Terapia antitumorale ed ipertensione arteriosa. Evento non infrequente nella clinica quotidiana. *Come affrontarlo*.

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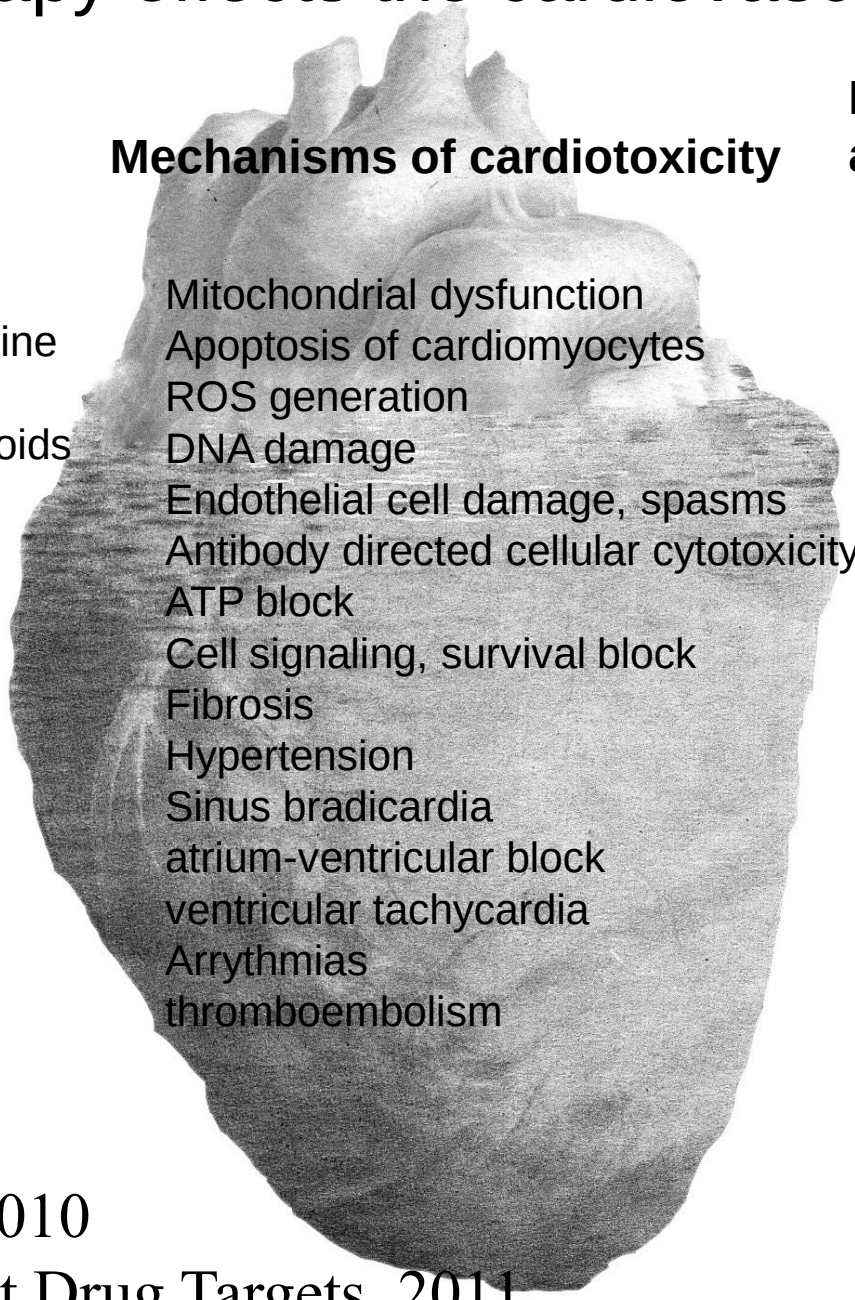
Cancer therapy effects the cardiovascular system

Anticancer drugs with possible cardiotoxicity

- Doxorubicin and other anthracyclines
- Capecitabine and cytarabine
- 5–Fluorouracil
- Paclitaxel and vinca alkaloids
- Cyclophosphamide
- TK Inhibitors:
  - *Trastuzumab*
  - *Imatinib*
  - *Bevacizumab*
  - *Sorafenib, sunitinib*
- COX–2 inhibitors
- Estrogen receptor modulators
- Irradiation to the thorax

Mechanisms of cardiotoxicity



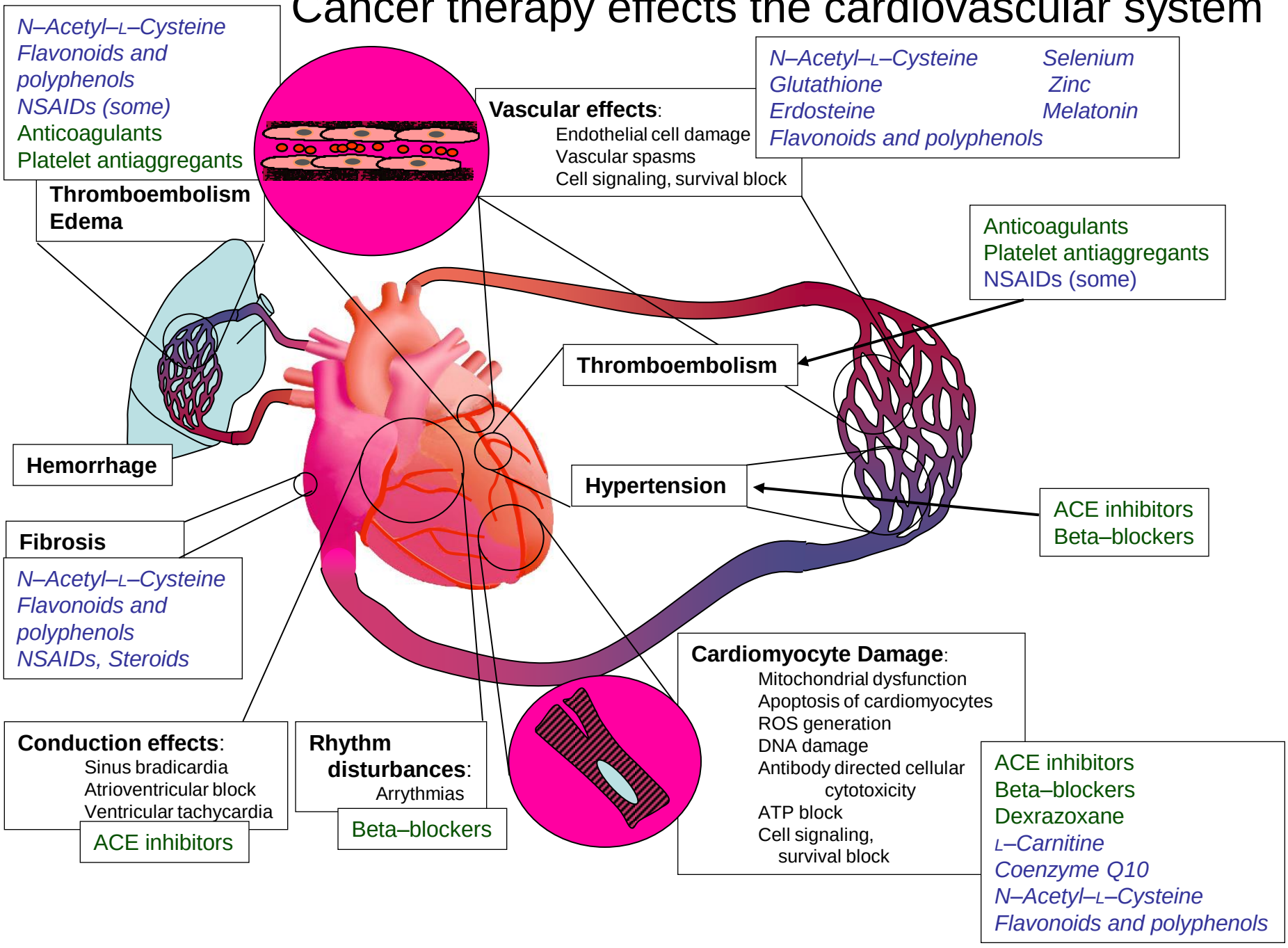
- Mitochondrial dysfunction
- Apoptosis of cardiomyocytes
- ROS generation
- DNA damage
- Endothelial cell damage, spasms
- Antibody directed cellular cytotoxicity
- ATP block
- Cell signaling, survival block
- Fibrosis
- Hypertension
- Sinus bradicardia
- atrium-ventricular block
- ventricular tachycardia
- Arrythmias
- thromboembolism

Potential protective agents

- Lipoic Acid
- Melatonin
- Coenzyme Q10
- Polyphenolic compounds
  - *Resveratrol*
  - *monoHER*
  - *Curcumin*
  - *Quercetin*
  - *Pycnogenol*
  - *Genisten*
  - *Naringenin*
- Garlic organosulfur compounds
- Cruceriferous Glucosinolates
  - *Sulforaphane*
  - *glucoraphanin*
- Grape Seed Pro-anthocyanin Extract
  - *Other anthocyanins*
- Calceolarioside

Albini et al, JNCI 2010
Ferrari et al, Current Drug Targets, 2011

Cancer therapy effects the cardiovascular system



Albini et al, **JNCI**, Jan 10 2010- Cardio-oncological prevention

The down-side of prevention- Thrombosis by COX2 inhibitors: Adverse Cardiovascular Events

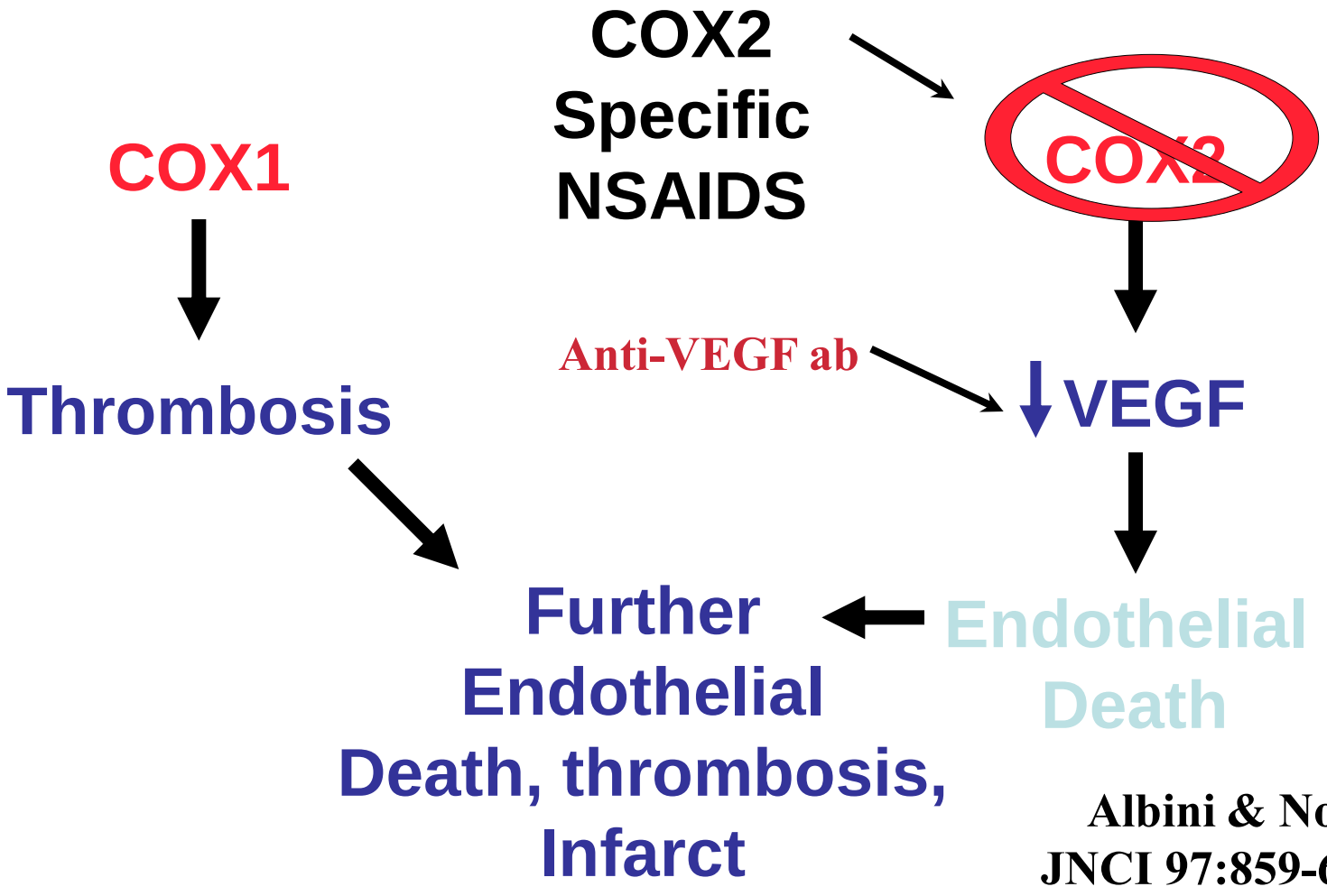
Vioxx

- Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial
  - Robert S. Bresalier, N Eng J. Medicine 2005

Celebrex

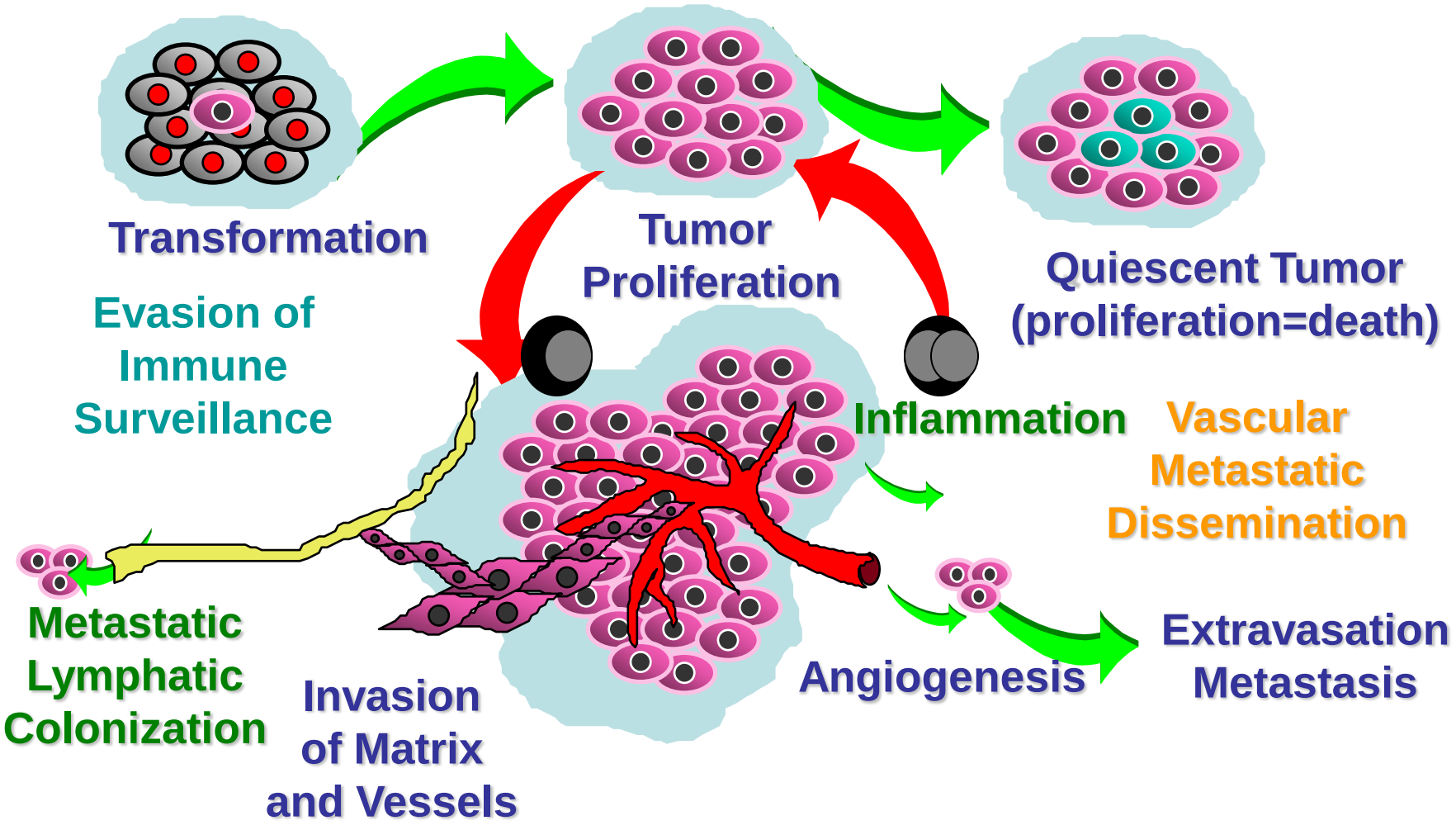
- Celecoxib for the Prevention of Colorectal Adenomatous Polyps
  - Nadir Arber, N Eng J. Medicine 2006
- Celecoxib for the Prevention of Sporadic Colorectal Adenomas
  - Monica M. Bertagnolli, N Engl J Med. 2006
- Effect of Celecoxib on Cardiovascular Events and Blood Pressure in Two Trials for the Prevention of Colorectal Adenomas
  - Scott D. Solomon, Circulation. 2006

COX2, Angiogenesis and cardiovascular complications

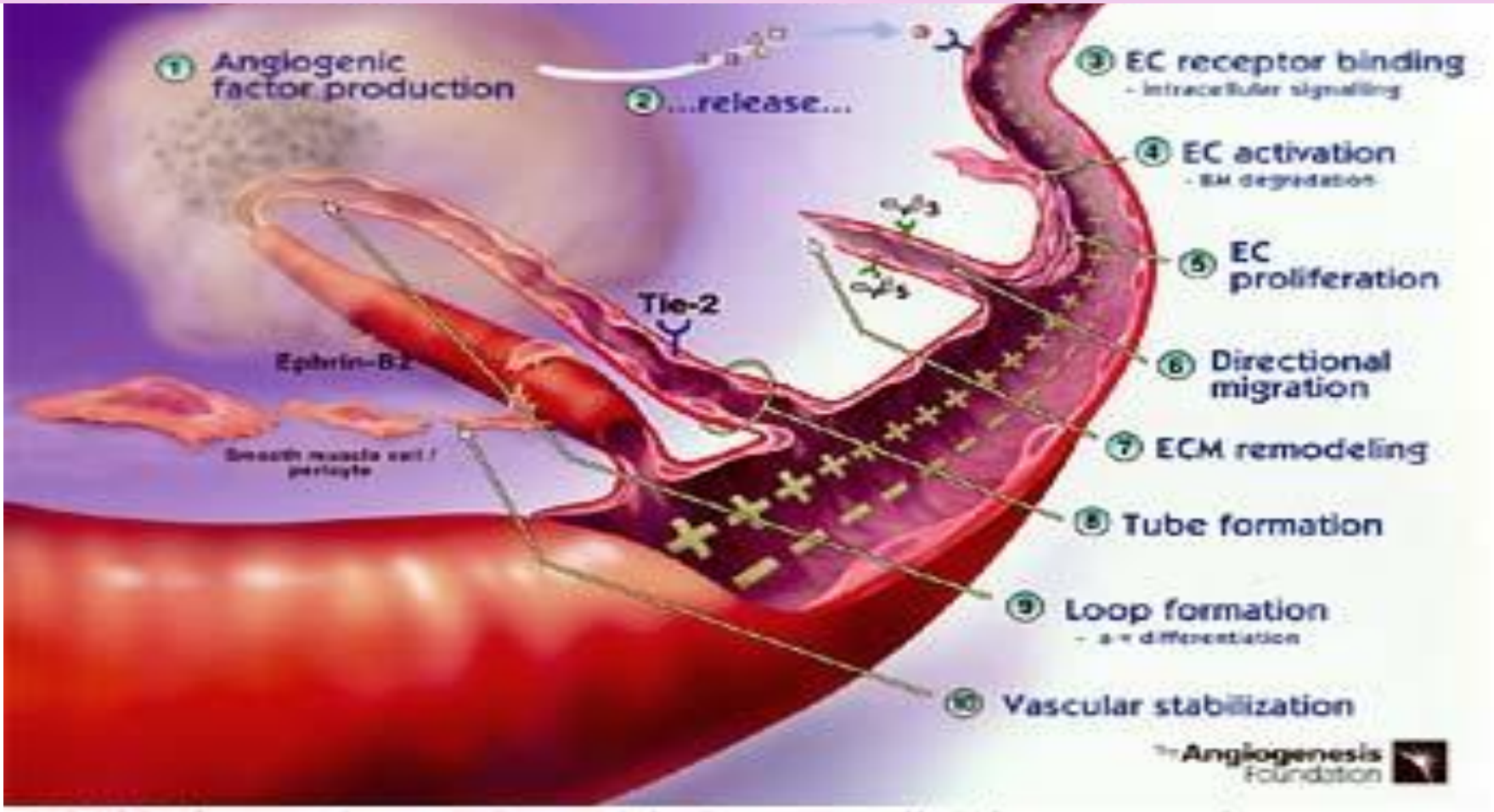


Albini & Noonan
JNCI 97:859-60, 2005

Tumor Progression



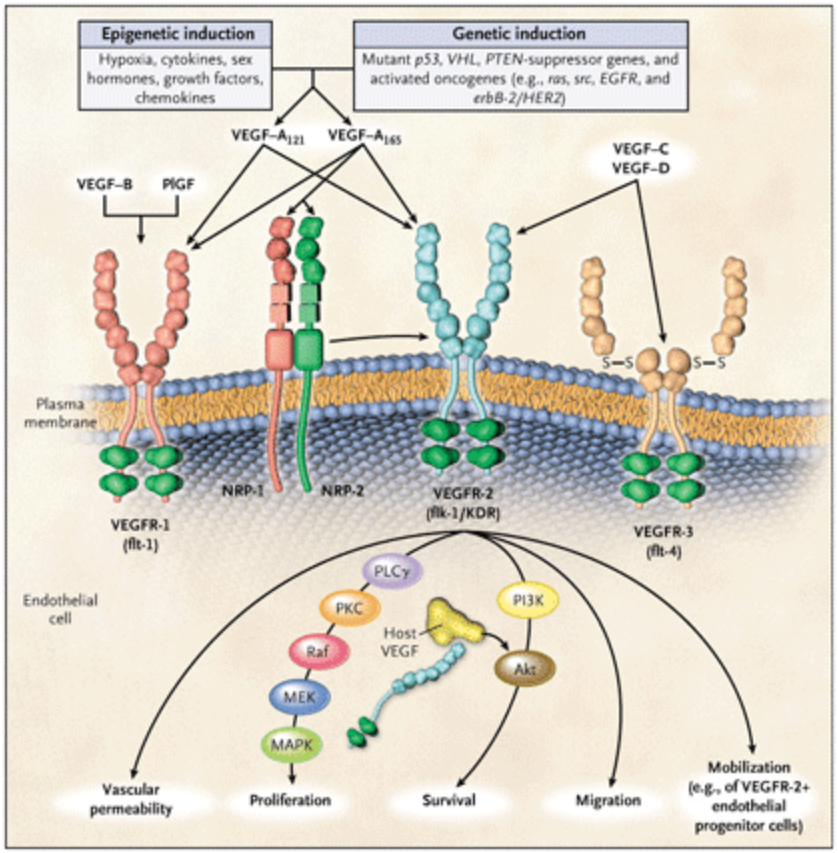
Angiogenesis: cascade of events



Angiogenic Factors Produced by Tumor Cells

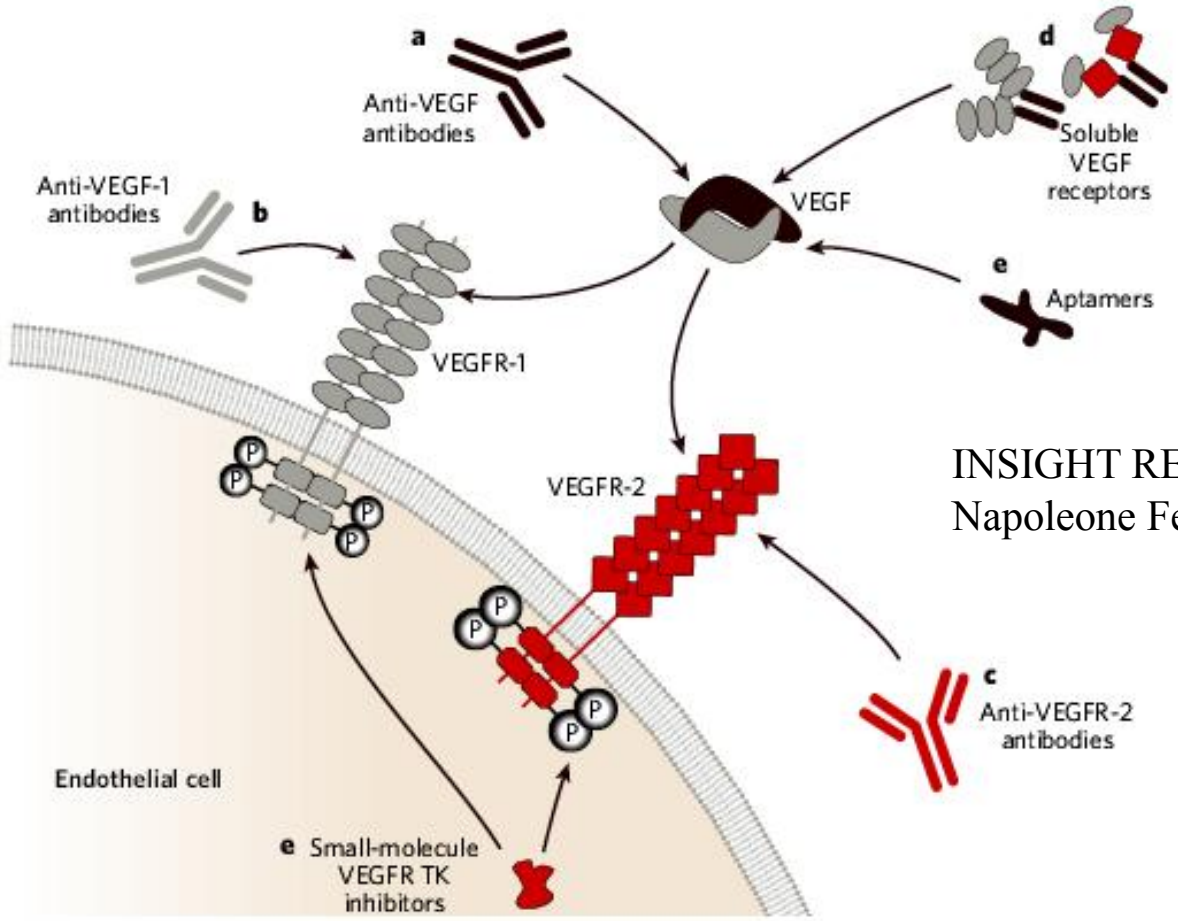
- VEGFs
- bFGFs
- HGF
- EGFs
- IL-8
- PlGF
- PDGF
- IGF-I
- TGF-α
- TGF-β
- TNF-α
- GM-CSF
- Angiopoietins
- Angiogenin

The Family of VEGF Molecules and Receptors



Tumor Angiogenesis-Robert Kerbel- NEJM May 8, 2008

Concepts of angiogenesis inhibition in the clinic



INSIGHT REVIEW NATURE 438: 967
Napoleone Ferrara & Robert S. Kerbel

Angiogenesis inhibitors approved for clinical use

Date of approval	Drug	Place	Disease
May 2003	**Velcade** (Bortezomib)	U.S. (FDA)	Multiple myeloma
December 2003	**Thalidomide**	Australia	Multiple myeloma
February 2004	***Avastin** (Bevacizumab)	U.S. (FDA)	Colorectal cancer
November 2004	**Tarceva** (Erlotinib)	U.S. (FDA)	Lung cancer
December 2004	***Avastin**	Switzerland	Colorectal cancer
December 2004	***Macugen**	U.S. (FDA)	Macular degeneration
January 2005	***Avastin**	European Union (25 countries)	Colorectal cancer
September 2005	***Endostatin** (Endostar)	China (SFDA)	Lung cancer
December 2005	***Nexavar** (Sorafenib)	U.S. (FDA)	Kidney cancer
December 2005	**Revlimid**	U.S. (FDA)	Myelodysplastic sindrome
January 2006	***Sutent** (Sunitinib**)**	U.S. (FDA)	Gastric (GIST), Kidney cancer
June 2006	***Lucentis**	U.S. (FDA)	Macular degeneration
October 2006-8	***Avastin**	U.S. (FDA)	Lung cancer and breast cancer

***** “pure” antiangiogenic agents

Cardiotoxicity of targeted drugs

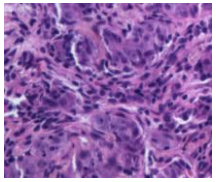
Agent	Class	Tyrosine kinase target(s)	Cancer target(s)	Other toxicity
*Drugs with known or likely cardiotoxicity**				
Trastuzumab (Herceptin)	mAb	ERBB2	ERBB2⁺ breast cancer	Infusion reactions, neutropaenia
Imatinib (Gleevec)	TKI	ABL1/2, PDGFRα/β, KIT	CML, Ph⁺ B-ALL, CMML, CEL, GIST	Oedema, nausea, myelosuppression, immunosuppression (?)
Dasatinib (Sprycel)	TKI	ABL1/2, PDGFRα/β, KIT, Src family	CML	Myelosuppression, oedema, pleural/pericardial effusion, panniculitis, QT prolongation, bleeding
Nilotibib (Tasigna)	TKI	ABL1/2, PDGFRα/β, KIT	CML	Myelosuppression, hyperbilirubinaemia, rash, QT prolongation
Sunitinib (Sutent)	TKI	VEGFR1–3, KIT, PDGFRα/β, RET, CSF1R, FLT3	Renal cell carcinoma, GIST	Haemorrhage, hypertension, adrenal dysfunction, hypothyroidism
Sorafenib (Nexavar)	TKI	VEGFR2, PDGFRβ, KIT, FLT3, RAF1, BRAF	Renal cell carcinoma, melanoma	Skin rash, hypertension, haemorrhage, acute coronary syndromes
Bevacizumab (Avastin)	mAb	VEGFA	Colorectal cancer, NSCLC	Haemorrhage, gastrointestinal perforation, poor wound healing, hypertension, neutropaenia, arterial thromboembolism
Drugs with low cardiotoxicity				
Lapatinib (Tykerb)	TKI	EGFR, ERBB2	Breast cancer	Skin rash, diarrhoea
Gefitinib (Iressa)	TKI	EGFR	NSCLC	Skin rash, diarrhoea, nausea, interstitial lung disease
Erlotinib (Tarceva)	TKI	EGFR	NSCLC, pancreatic cancer	Skin rash, diarrhoea, nausea, interstitial lung disease
Cetuximab (Erbitux)	mAb	EGFR	Colorectal cancer, squamous cell carcinoma of head/neck	Skin rash, infusion reactions, interstitial lung disease, hypomagnesaemia
Panitumumab	mAb	EGFR	Colorectal cancer	Skin rash

*Rate of cardiotoxicity is known only for trastuzumab and lapatinib. B-ALL, B-cell acute lymphoblastic leukaemia; CEL, chronic eosinophilic leukaemia; CML, chronic myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; CSF1R, colony-stimulating factor 1 receptor; EGFR, epidermal growth factor receptor; FLT3, FMS-related tyrosine kinase 3; GIST, gastrointestinal stromal tumour; mAb, humanized monoclonal antibody; NSCLC, non-small-cell lung cancer; PDGFR, platelet-derived growth factor receptor; Ph⁺, Philadelphia chromosome positive; QT prolongation, prolongation of the QT interval on electrocardiogram that may predispose to arrhythmia; RET, rearranged during transfection; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

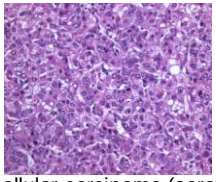
Force T et al. Nature Rev Cancer 2007; 7: 332-44

Systemic Effects of Anti-VEGF Therapy

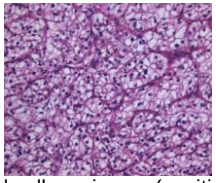
Tumor Tissues
(VEGF upregulated)



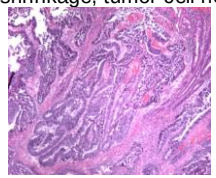
Lung cancer (bevacizumab)
Inhibition of tumor growth, tumor cavitation



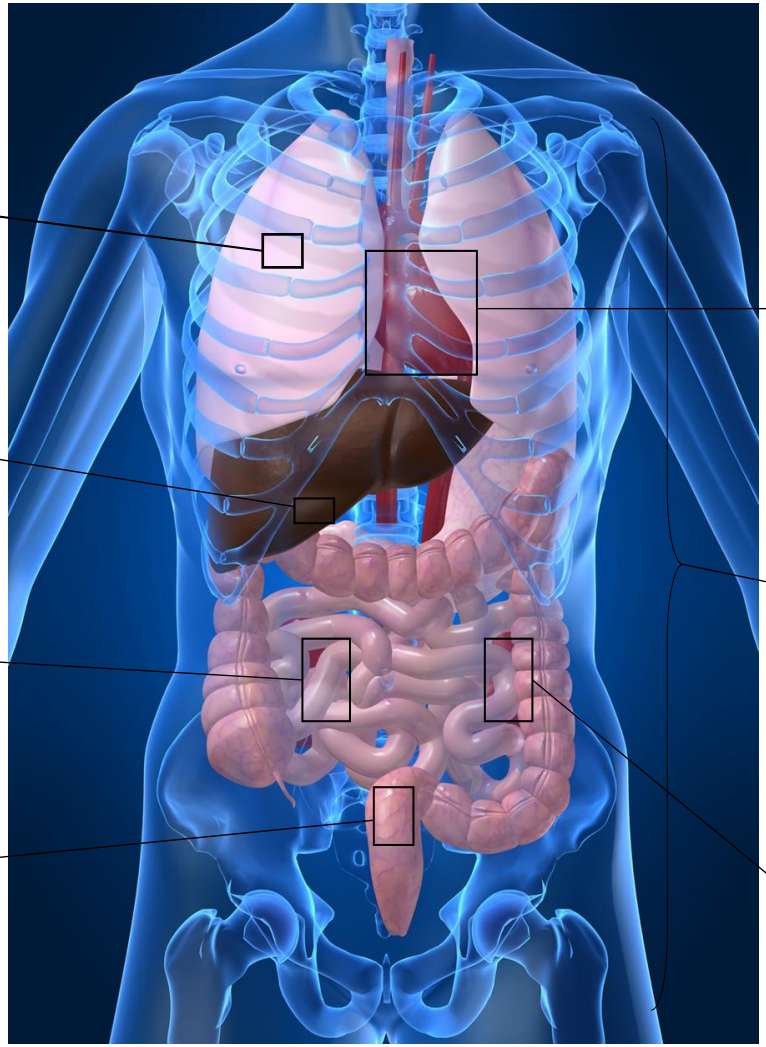
Hepatocellular carcinoma (sorafenib)
Tumor necrosis



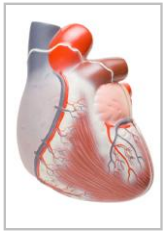
Renal cell carcinoma (sunitinib)
Tumor shrinkage, tumor cell necrosis



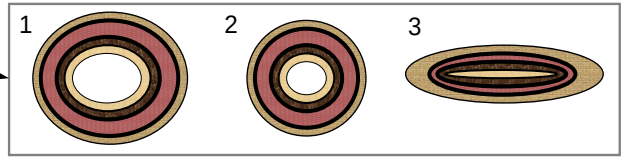
Colorectal cancer (bevacizumab)
Deceleration of tumor growth
efficient chemotherapy delivery



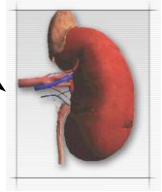
Normal Tissues
(VEGF constitutively expressed)



Hypertensive remodeling
Microvascular rarefaction
Cardiomyopathy (sunitinib and sorafenib)



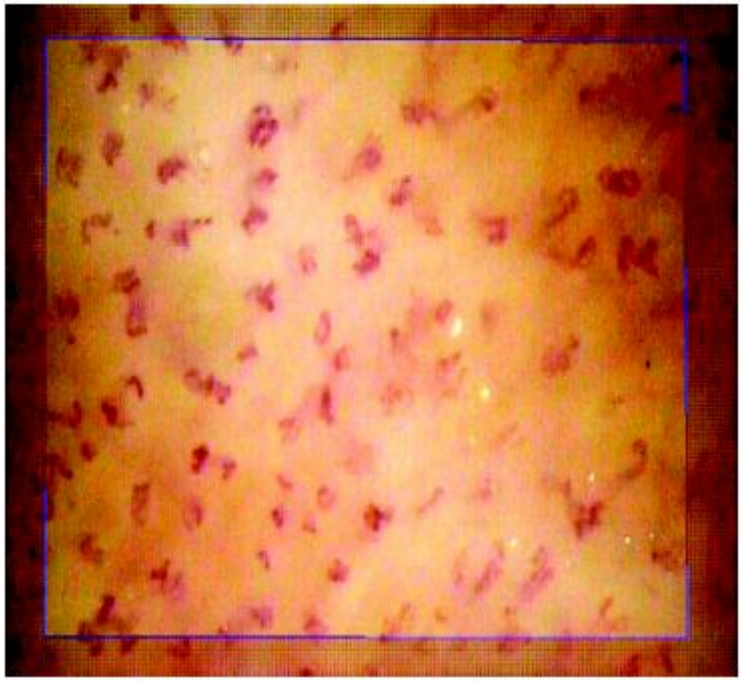
Microcirculation: 1. normal arteriole, 2. functional rarefaction
(endothelial dysfunction,vasoconstriction), 3. anatomic rarefaction



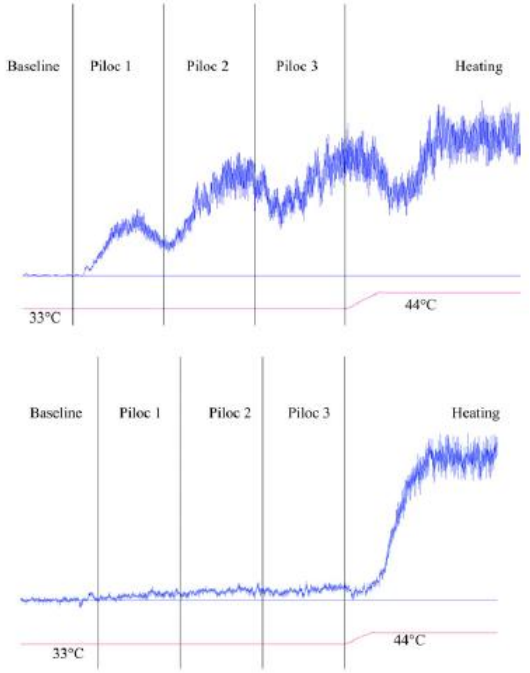
Thrombotic microangiopathy
Glomerulopathy / glomerulonephritis
Proteinuria
Hypertensive nephropathy

Vaklavos et al, Oncologist, 2010

Crucial role for microcirculation in the rising of blood pressure following angiogenesis inhibition by bevacizumab



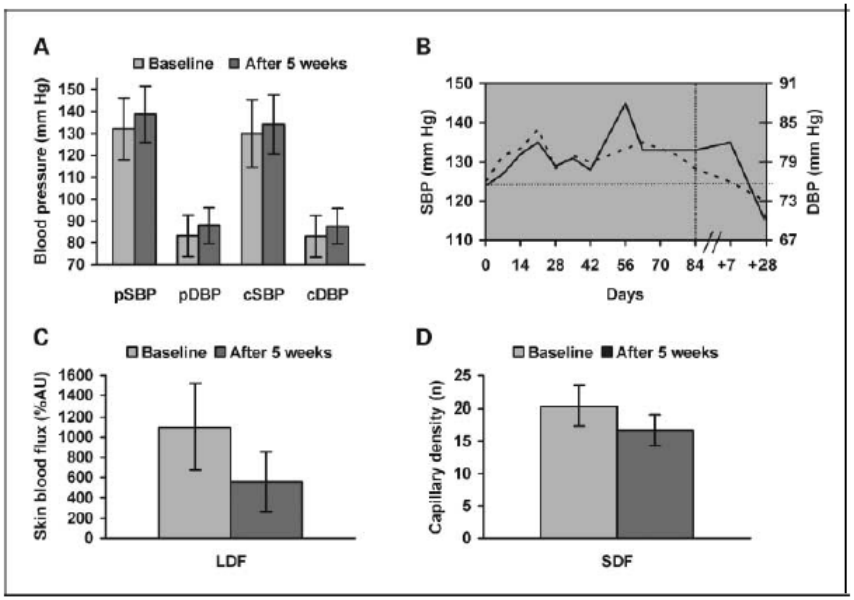
Typical video microscopic image of capillaries in the phalanx skin during venous occlusion. The blue rectangle represents a calibrated 1-mm^2 surface. The structural capillary density is the number of capillary structures in this surface area.



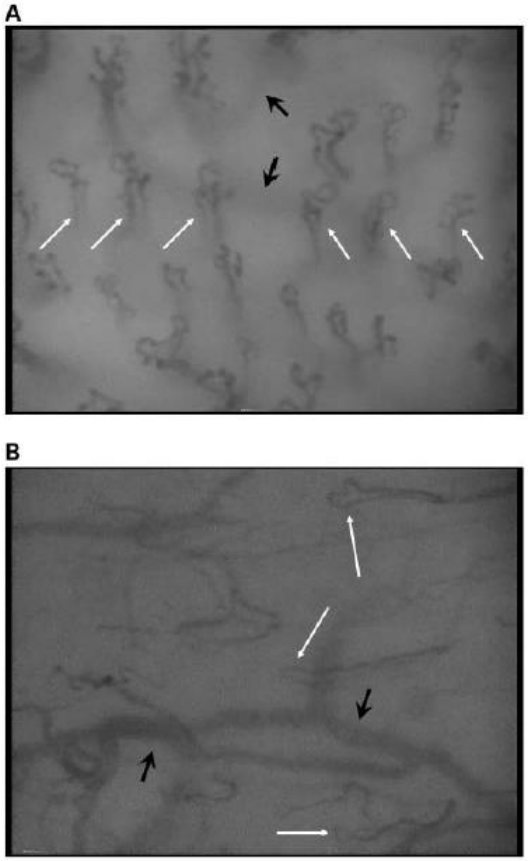
Typical examples of laser Doppler recordings before (upper figure, before treatment) and after a 6-month bevacizumab treatment (lower figure, altered response). Vertical lines indicate the successive administrations of pilocarpine. The red line represents the skin temperature maintained at 33°C during baseline and pilocarpine administrations and heated at 44°C for recording of the maximal skin flow under local vasodilation.

Mourad et al. Annals of Oncology 2008; 19: 927-934

Hypertension and rarefaction during treatment with telatinib



Blood pressure (A), skin blood flux (C), and capillary density (D) results at baseline and after 5 wk of treatment with telatinib. B, mean systolic blood pressure (continuous line) and mean diastolic blood pressure (dashed line) before treatment, weekly during treatment, and after discontinuation of telatinib treatment. A horizontal dashed line was added at baseline systolic blood pressure and baseline diastolic blood pressure for facilitation of reading. Left from the vertical line blood pressures measured in the first 84 d of treatment. Right from the vertical line blood pressures measured 7 and 28 d after discontinuation of treatment. pSBP, peripheral systolic blood pressure; pDBP, peripheral diastolic blood pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; LDF, laser doppler flow; %AU, percentage of change from baseline in arbitrary units; n, number.



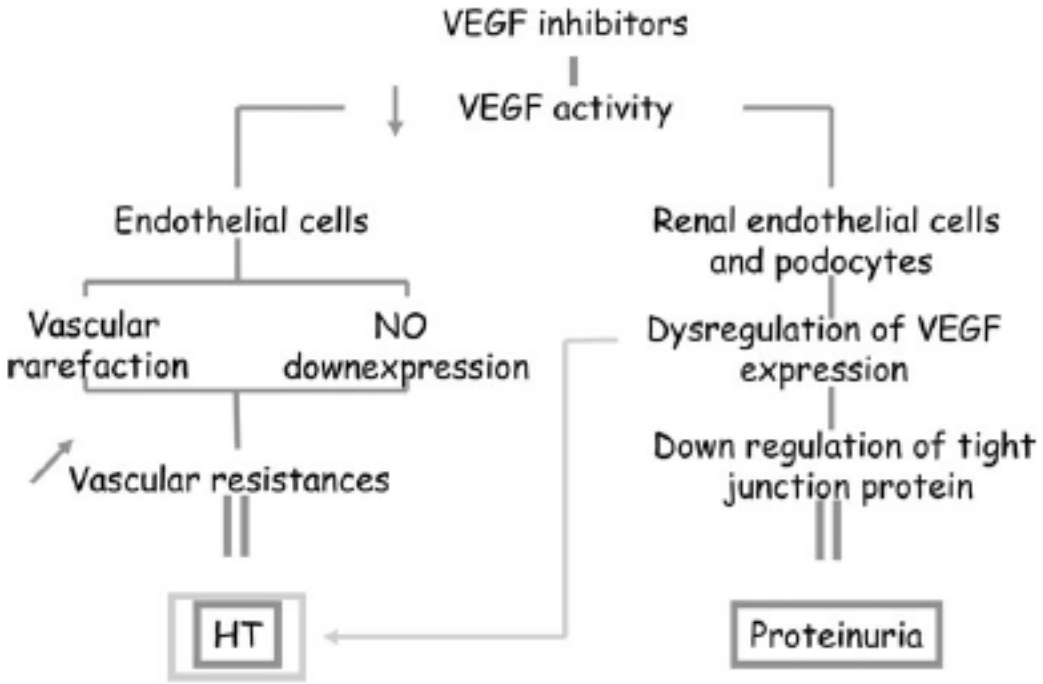
SDF images demonstrating visible capillary loops of a representative patient. A, at baseline. B, after 5wk of telatinib treatment. Black arrows, larger venules; white arrows, individual superficial capillary loops.

Steeghs et al. Clin Cancer Res 2008; 14: 3470-76

Hypertension during antiangiogenic therapy: friend or foe?

- Hypertension is one of the most frequent side-effects of systemic inhibition angiogenesis signaling.
- Its incidence and severity are dependent on the type of drugs, dose, and schedule used.
- The recognition of this side effect is an important issue since poorly controlled hypertension could lead to serious cardiovascular events.
- On the other hand, it may be a predictive factor of oncologic response

Mechanisms of hypertension induced by angiogenic inhibitors



The therapeutic low free VEGF activity contributes to the increase of systemic vascular resistances as a result of vascular rarefaction and down-regulation of nitric oxide production, dysregulation of renal endothelial cells and podocyte VEGF expression leading to thrombotic microangiopathy and thereby hypertension.

Incidence of VEGF inhibitors-associated hypertension compared with controls in randomized phase III clinical trials

Disease	Author	Regimen	Patient, *n*	Hypertension (%)	
				All grades	Grade 3/4
Bevacizumab					
mCRC	Hurwitz et al. [5]	IFL	397	8.3	2.3
		IFL + bevacizumab, 5 mg/kg	393	22.4	8.3
	Hurwitz et al. [6]	Placebo + IFL	98	14.3	3.1
		Fluorouracil + leucovorin + bevacizumab, 5 mg/kg	109	33.9	18.3
	Giantonio et al. [7]	FOLFOX4 + bevacizumab, 10 mg/kg	287	NA	6.2
		FOLFOX4	285	NA	1.8
		Bevacizumab, 10 mg/kg	234	NA	7.3
mRCC	Yang et al. [8]	Placebo	40	2.5	0
		Placebo + bevacizumab, 3 mg/kg	37	2.7	0
		Placebo + bevacizumab, 10 mg/kg	39	35.9	20.5
	Escudier et al. [9]	Placebo + interferon alpha	322	9	<1
		Interferon alpha + bevacizumab, 10 mg/kg	327	26	3
	Miles et al. [14]	Docetaxel + placebo	734	NA	1.3
		Docetaxel + bevacizumab, 7.5 mg/kg		NA	0.4
		Docetaxel + bevacizumab, 15 mg/kg		NA	3.2
NSCLC	Sandler et al. [10]	Carboplatin + paclitaxel	444	NA	0.7
		Carboplatin + paclitaxel + bevacizumab, 15 mg/kg	434	NA	7
	Manegold et al. [17]	Placebo	347	NA	2
		Bevacizumab, 7.5 mg/kg	345	NA	6
		Bevacizumab, 15 mg/kg	351	NA	9
mBC	Miller et al. [12]	Capecitabine	215	2.4	0.5
		Capecitabine + bevacizumab, 15 mg/kg	247	33.5	17.9
	Miller et al. [13]	Paclitaxel	346	NA	0
		Paclitaxel + bevacizumab, 10 mg/kg	365	NA	14.8
Sunitinib					
GIST	Demetri et al. [15]	Placebo	105	4	0
		Sunitinib, 50 mg/day (4 weeks on, 2 weeks off)	207	11	3
mRCC	Motzer et al. [16]	Interferon	360	1	1
		Sunitinib, 50 mg/day (4 weeks on, 2 weeks off)	375	24	8
Sorafenib					
mRCC	Escudier et al. [17]	Placebo	452	2	<1
		Sorafenib, 400 mg twice daily	451	17	4
Vatalanib					
mCRC	Hecht et al. [18]	Placebo + FOLFOX	583	NA	5.9
		Vatalanib + FOLFOX	585	NA	20.6
	Kohne et al. [19]	Placebo + FOLFOX	855	NA	5.9
		Vatalanib + FOLFOX		NA	20.6

VEGF, vascular endothelial growth factor; mBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; NA, not available; IFL, irinotecan, fluorouracil, leucovorin; mRCC, metastatic renal cell carcinoma; NSCLC, non-small-cell lung cancer; GIST, gastrointestinal stromal tumor.

Izzedine H et al. Annals of Oncology 2009; 20: 807-815

Bevacizumab-related hypertension in patients with metastatic colorectal cancer receiving bevacizumab as first-line therapy in combination with irinotecan and 5-FU in an Italian study
- patient characteristics-

	Patients with bevacizumab-related hypertension	Patients without bevacizumab-related hypertension	*P*
M/F	3/5	22/9	
Age at diagnosis (range)	53 years (48–70)	58 years (30-69)	
Primary tumor (colon/rectum)	6/2	24/7	
ECOG PS 0–1	5 (62.5%)	20 (64.5%)	
ECOG PS 2–3	3 (37.5%)	11 (35.5%)	
Medical history of arterial hypertension	2 (25%)	9 (29%)	
Antihypertensive treatment			
Diuretics/beta-adrenoceptor blocking drugs	5 (50%)	5 (55%)	
ACE inhibitors	4 (40%)	3 (33%)	
Others	1 (10%)	1 (12%)	
Previous adjuvant chemotherapy	3 (37.5%)	13 (42%)	
Primary tumor (colon/rectum)	6/2	24/7	
Sites of metastasis (%)			
Liver	6 (43%)	26 (60%)	
Lung	2 (14%)	6 (14%)	
Peritoneum	1 (7%)	4 (9%)	
Distant lymph nodes	4 (29%)	6 (14%)	
Bone	1 (7%)	1 (2%)	
Baseline CEA			
>30 ng/ml	2 (25%)	10 (32%)	
<30	5 (63%)	18 (58%)	
Not done	1 (12%)	3 (10%)	
Median duration of treatment (weeks)	56.4	12.2	
Dose administered (percentage of the planned dose)			
Irinotecan/5-FU bolus/infusional 5-FU	75/90/90	80/90/90	
Bevacizumab	100	100	
Second-line chemotherapy (*n*)	6 (75%)	28 (90%)	
Oxaliplatin based	5 (83%)	24 (86%)	
Others	1 (17%)	4 (14%)	
Response rate (%)	6/8 (75%)	10/31 (32%)	0.04
Median PFS (months)	14.5	3.1	0.04
Median OS (months)	Not reached	15.1	

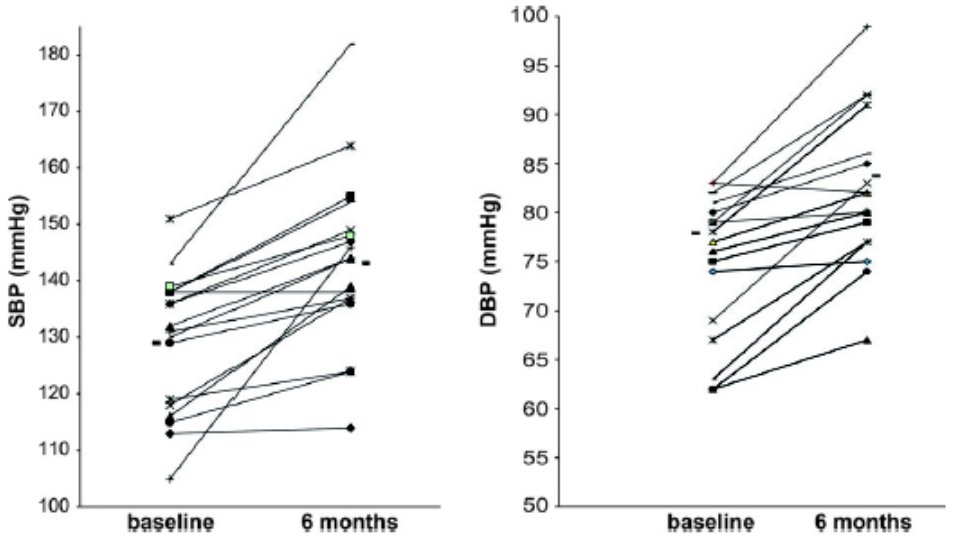
Only statistically significant *P* values have been indicated.
ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; 5-FU, 5-fluorouracil; PFS, progression-free survival; OS, overall survival.

Scartozzi M et al. Annals of oncology 2009; 20:227-230

Bevacizumab-related hypertension and microcirculation damage in patients with metastatic colorectal cancer treated with bevacizumab in a French study
- patient characteristics-

	Mean ± SD (range)
Age (years)	59 ± 9 (45–79)
Weight (kg)	74 ± 75 (42–104)
Body mass index (kg/m^2)	26.4 ± 4.8 (18.8–35.1)
Serum creatinine (μmol/l)	78 ± 18
Serum glucose (g/l)	1.16 ± 0.3
Bevacizumab cumulative dose (g)	3.16 ± 0.9 (1.57–4.8)

SD, standard deviation.



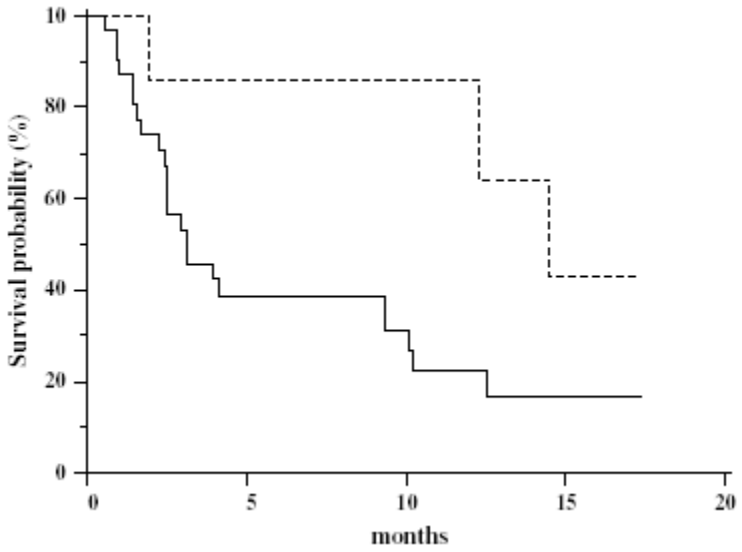
Scatter plot of systolic blood pressure (SBP) and diastolic blood pressure (DBP) at baseline and after 6 months of treatment with bevacizumab.

Mourad et al. Annals of Oncology 2008; 19: 927-934

Antiangiogenic therapy for cancer: is hypertension a good sign?

Arterial hypertension occurring during anti-angiogenic therapy has been correlated with the biological inhibition of angiogenesis-related pathways and, given its molecular link with anti-angiogenic mechanisms, it may represent a possible clinical marker for treatment efficacy, analogously to what has been demonstrated for skin rush.

Antiangiogenic therapy for cancer: is hypertension a good sign?
-the data-



Median progression-free survival of colorectal cancer patients with grades 2–3 bevacizumab-related arterial hypertension and without bevacizumab-related arterial hypertension. Patients with grades 2–3 bevacizumab-related arterial hypertension (-------) and without bevacizumab-related arterial hypertension (———) (P = 0.04).

Scartozzi M et al. Annals of oncology 2009; 20:227-230

Summary of the Italian study

Among patients with bevacizumab-related hypertension, a significant improvement in global clinical outcome, particularly in response rate and progression free survival, was observed.

It can be speculated that these results could be due to:

- bevacizumab-related hypertension may involve different biological pathways in comparison with other forms of hypertension;

<u>If confirmed</u>, these observation imply that the identification of a reliable clinical factor such as grades 2-3 arterial hypertension developing during bevacizumab therapy may constitute an early indicator of antitumor activity, whereas lack of this side-effect could represent an important warning of lack of activity and may ultimately suggest an early change in treatment strategy.

Scartozzi M et al. Annals of oncology 2009; 20:227-230

Hypertension at ASCO 2010

- **Brd. 19G Pulmonary hypertension (PH) in patients (pts) with CML treated with tyrosine kinase inhibitors (TKIs). (Abstract #6597)**
- S. Gaballa, A. Al-Kali, H. Kantarjian, E. Jabbour, A. Quintas-Cardama, M. Ayoubi, G. Borthakur, S. M. O'Brien, J. E. Cortes (pag 96)

  Brd. 6H Correlation between bevacizumab-related hypertension and response in mCRC patients. (Abstract #3581)
- A. De Stefano, L. Cannella, C. Carlomagno, A. Crispo, R. Bianco, R. Marciano, S. Pepe, S. De Placido (pag 260)
- **Brd. 5D A clinical and biological profile to predict risk of development of hypertension in patients with non-clear cell renal cell carcinoma treated with sunitinib. (Abstract #4601)**
- N. A. Ilias-Khan, A. Y. Khakoo, N. M. Tannir
- **Brd. 53B Pharmacoepidemiology of clinically relevant hypothyroidism and hypertension from sunitinib and sorafenib. (Abstract #9149)**
- C. M. Walko, R. E. Aubert, N. M. La-Beck, G. Hawk, V. Herrera, H. Kourlas, R. S. Epstein, H. L. McLeod
- **Brd. 8H Role of VEGF and VEGFR2 single nucleotide polymorphisms (SNPs) in predicting treatment-induced hypertension (HTN) and clinical outcome (CO) in metastatic clear cell RCC (mccRCC) patients (pts) treated with sunitinib.**
- **(Abstract #4629)**
- J. J. Kim, S. A. Vaziri, P. Elson, B. I. Rini, A. Patel, N. S. Basappa, M. Ganapathi,
- **Brd. 51B Sunitinib (SU)-related hypertension in a randomized placebo (P)-controlled trial of GIST patients (pts). (Abstract #10059)**
- M. Ewer, T. M. Suter, D. J. Lenihan, L. Niculescu, A. Breazna, R. J. Motzer, G. D. Demetri
- **Brd. 11A Analysis of early hypertension (HTN) and clinical outcome with bevacizumab (BV). (Abstract #3039)**
- H. Hurwitz, P. S. Douglas, J. P. Middleton, G. W. Sledge, D. H. Johnson, D. A. Reardon, D. Chen, O. Rosen
- **Brd. 5D A clinical and biological profile to predict risk of development of hypertension in patients with non-clear cell renal cell carcinoma treated with**
- **sunitinib. (Abstract #4601)**
- N. A. Ilias-Khan, A. Y. Khakoo, N. M. Tannir
- **Brd. 5E Risk of congestive heart failure with VEGF-targeted therapy: A systematic review and meta-analysis of clinical trials. (Abstract #4602)**
- F. A. Schutz, Y. Je, G. R. Azzi, T. K. Choueiri pag 361
- Hemorrages
- **Brd. 44F Baseline (BL) radiographic characteristics and severe pulmonary hemorrhage (SPH) in bevacizumab (BV)-treated non-small cell lung cancer (NSCLC) patients (pt): Results from ARIES, an observational cohort study**
- **(OCS). (Abstract #7619)**
- P. Kumar, N. A. Fischbach, J. R. Brahmer, D. R. Spigel, S. Beatty, S. Teng, E. D. Flick, A. Sing, T. J. Lynch, ARIES Investigators

Antiangiogenic therapy for cancer: is hypertension a good sign?

- Hypertension might be a good sign of oncologic response, but MUST be TREATED!
- If the oncologist suggests increasing the dose until the patient has hypertension, SAY NO! There is to date no cause-effect data

Significance of VEGF-signaling inhibition-induced proteinuria

Proteinuria can be a major clue to underlying renal disease or a transient finding in those patients. The onset of urinary protein excretion is of importance because proteinuria is a prognostic marker and an independent risk factor for cardiovascular diseases.

Proteinuria induced by VEGF signaling inhibition

Table 2 – Incidence of VEGF-targeted therapy-associated proteinuria compared to controls in selected randomised phase II/III clinical trials.

Disease	Author	Regimen	Patient, n	Proteinuria (%)	
				All grades	Grade 3/4
mCRC	Hurwitz et al., 2004	Irinotecan, Fluorouracil, leucovorin	397	21.7	0.8
		IFL + Bevacizumab 5 mg/kg	393	26.5	0.8
	Hurwitz et al., 2005	Fluorouracil + leucovorin + Placebo	98	25.1	0
		Fluorouracil + leucovorin + Bevacizumab 5 mg/kg	109	34.9	1.8
	Giantonio et al., 2007	FOLFOX4 + Bevacizumab 10 mg/kg	287	NA	0.7
		FOLFOX4	285	NA	0
			234	NA	0
	Tang et al., 2008	VEGF Trap 4 mg/kg every 2 weeks	51	49	7.8
mRCC	Yang et al., 2003	Placebo	40	15	0
		Placebo + Bevacizumab 3 mg/kg	37	15	2
		Placebo + Bevacizumab 10 mg/kg	39	25	3
	Motzer et al., 2007	Interferon alpha	375	NA	NA
		Sunitinib 50 mg once daily for 4 weeks	375	NA	NA
	Escudier et al., 2007	Placebo + Interferon alpha	322	3	0
		Interferon alpha + Bevacizumab 10 mg/kg	327	18	7
	Escudier et al., 2007	Placebo	452	NA	NA
		Sorafenib 400 mg twice daily	451	NA	NA
	Rini et al., 2008	Interferon alpha	349	NA	0
		Interferon alpha + Bevacizumab 10 mg/kg	366	NA	15
	Hutson et al., 2007	Placebo	27	NA	NA
		Pazopanib 800 mg daily		NA	NA
	Rixe et al., 2007	Axitinib 5 mg twice daily	52	36.7	0
	Sridhar et al., 2007	AZD2171 45 mg daily	37	NA	NA
NSCLC	Sandler et al., 2006	Carboplatin + Paclitaxel	444	NA	0
		Carboplatin + Paclitaxel + Bevacizumab 15 mg/kg	434	NA	3.1
	Massarelli et al., 2007	VEGF Trap 4 mg/kg every 2 weeks	33	NA	9
mBC	Miller et al., 2005	Capecitabine	215	7.4	0
		Capecitabine + Bevacizumab 15 mg/kg	247	25.3	0.9
	Miller et al., 2007	Paclitaxel	346	NA	0
		Paclitaxel + Bevacizumab 10 mg/kg	365	NA	3.5
Ad TC	Cohen et al., 2008	Axitinib 5 mg twice daily	60	18	5
AdPC	Spano et al., 2008	Gemcitabine	34	NA	0
		Gemcitabine + Axitinib 5 mg twice daily	69	NA	0
Hepatoma	Cheng et al., 2009	Placebo	76	NA	NA
		Sorafenib 400 mg twice daily	150	NA	NA
EOC	Tew et al., 2007	VEGF Trap 2 or 4 mg/kg every 2 weeks	162	7	4

mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; ARMD, age-related macular degeneration; GIST, gastrointestinal stromal tumour; mBC, metastatic breast cancer; mRCC, metastatic renal cell carcinoma; AdTC, advanced thyroid cancer; AdPC, advanced pancreatic cancer; EOC, epithelial ovarian cancer; NA, not available.

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Incidence of kidney diseases in anti-VEGF-treated patients

Table 3 – Biopsy-documented kidney diseases in anti-VEGF-treated patients.

Disease	Targeted therapy		Past medical history and/or other previous or concomitant therapies	Proteinuria		Kidney biopsy findings	Follow-up after anti-VEGF discontinuation		Ref.
	Agent	Dose		Onset	NCI Grade (g/24 h)		Month	Proteinuria Grade (g/day)	
RCC	BVZ	10 mg/kg	Nephrectomy IFN-α	2 weeks	Grade 3 (6g)	Glomerular TMA and IgA ICGN	2	Grade 2 (2.63)	34
RCC	BVZ	N/A	Nephrectomy, Diabetes IFN-α	9 months	Grade 2 (1.8)	Glomerular TMA	16	Grade 2 (1.8)	35
RCC	BVZ	N/A	IFN-α	7 months	Grade 1/2	Glomerular TMA	N/A	N/A	35
NSCLC	BVZ	7.5 mg/kg	Carboplatin/paclitaxel	N/A	Grade 4	Cryoglobulinemic GN	N/A	N/A	39
BC	BVZ	15 mg/kg	CKD Capecitabine/Pamidronate	N/A	Grade 4	Collapsing GN	N/A	N/A	15
PC	BVZ	5 mg/kg	Gemcitabine/Capecitabine	1 month	Grade 4 (9.6)	Proliferative ICGN	9	Grade 1 (0.4)	40
HC	BVZ	7.5 mg/kg	Unremarkable	9 months	Grade 2 (3.4)	Glomerular TMA	9	Grade 2 (1.7)	36
HC	BVZ	7.5 mg/kg	Unremarkable	3 months	Grade 2 (2.7)	Glomerular TMA	3	Grade 0–1 (0.03)	36
BAC	BVZ	15 mg/kg	Gemcitabine/Cisplatine	N/A	Grade 1 (0.16)	Glomerular TMA	N/A	N/A	36
SLC	BVZ	10 mg/kg	CKD, Diabetes Cisplatin/Docetaxel	3 months	Grade 1 (0.5)	Glomerular TMA	2	Resolved	36
PC	BVZ	10 mg/kg	Gemcitabine, Erlotinib	5 months	Grade 4 (4.6)	Glomerular TMA	N/A	N/A	36
OC	BVZ	15 mg/kg	Unremarkable	9 months	Grade 1 (0.8)	Glomerular TMA	N/A	N/A	36
MDA	BVZ	10 mg/kg	Paclitaxel/Pamidronate	3 months	Grade 4 (3.6)	Glomerular TMAand Collapsing GN	6	Grade 1 (0.99)	37
OC	VEGF Trap	4 mg/kg	Gemcitabine LV5FU2/CPT11	1 week	Grade 4 (16.6)	Glomerular TMA	2	Grade 1 (0.3)	33
RCC	Sorafenib	400 mg/d	Nephrectomy Sunitinib	10 days	Grade 2 (2.4)	AIN	N/A	N/A	42
SH	Sunitinib	37.5 mg/d	Radiotherapy Taxol, adriamycine	2 weeks	Grade 2 (1)	Glomerular TMA	3	Undetectable	38

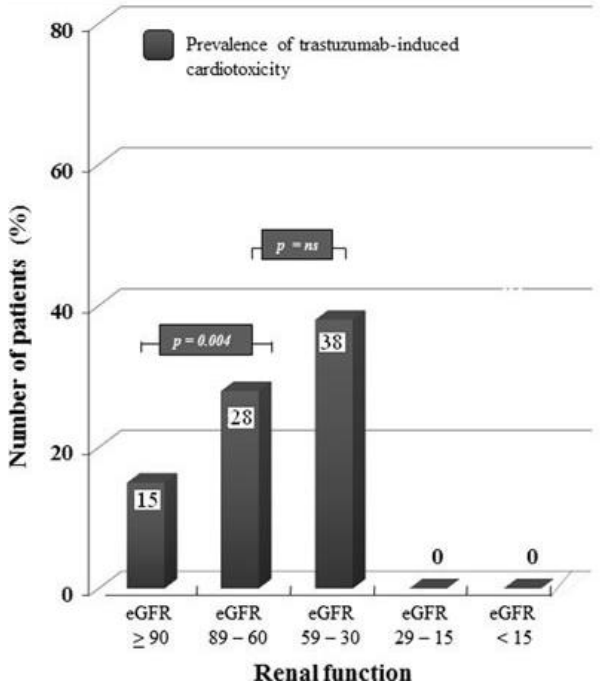
NCI, National Cancer Institute; VEGF, vascular endothelial growth factor; RCC, renal cell carcinoma; BVZ, bevacizumab; IFN-, interferon-alpha; TMA, thrombotic microangiopathy; ICGN, immune complex glomerulonephritis; N/A, not available; CKD, chronic kidney disease; NSCLC, non-small-cell lung cancer; BC, breast cancer; PC, pancreatic cancer; HC, hepatocarcinoma; BAC bronchoalveolar carcinoma; SLC small-cell lung carcinoma; OC, ovarian cancer; MDA: mammary ductal adenocarcinoma; LV5FU2, LV5FU2-CPT11, leucovorin5-fluorouracil/capecitabine; AIN, Acute interstitial nephritis; SH, skin hydradenoma.

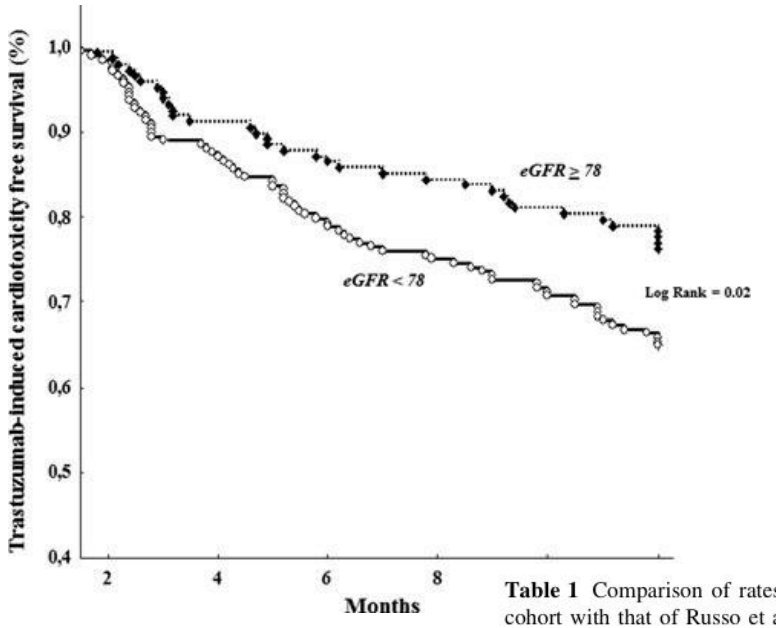
Izzedine H et al. Eur J Cancer 2010; 46: 439-48

Proteinuria as predictive marker

Whether the development of proteinuria might also serve as a surrogate marker of on-target effect (anti-tumor efficacy) and/or off-target effect (adverse event) is unknown.

Proteinuria as predictive marker of cardiotoxicity





Russo et al, Intern Emerg Med (2012) 7:439-46.

Table 1 Comparison of rates of RD in the InCHIANTI (untreated) cohort with that of Russo et al. (most treated with chemotherapy)

Kidney Function (eGFR)	Russo et al. [5] (all women)	Russo et al. [5] (women >60)	InCHIANTI [2] (women)
Class I (normal) >90	30 %	15 %	18.3 %
class II (mild RD)	61 % (eGFR 60–89)	69 % (eGFR 60–89)	40.6 % (eGFR 61–90)
class III (moderate RD)	9 % (eGFR 30–59)	16 % (eGFR 30–59)	37.8 % (eGFR 31–60)
(severe RD) <30	0 %	0 %	3.3 %

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