16% vs 3%).

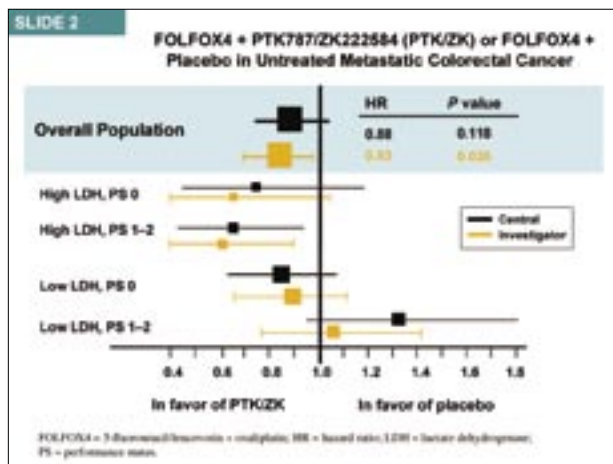
Hochster et al⁴ recently reported findings from 2 studies, one of oxaliplatin-based chemotherapy (3 treatment arms), and another of the same treatment arms plus bevacizumab. In the first study, patients with untreated metastatic disease were randomized to 1 of 2 combinations of oxaliplatin, 5-FU, and LV or 1 combination of oxaliplatin and capecitabine. The second trial randomized patients to each of these regimens plus bevacizumab 5 mg/kg every 2 weeks. A total of 147 and 213 patients were enrolled in the respective studies. The RRs were improved in each group with the addition of bevacizumab. The RRs among the 3 chemotherapy-only arms were 39% and 20% for the oxaliplatin, 5-FU, and LV arms and 29% in the oxaliplatin/capecitabine arm. The corresponding RRs for the groups with added bevacizumab were 49%, 34%, and 43%, respectively. The authors found that grade 3/4 AEs were acceptable and less common than those reported with IFL. This trial demonstrated that beva-

cizumab can be given safely with oxaliplatin-based therapy and appears to improve the response rate.

Small Molecule Inhibitors of VEGF in Colorectal Cancer

Several small molecule VEGFR antagonists are in various stages of development. The best-studied, PTK787/ZK222584 (PTK/ZK), potentially active against all known VEGFRs, has produced encouraging preclinical and phase I/II results, leading to 2 large randomized phase III trials.

Preliminary results of the first trial were presented at the 2005 ASCO meeting.⁵ In this trial, 1,168 patients with



untreated metastatic disease were randomized to receive FOLFOX4 with either oral PTK/ZK or placebo. The early primary endpoint was PFS, assessed by investigators and independent central radiology every 8 weeks. PTK/ZK was associated with a reduction in risk of progression by 12% when assessed by central radiologic review, but did not reach statistical significance. However, when PFS was assessed by the investigators, the risk of progression was reduced by a significant 17% ($P=.026$; Slide 2). In a subanalysis of patients with high lactate dehydrogenase (LDH), a marker for poor prognosis, PTK/ZK was associated with a 40% risk reduction. These data are preliminary and hypothesis-generating. Further data from this and a related ongoing study will help clarify the role of PTK/ZK in colorectal cancer.

Antiangiogenic Biologics in Refractory Colorectal Cancer

Antiangiogenic agents are being tested in patients who have failed multiple prior treatments. Chen et al presented data at the 2004 ASCO meeting from a trial that compared 5-FU/LV alone with 5-FU/LV plus bevacizumab in patients who had exhausted all therapeutic options. The response rate was

quite low (1%), but the final data have yet to be fully presented.⁶ A second interesting trial tested a combination of bevacizumab and cetuximab, a monoclonal antibody against epidermal growth factor receptor (EGFR).⁷ Here, 75 patients with metastatic disease who had failed 5-FU- and irinotecan-based treatments were randomized to receive cetuximab plus bevacizumab with or without the addition of irinotecan at the same dose and schedule as last received prior to the study. The RR (all partial responses [PRs]) was 35% in the triple-drug group and 23% in the double-drug group. The median TTP was 5.8 and 4.0 months, respectively. Toxicities were in line with those seen with each of these agents as monotherapies and, importantly, the combination of the 2 biologics with irinotecan appeared tolerable and feasible. Studies of combination cetuximab/bevacizumab with other first-line chemotherapeutics are ongoing.

In summary, much work remains to be done to determine the best dose, schedule, and setting for biologic agents in colorectal cancer. Bevacizumab has been shown to have a very robust and clinically significant benefit, especially as first-line therapy. Although in general this agent is well-tolerated, some toxicities are significant, and more studies are required to determine the best ways to manage them. Also, the role of bevacizumab in patients who have already progressed on bevacizumab-containing regimens is still unclear. Small molecule VEGFR antagonists or inhibitors present another exciting area of research, and further data will be forthcoming. Finally, studies of various combinations of anti-VEGF and anti-EGFR therapies, with and without traditional chemotherapeutics, are either planned or ongoing.

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Anti-VEGF Therapy in Renal Cell Carcinoma, Breast Cancer, and Lung Cancer

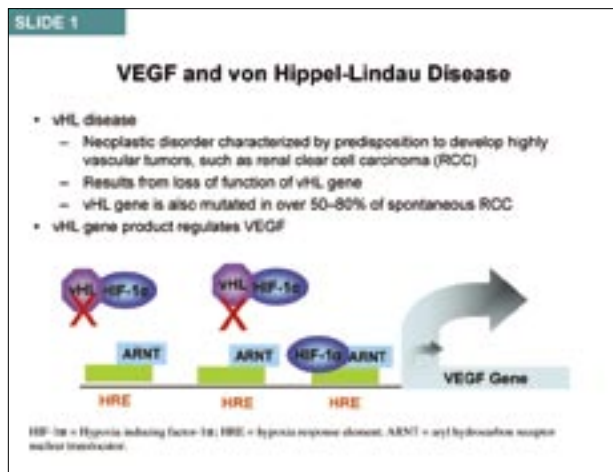


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Anti-VEGF Agents in Metastatic Renal Cell Carcinoma

Metastatic renal cell carcinoma (RCC) represents a very novel target for the use of antiangiogenic, and specifically anti-VEGF, agents. Clear cell carcinoma of the kidney, which makes up approximately 70% of the diagnoses of RCC, is predominantly associated with a mutation of the von Hippel-Lindau (vHL) gene, found on chromosome 3. Deletion and/or silencing of the vHL gene results in a significant increase in hypoxia-inducing factor-1 α (HIF-



1 α), which regulates the expression of VEGF. An increase in HIF-1 α is associated with an increase in a variety of factors, such as erythropoietin, GLUT-1, and VEGF. Disruption of the vHL pathway may play a pathophysiologic role in the development of clear cell carcinoma of the kidney, and therefore anti-VEGF may potentially have a more tumor-targeted effect, as opposed to simply being antiangiogenic.

The first clinical trial of anti-VEGF therapy was performed by Yang et al, who conducted a randomized placebo-controlled phase II trial of bevacizumab in patients who had metastatic clear cell carcinoma of the kidney without bone metastases.¹ A total of 116 patients were randomized to receive bevacizumab 3 or 10 mg/kg or placebo. Patients in the bevacizumab groups received an initial loading dose of 4.5 mg/kg in the low-dose group and 15 mg/kg in the

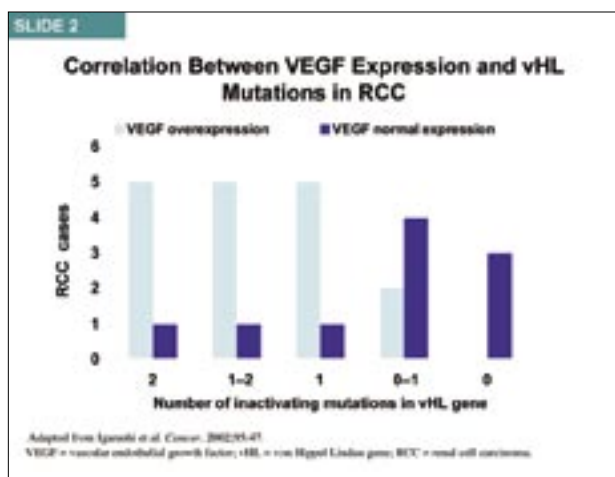
high-dose group. This trial was closed after an early analysis demonstrated a statistically significant benefit in the median TTP for the high-dose bevacizumab arm compared with the placebo arm (147 vs 41 days; $P < .001$). Response rates were low in this study, with the high-dose bevacizumab arm achieving a 10% RR and the placebo and low-dose bevacizumab arms showing no antitumor activity as defined by tumor response. High-dose bevacizumab was well-tolerated; hypertension and asymptomatic proteinuria were the most common AEs.

Several subsequent trials have been undertaken. Hainsworth et al² studied bevacizumab plus erlotinib, an EGFR TK inhibitor (TKI), in a phase II trial of 57 patients with metastatic disease. A PR was seen in 21% of patients, with an additional 66% having stable or minor responding disease. The toxicity profile was acceptable. Common grade 3/4 AEs were hypertension (8%), diarrhea (10%), rash (13%), nausea/vomiting (10%), pruritus (3%), and edema (2%). A larger, randomized phase II trial comparing single-agent bevacizumab with bevacizumab plus erlotinib in patients with previously untreated clear cell carcinoma is accrued.

After recognizing that VEGF inhibition may play a role in RCC, a number of investigators designed trials to test oral TKIs that block not only VEGF but other receptors that may be critical in angiogenesis or tumor development. Examples include BAY 43-9006 and SU11248, the 2 most significantly developed. Ratain et al performed a randomized discontinuation trial for BAY 43-9006, a dual-action Raf kinase and VEGFR inhibitor,³ enrolling 202 patients with previously treated metastatic RCC into a 12-week induction trial of this agent. The 65 patients with at least stable disease (SD) after this induction period were then randomized to receive continued BAY 43-9006 or placebo. The median PFS after randomization was greater with BAY 43-9006 than with placebo (24 vs 6 weeks; $P = .0001$). Grade 3/4 AEs occurred in 47% of patients randomized to the BAY 43-9006 arm, with the most common being hypertension (24%). Only 8% of patients discontinued the study drug due to AEs. This trial was notable in that these patients, who had progressive disease upon study entry, achieved an SD rate of nearly 40% during the induction phase.

That trial led to a randomized phase III study comparing BAY 43-9006 with placebo in patients with metastatic

clear cell carcinoma of the kidney who previously had progressive disease on first-line immunotherapy. Those data were presented at the 2005 ASCO meeting by Escudier and colleagues.⁴ This study enrolled 884 patients, of whom 769 were randomized to single-agent BAY 43-9006 or placebo. Patients receiving BAY 43-9006 had a median PFS of 24 weeks, versus 12 weeks with placebo ($P < .00001$). Interestingly, the initial data indicated low RRs of approximately 2%, with the majority of the patients on the investigational agent demonstrating minor response or SD. The final end-point of that trial, OS, is pending.



The other major agent that has been explored is SU11248, a multifaceted agent that inhibits not only VEGFRs but also platelet-derived growth factor receptors (PDGFR). Motzer and colleagues have conducted 2 phase II trials of second-line SU11248 in metastatic disease, which were presented at the 2005 ASCO meeting.⁵ Of the 63 patients in trial 1, 40% achieved a PR and 28% had SD. The median TTP was 8.7 months. For the 83 assessable patients out of 106 enrolled in trial 2, 39% had a greater than 30% decrease in tumor size. To date, AEs were reported to be mostly grade 1/2. SU11248 is subsequently being compared with interferon in a phase III trial for first-line therapy, with results expected within 2 years.

Finally, AG-013736, which effects VEGFR-1 and -2 and PDGFR- β , was investigated by Rini et al.⁶ In this study of 52 patients with cytokine-refractory metastatic disease, a PR was seen in 46% of patients, with approximately 69% of patients continuing on therapy with a median follow-up of 1 year with either responding or stable disease. The median TTP at the time of presentation had not been reached.

With all of these multifaceted inhibitory agents, the common toxicity seen is hypertension and mild proteinuria. However, this toxicity has not been a hindrance for these patients, who typically have only 1 kidney.

Bevacizumab in Breast and Non-Small Cell Lung Cancers

Bevacizumab has been studied in NSCLC in a phase III trial by Sandler et al.⁷ A total of 878 patients with previously untreated stage IIIb/IV nonsquamous NSCLC were randomized to receive paclitaxel/carboplatin or paclitaxel/carboplatin/bevacizumab. The RR was 10% in the chemotherapy-alone arm and 27% in the combination arm, and median OS was improved from 10.2 months to 12.5 months ($P = .0075$). Toxicities were not significantly worse in the bevacizumab arm, despite the fact that in earlier trials there had been a significant number of hemorrhagic deaths associated with the addition of bevacizumab. This seemed to be significantly reduced in this trial by excluding patients with centrally located squamous cell carcinomas.

Finally, in metastatic breast cancer, a large phase III study of capecitabine with or without bevacizumab in patients with anthracycline- and taxane-refractory disease found a significant improvement in RR with the addition of bevacizumab (19.8% vs 9.1%; $P = .001$). This response did not result in a longer PFS, OS, or time to deterioration in quality of life.⁸ Studies of first-line bevacizumab plus chemotherapy are in progress and showing promise.

Overall, VEGF inhibition appears to significantly improve the outcome for patients when used in combination with several kinds of chemotherapeutic regimens and represents a significant advance for many of our otherwise stagnant cancer therapies over the past decade.

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Question and Answer Forum

Drs. Ellis, Hecht, and Gordon answer further questions about anti-VEGF therapies.

Should anti-VEGF therapy be continued after a patient progresses on chemotherapy plus anti-VEGF therapy?

Dr. Lee Ellis We do not fully know the answer to that question, but at this time, the FDA does not support this approach in the product insert. Studies will be done in the future to determine if patients who progress on anti-VEGF therapy can benefit from continued anti-VEGF therapy. Despite a lack of data, this is often being done in clinical practice.

Proteinuria appears to be a somewhat common AE with bevacizumab and possibly other anti-VEGF therapies. What should be done when a patient presents with proteinuria on therapy?

Dr. Joel Randolph Hecht First, in many of these trials patients with significant proteinuria were excluded from enrollment, which is always a problem when extrapolating from clinical trials. The bevacizumab prescribing information states that rare but significant nephrotic syndrome has been reported in various trials,¹ but I have seen little of this side effect.

Dr. Michael Gordon In general, patients who develop clinically significant proteinuria based upon a 24-hour collection, that is, more than 1 gram in 24 hours, should be carefully monitored. If persistent moderate or severe proteinuria is seen, then the physician should consider temporarily stopping the medication.

How soon after stopping bevacizumab or other VEGF antagonists is it safe to proceed with elective surgery?

JRH While the numbers are small, data from the Hurwitz trial² indicate that patients who went to surgery less than 1 month after stopping bevacizumab had a 4-fold increase in wound complications, which were generally not clinically severe. Out of 39 patients who had surgery within 1 month of receiving the study drug, 6 had wound complications—approximately 15%. In the placebo group, 25

patients had surgery within 1 month of the study, but only 1 patient had wound complications. Among those patients who had surgery 29 to 60 days after treatment, the rates did not differ. From this, it appears that there is a difference in complications between those who had surgery less than 1 month after stopping bevacizumab and more than 1 month after stopping bevacizumab, but this difference is not large. If a patient needs urgent or emergency surgery, having been on bevacizumab should never preclude them from that.

LE From the surgeon's perspective, it is better to be more conservative. The mean half-life of bevacizumab is about 20 days,¹ whereas the mean half-life of most of the oral TKIs is several hours to 2 days. Therefore, elective surgery is not an issue with the oral inhibitors. Generally, when a patient is on bevacizumab and needs to undergo hepatic resection, I would recommend 1 course of chemotherapy without bevacizumab and waiting a total of 8 weeks, or 2 half-lives, from the last dose of bevacizumab before surgery. However, there are no data to support that practice.

I think we have to be cautious. It is important for the medical oncologist and surgeons to interact with one another so that they can form a strategy prior to proceeding with surgery. Certainly, for elective surgery, physicians can plan ahead. For emergency surgery, I think the surgeon must be aware that there is a higher risk of complications, and they should probably err on the side of caution. For example, in an emergent operation for perforated diverticulum, I think retention sutures are warranted, whereas in many normal circumstances the surgeon would not opt for these sutures.

JRH The other question is how long to wait to restart the medication after surgery. While it is generally recommended to wait 1 month, there is honestly not a large amount of data to support or reject this time frame.

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Targeting VEGF—Current and Future Research Directions

CME Post-Test: Circle the correct answer for each question below.

1. VEGF:
 - a. Activates endothelial cells
 - b. Enhances endothelial cell survival, migration, and proliferation
 - c. Induces vascular permeability
 - d. All of the above
2. Bevacizumab:
 - a. Is approved first-line treatment of patients with metastatic colorectal cancer in combination with intravenous 5-FU-based chemotherapy
 - b. Is a monoclonal antibody
 - c. Is not active against platelet-derived growth factor
 - d. All of the above
3. Proposed mechanisms of action of anti-VEGF therapy include:
 - a. Normalization of tumor vasculature shortly after initiation of treatment
 - b. Direct action of anti-VEGF therapy upon tumor cells
 - c. Inhibition of NO and the resulting tumor vasoconstriction
 - d. All of the above
4. HIF-1 α , increased by deletion or silencing of the vHL gene, is associated with an increase in:
 - a. Erythropoietin
 - b. GLUT-1
 - c. VEGF
 - d. All of the above
5. Tyrosine kinase inhibitors to VEGF receptors inhibit the activity of the following except:
 - a. VEGFR-1
 - b. VEGFR-2
 - c. VEGFR-3
 - d. Neuropilin
6. Metastatic renal cell carcinoma:
 - a. Is associated with mutations in the vHL gene
 - b. Is associated with an increase in erythropoietin, GLUT-1, and VEGF
 - c. Is thought to be particularly susceptible to VEGF antagonists and VEGFR inhibitors compared to other cancers
 - d. All of the above
7. Which of the following therapies has not been tested for metastatic renal cell carcinoma?
 - a. Cetuximab plus bevacizumab
 - b. Erlotinib plus bevacizumab
 - c. BAY 43-9006
 - d. AG-013736
8. BAY 43-9006:
 - a. Selectively targets VEGFRs
 - b. Can be used in combination with bevacizumab in metastatic colorectal cancer
 - c. Doubled PFS compared to placebo in a phase III randomized study of patients with metastatic clear cell carcinoma of the kidney
 - d. Produces proteinuria as its major side effect
9. In a study comparing bevacizumab/cetuximab/irinotecan with bevacizumab/cetuximab in refractory colorectal cancer, the respective response rates were:

a. 40% vs 28%	b. 35% vs 23%
c. 26% vs 33%	d. 21% vs 19%
10. In the phase III trial by Hurwitz et al, the median PFS among patients receiving IFL plus bevacizumab was:

a. 8.9 months	b. 4.5 months
c. 10.6 months	d. 14.2 months

CME Request Form

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Targeting VEGF—Current and Future Research Directions

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PART 1

Tell us about you

1. What is your primary specialty or occupation? (Check one)

- Medical Oncology Pathology Surgery
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3. For how many years have you been active in this area? (Check one)

- <5 years 5–10 years 11–19 years
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2. What is your main activity? (Check one)

- Patient care Clinical research
 Administration Teaching/Training
 Other _____

PART 2

Tell us about how you experienced this educational program

4. This program had a number of education objectives; to what extent were these objectives met?

(Please circle the number that best reflects your view: -2 = poor, +2 = outstanding)

Discuss the potential mechanisms of action behind the antitumor effectiveness of anti-VEGF plus chemotherapy combinations

-2 -1 0 +1 +2

Discuss the results of clinical trials evaluating antiangiogenic therapy in the treatment of colorectal cancer.

-2 -1 0 +1 +2

Discuss the results of clinical trials evaluating antiangiogenic therapy in the treatment of renal cell carcinoma

-2 -1 0 +1 +2

5. As a result of this program, do you feel that you:

- | | | |
|---|-----|----|
| • Have increased your professional knowledge? | Yes | No |
| • Will change your disease management approach? | Yes | No |

6. Do you feel that the overall content of this activity was in any way biased and therefore impacted your educational experience? Yes No

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