

Targeting Angiogenesis in Cancer Therapy: Moving Beyond Vascular Endothelial Growth Factor

YUJIE ZHAO, ALEX A. ADJEI

Roswell Park Cancer Institute, Buffalo, New York, USA

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ABSTRACT

Angiogenesis, or the formation of new capillary blood vessels, occurs primarily during human development and reproduction; however, aberrant regulation of angiogenesis is also a fundamental process found in several pathologic conditions, including cancer. As a process required for invasion and metastasis, tumor angiogenesis constitutes an important point of control of cancer progression. Although not yet completely understood, the complex process of tumor angiogenesis involves highly regulated orchestration of multiple signaling pathways. The proangiogenic signaling molecule vascular endothelial growth factor (VEGF) and its cognate receptor (VEGF receptor 2 [VEGFR-2]) play a central role in angiogenesis and often are highly expressed in human cancers, and initial clinical efforts to develop antiangiogenic treatments focused largely on inhibiting VEGF/VEGFR signaling. Such approaches, however, often lead to transient responses and further disease

progression because angiogenesis is regulated by multiple pathways that are able to compensate for each other when single pathways are inhibited. The platelet-derived growth factor (PDGF) and PDGF receptor (PDGFR) and fibroblast growth factor (FGF) and FGF receptor (FGFR) pathways, for example, provide potential escape mechanisms from anti-VEGF/VEGFR therapy that could facilitate resumption of tumor growth. Accordingly, more recent treatments have focused on inhibiting multiple signaling pathways simultaneously. This comprehensive review discusses the limitations of inhibiting VEGF signaling alone as an antiangiogenic strategy, the importance of other angiogenic pathways including PDGF/PDGFR and FGF/FGFR, and the novel current and emerging agents that target multiple angiogenic pathways for the treatment of advanced solid tumors. *The Oncologist* 2015; 20:660–673

Implications for Practice: Significant advances in cancer treatment have been achieved with the development of antiangiogenic agents, the majority of which have focused on inhibition of the vascular endothelial growth factor (VEGF) pathway. VEGF targeting alone, however, has not proven to be as efficacious as originally hoped, and it is increasingly clear that there are many interconnected and compensatory pathways that can overcome VEGF-targeted inhibition of angiogenesis. Maximizing the potential of antiangiogenic therapy is likely to require a broader therapeutic approach using a new generation of multitargeted antiangiogenic agents.

INTRODUCTION

Angiogenesis, a process that involves tight regulation of multiple signaling pathways, is the physiologic process by which new blood vessels form from pre-existing vessels. Although it is a homeostatic process that predominantly occurs during embryogenesis, angiogenesis also occurs in the adult during the ovarian cycle and in normal physiologic repair processes such as wound healing. Many cancers exploit angiogenic mechanisms to stimulate tumor growth and disease progression [1] (Fig. 1). Numerous proangiogenic and antiangiogenic factors, extracellular matrix components, and cell types act in concert to determine the type, location, and abundance

of the angiogenic response [2]. However, there is universal agreement that vascular endothelial growth factor (VEGF) and its cognate receptor (VEGF receptor 2 [VEGFR-2]) are the most prominent regulators of angiogenesis. VEGF signaling stimulates cellular pathways that lead to the formation and branching of new tumor blood vessels, promotes rapid tumor growth, and facilitates metastatic potential [3]. Accordingly, there was a long-held perception that inhibiting the VEGF/VEGFR pathway alone would cause a rapid and sustained antiangiogenic/antitumor response [4]. Indeed, several VEGF/VEGFR targeted inhibitors have been approved after improving

Correspondence: Alex A. Adjei, M.D., Ph.D., Roswell Park Cancer Institute, Buffalo, New York 14263, USA. Telephone: 716-845-4101; E-Mail: alex.adjei@roswellpark.org Received December 4, 2014; accepted for publication March 6, 2015; published Online First on May 22, 2015. ©AlphaMed Press 1083-7159/2015/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2014-0465>

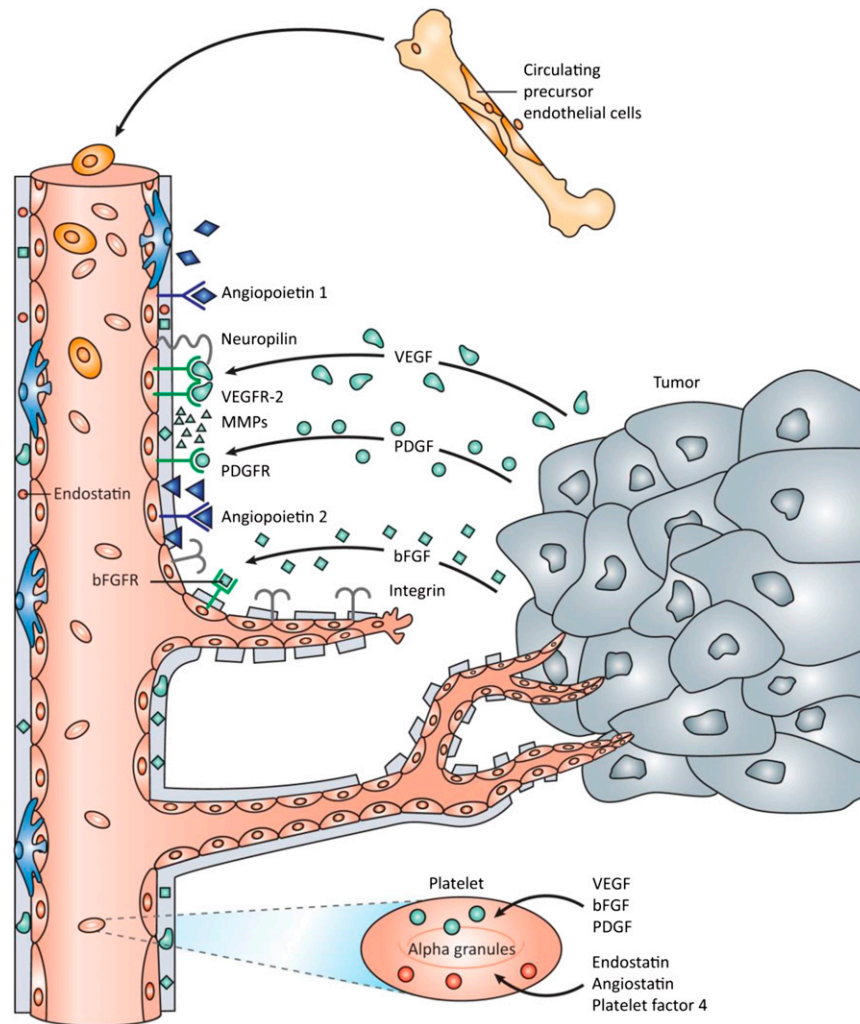


Figure 1. Tumor angiogenesis mechanisms. Soluble angiogenic factors (e.g., VEGF, PDGF, FGF) are secreted from the tumor and surrounding cells to induce and regulate key steps in angiogenesis. Reproduced with permission from [1].

Abbreviations: bFGF, basic fibroblast growth factor; bFGFR, basic fibroblast growth factor receptor; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

the prognosis of patients with cancer compared with chemotherapy alone across several indications [5–7]. However, because other mediators of angiogenesis, including the platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) signaling pathways also regulate angiogenesis, tumor growth, and metastasis, compensatory mechanisms may come into play when VEGF signaling is blocked. Consequently, more recent antiangiogenic treatments aim to simultaneously block both VEGF/VEGFR signaling and other pathways that are critical to angiogenesis and tumor growth. The purpose of this review is to discuss the relevant signaling pathways involved in tumor angiogenesis, growth, and resistance to anti-VEGF therapy and to highlight the potential clinical benefits related to their pharmacologic inhibition.

MATERIALS AND METHODS

To evaluate angiogenesis in cancer, a systematic review of the published literature during the period 2005–2014 was performed using PubMed. Following peer review, this paper was updated with any pertinent literature for the period

2014–2015. Articles were limited to the English language only, and the following key words were used: *angiogenesis, vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor, angiopoietins, TIE2, proto-oncogene protein RET, proto-oncogene protein MET, and hepatocyte growth factor*. In addition, abstracts from annual meetings of the American Society of Clinical Oncology and the European Society for Medical Oncology, among others, were searched to identify recent presentations related to angiogenesis in cancer. The discussion of antiangiogenic agents was limited to agents that have progressed to phase III clinical trial status.

Angiogenesis and the VEGF/VEGFR Pathway

VEGF was initially identified as an endothelial cell-specific mitogen with the ability to induce physiologic and pathologic angiogenesis [8, 9]. Since this finding, much has been learned about the nature of VEGF signaling and its role in angiogenesis. VEGF comprises a family of ligands (VEGF-A to -D and placental growth factor [PlGF]) that bind to VEGFR tyrosine kinases [2, 10, 11]. VEGF-A, VEGF-B, and PlGF have decisive roles in

angiogenesis. Although VEGF-A and -B have the greatest binding affinity for VEGFR-1 and -2, the majority of angiogenic effects are attributed to the interaction of VEGF-A with VEGFR-2 [11]. Less well understood, VEGFR-1 is thought to function predominantly as a decoy receptor by regulating the amount of free VEGF-A available to activate VEGFR-2 because VEGFR-1 negatively regulates VEGF-A/VEGFR-2 interaction [12]. The role of PlGF in angiogenesis remains controversial; however, gain- and loss-of-function experiments have shown that it may directly stimulate vessel growth and maturation and recruit proangiogenic bone marrow-derived progenitors and monocyte-macrophage lineage cells [13]. VEGF-C and -D appear to be the most important factors in lymphangiogenesis and have the greatest binding affinity for VEGFR-3 [14]. Not surprisingly, VEGFs are produced by several types of cells (Fig. 1), including fibroblasts, inflammatory cells, and many tumor cells, often in response to increasing tissue hypoxia [4].

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Inhibition of VEGF/VEGFR Signaling

Several agents, including bevacizumab, aflibercept, and, most recently, ramucirumab, that target the VEGF/VEGFR signaling pathway have been developed and are now approved across several indications.

Bevacizumab

Bevacizumab, a humanized monoclonal antibody (mAb) that targets VEGF-A to prevent its interaction with VEGFR-1 and -2, was the first targeted antiangiogenic approved for use in oncology [15]. Currently approved in the U.S. as combination therapy for first- and second-line treatment of metastatic colorectal cancer (mCRC) and metastatic renal cell carcinoma (mRCC) and for first-line therapy for unresectable, locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC), bevacizumab is also approved as monotherapy for adults with progressive glioblastoma [5]. Most recently, bevacizumab has also been approved in combination with chemotherapy for the first-line treatment of persistent, recurrent, or metastatic cervical cancer and platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer [5]. Notably, the U.S. Food and Drug Administration (FDA) revoked the product license in the U.S. for the treatment of breast cancer [16]. Although a positive impact on progression-free survival (PFS) and response rate had been demonstrated consistently, such an effect on overall survival (OS) had not. Coupled with an emerging unfavorable adverse events profile in this population, the use of bevacizumab in breast cancer was questioned [17], with the FDA concluding that the drug had not been shown to be safe and effective for that use [16].

Although an important advance in treatment, bevacizumab provides only a modest survival benefit, with inconsistent

effects in different tumor types [18]. The addition of bevacizumab to first-line irinotecan/5-fluorouracil/leucovorin for CRC, for example, increases OS by 4.7 months, whereas its addition to first-line carboplatin/paclitaxel for unresectable, locally advanced, recurrent, and metastatic nonsquamous NSCLC increases OS by 2 months [18]. Responses to bevacizumab are often transient, and many patients experience disease progression as an adaptive response to ongoing therapy or following treatment withdrawal [19–21]. Furthermore, early studies with bevacizumab across a variety of cancer types established a set of adverse events (AEs) attributed to antiangiogenic therapy, with the most documented toxicity being hypertension, which was reported in up to 36% of patients [22]. Because clinical trials are conducted under varying conditions and patient types (e.g., different treatment regimens, cancer types, age groups), the frequency of AEs varies widely. The most common AEs observed in bevacizumab-treated patients at a rate of >10% and at least twice the control arm rate are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, and exfoliation [23, 24].

Aflibercept

Aflibercept is a fusion protein that consists of VEGF-binding portions from the extracellular domains of human VEGFR-1 and -2 fused to the Fc portion of human immunoglobulin G1 (IgG1) [25]. Aflibercept functions as a decoy receptor by neutralizing the available VEGF-A and -B and PlGF and making the ligands unavailable to bind and activate VEGFRs. The ability of aflibercept to bind multiple VEGF ligands may provide a more complete blockade of angiogenesis than bevacizumab, which targets only VEGF-A [26]. Preclinical studies with aflibercept showed antitumor and antiangiogenic activity in a variety of xenograft models, including human colon cancer [25–27]. Indicated for patients with mCRC that is resistant to or that has progressed following an oxaliplatin-containing regimen, approval of aflibercept was based on findings from a phase III trial that showed its addition to folinic acid, fluorouracil, and irinotecan (FOLFIRI) significantly improved OS relative to placebo plus FOLFIRI in patients with mCRC who had previously received oxaliplatin (median: 13.50 vs. 12.06 months, respectively; hazard ratio [HR]: 0.817; 95% confidence interval [CI]: 0.713–0.937; $p = .0032$) [22, 28]. AEs with aflibercept compared with placebo were very similar to, although less severe than, those seen with bevacizumab and other antiangiogenic agents. The most common AEs ($\geq 20\%$) reported at a higher incidence ($\geq 2\%$) than with placebo are leukopenia, diarrhea, neutropenia, proteinuria, increased aspartate aminotransferase, stomatitis, fatigue, thrombocytopenia, increased alanine aminotransferase, hypertension, decreased weight, decreased appetite, epistaxis, abdominal pain, dysphonia, increased serum creatinine, and headache [22].

Ramucirumab

Recently approved in the U.S. for advanced gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma after prior fluoropyrimidine- or platinum-containing chemotherapy, ramucirumab is a fully humanized IgG1 mAb targeting the extracellular domain of VEGFR-2 [7]. The phase III REGARD

and RAINBOW trials, which were pivotal to FDA approval, evaluated ramucirumab as monotherapy and in combination with paclitaxel, respectively, in previously treated patients with advanced gastric cancer or GEJ adenocarcinoma [29]. The REGARD trial found that patients receiving ramucirumab with best supportive care (BSC) experienced median OS of 5.2 months compared with 3.8 months with placebo (HR: 0.776; 95% CI: 0.603–0.998; $p = .047$). In the phase III RAINBOW trial, the addition of ramucirumab significantly improved OS from 7.36 months to 9.63 months (HR: 0.807; 95% CI: 0.678–0.962; $p = .0169$) [30]. Ramucirumab has shown varying degrees of efficacy in renal, uterine, colorectal, and ovarian carcinoma [31, 32]. Most recently, results of ramucirumab trials in NSCLC and breast cancer have been reported. As a second-line treatment, ramucirumab plus docetaxel in the phase III REVEL study (NCT01168973) was reported to significantly increase OS among patients with stage IV NSCLC versus docetaxel alone (10.5 vs. 9.1 months; HR: 0.86; 95% CI: 0.75–0.98; $p = .023$) [33]. Furthermore, ramucirumab was well tolerated, with most treatment-emergent AEs occurring at a similar frequency in the ramucirumab and placebo arms. Ramucirumab is now approved in the U.S. in combination with docetaxel as a second-line therapy in advanced and/or metastatic NSCLC [7]. However, in metastatic, human epidermal growth factor receptor 2-negative (HER2-negative) breast cancer, results have been somewhat disappointing. In the ROSE/TRIO trial, ramucirumab in combination with docetaxel failed to demonstrate a meaningful improvement in important clinical outcomes versus docetaxel alone (OS: 27.3 vs. 27.2 months; HR: 1.01; 95% CI: 0.83–1.23; $p = .915$) [34]. Phase III trials of ramucirumab are also ongoing in mCRC, and results of its use in advanced hepatocellular carcinoma (HCC) as a second-line treatment (REACH trial) have been presented recently [35]. In that study, patients who had progressed during or following sorafenib or who were intolerant to it received ramucirumab plus BSC versus placebo plus BSC. A significant improvement in PFS (2.8 vs. 2.1 months; HR: 0.63; 95% CI: 0.52–0.75; $p < .0001$) was observed in the ramucirumab arm versus placebo, but this did not translate into a significant OS improvement (9.2 vs. 7.6 months; HR: 0.866; 95% CI: 0.717–1.046; $p = .1391$) [35].

Angiogenesis Beyond the VEGF/VEGFR Pathway

Although VEGF-mediated signaling can promote the growth, survival, migration, and invasion of cancer cells, a role for a number of signaling pathways working in combination with VEGF/VEGFR signaling is now appreciated. Studies of these proangiogenic signaling pathways have provided considerable insight into the molecular mechanisms that underlie tumor angiogenesis and provide a foundation for the development of antiangiogenic therapies that target these pathways (Fig. 2). Indeed, VEGF-independent signaling pathways have been shown to regulate tumor angiogenesis and serve as alternative inducers of tumor growth [36]. Several of these pathways have been well characterized, including the FGF/FGFR, PDGF/PDGFR, and hepatocyte growth factor (HGF)/MET signaling pathways.

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PDGF/PDGFR

The PDGF family consists of PDGF-A to -D polypeptide homodimers and the PDGF-AB heterodimer. These ligands exert their effects by binding to the PDGFR- α and - β tyrosine kinase receptors and activating pathways that are the same as and/or similar to those stimulated by VEGF [37, 38]. Accordingly, activation of PDGF signaling is implicated in growth, survival, and motility of a variety of cell types [39]. Overstimulation of PDGF signaling, either alone or in combination with FGF and VEGF, is associated with tumor vascularization in malignant disease, including but not limited to NSCLC, HCC, and ovarian cancer (OC) [39, 40]. Furthermore, direct activation of PDGF signaling has been observed in multiple tumor types, and coexpression of PDGF and its receptor suggests a role for autocrine and paracrine activation [41]. Roles for aberrant PDGF signaling in tumor angiogenesis include pericyte recruitment to vessels; secretion of proangiogenic factors; stimulation of endothelial cell proliferation, migration, sprouting, and tube formation in tumors; and promotion of lymphangiogenesis and subsequent lymphatic metastasis [42–45]. The importance of PDGF signaling in tumor angiogenesis is further supported by several studies demonstrating that PDGFR inhibitors improve the antitumor efficacy of VEGFR blocking agents [46]. Work is ongoing to clarify a role for PDGF in tumor angiogenesis, in the hope of developing more effective antiangiogenic treatments that reduce growth, maturation, and metastases of various tumor types.

FGF/FGFR

FGFs are heparin-binding growth factors that comprise a family of 23 members, 18 of which function as ligands for four receptor tyrosine kinases (RTKs), namely, FGFR-1 to -4 [47, 48]. FGFs and FGFRs are ubiquitously expressed and have numerous functions, including the regulation of normal cell growth and differentiation and of angiogenesis [49]. FGFR-1 is the primary FGFR expressed on endothelial cells, although FGFR-2 is also present in small amounts [50]. Among the FGFR ligands, FGF1 and FGF2 have been reported to have potent proangiogenic effects that induce the proliferation and migration of endothelial cells [51]. Overexpression of FGF and FGFR is reported in many cancers and is attributed to a number of mutations, including constitutive activation, gene amplification, translocations, gene fusions, and altered gene splicing, which may lead to enhanced angiogenesis through the stimulation and release of other proangiogenic factors [48, 49]. As discussed previously for PDGF, a collaborative interplay between FGF and VEGF signaling has also been demonstrated to be important for angiogenic and metastatic processes [52–54]. FGF can act synergistically with VEGF to amplify tumor angiogenesis; therefore, simultaneously targeting the FGF and VEGF pathways may more efficiently suppress angiogenesis and tumor growth than targeting either pathway alone. FGFs are implicated in the emerging phenomenon of resistance to VEGF inhibition. Resistance to VEGFR-2 blockade in late-stage tumors, for example, occurred in *in vivo* pancreatic cancer models, in which tumors regrew following an initial period of anti-VEGFR-2-mediated growth suppression [55].

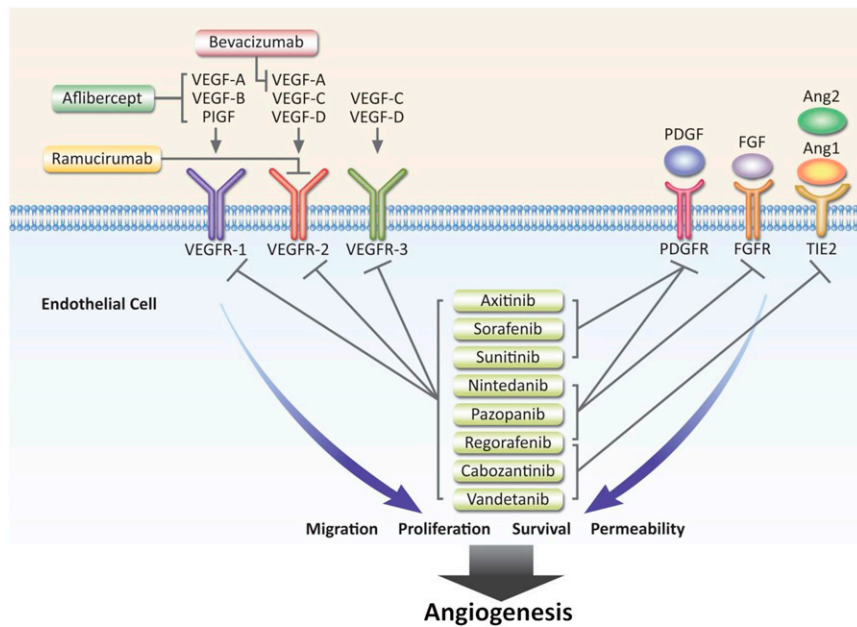


Figure 2. Angiogenesis signaling and targets of inhibition in approved antiangiogenic agents. Reproduced and adapted with permission from [74].

Abbreviations: Ang, angiopoietin; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

ANG/TIE2

Angiopoietins play a critical role in the maintenance of vessel quiescence and comprise a family of four ligands (ANG1 to ANG4). ANG1 and ANG2 are the best-characterized members and bind to the TIE2 receptor. ANG1 binding enhances perivascular-endothelial cell interaction and endothelial cell survival, which, in turn, promotes the stabilization of blood vessels, whereas ANG2 is predominantly synthesized and secreted by endothelial cells at sites of vascular remodeling in response to proangiogenic signals (e.g., inflammation, cytokines, hypoxia) [56]. Of note, ANG2 overexpression in many cancers correlates with poor survival and more invasive cancer phenotypes [53, 57]; however, studies indicate that, depending on the context, ANG/TIE2-targeting therapy can promote either protumor or antitumor effects. ANG2/TIE2-stimulated tumor vascular destabilization, for example, also may render established vasculature more resistant to antiangiogenic therapy, whereas TIE2 inhibition is believed to promote vascular regression. Hampered in part by a limited understanding of the biological complexity that is generated by agonistic and antagonistic signaling, development of treatments targeting the ANG/TIE2 pathway has proved to be challenging [58].

HGF/MET

Produced as a single-chain inactive precursor protein, HGF is a pleiotropic growth factor that binds MET RTK. Not only does HGF/MET signaling regulate normal cell proliferation, motility, and survival, it also mediates tumor angiogenesis and growth in a variety of cell and tissue types, including various carcinomas, sarcomas, hematopoietic malignancies, melanomas, and central nervous system tumors [59, 60]. Proangiogenic effects

of HGF/MET on tumors occur primarily by direct activation of endothelial cells to undergo motogenic or morphogenic changes and by indirect stimulation of the production of proangiogenic factors, including VEGF [61]. Comparisons of bevacizumab-resistant glioblastoma with pretreatment tumors from the same patients found increased MET expression in the former, suggesting that MET may play a role in antiangiogenic therapy resistance by compensating for the inhibition of VEGF and promoting an invasive tumor phenotype [62, 63]. The role of HGF/MET signaling in tumor angiogenesis continues to be a topic of intense investigation because better understanding could facilitate the development of MET-targeted therapies [59].

RET

The rearranged during transfection (RET) proto-oncogene encodes an RTK that is required for many biological processes, including normal development, maturation, and maintenance of several tissues and cell types [64]. When mutated, RET is associated with the growth, maintenance, and progression of several human cancers, including thyroid carcinoma, lung adenocarcinoma, chronic myelomonocytic leukemia, pancreatic cancer, breast cancer, acute myeloid leukemia, and colon carcinoma [64, 65]. Although a direct role in tumor angiogenesis and growth is not completely understood, RET appears to act in a tissue-specific manner by promoting tumor-associated inflammation and recruitment of proinflammatory mediators to stimulate tumor angiogenesis [64]. Furthermore, clinical studies of small-molecule tyrosine kinase inhibitors (TKIs) showed that inhibition of VEGFR-2 and epidermal growth factor receptor (EGFR) or MET also inhibits RET activity, suggesting that the effects of RET can occur, at least in part, through interaction among these pathways [66–68].

Overcoming Resistance to Antiangiogenic Agents: Targeting Multiple Angiogenic Signaling Pathways

Despite the efficacy that anti-VEGF/VEGFR targeted treatments can potentially provide, it is now apparent that many patients are intrinsically refractory or develop resistance to existing antiangiogenic agents that principally target VEGF-A or -B and VEGFR-2. Antiangiogenic resistance is most easily explained by the presence and utilization of various redundant and compensatory proangiogenic signaling pathways to recruit vasculature [69–71]. In support of this hypothesis, studies show that PlGF may mediate resistance by promoting proangiogenic signals when VEGF-A is blocked. In a phase II trial of FOLFIRI and bevacizumab in patients with previously treated mCRC, plasma levels of VEGF-C, VEGF-D, and PlGF were significantly elevated before or at the time of disease progression, suggesting that the increased levels of these proangiogenic factors may compensate for the anti-VEGF-A effects of bevacizumab [72]. Similar findings were reported in a study of bevacizumab-treated patients with CRC that demonstrated that those patients eventually developed increased levels of PlGF and VEGF-D, which coincided with resumption of angiogenesis [73]. Studies also show that, in the absence of VEGF-A activity, binding of VEGF-C and -D to VEGFR-2 and -3 may be sufficient to promote angiogenesis and tumor progression, which highlights another potential compensatory angiogenic mechanism in bevacizumab-treated patients [74].

Similarly, the suggestion of a role for FGF and PDGF signaling in the development of anti-VEGF resistance is borne out by clinical observations showing that increased plasma levels of FGF and PDGF precede disease progression in patients receiving bevacizumab chemotherapy [72]. FGF and PDGF are among the better-characterized proangiogenic pathways implicated in anti-VEGF resistance [55, 75–78]. Indeed, the VEGF, FGF, and PDGF signaling pathways appear to be closely integrated, as shown by data suggesting their redundancy and/or synergy in angiogenesis. FGF-dependent revascularization, for example, has been reported in anti-VEGF-resistant patients who have pancreatic tumors or recurrent glioblastoma [55, 79]. Similar findings are reported for PDGF signaling, with PDGFR expression found to be increased in a pancreatic cancer model that is resistant to VEGFR inhibition; combined targeting of VEGF and PDGF signaling induced regression of established tumor blood supply and inhibited tumor growth [77, 78].

Although data highlight the importance of VEGF signaling, it seems likely that, given the many intracellular pathways that influence tumorigenesis, treatments targeting this pathway alone may be less effective compared with multitargeting agents. A multitargeted approach to treatment is believed to limit the development of resistance and maximize antitumor efficacy [70].

Current and Emerging Multitargeting Antiangiogenic Agents

Antiangiogenic treatments that target multiple signaling pathways simultaneously have been and continue to be developed in the hope of increasing antitumor efficacy (Fig. 2). Several currently available cancer treatments aim to inhibit VEGF, FGF, PDGF, and/or other angiogenesis signaling pathways (Table 1) and have been approved across different cancer indications for a number of years. These agents include sorafenib,

sunitinib, axitinib, and pazopanib. Sorafenib, sunitinib, and axitinib are small-molecule TKIs that simultaneously inhibit the VEGF and PDGF pathways and target other signaling pathways, whereas pazopanib inhibits the VEGF, PDGF, FGF, and other pathways [6, 83, 85, 86]. Preclinical studies suggest that the antitumor and antiangiogenic effects of these agents occur in part through activation of endothelial cell apoptosis, decreased vessel permeability, and reduced blood flow [80, 104–110].

For some of the more recently approved agents, such as cabozantinib and vandetanib, their efficacy may also be attributed in part to their effects on other tumor growth signaling pathways and mechanisms. Cabozantinib targets the VEGFR family as well as c-Met, RET, c-KIT, TRKB, FLT-3, AXL, and TIE2 [66, 67], whereas vandetanib targets the VEGFR family and EGFR in addition to RET, BRK, TIE2, and EPH receptors and Src signaling [87]. Cabozantinib and vandetanib are both approved for advanced/metastatic medullary thyroid cancer, a relatively rare malignancy [66]. OS data are not yet available, but both compounds have demonstrated significant improvements in PFS versus placebo in this population [66, 68].

Regorafenib is a potent TKI with activity against VEGFR-1 to -3, PDGFR- α and - β , FGFR-1 and -2, TIE2, c-KIT, RET, RAF-1, and BRAF. Regorafenib was approved by the FDA in 2012 for the second-line treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with anti-VEGF therapy and, if KRAS wild type, with anti-EGFR therapy [83]. Clinical studies show that regorafenib significantly reduces tumor vascularity, delays tumor growth, and prevents metastasis in colon cancer models, supporting its use as an antiangiogenic treatment for CRC [111, 112].

In November 2014, the multitargeting antiangiogenic agent nintedanib was granted marketing authorization in the European Union for use in combination with docetaxel to treat locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology after first-line chemotherapy [113]. This approval was based on the LUME-Lung 1 trial, which demonstrated a significant improvement in OS to more than 1 year in patients with lung adenocarcinoma treated with nintedanib plus docetaxel versus docetaxel alone [90]. Phase I and II clinical studies initially demonstrated beneficial clinical effects with nintedanib monotherapy in advanced HCC, RCC, and CRC, and in addition to standard chemotherapy combination regimens in various tumor types, including prostate cancer and gynecologic malignancies [114–122]. Encouraging PFS data in OC have been reported (Table 2), and OS data for this indication are awaited [92]. Nintedanib is an orally available angiokinase inhibitor of VEGFR-1 to -3, PDGFR- α and - β , and FGFR-1 to -3, in addition to FLT-3 and Src [82, 114, 138]. Human tumor model studies show that nintedanib can reduce vessel density, vessel integrity, and tumor growth via effects on endothelial and smooth muscle cells, pericytes, and tumor cells [82].

Several other multitargeting antiangiogenic agents are currently in late-stage clinical trials or are under review for approval. These include cediranib, dovitinib, linifanib, brivanib, and lenvatinib (Table 2), which are all investigational antiangiogenic agents that inhibit various VEGFR, FGFR, and PDGFR family members and associated aspects of

Table 1. Currently available multitargeting antiangiogenics

Agent	Axitinib	Cabozantinib	Nintedanib	Pazopanib	Regorafenib	Sorafenib	Sunitinib	Vandetanib
U.S. approvals/indications	Advanced RCC (after failure of one prior systemic therapy)	Metastatic MTC (progressive)	Idiopathic pulmonary fibrosis	Advanced RCC, advanced STS (after prior chemotherapy)	Metastatic CRC (previously treated); GIST (locally advanced, unresectable or metastatic; previously treated with imatinib mesylate or sunitinib malate)	Unresectable HCC; advanced RCC; thyroid carcinoma (locally recurrent or metastatic); advanced RCC; differentiated; refractory to radioactive iodine treatment	GIST (after disease progression or intolerance to imatinib mesylate); advanced RCC; pNET (progressive, well differentiated; unresectable locally advanced or metastatic)	MTC (unresectable, locally advanced or metastatic)
EU therapeutic indications	Advanced RCC (after failure of prior sunitinib or cytokine)	MTC (progressive unresectable locally advanced or metastatic)	Advanced NSCLC (adenocarcinoma histology; after first-line chemotherapy); idiopathic pulmonary fibrosis	Advanced RCC; advanced STS (selected subtypes after prior chemotherapy)	Metastatic CRC (previously treated); GIST (unresectable or metastatic; previously treated with or intolerant to imatinib or sunitinib)	HCC; advanced RCC (after failed IFN- α or IL-2 therapy or unsuitable for such therapy); differentiated thyroid carcinoma (progressive locally advanced or metastatic; refractory to iodine)	GIST (unresectable and/or metastatic; after failure of imatinib mesylate); advanced/metastatic RCC; pNET (well-differentiated; unresectable or metastatic)	Aggressive, symptomatic MTC (unresectable, locally advanced or metastatic)
Targets	VEGFR-1 to -3, PDGFR- β , and c-KIT [6, 80]	VEGFR-1 to -3, c-Met, RET, c-KIT, TRKB, FLT-3, AXL, and TIE2 [81]	VEGFR-1 to -3, PDGFR- α and - β , and FGFR-1 to -3, FLT-3 and Src [82]	VEGFR-1 to -3, PDGFR- α and - β , FGFR-1 and -3, and c-KIT, Itk, Lck, c-Fms [83]	VEGFR-1 to -3, PDGFR- α and - β , FGFR-1 and -3, RET, RAF-1, and BRAF ^{mut} , DDR2, TrkA, EphA2, SAPPK2, PTK5 and Abl [84]	c-CRAF, BRAF, mutant BRAF, c-KIT, FLT-3, RET, RET/PTC, VEGFR-1 to -3, and PDGFR- β [85]	VEGFR-1 to -3, PDGFR- α and - β , FLT-3, c-KIT, CSF-1R, and RET [86]	VEGFR-2 and VEGFR-3, EGFR, RET, BRK, TIE2, EPH receptors, and Src signaling pathways [87, 88]
PFS, months, median (HR; 95% CI); p value ^a	RCC (vs. sorafenib) [89]: 6.7 vs. 4.7 (0.67; 0.54–0.81); $p < .0001$	MTC (vs. placebo) [66]: 11.2 vs. 4.0 (0.28; 0.19–0.40); $p < .001$	NSCLC (nintedanib plus docetaxel vs. placebo plus docetaxel) [90]: 3.4 vs. 2.7 (0.79; 0.68–0.92); $p = .0019$; NSCLC (nintedanib plus pemtrexed vs. placebo plus pemtrexed) [91]: 4.4 vs. 3.6 (0.83; 0.70–0.99); $p = .0435$; ovarian cancer (nintedanib plus paclitaxel and carboplatin vs. placebo plus paclitaxel and carboplatin) [92]: 17.3 vs. 16.6 (0.84; 0.72–0.98); $p = .0239$	RCC (vs. placebo) [93]: 9.2 vs. 4.2 (0.46; 0.34–0.62); $p < .0001$; STS (vs. placebo) [94]: 4.6 vs. 1.6 (0.31; 0.24–0.40); $p < .0001$	CRC (vs. placebo) [95]: 1.9 vs. 1.7 (0.49; 0.42–0.58); $p < .0001$; GIST (vs. placebo) [96]: 4.8 vs. 0.9 (0.27; 0.19–0.39); $p < .0001$	RCC (vs. placebo) [97]: 5.5 vs. 2.8 (0.44; 0.35–0.55); $p < .000001$; HCC [98]: NR; thyroid carcinoma (vs. placebo) [99]: 10.8 vs. 5.8 (0.59; 0.45–0.76); $p < .001$	GIST (vs. placebo) [100]: 5.3 vs. 1.4 (0.35; 0.25–0.48); $p < .001$; RCC (vs. IFN- γ ; treatment-naïve patients) [86, 101]: 10.9 vs. 5.1 (0.42; 0.32–0.54); $p < .000001$; pNET (vs. placebo) [86]: 10.2 vs. 5.4 (0.427; 0.271–0.673); $p = .0001$	MTC (vs. placebo) [68]: not yet reached; predicted 30.5 vs. observed 19.3 (0.46; 0.31–0.69); $p < .001$
OS, months, median (HR; 95% CI); p value ^a	RCC (vs. sorafenib) [102]: 20.1 vs. 19.2 (0.97; 0.80–1.17); $p = .374$	MTC (vs. placebo) [66]: no OS benefit shown; data not yet mature (0.98; 0.63–1.52)	NSCLC (nintedanib plus docetaxel vs. placebo plus docetaxel); adenocarcinoma histology [90]: 12.6 vs. 10.3 (0.83; 0.70–0.99); $p = .0359$; NSCLC (nintedanib plus pemtrexed vs. placebo plus pemtrexed) [91]: 12.2 vs. 12.7 (HR 1.03; 0.85–1.24); $p = .7921$; ovarian cancer (nintedanib plus paclitaxel and carboplatin vs. placebo plus paclitaxel and carboplatin) [92]: NR (data not yet mature)	RCC (vs. placebo) [103]: 22.9 vs. 20.5 (0.91; 0.71–1.16); $p = .224$; STS (vs. placebo) [94]: 12.5 vs. 10.7 (0.86; 0.67–1.11); $p = .2514$	CRC (vs. placebo) [95]: 6.4 vs. 5.0 (0.77; 0.64–0.94); $p = .0052$; GIST (vs. placebo) [96]: NR vs. NR (0.77; 0.42–1.41); $p = .199$	RCC (vs. placebo) [97]: 17.8 vs. 14.3 (0.78; 0.62–0.97); $p = .029$; HCC (vs. placebo) [98]: 10.7 vs. 7.9 (0.69; 0.55–0.87); $p = .00058$; thyroid carcinoma (vs. placebo) [85]: NR vs. 36.5 (0.88; 0.63–1.24); $p = .47$	GIST (vs. placebo) [100]: 16.7 vs. 14.9 (0.876; 0.68–1.13); $p = .306$; RCC (vs. IFN- γ ; treatment-naïve patients) [86]: 26.4 vs. 21.9 (0.82; 0.68–1.00); $p = NR$; pNET [86]: NR	MTC (vs. placebo) [68]: data not yet mature (0.89; 0.48–1.65)
AEs (three most frequent AEs in the investigational compound)	RCC (vs. sorafenib, treatment-emergent) [89]: diarrhea (55% vs. 53%), hypertension (40% vs. 29%), fatigue (39% vs. 32%)	MTC (vs. placebo) [66]: diarrhea (63% vs. 33%), hand-foot syndrome (50% vs. 2%), weight loss (48% vs. 10%)	NSCLC (nintedanib plus docetaxel vs. placebo plus docetaxel) [90]: diarrhea (42% vs. 22%), neutrophil decrease (37% vs. 36%), fatigue (30% vs. 27%); NSCLC (nintedanib plus pemtrexed vs. placebo plus pemtrexed) [91]: ALT increase (43% vs. 33%), AST increase (37% vs. 19%)	RCC (vs. placebo) [93]: diarrhea (52% vs. 9%), hypertension (40% vs. 10%), hair color change (38% vs. 3%), STS (vs. placebo) [94]: fatigue (65% vs. 49%), diarrhea (58% vs. 16%), nausea (54% vs. 28%)	CRC (vs. placebo, treatment-emergent) [95]: fatigue (47% vs. 28%), hand-foot syndrome (47% vs. 8%), diarrhea (34% vs. 8%); GIST (vs. placebo) [96]: hand-foot syndrome (67% vs. 15%), hypertension (59% vs. 27%), asthenia/fatigue (52% vs. 39%)	RCC (vs. placebo) [97]: diarrhea (48% vs. 11%), fatigue (29% vs. 16%), nausea (19% vs. 12%), HCC (vs. placebo) [98]: diarrhea (55% vs. 25%), fatigue (46% vs. 45%), abdominal pain (31% vs. 26%); thyroid carcinoma (vs. placebo) [85]: hand-foot syndrome (76% vs. 8%),	GIST (vs. placebo) [100]: fatigue (37% vs. 22%), diarrhea (34% vs. 6%), nausea (12% vs. 13%); RCC (vs. IFN- γ) [86]: diarrhea (66% vs. 21%), fatigue (62% vs. 56%), nausea (58% vs. 41%); pNET (vs. placebo) [86]: diarrhea (59% vs. 39%),	MTC (vs. placebo) [68]: diarrhea (56% vs. 26%), rash (45% vs. 11%), nausea (33% vs. 16%)

(continued)

Table 1. (continued)

Agent	Axitinib	Cabozantinib	Nintedanib	Pazopanib	Regorafenib	Sorafenib	Sunitinib	Vandetanib
Ongoing phase III trials (as of January 2015)	RCC in high-risk patients (NCT01599754); metastatic RCC (NCT00678392; NCT00920816 ^c)	HCC (NCT01908426); metastatic CRPC (NCT01605227; NCT01522443); metastatic RCC (NCT01865747); MTC (NCT00704730 ^c)	Ovarian cancer (NCT01015118 ^c); NSCLC (NCT022231164; NCT00805194; NCT00806819 ^c); IPF (NCT01979952; NCT01619085); refractory CRC (NCT02149108)	Ovarian cancer (NCT00866697 ^c); NSCLC (NCT00775307); RCC (NCT01613846; NCT01235962; NCT00720941 ^c ; NCT01575548; NCT00334282 ^c ; NCT00387764 ^c); STS (NCT02049905; NCT02180867)	HCC (NCT01774344); CRC (NCT01939223; NCT01853319; NCT01584830; NCT01189903; NCT01538680)	RCC (NCT01613846; NCT00326898; NCT01481870); AML (NCT01371981); HCC (NCT01829035; NCT01015833; NCT01730937; NCT01405573; NCT01932385; NCT01906216; NCT00901901 ^c); desmoid tumor (NCT02066181); breast cancer (NCT01234337); neoplasms (NCT00625378); melanoma (NCT00110019 ^c ; NCT00111007); thyroid cancer (NCT00984282 ^c)	RCC (NCT00375674; NCT00326898; NCT01481870); NSCLC (NCT00699392)	Thyroid cancer (NCT01876784); MTC (NCT01298323 ^c ; NCT00410761 ^c); NSCLC (NCT00364351 ^c ; NCT00418886 ^c)
Completed phase III trials (as of January 2015)	Advanced pancreatic cancer (NCT00471146)		IPF (NCT01335477; NCT01335464)	STS (NCT00753688); NSCLC (NCT01208064, terminated)	Metastatic CRC (NCT01103323); GIST (NCT01271712; NCT01646593)	HCC (NCT00105443; NCT00494299; NCT00692770; NCT00492752); NSCLC (NCT00449033; NCT00863746; NCT00300885, terminated); RCC (NCT00558636, terminated); RCC (NCT00492986; NCT00586105; NCT00073307; NCT00732914; NCT00478114; NCT00606866; NCT00111020; NCT00492258)	Breast cancer (NCT00393939; NCT00373256; NCT00435409; NCT00373113, terminated); HCC (NCT00699374, terminated); NSCLC (NCT00457392); RCC (NCT00838889; NCT00732914); Metastatic CRPC (NCT00676650, terminated); CRC (NCT00457691); Pancreatic cancer (NCT00428597, terminated); GIST (NCT00075218; NCT00372567, terminated)	NSCLC (NCT00404924; NCT00312377)

^aValues cannot be compared between trials due to differences in study design and methodology.

^bOnly grade 3–5 AEs if difference \geq 2%.

^cStudies listed as active, not recruiting patients on ClinicalTrials.gov as of January 2015.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; BRAF, v-raf murine sarcoma viral oncogene homolog B; BRK, breast tumor kinase; C/ confidence interval; c-MET, hepatocyte growth factor receptor; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; CSF-1R, colony stimulating factor-1 receptor; EGFR, epidermal growth factor receptor; EPH, ephrin receptor; EU, European Union; FGFR, fibroblast growth factor receptor; FLT, fms-related tyrosine kinase; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HER, human epidermal growth factor; HR, hazard ratio; IFN, interferon; IL, interleukin; IPF, idiopathic pulmonary fibrosis; MTC, medullary thyroid cancer; NR, not reported; NSCLC, non-small cell lung cancer; pNET, pancreatic neuroendocrine tumor; PTC, papillary thyroid carcinoma; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; RCC, renal cell carcinoma; RET, rearranged during transfection; STS, soft tissue sarcoma; TIE, tyrosine kinase with immunoglobulin-like and EGF-like domains; TRKB, tropomyosin-related kinase protein B; VEGFR, vascular endothelial growth factor receptor.

Table 2. Investigational antiangiogenic agents in phase III development for any indication^a

Agent	Brivanib	Cediranib	Dovitinib	Lenvatinib	Linifanib
Target	VEGFR-2 and FGFR-1 [123, 124]	VEGFR-1 to -3, PDGFR- α and - β , FGFR-1, and c-KIT [125]	VEGFR-1 to -3, FGFR-1 to -3, and PDGFR- β [126]	VEGFR-1 to -3, FGFR-1, and PDGFR- α and - β [127, 128]	VEGFR-1 to -3, PDGFR- α and - β , FGFR-1, and c-KIT, Csf-1R, and Flt-3 [129, 130]
Ongoing phase III trials (as of January 2015)	HCC (NCT00825955; NCT00908752)	Metastatic CRC (NCT00384176 ^b ; NCT00399035); recurrent glioblastoma (NCT00777153); relapsed ovarian cancer (platinum-sensitive) (NCT00532194); advanced NSCLC (NCT00245154 ^b)	Solid tumors (NCT02116803)	Thyroid cancer (NCT01321554); HCC (NCT01761266)	
Completed phase III trials (as of January 2015)	Metastatic CRC (NCT00640471); HCC (NCT00858871; NCT01108705, terminated)	Advanced NSCLC (NCT00795340); advanced biliary tract cancer ^b (NCT00939848)	Metastatic RCC (NCT01223027)		Advanced HCC (NCT01009593, terminated due to increased toxicity and no improvement in OS)
PFS, months; median (HR; 95% CI); <i>p</i> value ^c	HCC (vs. sorafenib) [123]; NR	Metastatic CRC (plus FOLFOLFOX/CAPOX vs. placebo plus FOLFOLFOX/CAPOX) [131]: 8.6 vs. 8.3 (0.84; 0.73–0.98); <i>p</i> = .0121; metastatic CRC (plus mFOLFOLFOX6 vs. bevacizumab plus mFOLFOLFOX6) [132]: 9.9 vs. 10.3 (1.10; 0.97–1.25); <i>p</i> = .119; recurrent glioblastoma (placebo plus lomustine vs. lomustine) [133]: 3.0 vs. 2.7 (1.05, 0.74–1.50); <i>p</i> = .90; cediranib plus lomustine vs. lomustine: 3.0 vs. 4.1 (0.76, 0.53–1.08); <i>p</i> = .16; relapsed ovarian cancer (platinum-sensitive; vs. platinum-based chemotherapy) [134]: 9.4 vs. 11.4 (0.68; NR; <i>p</i> = .0022); advanced NSCLC [135]: 5.5 vs. 5.5 (0.91; 0.71–1.18); <i>p</i> = .49	Metastatic RCC (vs. sorafenib) [136]: 3.7 vs. 3.6 (0.86; 0.72–1.04); <i>p</i> = .063	Thyroid cancer (vs. placebo) [137]: 18.3 vs. 3.6 (0.21; 99% CI: 0.14–0.31); <i>p</i> < .0001	HCC (vs. sorafenib) [129]: NR
OS, months; median (HR; 95% CI); <i>p</i> value ^c	HCC (vs. sorafenib) [123]: 9.5 vs. 9.9 (1.06; 0.94–1.23); <i>p</i> = .3116	Metastatic CRC (plus FOLFOLFOX/CAPOX vs. placebo plus FOLFOLFOX/CAPOX) [131]: 19.7 vs. 18.9 (0.94; 0.79–1.12); <i>p</i> = .012; Metastatic CRC (plus mFOLFOLFOX6 vs. bevacizumab plus mFOLFOLFOX6) [132]: 22.8 vs. 21.4 (0.95; 0.82–1.10); <i>p</i> = .546; recurrent glioblastoma (placebo plus lomustine vs. lomustine) [133]: 8.0 vs. 9.8 (1.43, 0.96–2.13); <i>p</i> = .10; cediranib plus lomustine vs. lomustine: 9.4 vs. 9.8 (1.15, 0.77–1.72); <i>p</i> = .50; relapsed ovarian cancer (platinum-sensitive; vs. platinum-based chemotherapy) [134]: 17.6 vs. 20.3 (0.70; NR; <i>p</i> = .0419); advanced NSCLC [135]: 12.2 vs. 12.1 (0.94; 0.69–1.30); <i>p</i> = .72	Metastatic RCC (vs. sorafenib) [136]: 11.1 vs. 11.0 (0.96; 0.75–1.22); NR	Thyroid cancer (vs. placebo) [137]: NR vs. NR (0.73; 0.50–1.07); <i>p</i> = .1032	HCC (vs. sorafenib) [129]: 9.1 vs. 9.8 (1.05; 0.90–1.22); NR
AEs (three most frequent AEs in the investigational compound ^c)	HCC (vs. sorafenib) [123]: decreased appetite (52% vs. 35%); fatigue (52% vs. 35%); diarrhea (49% vs. 50%)	Metastatic CRC (plus FOLFOLFOX/CAPOX vs. placebo plus FOLFOLFOX/CAPOX) [131]: diarrhea (71% vs. 48%), nausea (51% vs. 47%), vomiting (47% vs. 37%); metastatic CRC (plus mFOLFOLFOX6 vs. bevacizumab plus mFOLFOLFOX6) [132]: diarrhea (70% vs. 51%), nausea (51% vs. 50%), peripheral	Metastatic RCC (vs. sorafenib) [treatment-emergent] [136]: diarrhea (68% vs. 45%), nausea (53% vs. 45%)	Thyroid cancer (vs. placebo) [treatment-emergent] [137]: hypertension (68% vs. 9%), diarrhea (14% vs. 15%), AST increase (12% vs. 13%)	HCC (vs. sorafenib) ^d [129]: hypertension (21% vs. 11%), hand–foot syndrome (14% vs. 15%), AST increase (12% vs. 13%)

(continued)

Table 2. (continued)

Agent	Brivanib	Cediranib	Dovitinib	Lenvatinib	Linifanib
		neuropathy (50% vs. 51%); recurrent glioblastoma ^e [133]; cediranib: fatigue (16%), hypertension (14%), convulsion (9%); cediranib plus lomustine: thrombocytopenia (38%), neutropenia (20%), fatigue (15%); placebo plus lomustine: thrombocytopenia (22%), fatigue (9%), lymphopenia (8%); relapsed ovarian cancer (platinum-sensitive; vs. platinum-based chemotherapy) [134]; NR: advanced NSCLC (vs. placebo) [135]; anemia (92% vs. 97%), neutropenia (93% vs. 86%), fatigue (84% vs. 79%)	29%), vomiting (44% vs. 16%)	(60% vs. 8%), fatigue/asthenia (59% vs. 28%)	

^aRefers to agents and tumor types investigated in phase III trials.

^bPhase III follow-up study.

^cValues cannot be compared between trials due to differences in study design and methodology.

^dOnly grade 3–4 AEs > 3%.

^eOnly grade 3–4 AEs > 5%.

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; CAPOX, oxaliplatin plus oral capecitabine; CI, confidence interval; CRC, colorectal cancer; CSF-1R, colony stimulating factor-1 receptor; FGFR, fibroblast growth factor receptor; FLT, fms-related tyrosine kinase; FOLFOLX, 5-fluorouracil plus leucovorin plus oxaliplatin; HCC, hepatocellular cell carcinoma; HR, hazard ratio; mFOLFOLX, modified FOLFOLX; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; RCC, renal cell carcinoma; VEGFR, vascular endothelial growth factor receptor.

angiogenesis. Of these agents, cediranib is perhaps the furthest advanced in development, with completed or ongoing phase III trials for a number of indications, including CRC, NSCLC, ovarian cancer, glioblastoma, and biliary tract cancer. Most recently, in 2013, initial results from the ICON-6 trial of relapsed platinum-sensitive ovarian cancer showed significant improvement in PFS when cediranib was given concurrently with platinum-based chemotherapy versus chemotherapy alone and a positive effect on both PFS and OS when continued as a maintenance therapy [134]. Despite initial signs of activity as a monotherapy or in combination with chemotherapy in advanced tumors, cediranib has not yet been approved for use [139], and phase III clinical trials continue to evaluate the utility of this drug in combination with chemotherapy.

The investigational agent dovitinib, which targets FGFR as well as VEGFR and PDGFR, is being evaluated in RCC and has reached phase III development. In phase I trials, although dovitinib demonstrated activity in heavily pretreated patients [126], it was not shown to be superior to sorafenib in the third-line setting in patients with RCC who had progressed during treatment with previous VEGF-targeted therapies and mammalian target of rapamycin inhibitors [136]. RCC is a highly vascularized tumor, which is often due to von Hippel-Lindau gene mutations that drive proangiogenic signaling pathways [140]. The antiangiogenic agents axitinib and pazopanib have demonstrated significant antitumor activity and have been approved in advanced RCC as second-line therapy (Table 1).

Lenvatinib and linifanib, which target VEGFR, FGFR, and PDGFR, and brivanib, which targets VEGFR and FGFR, have reached phase III development in HCC. Hypervascularization is a key characteristic of HCC disease progression [141], making this an attractive indication for the investigation of antiangiogenic agents. Indeed, sorafenib has been approved for this indication for a number of years [85]; however, resistance to sorafenib has been observed [141, 142] and has led to the investigation of other antiangiogenic agents. The development of both linifanib and brivanib, however, appears to have faltered. Neither compound has demonstrated superiority or noninferiority to sorafenib (in terms of OS), and this is coupled with increased toxicity in first-line treatment [123, 129] and the termination of phase III HCC trials for both compounds (Table 2). The efficacy and safety of antiangiogenic agents in HCC continues to be debated [141].

DISCUSSION

Angiogenesis is a complex mechanism that depends on the tumor type. Indications including RCC, HCC, NSCLC, and OC, which are considered to be highly vascularized tumors, have been the focus of development for antiangiogenic agents. Several antiangiogenic agents are approved for these indications. Because multiple therapeutic options are available now, most patients on clinical trials receive additional lines of therapy when their tumors progress, thus it has been felt that the classic survival endpoint for approving novel compounds by the FDA may not be ideal. There is a push to move to PFS as an endpoint for approval by the FDA. Although this endpoint has not been fully adopted, there is evidence that the agency is moving in this direction.

It is interesting that few agents are continuing to be studied in solid tumors such as breast cancer, which are considered to

be less vascularized (Tables 1, 2). To date, the efficacy of antiangiogenic agents such as bevacizumab, sorafenib, and ramucirumab in breast cancer has been very variable [17]. The variability in response to antiangiogenic therapy in breast cancer is most likely explained by the extent of vascularization in this tumor type, the highly heterogeneous nature of the disease, the development of drug resistance, and the utilization of compensatory angiogenic mechanisms [17]. Recent results with ramucirumab plus docetaxel in the ROSE/TRIO trial in advanced HER2-negative breast cancer were disappointing [34]. No meaningful improvement in important clinical outcomes such as OS versus docetaxel alone were observed, and there was significantly more toxicity [34]. However, results from the TANIA and IMELDA trials in this indication demonstrated that continued second-line treatment with bevacizumab plus chemotherapy significantly improved PFS compared with bevacizumab alone [143, 144]. It is clear that the use of antiangiogenic therapy in breast cancer remains to be fully evaluated [17].

High variability in patient response to antiangiogenic therapy across different indications exists, and this is coupled with the development of therapy resistance [145]. As with other targeted compounds, a biomarker to identify patients with cancer who will benefit from antiangiogenic therapy is still needed. One of the main challenges in identifying potential biomarkers for antiangiogenic therapy is the complex nature of the angiogenic signaling process, which is characterized by multiple pathways that not only overlap but that continuously cross-talk, making it difficult to eliminate an angiogenic stimulus [146]. Several possible types of biomarkers are being investigated across different indications: circulating biomarkers (e.g., concentrations of soluble angiogenic receptor ligands), genetic biomarkers

(e.g., single nucleotide polymorphisms), tissue biomarkers (e.g., immunohistochemical staining of angiogenic receptors); and physiologic biomarkers (e.g., hypertension) [145]. However, the reproducibility of candidate biomarkers across indications is limited, and there is a paucity of studies comparing the same biomarkers for the same indication. The use of genomic and proteomic technologies will be key in improving our ability to match a target pathology with antiangiogenic therapy [17].

CONCLUSION

The focus of new and emerging antiangiogenic therapies is the simultaneous disruption of multiple signaling pathways. It is hoped that by using multitargeting, tumors will be less able to overcome the antiangiogenic and antitumor effects. Indeed, results from various clinical trials have already demonstrated the benefits of some multitargeting antiangiogenic agents in different tumor types.

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AUTHOR CONTRIBUTIONS

Conception/Design: Yujie Zhao, Alex A. Adjei
Data analysis and interpretation: Yujie Zhao, Alex A. Adjei
Manuscript writing: Yujie Zhao, Alex A. Adjei
Final approval of manuscript: Yujie Zhao, Alex A. Adjei

DISCLOSURES

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