David M

Vernon Ca

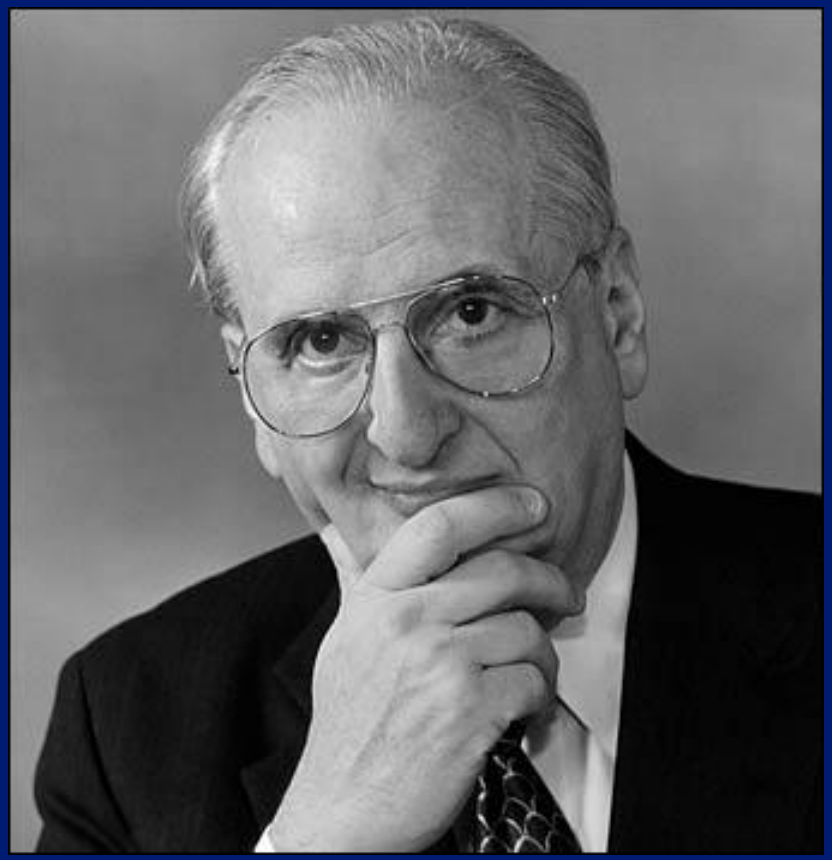
EACR Jo

Targeted therapies: Promises, successes, failures. Vienna September 2012

Disclaimer

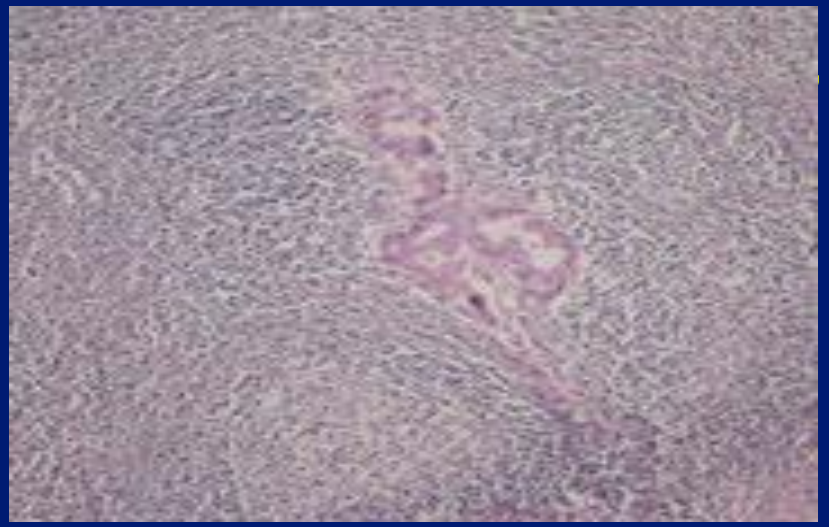
- I apologise (profusely) if I fail to mention:-
  - your favourite tumour type
  - your favourite anti-angiogenic agent
  - your favourite trial
  - your favourite clinical investigator (especially if it is you)
  - your favourite pharmaceutical company (especially if you are employed by one)

The Promise



Transplanted mouse tumours associated with microvasculature

Folkman J. Surg Forum 1962;13:81-83



Folkman J. N Engl J Med 1971;285:1182–6

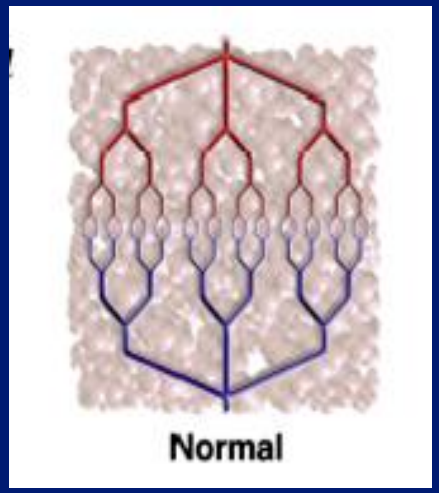
The hype

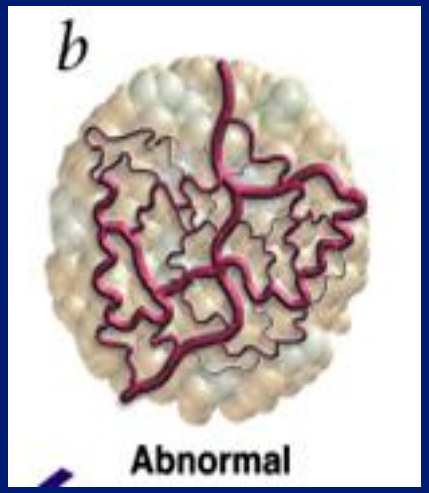
Folkman ‘will cure cancer within two years’

James Watson, Nobel Laureate

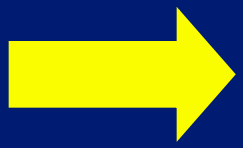
Some post-hoc rationalisation

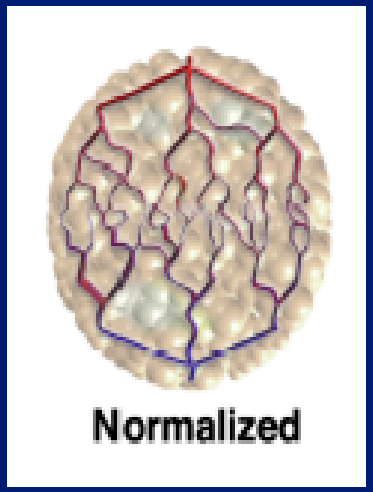
Anti-VEGF antibody ‘normalises’ tumour vasculature





Anti-VEGF

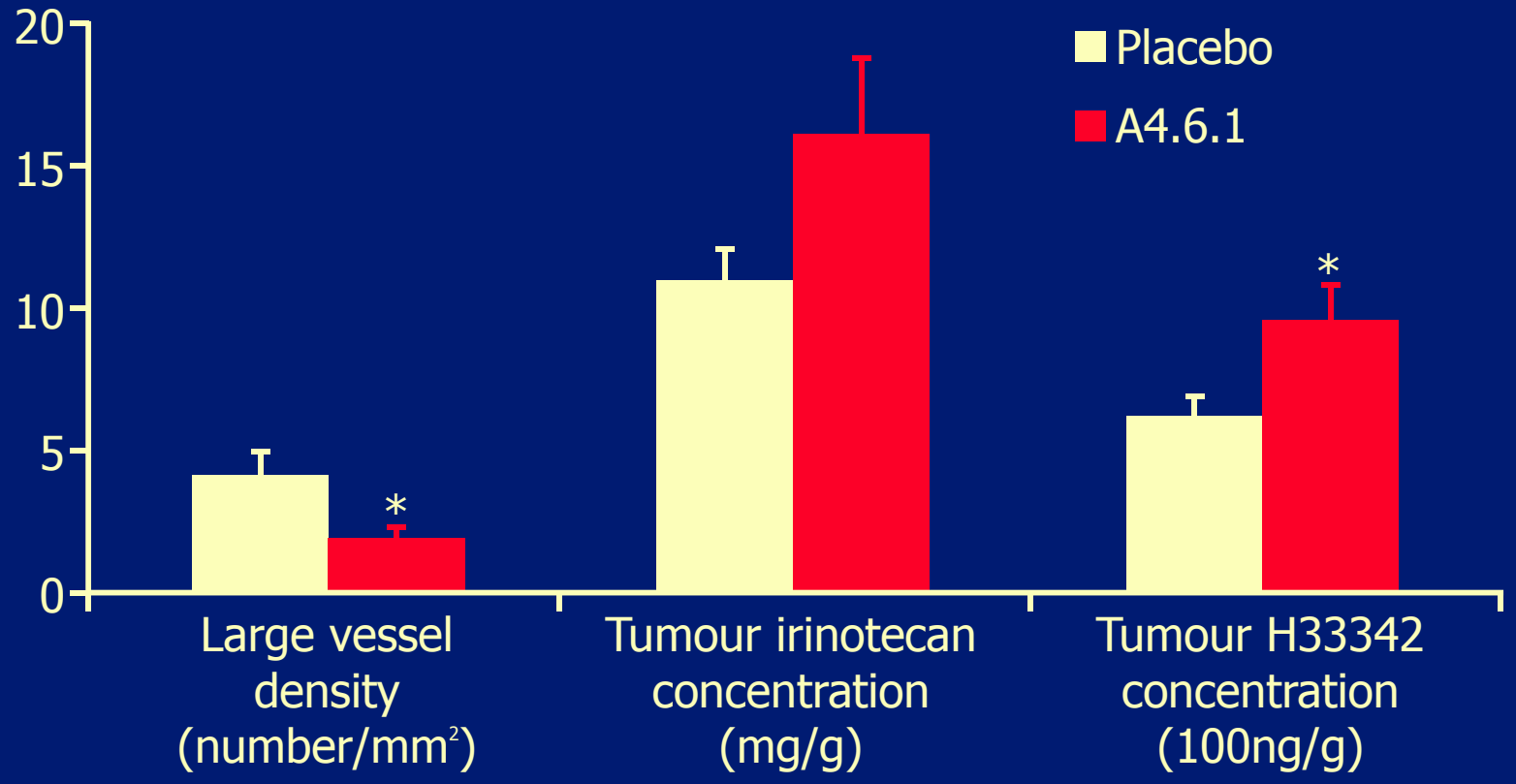




Reduces
interstitial fluid pressure
vessel density
Increases
drug delivery

Jain R. Nature Med 2001;7:987–9; Willett CG, et al. Nat Med 2004;10:145–7
Tong R, et al. Cancer Res 2004;64:3731–6

Pre-clinical studies of anti-VEGF therapy: ↑ delivery of chemotherapy



H33342 = tumour perfusion marker
*p<0.05 vs placebo

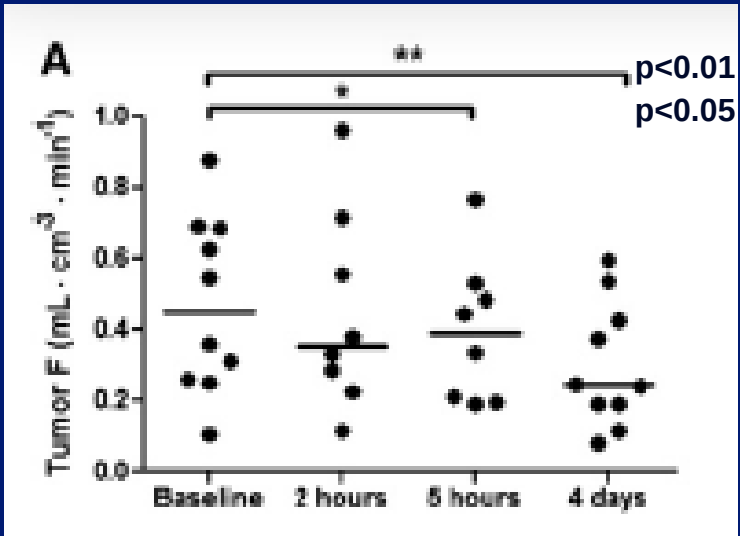
Wildiers H, et al. Br J Cancer 2003;88:1979–86

Cell PRESS

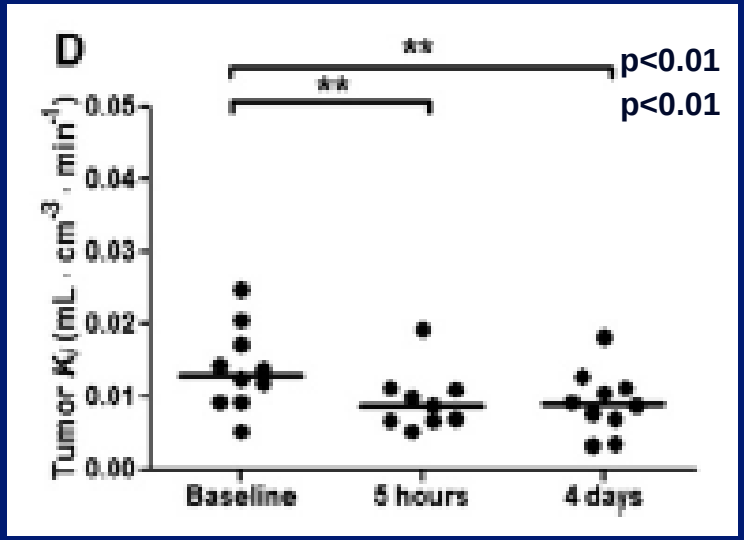
Cancer Cell
Article

Rapid Decrease in Delivery of Chemotherapy to Tumors after Anti-VEGF Therapy: Implications for Scheduling of Anti-Angiogenic Drugs

Perfusion

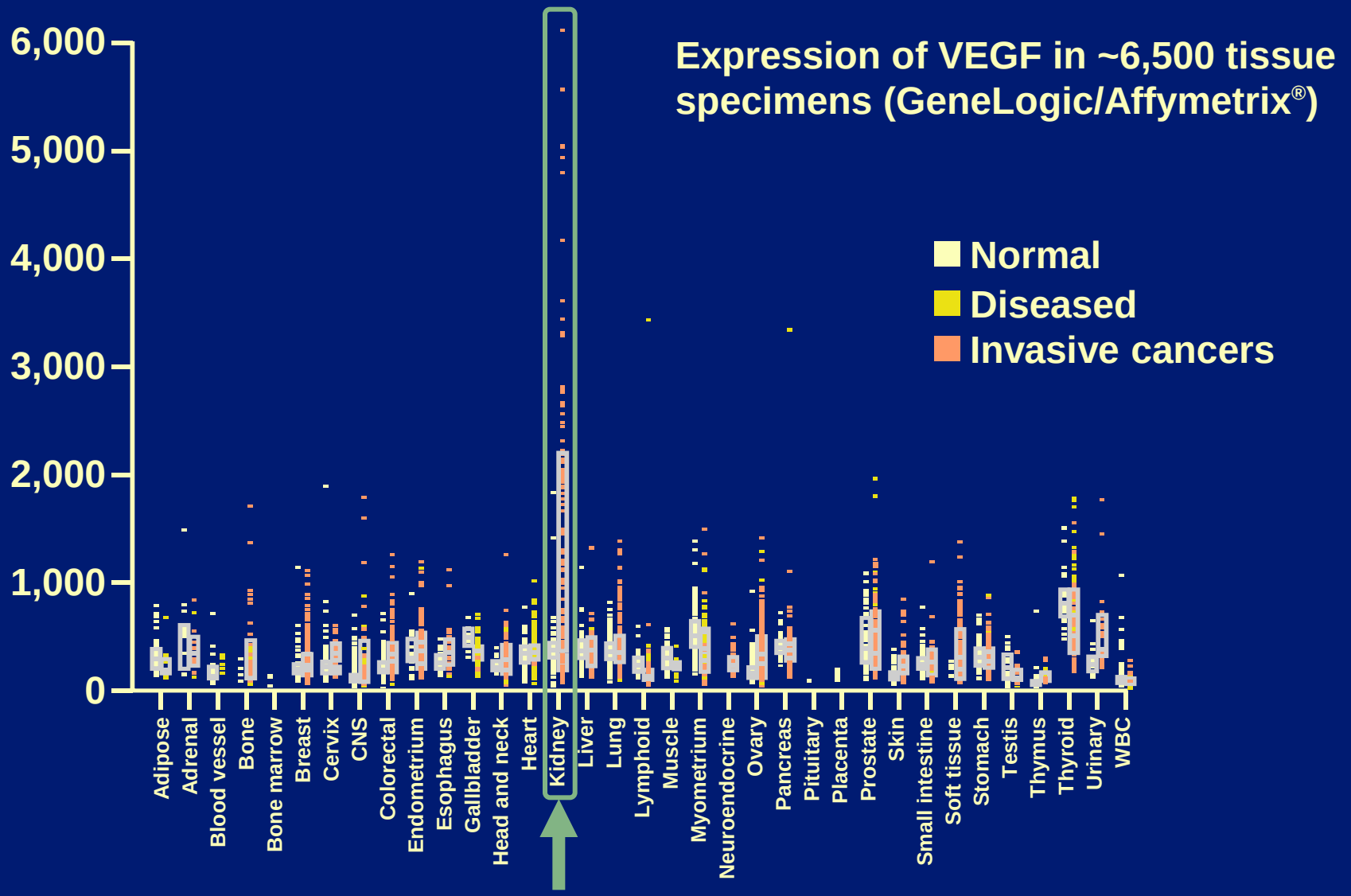


Net rate of influx of [^{11}C]docetaxel

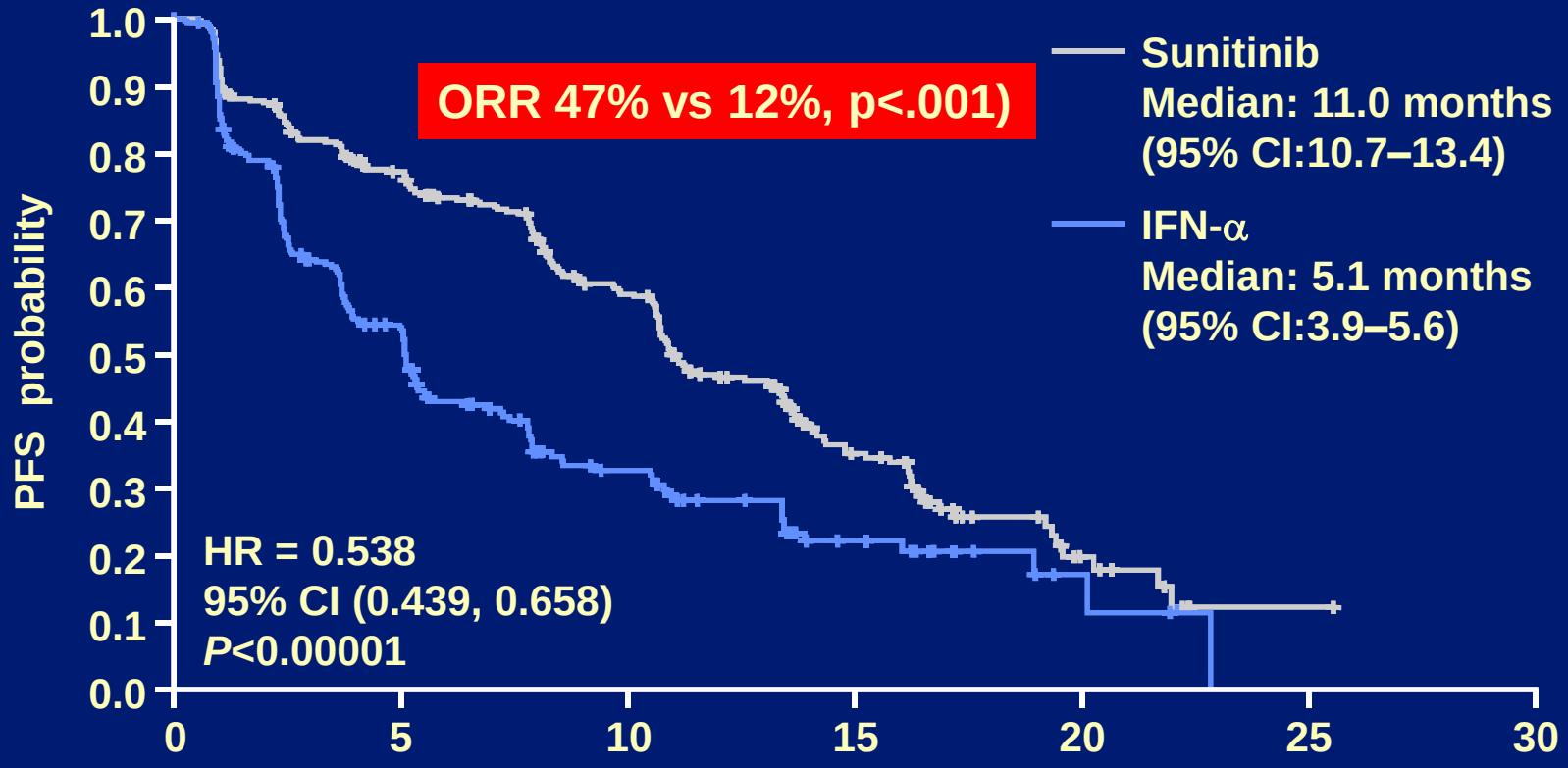


Van der Veldt et al, Cancer Cell (2012) 21:82-91

Overexpression of VEGF in human tissue



RCC Sunitinib vs. IFN-α: PFS by Independent Central Review



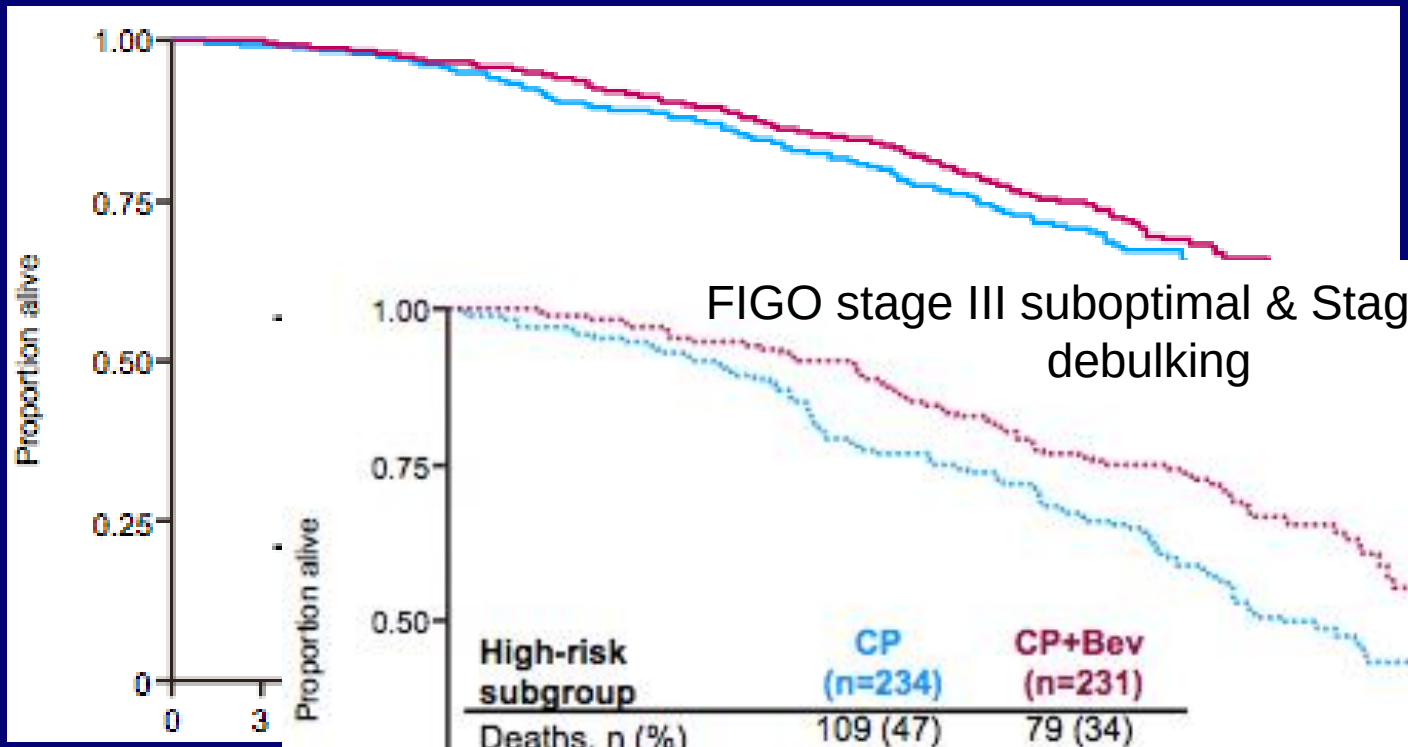
No. at Risk						
Sunitinib:	375	240	156	54	10	1
IFN-α:	375	124	46	15	4	0

HR = hazard ratio.

Motzer RJ, et al. *N Engl J Med.* 2007;356:115-124; Motzer RJ, et al. *J Clin* Oncol. 2007;20(Suppl 18s):5024 (Abstract).

ICON-7: carbo-taxol±bevacizumab OS update

ITT population

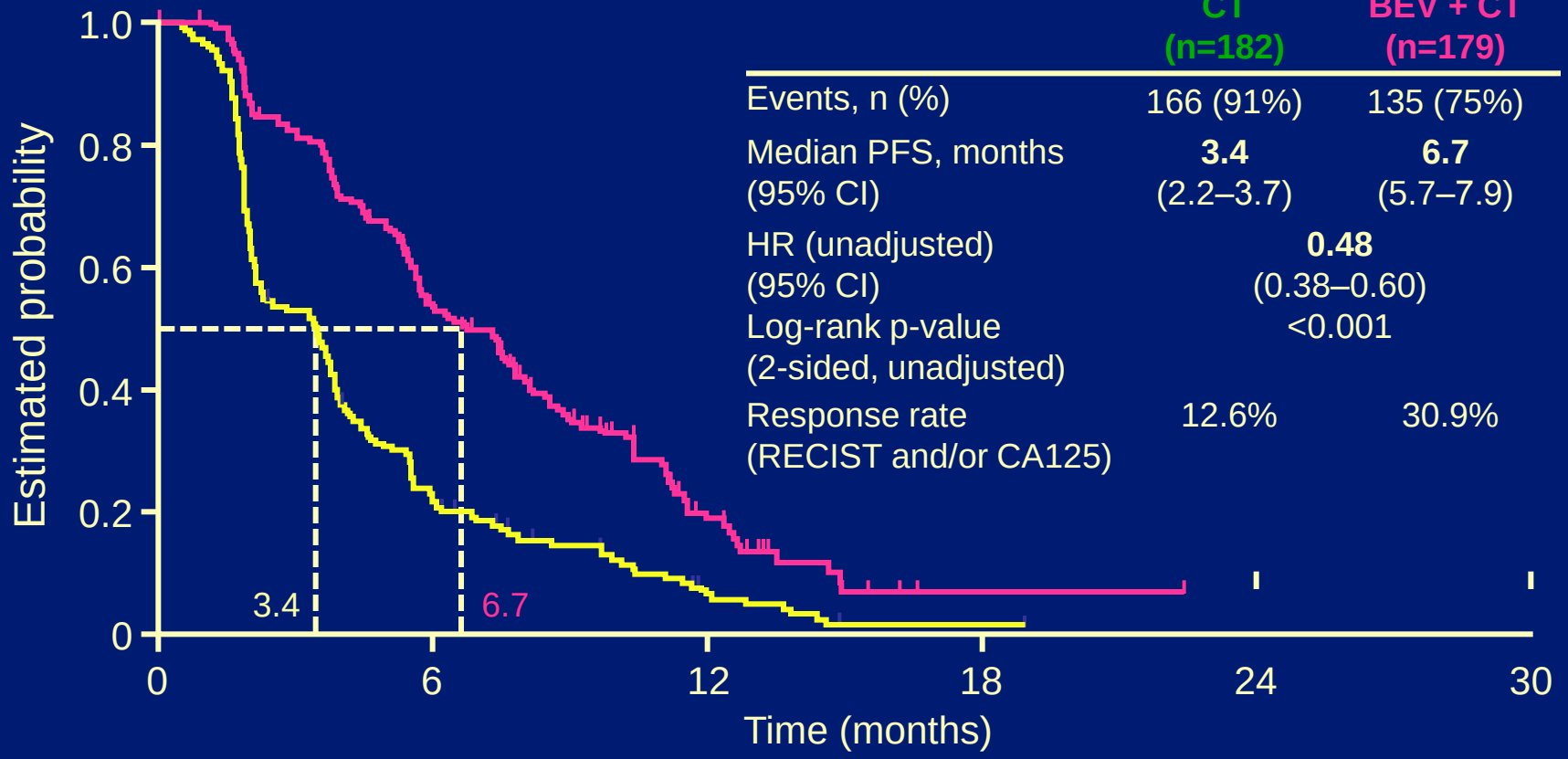


FIGO stage III suboptimal & Stage IV with debulking

High-risk subgroup	CP (n=234)	CP+Bev (n=231)
Deaths, n (%)	109 (47)	79 (34)
Median, months	28.8	36.6
Log-rank test	p=0.002	
HR (95% CI)	0.64 (0.48–0.85)	
1-year OS rate (%)	86	92

Kristensen *et al* ASCO 2011

Bevacizumab in platinum-resistant recurrent Ovarian Cancer



	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	
Response rate (RECIST and/or CA125)	12.6%	30.9%

Pujade-Lauraine et al ASCO 2012

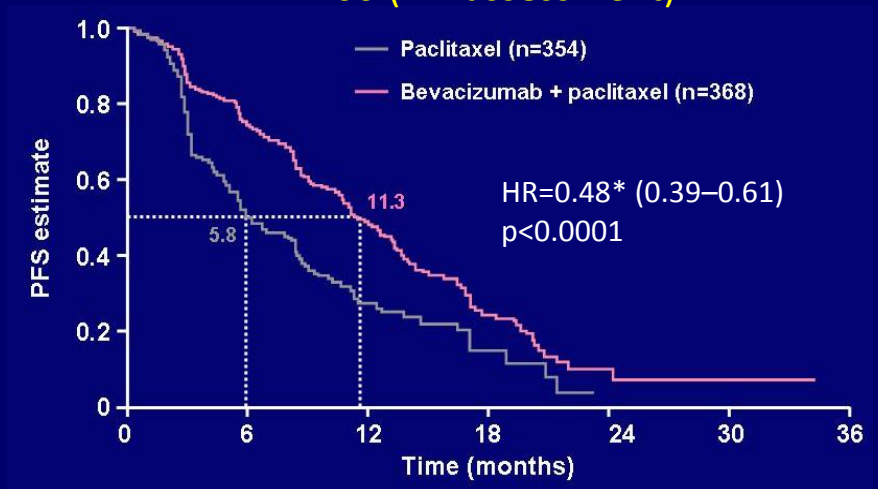
Recurrent Glioblastoma
Bevacizumab as a Single-Agent and in Combination

Bevacizumab Plus Chemotherapy								
BV Dose (mg/kg)	Chemotherapy	Study Design	Number of Patients	CR/PR (%)	PFS, Median (wk)	PFS-6 (%)	OS, Median (wk)	Reference
10	Carboplatin + cetuximab	Retrospective series	6	83	19	22	30	Francesconi et al.[71]
10	Etoposide	Phase II	27	23	18	45	46	Reardon et al.[72]
10	Irinotecan	Phase II	23	61	20	30	40	Vredenburgh et al.[10]
10	Irinotecan	Phase II	35	57	24	46	42	Vredenburgh et al.[11]
10	Irinotecan	Phase II	82	38	22	50	35	Friedman et al.[8]
10	Irinotecan	Retrospective series	37	68	30	64	46	Zuniga et al.[74]
	Irinotecan	Retrospective series	27	44	20	46	50	Kang et al.[73]
5	Irinotecan	Retrospective series	20	47	19	25	28	Bokstein et al.[76]
5 or 10	Irinotecan	Retrospective series	13	77	24	NR	27	Ali et al.[75]

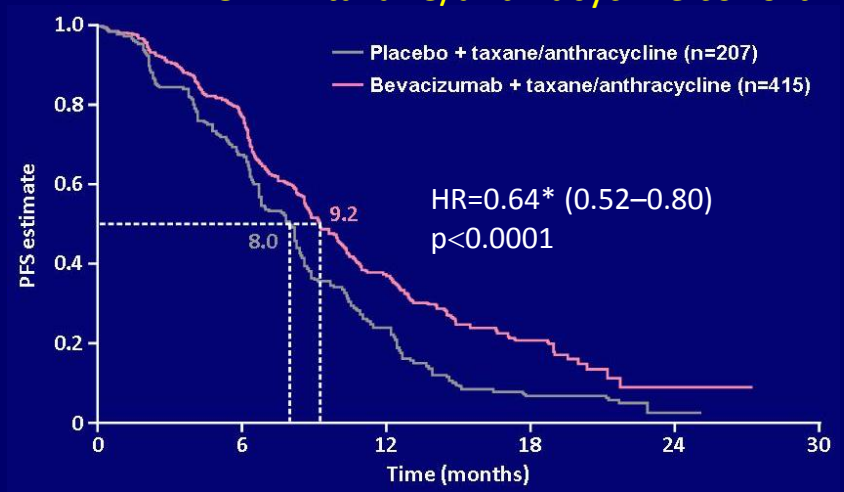
led to rapid approval for bevacizumab in Glioma by FDA May 2009

Breast Cancer: Bevacizumab and chemotherapy: PFS

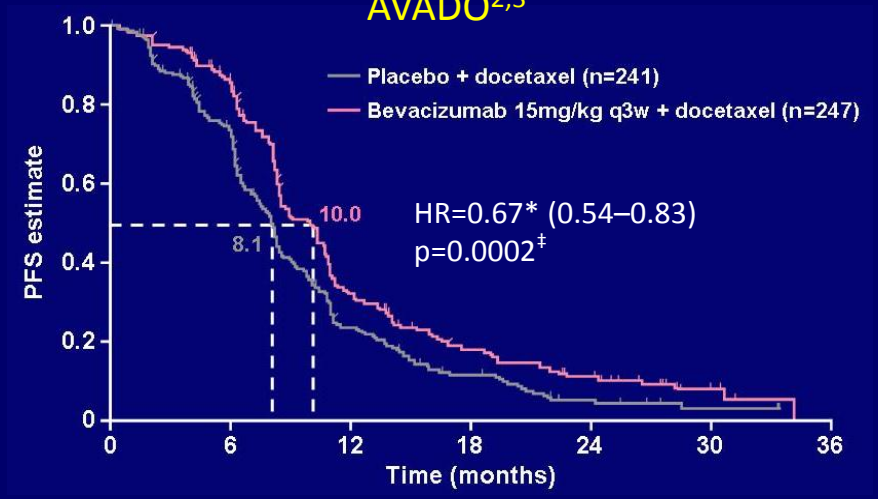
E2100 (IRF assessment)[1]



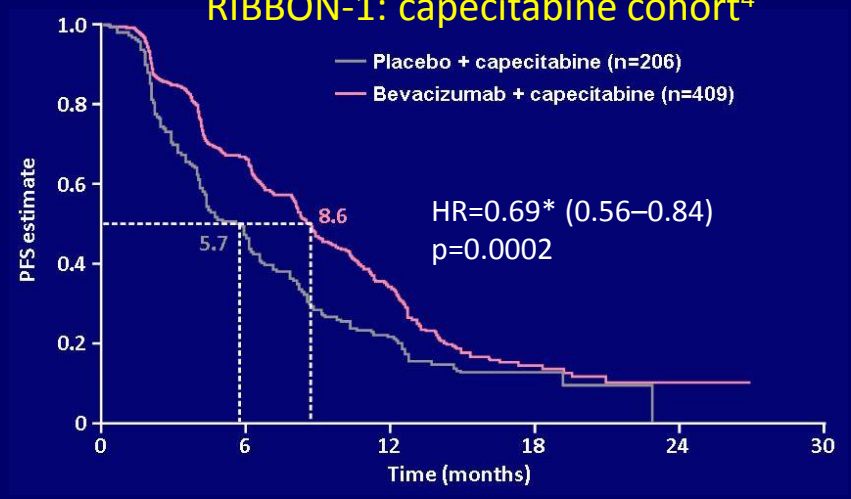
RIBBON-1: taxane/anthracycline cohort[4]



AVADO[2,3]



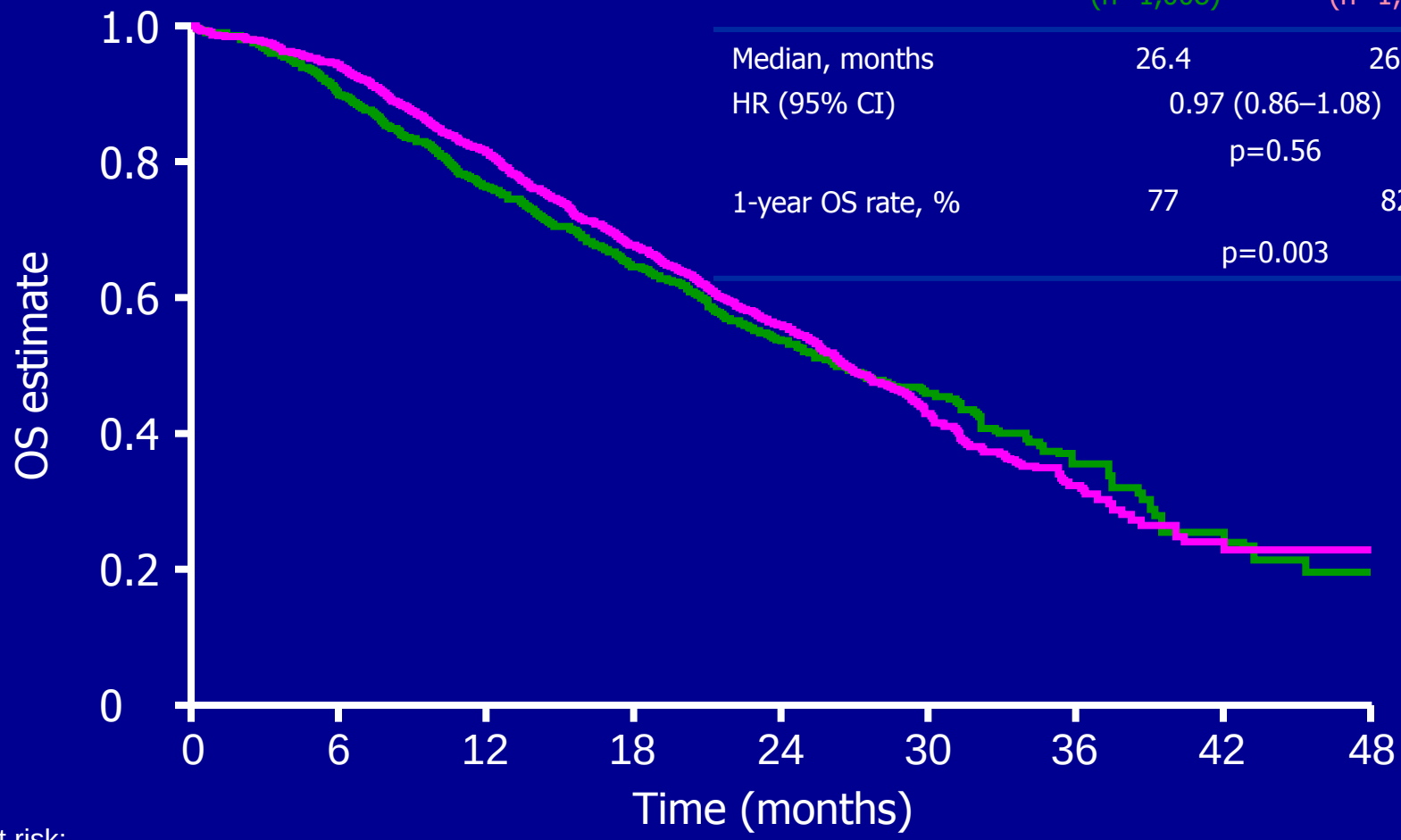
RIBBON-1: capecitabine cohort[4]



*Stratified and censored for non-protocol therapy before disease progression
‡p value is exploratory; IRF = independent review facility

1. Gray, et al. JCO 2009; 2. Miles, et al. SABCS 2009
3. Avastin SmPC; 4. Robert, et al. ASCO 2009

Bevacizumab in MBC: overall survival



Number at risk:

Non-bevacizumab	1008	892	746	621	426	178	51	19	8
Bevacizumab	1439	1333	1127	916	591	204	55	23	5

O'Shaughnessy, et al. ASCO 2010

U.S. Food and Drug Administration

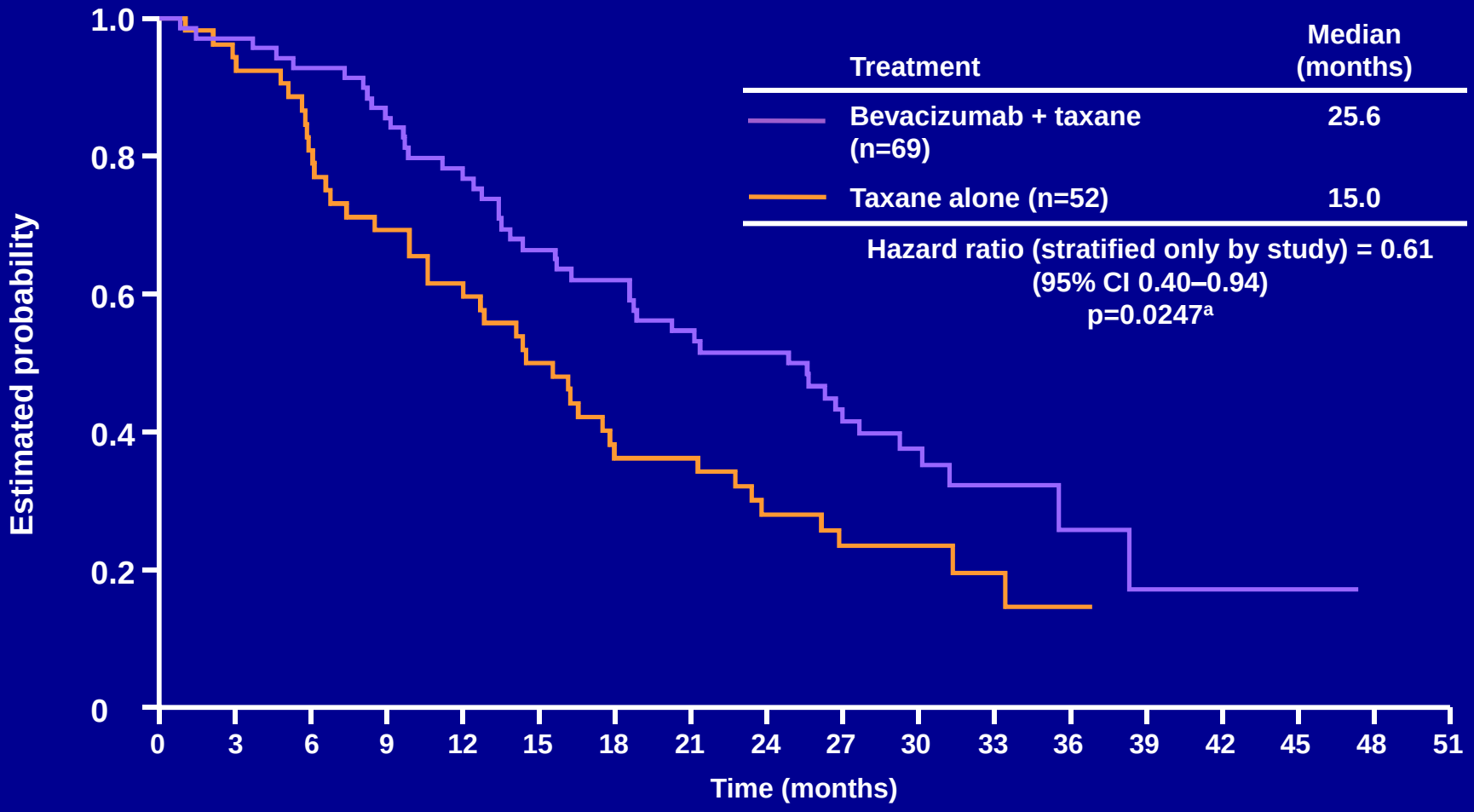
For Immediate Release: Nov. 18, 2011 Media Inquiries: Karen Riley, 301-796-4674, karen.riley@fda.hhs.gov Consumer Inquiries: 888-INFO-FDAFDA Commissioner announces Avastin decision *Drug not shown to be safe and effective in breast cancer patients*

FDA Commissioner announces Avastin decision *Drug not shown to be safe and effective in breast cancer patients FDA Commissioner Margaret A. Hamburg, M.D., said today she is revoking the agency's approval of the breast cancer indication for Avastin (bevacizumab) after concluding that the drug has not been shown to be safe and effective for that use.*

Avastin's risks include severe high blood pressure; bleeding and hemorrhaging; heart attack or heart failure; and the development of perforations in different parts of the body such as the nose, stomach, and intestines.

Taxane ± bevacizumab: Overall Survival

(taxane-pretreated hormone receptor-negative population)

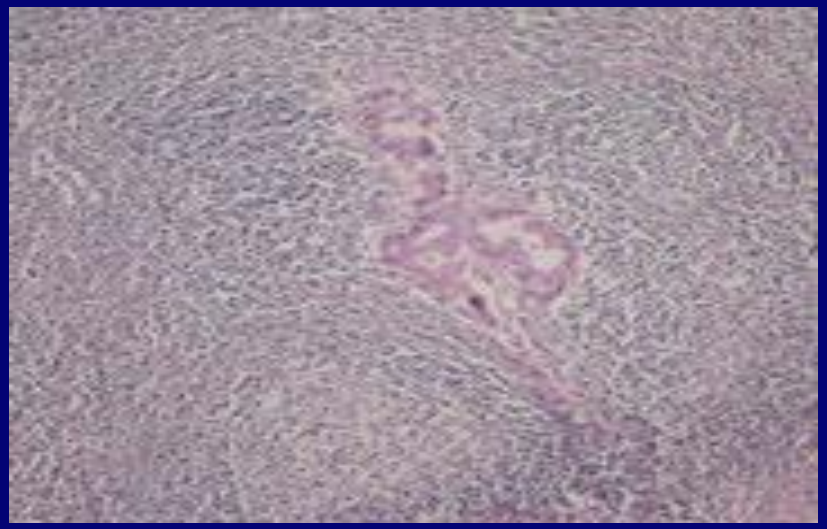


AVAB00092e October 2010

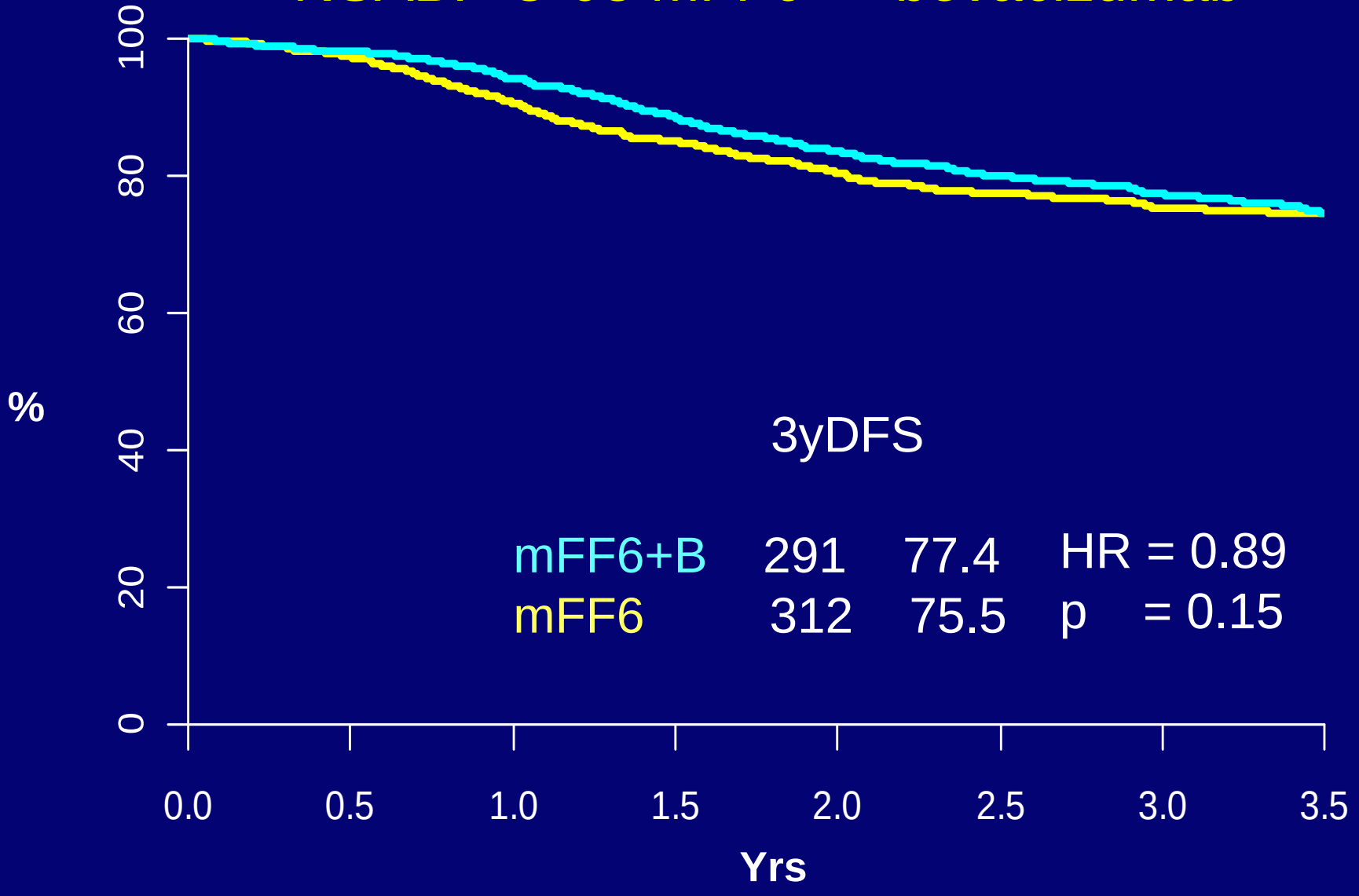
Miles et al. Ann Oncol 2010; Suppl

Anti-VEGF therapy in the adjuvant setting?

The wrong context?

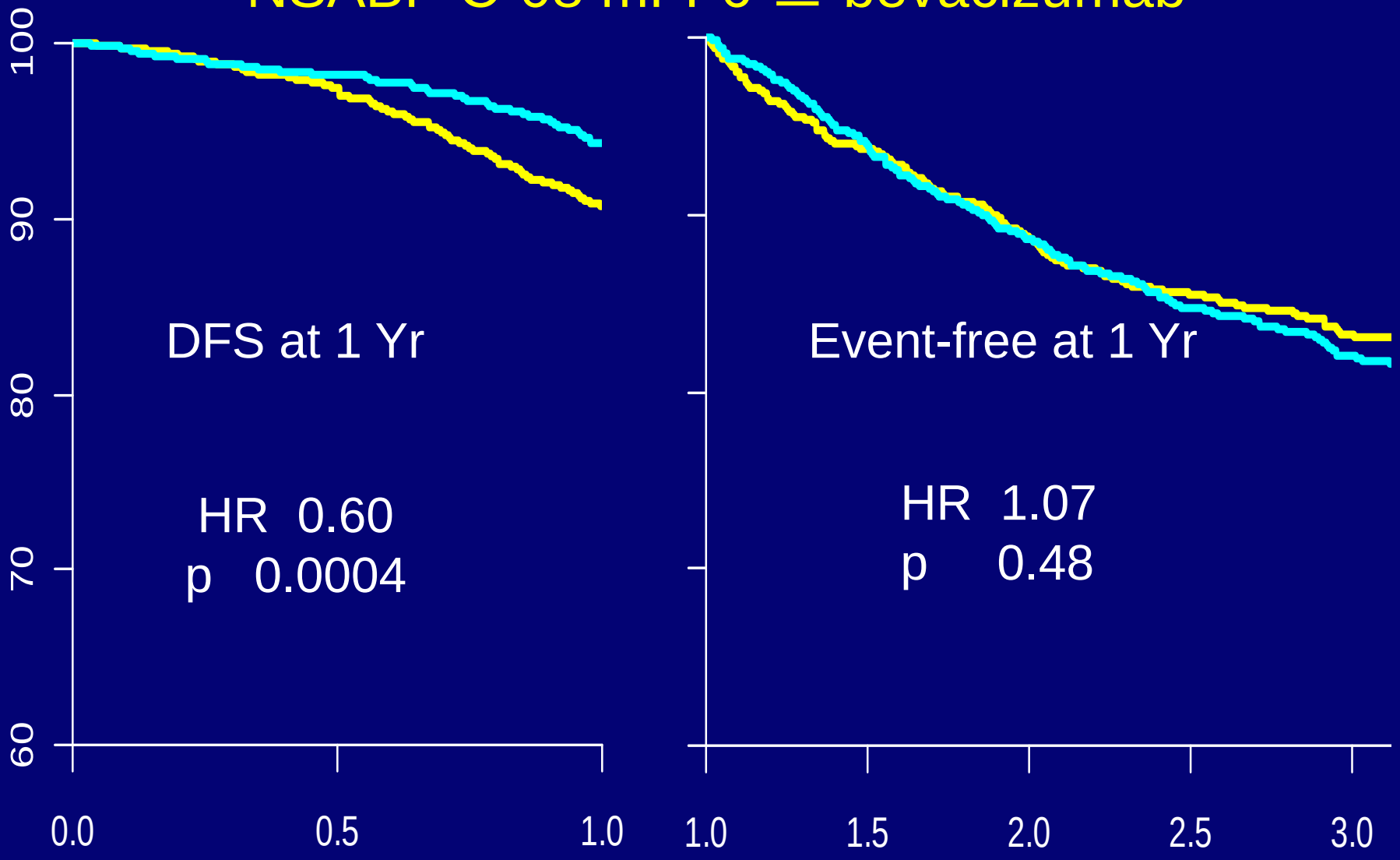


Adjuvant study in colorectal cancer
NSABP C-08 mFF6 ± bevacizumab



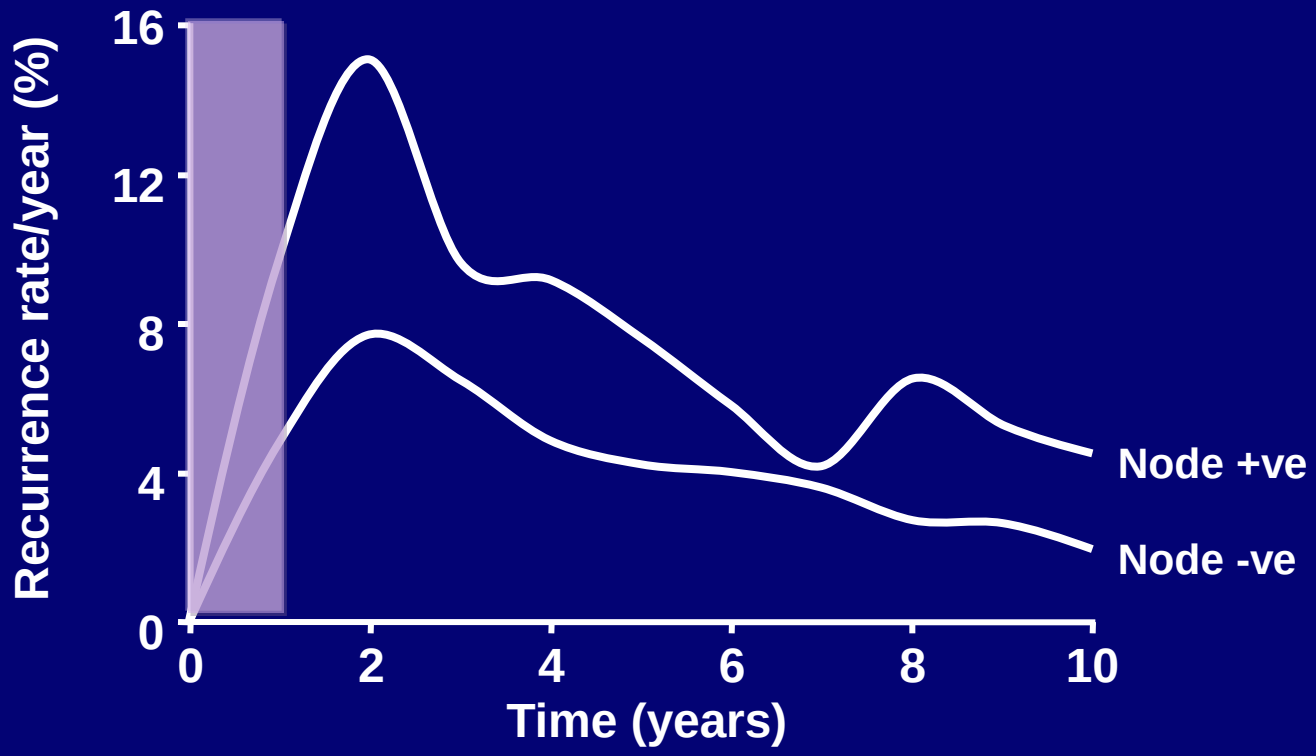
Allegra et al, JCO (2011) 29: 11-16

Adjuvant study in colorectal cancer
NSABP C-08 mFF6 ± bevacizumab



Allegra et al, JCO (2011) 29: 11-16

Angiogenesis:
is this a linear or stochastic behaviour?

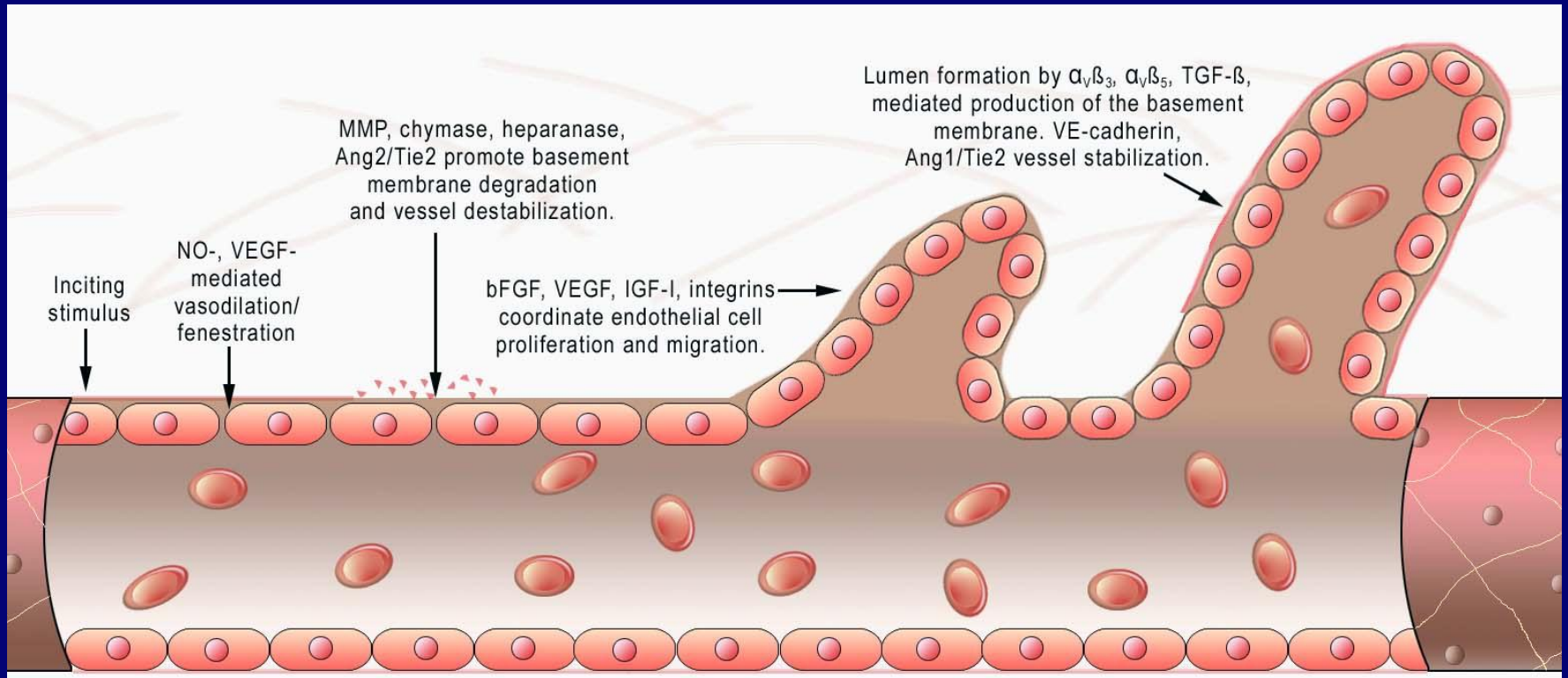


1 year of anti-angiogenic therapy
E5103 & Beatrice & BETH

Adapted from EBCTCG. Lancet 1998;352:930-942

Assumptions 20-40 yrs ago	Assumptions 2002-2010	What we know from clinical trial results (in 2012
Angio inhibition would induce dormancy in all tumor types	Angio inhibition would provide *benefit* across tumor types	Benefit is tumor dependent and context dependent (+/- chemo)

Angiogenesis: -multiple (non-mutating) factors -multiple targets

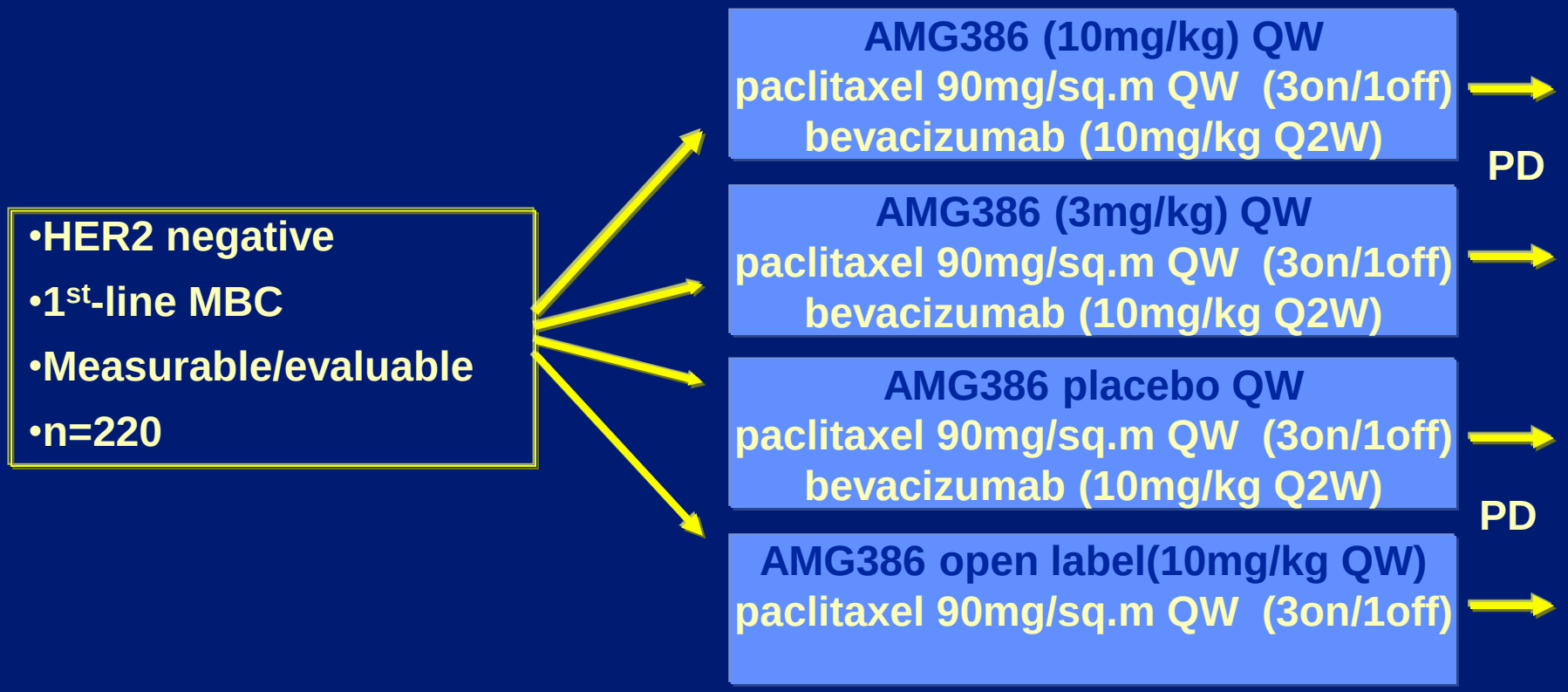


Extracellular VEGF, IL8, FGF, PDGF, Ang (HGF, heparanase)

Membrane RTK, Integrins, Cadherins, V-CAM, ephrin

Intracellular notch, mutations and receptor mutants

Inhibition of Angiopoetin1-2/Tie-2 axis



Dieras et al. ASCO 2011

The future?
Multikinase VEGFR inhibitors

	VEGFR	KIT	PDGFR	FGF	RET	MET	RAF	EGFR
Cediranib	*	*	*					
Sunitinib	*	*	*					
Pazopanib	*	*	*					
Intedanib	*		*	*				
Brivanib	*			*				
E7080	*		*	*				
Vandetanib	*				*			*
Sorafenib	*	*	*				*	
XL-184	*	*			*	*		

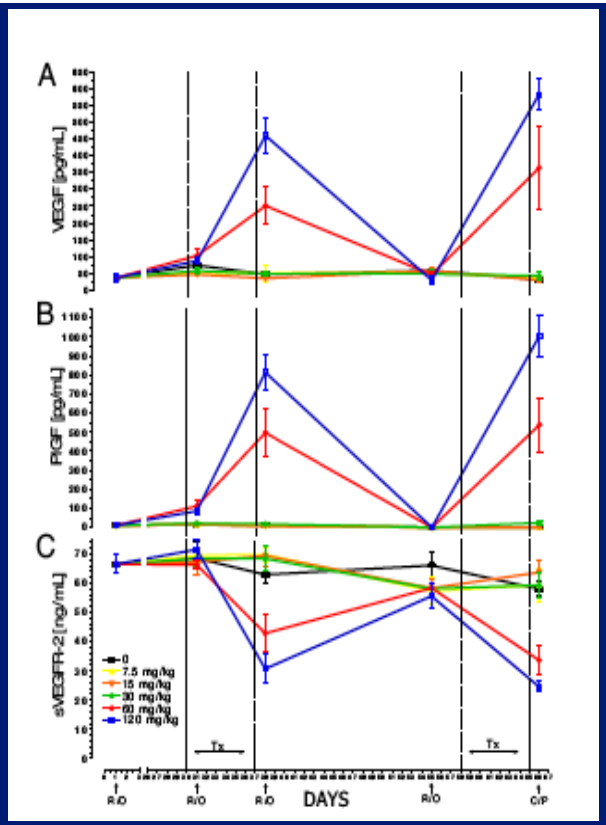
Assumptions 20-40 yrs ago	Assumptions 2002-2010	What we know from clinical trial results (in 2012
Angio inhibition would induce dormancy in all tumor types	Angio inhibition would provide *benefit* across tumor types	Benefit is tumor dependent and context dependent (+/- chemo)
Little discussion of multiplicity of angiogenic factors	Other angiogenic factors are important and may contribute to resistance	Dual targeting of bypass pathways have not led to major advances

Angiogenic factors increased by VEGF inhibition

Multiple circulating proangiogenic factors induced by sunitinib malate are tumor-independent and correlate with antitumor efficacy

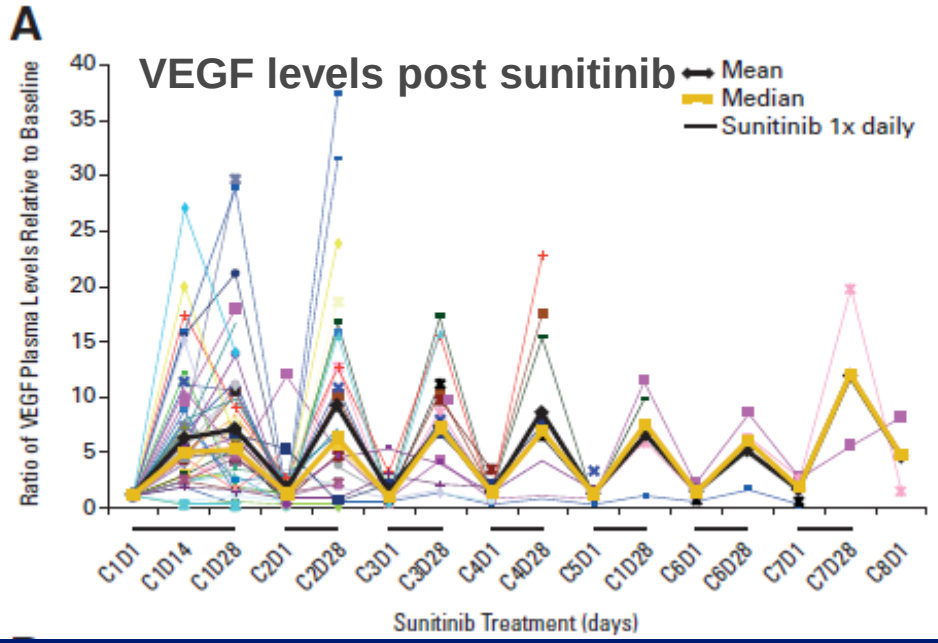
John M. L. Ebos*†, Christina R. Lee*, James G. Christensen‡, Anthony J. Mutsaers*†, and Robert S. Kerbel*†§

PNAS | October 23, 2007 | vol. 104 | no. 43 | 17069–17074



VOLUME 26 · NUMBER 11 · APRIL 10 2008
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Phase II Study of Sunitinib Malate, an Oral Multitargeted Tyrosine Kinase Inhibitor, in Patients With Metastatic Breast Cancer Previously Treated With an Anthracycline and a Taxane



Mediators of escape/rebound e.g., VEGF, FGF, PlGF, SDF1-α

Does inhibiting the VEGF pathway make things worse?

Anti-VEGFR2, SU10944, sunitinib, tumor VEGF KO

Cell PRESS

Cancer Cell
Article

Antiangiogenic Therapy Elicits Malignant Progression of Tumors to Increased Local Invasion and Distant Metastasis

Marta Pàez-Ribes,[1,6] Elizabeth Allen,[2,6] James Hudock,[3] Takaaki Takeda,[4] Hiroaki Okuyama,[4] Francesc Viñals,[1,5] Masahiro Inoue,[4] Gabriele Bergers,[3] Douglas Hanahan,[2,*] and Oriol Casanovas[1,*]
[1]Translational Research Laboratory, Catalan Institute of Oncology, IDIBELL, 08907 L'Hospitalet de Llobregat, Spain
[2]Department of Biochemistry & Biophysics, Diabetes Center, and Helen Diller Family Comprehensive Cancer Center
[3]Department of Neurosurgery and Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco, San Francisco, CA 94143, USA
[4]Department of Biochemistry, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka 537-8511, Japan
[5]Departament de Ciències Fisiològiques II, Universitat de Barcelona, IDIBELL, 08907 L'Hospitalet de Llobregat, Spain
[6]These authors contributed equally to this work
*Correspondence: dh@ucsf.edu (D.H.), ocasanovas@iconcologia.net (O.C.)
DOI 10.1016/j.ccr.2009.01.027

Sunitinib, Sorafenib, SU10944

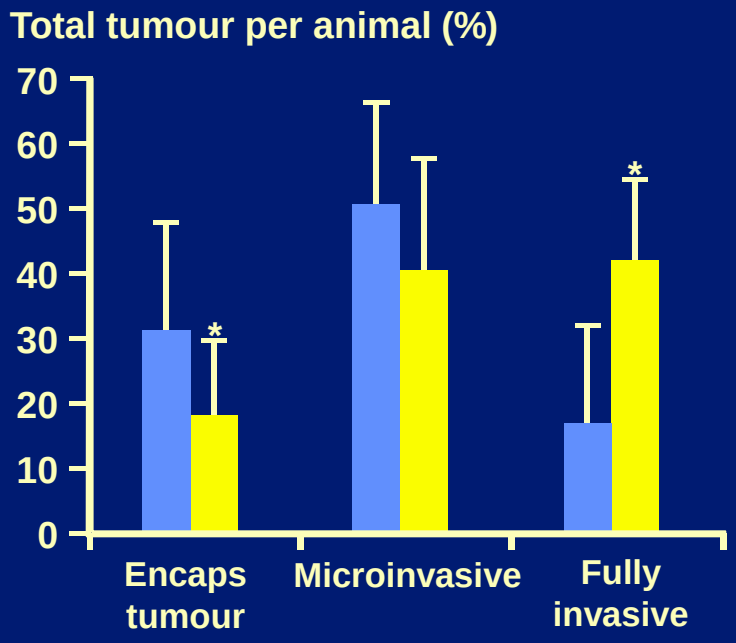
Cell PRESS

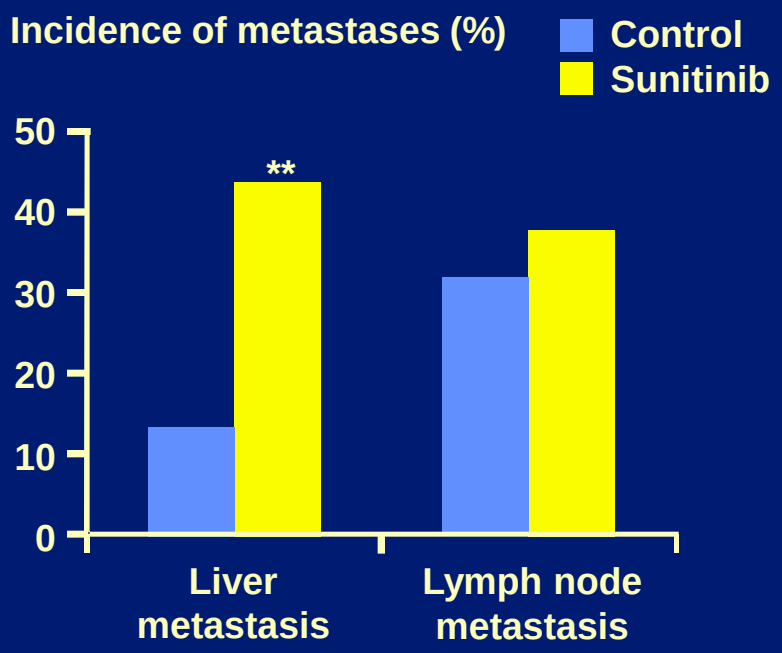
Cancer Cell
Report

Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

John M.L. Ebos,[1,2] Christina R. Lee,[1] William Cruz-Munoz,[1] Georg A. Bjarnason,[3] James G. Christensen,[4] and Robert S. Kerbel[1,2,*]
[1]Molecular and Cellular Biology Research, Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5, Canada
[2]Department of Medical Biophysics, University of Toronto, Toronto, ON M5G 2M9, Canada
[3]Sunnybrook Odette Cancer Centre, Toronto, ON M5G 2M9, Canada
[4]Pfizer Global Research and Development, La Jolla Labs, La Jolla, CA 92121, USA
*Correspondence: robert.kerbel@sunnybrook.ca
DOI 10.1016/j.ccr.2009.01.021

Rebound: increased invasiveness and metastatic potential when TKI is withdrawn



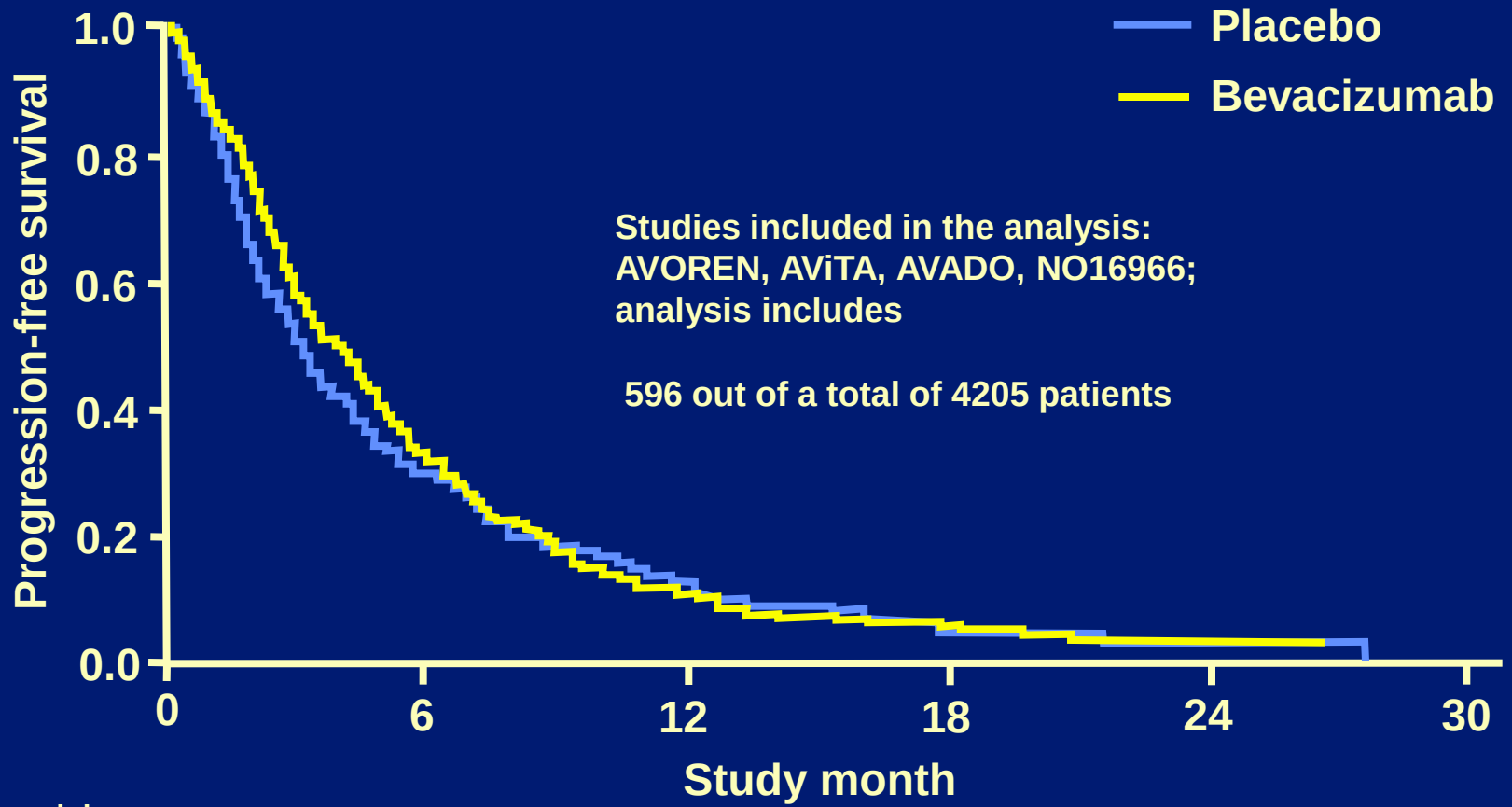


*p<0.05; **p<0.01 versus controls

- In genetically engineered mice with pancreatic neuroendocrine tumours, withdrawing sunitinib after limited-duration therapy and with tumours still responding resulted in
  - increased proportion of invasive tumour versus control
  - significant increase in number of liver metastases

Pàez-Ribes et al. Cancer Cell 2009;15:220–31

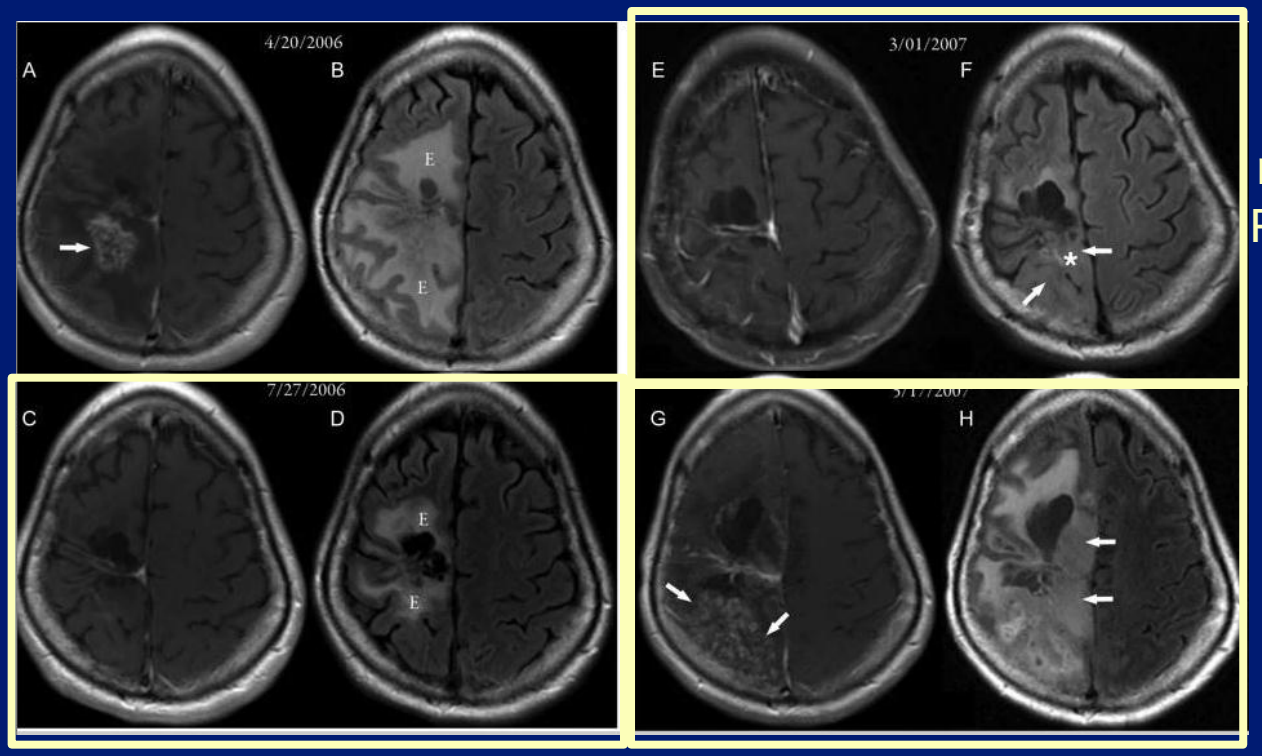
Time from bevacizumab discontinuation due to AEs to progressive disease/death: pooled dataset



Number remaining:						
Placebo	234	67	24	11	3	0
Bevacizumab	362	102	28	11	2	0

Miles et al JCO. 2011 29:83-88

Tumour invasion after treatment of glioblastoma with bevacizumab



3/12 bev decreased enhancement & oedema

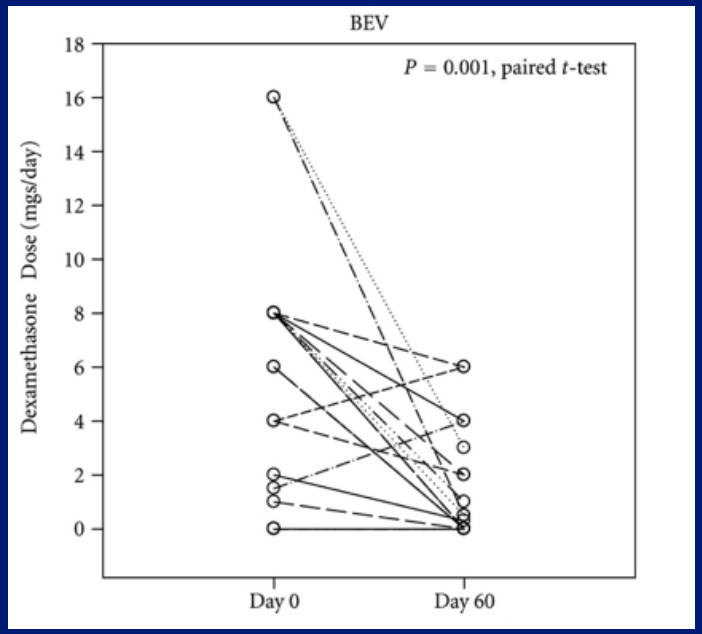
8/12 bev non-enhancing FLAIR changes

2/12 post bev increase non-enhancing & enhancing tumour

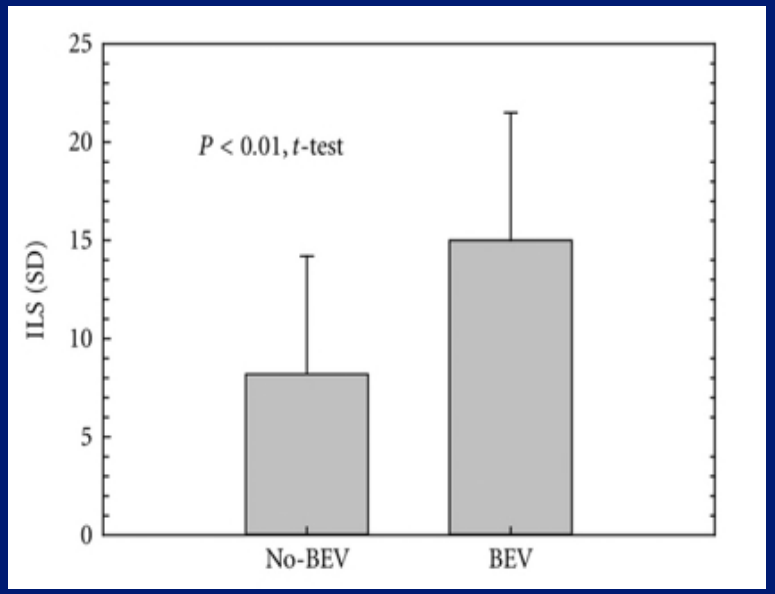
increases in IGFBP2, CA9, MMP2 by IHC

de Groot et al, Neuro Oncol 2010;12:233–42

Bevacizumab improves quality of life in patients with recurrent glioma



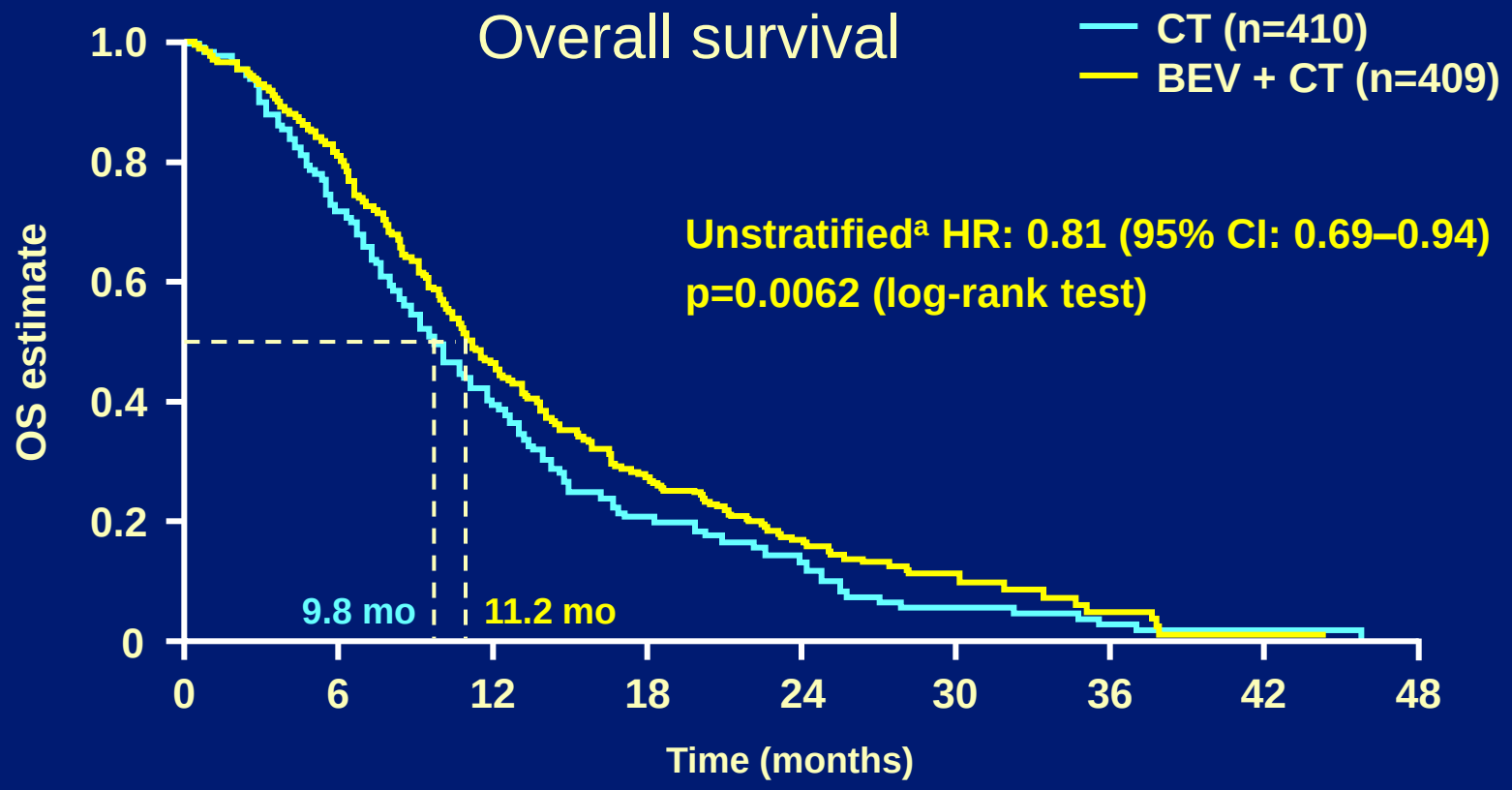
reduced steroid requirement



Improved
Independent Living Scores

Nagpal, et al **Chemother Res Pract** 2011;2011:602812. Epub 2011

Bevacizumab beyond progression in patients with mCRC



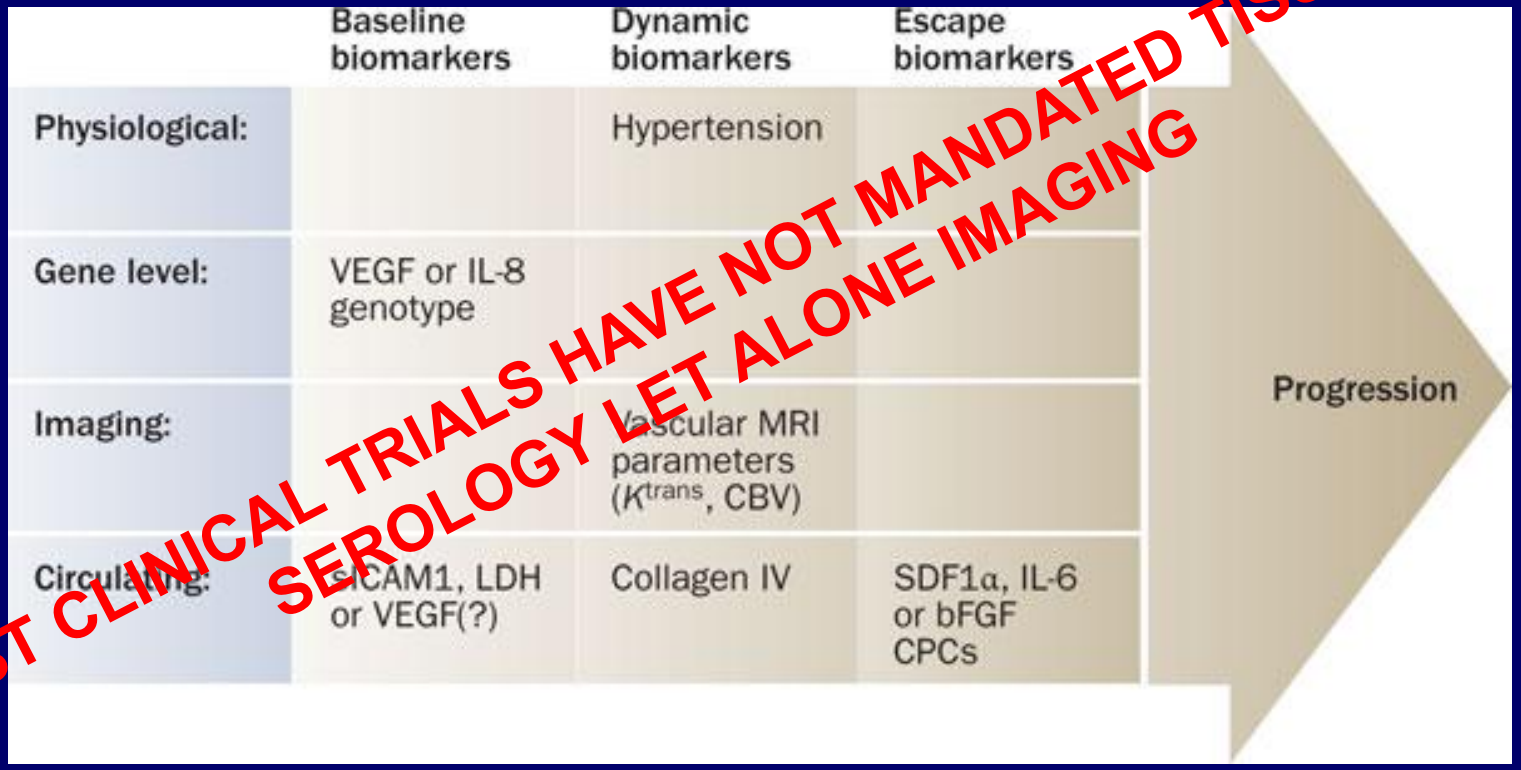
Arnold et al ASCO 2012

Assumptions 20-40 yrs ago	Assumptions 2002-2010	What we know from clinical trial results (in 2012
Angio inhibition would induce dormancy in all tumor types	Angio inhibition would provide *benefit* across tumor types	Benefit is tumor dependent and context dependent (+/- chemo)
Little discussion of multiplicity of angiogenic factors	Other angiogenic factors are important and may contribute to resistance	Dual targeting of bypass pathways have not led to major advances
Resistance would not occur	Resistance is inevitable	Continuation of therapy may be of some benefit
Did not consider consequences of withdrawal	Preclinical and anecdotes- Withdraw may lead to “flare”	No hard data to support that withdrawal leads to “flare”
Did not consider consequences of induction of hypoxia	VEGF inhibitors may increase tumor aggressiveness	In GBM, VEGF inhibitors may increase invasion and metastasis, but patients may still benefit from therapy

Candidate biomarkers of response and resistance to antiangiogenic therapy

Do all patients benefit a bit, or do a few benefit a lot?

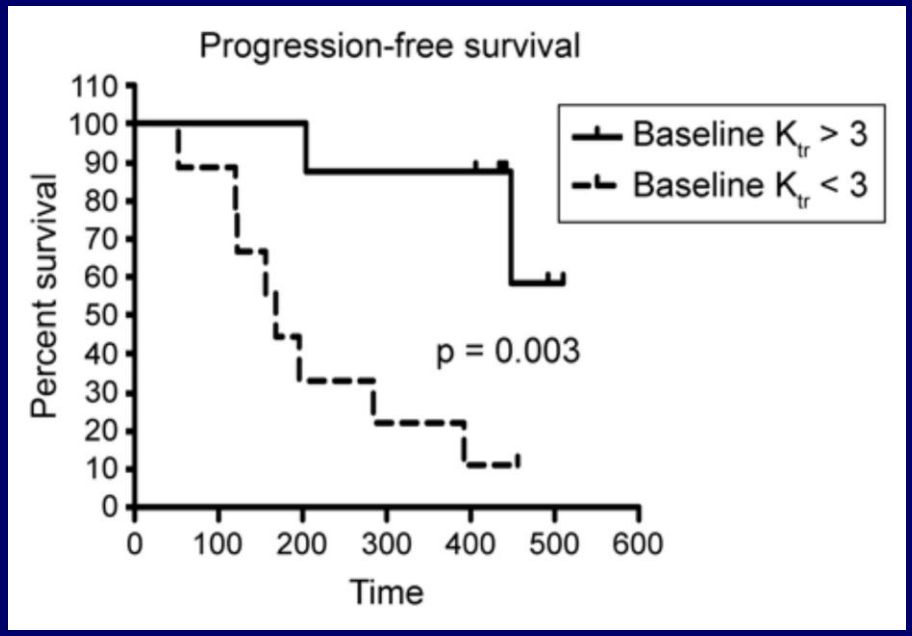
Conventional criteria (patient, tumour, pre-Rx characteristics)

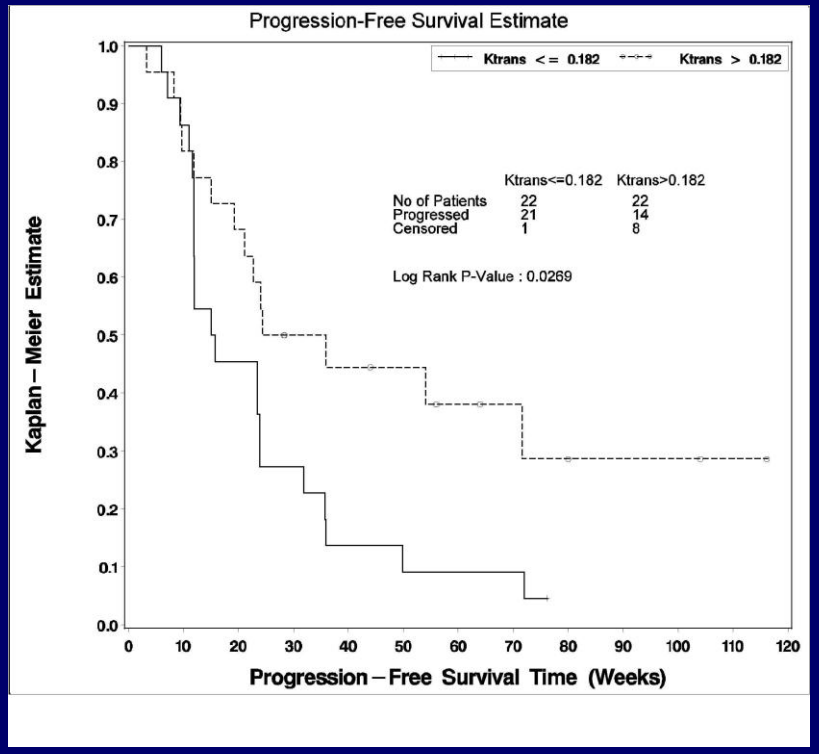


MOST CLINICAL TRIALS HAVE NOT MANDATED TISSUE OR SEROLOGY LET ALONE IMAGING

Jain R K *et al.* (2009) Biomarkers of response and resistance to antiangiogenic therapy *Nat Rev Clin Oncol* doi:10.1038/nrclinonc.2009.63

DCE-MRI as biomarker of response to VEGF inhibition: baseline K_{trans} (RCC)





Flaherty, K.T., Rosen, M.A., Heitjan, D.F., Gallagher, M.L., Schwartz, B., Schnall, M.D., O'Dwyer, P.J. Cancer Biology & Therapy 2008 7 (4) 1-6

Hahn,O.M., Yang,C., Medved,M., Karczmar,G., Kistner,E., Karrison,T.,Manchen,E. Mitchell, M/. Ratain, MJ., Stadler, W.M.

A dynamic contrast-enhanced MRI pharmacodynamic biomarker study of sorafenib in metastatic renal cell carcinoma. In press.

Summary of plasma VEGF-A findings across tumour types

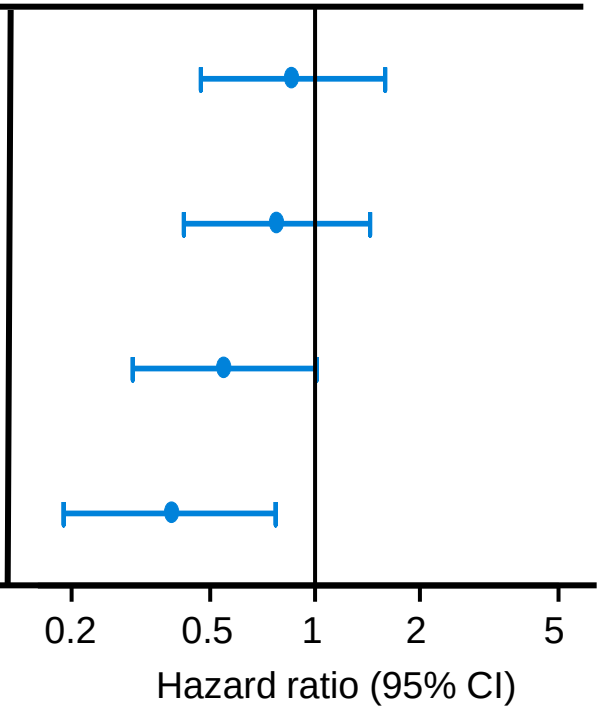
Tumour type	Trial	Prognostic		Potentially predictive		Sample buffer
		PFS	OS	PFS	OS	
mBC	AVADO	✓	✓	✓	X[a]	EDTA
mBC	AVEREL	✓	?	✓	?	
GaC	AVAGAST	✓	✓	✓	✓	
mPaC	AViTA	✓	✓	✓	✓	
mCRC	AVF2107g	X	✓	X	X	Citrate
NSCLC	AVAiL	✓	✓	X	X[a]	
RCC	AVOREN	✓	✓	X	X[a]	

[a]Result might have been confounded by crossover

Jayson et al. EMCC 2011; Gianni et al. SABCS 2011

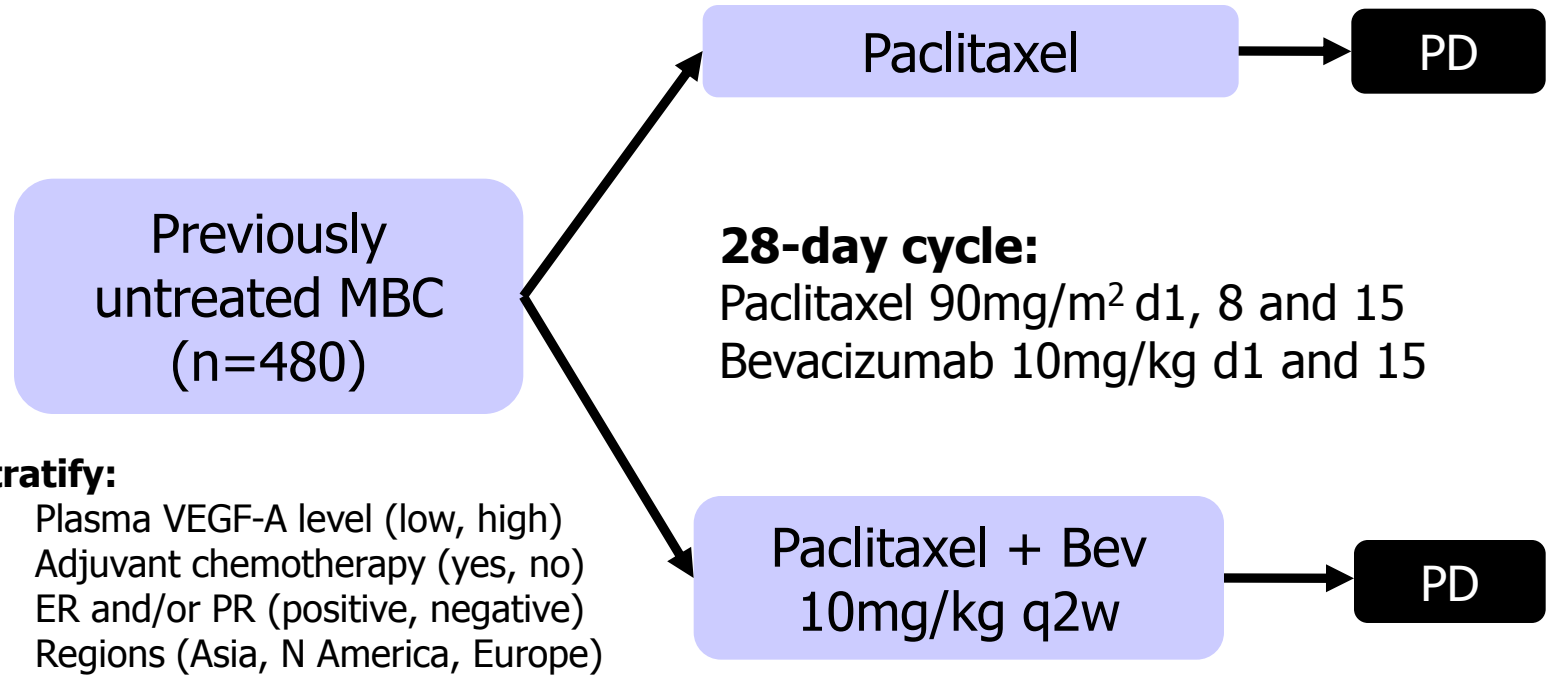
Docetaxel ± bevacizumab (AVADO)
PFS according to VEGF-A quartiles

VEGF-A quartile (pg/mL)	No. of patients	No. of events	Median PFS (months) Bevacizumab 15 mg/kg + docetaxel	Median PFS (months) Placebo + docetaxel	HR (95% CI)
1st	71	43	8.6	8.3	0.86 (0.47–1.59)
2nd	68	43	8.5	7.2	0.78 (0.42–1.44)
3rd	65	43	8.4	6.5	0.55 (0.30–1.01)
4th	61	36	10.3	7.5	0.39 (0.19–0.77)



Miles DW, et al. Cancer Res 2010;70(24 Suppl.):558 (abstract P2-16-04)

MERiDiAN (GO25632): Study Design



Assumptions 20-40 yrs ago	Assumptions 2002-2010	What we know from clinical trial results (in 2012
Angio inhibition would induce dormancy in all tumor types	Angio inhibition would provide *benefit* across tumor types	Benefit is tumor dependent and context dependent (+/- chemo)
Little discussion of multiplicity of angiogenic factors	Other angiogenic factors are important and may contribute to resistance	Dual targeting of bypass pathways have not led to major advances
Resistance would not occur	Resistance is inevitable	Continuation of therapy may be of some benefit
Did not consider consequences of withdrawl	Preclinical and anecdotes- Withdraw may lead to “flare”	No hard data to support that withdrawal leads to “flare”
Did not consider consequences of induction of hypoxia	VEGF inhibitors may increase tumor aggressiveness	In GBM, VEGF inhibitors may increase invasion and metastasis, but patientsmay still benefit from therapy
Did not think about biomarkers	Biomarkers are elusive	Maybe? Need validation, sometimes complex

Angiogenesis therapies in the clinic a two-edged sword?

- Promises
  - a non-mutating target on which most cancers seem to depend
  - a complex multi-factorial process
- Successes
  - improved outcome in several tumour types
  - clinical benefits are tumour AND context dependent
- Failures (largely our own)
  - agents developed along the lines of cytotoxic drugs
  - negligible collection of relevant information in trials
  - failure to understand the underlying mechanisms
  - implications for scheduling, biomarkers

Angiogenesis therapies in the clinic a two-edged sword?

We can do a lot better than this.

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Thank you!