Targeted therapy and surgery in RCC

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BAUS oncology, London 2014

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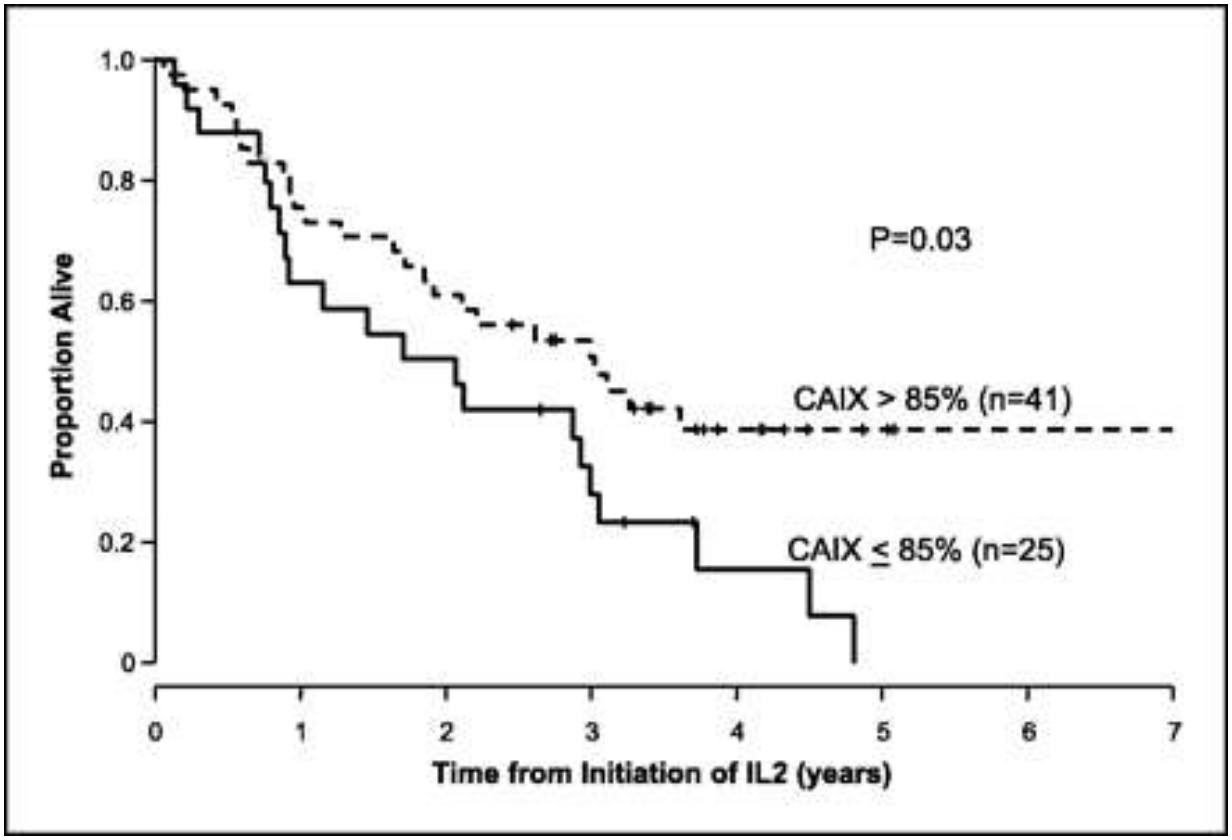
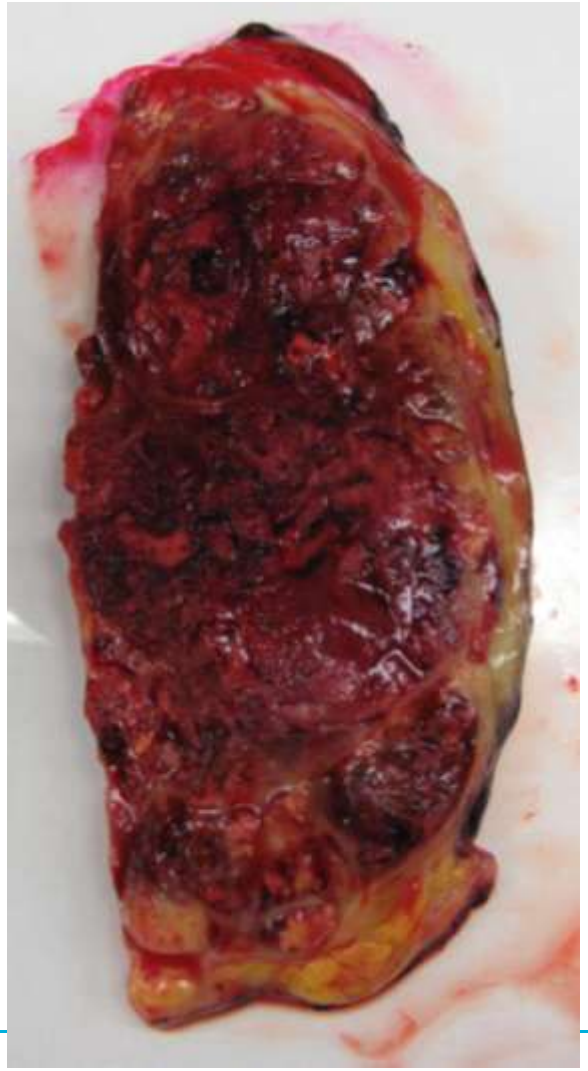
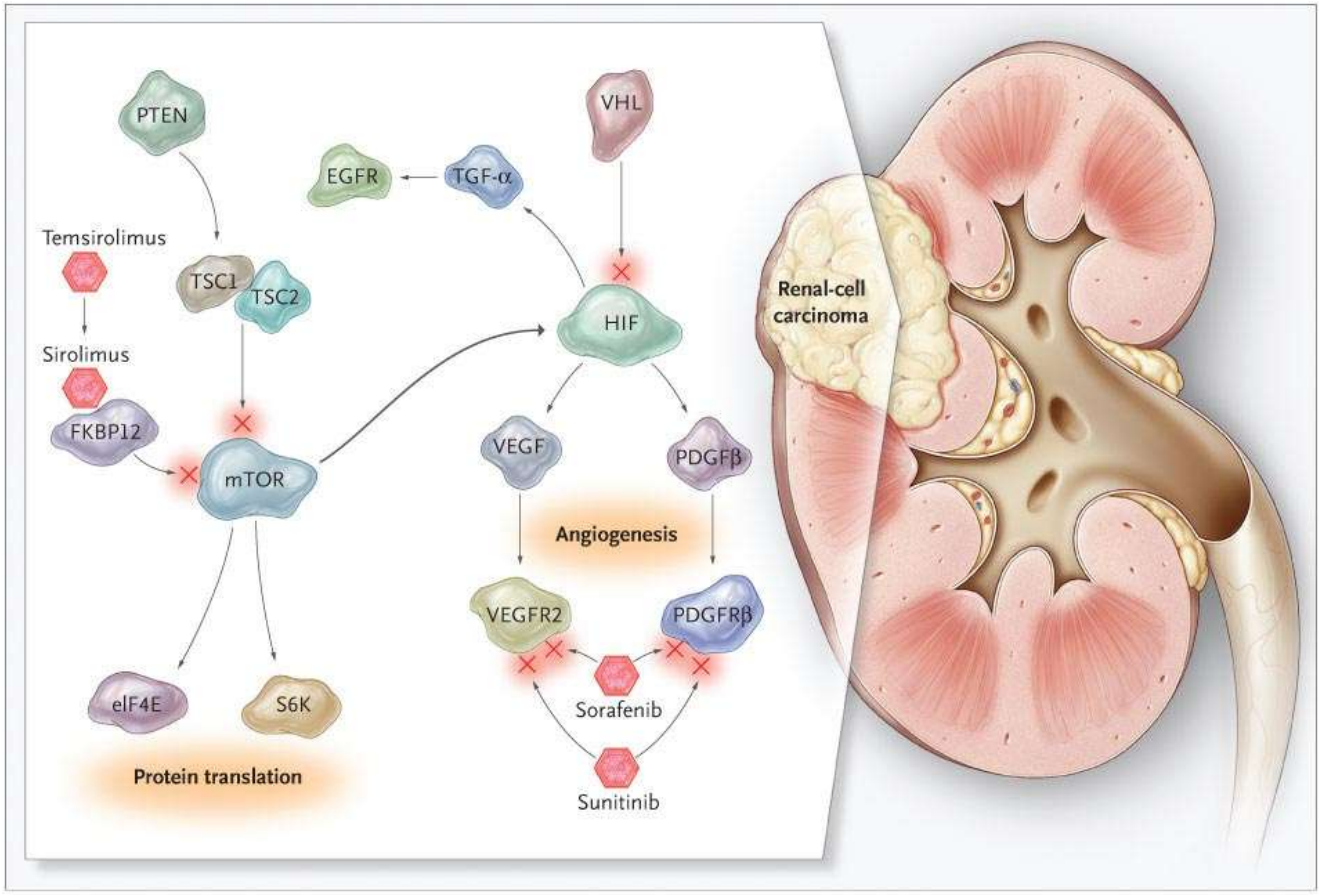
Survival of >5 years was only seen in patients with high CAIX expressing tumors.



Angiogenesis



Targeted therapy



Brugarolas et al. NEJM 2007;256: 185

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2007 VOL. 356 NO. 2

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

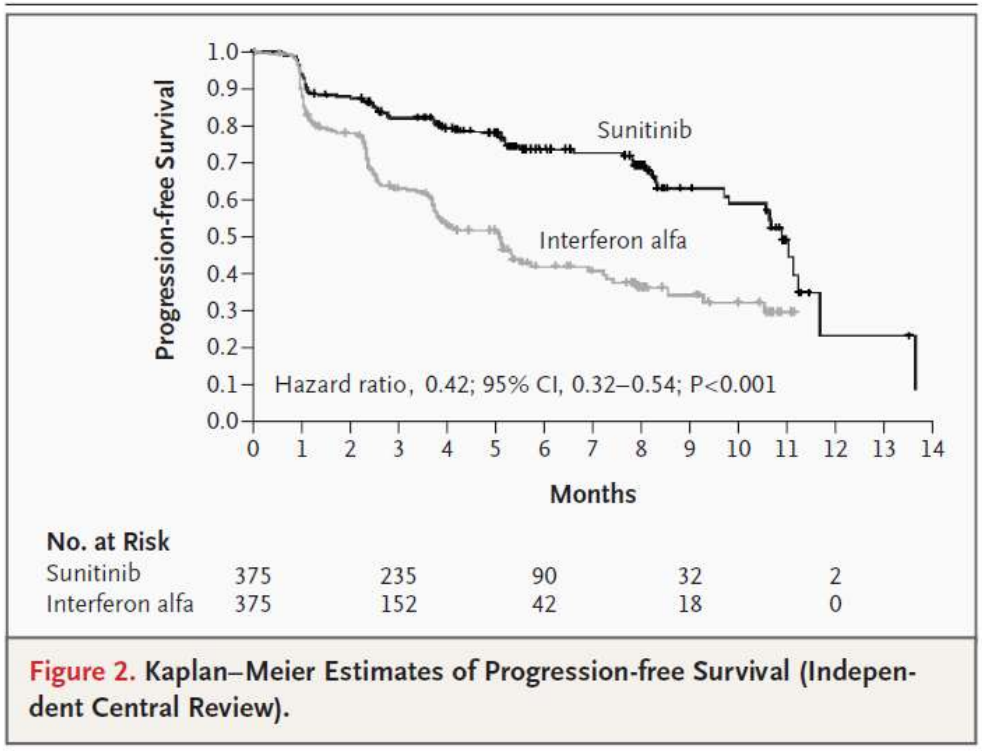


Figure 2. Kaplan–Meier Estimates of Progression-free Survival (Independent Central Review).

ORIGINAL ARTICLE

Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma

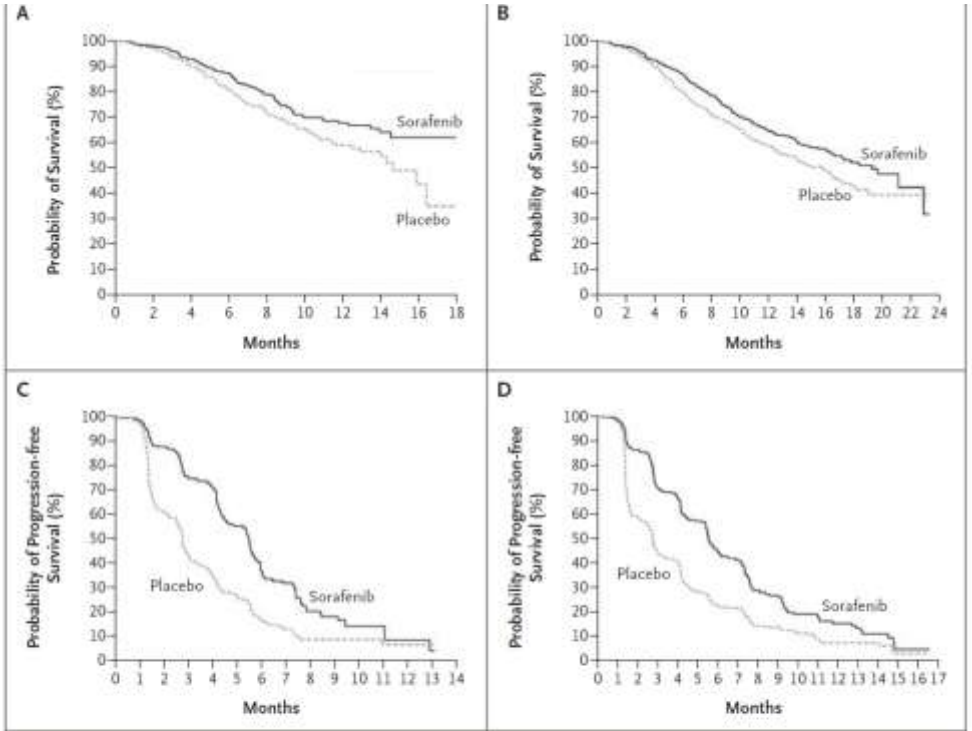


Figure 2. Kaplan–Meier Analysis of Overall Survival and Progression-free Survival.

Panel A shows the probability of overall survival among 903 patients — 451 receiving sorafenib and 452 receiving placebo — in May 2005, when patients receiving placebo were allowed to switch to sorafenib ($P=0.02$ for the comparison between the two study groups; O'Brien–Fleming threshold for statistical significance, $P=0.0005$). Panel B shows the probability of overall survival among the same patients in November 2005 ($P=0.02$; O'Brien–Fleming threshold for statistical significance, $P=0.0094$). Panel C shows the probability of progression-free survival among 769 patients — 384 patients receiving sorafenib and 385 patients receiving placebo — who were assessed in an independent review in January 2005 ($P<0.001$). Panel D shows the probability of progression-free survival among all 903 patients, according to a review by investigators in May 2005 ($P<0.001$).

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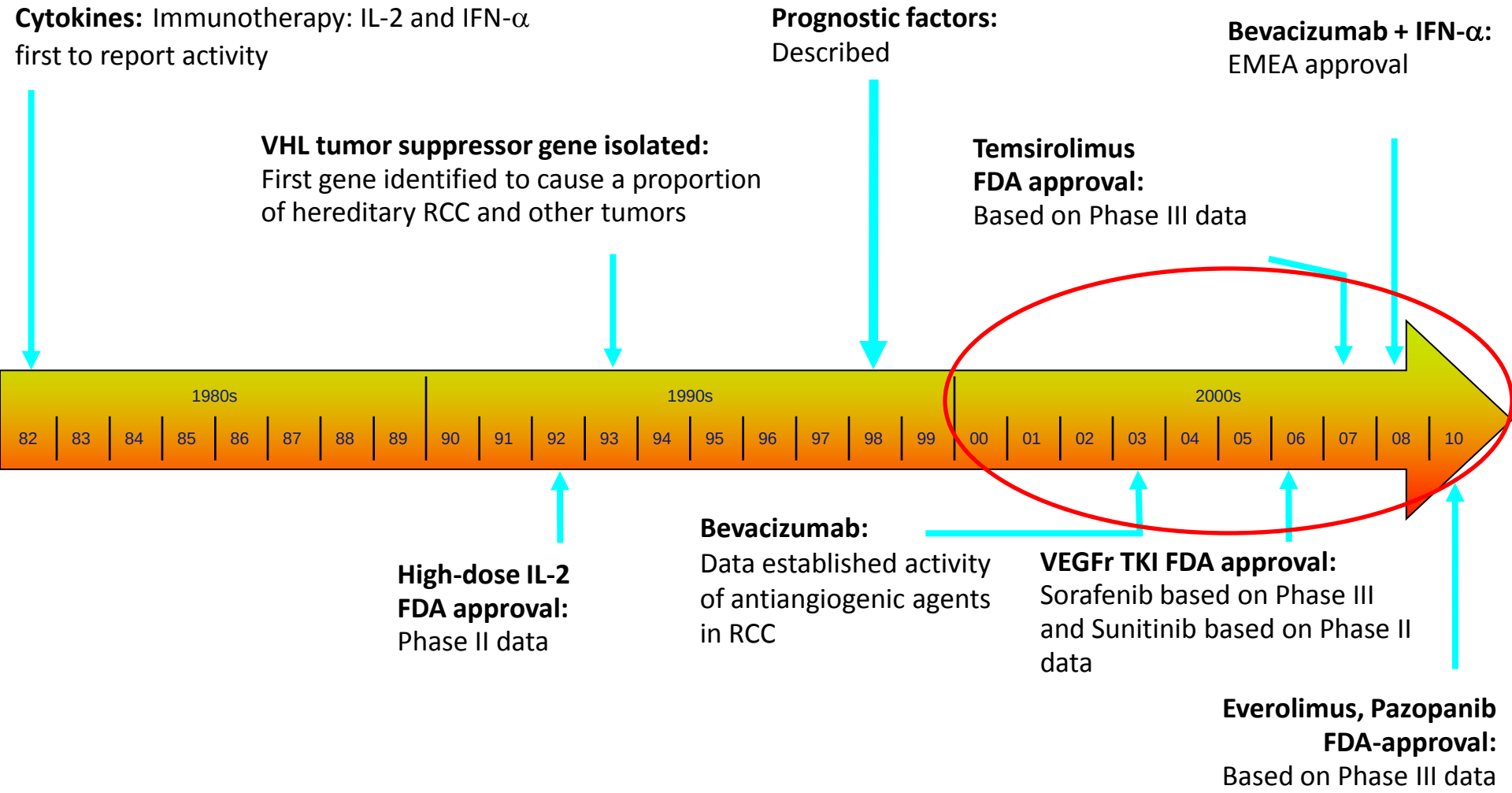
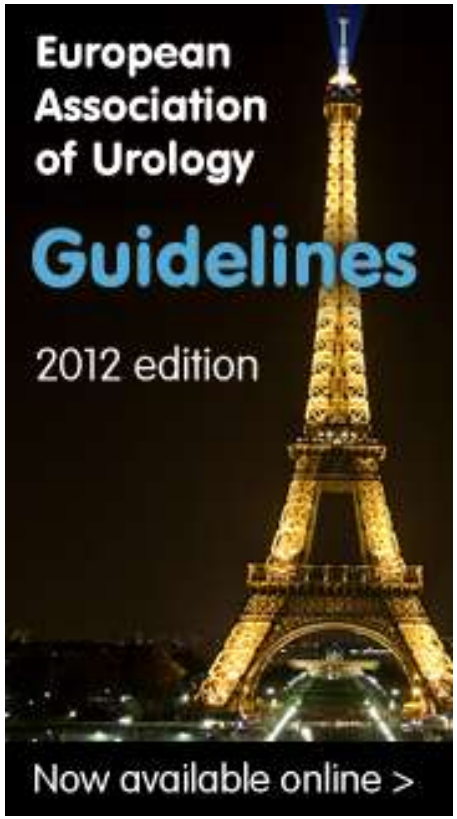
Immunotherapy was the standard of care for patients with RCC for decades



Guidelines on Renal Cell Carcinoma

B. Ljungberg, N. Cowan, D.C. Hanbury, M. Hora, M.A. Kuczyk, A.S. Merseburger, P.F.A. Mulders, J-J. Patard, I.C. Sinescu



Side-effect profile

	Incidence of AEs* (%)			
	Sorafenib (n=451)		Placebo (n=451) †	
	Any grade	Grades 3 –4	Any grade	Grades 3 –4
Diarrhoea	43	2	13	1
Rash/desquamation	40	1	16	<1
Fatigue	37	5	28	4
HFSR	30	6	7	–
Hypertension	17	4	2	<1
Dyspnoea	14	4	12	2
Decreased haemoglobin	8	3	7	4
Bone pain	8	1	8	3
Tumour pain	6	3	5	2

Treatment discontinuation rates were similar: 10% sorafenib, 8% placebo

*National Cancer Institute-Common Toxicity Criteria (NCI-CTC, version 3) treatment-emergent AEs occurring in ≥2% of patients; †One patient was not evaluable for safety

AEs = adverse events; HFSR = hand–foot skin reaction

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Escudier B, et al. N Engl J Med 2007;356:125–34

Management of sorafenib AEs

- Common adverse reactions associated with sorafenib are
  - HFSR/rash
  - gastrointestinal side effects
  - hypertension
  - fatigue
- The majority of AEs are manageable and reversible

Hand–foot skin reaction

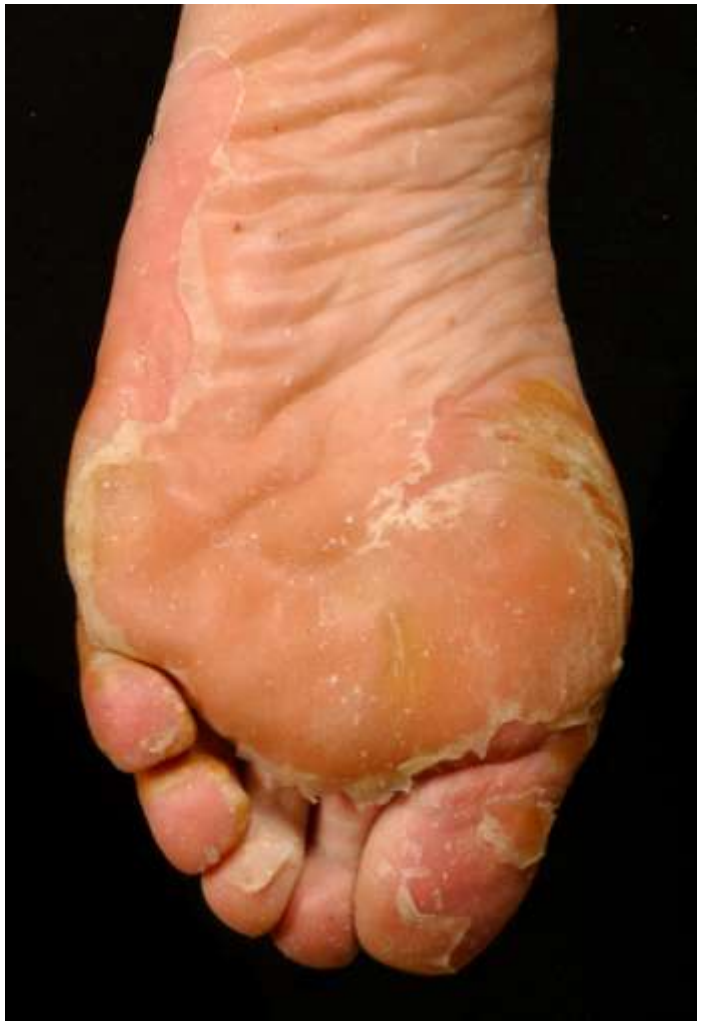
- HFSR occurs in 30% of patients (grade 3–4 = 7%)
- Initial recommended management strategies are
  - manicure and pedicure before and during treatment
  - shock absorbing soles etc. for pressure points, sandals
  - application of alcohol-free moisturiser immediately after bathing
- Recommended pharmacological interventions include
  - treatment delay and adjustments if grade 3 toxicity occurs
- Corticosteroids have no proven efficacy

Bhojani N, et al. Eur Urol 2007.

Grade 2 Hand–Foot Syndrome

- Thick stratum corneum
- Erythema
- Pseudo blisters without fluid
- Minimal pain
- No loss of function
- Impairment in certain activities

Example of Grade 3 Hand–Foot Syndrome with TKI Treatment



- Erythema and desquamation over entire surface of sole
- Pain
- Complete loss of function

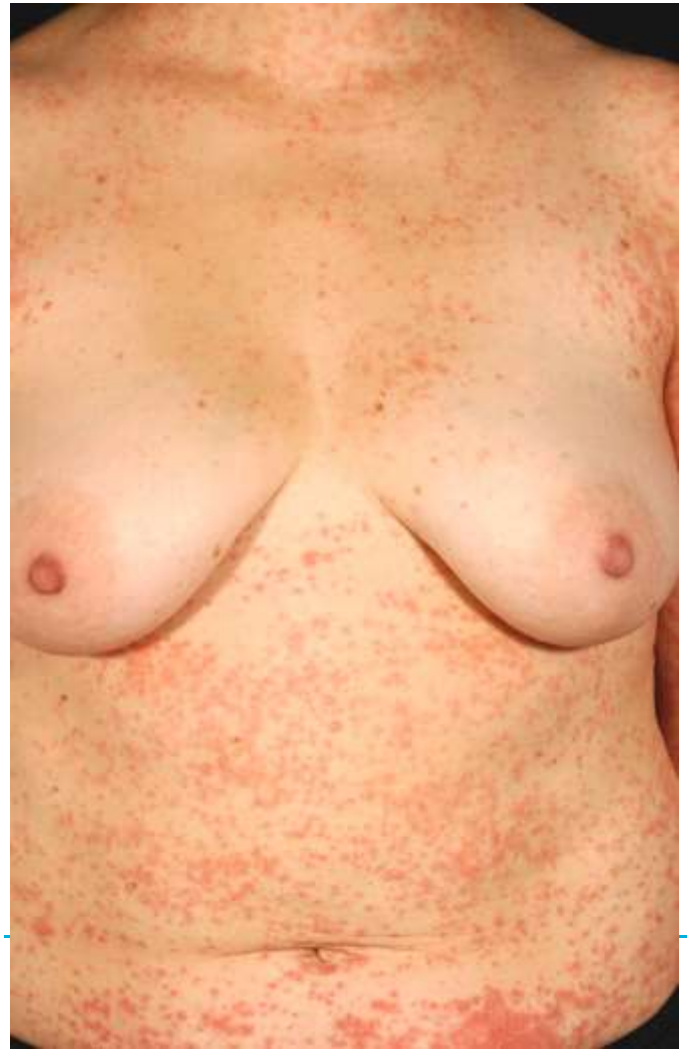
Rash/desquamation

- Rash occurs in 40% of patients (grade 3–4 <1%)
- Initial recommended management strategies are
  - grade 1: moisturising cream twice daily
  - colloidal oatmeal lotions and soap
  - antidandruff shampoo
  - loose clothing
  - avoidance of direct sunlight, detergents, antibacterial soaps, alcohol-based perfume
  - use sun protection of factor ≥30
- Recommended pharmacological interventions include
  - grade 1–2: hydrocortisone 1% cream
  - grade 3: prednisone 25mg p.o. daily for 2 days, then 10mg p.o. q.d. for 7–14 days
  - grade 4: referral to dermatologist

p.o. = orally

Bhojani N, et al. Eur Urol 2007.

Grade 2 Rash



- Prominent on trunk
- Small erythema
- Tendency for confluence

Diarrhoea

- Diarrhoea occurs in 43% of patients (grade 3–4 = 2%)
- Initial recommended management strategies are
  - avoidance of foods that would aggravate the diarrhoea (spicy, fatty foods, caffeine)
  - avoidance of stool softeners and fibre supplements
  - aggressive oral rehydration with fluids containing water, salt and sugar
- Recommended pharmacological interventions include
  - loperamide and diphenoxylate
    - standard dose (loperamide): initial 4mg doses followed by 2mg every 4 hours or after every loose stool
    - more aggressive: 4mg initially, then 2mg every 2 hours
  - cholestyramine: 4g p.o. 30 min prior to treatment and every 6 hours as needed

Bhojani N, et al. Eur Urol 2007.

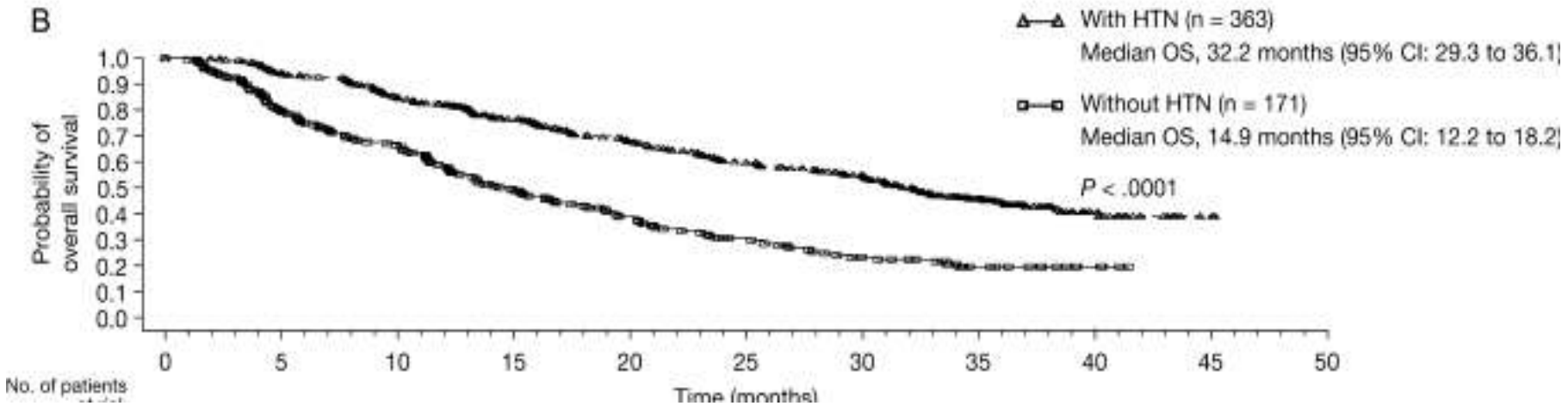
Hypertension

- Hypertension occurs in 17% of patients (grade 3–4 = 4%)
- Initial recommended management strategies are
  - blood pressure monitoring weekly during the first 6 weeks of therapy
  - weekly blood pressure in a home setting for patients with pre-existing hypertension
- Recommended pharmacological interventions include
  - standard antihypertensive therapy
  - angiotensin II receptor blockers, β-blockers, and diuretics
    - optimal drug choices: telmisartan (20–80mg q.d.); valsartan (80–320mg q.d.); atenolol (50–100mg q.d.); HCTZ (12.5–100mg q.d.)
- Non-dihydropyridine calcium channel blockers (verapamil, diltiazem) are contraindicated

HCTZ = hydrochlorothiazide

Bhojani N, et al. Eur Urol 2007. Epub ahead of print

Hypertensie is een biomarker bij VEGFR-I



Rini J Nat Cancer Inst 2011;103:763

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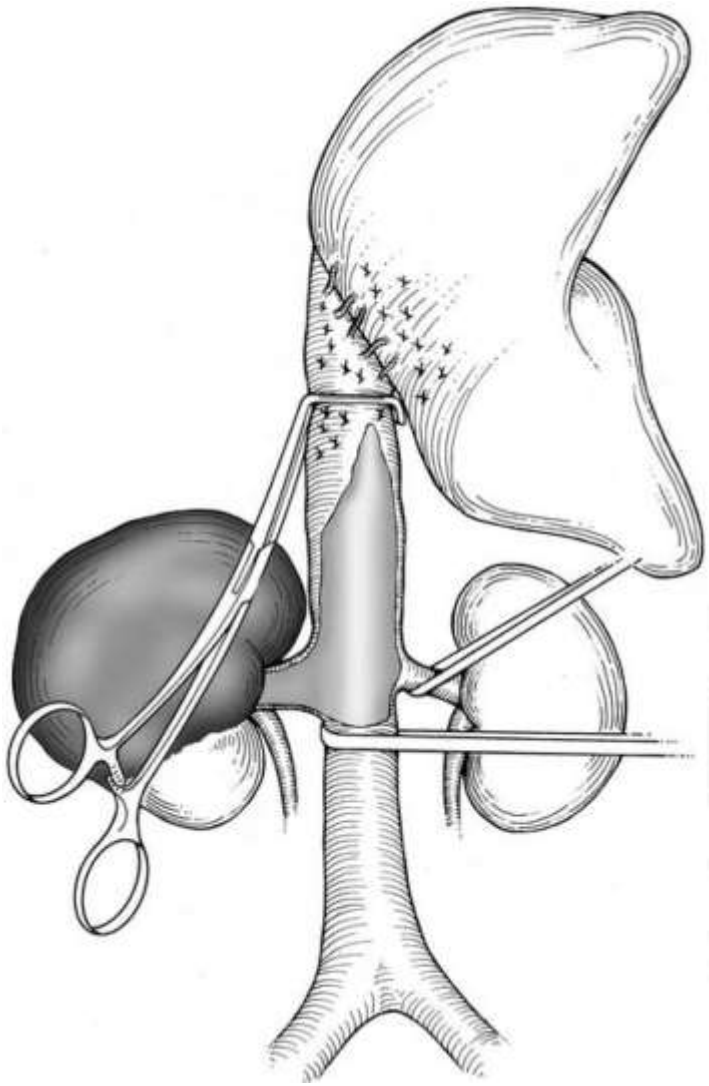
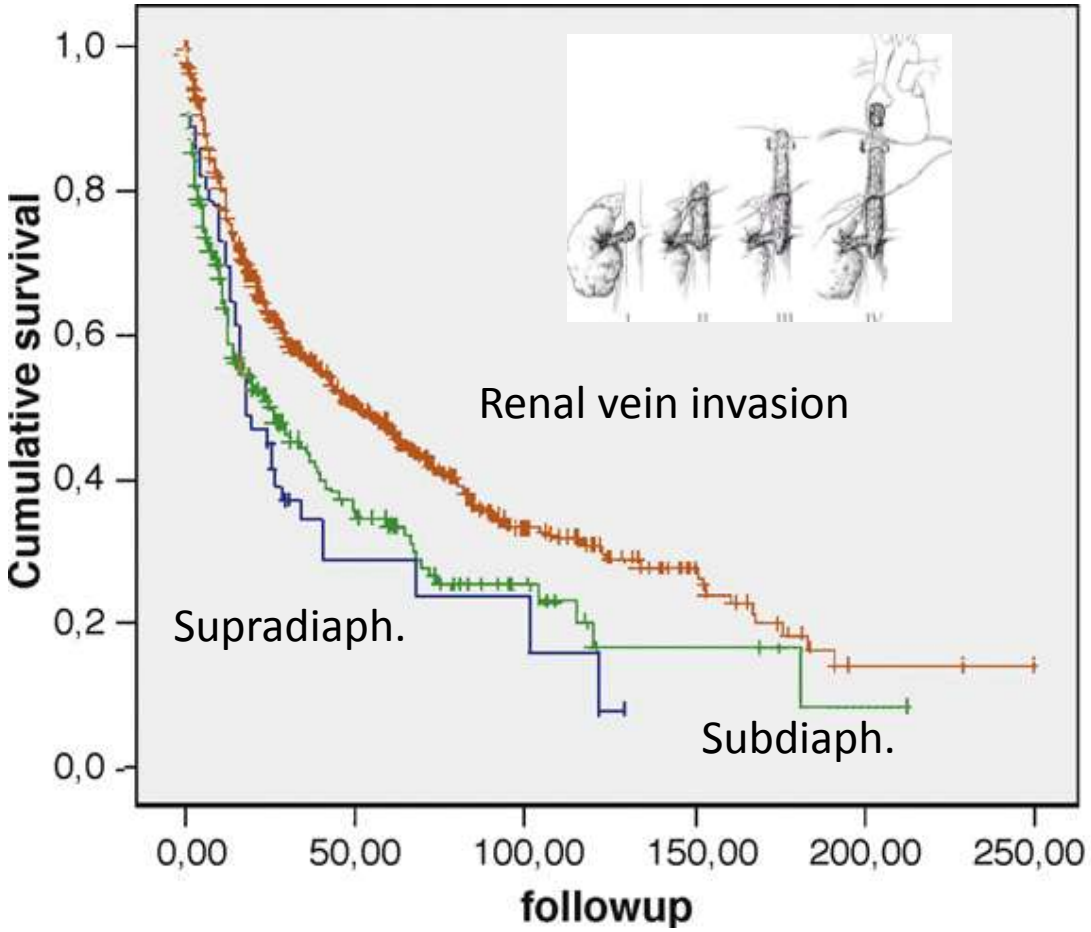
Sequencing Surgery and Drugs

-RCC

-mRCC





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Wagner et al., Eur Urol 55:452, 2009

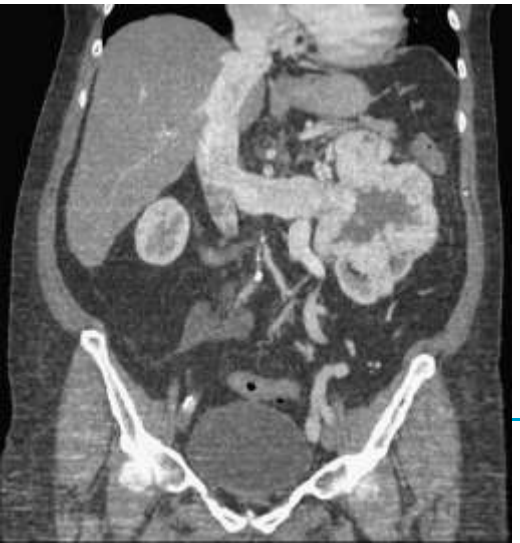
Sunitinib and caval involvement

- Several cases reported[1,2,3], but progression was observed[4]

[1]Harshman et al., Nat Rev Urol, 2009: M1
[2]Robert et al., Eur Urol 55:1477, 2009
[3]Karakiewicz et al., Eur Urol 53:845, 2008
[4]Bex et al., Acta Oncol 2010

No increase in side-effects (trombo-embolic events)

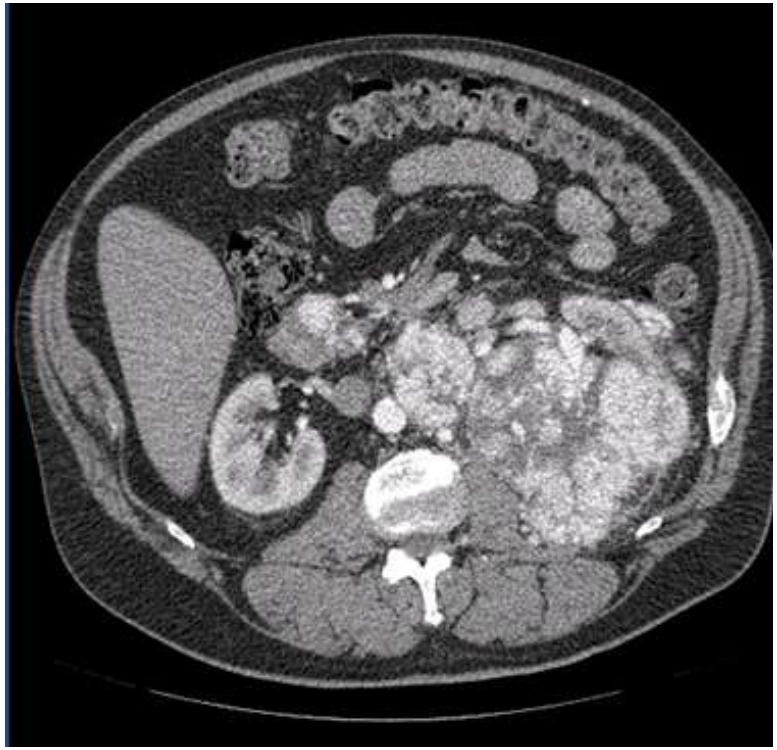
No consistent decrease in size of tumor/trombus

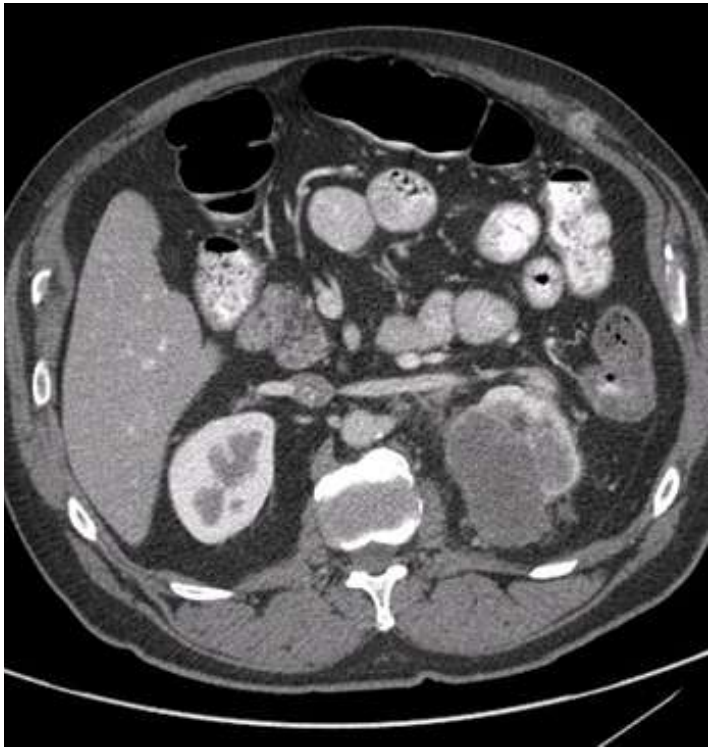


[1]Zangari et al., JCO 27:4865, 2009
[2]Ranpura et al., ASCO-GU2010 #331
[3]Schutz et al., ASCO-GU2010 #348

Neoadjuvant therapy

Preoperative Sunitinib





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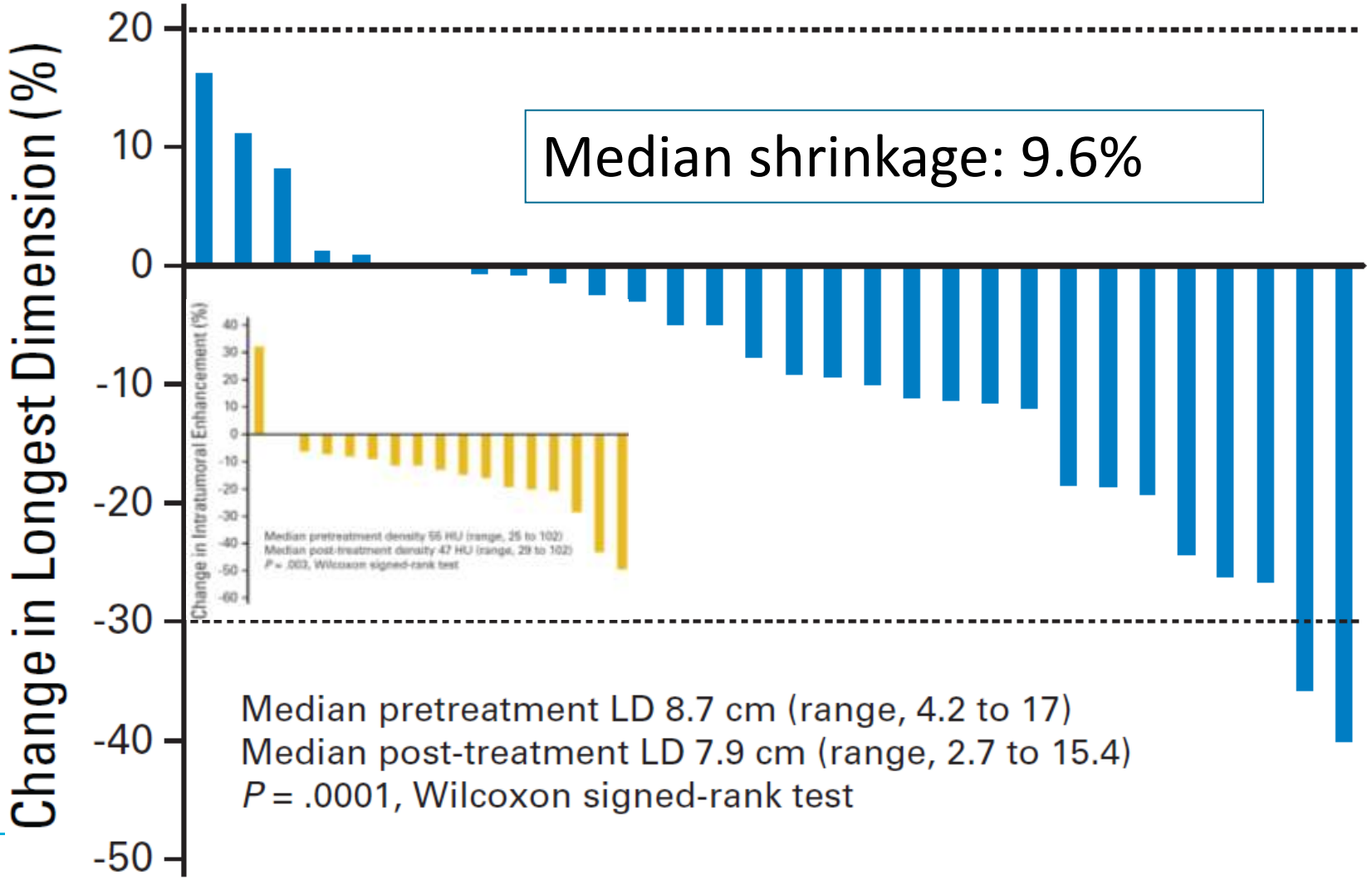
Wood et al., EAU 2010

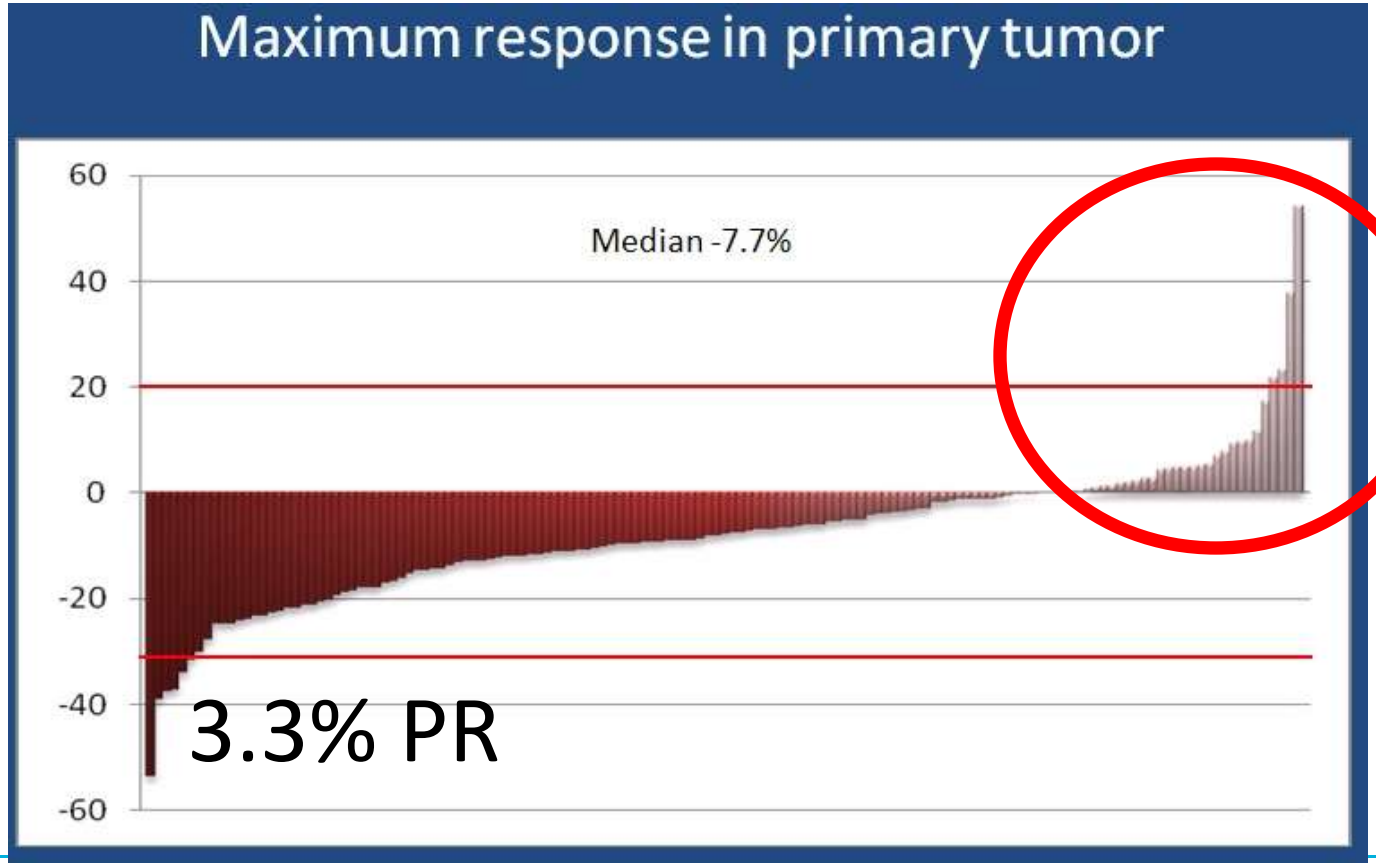
Neoadjuvant sorafenib



Cowey et al., JCO 28:1502, 2010

Neoadjuvant

- ~8% tumor reduction



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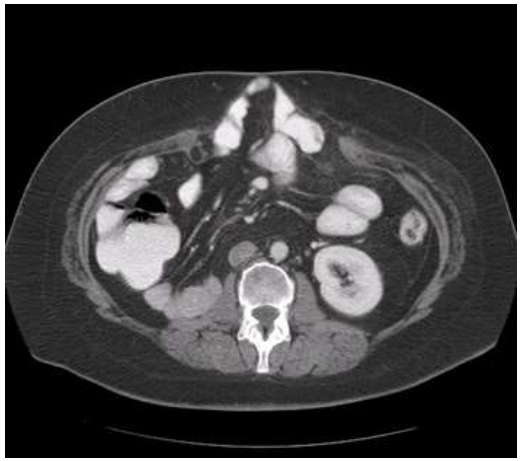
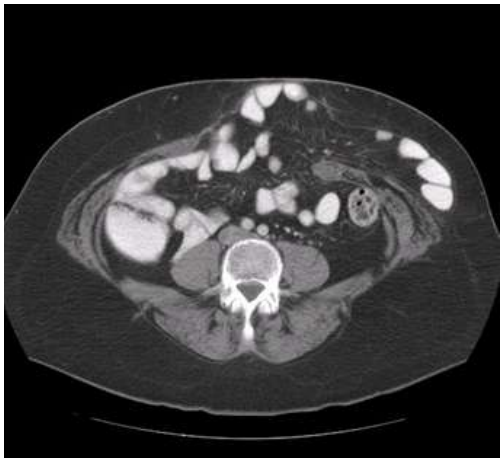
Abel & Wood, ASCO-GU2010 #318

Neoadjuvant toxicity

- **Wound healing** problems[1]





- Increased chance of **bleeding**[2]
  - Sunitinib RR 3.98
  - Bevacizumab RR 3.65
  - Sorafenib RR 1.78

[1]Abel & Wood, ASCO-GU2010 #318

[2]Nasir et al. ASCO-GU2010

Cytoreductive Nephrectomy

The Impact of Cytoreductive Nephrectomy on Survival of Patients With Metastatic Renal Cell Carcinoma Receiving Vascular Endothelial Growth Factor Targeted Therapy

Toni K. Choueiri,* Wanling Xie, Christian Kollmannsberger, Scott North, Jennifer J. Knox, J. Geoffrey Lampard, David F. McDermott, Brian I. Rini and Daniel Y. C. Heng

From the Kidney Cancer Center, Dana Farber Cancer Institute (TKC, WX) and Beth Israel Deaconess Medical Center (DFM), Boston, Massachusetts, British Columbia Cancer Agency, Vancouver, British Columbia (CK), Cross Cancer Institute, Edmonton (SN), Tom Baker Cancer Center (DYCH), University of Calgary, Calgary (JGL), Alberta, and Princess Margaret Hospital, Toronto, Ontario (JJK), Canada, and Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio (BIR)

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Printed in U.S.A.
DOI:10.1016/j.juro.2010.09.012

Cytoreductive Nephrectomy

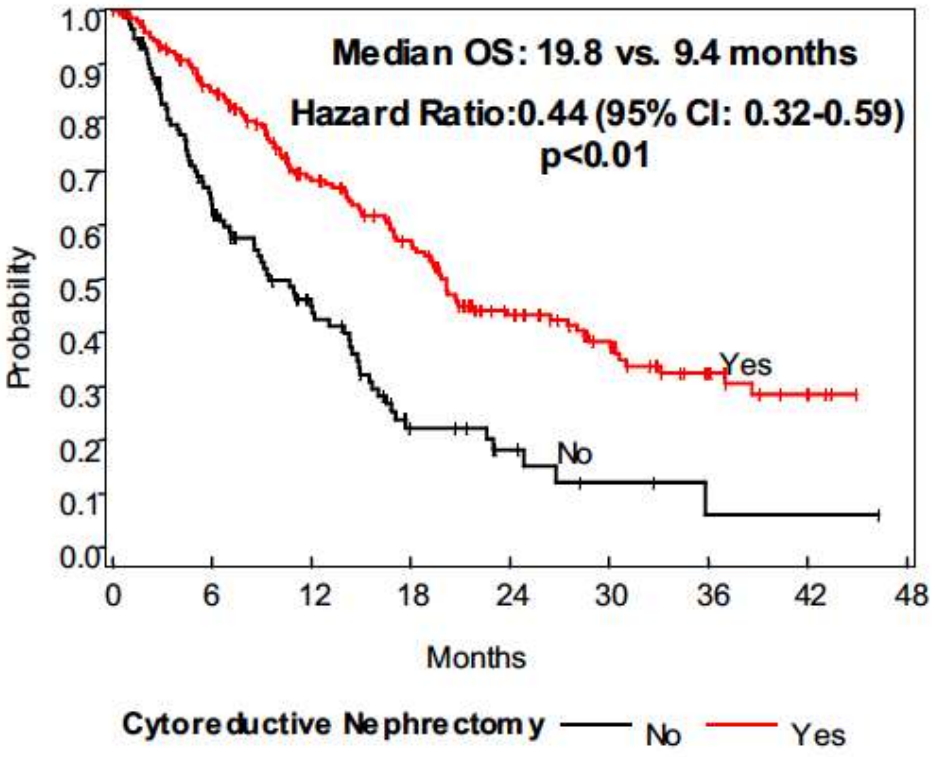


Figure 1. Kaplan-Meier curve depicting overall survival from initiation of VEGF targeted therapy for 314 patients who did or did not receive cytoreductive nephrectomy.

Cytoreductive Nephrectomy

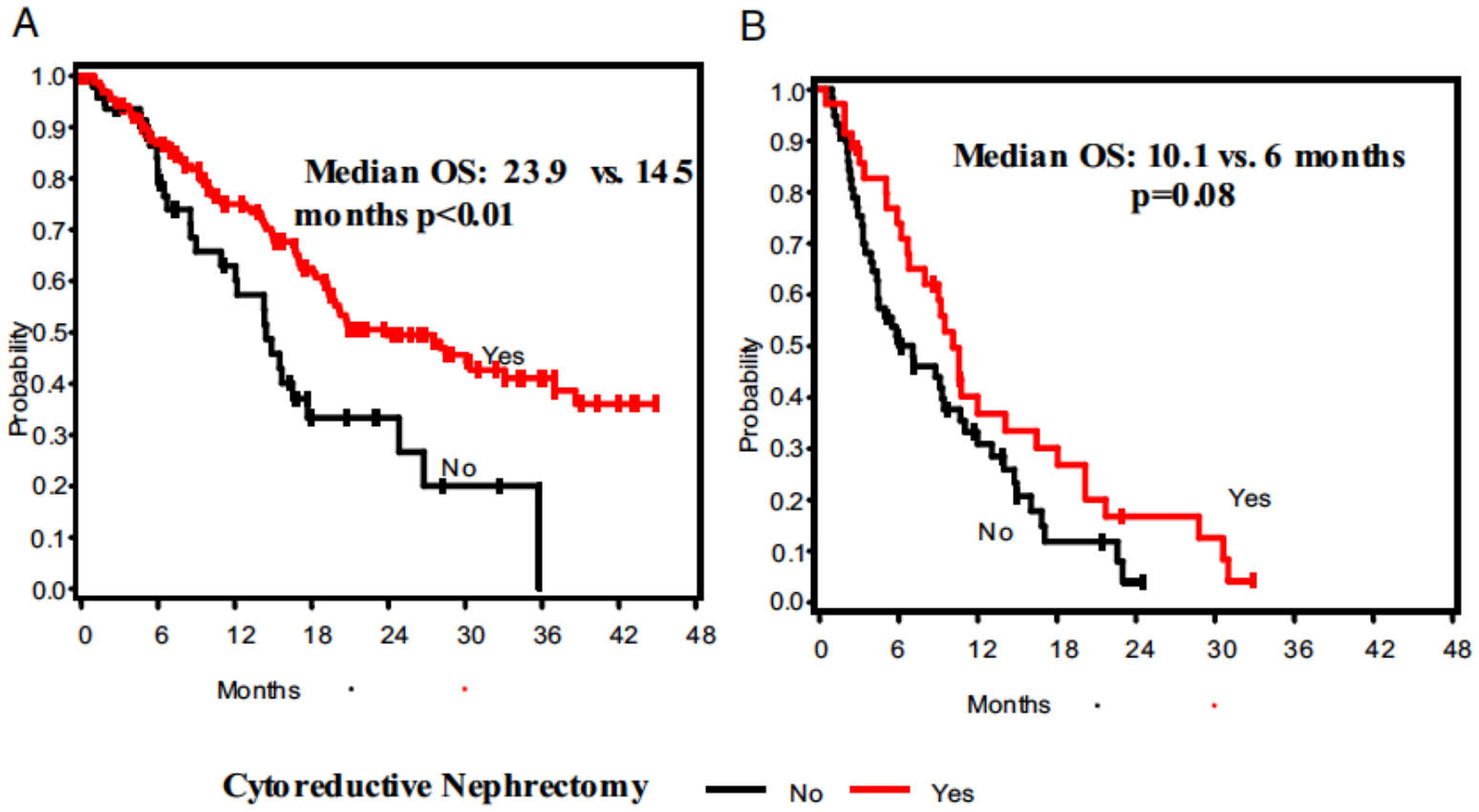


Figure 2. Kaplan-Meier curve of overall survival from initiation of VEGF targeted therapy by cytoreductive nephrectomy, and KPS 80 or greater (*A*) or KPS less than 80 (*B*).

Cytoreductive nephrectomy - morbidity

- Higher morbidity for Nx in M+:

	M-	M+
%male	62%	68%
emergencies	19%	28%
admission	6.7d	9.5d
complications	23%	30%
mortality	1.2%	3%

P<0.001

Lughezzani et al., AUA 2010 #1659

Conclusions

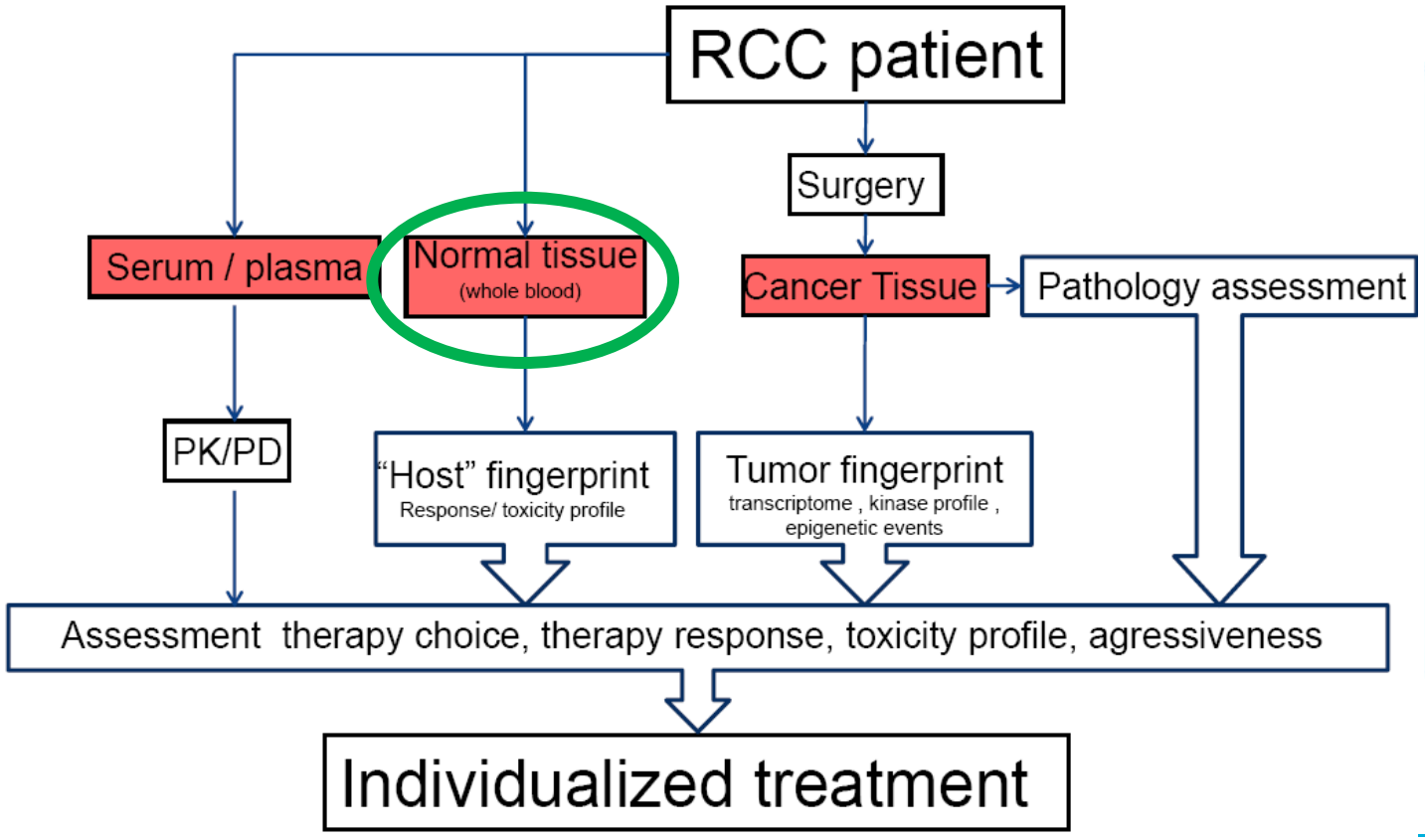
- Surgery most important in locally advanced RCC
- Need for adjuvant therapies
- Neo-adjuvant therapy anecdotal
- In mRCC surgery has a place in sequencing with drugs

- Multidisciplinary decision making is key in optimizing results in patients with RCC

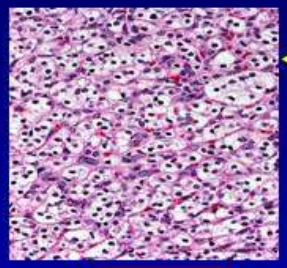
But still need for improvement

Mechanisms of resistance

A **EURO**pean collaborative project on **TA**rgeted therapy in **R**enal cell cancer:
GEnetic and **T**umour-related biomarkers for response and toxicity

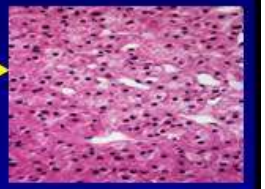


RCC : Histologic and Molecular Characteristics



Proximal Nephron

Distal Nephron

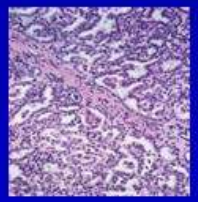


Oncocytoma (5%)

Clear Cell Carcinoma (75%)

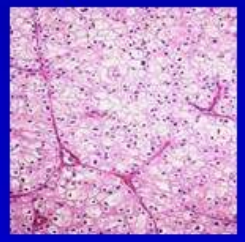
- LOH - 3p25
- VHL mutation (50-80%)
- Hypermethylation (5-20%)
- Anti-VEGF and VEGFr therapy

Papillary Carcinoma (15%)



Type 1 c-met mutation

Type 2 FH mutation



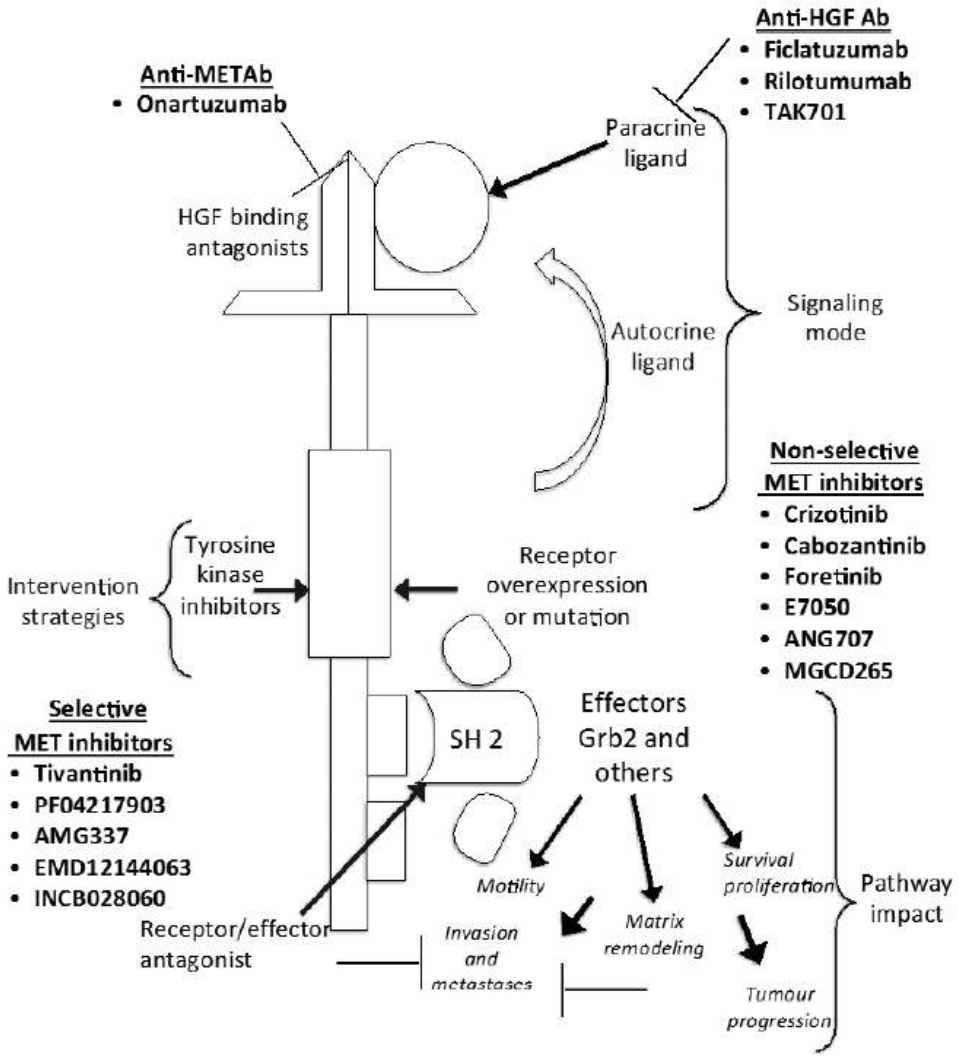
Chromophobe (5%)

Collecting Duct, Undifferen-tiated (rare)

EORTC studie: CREATE studie

- Crizotinib is a compatative TKI of the ALK and MET/HGF receptor

- In papillary RCC type I



Immunotherapy?

Available at www.sciencedirect.com

ScienceDirect

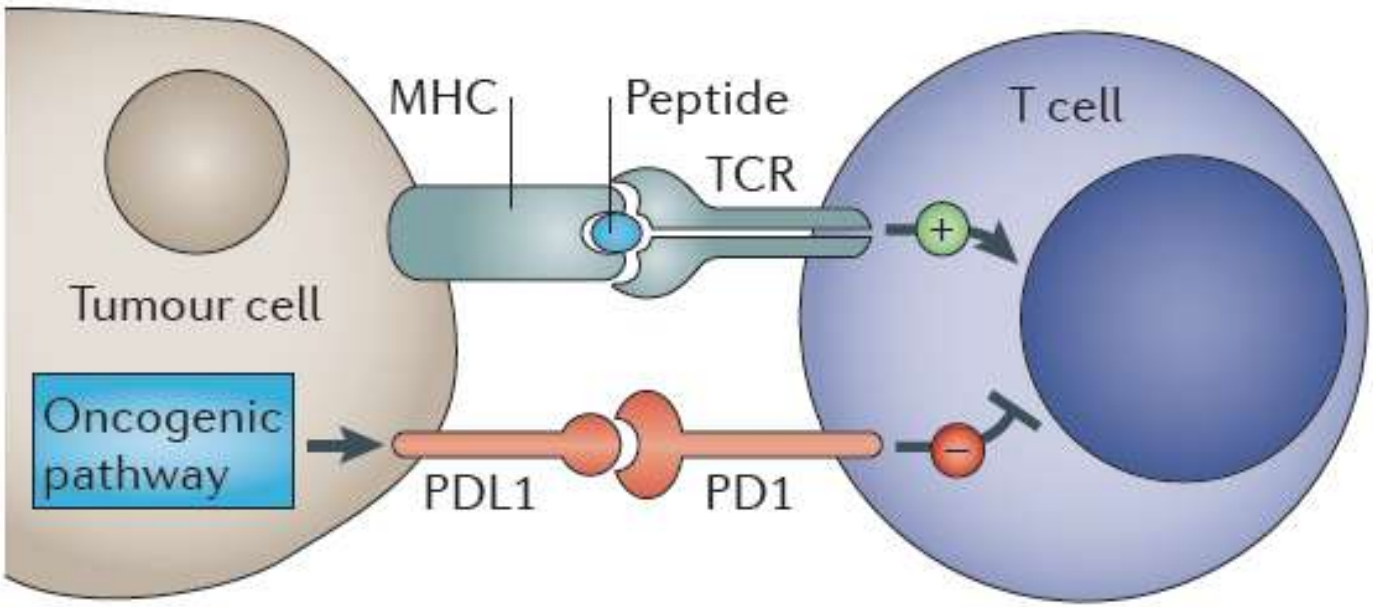
journal homepage: www.ejcancer.com

Drug of the year: Programmed Death-1 receptor/Programmed Death-1 Ligand-1 receptor monoclonal antibodies

Caroline Robert, Jean-Charles Soria, Alexander M.M. Eggermont *

Gustave Roussy Comprehensive Cancer Center, 114 Rue Edouard Vaillant, 94800 Villejuif/Paris-Sud, France

PD-L1 on human tumor cells mediates T cell inhibition –resistance



Pardoll DM,Nat Rev Cancer 2012

PD1 en PDL1 inhibitie

- Anti-PD1
  - Nivolumab (BMS-936558; BMS)
  - MK-3475 (Merck)
  - AMP-514 (Medimmune/AZ)
- Anti-PDL1
  - MPDL3280A (Roche)
  - MEDI-4736 (Medimmune/AZ)

PD-1/PD-L1 blokkage

- 31% mRCC patients heavily treated are responding
- Responses can be long lasting (> 1 year)
- Less graad 3 toxicity
- Biomarker: possibly: PD-L1 expression on the tumor cells

Topalian N Engl J Med. 2012;366: 2443-2454.

Remarks on the future

- TKI still needs to be optimized in RCC and mRCC
- Surgery and TKI needs adequate sequencing
- Implementation of immune modulation and TKI
- Smart trials are neccessary


Thank you