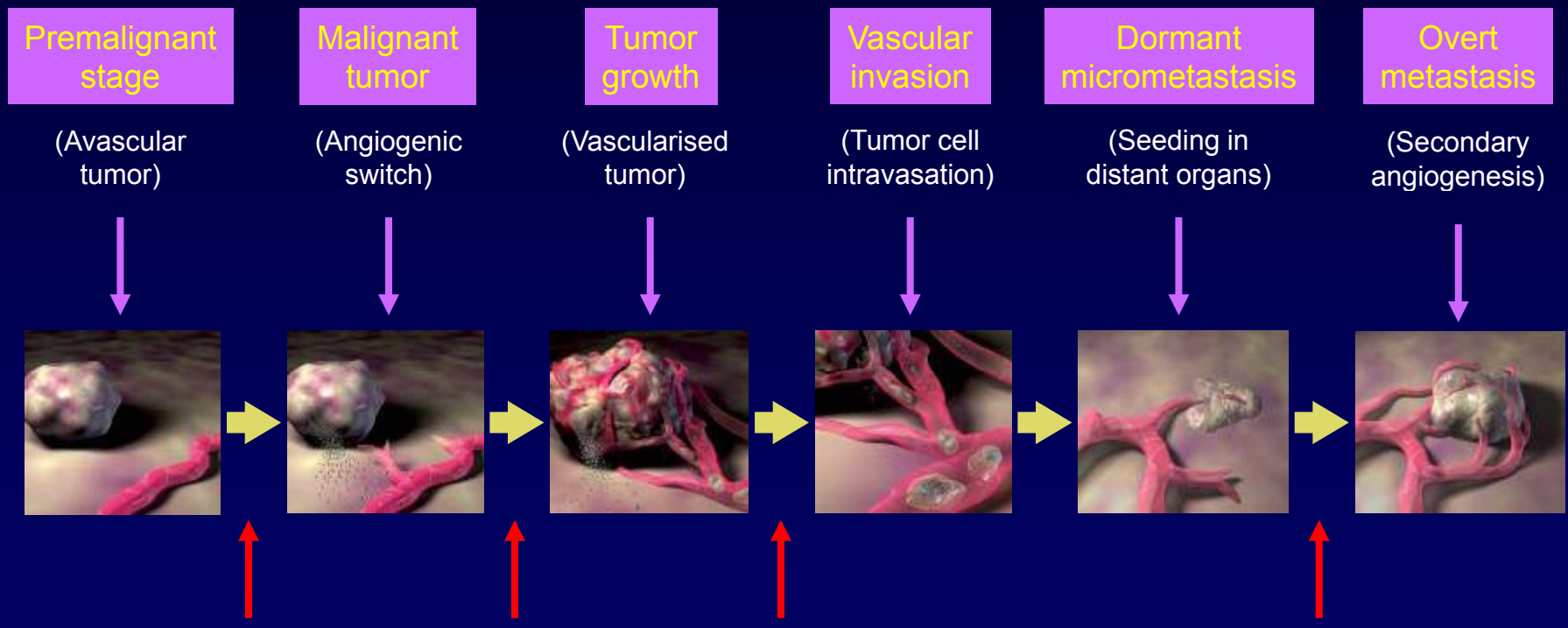
Angiogenesis and Ovarian Cancer

Andrew Clamp, MD, PhD
Senior Lecturer in Medical Oncology
The Christie
Manchester, United Kingdom

Angiogenesis



Stages at which angiogenesis plays a role in tumor progression

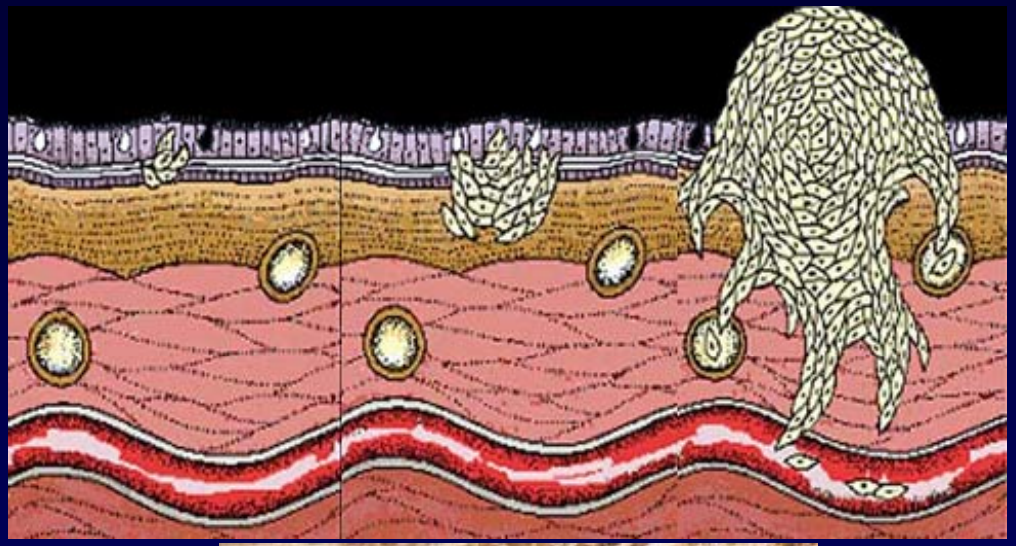
Poon RT, et al. *J Clin Oncol.* 2001;19(4):1207-1225.

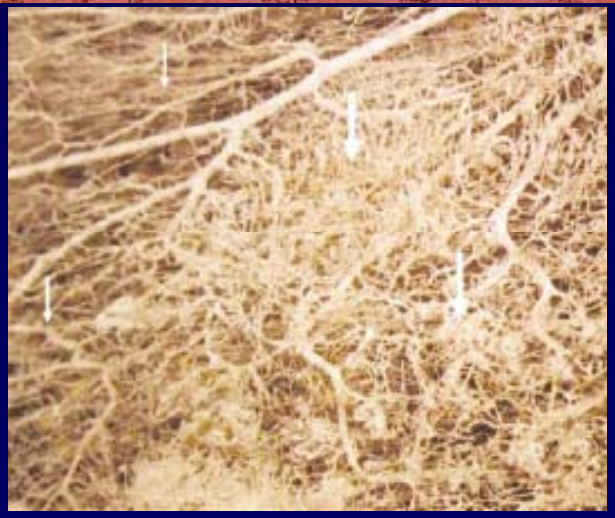
Regulation of Angiogenesis

Angiogenic factors

Cytokines
- **VEGF**
- FGF
- HGF
- HB-EGF
- Angiogenin
- IL-8
- PDGF

Enzymes
- TP





Anti-angiogenic proteins

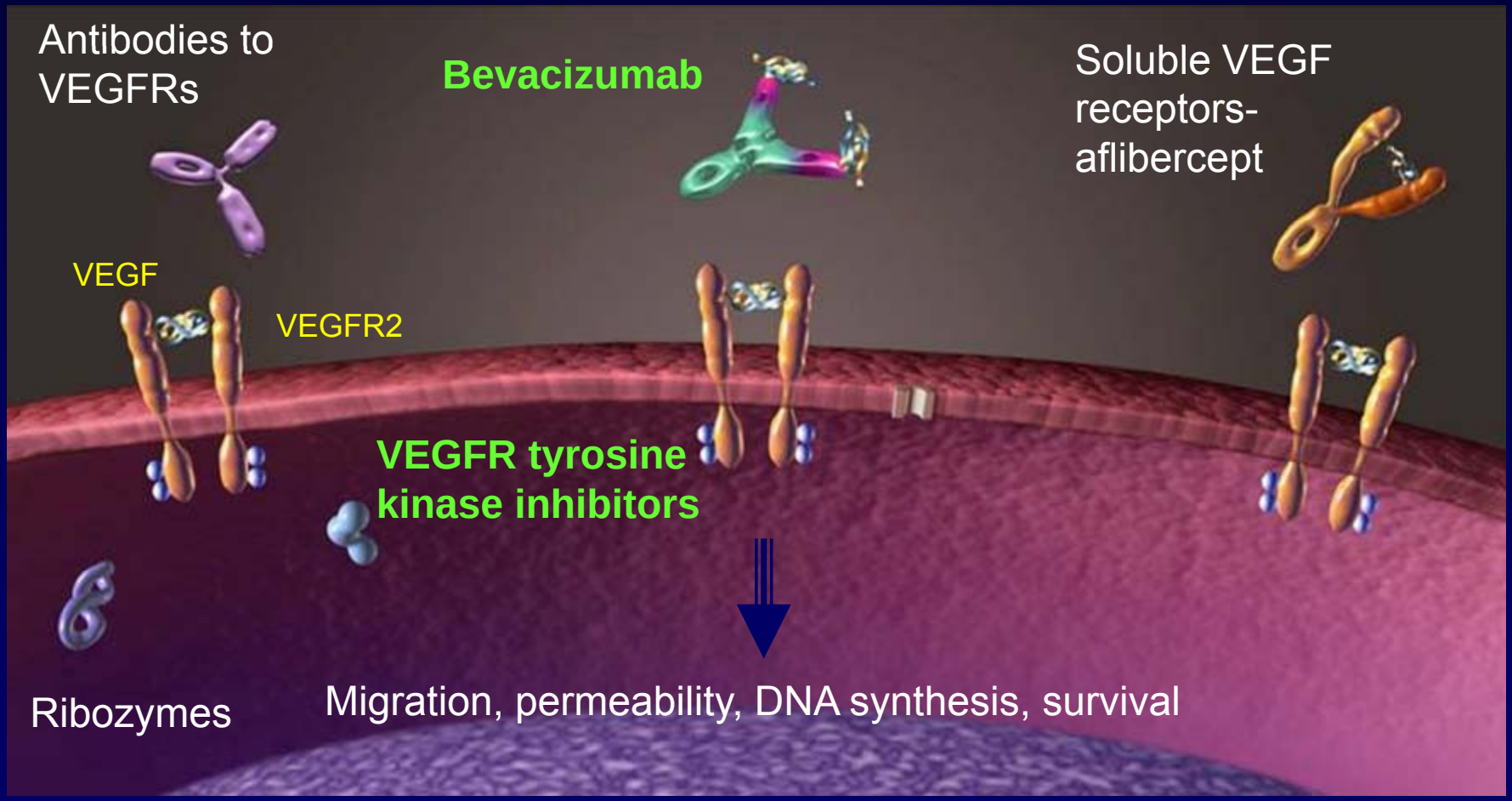
Protein fragments
- Endostatin
- Angiostatin

Inhibitory proteins
- PF4

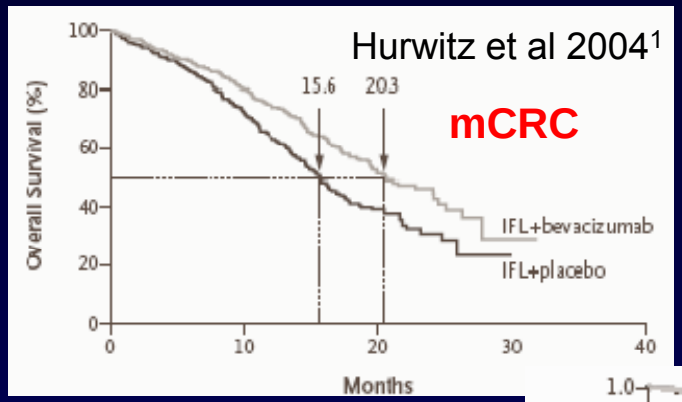
Soluble receptors
- s-flt
- s-FGF R

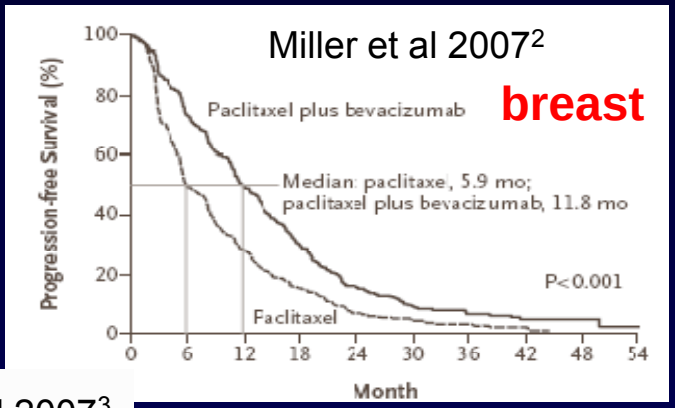
Hinnen P, et al. *Br J Cancer.* 2007;96(8):1159-1165.

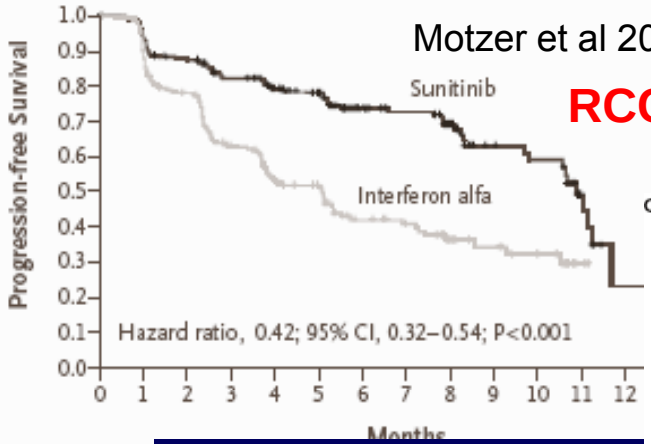
VEGF Targeting Strategies

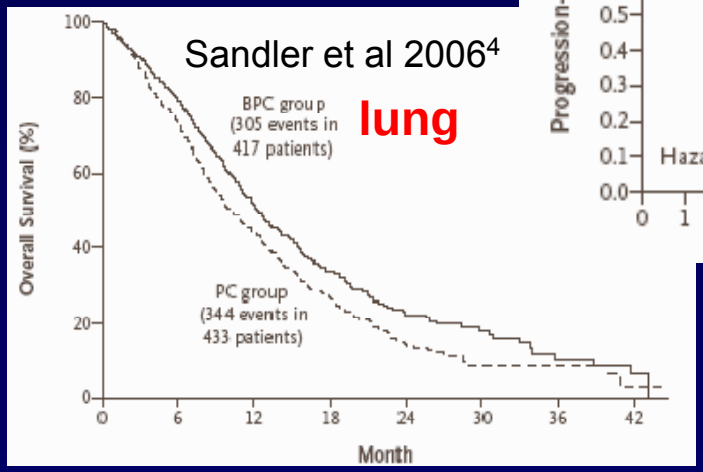


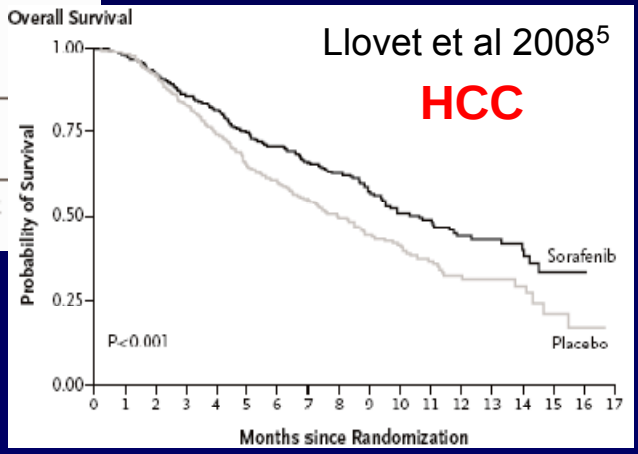
Anti-VEGF Therapies in Solid Tumors





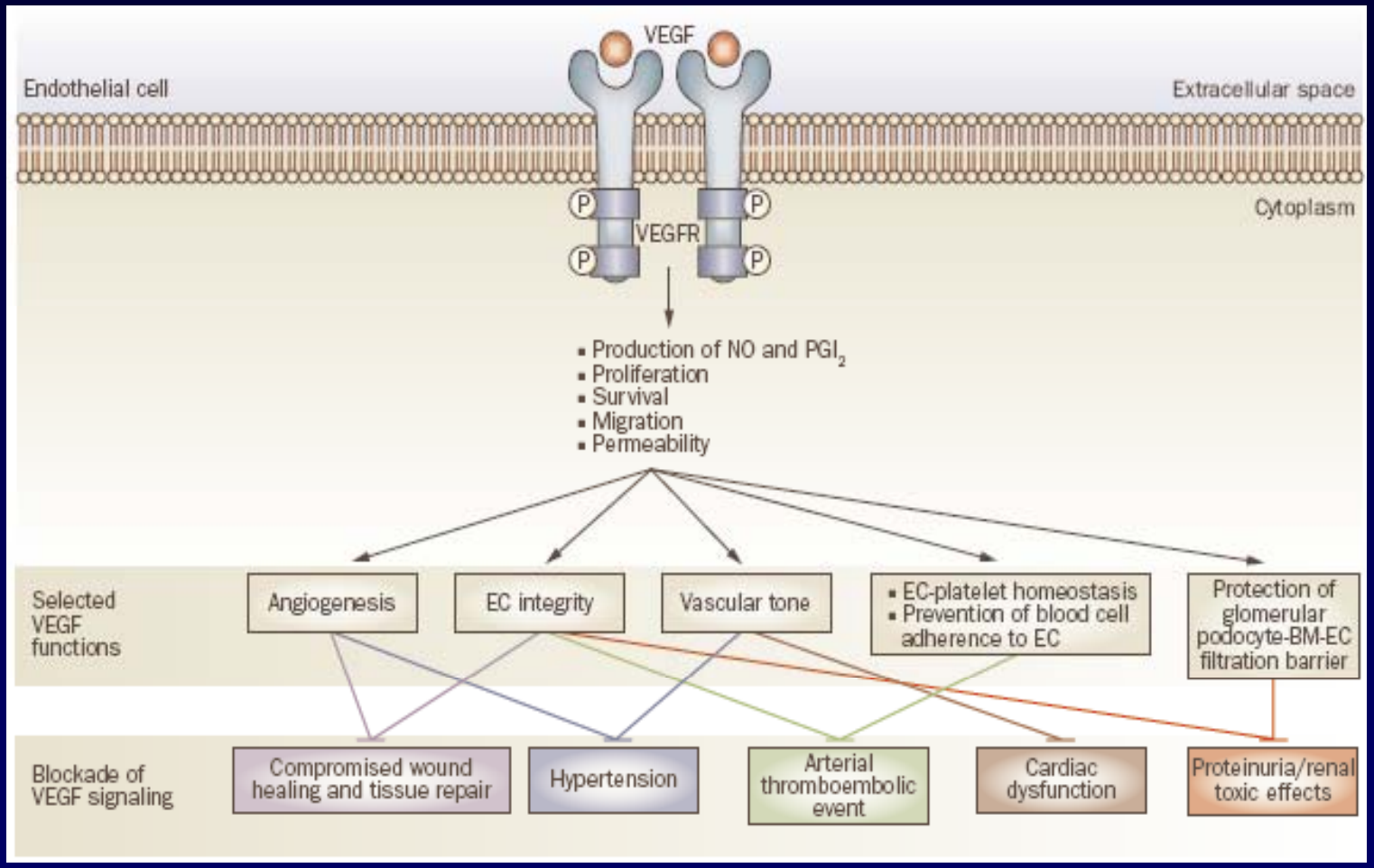






1. Hurwitz H, et al. *N Engl J Med.* 2004;350(23):2335-2342. 2. Miller K, et al. *N Engl J Med.* 2007;357(26):2666-2676. 3. Motzer RJ, et al. *J Clin Oncol*. 2009;27(22):3584-3590. 4. Sandler A, et al. *N Engl J Med.* 2006;355(24):2542-2550. 5. Llovet JM, et al. *N Engl J Med.* 2008;359(4):378-390.

Toxicities of VEGF Inhibition



Chen HX, et al. *Nat Rev Clin Oncol.* 2009;6(8):465-477.

Angiogenesis and Ovarian Cancer Prognosis

- Poor prognostic factors in retrospective studies[1-6]
  - High microvessel density
  - High intratumoral VEGF expression
  - VEGF gene polymorphisms
  - Angiogenic gene profile

- Animal models- VEGF blockade inhibits ascites formation and slows tumor growth[7]

1. Shen GH, et al. *Br J Cancer*. 2000;83(2):196-203. 2. Goodheart MJ, et al. *Clin Cancer Res.* 2005;11(10):3733-3742. 3. Hefler LA, et al. *Clin Cancer Res.* 2007;13(3):898-901. 4. Mendiola M, et al. *PLoS One.* 2008;3(12):e4051. 5. Duncan TJ, et al. *Clin Cancer Res.* 2008;14(10):3030-3035. 6. Rubatt JM, et al. *Gynecol Oncol*. 2009;112(3):469-474. 7. Byrne AT, et al. *Clin Cancer Res*. 2003;9(15):5721-5728.

Single-Agent Bevacizumab in Ovarian Cancer

15 mg/kg Bevacizumab q3w

	Burger et al (2007)[1]	Cannistra et al (2007)[2]
Patients	62	44
Prior chemo regimens	1-2	1-3
Platinum-resistant	58%	100%
Median number of cycles	7 (1-35)	5 (2-16)
Response rate	21%	16%
6-month PFS	40%	28%
Median PFS	4.7 months	4.4 months
Median OS	17.0 months	10.7 months

1. Burger RA, et al. *J Clin Oncol.* 2007;25(33):5165-5171. 2. Cannistra SA, et al. *J Clin Oncol.* 2007;25(33):5180-5186.

Bevacizumab Combination Regimens in Ovarian Cancer

- Case series of bevacizumab in combination with several chemotherapeutic regimens
- Safety in combination with carboplatin-paclitaxel established

	Cyclophosphamide	Erlotinib	Sorafenib
Ref.	Garcia et al (2008)[1]	Nimeiri et al (2008)[2]	Azad et al (2008)[3]
Regimen	BEV 10 mg/kg q2w Cyclo. 50 mg od	BEV 15 mg/kg q3w Erlotinib 150 mg od	BEV 5 mg/kg q2w Sora. 200 mg bid
No. patients	70	13	13
RR	24%	15%	43%
6-mo PFS	56%	38%	NA
Median OS	16.9	11.0	NA

1. Garcia AA, et al. *J Clin Oncol*. 2008;26(1):76-82. 2. Nimeiri HS, et al. *Gynecol Oncol.* 2008;110(1):49-55. 3. Azad NS, et al. *J Clin Oncol.* 2008;26(22):3709-3714.

Bevacizumab Toxicity in Ovarian Cancer

- Typical toxicity profile- hypertension, thromboembolic events
- BUT….
- Gastrointestinal perforations/ fistulae[1]
- Cannistra et al early discontinuation- five GI perforations[2]
- Safety signal in other phase II studies
- Can we predict patients most at risk?[3]
  - Multiple lines of therapy
  - Diffuse serosal involvement
  - Radiological evidence of bowel obstruction

- Can we extrapolate form other tumor types?[4]

1. Sfakianos GP, et al. *Gynecol Oncol.* 2009;114(3):424-42. 6 2. Cannistra SA, et al. *J Clin Oncol.* 2007;25(33):5180-5186. 3. Wright JD, et al. *Int J Gynecol Cancer*. 2008;18(3):400-406. 4. Hapani S, et al. *Lancet Oncol.* 2009;10(6):559-568.

Phase III Bevacizumab Trials

- First-line
  - ICON-7
  - GOG-218
- Recurrent disease
  - OCEANS
  - GOG-213
  - Aurelia

ICON7

Bevacizumab in Ovarian Cancer

GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

AGO-AUST
AGO-OWAR
ANZGOG
EORTC
GEICO
GINECO
GOG
JGOG
MITO
MRC/NCRI
NCI
NCIC CTG
NSGO
RTOG
SGCTG

EOC/FTC/PPC after surgery/biopsy

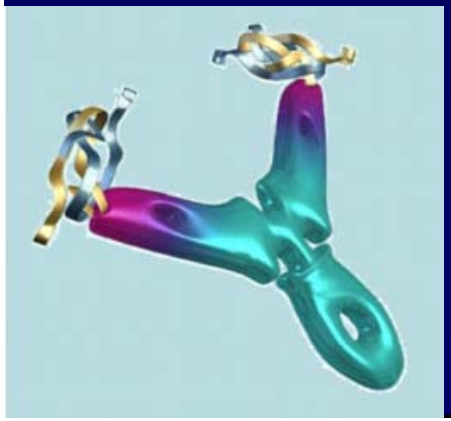
I-IIa (Gd3 or clear cell)

IIb-IV

(1520 patients)

Carboplatin/ paclitaxel + bevacizumab x 6 → **Bevacizumab x 12**

Carboplatin/ paclitaxel x 6



1º Outcome- PFS

Results Autumn 2010

Translational research

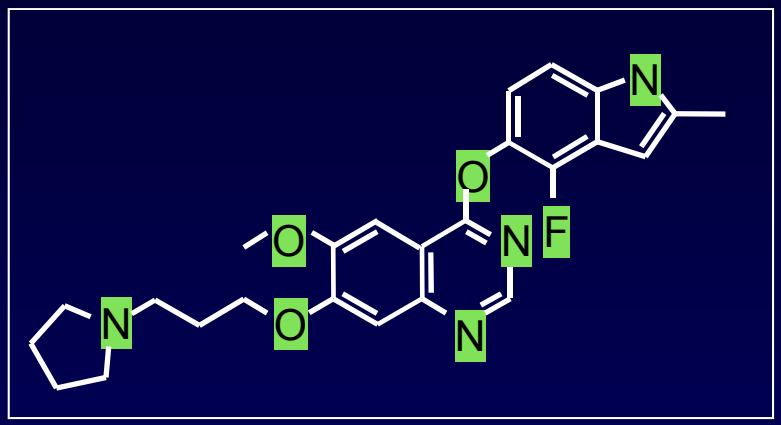
Biomarkers of response/progression

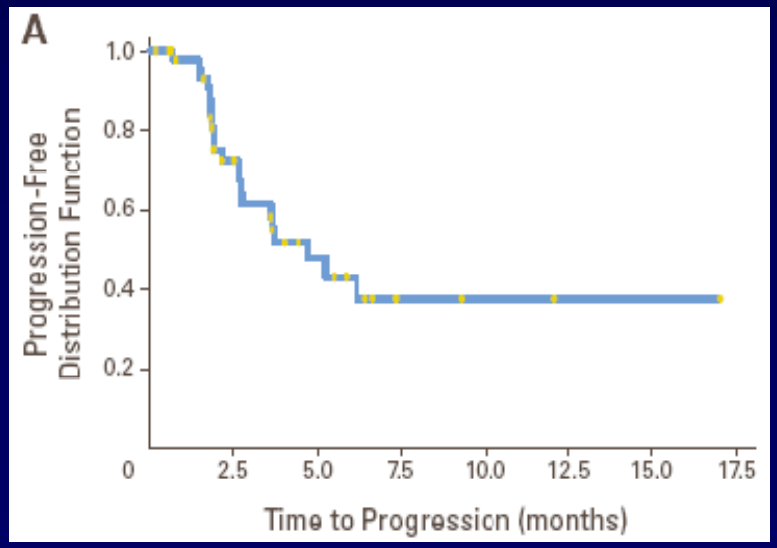
ICON7 vs GOG218

	ICON7	GOG218
Stage	Ic-IV	IIIa-IV
Bevacizumab dose	2.5 mg/kg/wk	5 mg/kg/wk
Design	2 arm	3 arm with placebo maintenance
Duration of maintenance	39 weeks	48 weeks

Cediranib and Ovarian Cancer

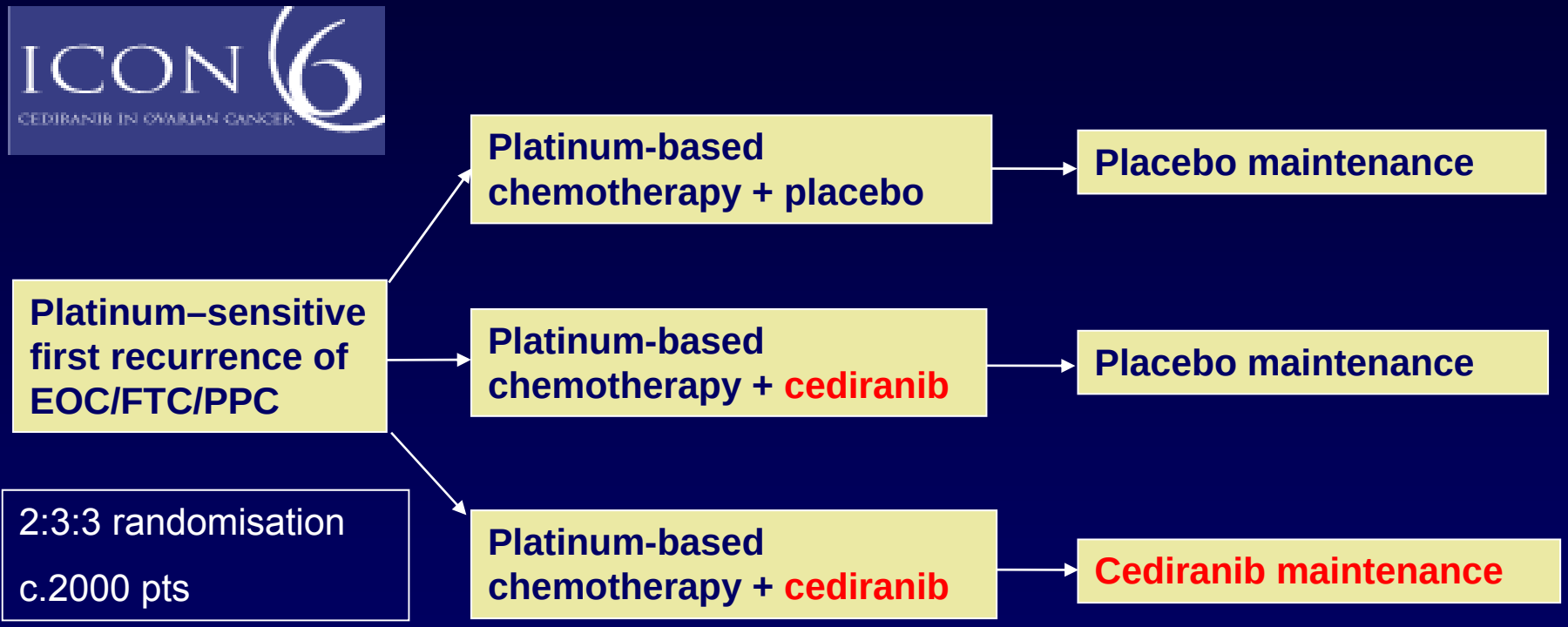
- Oral inhibitor of VEGFR-2, VEGFR-1,-3 and c-kit
- 2 phase II trials
- Relapsed ovarian cancer
- Mixed platinum sensitivity
- 30 mg od
- RR-17%
- Median PFS 5.2 months
- Hypertension, fatigue, diarrhea





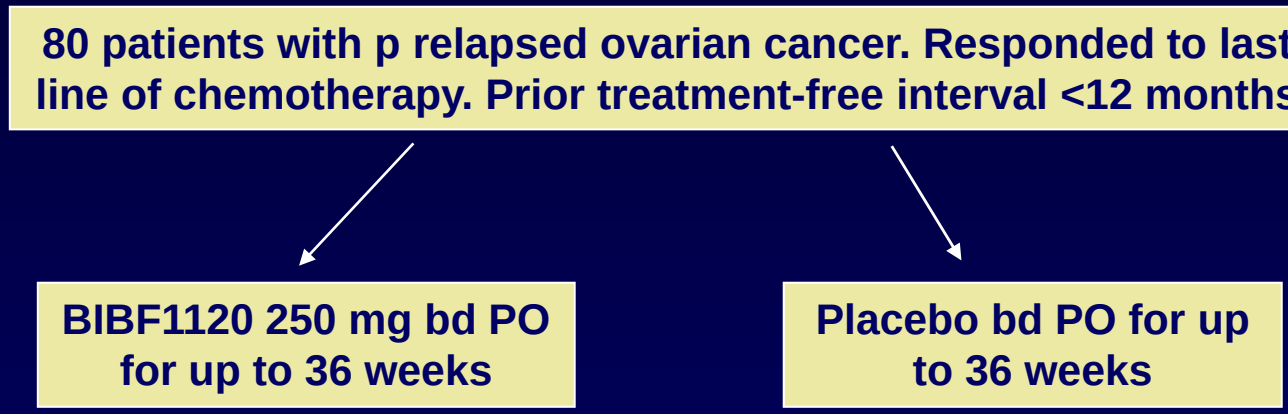
Matulonis UA, et al. *J Clin Oncol.* 2009;27(33):5601-5606. Hirte HW, et al. *J Clin Oncol.* 2008;26(May 20 Suppl): Abstract 5521.

Cediranib in Ovarian Cancer



- **Cediranib dose 20 mg od**
- **Carboplatin-paclitaxel, gemcitabine-carboplatin, carboplatin**

BIBF1120 and Ovarian Cancer



- Phase II maintenance screening study
- BIBF1120—oral angiokinase inhibitor (VEGFR, FGFR, PDGFR)
- PFS at 36 weeks—BIBF 1120,14.3%, placebo 5.0%
- 2 prolonged remission patients in BIBF1120 arm

Ledermann JA, et al. *J Clin Oncol.* 2009;27(15S): Abstract 5501.

BIBF1120 and Ovarian Cancer II

- Phase I in combination with carboplatin-paclitaxel*
- Recommended dose BIBF1120 200 mg bd

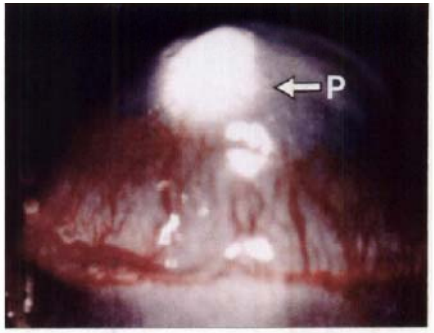
- AGO-OVAR12
- Phase III—1300 patients with IIB-IV disease
- BIBF1120 vs placebo—2 years
- In combination with carboplatin-paclitaxel

- AGO OVAR16—pazopanib

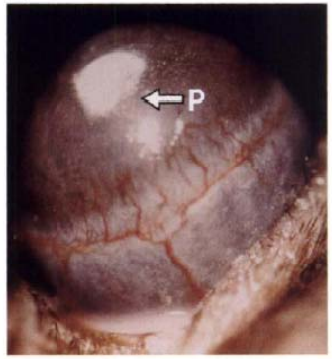
*du Bois A, et al. *Ann Oncol.* 2010;21(2):370-375.

Weekly Paclitaxel—An Anti-Angiogenic Therapy in Ovarian Cancer?

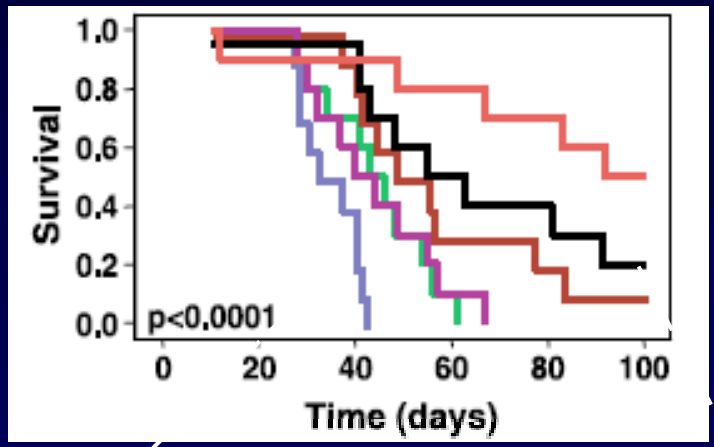
Methylcellulose



Paclitaxel



Klauber N, et al. *Cancer Res.* 1997;57(1):81-86.



PBS

Kamat AA, et al. *Cancer Res.* 2007;67(1):281-288.

VEGFRTKI and met. taxane

- Weekly paclitaxel effective in ovarian cancer resistant to three-weekly platinum-taxane chemotherapy

Markman M, et al. *J Clin Oncol.* 2002;20(9):2365-2369.
Markman M, et al. *Gynecol Oncol.* 2006;101(3):436-440.

Weekly Paclitaxel—An Anti-Angiogenic Therapy in Ovarian Cancer?

FIGO III <1 cm

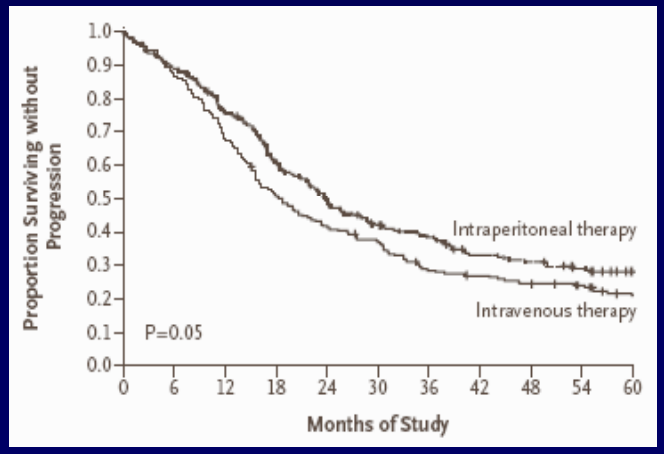
Paclitaxel
135 mg/m²/24 hours d1 IV

Cisplatin
75 mg/m² d2 IV

Paclitaxel
135 mg/m²/24 hours d1 IV

Cisplatin
100 mg/m² d2 IP

Paclitaxel
60 mg/m² d8 IP



Armstrong DK, et al. *N Engl J Med.* 2006;354(1):34-43.

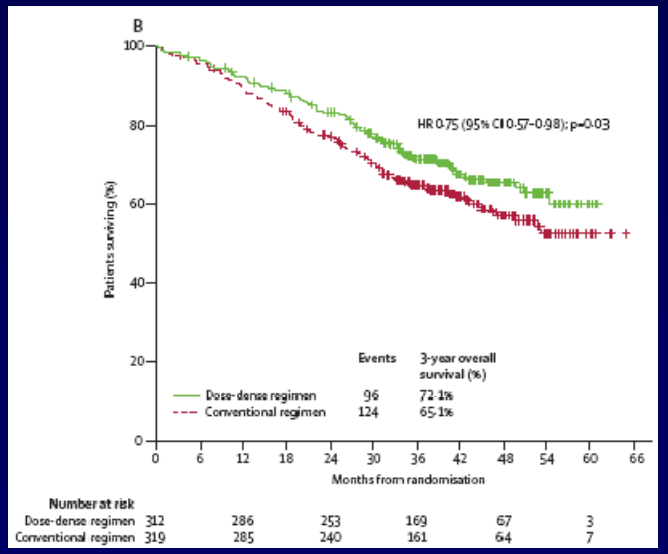
FIGO II-IV

Paclitaxel
180 mg/m² d1

Carboplatin
AUC6

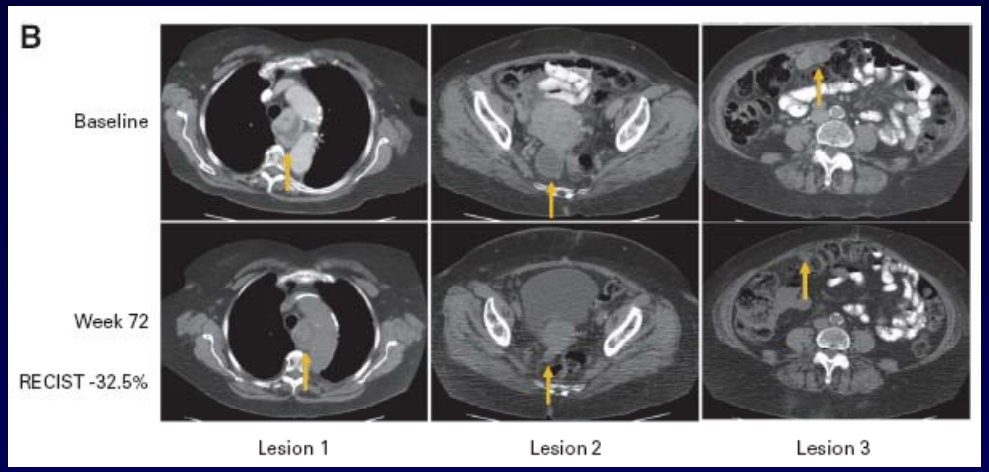
Paclitaxel
80 mg/m² d1,8,15

Carboplatin
AUC6



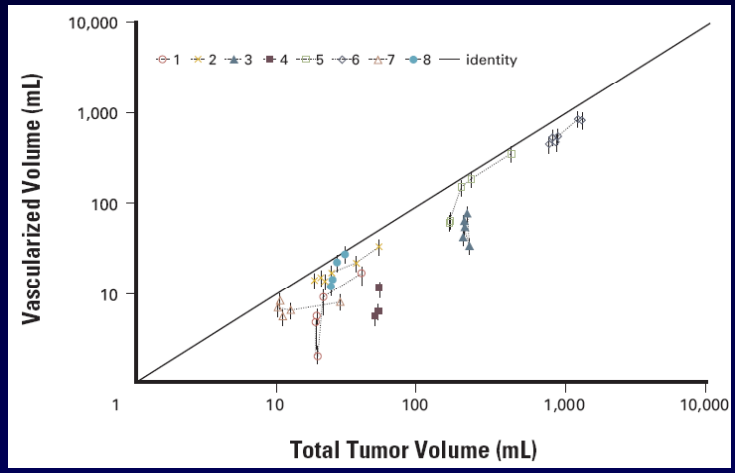
Katsumata N, et al. *Lancet.* 2009;374(9698):1331-1338.

Other Targets



Herbst RS, et al. *J Clin Oncol*. 2009;27(21):3557-3565.

- **AMG386**
- Angiopoietin 1/2 Peptibody
- 156 wk PR

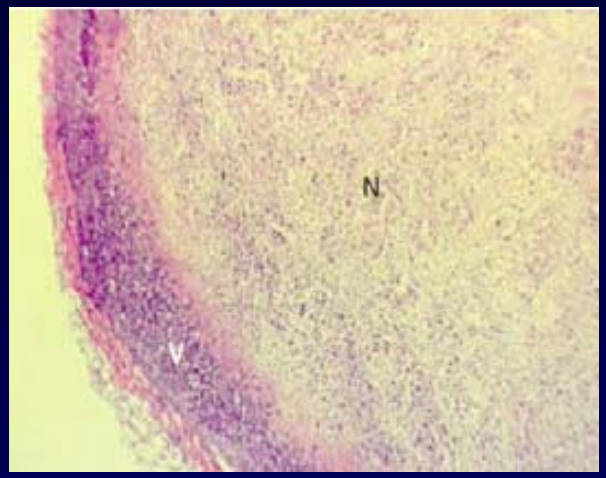


Jayson GC, et al. *J Clin Oncol.* 2005;23(5):973-981.

- **CDP860**
- PDGFRβ Fab
- Ascites accumulation

Vascular Disrupting Agents

- Acute shutdown of tumor vasculature
- Hypoxia and necrosis
- Combretastatin and DMXAA



Hinnen P, et al. *Br J Cancer.* 2007;96(8):1159-1165.

- Phase II CA4P and carboplatin-paclitaxel
- 44 patients platinum-resistant ovarian cancer
- 25% response rate (RECIST/CA-125)
- Tumor pain, hypertension

Zweifel M, et al. *J Clin Oncol.* 2009;27(15S): Abstract 5502.

Biomarkers for Anti-VEGF Therapies

..'characteristic that is objectively measured and evaluated as an indicator of a normal biological process, a pathogenic process or of a pharmacological response to a therapeutic intervention'

Atkinson AJ, et al. *Clin Pharmacol Ther.* 2001;69:89-95

- **Predictive biomarker**
- **Surrogate response**
- **Resistance biomarker**
- **Pharmacodynamic biomarker**

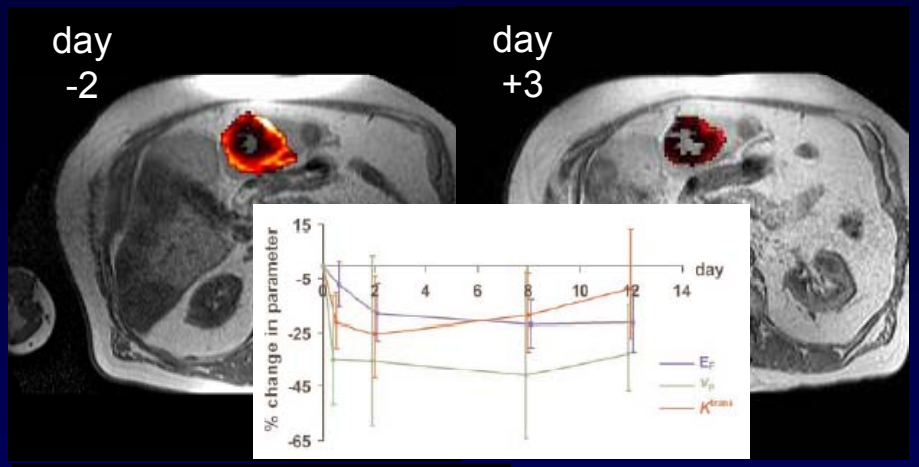
Imaging Biomarkers

- DCE-MRI
- Clear PD signal
- K^{trans}

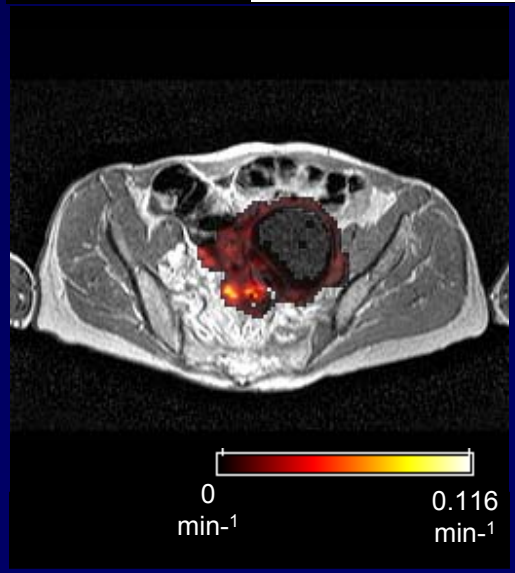
- May predict benefit from VEGFI in RCC

  Hahn OM, et al. *J Clin Oncol*. 2008;26(28):4572-4578.

- BUT.. reproducibility
- Cost



O'Connor et al. 2009

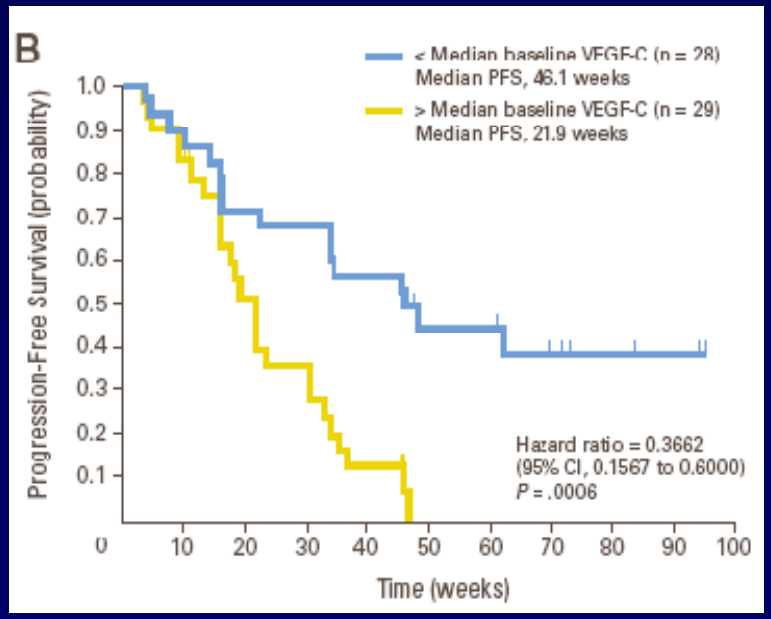


Mitchell et al. 2010. In press

Circulating Biomarkers

- Angiomodulatory cytokines
- PD signature- elevated VEGF, PlGF, reduction sVEGFR-2 and sVEGFR-3
- Lower baseline VEGF-C assoc with longer PFS/RR in RCC

Rini BI, et al. *J Clin Oncol.* 2008;26(22):3743-3748.



Circulating Biomarkers

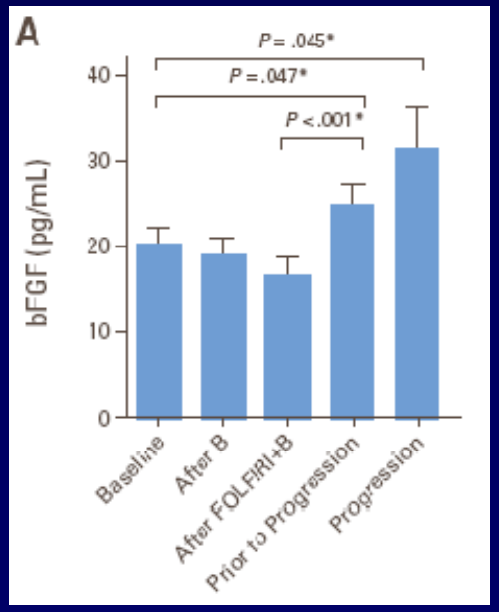
- Angiomodulatory cytokines
- PD signature- elevated VEGF, PlGF, reduction sVEGFR-2 and sVEGFR-3
- Lower baseline VEGF-C assoc with longer PFS/RR in RCC

Rini BI, et al. *J Clin Oncol.* 2008;26(22):3743-3748.

- Early markers of progression- FGF2, HGF, PlGF, SDF-1

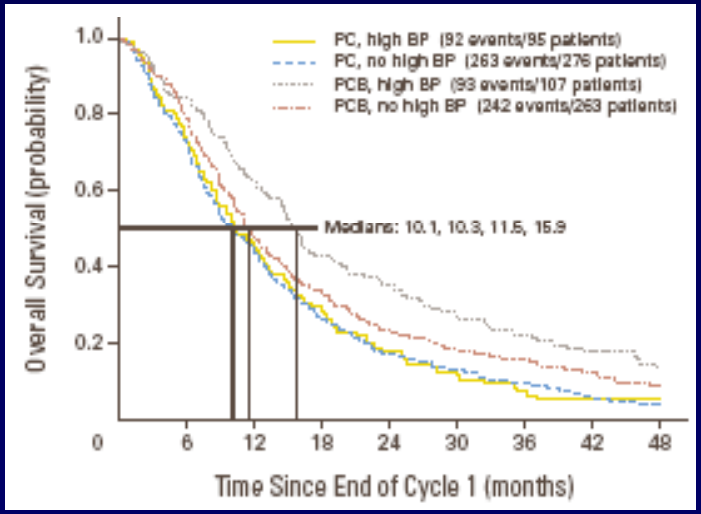
Batchelor et al 2007. Kopetz S, et al. *J Clin Oncol.* 2010;28(3):453-459.

- Currently exploratory- biomarker profile



Biomarkers

- Circulating endothelial cells
- Hypertension?
  - Marker of degree of inhibition
  - May be predictive of benefit from bevacizumab



Schneider BP, et al. *J Clin Oncol*. 2008;26(28):4672-4678. Dahlberg SE, et al. *J Clin Oncol.* 2010;28(6):949-954.

Biomarkers

- Circulating endothelial cells
- Hypertension?
  - Marker of degree of inhibition
  - May be predictive of benefit from bevacizumab
- Obesity?
  - Adipose tissue secretes proangiogenic factors
  - Obese mice resistant to anti-VEGF treatments
  - In mCRC obesity may be predictive factor

Guiu et al 2010. In press.

Key Questions

- Does the addition of an anti-angiogenic agent to standard chemotherapy improve outcomes in first-line setting/relapsed disease?
- Is maintenance therapy necessary?
- In platinum-resistant disease, is combination therapy superior to single modality therapy?
- Is dose-dense paclitaxel as effective as anti-VEGF treatment strategies?
- Will modulation of other angiogenesis targets improve the efficacy of anti-VEGF treatment strategies?
- Can we identify predictive biomarkers?