Antiangiogenic Therapy for Advanced Non-Small Cell Lung Cancer

Edited by Alex Adjei, M.D., Ph.D., Alan Sandler, M.D., and Mark Socinski, M.D.

Lung cancer causes over 160,300 deaths annually in the US, more than cancers of the breast, colon and prostate combined[1]. Approximately 85% of lung cancers are of non-small cell-type (NSCLC), a form comprised of diverse histological subtypes originating in lung epithelial cells[2]. Most patients with advanced or metastatic disease treated with standard first-line platinum-based chemotherapy regimens survive for less than a year[3].

Because of this poor prognosis, agents that disrupt critical growth factor/receptor signaling pathways in tumor angiogenesis and lymphangiogenesis are being intensively researched for NSCLC. Of the many known proangiogenic cytokines, vascular endothelial growth factor (VEGF) has been the best studied as a therapeutic target. VEGF induces the proliferation, migration and survival of vascular endothelial cells, and stimulates the recruitment of bone marrow-derived endothelial progenitor cells to the new vasculature. VEGF also increases vascular permeability, contributing to malignant pleural effusion in NSCLC[3, 4]. Inhibition of VEGF and its receptors in human tumor xenografts has been shown to curtail tumor vascularization, promote apoptosis, and enhance intratumor penetration of cytotoxic chemotherapy through transient normalization of tumor vasculature and lowering of elevated interstitial tumor pressure[3, 5].

Clinical Evidence for Antiangiogenic Therapy

Anti-VEGF therapies disrupt angiogenesis by either: 1) binding extracellular circulating VEGF (monoclonal antibodies, VEGF Trap), or 2) intracellular targeting of the VEGF receptors (tyrosine kinase inhibitors).

The FDA approval of **bevacizumab** (Avastin), a humanized VEGF-targeting monoclonal antibody, for the first-line treatment of advanced or metastatic non-squamous cell NSCLC was based on results from a randomized, open-label phase 3 trial (ECOG 4599) that showed that the addition of 15 mg/kg bevacizumab (BV) to carboplatin/paclitaxel (CP) reduced the risk of death by ~20% vs. CP alone (HR, 0.79)[6]. Median overall survival (OS) in the BV/CP arm was 12.3 mo. compared with 10.3 mo. for CP (P=0.003). ECOG 4599 was followed by a second randomized phase 3 trial (AVAiL) of BV 7.5 or 15 mg/kg plus cisplatin/gemcitabine (CG) compared with CG plus placebo in 1043 chemo-naïve patients with advanced or recurrent NSCLC[7]. While OS data are not yet available, both BV doses used in combination with CG reduced the risk of disease progression vs. CG/placebo (BV 7.5 mg/kg: HR, 0.75; P=0.0026; BV 15 mg/kg: HR, 0.82; P=0.03).

VEGF Trap (AVE0005, Aflibercept) is a soluble, recombinant fusion molecule combining portions of the extracellular domains of human VEGF receptors -1 and -2 fused to the F_c segment of human immunoglobulin IgG1. This agent, which acts as a receptor decoy for circulating VEGF, has been shown to induce both regression and apoptosis of tumor vasculature in established human lung tumor xenografts and metastases[8]. An ongoing, open-label phase 2 trial is planning to enroll 94 patients with platinum- and erlotinib-resistant advanced NSCL adenocarcinoma to receive intravenous VEGF Trap every 2 weeks[9]. In a preliminary analysis of the first 54 patients treated in this study, 2 experienced a partial response (PR) and 34 had stable disease (SD). A phase 3 trial of VEGF Trap in combination with docetaxel as second-line treatment in 900 patients with metastatic NSCLC began enrollment in September 2007.

Tyrosine Kinase Inhibitors

Most small molecule tyrosine kinases inhibitors (TKIs) disrupt intracellular angiogenic signaling by binding competitively to the ATP binding site on growth factor receptors. Inhibitors of the epidermal growth factor receptor (EGFR) were among the first targeted agents approved for advanced NSCLC. These agents can produce dramatic responses in patients harboring certain EGFR TK-activating mutations[10]. In a landmark phase 3 trial, the EGFR inhibitor **erlotinib** (Tarceva) improved median OS by 2 months compared to placebo (6.7 vs. 4.7 mo., P<0.001) as second- or third-line NSCLC therapy, leading to its current indication for patients who have failed ≥1 prior chemotherapy regimen[11].

The majority of TKIs in clinical development for NSCLC are oral agents that target VEGFR-2, a key receptor involved in VEGF-mediated angiogenesis, in addition to other angiogenic targets (see Table). **Sunitinib** (Sutent) 50 mg/kg/day (4 weeks on, 2 weeks off) was evaluated in a single-arm phase 2 study of 63 treatment-refractory NSCLC patients[12]. Median PFS and OS were 2.8 mo. and 6 mo., respectively, with an objective response rate of 11.1%. In a subsequent phase 2 trial, a median PFS and OS of 3.1 mo. and 9.3 mo. were reported using continuous dosing of sunitinib 37.5 mg/day in 47 treatment-refractory NSCLC patients[13]. **Sorafenib** (Nexavar) 400 mg bid continuous dosing produced a median PFS of 2.7 mo. and OS of 6.7 mo. in a phase 2 trial involving 52 patients with relapsed/refractory NSCLC[14]. Both agents are now in phase 3 trials for advanced NSCLC—sunitinib plus erlotinib in the refractory setting, and sorafenib in combination with CP as front-line therapy.

Kinase Inhibitors in Clinical Trials for NSCLC

Agent	Molecular Targets	Trial Phase/Setting
ABT-869	VEGFR-1, -2, -3, PDGFR-α & -β, c-Kit, Flt-3	Phase 2, refractory
Axitinib (AG-013736)	VEGFR-1, -2, -3, PDGFR-β, c-Kit	Phase 2, refractory
BIBF 1120	VEGFR, PDGFR, FGFR	Phase 2, refractory
Cediranib (AZD2171)	VEGFR-1, -2, -3, PDGFR-α & -β, c-Kit	Phase 2/3, front-line and refractory
Enzastaurin	PKCβ, PI3/AKT signaling pathway, GSK3-β phosphorylation	Phase 2, front-line and refractory
Motesanib diphosphate (AMG 706)	VEGFR-1, -2, -3, PDGFR, c-Kit, RET	Phase 3, front-line
PTK787/ZK	VEGFR-1, -2, -3	Phase 2, refractory
Sorafenib (Nexavar)*	VEGFR-1, -2, -3, Raf-1, PDGFR-β, Flt-3, c-Kit, RET	Phase 3, front-line
Sunitinib (Sutent)**	VEGFR-1, -2, -3, Flt-3, PDGFR-α & -β, c-Kit, RET	Phase 3, refractory
Vandetanib (ZD6474; Zactima)	VEGFR-2, EGFR/HER2, RET	Phase 3, refractory
XL647	VEGFR-2, EGFR/HER2, EphB4	Phase 2, refractory
XL999	VEGFR-2, FGFR-1, -3, PDGFR-β, Flt-3, RET, c-Kit, SRC	Phase 2, refractory

* Approved for advanced renal cell carcinoma (RCC) and unresectable hepatocellular carcinoma (HCC)
** Approved for advanced RCC and gastrointestinal stromal tumor (GIST)

Antiangiogenic Escape and Treatment Strategies

Most tumors eventually compensate for therapy-induced VEGF interruption through one or more proposed escape mechanisms, which may include upregulation of VEGF and other growth factors, contribution of VEGF by host stroma, hyperactivation of alternate signaling pathways, co-option of existing vessels, or transformation of the tumor vasculature to a more mature, less VEGF-dependent phenotype[15, 16]. Resistance to TKIs may incorporate elements of both VEGF escape and EGFR resistance. There is some evidence that inhibiting EGFR may make tumors more angiogenesis-dependent, and thus more susceptible to VEGF inhibitors[17]. Therefore, simultaneously targeting both VEGF and EGFR is being explored as a potential strategy for circumventing anti-VEGF escape and increasing efficacy.

In a phase 2 trial involving 120 patients with recurrent/refractory NSCLC, the combination of BV and erlotinib was comparably effective and somewhat better tolerated than BV plus chemotherapy (median OS = 13.7, 12.6 mo. for BV/erlotinib, BV/chemotherapy vs. 8.6 mo. for chemotherapy alone)[18]. Following on these results, two phase 3 trials have been initiated: erlotinib ± BV as second-line therapy in NSCLC patients who have had no prior anti-VEGF or anti-EGFR therapy (BeTa Lung); and front-line BV/chemotherapy (4 cycles) followed by BV ± erlotinib in NSCLC patients with squamous or non-squamous histology (ATLAS). Single agents that target both VEGF and EGFR are also in development. Of these, **vandetanib** (ZD6474), a once-daily oral TKI, is the most clinically mature for NSCLC. Results from several phase 2 studies in different NSCLC treatment settings have produced encouraging results, and four randomized phase 3 trials of vandetanib have been initiated in refractory NSCLC: vandetanib vs. placebo; vs. erlotinib; ± docetaxel; and ± pemetrexed. Therapies directed at other angiogenic targets, such as the insulin-like growth factor receptor-1 (IGFR-1) and mammalian target of rapamycin (mTOR), part of the PI3/Akt pathway, are also being investigated for advanced NSCLC.

Safety Issues of Antiangiogenic Therapy in NSCLC

BV is presently contraindicated in NSCLC patients with squamous cell histology and in those with brain metastases (BM) due to concerns of increased bleeding risk. Squamous cell tumors appear particularly susceptible to hemorrhage resulting from central tumor necrosis or cavitation induced by VEGF inhibition. Two phase 2 trials are being planned to assess the safety of BV in patients with squamous cell NSCLC: AVASQ, which will examine whether radiotherapy prior to CP/BV might mitigate bleeding risk; and BRIDGE, in which patients will receive CP followed by CP/BV. A third open-label phase 2 study (PASSPORT) is enrolling non-squamous NSCLC patients with previously treated, non-progressive BM to receive BV as part of first- or second-line systemic therapy. These studies will help determine whether BV may in fact be safe for patients with squamous cell carcinoma or BM in certain circumstances. In addition to these NSCLC-specific safety concerns, VEGF inhibition may be associated with hypertension, impaired wound healing, and, very infrequently, gastrointestinal perforations, fistula formation, thromboembolic complications, and reversible posterior leukoencephalopathy.

Side effects from sunitinib or sorafenib therapy may include diarrhea, fatigue, nausea, stomatitis, hypertension, and mucosal inflammation. Both agents have also been associated with a number of dermatological toxicities, including hand-foot skin reaction and rash (primarily sorafenib), hair depigmentation (sunitinib), and subungual splinter hemorrhages (both agents). Sunitinib has been associated with both pulmonary and cerebral hemorrhage in NSCLC patients[12]. Additionally, patients receiving sunitinib may require monitoring for development of hypothyroidism, reduced left ventricular ejection fraction (LVEF), and QT interval prolongation[19, 20].

Future Directions

The use of biomarkers for identifying NSCLC patients most likely to respond to antiangiogenic therapies remains an active area of research, but requires validation. From a therapeutic standpoint, vascular disrupting agents (VDAs) represent a novel antivascular approach to NSCLC. VDAs selectively target existing tumor vasculature, resulting in rapid tumor necrosis. In a single-arm phase 2 study in chemo-naïve patients with advanced NSCLC, 11 of 30 who received the VDA **DMXAA** (ASA404) plus CP achieved a PR and 14 had SD; median survival was 14.9 mo.[21]. A second VDA, **MPC-6827** (Azixa) is being evaluated in a phase 2 trial in NSCLC patients with BM. With numerous agents/combinations under investigation for NSCLC, clinicians should consider referring appropriate patients for participation in clinical trials, which provide the best opportunity to take advantage of evolving therapies and strategies.

Abbreviated References:

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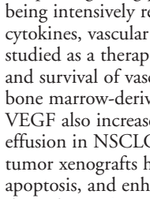

From the Editor-in-Chief

The Angiogenesis Foundation is pleased to present this CME issue of *Targeting Tumor Angiogenesis* focused on advanced non-small cell lung cancer. I have invited three preeminent experts, Drs. Alex Adjei, Alan Sandler, and Mark Socinski, to discuss the latest evidence on antiangiogenic therapies for advanced NSCLC and what the future holds for new therapeutic targets under investigation.

– *William W. Li, M.D., President, The Angiogenesis Foundation*

Guest editors:

Alex Adjei, M.D., Ph.D.

Alan Sandler, M.D.

Mark Socinski, M.D.

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RELEASE AND EXPIRATION
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INTENDED AUDIENCE
Practicing oncologists and oncology nurses in the U.S.

EDUCATIONAL OBJECTIVES
- Describe angiogenesis targets and pathways in cancer
- Describe the paradigm shifts in cancer management accompanying antiangiogenic therapy
- Review clinical data regarding the use of antiangiogenic agents in treating advanced non-small cell lung cancer

METHOD OF PARTICIPATION
Review the illustration and article(s) on this publication, and then visit www.angio.org and click on CME Information for additional content, CME registration and evaluation. There you can access additional program content, related articles, and detailed instructions to obtaining CME credits for this activity.

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Alex Adjei, M.D., Ph.D.
- Has no relationships to disclose that are germane to this CME activity

William W. Li, M.D.
- Has no relationships to disclose that are germane to this CME activity

Alan Sandler, M.D., has a financial interest/relationship or affiliation in the form of:
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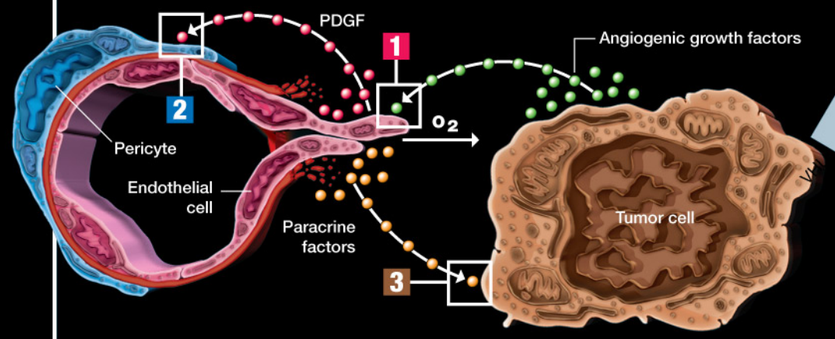
Written by Rod Smith, Medical Writer and Editor, The Angiogenesis Foundation
- Has no relationships to disclose that are germane to this CME activity

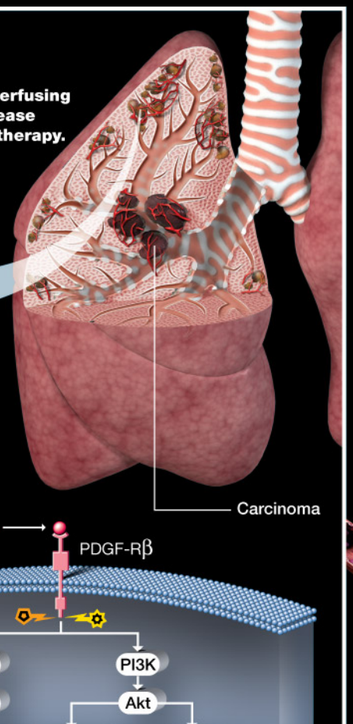
DISCUSSION OF UNLABELED USE
This CME activity contains discussion of published and/or investigational use of bevacizumab (Avastin), DMXAA (ASA404), erlotinib (Tarceva), MPC-6827 (Azixa), sorafenib (Nexavar), sunitinib (Sutent), vandetanib (ZD6474), and VEGF Trap (Aflibercept).

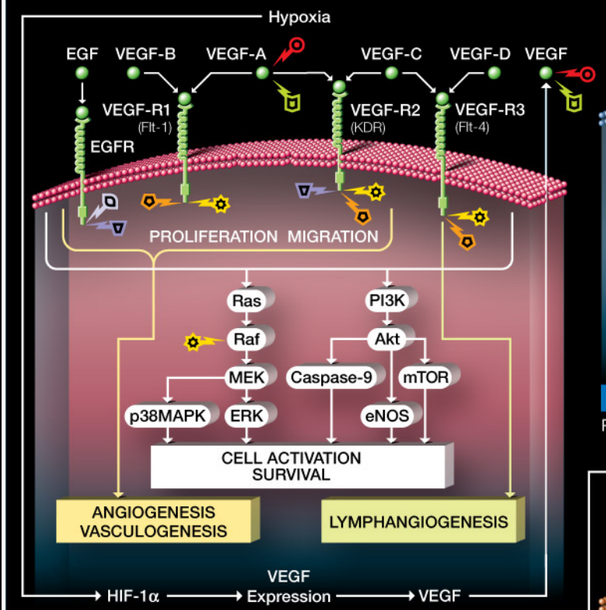
The Angiogenesis Foundation
PO Box 382111
Cambridge, MA 02238
t: 617.576.5708 f: 617.576.5808
www.angio.org

Targeting Cells and Pathways in Lung Cancer

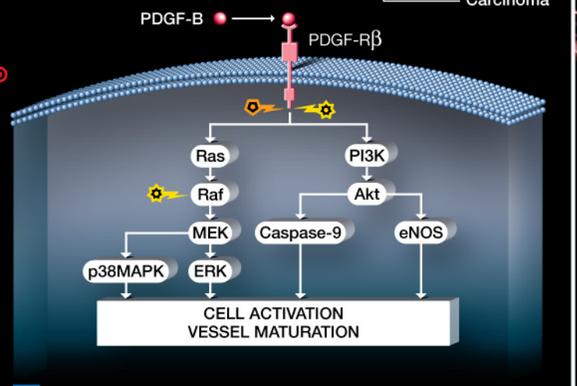
During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels perfusing tumors. Endothelial cells also provide paracrine factors to tumor cells which, in turn, release growth factors that sustain angiogenesis. Key pathways in each cell can be targeted for therapy.



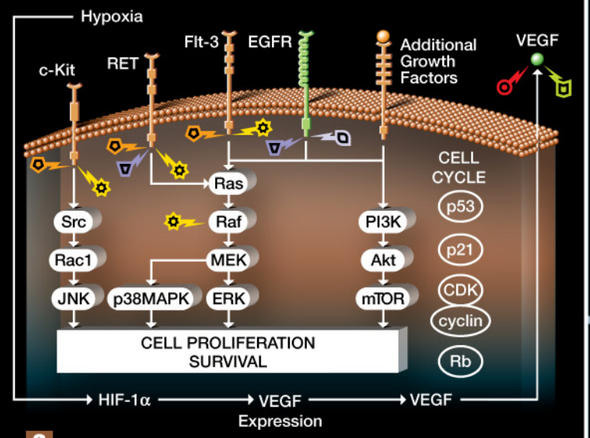




1 ENDOTHELIAL CELL The vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGF-R1, VEGF-R2, VEGF-R3, activating signal transduction to promote angiogenesis,vasculogenesis, and lymphangiogenesis.



2 PERICYTE Platelet-derived growth factor (PDGF) and its receptor PDGF-Rβ mediate vessel maturation.



3 TUMOR CELL Multiple growth factors and receptors activate signal transduction and cell cycle pathways to stimulate tumor cell growth.

Targeted Agents

(Targets shown in diagram above and to the right)

- **Bevacizumab** (Avastin)
- **Erlotinib** (Tarceva)
- **Sunitinib** (Sutent)
- **Sorafenib** (Nexavar)
- **Vandetanib** (ZD6474)
- **VEGF Trap** (Aflibercept)

Targeting Tumor Angiogenesis

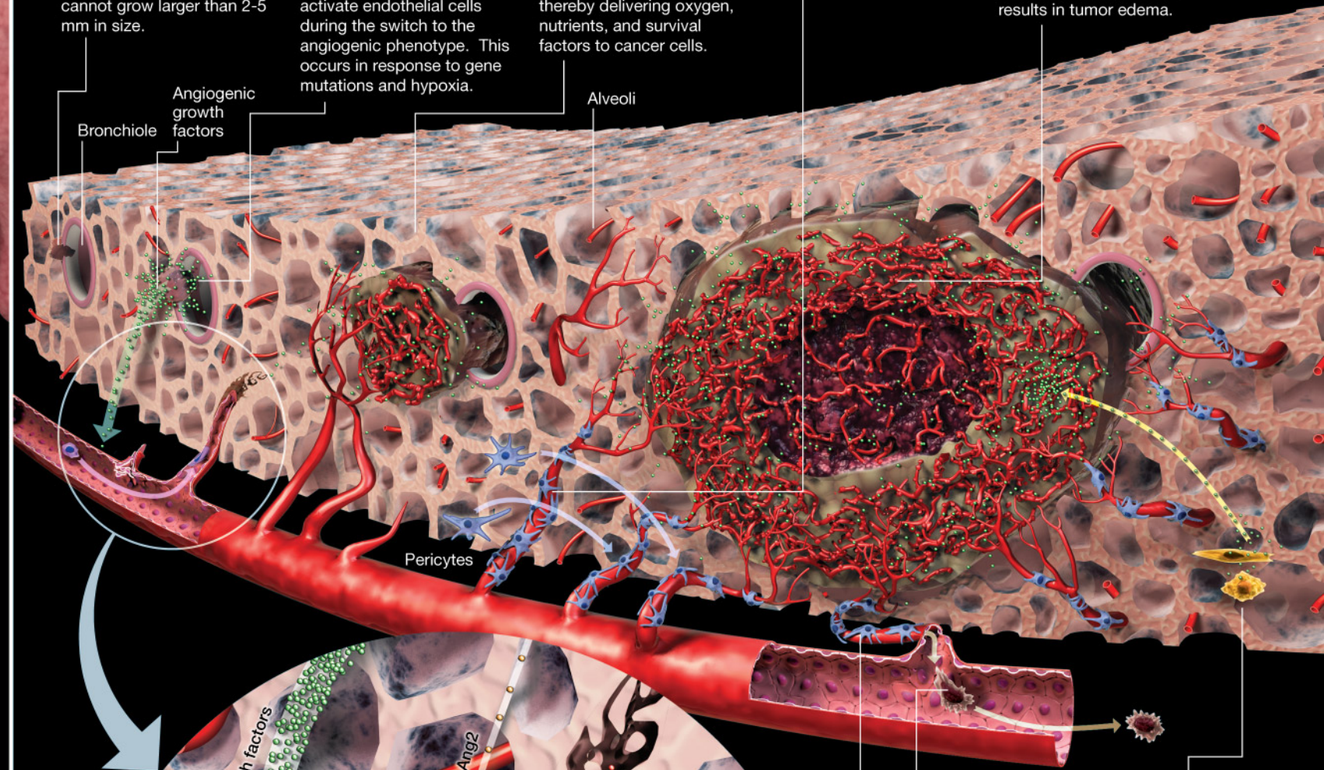
1 Incipient cancers lack a blood supply and cannot grow larger than 2-5 mm in size.

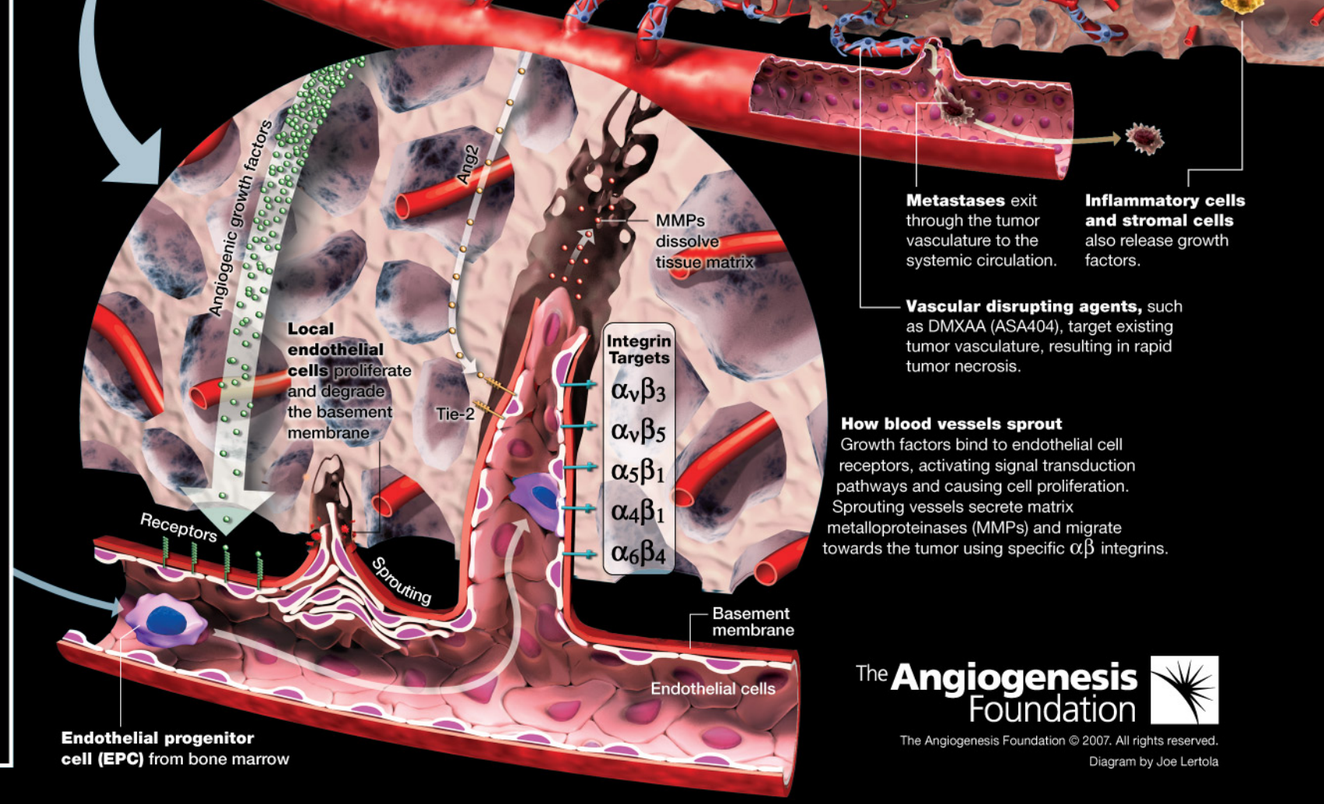
2 Cancer cells release growth factors that activate endothelial cells during the switch to the angiogenic phenotype. This occurs in response to gene mutations and hypoxia.

3 Angiogenic vessels form tubes and loops, thereby delivering oxygen, nutrients, and survival factors to cancer cells.

4 Vessels mature as pericytes are recruited by endothelial cells to stabilize new capillaries.

5 Unabated angiogenesis enables tumor expansion and local invasion. Abnormal blood flow leads to central hypoxia. Vessel hyperpermeability results in tumor edema.





Metastases exit through the tumor vasculature to the systemic circulation.

Inflammatory cells and stromal cells also release growth factors.

Vascular disrupting agents, such as DMXAA (ASA404), target existing tumor vasculature, resulting in rapid tumor necrosis.

How blood vessels sprout
Growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation. Sprouting vessels secrete matrix metalloproteinases (MMPs) and migrate towards the tumor using specific αβ integrins.

The Angiogenesis Foundation

Diagram by Joe Lertola