Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

Anti-VEGF Therapies in the Clinic

Kellen L. Meadows and Herbert I. Hurwitz

Duke University Medical Center, Durham, North Carolina 27710

Correspondence: hurwi004@mc.duke.edu

The development and use of antiangiogenesis agents, particularly those targeting vascular endothelial growth factor (VEGF), has become an integral component of anticancer regimens for many tumor types. This review is intended to highlight some of the most important clinical successes and failures of anti-VEGF therapies, and where possible, to suggest important lessons that have been learned. This review emphasizes data from agents that have been FDA approved and/or have completed phase III studies.

Antiangiogenesis agents are among the most commonly used anticancer agents in the clinic today. By far the most commonly used antiangiogenesis agents are those targeting vascular endothelial cell growth factor (VEGF). This class is the primary focus of this review.

Bevacizumab was the first VEGF inhibitor approved for the treatment of cancer. Bevacizumab is currently approved by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMEA), and many other regulatory authorities for the treatment of colorectal, non-small-cell lung, breast, and renal cell cancers, and glioblastoma; as of the summer of 2011, the continuation of U.S. FDA approval for breast cancer is uncertain (Monthly Prescribing Reference 2011). Except for the glioblastoma indication, all of the bevacizumab approvals have been in combination with chemotherapy. Sunitinib (Sutent; Pfizer) is a multikinase inhibitor that inhibits VEGFR1, 2, 3, PDGFR, c-Kit, and RET. Sunitinib is FDA and EMEA approved for the treatment of renal cell cancer and for gastrointestinal stromal tumors (GISTs). The activity in GISTs is likely driven mostly by this agent's effects on c-Kit, the canonical driver mutation in that tumor type. Sorafenib (Nexavar; Onyx and Bayer) is a multikinase inhibitor that inhibits VEGFR1, 2, 3, PDGFR, c-Kit, RET, and Raf. Sorafenib is FDA and EMEA approved for the treatment of renal cell cancer and hepatocellular carcinoma (hepatoma). Pazopanib (Votrient; GlaxoSmithKline) is a multikinase inhibitor that inhibits VEGFR1, 2, 3, PDGFR, and c-Kit. Pazopanib is FDA and EMEA approved for the treatment of advanced renal cell cancer. Sunitinib, sorafenib, and pazopanib have been approved as monotherapies. Numerous other VEGF inhibitors are in various stages of clinical development. Those in late-stage (i.e., phase III) studies include brivanib alaninate (BMS-582664; Bristol-Myers Squibb), cediranib (Recentin; AstraZeneca; http://www.astrazeneca.com/Media/Press-releases/Article/20100528-AstraZeneca-Announces-Results-of-Recentin-HORIZON-II-), vandetanib (ZD6474, Zactima; AstraZeneca), motesanib (AMG 706, Amgen),

Editors: Michael Klagsbrun and Patricia D'Amore
Additional Perspectives on Angiogenesis available at www.perspectivesinmedicine.org

 doi: 10.1101/cshperspect.a006577
Cite this article as *Cold Spring Harb Perspect Med* 2012;2:a006577

linifanib (ABT 869, Abbott), and axitinib (AG-013736, Pfizer). A partial listing of these agents is in Table 1.

The question of whether antiangiogenesis agents "work" in the clinic depends in large part on what definition of "work" is used. The most common definition is usually regulatory approval (e.g., by the FDA or EMEA). It should be noted that the careful vetting by regulatory bodies is usually limited to large phase III studies. The end points for approvals may differ, such as overall survival (OS), progression-free survival (PFS) (tumor control), or response rate (RR) (tumor shrinkage). These end points, and their adjudication, can be complicated by many factors. These include access to the same or a similar treatment off protocol, in which case the question may not be simply comparing a new drug versus a standard comparator, but whether to use the new drug sooner versus later. Clinical efficacy and toxicity may be influenced by concurrent chemotherapy, the patient's cancer, and noncancer conditions that patients also have, particularly among older patients. Despite this complexity, anti-VEGF therapy has established itself as one of the most important classes of drugs for the treatment of human cancer.

EARLY CLINICAL DEVELOPMENT OF BEVACIZUMAB

The initial phase I studies with bevacizumab were notable for demonstrating that bevacizumab had good pharmacokinetic properties and was remarkably well tolerated (Gordon et al. 2001; Margolin et al. 2001). The plasma half-life was 21 d, which allowed dosing on an every 2 or 3 wk schedule. One patient did have a cerebrovascular bleed, but it was later noted that this patient had an occult central nervous system (CNS) metastasis that likely predisposed to this event. However, this event reenforced caution in treating patients who might also be at increased risk for vascular toxicities and was one of the reasons patients with brain metastases were excluded from early studies of bevacizumab. Doses of bevacizumab $\geq$0.3 mg/kg achieved target plasma levels that were predicted to be active based on preclinical models (Kim et al. 1993). These levels also appeared to clear all circulating VEGF (Gordon et al. 2001), although this determination was based on extrapolation because distinguishing free and bound VEGF was not possible on bevacizumab treatment. No clear signs of clinical activity were seen in this phase I study. Despite high enthusiasm for angiogenesis inhibitors at the time (Kolata 1998), the lack of single activity with bevacizumab was predictable because patients who participate in phase I studies usually have highly refractory cancers and preclinically bevacizumab was shown to slow or stop tumor growth but not to induce single agent responses (Warren et al. 1995).

A series of four randomized phase II studies with bevacizumab was initiated, three conducted by Genentech and one overseen by the National Cancer Institute (Cobleigh et al. 2003; Kabbinavar et al. 2003; Yang et al. 2003; Johnson et al. 2004). Two studies, one in colorectal and one in non-small-cell lung cancer, included standard chemotherapy and chemonaive patients. Two studies, one in metastatic breast cancer and one in metastatic renal cell cancer, used bevacizumab monotherapy and included patients who had progressed on prior treatments. All studies included a high and low dose of bevacizumab and a placebo. All studies strongly suggested that bevacizumab improved PFS, with trends for improved OS. Tumor RRs were increased in those patients treated with chemotherapy, and some tumor responses were also seen in the monotherapy studies. In general, very few side effects were attributable to bevacizumab, and the toxicity profile of the standard chemotherapy seemed unchanged. The lung cancer study, however, was complicated by several patients having severe hemoptysis, which was sometimes fatal. These events occurred primarily in subjects with central (vs. peripheral) lesions of squamous cell histology. Clinically, most lung cancers that are centrally located are of squamous cell histology, and these lesions are almost always near or abutting major vessels. Interestingly, many of the bleeding events occurred in the setting of tumor responses associated with cavitation. For this reason, patients with squamous cell histology

Table 1. Antiangiogenesis agents

Therapeutic agent	Agent description	FDA-approved indication	Selected phase III studies in nonapproved tumor types
Bevacizumab (Avastin; Genentech)	Humanized anti-VEGF mAb	1st line mCRC with intravenous 5′-FU-based chemotherapy 2nd line mCRC with intravenous 5′-FU-based chemotherapy 1st line NSCLC with carboplatin and paclitaxel 1st line renal with interferon alfa 2nd line GBM as monotherapy 1st line MBC with paclitaxel; currently being reconsidered	Ovarian: NCT00976911 (AURELIA), NCT01239732, NCT00483782 (ICON7), NCT00434642 (OCEANS) Gastric: NCT00548548 (AVAGAST), NCT00887822 Prostate: NCT00110214 Urinary tract: NCT00942331 Lymphoma (DLBCL): NCT00486759 Carcinoid: NCT00569127 GIST: NCT00324987 Head and neck: NCT00588770 Pancreas: NCT00088894
Sunitinib (Sutent; Pfizer)	Small molecule TKI: VEGFRs, PDGRs, c-kit, Flt3, Ret	1st line renal as monotherapy 2nd line GIST as monotherapy	PNET: NCT00428597; stopped early because of favorable efficacy interim results NSCLC: NCT00457392 Breast: NCT00393939, NCT00373256, NCT00373113 Colorectal: NCT00457691 HCC: NCT00699374; discontinued because of safety concerns
Sorafenib (Nexavar; Onyx/Bayer)	Small molecule TKI: VEGFRs, PDGRs, c-kit, Ret, Raf	1st line renal as monotherapy 1st line HCC as monotherapy	NSCLC: NCT00300885; terminated early because unable to meet primary end points NCT00449033 (NEXUS) NCT00863746 (MISSION) Thyroid: NCT00984282

Continued

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

Table 1. *Continued*

Therapeutic agent	Agent description	FDA-approved indication	Selected phase III studies in nonapproved tumor types
Pazopanib (Votrient; GlaxoSmithKline)	Small molecule TKI: VEGFRs, PDGRs, c-kit	1st line renal as monotherapy	Ovarian: NCT00866697 Sarcoma: NCT00753688 (PALETTE), NCT00794521 Breast: NCT00558103 NSCLC: NCT01208064
Brivanib alaninate (Bristol-Myers Squibb)	Small molecule TKI: VEGFs, PDGFRs, FGFRs	None to date	Colorectal: NCT00640471 HCC: NCT00908752 (BRISK-TA), NCT00858871 (BRISK FL), NCT01108705 (BRISK–APS)
Cediranib (Recentin; AstraZeneca)	Small molecule TKI: VEGFRs, c-kit, PDGFRs	None to date	Colorectal: NCT00399035 (HORIZON II), NCT00384176 (HORIZON III) NSCLC: NCT00795340 Ovarian: NCT00544973 GBM: NCT00777153 (REGAL)
Vandetanib (Zactima; AstraZeneca)	Small molecule TKI: VEGFRs, PDGFRs, EGFR, Ret	None to date	NSCLC: NCT00404924, NCT00312377 (ZODIAC), NCT00418886 (ZEAL), NCT00364351 (ZEST)
Linifinib (Abbott)	Small molecule TKI: VEGRs, PDGFRs	None to date	HCC: NCT01009593
Axitinib (Pfizer)	Small molecule TKI: VEGRs, PDGFRs, c-kit	None to date	Pancreatic: NCT00471146 Renal: NCT00920816, NCT00678392
Aflibercept (VEGF-Trap; Regeneron/ Sanofi-Aventis)	Recombinant VEGFR fusion protein that binds VEGF A and B, PIGF	None to date	Pancreatic: NCT00574275 (VANILLA); study terminated after interim analysis showed unable to show improved survival NSCLC: NCT00532155 (VITAL) Colorectal: NCT00561470 (VELOUR) Prostate: NCT00519285 (VENICE)

were excluded from the next series of non-small-cell lung cancer trials, until strategies to better understand and minimize this risk were worked out. Taken together, this suite of studies suggested that bevacizumab was sufficiently active and safe to justify phase III studies.

These phase II studies informed but did not definitively answer the optimal dose of bevacizumab in each setting. In the randomized colorectal cancer study, the lower-dose bevacizumab group (5 mg/kg every 2 wk = 2.5 mg/kg per week) appeared superior to the higher-dose group (10 mg/kg every 2 wk = 5.0 mg/kg per week equivalent). The reasons for this unexpected finding were unclear, although the patients in the higher-dose group may have had more unfavorable prognostic features. For this reason, the initial phase III study in the first line metastatic colorectal cancer (AVF2107g) selected the lower-dose bevacizumab, whereas the second line study (E3200) selected the higher dose (see below). Both studies were positive, which has led to some controversy related to which dose of bevacizumab is preferred in first versus second line and with different chemotherapy regimens. For essentially all subsequent first line studies in colorectal cancer, the 5 mg/kg dose has been used as the consensus standard or preferred dose. In the lung, breast, and renal cell cancer randomized phase II studies, trends favored the higher-dose groups, and for this reason, all phase III studies outside of colorectal cancer have tended to use the higher dose of bevacizumab (5 mg/kg per week equivalent).

COLORECTAL CANCER

The first FDA approval of a targeted antiangiogenesis treatment was for bevacizumab (Avastin; Genentech/Roche) when used in combination with an intravenous 5-fluorouracil (5-FU)-based chemotherapy regimen. The study leading to this approval randomized more than 800 patients to either standard chemotherapy consisting of Irinotecan, 5-FU, leucovorin (known as the "IFL" regimen) with placebo versus the same chemotherapy plus bevacizumab (Hurwitz et al. 2004). The bevacizumab dose was 5 mg/kg every 2 wk. The median survival improved from 15.6 to 20.3 mo, which was highly statistically significant and was one of the largest improvements ever reported in this patient group. The hazard ratio (HR) for OS was 0.65, meaning that the risk or hazard of dying over the period of follow-up was reduced by approximately one-third. The HR for PFS was 0.54, meaning that the risk of either disease progression or death was reduced by approximately half. The median PFS was increased from 6.2 to 10.6 mo. Interestingly, tumor RRs were also increased, from 34% to 45%.

This study helped to further define the safety profile of bevacizumab. Several side effects, which are now considered largely anti-VEGF class toxicities, were noted. Grade 3–5 (severe, life-threatening, or lethal) side effects were uncommon. Grade 3 hypertension, which at the time corresponded to the use of an additional outpatient antihypertensive medication, was seen in 11% of patients. No grade 4 hypertensive events were seen in this study. Other anti-VEGF toxicities occurred at rates ~1% higher in the bevacizumab group compared with the control group. These included arterial thromboembolic events, such as myocardial infarction or cerebrovascular events (2% vs. 1%), bleeding (3.1% vs. 2.5%), gastrointestinal perforation (1.5% vs. 0%), wound healing complications (1.3% vs. 0.5%), and proteinuria (any proteinuria 26% vs. 21%, but no difference in grade 2 or grade 3 proteinuria), respectively (Scappaticci et al. 2005, 2007; Avastin Prescribing Information, http://www.avastin.com/avastin/hcp/index.html).

Subsequent studies demonstrated that bevacizumab improved clinical outcomes with essentially all chemotherapy regimens with which it was combined, including IV 5-FU/leucovorin (Kabbinavar et al. 2005), oral 5-FU (capecitabine or Xeloda) (Tebbutt et al. 2010), and IV or oral 5-FU combined with oxaliplatin (FOLFOX or XELOX regimens) (Giantonio et al. 2007; Saltz et al. 2008). Improvements were also suggested when bevacizumab was combined with infusional 5-FU and irinotecan (FOLFIRI regimen) (Fuchs et al. 2007),

although this study's design precluded formal comparisons related to bevacizumab. PFS was improved in all of these studies. OS was significantly improved in only a few studies, although favorable trends were seen in all studies. RRs were increased in the majority, but not all, of these studies (Table 2).

The reasons for different outcomes remain controversial. All of these studies used bevacizumab at the 2.5 mg/kg equivalent (5 mg/kg every 2 wk or 7.5 mg/kg every 3 wk), except the one second line E3200 study. This makes dose an unlikely explanation, or at least one that is not readily testable. Differing biological effects with different chemotherapy regimens is another explanation, although the majority of clinical data do not support this hypothesis (Bendell et al. 2011). Another explanation is the potential for the cumulative toxicities and inconveniences of chemotherapy to preclude long-term treatment. When patients stop some of their treatment regimen, they are likely to stop all treatment. With the FOLFOX4 regimen, patients receive IV bolus and infusional 5-FU on Day 1 and Day 2, either in the clinic or hospital ward, every 14 d. This translates into 2–4 d out of every 2 wk dedicated to chemotherapy treatments, which can be hard to maintain for patients and their families, particularly for prolonged periods of time and particularly where treatment "holidays" are not part of the study protocol. In first line colon cancer therapy, most patients would be expected to stay on treatment for at least 9–11 mo (Hurwitz et al. 2004; Saltz et al. 2008; Hecht et al. 2009; Tol et al. 2009). No clinical subgroup (e.g., age, gender, performance status) appeared to benefit more or less from therapy (Kohne et al. 2002; Hurwitz et al. 2004).

The second line study conducted by ECOG randomized patients to FOLFOX, FOLFOX + bevacizumab, or bevacizumab monotherapy. The latter arm of this study is the largest bevacizumab monotherapy experience in metastatic colorectal cancer. The regimen of FOLFOX plus bevacizumab was superior for all outcomes; outcomes with FOLFOX alone were next best, and outcomes with bevacizumab monotherapy were the worst of the three groups. In the 243 patients who received bevacizumab monotherapy, the RR was 3%, which is biologically interesting but clinically not meaningful. Similarly, in this group the median PFS was 2.7 mo, which is similar to the PFS reported with best supportive care alone in this setting in other studies. These data suggested that bevacizumab, at least for colorectal cancer, is most active when given with chemotherapy and that 5-FU should be continued with bevacizumab until disease progression, even if the other cytotoxic parts of the chemotherapy regimen need to be stopped.

The issues of whether and how to continue bevacizumab after the chemotherapy regimen is no longer tolerable—so-called maintenance therapy—are controversial. Trial data are not mature enough to draw conclusions related to whether maintenance therapy is better than watchful waiting (complete treatment breaks) with retreatment at progression, or whether maintenance therapy should use bevacizumab as monotherapy or in combination with some chemotherapy (Dutch Colorectal Cancer Group, CAIRO 3, http://www.dccg.nl/trials/cairo3; Tabernero et al. 2010). Similarly, the issue of whether to continue bevacizumab after progression is also controversial, including the amount of progression and rate of progression that should trigger changes in treatment for an individual patient. Data from observational registries (not clinical trials) suggest that treatment with bevacizumab past progression improves patient outcomes, including survival (Kozloff et al. 2009). Importantly, these findings could be explained by patient selection factors alone (patients with more indolent biology are destined to receive more treatment), by a continued benefit with bevacizumab, or a hybrid of both explanations. Trials to formally address these issues are currently ongoing. These controversies highlight important fundamental questions related to the nature of tumor progression and resistance to anti-VEGF therapy.

Several small molecule inhibitors have also been tested in metastatic colorectal cancer, although all of these studies have been negative to date. These include phase III trials with

Table 2. Bevacizumab trials for FDA-approved tumor types

Clinical trial	Indication	Clinical stage	Treatment assignment	Median PFS (mo)	Response rate	Median overall survival (mo)
Colorectal						
Kabbinavar et al. 2003	1st line	Randomized Phase II	5-FU/LV alone	5.2	17%	13.8
			5-FU/LV/High dose bevacizumab: 10 mg/kg every 2 wk	7.2	24%	16.1
			5-FU/LV/Low dose bevacizumab: 5 mg/kg every 2 wk	9.0	40%	21.5
Kabbinavar et al. 2005	1st line for subjects deemed nonoptimal for 1st line irinotecan	Randomized Phase II	5-FU/LV/ bevacizumab	9.2	26.0%	16.6
			5-FU/LV alone	5.5	15.2%	12.9
			Bevacizumab 5 mg/kg every 2 wk	HR = 0.50, $p = 0.0002$	$p = 0.055$	HR = 0.79, $p = 0.16$
Hurwitz et al. 2004	1st line	Phase III	IFL/bevacizumab	10.6	44.8%	20.3
			IFL/placebo	6.2	34.8%	15.6
			Bevacizumab 5 mg/kg every 2 wk	HR = 0.54, $p < 0.001$	$p = 0.004$	HR = 0.66, $p < 0.001$
MAX III (Tebbutt et al. 2010)	1st line	Phase III	Capecitabine (C)	5.7	30.3%	18.9
			Capecitabine/bev (CB)	8.5	38.1%	18.9
			Capecitabine/bev/ mitomycin (CBM)	8.4	45.9%	16.4
			Bevacizumab at 7.5 mg/kg every 3 wk	C vs. CB: HR = 0.63, $p < 0.001$ C vs. CBM: HR = 0.59, $p < 0.001$	C vs. CB: $p = 0.16$ C vs. CBM: $p = 0.006$	[a]
E3200 (Giantonio et al. 2007)	2nd line	Phase III	FOLFOX4/ bevacizumab	7.3	22.7%	12.9
			FOLFOX4 alone	4.7	8.6%	10.8
			Bevacizumab monotherapy	2.7	3.3%	
			Bevacizumab 10 mg/ kg every 2 wk	FOLFOX/bev vs. FOLFOX alone: HR = 0.61, $p < 0.0001$	FOLFOX/bev vs. FOLFOX alone: $p < 0.0001$	HR = 0.75, $p = 0.0011$

Continued

Table 2. *Continued*

Clinical trial	Indication	Clinical stage	Treatment assignment	Median PFS (mo)	Response rate	Median overall survival (mo)
NO16966 (Saltz et al. 2008)	1st line	Phase III	FOLFOX4/ bevacizumab 5 mg/ kg every 2 wk XELOX/bevacizumab 7.5 mg/kg q 3 wk	FOLFOX 4 or XELOX/ bevacizumab = 9.4	FOLFOX4 or XELOX/bev = 47%	FOLFOX4 or XELOX/bev = 21.3
			FOLFOX4/placebo	FOLFOX4 or XELOX/ placebo = 8.0	FOLFOX4 or XELOX/placebo = 49%	FOLFOX4 or XELOX/placebo = 19.9
			XELOX/placebo	HR = 0.83, $p = 0.0023$	$p = 0.31$	HR = 0.89, $p = 0.0769$
BICC-C (Fuchs et al. 2007)	1st line	Phase III	FOLFIRI/ bevacizumab 5 mg/ kg every 2 wk	11.2	57.9%	[b]
			Modified bolus IFL/ bevacizumab 7.5 mg/kg every 3 wk	8.3 $p = 0.28$	53.3% [a]	19.2 $p = 0.007$
Breast						
Miller et al. 2005	Refractory	Phase III	Capecitabine/ bevacizumab 15 mg/kg every 3 wk	4.86	19.8%	15.1
			Capecitabine alone	4.17 HR = 0.98, $p = 0.857$	9.1% $p = 0.001$	14.5
ECOG 2100 (Miller et al. 2007)	1st line HER2 negative	Phase III	Paclitaxel/ bevacizumab 10 mg/kg every 2 wk	11.8	36.9%	26.7
			Paclitaxel alone	5.9 HR = 0.60, $p < 0.001$	21.2% $p < 0.001$	25.2 HR = 0.88, $p = 0.16$
AVADO (Miles et al. 2010)	1st line HER2 negative	Phase III	Docetaxel/ bevacizumab 15 mg/kg every 3 wk	10.0 P vs. placebo: $p < 0.001$	64.1% P vs. placebo: $p < 0.001$	30.2 P vs. placebo: $p = 0.85$
			Docetaxel/ bevacizumab 7.5 mg/kg every 3 wk	9.0 P vs. placebo: $p = 0.045$	55.2% P vs. placebo: $p = 0.07$	30.8 P vs. placebo: $p = 0.72$
			Docetaxel/placebo	8.1	46.4%	31.9

RIBBON-1 (Robert et al. 2009)	1st line HER2 negative	Phase III	Capecitabine/ bevacizumab 15 mg/kg every 3 wk	8.6	35.4%	29.0[c]
			Capecitabine/placebo	5.7 HR = 0.688, P vs. placebo: $p = 0.0002$	23.6% P vs. placebo: $p = 0.0097$	21.2[c] HR = 0.847, P vs. placebo: $p = 0.2706$
			Taxane or anthracycline/ bevacizumab 15 mg/kg every 3 wk	9.2	51.3%	25.2[c]
			Taxane or anthracycline/ placebo	8.0 HR = 0.644, P vs. placebo: $p < 0.0001$	37.9% P vs. placebo: $p = 0.0054$	23.8[c] HR = 1.032, P vs. placebo: $p = 0.8298$
RIBBON-2 (Brufsky et al. 2009)	2nd line HER2 negative	Phase III	Chemotherapy (taxane, gemcitabine, capecitabine, or vinorelbine)/ bevacizumab 10 mg/kg every 2 wk or 15 mg/kg every 3 wk depending on chemo regimen	7.2	39.5%	18.0
			Chemotherapy (taxane, gemcitabine, capecitabine, or vinorelbine)/ placebo	5.1 HR = 0.775, $p = 0.0072$	29.6% $p = 0.0193$	16.4 HR = 0.90, $p = 0.3741$
Non-small-cell lung cancer						
ECOG E4599 (Sandler et al. 2006)	1st line	Phase III	Paclitaxel/ carboplatin/ bevacizumab 15 mg/kg every 3 wk	6.2	35%	12.3
			Paclitaxel/carboplatin alone	4.5 HR = 0.66, $p < 0.001$	15% $p < 0.001$	10.3 HR = 0.79, $p = 0.003$

Continued

Table 2. *Continued*

Clinical trial	Indication	Clinical stage	Treatment assignment	Median PFS (mo)	Response rate	Median overall survival (mo)
Renal						
AVOREN (Escudier et al. 2010)	1st line	Phase III	Interferon/ bevacizumab 10 mg/kg every 2 wk	10.2	31%	23.3
			Interferon/placebo	5.4 HR = 0.63, $p < 0.001$	13% $p < 0.001$	21.3 HR = 0.86, $p = 0.1291$
Glioblastoma						
Friedman et al. 2009	Refractory	Randomized Phase II	Irinotecan/ bevacizumab 10 mg/kg every 2 wk	5.6	37.8%	9.2
			Bevacizumab 10 mg/ kg every 2 wk	4.2	28.2%	8.7
Kreisl et al. 2009	Refractory	Phase II	Bevacizumab 10 mg/ kg every 2 wk After tumor progression, bevacizumab 10 mg/kg every 2 wk/ irinotecan	16 wk	71% (Levin criteria)	31 wk

PFS, progression-free survival; HR, hazard ratio.
[a]Not statistically significant.
[b]Not yet reached at analysis.
[c]Represents 33% overall survival data.

SU5416 (semaxanib; SUGEN/Pfizer) (PR News Wire 2002), vatalinib (PTK787; Novartis) (Hecht et al. 2005), sunitinib (Sutent; Pfizer) (Murphy 2009), and cediranib (Recentin; AstraZeneca) (Robertson et al. 2009). The reasons for these failures where bevacizumab seems active remain to be elucidated. One possible explanation is that several of these agents have significant pharmacokinetic limitations, such as limited half-lives, limited absorption, and marked protein binding. Compared with bevacizumab, small molecule VEGF inhibitors tend to cause more fatigue and/or other CNS side effects (e.g., dizziness or ataxia) and more myelosupression (Hecht et al. 2005; Kohne et al. 2007; Yamamoto et al. 2009; Sutent Prescribing Information, http://www.pfizerpro.com/hcp/oncology/sutent/indication?rid=/wyeth_html/home/minisites/oncology/sutent/pi/highlights.html). When combined with chemotherapy, increases in these toxicities could lead to more dose reductions, interruptions, or discontinuations of chemotherapy and/or the anti-VEGF agent, adjustments that could affect efficacy. Several of these studies also included chemotherapy regimens that can be hard to maintain for prolonged periods of time, which may have obscured any ongoing benefit from the anti-VEGF therapy.

Interestingly, most small molecule VEGF inhibitors have been reported to increase plasma levels of VEGF on treatment (Herbst et al. 2007; Beaudry et al. 2008; Jain et al. 2009; Gerstner et al. 2010; Kopetz et al. 2010; Nikolinakos et al. 2010). Whether these elevations in VEGF are derived from the tumor or normal vasculature, or both, remains controversial (Kerbel 2008; Ebos et al. 2009b). In theory, up-regulated VEGF in the setting of subtherapeutic drug levels (because of pharmacokinetic issues and/or dose modifications or interruptions) could lead to increased VEGF signaling. This concern is theoretically more likely with small molecular inhibitors (most half-lives reported as 24 h or less) compared with bevacizumab (half-life of 21 d). There may be other ways in which depleting the VEGF ligand versus competitively inhibiting the VEGF receptor at the ATP binding site of its catalytic domain may have differing biological consequences.

Preclinical models suggested that antiangiogenesis therapy may be most effective for smaller tumors, where the "angiogenic switch" was easiest to stop or reverse (Hanahan and Folkman 1996; Korsisaari et al. 2007). For patients with localized colon cancer that has spread to the local lymph nodes, but no further, there is a significant risk of disease recurrence after the primary cancer has been surgically resected. This risk is reduced by the administration of chemotherapy (usually FOLFOX type regimen). Two studies have tried to address whether adding bevacizumab to this chemotherapy would help to further reduce disease recurrence and/or improve survival. The CO-8 trial was conducted by the NSABP (National Surgical Adjuvant Bowel and Breast Project) and compared 6 mo of standard chemotherapy with FOLFOX 6 to the same chemotherapy plus bevacizumab followed by 6 mo of additional bevacizumab monotherapy (Allegra et al. 2011). There was no difference in either disease-free survival or OS. A similarly designed international phase III study, known as AVANT, was conducted by Roche and also reported no significant difference among the arms for disease-free survival (Murphy 2010; De Gramont et al. 2011). Interestingly, this study reported a small but unexpected trend for worse disease-free survival in the bevacizumab groups. In both studies, a trend for improved disease-free survival was seen at the 1-yr time point, which coincided with the completion of the prescribed bevacizumab monotherapy. However, any suggested benefit at that time point was lost with longer follow-up. In addition, it appeared that tumor recurrence was only delayed but not prevented, and there was no impact on OS. Whether there was a modest effect during bevacizumab therapy and whether this effect was lost or there was some form of posttreatment tumor acceleration remain controversial. At this time, given the limited available data, it is not known whether these intriguing findings were due to biology or simply an artifact of study conduct.

BREAST CANCER

The first phase III study reported with bevacizumab was a study of capecitabine ± bevacizumab in refractory breast cancer (Miller et al. 2005). This study of 462 patients noted an improvement in RR (from 9% to 19%), but there was no difference in PFS or OS. The second phase III study in breast cancer tested a different chemotherapy and a different setting: weekly paclitaxel ± bevacizumab in first line metastatic breast cancer (Miller et al. 2007). This study, conducted by the Eastern Cooperative Oncology Group (ECOG Trial 2100), reported a marked improvement in PFS (HR 0.60; median PFS 11.8 vs. 5.9 mo) and RRs (27% vs. 21%) (Miller et al. 2007). These results were highly statistically significant. OS results were not as impressive (HR 0.88; median OS 26.7 vs. 25.2 mo). These data led the U.S. FDA to extend bevacizumab's approval to first line breast cancer. The reasons for the discordance between PFS and OS benefits remain controversial. Possible explanations include less mature data for survival (which usually occurs much later than disease progression) and confounding by numerous postprotocol therapies, including bevacizumab, and "rebound" of the tumor vasculature, where tumor growth may have been accelerated, at least temporarily, after discontinuation of bevacizumab. Preclinically, increased aggressiveness or invasiveness of tumors treated with different VEGF inhibitors, particularly when treatment is interrupted, has been reported in several, but not all, tumor models (Paez-Ribes et al. 2009). Modeling this effect in the clinic is difficult. The largest and most systematic analysis of how patients progressed after bevacizumab was discontinued analyzed data from 4205 patients and found no evidence for "rebound," although this analysis was not designed to formally exclude this possibility, particularly if this phenomenon might apply only to a minority of patients (Miles et al. 2011).

More recently, several additional studies in first and second line advanced breast cancer have been reported: AVADO (docetaxel ± bevacizumab, 1st line), RIBBON-1 (Avastin with either capecitabine, taxane, or anthracycline, first line), and RIBBON-2 (Avastin with either capecitabine, gemcitabine, taxane, or vinorelbine, second line). AVADO, which included 736 patients, was a randomized double-blinded study comparing every 3 wk docetaxel, docetaxel plus low-dose bevacizumab (7.5 mg/kg every 3 wk, 2.5 mg/kg equivalent), or docetaxel plus high-dose bevacizumab (15 mg/kg every 3 wk, 5.0 mg/kg equivalent) (Miles et al. 2010a). RIBBON-1, which included 1237 patients, compared several standard chemotherapy regimens (taxane, anthracycline-based combination, or capecitabine) with or without bevacizumab (Robert et al. 2009). RIBBON-2 enrolled 684 patients and compared several standard chemotherapies (taxane, gemcitabine, capecitabine, vinorelbine) with or without bevacizumab (Brufsky et al. 2009). In these studies, bevacizumab added no survival advantage, and the PFS benefits were more modest than those seen in the ECOG Trial E2100 above (Table 2). The HR for PFS in AVADO was 0.67 for higher-dose bevacizumab and 0.80 for the lower-dose bevacizumab; in RIBBON-1, the HR for PFS was 0.64 for the taxane/anthracycline subgroup and 0.69 for the capecitabine subgroup. Although all of these improvements were statistically significant, they translated into median improvements in PFS of only 1.9, 0.9, 2.9, and 1.2 mo, respectively. AVADO was designed to compare higher and lower doses of bevacizumab to placebo, but not to each other. Although there was no statistically significant difference between the higher- versus lower-dose bevacizumab groups, PFS and tumor responses were numerically superior in the higher-dose group (PFS HR, 0.67 vs. 0.80; relative risk [RR], 64% vs. 55%). The second line RIBBON-2 study had an HR for PFS of 0.78, which was statistically significant, and an HR for OS of 0.90, which was not statistically significant. In later lines of therapy, the end point of overall survival is particularly important, because there are fewer subsequent lines of therapy that may confound that end point.

Interpretations of these data are highly controversial. These data could reflect true biological differences and/or interaction with different

chemotherapies. These results may also have been affected by variation in study conduct, limited maturity of survival data, access to bevacizumab off protocol, and the amount of treatment and relatively long time patients survived after protocol-defined treatment. Interesting, ~50% of patients on the control arms and ~40% of patients in the bevacizumab arms of these studies received bevacizumab as some component of their postprotocol therapy (O'Shaughnessy et al. 2010). Regardless of these potential confounders, these improvements in PFS taken as a whole were considered sufficiently modest that the FDA has recommended removing bevacizumab's approval for the treatment of metastatic breast cancer (FDA 2010). Small molecule VEGF inhibitors have also been studied in metastatic breast cancer, although there have been only a few phase III studies reported to date, and most of these studies have not yet been published. Sunitinib was evaluated in two phase III studies: a first line study with docetaxel ± sunitinib (SUN1064 study) in Her2/neu-negative cancers and a second line study of capecitabine ± sunitinib (SUN1099 study). Both studies failed to meet their primary end points.

NON-SMALL-CELL LUNG CANCER

There have been several studies evaluating VEGF inhibitors in non-small-cell lung cancer. Patients with non-small-cell lung cancer have several special management issues. These patients will often have some degree of hemoptysis, tumors that are near major blood vessels, active coronary or cerebrovascular disease, and brain metastases at some point in their disease course. The first positive lung cancer study was ECOG E4599 (Sandler et al. 2006). This study randomized 878 patients to standard every-3-wk carboplatin plus paclitaxel chemotherapy with or without bevacizumab (15 mg/kg every 3 wk; 5 mg/kg per week equivalent). All end points of clinical benefit were improved. The HR for OS was 0.79, and the median OS increased from 10.3 to 12.3 mo. The HR for PFS was 0.69, and the median PFS increased from 4.5 to 6.2 mo. Tumor RRs improved from 15% to 35%. All of these results were highly statistically significant. To minimize the risk of severe bleeding, which had been noted in the earlier phase II studies, patients with squamous cell histology, more than scant hemoptysis (more than one-half teaspoon per event), brain metastases, or who needed full-dose anticoagulation or more than baby doses of aspirin were excluded from this study. With these precautions, the rates of clinically significant bleeding were 4.4% versus 0.7%, for the bevacizumab versus control groups, respectively.

This initial U.S.-based phase III was followed up by an international phase III study known as the AVAiL (AVastin in Lung Cancer) study (Reck et al. 2010). In AVAiL, 1043 patients with advanced, non-squamous non-small-cell lung cancer were randomly assigned to gemcitabine and cisplatin, this chemotherapy plus higher-dose bevacizumab (15 mg/kg every 3 wk, 5 mg/kg per week equivalent) or this chemotherapy plus lower-dose bevacizumab (7.5 mg/kg every 3 wk, 2.5 mg/kg per week equivalent). As with the AVADO breast cancer study, AVAiL was designed to compare higher-dose bevacizumab and lower-dose bevacizumab with placebo but not with each other. AVAiL confirmed a PFS and tumor response benefit with the addition of bevacizumab. There was no difference in outcomes between the higher- and lower-dose bevacizumab groups. A minor numerical advantage was noted for the lower-dose group (PFS HR, 0.75 vs. 0.82; RR, 34% vs. 30%), although these differences were statistically nonsignificant. The suggestion of small but potentially clinically meaningful differences between the E4599 and AVAiL studies, which differed in their chemotherapy regimens, again raises the possibility, however unlikely, of special interactions between bevacizumab and different chemotherapies.

Multiple small molecule VEGF inhibitors have been evaluated in non-small-cell lung cancer. To date, all reported phase III results have been negative; unfortunately, few of the negative trials have yet been published. Sunitinib was evaluated in a large second line phase III study of erlotinib ± sunitinib (PR News Wire 2010). Sorafenib was evaluated in two large first line

phase III studies: carboplatin and paclitaxel ± sorafenib (ESCAPE trial) (Scagliotti et al. 2010) and gemcitabine and cisplatin ± sorafenib (Nexus study). Vandetanib (Zactima; AstraZeneca), which inhibits VEGF receptors as well as EGFR, was evaluated in four large phase III trials: a second line study of docetaxel ± vandetanib (ZODIAC trial); a second line study of pemetrexed ± vandetanib (ZEAL trial); a second line study of erlotinib versus vandetanib (ZEST trial); and a third line study of best supportive care (placebo) versus vandetanib (ZEPHYR) (De Boer et al. 2009; Natale et al. 2009; Herbst et al. 2010; Mirshahidi and Hsueh 2010).

RENAL CELL

Renal cell cancer appears to be the most responsive tumor type to VEGF inhibitors in the clinic. This is likely due to the highly angiogenic phenotype in these cancers driven by the frequent mutation of the VHL (von Hippel–Lindau) gene in these cancers. VHL targets Hif1α, among other proteins, for degradation in the proteosome. When VHL is mutated, Hif levels increase, leading to up-regulation of numerous Hif-responsive angiogenic genes and their proteins, including VEGF, PDGF, HGF, angiopoetins, and inflammatory cytokines such as SDF1 and IL6 (Schioppa et al. 2003; Staller et al. 2003; Carmeliet 2005). The constitutive up-regulation of many factors beyond VEGF may make this tumor type particularly sensitive to agents such as multikinase VEGF inhibitors that block several factors concurrently.

All four VEGF inhibitors (sorafenib, sunitinib, pazopanib, bevacizumab) and the two mTOR inhibitors (temsirolimus, everolimus) that are FDA approved for the treatment of cancer are approved for the treatment of renal cell cancer. Sorafenib was approved based on a large phase III comparison of sorafenib versus best-supportive-care patients with clear cell RCC who experienced treatment failure with one prior systemic therapy (Treatment Approaches in Renal Cancer Global Evaluation Trial, TARGET) (Escudier et al. 2007, 2009). Sorafenib markedly improved PFS (HR 0.44, median PFS 5.5 vs. 2.8 mo), a result that was highly statistically significant. Once mature survival data were available, the group assigned to sorafenib was found to have modestly improved OS compared with the placebo control group (HR .88, median OS 17.8 vs. 15.2 mo), a result that was of only borderline statistical significance. The survival end point was likely confounded by the frequent crossover to sorafenib by patients in the control group at progression, which meant that the comparison was not simply sorafenib versus placebo, but earlier versus later use of sorafenib. When this crossover was accounted for, the impact on survival was more robust (HR 0.78, median OS 17.8 vs. 14.3 mo), a result that was statistically significant.

Sunitinib was approved based on a large phase III study in treatment naive patients with clear cell renal cell cancer who were randomized to sunitinib versus interferon-α (Motzer et al. 2007). PFS was markedly improved (HR 0.42, median PFS 11 vs. 5 mo), as was tumor response (RRs, 31% vs. 6%). Survival data were not mature enough for analysis, but trends also favored the sunitinib group. Sunitinib also appears active in cytokine (interferon and/or IL2) refractory patients. In two non-randomized single arm studies, ~35% of patients achieved a partial response (Rosenberg et al. 2007; Sutent Prescribing Information, http://www.pfizerpro.com/hcp/oncology/sutent/indication?rid=/wyeth_html/home/minisites/oncology/sutent/pi/highlights.html).

Pazopanib was approved for the treatment of renal cell cancer based on a large phase III study that included patients with treatment-naive and cytokine-refractory renal cell cancer (Sternberg et al. 2010). Patients were randomized to pazopanib versus best supportive care. PFS was significantly prolonged in the treatment-naive subgroup (HR 0.40, median PFS 11.1 vs. 2.8 mo), and the cytokine-pretreated subgroup (HR 0.54, median PFS 7.4 vs. 4.2 mo). The tumor RRs were also increased (30% vs. 3%).

Bevacizumab was approved for the treatment of renal cell cancer based on a large phase III study that randomized 649 patients to interferon alfa2a ± bevacizumab (AVOREN, Avastin and Roferon in renal cell cancer) (Escudier et al. 2010). PFS was significantly improved

(HR 0.60, median PFS 10.2 vs. 5.4 mo), as was tumor RR (30% vs. 12%). Both results were highly statistically significant. OS, which may have been confounded by access to various VEGF inhibitors outside of the study, was numerically but not statistically significantly better (HR 0.86, median OS 23.3 vs. 21.3 mo). A similarly designed study of more than 700 patients conducted in the United States (CALBG 90206) found comparable results. PFS was improved (HR 0.71, median PFS 8.5 vs. 5.2 mo), as was tumor response (26% vs. 13%) (Rini et al. 2008a).

Reliable comparisons between individual studies are not possible. Patient populations differed with respect to prior treatment and percent of patients with favorable or unfavorable prognostic factors; comparator treatments also varied (best supportive care, interferon vs. new treatment, or interferon ± new treatment) (Motzer et al. 2002; Negrier et al. 2002; Mekhail et al. 2005). Nevertheless, the similarity in reported PFS and RRs across these studies is intriguing. In addition, when tumor responses occurred, they were remarkably durable, lasting on average approximately a year or more (Motzer et al. 2007; Escudier et al. 2009; Sternberg et al. 2010). Interestingly, antitumor activity has been reported in some patients who have progressed on one VEGF inhibitor when they are rechallenged with a different VEGF inhibitor (Medical News Today 2010; Hutson et al. 2011). These findings raise important questions related to the mechanisms of resistance to anti-VEGF therapy, including whether those mechanisms can be reversed by a treatment interruption and/or by switching the inhibitor.

Two mTOR inhibitors have also been approved for the treatment of renal cell carcinoma. mTOR is a key downstream signaling node for many receptor tyrosine kinases, including VEGF receptors. In addition, mTOR serves as a critical nutrient sensor, linking numerous metabolic, proliferative, survival, and angiogenic responses (Dancey 2010). mTOR is also a regulator of Hif-α (Hudson et al. 2002). Temsirolimus is an esterified prodrug of rapamycin that is administered intravenously. In a large phase III trial, chemo-naive patients with poor prognostic features were randomized to temsirolimus (25 mg weekly), interferon alfa (3–18 MU three times per week), or a combination of temsirolimus (15 mg weekly) plus reduced dose interferon alfa (3–6 MU three times per week) (Hudes et al. 2007; Torisel Prescribing Information, http://www.torisel.com/Prescribing-Information.aspx). Compared to interferon alone, temsirolimus monotherapy improved OS (HR 0.73, median 10.9 vs. 7.3 mo), PFS (HR 0.63, median 5.5 vs. 3.1 mo), and RR (8.6% vs. 4.8%). Everolimus (Afinitor in the United States; Novartis) is an oral rapamycin analog that was initially developed as an immunosuppressant to prevent allograft rejection following solid tumor transplant (Certican in Europe) (Afinitor Prescribing Information, http://www.afinitor.com/index.jsp?site=PC018103&source=01030&irmasrc=ONCWB0042; Certican Prescribing Information, http://www.health.gov.il/units/pharmacy/trufot/alonim/CERTICAN_DR_Alon_ Doctor_Internet_1265520370563.pdf). In a large phase III study, patients with advanced clear cell renal cell carcinoma who had disease progression on a VEGF inhibitor were randomized to everolimus versus placebo with best supportive care (Motzer et al. 2008). PFS was significantly improved (HR 0.33, median PFS 4.0 vs. 1.9 mo). Tumor responses were rare, only 1% versus 0%. OS, which may have been confounded by patients in the control arm crossing over to everolimus at progression, had a nonsignificant trend in favor of everolimus (HR 0.87, median 14.8 vs. 14.4 mo). When the confounding from crossover was accounted for, survival was 1.9-fold longer for patients randomized to everolimus; these results were statistically significant (CI 0.5–0.85, median 14.8 vs. 10.0 mo) (Motzer et al. 2010).

GLIOBLASTOMA

Glioblastoma is known to be highly vascular and to overexpress VEGF, among many other angiogenic factors. Tumor vascularity is used as a criterion for the pathological grading of glioblastoma. Because the skull limits the capacity of the brain to deal with swelling, VEGF-driven tumor edema, beyond isolated

tumor enlargement or invasion, is a significant clinical issue in these patients because the associated increases in intracranial pressure can directly compromise neurological function. Tumor bleeding related to vascular fragility can also be devastating. Common supportive care treatments for these patients raise special issues. For example, steroids, which are commonly used for the control of tumor edema, can have significant side effects. Venous thromboembolic disease, which requires full-dose anticoagulation, is also common in these patients. Steroids and anticonvulsants, which can up-regulate the cytochrome p450 system, can markedly affect the metabolism of many drugs. In addition, antibodies and many small molecules cannot cross the normal blood–brain barrier. The clinical importance of these findings with anti-VEGF treatments for brain tumor patients is not clear because the blood–brain barrier is already disrupted in hyperpermeable tumor blood vessels. VEGF drives this hyperpermeability, which, in turn, leads to tumor edema and contrast enhancement on CT and MRI scans. Improvement in these parameters has sometimes been attributed to "normalization" of the vasculature, particularly in the setting of additional changes in vessel anatomy and pericyte coverage (Jain 2005, 2007). Vascular normalization is usually expected to improve drug delivery, but this may not apply in all settings; in addition, the extent and duration of any normalization may also vary among patients and among tumor types. Changes in edema and permeability with anti-VEGF treatment could also be distinct from changes in tumor size per se but might still be clinically beneficial. The fixed structure of the brain greatly facilities the use of high-resolution MRI and PET scans, and for these reasons, some of the most elegant work on tumor perfusion has been done in brain tumor patients (Batchelor et al. 2007). These issues, not unexpectedly, have both enabled and complicated the development of antiangiogenesis treatment in patients with brain tumors.

In this context, bevacizumab was FDA approved for the treatment of refractory glioblastoma when used as monotherapy. This approval was based on tumor responses that were seen in ~20%–25% of patients treated with bevacizumab monotherapy in two modest-sized studies (Friedman et al. 2009; Kreisl et al. 2009). The first study randomized 167 patients to bevacizumab or to bevacizumab plus irinotecan, based on earlier promising activity of that combination (Friedman et al. 2009). The second study was a single arm study of 56 patients (Kreisl et al. 2009). In both studies, bevacizumab was well tolerated and significant toxicities, including CNS bleeding, were rare. Many other VEGF inhibitors and other antiangiogenesis agents are in clinical trials in glioblastoma. The only phase III study reported to date, the REGAL study, evaluated cediranib monotherapy (at 30 mg/d) versus lomustine plus cediranib (20 mg/d) versus lomustine plus placebo (Johnson 2010). Although there was a numerical trend in PFS favoring the combination of lomustine plus cediranib, the difference was not statistically significant, and there was no difference in OS. Interestingly, an earlier phase II study used a dose of 45 mg/d of cediranib (Ramalingam et al. 2010) but found that that dose was not well tolerated, mostly because of fatigue, which is a common problem in many cancer patients, especially brain tumor patients. The potential for otherwise modest toxicities to limit the long-term tolerability of small molecule VEGF tyrosine kinase inhibitors has been seen with other agents and other diseases as well (Hecht et al. 2005; Kohne et al. 2007; Cunningham et al. 2008; Robertson et al. 2009; Docguide 2010). It is intriguing to speculate whether the apparent differences in outcomes with different anti-VEGF therapies are driven by differing biological effects or differences in tolerability and dose intensity.

HEPATOCELLULAR CARCINOMA

The development of treatments for patients with hepatocellular cellular cancer or hepatoma has been complicated by the medical complications associated with liver dysfunction and cirrhosis, which are the major risk factors for developing this cancer. The consequences of

cirrhosis include portal hypertension, varices that are prone to bleeding, coagulopathies, thrombocytopenia, and abnormal drug metabolism. Given these difficulties, the impact of sorafenib on this cancer was a key advance for the treatment of these patients, which is currently only VEGF inhibitor approved for the treatment of hepatoma. Sorafenib was approved by the U.S. FDA, EMEA, and other regulatory bodies for the treatment of hepatoma based on a large randomized trial known as SHARP (Llovet et al. 2008). In this trial, patients with chemo-naive hepatocellular cancer and no worse than mild cirrhosis (Childs A classification) were randomized to sorafenib versus placebo. OS was improved (HR 0.69, median 10.7 vs. 7.9 mo), as was PFS (HR 0.58, median 5.5 vs. 2.8 mo); both results were highly statistically significant. Despite this notable effect on tumor control, only 2% of patients on sorafenib had a partial response. Several other VEGF inhibitors are in large clinical trials in hepatoma. The only phase III study reported to date is a phase III trial of sunitinib versus sorafenib (SUN 1170 study). Although study details have not yet been released, this study was discontinued early because of a higher incidence of serious adverse events and inferior activity in the sunitinib arm (News Medical 2010). Additional studies with other VEGF inhibitors are expected to be completed in the near future.

OTHER TUMOR TYPES

Despite many successes, there have been numerous studies in other tumor types with VEGF inhibitors with only modestly positive or frankly negative results. A large phase III advanced pancreatic cancer study of gemcitabine ± bevacizumab found no difference in overall or PFS between the two treatment arms (Kindler et al. 2010). A similarly designed study in pancreatic cancer with gemcitabine + erlotinib + bevacizumab found a modest improvement in PFS but no difference in OS (Van Cutsem et al. 2009b). Other pancreatic phase III studies of gemcitabine + aflibercept (VANILLA study) and gemcitabine + axitinib have been reported as negative also, although these results are not yet published (Medical News Today 2009; Sanofi-Aventis 2009).

In metastatic gastric cancer, a large phase III study of capecitabine + cisplatin + bevacizumab (AVAGAST study) found a modest but statistically significant improvement in PFS; a favorable trend in OS, the study's primary end point, was not statistically significant (Kang et al. 2010). Intriguingly, preplanned subset analyses suggest that treatment efficacy may differ in different regions of the world. The epidemiology of gastric cancer, as well as the non-study-related management of this cancer, is known to vary in different geographic regions (Shah and Kelsen 2010).

In metastatic castrate-resistant prostate cancer, a large phase III study randomized more than 1000 men to docetaxel with dexamethasone and prednisone versus the same treatment plus bevacizumab (Kelly et al. 2010). This study found that the addition of bevacizumab conferred modest but statistically significant improvements in PFS (HR 0.77, median 9.9 vs. 7.5 mo), tumor response (53% vs. 42%), and blood PSA (prostate-specific antigen) response (70% vs. 58%). However, OS, the primary end point for the study, was not significantly improved (HR 0.91).

In ovarian cancer, a large randomized study (GOG -0218) showed mixed results. More than 1800 women with epithelial ovarian cancer were randomized to standard chemotherapy with carboplatin + paclitaxel (6 mo) versus carboplatin + paclitaxel + bevacizumab during chemotherapy (6 mo), or carboplatin + paclitaxel + bevacizumab (during chemotherapy and for six additional months as monotherapy) (Burger et al. 2010). There was no improvement in any outcome with the addition of only bevacizumab during chemotherapy. The third arm, which added bevacizumab during and after chemotherapy, improved PFS (HR 0.72, median 14.1 vs. 10.3 mo), which was statistically significant; however, OS was not increased.

ANTI-VEGF TOXICITIES

Anti-VEGF treatments in general have been relatively well tolerated, particularly compared with traditional chemotherapy. This may relate

to the tumor specificity of VEGF expression and/or the redundancy of angiogenesis in the host. Themes have emerged related to what are likely class-related side effects, which provide important insights into the effect of target modulation in the host, not just the tumor. However, biologically and clinically important differences among these agents are likely, related to distinct mechanisms of target modulation, off-target effects, pharmacokinetic differences, and ability to cross the blood–brain barrier. Cross-study comparisons, among agents and even for the same agent, are difficult because the reported side effects may differ owing to differences in patient populations, durations of treatment, concurrent chemotherapies, and methods of tracking and attributing side effects. The largest analyses, particularly across different studies, have so far been largely limited to bevacizumab.

Hypertension that requires some medical intervention has been reported in ~10%–20% of patients treated with VEGF inhibitors (Afinitor Prescribing Information, http://www.afinitor.com/index.jsp?site=PC018103&source=01030&irmasrc=ONCWB0042; Avastin Prescribing Information, http://www.avastin.com/avastin/hcp/index.html; Sorafenib Prescribing Information, http://www.pfizerpro.com/hcp/oncology/sutent/indication?rid=/wyeth_html/home/minisites/oncology/sutent/pi/highlights.html; Torisel Prescribing Information, http://www.torisel.com/Prescribing-Information.aspx; Votrient Prescribing Information, https://www.gsksource.com/gskprm/en/US/adirect/gskprm?cmd=ProductDetailPage&product_id=1279563278373&featureKey=601903). Severe hypertension is uncommon, usually in <0.1% of patients. Blood pressure is a complex outcome because it can be influenced by many factors, including preexisting conditions (including hypertension), chemotherapy and its side effects, other medications, activity, and diet, many of which may change over the course of a patient's course of treatment. In preclinical models and in patients, anti-VEGF-related hypertension is likely mediated by alterations in nitric oxide signaling (Nixon et al. 2007; Facemire et al. 2009). Multiple anti-hypertensives agents have been used, with none clearly superior in the clinic.

Because blood pressure is a known on-target effect for anti-VEGF agents, blood pressure is a potential pharmacodynamic marker for anti-VEGF therapy. For this reason, there have been several reports correlating treatment-related blood pressure changes with clinical outcome (Friberg et al. 2005; Holden et al. 2005; Rixe et al. 2007; Rini et al. 2008b; Bono et al. 2009). The majority of pilot and cooperative group studies have used the NCI common toxicity criteria, which are largely based on the treating oncologist's decision that the patient's blood pressure requires additional antihypertensive medications [NIH 2006, "Common Terminology Criteria for Adverse Events v3.0 (CTCAE)"]. The largest and most detailed analysis on the topic analyzed eight phase III controlled trials with bevacizumab that were conducted by Genentech or Roche. This analysis used patient-specific data, including individual blood pressure values (Hurwitz et al. 2010). This analysis found that treatment-related hypertension did not predict for benefit from bevacizumab. It is not uncommon for a pharmacodynamic marker to not also be a predictive marker, likely because different outcomes can have different dose–response relationships. Because hypertension is a known risk for more severe complications, such as myocardial infarction and cerebrovascular events, these data suggest that hypertension should be managed with standard treatments and that strategies to not treat hypertension or to increase the dose of treatment to a given point of hypertension are likely not useful (Ryanne Wu et al. 2009).

Arterial thromboembolic events (ATEs), such as myocardial infarction and cerebrovascular events, are increased with anti-VEGF therapies (Avastin Prescribing Information, http://www.avastin.com/avastin/hcp/index.html; Sorafenib Prescribing Information, http://www.pfizerpro.com/hcp/oncology/sutent/indication?rid=/wyeth_html/home/minisites/oncology/sutent/pi/highlights.html; Votrient Prescribing Information, https://www.gsksource.com/gskprm/en/US/adirect/gskprm?cmd=ProductDetailPage

&product_id=1279563278373&featureKey=601903). In unselected patients, bevacizumab increases this risk by approximately twofold, from ~1% to 2% (Scappaticci et al. 2007). This risk is increased further by other known risk factors for ATE, including older age and history of a prior ATE.

GI perforation and wound healing complications have also been reported in ~1%–2% of patients treated with bevacizumab plus chemotherapy (Scappaticci et al. 2007). It is likely that several conditions predispose to the risk of perforation, including intraperitoneal cancer, prior abdominal surgery, and chemotherapy-related enteritis. It does not appear that perforation risk is significantly increased by the presence of an otherwise asymptomatic primary tumor (Poultsides et al. 2009).

Wound healing complications also appear to be increased. In the setting of surgery followed by treatment once the wound has healed, the risk of a significant wound healing complications is increased from ~0.5% to 1.3% (Scappaticci et al. 2005; Allegra et al. 2011). In high-risk settings, when patients undergo emergent surgery usually involving a large laparotomy for complications of cancer progression, the risk of surgical complications appears to be increased from ~3% to 13%. Under more controlled circumstances, such as elective resection of liver metastases where bevacizumab is discontinued at least a month before surgery, the rate of surgical complications does not appear to be increased compared with historical controls (Grothey et al. 2008; Kesmodel et al. 2008; Van Cutsem et al. 2009a).

The contribution of bevacizumab to venous thromboembolism is controversial (Nalluri et al. 2008; Lyman and Khorana 2009; Cassidy et al. 2010). One meta-analysis found that bevacizumab increased this risk (Nalluri et al. 2008). The largest analysis of the topic used patient-specific data across 10 phase III Genentech- or Roche-sponsored studies (Cassidy et al. 2010). This analysis found no increased risk related to bevacizumab, using either crude event rates or after adjusting for observation time, which was generally longer in the bevacizumab groups. The apparent differences in ATE versus VTE (venous thromboembolic event) risks may have many explanations, including distinct pathophysiologies underlying these events. For example, arterial events may be more dependent on endothelial cell function, and venous events may depend more on alterations in coagulation, which may even be improved to the degree the tumor vasculature is normalized.

BIOMARKERS

Multiple groups have shown that increased levels of various angiogenesis factors, including VEGF, correlate with worse prognosis or outcome in general (Poon et al. 2001). Similarly, several groups have described in patients changes in various angiogenesis factors with anti-VEGF treatment, including VEGF, PlGF, SDF1, Ang2, and sVEGFR2, among others (Hanrahan et al. 2009, 2010; Jain et al. 2009; Nixon et al. 2010). Many of these changes are seen in preclinical models, even in non-tumor-bearing mice, suggesting that these responses are at least partially host-derived (Ebos et al. 2007, 2009a). In preclinical models, factors mediating resistance to anti-VEGF therapy have been well described (Shojaei et al. 2007; Crawford et al. 2009). In the clinic, however, markers that predict which patients will derive greater or lesser benefit from anti-VEGF therapy have been elusive. This may relate to many factors, including technical limitations in assay methods and target abundance or stability. The difficulty in identifying such biomarkers may also relate to the context and complexity of coregulation and counterregulation of angiogenesis. Lastly, this information can only be reliably derived from large randomized trials.

Several studies have sought to identify markers that would predicted which patients would or wound not benefit from anti-VEGF therapy, Initial studies using randomized trials evaluated tumor and stromal VEGF expression by immunohistochemistry and by in situ hybridization using archived paraffin-embedded tumor samples (Jubb et al. 2003); these studies also evaluated vascular density and a limited number of other angiogenic

factors and oncogenes known to regulate important angiogenesis factors (Jubb et al. 2006). Although many of these factors were found to be prognostic, none predicted benefit (or lack of benefit) from bevacizumab. Interestingly, in several tumor types, plasma VEGF levels did not predict for benefit from bevacizumab (Bernaards et al. 2010).

Analysis of multiple cytokines at the same time may allow for more nuanced, if somewhat more complicated, predictive models. Using the E4599 non-small-cell lung cancer trial, Dowlati and colleagues measured several angiogenic factors and found that baseline ICAM levels were prognostic for survival and predictive of response to chemotherapy with or without bevacizumab; VEGF levels were predictive of tumor response to bevacizumab but not OS (Dowlati et al. 2008). Heymach and colleagues evaluated baseline and treatment-related changes in multiple angiogenic factors in patients on several phase II trials; in these trials, patients were treated with vandetanib versus erlotinib, docetaxel ± vandetanib, and vandetanib versus carboplatin/paclitaxel, respectively (Hanrahan et al. 2009, 2010). All three studies suggested that lower baseline VEGF correlated with improved PFS and higher baseline VEGF levels correlated with similar or worsened PFS. Changes in cytokine profiles on treatment and progression were distinct for different treatments and suggested a role for several inflammatory cytokines, including IL8, MMP9, VEGF, and ICAM-1. Although intriguing, conclusions from these studies are limited by the modest number of patients in each group and the fact that vandetanib failed to meet its primary end point in similarly designed phase III studies (Natale et al. 2009; Herbst et al. 2010).

Several more recent analyses of phase III studies have reported more promising results, with the identification of several markers of sensitivity and resistance to VEGF inhibitors. The largest effort to date has been conducted by the team from Roche on several of their phase III studies. This effort also used novel reagents to measure VEGF. Using a novel multiplex assay, Scherer and colleagues analyzed baseline plasma samples for VEGF-A, ICAM-1, VEGF receptors 1 and 2, E-selectin, and VCAM-1 using samples from the phase III AVADO breast cancer study (Miles et al. 2010b). VEGF-A and VEGF-R2 predicted for PFS with bevacizumab. Results with other analytes were reported to be either not strong or not consistent. VEGF and VEGFR2 levels did not correlate with each other nor with other known prognostic factors. Findings from a phase III pancreatic cancer trial were noted to be similar. The same team reported that neuropillin1 level as measured by immunohistochemistry in archived formalin-fixed, paraffin-embedded tumor samples predicted for benefit from bevacizumab in both metastatic colorectal cancer and in metastatic gastric cancer (Foernzler et al. 2010; Shah et al. 2010). Details on ELISA and IHC reagents and the nature of any trends seen with other analytes are not yet published.

Using a different multiplex platform, Nixon and colleagues analyzed more than 40 angiogenic factors using plasma from patients on the CALGB phase III pancreas cancer study of gemcitabine ± bevacizumab (Kindler et al. 2010; Nixon et al. 2011). This work identified VEGF-D levels as a strong candidate marker for predicting for both benefit and lack of benefit from bevacizumab. Other candidate makers included SDF1, Ang2, and osteopontin (Nixon et al. 2011). Multiple angiogenic factors were found to be highly prognostic of outcome independent of treatment, further supporting the clinical relevance of tumor angiogenesis. Interestingly, immunohistochemistry analyses of archived formalin-fixed, paraffin-embedded tumor samples from the phase III MAX trial in metastatic colorectal cancer identified VEGF-D expression as a candidate marker of resistance to bevacizumab (Weickhardt et al. 2011). VEGF-D was also independently implicated in a modest-sized non-randomized study in patients with metastatic colorectal cancer conducted by Lieu et al. (2011); these investigators found that plasma VEGF-D levels as well as VEGF-C rose in the setting of disease progression.

For the VEGF inhibitor pazopanib, using data from the phase III study of pazopanib versus best supportive care, Lieu et al. (2011)

analyzed seven angiogenic factors previously suggested to predict benefit from pazopanib in non-randomized studies. Circulating baseline IL6, IL8, HGF, OPN, TIMP1, and VEGF correlated with baseline tumor burden, whereas higher levels of IL6, HGF, and OPN were associated with lesser tumor responses to treatment with pazopanib (Liu et al. 2011). The differences in results across studies may easily be explained by differences in the targets and assay methods used in each study, differences in tumor biology, and the use of different VEGF inhibitors. It is anticipated that additional analyses and further technical advances will allow these findings to be reconciled in the near future.

FUTURE DIRECTIONS

Taken together, anti-VEGF therapy and anti-angiogenesis therapy are important components of current anti-cancer treatments. However, many issues remain. These include the development and validation of biomarkers that identify those patients most likely to benefit from treatment and the mechanisms underlying primary and acquired resistance. The progress in biomarker development to date highlights both the biological complexity and technical demands of this effort. There are many novel anti-angiogenesis therapies now being developed. How to develop these agents and how to potentially combine complementary anti-angiogenesis therapies will require attention not only to the mechanisms of resistance, but also to mechanisms of toxicity. Fortunately, the tools to help understand these mechanisms in preclinical models and in patients are advancing rapidly. In addition, because large clinical and biomarker data sets are now in principle available from multiple phase III trials, the pace of biomarker and therapeutic angiogenesis research is likely to accelerate significantly in the coming years.

REFERENCES

NCT00393939: A randomized phase 3 study of docetaxel in combination with sunitinib versus docetaxel in the first-line treatment of advanced breast cancer patients. http://clinicaltrials.gov/ct2/show/NCT00393939.

NCT00435409: A randomized, phase 3 study of sunitinib in combination with capecitabine compared with capecitabine in patients with previously treated breast cancer. http://clinicaltrials.gov/ct2/show/NCT00435409.

NCT00449033: A phase III randomized, double-blind, placebo controlled trial comparing the efficacy of gemcitabine, cisplatin and sorafenib to gemcitabine, cisplatin and placebo in first-line treatment of patients with Stage IIIb with effusion and Stage IV non-small cell lung cancer (NSCLC). http://clinicaltrials.gov/ct2/show/NCT00449033.

NCT00700102: A study of avastin (bevacizumab) plus crossover fluoropyrimidine-based chemotherapy in patients with metastatic colorectal cancer. http://clinicaltrials.gov/ct2/show/NCT00700102.

NCT00777153: Cediranib in combination with lomustine chemotherapy in recurrent glioblastoma (REGAL). http://clinicaltrials.gov/ct2/show/NCT00777153.

NCT00858871: A randomized, double-blind, multi-center phase III study of brivanib versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. http://clinicaltrials.gov/ct2/show/NCT00858871.

NCT01009593: Efficacy and Tolerability of ABT-869 versus Sorafenib in Advanced Hepatocellular Carcinoma (HCC). http://clinicaltrials.gov/ct2/show/NCT01009593.

Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Colangelo LH, Atkins JN, Seay TE, Fehrenbacher L, Goldberg RM, et al. 2011. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: Results of NSABP protocol C-08. *J Clin Oncol* **29:** 11–16.

Batchelor TT, Sorensen AG, di Tomaso E, Zhang WT, Duda DG, Cohen KS, Kozak KR, Cahill DP, Chen PJ, Zhu M, et al. 2007. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell* **11:** 83–95.

Beaudry P, Nilsson M, Rioth M, Prox D, Poon D, Xu L, Zweidler-Mckay P, Ryan A, Folkman J, Ryeom S, et al. 2008. Potent antitumor effects of ZD6474 on neuroblastoma via dual targeting of tumor cells and tumor endothelium. *Mol Cancer Ther* **7:** 418–424.

Bendell JC, Bekaii-Saab TS, Cohn AL, Hurwitz HI, Kozloff M, Tezcan H, Feng S, Flick ED, Sing A, Grothey. 2011. Similarities in treatment (Tx) patterns and clinical outcomes (CO) in patients (pts) with metastatic colorectal cancer (mCRC) initially treated with FOLFOX/BV or FOLFIRI/BV: Results from ARIES, a bevacizumab (BV) observational study. *J Clin Oncol* **29** (suppl 4; abstr 480). http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view &confID=103&abstractID=70777.

Bernaards C, Hegde P, Chen D, Holmgren E, Zheng M, Jubb AM, Koeppen H, Scherer SJ, Chen DS. 2010. Circulating vascular endothelial growth factor (VEGF) as a biomarker for bevacizumab-based therapy in metastatic colorectal, non-small cell lung, and renal cell cancers: Analysis of phase III studies. *J Clin Oncol* **28:** 15s.

Bono P, Elfving H, Utriainen T, Osterlund P, Saarto T, Alanko T, Joensuu H. 2009. Hypertension and clinical benefit of bevacizumab in the treatment of advanced renal cell carcinoma. *Ann Oncol* **20:** 393–394.

Brufsky A, Bondarenko I, Smirnov V, Hurvitz S, Perez E, Ponomarova O, Vynnychenko I, Swamy R, Mu H, Rivera R. 2009. RIBBON-2: A randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of HER2-negative metastatic breast cancer. *Cancer Res* **69** doi: 10.1158/0008-5472.SABCS-09-42.

Burger RA, Brady MF, Bookman MA, Walker JL, Homesley HD, Fowler J, Monk BJ, Greer BE, Boente M, Liang SX. 2010. Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study. *J Clin Oncol* **28:** 18.

Carmeliet P. 2005. VEGF as a key mediator of angiogenesis in cancer. *Oncology* **69:** 4–10.

Cassidy J, Saltz L, Van Cutsem E, Hedrick EE, Lasserre S, Sirzen F, Rohr UP, Hurwitz H. 2010. Venous thromboembolic events with chemotherapy plus bevacizumab: A pooled analysis of over 6,000 patients in randomized phase II and III studies. *J Clin Oncol* **28:** 15s.

Cobleigh MA, Langmuir VK, Sledge GW, Miller KD, Haney L, Novotny WF, Reimann JD, Vassel A. 2003. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. *Semin Oncol* **30:** 117–124.

Crawford Y, Kasman I, Yu L, Zhong C, Wu X, Modrusan Z, Kaminker J, Ferrara N. 2009. PDGF-C mediates the angiogenic and tumorigenic properties of fibroblasts associated with tumors refractory to anti-VEGF treatment. *Cancer Cell* **15:** 21–34.

Cunningham D, Wong RP, D'haens G, Douillard J, Robertson J, Saunders O, Stone AM, Van Cutsem E, HORIZON I Study Group. 2008. A phase II, double-blind, randomized multicenter study of cediranib with FOLFOX versus bevacizumab with FOLFOX in patients with previously treated metastatic colorectal cancer (mCRC): Final PFS results. *J Clin Oncol* **26** (20 May suppl; abstr 4028).

Dancey J. 2010. mTOR signaling and drug development in cancer. *Nat Rev Clin Oncol* **7:** 209–219.

De Boer R, Arrieta Ó, Gottfried M, Blackhall FH, Raats J, Yang CH, Langmuir P, Milenkova T, Read J, Vansteenkiste; J. 2009. Vandetanib plus pemetrexed versus pemetrexed as second-line therapy in patients with advanced non-small cell lung cancer (NSCLC): A randomized, double-blind phase III trial (ZEAL). *J Clin Oncol* **27:** 15s.

De Gramont A, Van Cutsem E, Tabernero J, Moore MJ, Cunningham D, Rivera F, Im S, Makrutzki M, Shang A, Hoff PM, et al. 2011. AVANT: Results from a randomized, three-arm multinational phase III study to investigate bevacizumab with either XELOX or FOLFOX4 versus FOLFOX4 alone as adjuvant treatment for colon cancer. *J Clin Oncol* **29** (Suppl 4; abstr 362).

Docguide. 2010. Addition of sunitinib to FOLFOX6 or FOLFIRI adds no survival benefit for patients with metastatic colorectal cancer. http://www.docguide.com/addition-sunitinib-folfox6-or-folfiri- adds-no-survival-benefit-patients-metastatic-colorectal-cancer.

Dowlati A, Gray R, Sandler AB, Schiller JH, Johnson DH. 2008. Cell adhesion molecules, vascular endothelial growth factor, and basic fibroblast growth factor in patients with non-small cell lung cancer treated with chemotherapy with or without bevacizumab—An Eastern Cooperative Oncology Group Study. *Clin Cancer Res* **14:** 1407–1412.

Ebos JM, Lee CR, Christensen JG, Mutsaers AJ, Kerbel RS. 2007. Multiple circulating proangiogenic factors induced by sunitinib malate are tumor-independent and correlate with antitumor efficacy. *Proc Natl Acad Sci* **104:** 17069–17074.

Ebos JM, Lee CR, Cruz-Munoz W, Bjarnason GA, Christensen JG, Kerbel RS. 2009a. Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. *Cancer Cell* **15:** 232–239.

Ebos JM, Lee CR, Kerbel RS. 2009b. Tumor and host-mediated pathways of resistance and disease progression in response to antiangiogenic therapy. *Clin Cancer Res* **15:** 5020–5025.

Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, et al. 2007. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* **356:** 125–134.

Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, Negrier S, Chevreau C, Desai AA, Rolland F, et al. 2009. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* **27:** 3312–3318.

Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S, Ravaud A, Golding S, Jethwa S, Sneller V. 2010. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): Final analysis of overall survival. *J Clin Oncol* **28:** 2144–2150.

Facemire CS, Nixon AB, Griffiths R, Hurwitz H, Coffman TM. 2009. Vascular endothelial growth factor receptor 2 controls blood pressure by regulating nitric oxide synthase expression. *Hypertension* **54:** 652–658.

FDA. 2010. FDA begins process to remove breast cancer indication from Avastin label. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm237172.htm.

Foernzler D, Delmar P, Kockx M, Cassidy J, Saltz L, Scherer S. 2010. Tumor tissue based biomarker analysis in NO16966: A randomized phase III study of first-line bevacizumab in combination with oxaliplatin-based chemotherapy in patients with mCRC. *2010 Gastrointestinal Cancers Symposium* Abstract 374. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view& confID=72&abstractID=2207.

Friberg G, Kasza K, Vokes EE, Kindler HL. 2005. Early hypertension (HTN) as a potential pharmacodynamic (PD) marker for survival in pancreatic cancer (PC) patients (pts) treated with bevacizumab (B) and gemcitabine (G). *J Clin Oncol* **23:** 16S.

Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas MK, Jensen R, et al. 2009. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* **27:** 4733–4740.

Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, Schulz J, Richards D, Soufi-Mahjoubi R, Wang B, et al. 2007. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-

line treatment of metastatic colorectal cancer: Results from the BICC-C Study. *J Clin Oncol* **25:** 4779–4786.

Gerstner ER, Eichler AF, Plotkin SR, Drappatz J, Doyle CL, Xu L, Duda DG, Wen PY, Jain RK, Batchelor TT. 2010. Phase I trial with biomarker studies of vatalanib (PTK787) in patients with newly diagnosed glioblastoma treated with enzyme inducing anti-epileptic drugs and standard radiation and temozolomide. *J Neurooncol* **103:** 325–332.

Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson ABIII. 2007. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* **25:** 1539–1544.

Gordon MS, Margolin K, Talpaz M, Sledge GW Jr, Holmgren E, Benjamin R, Stalter S, Shak S, Adelman D. 2001. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. *J Clin Oncol* **19:** 843–850.

Grothey A, Sugrue MM, Purdie DM, Dong W, Sargent D, Hedrick E, Kozloff M. 2008. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: Results from a large observational cohort study (BRiTE). *J Clin Oncol* **26:** 5326–5334.

Hanahan D, Folkman J. 1996. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* **86:** 353–364.

Hanrahan EO, Ryan AJ, Mann H, Kennedy SJ, Langmuir P, Natale RB, Herbst RS, Johnson BE, Heymach JV. 2009. Baseline vascular endothelial growth factor concentration as a potential predictive marker of benefit from vandetanib in non-small cell lung cancer. *Clin Cancer Res* **15:** 3600–3609.

Hanrahan EO, Lin HY, Kim ES, Yan S, Du DZ, McKee KS, Tran HT, Lee JJ, Ryan AJ, Langmuir P, et al. 2010. Distinct patterns of cytokine and angiogenic factor modulation and markers of benefit for vandetanib and/or chemotherapy in patients with non-small-cell lung cancer. *J Clin Oncol* **28:** 193–201.

Hecht JR, Trarbach T, Jaeger E, Hainsworth J, Wolff R, Lloyd K, Bodoky G, Borner M, Laurent D, Jacques C. 2005. A randomized, double-blind, placebo-controlled, phase III study in patients (Pts) with metastatic adenocarcinoma of the colon or rectum receiving first-line chemotherapy with oxaliplatin/5-fluorouracil/leucovorin and PTK787/ZK 222584 or placebo (CONFIRM-1). *J Clin Oncol* **23:** 16S.

Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, Marshall J, Cohn A, McCollum D, Stella P, et al. 2009. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* **27:** 672–680.

Herbst RS, Heymach JV, O'Reilly MS, Onn A, Ryan AJ. 2007. Vandetanib (ZD6474): An orally available receptor tyrosine kinase inhibitor that selectively targets pathways critical for tumor growth and angiogenesis. *Expert Opin Investig Drugs* **16:** 239–249.

Herbst RS, Sun Y, Eberhardt WE, Germonpre P, Saijo N, Zhou C, Wang J, Li L, Kabbinavar F, Ichinose Y, et al. 2010. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): A double-blind, randomised, phase 3 trial. *Lancet Oncol* **11:** 619–626.

Holden SN, Eckhardt SG, Basser R, de Boer R, Rischin D, Green M, Rosenthal MA, Wheeler C, Barge A, Hurwitz HI. 2005. Clinical evaluation of ZD6474, an orally active inhibitor of VEGF and EGF receptor signaling, in patients with solid, malignant tumors. *Ann Oncol* **16:** 1391–1397.

Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, Sosman J, McDermott D, Bodrogi I, et al. 2007. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* **356:** 2271–2281.

Hudson CC, Liu M, Chiang GG, Otterness DM, Loomis DC, Kaper F, Giaccia AJ, Abraham RT. 2002. Regulation of hypoxia-inducible factor 1α expression and function by the mammalian target of rapamycin. *Mol Cell Biol* **22:** 7004–7014.

Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, et al. 2004. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* **350:** 2335–2342.

Hurwitz H, Douglas PS, Middleton JP, Sledge GW, Johnson DH, Reardon DA, Chen D, Rosen O. 2010. Analysis of early hypertension (HTN) and clinical outcome with bevacizumab (BV). *J Clin Oncol* **28:** 15s.

Hutson TE, Bukowski RM, Cowey CL, Figlin R, Escudier B, Sternberg CN. 2011. Sequential use of targeted agents in the treatment of renal cell carcinoma. *Crit Rev Oncol Hematol* **77:** 48–62.

Jain RK. 2005. Normalization of tumor vasculature: An emerging concept in antiangiogenic therapy. *Science* **307:** 58–62.

Jain RK, di Tomaso E, Duda DG, Loeffler JS, Sorensen AG, Batchelor TT. 2007. Angiogenesis in brain tumours. *Nat Rev Neurosci* **8:** 610–622.

Jain RK, Duda DG, Willett CG, Sahani DV, Zhu AX, Loeffler JS, Batchelor TT, Sorensen AG. 2009. Biomarkers of response and resistance to antiangiogenic therapy. *Nat Rev Clin Oncol* **6:** 327–338.

Johnson K. 2010. Cediranib falls short in phase III glioblastoma trial. *Internal Med News* http://www.internalmedicinenews.com/news/neurology/single-article/cediranib-falls-short-in-phase-iii-glioblastoma-trial/d9b36de685.html.

Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore RFIII, Gaudreault J, Damico LA, et al. 2004. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* **22:** 2184–2191.

Jubb AM, Landon TH, Burwick J, Pham TQ, Frantz GD, Cairns B, Quirke P, Peale FV, Hillan KJ. 2003. Quantitative analysis of colorectal tissue microarrays by immunofluorescence and in situ hybridization. *J Pathol* **200:** 577–588.

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

Jubb AM, Hurwitz HI, Bai W, Holmgren EB, Tobin P, Guerrero AS, Kabbinavar F, Holden SN, Novotny WF, Frantz GD, et al. 2006. Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer. *J Clin Oncol* **24:** 217–227.

Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S, Bergsland E. 2003. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* **21:** 60–65.

Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR, Mass R, Perrou B, Nelson B, Novotny WF. 2005. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: Results of a randomized phase II trial. *J Clin Oncol* **23:** 3697–3705.

Kang Y, Ohtsu A, Van Cutsem E, Rha SY, Sawaki A, Park S, Lim H, Wu J, Langer B, Shah MA. 2010. AVAGAST: A randomized, double-blind, placebo-controlled, phase III study of first-line capecitabine and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer (AGC). *J Clin Oncol* **28:** 18s.

Kelly WK, Halabi S, Carducci MA, George DJ, Mahoney JF, Stadler WM, Morris MJ, Kantoff P, Monk III JP, Small EJ, et al. 2010. A randomized, double-blind, placebo-controlled phase III trial comparing docetaxel, prednisone, and placebo with docetaxel, prednisone, and bevacizumab in men with metastatic castration-resistant prostate cancer (mCRPC): Survival results of CALGB 90401. *J Clin Oncol* **28:** 18.

Kerbel RS. 2008. Tumor angiogenesis. *N Engl J Med* **358:** 2039–2049.

Kesmodel SB, Ellis LM, Lin E, Chang GJ, Abdalla EK, Kopetz S, Vauthey JN, Rodriguez-Bigas MA, Curley SA, Feig BW. 2008. Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases. *J Clin Oncol* **26:** 5254–5260.

Kim KJ, Li B, Winer J, Armanini M, Gillett N, Phillips HS, Ferrara N. 1993. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. *Nature* **362:** 841–844.

Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, et al. 2010. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: Phase III trial of the cancer and leukemia group B (CALGB 80303). *J Clin Oncol* doi: 10.1200/JCO.2010.28.1386.

Kohne CH, Cunningham D, Di CF, Glimelius B, Blijham G, Aranda E, Scheithauer W, Rougier P, Palmer M, Wils J, et al. 2002. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: Results of a multivariate analysis of 3825 patients. *Ann Oncol* **13:** 308–317.

Kohne C, Bajetta E, Lin E, Valle JW, Van Cutsem E, Hecht JR, Moore M, Germond CJ, Meinhardt G, Jacques C. 2007. Final results of CONFIRM 2: A multinational, randomized, double-blind, phase III study in 2nd line patients (pts) with metastatic colorectal cancer (mCRC) receiving FOLFOX4 and PTK787/ZK 222584 (PTK/ZK) or placebo. *J Clin Oncol* **25:** 18S.

Kolata G. 1998. A cautious awe greets drugs that eradicate tumors in mice. *New York Times* (3 May 1998).

Kopetz S, Hoff PM, Morris JS, Wolff RA, Eng C, Glover KY, Adinin R, Overman MJ, Valero V, Wen S, et al. 2010. Phase II trial of infusional fluorouracil, irinotecan, and bevacizumab for metastatic colorectal cancer: Efficacy and circulating angiogenic biomarkers associated with therapeutic resistance. *J Clin Oncol* **28:** 453–459.

Korsisaari N, Kasman IM, Forrest WF, Pal N, Bai W, Fuh G, Peale FV, Smits R, Ferrara N. 2007. Inhibition of VEGF-A prevents the angiogenic switch and results in increased survival of Apc^{+}/min mice. *Proc Natl Acad Sci* **104:** 10625–10630.

Kozloff M, Yood MU, Berlin J, Flynn PJ, Kabbinavar FF, Purdie DM, Ashby MA, Dong W, Sugrue MM, Grothey A. 2009. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: The BRiTE observational cohort study. *Oncologist* **14:** 862–870.

Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, Garren N, Mackey M, Butman JA, Camphausen K, et al. 2009. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol* **27:** 740–745.

Lieu CH, Tran HT, Jiang Z, Mao M, Overman MJ, Eng C, Morris J, Ellis LM, Heymach J, Kopetz S. 2011. The association of alternate VEGF ligands with resistance to anti-VEGF therapy in metastatic colorectal cancer. *J Clin Oncol* **29** (Suppl; abstr 3533).

Liu Y, Tran HT, Lin Y, Martin A, Zurita AJ, Sternberg CN, Amado RG, Pandite LN, Heymach J, Team V. 2011. Circulating baseline plasma cytokines and angiogenic factors (CAF) as markers of tumor burden and therapeutic response in a phase III study of pazopanib for metastatic renal cell carcinoma (mRCC). *J Clin Oncol* **29** (Suppl; abstr 4553).

Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, et al. 2008. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* **359:** 378–390.

Lyman GH, Khorana AA. 2009. Cancer, clots and consensus: New understanding of an old problem. *J Clin Oncol* **27:** 4821–4826.

Margolin K, Gordon MS, Holmgren E, Gaudreault J, Novotny W, Fyfe G, Adelman D, Stalter S, Breed J. 2001. Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: Pharmacologic and long-term safety data. *J Clin Oncol* **19:** 851–856.

Medical News Today. 2009. http://www.medicalnewstoday.com/articles/137485.php. Pfizer discontinues global phase III trial of axitinib for futility in advanced pancreatic cancer. http://www.medicalnewstoday.com/articles/137485.php.

Medical News Today. 2010. http://www.medicalnewstoday.com/articles/208748.php. Pfizer announces positive phase 3 trial results for axitinib in patients with previously-treated metastatic renal cell carcinoma

(mRCC). http://www.medicalnewstoday.com/articles/208748.php.

Mekhail TM, Abou-Jawde RM, Boumerhi G, Malhi S, Wood L, Elson P, Bukowski R. 2005. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J Clin Oncol* **23:** 832–841.

Miles DW, Chan A, Dirix LY, Cortes J, Pivot X, Tomczak P, Delozier T, Sohn JH, Provencher L, Puglisi F, et al. 2010a. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* **28:** 3239–3247.

Miles DW, de Haas SL, Dirix L, Chan A, Pivot X, Tomczak P, Provencher L, Delmar P, Scherer S. 2010b. Plasma biomarker analyses in the AVADO phase III randomized study of first-line bevacizumab + docetaxel in patients with human epidermal growth factor receptor (her) 2-negative metastatic breast cancer. *San Antonio Breast Cancer Symposium* December 8–12, 2010.

Miles D, Harbeck N, Escudier B, Hurwitz H, Saltz L, Van Cutsem E, Cassidy J, Mueller B, Sirzen F. 2011. Disease course patterns after discontinuation of bevacizumab: Pooled analysis of randomized phase III trials. *J Clin Oncol* **29:** 83–88.

Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, et al. 2005. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol* **23:** 792–799.

Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. 2007. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* **357:** 2666–2676.

Mirshahidi HR, Hsueh CT. 2010. Updates in non-small cell lung cancer—Insights from the 2009 45th annual meeting of the American Society of Clinical Oncology. *J Hematol Oncol* **3:** 18.

Monthly Prescribing Reference. 2011. FDA Update on Avastin for metastatic breast cancer. http://www.empr.com/fda-update-on-avastin-for-metastatic-breast-cancer/article/206504/.

Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. 2002. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* **20:** 289–296.

Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, et al. 2007. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* **356:** 115–124.

Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V, Thompson JA, Figlin RA, Hollaender N, et al. 2008. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. *Lancet* **372:** 449–456.

Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V, Thompson JA, Figlin RA, Hollaender N, et al. 2010. Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. *Cancer* **116:** 4256–4265.

Murphy K. 2009. Phase III Sutent trial for colorectal cancer discontinued. *Fight Colorectal Cancer Research News*. http://fightcolorectalcancer.org/research_news/2009/07/phase_iii_sutent_trial_for_colorectal_ cancer_discontinued.

Murphy K. 2010. Second Avastin trial shows no benefit in early stage colon cancer. *Fight Colorectal Cancer Research News*. http://fightcolorectalcancer.org/research_news/2010/09/second_avastin_trial_shows_no_benefit_in_early_stage_colon_cancer.

Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. 2008. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: A meta-analysis. *JAMA* **300:** 2277–2285.

Natale RB, Thongprasert S, Greco FA, Thomas M, Tsai CM, Sunpaweravong P, Ferry D, Langmuir P, Rowbottom JA, Goss GD. 2009. Vandetanib versus erlotinib in patients with advanced non-small cell lung cancer (NSCLC) after failure of at least one prior cytotoxic chemotherapy: A randomized, double-blind phase III trial (ZEST). *J Clin Oncol* **27:** 15s.

Negrier S, Escudier B, Gomez F, Douillard JY, Ravaud A, Chevreau C, Buclon M, Perol D, Lasset C. 2002. Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: A report from the Groupe Francais d'Immunotherapie. *Ann Oncol* **13:** 1460–1468.

News Medical. 2010. Pfizer announces discontinuation of SUN 1170 phase 3 study of Sutent in HCC. http://www.news-medical.net/news/20100423/Pfizer-announces-discontinuation-of-SUN-1170-Phase-3-study-of-Sutent-in-HCC.aspx.

Nikolinakos PG, Altorki N, Yankelevitz D, Tran HT, Yan S, Rajagopalan D, Bordogna W, Ottesen LH, Heymach JV. 2010. Plasma cytokine and angiogenic factor profiling identifies markers associated with tumor shrinkage in early-stage non-small cell lung cancer patients treated with pazopanib. *Cancer Res* **70:** 2171–2179.

Nixon A, Allen J, Miller E, Savage S, Kaplan N, Starr M, Bendell J, Uronis H, Fernando N, Hurwitz H. 2007. Clinical evaluation of nitric oxide responses to anti-VEGF therapy with bevacizumab. *J Clin Oncol* **25:** 18S.

Nixon A, Starr M, Pang H, Bulusu A, Honeycutt W, Amara A, Bendell JC, Hurwitz HI. 2010. Use of plasma angiome to predict PFS in patients with metastatic colorectal cancer (mCRC) treated with capecitabine, oxaliplatin, and bevacizumab (XELOX-A). *J Clin Oncol* **28** (suppl; abstr e21009).

Nixon AB, Pang H, Starr M, Hollis D, Friedman PN, Bertagnolli MM, Kindler HL, Goldberg RM, Venook AP, Hurwitz H. 2011. Prognostic and predictive blood-based biomarkers in patients with advanced pancreatic cancer: Results from CALGB 80303. *J Clin Oncol* **29** (Suppl; abstr 10508).

O'Shaughnessy J, Miles D, Gray RJ, Dieras V, Perez EA, Zon R, Cortes J, Zhou X, Phan S, Miller K. 2010. A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC). *J Clin Oncol* **28:** 15.

Paez-Ribes M, Allen E, Hudock J, Takeda T, Okuyama H, Vinals F, Inoue M, Bergers G, Hanahan D, Casanovas O. 2009. Antiangiogenic therapy elicits malignant

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

progression of tumors to increased local invasion and distant metastasis. *Cancer Cell* **15:** 220–231.

Poon RT, Fan ST, Wong J. 2001. Clinical implications of circulating angiogenic factors in cancer patients. *J Clin Oncol* **19:** 1207–1225.

Poultsides GA, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, Weiser M, Temple LK, Wong WD, Paty PB. 2009. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol* **27:** 3379–3384.

PR News Wire. 2002. http://www.prnewswire.com/news-releases/pharmacia-announces-closing-of-su5416-semaxanib-clinical-trials-75895232.html. Pharmacia announces closing of SU5416 (semaxanib) clinical trials. http://www.prnewswire.com/news-releases/pharmacia-announces-closing-of-su5416-semaxanib-clinical-trials-75895232.html.

PR News Wire. 2010. http://www.prnewswire.com/news-releases/topline-results-from-phase-3-trial-of-sunitinib-with-erlotinib-in-advanced-non-small-cell-lung-cancer-nsclc-101330169.html. Topline results from phase 3 trial of sunitinib with erlotinib in advanced non-small cell lung cancer (NSCLC). http://www.prnewswire.com/news-releases/topline-results-from-phase-3-trial-of-sunitinib-with-erlotinib-in-advanced-non-small-cell-lung-cancer-nsclc-101330169.html.

Ramalingam SS, Belani CP, Mack PC, Vokes EE, Longmate J, Govindan R, Koczywas M, Ivy SP, Gandara DR. 2010. Phase II study of Cediranib (AZD 2171), an inhibitor of the vascular endothelial growth factor receptor, for second-line therapy of small cell lung cancer (National Cancer Institute #7097). *J Thorac Oncol* **5:** 1279–1284.

Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, et al. 2010. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for non-squamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol* **21:** 1804–1809.

Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, Archer L, Atkins JN, Picus J, Czaykowski P, et al. 2008a. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol* **26:** 5422–5428.

Rini BI, Schiller JH, Fruehauf JP, Cohen EE, Tarazi JC, Rosbrook B, Ricart AD, Olszanski AJ, Kim S, Spano J. 2008b. Association of diastolic blood pressure (dBP)>90 mmHg with overall survival (OS) in patients treated with axitinib (AG- 013736). *J Clin Oncol* **26** (20 May suppl; abstr 3543).

Rixe O, Billemont B, Izzedine H. 2007. Hypertension as a predictive factor of Sunitinib activity. *Ann Oncol* **18:** 1117.

Robert NJ, Dieras V, Glaspy J, Brufsky A, Bondarenko I, Lipatov O, Perez E, Yardley D, Zhou X, Phan S. 2009. RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). *J Clin Oncol* **27:** 155.

Robertson JD, Botwood NA, Rothenberg ML, Schmoll HJ. 2009. Phase III trial of FOLFOX plus bevacizumab or cediranib (AZD2171) as first-line treatment of patients with metastatic colorectal cancer: HORIZON III. *Clin Colorectal Cancer* **8:** 59–60.

Rosenberg JE, Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Bukowski RM, George DJ, Kim ST, Baum CM, Wilding G. 2007. Sunitinib therapy for patients (pts) with metastatic renal cell carcinoma (mRCC): Updated results of two phase II trials and prognostic factor analysis for survival. *J Clin Oncol* **25:** 18S.

Ryanne Wu R, Lindenberg PA, Slack R, Noone AM, Marshall JL, He AR. 2009. Evaluation of hypertension as a marker of bevacizumab efficacy. *J Gastrointest Cancer* **40:** 101–108.

Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, et al. 2008. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol* **26:** 2013–2019.

Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. 2006. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* **355:** 2542–2550.

Sanofi-Aventis. 2009. Phase 3 trial of aflibercept in metastatic pancreatic cancer discontinued. http://en.sanofi-aventis.com/press/press_releases/2009/ppc_26186.asp.

Scagliotti G, Novello S, von Pawel J, Reck M, Pereira JR, Thomas M, Abrao Miziara JE, Balint B, De Marinis F, Keller A, et al. 2010. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. *J Clin Oncol* **28:** 1835–1842.

Scappaticci FA, Fehrenbacher L, Cartwright T, Hainsworth JD, Heim W, Berlin J, Kabbinavar F, Novotny W, Sarkar S, Hurwitz H. 2005. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol* **91:** 173–180.

Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, Bergsland E, Ngai J, Holmgren E, Wang J, et al. 2007. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst* **99:** 1232–1239.

Schioppa T, Uranchimeg B, Saccani A, Biswas SK, Doni A, Rapisarda A, Bernasconi S, Saccani S, Nebuloni M, Vago L, et al. 2003. Regulation of the chemokine receptor CXCR4 by hypoxia. *J Exp Med* **198:** 1391–1402.

Shah MA, Kelsen DP. 2010. Gastric cancer: A primer on the epidemiology and biology of the disease and an overview of the medical management of advanced disease. *J Natl Compr Canc Netw* **8:** 437–447.

Shah M, Kang Y-K, Ohtsu A, Delmar P, Foernzler D, Langer B, Scherer S, Van Cutsem E. 2010. Tumour biomarker analyses in the avagast phase III randomized study of first-line bevacizumab + capecitabine/cisplatin in patients with advanced gastric cancer. *Ann Oncol* **21** (Supplement 8; abstr 174PD).

Shojaei F, Wu X, Malik AK, Zhong C, Baldwin ME, Schanz S, Fuh G, Gerber HP, Ferrara N. 2007. Tumor refractoriness to anti-VEGF treatment is mediated by $CD11b^{+}Gr1^{+}$ myeloid cells. *Nat Biotechnol* **25:** 911–920.

Staller P, Sulitkova J, Lisztwan J, Moch H, Oakeley EJ, Krek W. 2003. Chemokine receptor CXCR4 downregulated by von Hippel–Lindau tumour suppressor pVHL. *Nature* **425:** 307–311.

Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, et al. 2010. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* **28:** 1061–1068.

Tabernero J, Aranda E, Gomez A, Massuti B, Sastre J, Abad A, Valladares M, Rivera F, Safont M, Diaz-Rubio E. 2010. Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single-agent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC): The MACRO Trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]). *J Clin Oncol* **28:** 15s.

Tebbutt NC, Wilson K, Gebski VJ, Cummins MM, Zannino D, van Hazel GA, Robinson B, Broad A, Ganju V, Ackland SP, et al. 2010. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: Results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. *J Clin Oncol* **28:** 3191–3198.

Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG, Erdkamp FL, Vos AH, van Groeningen CJ, Sinnige HA, et al. 2009. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* **360:** 563–572.

Van Cutsem E, Rivera F, Berry S, Kretzschmar A, Michael M, DiBartolomeo M, Mazier MA, Canon JL, Georgoulias V, Peeters M, et al. 2009a. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: The BEAT study. *Ann Oncol* **20:** 1842–1847.

Van Cutsem E, Vervenne WL, Bennouna J, Humblet Y, Gill S, Van Laethem JL, Verslype C, Scheithauer W, Shang A, Cosaert J, et al. 2009b. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol* **27:** 2231–2237.

Warren RS, Yuan H, Matli MR, Gillett NA, Ferrara N. 1995. Regulation by vascular endothelial growth factor of human colon cancer tumorigenesis in a mouse model of experimental liver metastasis. *J Clin Invest* **95:** 1789–1797.

Weickhardt AJ, Williams D, Lee C, Simes J, Murone C, Wilson K, Cummins M, Asadi K, Price TJ, Mariadason J, et al. 2011. Vascular endothelial growth factors (VEGF) and VEGF receptor expression as predictive biomarkers for benefit with bevacizumab in metastatic colorectal cancer (mCRC): Analysis of the phase III MAX study. *J Clin Oncol* **29** (Suppl; abstr 3531).

Yamamoto N, Tamura T, Yamada K, Yamada Y, Nokihara H, Fujiwara Y, Takahashi T, Murakami H, Boku N, Yamazaki K, et al. 2009. Phase I, dose escalation and pharmacokinetic study of cediranib (RECENTIN), a highly potent and selective VEGFR signaling inhibitor, in Japanese patients with advanced solid tumors. *Cancer Chemother Pharmacol* **64:** 1165–1172.

Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, Steinberg SM, Chen HX, Rosenberg SA. 2003. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* **349:** 427–434.

Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org