Behandling av metastatisk og avansert nyrekreft – en liten revolusjon!

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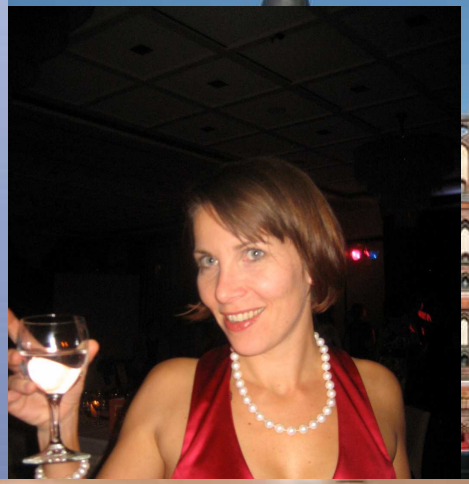
Miele®

Anything else is a compromise



MEDISIN OG VITENSKAP Diagnostikk og behandling

Behandling av nyrekreft med fjernmetastaser

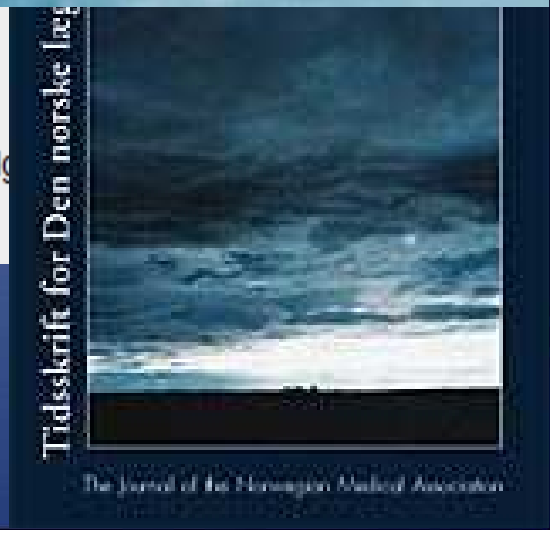
S D Fosså N Aass K Tveter O Dahl

Det finnes ingen effektiv standardbehandling av nyrekreft med fjernmetastaser, men legene som ser disse pasientene, bør kjenne til indikasjon for og effekt av de forskjellige terapitilbud ved denne tilstanden.

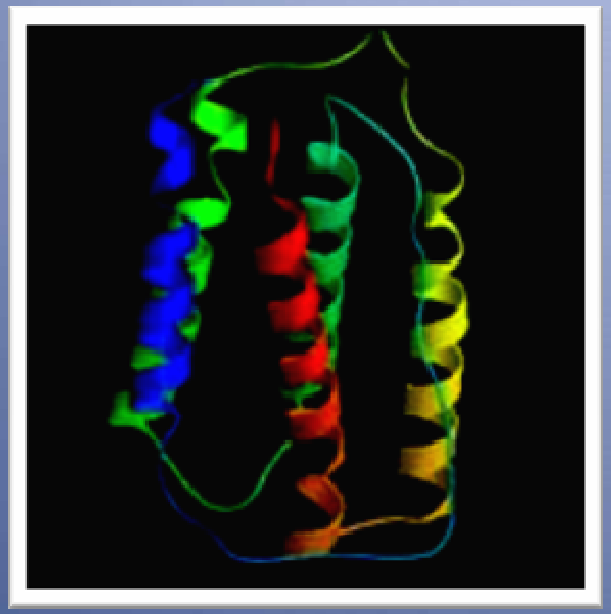
Aktuell relevant litteratur blir omtalt sammen med erfaringene fra Det Norske Radiumhospital. Hovedvekten blir lagt på systemisk behandling.

Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av pasienter med nyrecellekreft (RCC)

Pasienter med metastaserende nyrekreft som skal ha systemisk behandling, bør prinsipielt inkluderes i kliniske studier. Hvis dette ikke er mulig, ansees interferon- α - monoterapi, administrert av lokalsykehus, som standard systemisk behandling for utvalg og godt informerte pasienter.



The excitement of the cytokine era



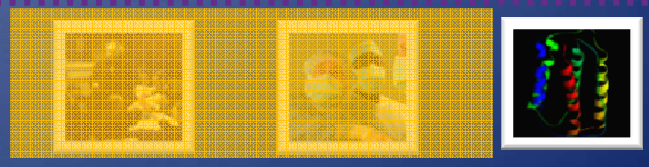
1950s: IFN discovered
Isaacs and Lindenmann

1980s: clinical trials using IFN

IFN: proven efficacy, increased OS

Therapy of choice in Europe

1980s



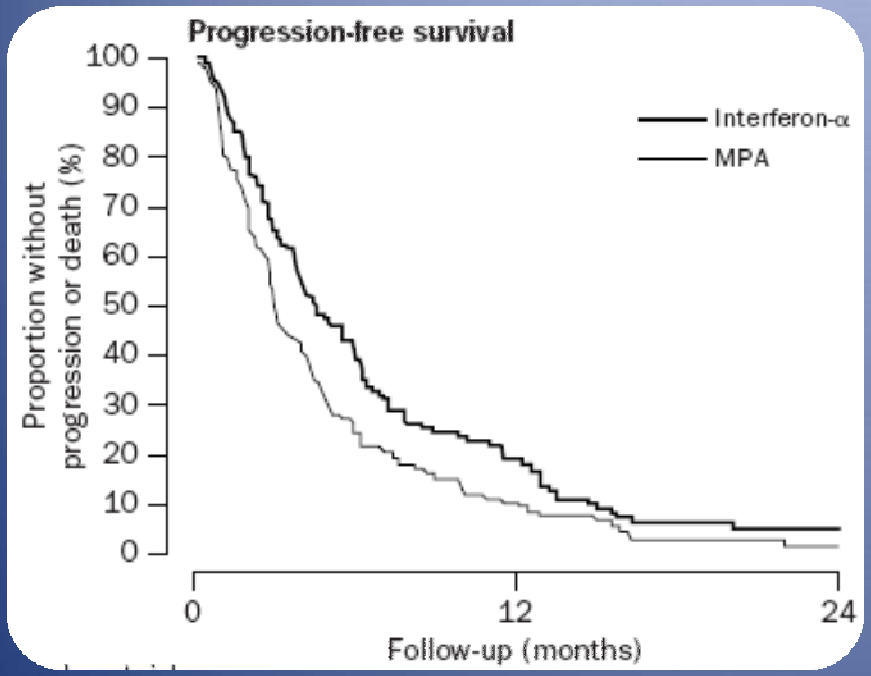
Haemangiomas

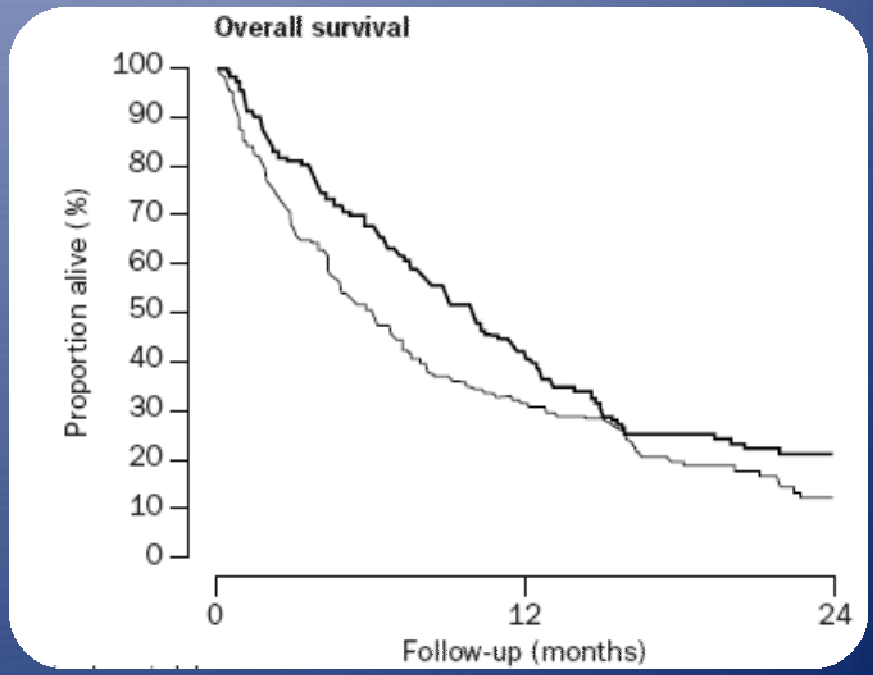
Some therapy resistant and life threatening

After 11 months of IFN treatment

Folkman, et al.

Interferon

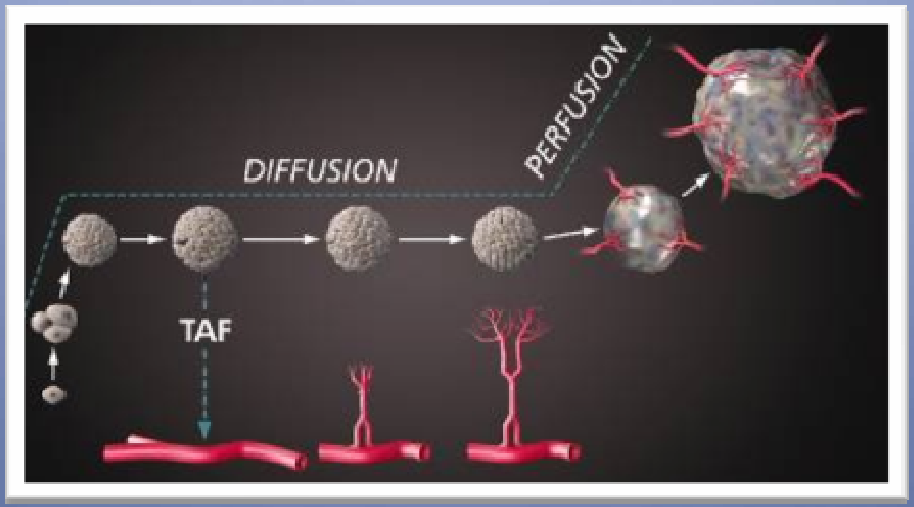




PFS 5,0 mnd
OS 11,4 mnd

MRCRCC, Lancet 1999

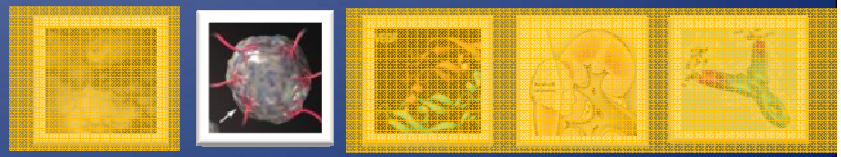
The anti-angiogenesis theory, a new way of thinking



Judah Folkman

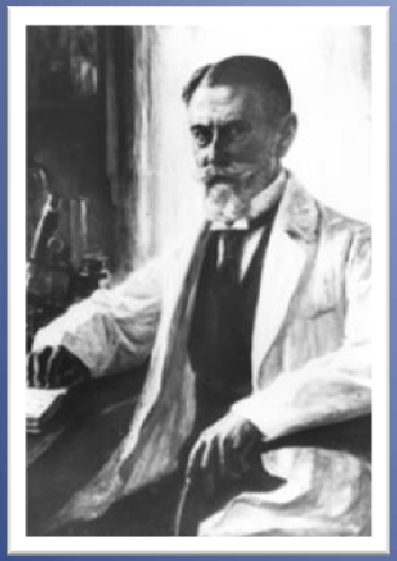
- **Isolates *'a tumour factor responsible for angiogenesis'*[1]**
- **Controversial hypothesis *'tumours are dependent on angiogenesis'*[2]**

1971

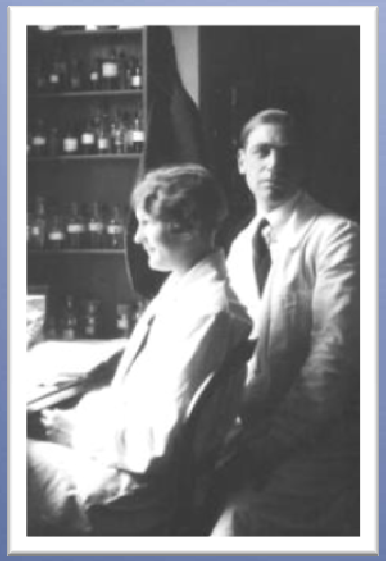


1. Folkman, J Exp Med 1971; **2.** Folkman, NEJM 1971

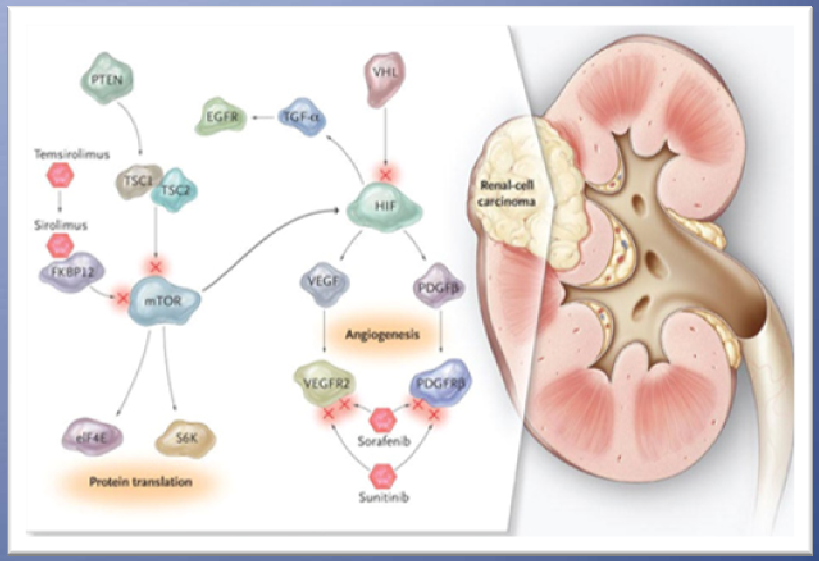
Identification of VHL



Eugen von Hippel (1904)

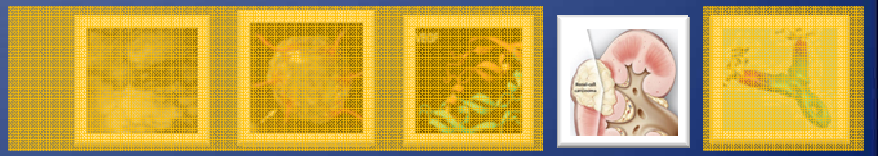


Arvid Lindau (1926)

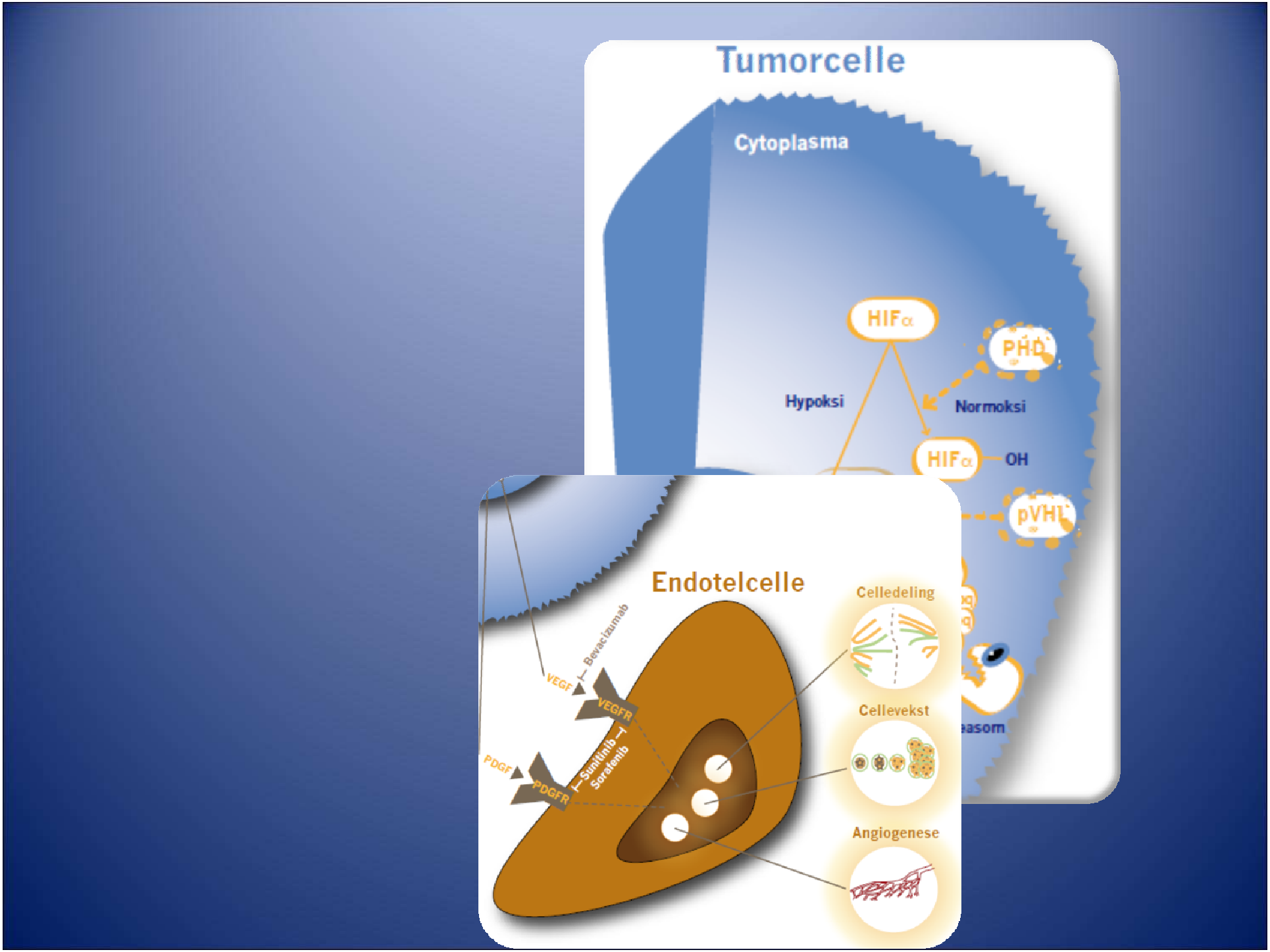


- Latif et al (1993) identify VHL gene mutation and link to clear-cell RCC

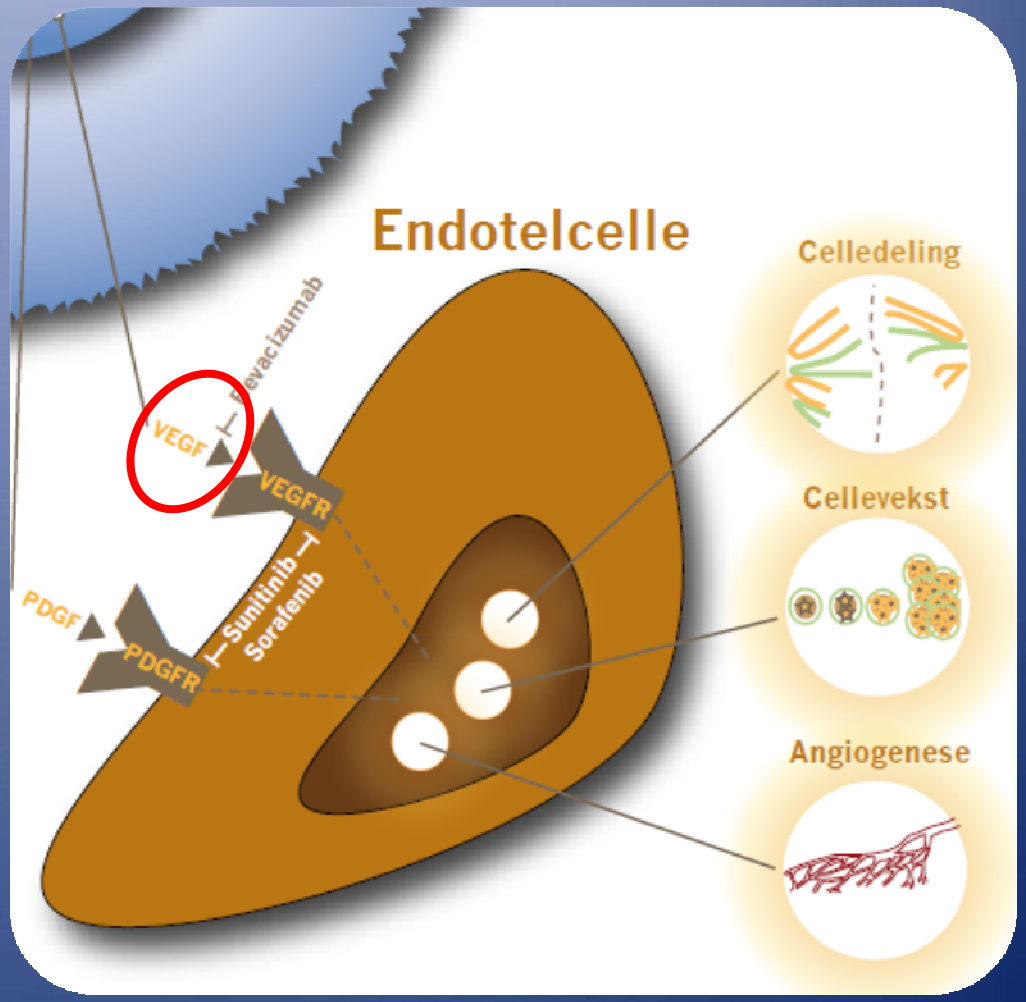
1993



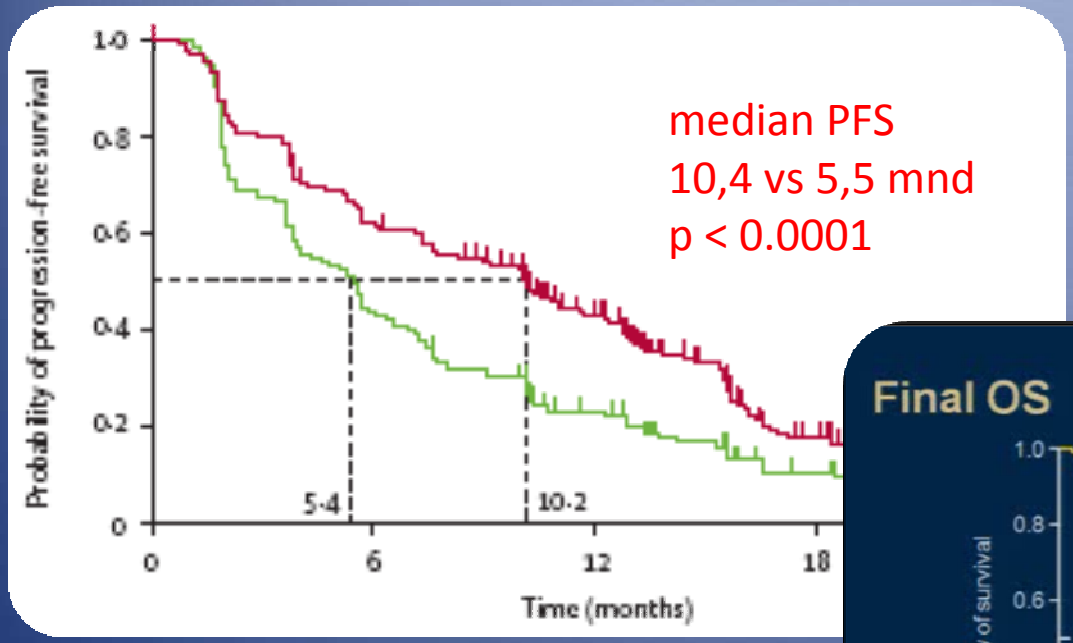
Latif et al. Science 1993


Tumorcelle
Cytoplasma
HIFα
PHD
Hypoksi
Normoksi
HIFα
OH
pVHL
Endotelcelle
Bevacizumab
VEGF
VEGFR
PDGF
PDGFR
Sunitinib
Sorafenib
Celledeling
Cellevekst
Angiogenese

Bevacizumab

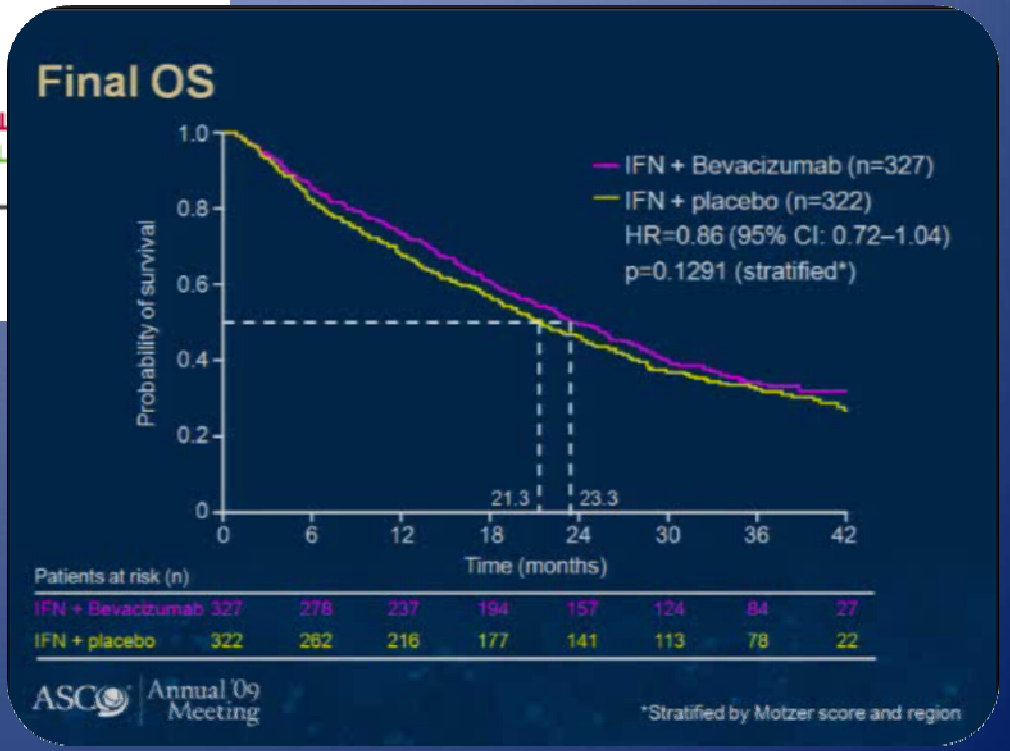


Bevacizumab (AVOREN)



median PFS
10,4 vs 5,5 mnd
p < 0.0001

median OS
23,3 vs 21,3 mnd
n.s.



Escudier et al., Lancet 2007

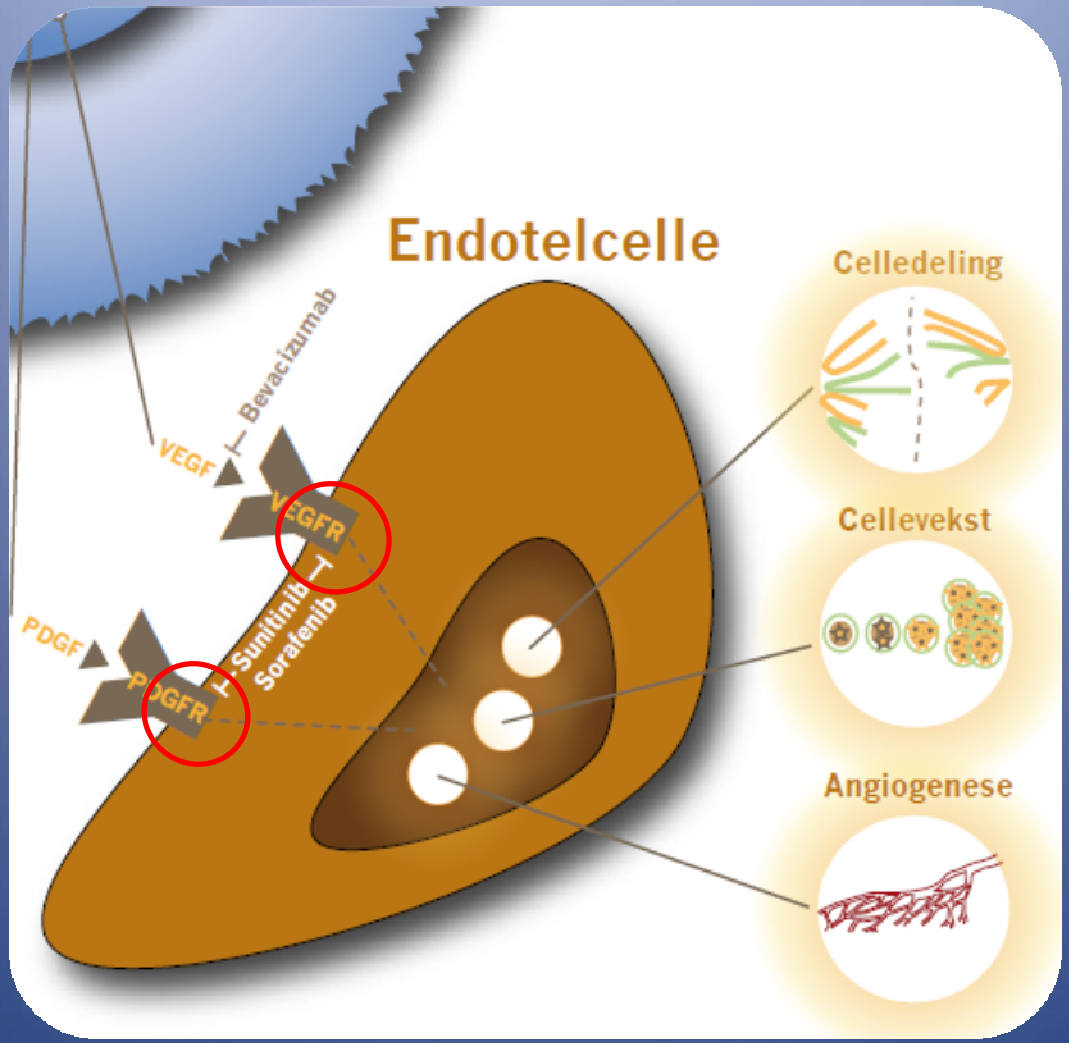
Escudier, B; ASCO 2009

Bev + Interferon – subsequent therapies

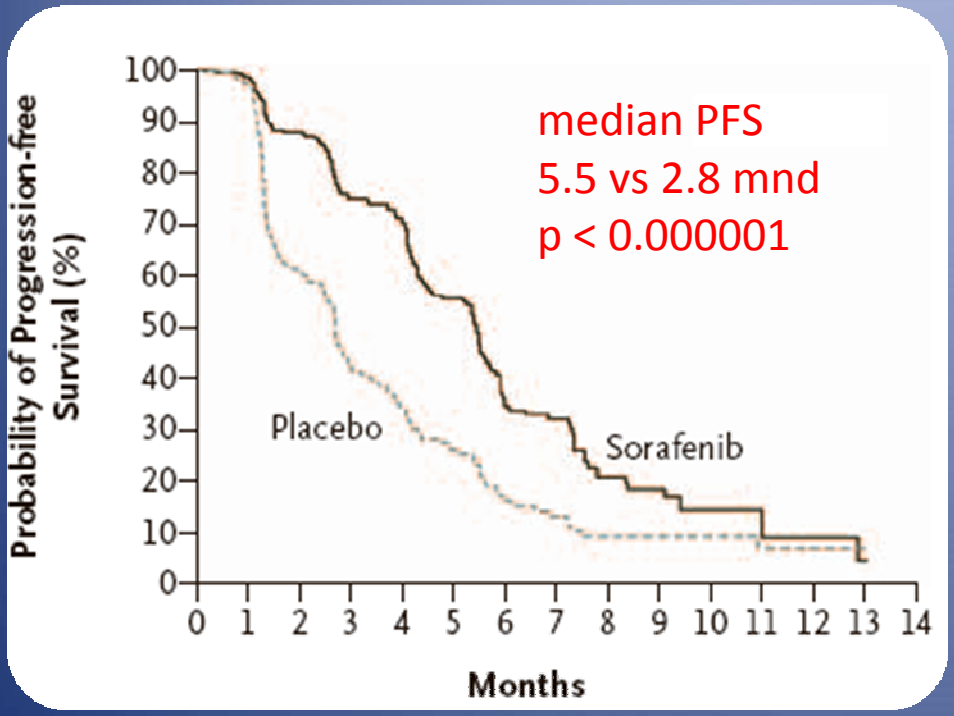
TABLE 4 Median OS in patients receiving post-protocol therapy

	Bevacizumab + IFN		IFN + placebo	
	n	Median OS (months)	*n*	Median OS (months)
All patients	327	23.3	322	21.3
Subsequent TKI	113	38.6	120	33.6
Subsequent sunitinib	83	43.6	92	39.7
Subsequent sorafenib	60	38.6	50	30.7
Subsequent sunitinib + sorafenib	32	43.6	27	41.2

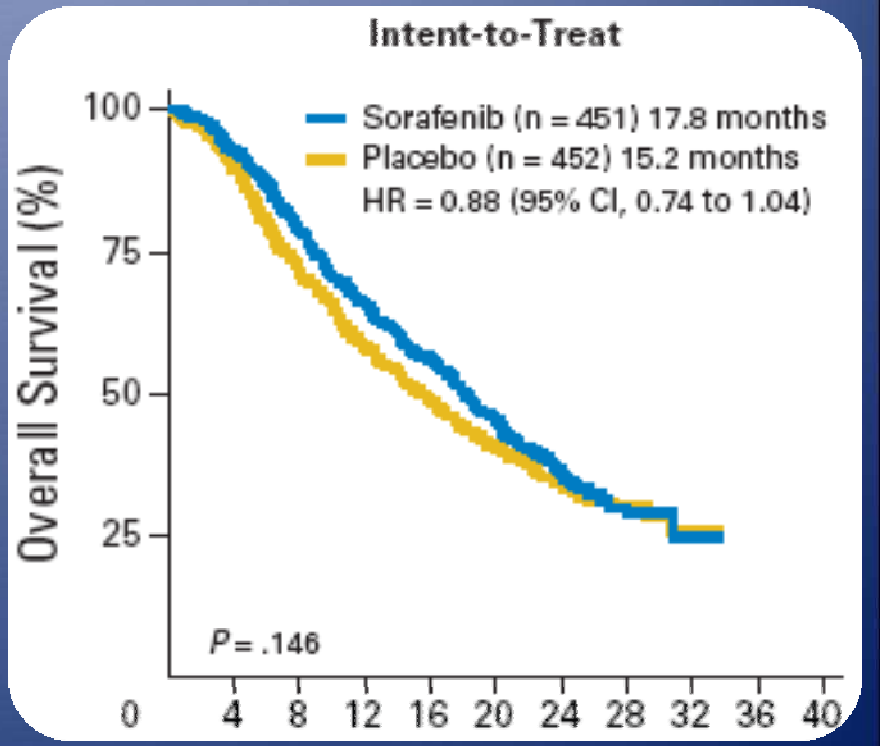
Bracarda et al., BJU Int 2011


Endotelcelle
Celledeling
Cellevekst
Angiogenese
Bevacizumab
VEGF
VEGFR
PDGF
PDGFR
Sunitinib
Sorafenib

Sorafenib (TARGET)



median PFS
5.5 vs 2.8 mnd
p < 0.000001

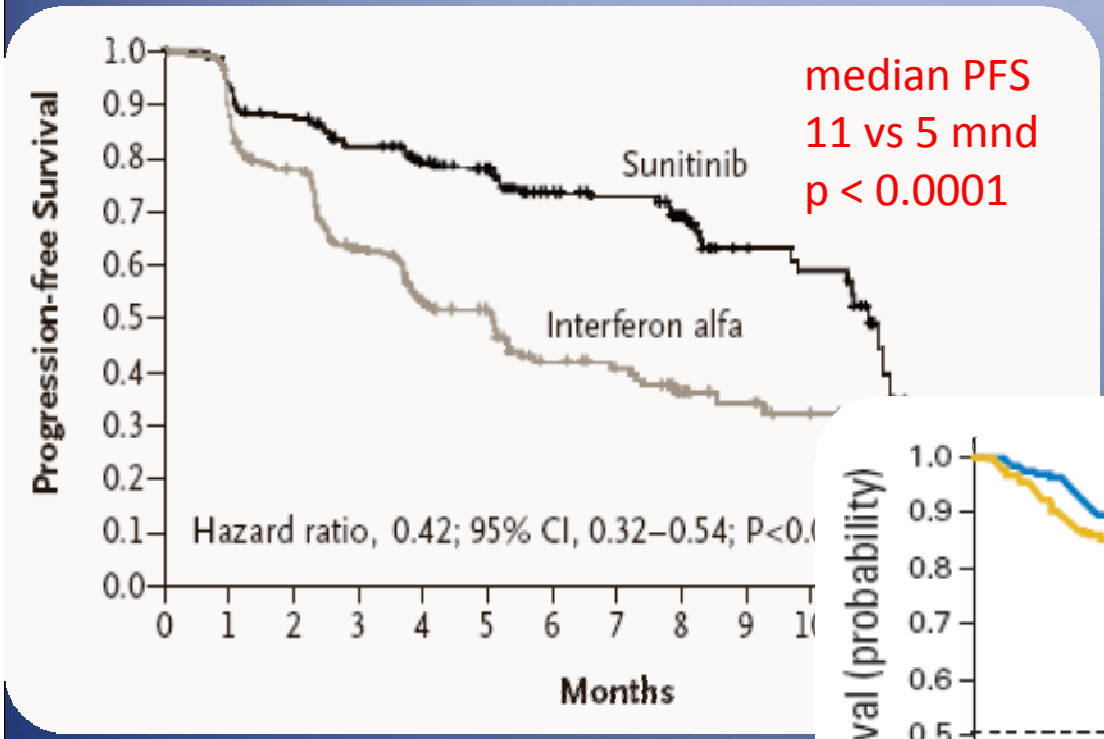


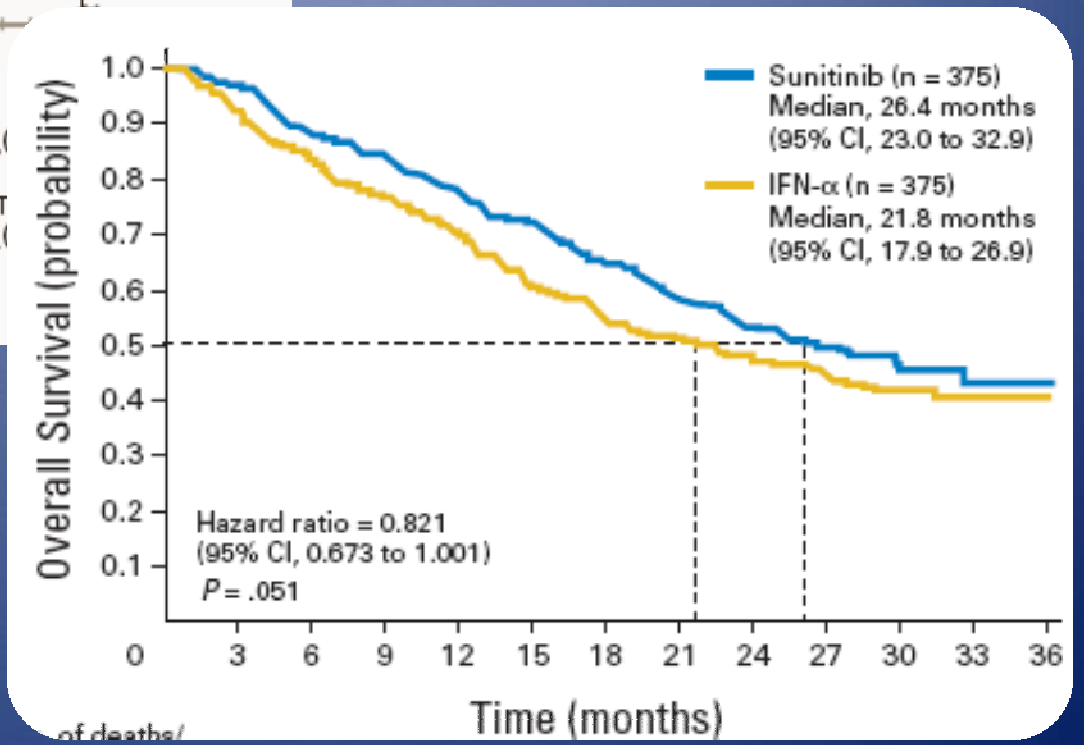
Escudier et al., N Engl J Med 2007

Escudier et al., J Clin Oncol 2009

Sunitinib

median PFS
11 vs 5 mnd
p < 0.0001

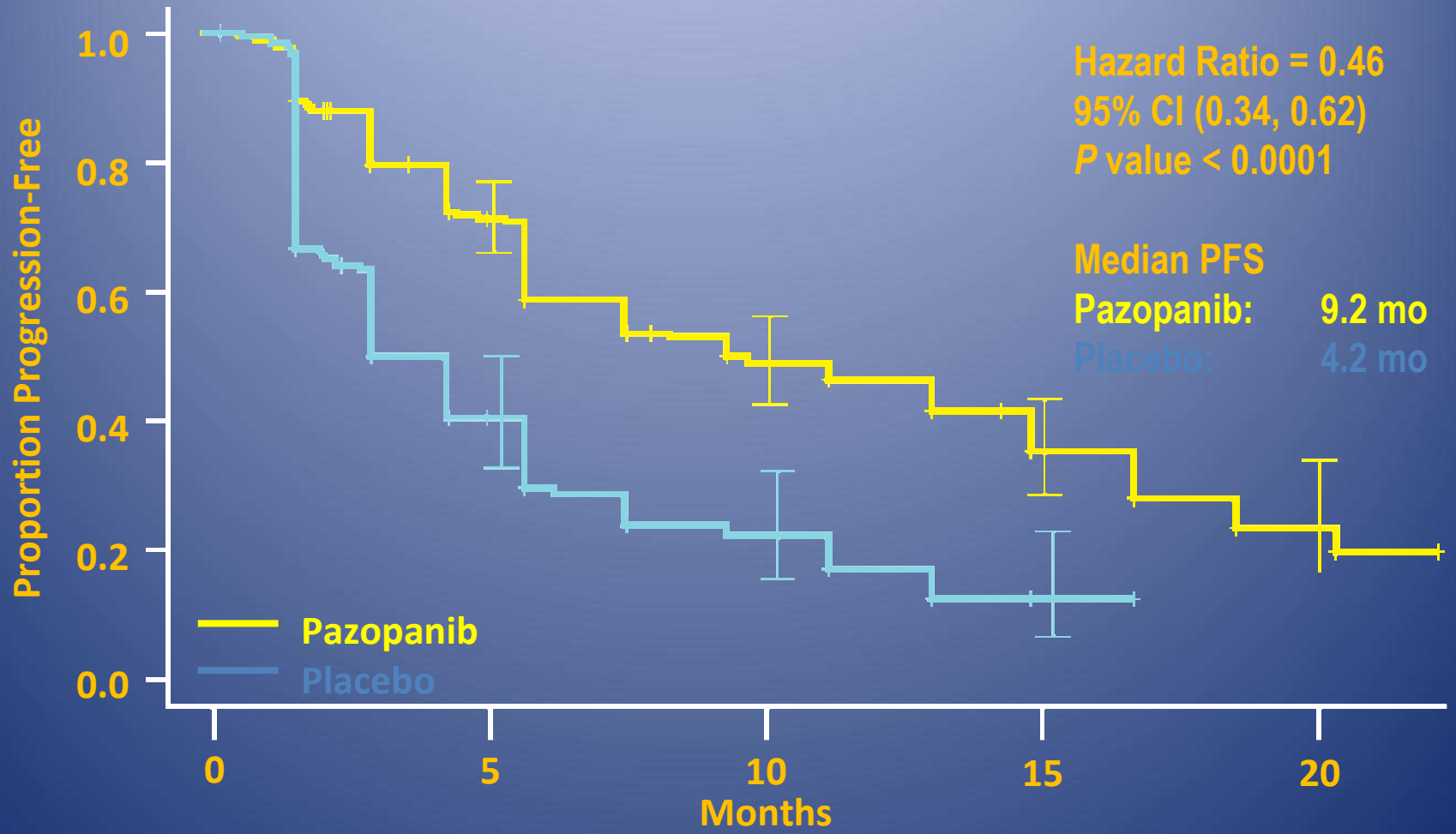




Motzer et al., N Engl J Med 2007

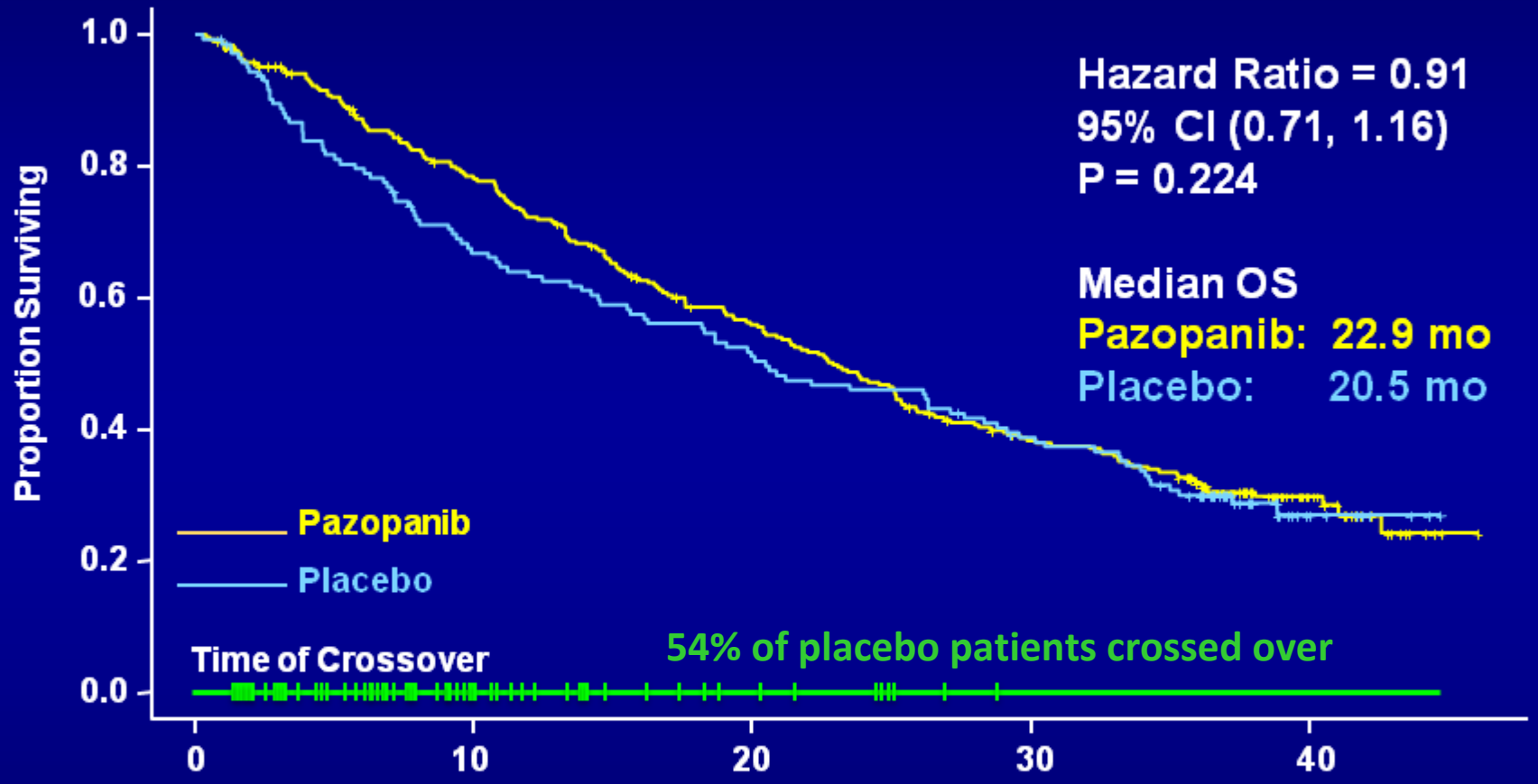
Motzer et al., J Clin Oncol 2009

Pazopanib



Reproduced with permission from Sternberg CN, et al. *J Clin Oncol*. 2010;28:1061-8.

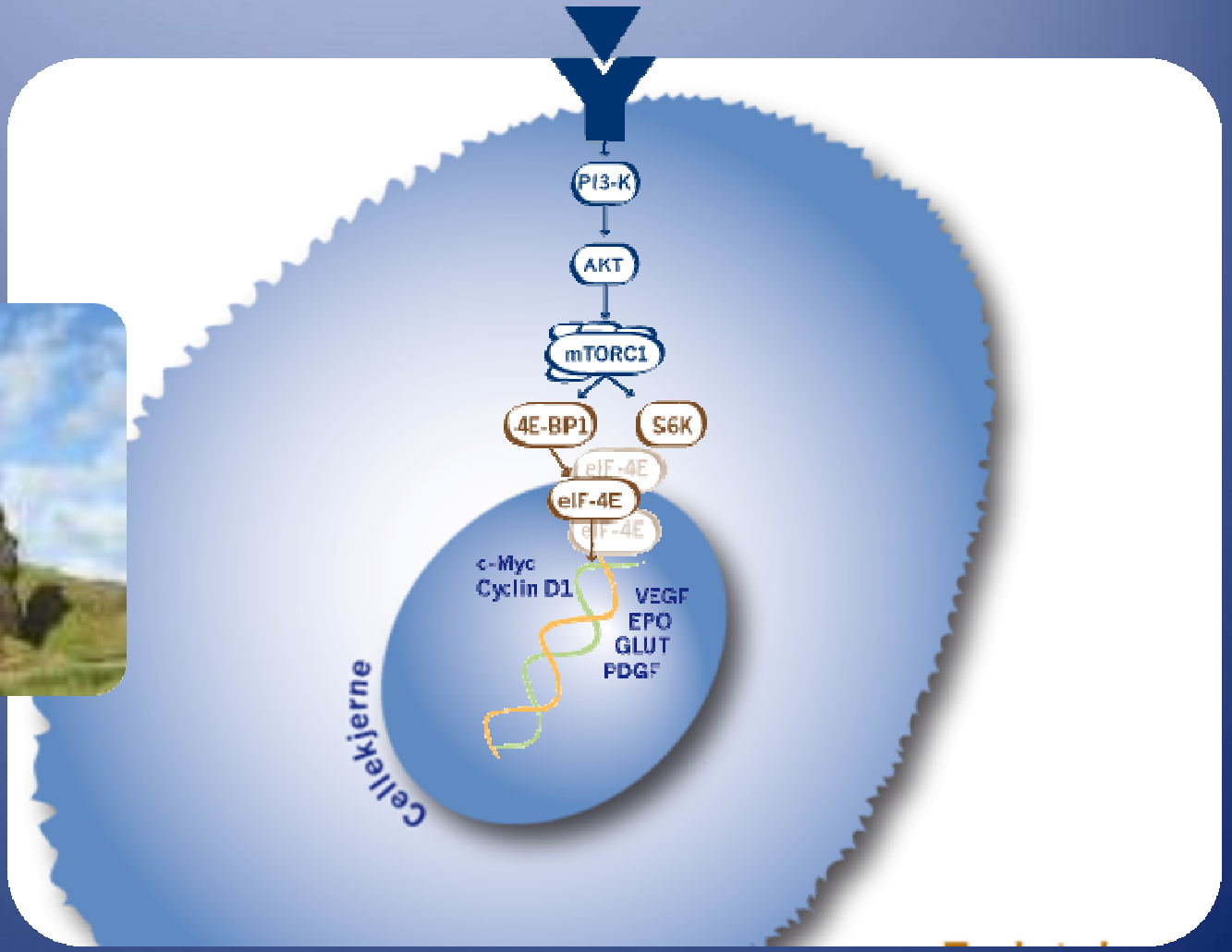
Final Overall Survival Results



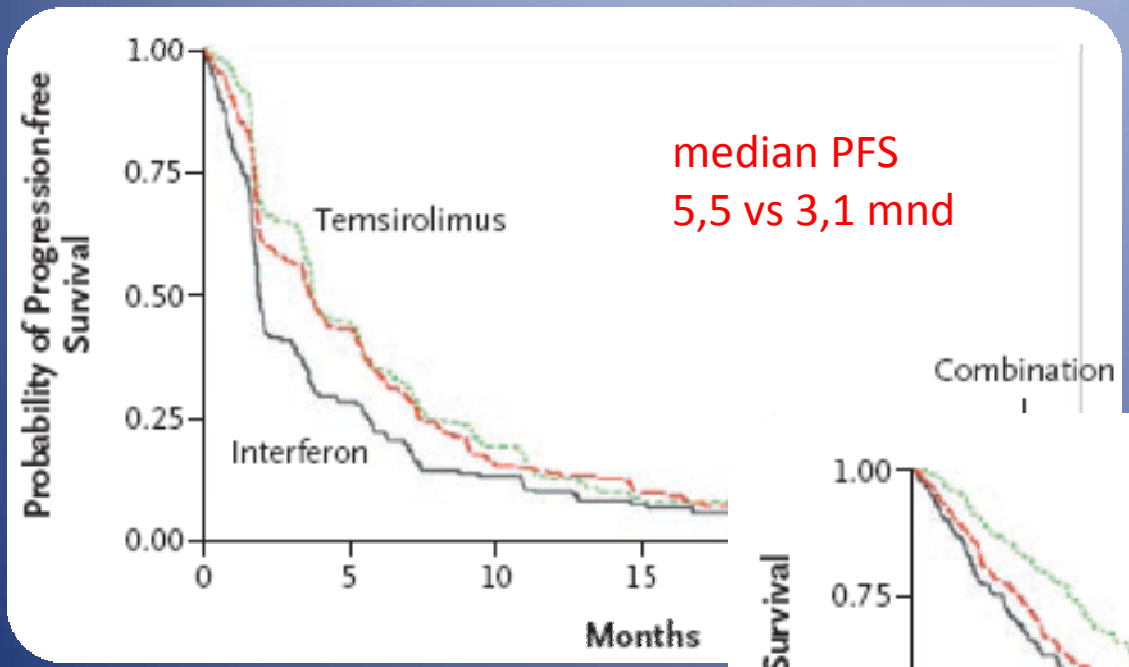
Patients at Risk					
Pazopanib	290	213	147	95	25
Placebo	145	93	71	53	9


Behandling av
nyrekreft

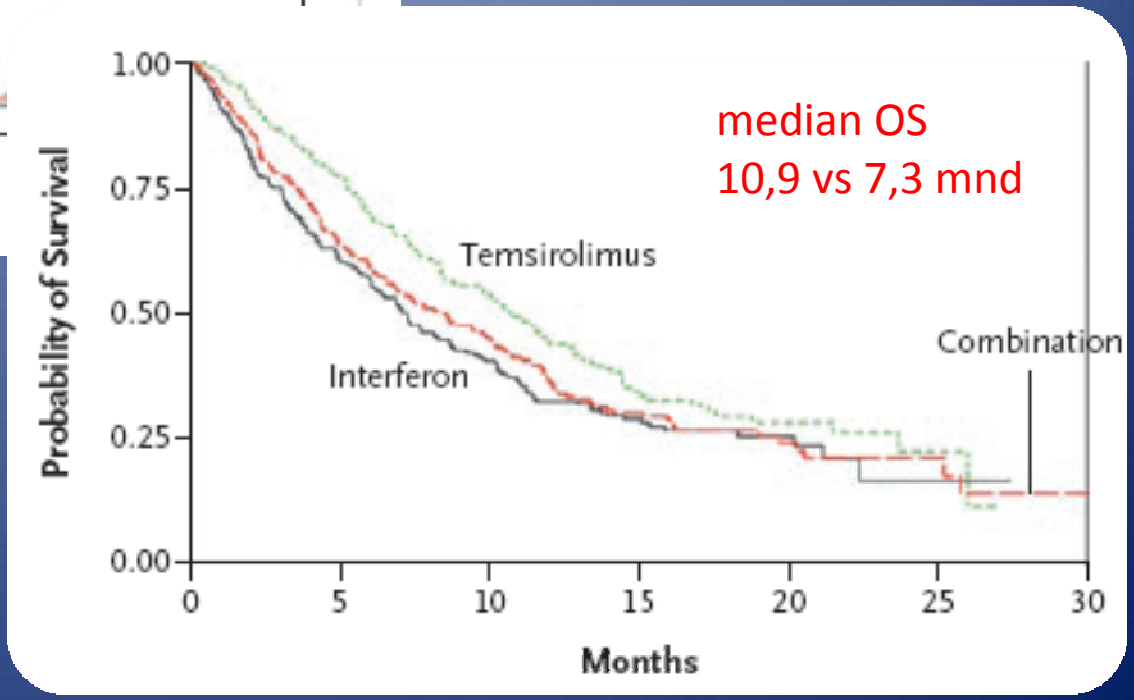
mTOR


PI3-K
AKT
mTORC1
4E-BP1
S6K
eIF-4E
eIF-4E
c-Myc
Cyclin D1
VEGF
EPO
GLUT
PDGF
Cellekjerne

Temsirolimus

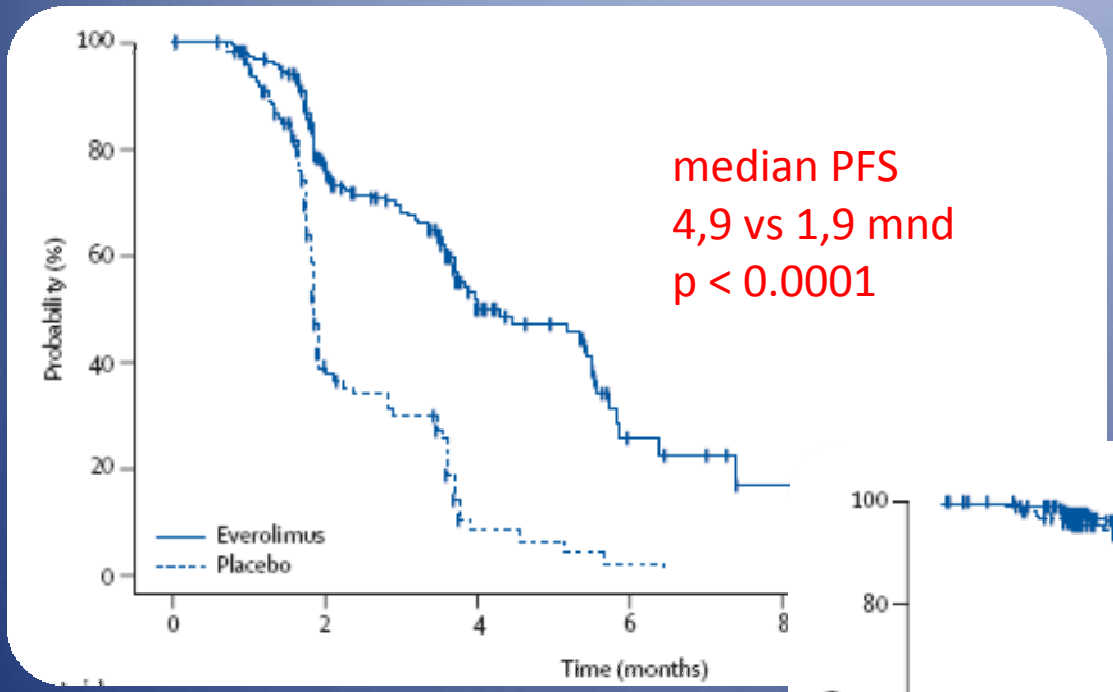


median PFS
5,5 vs 3,1 mnd

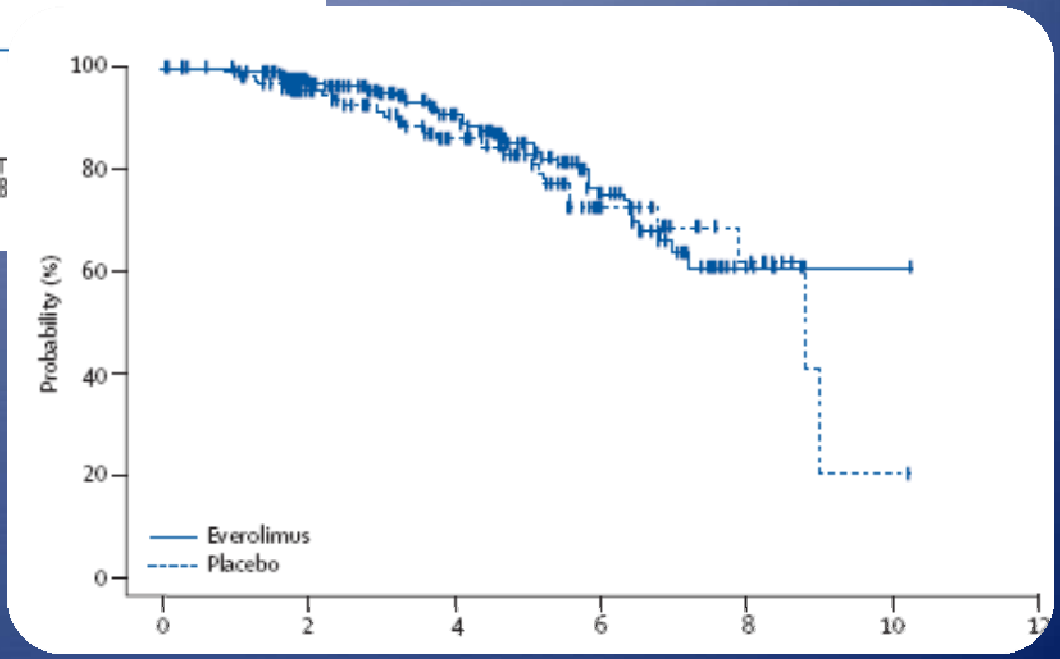


median OS
10,9 vs 7,3 mnd

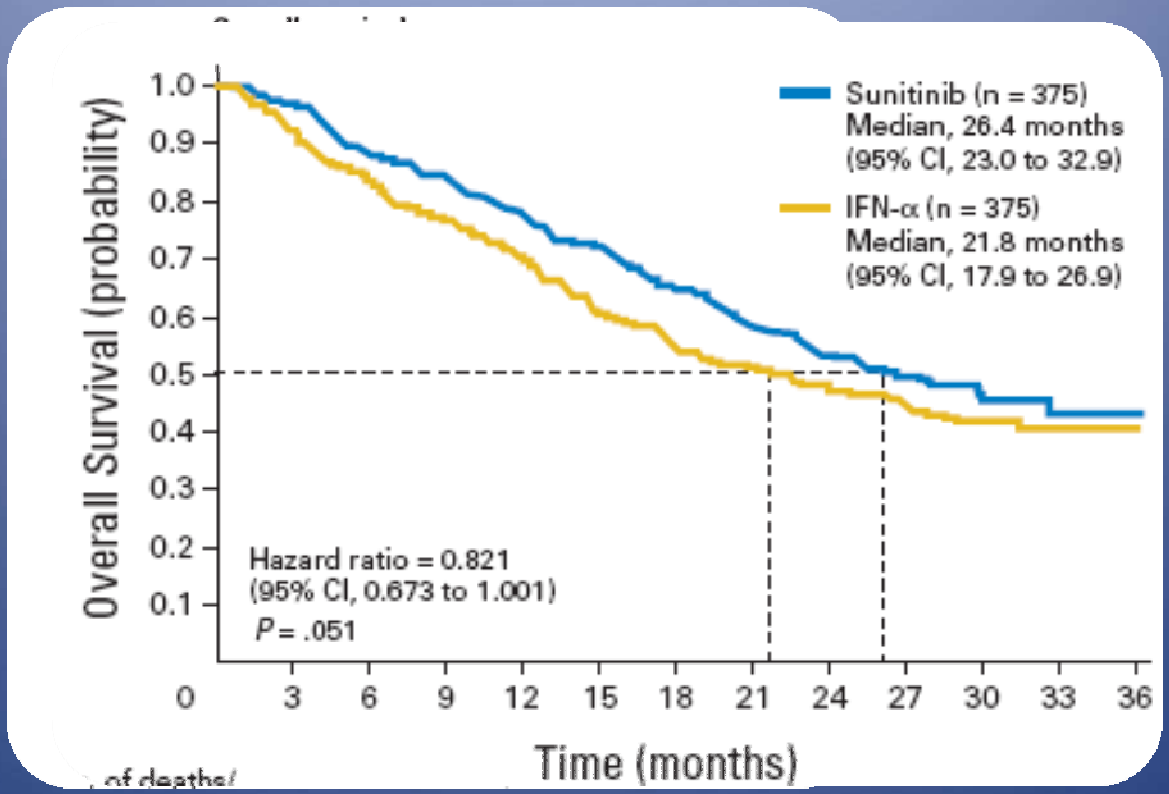
Everolimus



median PFS
4,9 vs 1,9 mnd
p < 0.0001



Revolution?


Overall Survival (probability)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3
6
9
12
15
18
21
24
27
30
33
36
Time (months)
Sunitinib (n = 375)
Median, 26.4 months
(95% CI, 23.0 to 32.9)
IFN-α (n = 375)
Median, 21.8 months
(95% CI, 17.9 to 26.9)
Hazard ratio = 0.821
(95% CI, 0.673 to 1.001)
P = .051

Future!

LETTER

doi:10.1038/nature09639

Exome sequencing identifies frequent mutation of the SWI/SNF complex gene *PBRM1* in renal carcinoma

Ignacio Varela[1], Patrick Tarpey[1], Keiran Raine[1], Dachuan Huang[2], Choon Kiat Ong[2], Philip Stephens[1], Helen Davies[1], David Jones[1], Meng-Lay Lin[1], Jon Teague[1], Graham Bignell[1], Adam Butler[1], Juok Cho[1], Gillian L. Dalgliesh[1], Danushka Galappaththige[1], Chris Greenman[1], Claire Hardy[1], Mingming Jia[1], Calli Latimer[1], King Wai Lau[1], John Marshall[1], Stuart McLaren[1], Andrew Menzies[1], Laura Mudie[1], Lucy Stebbings[1], David A. Largaespada[3], L. F. A.Wessels[4], Stephane Richard[5,6], Richard J. Kahnoski[7], John Anema[7], David A.Tuveson[8], Pedro A. Perez-Mancera[8], Ville Mustonen[9], Andrej Fischer[9,10], David J. Adams[11], Alistair Rust[11], Waraporn Chan-on[2], Chutima Subimerb[2], Karl Dykema[12], Kyle Furge[12], Peter J. Campbell[1], Bin Tean Teh[2,13,14], Michael R. Stratton[1,15] & P. Andrew Futreal[1]

Cure for metastatic disease?

	PR (%)	CR (%)
Sorafenib (TARGET)	10	<1
Sunitinib	31	0
Temsirolimus (Global ARCCS)	8.6	0
Bevacizumab + INF-α (AVOREN)	30	1
Everolimus (RECORD-1)	1	0
Pazopanib	30	<1
HD IL-2 (SELECT)	22	6

Complete remission with TKI

- 64 CR pts from France
- 36 TKI alone, 28 + local treatment
- Median time from treatment initiation to CR 12.6 and 18,5 months resp.

- 29/53 pts who stopped treatment after CR still in complete remission

Albiges et al., ASCO annual meeting 2010

Revisiting cytokines

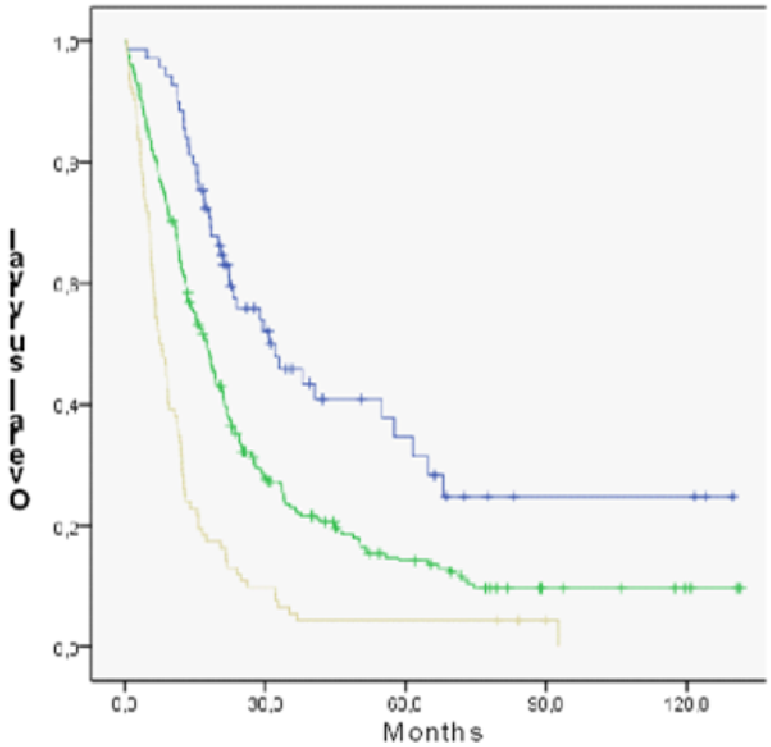
- LD IL-2 s.c. + INF s.c. (for max. 9 months)
- 422 consecutive pts
- 10 year median OS 10 % (25 % in MSKCC good risk)
- CR 4% PR 12%

- In combination with surgery in PR pts a total of 9 % with NED after 10 years

Donskov, Agerbeck et al. Abstract 4591, ASCO annual meeting 2010

Revisiting cytokines

Survival stratified by MSKCC



	N	Med	5-Y	10-Y
FAV	69	32.1 mo	35%	25%
INT	255	17.6 mo	14%	10%
POOR	92	7.4 mo	4%	0%

Single- or Oligomets

- Low CR rates with both cytokines and targeted therapy …
- Surgery may provide cure in some part of patients suitable

Oligomets – surgical resection

- 887 nephrectomy patients from the Mayo Clinic (1976-2006), 125 with subsequent complete metastasectomy
- Median OS with complete metastasectomy 3,6 years vs 1,3 years without
- Lung mets only > 10 years vs 1,6

Alt et al., ASCO GU 2010 #317

Single- or Oligomets

- … but response rates of 30-45 % and at least stable disease in another 30-45 %

- What is the best combination of surgery and systemic therapy in this setting and what the best timing?

Patient selection for metastasectomy

- Good performance status
- Metachronous > synchronous
- All disease surgically removable
- No prohibitive medical comorbidities
- (heavily symptomatic)

Singel- and Oligomet - Options

- Stereotactic radiotherapy
  - 3-5 fractions of 8 -15 Gy
  - Local control rates (PR + CR): >90%
  - CR 30% (may take up to 3 years until CR)
  - No significant side effects

Wersäll et al., Radiother Oncol; 2005

Cure for metastatic disease?

- Probable not with systemic therapy alone
- … but new treatment options provide the chance of secondary metastasectomy
- Re-consult your multidisciplinary tumorboard when achieving partial responses
- (new agents may provide even higher response rates)

Cure for metastatic disease?

- … and if you don´t try, you can´t cure anyone!!!