What Do My Genes Tell Me About Kidney Cancer?

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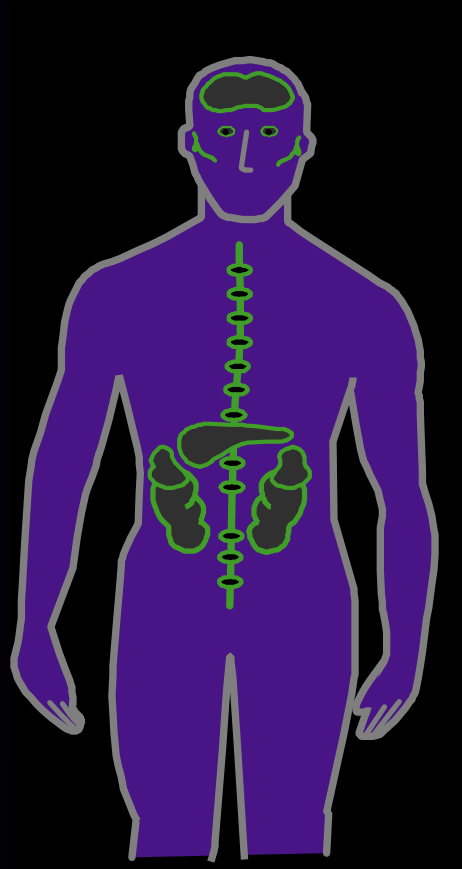
Urologic Oncology Branch, Center for Cancer Research

National Cancer Institute

von Hippel Lindau Disease

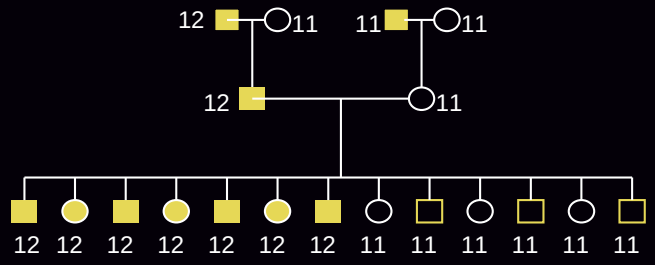
- Tumors develop in:
  - Both Kidneys
  - Adrenal Glands
  - Pancreas
  - Brain or Spine
  - Eyes
  - Inner Ears



Identification of the VHL gene

(W. Marston Linehan and Berton Zbar, NCI)

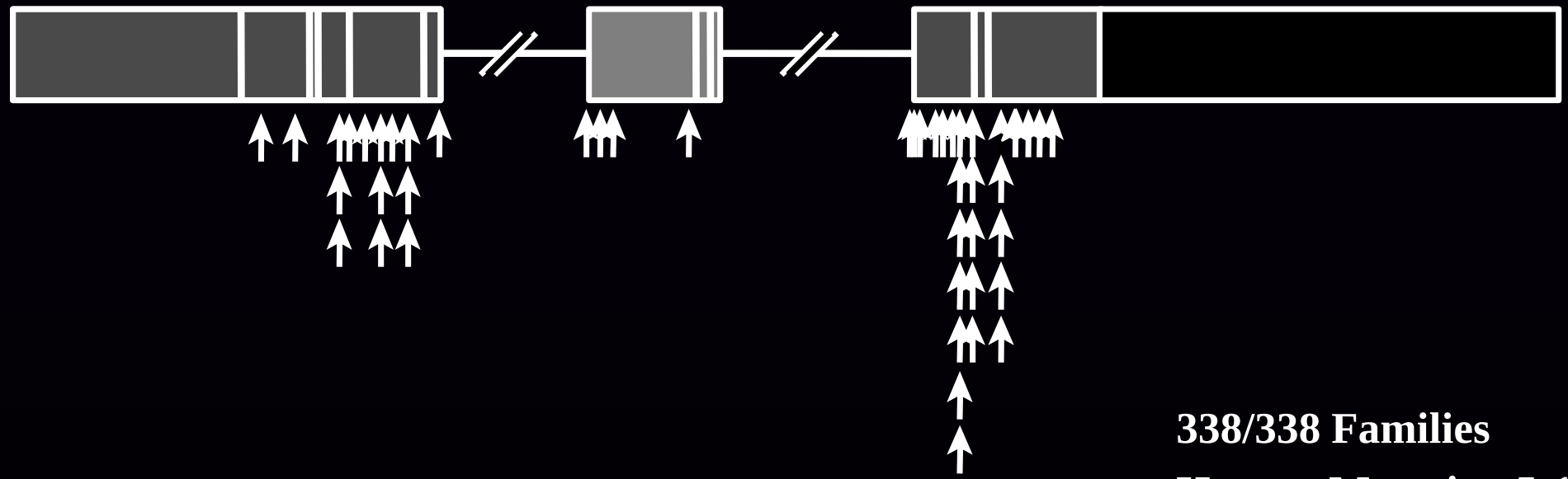
Collect families



Linkage analysis

Physical mapping

Germline VHL Mutations

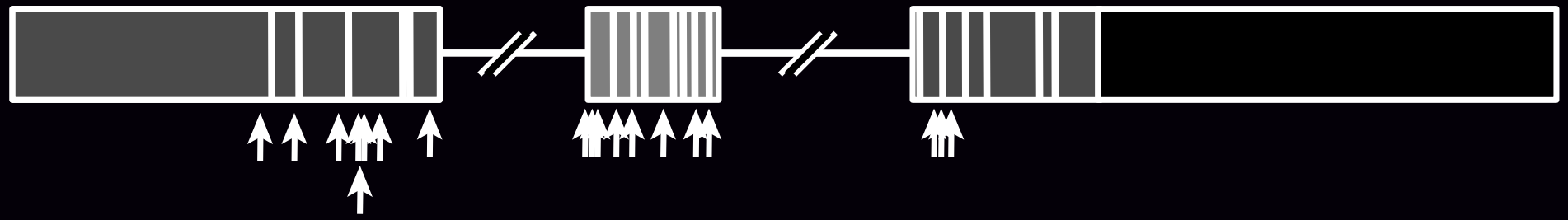


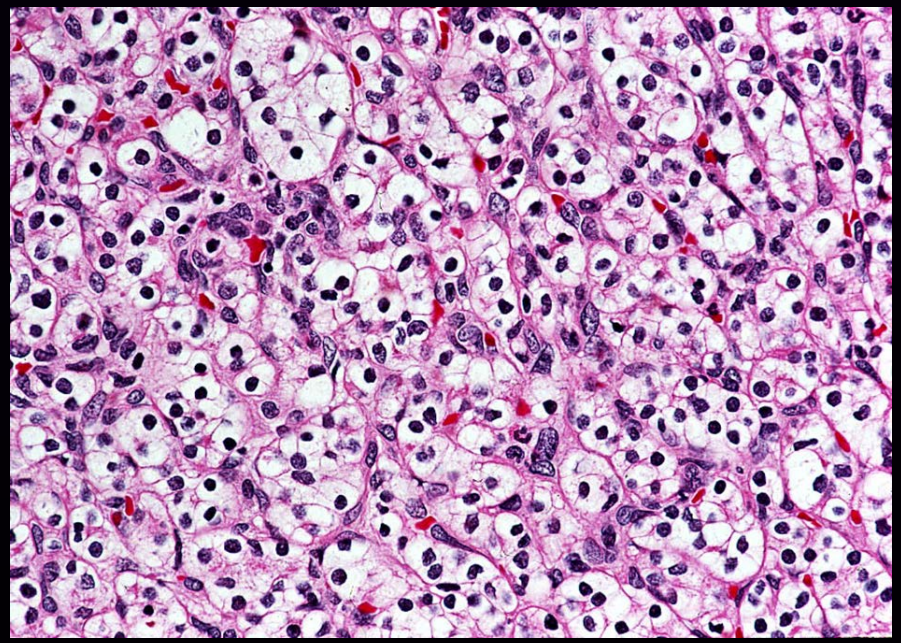
338/338 Families

Human Mutation 5:1995

Corbin et al. In Prep

Sporadic Clear Cell RCC
VHL Gene Mutations



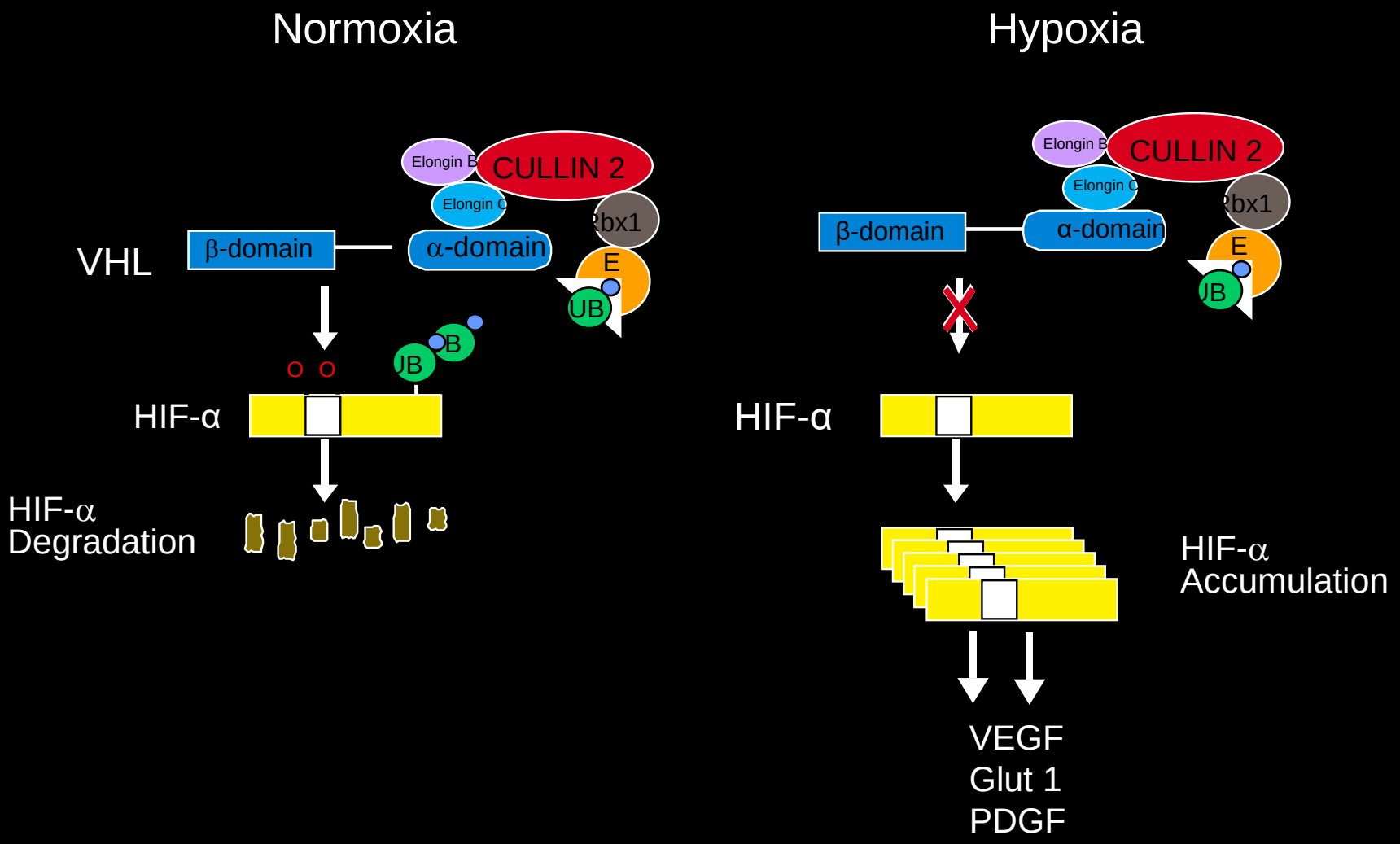


Science 260:1993

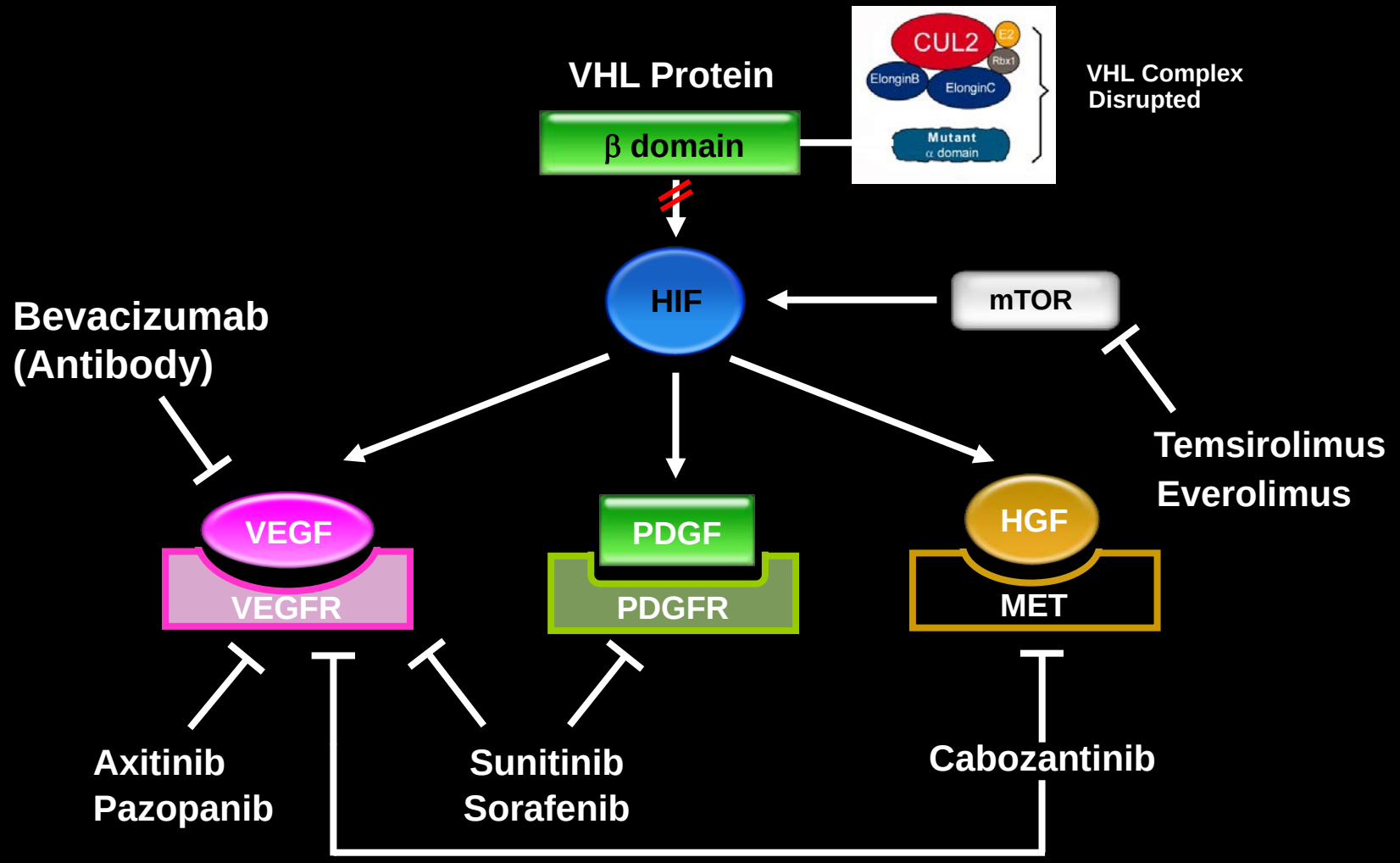
Nature Genetics 7:1994

Clin Cancer Res 14:2008

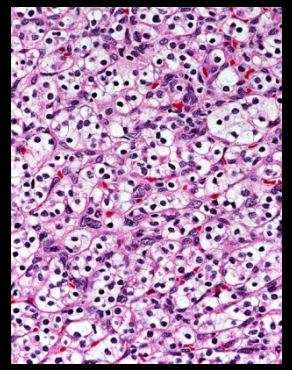
HIFα is targeted for degradation in normoxic, but not hypoxic cells



Targeting the VHL Pathway in Sporadic Clear Cell RCC

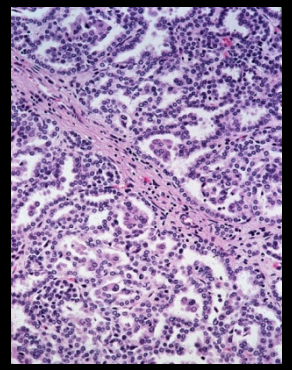


Histologic and Genetic Heterogeneity in Human Renal Epithelial Neoplasms



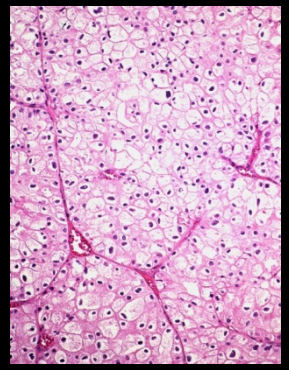
Clear Cell

VHL, BAP1, PBRM1

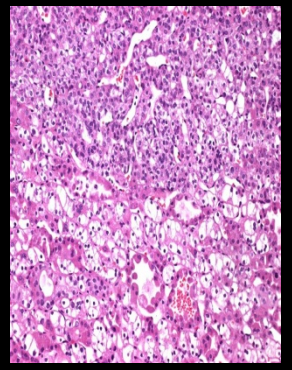


Papillary Type 1

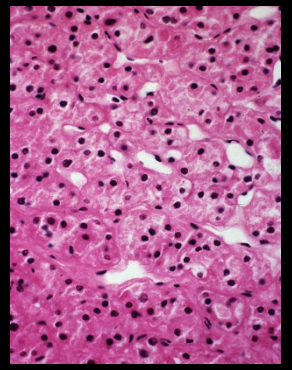
MET



Chromophobe

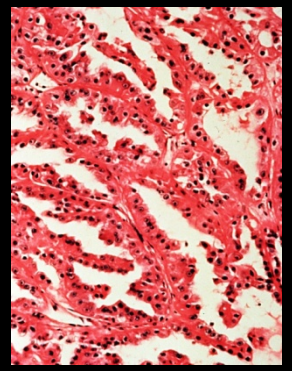


Hybrid



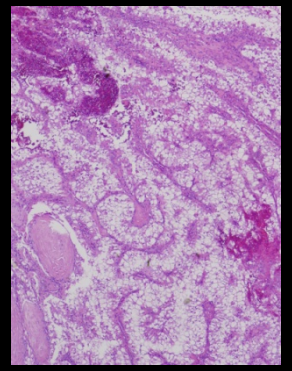
Oncocytoma

FLCN



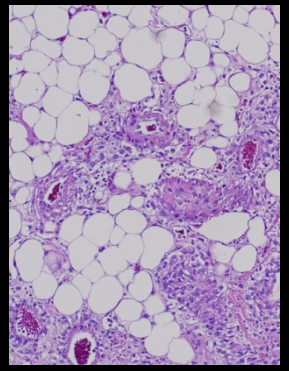
Papillary Type 2

FH



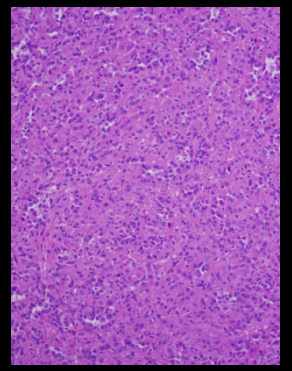
TFE3

TFE3, TFEB, MITF



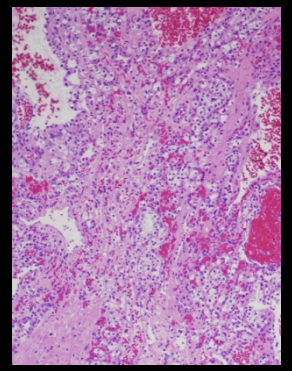
Angiomyolipoma

TSC1, TSC2



Oncocytic

SDHB, SDHC, SDHD



Clear/Chromophobe

PTEN

Genetic Alterations: Germline versus Somatic

- **Germline Alteration**
  - Identified by testing in blood cells, buccal mucosa etc
  - Affects one allele in cells throughout the body
  - Inherited (patients are born with these changes)
  - Can be transmitted to offspring, usually in an autosomal dominant manner
  - Cancer predisposition
- **Somatic Alteration**
  - Identified by testing tumor
  - Alterations restricted to the tumor
  - Not inherited

Who Should Undergo Germline Testing?

- **Guidelines: e.g. American College of Medical Genetics and Genomics**
- **Factors to consider while referring for genetic evaluation**
  - Presence of bilateral, multifocal tumors
  - Young age at diagnosis (generally < 50 years)
  - Histology- papillary type 1 and 2, collecting duct, tubulopapillary etc
  - Presence of other clinical features associated with herediatry RCC (e.g. multiple cutaneous leiomyomas)
  - Strong family history
- **Patients should be assessed/counseled by a genetic counselor**

I Have a Germline Mutation: Will I Get Kidney Cancer?

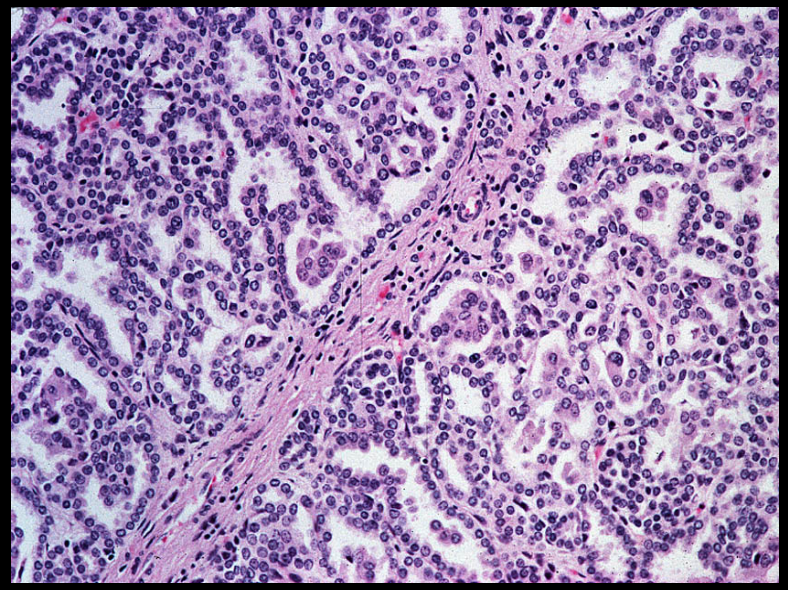
- Depends on the specific gene affected
- *MET* mutations highly penetrant
  - Almost all affected individuals will develop tumors by age 80
- Fumarate Hydratase Mutations
  - 15-30% of individuals with the mutation will develop kidney cancer
- No reliable way to predict who will develop cancer
  - Lifelong screening recommended for most patients

Identifying Genetic Alterations: How Does it Help?

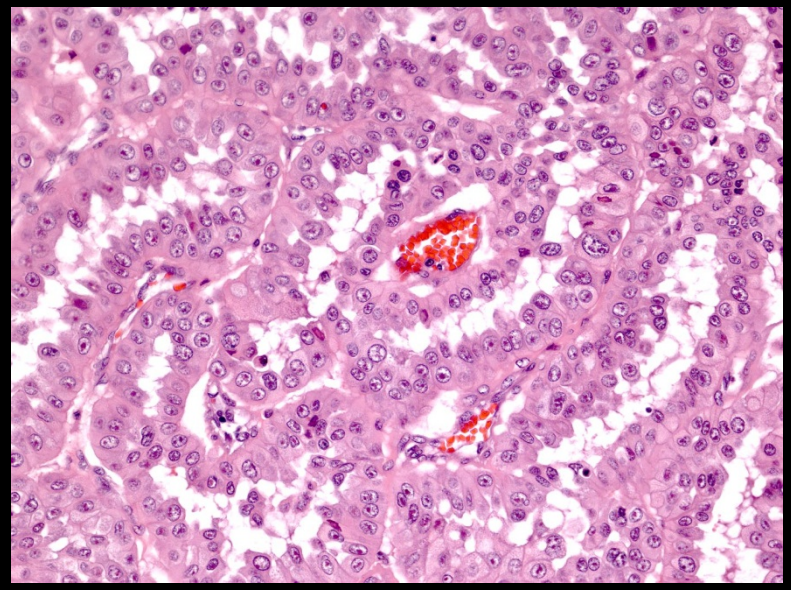
- Identification of specific genetic alterations can
  - Help establish a diagnosis
  - Identify families at risk and enable appropriate screening
  - Dictate choice of treatment
  - ? Serve as a prognostic factor

Can my Genes Help Guide Therapy?

Papillary RCC: Histologic Subtypes

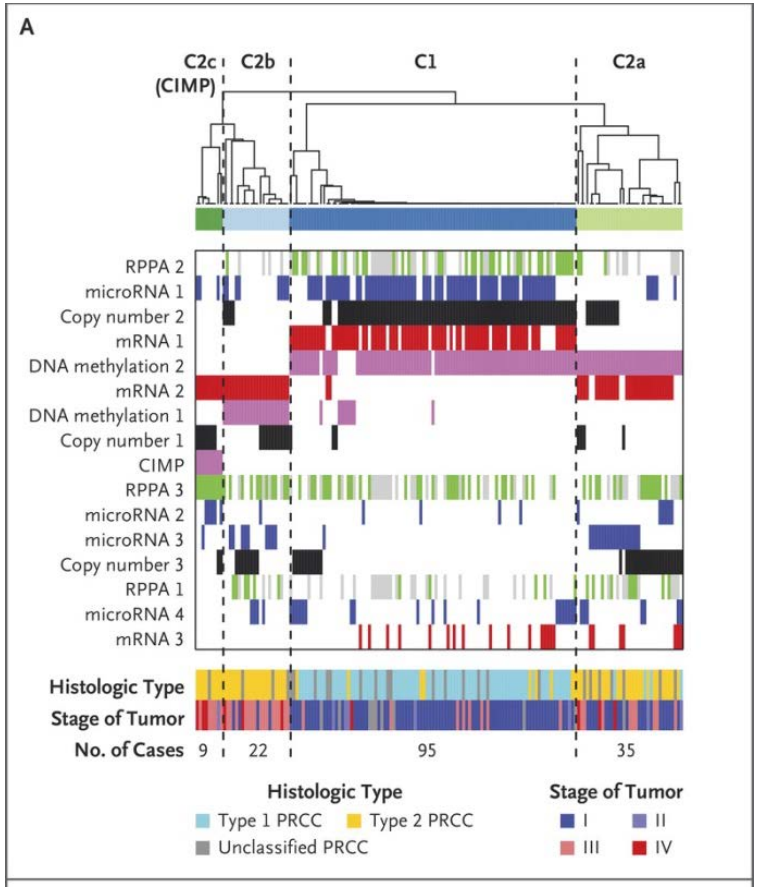


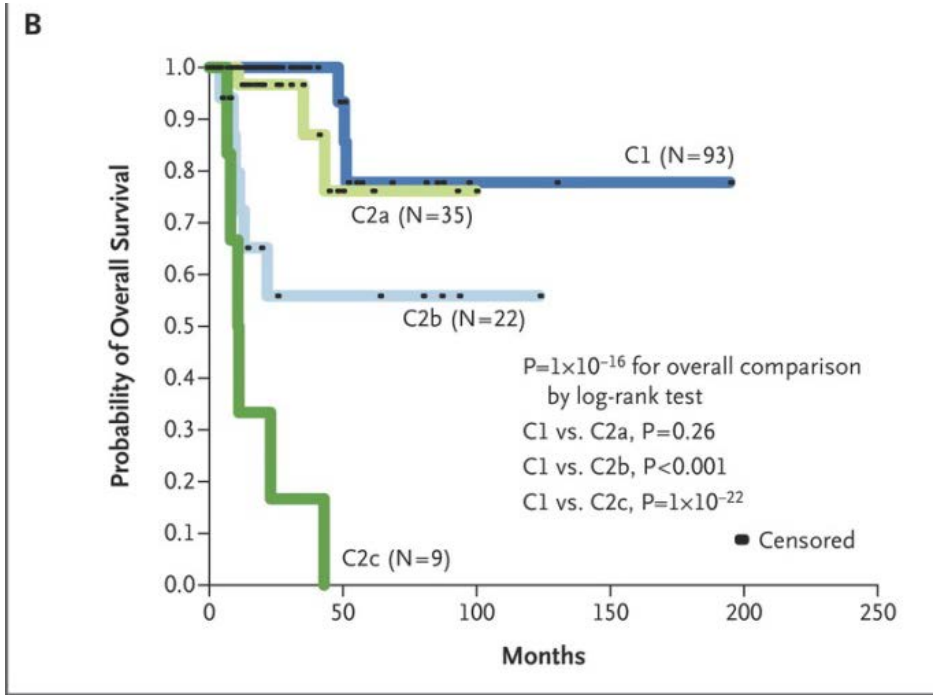
Type 1



Type 2 (Non Type 1)

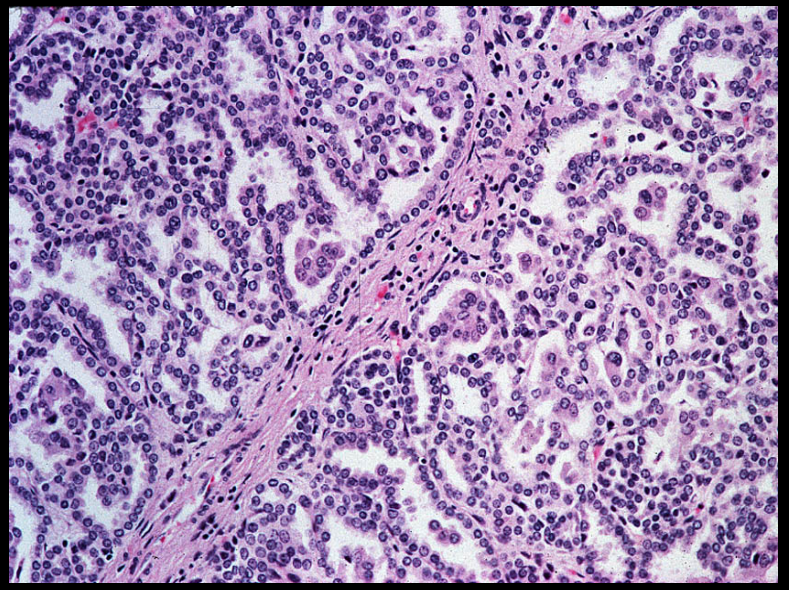
TCGA: Genetic Profiling of Papillary RCC: 4 Distinct Subgroups

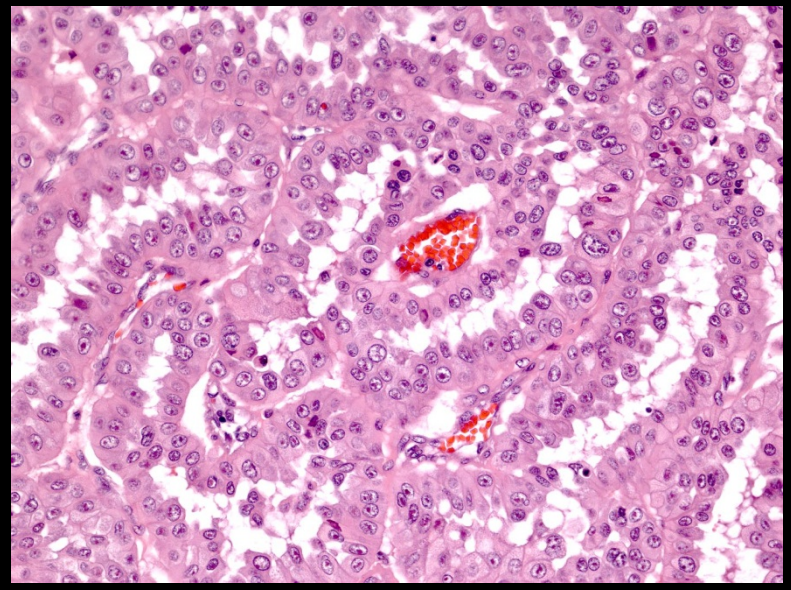




NEJM 2016

Papillary RCC: Histologic Subtypes





Type 1

MET
TERT Promoter
EGFR
CDKN2A/B

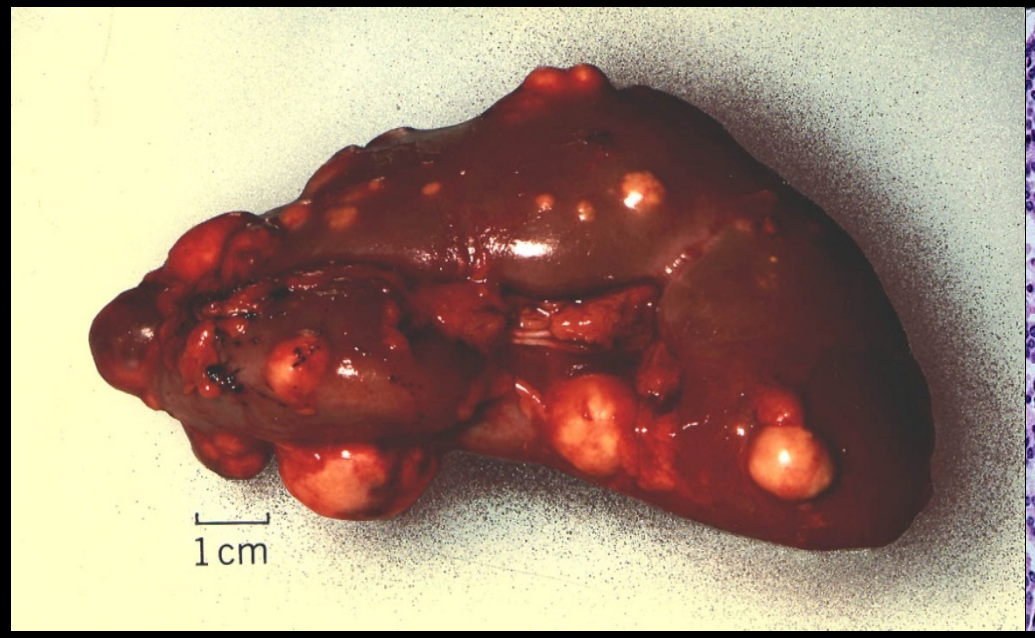
Type 2 (Non Type 1)

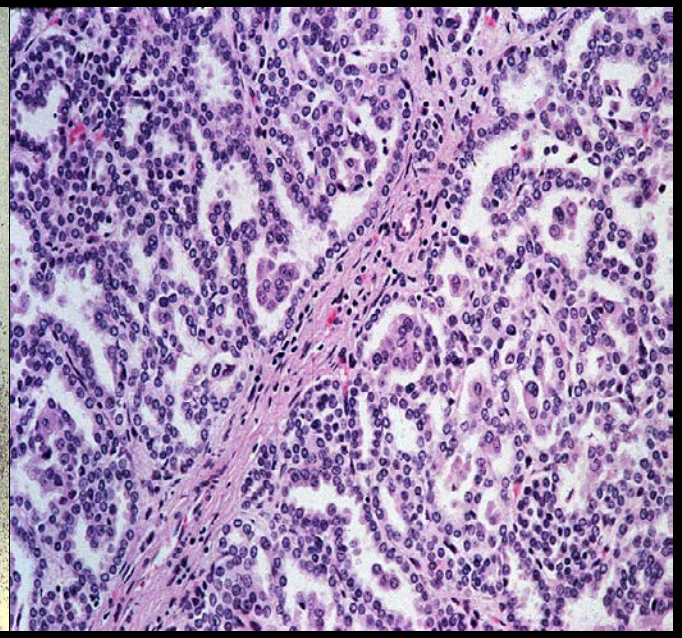
Fumarate Hydratase
NRF2 Pathway
CDKN2A/B
SWI/SNF, Chromatin Remodeling

Hereditary Papillary Renal Cancer (HPRC)

- Familial form of type I papillary RCC

- Affected individuals present with bilateral multifocal papillary RCC

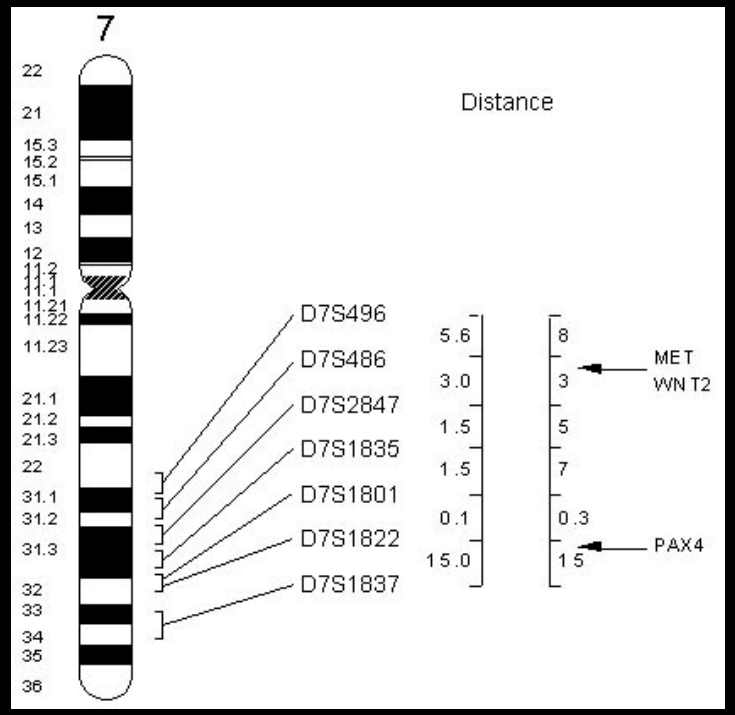




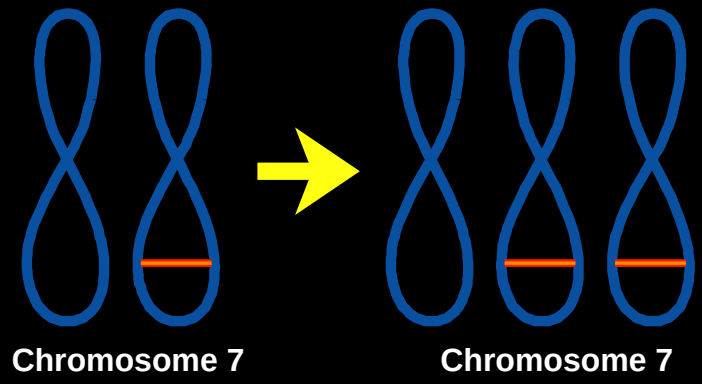
MET- The Gene for Hereditary Papillary Renal Cancer

Germline mutations in *MET* are the hallmark of HPRC

Location of *MET* on chromosome 7



Nonrandom duplication of chromosome bearing mutated *MET* allele



Schmidt et al., Nat Genetics, 1997

Met ‘Activation’ in Sporadic Papillary RCC

- **Activating Mutations in *MET***
  - Somatic activating mutations seen in ~10% of sporadic papillary RCC
  - *MET* fusion or splice variants~ 5-7%
- **Gain of chromosome 7**
  - ~ 80% of type 1 papillary RCC
  - Both *MET* and its activating ligand *HGF* located on Ch 7
- **Focal Amplification relatively rare**
- **MET and Ch7 alterations seen predominantly in type 1 papillary RCC (TCGA)**

Nat Genet 1997; Am J Path 1999; Clin Can Res 2014;TCGA, NEJM 2015; Nat Genet 2015;

VOLUME 31 · NUMBER 2 · JANUARY 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II and Biomarker Study of the Dual MET/VEGFR2 Inhibitor Foretinib in Patients With Papillary Renal Cell Carcinoma

Toni K. Choueiri, Ulka Vaishampayan, Jonathan E. Rosenberg, Theodore F. Logan, Andrea L. Harzstark, Ronald M. Bukowski, Brian I. Rini, Sandy Srinivas, Mark N. Stein, Laurel M. Adams, Lone H. Ottesen, Kevin H. Laubscher, Laurie Sherman, David F. McDermott, Naomi B. Haas, Keith T. Flaherty, Robert Ross, Peter Eisenberg, Paul S. Meltzer, Maria J. Merino, Donald P. Bottaro, W. Marston Linehan, and Ramaprasad Srinivasan

Primary Endpoint: Overall Response Rate

	Dosing Cohort A (n=37)	Dosing Cohort B (n=37)	TOTAL (N=74)
Overall Response Rate	5 (13.5%)	5 (13.5%)	10 (13.5%)

- Duration of response: 18.5 months
- Median PFS: 9.3 months

JCO2013

Germline *MET* Mutations Associated with High Response Rate

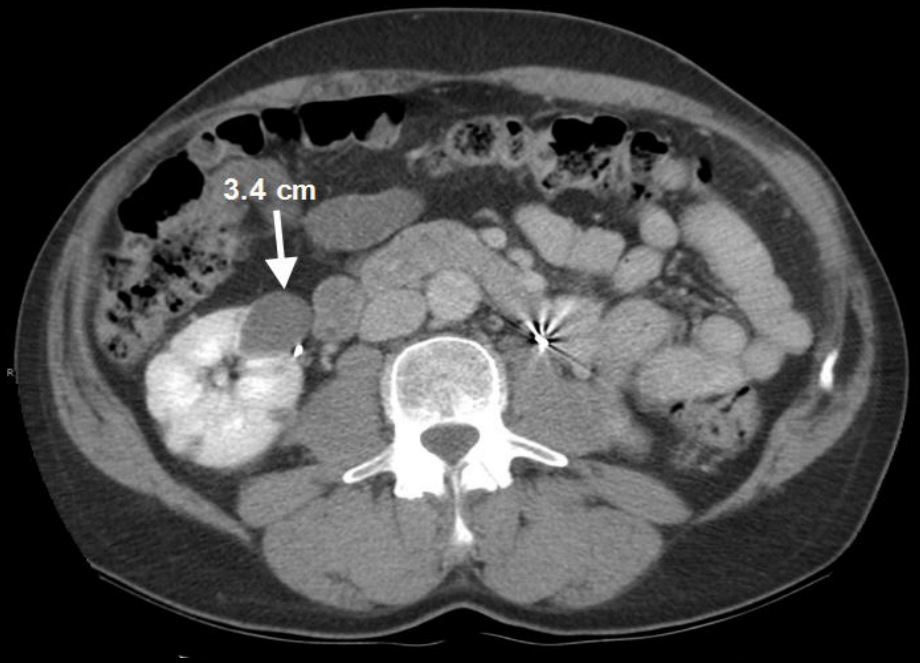
N=67 evaluable:

- **Germline *MET* mutation (N=10)**
  - **Mutated *MET:***
    - **5/10 PR (50%)**
    - **5 SD (4 with >10% reduction in SLD of tumors)**
  - **WT MET:**
    - **5/57 (9%)**

- **Other *MET* alterations**
  - ***MET* amplification (N=2):** **No responses**
  - **Gain chromosome 7 (N=18):** **ORR 5%**

JCO2013

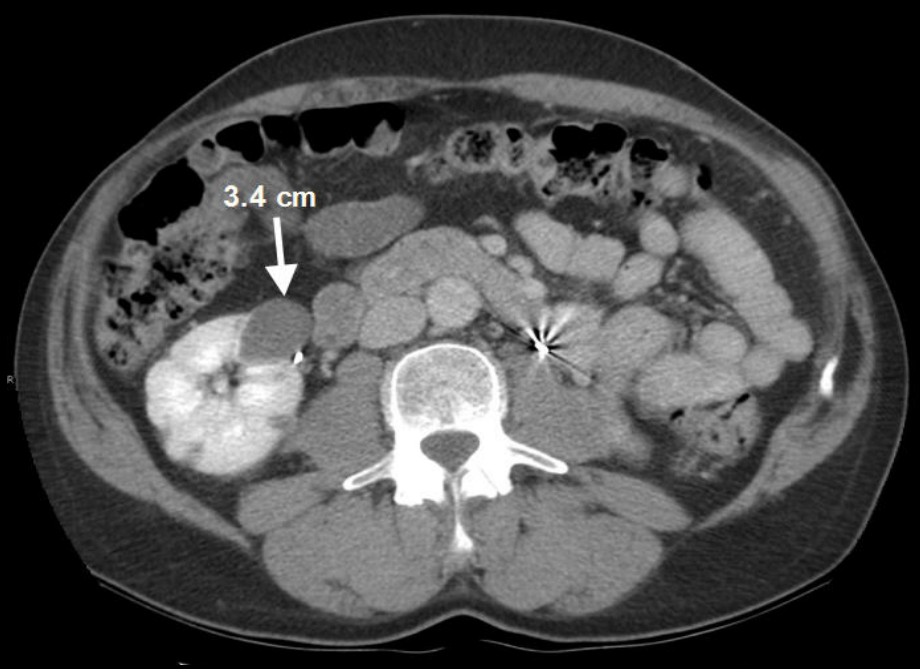
Regression of a renal tumor in a patient with HPRC treated with Foretinib



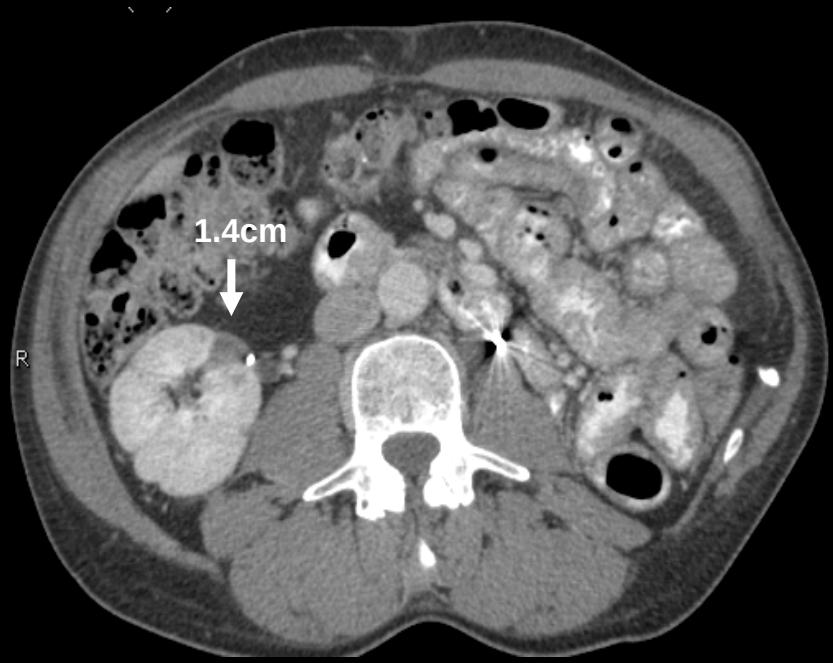
Pre-Treatment

Srinivasan, et al ASCO 2009

Regression of a Renal Tumor in a Patient with HPRC Treated with Foretinib



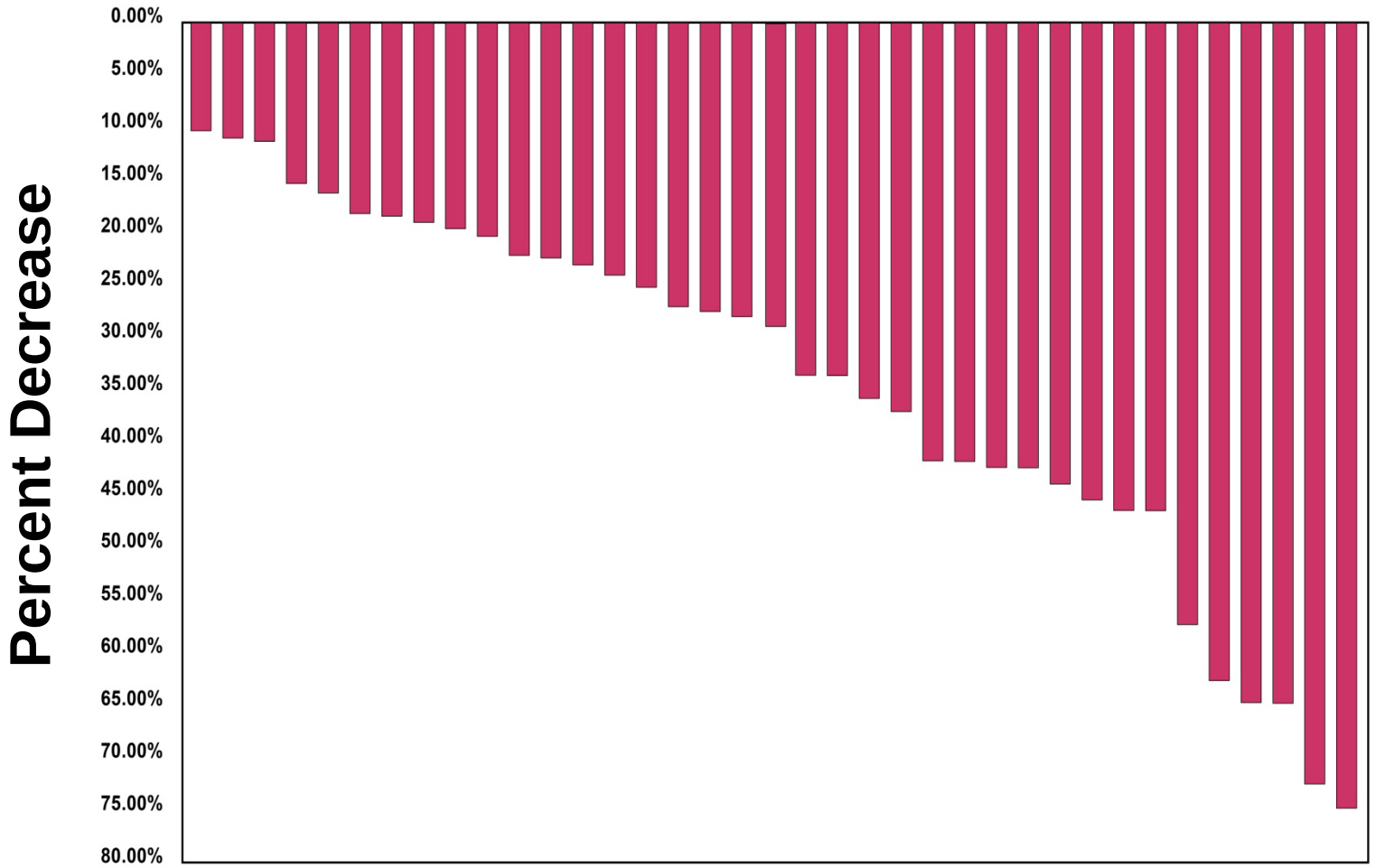
Pre-Treatment



Following 49 cycles of therapy

Srinivasan, et al ASCO 2009

Targeted Lesions in Patients with Germline *MET* Mutations



VOLUME 35 · NUMBER 26 · SEPTEMBER 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Biomarker-Based Phase II Trial of Savolitinib in Patients With Advanced Papillary Renal Cell Cancer

Toni K. Choueiri, Elizabeth Plimack, Hendrik-Tobias Arkenau, Eric Jonasch, Daniel Y.C. Heng, Thomas Powles, Melanie M. Frigault, Edwin A. Clark, Amir A. Handzel, Humphrey Gardner, Shethah Morgan, Laurence Albiges, and Sumanta Kumar Pal

European Journal of Cancer 87 (2017) 147–163

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Crizotinib achieves long-lasting disease control in advanced papillary renal-cell carcinoma type 1 patients with *MET* mutations or amplification. EORTC 90101 CREATE trial☆

Patrick Schöffski [a,b,*], Agnieszka Wozniak [b], Bernard Escudier [c],

Impact of Met Status on Efficacy

	Foretinib (N=74)	Crizotinib (N=23)	Savolitinib (N=109)
Histology	All papillary	Type 1 Papillary	All Papillary
Stratification by Met Status (Post Hoc)	Yes	Yes	Yes
Stratification Criteria	Met Mutation	Met TK Mutation	Met TK Mutation Chromosome 7 Gain Focal Met amplification
Number MET + Number MET-	10 57	4 16	44 46
ORR MET+ MET-	 50% 9%	 50% 6%	 18% 0%
PFS (Median) MET+ MET-	NA	? 3	6.2 1.4

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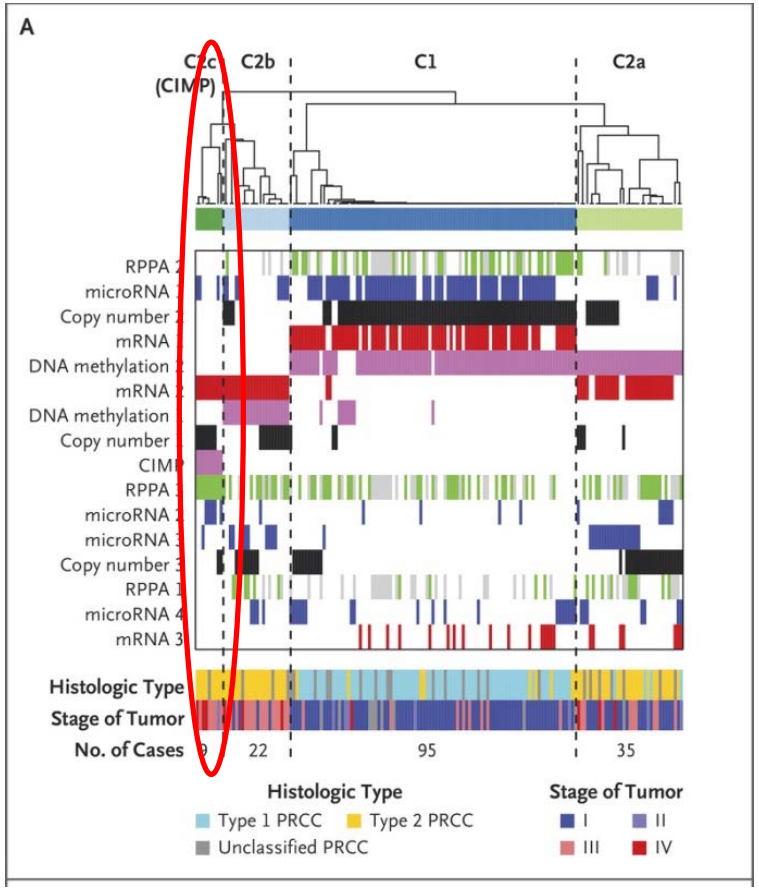
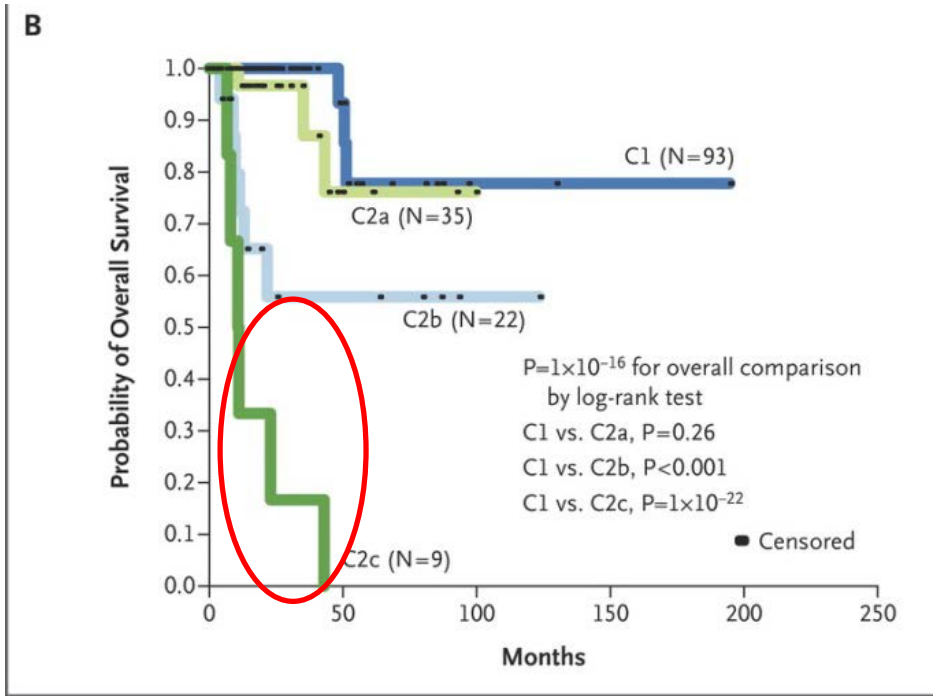
Comparable to VEGFR TKIs (Historical)

Hereditary Leiomyomatosis Renal Cell Carcinoma: HLRCC

- Cutaneous leiomyomas
- Uterine leiomyomas (fibroids)
- Renal cell carcinoma (Type 2 papillary RCC)

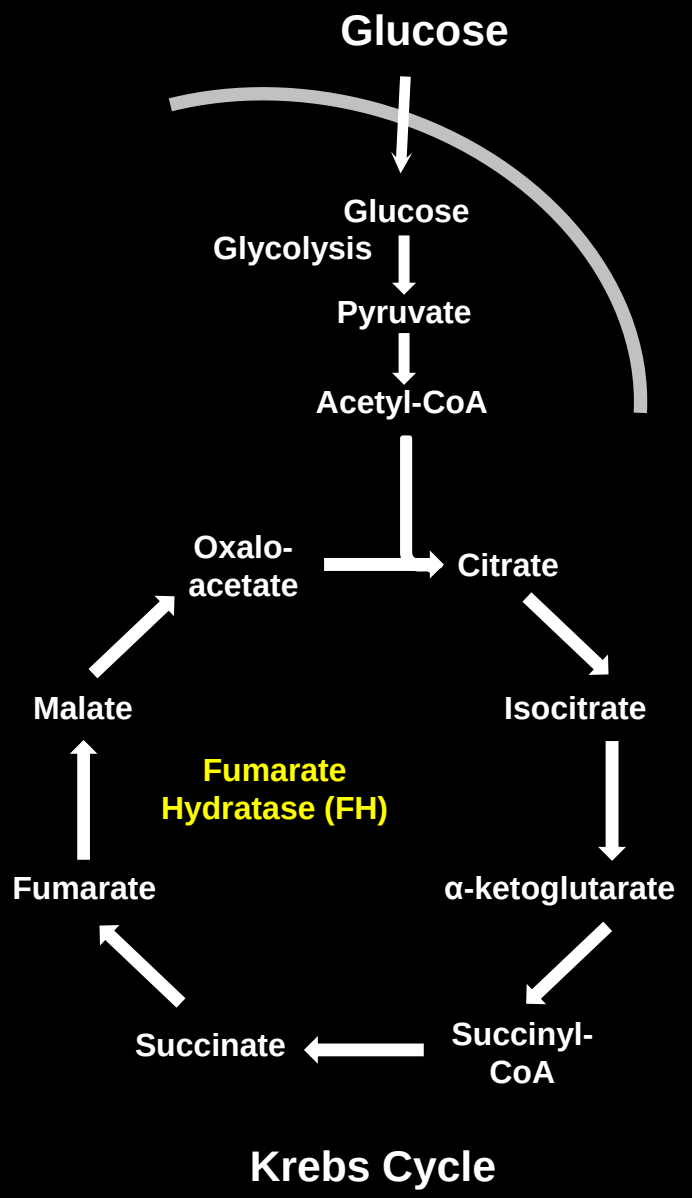
TCGA: Genetic Profiling of Papillary RCC: HLRCC Associated with Poor Prognosis





NEJM 2016

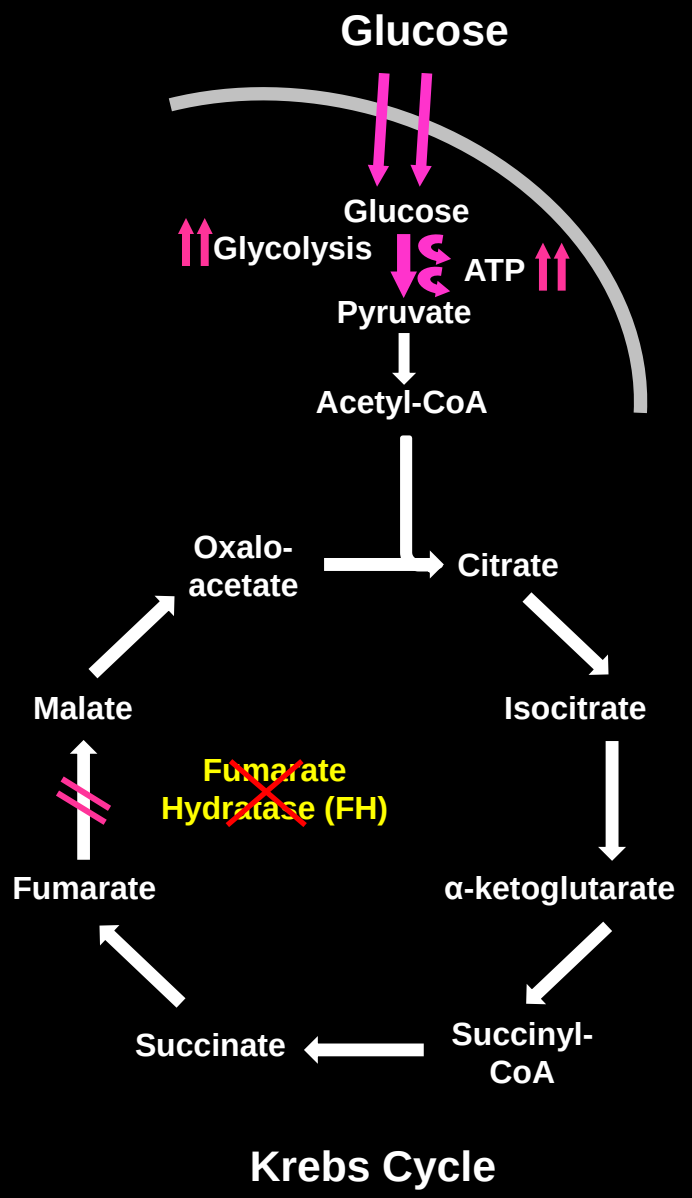
Fumarate Hydratase: HLRCC Kidney Cancer



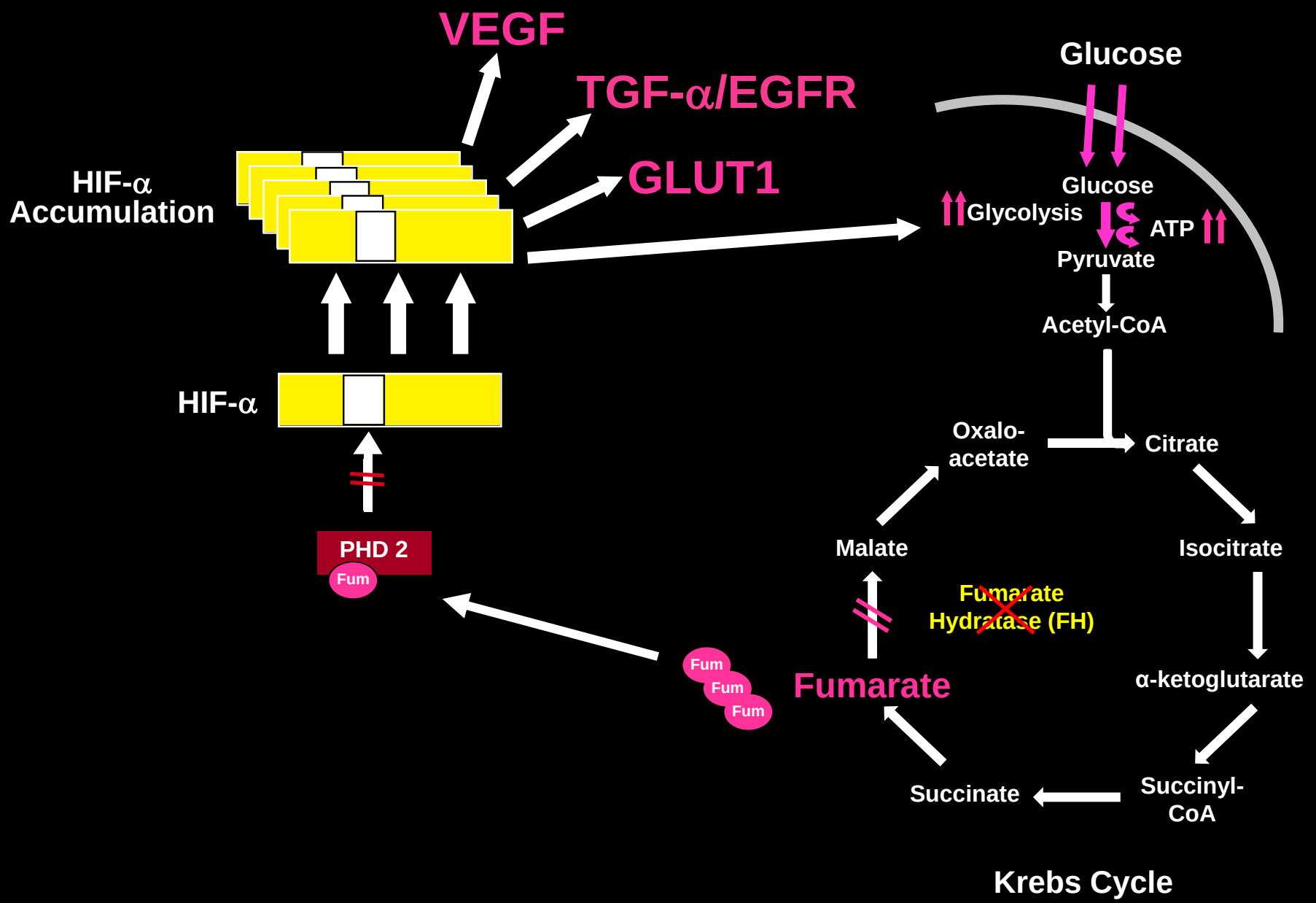
Krebs Cycle

Isaacs, Cancer Cell, 2005
Tong, Cancer Cell, 2011

Fumarate Hydratase: HLRCC Kidney Cancer



Cancer Cell, 2005
Cancer Cell, 2011



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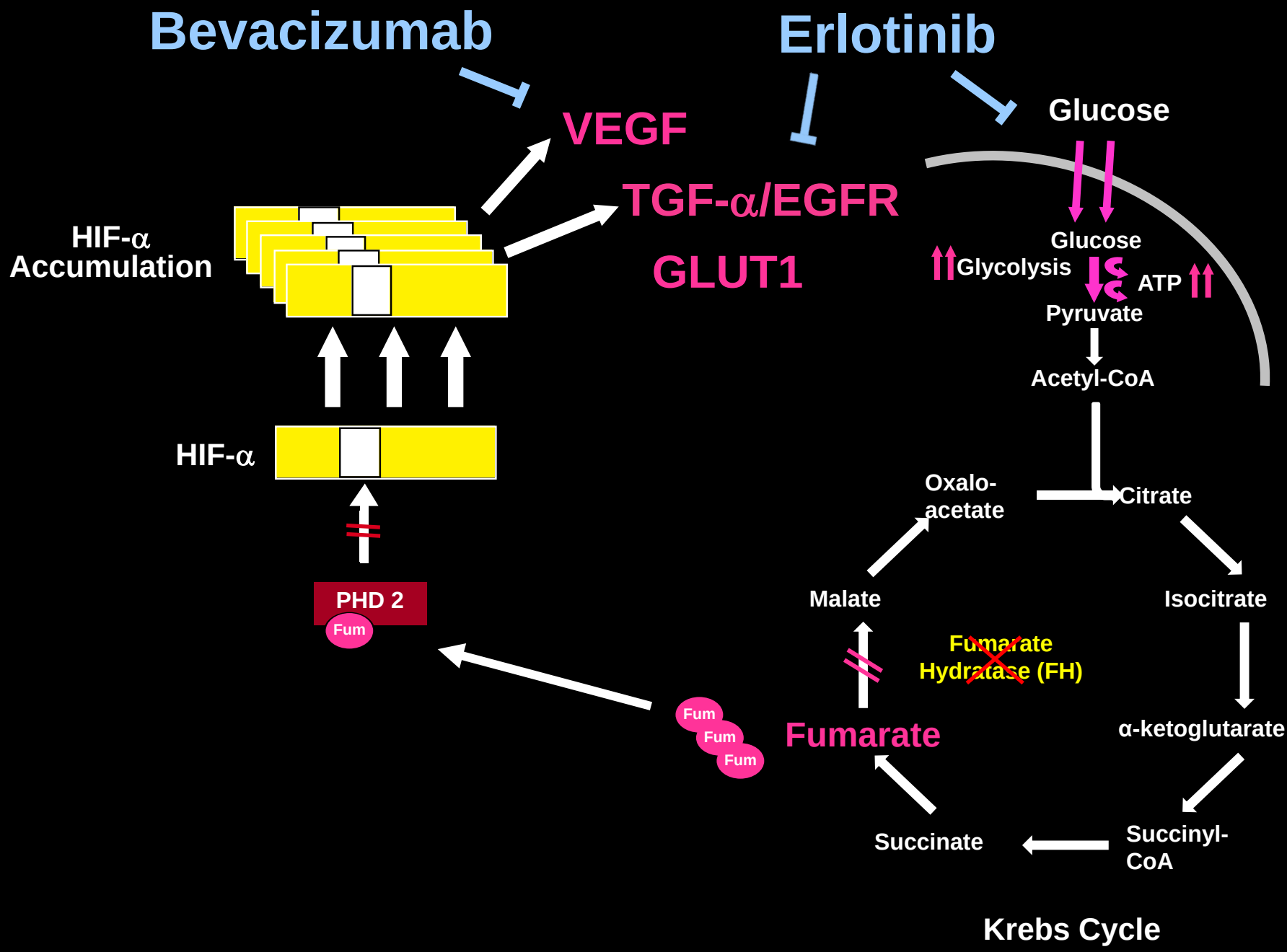
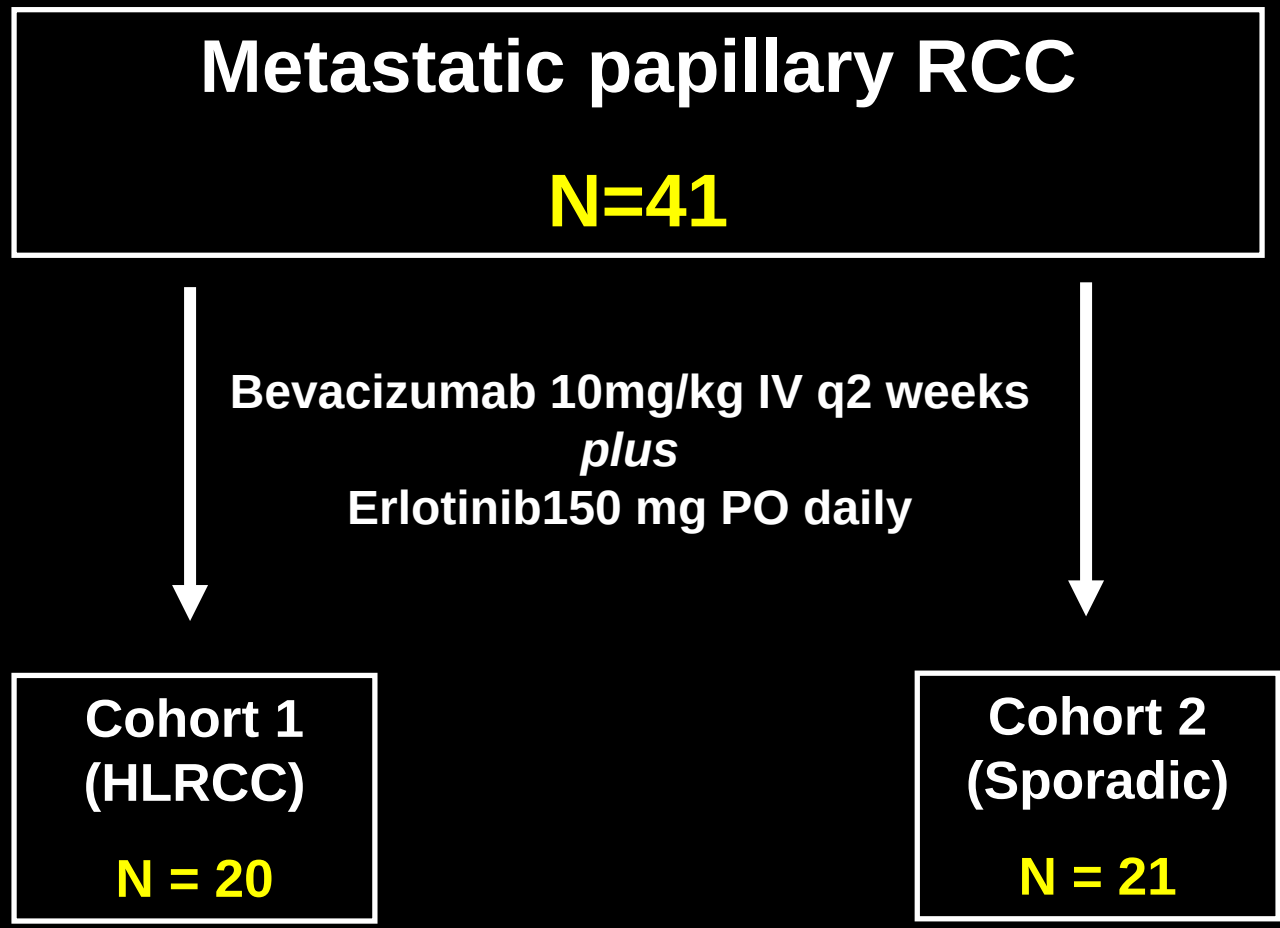

Bevacizumab
Erlotinib
VEGF
TGF-α/EGFR
GLUT1
HIF-α Accumulation
HIF-α
PHD 2
Fum
Glucose
Glucose
Glycolysis
ATP
Pyruvate
Acetyl-CoA
Oxalo-acetate
Citrate
Isocitrate
α-ketoglutarate
Succinyl-CoA
Succinate
Fumarate
Malate
Fumarate Hydratase (FH)
Fum
Fum
Fum
Krebs Cycle

Study Design



Patient Demographics

	Cohort 1 [HLRCC]	Cohort 2 [Sporadic]	Total
Number of Patients	20	21	41
Median Age (range), years	46 (22 – 63)	55 (35 – 73)	52 (22 – 73)
Gender (%)			
Male	11 (55%)	15 (71%)	26 (63%)
Female	9 (45%)	6 (29%)	15 (37%)
MSKCC Risk Groups			
Favorable	5	1	6 (15%)
Intermediate	12	17	29 (70%)
Poor	3	3	6 (15%)
Prior Systemic Therapy			
No	14	9	23 (56%)
Yes	6	12	18 (44%)

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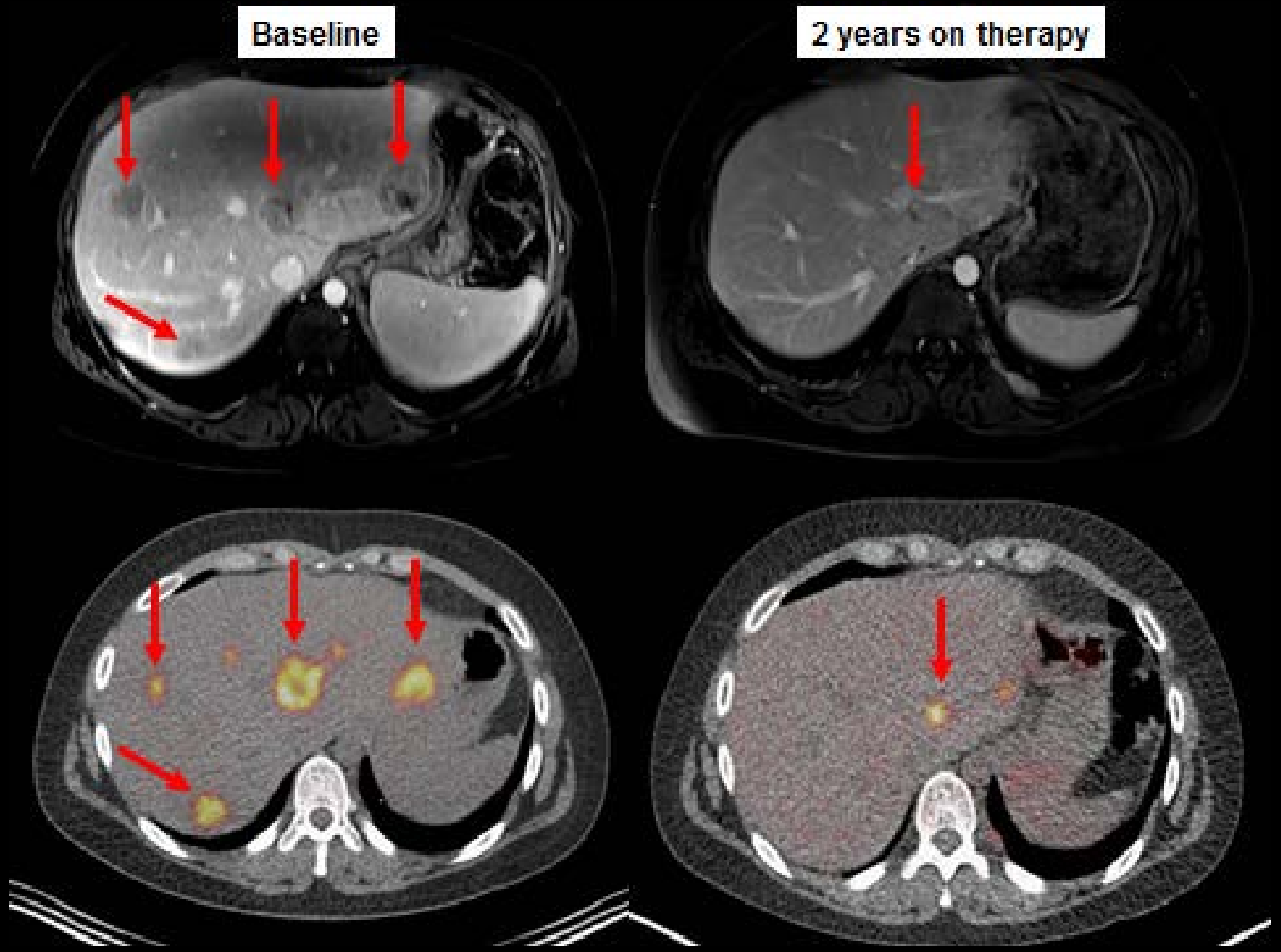
Median Age (range), years	46 (22 – 63)	55 (35 – 73)	52 (22 – 73)
Gender (%)			
Male	11 (55%)	15 (71%)	26 (63%)
Female	9 (45%)	6 (29%)	15 (37%)
MSKCC Risk Groups			
Favorable	5	1	6 (15%)
Intermediate	12	17	29 (70%)
Poor	3	3	6 (15%)
Prior Systemic Therapy			
No	14	9	23 (56%)
Yes	6	12	18 (44%)

Bevacizumab plus Erlotinib in Papillary RCC - Efficacy

Best Response by RECIST	Cohort 1 [HLRCC] (%) N=20	Cohort 2 [Sporadic] (%) N=21	Total (%)
Confirmed Partial Response (PR)	13 (65%)	6 (29%)	19 (46%)
Overall Response Rate	65%	29%	46%
Stable disease (SD)	7 (35%)	13 (62%)	20 (49%)
Disease Control Rate (SD+PR)	100%	91%	95%

36 Year Old Woman with HLRCC Associated Papillary RCC



Summary

- The term kidney cancer encompasses several different subtypes
- Individual subtypes are characterized by distinct genetic, clinical and histologic features
- Understanding genetic alterations is
  - Critical to the development of tailored treatment options
  - Increasingly becoming an integral part of the management of kidney cancer

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