Terapia Anti-VEGF: Dieci Anni di Esperienza

Napoleone Ferrara, M.D.
University of California, San Diego

Catania, Ottobre 22, 2015

Am. J. Roentgenol., 41:891-9, 1939

Vol. 42, No. 6

VASCULARIZATION OF THE BROWN-PEARCE RABBIT EPITHELIOMA TRANSPLANT AS SEEN IN THE TRANSPARENT EAR CHAMBER*†

By A. GORDON IDE, M.D., NORMAN H. BAKER, M.D.,‡ *and* STAFFORD L. WARREN, M.D.
ROCHESTER, NEW YORK

THE readiness with which metastatic tumor cells grow in tissues distant from the original site is dependent to a great extent upon their ability to maintain their nutrition by developing a blood supply in their new location. It seems of some moment to study the development of the vascular supply to a tumor transplant placed in a rabbit ear chamber, and particularly to find out if possible whether the pattern of the vascular response to the transplanted tumor tissue resembles that of other transplanted tissues and repair reactions. These data are to be used as controls for a study of the effects of roentgen radiation upon the blood vessels of the tumor transplant which follows in another paper of this series.

following testicular transplantation. If the transplant takes, growth is rapid and uniform until the window area is filled; then regression occurs. The vascularization of the newly transplanted tumor fragment from the time of implantation up to the time that tumor growth is definitely established is the main concern of this study.

Since the ear is a specialized organ in the rabbit, blood vessel distribution differs in some respects from that of other organisms. Yet these vessels in their responses to stimuli (especially those stimuli presented by foreign material or by the tumor transplant) should follow the fundamental reactions of blood vessels generally. It was felt that the tumor transplant in the ear could be considered as an analogue to a

SEMINARS IN MEDICINE
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LOUIS M. SHERWOOD, M.D., *Editor*
EDITH E. PARRIS, *Assistant Editor*

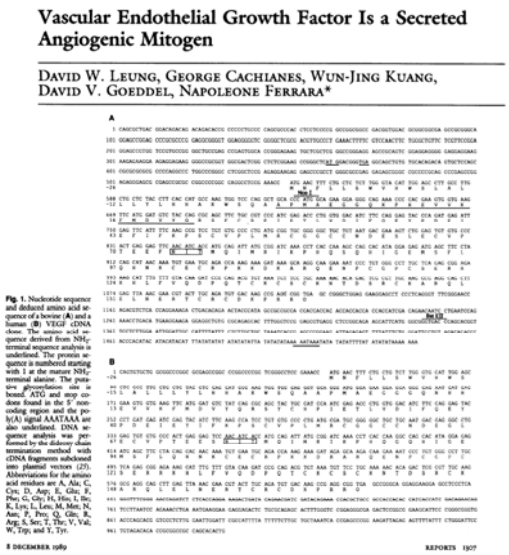
TUMOR ANGIOGENESIS: THERAPEUTIC IMPLICATIONS

JUDAH FOLKMAN, M.D.

"Anti-angiogenesis may provide a form of cancer therapy worthy of serious exploration".

N. Engl. J. Med. 285:1182-6, 1971

Isolation and cloning of VEGF, an endothelial cell-specific mitogen secreted by follicular cells



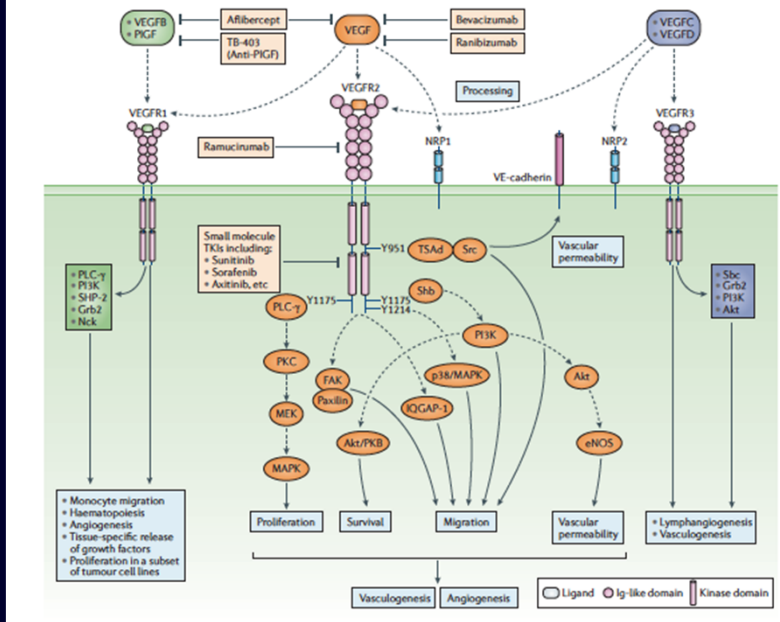
Vascular Endothelial Growth Factor Is a Secreted Angiogenic Mitogen

DAVID W. LEUNG, GEORGE CACHIANES, WUN-JING KUANG, DAVID V. GOEDDEL, NAPOLEONE FERRARA*

Science, 246:1306-09, 1989

Inactivation of a single *vegfa* allele results in defective vascularization and embryonic lethality in mice

Ferrara N, et al. *Nature* 380:439–42, 1996



In press, 2015

Nature Reviews | Drug Discovery

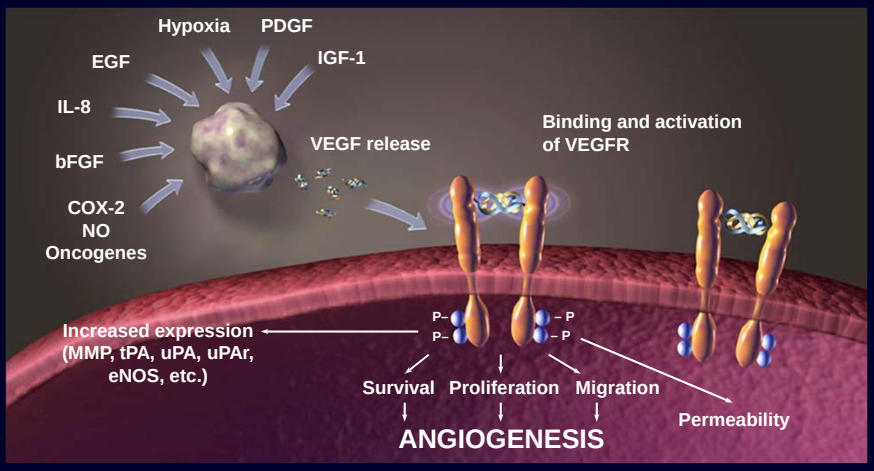
Table 2 Anti-angiogenic drugs that are approved and/or in clinical development

Drug name	Type	Mechanism of action	Clinical stage	Company
Bevacizumab (Avastin)	Humanized mAb	Blocks VEGF-A binding to receptors	Approved for metastatic CRC, NSCLC, RCC; recurrent GBM	Genentech/Roche (Basel, Switzerland)
Sunitinib (Sutent)	Small molecule RTK inhibitor	Inhibits signaling of VEGFRs, PDGFRs, FLT-3, CSF1R	Approved for metastatic RCC, imatinib-resistant GIST, PNET	Pfizer (New York, NY)
Sorafenib (Nexavar)	Small molecule RTK inhibitor	Inhibits signaling of VEGFRs Raf, PDGFRs, KIT	Approved for metastatic RCC, HPCC	Bayer/Onyx (South San Francisco, CA)
Pazopanib (Votrient)	Small molecule RTK inhibitor	Inhibits signaling of VEGFRs PDGFRs, KIT	Approved for metastatic RCC	GlaxoSmithKline (London, UK)
Vandetanib (Caprelsa)	Small molecule RTK inhibitor	Inhibits signaling of VEGFRs PDGFRs, EGFR	Approved for metastatic medullary thyroid cancer	AstraZeneca (London, UK)
Axitinib (Inlyta)	Small molecule RTK inhibitor	Inhibits signaling of VEGFRs PDGFRs, KIT	Approved for RCC that failed first-line therapy	Pfizer (New York, NY)
Aflibercept (Zaltrap)	Chimeric soluble receptor	Binds VEGF-A, VEGF-B and PlGF	Phase 3 multiple tumor types	Regeneron/Sanofi Aventis (Paris)
AGM386	Peptidobody	Binds Angiopoietin-1 and -2	Phase 3 multiple tumor types	Amgen (Thousand Oaks, CA)
Motesanib	Small-molecule RTK inhibitor	Inhibits signaling of VEGFRs PDGFRs, KIT	Phase 3 multiple tumor types	Amgen
Cediranib (Recentin)	Small molecule RTK inhibitor	Inhibits signaling of VEGFRs PDGFRs, KIT	Phase 3 multiple tumor types	AstraZeneca
Cabozantinib	Small molecule RTK inhibitor	Inhibits signaling of VEGFRs, PDGFR, cMET, RET, KIT	Phase 3 multiple tumor types	Exelixis (South San Francisco, CA)
Tivozanib	Small molecule RTK inhibitor	Inhibits signaling of VEGFRs PDGFRs, KIT	Phase 3 metastatic RCC	Aveo (Cambridge, MA)
Regorafenib	Small molecule RTK inhibitor	Inhibits signaling of VEGFRs Raf, PDGFRs, KIT	Phase 3 relapsed CRC and other tumors	Bayer/Onyx
Ramucirumab	Human mAb	Blocks VEGFR-2 signaling	Phase 3 multiple tumor types	ImClone/Lilly (Indianapoilis, IN)
Cilengitide	Cyclic peptide	Blocks αv integrins	Phase 3 GBM	Merck KGaA (Darmstadt, Germany)
Volociximab	Chimeric mAb	Blocks α5β1 integrin	Phase 2 multiple tumor types	PDL/Biogen Idec (Cambridge, MA)
IMC-18F1	Human mAb	Blocks VEGFR-1 signaling	Phase 2 multiple tumor types	ImClone/Lilly
TB-403	Humanized mAb	Blocks PlGF binding to VEGFR-1	Phase 2 multiple tumor types	Thrombogenix/Roche
Anti-EGFL7	Humanized mAb	Blocks EGFL7, a protein implicated in vascular maturation	Phase 2 multiple tumor types	Genentech/Roche

TKI, tyrosine kinase inhibitor; CRC, colorectal cancer; NSCLC, non-small cell lung carcinoma; RCC, renal-cell carcinoma; GBM, glioblastoma multiforme; GIST, gastrointestinal stromal tumor; HPCC, hepatocellular carcinoma.

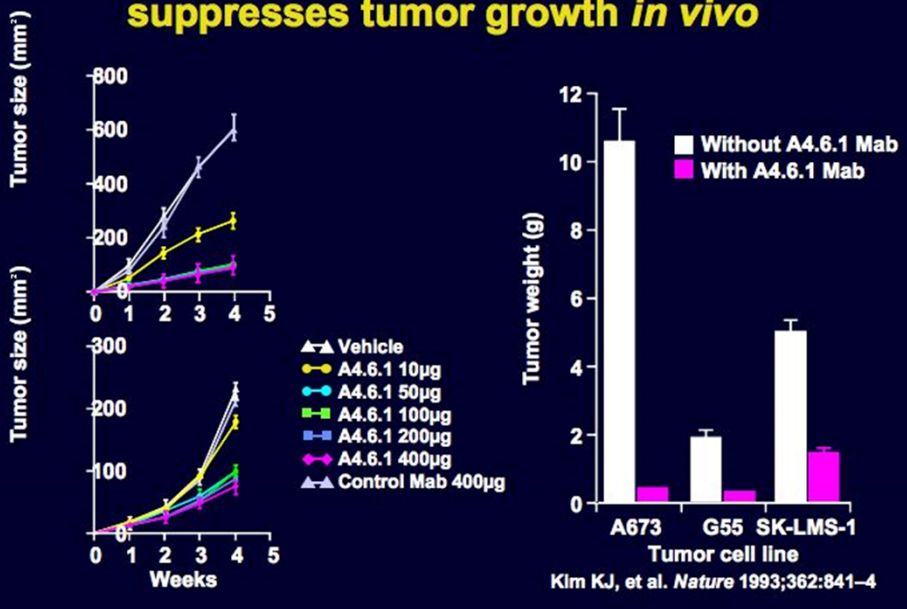
Singh,M & Ferrara,N. *Nature Biotechnol.*, 30:648-57,2012

Hypoxia, Oncogenes and Cytokines Induce VEGF Expression in Tumor Cells



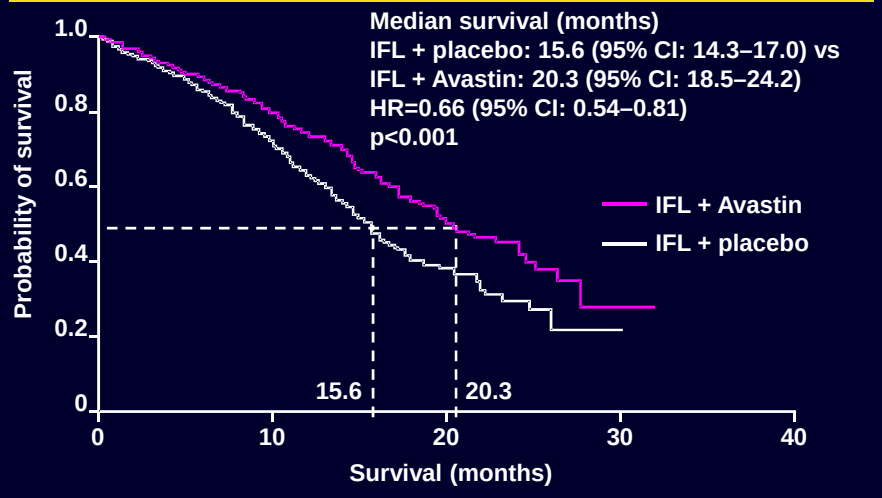
PDGF = platelet-derived growth factor; IGF-1 = insulin-like growth factor 1
IL-8 = insulin-like growth factor 8

Inhibition of VEGF-mediated angiogenesis suppresses tumor growth *in vivo*



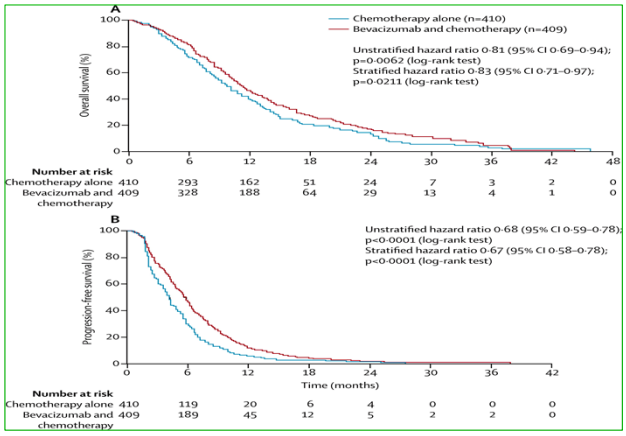
Kim KJ, et al. *Nature* 1993;362:841–4

Phase III trial AVF2107g: bevacizumab increases survival in previously untreated metastatic CRC



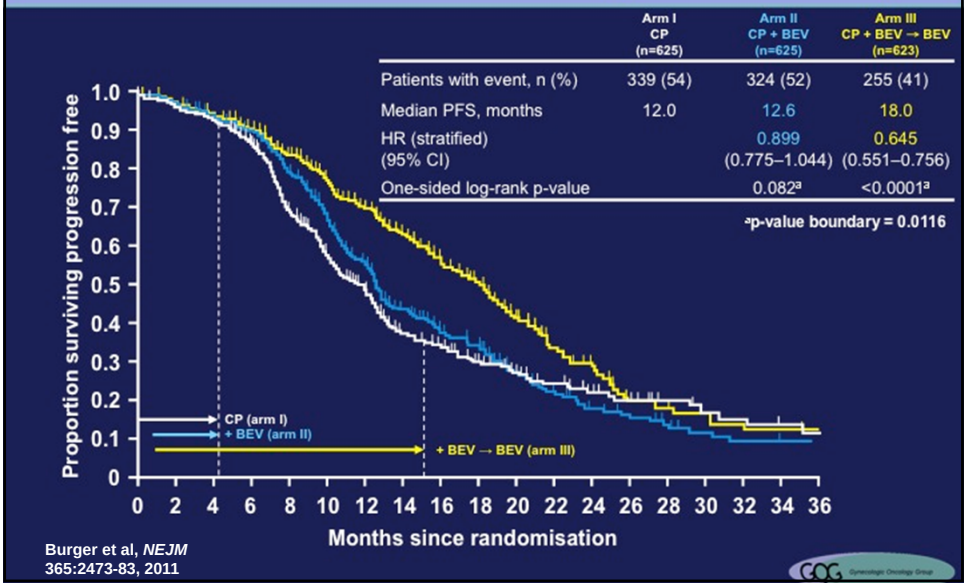
Hurwitz H, et al. *N Engl J Med* 2004;350:2335–42

VEGF inhibition with bevacizumab plus standard second-line chemotherapy beyond disease progression has clinical benefits in patients with metastatic colorectal cancer



Bennouna et al, *Lancet Oncol* 2013; 14: 29–37

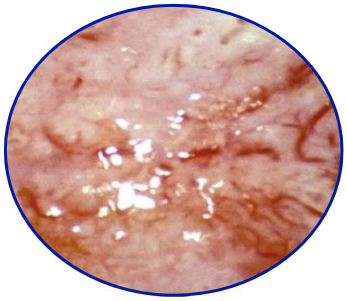
Progression-free survival in ovarian cancer patients is dependent on the duration of bevacizumb treatment (GOG-0218 trial)



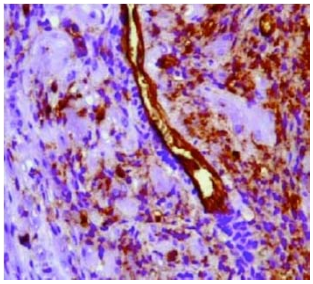
Burger et al, *NEJM* 365:2473-83, 2011

Angiogenesis In Cervical Cancer

Accumulating evidence supports the concept that angiogenesis plays a central role in cervical carcinogenesis and disease progression



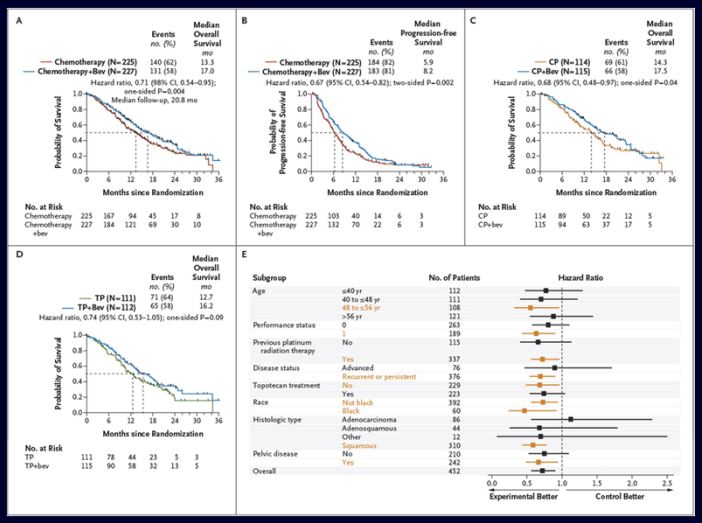
Atypical vessels on colposcopy



– Intratumoral microvessel density

Tewari KS, Monk BJ. Invasive Cervical Cancer. In: Clinical Gynecologic Oncology, 8th ed. DiSaia PJ, Creasman WT (eds). Mosby,

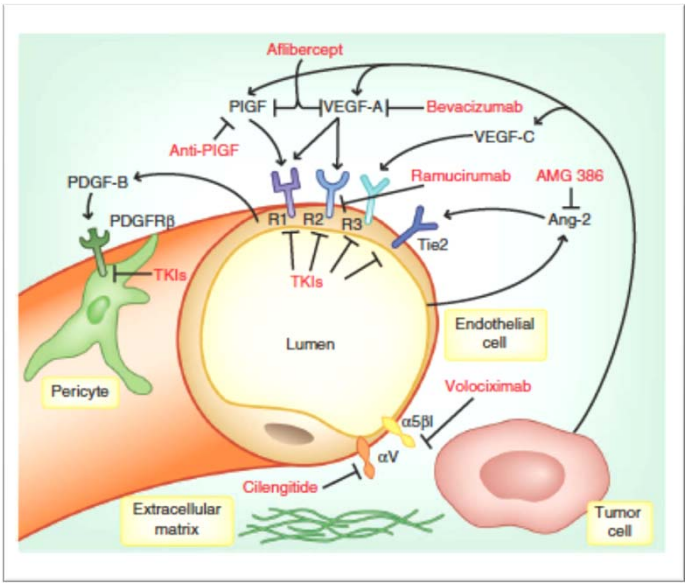
Improved Survival with Bevacizumab in Advanced Cervical Cancer



Tewari KS et al. N Engl J Med 2014;370:734-743.

The NEW ENGLAND JOURNAL of MEDICINE

Can we improve the efficacy of anti-VEGF agents by combinations with inhibitors of other angiogenic pathways?



Singh,M & Ferrara,N. *Nature Biotechnol.*, 30:648-57,2012

Neuro-Oncology

Neuro-Oncology 17(7), 1007–1015, 2015
doi:10.1093/neuonc/nov019
Advance Access date 9 February 2015

Phase 1 dose-escalation study of the antiplacental growth factor monoclonal antibody RO5323441 combined with bevacizumab in patients with recurrent glioblastoma

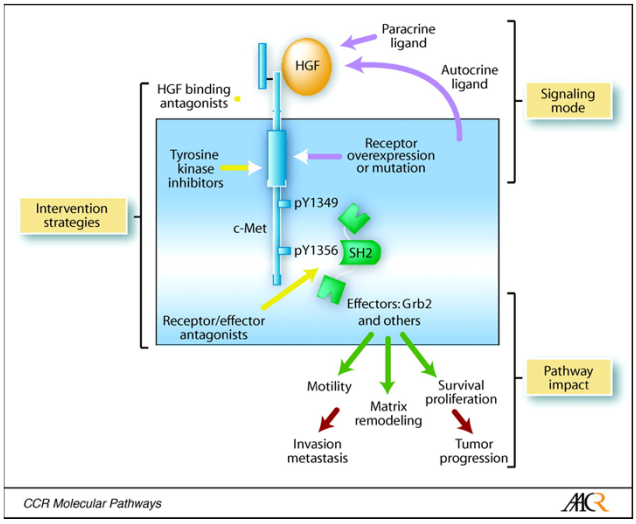
Ulrik Lassen, Olivier L. Chinot, Catherine McBain, Morten Mau-Sørensen, Vibeke Andrée Larsen, Maryline Barrie, Patrick Roth, Oliver Krieter, Ka Wang, Kai Habben, Jean Tessier, Angelika Lahr, and Michael Weller

Department of Oncology, Rigshospitalet, Copenhagen, Denmark (U.L., M.M.-S.); Department of Radiology, Rigshospitalet, Copenhagen, Denmark (V.A.L.); Aix-Marseille University A.P.-H.M., Department of Neuro-Oncology, University Hospital Timone, Marseille, France (O.L.C., M.B.); Department of Clinical Oncology, The Christie Hospital N.H.S Foundation Trust, Manchester, England (C.M.); Department of Neurology, University Hospital Zurich, Zurich, Switzerland (P.R., M.W.); Roche Diagnostics GmbH, Penzberg, Germany (O.K., K.H., A.L.); Hoffmann La Roche Pharmaceuticals, Nutley, NewJersey (K.W.); F. Hoffmann-La Roche Ltd, Basel, Switzerland (J.T.)

Corresponding Author: Ulrik Lassen, MD, PhD, Department of Oncology 5072, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark (ulrik.lassen@rh.regionh.dk).

Conclusion. The toxicity profile of RO5323441 plus bevacizumab was acceptable and manageable. The observed clinical activity of the combination does not appear to improve on that obtained with single-agent bevacizumab in patients with recurrent glioblastoma.

c-Met-mediated oncogenic signaling.



Benedetta Peruzzi, and Donald P. Bottaro Clin Cancer Res 2006;12:3657-3660

Clinical Cancer Research
AACR American Association for Cancer Research

Clinical trials with HGF/cMet inhibitors so far have been largely negative

Onartuzumab (Met-Mab) in combination with erlotinib failed to show any PFS or OS benefit relative to erlotinib plus placebo in NSCLC (phase III).

In phase III studies, an anti-HGF antibody (Amgen) had detrimental effects on survival of gastric cancer patients.

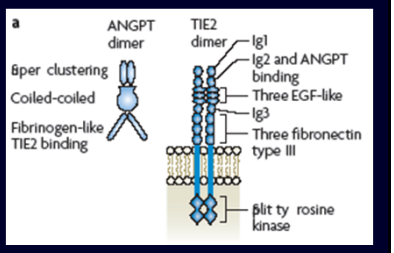
Various small molecule TKIs also did not show benefit in NSCLC.

Combination of onartuzumab with bevacizumab did not appear to provide benefit relative to bevacizumab monotherapy in GBM (Cloughesy et al, ASCO 2015).

Combination of onartuzumab and bevacizumab with paclitaxel did not improve PFS relative to bevacizumab plus paclitaxel in triple negative breast cancer (Dieras et al. Annals Oncol, 2015).

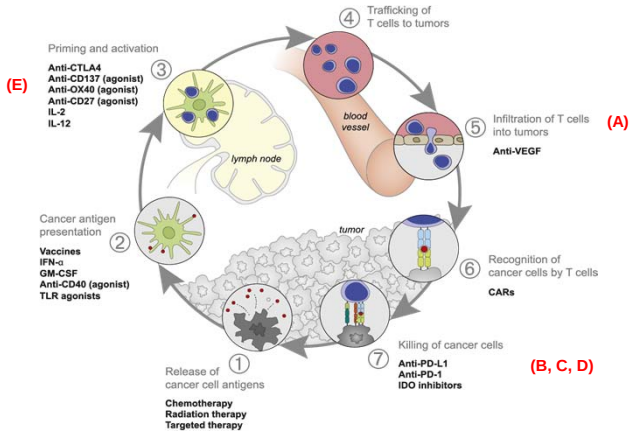
The Angiopoietin/TIE2 system in angiogenesis

- *TIE2*
  - Transmenbrane Tyr kinase receptor expressed by endothelial cells and perivascular macrophages
- *ANG1*
  - Vascular maturation factor
    - promotes the recruitment of pericytes and smooth muscle cells
    - survival factor for endothelial cells
- *ANG2*
  - Expressed and released at sites of vessel remodeling
  - Vascular destabilization factor
    - In the presence of other proangiogenic factors → ANGIOGENESIS



Huang et al., *Nat Rev Cancer* 2010

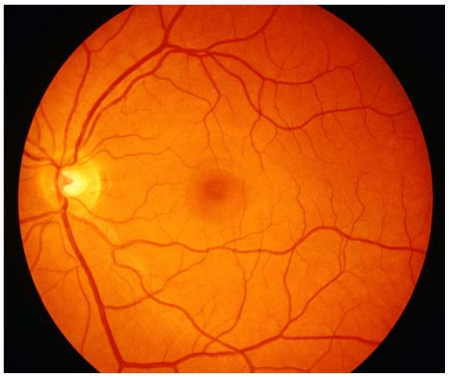
Anti-PDL-1 and anti-VEGF could cooperate to increase T-cell activation at multiple stages of the cancer immunity cycle.



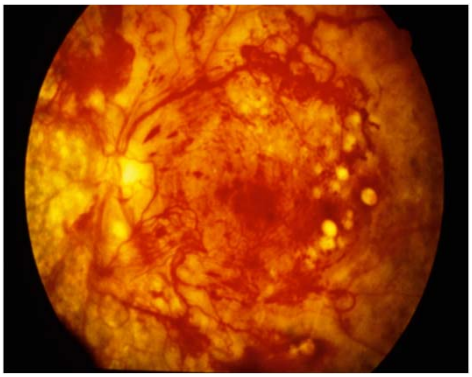
Anti-VEGF increases immune response: Potential synergy between MPDL3280A and bevacizumab

A. **Increases trafficking of T cells into tumors** (Can Res 2010: 70; 6171; Clin Cancer Res 2007 13:3951)
B. **Reduces frequency of myeloid-derived suppressor cells (MDSC)** (JI 2008: 181; 346)
C. **Reduces suppressive cytokines and tumor-infiltrating Tregs and MDSCs** (Plos One 2009: 4; e7669)
D. **Increases both CD8+ and CD4+ central memory T cells in combination with Ipilimumab** (Hodi, JCO suppl. 2010)
E. **Increases dendritic cell maturation and function** (Nature Medicine 1996 1096-113)

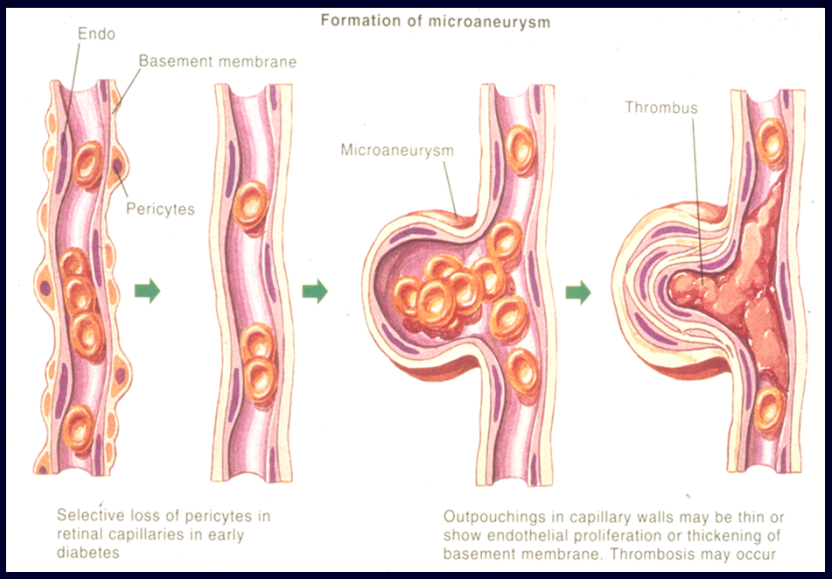
Normal Retina



Diabetic Retinopathy



Pericyte Loss and Microaneurysms Result in Abnormal Leakage/Bleeding in Retinal Vessels



N. Engl. J. Med., 331:1480-7, 1994

VASCULAR ENDOTHELIAL GROWTH FACTOR IN OCULAR FLUID OF PATIENTS WITH DIABETIC RETINOPATHY AND OTHER RETINAL DISORDERS

Lloyd Paul Aiello, M.D., Ph.D., Robert L. Avery, M.D., Paul G. Arrigg, M.D., Bruce A. Keyt, Ph.D., Henry D. Jampel, M.D., Sabera T. Shah, M.D., Louis R. Pasquale, M.D., Hagen Thieme, Mami A. Iwamoto, M.D., John E. Park, Ph.D., Hung V. Nguyen, M.S., Lloyd M. Aiello, M.D., Napoleone Ferrara, M.D., and George L. King, M.D.

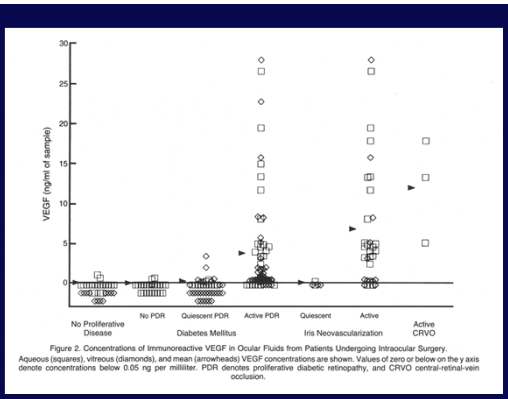
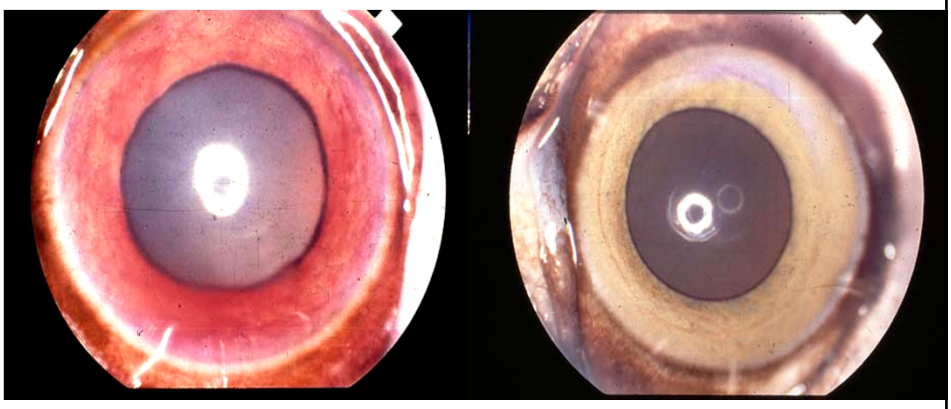


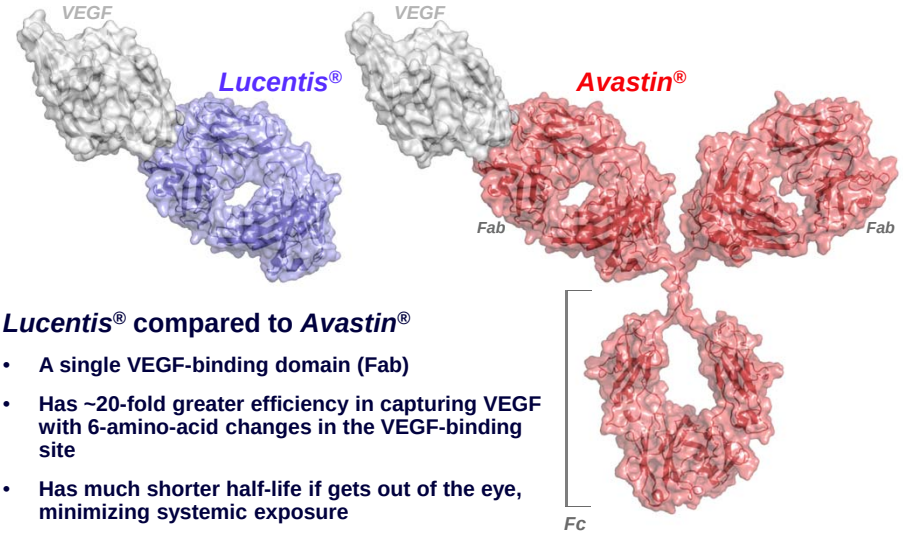
Figure 2. Concentrations of Immunoreactive VEGF in Ocular Fluids from Patients Undergoing Intraocular Surgery. Aqueous (squares), vitreous (diamonds), and mean (arrowheads) VEGF concentrations are shown. Values of zero or below on the y axis denote concentrations below 0.05 ng per milliliter. PDR denotes proliferative diabetic retinopathy, and CRVO central-retinal-vein occlusion.

Suppression of Iris Neovascularization by anti-VEGF mAb in a Primate Model

Control mAb **mAb A.4.6.1**



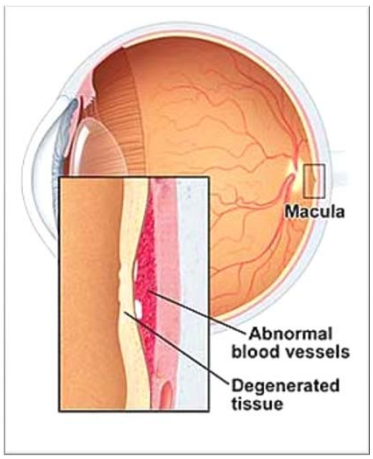
Adamis et al., Arch Ophthalmol 1996;114:66-71

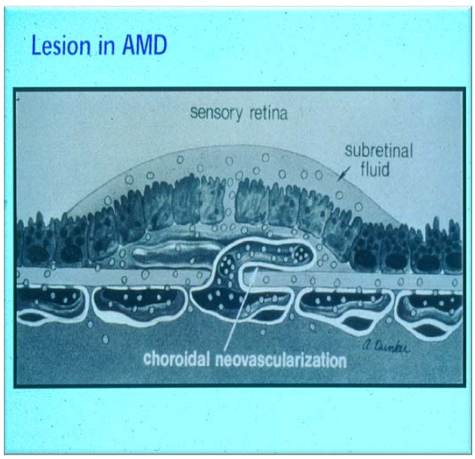


Lucentis®* compared to *Avastin®

- A single VEGF-binding domain (Fab)
- Has ~20-fold greater efficiency in capturing VEGF with 6-amino-acid changes in the VEGF-binding site
- Has much shorter half-life if gets out of the eye, minimizing systemic exposure
- Potentially less likely to initiate inflammation because of lack of Fc

Neovascular age-related macular degeneration



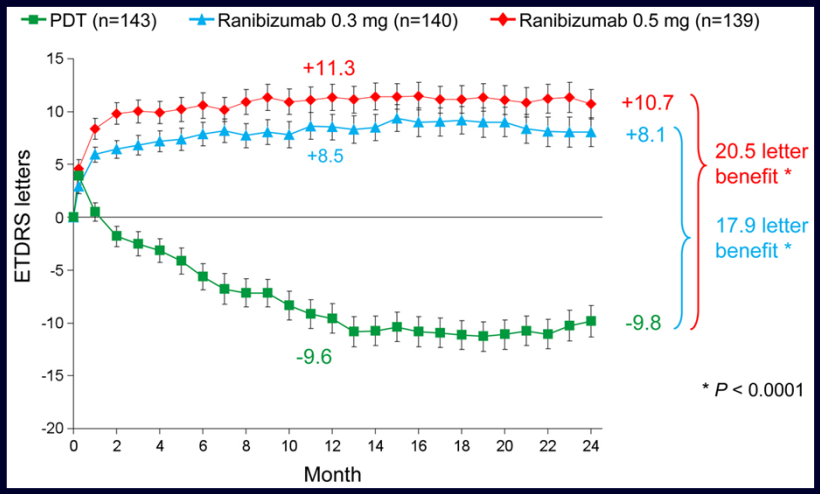


Age-related macular degeneration produces a loss of central visual acuity

normal vision

macular degeneration

Ranibizumab results in increased visual acuity in wet AMD patients



D.M. Brown et al, *Ophthalmology*, 116:57-65, 2009

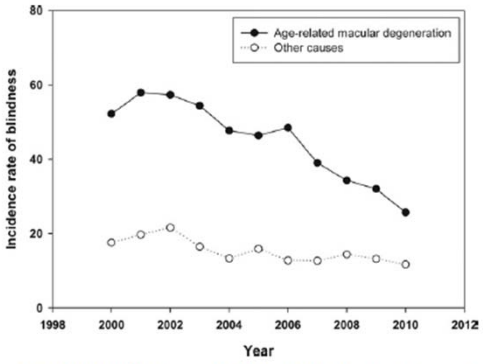
Impact of Availability of Anti–VEGF Therapy on Visual Impairment and Blindness Due to Neovascular AMD and DME

- Ranibizumab as given in MARINA and ANCHOR would reduce the number of cases of legal blindness by 72% (95% CI: 70% to 74%)
- Only 4,484 (3.0%) of 151,340 incident cases of CNV in 2008 would go on to legal blindness in U.S. by 2010
- Every 4-week ranibizumab substantially reduced legal blindness by 78% and visual impairment by 33% within 2 years after diagnosis and treatment of non-Hispanic white and Hispanic patients with DME involving the center of the macula with vision

Bressler et al., *Arch Ophthalmol.* 2011;129:709-17; **Campbell et al.,** *Arch Ophthalmol.* 2012;130:794-95.

Incidence of Legal Blindness From Age-Related Macular Degeneration in Denmark: Year 2000 to 2010

SARA BRANDI BLOCH, MICHAEL LARSEN, AND INGER CHRISTINE MUNCH



• CONCLUSION: From 2000 to 2010 the incidence of legal blindness from AMD fell to half the baseline incidence. The bulk of the reduction occurred after the introduction of intravitreally injected inhibitors of vascular endothelial growth factor in 2006. (Am J Ophthalmol 2012;153:209–213. © 2012 by Elsevier Inc.

Holz FG, *et al. Br J Ophthalmol* 2015;**99**:220–226.

Clinical science

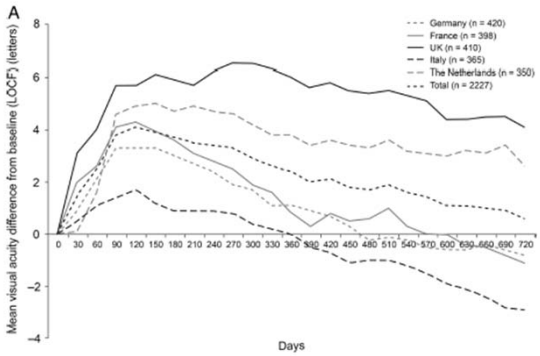
OPEN ACCESS

Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration

Frank G Holz,[1] Ramin Tadayoni,[2] Stephen Beatty,[3] Alan Berger,[4] Matteo G Cereda,[5] Rafael Cortez,[6] Carel B Hoyng,[7] Philip Hykin,[8] Giovanni Staurenghi,[5] Stephanie Heldner,[9] Timon Bogumil,[10] Theresa Heah,[10] Sobha Sivaprasad[8,11]

Clinical science

Figure 2 Mean change in visual acuity score from baseline over time for all patients by country: Germany, France, UK, Italy and the Netherlands (A) and Canada, Ireland and Venezuela (B). Data based on effectiveness analysis set using a last observation carried forward (LOCF) approach.



- **Impact of VEGF Inhibitors on Disease**
- **Benefit in several tumor types. VEGF inhibitors now represent standard of therapy for multiple malignancies.**
- **Dramatic benefits in intraocular neovascular diseases such as wet AMD following treatment with ranibizumab, bevacizumab or aflibercept**
- **Present Challenges**
- **Identification of predictive biomarkers**
- **Establishing optimal treatment duration/combinations**
- **Elucidating mechanisms of inherent refractoriness/resistance**

Acknowledgments

- Xiumin Wu
- Alicia Chung
- Farbod Shojaei
- Cuiling Zhong
- Marcin Kowanetz
- Xueping Qu
- Lanlan Yu
- Mallika Singh
- Carlos Bais
- Tony Adamis
- Len Presta
- Leisa Johnson
- Yongping Crawford
- Germaine Fuh
- Nick Van Bruggen
- Rick Carano
- Franklin Peale
- Max Tejada

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