



# Angiogenesis as a hallmark of solid tumors - clinical perspectives

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## Abstract

**Background** Angiogenesis is a key and early step in tumorigenesis, and is known as a hallmark of solid tumors and a key promoter of tumor recurrence. Unlike normal tissue vessels, the architecture of the tumor vasculature is abnormal, being leaky, tortuous, fragile and blind-ended. Perivascular cells are either detached or absent, causing reduction of vascular integrity, an increase in vessel immaturity, incoherent perfusion, defective functionality and enhanced tumor dissemination and metastasis. The abnormal tumor vasculature along with the defective tumor vessel functionality finally causes bouts of hypoxia and acidity in the tumor microenvironment (TME), further reinvigorating tumor aggression. Interstitial hypertension or high interstitial fluid pressure (IFP) is an outcome of tumor hyper-permeability. High IFP can be a barrier for either effective delivery of anti-cancer drugs toward the TME or accumulation of drugs within the tumor area, thus promoting tumor resistance to therapy. Some tumors do, however, not undergo angiogenesis but instead undergo vessel co-option or vascular mimicry, thereby adding another layer of complexity to cancer development and therapy.

**Conclusions** Combination of anti-angiogenesis therapy with chemotherapy and particularly with immune checkpoint inhibitors (ICIs) is a promising strategy for a number of advanced cancers. Among the various approaches for targeting tumor angiogenesis, vascular normalization is considered as the most desired method, which allows effective penetration of chemotherapeutics into the tumor area, thus being an appropriate adjuvant to other cancer modalities.

**Keywords** Angiogenesis · Normalization · Vascular endothelial growth factor (VEGF) · Endothelial cell (EC) · Tumor microenvironment (TME) · Pericyte · Hypoxia · Cancer stem cell (CSC) · Bevacizumab · Sunitinib · Pazopanib · Combination therapy · Vessel co-option · Vascular mimicry · Programmed death-1 receptor (PD-1) · Programmed death-ligand 1 (PD-L1) · Chemotherapy

## Highlights

- Structural (architectural) and functional abnormalities in tumor vasculature favor immune evasion, drug impedance and metastasis.
- Aberrant angiogenesis and abnormal tumor vasculature account for increased hypoxia and acidity in the TME, as well as causing high IFP.
- Exploiting vascular mimicry and vessel co-option by cancer type indicates that anti-angiogenic therapy is not effective for all cancers.
- A suggestive strategy is to use combinations of anti-angiogenic therapy with other treatment modalities, including chemotherapy and particularly ICIs.
- Selection of appropriate adjuvants and considering the time and dose of administration are useful modalities for improving the efficacy of therapy and reducing the chance of tumor relapse and resistance.
- Vascular normalization is an effective strategy for potentiating the delivery of chemotherapeutic drugs and enhancing their efficacy, as well as reducing the chance of tumor recurrence and metastasis.

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## 1 Introduction

Angiogenesis or aberrant vascularization is considered as both a hallmark of solid tumors [1–4] and a hallmark of tumor recurrence [5]. Tumors establish blood supply early in their development [6] upon growing beyond a few millimeters [7]. Blood and lymphatic vessels are conduits for cancer cell transportation toward new sites, i.e., metastasis [8]. They are also required for sustained cancer growth [9], as well as for satisfying O<sub>2</sub> and metabolic demands [10]. Endothelial cells (ECs) are known as critical players in tumor angiogenesis and in the supply of O<sub>2</sub> and nutrients to tumor cells [11]. Each EC can support the growth of approximately 2000 tumor cells [12], which is huge.

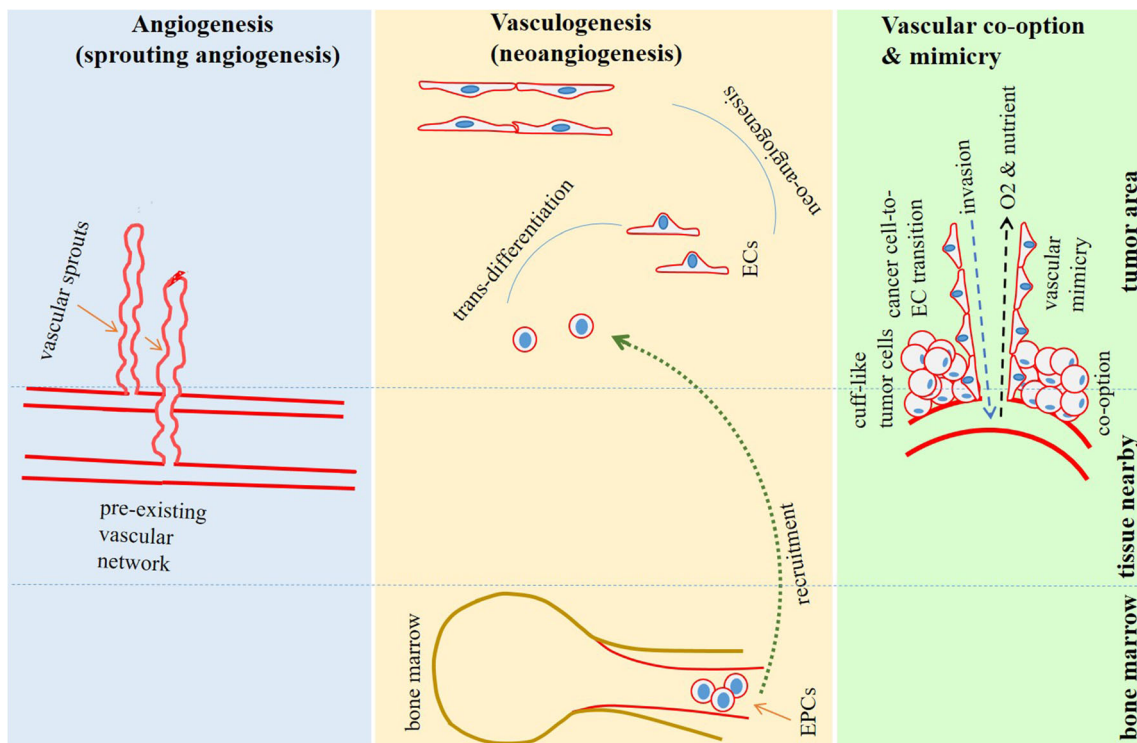
Limited knowledge on angiogenesis and the key implications of this hallmark of cancer has stimulated several lines of investigation aimed at obtaining a better understanding of the architecture of tumor vessels, their actual role in tumorigenesis beyond their usual circulatory functions and the design of therapeutic approaches benefiting from durability and efficacy. Data published up to now have successfully uncovered several of the roles taken by tumor cells to harness angiogenic-related events in their favor. The aim of this narrative review is to discuss the various aspects of angiogenesis in solid tumors, specifically the architecture of tumor vessels and the pros and cons related to anti-angiogenic therapies, combinational therapies, as well as exploiting vascular normalization strategies as an approach for targeting tumor angiogenesis. We will also discuss the prognostic value of angiogenic markers in tumor diagnosis and therapy.

## 2 Origin of tumor vessels

There are three different origins of tumor vessels: (1) angiogenesis or sprouting angiogenesis, which is defined by the growth of new blood vessels from a pre-existing network of vessels and their infiltration into the tumor, (2) vasculogenesis, which is also called neo-angiogenesis, and is characterized by de novo formation of vessels from tumor-recruited bone marrow-derived endothelial progenitor cells (EPCs) [13, 14], and (3) vessel co-option, which is defined by a cuff-like organization of cancer cells around pre-existing vasculature [13, 15] (Fig. 1). Angiogenesis is the most common form, which occurs in tumors mostly as a response to hypoxia in the tumor microenvironment (TME). Angiogenesis is subdivided into classic sprouting, and glomeruloid and intussusceptive microvascular growth. Glomeruloid angiogenesis is vascular development into glomeruli like structures, and intussusceptive growth is longitudinal splitting of pre-existing vessels [16].

## 3 Architecture of the tumor vasculature

Tumor vessels show an anomalous and immature architecture [17]. They exhibit intensive sprouting orchestrated in an irregular convoluted manner (a tortuous feature) that tends to raise flow resistance. Tumor vessels are also distinguished by large holes in their walls (pores with diameters ranging from 400 to 600 nm [18]), which is a characteristic of a leaky or hyperpermeable vasculature. The leaky architecture differs within and among tumors, and acquisition of such a feature is due mainly to a defective basement membrane and poor tight junction development between ECs. The basement membrane of the tumor vasculature is irregular in composition and thickness, and can be too thick or even absent. Tumor vessels are also fragile and blunt-ended. The diameter of the tumor vasculature varies from abnormally wide to unusually thin channels with small or even compressed lumens. Thus, there is no virtual association between tumor vessel diameter and flow velocity due to the heterogeneous vascular network causing functional shunts in the tumor vasculature. Tumor vessels also share characteristics of arterioles, venules and capillaries, but do not exhibit a distinct identity. This sharing feature causes extensive shunts between arterial and venous tumor systems (anatomical shunts). Multi-layering occurs occasionally in the tumor vasculature. Smooth muscle cells (SMCs) may be absent and, instead, tumor blood vessel walls may be integrated with cancer cells. In addition, tumor vessels exhibit limited coverage by pericytes. Normally, pericytes must be present in a sufficient fraction in order to stabilize newly formed vessels, guide optimal blood flow and limit further sprouting. Pericytes maintain stability of the microvasculature through facilitating vascular maturation. In tumors, pericytes wrap around the endothelium in an abnormal loose manner, called detached pericytes, or may even be absent, which can promote cancer metastasis. When being present, the activity of pericytes is important for maintaining the function and integrity of the tumor vasculature and, thus, their absence and detachment from the tumor endothelium may enhance tumor dissemination. A low fraction of pericytes in tumors compared to normal tissues possibly contributes to an immature tumor vasculature. This abnormal orchestration in the tumor vasculature is due to an imbalance in signaling appertained to pro- and anti-angiogenesis, the result of which is spatial and temporal blood flow heterogeneity and incoherent perfusion. The general representation for such incoherent perfusion is a low blood flow and subsequent hypoxia and acidosis within the TME, and a high interstitial fluid pressure (IFP) (also called interstitial hypertension). Such inadequate perfusion and high IFP may have a profound impact on tumor progression including immunosuppression, therapy resistance (radio- and chemotherapy) and metastasis [4, 9, 10, 14, 19–31]. Architectural abnormalities in the tumor vasculature may have diagnostic value, i.e., patient responses to anti-angiogenic therapy can be



**Fig. 1** Origins of tumor vessels. Tumors can take three routes for meeting their demands: angiogenesis, vasculogenesis and vascular co-option and mimicry. Angiogenesis is characterized by vascular sprouts from a pre-existing vascular network, while vasculogenesis is based on recruitment of endothelial progenitor cells (EPCs) from bone marrow into the tumor area and their further transformation into endothelial cells (ECs). Vessel

co-option is a process occurring in cancers like those in brain, lung and liver, during which cancer cells form cuff-like structures around pre-existing vasculature. Vascular mimicry is a channel-like orchestration of endothelial-like cells derived from cancer cells, which helps tumors to meet their metabolic and O<sub>2</sub> demands. In addition, they may serve as a route for tumor metastasis

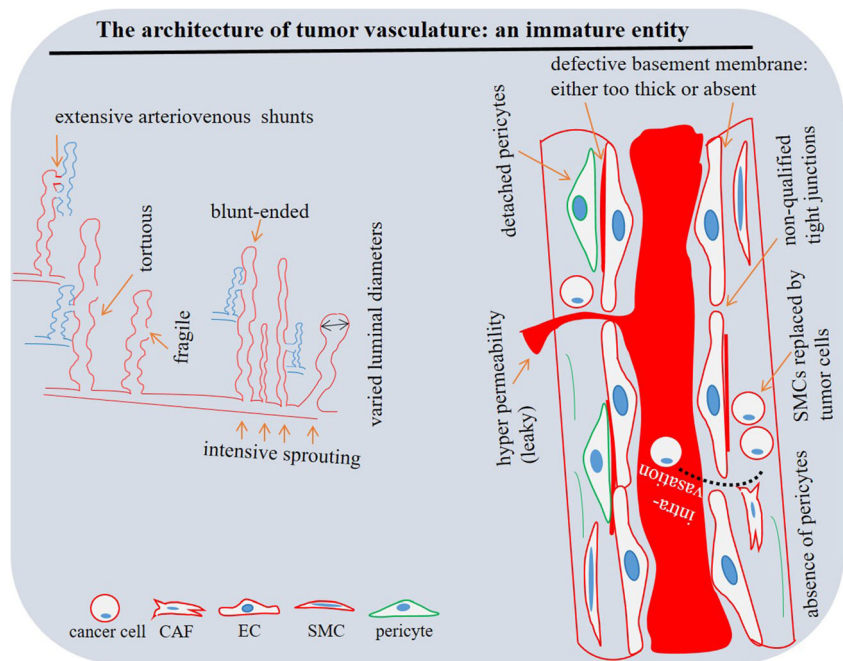
evaluated by architectural imaging of the tumor vasculature [32]. Contrast enhanced sonography is a useful tool for this. Vascular penetration can be evaluated in this way, and has a specificity of ~88.6% for the diagnosis of malignancy. Assessment of intra-tumoral dilation in patients with breast cancer can increase the diagnostic reliability to ~89% [33] (Fig. 2).

#### 4 Blood flow in tumors

The blood flow is disorganized in many solid tumors. Normally, arteries have a higher pressure than veins with a flow rate directly proportional from arteries to veins, and inversely correlated with geometric resistance. By contrast, in tumors there is little difference in pressure between arteries and veins, causing an increase in the rate of geometric resistance [27]. In fact, aberrant blood flow and vascular permeability will lead to a constitutive deposition of plasma into the extracellular matrix (ECM), which is called vasogenic edema [34]. The ECM is occupied by dysfunctional lymphatic vessels, or even lacks these vessels. In metastatic melanoma, for instance, lymphatic vessels have been found to be less frequent or nearly absent compared to those in the primary

tumor, with extensive micro-neovascularization within the metastases [35]. When present, lymphatic vessels are under constitutive compression by the growing tumor, turning them into abnormal or malfunctioning vessels. The abnormal lymphatic vessels preclude effective clearance and draining of excess plasma within the extracellular space. The rise in IFP is, in fact, a result of a malfunctioning lymphatic system along with hyper-permeability of the tumor vasculature [30, 36]. This rise in IFP can reach up to the 5–10 mmHg or even higher and can cause a reduction in the trans-vascular hydrostatic pressure gradient to near zero, thus precluding distribution of large molecules and impeding diffusion of systemic drug delivery and nutrients into the TME [30, 37, 38]. High IFP can also be a result of increased deposition of hyaluronan within the ECM stroma. Hyaluronidases can be used for targeting high IFP and, as such, has been found to be an effective approach for ECM disruption [39, 40]. High IFP compresses the existing blood vasculature within tumors, such that the blood flow is diverted from the core or center toward the edge or periphery of the tumor mass [27]. The core-to-edge flow of blood restricts drug accumulation within the tumor area [41]. Such core-to-edge transition can also be pertained to the tumor cellularity. Cancer stem cells (CSCs) are an example in this context. A study by Liu and colleagues on invasive breast

**Fig. 2** Architecture of the tumor vasculature. Characteristics of the tumor vasculature that distinguishes it from normal vessels are shown. Pericytes and smooth muscle cells (SMCs) are perivascular cells located around the tumor endothelium. Pericytes are either detached or absent. Detachment of pericytes favors a leaky tumor vasculature. The detached cells may differentiate into cancer associated fibroblasts (CAFs) that, in turn, may be involved in cancer cell invasion and their intrusion from leaky vessels into the bloodstream



carcinoma has come to an interesting finding. The authors assessed the presence of CD44<sup>+</sup> CSCs in three tumor areas: the inferior front (core area), the intermediate area and the invasive front (edge area). They noticed a low presence of CD44<sup>+</sup> CSCs in the core, a higher fraction in the intermediate zone, and the highest fraction in the edge area [42]. This has led to the concept of core-to-edge transition of CSCs, and a critical promoter of this process is hypoxia [41, 43]. This implies that tumor cells including cancer cells and CSCs, when transitioned from the core to the edge, will result in more resistance to therapy. Since the edge of a tumor is the place for invasive adaptive tumor cells, mostly the site for therapy resistant CSCs, complete removal of the edge area is warranted, without which recurrence is to be expected. Due to being leaky, the aberrant tumor vasculature will lead to a rise in hypoxia and, thus, to cellular transitioning (Fig. 3).

## 5 Perivascular cells and tumor angiogenesis

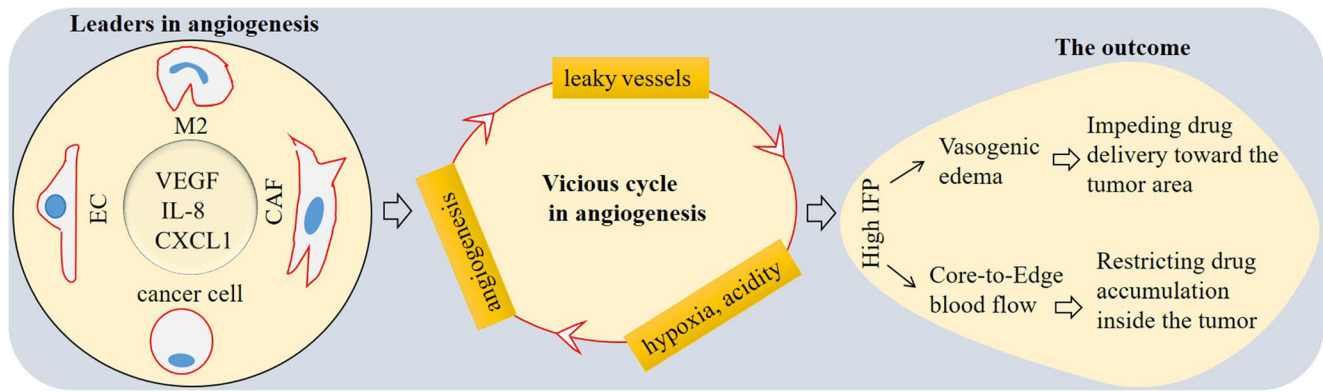
Pericytes and SMCs are perivascular cells that envelop ECs [44]. Pericytes generally act to maintain the viability of ECs and induce the formation of tight junctions between them [45]. In tumorigenic conditions, as discussed above, ECs are loosely covered by pericytes [46], which leads to a poor development of tight junctions between ECs, and, thereby, a leaky architecture. Pericytes in the TME are partly derived from CSCs, and contribute to immunosuppression [47] and chemotherapy resistance [47]. Pericytes shield the endothelium to preclude it from anti-angiogenic therapy [5]. Pericytes dissociated or detached from the tumor vasculature undergo

fibroblast differentiation, which contributes to tumor invasion and metastasis [48]. Pericyte detachment initiates vascular destabilization, tip cell generation and migration [49] (Fig. 2).

The activity of pericytes is well-defined in glioblastoma (GBM). GBM is equipped with a blood-tumor barrier (BTB) at the interface between blood and tumor cells. The BTB lacks tight junctions due to abnormal orchestration of pericytes in its structure. Compared to the blood-brain barrier (BBB) the BTB is leakier, which allows penetration of metastatic tumor cells into the brain area. Surprisingly, the BTB is also equipped with efflux transporters for impeding the penetration of anti-cancer drugs within the tumor area [45, 50, 51]. It seems that part of the unidirectional efflux pump activity within perivascular niches is due to the activity of CSCs. CSCs represent one of the constituents of perivascular niches [31], and can be formed from perivascular cells via phenotype switching [52], which infers that perivascular cells have plasticity to form cells required for tumor progression. CSCs can also be attracted toward these niches through the C-X-C chemokine ligand 12 (CXCL12)/C-X-C chemokine receptor type 4 (CXCR4) signaling axis [53]. Thereby, CSCs can undergo pericyte differentiation, which is mainly promoted under the influence of transforming growth factor-beta (TGF- $\beta$ ) [31]. Blocking of this pleiotropic immunosuppressive cytokine by inhibitory drugs is pivotal for the suppression of cancer growth and progression [54, 55].

Pericytes derived from CSCs within perivascular niches are involved in maintaining the structure and function of the BTB. In fact, the drug efflux ability of the BTB may be enhanced under the influence of CSC-derived pericytes. Thus, CSCs and CSC-derived pericyte-like cells can be targeted for





**Fig. 3** Angiogenesis, vicious cycling in angiogenesis, and its relevance to resistance to chemotherapy. Four players of angiogenesis within the tumor microenvironment (TME) are cancer associated fibroblasts (CAFs), cancer cells, type 2 macrophages (M2) cells and endothelial cells

(ECs). Due to the abnormal architecture of the tumor vasculature, tumors exacerbate the rate of hypoxia and acidity which further increases the rate of interstitial fluid pressure (IFP). A high IFP impedes drug delivery into the tumor area, and restricts drug accumulation within tumors

enhancing the permeability of a tumor for chemotherapeutic drugs, the main mechanism of which is BTB breakdown [50]. Targeting CSCs and pericytes derived from them can also be an effective approach for disrupting the tumor neo-vasculature and for suppressing tumor growth [31]. There exists a large overlap in the expression of biomarkers between pericytes and SMCs, which indicates a close cooperation among the two cell types in the formation of new blood vessels. Oct4 is considered as a marker of CSCs. Interestingly, Oct4 knockout in perivascular cells (SMCs + pericytes) has been found to suppress angiogenesis [44]. These data show how CSCs are related to the promotion of angiogenesis in perivascular niches.

## 6 Vascular endothelial growth factor: a key promoter of (sprouting) angiogenesis

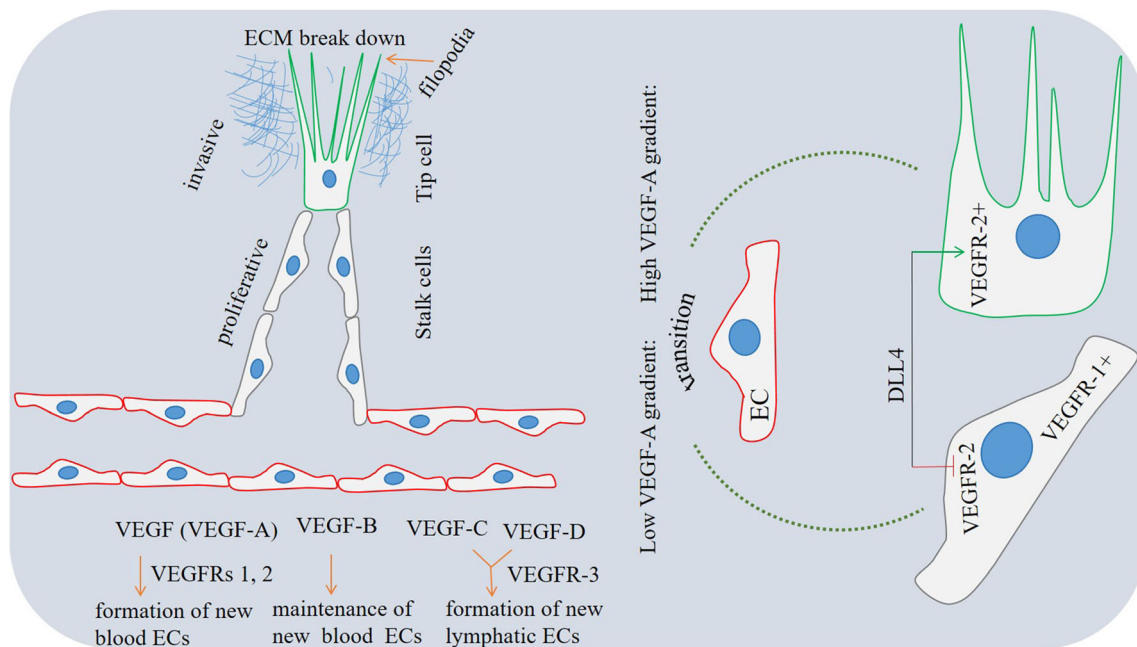
Vascular endothelial growth factor (VEGF) is an inflammatory and regulatory cytokine that is known as the main component and critical driver of angiogenesis. VEGF acts as promoter of both blood vessel growth [56, 57] and vascular permeability [58, 59]. Blood vessels are formed in response to VEGF-A, whereas lymphatic vessels are formed in response to VEGF-C and VEGF-D. Thus, VEGF-A is known as an inducer of blood ECs, and VEGF-C and VEGF-D as inducers of lymphatic ECs [60]. VEGF-A is the circulating form, and is referred to as VEGF in general. VEGF-A is a cardinal mediator of angiogenesis in the vast majority of solid tumors [61, 62]. By contrast, the role of VEGF-B in angiogenesis is restricted to some organs, such as heart. VEGF-B acts to promote growth in cardiac vasculature without bearing adversarial effects like increased leakage or permeability, as is seen in the tumor vasculature [15]. Generally, VEGF-B acts to maintain new blood vessels [62]. VEGF exists as matrix-bound or soluble isoforms. The matrix-bound isoform stimulates vascular branching, while the soluble isoform promotes the enlargement of vessels

[15]. Vascular enlargement occurs via the formation of motile ECs, called tip cells (see above). Tip cells develop in response to a high VEGF-A gradient [10] (Fig. 4).

Cancer cells, macrophage type 2 (M2) cells, cancer-associated fibroblasts (CAFs) and ECs are the four key cells responsible for the release of VEGF into the tumor stroma (Fig. 3). Autocrine release of VEGF from ECs contributes to the maintenance of vascular homeostasis, while its paracrine release from cancer cells and other cells within the tumor stroma is responsible for vascular branching, the latter of which renders the tumor vasculature abnormal. VEGFR-1 (also called FLT1), VEGFR-2 (also called FLK1) and VEGFR-3 are the three known VEGF receptors [15]. The activity of VEGFR-1 is context dependent, and can exert a negative effect on VEGFR-2. VEGF-C and VEGF-D promote lymphangiogenesis through binding to VEGFR-3 [24].

### 6.1 Selection of tip/stalk cells in tumor angiogenesis: The role of vascular endothelial growth factor/Notch signaling

VEGF-A acts through binding to VEGFR-1 and VEGFR-2. Among the two receptors, VEGFR-2 plays a predominant role in the stimulation of EC mitogenesis and vascular permeability [24]. VEGFR-2 is highly expressed on tip cells, whereas VEGFR-1 is expressed predominantly on stalk cells [28]. Interactions between VEGF-A and VEGFR-2 in a high VEGF-A gradient enable EC-to-tip cell transformation, thereby acquiring a migratory phenotype. By contrast, in a low VEGF-A gradient, the neighboring ECs are committed to become stalk cells, thus acquiring a proliferative phenotype [63, 64]. Tip cells are motile and invasive ECs (so called migratory phenotype) and are able to break down the nearby ECM, which is mediated by protrusion of filopodia. Tip cells are thus promoting the growth of newly formed vascular sprouts [10]. Stalk cells, on the other hand, preferentially undergo proliferation. So



**Fig. 4** Vascular sprouting in tumors: mechanism of tip and stalk cell selection. Tip cells are migratory cells with filopodia for extracellular matrix (ECM) breakdown and are differentiated from endothelial cells (ECs) upon exposure to high vascular endothelial growth factor (VEGF)-A gradients. Tip cells pave the path for proliferative stalk cells for elongation of newly formed vascular sprouts. These cells are transformed from ECs when the VEGF-A gradient is low. Specification

toward either one of the two phenotypes is under control of Notch signaling. High Delta-like 4 (DLL4) activity in ECs under commitment to tip cells renders them highly responsive to VEGF-A through enhancing the expression of VEGFR-2, whereas the activity of Notch signaling in ECs undergoing stalk cell transformation causes low expression of VEGFR-2, thus making them irresponsive to VEGF-A

filopodia extensions are infrequent in stalk cells compared to tip cells. Stalk cells act by establishing a lumen and supporting elongation of vascular sprouts. After vascular sprouts are formed, lumenized and elongated, the next step will be the formation of vascular loops, mediated by anastomosis development between tip cells and nearby sprouts [28] (Fig. 4).

Specification toward either phenotype (tip or stalk cells) is under the control of Notch signaling. VEGFR-2-positive ECs (the final tip cells) show increased expression of Delta-like 4 (DLL4). DLL4 is the Notch ligand that upon binding to its receptors on neighboring ECs (the final stalk cells) cause release of the Notch intracellular domain (NICD). This is for rendering the final stalk cells irresponsive to VEGF-A, and is mediated by reducing the expression of VEGFR-2 in the cells [65]. Thus, VEGF-A/VEGFR-2 blockade can be used to normalize the tumor vasculature, as further outlined below. Blockade within this axis will suppress vascular permeability, thus reducing IFP, improving tumor oxygenation and augmenting drug delivery into the tumor area [59] (Fig. 4).

## 7 The tumor vasculature, tumor cell spreading and drug resistance

Tumor ECs express FASL that restricts the infiltration of CD8<sup>+</sup> T cells [21]. A leaky tumor vasculature causes

accumulation of waste products and raises TME acidity, thus influencing tumor cell metabolism [66]. In early or pre-metastatic lesions of epithelial tumors, infiltration of blood vessels rarely happens. This is due to the presence of basal lamina, which function as a barrier between tumor cells and the surrounding vascular stroma. By contrast, malignant tumors show a stromal response, which removes the constraint or barrier between the vascular stroma and the tumor, and is a trigger for the development of vascular networks. The type and grade of a tumor influence the intensity of the stromal response [10].

A point for consideration here is that a low coverage of tumor vessels by pericytes and a resulting aberrant architecture along with a rapid rate of EC proliferation in the TME renders these ECs more sensitive to radio/chemotherapy compared to normal ECs [12, 31]. The impact of aberrant tumor vessels on the surrounding TME can, thus, secondarily cause therapy resistance. The consequences are intensification of hypoxia and a higher IFP, as discussed above. Radiation therapy along with several chemotherapeutic drugs rely mainly on the production of O<sub>2</sub> radicals in order to kill tumor cells. Therefore, tumor hypoxia, which is a secondary response to aberrant angiogenesis, can attenuate the efficacy of such therapeutic approaches [15]. This, along with the clearance of chemotherapeutic drugs from the circulation, requires the use of increasing amounts of drugs for tumor cell eradication.

This results in a rise in normal tissue toxicity and in limiting the delivery of efficient radiation doses, which in turn leads to interruption of the course of cancer therapy [67, 68] (Fig. 3).

## 8 Anti-angiogenic therapy

### 8.1 Direct and indirect ways for targeting endothelial cells

ECs and perivascular cells are the two major cell types required for angiogenesis [44]. ECs are genetically stable, so they can be targeted without ensuing resistance. Angiogenesis can be harnessed in either a direct or an indirect way. The direct way acts through combating ECs, and the indirect way through targeting pro-angiogenic proteins. Angiostatin and vitaxin are drugs that take the direct way, whereas herceptin is an example of a drug that acts indirectly [6]. Angiogenesis can also be prevented in the TME as part of the function of efficient chemo-preventive drugs, such as the epidermal growth factor receptor (EGFR) inhibitor cetuximab [69, 70]. Tyrosine kinase inhibitors (TKIs) can be used to hamper angiogenesis via VEGFRs, axitinib being an example. This drug is highly selective for VEGFR and is approved by the FDA for targeting advanced renal cell carcinoma (RCC) [57]. Other TKIs for targeting VEGFR are sorafenib, sunitinib and pazopanib [71]. Pazopanib suppresses VEGFR-1, 2 and 3, and inhibits c-KIT and platelet-derived growth factor receptor (PDGFR) tyrosine kinases (TKs) [72]. Pre-treatment with pazopanib in patients with localized RCC required for partial nephrectomy has been found to be effective for maintaining renal parenchyma [73].

Sunitinib can be used for patients with liver metastases from e.g. neuroendocrine cancers derived from the aerodigestive tract. The primary source of vascular supply in liver cancer is the hepatic artery, and trans-arterial embolization (TAE) of the branches of this artery is used as a treatment modality in these patients. Embolization, however, stimulates VEGF release into the circulation, so a high serum VEGF may be the result. Administration of the VEGFR inhibitor sunitinib for patients treated with TAE has been found to be an effective modality and an appropriate combination. A rise in overall survival (OS) and progression-free survival (PFS) rates has been found to occur after such combination therapy [74]. This is indicative of a role of sunitinib in abrogating the TAE counter-effect on the VEGF level, thus reducing the pro-tumor activity occurring secondary to such a procedure. Recently, Sheng and colleagues compared the efficacy of pazopanib and sunitinib in patients with advanced or metastatic RCC. The authors noticed similar median PFS rates between the two treatment arms, while the overall response rate was considerably higher in the pazopanib group compared to the sunitinib group [75].

Bevacizumab (also called avastin) is an inhibitor of VEGF-A. In lung cancer, bevacizumab has been shown to be beneficial for patients with the non-squamous type. The administration of this drug is not recommended for patients with non-resected squamous lung cancer due to complications like hemoptysis, which occur in the squamous cancer type [76]. Several clinical trials for anti-angiogenic therapy and their results are listed in Table 1.

### 8.2 Combination of anti-angiogenic therapy with other treatment modalities

#### 8.2.1 Why is there a need for combination therapy?

Anti-angiogenic therapy may benefit from combination therapy in order to strengthen its efficacy and to reduce drug resistance and recurrence. For example, colorectal cancer (CRC) patients receiving bevacizumab need adjuvant chemotherapy in order to reach reasonable clinical outcomes [59]. GBM is a tumor type with a high vascularization rate. In a phase II clinical trial, treatment of recurrent GBM patients with the pan-VEGFR inhibitor tivozanib has shown reduced vascular abnormality and improved tissue oxygenation and blood flow. However, the structural changes in the tumor vasculature were not substantial, so mono-therapy with tivozanib yielded a limited anti-tumor efficacy [77]. Patients with malignant brain cancers, such as glioma, usually show a tumor-induced disruption of the BBB. This disruption is incomplete and heterogeneous and, as such, hampers effective penetration of some drugs toward the tumor area. Bevacizumab is large in size and cannot be delivered effectively into the tumor area. Such patients may benefit from the application of drugs able to promote transient disruption of the BBB. Mannitol is a solution with high osmotic pressure. Intra-carotid administration of mannitol to malignant glioma patients has been found to go well with intra-arterial administration of bevacizumab. These patients showed reduced tumor volumes, and the outcomes were better in patients without a previous history of bevacizumab administration [78]. This work underscores (1) the need for combination regimens for enhancing the efficacy of anti-angiogenic therapy, (2) a presumable superiority of the intra-arterial bevacizumab route over intra-venous application and (3) a seemingly higher efficacy of anti-angiogenic therapy in patients with no previous history of anti-angiogenic treatment. With respect to the higher efficacy of intra-arterial administration (2), there is evidence indicating that CRC patients administered with intra-venous bevacizumab may experience thromboembolism [79], an undesired side-effect of this route of administration. Clinical trials for anti-angiogenic combination therapy and their results are listed in Table 2.

**Table 1** Agents with anti-angiogenic activities for targeting solid cancers: clinical trials

Agent name	Activity	Type of cancer	Mechanism	Ref
tivozanib	pan-VEGFR inhibitor, 1.5 mg, p.o	recurrent GBM, (phase 2)	Reduction of tissue oxygenation, abnormal vascular permeability and plasma levels of Svegfr-2, increase of plasma VEGF. No effect on tumor vascular architecture, no significant effect on tumor volume	[77]
eribulin vs. bevacizumab	eribulin: A microtubule dynamics suppressor, 1.4 mg m <sup>2</sup> i.v. bevacizumab: Anti VEGF-A monoclonal antibody, 10 mg kg <sup>-1</sup> , i.v.	breast cancer, stage III/IV	Eribulin suppressed cytokines related to angiogenesis (VEGF & bFGF) and EMT (TGF-β), and increased tumor reoxygenation (high SO <sub>2</sub> ). Bevacizumab did not improved tumor reoxygenation and EMT, but it suppressed cytokines related to angiogenesis.	[78]
pazopanib vs. sunitinib	pazopanib: VEGFR inhibitor, 800 mg sunitinib: a VEGFR TKI, 50 mg	advanced or metastatic RCC (phase 3)	Median PFS was similar between the two treatment arms. The overall response rate was considerable higher in the pazopanib arm	[75]
pazopanib	800 mg, p.o	localized RCC, (phase 2)	Tumor volume was reduced in 92% of cases. This allows for optimal parenchymal preservation in patients undergoing partial nephrectomy.	[73]
pazopanib	600 mg, p.o	advanced HCC, (phase 1)	Pazopanib at the maximum tolerated dose (600 mg) attenuated vascular leakage within tumor. However, 73% of patients showed incomplete response or steady disease.	[79]
sorafenib	400 mg, p.o	HCC	Sorafenib reduced portal blood flow, but it was reversible	[80]

GBM, glioblastoma; VEGF, vascular endothelial growth factor; TGF, transforming growth factor; FGF, fibroblast growth factor; EMT, epithelial-mesenchymal transition; TKI, tyrosine kinase inhibitor; SO<sub>2</sub>, oxygen saturation; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma

### 8.2.2 Combining anti-angiogenic therapy with chemotherapy

Combination of bevacizumab with chemotherapy is approved in patients with ovarian cancer. Pignata and colleagues used bevacizumab in combination with carboplatin-based doublet for platinum-sensitive recurrent ovarian cancer patients. In this phase 3 trial, the authors noticed an improved PFS for patients receiving combination therapy. These promising results may be considered for further clinical practice [80].

The effect of anti-angiogenic combination therapy has been well-studied in patients with CRC. The first-line therapeutic regimen and most effective schedule for patients with metastatic CRC is the combination of bevacizumab with FOLFOXIRI [81, 82]. Shinozaki and colleagues evaluated the efficacy of this combinational therapy in metastatic CRC patients, and found that the results were highly beneficial (overall response rate of 63.6%) in selected patients who tolerated an intensive therapeutic course [81]. In another study, bevacizumab was added to oxaliplatin-based chemotherapy in patients with stage II (high-risk) CRC. In this case, however, combination with bevacizumab did not improve the OS or DFS in the adjuvant setting. Interestingly, different tumor biology was noted in left and right colon cancers, representing differential responses to bevacizumab therapy [83]. DFS was not found to be improved after bevacizumab/FOLFOX4 treatment of stage III CRC in a study by André and colleagues [84]. Bevacizumab may elicit an optimal response when used after EGFR inhibitor cetuximab therapy, as noted by Liu and colleagues on left-sided *RAS* oncogene wild-type metastatic CRC [85]. A point important to consider here is the

development of bevacizumab resistance in patients with a previous history of treatment with this anti-angiogenic drug. Thus, it is expected that resistant patients may have higher blood levels of angiogenic factors, as reported by Cutsem and colleagues who noticed significantly higher blood levels of placental growth factor (PLGF) and VEGF-A in patients with metastatic CRC previously treated with bevacizumab, compared to patients without a previous history of bevacizumab therapy [86].

Taylor and colleagues evaluated the effect of combination of bevacizumab with the mammalian target of rapamycin (mTOR) inhibitor everolimus on patients with recurrent ovarian, peritoneal and fallopian tube cancers. Traditional therapies generally show limited efficacies for these cancer types. It was found that the combination therapy improved the 6-month PFS by 24%, i.e., in 13/50 patients [87]. The efficacy of combination pazopanib + gemcitabine therapy has also been evaluated in recurrent ovarian, primary peritoneal and fallopian tube cancer patients. In this phase 2 trial, Duska and colleagues reported a higher efficacy (improved median PFS, overall response rate and disease control rate) for the combination group over mono-gemcitabine therapy. Interestingly, the effect of combination therapy on PFS was more pronounced in patients resistant to platinum therapy. Therefore, patients resistant to platinum therapy may benefit from the use of combined pazopanib-gemcitabine therapy [72]. Recently, the effect of bevacizumab combination therapy for phase 3 recurrent ovarian, peritoneal and fallopian tube cancers has been assessed by Pfisterer and colleagues. In this study, two combinational groups were assessed, i.e., a



**Table 2** Adjuvant anti-angiogenic regimens in patients with solid cancers

Cancer type	Drug combination: name and activity	Toxicity	The effects of adjuvant therapy	Ref
recurrent GBM (phase 3)	cediranib: *Pan-VEGFR inhibitor, 30 mg p.o cilengitide: an integrin suppressor with anti-angiogenic and anti-invasive activities, 2000 mg i.v.	16% of patients had to stop therapy due to toxicity, which was independent on drug dosage.	No clinical advantage for (only 2 out of 45 patients showed complete response). combination therapy reduced plasma VEGFR-2, vascular permeability, angiogenesis and tumor infiltration.	[83]
recurrent breast cancer (phase 2)	bevacizumab: 15 mg/m <sup>2</sup> , i.v. vinorelbine: A mitotic inhibitor, 55 mg/m <sup>2</sup> , p.o capecitabine: A fluoropyrimidine prodrug that its active metabolite is fluorouracil 2000 mg/m <sup>2</sup> , p.o	neutropenia (n=10) & hypertension (n=3) for concurrent therapy, and neutropenia (n=4) & leukopenia (n=2) for sequential therapy.	The counts for CEPs and CECs (viable) were below the median rate, indicating improvement of OS.	[84]
stage III/IV ovarian cancer (phase 2)	bevacizumab: 15 mg/kg carboplatin: a platinum compound that reacts with nucleic DNA Paclitaxel: a microtubule-stabilizing agent	**Not addressed	The combination therapy improved PFS and OS particularly in subjects with high MVD.	[85]
advanced ovarian cancer (phase 3)	olaparib: PARP inhibitor, 300 mg, p.o bevacizumab: 15 mg/kg	fatigue, nausea and anemia	The combination therapy showed considerable PFS benefit for patients with BRCA	[86]
recurrent ovarian, fallopian tube & peritoneal cancers (phase 2)	bevacizumab: 10 mg/kg everolimus: mTOR inhibitor, 10 mg	Toxicities were almost grade 1 and 2 including mucositis, gastrointestinal, pain, nausea/vomiting	The combination therapy improved 6-month PFS (26%).	[87]
recurrent ovarian, fallopian tube or primary peritoneal cancers (phase 2)	pazopanib: VEGFR inhibitor, 800 mg gemcitabine: 1000 mg/m <sup>2</sup>	grade 3 or higher neutropenia, hypertension and thrombocytopenia	The combination therapy showed higher median PFS, overall response rate and disease control rate (5.3 months, 20% & 80%) vs. gemcitabine therapy (2.9 months, 11% & 60%).	[72]
recurrent ovarian, peritoneal & fallopian tube cancers (phase 3)	bevacizumab: 15 mg/kg Platinum-based combinations <sup>3</sup>	grade 3/4 hypertension and neutropenia	Median PFS in the experimental group: 13.3 months Median PFS in the standard group: 11.6 months.	[88]
advanced solid cancers (phase 1b)	bevacizumab: 10 mg/kg TRC105: an anti-endoglin monoclonal antibody, dose escalated from 10 mg/kg	Headache was the most common adverse effect. concurrent therapy did not augmented toxicities related to the bevacizumab monotherapy.	The combination therapy reduced the tumor volume and the ceased the progression	[89]
GBM (phase 1b)	cediranib standard chemoradiation: temozolomide	Not addressed	The combination therapy normalized tumor vasculature (improved vascular perfusion & integrity) in half of patients, and improved patient survival	[90]
NSCLC (phase 2)	endostatin carboplatin Paclitaxel: 175 mg/m <sup>2</sup>	Only 2 patients showed a rise in AST levels (liver toxicity), which can be manageable.	The combination therapy reduced CECs, and increased ccCK18, predicting longer PFS and OS.	[91]
advanced rectal cancer (phase 2)	bevacizumab: 5 mg/kg capecitabine: 825 mg/m <sup>2</sup> p.o radiation: 50.4 Gy/28 fractions	Patients experienced mostly mild adverse events including diarrhea, proctitis <sup>1</sup> , hypertension and rectal bleeding, and the adjuvant regimen was well-tolerated.	Although the neoadjuvant regimen was safe, addition of bevacizumab did not improve ypCR <sup>2</sup> and local control in long-term.	[92]

\* pan VEGFR = VEGFR-1, VEGFR-2 and VEGFR-3.

\*\*not addressed means that the designated item has not been assessed or included in the study.

<sup>1</sup> Proctitis is defined by inflammation of inner lining of rectum.

<sup>2</sup> ypCR is a pathogenic complete response.

<sup>3</sup> either carboplatin plus gemcitabine (with 15 mg/kg bevacizumab) [standard group] or carboplatin plus pegylated liposomal doxorubicin (with 10 mg/kg bevacizumab) [experimental group]

GBM, glioblastoma, VEGF, vascular endothelial growth factor; CEP, circulating endothelial progenitor; CEC, circulating endothelial cell; mTOR, mammalian target of rapamycin; PARP, poly (ADP-ribose) polymerase; OS, overall survival; MVD, microvessel density; PFS, progression-free survival; CRC, colorectal cancer; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; NSCLC, non-small cell lung cancer; ccCK18, caspase-cleaved CK18; AST, aspartate aminotransferase

standard group, which included carboplatin plus gemcitabine (with 15 mg/kg bevacizumab), and an experimental group, which included carboplatin plus pegylated liposomal doxorubicin (with 10 mg/kg bevacizumab). The median PFS was higher in the experimental group (13.3 months) compared to that in the standard group (11.6 months). Therefore, in patients with recurrent ovarian cancer, carboplatin–pegylated liposomal doxorubicin plus bevacizumab may serve as a new therapeutic regimen [88]. Bevacizumab plus the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib has also been evaluated in advanced ovarian cancer patients. Addition of olaparib for patients treated with bevacizumab provided a considerable PFS benefit. The outcomes were more pronounced in homologous recombination deficiency (HRD) positive cancer patients [89] (Table 2).

### 8.2.3 Combining anti-angiogenic therapy with immunotherapy

Anti-angiogenic therapy can be used in combination with immunotherapy to synergistically target human cancers. Such combination therapy can form a cycle of vascular remodeling and immune-stimulation within tumors [90]. There is a positive link between angiogenesis and immune escape in tumors. Interaction with VEGF enables dendritic cells (DCs) to take an angiogenic route. DCs express VEGFRs [91]. Interactions between VEGFR and VEGF may either lead to suppression of DC maturation [92] or to promoting their differentiation into cells with an EC-like phenotype. VEGFRs are also expressed by lymphocytes and macrophages [91]. Activation of T cells is suppressed by VEGF [93, 94]. VEGF also promotes macrophage infiltration into the tumor area. In addition, VEGF stimulates chemotaxis of regulatory T cells (Tregs) and maintains the activity of these cells in the tumor area [91]. Anti-angiogenic therapy can cause immune activation, whereas immunotherapy can cause anti-vascular effects. The anti-vascular effects are mediated by changes induced by immunotherapy in the tumor vasculature [90].

Cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) is a checkpoint mediator that acts primarily in the priming phase of immune responses. CTLA-4 blockade promotes T cell priming and activation and suppresses Treg function [95]. Hodi and colleagues evaluated the effect of bevacizumab combined with ipilimumab in patients with metastatic melanoma. The outcomes of this clinical trial were promising, i.e., the combination therapy could stimulate inflammatory events and promote the circulation of memory cells within the peripheral blood. The combination therapy also augmented effector T cell trafficking within the tumor area and potentiated responses from the humeral immune system to galectins. Antibody related to the galectin members was detected as a witness of coordinated responses of B and T cells [92].

Programmed death-1 receptor (PD-1) is another checkpoint mediator that upon interaction with its ligand programmed death-ligand 1 (PD-L1) can promote an immunosuppressive state in the TME. PD-1/PD-L1 interactions are active during late phases of T cell development, namely T cell maturation and expansion. PD-1 or PD-L1 blockade can thus offer promising therapeutic options for patients with advanced cancers [95]. Li and colleagues evaluated the efficacy of an anti-PD-1 antibody with different doses of anti-VEGFR-2 therapy in a mouse model of breast cancer. The authors noticed a synergistic effect, and a positive anti-angiogenic dosage effect on the outcome of therapy. A low dose of anti-angiogenic therapy was found to be effective for sensitizing tumor cells to the anti-PD-1 therapy [96]. The results of this study may have implications for dose modulations in patients receiving combination therapy. In another study, Zimmer and colleagues evaluated the effects of combinations of the PD-L1 inhibitor durvalumab with olaparib and the pan-VEGFR (VEGFR1-3) inhibitor cediranib in patients with ovarian, endometrial and triple-negative breast cancer (TNBC). The authors noted a promising objective response rate (ORR: 44 %) in patients receiving combination therapy. In addition, a desirable stable disease (SD: 33 %) was observed in patients receiving combination therapy. As yet, however, it is not fully clear whether the therapeutic benefits are related to the anti-VEGFR therapy, the PARP inhibitor, or both.

Combination of the VEGF inhibitor bevacizumab with the PD-L1 inhibitor atezolizumab has been assessed by Lee and colleagues on unresectable hepatocellular carcinoma (HCC) in a phase 1b clinical trial. Patients receiving combination therapy showed an improved median PFS rate (5.6 months vs. 3.4 months for atezolizumab monotherapy) [97]. In addition, it was found that the combination therapy creates an immunogenic microenvironment for tumor regression [98]. This study was continued by another group in a phase 3 trial. As compared to the phase 1b trial (Lee and colleagues), combinational atezolizumab-bevacizumab improved the median PFS (6.8 months) compared to the phase 3 trial, with an outstanding OS rate of 67.2 % [99].

It is important to consider the immune context of the tumor when designing therapeutic schedules. CRC, for instance, entails two subsets with distinct responses to combination therapies. The mismatch repair deficient/microsatellite instability-high (dMMR/MSI-high) subset is considered to be an immune-enriched subset, showing higher responses to combination therapies than patients with mismatch repair proficient/microsatellite stable (pMMR/MSS) tumors. VEGF blockade therapies are expected to increase CD8<sup>+</sup> T cell infiltration and reduce Treg expansion, thus increasing the immunogenic context within tumors [100].

The next point important to consider is the level of PD-L1 expression in a tumor. Patients with PD-L1<sup>+</sup> cancers generally show higher response rates to anti-VEGF/anti-PD-L1

combination therapy. McGregor and colleagues, for example, noticed higher overall response rates for PD-L1<sup>+</sup> metastatic RCC patients (60 %) than for patients with PD-L1<sup>-</sup> cancers (19 %) [101]. Another study on metastatic RCC evaluating the effect of combination of bevacizumab plus PD-1 inhibitor pembrolizumab by Dudek and colleagues found higher overall responses and PFS rates in patients in a phase 2 (60.9 % and 20.7 months) than those in a phase 1b (41.7 % and 9.9 months) trial. Another outcome of this study was a higher response rate in patients with tumor-infiltrating lymphocytes (TILs) than in those with PD-L1 expression [102]. A phase 3 clinical trial with avelumab-axitinib combination therapy has also been carried out for advanced RCC patients with results promising for patients with PD-L1<sup>+</sup> cancers, i.e., they had an improved PFS compared to those receiving sunitinib therapy [103]. A higher efficacy of avelumab-axitinib combination therapy over sunitinib therapy was also noted by Motzer and colleagues in advanced RCC patients. In this study, the authors noticed no relation between CD8<sup>+</sup> T cells and PD-L1 expressions status with PFS in the combination arm [104]. A similar study was continued by another group using pembrolizumab as checkpoint inhibitor, with similar outcomes (higher PFS for pembrolizumab-axitinib vs. sunitinib), suggesting the use of checkpoint inhibitors in combination with axitinib as a standard of care for advanced RCC patients [105]. In another recent report Motzer and colleagues compared the efficacy of nivolumab-ipilimumab combination therapy with that for sunitinib in patients with advanced RCC, and more favorable long-term clinical benefits were noted for the combination therapy compared to the sunitinib therapy, including lower grade 3 adverse events [106]. This study also indicated that combination of a CTLA-4 inhibitor with a PD-1 inhibitor can be well-tolerated among patients with advanced cancer. This is due to the effect of CTLA-4 inhibition on rescuing the priming phase of T cell development, and the impact of PD-1 inhibition on recovering the maintenance phase of T cell maturity, so the two can go well as a combination regimen for boosting the immune system. From the work published so far, the importance of both PD-L1 expression status and TIL presence in determining responses to immune checkpoint inhibitor (ICI) therapy may be asserted. Another postulation is that anti-angiogenic therapy can influence the efficacy of ICIs in patients with advanced cancer, and that understanding the immune context of a tumor prior to the start of therapy is relevant (Table 3).

## 9 Issues related to anti-angiogenic therapies

Administration of anti-angiogenic agents to patients with advanced-staged cancers including liver, brain and lung cancer, and some other solid cancers including pancreas, ovary, cervix and breast cancer, and tumors of the gastrointestinal

system has received wide approval [107], and hundreds of thousands cancer patients around the world are treated with these agents [56]. Anti-angiogenic therapy has resulted in improvements in OS and PFS for certain cancers, such as HCC, RCC and CRC. As yet, however, the effects of this approach are not always durable [107] and limited to only a subset of tumors [56, 107]. The OS in patients with advanced breast cancer is, for example, marginal (only 12 %) [56], and nearly all patients with RCC acquire resistance to anti-angiogenic therapy [108]. Below, we will discuss common issues related to anti-angiogenic therapy in patients with solid tumors.

### 9.1 Vessel co-option

Not all tumors are responsive to anti-angiogenic therapy, and not all tumors are dependent on neo-angiogenesis for their growth and proliferation. Examples of these are tumors exploiting vessel co-option to meet their demands (Fig. 1). Vessel co-option can be seen in tumors of the liver, lung and brain. The first evidence for the acquisition of vessel co-option was obtained in patients with GBM. Vessel co-option is defined as using nutrients and O<sub>2</sub> from pre-existing vasculature in nearby tissue. Vessel co-option adds a layer of complexity to cancer development and resistance to anti-angiogenic therapy. As in lung cancer not all cases exploit vessel co-option, anti-angiogenic therapy may lead to desirable outcomes [16, 62, 107, 109]. Conversely, although GBM is a highly vascularized cancer, responses to anti-VEGF therapy are only transient, which is due to vascular co-option in this cancer type [110]. A point important to consider here is the positive link between vessel co-option and hypoxia. In fact, hypoxic tumors in order to migrate through a host organ need to co-opt with normal blood vessels [62]. What can be understood from the importance of vessel co-option is (1) its impact on reducing the efficacy of anti-angiogenic therapy in certain tumor types and (2) its positive link with hypoxia for tumor cell migration and metastasis [62, 107, 111].

### 9.2 Vascular mimicry

Vascular mimicry is an independent route taken by solid cancers to meet their demands [112]. Vascular mimicry is defined by cancer cell-derived channels similar to blood vessels. These structures serve as alternative sources for nutrient and O<sub>2</sub> supply and are important for tumor growth and invasion [113] (Fig. 1). A difference between vascular mimicry and blood vessels is the origin of ECs, which cover the endothelium. The tube-like structures of vascular mimicry are lined by ECs derived from cancer cells, i.e., vascular mimicry represents transformation of cancer cells into EC-like cells. To do this, cancer cells undergo epithelial-to-endothelial transition, which is a subtype of epithelial-to-mesenchymal transition (EMT) [112]. Vascular mimicry can e.g. be seen in patients

**Table 3** Combining anti-angiogenesis with immune checkpoint inhibitors (ICIs)

Cancer type	Drug combination: name and activity	Toxicity	The effects of adjuvant therapy	Ref
unresectable HCC, phase 1b	atezolizumab: PD-L1 inhibitor, 1200 mg bevacizumab: 15 mg/kg	grade 3/4 hypertension and proteinuria	The combination therapy improved median PFS: 5.6 months.	[107]
unresectable HCC, phase 3	atezolizumab: 1200 mg bevacizumab: 15 mg/kg	grade 3/4 hypertension	The combination therapy improved overall survival (67.2%) and median PFS (6.8 months).	[109]
metastatic RCC, phase 2	atezolizumab: 1200 mg bevacizumab: 15 mg/kg	fatigue, musculoskeletal pain, proteinuria, diarrhea, nausea, dyspnea and hypertension were the most common adverse events.	The combination therapy improved overall response rate, particularly in patients with a PD-L1 <sup>+</sup> cancer (60% vs. 19% for PD-L1 <sup>-</sup> cancer cases).	[111]
metastatic RCC, phase 2	pembrolizumab: PD-1 inhibitor, 200 mg bevacizumab: 15 mg/kg	hypertension and proteinuria	The combination therapy improved overall response rate (60.9%)	[112]
advanced RCC, phase 3	avelumab: PD-L1 inhibitor: 10 mg/kg axitinib: a VEGFR TKI, 5 mg sunitinib: a VEGFR TKI, 50 mg	Not addressed	The combination of avelumab with axitinib better improved PFS than that for sunitinib.	[113]
advanced RCC, phase 3	avelumab: 10 mg/kg <sup>-1</sup> axitinib: 5 mg sunitinib: 50 mg	Not addressed	The combination of avelumab with axitinib better improved PFS than that for sunitinib.	[114]
advanced RCC, phase 3	pembrolizumab: 200 mg axitinib: 5 mg sunitinib: 50 mg	hypertension, increase of alanine aminotransferase and diarrhoea	The combination of pembrolizumab with axitinib better improved PFS than that for sunitinib (24-month PFS 37.6% vs. 26.5%)	[115]
advanced RCC, phase 3	nivolumab: PD-1 inhibitor, 3 mg/kg ipilimumab: A monoclonal antibody for targeting CTLA-4, 1 mg/kg sunitinib: 50 mg	Any-grade adverse events was similar between the combination group (nivolumab+ipilimumab) and sunitinib. Grade 3 adverse events was fewer in the combination group	The combination of nivolumab plus ipilimumab showed higher 30-month overall survival, 30-month PFS and complete response, compared to that for sunitinib therapy	[116]
metastatic melanoma (phase 1)	ipilimumab: 3 or 10 mg/kg bevacizumab, 7.5 or 15 mg/kg	Fatigue, rash, headache and cough are among the most common adverse effects reported for such therapy.	The combination therapy improved responses from immune system against tumor by augmenting T cell trafficking across tumor vessels, and increasing the number of anti-galectin antibodies.	[102]

HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; PD-1, programmed death-1 receptor; PD-L1, programmed death ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; PFS, progression-free survival; TKI, tyrosine kinase inhibitor

with breast cancer [113]. It is presumed that such patients, when receiving anti-angiogenic therapy, may develop vascular mimicry, thereby acquiring increased resistance to chemotherapy [112]. CAFs are the key cells contributing to cancer cell-to-EC transition in patients with vascular mimicry. CAFs send stimulatory signals to cancer cells to pursue such transitioning. The two key signaling factors excreted by CAFs are TGF- $\beta$  and CXCL12. Both contribute to EMT and stemness [113, 114], the two transcriptional signatures in vascular mimicry known to promote tumor plasticity at the time of drug resistance and metastasis [112].

The channel-like orchestration of vascular mimicry is acting as a route for cancer invasion and metastasis. Vascular mimicry is also induced by thrombin, an enzyme acting in catalyzing coagulation-related reactions. Coagulation and blood clotting is common in patients developing metastasis, and the activity of platelets is important in this context [112].

Taking these two points together, a close link could be asserted between vascular mimicry and the activity of platelets, and the promotion of metastasis. Vascular mimicry is thus a real concern, bypassing the activity of angiogenic systems for tumor growth and aggression. Vascular mimicry can thus act as another route for a tumor to suppress the activity anti-angiogenic therapy. Therefore, suppression of EC-dependent angiogenesis is not sufficient for retarding tumor progression, implying the need for targeting both ECs and growing tumor cells for a durable therapy response.

### 9.3 Limited activity of anti-angiogenic therapy in late-stage cancers

Targeting angiogenesis or angio-prevention is most effective in early-stage or pre-malignant lesions. Thus, predisposing conditions, such as pre-neoplastic or hyperplastic lesions,



chronic inflammation and occult tumors might be addressed by anti-angiogenic therapy [69]. Angio-prevention may be an appropriate choice for occult tumors, such as those of the lung, breast, pancreas and thyroid. Occult tumors do not always progress into malignant behavior [115].

Unfortunately, early diagnosis is not available for most malignancies [69]. Lung cancer is, for example, typically asymptomatic at early stages. This asymptomatic characteristic results in a delayed diagnosis in about half of the patients [116, 117]. What makes things even worse is the promotion of vascular invasion already in low-stage lung cancer patients [117]. A reason for delayed diagnosis in pancreatic cancer is tumor-mediated pain suppression at early stages [118], rendering them asymptomatic. A major predicament of delayed diagnosis in pancreatic cancer patients receiving anti-angiogenic therapy is the evolution of tumor escape from therapy [69].

#### 9.4 Tumor necrosis and hypoxia secondary to anti-angiogenic therapy

Anti-angiogenic agents may cause necrosis [119] and hypoxia [120, 121], particularly at the invasive front or edge of a tumor. Necrotic areas have been found to sensitize tumors to anti-PD-1 immunotherapy [119], but within highly proliferative tumors they may also be the places for nurturing CSCs due to their usually hypoxic nature. In fact, tumor necrosis finally results in hypoxia [34] and, thereby, predisposition to drug resistance, relapse and metastasis [120, 122]. This is important when considering the use of tyrosine kinase inhibitors, such as sorafenib and sunitinib, necessitating a close patient follow up due to the risk to develop drug resistance through intra-tumoral hypoxia induction and subsequent CSC enrichment [123]. The expansion of CSCs may secondarily augment angiogenic-related events [5]. Cells adjacent to the tumor vasculature may experience  $O_2$  concentrations of  $\sim 5\%$ , while cells close to the necrotic areas of a tumor often survive  $O_2$  concentration of  $\sim 0.1\%$ , which is almost anoxic [124].

#### 9.5 Effect of anti-angiogenic therapy on drug penetration

Anti-angiogenic therapy can blunt drug penetration into the tumor area [9]. As discussed earlier, tumor angiogenesis and anti-angiogenic therapy can both strengthen the promotion of hypoxia within the TME, and may be positively linked with stromal aggregation of fibrotic contents in the form of desmoplasia [125]. Hypoxia can recruit fibroblasts toward the tumor area [55], and is linked positively to the continuous production of TGF- $\beta$ , which is a key fibrogenic mediator. The presence of TGF- $\beta$  within the TME results from the differentiation of fibroblasts recruited into the tumor area into myofibroblastic CAFs, which are responsible for the

promotion of desmoplasia. Desmoplasia hampers the penetration of drugs into the tumor area [125]. Vascular disruption promoted by conventional anti-angiogenic therapy is another way for restricting drug delivery into a tumor.

#### 9.6 Vasculogenic rebound

Vasculogenic rebound is a term that refers primarily to the late mobilization of bone marrow-derived circulatory endothelial progenitor cells (EPCs). These EPCs contribute to the *de novo* formation of vessels and may cause tumor recurrence. A late burst in circulatory ECs may occur secondary to the application of vascular disrupting agents. In animal tumor models, Taylor and colleagues explored the efficacy of combretastatin A-4 (CA4P) either alone or in combination with anti-angiogenic regimens. CA4P is a vascular disrupting agent. The anti-angiogenic drugs used in this study were sunitinib and DC-101, the latter being a monoclonal antibody directed against VEGFR-2. Vasculogenic rebound was found to occur only after CA4P monotherapy, and it was counteracted when used in combination with sunitinib and DC-101 [126]. Vasculogenic rebound is another predicament for conventional anti-angiogenic therapies aimed at disrupting tumor vessels.

#### 9.7 Exploiting pathways beyond VEGF for endothelial cell activation

VEGF, as discussed above, is a key promoter of EC activation and angiogenesis in cancer, but it is not the sole promoter. Dependent on the conditions present, tumors can take other ways to activate ECs [127]. Factors secreted by cancer cells that contribute to angiogenesis are PDGF, angiopoietin and basic fibroblast growth factor (bFGF) [128]. PLGF is considered as a member of the VEGF subfamily that contributes to angiogenesis. PLGF has also been found to be increased in patients resistant to anti-angiogenic therapy [86]. The acquisition of such a subsidiary route may represent an escape mechanism from VEGF inhibitors. Transition into alternative pathways of angiogenesis is in fact a general concern for anti-angiogenic therapies. The Notch inhibitor RO4929097 is able to modulate the population of CSCs and may, as such, have an anti-angiogenic effect. Xu and colleagues administered RO4929097 as adjuvant with temozolomide and radiation to high-grade glioma patients (phase 0/1 clinical trial), and observed a tumor escape from Notch dependence and alternative neo-angiogenesis independent of Notch. Angiogenic markers, such as VEGF-A, angiopoietins and PECAM (CD31) were found to be upregulated in patients with recurrent tumors [129]. VEGF inhibitors, such as cediranib used for GMB patients, can secondarily cause integrin upregulation [110]. Integrins are transmembrane proteins that play important roles in angiogenesis, invasion and metastasis [130], thus defining a secondary route to promote resistance to anti-angiogenic

therapy. Interestingly, combination therapy of cediranib with the integrin inhibitor cilengitide in GBM patients did not lead to a desirable clinical outcome [110], which is indicative for the involvement of pathways beyond integrin signaling in promoting drug resistance. As discussed above, GBM is a cancer that can take vessel co-option to meet the demands for O<sub>2</sub> and nutrient supply. This may be a way for bypassing the effect of combination therapy.

## 10 Current strategies in cancer angiogenesis and therapy

### 10.1 Vascular normalization: a promising therapeutic approach

Abnormal vascular growth and function (incoherent or hypo-perfused vasculature) is a known hallmark of most solid cancers, facilitating immune evasion [20, 28, 131]. The aim of vascular normalization approaches is to improve tumor perfusion, implemented by attenuation of the leaky vasculature and increasing pericyte coverage [39]. Vascular normalization approaches by fixing abnormal vasculature and repairing blood vessel function result in normalization of the rate of O<sub>2</sub> delivery (relieving tumor hypoxia [132]). Augmenting tumor oxygenation promotes the differentiation of cancer cells (through reducing tumor hypoxia-related EMT) and suppresses their metastasis. Vascular normalizing strategies may be feasible for combating tumor angiogenesis and metastasis when used in combination with cytotoxic therapeutics [9, 19, 39, 133, 134].

#### 10.1.1 Virtues of vascular normalization over conventional anti-angiogenic therapies

Vascular normalization resolves the possibility of increased tumor metastasis related to angiogenic blockade therapy [135], thus rendering a tumor less invasive, more benign and less metastatic [64]. This approach is also expected to boost anti-tumor immunity [19]. This is mediated by facilitating Teff cell extravasation [119] and increasing the number of TILs in the tumor area [136]. Vascular normalization counteracts the inhibitory effect of a pericyte-low tumor vasculature on T cell trafficking into the tumor area. Vascular normalization also potentiates reprogramming of macrophages toward attaining an anti-tumor type 1 (M1) phenotype. This is mediated by abrogating hypoxia-induced M2 polarity [39], which can be a feasible strategy in particular for cancer patients who are obese [137]. One of the key functions of M2 cells is to induce CAFs. CAFs act by precipitating fibrotic contents in the form of desmoplasia in cancers, like those of the pancreas. These desmoplastic aggregates, indicative of an abnormal stroma, hamper the penetration of Teff cells, thus promoting

an immune evasive TME, activation of M2 cells and polarization of TAMs into a M2 phenotype [125].

In addition, conventional therapies that cause destruction of the tumor vasculature (also called tumor devascularization) can reduce the delivery of cytotoxic therapies into the tumor [14, 138]. Conversely, normalization of the tumor vasculature through fixing the delivery system may enhance the distribution of anti-cancer drugs. The idea behind vascular normalization is to prune inefficient and immature tumor vasculature to elimination of excess ECs and, thus, removal of unproductive vessels, thereby enabling efficient intra-tumoral delivery of therapeutics (administered via the intravenous route) [39].

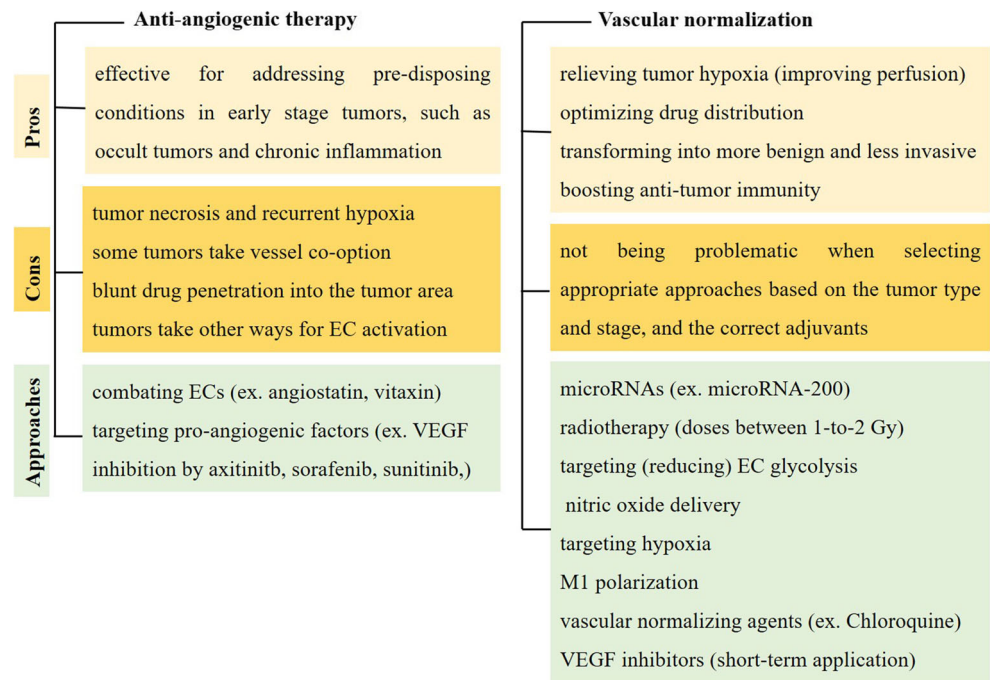
Hypo-perfusion and tumor hypoxia are the main predicaments related to conventional anti-angiogenic therapy, which may potentially cause treatment resistance. The vascular normalizing approach avoids this unfavorable event through enhancing O<sub>2</sub> delivery into the tumor area. Vascular normalization and vascular decompression (solid stress alleviation) are both effective strategies for improving blood perfusion and optimizing drug distribution. The former is more beneficial for tumors with un-compressed, high-permeable vessels, such as GBM, while the latter is more effective for tumors with high-compressed, low-permeable vessels, such as pancreatic ductal adenocarcinoma (PDAC) [139]. The diagram presented in Fig. 5 summarizes the pros and cons related to anti-angiogenic therapy, and the virtues of vascular normalization over conventional angiogenic targeting agents.

#### 10.1.2 Vascular normalizing strategies

There are several strategies to promote tumor vasculature normalization: (1) microRNA targeting [133], (2) radiotherapy [140], (3) EC glycolysis targeting [127], (4) hypoxia control [141], (5) nitric oxide delivery [9], (6) M2-to-M1 polarization of tumor macrophages [131], (7) application of agents with vascular normalizing activity, such as chloroquine (an anti-malaria drug) [142] and (8) VEGF inhibitors. Lowering (not eliminating) glycolysis in tumor ECs can normalize vascular abnormalities, ameliorate the chance of metastasis and improve the efficacy of chemotherapy without causing systemic toxicity [127].

**Radiation doses and vascular normality** Regarding radiotherapy, diverse reactions may occur using different radiation doses. High single radiation doses (> 5–10 Gy) may promote severe vascular damage, i.e., EC death and vascular dysfunction, which further induces hypoxia and reduces infiltration of immune cells, whereas low single doses (< 5–10 Gy) may cause mild vascular damage and improve anti-tumor immunity through enhancing the infiltration of immune cells (T cells) [143]. This enhanced infiltration of T cells is mediated by M1 reprogramming of TAMs at radiation doses lower than 2 Gy and a positive influence of M1 cells on vascular normalization

**Fig. 5** Anti-angiogenic therapy versus vascular normalization. Vascular normalization has more advantages and lower adverse effects in comparison with anti-angiogenic therapy. EC, endothelial cell; VEGF, vascular endothelial growth factor; M1, macrophage type 1



[144]. Even lower doses (< 1 Gy) are linked to EC activation and neo-angiogenesis, thus supporting tumor growth and metastasis [143].

**MicroRNAs and vascular normality** MicroRNAs can be exploited to regulate tumor angiogenesis. MicroRNA-200, for example, has been found to inhibit angiogenesis in a number of cancers, and its intra-endothelial delivery has been reported to induce vascular normalization [145]. MicroRNA-23a released from cancer cells has been found to exacerbate hypoxia-induced angiogenesis and inhibit tight junctions between ECs, thus increasing vessel permeability and trans-endothelial migration (invasion) of cancer cells [146]. Thus, microRNAs may serve as targets to counteract hypoxic reactions within the TME.

**Targeting hypoxia for normalizing tumor vasculature** The hypoxic TME controls interactions between ECs and tumor cells, and boosts the production of pro-angiogenic factors including VEGF for the initiation of angiogenesis. This will result in the formation of a network of abnormal tumor blood vessels. Therefore, control over hypoxia through partial O<sub>2</sub> pressure regulation inside the tumor mass may be considered as a promising approach to normalize the tumor vasculature [131, 141, 147].

**VEGF inhibitors for normalizing tumor vasculature** Finally, some anti-angiogenic therapies represent vascular normalizing activities. Examples are VEGFR inhibitors, such as sunitinib and sorafenib, and VEGF-A inhibitors, such as bevacizumab (Avastin) [9, 71, 148, 149]. Inhibition of

VEGF partly destroys the tumor vasculature, normalizes some of the tumor vessels, reduces primary tumor growth, and enhances the efficacy of some chemotherapeutic drugs [56]. Reduction of vascular leakiness is a mark of vascular architectural normalization. Bevacizumab has been administered along with paclitaxel in a human xenograft model of breast cancer. By doing so, Yanagisawa and co-workers found an increase in the tumoral concentration of paclitaxel, which was related to a reduction in vascular permeability (leakiness) [150].

## 11 Novel diagnostic/therapeutic windows related to cancer angiogenesis and therapy

### 11.1 Clinicopathological and prognostic value of angiogenic markers

#### 11.1.1 Micro-vessel density

The identification of patients likely to reply to anti-angiogenic therapy is of prime importance [151]. A major predicament for using bevacizumab in patients with recurrent GBM is the short time period in which the tumors tend to relapse (< 4 to 5 months) [110]. This also infers that bevacizumab monotherapy is not sufficient for such patients, requiring the use of combination therapies. Interestingly, in a phase 3 retrospective study of ovarian cancer (stage III/IV) it was found that bevacizumab as adjuvant with carboplatin and paclitaxel was effective in improving the PFS and OS, particularly in patients with a high micro-vessel density (MVD). MVD is

measured by counting CD31<sup>+</sup> ECs in tumor tissues [152], and can be visualized using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) [153]. CD31-MVD is used as a surrogate angiogenic measure of a tumor, and can be employed as a predictive biomarker for tracing the efficacy of bevacizumab therapy [152, 154]. Endoglin is considered as a marker for the evaluation of high MVD in tumors. VEGF inhibition upregulates endoglin expression on the surface of proliferating ECs. Upregulation of this receptor on tumor vessels is important for angiogenesis, which infers that endoglin can act as a mediator of tumor resistance to VEGF suppressors. Therefore, combination of anti-VEGF agents, such as bevacizumab, with anti-endoglin drugs like TRC105 may offer a therapeutic option for cancer patients. Gordon and colleagues used bevacizumab/TRC105 adjuvant therapy for the treatment of advanced solid cancer patients and the results were promising, as indicated by reduction of tumor volume and cessation of tumor progression [155]. MVD may be representative of tumor blood flow, and a higher blood flow may be positively correlated to the anti-angiogenic activity of drugs. Tumor blood flow [156] and vascular leakage [157] can also be measured by DCE-MRI.

### 11.1.2 Circulating endothelial cells

Evaluation of circulating ECs (CECs) is another way of predicting the efficacy of therapy and depicting patient survival. Generally, CECs show increases in blood of cancer patients, while after treatment these increases are reduced. Such a reduction can predict a longer median survival in patients with cancer [158].

### 11.1.3 Epidermal growth factor-like domain 7

Epidermal growth factor-like domain 7 (EGFL7) is another essential regulator of angiogenesis and is upregulated when angiogenesis reaches a pathogenic condition. It can be considered as a biomarker for evaluation of responses to therapy. EGFL7 is implicated in the formation of vascular tubes, guiding EC migration during angiogenic sprouting. EGFL7 also suppresses immune cell infiltration into the tumor area, thereby escalating tumor growth and resistance. Hansen and co-workers who treated metastatic CRC with a bevacizumab/first-line chemotherapy combination found that EGFL7 served as a predictive biomarker of therapy response, highlighting the value of dual anti-VEGF-A/anti-EGFL7 for targeting angiogenesis [151].

### 11.1.4 Other markers

Also other markers may be used for the prognosis of angiogenesis, such as serum VEGF as described above, p53 and thrombospondin-1 (TSP1)-IA. The former is used as a

potential marker of poor OS, while the other two are used as markers for an improved OS, as reported in a study on gynecologic cancers [154]. <sup>18</sup>F-FDG uptake has also been found to be effective for detecting angiogenesis in early-stage breast cancer [159].

## 12 Modulation of 'dose' and 'time' of exposure is key to improving the efficacy of anti-angiogenic therapy

The dose of anti-angiogenic therapy is important for exerting a desired outcome. A low-dose regimen can sensitize breast cancer cells to anti-PD-1 therapy, as discussed above [96]. Jain reported on human colon carcinoma, and came up with two interesting findings: (1) anti-angiogenic therapies initially improve both the structure and function of tumor vessels, and (2) sustained or aggressive anti-angiogenic regimens may eventually cause drug resistance and vessel abnormality [14]. In addition to resistance and abnormality, long-term application of anti-angiogenic therapy may cause tumor devascularization, thereby exacerbating tumor hypoxia. In GBM treated with bevacizumab, tumor progression is expected in 40–60 % of patients after initial therapy success [138].

Sometimes pro-angiogenic recovery may result from a long duration of time intervals of chemotherapy. For instance, taxane combination therapy (carboplatin and docetaxel) prescribed every three weeks has been found to increase MVD in advanced ovarian cancer patients (epithelial subtype). Therefore, short-time intervals for the administration of chemotherapy is suggested to abrogate recovery in angiogenic-related systems [160].

## 13 Conclusions and future directions

Targeting tumor angiogenesis is an important issue in cancer therapy, and is based on the fact that tumors are trying to adapt their need to O<sub>2</sub> and nutrients available within the surrounding milieu. This adaptation helps them to maintain their survival in O<sub>2</sub> and nutrient low conditions, to promote their growth, invasion and metastasis, and even to cause recurrence after tumor therapy. To pursue such aims, tumors make essential changes in their vasculature bed, either architecturally or functionally, thereby behaving in an abnormal manner for their own favor. These changes led us to think of other modalities than conventional anti-angiogenic therapies for targeting tumor angiogenesis since tumor vascular beds are distinct from those in tissue vessels. Thus, different modalities are needed to combat this key promoter of tumor aggression. As discussed above, there are three major issues with regard to anti-angiogenic therapy: (1) causing recurrent hypoxia when the anti-angiogenic regimen is not selected appropriately, (2) tumors



are able to bypass the effectiveness of anti-VEGF sunitinib, sorafenib and pazopanib by exploiting other ways for EC activation and (3) there are tumors that do not use angiogenesis but, instead, vascular mimicry. Besides, the efficacy of anti-angiogenic therapy *in solo* is superficial (transient) and may not be durable. Heterogeneity of tumors is another issue that results in complex responses to anti-angiogenic therapy. In addition, some tumors use, next to the pre-existing vasculature, strategies to use pre-existing stromal structures, which enables them to grow further and escape surveillance. Vascular normalization has some virtues over conventional approaches for targeting tumor angiogenesis. The virtues of this strategy are desirable, and deserve careful consideration when seeking adjuvant therapy aiming for effective and durable results. Considering vascular normalization for the design of adjuvant or combination anti-angiogenic strategies may pave the way for effective and durable therapies for patients with advanced cancers.

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## Declarations

**Conflicts of interest/competing interests** The authors declare to conflict of interest.

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**Abbreviations** *EC*, endothelial cell; *EPC*, endothelial progenitor cell; *TME*, tumor microenvironment; *IFP*, interstitial fluid pressure; *SMC*, smooth muscle cell; *ECM*, extracellular matrix; *CSC*, cancer stem cell; *BTB*, blood-tumor barrier; *CXCL12*, C-X-C chemokine ligand 12; *CXCR4*, C-X-C chemokine receptor type 4; *TGF- $\beta$* , transforming growth factor-beta; *VEGF*, vascular endothelial growth factor; *M2*, macrophage type 2; *CAF*, cancer-associated fibroblast; *EGFR*, epidermal growth factor receptor; *TKI*, tyrosine kinase inhibitor; *PDGFR*, platelet-derived growth factor receptor; *DC*, dendritic cell; *CTLA-4*, cytotoxic T-lymphocyte-associated protein-4; *PD-1*, programmed death-1 receptor; *PD-L1*, programmed death ligand 1; *dMMR/MSI*, deficient/microsatellite instability; *pMMR/MMS*, mismatch repair proficient/microsatellite stable; *TIL*, tumor-infiltrating lymphocyte; *ICI*, immune checkpoint inhibitor; *EMT*, epithelial-to-mesenchymal transition; *MVD*, micro-vessel density

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