

# Systemic Management of non-clear cell Renal Cell Cancer

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Asian Oncology Summit  
April 2010  
Bali, Indonesia

# Disclosure & Disclaimer

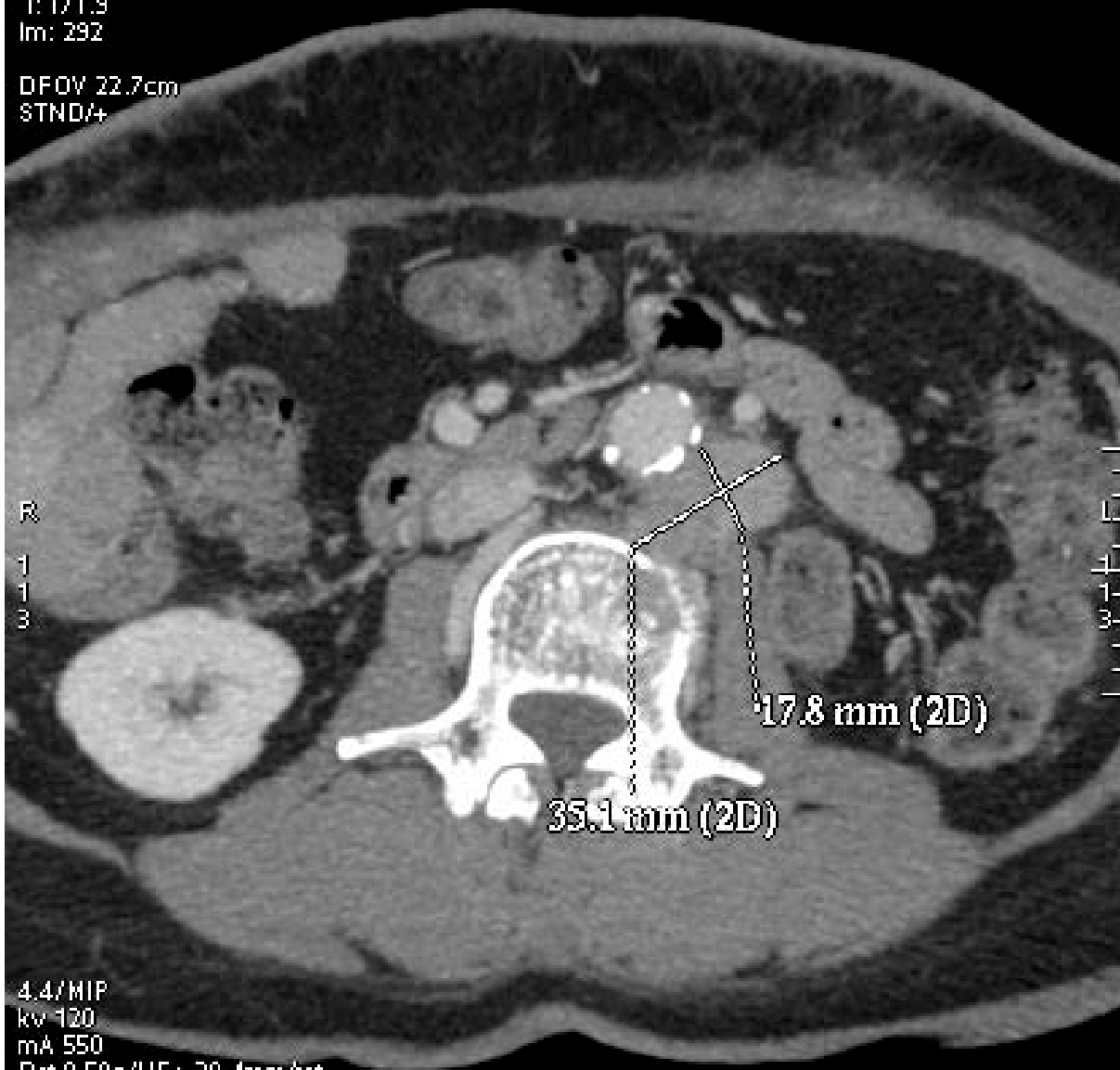
- Honoraria from GSK, Pfizer, Novartis, Bayer
- Evidence for treatment for nccRCC is not-Level 1.

Axial Volume 1  
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I: 171.9  
Im: 292

A 85

DFOV 22.7cm  
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# Overview

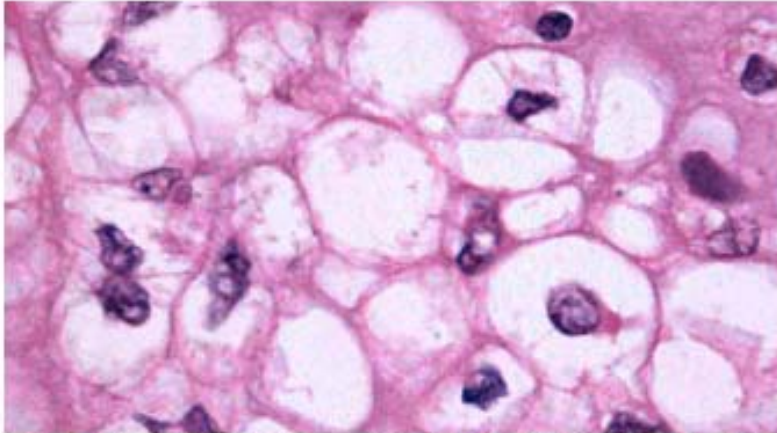
- Epidemiology
- Classification of non-clear RCC
- Molecular and cytogenetic aspects of non-clear RCC
- Treatment options

# Epidemiology

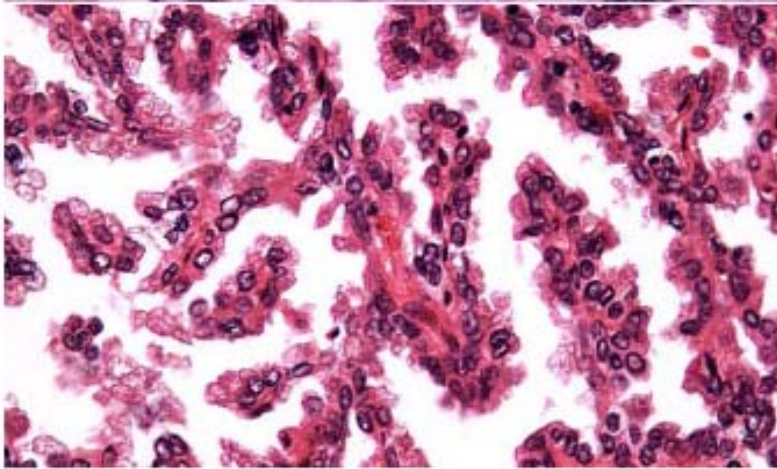
- RCC: 13<sup>th</sup> most common cancer in the world
- Trend is increasing with 35% increase in past 25 years in USA alone
- RCC is a wide spectrum of various types

# Classification of RCC

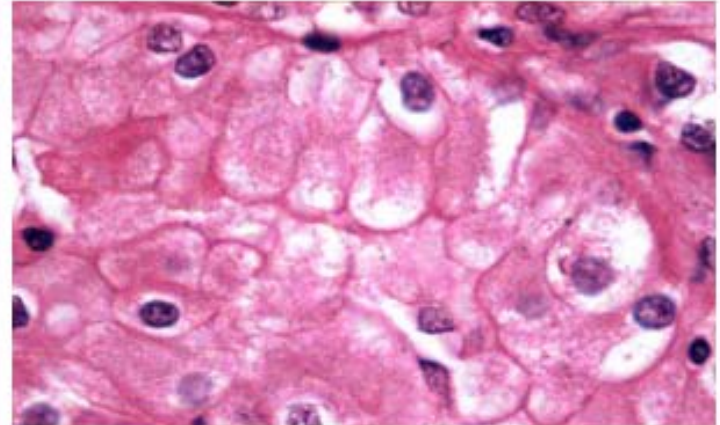
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# WHO Classification of RCC (2004)

- Clear cell
- Multi-locular ccRCC
- Papillary RCC
- Chromophobe RCC
- Collecting ducts of Bellini
- Renal medullary
- Xp11 translocation
- Carcinoma associated with neuroblastoma
- Mucinous tubular and spindle cell
- RCCs, non-specified

# WHO Classification of RCC (2004)

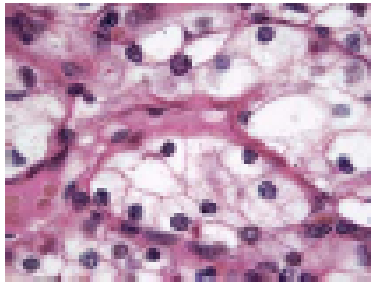
- Clear cell (70-85%)
- Multi-locular ccRCC
- Papillary RCC (7-15%)
- Chromophobe RCC (5-10%)
- Collecting ducts of Bellini
- Renal medullary
- Xp11 translocation
- Carcinoma associated with neuroblastoma
- Mucinous tubular and spindle cell
- RCCs, non-specified

# Epidemiology

Prevalence of PRCC and ChrRCC amongst all the RCC for the past 5 years (2005 -2010)

ccRCC	329	59.6
prRCC	53	9.6
chrRCC	12	2.2
Others	158	28.6
total	552	100%

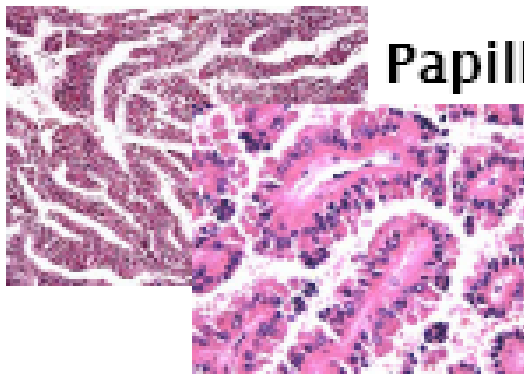
# Most Common RCC



Clear cell

**-3p, +5q22, -6q, -8p, -9p, -14q**

gene *VHL*



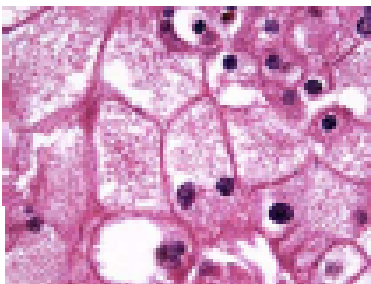
Papillary I

gene *c-MET*

**+3q, +7, +8, +12, +16, +17, +20, -Y**

Papillary II

gene *FH*



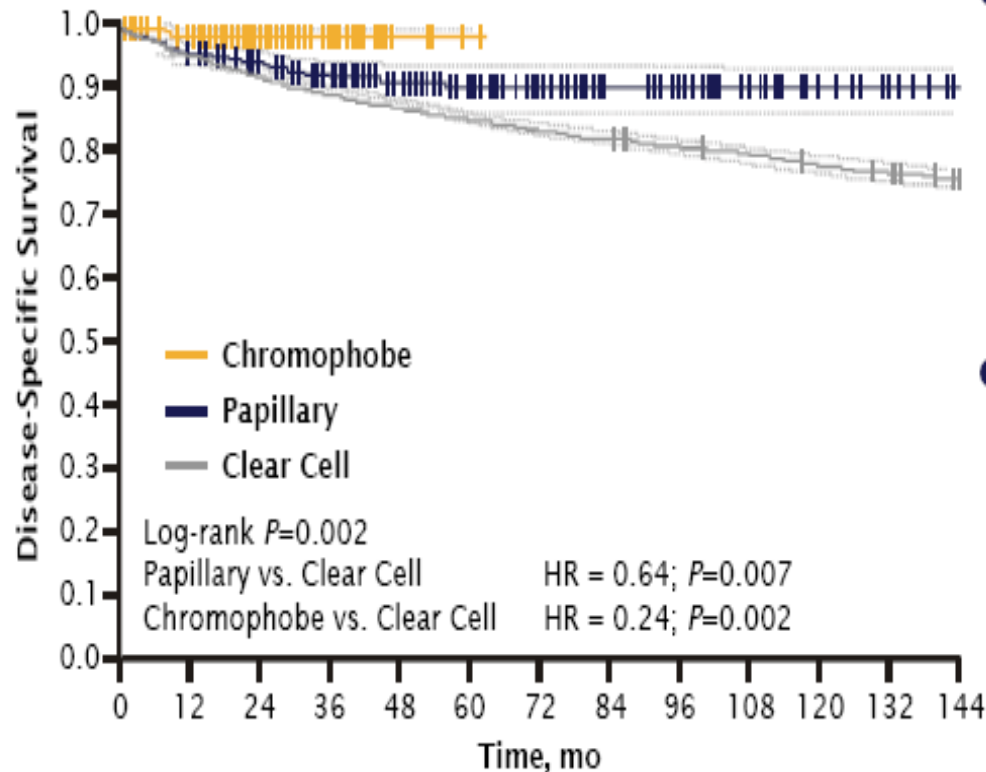
Chromophobe

**(-) 1, 2, 6, 10, 13, 17, 21**

gene *c-kit*

# Prognostic Value Of RCC

## Histology: Population-based stdy

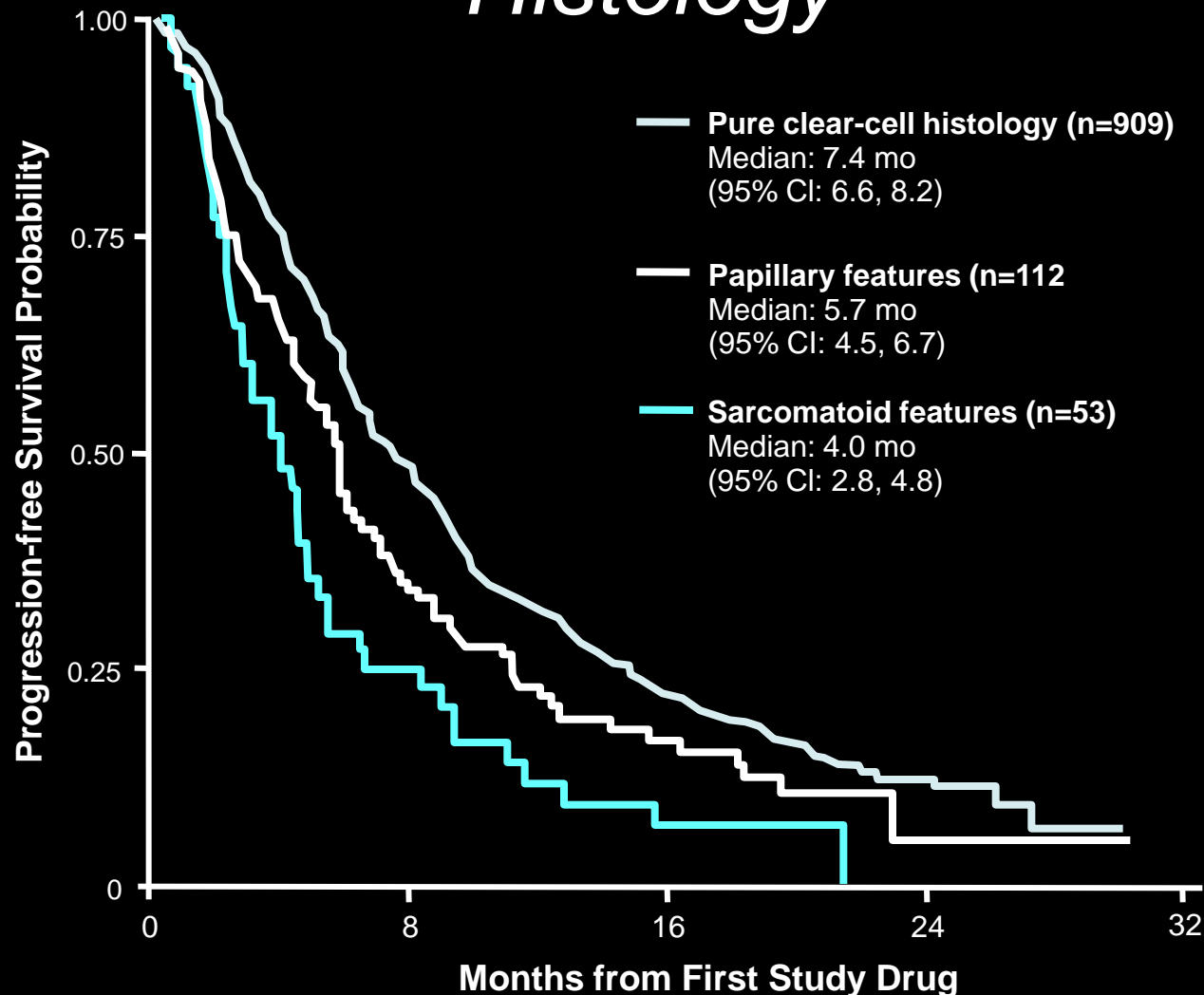


Number of Patients at Risk

Chromophobe	195	104	57	23	4	1	0	0	0	0	0	0	
Papillary	717	441	317	207	125	101	85	62	56	42	32	26	17
Clear Cell	10706	8330	6987	5957	5007	4064	3318	2660	2095	1646	1236	902	656
Total	11618	8875	7361	6187	5136	4166	8539	2722	2151	1688	1268	928	673

- Significance for histology in univariate cause-specific mortality analysis of 11,618 patients post-nephrectomy
- However, no added value for histology in multi-variate model including
  - Age
  - Year of surgery
  - TNM staging
  - Fuhrman grade

# *EU-ARCCS: Median PFS is Longest in Patients with RCC of Clear-cell Histology*



# Metastatic nccRCC

- Chromophobe have a longer median survival than papillary
- Metastatic Papillary have poorer prognosis than clear-cell type<sup>1</sup>
  - More local recurrence
  - Less response to immuno(chemo)therapy
  - Shorter median survival

<sup>1</sup>Stenier T ASCO 2006

<sup>1</sup>Kassouf Urol. 2007 Nov;178(5):1896-900. Epub 2007 Sep 17

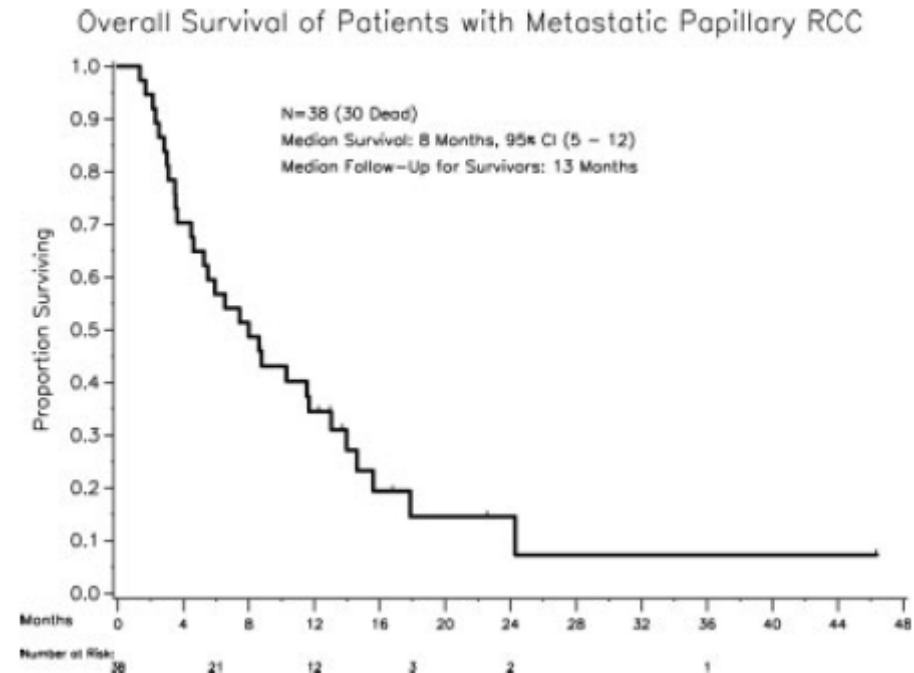
# Treatment of Metastatic Renal Cell Carcinoma of Non-Clear-Cell Subtypes

- Dearth of treatment options
- Heterogeneous group constituting <10% of patients in clinical trial

# Treatment outcome for metastatic papillary renal cell carcinoma patients

**TABLE 2**  
**Systemic Treatments and Outcomes in Metastatic Papillary RCC**

Treatment therapies	No. (N = 44) (%)	Partial response	Stable disease
Cytokine			
IFN	4 (9)	0	0
IL-2	2 (5)	0	0
IFN or IL-2 based-combination	6 (14)	0	1
Cytotoxic and hormonal agents	7 (16)	0	2
Novel agents	25 (57)	1	9



# Metastatic Papillary RCC

Herrmann E et al ASCO 2007

- 22 patients with metastatic papillary RCC treated with immunochemotherapy
- ZERO responders after 2 cycles



Judah  
Folkman

# Hypoxia and Angiogenesis: Molecular Basis of Cancer Progression

- All solid tumors do start as nonvascular cellular aggregates (microscopic disease) that is, tumor cell hypoxia is a very early event

*“In the absence of vascularization, solid tumors remain dormant 2–3 mm<sup>3</sup> in size, with GROWTH being limited by the ability of oxygen and nutrients to diffuse into the tumor”*



# Angiogenic Switch in Tumors

Small tumor (1–2 mm)

- Avascular
- Dormant
- Hypoxic

• VEGF  
• VEGF

• VEGF

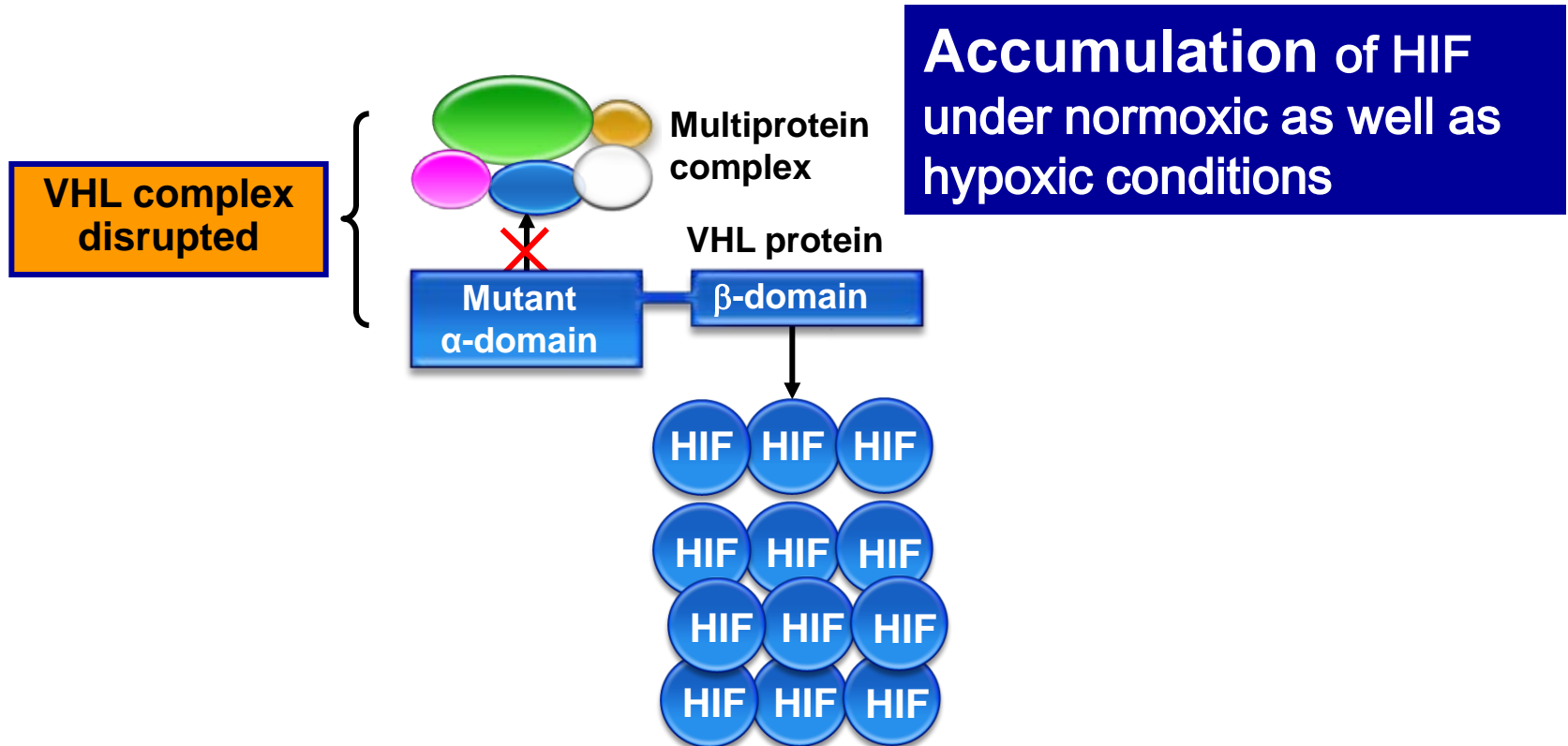
• VEGF

Angiogenic switch

Larger tumor

- Vascular
- Metastatic potential

# VHL Gene Mutation



**Mutant pVHL = no degradation of HIF**

# Treatments for mRCC

## Cytokines

Immunotherapy  
IL-2 and IFN- $\alpha$   
first to report activity

**VHL tumour suppressor gene isolated**  
First gene identified to cause a proportion  
of hereditary RCC and other tumours

**Bevacizumab + IFN- $\alpha$**   
FDA (2009) and EMA (2007) approval

**Everolimus**  
FDA and EMA  
approval

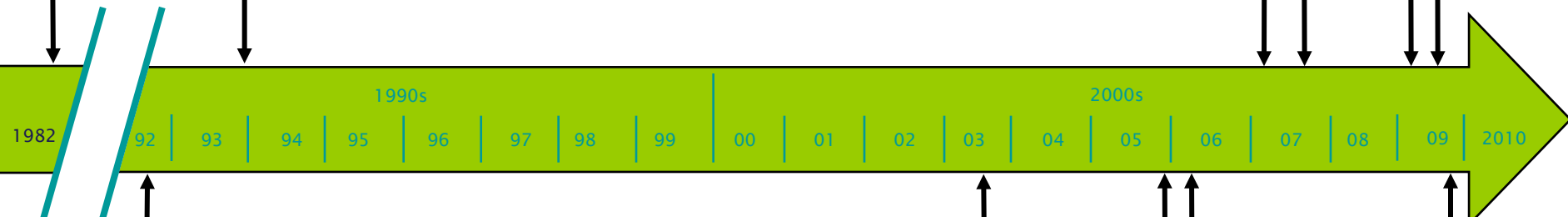
**Temsirolimus**  
FDA and EMA approval

**High-dose IL-2**  
FDA approval based on  
phase II data

**Bevacizumab**  
Data established  
activity of anti-  
angiogenic agents  
in RCC

**Sorafenib and  
sunitinib**  
FDA and EMA  
approval

**Pazopanib**  
FDA approval



FDA = US Food Drug Administration;  
EMA = European Medicines Agency.

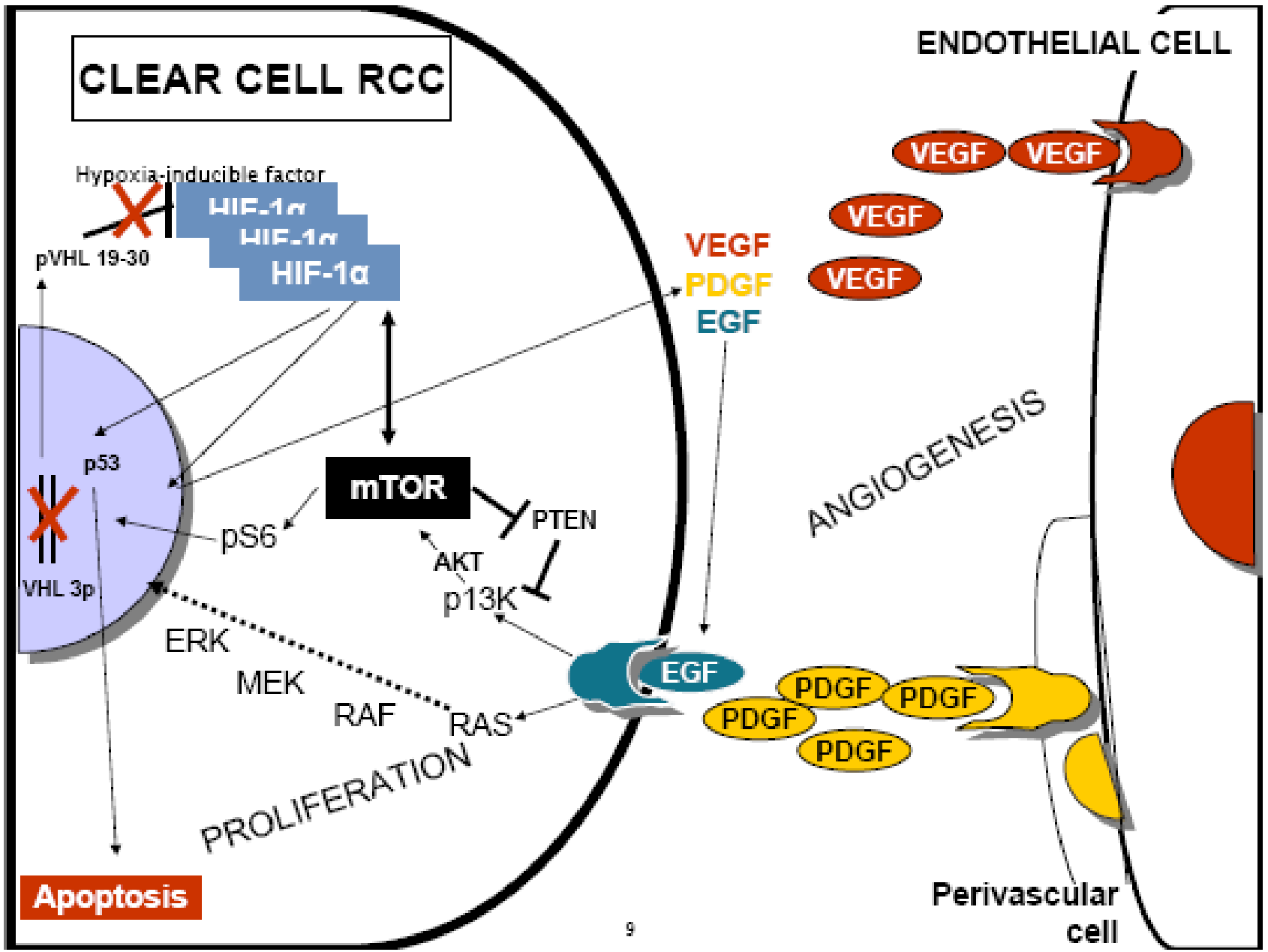
Quesada, et al. *Cancer Res.* 1983;43:940-947; deKernion, et al. *J Urol.* 1983;130:1063-1066; Rosenberg, et al. *N Engl J Med.* 1985;313:1485-1492; Latif, et al. *Science.* 1993;260:1317-1320; Yang, et al. *N Engl J Med.* 2003;349:427-434

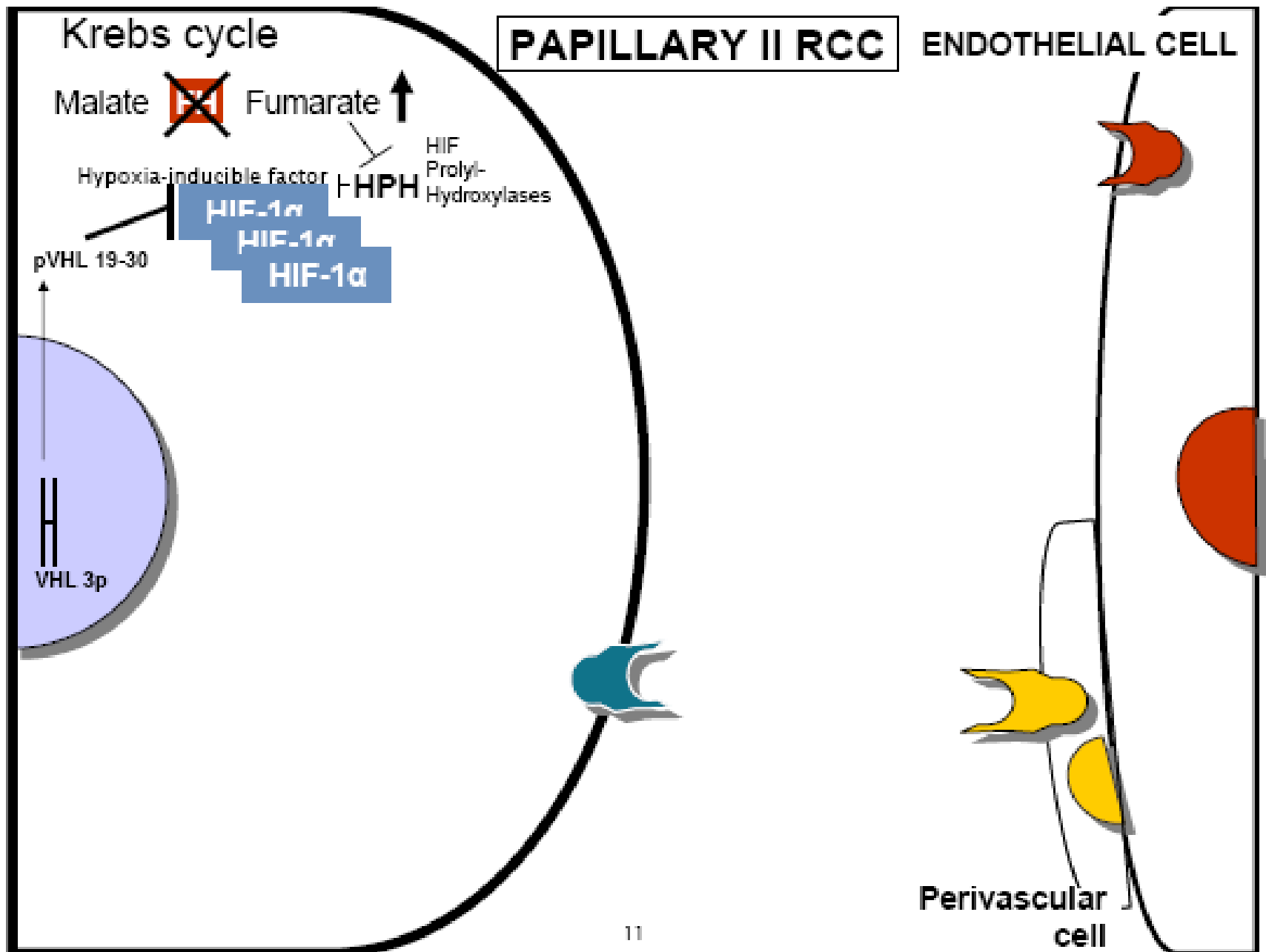


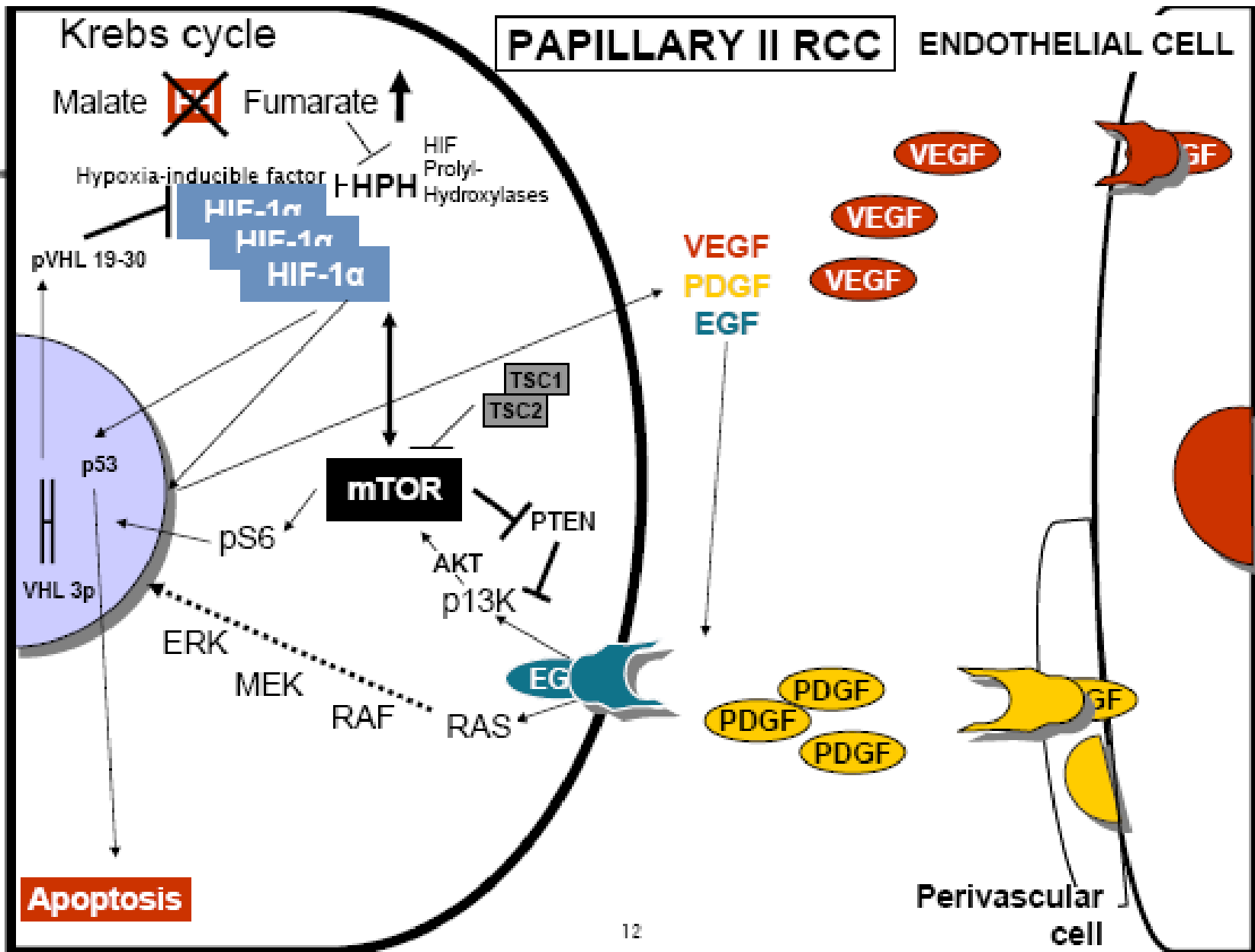
# Serum VEGF amongst RCC subtypes

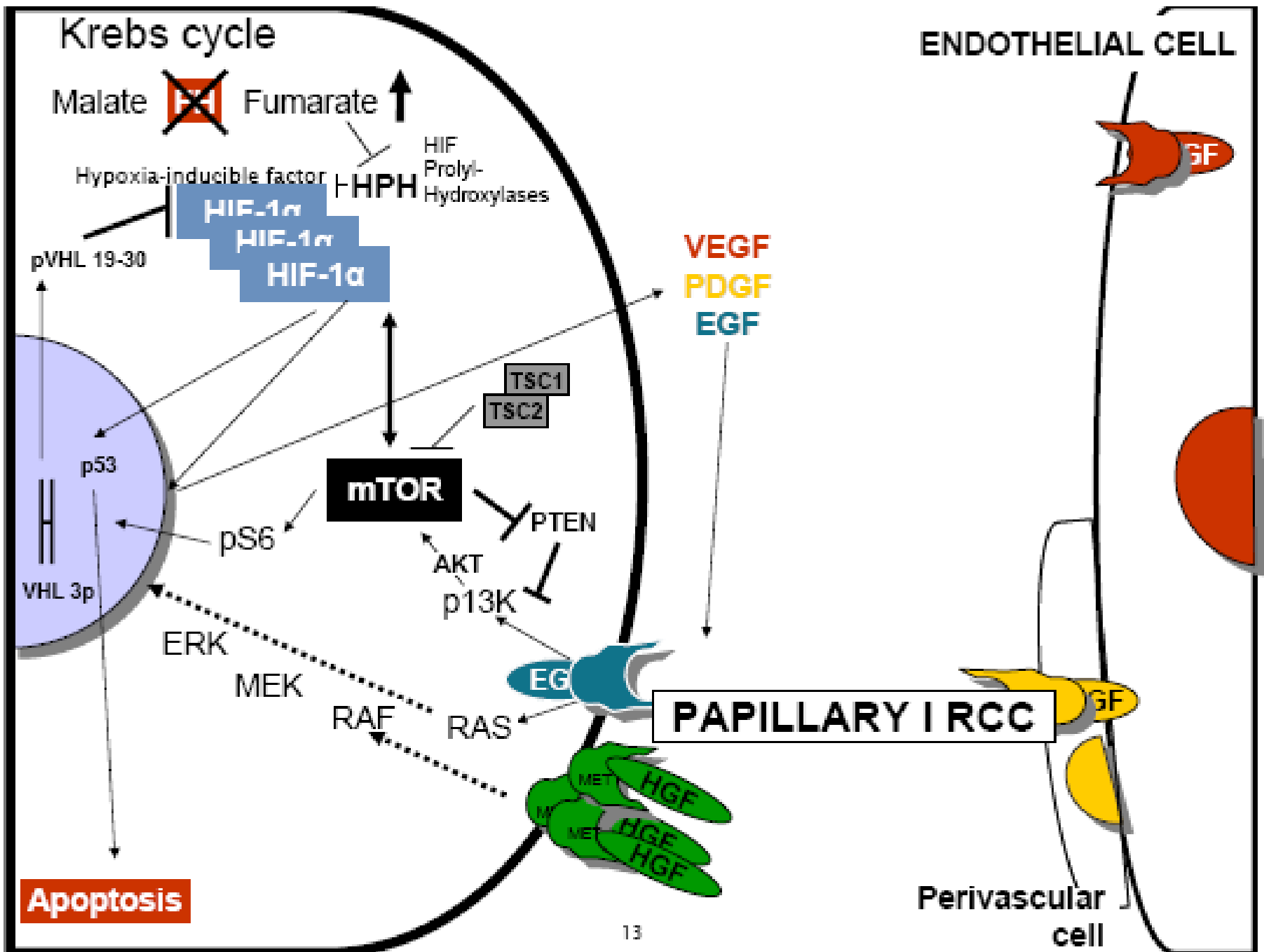
Histotype	VEGF (ng/mL ± SD)
Clear cell carcinoma	3.6 ± 6.9
Papillary type 1	2.4 ± 2.3
Papillary type 2	1.6 ± 2.6
Chromophobe	5.2 ± 3.5
Granular	2.0 ± 3.2
<i>P</i> value*	0.232

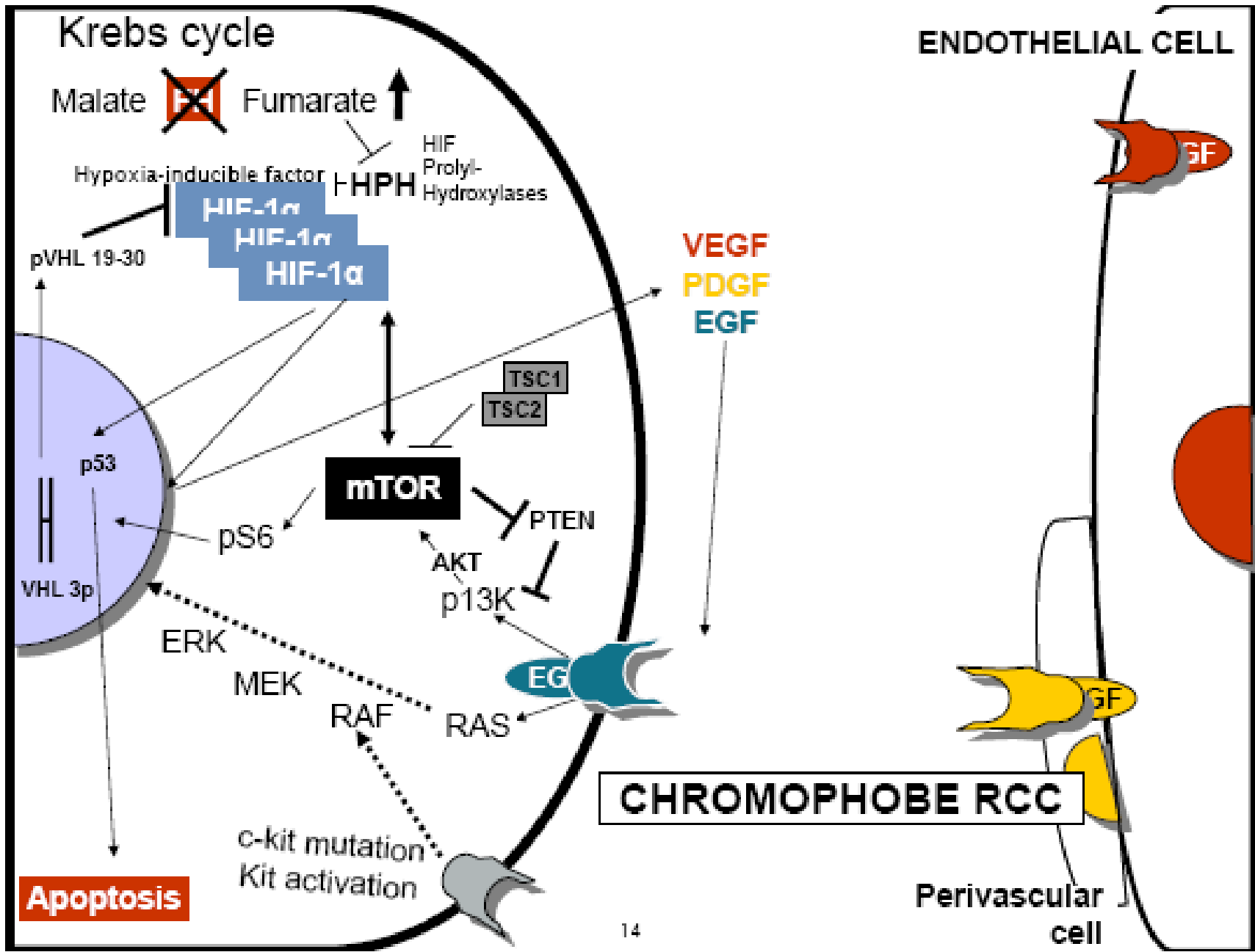
- Serum VEGF are elevated in all types of RCC, suggesting possibility of targeting VEGF + VEGFRs













# **Treatment of nccRCC in era of Biologics**

# Sunitinib EAP: Subgroup analysis

	Patient subgroups			
	Brain mets n = 213	ECOG PS $\geq 2$ n = 319	Non-clear-cell histology n = 588	Age $\geq 65$ years n = 1,056
Objective response	12%	9%	11%	17%
CR	<1%	0%	<1%	<1%
SD $\geq 3$ months	52%	52%	57%	60%
Progressive of SD<3 months	36%	39%	32%	23%
Clinical benefit*	64%	61%	68%	77%

# Sunitinib EAP: Subgroup analysis

	Patient subgroups				
	All patients	Brain mets	ECOG PS>2	Non-clear cell	Age >65 years
Evaluable patients	4,349	320	582*	588	1,414
PFS (months)	10.9	5.6	5.1	7.8	11.3
OS (months)	18.4	9.2	6.7	13.4	18.2

# *EU-ARCCS: Sorafenib Can Benefit Patients with a Spectrum of RCC Histologies*

	Total (N = 1048)	Clear-cell (n = 836)	Papillary (n = 101)	Sarcomato id (n = 48)
<b>CR + PR</b>	<b>46 (4.4)</b>	<b>43 (5.1)</b>	<b>1 (1.0)</b>	<b>0 (0)</b>
<b>CR + uPR</b>	<b>182 (17.4)</b>	<b>168 (20.1)</b>	<b>5 (5.0)</b>	<b>2 (4.2)</b>
<b>SD</b>	<b>765 (73.0)</b>	<b>594 (71.1)</b>	<b>86 (85.1)</b>	<b>41 (85.4)</b>
<b>PD</b>	<b>101 (9.6)</b>	<b>74 (8.9)</b>	<b>10 (9.9)</b>	<b>5 (10.4)</b>
<b>DCR ≥8 wks</b>	<b>895 (85.4)</b>	<b>726 (86.8)</b>	<b>83 (82.2)</b>	<b>39 (81.3)</b>
<b>DCR ≥12 wks</b>	<b>815 (77.8)</b>	<b>669 (80.0)</b>	<b>74 (73.3)</b>	<b>30 (62.5)</b>

uPR, unconfirmed partial response; DCR, disease control rate

# Multi-targeted Tyrosine Kinases Inhibitors in nccRCC

- Sorafenib

- ARCCS study Stadler WM, et al., *J Clin Oncol*, 2007
- N: 2488
- Median Progression free survival of 8.9 mths and overall survival of 12.2 mths

Types	PFS/OS (mth)	Response (PR/SD)
Papillary (n:174)	6.6	3.4%/77%
Chromophobe (n:25)	9.3	5.6%/89%
ALL	8.9/12.2	

# Sunitinib and Sorafenib in Chromophobe RCC

<b>PFS: Chromophobe Tumors</b>		
<b>Factor</b>	<b>No. of Patients*</b>	<b>Median PFS†‡ (months)</b>
<b>Overall</b>	<b>13 (no. of responders)</b>	<b>10.8</b>
<b>Treatment</b>		
<b>Sunitinib</b>	<b>7(1)</b>	<b>8.9</b>
<b>Sorafenib</b>	<b>6(2)</b>	<b>27.5</b>

*Choueiri J Clin  
Oncol. 2008  
Jan  
1;26(1):127-31*

# Sunitinib and Sorafenib in Papillary RCC

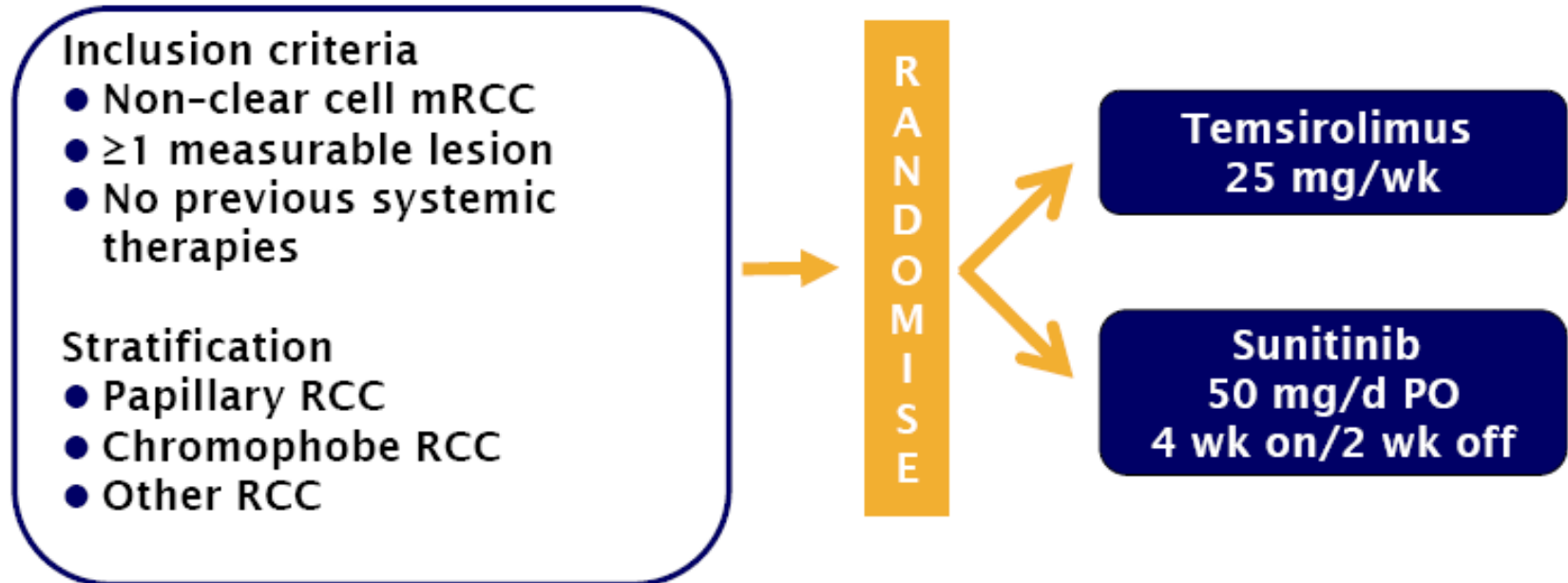
	No. of Patients*	Median PFS (months)
<b>Overall</b>	<b>41(no. of responders)</b>	<b>7.6</b>
<b>Treatment</b>		
<b>Sunitinib</b>	<b>13(2)</b>	<b>11.9</b>
<b>Sorafenib</b>	<b>28(0)</b>	<b>5.1</b>

# Temsirolimus

Median OS, by Subgroup	IFN- $\alpha$	TEM	HR (95% CI) TEM vs. IFN- $\alpha$
<b>Histology Type</b>			
Clear cell	8.2 months	10.6 months	0.85 (0.64–1.06)
<b>Other</b>	<b>4.3 months (36)</b>	<b>11.6 months (37)</b>	<b>0.55 (0.33–0.90)</b>
<b>Age</b>			
<65 yrs	6.9 months	12.0 months	0.67 (0.52–0.87)
$\geq$ 65 yrs	8.3 months	8.6 months	1.15 (0.78–1.68)
<b>Risk Group</b>			
Intermediate	17.7 months	13.0 months	1.17 (0.74–1.84)
Poor	6.0 months	10.2 months	0.70 (0.55–0.89)

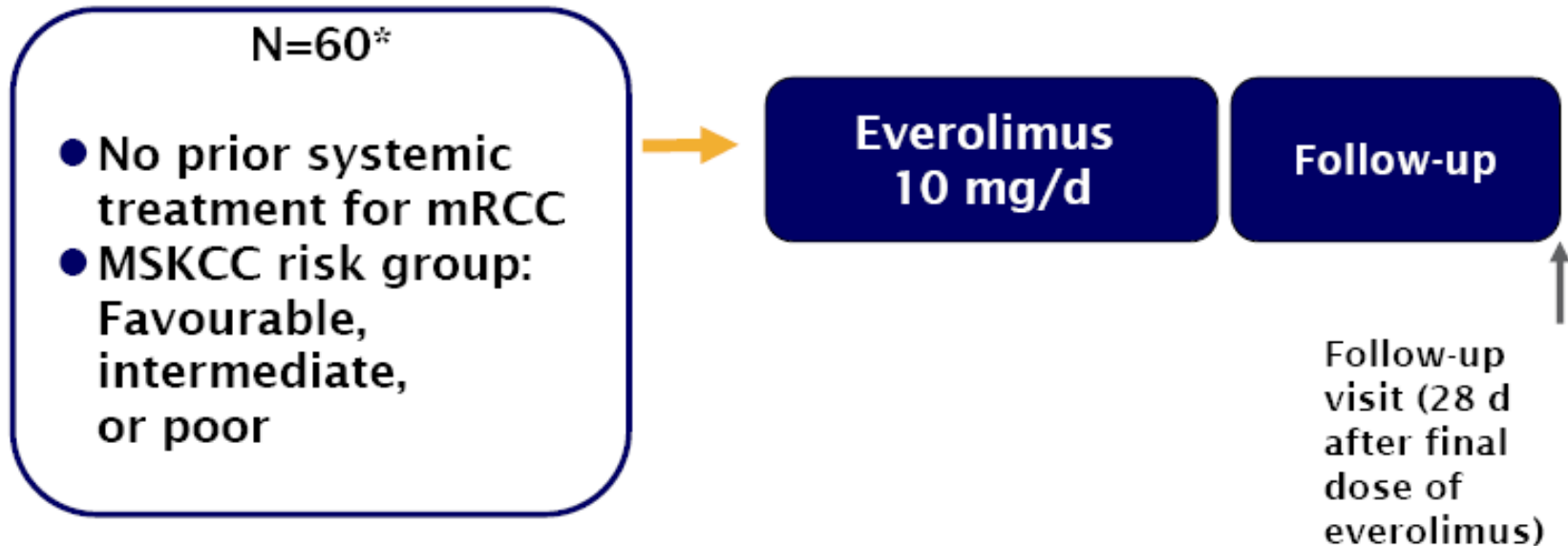
HR = hazard ratio

# On-going Study: Phase II of Temsirolimus in nccRCC



- Prospective randomised phase II study
- Primary endpoint: PFS
- Secondary endpoints: Response rate, OS, tolerability

# On-going: Phase II study of Everolimus in Advanced Papillary RCC (RAPTOR)



- Phase 2 trial at multiple sites in Europe
- Primary endpoint: PFS at 6 months
- Secondary endpoints: Disease control rate, ORR, duration of response, median PFS, safety

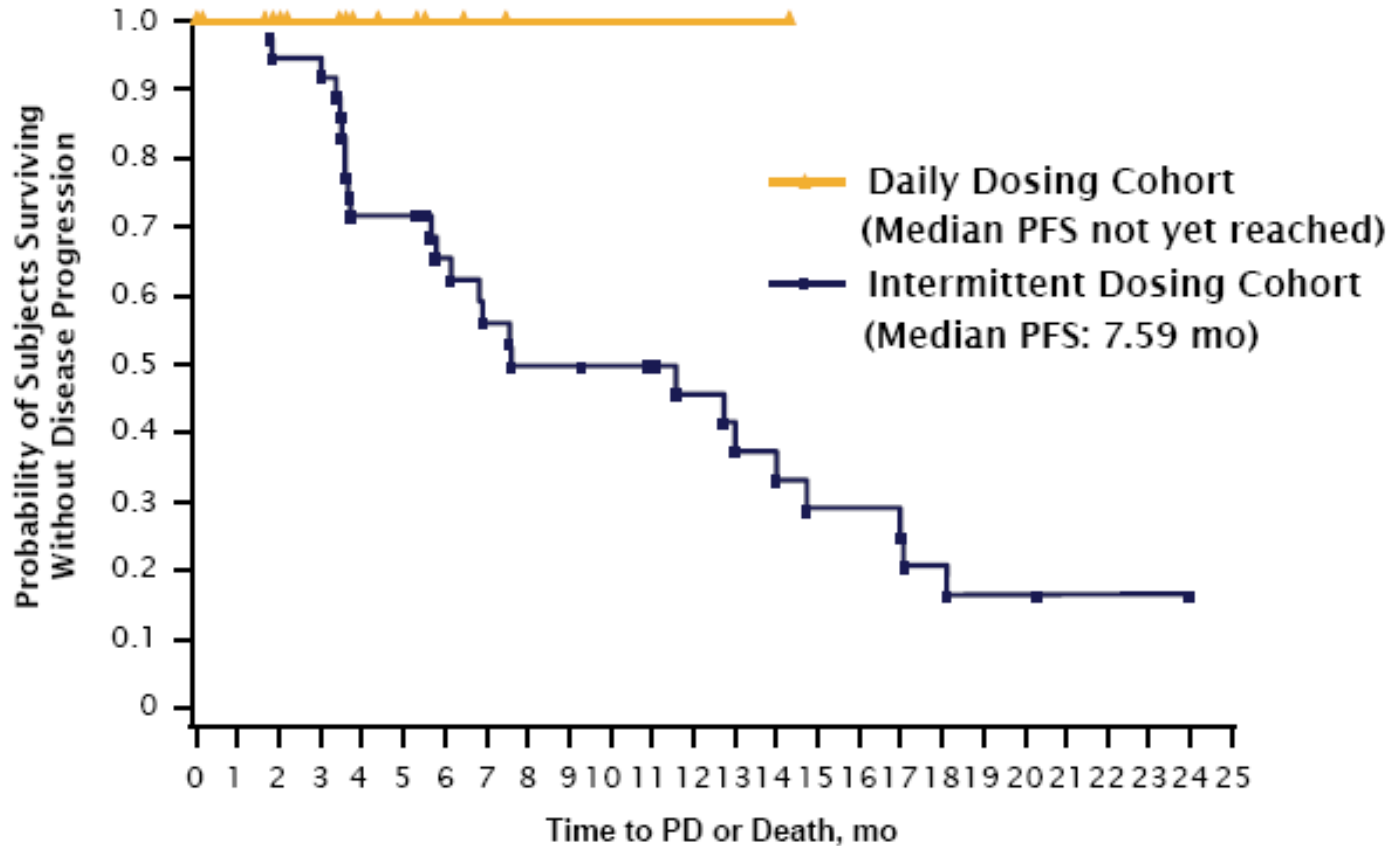
# Phase II study of Foretinib in pap RCC

- Foretinib is a TKI of c-Met and VEGFR
- Stratum A
  - Patients with germline mutation of c-Met or molecular evidence suggestive of c-Met pathway activation (somatic c-Met mutation, trisomy 7 or 7q31 amplification)
- Stratum B
  - Patients without apparent molecular evidence suggestive of c-Met pathway activation in their renal cell cancer or available tumour samples
- Rx: a. foretinib 240 mg .day x 5 days and rest 9 days.  
b. foretinib 80 mg daily

# Phase II study of Foretinib in pap RCC: PFS

Response, n (%)	Dosing Regimen					
	5 d on/9 d off			Daily		
	Stratum A (N=21)	Stratum B (N=16)	All (N=37)	Stratum A (N=5)	Stratum B (N=11)	All (N=16)
Confirmed PR	2* (10)	2 (13)	4 (11)	1* (20)	2 (18)	3 (19)
Unconfirmed PR	2 (10)	0	2 (5)	0	0	0
SD	15 (71)	13 (81)	28† (76)	4 (80)	7 (64)	11 (69)
PD	1 (5)	1 (6)	2 (5)	0	0	0
Not evaluated	1 (5)	0	1 (3)	0	2 (18)	2 (13)
ORR	2 (10)	2 (13)	4 (11)	1 (20)	2 (18)	3 (19)

# Phase II study of Foretinib in pap RCC: PFS



Srinivasan, et al. *J Clin Oncol.* 2009;27:ab5103.

# Epidermal Growth Factor Receptor (EGFR) Inhibitors

- Normal vHL expression is associated with greater EGFR inhibitor activity<sup>1</sup>
- Erlotinib 39 patients
- Response: 11% (target was 20%) with 12% stable disease
- 6 months PFS: 30%
- MS: 27 months
- Although this was a negative study, it yielded encouraging extended disease control rate and overall survival rate.

1. Clin Can Res 6:1518, 2000

2. Pan C, et al., *J Clin Oncol*, 2007

# Role of c-kit gene in chrRCC

- CD-117 +ve in 88-100% of chrRCC
- Upregulation of c-kit gene expression reported
- Mechanism of KIT overexpression is unknown

crine way [19]. In summary 70 cases, based on 4 reports investigators were unable to detect activating mutations within exon 17 of the *c-kit* gene [19-22]. Absence of *c-kit* mutation could be argue for potential effectiveness of imatinib therapy in patients with metastatic ChRCCs.



# Summary

- Treatment of non-clear cell type is no different from clear cell subtype
- Current evidence is not level 1
- Targeted therapy are being used treat non-clear cell RCC but the full potential is not unknown without being tested in sufficiently large number of patients.
- There is an urgent need for more focused research and dedicated clinical trials amongst patients with these disease.