Angiogenesis Inhibitors in Primary and Secondary Brain Tumors

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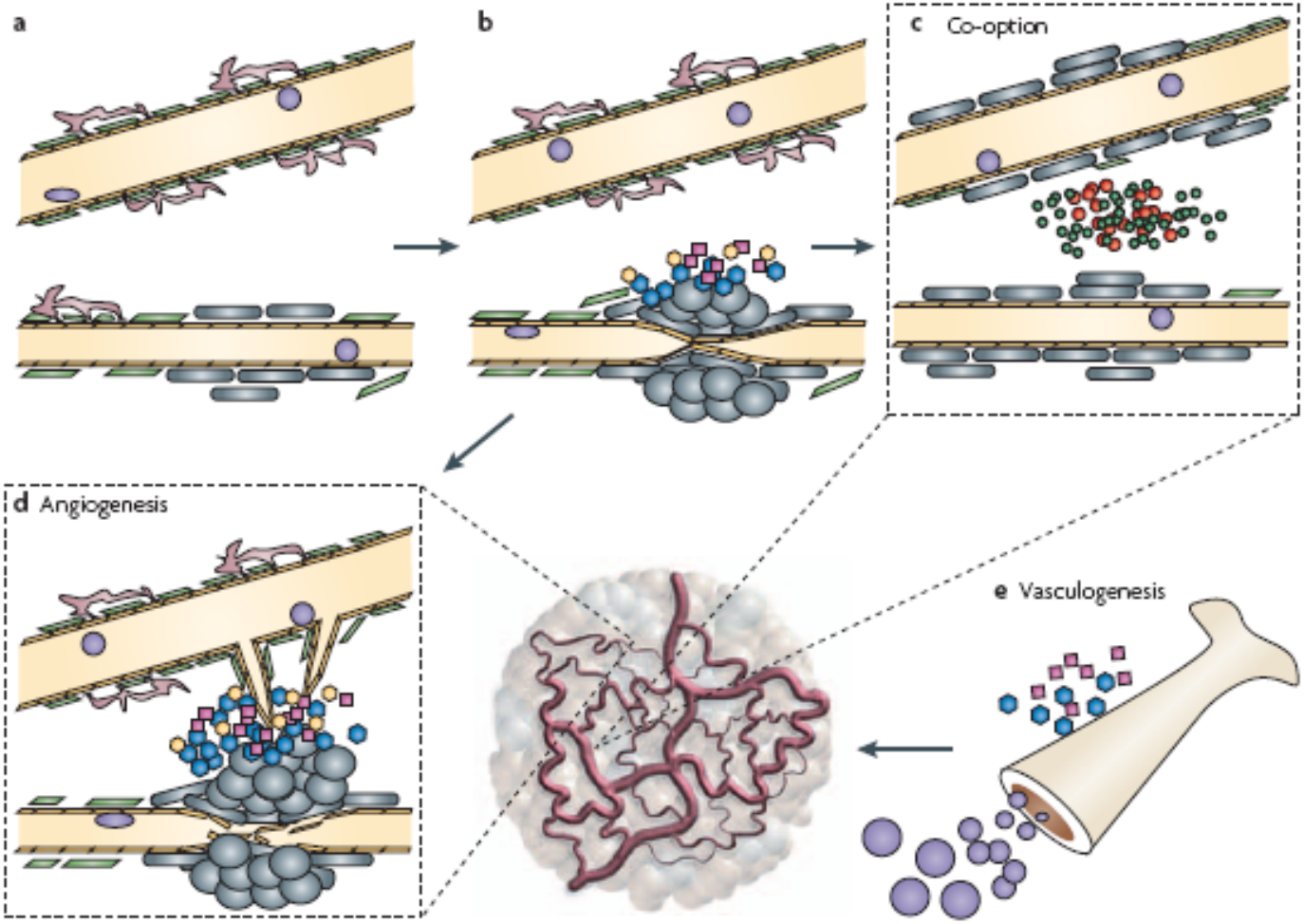
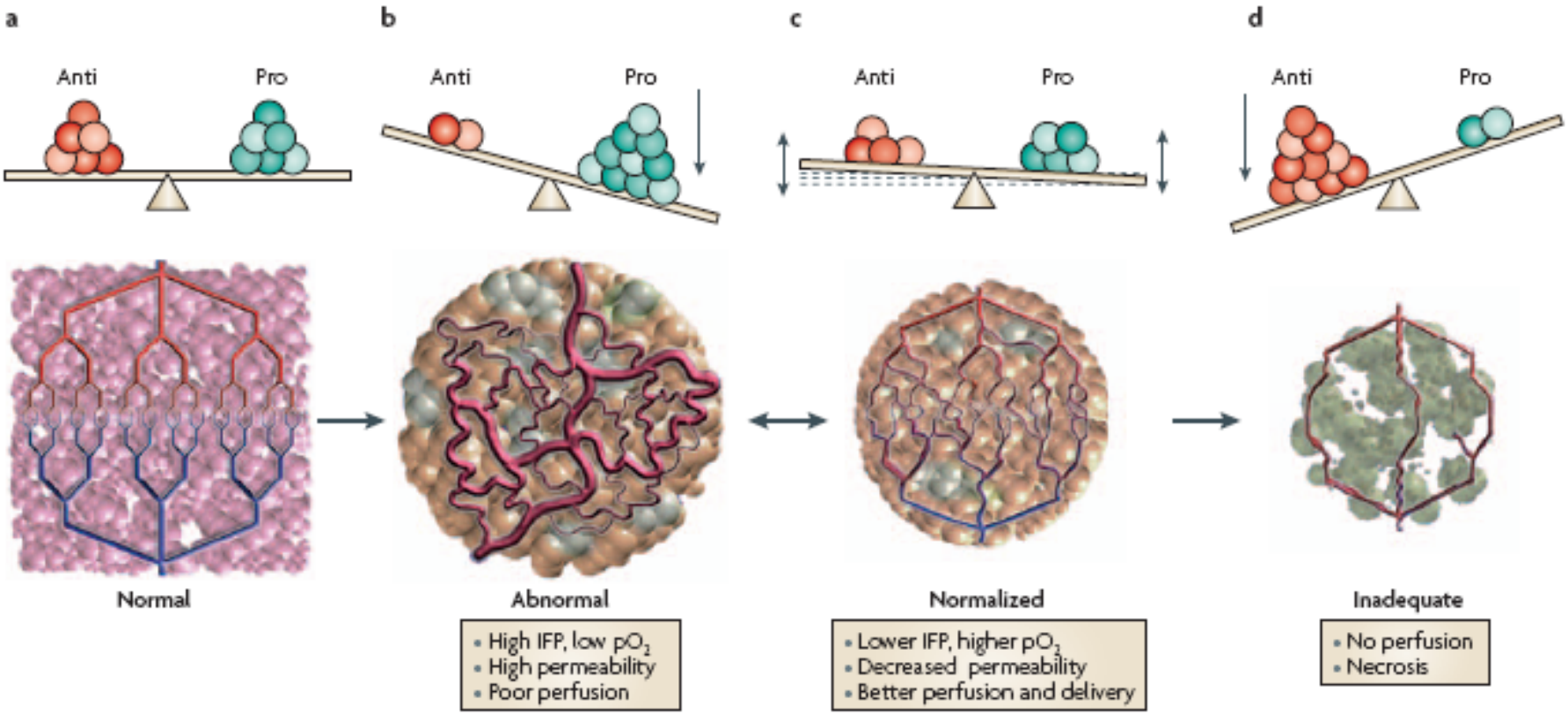
Mechanisms of tumor-related angiogenesis



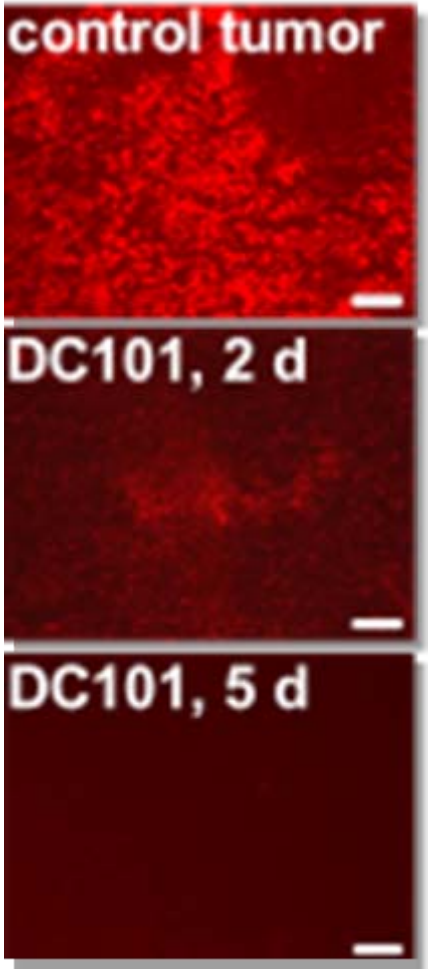
Jain R, et al. *Nat Rev Neurosci* 2007

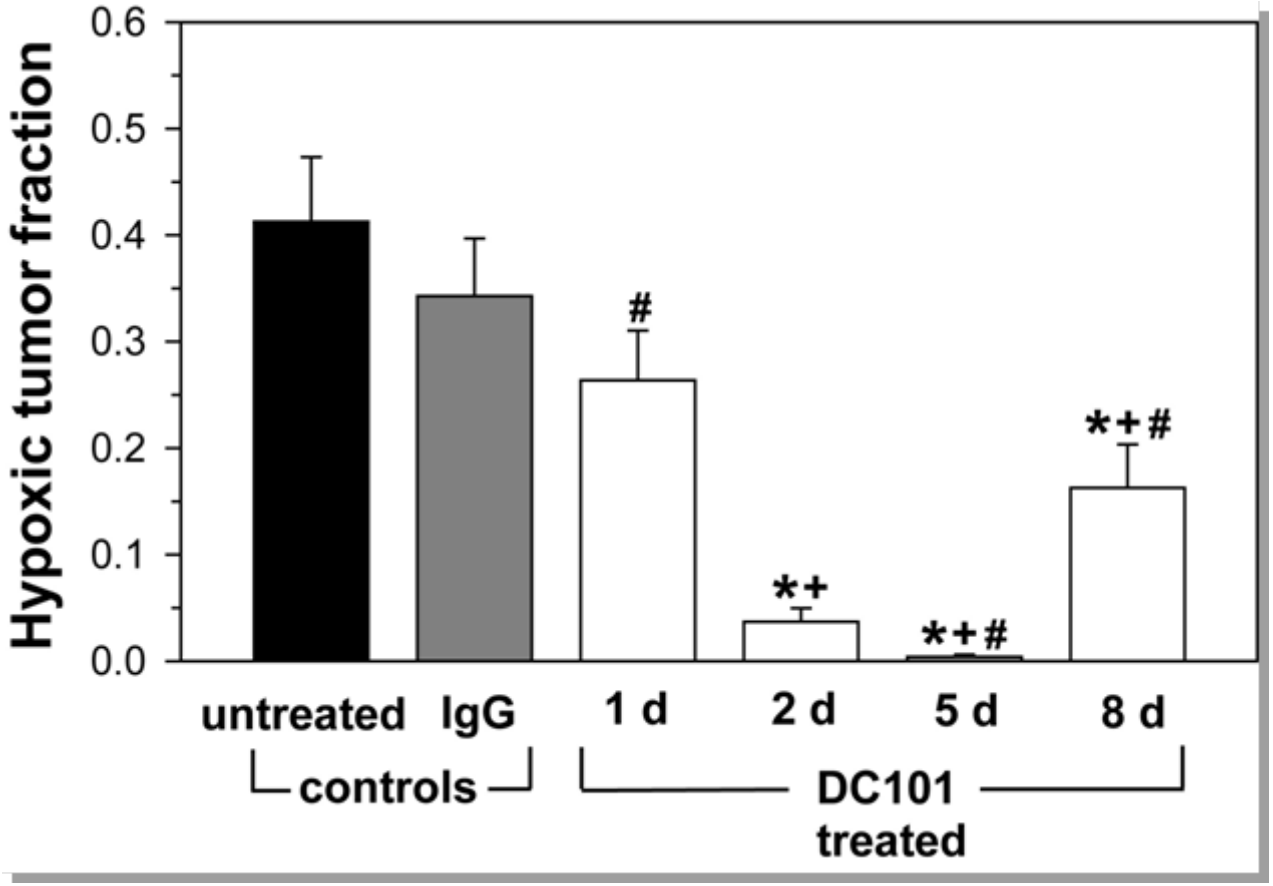
Normalization Hypothesis



Jain, *Nat Med* 2001

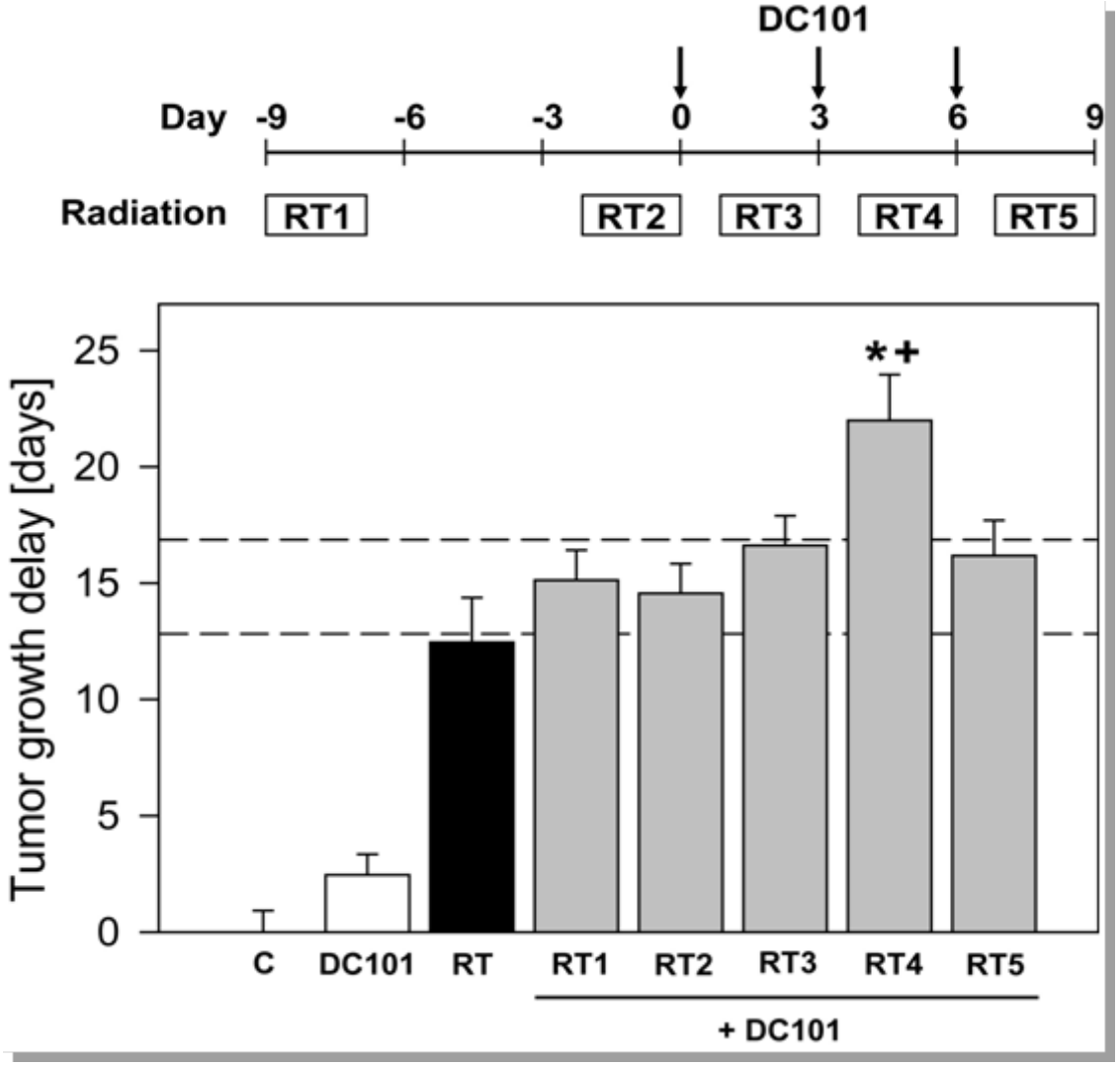
DC101 Decreases Tumor Hypoxia During the Vascular Normalization Time Window





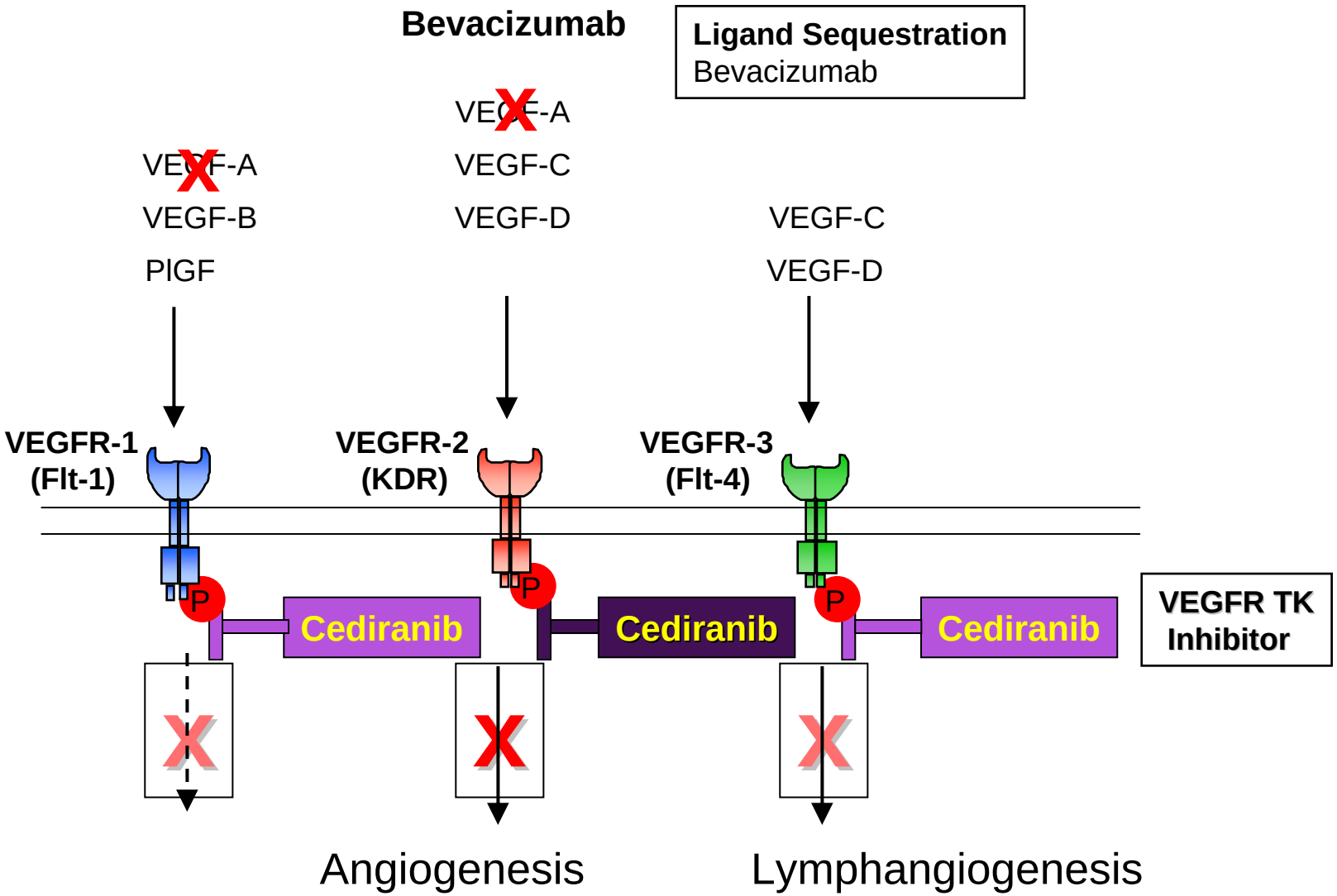
Winkler, Kozin et al., *Cancer Cell* 2004

Radiation Acts Synergistically with VEGFR2 Blockade During the Normalization Time Window

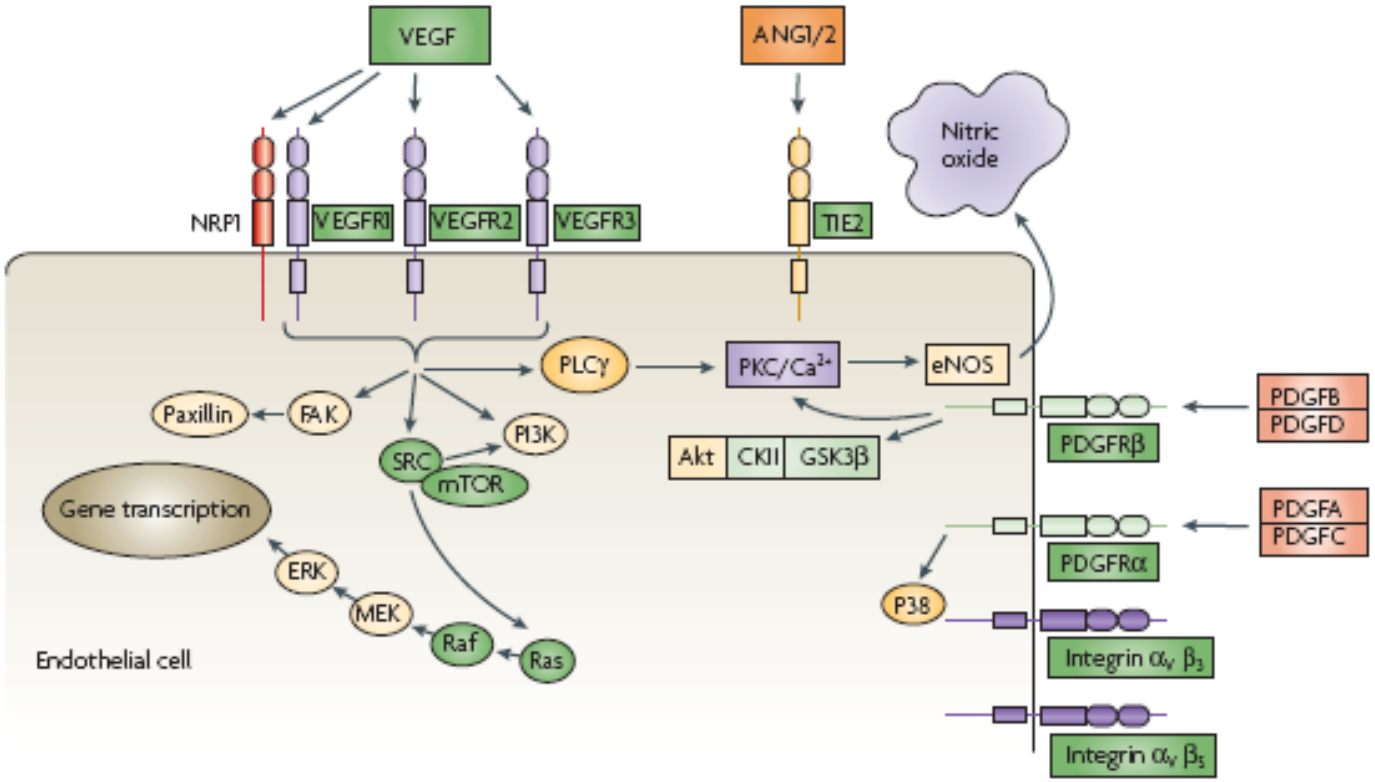


Winkler, Kozin et al., *Cancer Cell* 2004

MOA of Bevacizumab and Cediranib



Molecules targeted by angiogenesis inhibitors currently in clinical trials

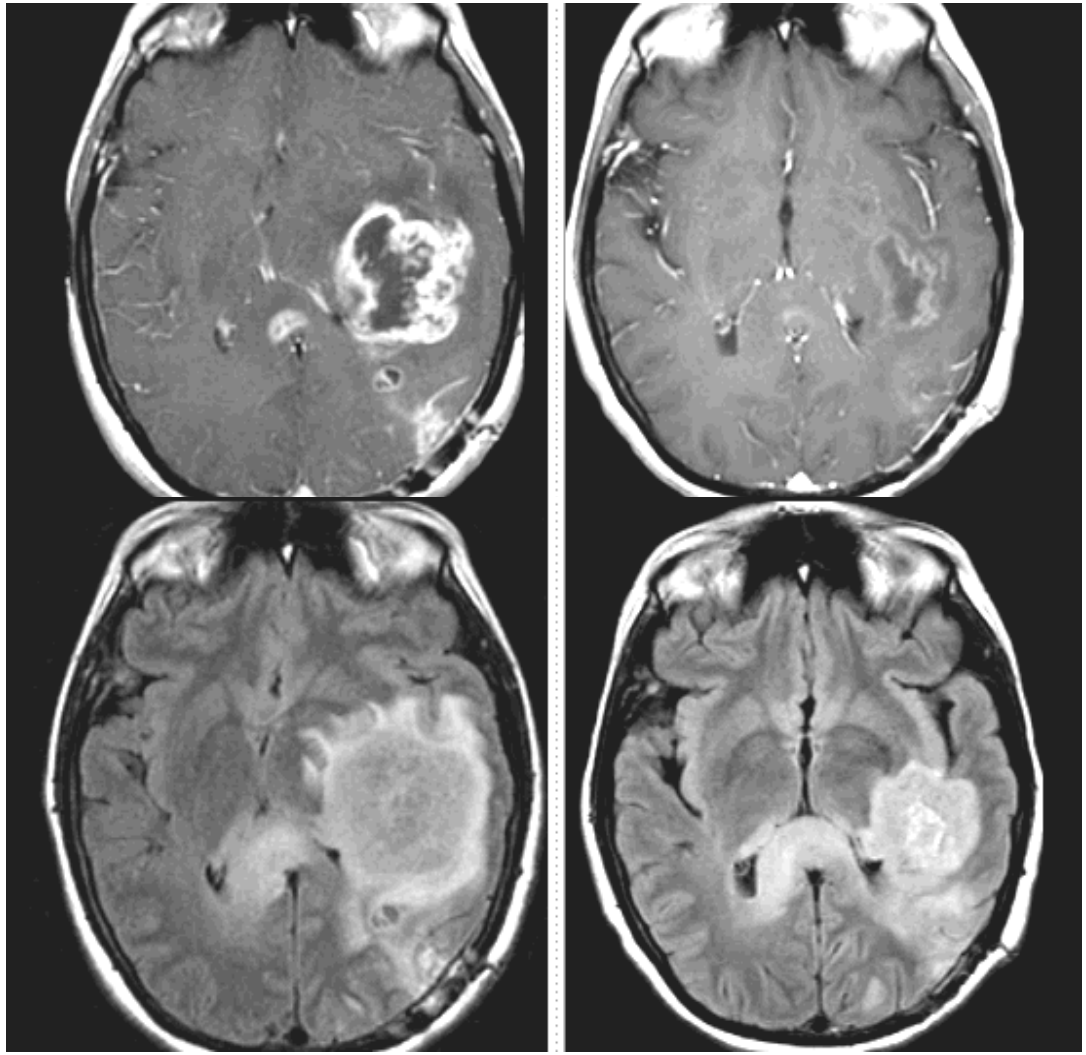


Jain R, et al. *Nat Rev Neurosci* 2007

Bevacizumab Trials in GBM

Study	Regimen	Radiographic Responses	APF6
Vredenburgh, et al (N = 35)	Bev 10mg/kg Q2W or 15mg/kg Q3W + CPT-11 (125, 340*, 350* mg/m2)	57%	46%
Chen, et al (N = 21)	Bev 10mg/kg Q2W + CPT-11 (125, 350* mg/m2)	67%	-
Cloughesy, et al (N = 82)	Bev 10mg/kg Q2W + CPT-11 (125, 340* mg/m2)	37.8%	50.3%
Ali, et al (N = 13)	Bev 10-15mg/kg Q2W + CPT-11 (125mg/m2)	77%	-
Cloughesy, et al (N = 85)	Bev 10mg/kg Q2W	28.2%	42.6%
Kriesl, et al (N = 48)	Bev 10mg/kg Q2W	35%	29%

Response to Bevacizumab in GBM



Baseline **4 weeks later**

Toxicity in BEV/CPT11 Randomized Phase II GBM Trial

Adverse Event	Bev (n=84)	Bev + CPT-11 (n=79)
Hemorrhage	0	2 (2.5)
Intracerebral hemorrhage	0	1 (1.3)
GI perforation	0	1 (1.3)
ATE	1 (1.2)	2 (2.5)
VTE	3 (3.6)	7 (8.9)
RPLS	0	1 (1.3)
Proteinuria	0	1 (1.3)
Wound healing	2 (2.4)	1 (1.3)
CHF	0	0
Infection	8 (9.5)	11 (13.9)

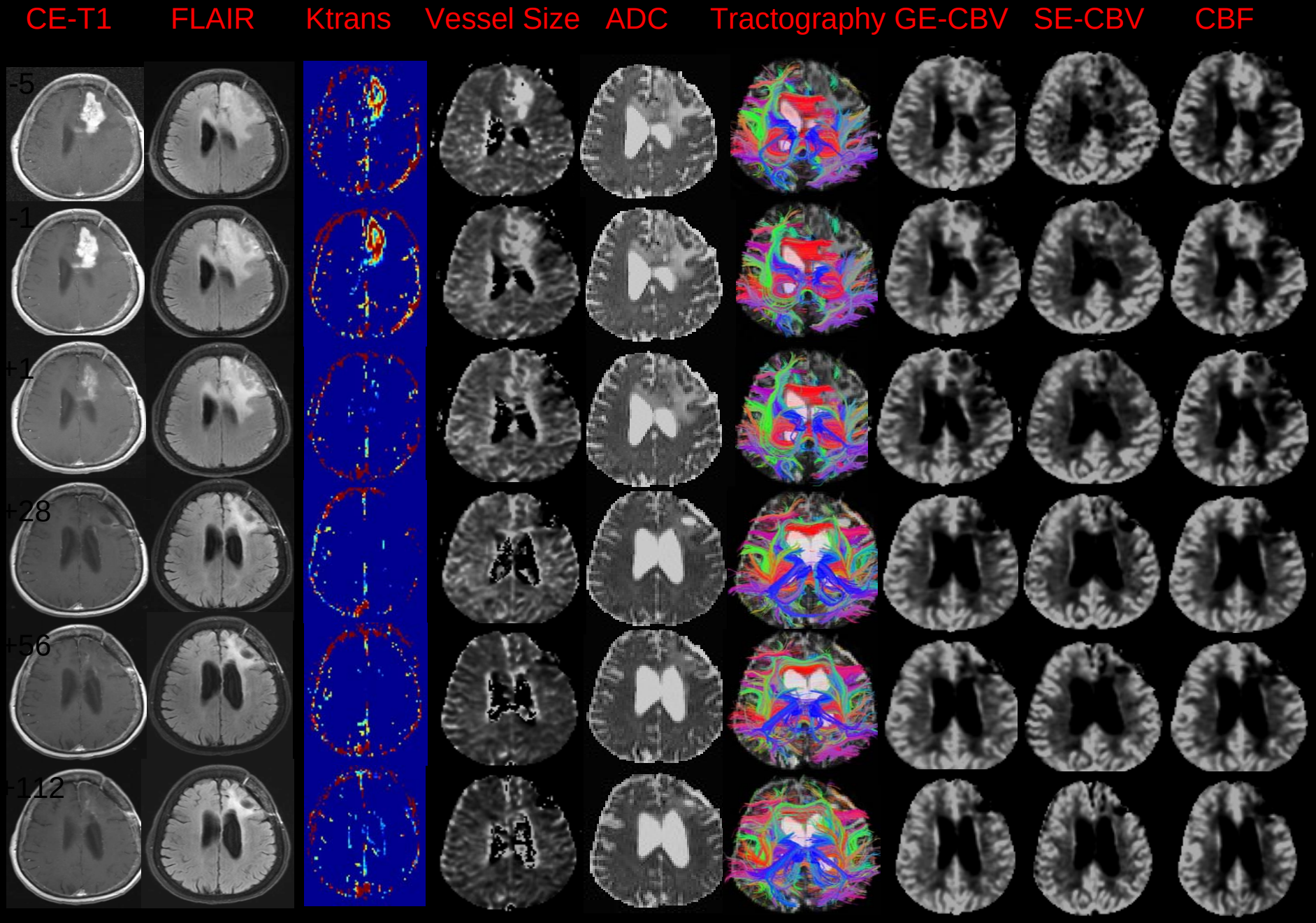
Cloughesy et al. ASCO 2008.

Cancer Cell
Article

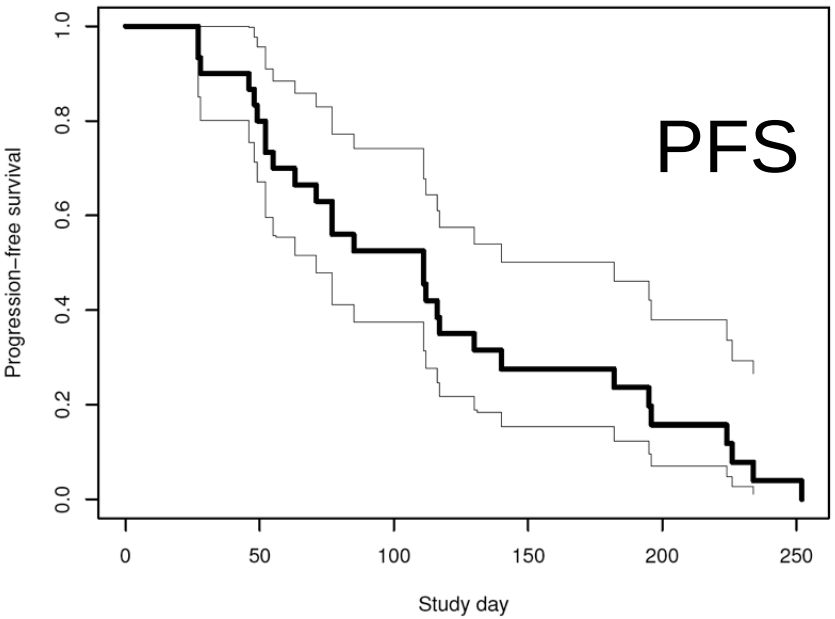
AZD2171, a Pan-VEGF Receptor Tyrosine Kinase Inhibitor, Normalizes Tumor Vasculature and Alleviates Edema in Glioblastoma Patients

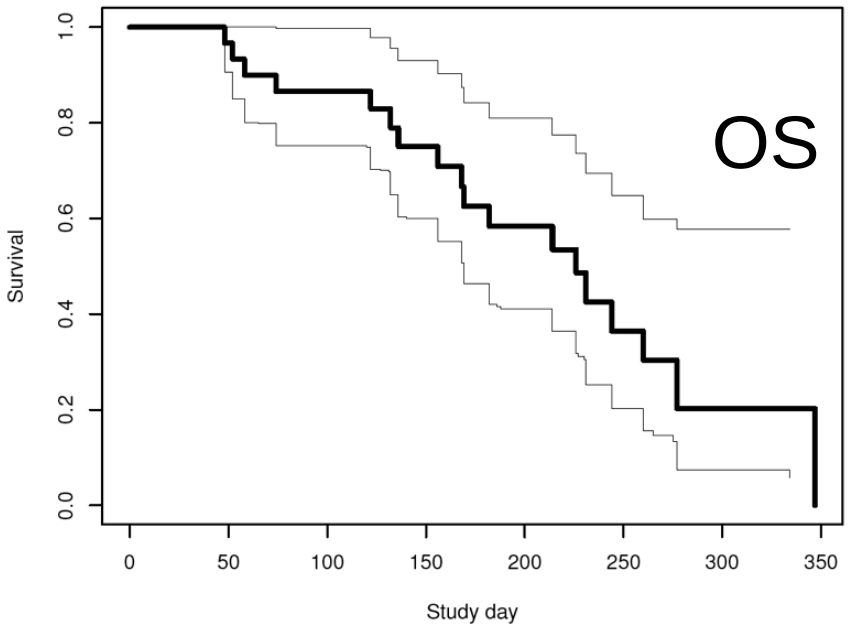
Tracy T. Batchelor,[1,2,10,*] A. Gregory Sorensen,[3,6,10] Emmanuelle di Tomaso,[2,11] Wei-Ting Zhang,[3,6,11] Dan G. Duda,[2,11] Kenneth S. Cohen,[4] Kevin R. Kozak,[2] Daniel P. Cahill,[5] Poe-Jou Chen,[3,6,7] Mingwang Zhu,[3,6] Marek Ancukiewicz,[2] Maciej M. Mrugala,[1] Scott Plotkin,[1] Jan Drappatz,[8] David N. Louis,[5] Percy Ivy,[9] David T. Scadden,[4] Thomas Benner,[3] Jay S. Loeffler,[2] Patrick Y. Wen,[8] and Rakesh K. Jain[2,*]

- **NCI-Funded, Phase II Study (1R21CA117079-01)**
  - Massachusetts General Hospital Cancer Center
  - Dana-Farber Cancer Institute
- **Endpoints**
  - APF6 (primary)
  - Radiographic Response (MRI on days -1, -5 ,1, then q28 days)
  - Overall Survival
  - Toxicity
  - Correlative biomarker and imaging studies
- **Accrual**
  - N = 31 recurrent glioblastoma patients (01/06-10/06)
  - 30/31 patients have progressed as of February 05, 2009
  - One patient remains alive with progression at 1159 days


CE-T1
FLAIR
Ktrans
Vessel Size
ADC
Tractography
GE-CBV
SE-CBV
CBF
-5
-1
+1
+28
+56
+112

Clinical Outcomes



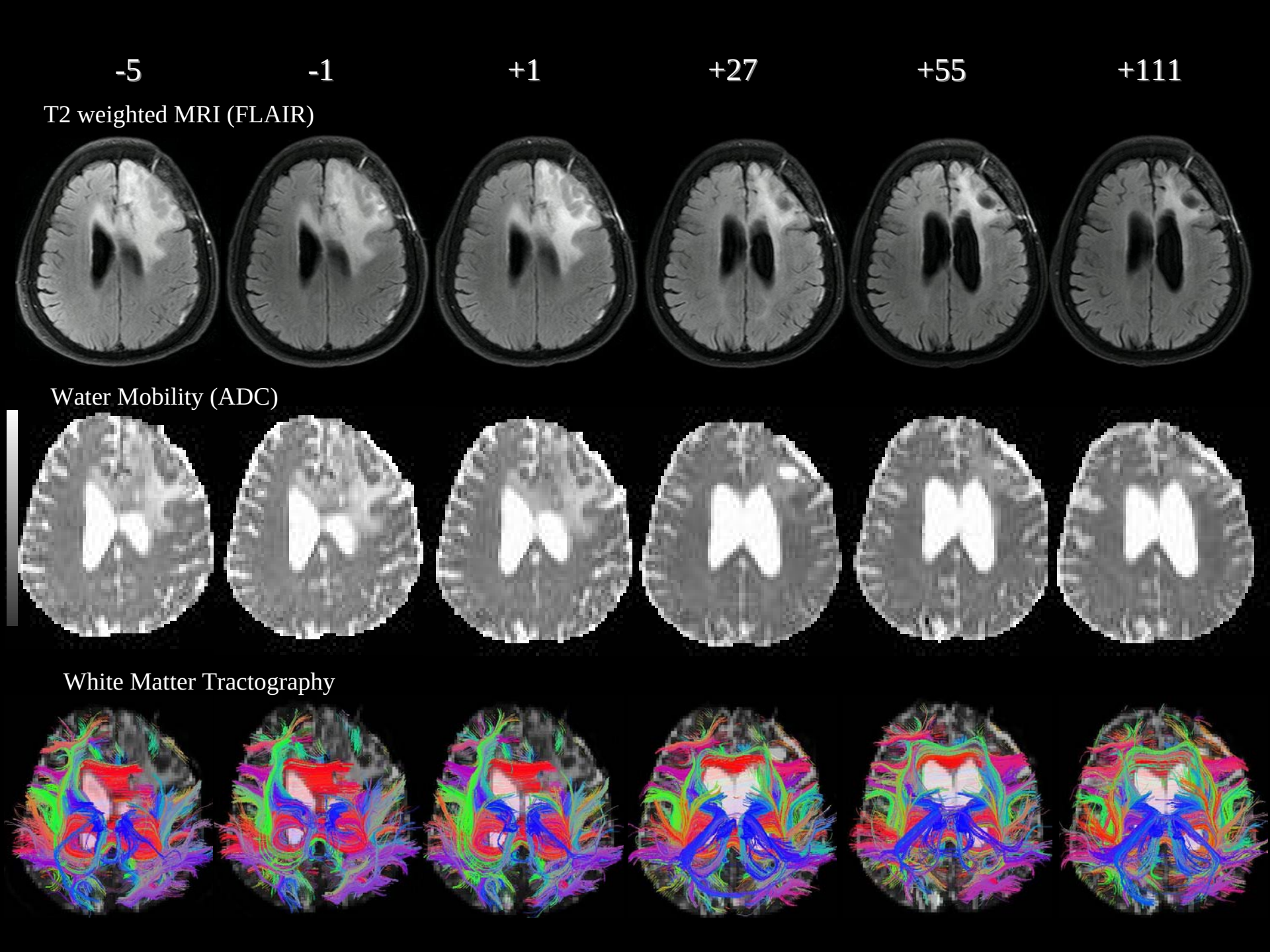


	Radiographic Responses (N = 16)	**APF6** [95% CI] (N = 30)	**PFS** [95% CI] (N = 30)	**OS** [95% CI] (N = 30)
Cediranib *Cancer Cell 2007*	**PR: 17/30 (56%)**	**25.8% [14.7%, 46.9%]**	**117 days [82, 145]**	**227 days [177, 293]**
Wong, et al *J Clin Oncol* 1999	N/A	15%	63 days	175 days
Ballman, et al *Neuro-oncol* 2007	N/A	9%	54 days	150 days

Phase II Study of Cediranib in Recurrent Glioblastoma

- **Steroid-Sparing Effects of Cediranib**
  - Kofman introduced the use of corticosteroids to treat brain tumor associated edema in 1957
  - Most patients with recurrent glioblastoma require steroid therapy for cerebral edema
  - 6/15 patients who were not taking steroids at the start of cediranib did NOT require steroids during treatment
  - 16 patients entered the trial on some dose of steroids, *15/16 had their dose reduced* over time and *5/16 had the steroids discontinued*
  - All patients who developed PD on cediranib required administration of steroids after discontinuation of cediranib

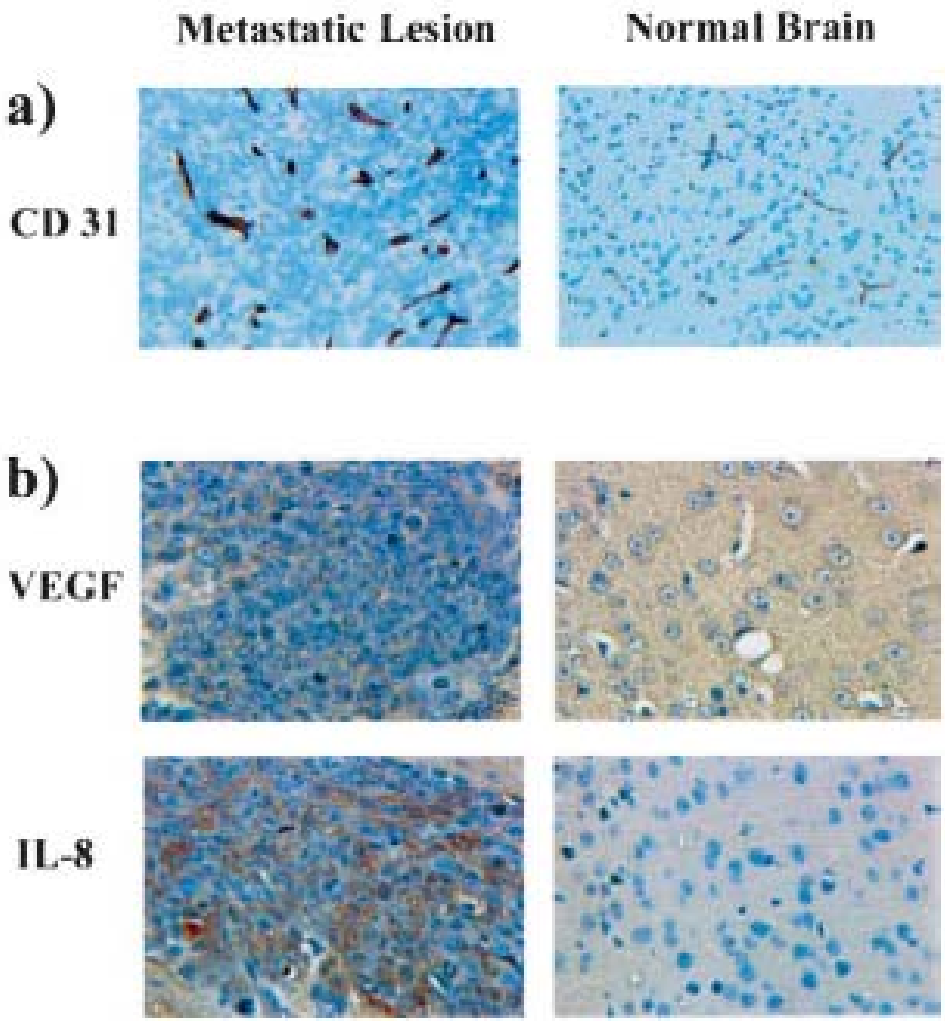
MRI and clinical data support an anti-edema effect of cediranib


-5
-1
+1
+27
+55
+111
T2 weighted MRI (FLAIR)
Water Mobility (ADC)
White Matter Tractography

Selected VEGF TKI Trials in GBM

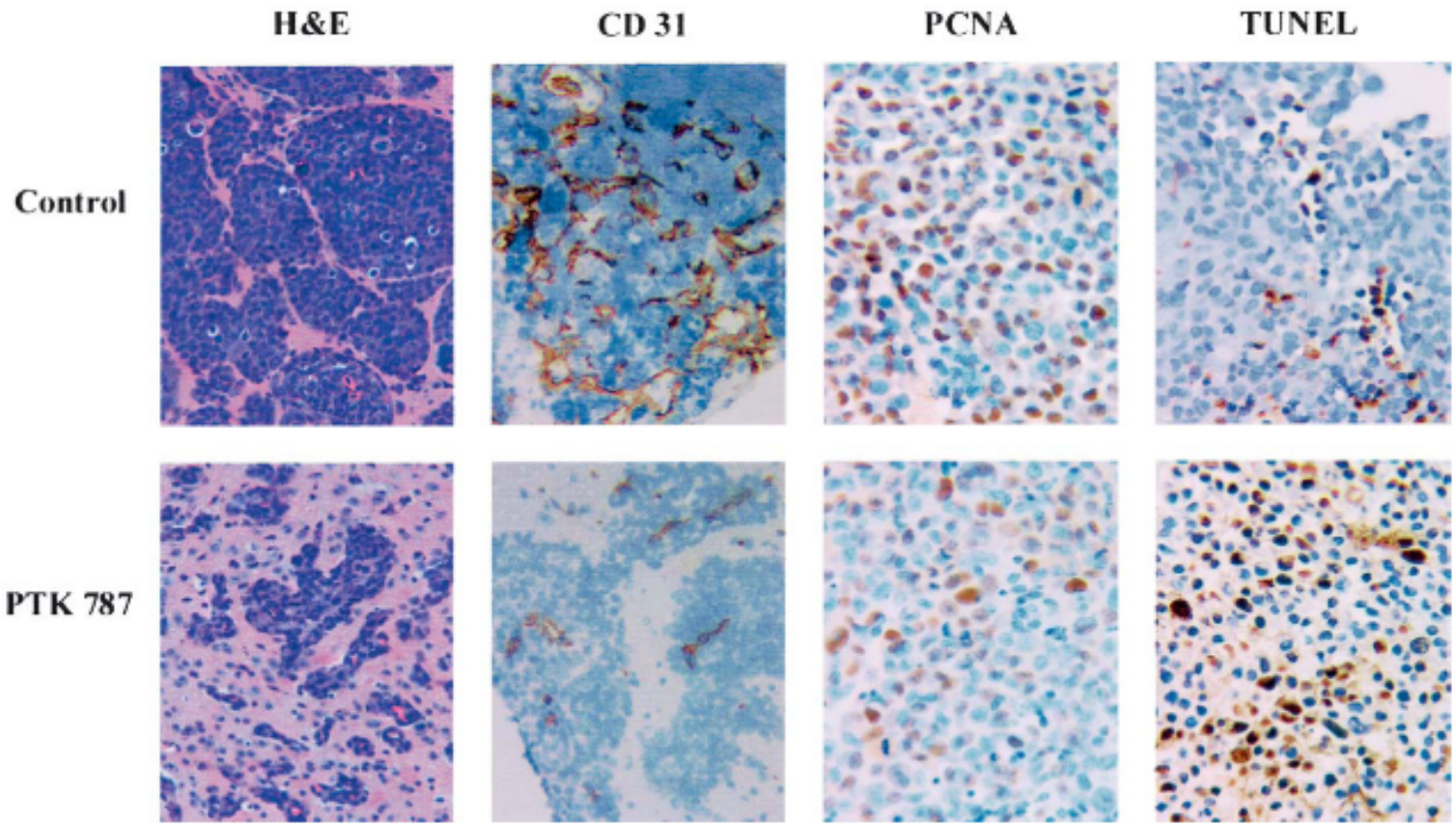
Agent(s)	Phase	Diagnosis	Sponsor	Primary Endpoint	Sites
Cediranib, lomustine, or both	III	Recurrent GBM	AZ	PFS	Multiple
Cediranib, TMZ, and RT	I/II	New GBM	NCI	MTD/PFS	MGH, DFCI
Sorafenib and erlotinib, tipifarnib, or temsirolimus	I/II	Recurrent GBM	NCI	MTD/PFS6	NABTC
Sorafenib and TMZ	II	Recurrent GBM	Bayer, S-P	PFS6	Duke
Sorafenib, TMZ, and RT	I	CNS tumor	Bayer	MTD	Thomas Jefferson University
Sunitinib	II	Recurrent MG	NCI	PFS6	Multiple
Sunitinib and irinotecan	I	Recurrent MG	Pfizer	MTD	Duke
Vandetanib	I/II	Recurrent glioma	NCI	MTD/PFS	NCI
Vandetanib, imatinib, and hydroxyurea	I	Recurrent MG	Novartis, AZ	MTD	Duke
Vandetanib, TMZ, and RT	I/II	New GBM	AZ	MTD/OS	Multiple
XL184	II	Recurrent GBM	Exelixis	PFS6	DFCI, UCSF, MDACC

MVD in BM of MDA-231 GFP in mouse brain



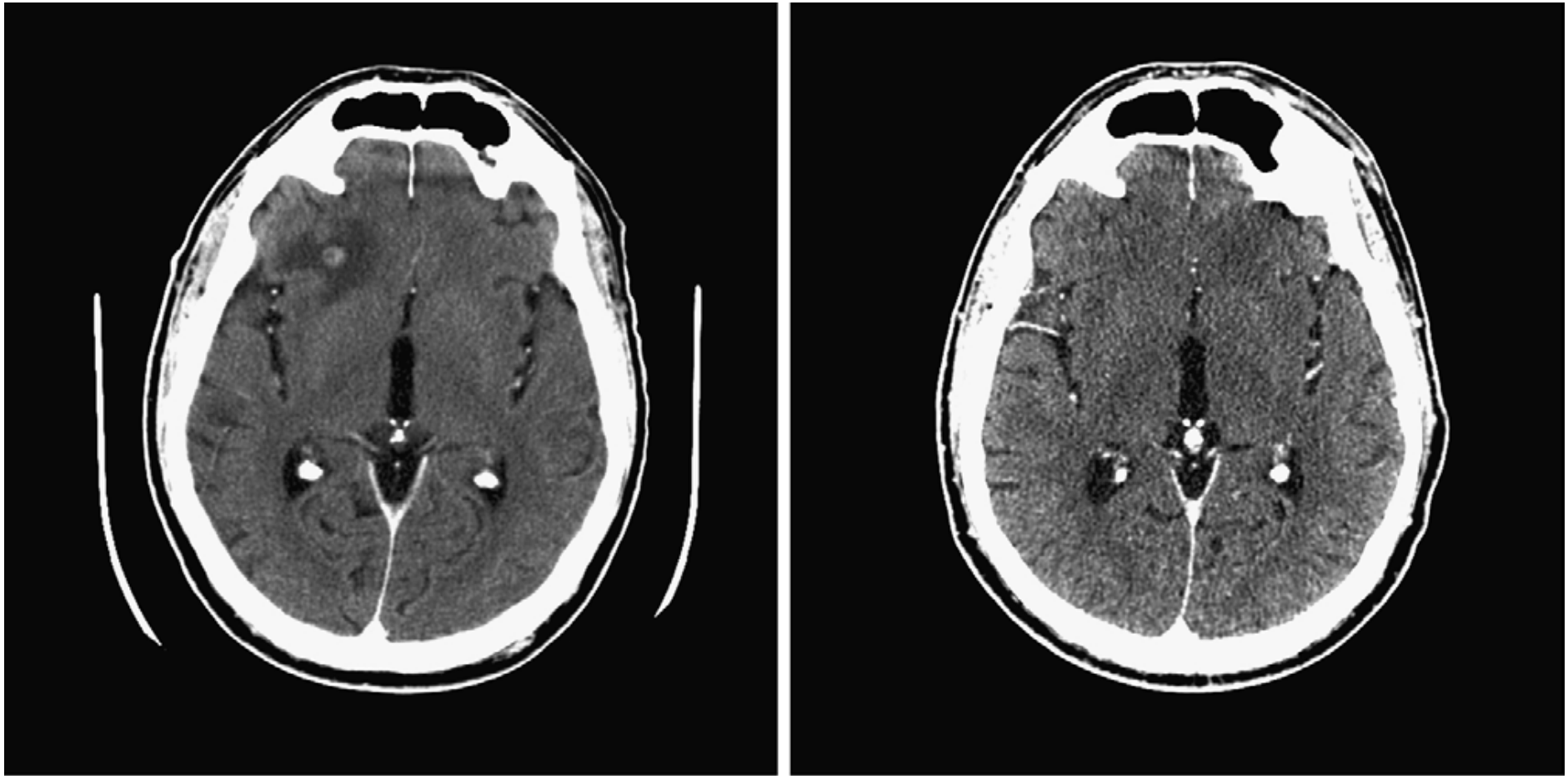
Kim LS et al. Clin Experimental Metastasis 2004

Breast cancer BM in nude mice treated with PTK787



Kim LS et al. Clin Experimental Metastasis 2004

Complete CNS response with Sunitinib for RCC



Medioni J. Annals of Oncol 2007

CNS Bleeding with anti-VEGF Therapy in Cancer

Table 1. Phase I and II studies of anti-VEGF agents that excluded brain metastases

Drug	Patient Number	Grade 3 Thrombocytopenia	Rate of CNS Bleeding	≥Grade 3 Bleed Outside CNS
Bevacizumab[29–38]	669	13 (2%)	1 (0.2%)	30 (5%)
Sorafenib[39–47]	499	15 (3%)	1 (0.2%)	9 (2%)
Semaxanib[48–54]	99	8 (8%)	0	4 (4%)
Sunitinib[55–57]	197	12 (6%)	0	0
Vatalanib[58, 59]	70	0	0	0
Axitinib[60]	36	0	0	1 (3%)
Vandenitib[61–63]	141	1 (0.7%)	0	0
Total	1,711	49 (3%)	2 (<1%)	44 (3%)

Table 2. Phase I and II studies of anti-VEGF agents that included brain metastases

Drug	Patient Number	Grade 3 Thrombocytopenia	Rate of CNS Bleeding	≥Grade 3 Bleed Outside CNS
Bevacizumab[64–67]	187	2 (1%)	0	7 (4%)
Sorafenib[23,68]	174	0	1 (1%)	0
Semaxanib[69–73]	163	1 (1%)	0	1 (1%)
Sunitinib	0	0	0	0
Vatalanib	0	0	0	0
Total	524	3 (<1%)	1 (<1%)	8 (2%)

Carden et al. Neuro-Oncol 2008

CNS Bleeding with anti-VEGF Therapy in Cancer

Table 4. Trials of anti-VEGF therapy targeted at or including brain metastases

First Author	Agent	Cancer	Patient Number	Number of Patients with Brain Metastases	Grade 3 Thrombo-cytopenia	Rate of CNS Bleeding	≥Grade 3 Bleed Outside CNS
Tamaskar[78]	Sunitinib	Renal cell carcinoma	35	5	0	0	0
Heymach[79]	ZD6474 ± docetaxel	Lung	127	13	0	0	2 (2%)
Amaravadi[80]	Sorafenib with temozolamide	Melanoma	38	38	6 (16%)	0	0
Henderson[81]	Sorafenib	RCC	2,488	65	0	0	0

Carden et al. Neuro-Oncol 2008

Conclusions

- Angiogenesis inhibitors are active in primary brain tumors, despite BEV being a monoclonal antibody
- Angiogenesis inhibitors are safe and tolerable in primary brain tumor patients, with potent anti-edema effects
- Existing data suggests that risk of intracranial hemorrhage is low
- Angiogenesis inhibitors may be useful in combination with RT or as salvage therapy in brain metastases