# Anti-angiogenic therapies in the management of glioblastoma

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**Abstract:** Angiogenesis is a central feature of glioblastoma (GBM), with contribution from several mechanisms and signaling pathways to produce an irregular, poorly constructed, and poorly connected tumor vasculature. Targeting angiogenesis has been efficacious for disease control in other cancers, and given the (I) highly vascularized environment in GBM and (II) correlation between glioma grade and prognosis, angiogenesis became a prime target of therapy in GBM as well. Here, we discuss the therapies developed to target these pathways including vascular endothelial growth factor (VEGF) signaling, mechanisms of tumor resistance to these drugs in the context of disease progression, and the evolving role of anti-angiogenic therapy in GBM.

**Keywords:** Brain tumor; glioblastoma (GBM); angiogenesis; vascular endothelial growth factor (VEGF); resistance; radiation necrosis

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Glioblastoma (GBM) is the most aggressive and unfortunately most common, malignant primary brain tumor, with a median survival of 10–31 months depending on age at diagnosis, extent of resection, treatment and molecular prognostic factors (1-4). Angiogenesis is a central feature of GBM, with microvascular glomeruloid proliferation requisite for histological diagnosis (5,6). Endothelial cells comprise the tumor blood vessels, facilitating delivery of nutrients and oxygen. In addition, endothelial cells directly support glioma progenitor cell proliferation through intercellular signaling pathways, contributing to tumor growth and resilience (7).

## Mechanisms of angiogenesis

Angiogenesis in gliomas involves various mechanisms: co-option of preexisting vessels (8); *de novo* angiogenesis through extension of nearby vessels (9); differentiation of bone marrow-derived endothelial progenitors (10); multiplication of vessels through splitting of existing vessels (also known as intussusception) (11); and vascular mimicry by glioma stem cells that form luminal cylinders resembling vessels (12-15).

Angiogenesis is regulated by intricate and overlapping signaling pathways, which involve both hypoxia-dependent and -independent processes. In hypoxic environments, hypoxia inducible factor 1 subunit alpha (*HIF-1α*) is upregulated, driving expression of pro-angiogenic genes such as vascular endothelial growth factor (*VEGF*). VEGF protein binds to its receptor VEGFR and activates additional growth factors that mediate endothelial sprouting, migration, and endovascular permeability. Hypoxia also induces matrix metalloproteinase (*MMP*) production that mediates stromal disintegration and endothelial migration (16,17). Angiopoietin 1 (*ANG1*) and *ANG2* have a complicated interplay, but work together to help formalize these primitive vessels. ANG1 protein stabilizes vessels by facilitating cell interactions that support vasculature integrity (18). The role of ANG2 depends on the presence or absence of VEGF. When VEGF is present,

ANG2 acts via tyrosine kinase with immunoglobulin-like and EGF-like 1 (TIE1) receptors to promote angiogenesis and stimulate the migration and differentiation of endothelial cells, through Notch and ephrin-A2 signaling, respectively (19-22). When VEGF is absent, ANG2 acts via TIE2 receptors to destabilize blood vessels, causing endothelial apoptosis and vessel regression (19). In low nutrient environments, *VEGF* can be upregulated through peroxisome-proliferator-activated receptor-γ coactivator-1α (*PGC-1-α*) independently of hypoxia (23). In addition, several different gene mutations that are common in gliomas, including platelet-derived growth factor (*PDGF*), epithelial growth factor receptor (*EGFR*), p53 (*TP53*), RB transcriptional corepressor 1 (*RB1*), von Hippel-Lindau tumor suppressor (*VHL*) and phosphate and tensin homolog (*PTEN*), all stabilize HIF-1α causing subsequent upregulation of *VEGF* (24,25).

In addition to *VEGF*-related actions on angiogenesis, stromal cell-derived factor 1 protein (SDF-1, also known as C-X-C motif chemokine ligand 2, CXCL2), and its receptor CXCR4 (C-X-C motif chemokine receptor 4), also recruit bone marrow-derived progenitors from the circulation into the tumor that subsequently differentiate into endothelial cells and pericytes (26-28). Other growth factor pathways including fibroblast growth factor (*FGF*), phosphoinositide 3-kinase (*PIK3*), *PDGF*, and transforming growth factor β1 (*TGFβ1*), mediate angiogenesis through a combination of mechanisms that regulate *VEGF* expression, stimulate endothelial cell proliferation, and regulate expression of proteases implicated in vessel dissolution and migration (29-32). As these processes unfold, the tumor vasculature manifests as irregular, poorly constructed, and poorly connected vessels (33). This disorganized and leaky system creates spatiotemporal heterogeneity in tumor oxygenation that may impact the development and expansion of the tumor's genetic subclone populations.

## Therapeutic strategies targeting angiogenesis

Targeting angiogenesis through *VEGF* blockade and other mechanisms has been efficacious in other cancers. In addition to triggering tumor cell death via deprivation of oxygen and nutrients, targeting angiogenesis may lead to the transient normalization of the tumor vasculature and improved uptake of cytotoxic chemotherapy (34). In addition to observations that GBM is a highly vascularized tumor, several studies correlated *VEGF* expression with glioma grade and prognosis (16,35,36). Thus, angiogenesis became a prime target of therapy in GBM as well.

While there are many inhibitors targeting different parts of the angiogenesis cascade, the only approved treatment in the United States (US) is bevacizumab, a recombinant human monoclonal antibody that binds to and sequesters VEGF, preventing activation of its receptors. In 2004, it was first FDA-approved for treatment of advanced colorectal cancer, where it reduced microvascular density and blood perfusion (37). The first clinical trials of bevacizumab in GBM were in recurrent disease in the "AVF3708g/BRAIN" and "NCI 06-C-0064E" phase II trials. In these trials, bevacizumab monotherapy or combination therapy with irinotecan, demonstrated objective response rates (28–40%) and progression-free survival at 6 months (PFS6) of 40–50% that were markedly improved compared to higher historical controls, but no improvement in overall survival (OS) (38-40). These studies led to conditional accelerated FDA approval of bevacizumab in recurrent GBM in 2009, approved as monotherapy given the added toxicity in the combination arm (38,39). The phase III European Organization of Research and Treatment of Cancer (EORTC) 26101 trial in recurrent GBM investigated lomustine with or without bevacizumab, and combination therapy also demonstrated improvement in PFS (1.5 to 4.2 months) but no change in OS (41). Both the AVF3708g and EORTC 26101 trials demonstrated reduced reliance on steroids. In EORTC 26101, more patients on bevacizumab were able to completely stop steroids than patients in the control arm (23% *vs.* 12%). Based on the results of this trial, bevacizumab received full approval for treatment of recurrent GBM in 2017.

Bevacizumab was also investigated in newly diagnosed GBM in two large randomized, double-blinded, phase III trials—Radiation Therapy Oncology Group (RTOG) 0825 and AVAglio. Both trials demonstrated an improvement in PFS by 3.4–4.4 months with addition of bevacizumab to standard temozolomide and radiation, but no improvement in OS (42,43).

Aflibercept, also known as VEGF trap, is a recombinant fusion protein that binds to circulating VEGF-A and VEGF-B, as well as placenta growth factor (PGF), and inhibits binding to VEGF receptors and downstream signaling. A phase II trial in recurrent malignant glioma demonstrated PFS6 of 7.7% in GBM, however the study was notable for high dropout attributed to significant toxicities (44).

Tyrosine kinase inhibitors (TKIs) are small molecules that target one or many tyrosine kinase receptors, including

VEGFR, EGFR, PDGFR, and FGFR. Sunitinib and sorafenib both target VEGFR in addition to c-Kit and PDGFR, and are shown to improve survival in other cancers including metastatic renal and hepatic cell carcinoma (45,46). However, a phase II trial looking at sunitinib monotherapy in bevacizumab-naïve and -resistant recurrent GBM demonstrated no improvement in PFS or OS (47). Sorafenib was tested in a phase I trial of recurrent GBM with modest effect on outcomes (median PFS 7.9 months and OS 17.8 months), but several dose-limiting toxicities (48). Phase III trial of cediranib, another inhibitor of VEGFR, c-Kit and PDGFR, versus lomustine versus combination failed to meet its primary endpoint of PFS in recurrent GBM (49). Enzastaurin, which targets the protein kinase C and *PI3K/AKT* serine/threonine 1 pathways, also failed to meet its primary endpoint of improvement in PFS or OS in a phase III trial in recurrent GBM comparing enzastaurin versus lomustine (50).

Unfortunately, targeting other components of angiogenesis has also demonstrated limited efficacy. Trebananib (AMG386), a peptide fused to the Fc immunoglobulin protein, inhibits ANG1 and ANG2 ligands from interacting with the TIE2 receptor. Phase II study of trebananib versus combination with bevacizumab in recurrent GBM showed no improvement compared to historical OS of bevacizumab monotherapy (51). Cilengitide, an antagonist of integrins αvβ3 and αvβ5 that mediate vascular stability, did not improve PFS or OS in combination with standard therapy for newly diagnosed GBM (52). In addition to the treatments discussed above, there are many additional clinical trials using medications targeted toward angiogenesis, in different phases of development (*Table 1*).

## Pathways of resistance

Despite the biologic rationale and early promise of anti-angiogenic therapies, no agent in isolation or in combination has yet demonstrated an improvement in survival in GBM. Mechanisms of resistance are multifactorial and involve (I) upregulation of *VEGF*-independent angiogenesis; alternative methods of vasculogenesis including (II) recruitment of bone marrow-derived progenitors, (III) vascular mimicry and (IV) vessel co-option; (V) tumor cell autophagy; and (VI) tumor cell migration away from the tumor center and invasion into surrounding brain tissue (*Figure 1*). In addition to these pathways, there is some data that tumors treated with TKIs may acquire mutations in tyrosine kinase domain that dampen the response to TKIs, as seen with EGFR inhibitors gefitinib and erlotinib (90).

Downregulation of *VEGF* leads to upregulation of other proangiogenic pathways, including *PDGF*, *FGF*, phosphatidylinositol glycan anchor biosynthesis class F (*PlGF*), hepatic growth factor (*HGF*)/*c-MET* protooncogene, *ANG1*, *ANG2*, delta4-notch (*DLL4-Notch*), and interleukins (12,91,92). Hypoxia resulting from treatment with VEGF inhibitors upregulates *HIF-1α*, which in turn increases expression of *ANG2* (93). *FGF*, which is involved in developmental and oncologic angiogenesis, may mediate resistance to VEGF inhibitors such as cediranib (94,95). In addition to regulation of *FGF* and ephrin signaling pathways, the *DLL4-Notch* pathway may also mediate resistance to VEGF inhibition by stabilization of larger vessels (96).

Blockade of *VEGF/VEGFR* signaling drives compensatory mechanisms of tumor vasculogenesis. Increased vascular co-option was seen in *HIF-1α* transgenic knockout mice, as well as GBM mouse xenograft models treated with a neutralizing VEGF antibody (10,97). In humans, co-option was observed in resected tumor samples after pre-surgery exposure to bevacizumab or cediranib (98,99). *VEGF/VEGFR* blockade also leads to *de novo* blood vessel formation and stabilization via the *VEGF*-independent pathways described above (10,99-106).

Independent of increasing angiogenesis, disease resistance to anti-angiogenic agents may be mediated by other mechanisms of tumor perseverance. The hypoxia-induced pathways above also drive tumor progression through expansion of a *HIF*-regulated tumor progenitor population (107). Tumor cells under hypoxic stress may also evade immediate cell death with autophagy-driven sequestering of damaged cell components, mediated by HIF-1α and B-cell CLL/lymphoma 2 (*BCL2*)-interacting protein 3 (*BNIP3*) (100). In addition to *in situ* resilience, tumor cells treated with anti-angiogenic agents migrate and invade away from hypoxic areas, demonstrated both in mouse models of GBM (108,109) and in humans (110,111). This invasion is often perivascular in nature along blood vessels remaining after anti-angiogenic treatment, with tumor cells co-opting pre-existing vessels in a *VEGF*-independent manner (97). This invasion is seen on MRI as non-enhancing disease and can be multifocal and thus more difficult to address with focal treatments (surgery, radiation, etc.) at the time of recurrence (26,101,108). This invasive phenotype may be mediated through upregulation of genes that facilitate cellular motility as

**Table 1** Clinical trials with anti-angiogenic treatment

| Drug | Target | Farthest trial design | Results |
|---|---|---|---|
| Antibodies | | | |
| Andecaliximab (GS-5745) | MMP9 | Phase II recurrent GBM | Ongoing (NCT03631836) |
| Bevacizumab | VEGF-A | Phase III newly diagnosed GBM | RT/TMZ ± BEV; AVAGlio: mOS 16.8 *vs.* 16.7 months; mPFS 8.4 *vs.* 4.3 months (43); RTOG 0825: mOS 15.7 *vs.* 16.1 months; mPFS 10.7 *vs.* 7.3 months (42) |
| | | Phase III recurrent GBM | CCNU ± BEV—EORTC 26101; mOS 9.1 *vs.* 8.6 months; mPFS 4.2 *vs.* 1.5 months. Grade 3 to 5 adverse events 63.6% *vs.* 38.1% (41) |
| Carotuximab (TRC184) | Endoglin (CD105) | Phase II recurrent GBM | In combination with BEV, mPFS 1.8–2.9 months and mOS 5.75–10 months (53,54) |
| PF-04856884 | Ang2 | Phase I recurrent GBM | Terminated due to high toxicity (55) |
| Ramucirumab | VEGFR-2 | Phase II recurrent GBM | PFS6 12.5%, mOS 11.4 months (clinicaltrials.org, NCT00895180) |
| Tanibirumab (TTAC-0001) | VEGFR-2 | Phase II recurrent GBM | Ongoing (NCT03856099) |
| Tyrosine kinase inhibitor | | | |
| AEE788 | VEGFR-1/2, EGFR | Phase I recurrent GBM | Significant toxicity leading to discontinuation in 17% of patients (56) |
| Anlotinib | VEGFR-1/2/3, c-Kit, PDGFR-α, FGFR-1/2/3 | Phase I/II newly diagnosed GBM | Ongoing (NCT04119674, NCT04157478) |
| | | Phase I/II recurrent GBM | Ongoing (NCT04004975) |
| Apatinib | VEGFR-2, c-Kit, c-Src | Phase II recurrent GBM | mPFS 6 months, mOS 9.3 months (57) |
| Axitinib | VEGFR-1/2/3 | Phase II recurrent GBM | PFS6 26% as monotherapy or in combination with lomustine (58); GLIAVAS: PFS6 18% as monotherapy or in combination with PD-1 inhibitor avelumab (59) |
| Cabozantinib (XL184) | VEGFR-2,3, REF, c-kit, c-MET | Phase II newly diagnosed GBM | In patients naïve to anti-angiogenic therapy and those with prior exposure, respectively, mOS 10.4 and 4.6 months PFS6 27.8% and 8.5%, mPFS 3.7 and 2.3 months, Grade 3/4 toxicities 84.7% and 72.4% of patients (60,61) |
| Cediranib | VEGFR-1/2/3 PDGFR-α/β, c-kit | Phase III in recurrent GBM | No improvement over lomustine alone (49,62,63) |
| | | Phase II in newly diagnosed GBM | Ongoing (NCT01062425) |
| Dovitinib | VEGFR-1/2/3, FGFR-1/2/3, PDGFR-β | Phase II recurrent GBM | mOS 3–7.9 months, PFS6 5% (64,65) |
| Enzastaurin | PKC-β PI3K/AKT | Phase III in recurrent GBM | Stopped at interim analysis due to no benefit compared to lomustine (mOS 6.6 months, mPFS 1.6 months) (50) |
| | | Phase II in newly diagnosed GBM | In combination with RT + TMZ, mOS 17.1 months, mPFS 8.31 months (66) |

**Table 1** (*Continued*)

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| Drug | Target | Farthest trial design | Results |
|---|---|---|---|
| Lenvatinib (E7080) | VEGFR-2/3 FGFR1 PDGFR-β | Phase II recurrent GBM | mOS 4.11 months, PFS6 8.3%, mPFS 1.9 months (67) |
| | | Phase II advanced solid tumors (including GBM) | Combined with pembrolizumab; ongoing (NCT03797326) |
| Nintedanib | VEGFR-1/2/3, FGFR1/2/3 and PDGFRα/β | Phase II recurrent GBM | mOS 6.9 months, PFS6 0% (68) |
| Pazopanib | VEGR-1/2/3 PDGFR- α/β c-kit | Phase I/II newly diagnosed GBM | Ongoing (NCT02331498) |
| | | Phase II recurrent GBM | mOS 8.03 months, PFS6 3%, mPFS 2.77 months (69) |
| | | Phase I/II recurrent GBM | Combined with lapatinib (HER2/neu, EGFR inhibitor), early termination due to PFS6 0% and 15% in EGFRvIII mutant and EGFR wildtype, respectively (70) |
| Ponatinib | VEGFR-2 | Phase II in recurrent GBM | mOS 98 days, mPFS 28 days (71) |
| Regorafenib | VEGFR1/3, PDGFR-β, FGFR 1 | Phase II in recurrent GBM | Ongoing (NCT04051606) |
| Sorafenib | VEGFR-2/3, PDGFR-β, FLT3, Raf kinase | Phase II newly diagnosed GBM | mOS 12 months, mPFS 6 months (72) |
| | | Phase II in recurrent GBM | In combination with BEV, mOS 5.6 months, PFS6 20.4% (73); in combination with TMZ, mOS 41.5 weeks, PFS6 9.4%, mPFS 6.4 weeks (74); in combination with Temsirolimus in anti-VEGF naïve patients, mOS 6.3 months, PFS6 17.1%, mPFS 2.6 months (75); in combination with erlotinib, mOS 5.7 months, PFS6 14% mPFS 2.5 months (76) |
| Sunitinib | VEGFR-2, PDGFR-α/β, c-kit | Phase II in recurrent GBM | mOS 9.6-12.6 months, PFS6 12.5–21.5%, PFS 2.2 months, no improvement in combination with irinotecan (77,78) |
| | | Phase III in recurrent GBM | Ongoing (NCT02239952) |
| Tandutinib (MLN 518) | PDGFR, FLT3, c-kit | Phase II recurrent GBM | OS 8.8–11 months, PFS6 16–23%, PFS 1.9–4.1 months; increased toxicity compared to bevacizumab, no significant benefit of combination (79,80) |
| Tesevatinib | EGF, HER2, VEGF, ephrin B4 | Phase II recurrent GBM | Ongoing (NCT02844439) |
| Tivozanib | VEGFR-2/3 | Phase II recurrent GBM | mOS 8.1 months, mPFS 2.3 months (81) |
| Vandetanib | VEGFR-1/2, EGFR, RET | Phase II newly diagnosed GBM | mOS 16.6 months, PFS 7.7 months [addition of vandetanib not significantly improved compared to RT + TMZ alone (82)] |
| | | Phase II recurrent anaplastic astrocytoma | Given after carboplatin, mOS 9.27 months, PFS6 17.4 months [worse PFS6 and OS when given concurrently with carboplatin (83)] |
| | | Phase II recurrent GBM | mOS 5.6 months, mPFS 1.7 months; No added benefit with addition of vandetanib compared to carboplatin monotherapy (84) |

**Table 1** (*Continued*)

**Table 1** (*Continued*)

| Drug | Target | Farthest trial design | Results |
|---|---|---|---|
| Other | | | |
| Aflibercept (VEGF-Trap) | IgG fused to receptor sequences of VEGFR-1,2 | Phase II recurrent AA | mOS 39 weeks, PFS6 25%, mPFS 4 weeks (44) |
| | | Phase II GBM | mOS 55 weeks, PFS6 7.7%, mPFS 12 weeks (44) |
| Cilengitide | SMI to αvβ3, αvβ5, αvβ1 Integrins | Phase III in newly diagnosed GBM | mOS 26.3 months; no benefit of adding cilengitide to TMZ + RT alone (52) |
| | | Phase II in recurrent GBM | mOS 9.9 months, PFS6 15%, mPFS 8.1 weeks (85) |
| CT-322 | Pegylated Adnectin binding VEGFR-2 | Phase II recurrent GBM | Terminated due to inefficacy (86) |
| Macitentan | SMI to Endothelin-1A/B receptor | Phase I in newly diagnosed and recurrent GBM | Terminated due to poor accrual |
| PT2385 | SMI to HIF-2alpha | Phase II recurrent GBM | mPFS 6.7 months (87) |
| RO5323441 | PlGF inhibitor (binds to and activated VEGFR) | Phase I recurrent GBM | Increased serum concentration when combined with bevacizumab; brain concentration not studied (88) |
| Trebananib (AMG 386) | Ang-1/2 peptide-Fc fusion protein | Phase II recurrent GBM | In combination with bevacizumab, mOS 9.5 months, 6PFS 24.3%, mPFS 3.6 months (51) |
| VB-111 | adenovirus with pre-pro-endothelin1 driving apoptotic receptor | Phase III recurrent GBM | Ongoing (NCT02511405) |
| VXM01 | Oral vaccine against VEGFR-2 | Phase II recurrent GBM | Ongoing (NCT03750071) |

List of therapies targeted toward angiogenesis in GBM, the molecular target, highest available trial phase (phase I, II, and III) and brief summary of the results of these trials. For ongoing trials, the National Clinical Trials (NCT) registration number is provided. AA, anaplastic astrocytoma; Akt, AKT serine/threonine kinase 1; Ang2, angiopoietin-2; BEV, bevacizumab; CCNU, lomustine; EGF/EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FLT3, Fms-like tyrosine kinase; GBM, glioblastoma multiforme; HER2, human epidermal growth factor receptor 2; MMP, matrix metalloprotease; PFS6, 6-month progression-free survival; mPFS, median progression-free survival; mOS, median overall survival; PDGFR, platelet derived growth factor receptor; PIK3, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKC-β, protein kinase c beta HIF, hypoxia inducible factor; PKC, protein kinase C; PI3K, phosphatidylinositol 3-kinase; PlGF, placental derived growth factor; REF, Aly/REF exporter; RET, RET proto-oncogene; RT, radiation therapy; SMI, small molecular inhibitor; SRC, SRC proto-oncogene; TMZ, temozolomide; VEGFR, vascular endothelial growth factor receptor.

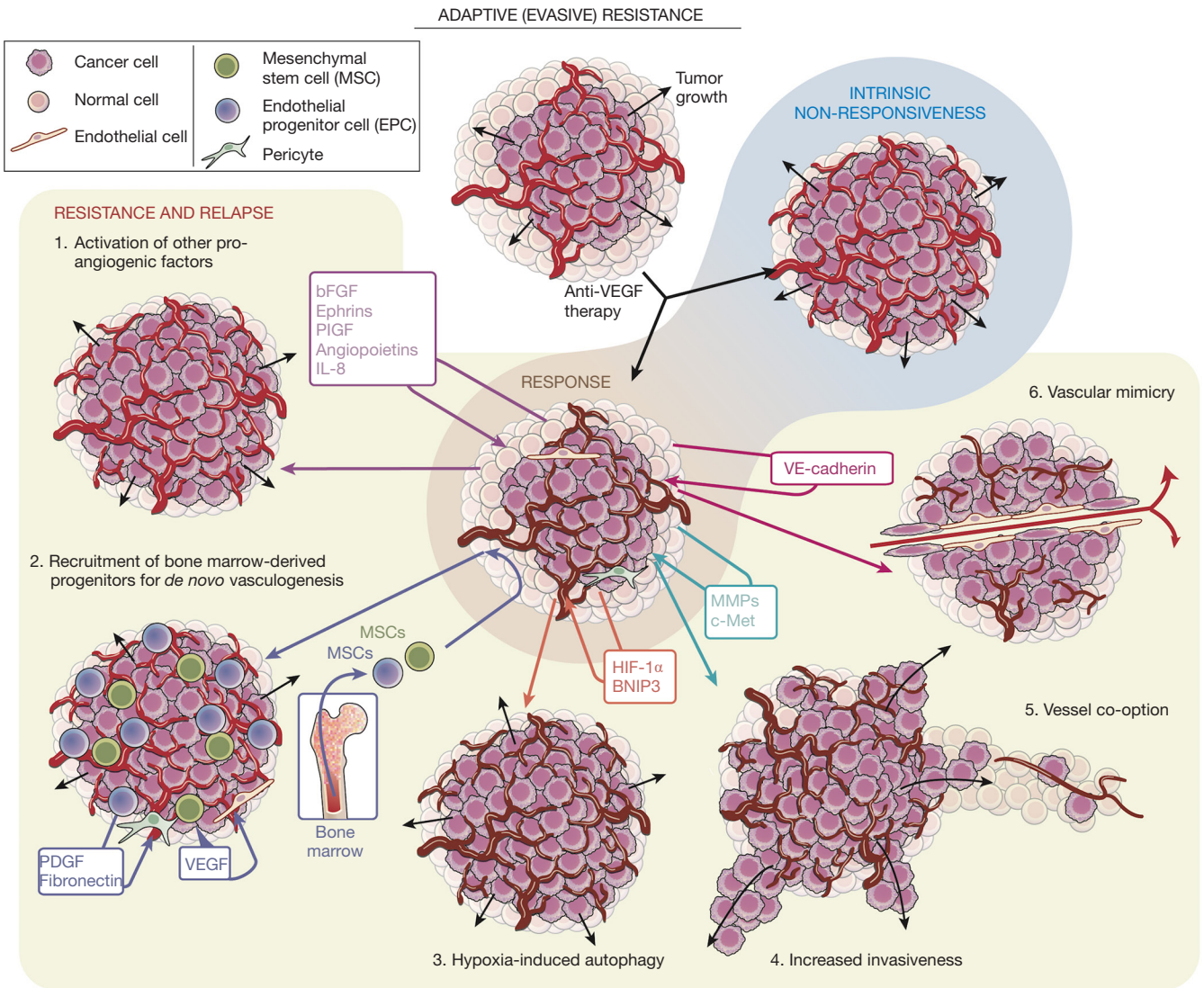


**Figure 1** Mechanisms of resistance to anti-VEGF therapy. Resistance to VEGF targeted therapy is multifactorial, involving initial non-responsiveness of tumor cells to anti-VEGF therapy, as well as later acquired resistance via several mechanisms. [1] Upregulation of angiogenesis through VEGF-independent pathways, including FGF, PlGF, HGF, c-MET, ANG1, ANG2, and interleukins. [2] Increased recruitment of bone-marrow derived progenitors, including mesenchymal stem cells and endothelial progenitor cells, which differentiate into pericytes and endothelial cells, respectively, to populate new blood vessels. [3] Tumor cells under hypoxic stress sequester damaged cell components, in a process called "autophagy", which delays cellular apoptosis. [4] Tumor cells treated with anti-angiogenic agents migrate and invade away from hypoxic areas, making treatment with surgery and radiation more difficult. [5] Tumor cells in hypoxic environments will migrate toward blood vessels in the nearby normal brain, and "co-opt" these vessels for their supply of oxygen and nutrients. [6] Tumor cells can change their shape to resemble endothelial cells, and will aggregate with normal endothelial cells to create cylindrical structures with lumen, which behave as blood vessels. Adapted from Chandra *et al.* (89). ANG1/2, angiopoietin 1/2; bFGF, basic fibroblast growth factor; BNIP3, B-cell CLL/lymphoma 2 (BCL2)-interacting protein 3; c-MET, c-MET proto-oncogene; HIF-1α, hypoxia inducible factor 1 subunit alpha; HGF, hepatic growth factor; IL-8, interleukin-8; PDGF, platelet-derived growth factor; PlGF, placental growth factor; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; VE-cadherin, vascular endothelial cadherin.

well as proteins that allow invasion of cells through the extracellular matrix including MMPs -2, -9, and -12; and secreted protein acidic and rich in cysteine (SPARC) (112). Among other pro-migratory mechanisms, tumor cells may transition to a mesenchymal phenotype mediated via *PDGF* and HGF-dependent *MET* signaling (105,113). This was demonstrated after exposure to either bevacizumab or cediranib (99,114), and led to interest in targeting the *MET* pathway in conjunction with VEGF manipulation, as *MET* may also contribute to tumor growth. Although a phase II trial evaluating bevacizumab with or without onartuzumab, a monovalent MET inhibitor, failed to improve PFS or OS (115), trials of other c-MET inhibitors are in progress (NCT02386826, NCT02270034).

## Evolving use of anti-angiogenic therapy

Though anti-angiogenic therapies to date have failed to extend survival in new or recurrent GBM, their contribution to PFS suggests some degree of benefit, possibly through alleviation of peritumoral edema (116). Corticosteroids are first line therapy for peritumoral edema, but have a broad and high-frequency side effect profile particularly in the setting of prolonged use, including myopathy, hyperglycemia, weight gain, hypertension, osteoporosis, insomnia, anxiety, and rarely avascular necrosis among other toxicities (117). Bevacizumab carries a distinct range of side effects, including hypertension and poor wound healing, but also rare risks of thromboembolism, hemorrhage, gastrointestinal perforation and nephrotic syndrome (118). Several clinical trials suggested that bevacizumab can reduce reliance on corticosteroids in GBM patients. These observations emerged from the AVF3708g trial, EORTC26101 trial, and other observational studies (38,39,119). Likewise, use of cediranib and cabozantinib (which inhibits VEGF2, MET, AXL tyrosine kinase, and ret protooncogene RET) also correlated with reduced corticosteroid use over time (60,94). In regards to quality-of-life and symptom control, there is conflicting evidence as to whether bevacizumab is beneficial. The AVAglio trial in newly diagnosed GBM noted delayed deterioration of quality-of-life metrics (including global health status, cognitive, emotional, and social functioning, and ability to communicate) with bevacizumab compared to control, and stable Mini Mental Status Examination (43). However, the RTOG0825 study reported decreased quality-of-life measures (symptom control and neurocognitive function) with bevacizumab compared to placebo (42).

Bevacizumab is also used to treat the clinical and radiographic changes associated with radiation necrosis in the brain. Radiation may underlie short- and long-term changes to the vasculature including increased vascular permeability, vasculopathy, ischemia, necrosis, and resultant edema (120). These pathological changes underlie MRI findings including increased contrast enhancement and edema that are often difficult to distinguish from tumor progression. Radiation necrosis can be symptomatic with focal deficits including weakness and aphasia, headaches, and seizures. Recent studies demonstrated bevacizumab to be a powerful tool for managing radiation-associated edema (121,122). There is an ongoing phase II clinical trial comparing corticosteroids plus bevacizumab versus placebo for the treatment of radiation necrosis in brain metastasis (NCT02490878).

In addition to symptomatic treatment, there is still hope that anti-VEGF agents may be helpful in combination with other therapies, including cytotoxic chemotherapy, TKIs, and immunotherapy, in improving survival in GBM. Many of these combinatorial strategies rely on the recent mechanistic understanding that anti-VEGF therapies may act to normalize the blood vasculature, improving spatial and temporal delivery of therapeutic agents across the tumor (34,123). Improved efficacy of combinatory treatment may require specific timing of anti-VEGF agents with cytotoxic/cytostatic agents. For example, a phase II trial looking at cediranib demonstrated vascular normalization occurs day 1 to 28 after drug dosage (94). Experiments looking at the time frame for vascular normalization after bevacizumab have yet to be been done in GBM, but mouse models suggest it starts as early as 1 day after infusion and clinical trials in rectal carcinoma suggest half of the tumor vasculature is normalized by day 12 (124). The dosing of bevacizumab may influence response as well, with some studies suggesting that a reduced dose may be more efficacious (125,126).

The interaction of VEGF signaling and the immune system is of particular interest given the impact of immunotherapies in several cancers. VEGF signaling inhibits differentiation of circulating hemopoietic progenitor cells, dendritic cells, and T cells through nuclear factor kappa B (*NFκB*) signaling (127,128). Aflibercept also increases the mature dendritic cell population in solid tumors (129). In a study of colorectal cancer, bevacizumab increased CD4+ and CD8+ T cells, as well as CD20+ B cells in peripheral blood (130). However, these studies suggesting that VEGF inhibition may alleviate VEGF-mediated immunosuppression was countered by a study in

which VEGF inhibition was tied to impaired lymphocyte recruitment (131). A better understanding of the role of VEGF in regulating the brain immune niche and GBM tumor microenvironment is clearly needed.

## Conclusions

Angiogenesis is a hallmark feature of GBM and the role of anti-angiogenic agents in GBM treatment has evolved over time. While initial trials were promising that these agents could impact prognosis, many agents including anti-VEGF antibody failed to prolong survival in both newly diagnosed and recurrent GBM, either as monotherapy or in combination with traditional chemotherapies and other targeted agents. Despite these challenges, anti-angiogenic agents still have utility for managing vasogenic and radiation-related edema, being used in combination to target multiple angiogenic pathways, and to promote the intratumoral uptake of other chemotherapies.

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