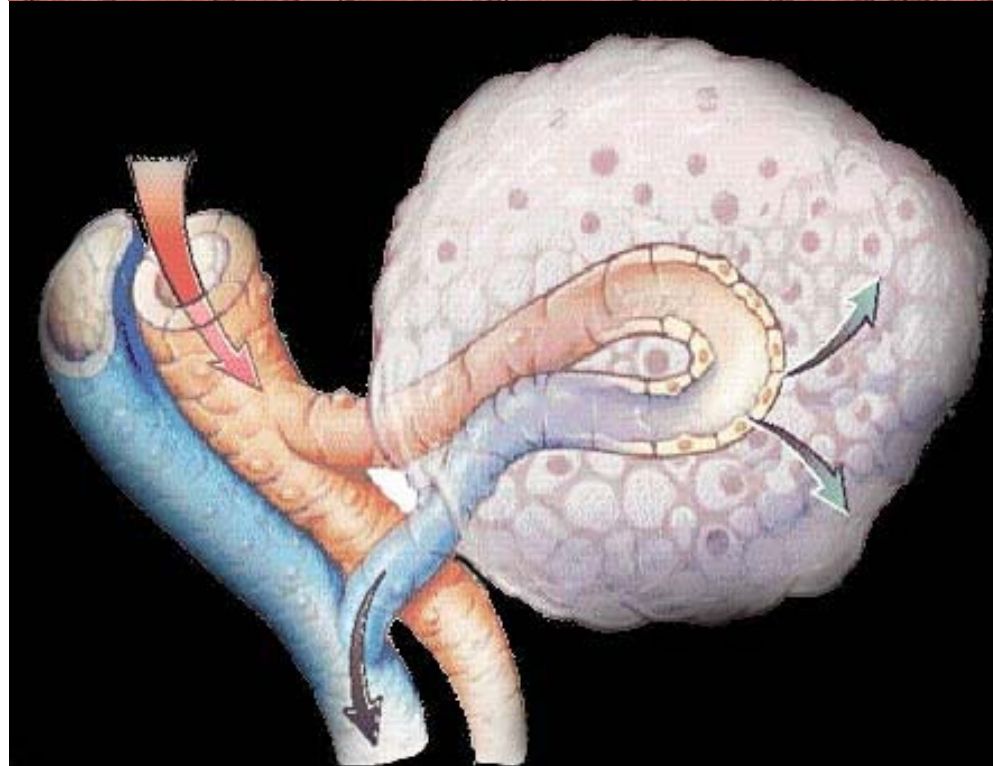
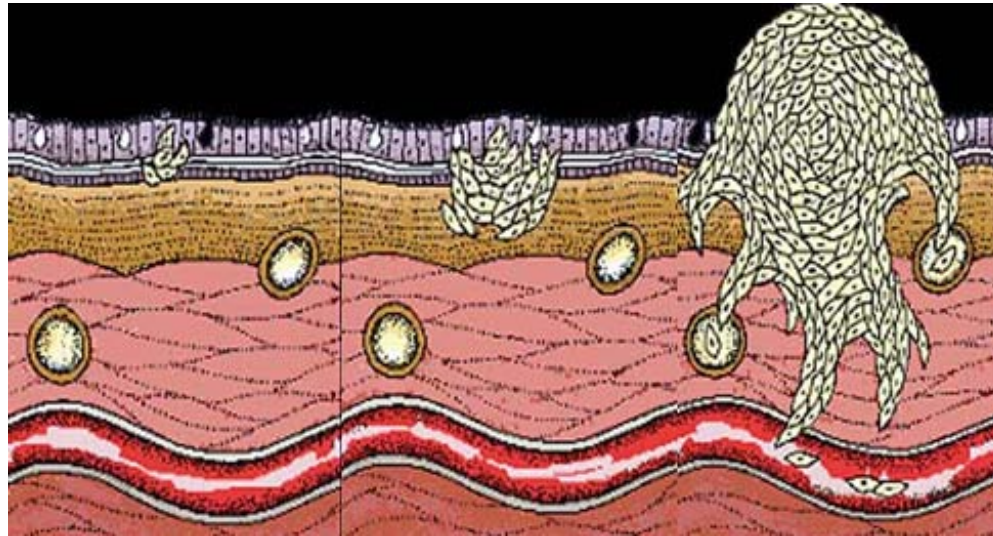


IMAGING ANGIOGENESIS

Gordon Jayson

Manchester UK

REGULATION OF ANGIOGENESIS



Angiogenic factors

Cytokines

•VEGF

- FGF
- HGF
- HB-EGF
- Angiogenin
- IL-8
- PDGF

Enzymes

- TP

Anti-Angiogenic proteins

Protein fragments

- endostatin
- angiostatin

Inhibitory proteins

- PF4

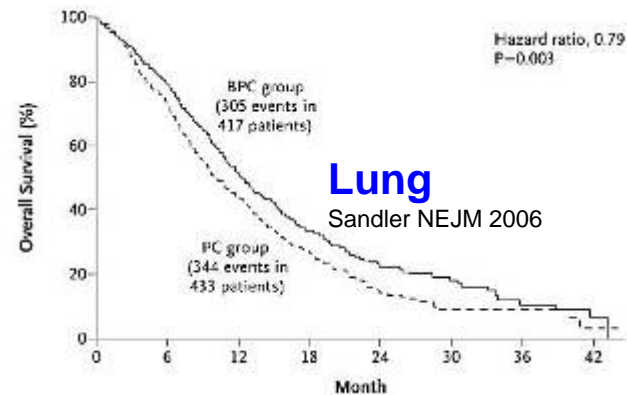
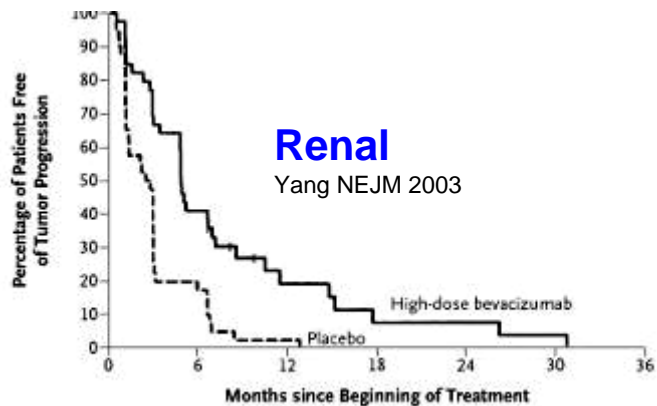
Soluble receptors

- s-flt
- s-FGF R

VEGF_i INCREASE RR, PFS +/- OS IN SOLID TUMOURS

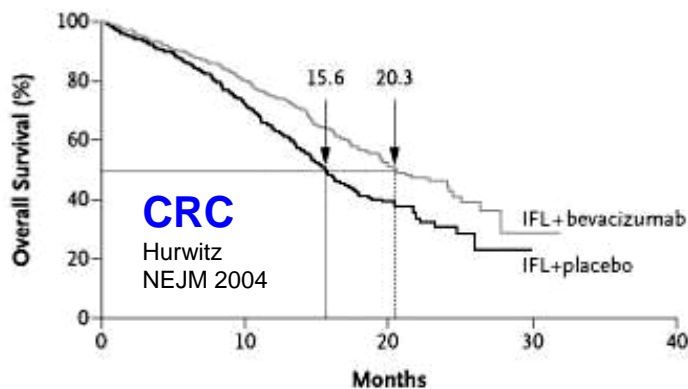
Renal

Yang NEJM 2003



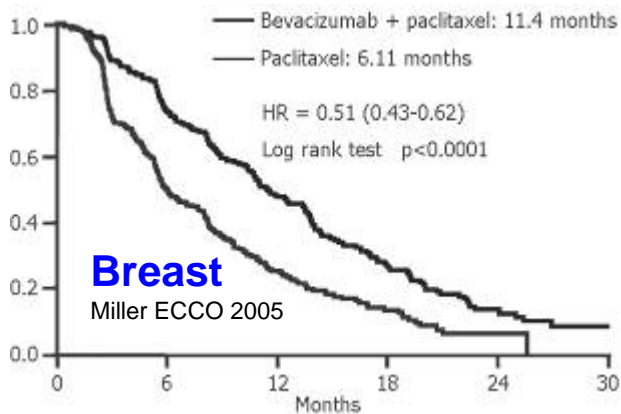
Lung

Sandler NEJM 2006



CRC

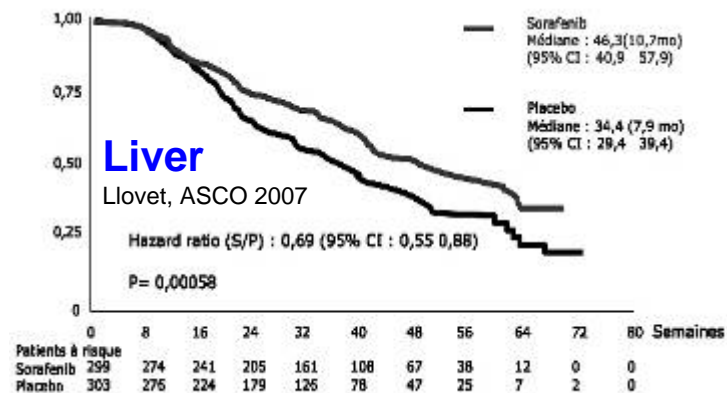
Hurwitz
NEJM 2004



Breast

Miller ECCO 2005

Who?
Schedule?
How Long?



Liver

Llovet, ASCO 2007

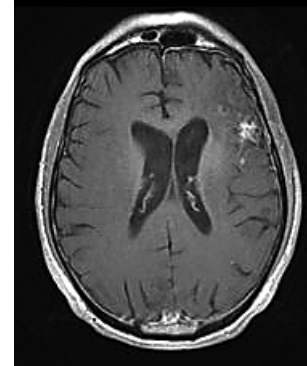
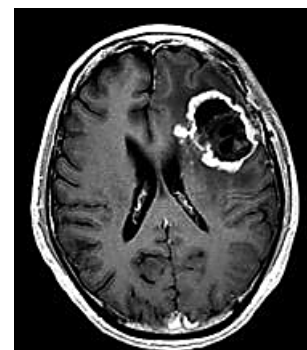
NEW AND FUTURE TARGETS

Integrins

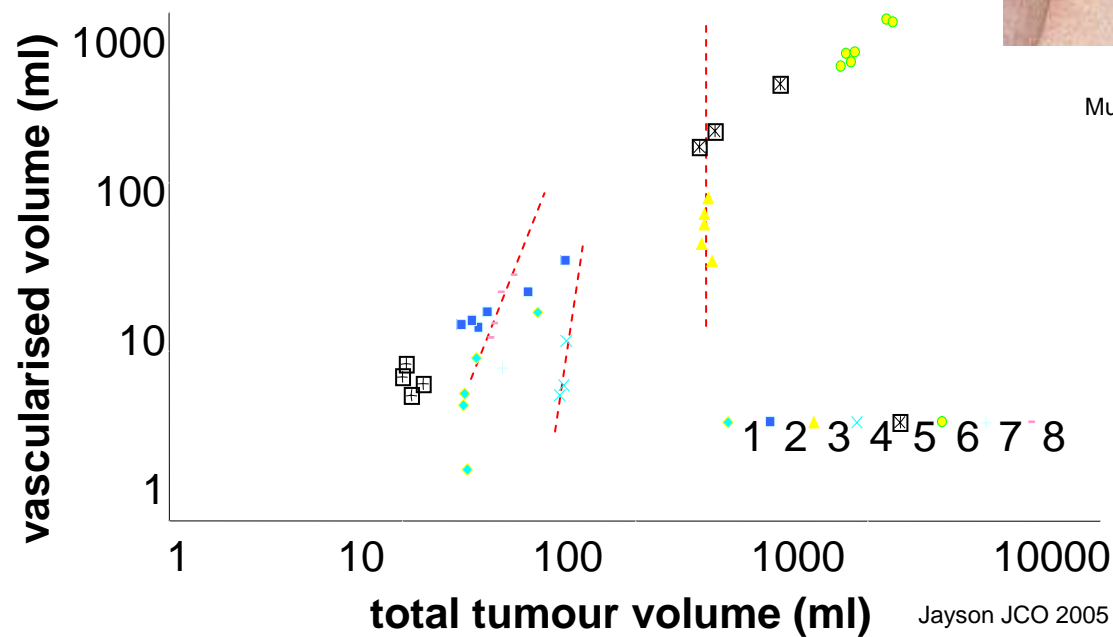
PDGF: CP-868,596 Lewis, ASCO 2007
 Sarcoma, Spindle Cell, NSCLC



CNTO 95
 Mullamitha, Clin Cancer Res 2007



Cilengitide
 Reardon, ASCO 2007



NEW AND FUTURE TARGETS

Integrins

PDGF: CP-868,596 Lewis, ASCO 2007

Ang: AMG 386 (Ang 1, 2) Rosen ASCO 2007

Ovarian

HGF: ARQ 197 (c-met RTKi) Garcia ASCO 2007

XL880 (c-met, VEGFR2 RTKi) Eder ASCO 2007

Prostate, NET, Testicular

VDAs Combretastatin

CT Metronomic

DLL4

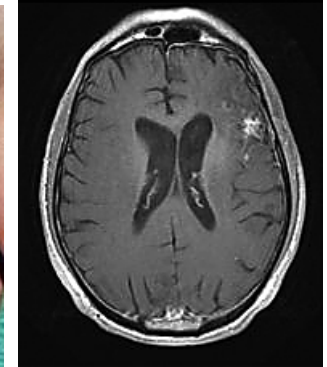
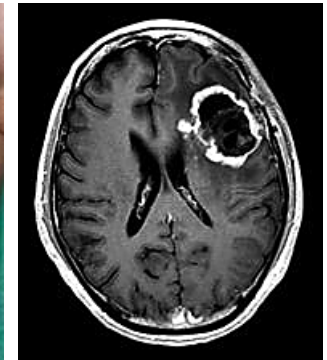
Neuropilin

FGFs



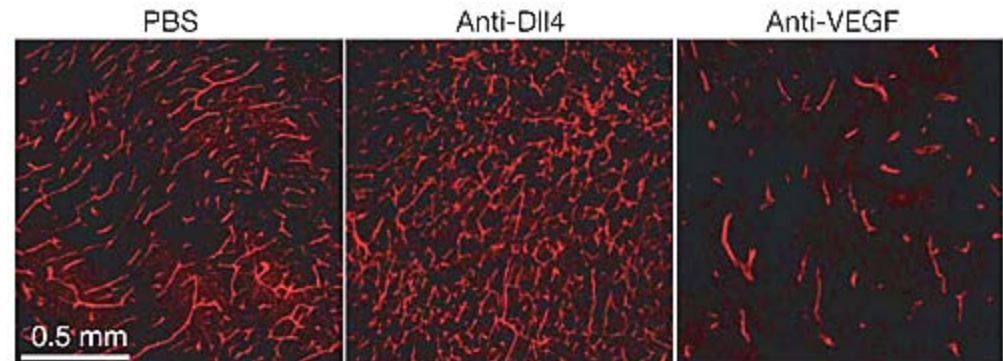
CNTO 95

Mullamitha, Clin Cancer Res 2007



Cilengitide

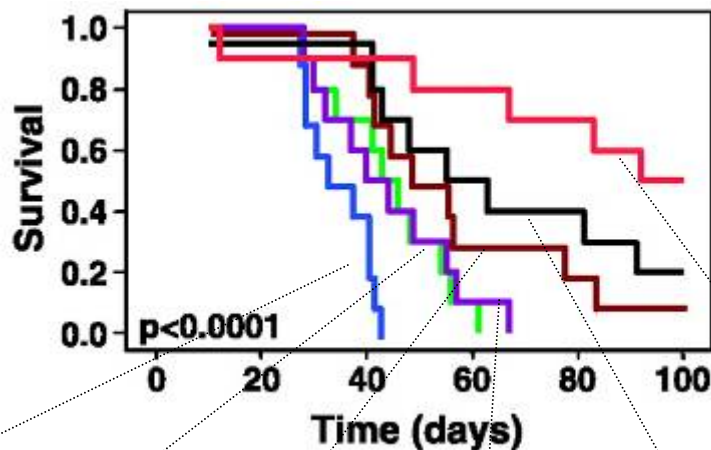
Reardon, ASCO 2007



Ridgeway, Nature 2006

ANTI-VASCULAR COMBINATION REGIMENS

Docetaxel, AEE778
HeyA8 cell line



VEGF, Cytotoxic

Kamat et al., Cancer Res 2007

PBS

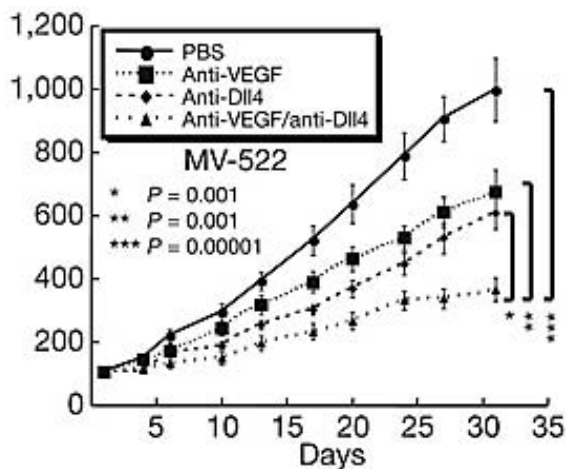
MTD CT

MET CT

VEGF RTKi

MTD CT
VEGF RTKi

MET CT
VEGF RTKi

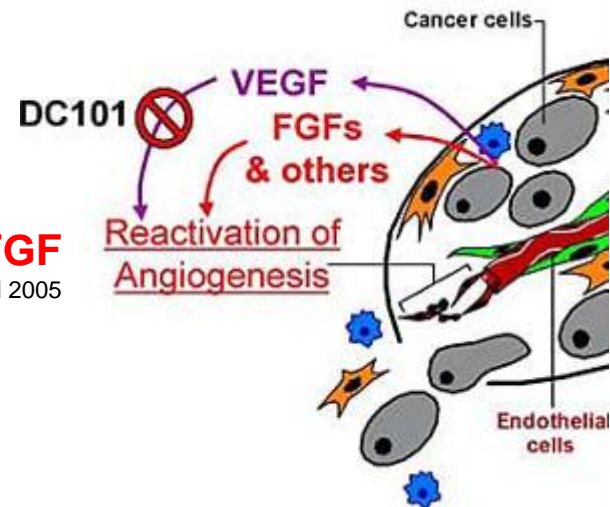


VEGF, DLL4

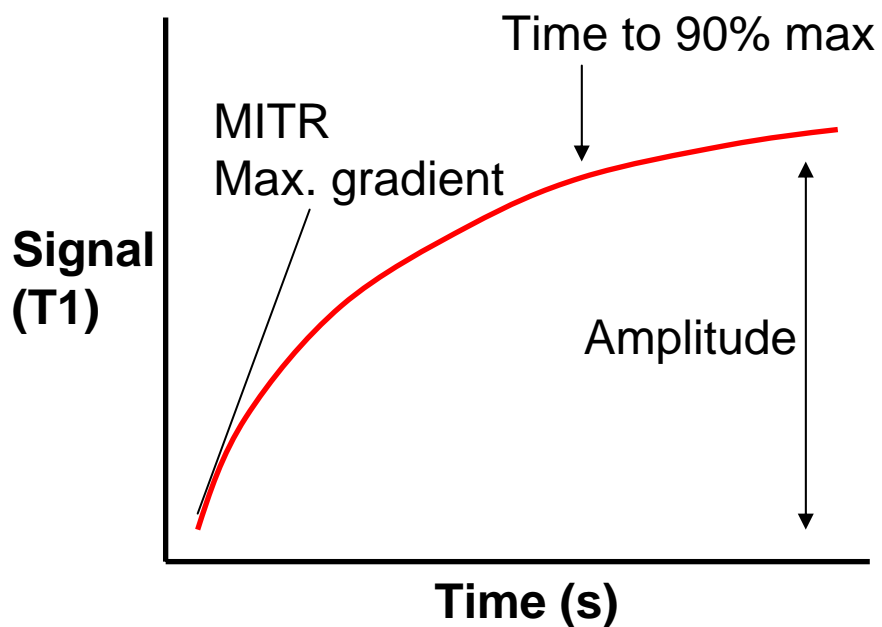
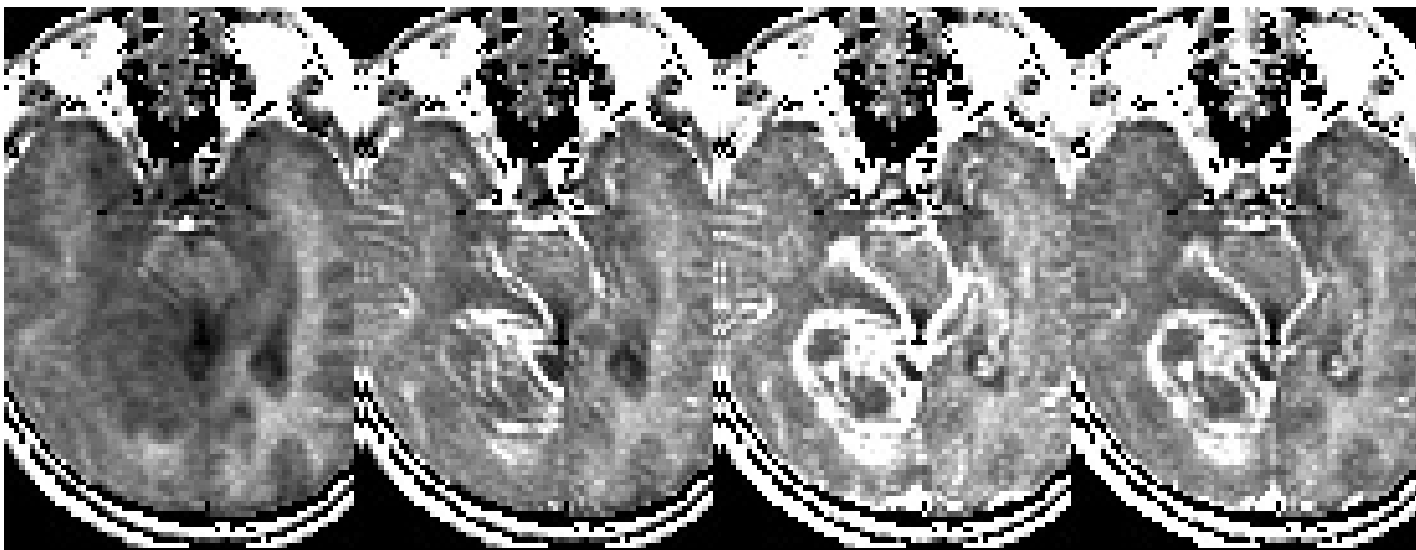
Ridgeway, Nature 2006

VEGF, FGF

Casanovas Cancer Cell 2005

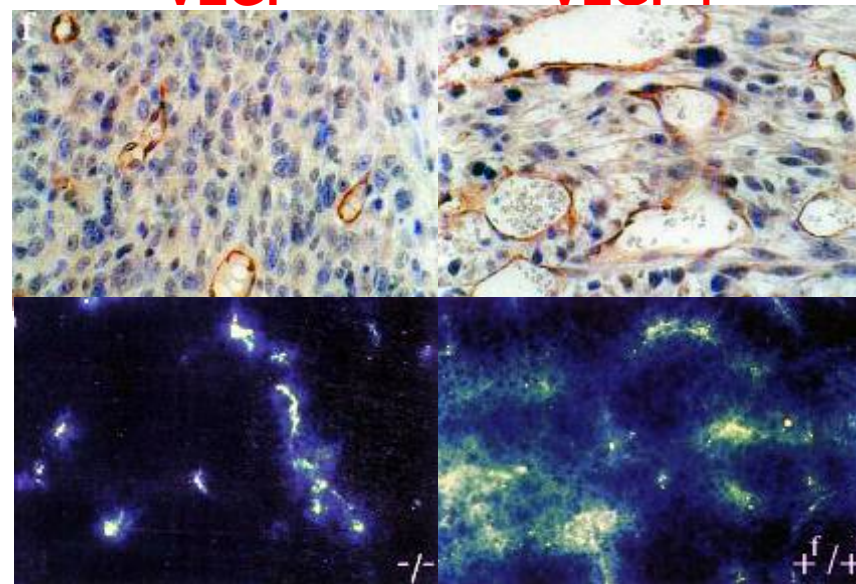


IMAGING THE VASCULATURE



VEGF -

VEGF +

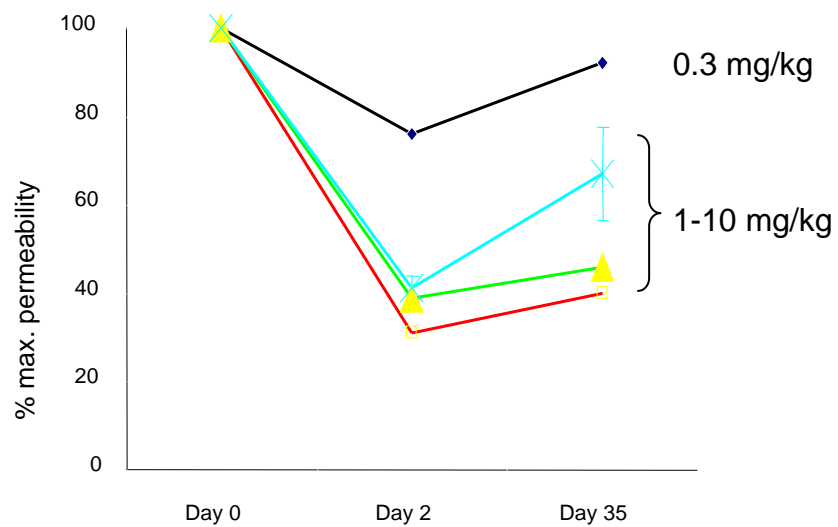
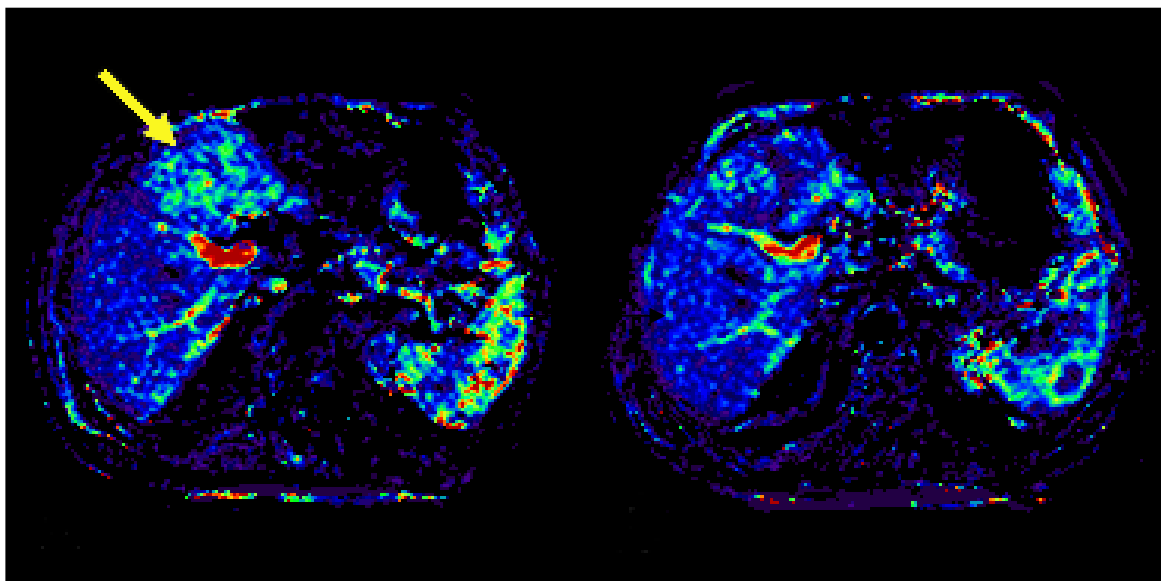


K_{trans}

Endothelial permeability surface area product

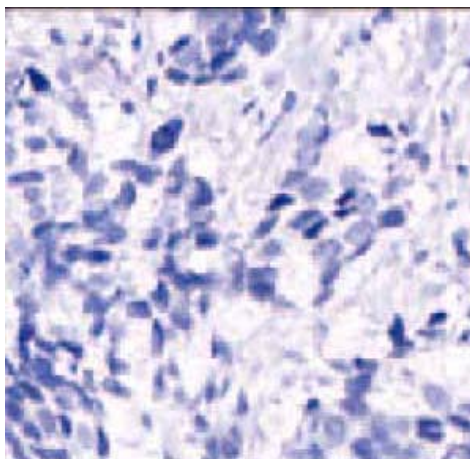
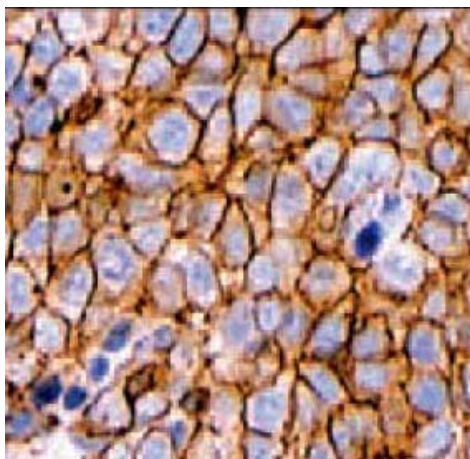
PHARMACODYNAMIC/ BIOMARKER IMAGING OF ANGIOGENESIS

Jayson JNCI 2002

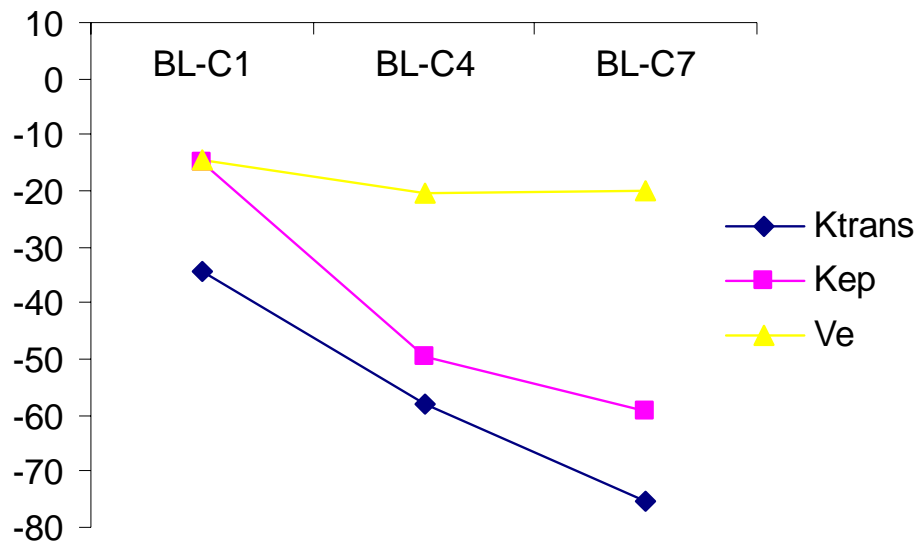


PROOF THAT VEGF IS INHIBITED IN PATIENTS

Wedam JCO 2006



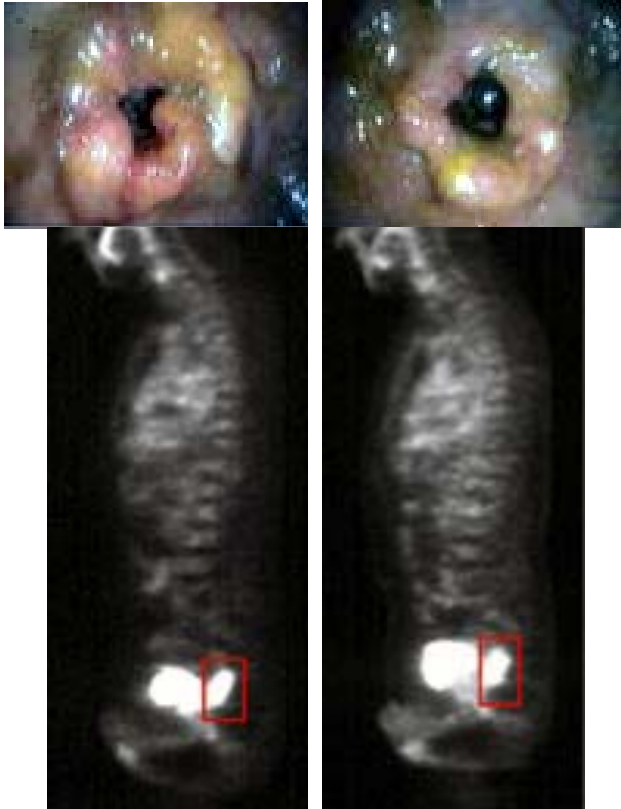
	BL-C1	BL-C4/7
Ki-67	2.1	-35.1
MVD	-14.6	16.6
VEGF-A	-50.0	-44.9
pVEGFR2	-69.2	-88.9
pVEGFR2	-66.7	-76.4
VEGFR2	69.7	-28.3
TUNEL	128.9	72.7



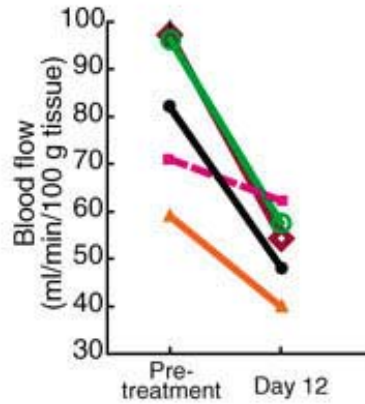
ANTI-VEGF Ab INHIBIT THE VASCULATURE

Willett Nat Med 2004

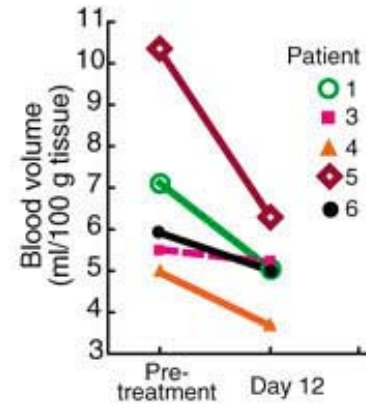
Bevacizumab 5mg/kg
Days 0 and 12



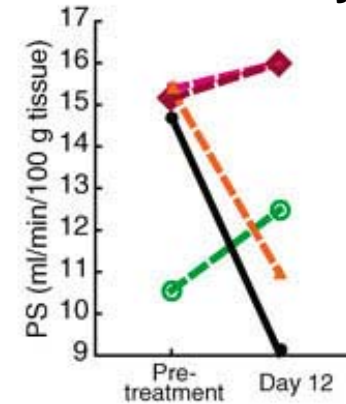
Flow



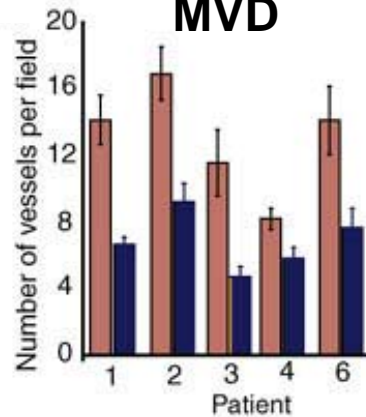
Volume



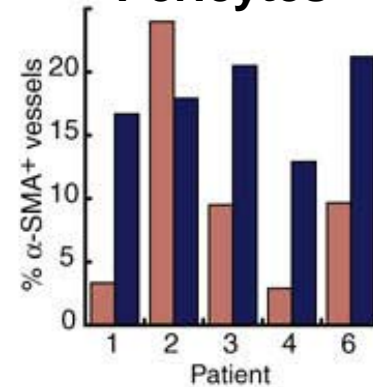
Permeability



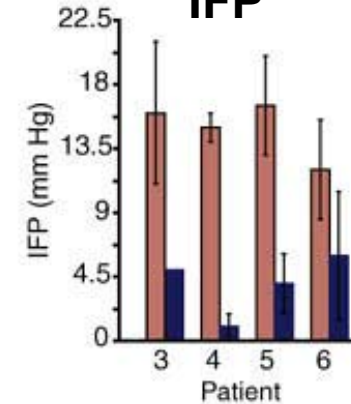
MVD



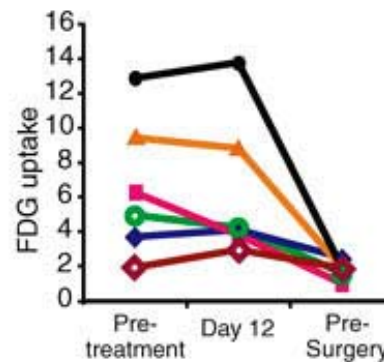
Pericytes



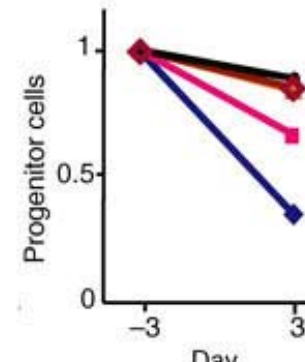
IFP



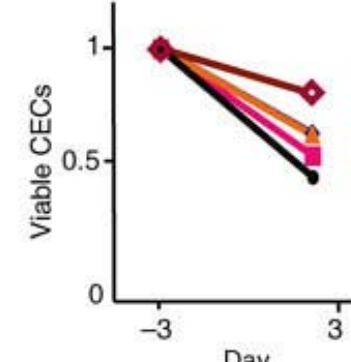
FDG-PET



CEPs



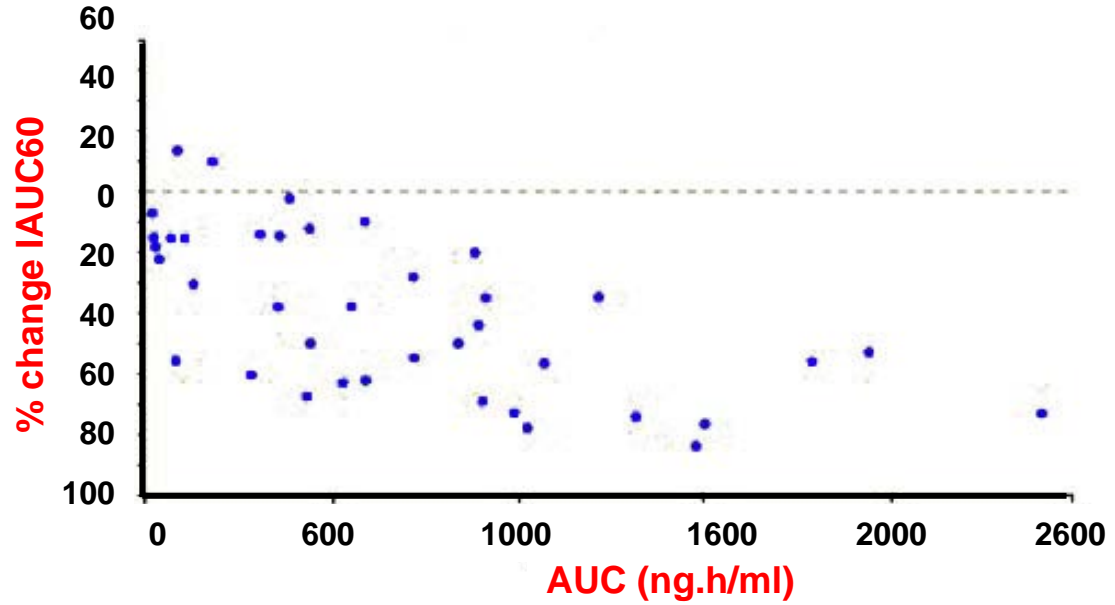
CECs



Δ DCE-MRI PROPORTIONAL TO DOSE OF VEGFi

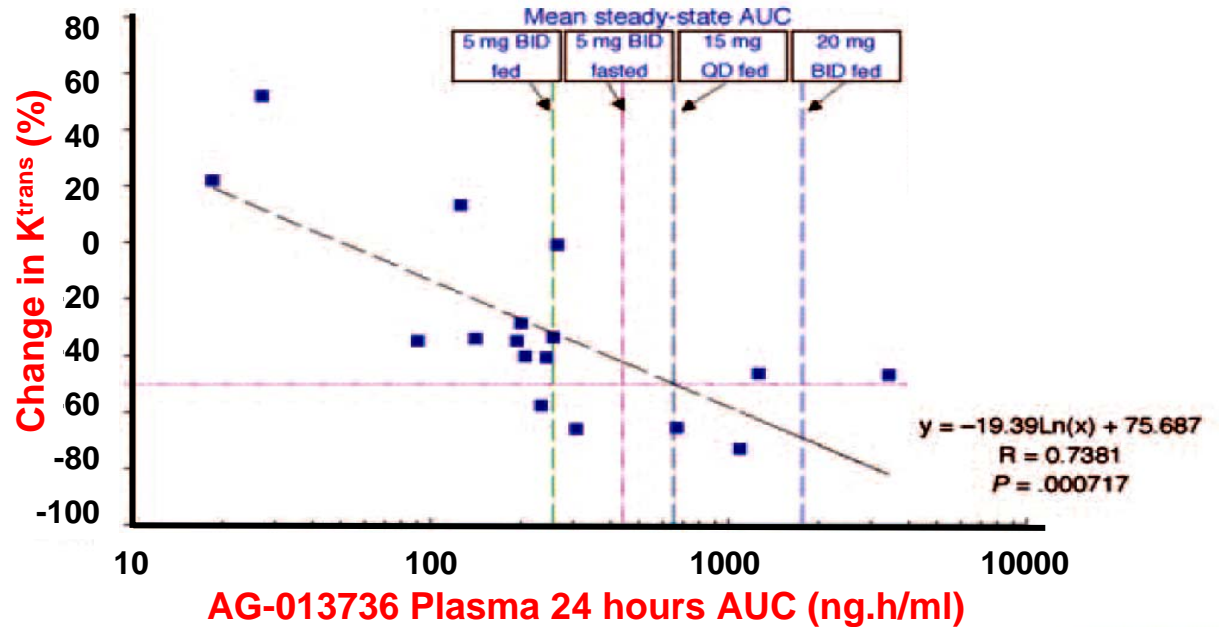
AZD2171

Dreys (ASCO 2007)



AG-013736

Liu (JCO 2005)



BIBF1120

Mross ASCO 2005,

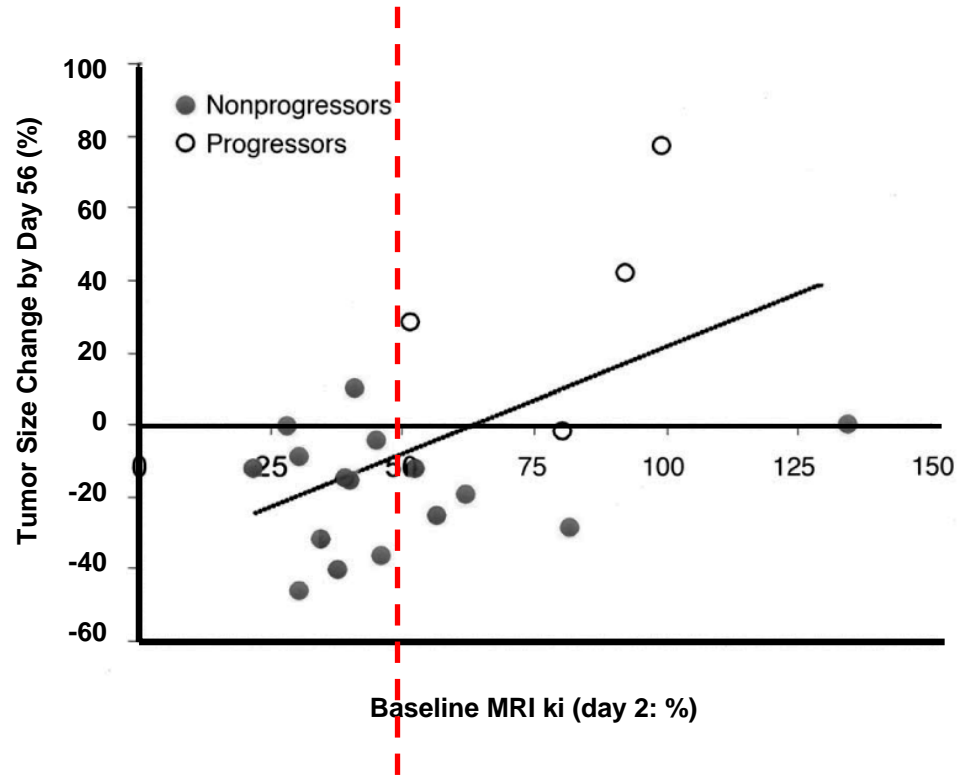
PTK/ZK

Morgan JCO 2003
 Thomas JCO 2005

Δ DCE-MRI IS RELATED TO OUTCOME

PTK/ZK

Morgan JCO 2003
Thomas JCO 2005

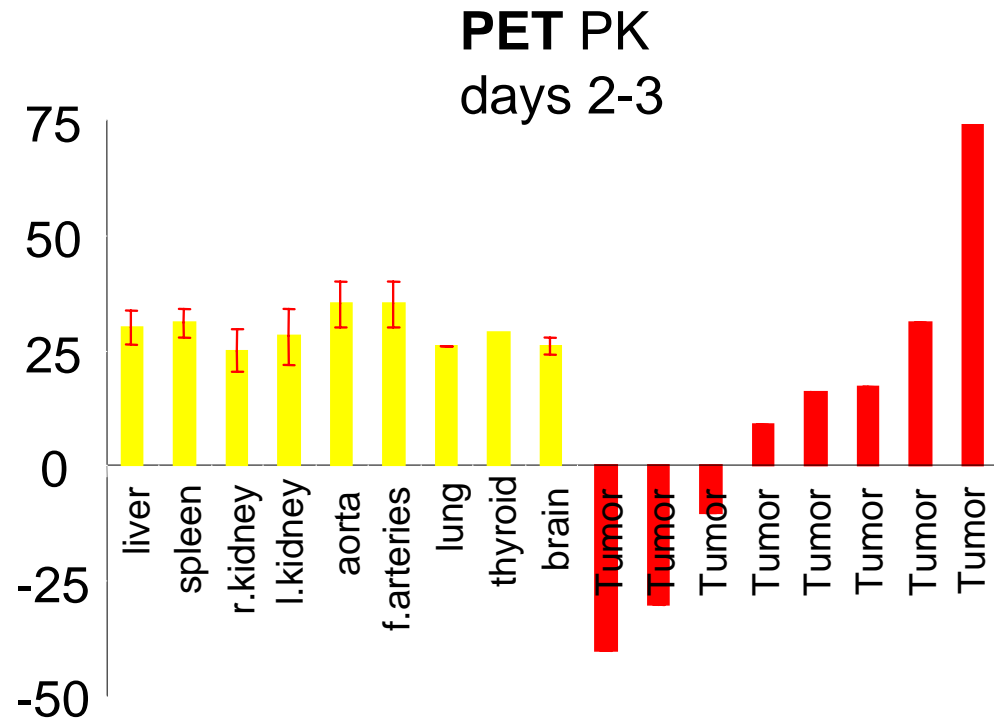
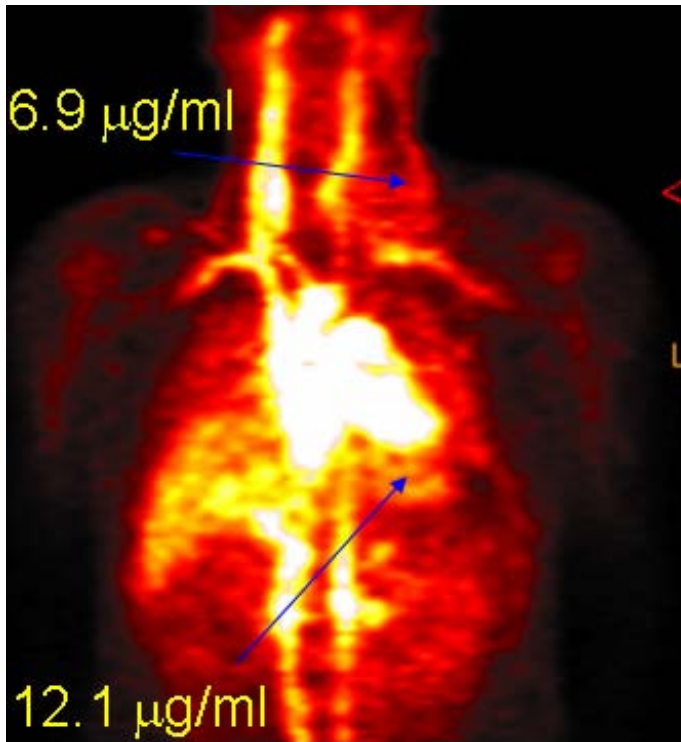


Reductions of >50% K^{trans} are associated with stabilization

Relationship between K^{trans} and PFS reported with **Sorafenib** in renal cancer (O'Dwyer ASCO 2005)

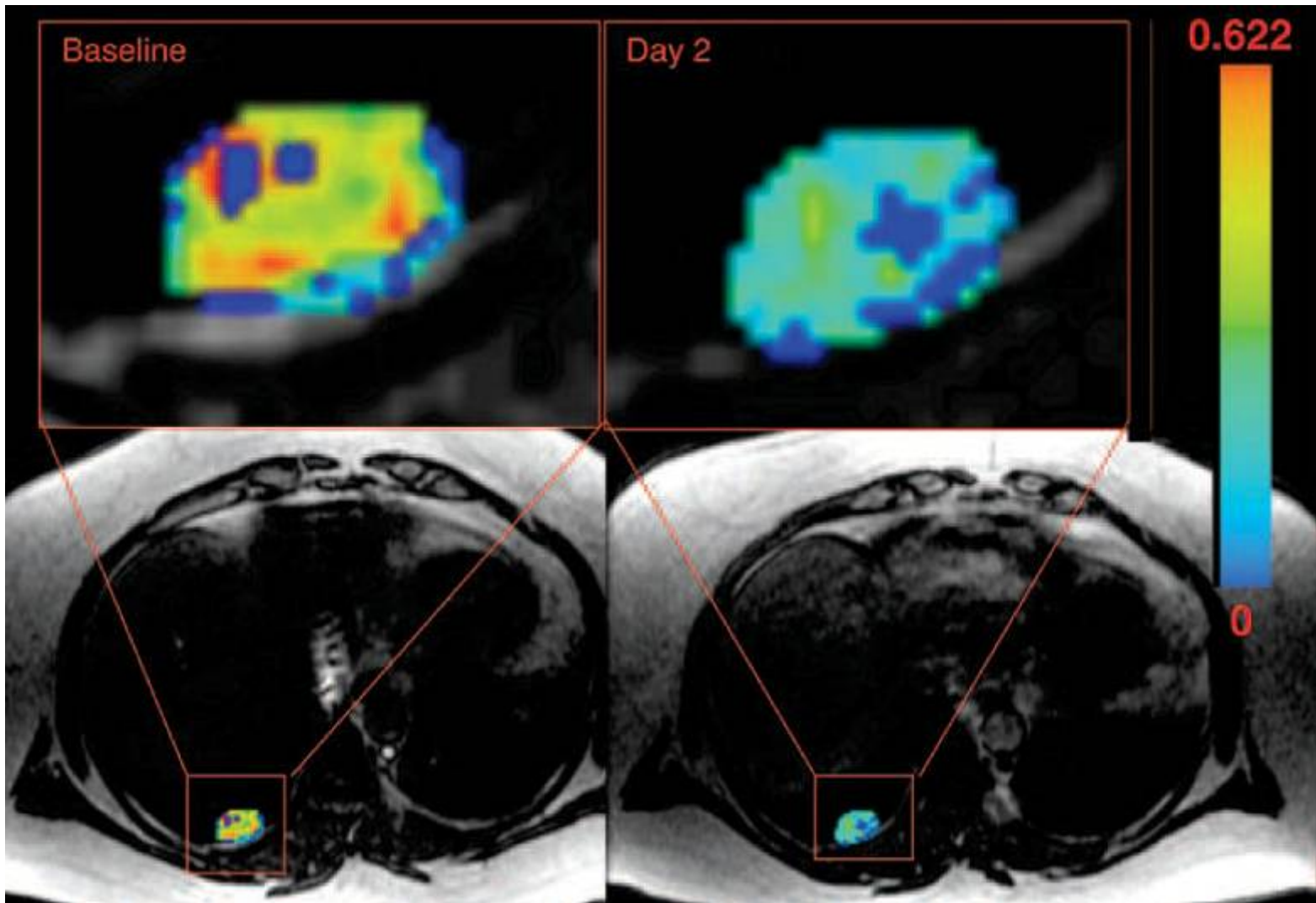
VASCULAR HETEROGENEITY

Jayson, JNCI, 2002



	AIF	Parameter	Model	ROI	Stats
Anti-VEGF Ab					
HuMV833 ^{Jayson 2002}	Manual	K^{trans} , K_{fp} , V_p	Tofts, ET	Entire tumor	Mean +/-SD
Bevacizumab ^{Overmoyer 2004}		K_{ep}			
Bevacizumab ^{Doshi 2005}		K^{trans} , K_p , V_e , IAUGC	Brix, Kety	Enhancing reg	Base, single Δ
Bevacizumab ^{Wedam 2006}		K^{trans} , K_{ep} , V_e	Brix		
VEGF R					
AZD2171 ^{Dreys 2005}		IAUGC			Decrease
CDP791 ^{Jayson 2006}	Standard	K^{trans} , V_p , V_e , flow VTV, IAUGC		Entire tumor	
VEGFR/PDGFR TKi					
SU5416 ^{Medved 2004}	Not required	IAUGC, washout,	Heuristic		Δ Mean
SU5416 ^{O'Donnell 2005}		C_{max} , K^{trans} , V_e	NS	Pixel based	Median
PTK/ZK ^{Morgan 2003}	Standard	K_i	Larsson	Section	Δ baseline
PTK/ZK ^{Yung 2003}		K_i , CBV	NS		Δ Mean
PTK/ZK ^{Mross 2005}	Standard	K_i	Larsson	Entire tumor	Δ baseline
PTK/ZK ^{Thomas 2005}		K_i	Larsson	Entire tumor	Δ Mean
AG013736 ^{Liu 2005}	Rijpkema	K^{trans} , IAUGC	Tofts, Heur	Entire tumor	Δ Mean
BAY 43-9006 ^{O'Dwyer 2005}	Manual	K^{trans}	Tofts		Δ baseline
VEGFR/PDGFR/FGFR TKi					
SU6668 ^{Xiong 2004}		IAUGC, slope	Heuristic	CT	Δ baseline
BIBF1120 ^{Mross 2005}		K^{trans} , IAUGC			Δ baseline
Anti-PDGFRβ					
CDP860 ^{Jayson 2005}	Standard	K^{trans} , V_e , V_p , flow, VTV, IAUGC	Tofts, ET, LL Heur	Entire tumor	Median, mean
Anti-Integrin					
CNT095 ^{Jayson 2005}	Standard	K^{trans} , V_e , V_p , flow, VTV, IAUGC	Tofts, ET LL, Heur	Entire tumor	Median, mean
Endostatin ^{Eder 2002}	Manual	K^{trans} , V_e	Tofts	Entire tumor	

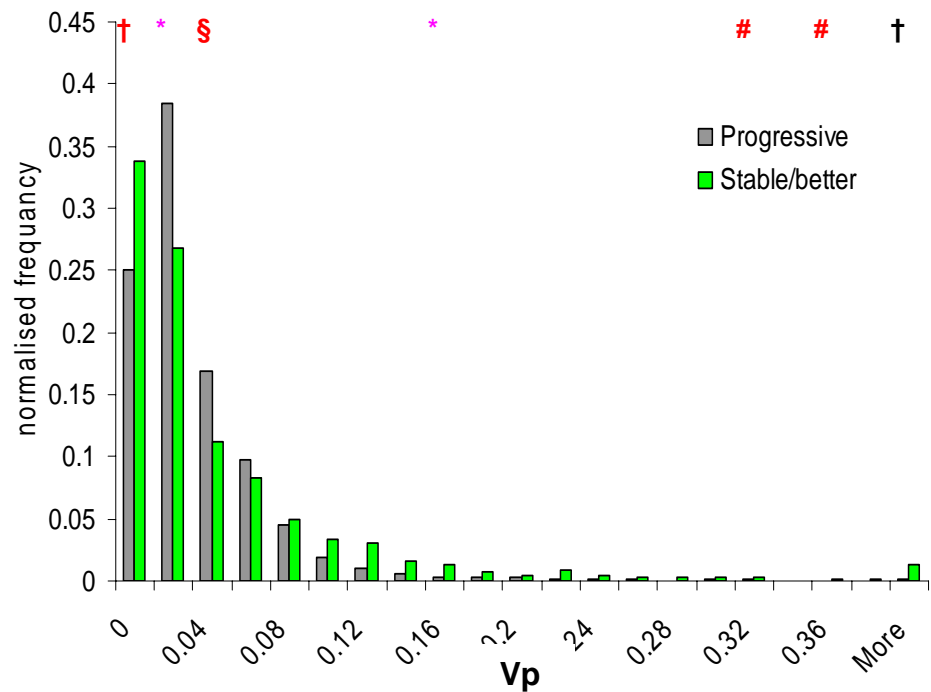
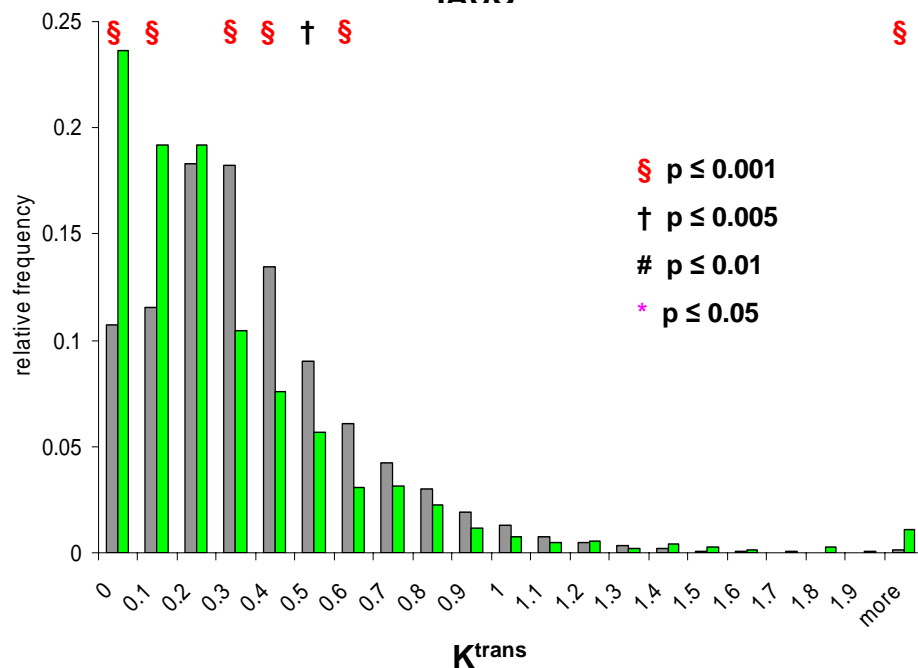
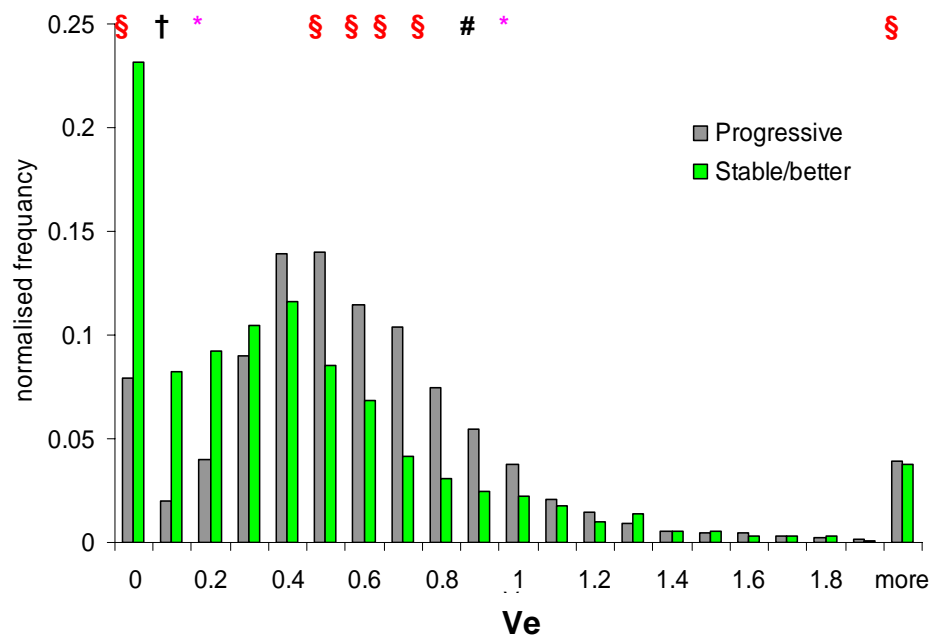
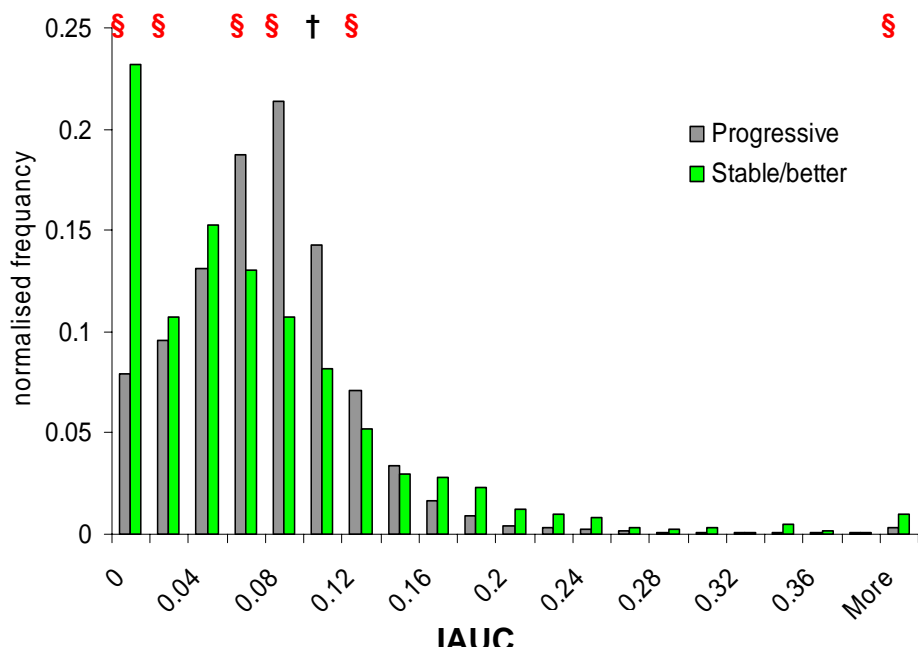
STATISTICAL ANALYSIS OF DATA IS PROBLEMATIC



From Liu JCO 2005

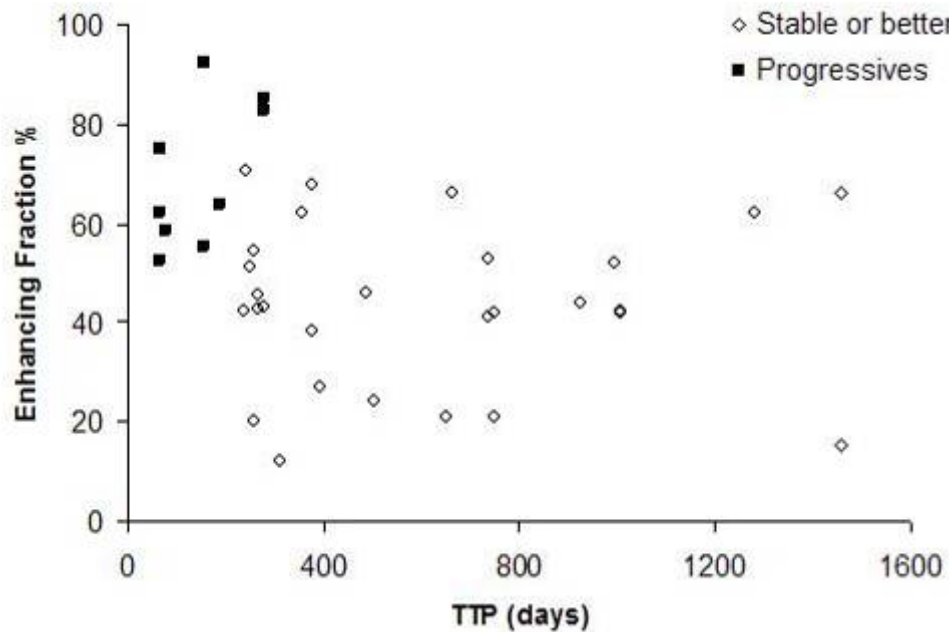
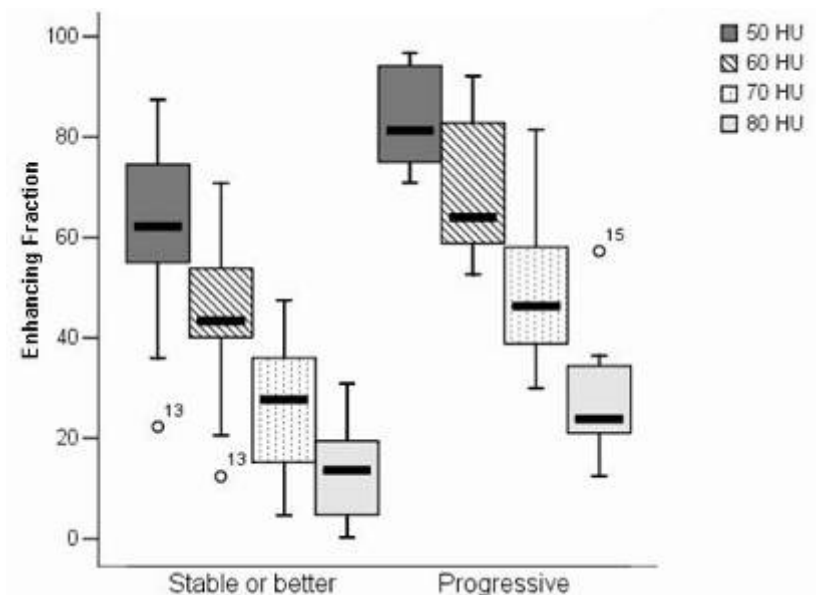
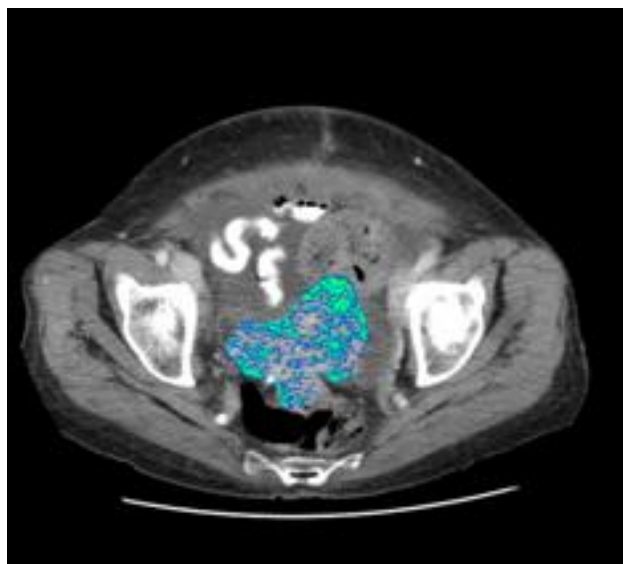
**Perfusion in pulmonary metastasis
from renal cancer**

VASCULAR PARAMETERS, HETEROGENEITY AND PROGRESSION



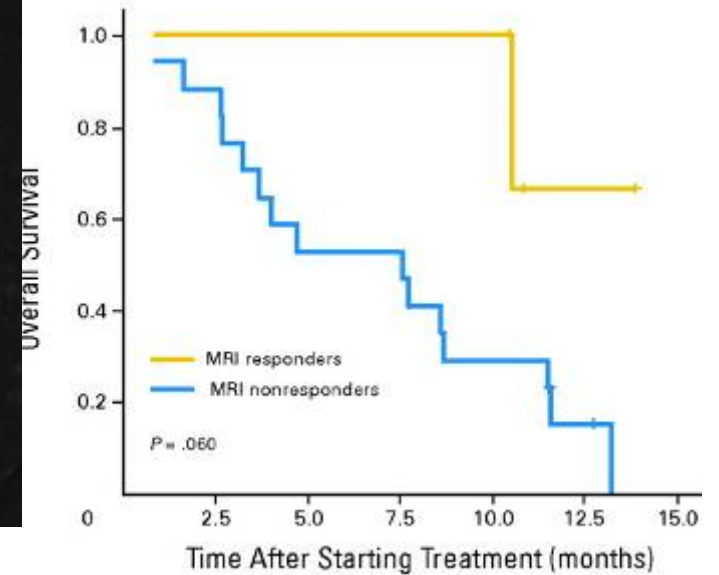
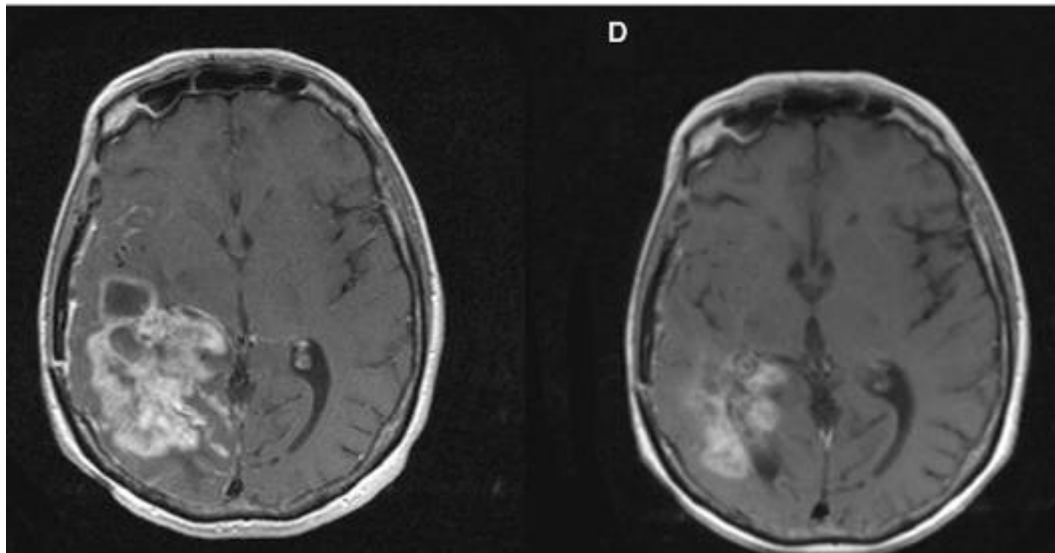
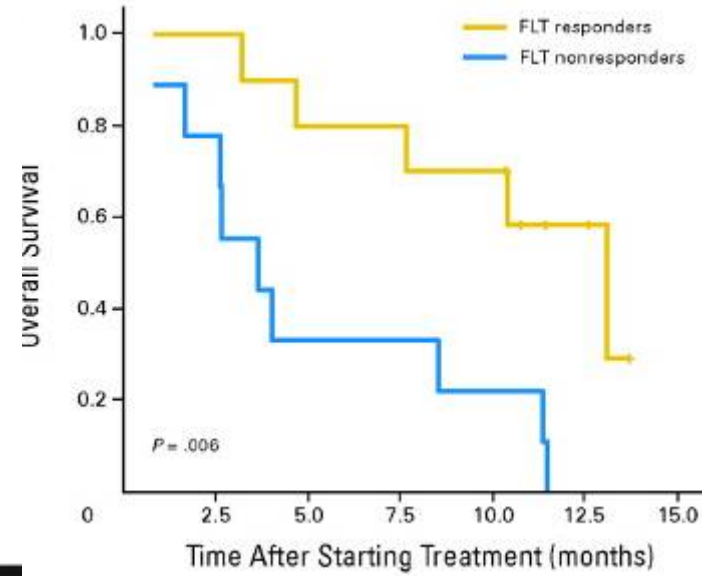
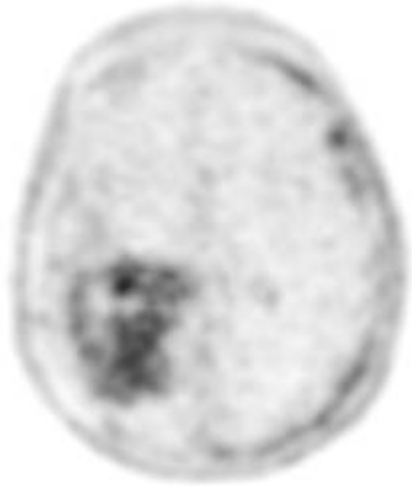
BASELINE ENHANCING FRACTION PREDICTS OUTCOME IN OVARIAN CANCER

O'Connor, Clin Cancer Res (In press)



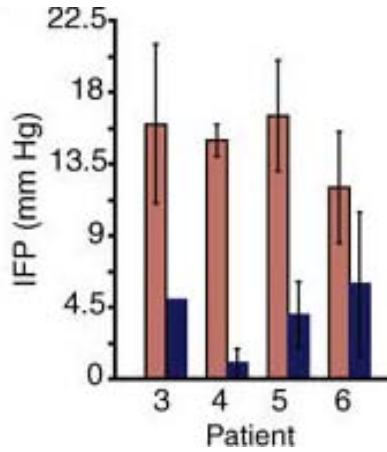
[¹⁸F]-FLT: BIOMARKER FOR BEVACIZUMAB IN GLIOMA

Chen, JCO 2007



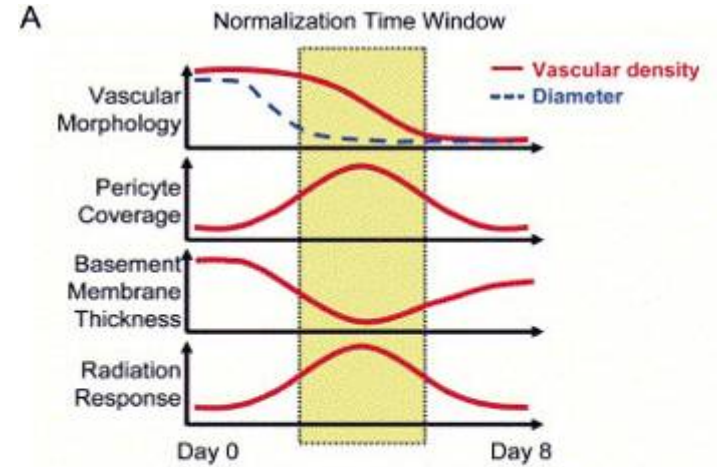
INTERSTITIAL PRESSURE

Willett, Nat Med 2004



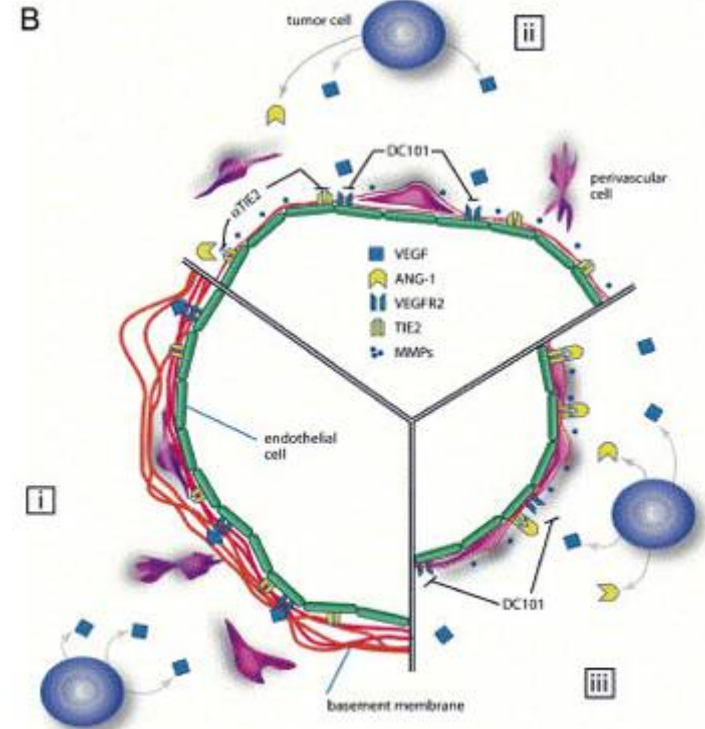
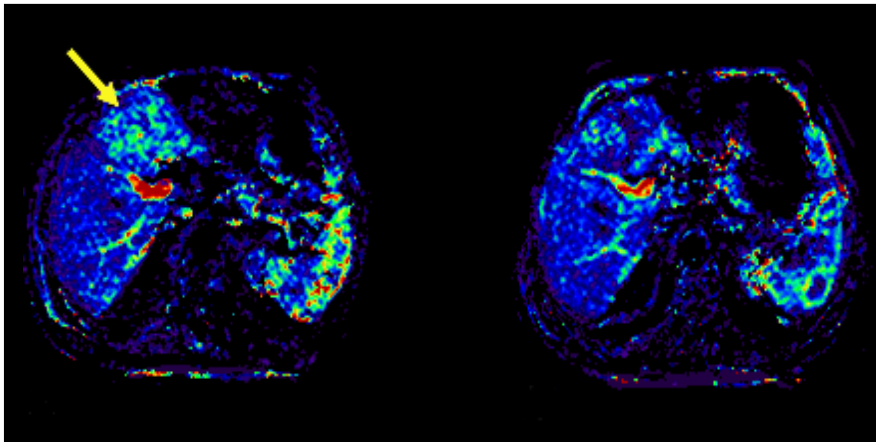
NORMALISATION

Winkler, Cancer Cell, 2004

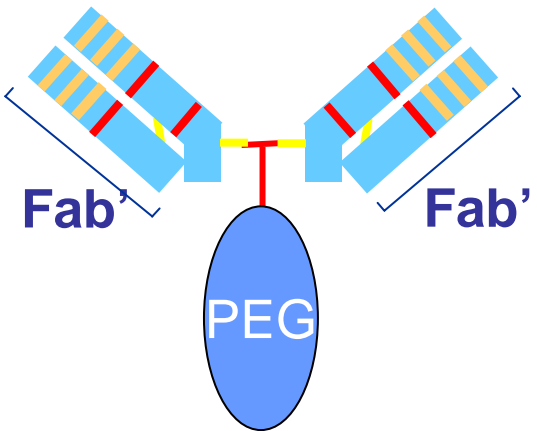


VASCULAR PERMEABILITY

Jayson JNCI 2002

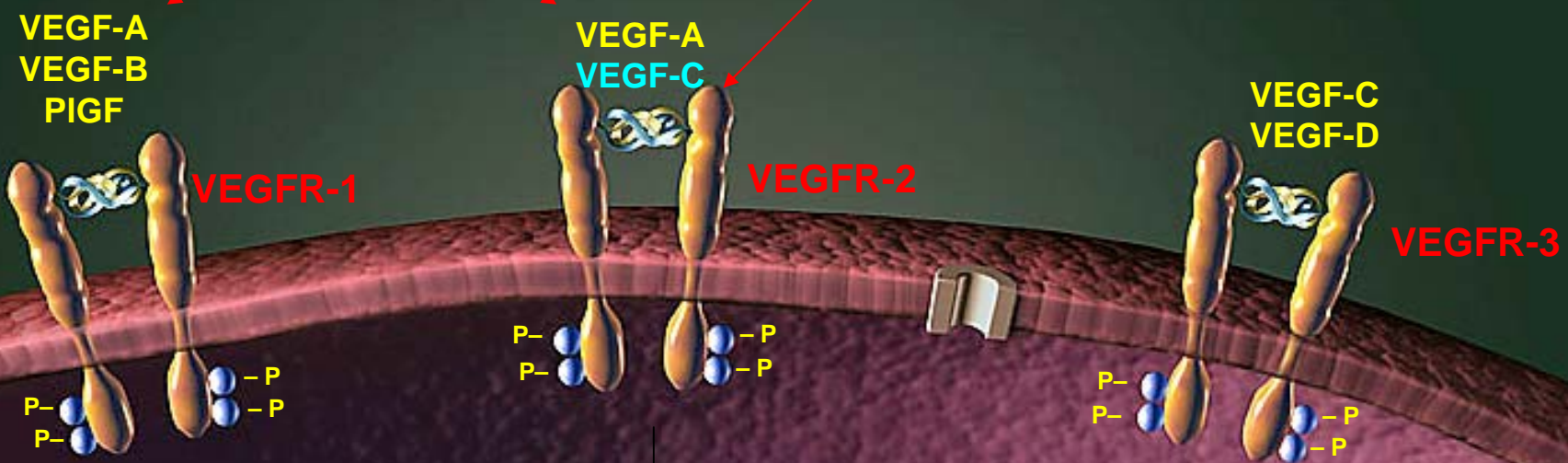


THE VEGF FAMILY AND ITS RECEPTORS



Bevacizumab

CDP 791

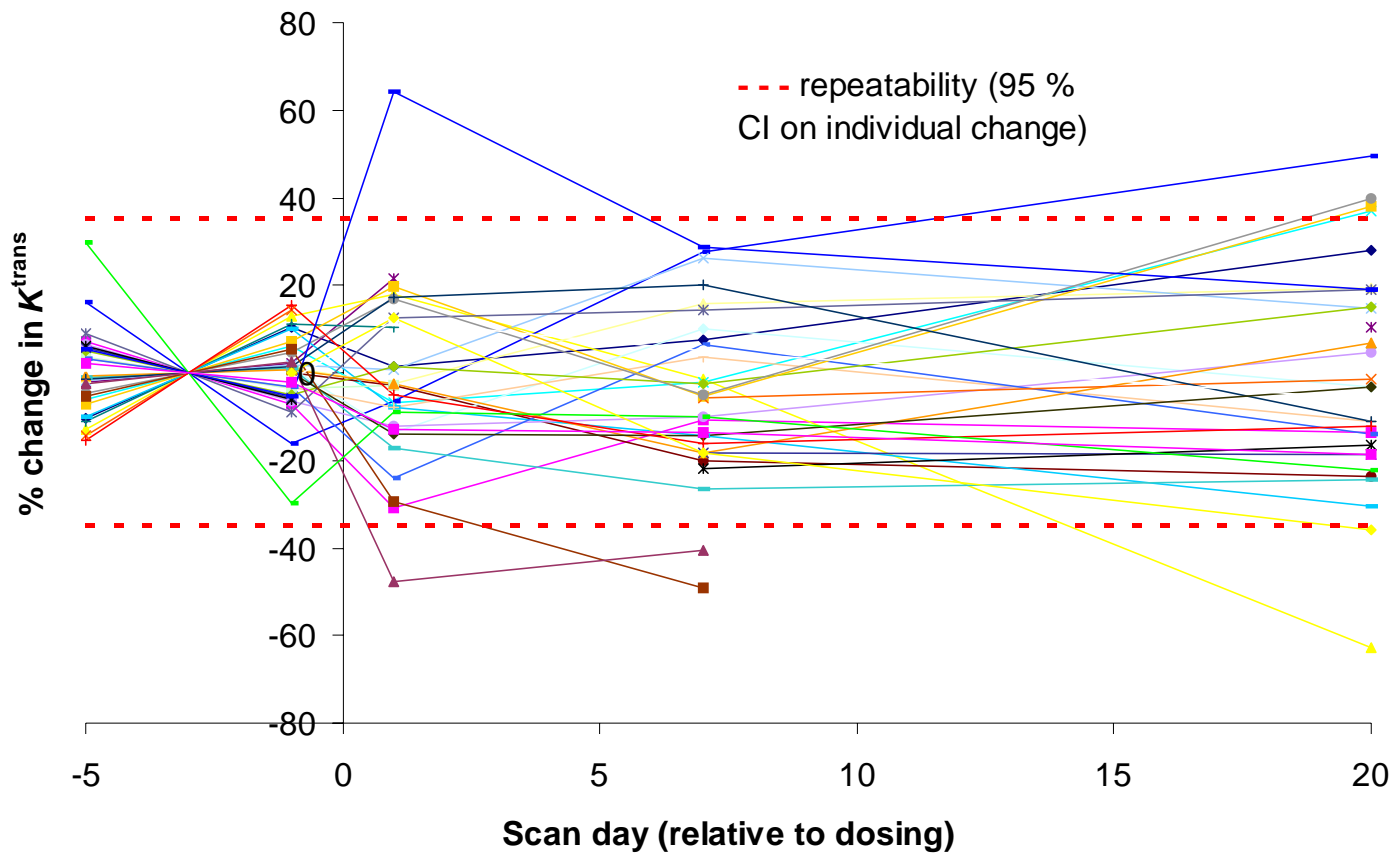


Migration, Permeability, DNA synthesis, Survival

Angiogenesis

Lymphangiogenesis

EFFECT OF CDP791 ON k^{trans}



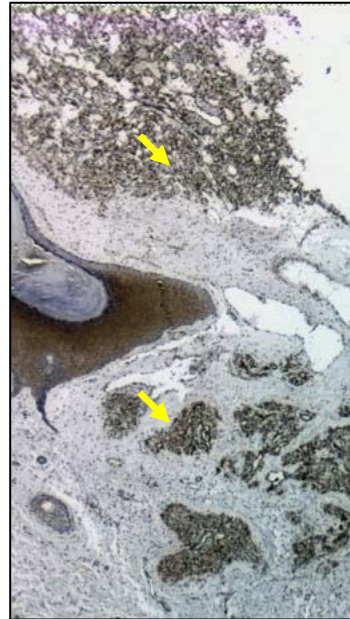
CDP-791 IS A BIOLOGICALLY ACTIVE KDR ANTAGONIST

Ton, Clin Cancer Res (In Press)

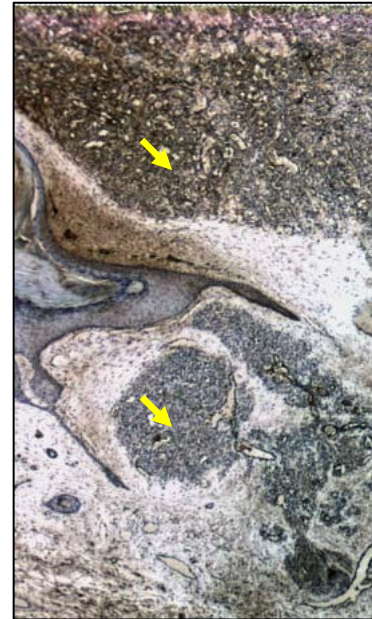
Dose related HT
Disease stabilisation



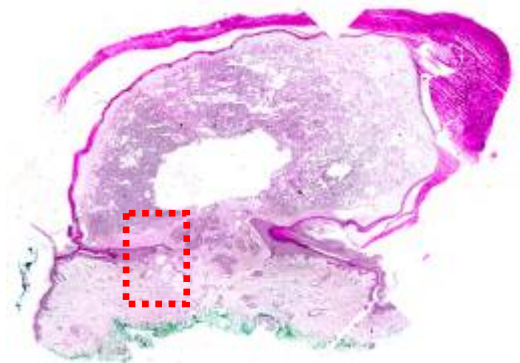
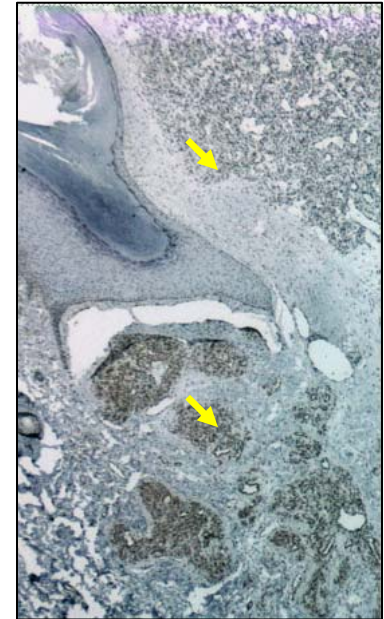
KDR



CDP-791

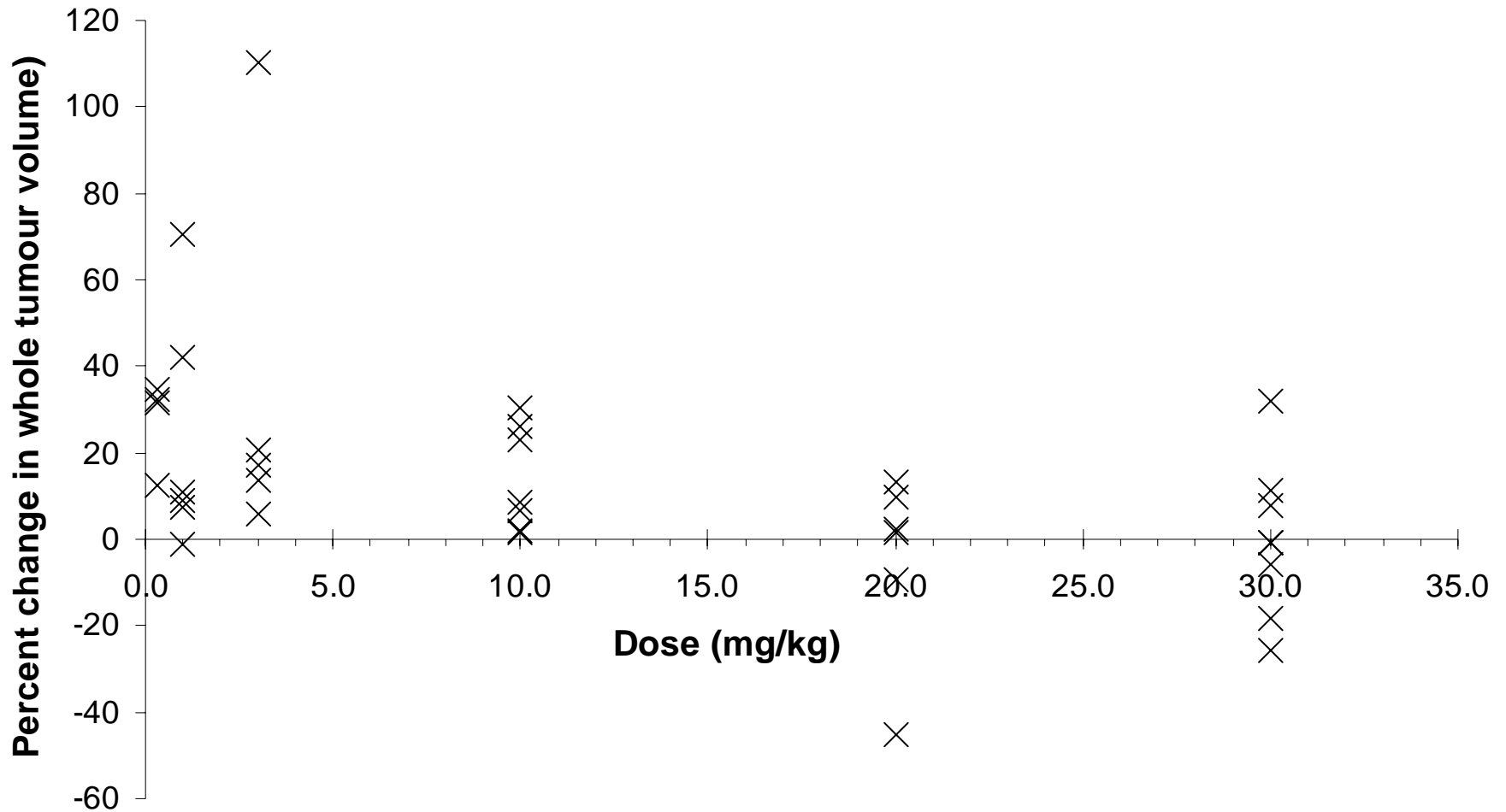


p-KDR



⇒ CDP791 inactivates KDR in humans

DOSE-LEVEL RELATED INHIBITION OF 3D TUMOR GROWTH



SUMMARY

DCE-MRI

Evaluated in several phase I/II trials of VEGF inhibitors

Δ DCE-MRI \propto Dose

Δ DCE-MRI \propto Disease Stabilisation

Heterogeneity is clinically significant

Pure KDR antagonists might not impact on tumour permeability

Phase III evaluation

Volumetrics

Who?

Schedule?

How Long?

ACKNOWLEDGEMENTS

Clinical

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Gio Buenocorsi
James O'Connor

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