

Non Clear Cell Renal Cancer

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Barts Cancer Institute

Disclosures

Educational/funding Grants

- GSK
- Pfizer
- Novartis
- AZ

Non-clear cell renal cancer has often been considered part of the clear cell 'team' and treated in the same way.



So this group of tumors has distinct features

Clear cell renal cancer

- VHL mutation
- VEGF driving the cancer
- Randomised phase III data

Non-clear cell

- Heterogeneous group of cancers
- Specific genetic alterations (MET BHD)
- Lack of data with specific therapies

So its different but does that matter?

Clear cell renal cancer

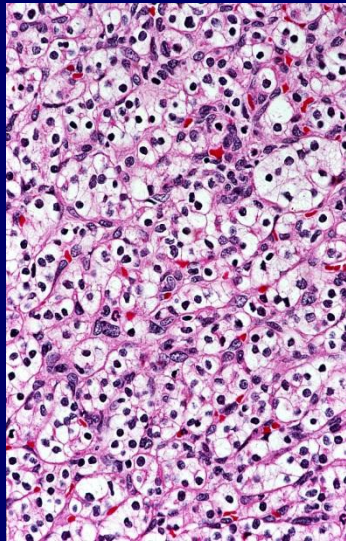
- VHL mutation
- VEGF driving the cancer
- Randomised phase III data

Non-clear cell

- Heterogeneous group of cancers
- Specific genetic alterations (MET BHD)
- Lack of data with specific therapies

Probably, but we really don't know

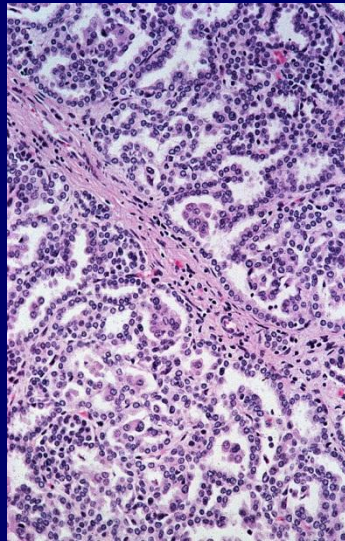
Even the subset are likely to behave in a distinct manner



Clear Cell

VHL

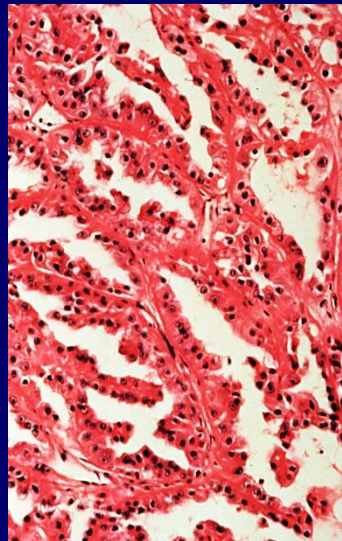
75%



Papillary Type 1

Met

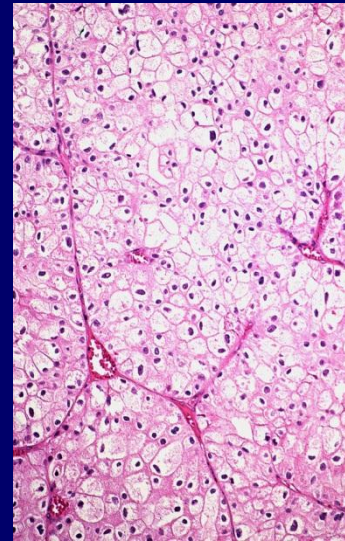
5%



Papillary Type 2

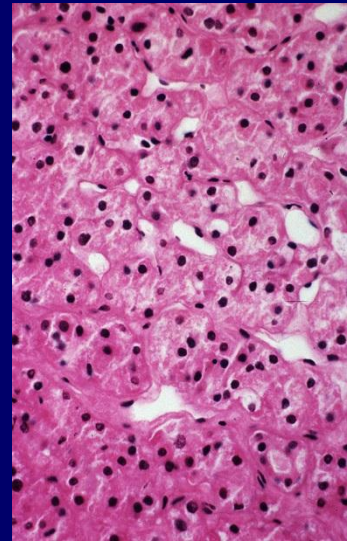
FH

10%



Chromophobe

5%

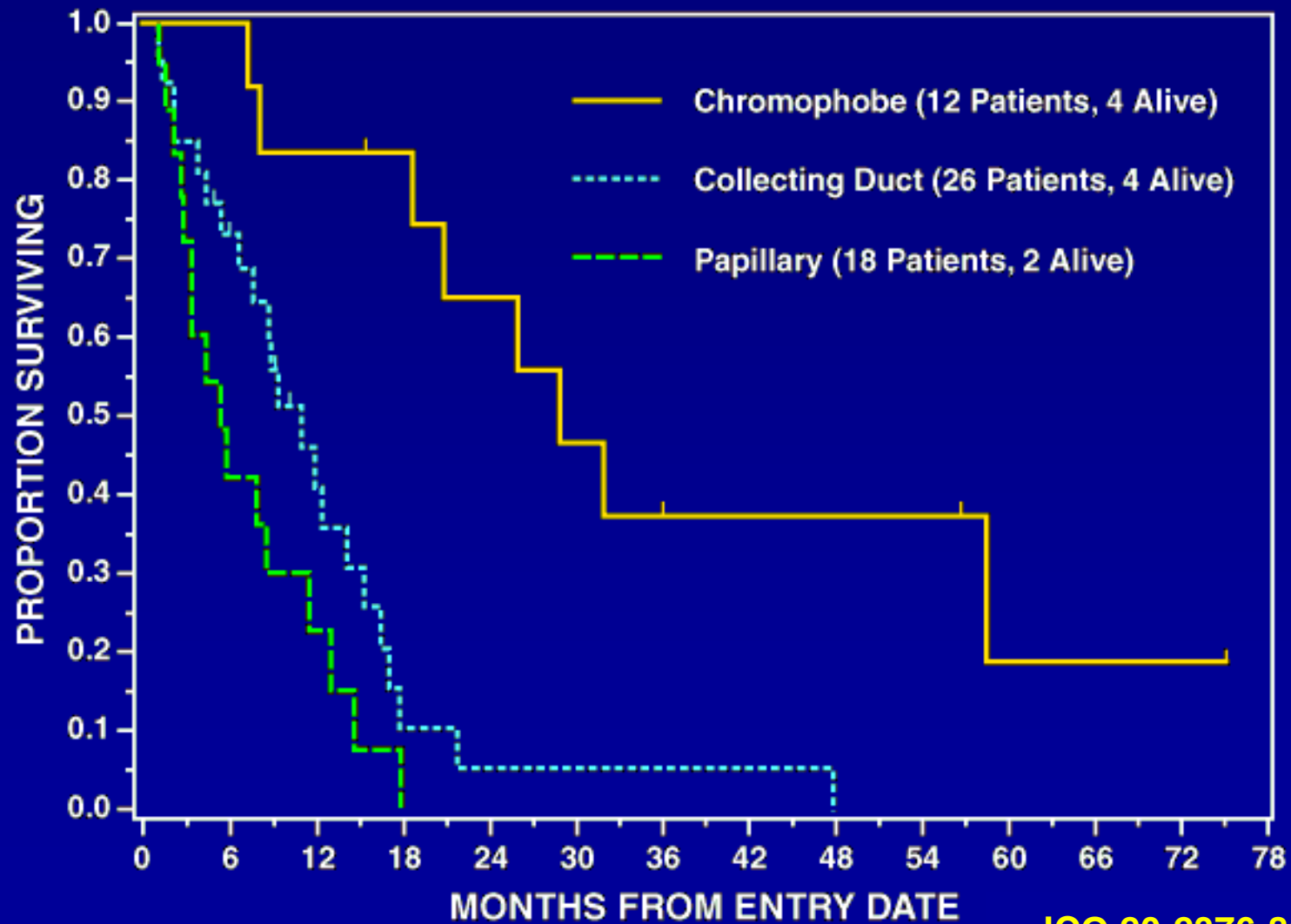


Oncocytoma

5%

BHD

Non-Clear-Cell Histology Survival by Cell Type (MSK Experience)



Non-clear cell renal cancer patients treated with VEGF TKIs

Study design	Patient population	Response rate	PFS	OS
Expanded access programme (n=588)	non-clear cell Sunitinib	11%	7.8	13.2
Prospective phase II (n=47)	Non-clear cell sunitinib 1 st -3 rd line	5%	2.7	14.0
Retrospective analysis (n=53)	Non clear cell VEGF TKIs 1 st -3 rd line	10%	8.6	19.6

Gore et al Lancet Oncology 2010
Tannir et al European Urology 2012
Choueri et al JCO 2008

Papillary renal cancer patients treated with VEGF TKIs

Study design	Patient population	Response rate	PFS	OS
Expanded access programme (n=588)	Sunitinib	11%	7.8	13.2
Prospective phase II (n=25)	Sunitinib 1 st -3 rd line	0%	1.6	12.6.
Retrospective analysis (n=47)	VEGF TKIs 1 st -3 rd line	3%	7.6	NA

Gore et al Lancet Oncology 2010
Tannir et al European Urology 2012
Choueri et al JCO 2008

First line sunitinib in type I and II papillary renal cell carcinoma (PRCC): SUPAP- a phase II study of the French Genito-Urinary Group (GETUG) and the Group of Early Phase trials (GEP)

A.Ravaud⁽¹⁾, S. Oudard⁽²⁾, M. de Fromont⁽³⁾, C. Chevreau⁽⁴⁾, G. Gravis-Mescam⁽⁵⁾, S. Zanetta⁽⁶⁾, C. Théodore⁽⁷⁾, M. Jimenez⁽⁸⁾, E. Sevin⁽⁹⁾, B. Escudier⁽¹⁰⁾

(1) Hôpital Saint André CHU, Bordeaux, France; (2) Hôpital Européen Georges Pompidou, Paris; (3) Prado-Pathologie, Marseille; (4) Institut Claudius Régaud, Toulouse; (5) Institut Paoli-Calmettes, Marseille; (6) Centre Georges-François Leclerc, Dijon, France; (7) Hôpital Foch, Suresnes; (8) Unicancer, Paris, (9) Centre François Baclesse, Caen; (10) Institut Gustave Roussy, Villejuif.

Patients characteristics

TYPE I	15 pts
NON TYPE 1	46 pts
Median age (years)	64
NEPHRECTOMY	53 pts (87%)
PS 0	31 pts
PS 1	30 pts
MSKCC favorable	12 pts (22%)
intermediate	33 pts (61%)
poor	9 pts (17%)
undetermined	7 pts

Study design and results

- Single arm phase II study
- Sunitinib 50mg 4/2
- Papillary cancer type I and II
- Primary endpoint –PFS
- Secondary endpoint- RR OS Toxicity

RESPONSE RATE = 12%

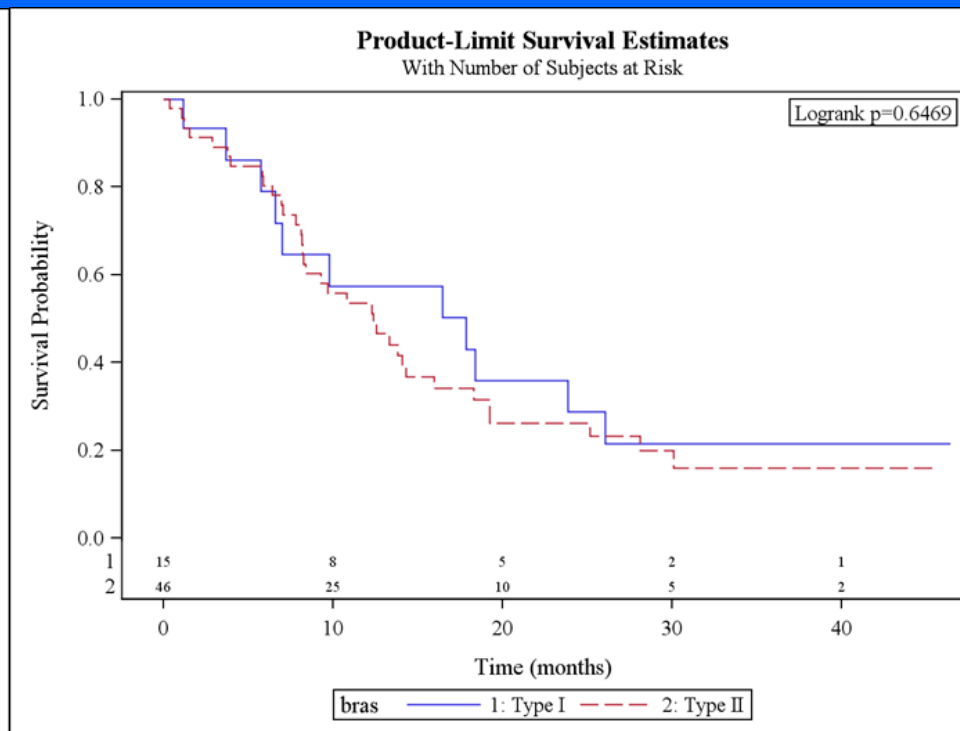
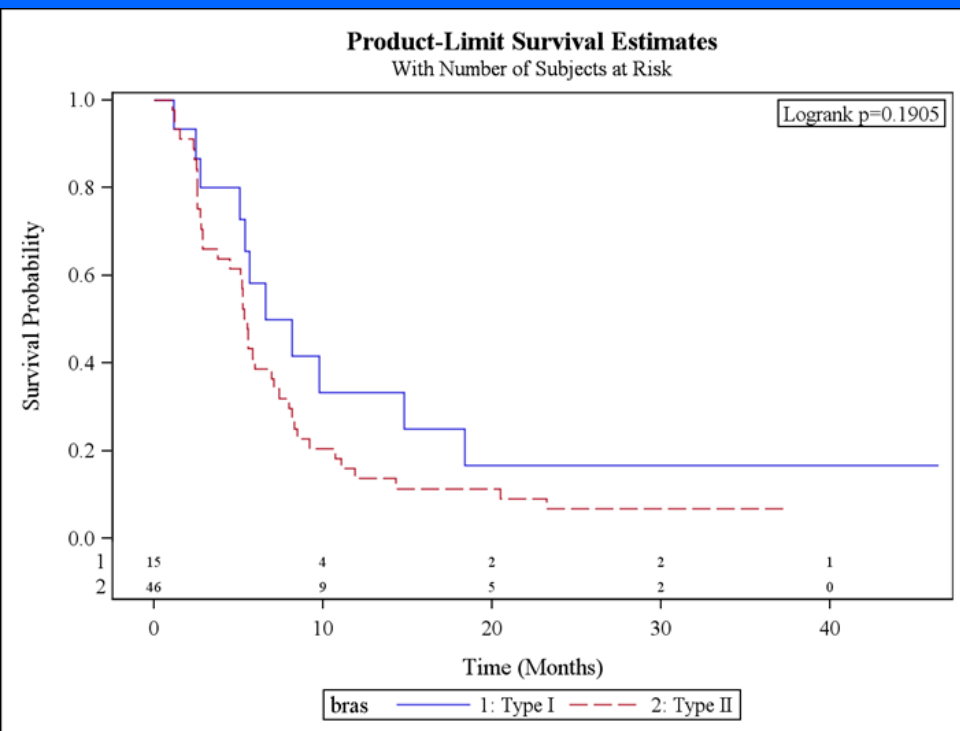
PFS = 5.6 months (5.1-7.4)

OS = 12.5 months (8.2-17.8)

Outcome of type 1 v.s. 2 papillary RCC

PFS

OS



Rational for mTOR inhibition in non-clear cell renal cancer

- **Study design:** RIII Temsirolimus v.s. interferon in poor risk RCC
- **Results:** non-clear cell groups had a survival advantage with Temsirolimus

Open-label Phase II Trial of First-line Everolimus Monotherapy in Patients With Advanced Papillary Renal Cell Carcinoma: RAPTOR Interim Analysis

B. Escudier,¹ S. Bracarda,² J. P. Maroto,³ C. Szczylik,⁴ P. Nathan,⁵
S. Negrier,⁶ , V. Molinie, ⁷ K. Slimane,⁸ C. May,⁹ C. Porta,¹⁰ V. Grunwald¹¹

¹Institut Gustave Roussy, Villejuif, France; ²Ospedale San Donato, Arezzo, Italy; ³Hospital de la Santa Creu i Sant Pau, Oncology Department, Barcelona, Spain; ⁴Warsaw , Poland; ⁵Mount Vernon Cancer Centre, Northwood, UK; ⁶University Lyon, Lyon, France; ⁷Saint Joseph Hospital, Paris, France; ⁸Novartis Pharma SAS, Cedex, France; ⁹Novartis Pharmaceuticals Corporation, Nuernberg, Germany; ¹⁰IRCCS San Matteo University Hospital Foundation, Pavia, Italy; ¹¹Clinic for Haematology, Haemostaseology, Oncology, and Stem Cell Transplantation, Medical School Hannover, Hannover, Germany

RAPTOR, RAD001 in Advanced Papillary Tumor Program
in Europe (ClinicalTrials.gov, NCT00688753)

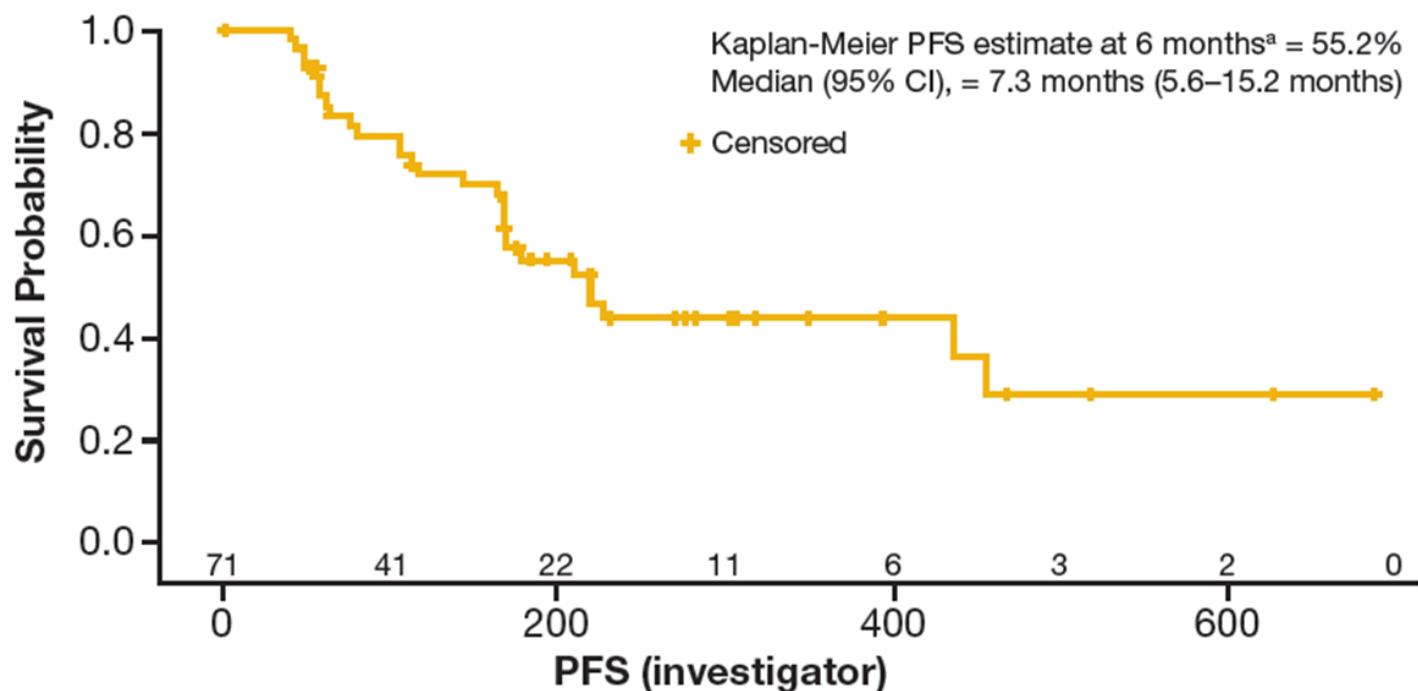
Study Design and Patient Characteristics

- **Design:** open-label, single-arm, non-randomized, multicentre phase II trial
- **Primary end point:** proportion of patients progression-free at 6 months
- **Treatment:** everolimus 10 mg once daily until disease progression or unacceptable toxicity
 - Dose reduction to 5 mg once daily permitted

N = 92	
Sex	
Female	20 (21.7%)
Male	72 (78.3%)
Age	
n	92
Mean (SD)	59.9 (14.9)
Median	62.0
Range	23–84
Patients with PS	
0	56 (60.9%)
1	36 (39.1%)
MSKCC	
Favourable	48 (52.2%)
Intermediate	38 (41.3%)
Poor	1 (1.1%)
Missing	5 (5.4%)
Nephrectomised patients	
No	16 (17.4%)
Yes	76 (82.6%)
Metastatic sites	
1	13 (14.1%)
2	23 (25.0%)
> 2	48 (52.2%)
Missing	8 (8.7%)
Time from diagnosis to treatment	
n	88
Mean (SD)	788.56 (1218.70)
Median	209.50
Range	14.0–5451.0
Type	
Type 1	23 (25.0%)
Type 2	39 (42.4%)
Missing	30 (32.6%)

MSKCC, Memorial Sloan-Kettering Cancer Centre.

Progression-free Survival



^aKaplan-Meier estimate for the proportion of patients without PFS event (progression or death due to any cause).

PFS assessment of patients still receiving treatment and the independent radiology review are ongoing

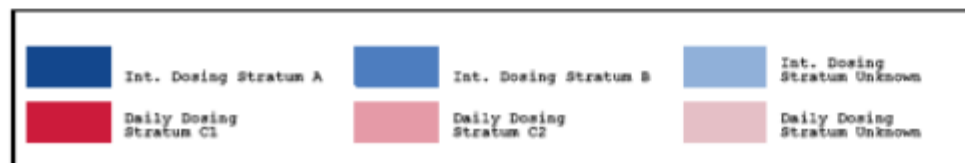
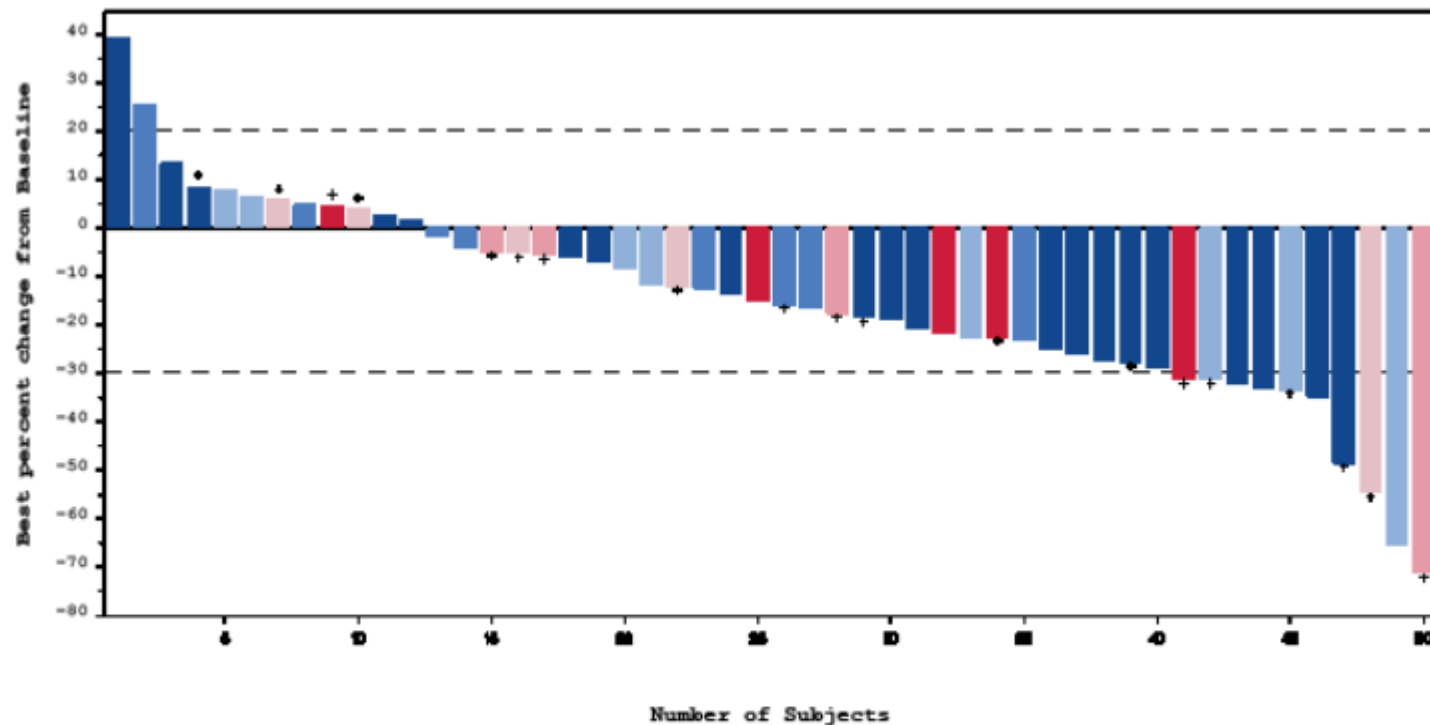
Papillary renal cancer patients treated with VEGF TKIs

Study design	Patient population	PFS mnths
Expanded access programme (n=588)	Sunitinib	7.8
Prospective phase II (n=25)	Sunitinib 1 st -3 rd line	1.6
Retrospective analysis (n=47)	VEGF TKIs 1 st -3 rd line	7.6
Ravault et al	Sunitinib 1st line	5.6 (5-7)
Escudier et al	everolimus	7.3 (5-12)

Do the same prognostic factors apply
as those seen in clear cell RCC?



A Phase II Study of Foretinib (MET/VEGFR2 TKI) in Papillary RCC

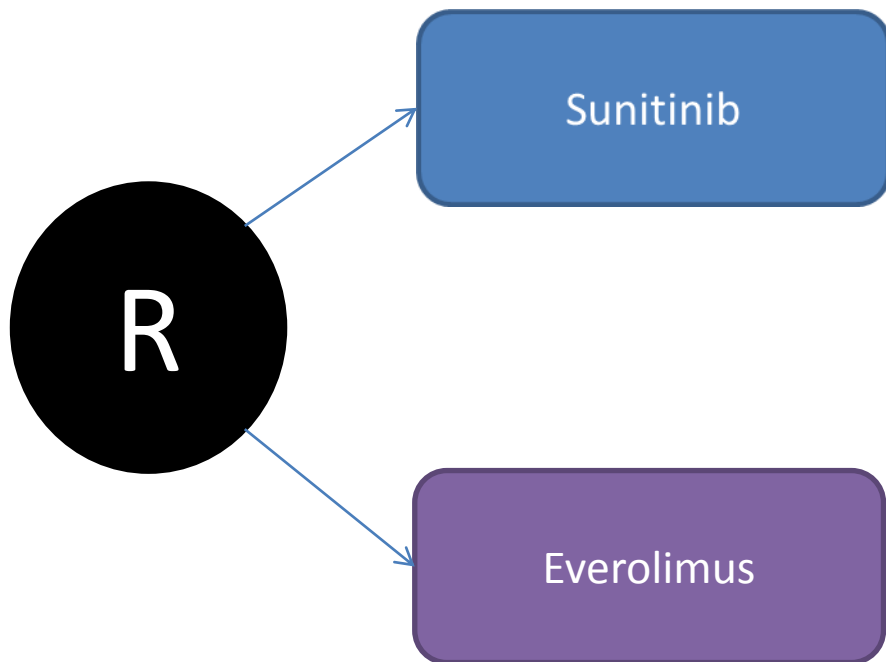


70% Clinical benefit

Choueiri et al 2011

ASPEN trial for papillary RCC

- First line therapy for papillary cancer
- Randomised phase II study
- PFS is the primary endpoint
- Collaboration between industrial partners



Overview of treatment for non-clear cell histology

Tumor	Therapy
Sarcomatoid	VEGF TKI therapy/chemotherapy
Papillary type 1	Sunitinib or everolimus
Papillary type 2	Sunitinib or everolimus
Chromophobe	Don't know maybe mTOR
Collecting Duct	Chemotherapy