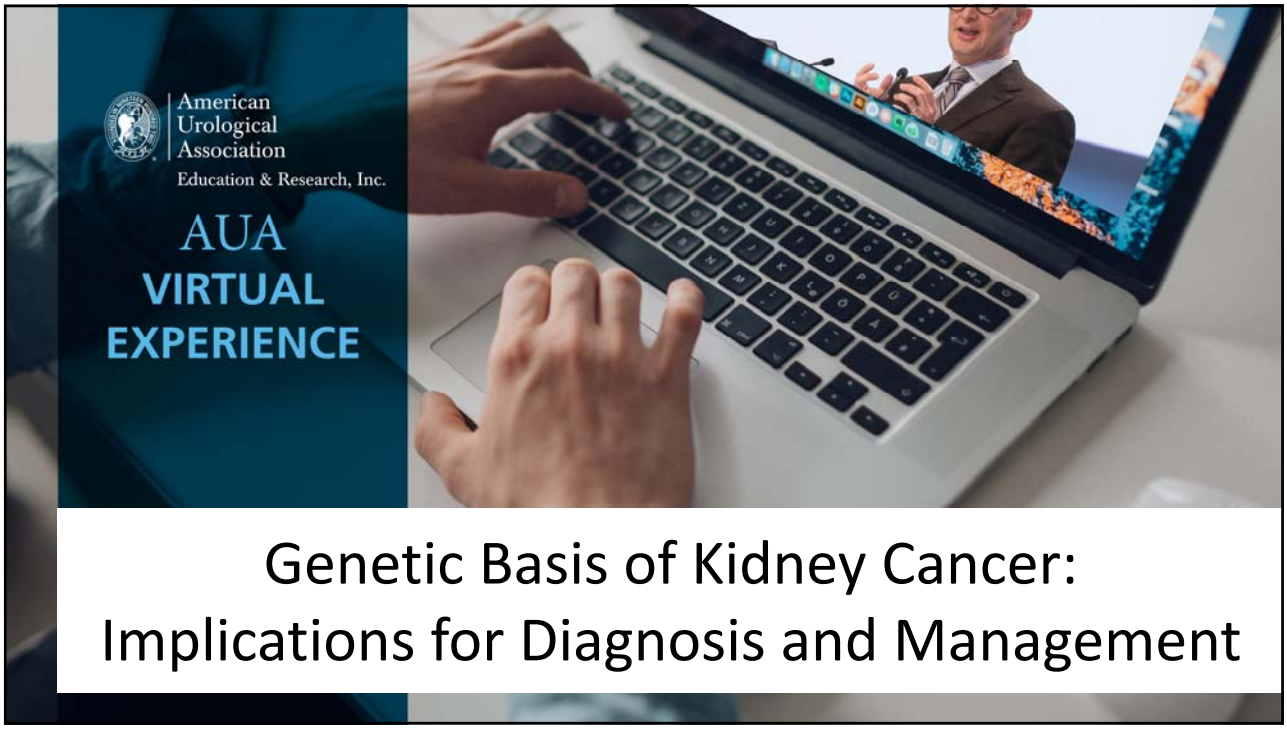


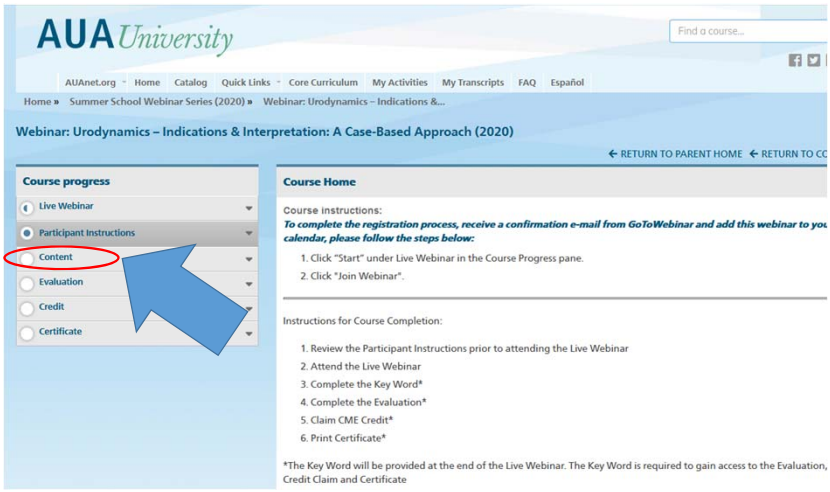
American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

Accreditation: The American Urological Association (AUA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation: The American Urological Association designates this internet live activity for a maximum of 1.50 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Course Handouts



1. Take Course
2. Course Progress/Content
3. Download PDF

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Course Evaluations & CME Credits

Evaluations: Course evaluations will be administered electronically on AUA*University* at the end of this program. These are very important and read carefully by faculty members and are used for our ongoing needs assessment in selecting core subjects and faculty for future meetings.

CME Credits: Upon completion of course evaluations, you will have the opportunity to claim CME credits and obtain a certificate.

AUA Disclosure Policy

All persons in a position to control the content of an educational activity (i.e., activity planners, presenters, authors) are required to disclose to the provider any relevant financial relationships with any commercial interest. The AUA must determine if the individual's relationships may influence the educational content and resolve any conflicts of interest prior to the commencement of the educational activity. The intent of this disclosure is not to prevent individuals with relevant financial relationships from participating, but rather to provide learners information with which they can make their own judgments.

- AUA Office of Education Staff has nothing to disclose.
- Visit AUA*University* to view Faculty and Education Council disclosures.

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

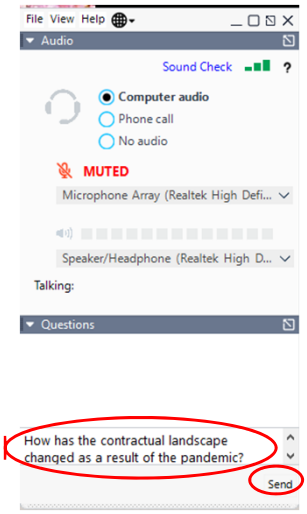
Coding Advice

- Coding advice given during presentations are the opinions of the presenters and may not have been vetted through the AUA for accuracy.
- Verify accuracy prior to reporting on medical claims.

American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

We Need YOU To Actively Participate!



Submit Questions for Faculty or AUA Staff

Acknowledgments

This educational activity is supported by independent educational grants from:

Astellas

AstraZeneca

Bristol-Myers Squibb

Genentech

Merck

Pfizer, Inc.

Sanofi Genzyme

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Course Director

W. Marston Linehan, M.D.

Chief, Urologic Oncology Branch

National Cancer Institute

National Institutes of Health

Course Faculty

Mark Ball, MD
Senior Attending Surgeon
National Cancer Institute

David F. McDermott, MD
Chief Medical Oncology
Leader Kidney Cancer Program
Beth Israel Deaconness/Dana Farber Harvard Cancer Center

Ramaprasad Srinivasan, MD, PhD
Head, Molecular Therapeutics Section
National Cancer Institute

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Learning Objectives

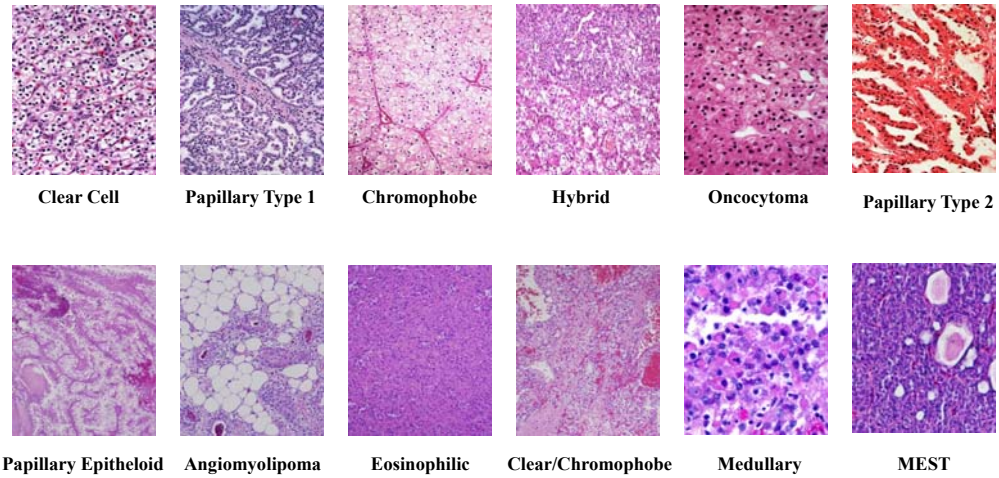
After participating in this course, attendees will be able to:

1. Differentiate among the subtypes of kidney cancer, with emphasis on clinical management decisions and outline ways in which knowledge of kidney cancer subtypes can alter surgical approach.
2. Apply advanced strategies for partial nephrectomy for patients with endophytic, hilar and multiple tumors including role of warm ischemia, intraoperative ultrasound, techniques for hemostatic control, the role of off-clamp and selective hilar clamping, the use of the retroperitoneal approach, and methods for renorrhaphy.
3. Describe techniques for management of large and/or locally advanced tumors including management of renal vein or inferior vena cava invasion and the use of lymphadenectomy.
4. Identify the role of cytoreductive nephrectomy and/or resection of metastatic foci in patients with advanced disease.
5. Describe new and emerging targeted therapy and immuno-oncology options for patients with locally-advanced and advanced kidney cancer and the role of adjuvant therapy.

Knowledge Assessment

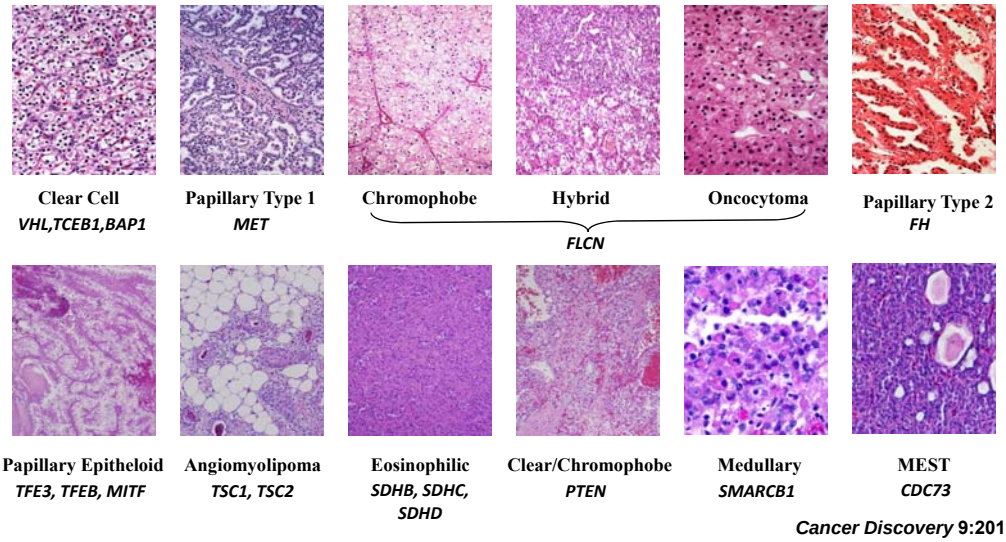
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Kidney Cancer



Cancer Discovery 9:2019

Kidney Cancer Genes



Cancer Discovery 9:2019

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

RCC Genes Guide Management of Localized Disease

- Active surveillance or surgery?
- What type of surgical procedure?
  - Robotic versus Open?
  - Enucleation?
  - Wide margins?

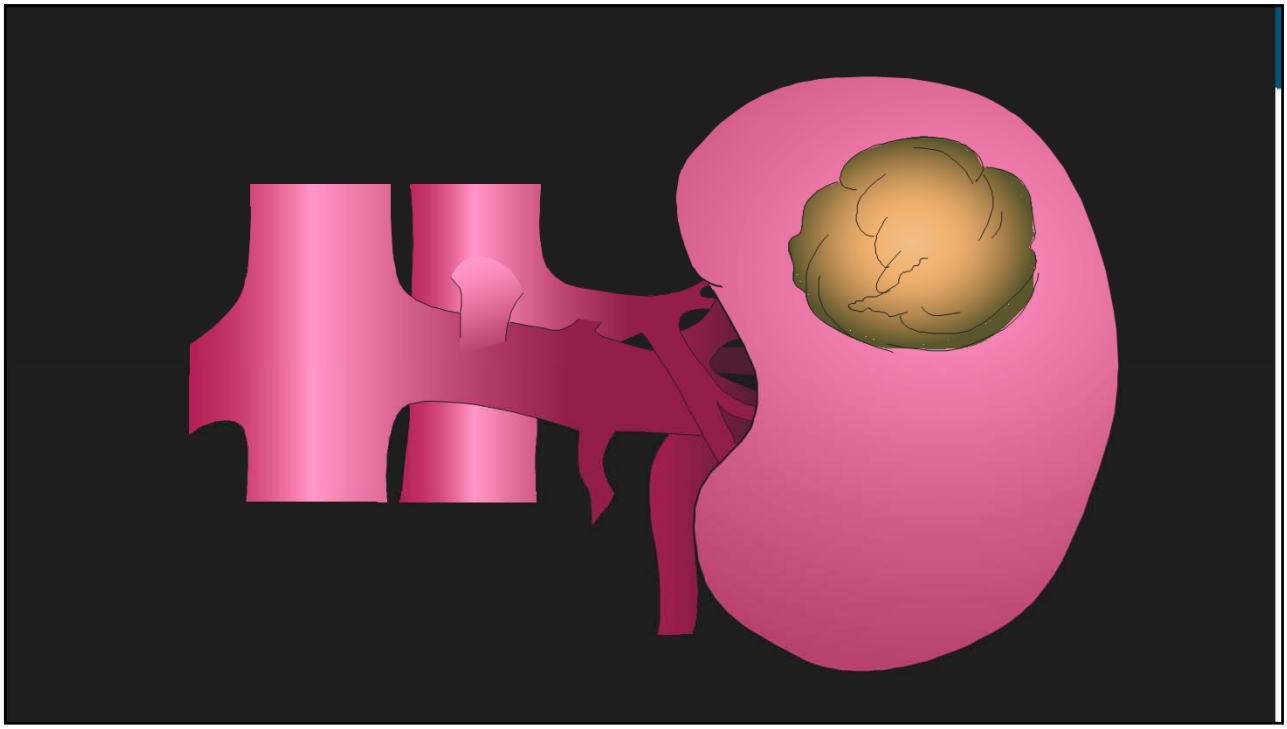
RCC Genes Guide Management of Advanced Disease

- Active surveillance or treatment?
- What types of therapy?
  - Agents targeting the VHL/HIF/VEGF pathway?
  - Agents targeting the MET pathway?
  - Agents targeting PD-1, PDL-1, CTLA4

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Genetically Defined Renal Cell Carcinoma

1. Clear Cell RCC
   - Sporadic Clear Cell RCC
   - Von Hippel Lindau (VHL)
2. Type 1 Papillary RCC
   - Sporadic Type 1 Papillary RCC
   - Hereditary Papillary Renal Carcinoma (HPRC)
3. Type 2 Papillary RCC
   - Sporadic Type 2 RCC
   - Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC)
4. Translocation RCC
   - TFE3/TFEB RCC
   - Hereditary MITF RCC (MITF)



American Urological Association
Education & Research, Inc.

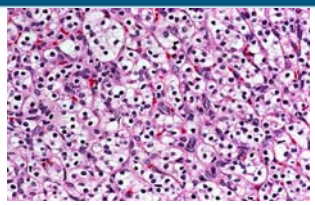
AUA VIRTUAL EXPERIENCE

Nature
Vol. 327, No. 6124, pp 721-727, 25 June 1987

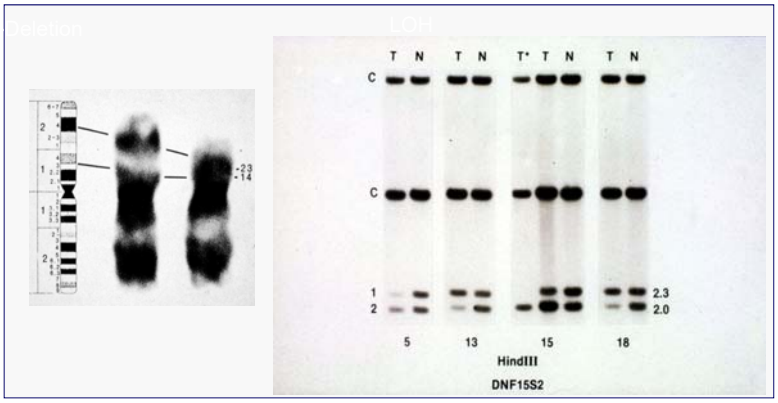
Loss of alleles of loci on the short arm of chromosome 3 in renal cell carcinoma

B. Zbar*, H. Brauch*, C. Talmadge*, & W. M. Linehan†

*Laboratory of Immunobiology, National Cancer Institute- Frederick Cancer Research Facility, Frederick Maryland 21701, USA
†Surgery Branch, National Cancer Institute, Bethesda, Maryland 20892, USA



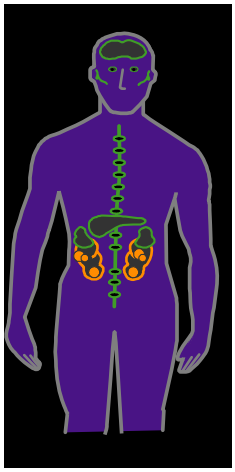
ccRCC



Chromosome 3 Locus DNF15S2

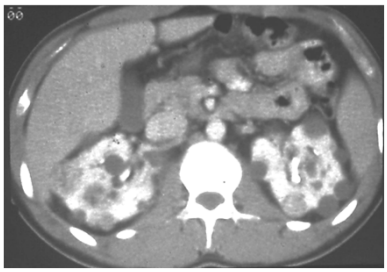
VHL Clinical Features

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



American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

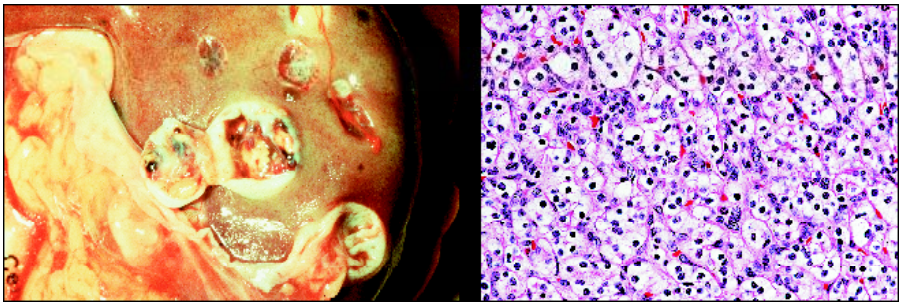
VHL: Renal Cell Carcinoma



CT Scan: Bilateral, Multifocal RCC

VHL Kidney: Multifocal RCC

von Hippel-Lindau (VHL)
Multiple Clear Cell Renal Carcinomas



Multiple Renal Cysts Containing RCC

Clear Cell RCC

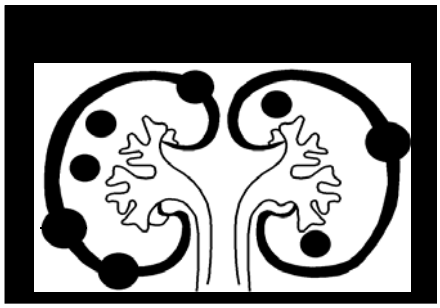
J Urol 153:1995

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

NCI VHL Kindreds N=392

- 783 affected from 413 VHL families have been evaluated
- 649 nephrectomies/partial nephrectomies

Surgical Management of VHL-Associated Renal Carcinoma



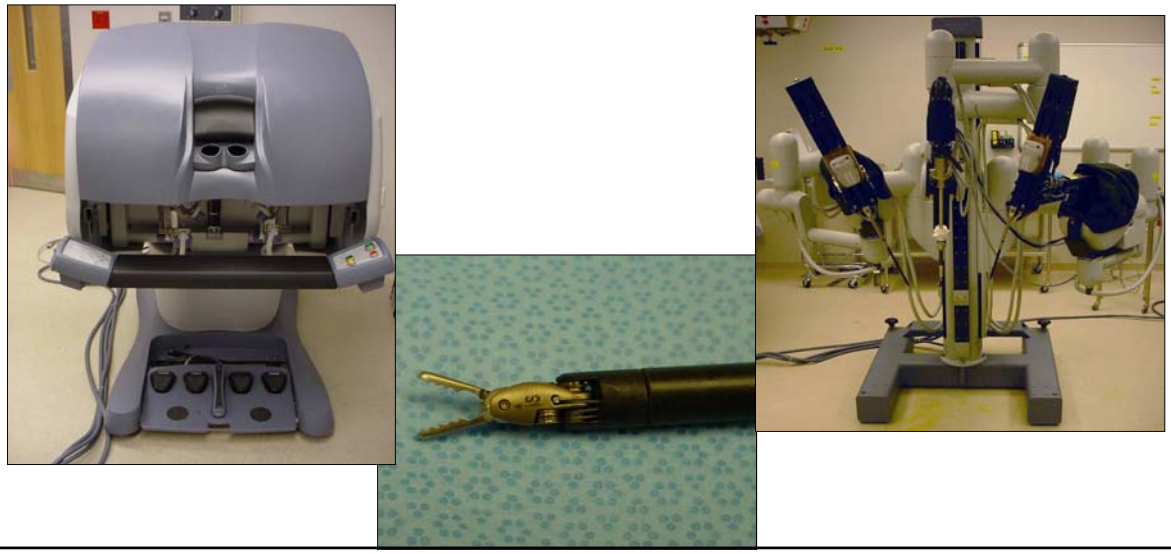
Surgery = nephron sparing enucleation

"3 cm rule"
Delay surgery until diameter of largest renal tumor = 3 cm

Radiology 174: 1990
J Urol: 153:1995
J Urol 165:2001
J Urol 165:2001
J Urol 172:2004
J Urol 173 2005

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

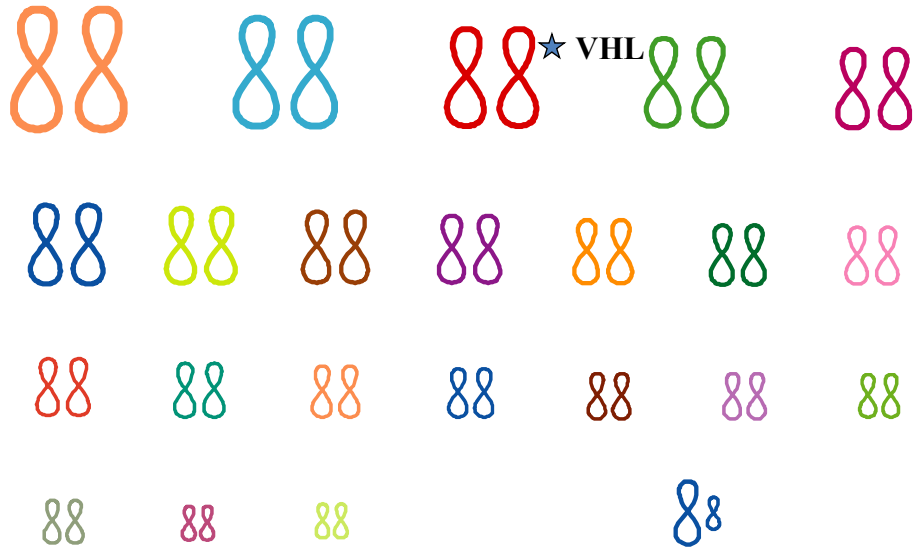
Robotic Assisted Partial Nephrectomy



Robotic Assisted Partial Nephrectomy

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

NIH Clinical Center Hospital



VHL Gene: Clear Cell RCC

American Urological Association Education & Research, Inc.

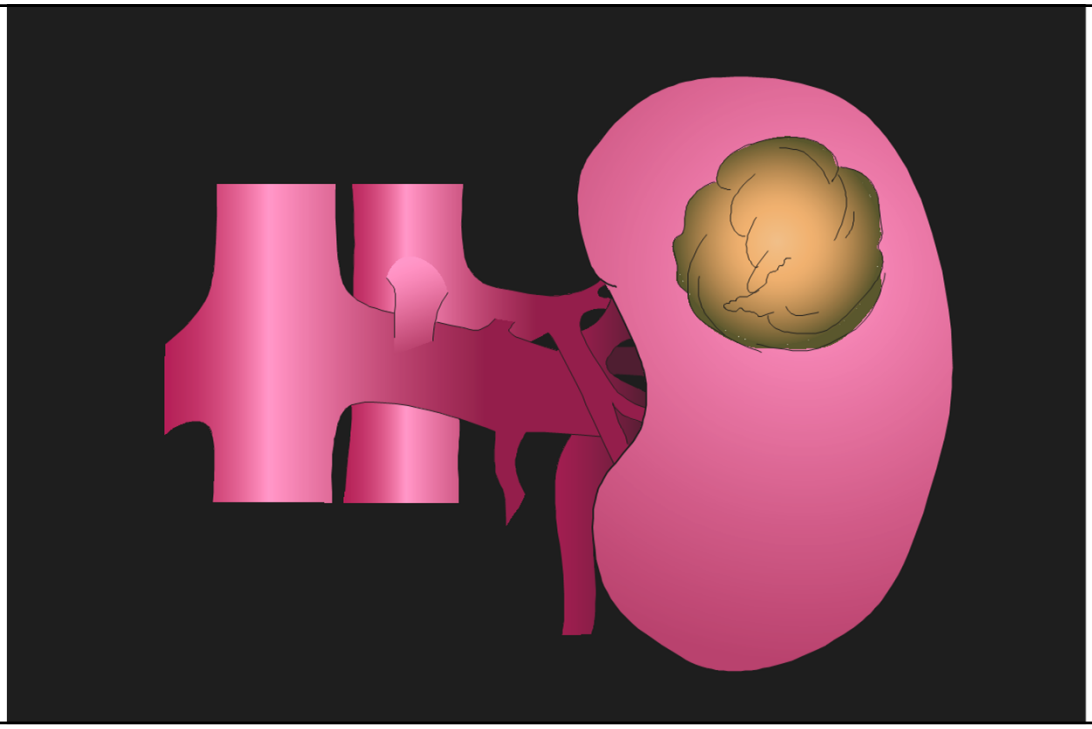
AUA VIRTUAL EXPERIENCE

VHL Gene

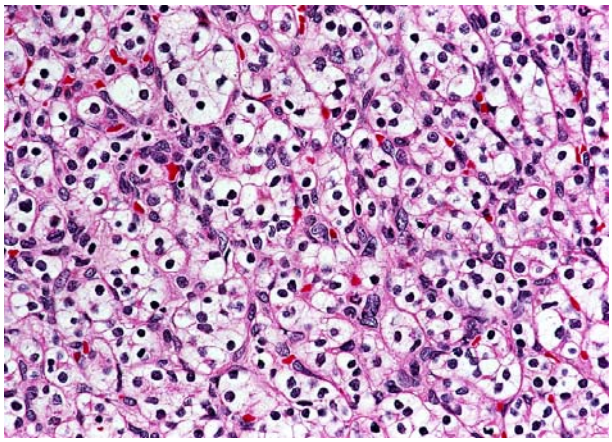
Science 260:1993

Germline *VHL* Gene Mutations

397/397 Families

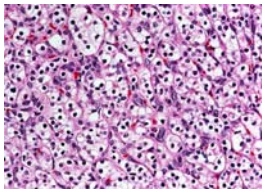


Clear Cell Renal Carcinoma



American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Sporadic Clear Cell RCC
VHL Gene Mutations

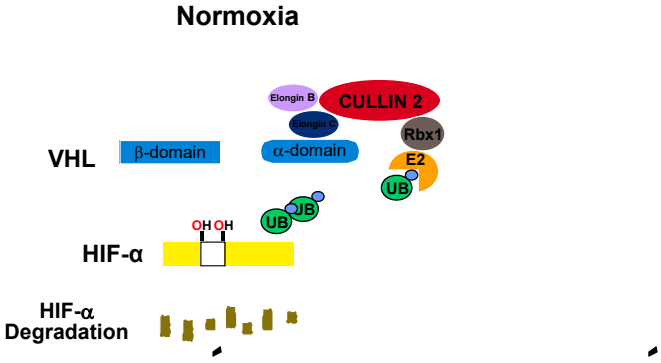


Science 260:1993
Nature 469:2013
Nature Genetics 7:1994

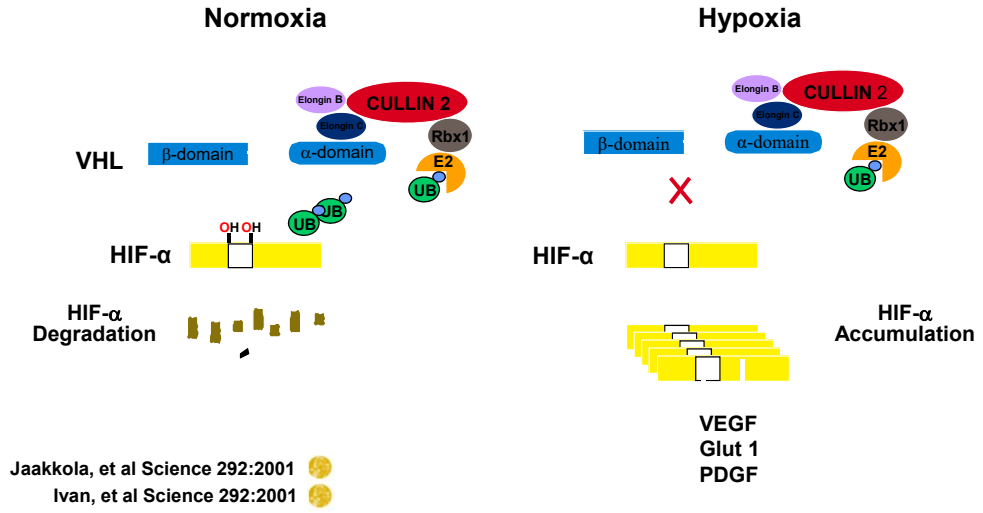
How Does the VHL Gene Function?

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

HIFα is targeted for degradation in normoxic,

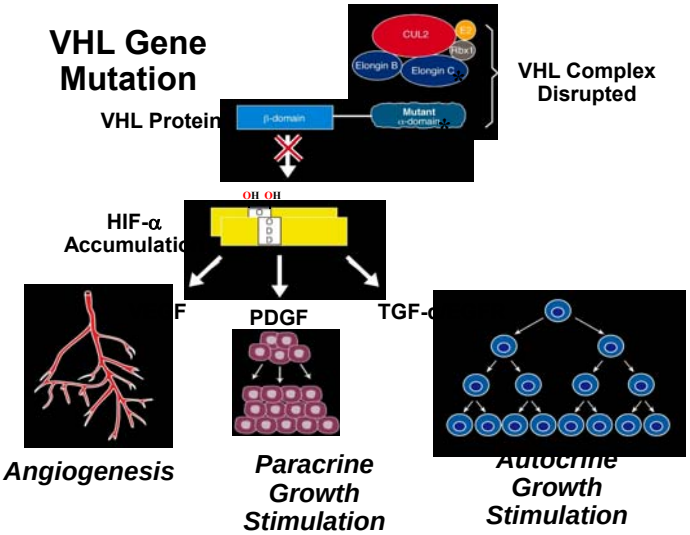


HIFα is targeted for degradation in normoxic, but not hypoxic cells

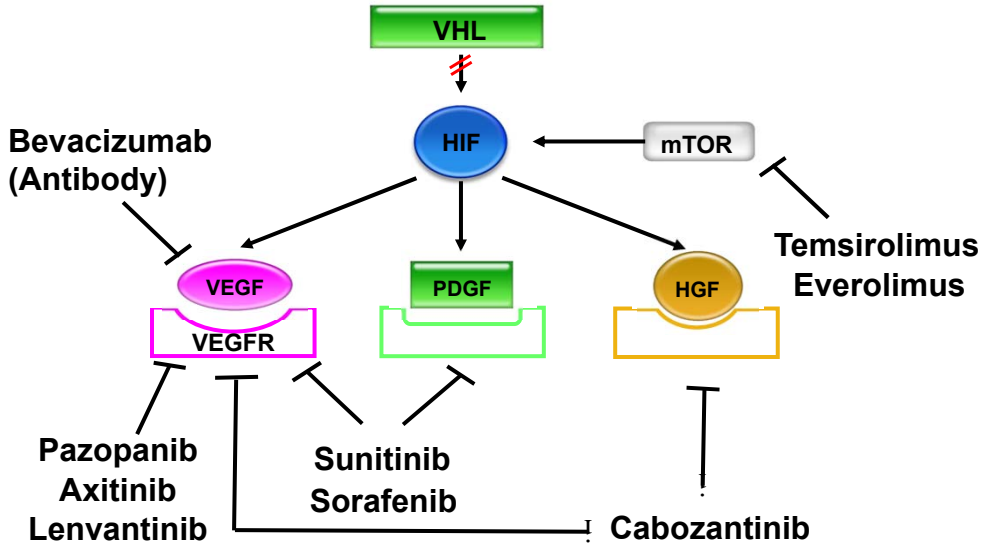


Jaakkola, et al Science 292:2001
Ivan, et al Science 292:2001

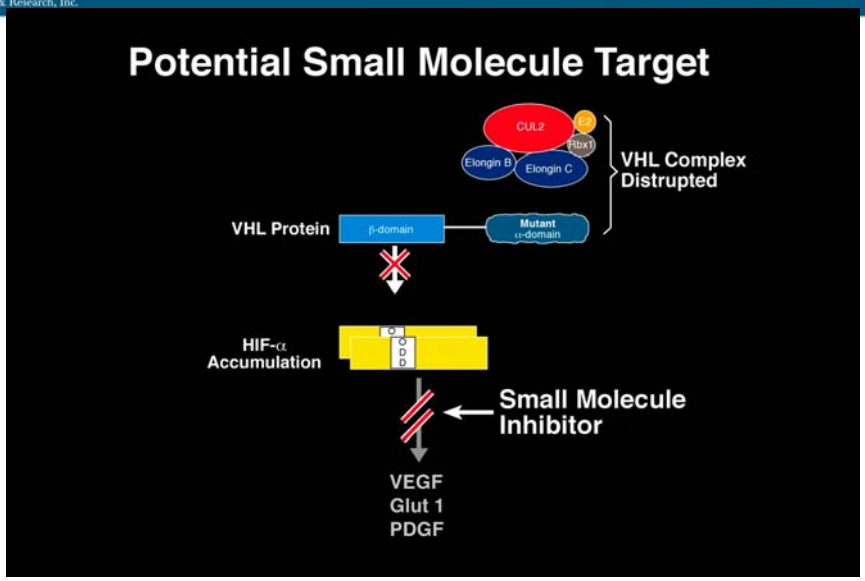
ccRCC: *VHL/TCEB1* mutation



Targeting VHL/HIF in Clear Cell RCC

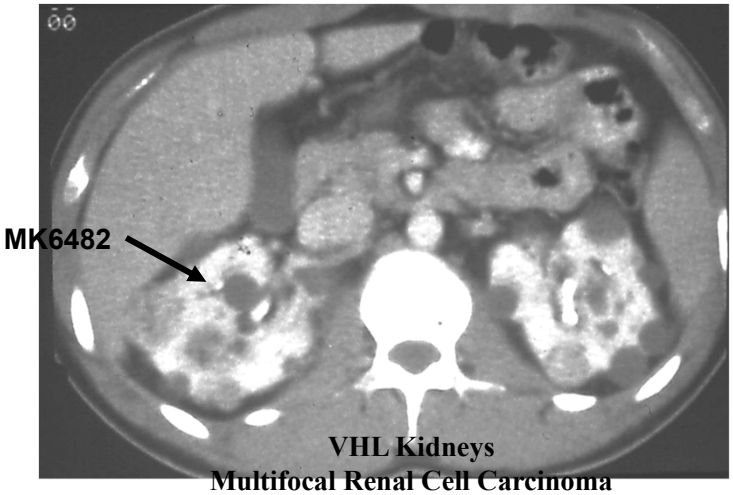


American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE



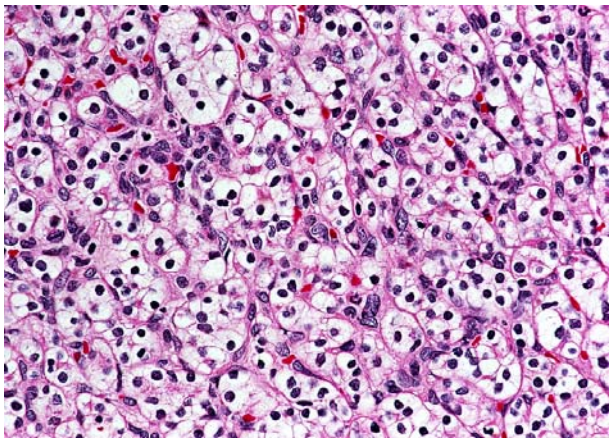
Chen, *et al Nature* 539:2016 Cho, *et al Nature* 539:2016 Scheuermann, *et al Nat Chem Bio* 9:2013

VHL Clinical Trial
MK6482 Targeting HIF2α



VHL Kidneys
Multifocal Renal Cell Carcinoma

Clear Cell Renal Carcinoma



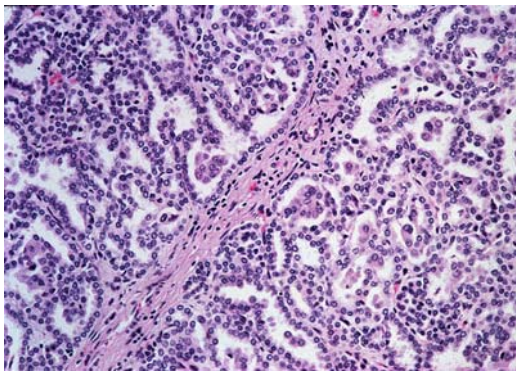
Non-Clear Cell RCC

What possible approaches are there for developing therapeutic approaches for patients with:

1. Type 1 Papillary RCC
2. Type 2 Papillary RCC
3. TFE3 RCC

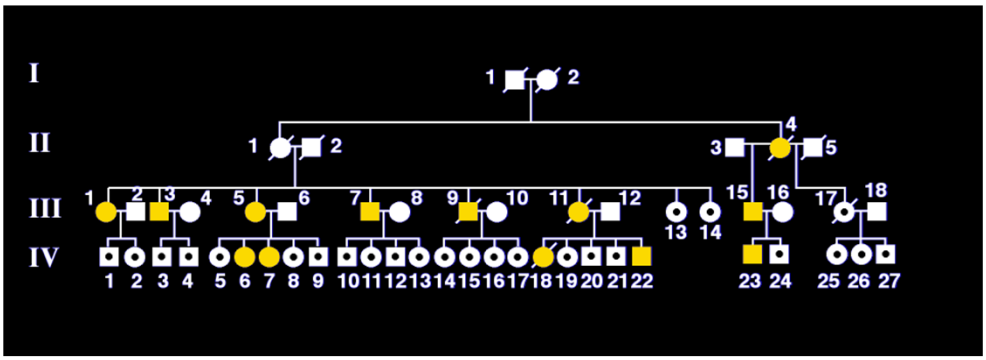
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Papillary Renal Carcinoma



Type 1 Papillary RCC

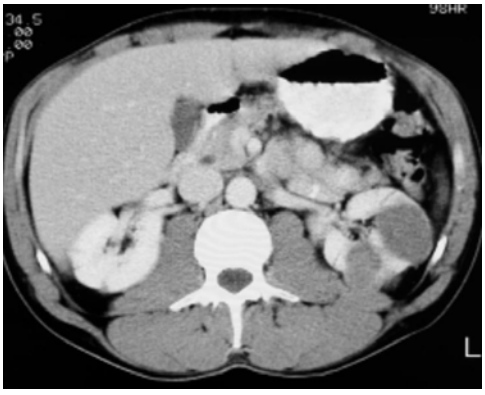
Hereditary Papillary Renal Carcinoma (HPRC)



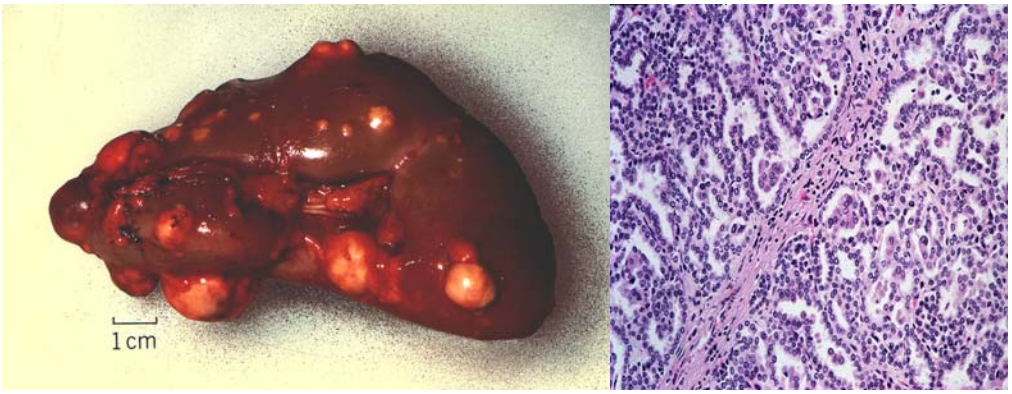
J. Urol 151: 1994
J. Urol 153: 1995

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

HPRC: Renal Tumors

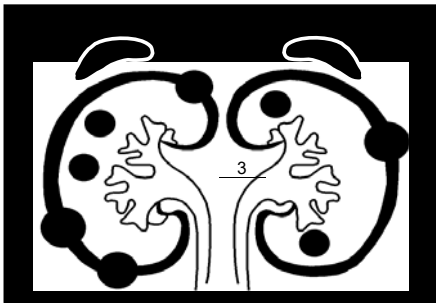


Hereditary Papillary Renal Carcinoma Type 1 papillary renal carcinoma



American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Surgical Management of HPRC-Associated Renal Carcinoma

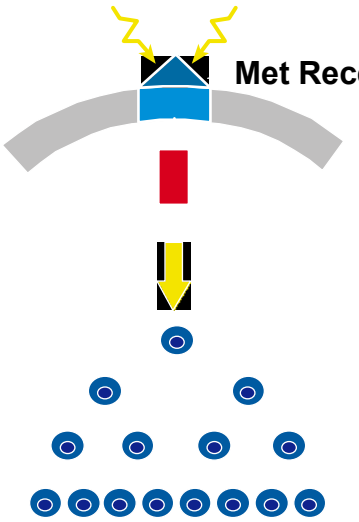


"3 cm rule"
Delay surgery until diameter of largest renal tumor = 3 cm

Surgery = nephron sparing enucleation

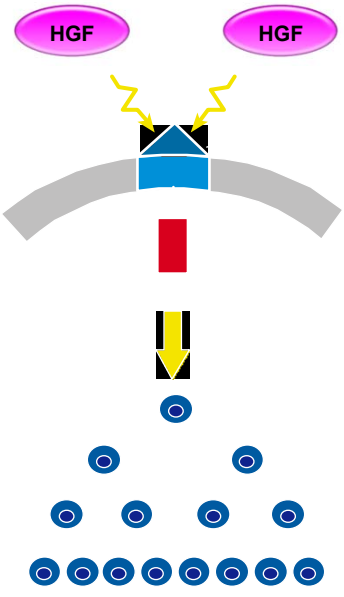
W J Urol 13: 1995
J Urol: 153:1995
J Urol 165:2001
J Urol 165:2001
J Urol 172:2004
J Urol 173 2005

MET is the HPRC Gene



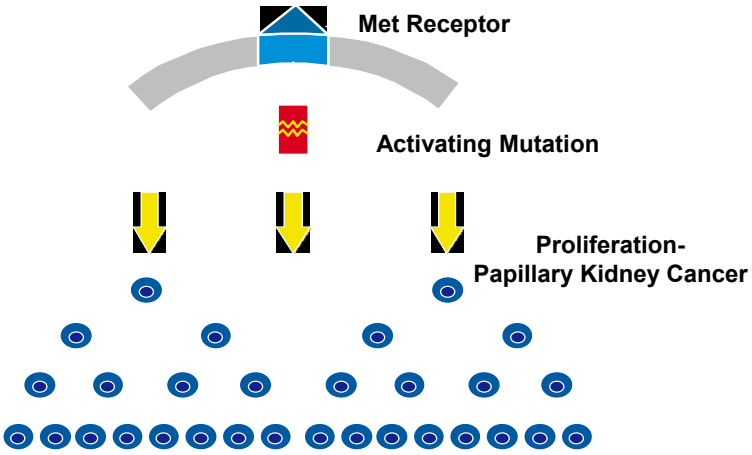
Nature Genetics 16:1997

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE



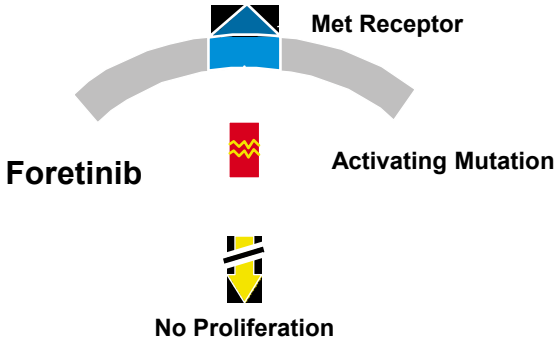
Nature Genetics 16:1997

HPRC: Activating Mutations in the Tyrosine Kinase Domain of *MET*



American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

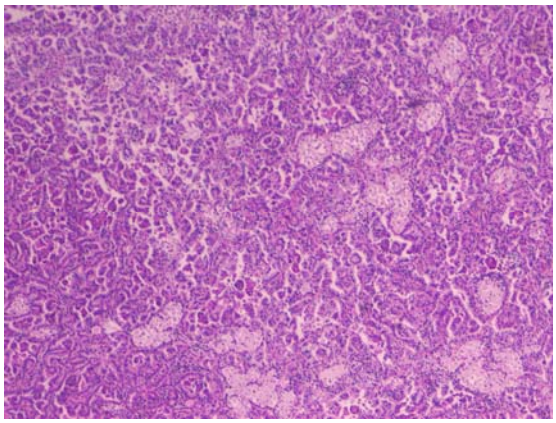
Foretinib: Dual VEGFR and MET Inhibitor



J Clin Oncol 10:2012

Sporadic Type 1 Papillary RCC

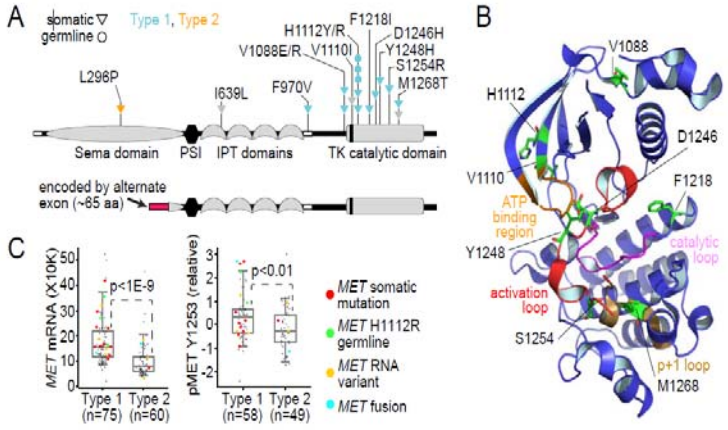
Type 1
Papillary RCC



N Engl J Med 143:2016

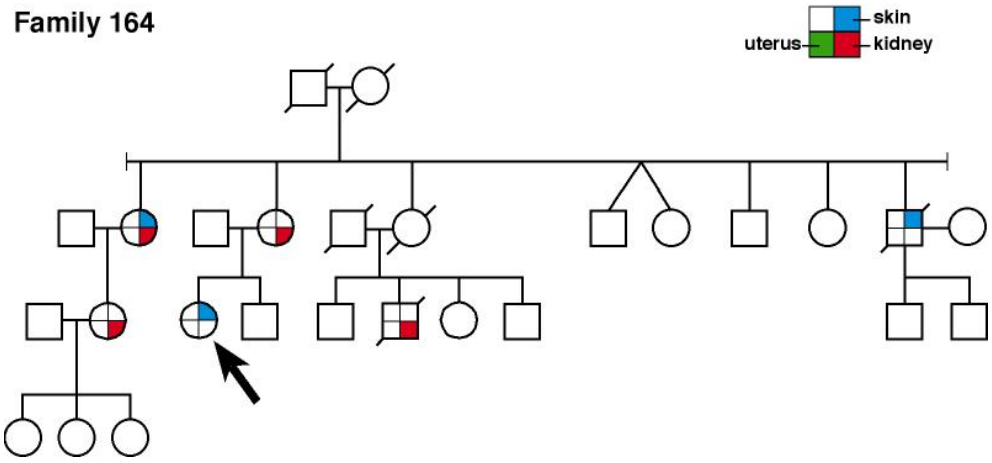
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Type 1 Papillary RCC
MET Mutation, Splice, Fusion, Phosphorylation



N Engl J Med 143:2016

Hereditary Papillary Renal Carcinoma Type 2



J Urol:153 1995

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

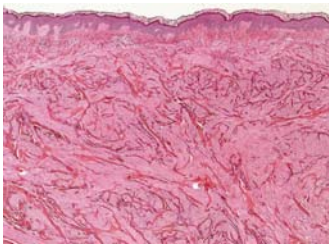
Hereditary Leiomyomatosis Renal Cell Carcinoma: HLRCC

- Cutaneous leiomyomas
- Uterine leiomyomas (fibroids)
- Renal cell carcinoma

Launonen PNAS 98:2001

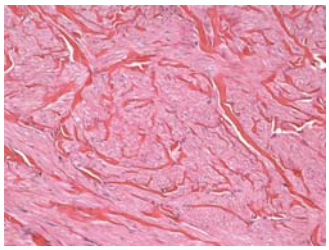
HLRCC: Cutaneous Leiomyomas

Leiomyomas



2.5 X

Upper Dermis



10 X

Middle Dermis

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

HLRCC: Uterine leiomyomas

Am J Hum Genet 71:2003

Papillary Kidney Cancer: Patient 2

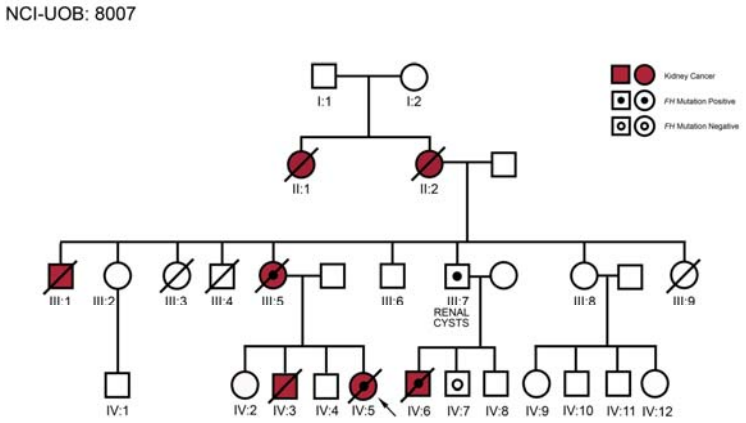
5/23/89

2/01/90

18 Year Old Female

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

HLRCC Kidney Cancer



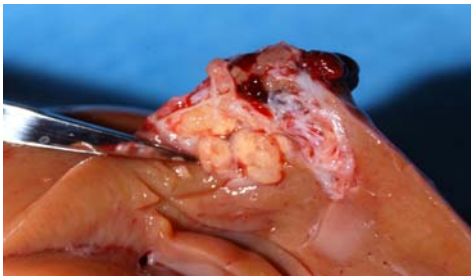
Germline FH Mutation: c.240dupA, NT 110, p.Ile81AspfsX14 , AA# 38, Exon 1, Frameshift

American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

HLRCC Cystic Renal Mass

2.5 Cm Renal Cyst



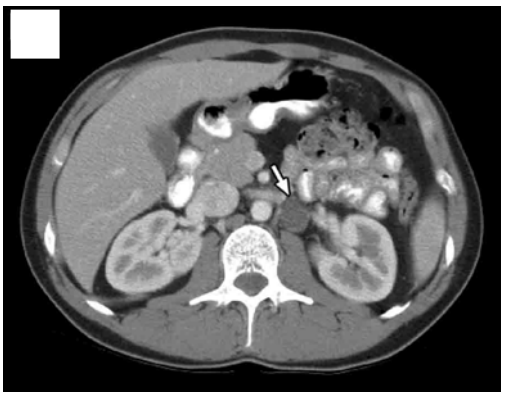
½ cm Renal Tumor

American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

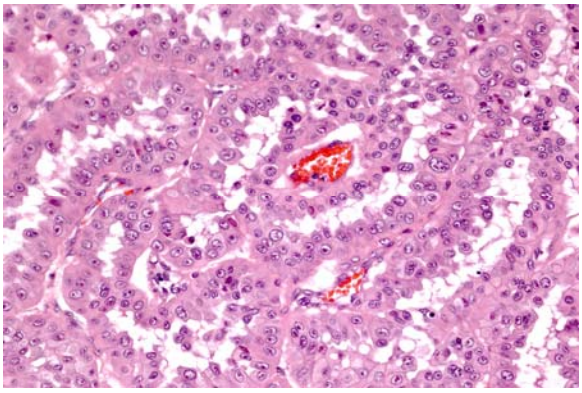
HLRCC Cystic Renal Mass
2 cm Hilar Node

2.5 Cm Renal Cyst

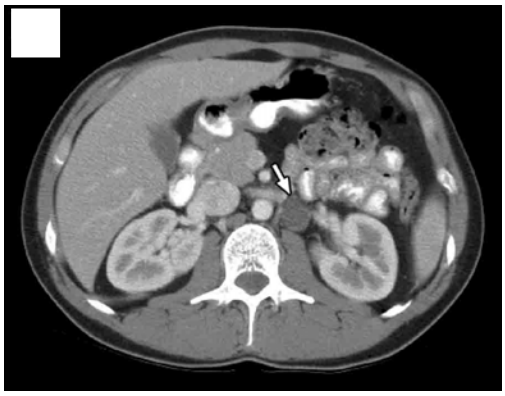


2 cm Hilar Node

HLRCC Cystic Renal Mass
2 cm Hilar Node



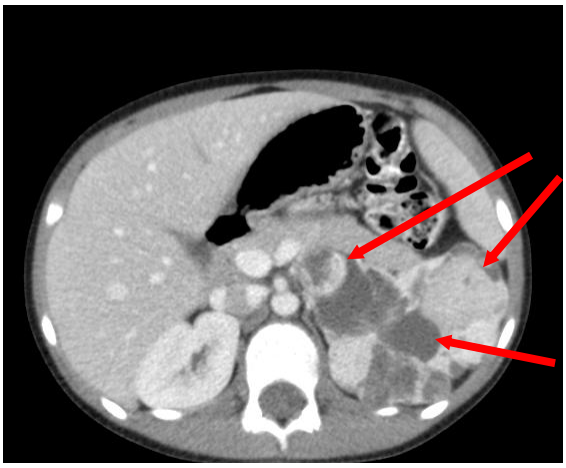
Type 2 Papillary RCC



2 cm Hilar Node

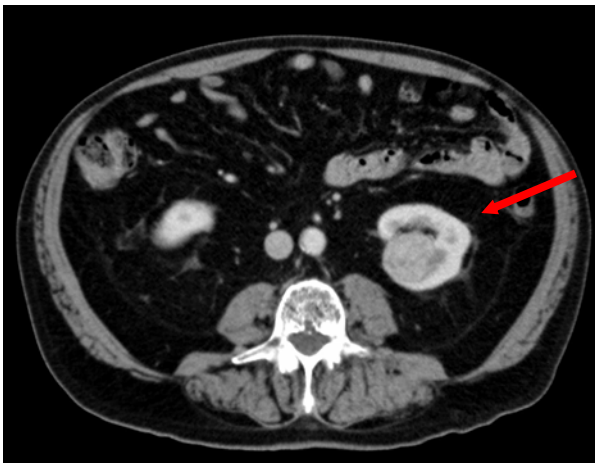
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

HLRCC Kidney Cancer
10 Year Old Female



Germline *FH* mutation: C>T, NT 172, Arg58 Stop, Nonsense

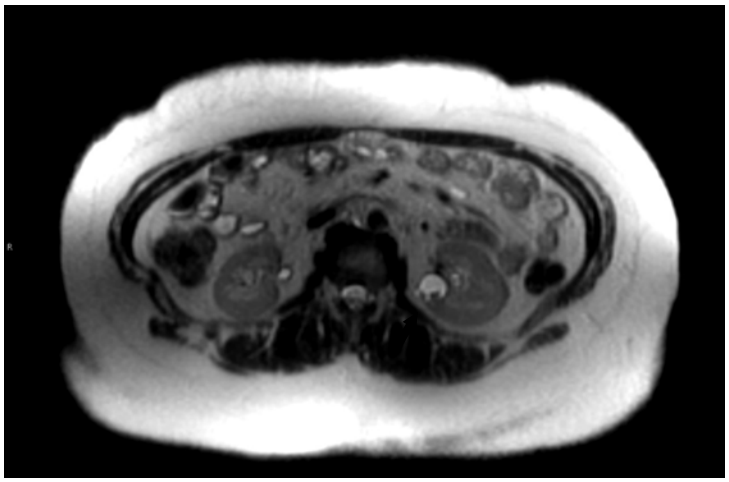
HLRCC Kidney Cancer
77 Year Old Male



Tumor

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

24 Year Old Female HLRCC Patient
04/09/08

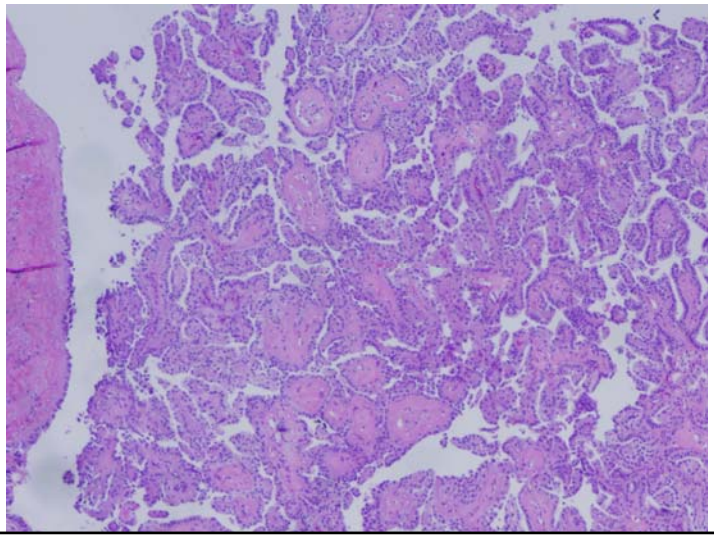


24 Year Old Female HLRCC Patient
04/09/08

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

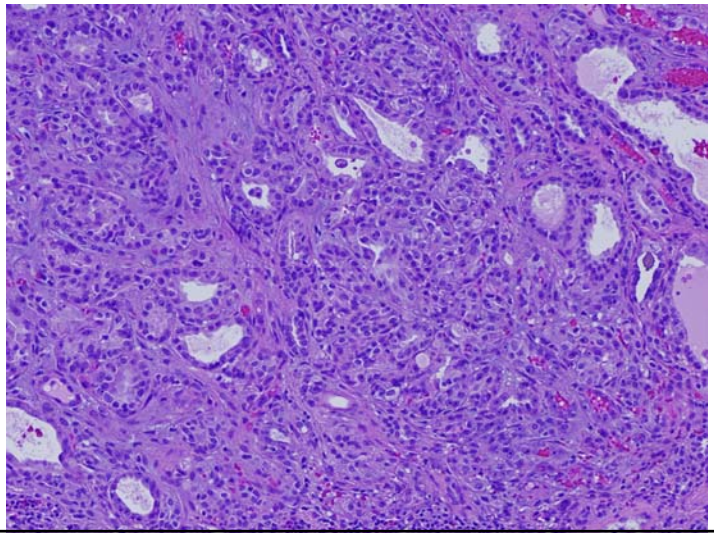
24 Year Old Female HLRCC Patient
06/06/08

Tumor Inside Cyst



24 Year Old Female HLRCC Patient
06/06/08

Tumor Invading Renal Parenchyma

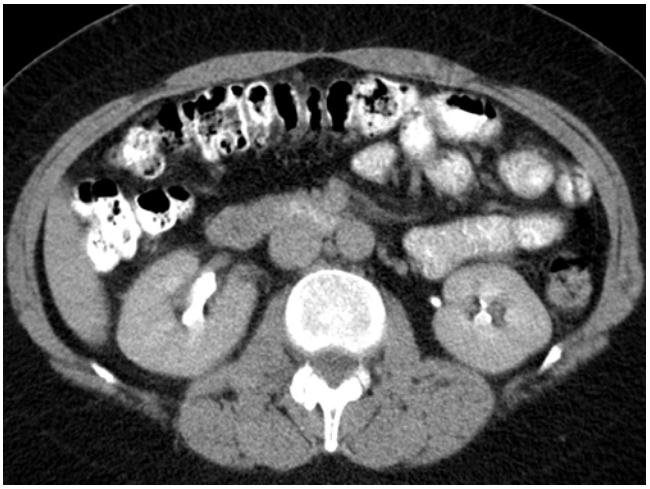


American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

43 Year Old Female HLRCC Patient
3/3/03

FH: T>G, NT 602, Leu201Arg, Exon 4, Missense

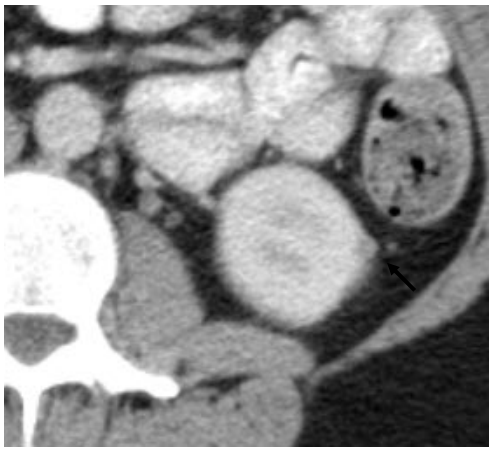
46 Year Old Female HLRCC Patient
September 2006



FH: T>G, NT 602, Leu201Arg, Exon 4, Missense

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

46 Year Old Female HLRCC Patient
September 2006

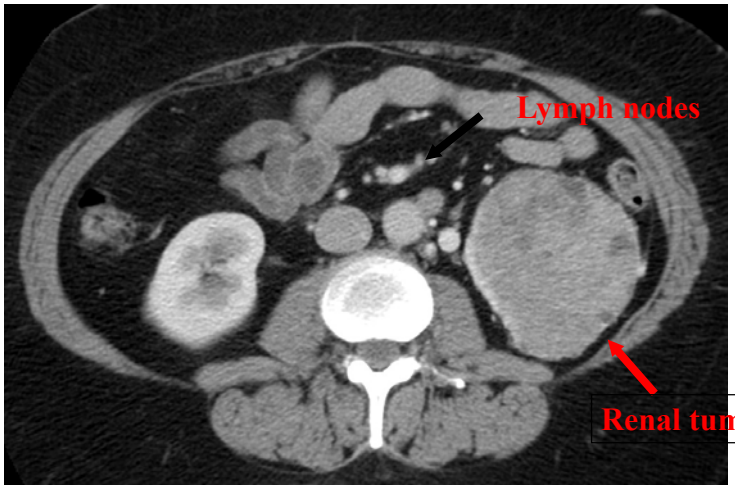


FH: T>G, NT 602, Leu201Arg, Exon 4, Missense

American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

50 Year Old Female HLRCC Patient December 2010



FH: T>G, NT 602, Leu201Arg, Exon 4, Missense

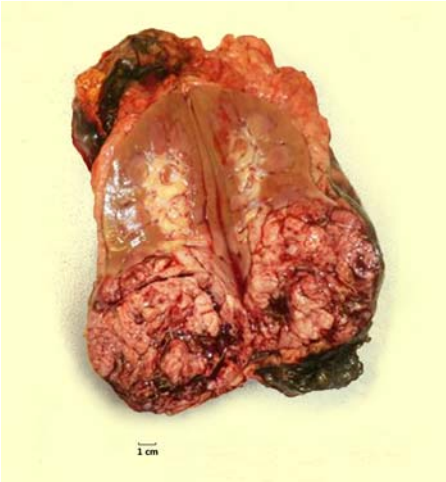
American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

50 Year Old Female HLRCC Patient December 2010

FH: T>G, NT 602, Leu201Arg, Exon 4, Missense

50 Year Old Female HLRCC Patient



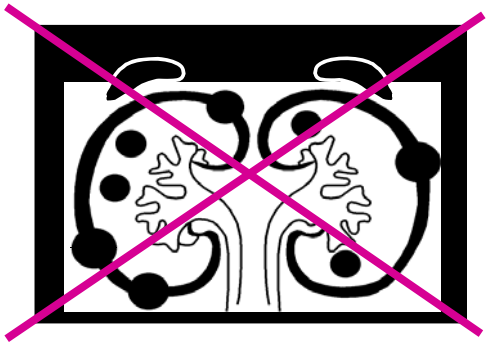
9 cm Type 2 Papillary Renal Cancer

10/59 lymph nodes positive

FH: T>G, NT 602, Leu201Arg, Exon 4, Missense

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

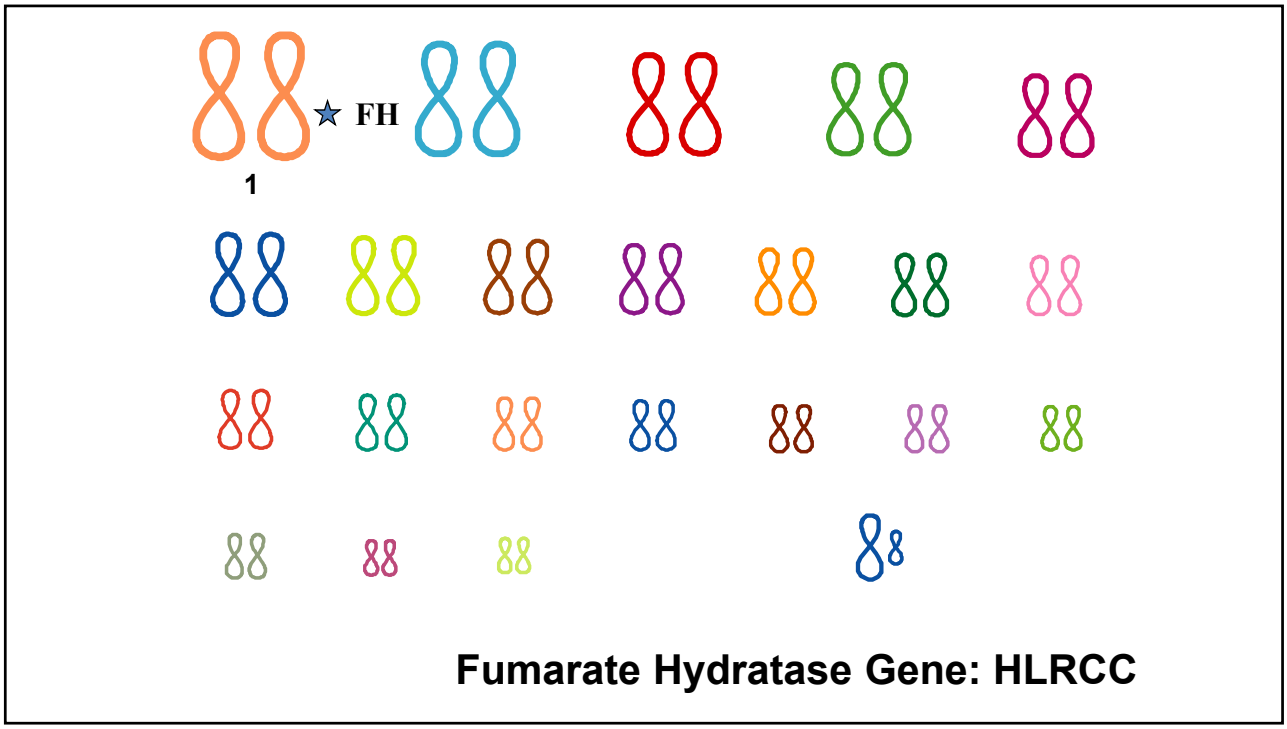
Surgical Management of HLRCC-Associated Renal Carcinoma

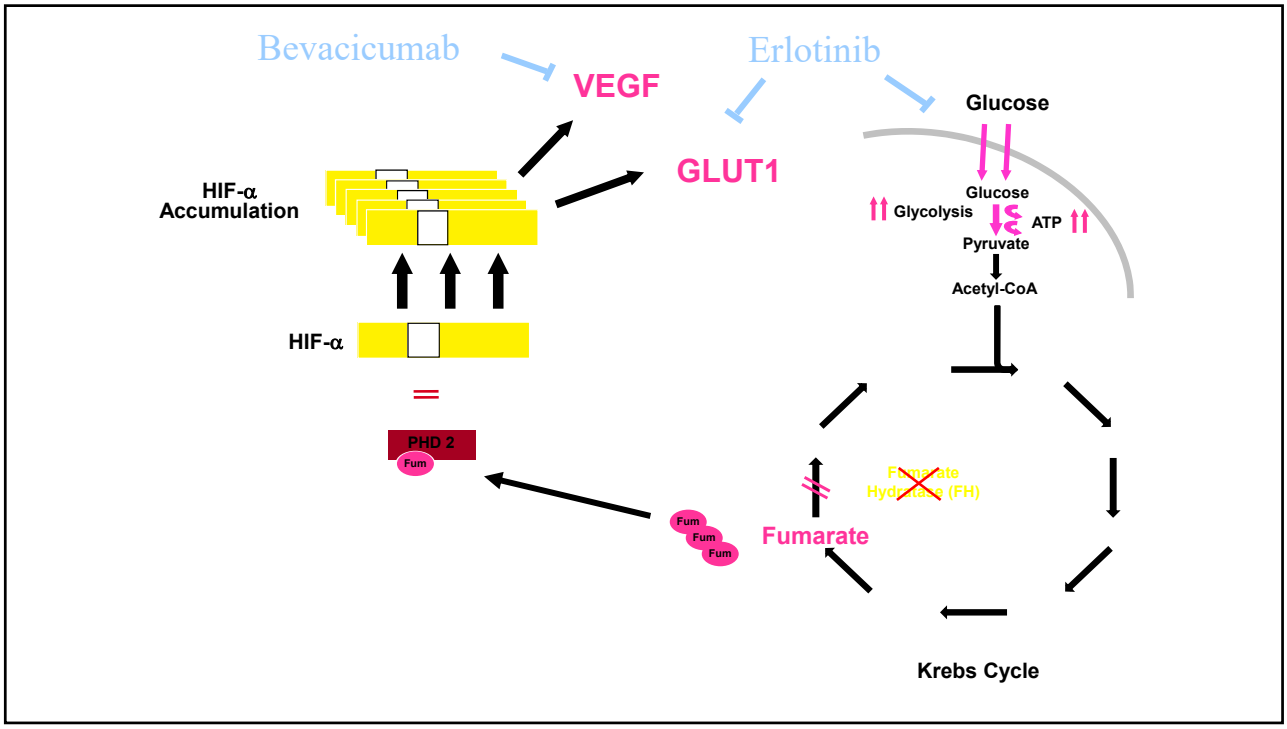


"3 cm rule"
Delay surgery until diameter of largest renal tumor = 3 cm

Surgical management should NOT be delayed
Wide Surgical Margins
Mostly Open Procedures
Can be bilateral and multifocal

Nature CPU 3:2007
J Urol 177:2007

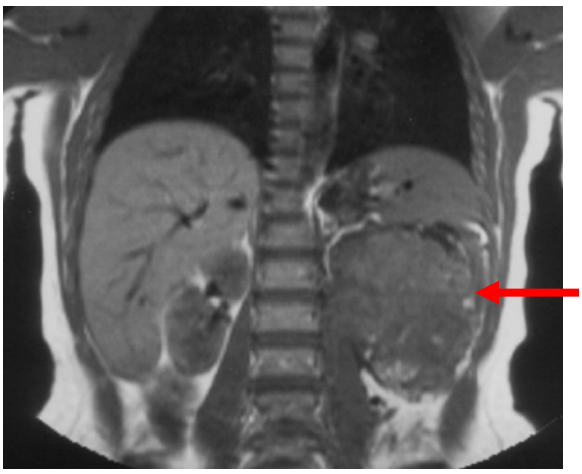




Locally Advanced Kidney Cancer

Surgery 4/21/87

Died 1/08/88

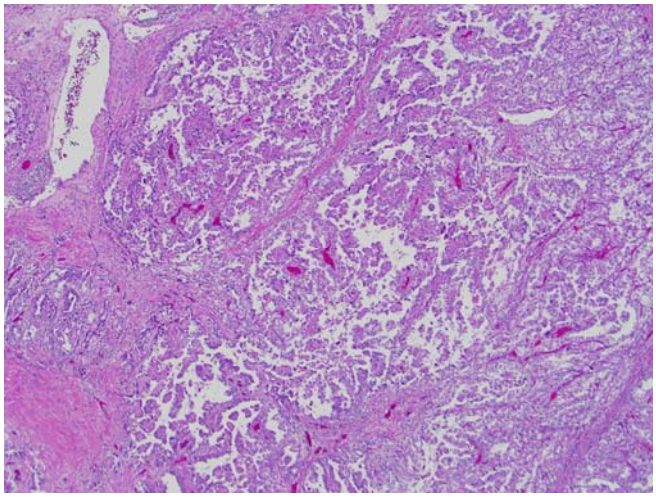


11 cm
T3A

21 Year Old Female

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Locally Advanced Kidney Cancer



"Papillary Kidney Cancer"

Translocation
Papillary Kidney Cancer

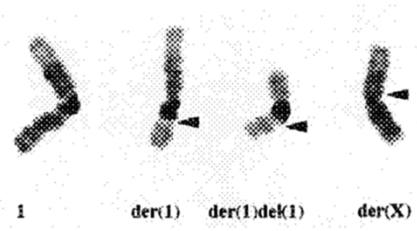


Fig. 1. Partial karyotype of the cell line UOK124 illustrating the rearrangements involving chromosomes X and 1. The karyotype contained a normal chromosome 1 but no normal X. The der(1) and the der(X) result from the t(X;1)(p11.2;q21.2) that is associated with papillary renal cell carcinoma and the der(1)del(1)(p31)t(X;1)(p11.2;q21.2) is thought to be derived by deletion following the duplication of the der(1) chromosome. The arrows indicate the position of the translocation breakpoints.

Cytogenet Cell Genet 71:1995

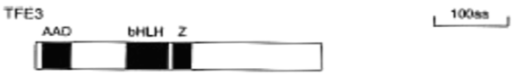
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

TFE3 Kidney Cancer

Chromosome 1q21.2

+

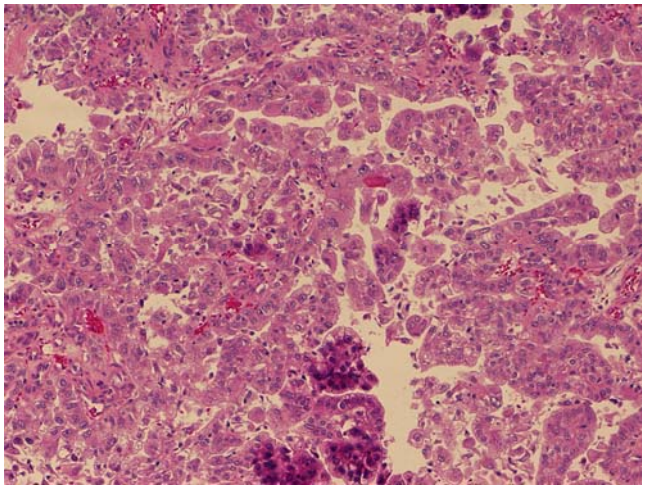
Chromosome Xp11.1



t(X;1)(p11.2;q21.2)

Human Mol Genetics 5:1966

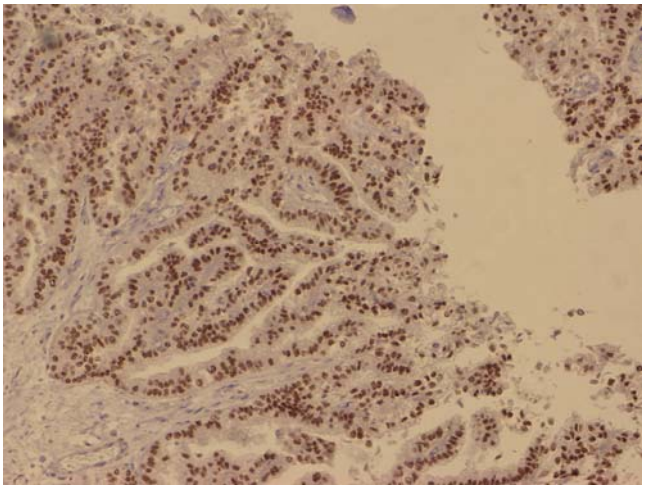
TFE3 Kidney Cancer



Type 2 Papillary RCC

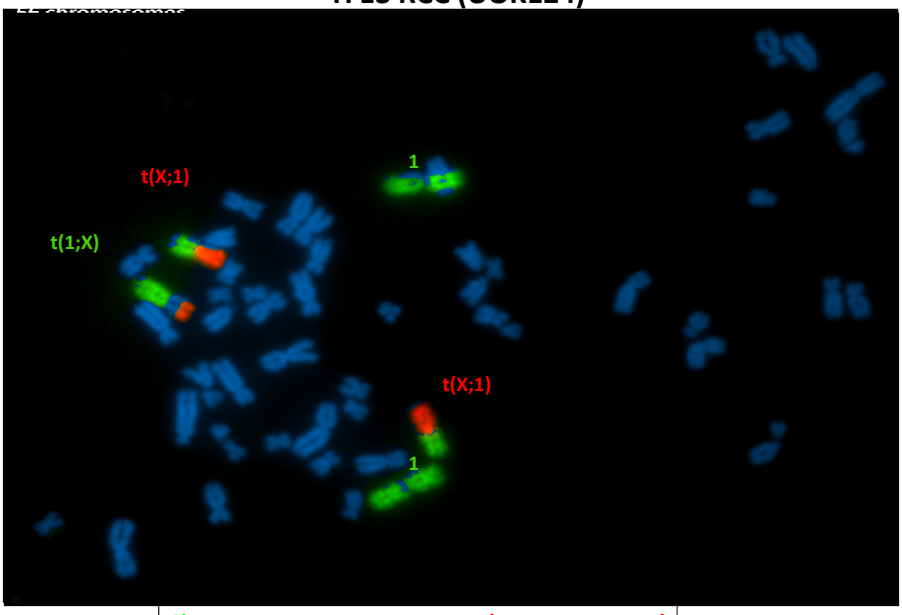
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

TFE3 Kidney Cancer



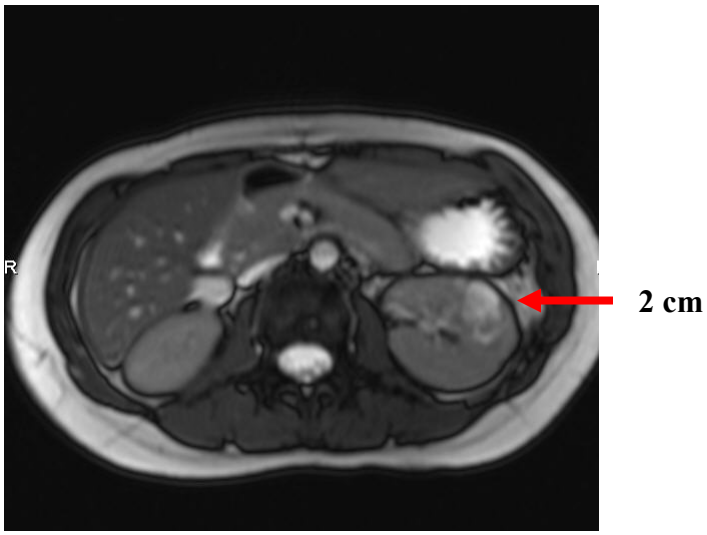
TFE3 Immunohistochemistry

TFE3 RCC (UOK124)



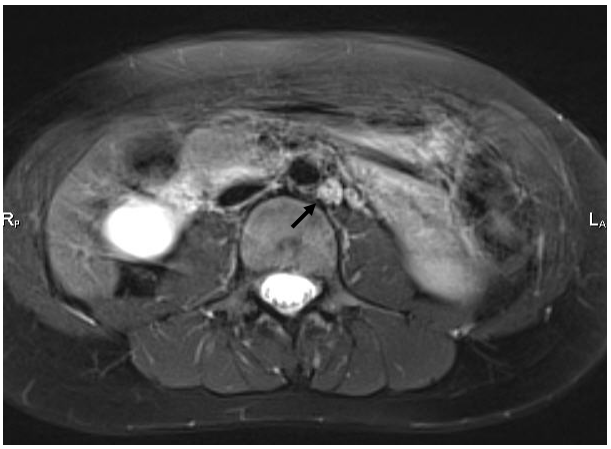
Chromosome 1 = green X- chromosome = red

TFE3 t(X;1)(p11.2;q21.2) Translocation
Papillary Kidney Cancer



23 Year Old Female

TFE3 t(X;1)(p11.2;q21.2) Translocation
Papillary Kidney Cancer

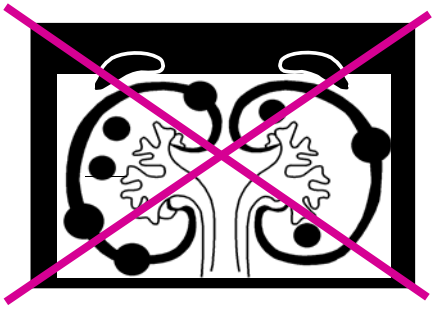


Positive
Hilar node

23 Year Old Female

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Surgical Management of
TFE3/TFEB Renal Cell Carcinoma



"3 cm rule"
Delay surgery until diameter of largest renal tumor = 3 cm

Surgical management should NOT be delayed
Wide Surgical Margins
May Need Open Procedures

TFE3 Translocation RCC
12 Year Old Male

42% of RCC in Children & Young Adults

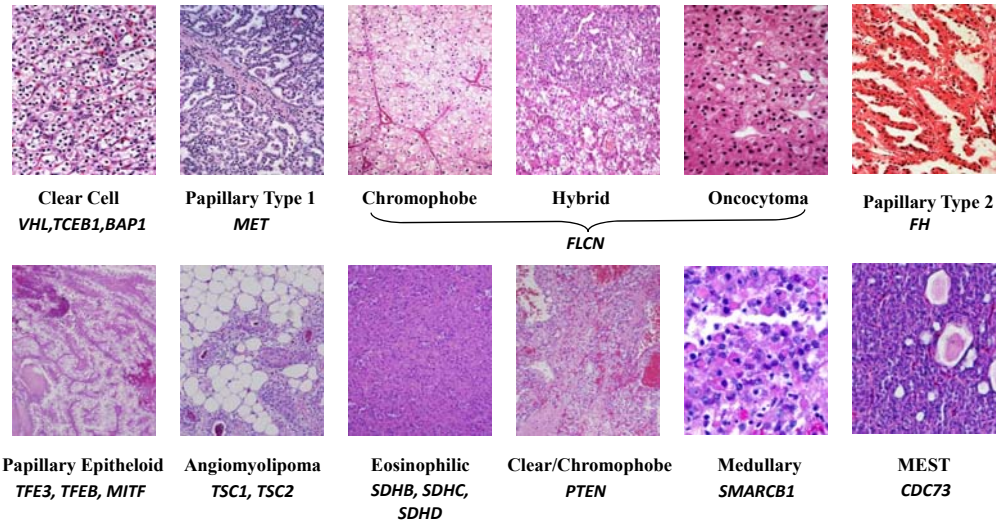
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

TFE3/TFEB Papillary RCC

- **TFE3/TFEB Translocation kidney cancer**
  - **12% of Type 2 papillary RCC**
  - **Mean Age: 55 (37-71)**
  - **TFEB fusions found in patients 64 and 71 years of age**

N Engl J Med 143:2016

Kidney Cancer Genes



Clear Cell *VHL,TCEB1,BAP1*

Papillary Type 1 *MET*

Chromophobe

Hybrid

Oncocytoma

FLCN

Papillary Type 2 *FH*

Papillary Epitheloid *TFE3, TFEB, MITF*

Angiomyolipoma *TSC1, TSC2*

Eosinophilic *SDHB, SDHC, SDHD*

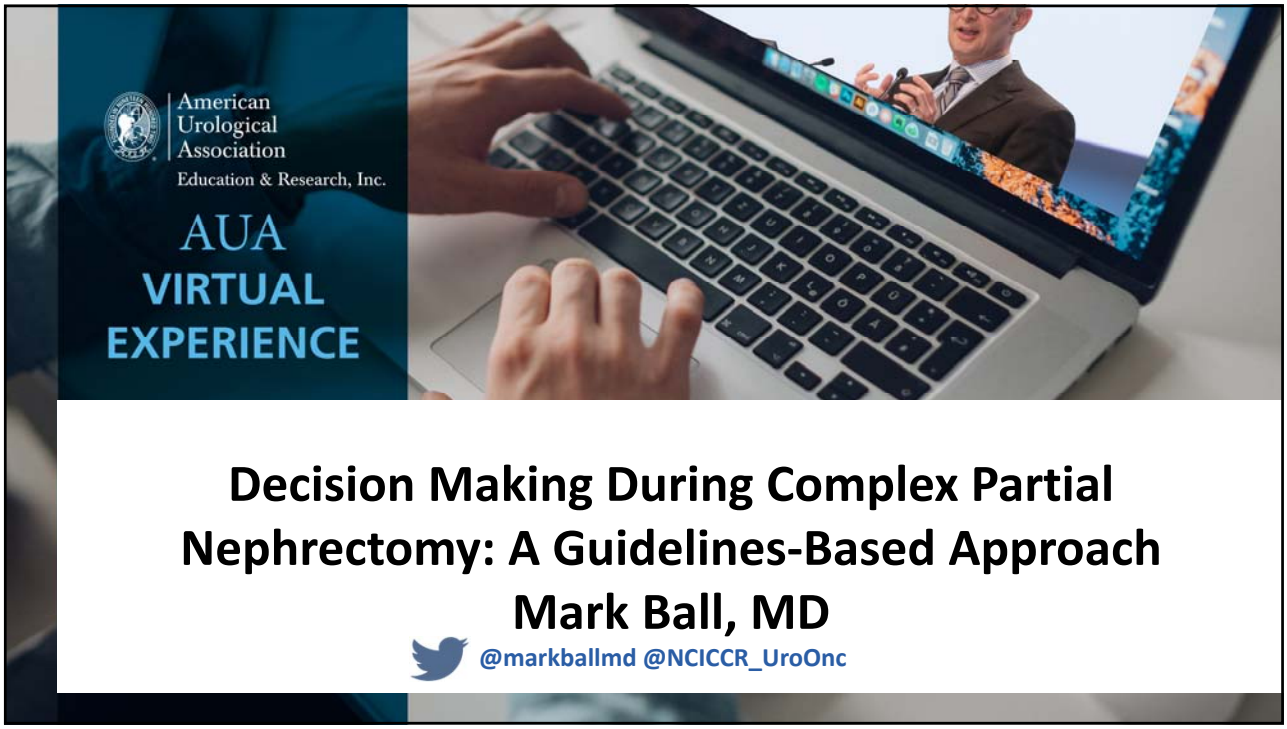
Clear/Chromophobe *PTEN*

Medullary *SMARCB1*

MEST *CDC73*

American Urological Association

Urologic Oncology Branch
National Cancer Institute



Decision Making During Complex Partial Nephrectomy: A Guidelines-Based Approach

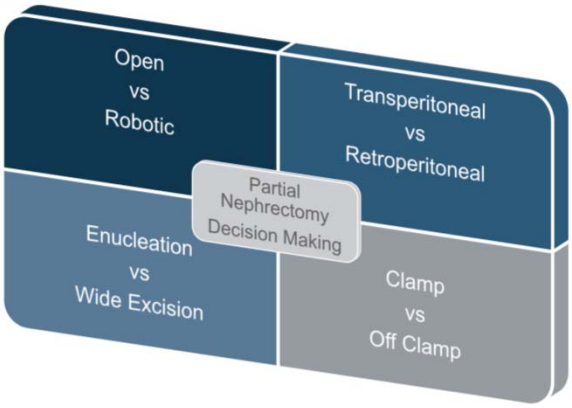
Mark Ball, MD

@markballmd @NCICCR_UroOnc

No Disclosures

Outline

- When to perform partial nephrectomy
- Decision making during PN
  - Rubric
  - Cases



American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Choosing candidates for partial nephrectomy: a Goldilocks approach

When to operate

Too cold = Active Surveillance

Renal Mass and Localized Renal Cancer: AUA Guideline

- For patients with small renal masses, especially those <2cm, AS is an option for initial management.
- Physicians should prioritize AS when the anticipated risk of intervention or **competing risks of death outweigh the potential oncologic benefits** of active treatment. (Clinical Principle)

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

When to operate

Too hot = Radical Nephrectomy

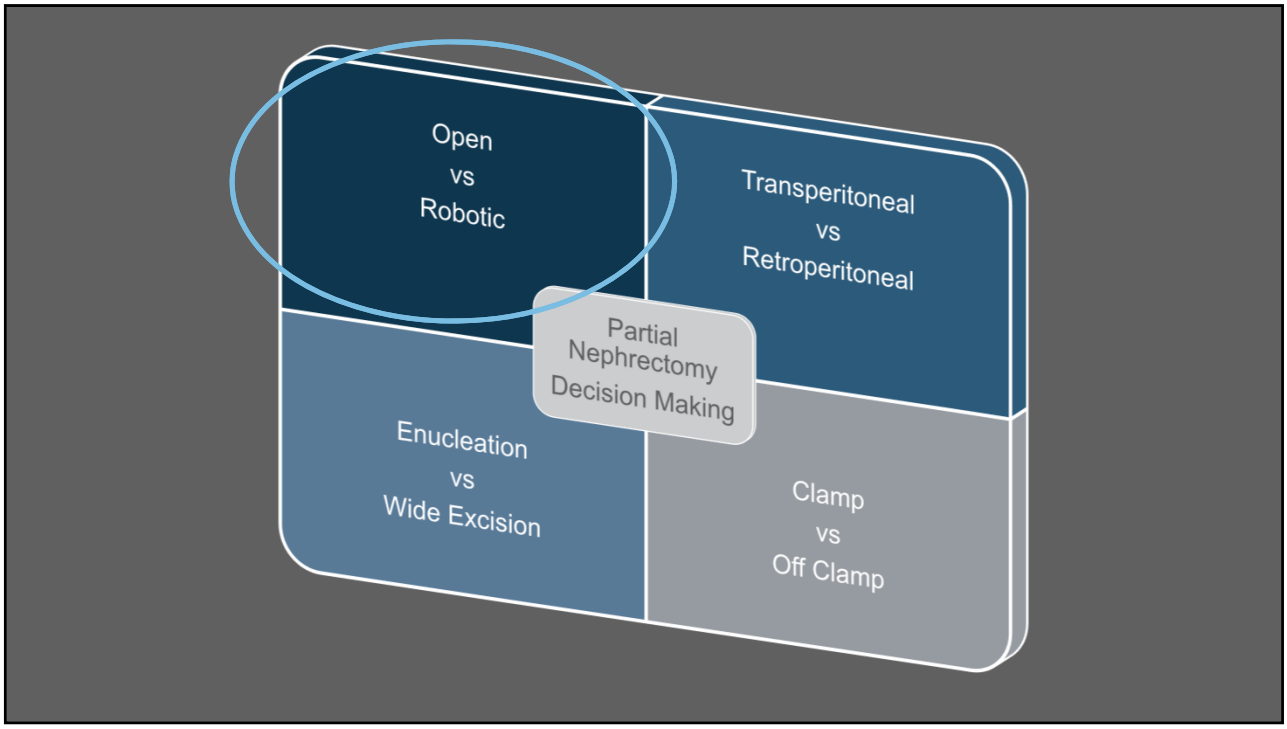
Renal Mass and Localized Renal Cancer: AUA Guideline

- Physicians should consider RN for patient where **increased oncologic potential** is suggested.
- RN is preferred if **all** of the following criteria are met:
  - 1) high tumor complexity and PN would be challenging even in experienced hands;
  - 2) no preexisting CKD or proteinuria; and
  - 3) normal contralateral kidney and new baseline eGFR will likely be greater than 45 ml/min/1.73m^2.

When to operate

Just right = Partial Nephrectomy

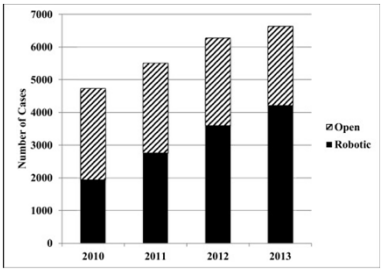
Anticipated oncologic benefits of intervention outweigh the risks of treatment and competing risks of death, physicians should recommend active treatment.



Open versus Robotic

22. In patients undergoing surgical excision of a renal mass, a minimally invasive approach should be considered when it would not compromise oncologic, functional and perioperative outcomes. **(Expert Opinion)**

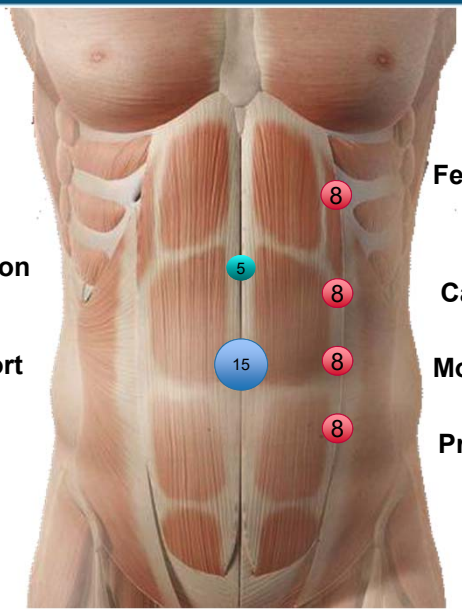
- Open surgery may be favored if:
  - 1. Surgeon experience and comfort ***
  - 2. Need for cold ischemia
  - 3. HLRCC/SDH Tumors
  - 4. Prior renal surgery (?)



Alameddine, M et al.
European Urology Focus, Volume 5, Issue 3, 482 - 487

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Left-Sided Port Placement



Fenestrated Bipolar

AirSeal Insufflation

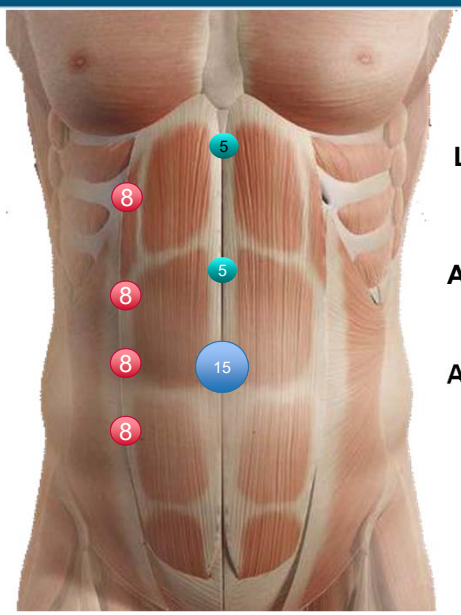
Camera

Assistant Port

Monopolar Scissors

Prograsp

Right-Sided Port Placement



Monopolar Scissors

Camera

Fenestrated Bipolar

Prograsp

Liver Retractor

AirSeal Insufflation

Assistant Port

Operative Approach

Mini-flank incision
Between 10th and 11th Rib

AUA Core Curriculum

Surgical Approach for Redo Surgery

- Traditionally, reoperative surgery was always done with an open approach.
- We are increasingly using robotics for 2nd, 3rd and 4th time kidney surgeries.

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Reoperative Surgery

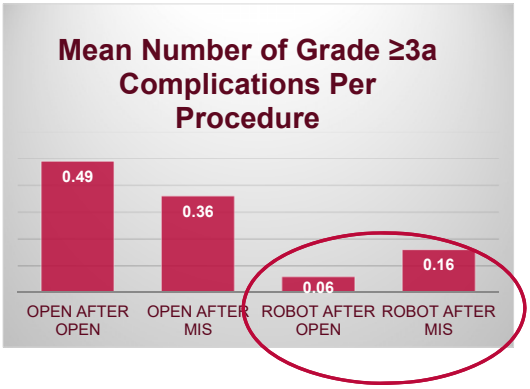
Consideration for Robotic Redo Surgery

- Anatomy can be distorted – place a ureteral catheter
- Preserve Gerota's fascia
  - Open in Clamshell fashion
  - Suture close
- Ultrasound early and often – can identify ureter and hilum
- Approach hilum with caution if previously dissection.

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Reoperative Surgery

215 Redo PN at the NCI



Factors Leading to More Complications

Univariate Analysis	Multivariate Analysis
Number of prior surgeries	Final intended surgical approach
Final intended surgical approach	(p = .001, OR: 4.3)

In the well selected patient, robotic redo PN is as safe as open PN

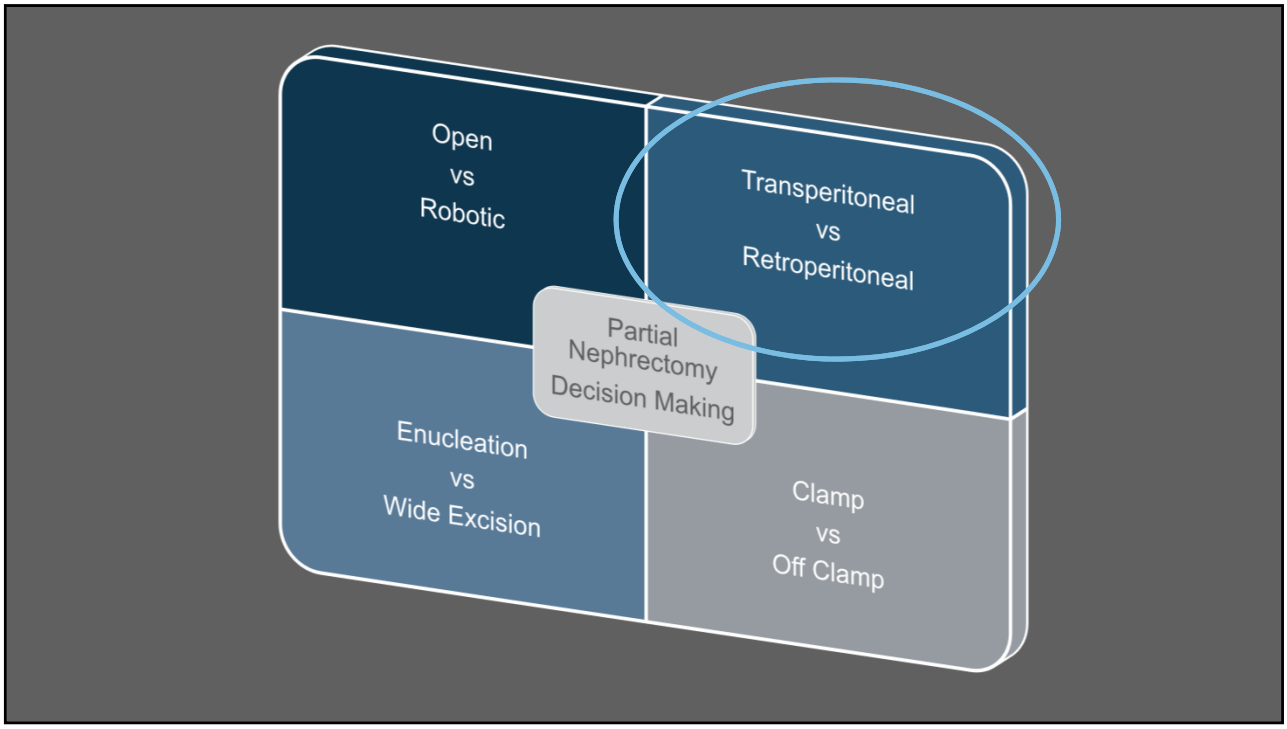
Gurram et al GU ASCO 2020

Open versus robotic partial nephrectomy: Systematic review and meta-analysis of contemporary studies

Sheng-Han Tsai[1,2†] | Ping-Tao Tseng[3,4†] | Benjamin A. Sherer[5] | Yi-Chen Lai[2,6] | Pao-Yen Lin[7,8] | Ching-Kuan Wu[3] | Marshall L. Stoller[5]

Int J Med Robotics Comput Assist Surg. 2019;**15**:e1963.

- 34 studies with 60,808 patients.
- Compared to open, robotic surgery had
  - less blood loss,
  - less transfusion,
  - longer operative time,
  - less postoperative complications,
  - lower readmission rate,
  - shorter length of stay, and
  - less estimated glomerular filtration rate (eGFR) decline

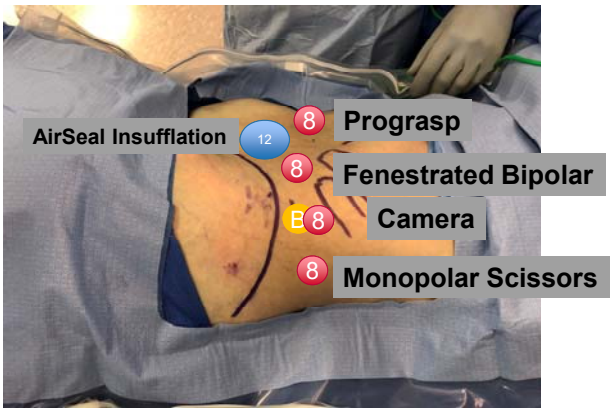


Transperitoneal versus Retroperitoneal

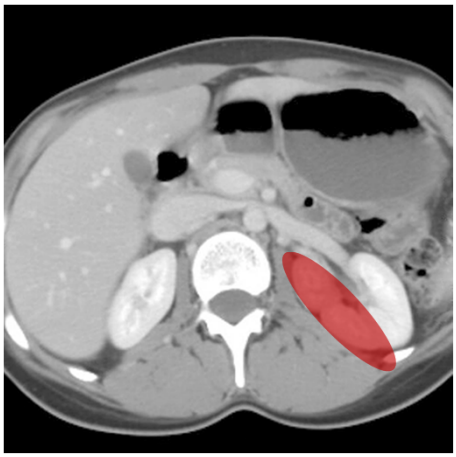
- Transperitoneal = default option
  - Most familiar anatomy
  - More working space
- Retroperitoneal
  - Good for posterior tumors
  - No bowel manipulation
  - Quicker access to hilum
  - Can see the base of a posterior tumor better

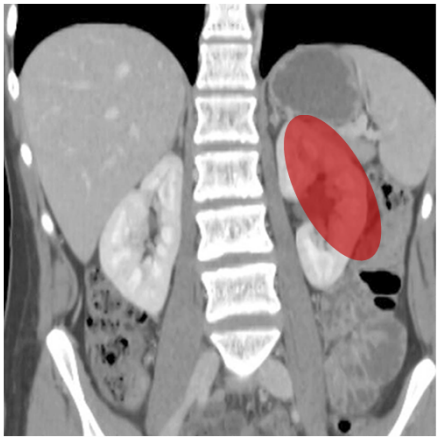
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Retroperitoneal port placement



Retroperitoneal Candidates

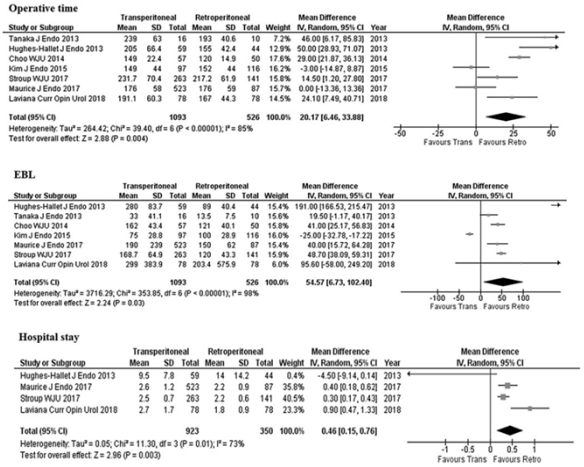


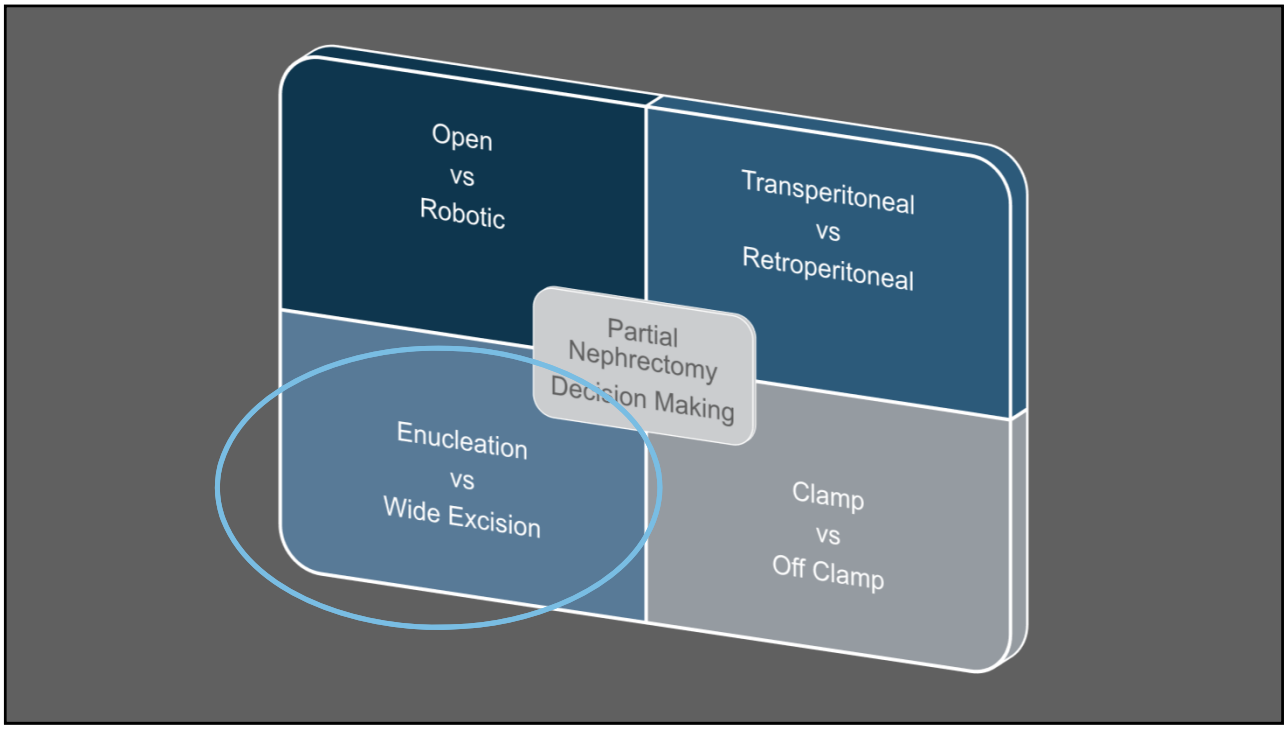


Retroperitoneal Robotic Partial Nephrectomy: Systematic Review and Cumulative Analysis of Comparative Outcomes

JOURNAL OF ENDOUROLOGY
Volume 32, Number 7, July 2018

- Seven retrospective case–control studies were identified and included in the analysis, with a total number of 1379 patients (866 for transperitoneal group; 513 for retroperitoneal group).



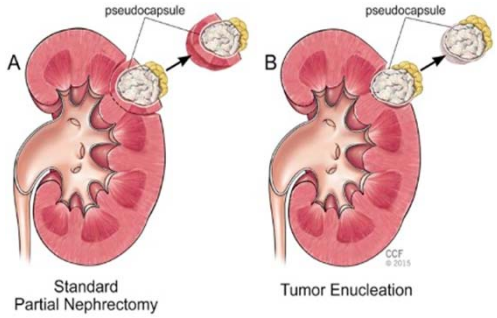


American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

Partial Nephrectomy versus Tumor Enucleation

- Benefits of tumor enucleation:
  - Preserve more parenchyma
  - See the tumor – no guessing the depth of resection
  - Avoid colleting system entry
  - Even off clamp -> less blood loss
- Candidates
  - familial RCC, multifocal disease, or severe CKD
  - Unifocal sporadic – enucleation not necessary



Tumor enucleation

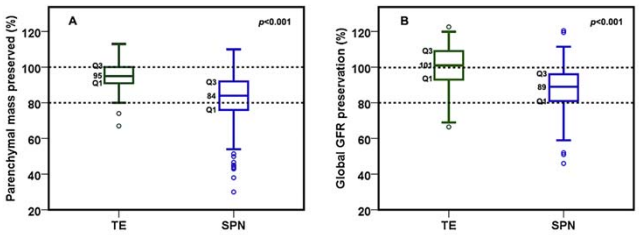
18. For patients undergoing PN, negative surgical margins should be a priority. The extent of normal parenchyma removed should be determined by surgeon discretion taking into account the clinical situation, tumor characteristics including growth pattern, and interface with normal tissue. Tumor enucleation should be considered in patients with familial RCC, multifocal disease, or severe CKD to optimize parenchymal mass preservation. **(Expert Opinion)**

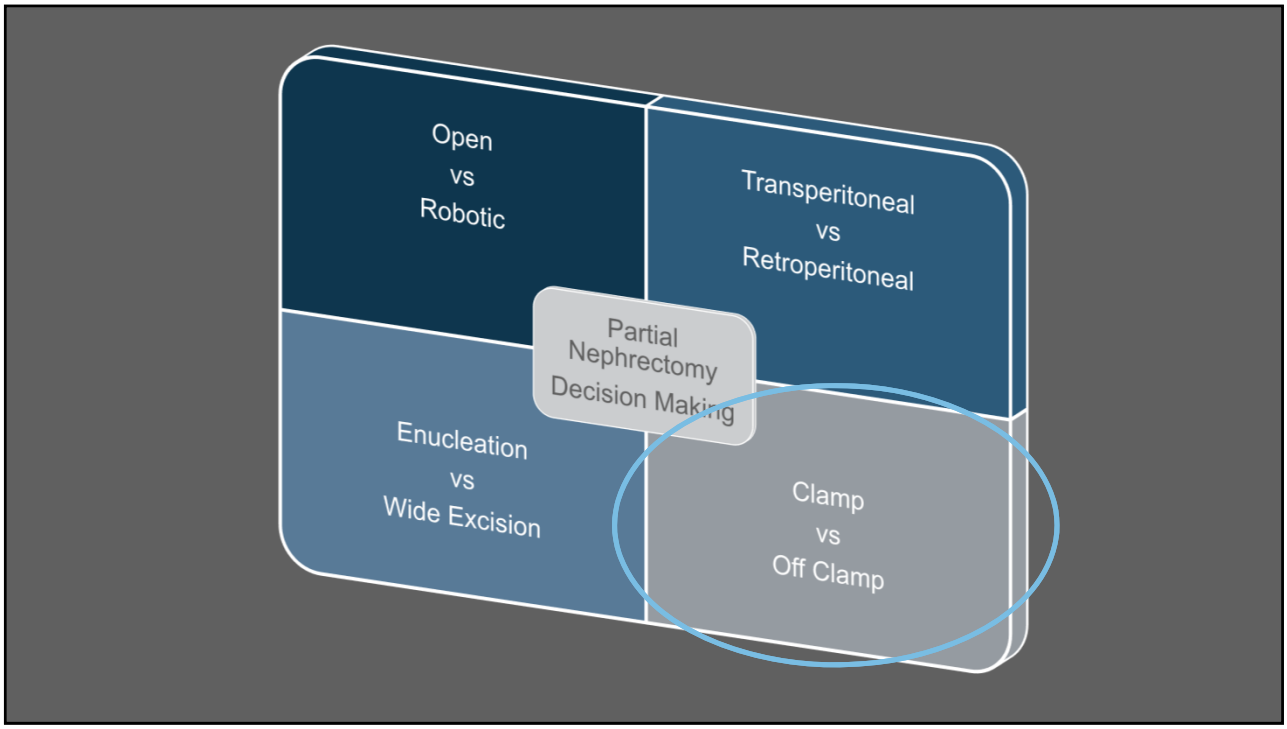
Functional Comparison of Renal Tumor Enucleation Versus Standard Partial Nephrectomy

Wen Dong[a,b,†], Gopal N. Gupta[c,†], Robert H. Blackwell[c], Jitao Wu[a,d], Chalairat Suk-Ouichai[a,e], Arpeet Shah[c], Sarah E. Capodice[c], Marcus L. Quek[c], Elvis Caraballo Antonio[a], Diego Aguilar Palacios[a], Erick M. Remer[a,f], Jianbo Li[a,g], Joseph Zabell[a], Sudhir Isharwal[a], Steven C. Campbell[a,]*

- 71 TE VS 373 PN cases.
- For TE, warm ischemia and zero ischemia were used in 51% and 49% ofcases, respectively.
- For PN, warm ischemia and cold ischemia were used in 72% and 28%of patients, respectively.
- Positive margins were found in 8.5% of TE and 4.8% of PN patients(p= 0.2).

EUROPEAN UROLOGY FOCUS 3 (2017) 437–443





American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

Considerations for Off Clamp

- Indications
  - multiple tumors not amenable to extended warm ischemia
  - Solitary kidney
  - Existing CKD
  - Previous kidney surgery – scarred hilum
  - Planning for future kidney surgeries – prevent scarred hilum
- Enucleation

Considerations for Off Clamp PN

- Enucleation > wide resection
- Have lap pad or bolster in the body for manual compression

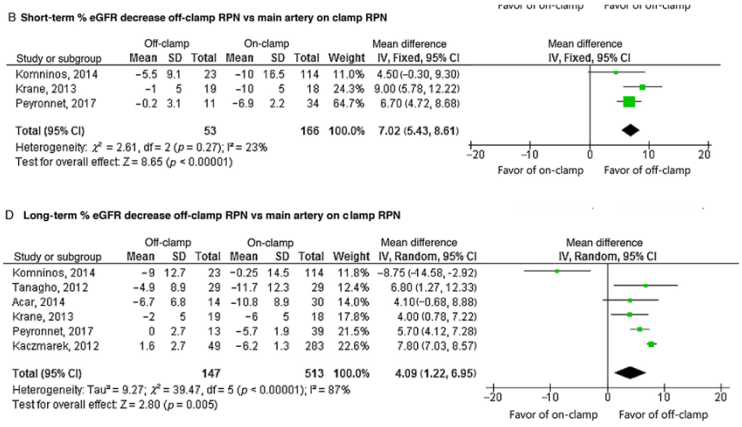
Impact of Renal Hilar Control on Outcomes of Robotic Partial Nephrectomy: Systematic Review and Cumulative Meta-analysis

Giovanni E. Cacciamani[a,b,†], Luis G. Medina[a,†], Tania S. Gill[a], Alec Mendelsohn[a], Fatima Husain[a], Lokesh Bhardwaj[a], Walter Artibani[b], Renè Sotelo[a], Inderbir S. Gill[a,]*

EUROPEAN UROLOGY FOCUS 5 (2019) 619–635

Off clamp versus on clamp:

Similar:
Transfusion requirements
Complications
Positive surgical margins



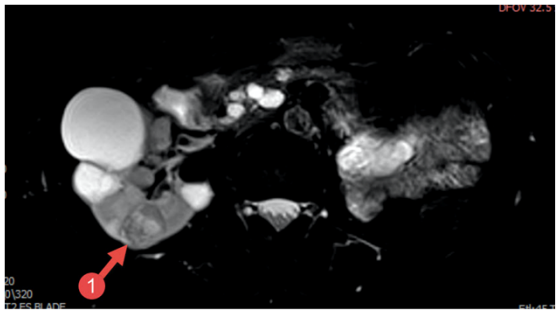
Putting it together

- My population – large percentage of either hereditary or non-hereditary but multifocal kidney tumors
  - Robotic off-clamp enucleation (mostly transperitoneal)
  - The combination of robotic, off clamp, enucleation → maximal preservation of renal function, while minimizing blood loss and complications

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Case 1

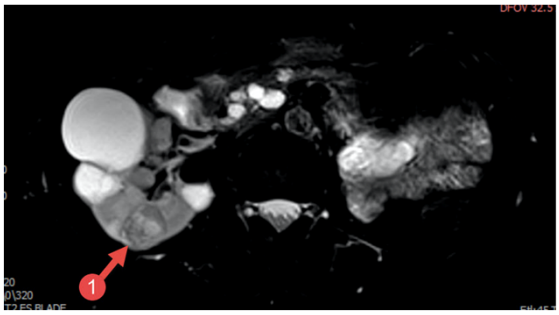
- Woman in her 60s, previous right PN, previous left RN
- Cr 1.6, eGFR 35

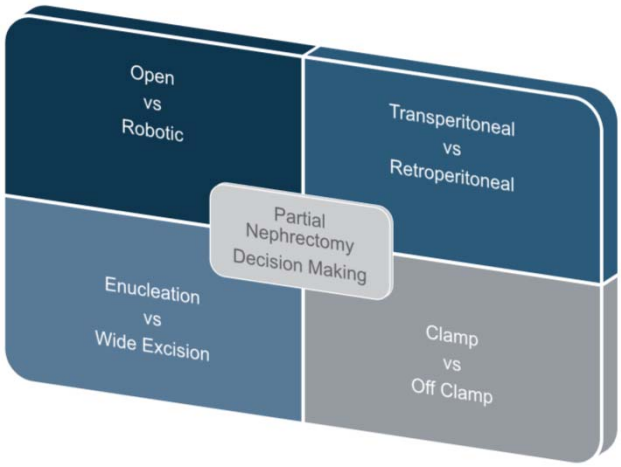


American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

Decision-making

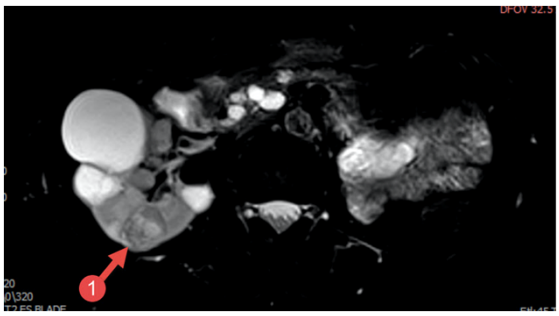


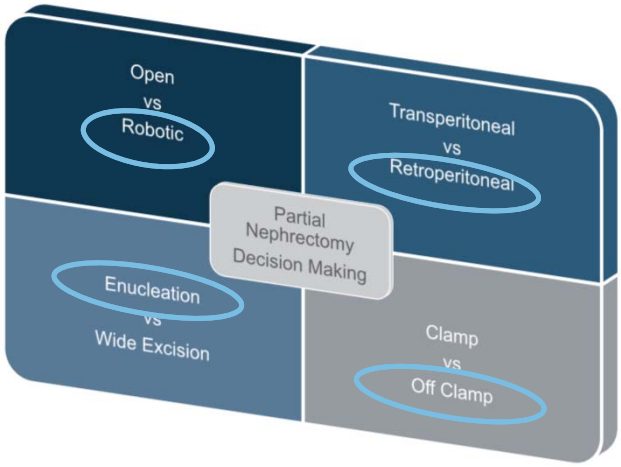


American Urological Association Education & Research, Inc.

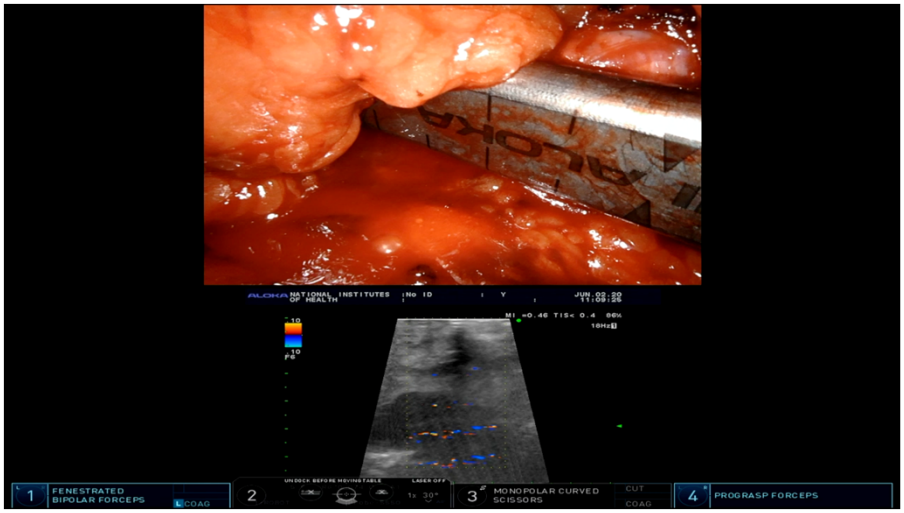
AUA VIRTUAL EXPERIENCE

Decision-making





Case 1



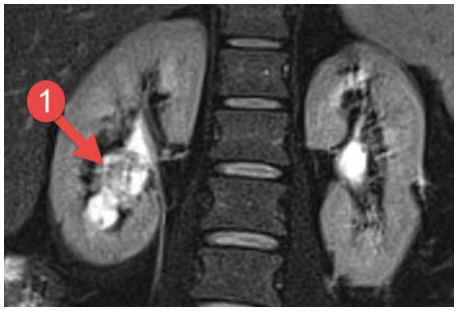
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

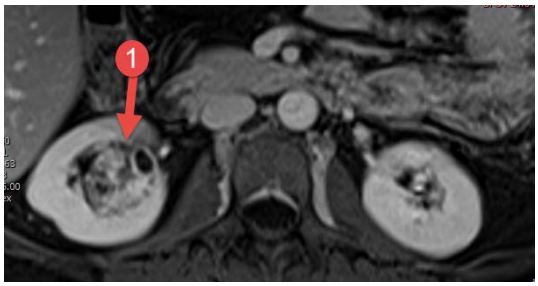
Case 1 Outcomes

- Perioperative: WIT 0 min, EBL 100 cc
- Pathology: FG2, cRCC, negative margins
- Renal function: Cr 1.3, eGFR 43

Case 2

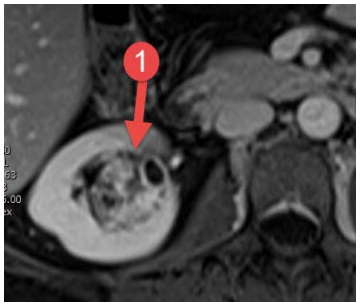
- 31-year-old woman with history of left partial nephrectomy
- Germline panel negative
- Cr 0.76, eGFR 100

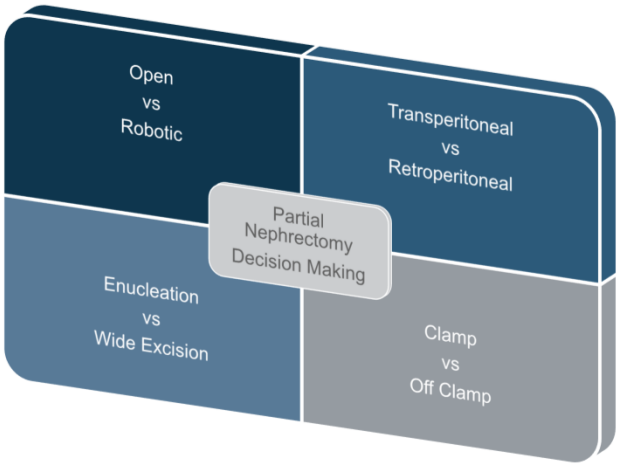




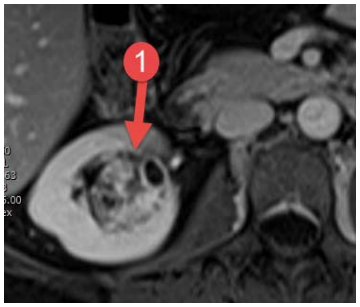
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

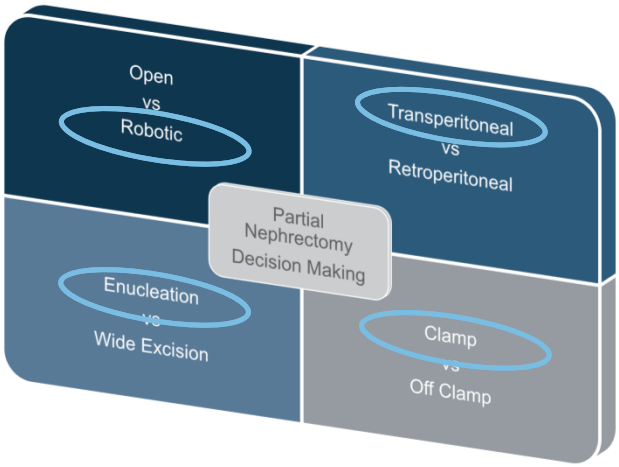
Decision Making



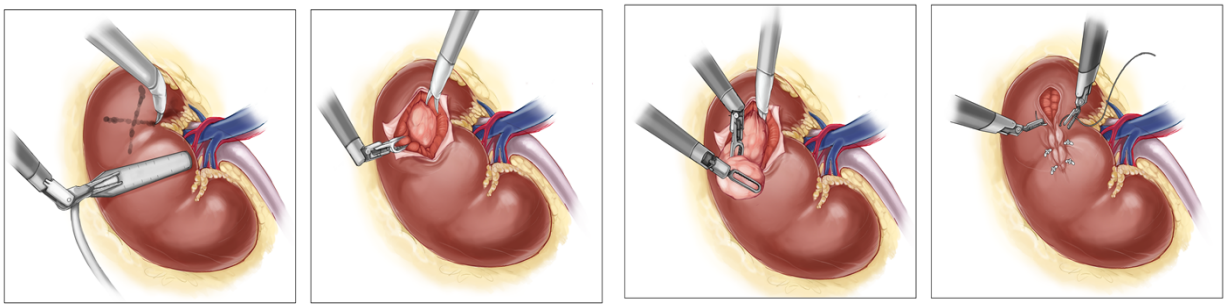


Decision Making



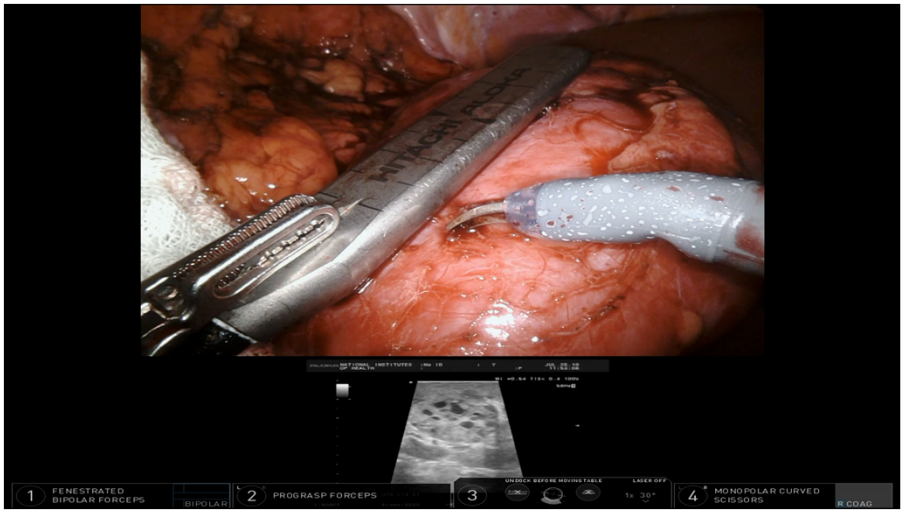


Endophytic Tumors



Lebastschi A. et al In Preparation

Case 2



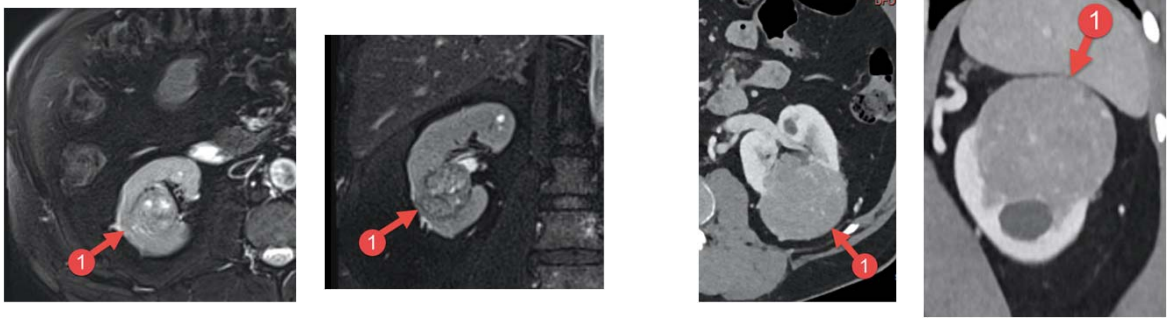
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Case 2 Outcomes

- Perioperative: WIT 19 min, EBL 55 cc
- Pathology: FG2, ccRCC, negative margin
- 12 month Cr: 0.78, eGFR 113
- No recurrent or de novo disease at 24 months.

Case 3

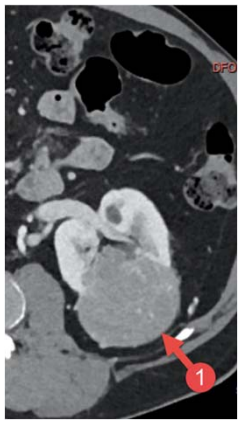
- 71-year-old man with bilateral masses, genetic work up negative
- Right biopsy: clear cell RCC, left not biopsied
- Cr 0.96 eGFR 79

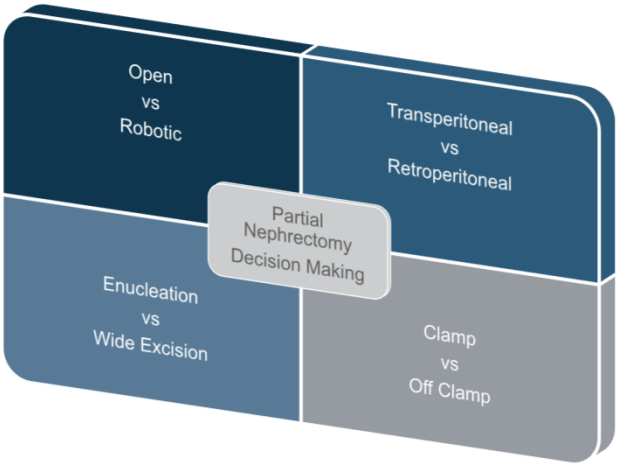


American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Decision Making

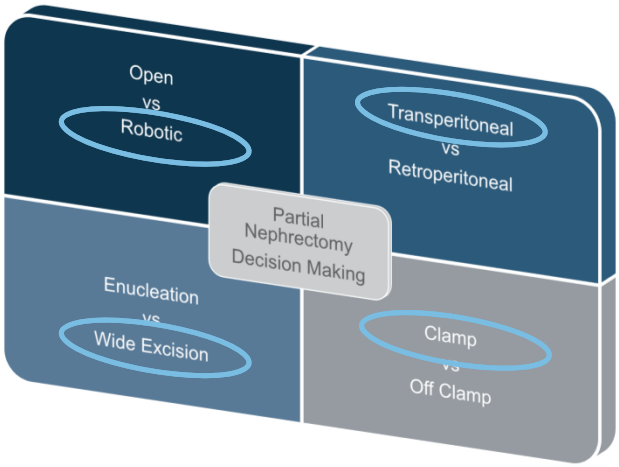
- Left first – bigger, but higher chance of partial



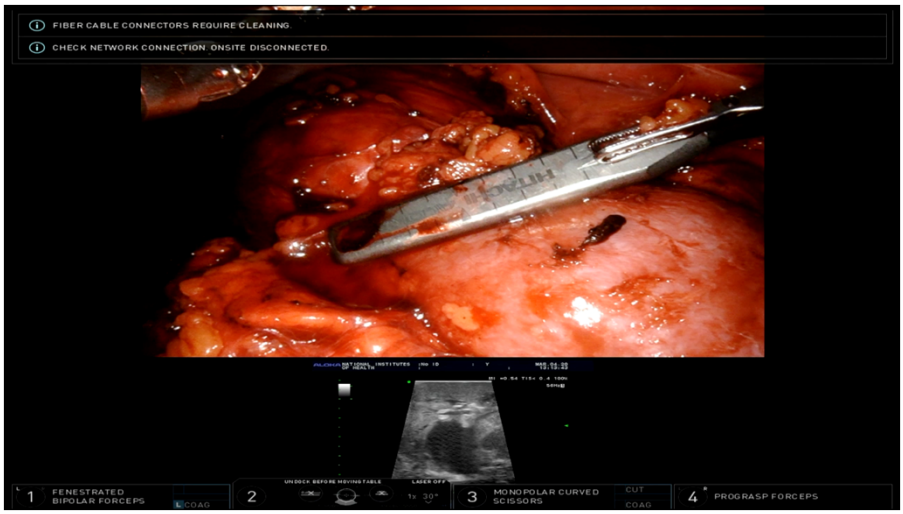


Decision Making

- Left first – bigger, but higher chance of partial



Case 3 - Left



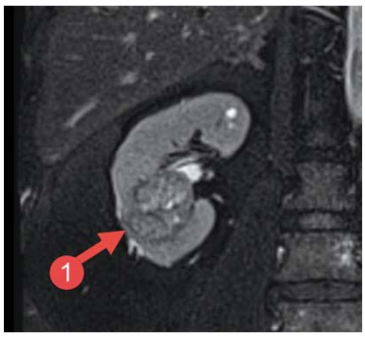
Case 3 Outcomes

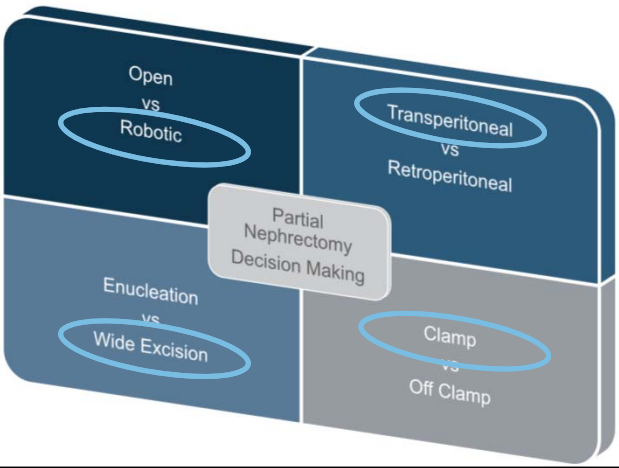
- Perioperative: WIT 29 min, EBL 350 cc
- Pathology: 8.5 cm chromophobe RCC, negative margin
- Discharge Cr 1.3, GFR 60

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

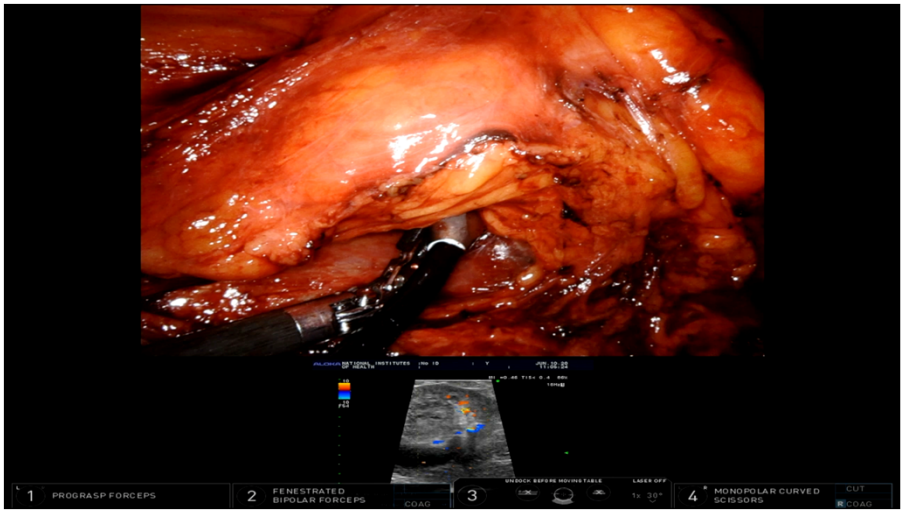
Decision Making

- 6 weeks later – right side





Case 3- Right



American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Case 3 – Right Side

- Too hot = Radical Nephrectomy
- 3 cm FG 3 ccRCC invading sinus fat (pT3a), negative margins
- Discharge Cr 2.0, GFR 38

Conclusion

- Decision to perform PN – weigh oncologic risk versus competing risks of surgery.
- Decision making during PN requires input of patient, tumor and surgeon factors.
- Being facile with each of the options give you more tools in the armamentarium (2^4 = 16 surgical options).

HOW IMMUNOTHERAPY FITS IN THE TREATMENT ALGORITHM FOR PATIENTS WITH RENAL CELL CARCINOMA

David McDermott, MD
Beth Israel Deaconess Medical Center
Harvard Medical School

Beth Israel Lahey Health

Beth Israel Deaconess Medical Center | HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Disclosure Information

David F. McDermott, MD

Consultant for: Merck, Bristol-Myers Squibb, Genentech, Pfizer, Exelixis, Alkermes Inc, Iovance

Grant/Research support from: Prometheus Labs, BMS, Merck

Speaker's Bureau for: None

Stockholder in: None

Honoraria from: None

Employee of: None

DF/HCC
DANA-FARBER / HARVARD CANCER CENTER

Kidney Cancer Program

July 16th, 2020

Leader:

David McDermott[BIDMC]

Co-Leaders:

Bill Kaelin[DFCI]

Sabina Signoretti[BWH]

Toni Choueiri[DFCI]

Othon Iliopoulos[MGH]

M. Dror Michaelson[MGH]

Identify the drug target: block PD-1/PD-L1

Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation

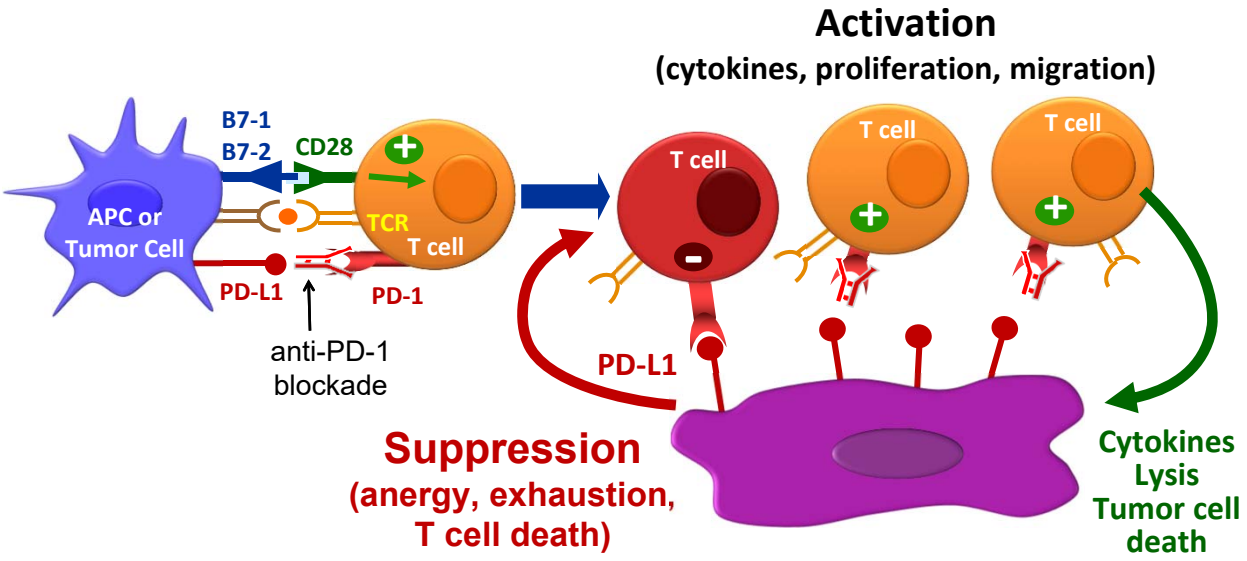
By Gordon J. Freeman,* Andrew J. Long,‡ Yoshiko Iwai,§ Karen Bourque,‡ Tatyana Chernova,* Hiroyuki Nishimura,§ Lori J. Fitz,‡ Nelly Malenkovich,* Taku Okazaki,§ Michael C. Byrne,‡ Heidi F. Horton,‡ Lynette Fouser,‡ Laura Carter,‡ Vincent Ling,‡ Michael R. Bowman,‡ Beatriz M. Carreno,‡ Mary Collins,‡ Clive R. Wood,‡ and Tasuku Honjo§

J. Exp. Med. © The Rockefeller University Press • 0022-1007/2000/10/1027/08 $5.00
Volume 192, Number 7, October 2, 2000 1027–1034



CANCER CENTER AT BETH ISRAEL DEACONESS MEDICAL CENTER

Anti-PD-1: Blocking T cell Suppression



Keir ME et al, *Annu Rev Immunol* 2008; Pardoll DM, *Nat Rev Cancer* 2012

Kidney Cancer: Most Applied Sequence 2015

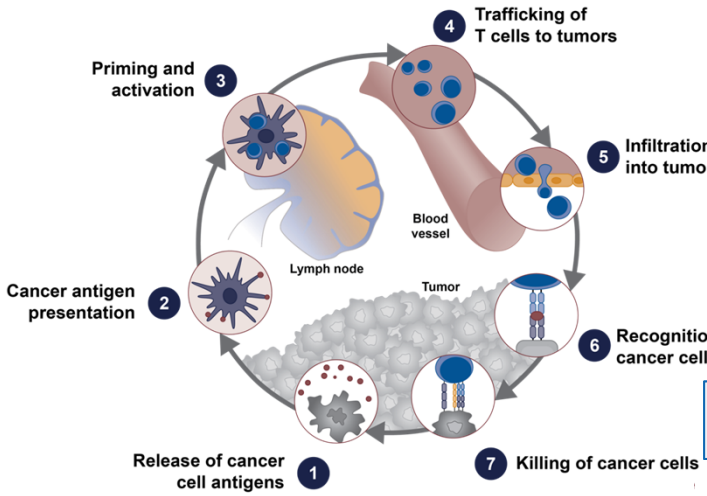
Setting	NCCN	Alternative
1st-Line Therapy	VEGF Blockade	
2nd-Line Therapy	PD-1 Blockade	

DF/HCC
DANA-FARBER / HARVARD CANCER CENTER

Can we combine therapies to increase remissions?

Slide courtesy of R. Sullivan, MGH

Is VEGF Inhibition Synergistic With Anti–PD-1?[1]



VEGF blockade[2-4]

PD-L1, PD-1 inhibitors

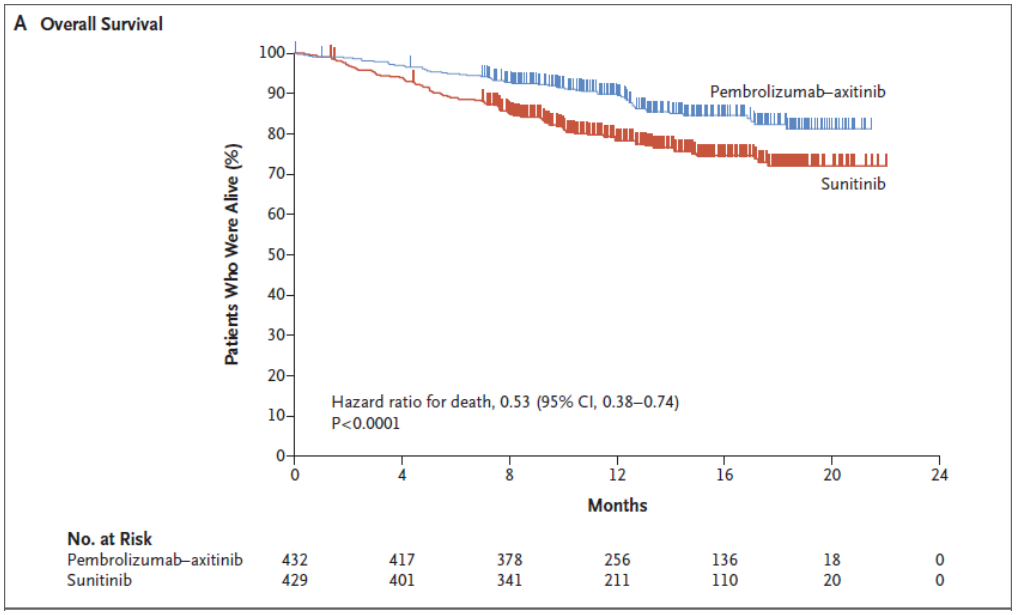
1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10. 2. Shrimali RK et al. *Can Res.* 2010;70:6171-6180. 3. Manning EA et al. *Clin Cancer Res.* 2007;13:3951-3959. 4. Motz GT et al. *Nat Med.* 2014;20:607-615.

PeerView.com

Fusion of First and Second-line Therapy

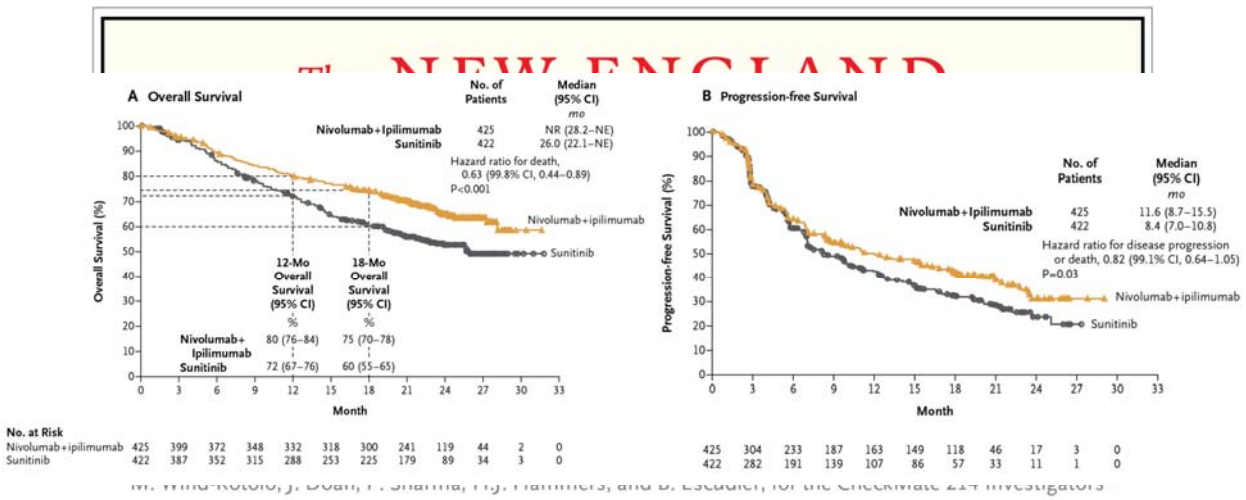
Setting	NCCN	Alternative
Treatment Naïve	**PD-1 + VEGF Blockade**	
3rd-Line Therapy	 Hodi[DFCI]	

DF/HCC DANA-FARBER / HARVARD CANCER CENTER



mRCC: Era of Front-Line Combination Therapy

Setting	NCCN	Alternative
1st-Line Therapy	PD-1 + CTLA-4 Blockade	
2nd-Line Therapy		



N Engl J Med 2018;378:1277-90

First-Line Phase 3 Trials in Advanced Kidney Cancer

Control	Experimental Arm
Sunitinib	**Axitinib + avelumab**
Sunitinib	**Bevacizumab + atezolizumab**
Sunitinib	**Nivolumab + cabozantinib**
Sunitinib	Lenvatinib + everolimus or lenvatinib + pembrolizumab
Sunitinib	**Axitinib + pembrolizumab**
Sunitinib	**Nivolumab + ipilimumab**

Should these approaches be applied to all patients?

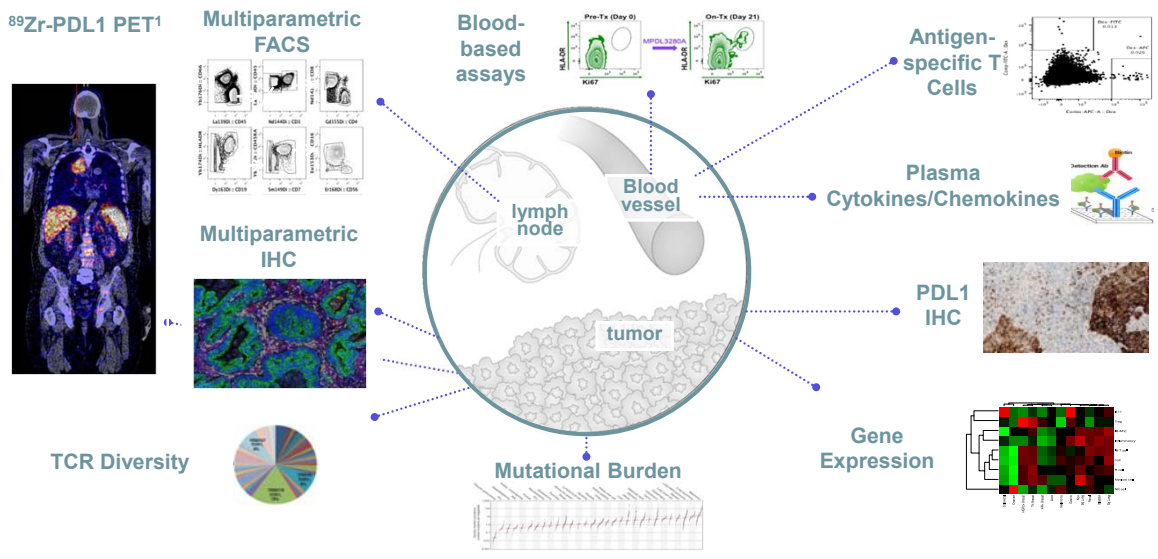
DF/HCC DANA-FARBER / HARVARD CANCER CENTER

Bold – met 1st endpoint

Making Remissions More Common in Solid Tumors

- **Patient Selection**
- Trial Design
- Novel Targets
- Novel Endpoints

Comprehensive Biomarker Platform



Modified from Chen DS SITC 2015
[1]De Vries, NIH workshop 2016

Chen DS, FDA-AACR

nature medicine

ARTICLES

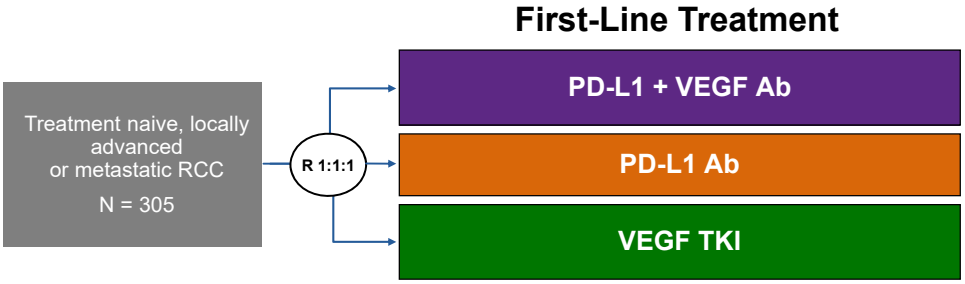
https://doi.org/10.1038/s41591-018-0053-3

Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma

David F. McDermott[1*], Mahrukh A. Huseni[2], Michael B. Atkins[3], Robert J. Motzer[4], Brian I. Rini[5], Bernard Escudier[6], Lawrence Fong[7], Richard W. Joseph[8], Sumanta K. Pal[9], James A. Reeves[10], Mario Sznol[11], John Hainsworth[12], W. Kimryn Rathmell[13], Walter M. Stadler[14], Thomas Hutson[15], Martin E. Gore[16], Alain Ravaud[17], Sergio Bracarda[18], Cristina Suárez[19], Riccardo Danielli[20], Viktor Gruenwald[21], Toni K. Choueiri[22], Dorothee Nickles[2], Suchit Jhunjhunwala[2], Elisabeth Piault-Louis[2], Alpa Thobhani[23], Jiaheng Qiu[2], Daniel S. Chen[2], Priti S. Hegde[2], Christina Schiff[2], Gregg D. Fine[2] and Thomas Powles[24]

DF/HCC DANA-FARBER / HARVARD CANCER CENTER

IMmotion150 Trial Design: Randomized P2



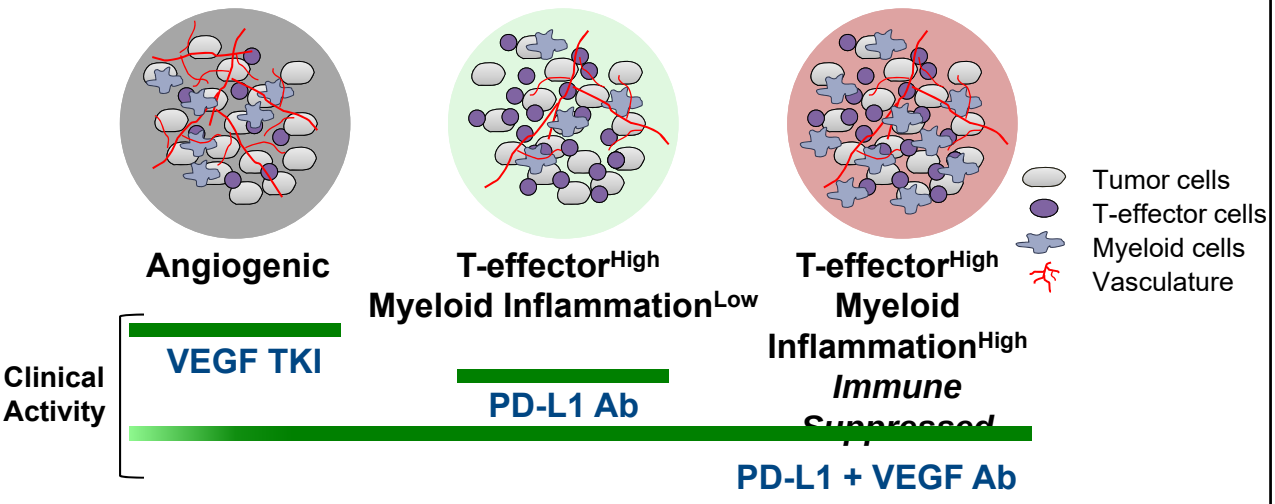
- IMmotion150 was designed to be **hypothesis generating** and inform the Phase III study IMmotion151
- **First Randomized Trial to:**
  - Explore ICB (atezo) + Targeted Therapy (bev)
  - Explore the association between outcome and TME gene signatures

TME, tumor microenvironment; ICB, immune checkpoint blockade

DF/HCC DANA-FARBER / HARVARD CANCER CENTER

McDermott D, et al. Nature Med 2018

Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mKC



DF/HCC DANA-FARBER / HARVARD CANCER CENTER

McDermott D, et al. Nature Med 2018

MUNICH 2018 ESMO congress

Molecular correlates differentiate response to atezolizumab + bevacizumab vs sunitinib: results from a Phase III study (IMmotion151) in untreated metastatic renal cell carcinoma

Brian I. Rini,[1] Mahrukh Huseni,[2] Michael B. Atkins,[3] David F. McDermott,[4] Thomas Powles,[5] Bernard Escudier,[6] Romain Banchereau,[2] Li-Fen Liu,[2] Ning Leng,[2] Jinzhen Fan,[2] Jennifer Doss,[2] Stefani Nalle,[2] Susheela Carroll,[2] Shi Li,[2] Christina Schiff,[2] Marjorie Green,[2] Robert J. Motzer[7]

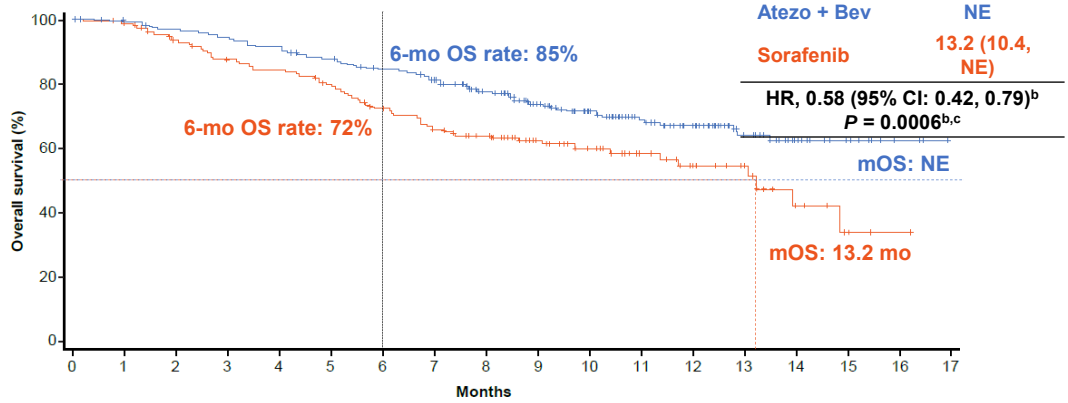
Rini et al, Lancet 2019 esmo 2019

Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150

Ann-Lii Cheng,[1] Shukui Qin,[2] Masafumi Ikeda,[3] Peter R. Galle,[4] Michel Ducreux,[5] Andrew X. Zhu,[6] Tae-You Kim,[7] Masatoshi Kudo,[8] Valeriy Breder,[9] Philippe Merle,[10] Ahmed Kaseb,[11] Daneng Li,[12] Wendy Verret,[13] Derek-Zhen Xu,[14] Sairy Hernandez,[13] Juan Liu,[14] Chen Huang,[14] Sohail Mulla,[15] Ho Yeong Lim,[16] Richard S. Finn[17]

[1]National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; [2]People's Liberation Army Cancer Center, Jinling Hospital, Nanjing, People's Republic of China; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]University Medical Center Mainz, Mainz, Germany; [5]Gustave Roussy Cancer Center, Villejuif, France; [6]Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]Seoul National University College of Medicine, Seoul, Korea; [8]Kindai University Faculty of Medicine, Osaka, Japan; [9]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Hospital La Croix-Rousse, Lyon, France; [11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [13]Genentech, Inc., South San Francisco, CA, USA; [14]Roche Product Development, Shanghai, People's Republic of China; [15]Hoffmann-La Roche Limited, Mississauga, ON, Canada; [16]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [17]Jonsson Comprehensive Cancer Center, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

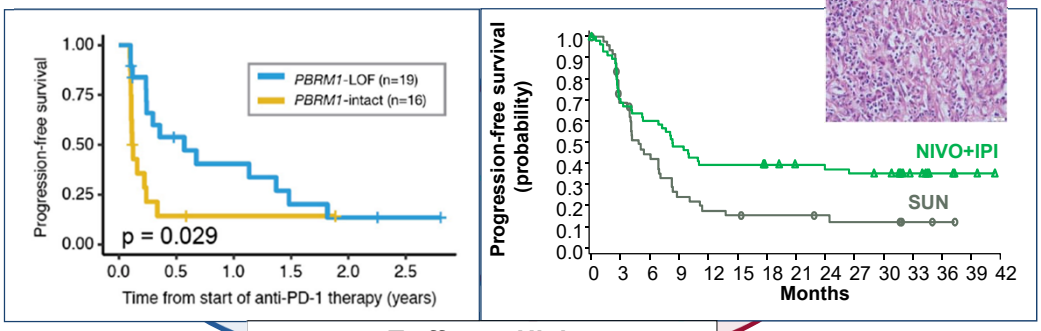
OS: co-primary endpoint

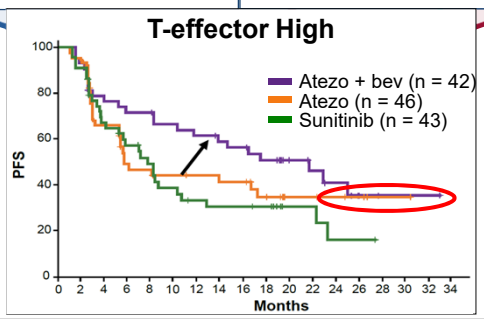


No. at risk																	
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Biomarker Model





- All inter-related
- Some tumors may have a larger sweet spot

DF/HCC
DANA-FARBER / HARVARD CANCER CENTER

Making Remissions More Common in Kidney Cancer

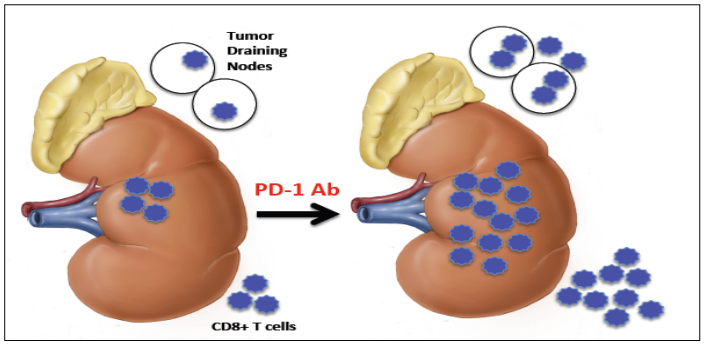
- Patient Selection
- **Trial Design**
- Novel Targets – from Human Tissue
- Novel Endpoints

Phase 3 Trials Assessing Adjuvant Immunotherapy for High-Risk Localized RCC[1]

Treatment Arms	Primary Endpoint	Trial	ClinicalTrials.gov ID
Atezolizumab vs placebo	DFS	IMmotion010	NCT03024996
Pembrolizumab vs placebo	DFS	KEYNOTE-564	NCT03142334
Neoadjuvant nivolumab → surgery → adjuvant nivolumab vs observation	RFS	PROSPER RCC	NCT03055013
Nivolumab + ipilimumab vs placebo	DFS	CheckMate 914	NCT03138512
Durvalumab vs durvalumab + tremelimumab vs active surveillance	DFS and OS	RAMPART	NCT03288532

1. https://www.clinicaltrials.gov. Accessed August 15, 2019.

Rationale for Pre-Surgery Anti-PD-1 Priming

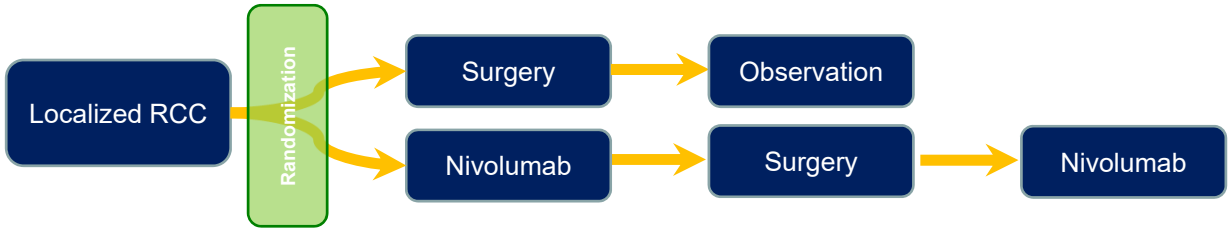


Harshman Cancer J 2014.

- Ongoing but unsuccessful anti-tumor T cell response in the tumor, tumor microenvironment, and draining lymph nodes
- Post-PD-1 blockade anti-tumor CD8 T cells may preferentially expand in these areas → traffic to distant sites as memory cells → eradicate micrometastases
- Nephrectomy will remove the majority of these effector cells and cytokines potentially resulting in a less potent response
- We know nivolumab can work when there is tumor present; no idea if it does when there is little or no antigen

Woo Cancer Res 2012, C Drake personal comm.

PROSPER RCC: Phase III Perioperative PD-1 Blockade



Harshman[DFCI]

Drake[CUMC]

DF/HCC
DANA-FARBER / HARVARD CANCER CENTER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

2018

Making Remissions More Common in Kidney Cancer

- Patient Selection
- Trial Design
- **Novel Targets**
- Novel Endpoints

The Landscape of Novel Agents in RCC

Agent	Mechanism of Action	Results from Ongoing Early-Phase Studies
PT2977/MK-6482[1-3]	Binds to HIF-2α and prevents heterodimerization with HIF-1β	N = 55; PR 24%, PFS 11 mo
NKTR-214[4]	Pegylated IL-2	N = 26; ORR 46% (in combo with nivolumab)
TRC105 + axitinib[5]	Anti-Endoglin/anti-VEGFR	N = 150; mPFS 6.7 mo combo (HR 1.4 vs axi)

1. Choueiri TK, et al. IKCS 2019. 2. Jonasch E, et al. ESMO 2019. Abstract 3170. Choueiri TK, et al. GU Ca Symp 2020. Abstract 611. 4. Diab A, et al. ASCO 2018. Abstract 3006. 5. Choueiri TK, et al. ESMO 2019. Abstract 3527.

Making Remissions More Common in Kidney Cancer

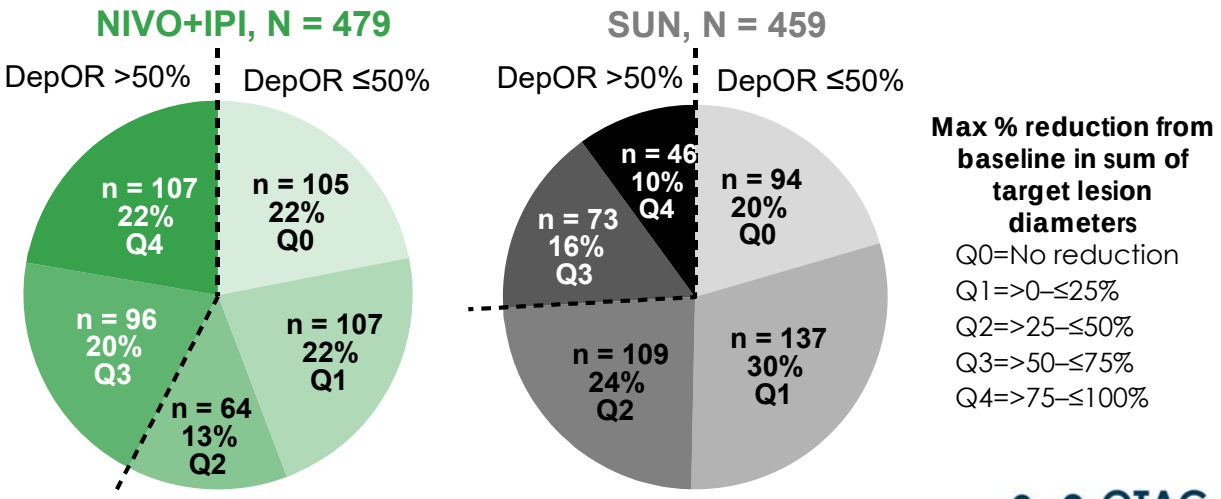
- Patient Selection
- Trial Design
- Novel Targets
- **Novel Endpoints**

mRCC: Era of Front-Line Combination Therapy

Setting	NCCN	Alternative
1st-Line Therapy	PD-1 + CTLA-4 Blockade	
2nd-Line Therapy		

Median follow-up: 32.4 months

Depth of Response: Proportion of Evaluable Patients by Quartile in ITT



Max % reduction from baseline in sum of target lesion diameters

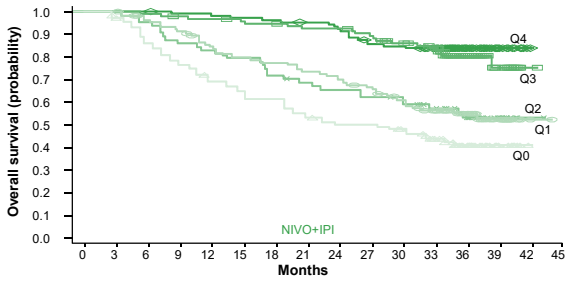
Q0=No reduction
Q1=>0–≤25%
Q2=>25–≤50%
Q3=>50–≤75%
Q4=>75–≤100%

Grünwald V et al. Poster presentation at ESMO 2019. Abstract 2368.

OTAC ONCOLOGY TUMOR ADVISORY COUNCIL

Median follow-up: 32.4 months

Depth of Response: Associated with improved Overall Survival

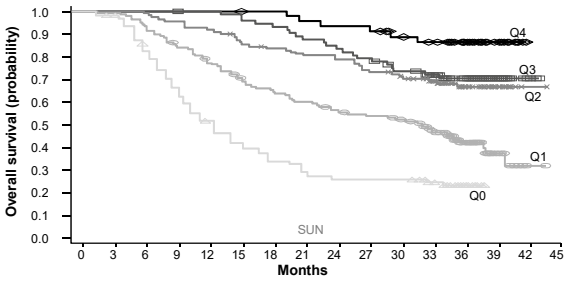


No. at risk

Q0	105	100	89	79	71	64	62	56	50	49	46	36	22	7	0	0
Q1	107	106	100	95	86	80	78	74	70	66	57	48	33	14	1	0
Q2	64	64	61	55	53	51	46	43	41	39	37	32	23	10	1	0
Q3	96	96	95	93	92	90	89	86	86	82	76	61	30	9	1	0
Q4	107	107	107	105	104	103	102	100	96	89	88	75	39	12	1	0

Quartile	Events	Median OS, mo (95%CI)	HR (95% CI) [a]
Q0	59/105	26.9 (18.6–NE)	–
Q1	46/107	NR (29.9–NE)	0.63 (0.43–0.93)
Q2	29/64	NR (26.1–NE)	0.65 (0.42–1.01)
Q3	18/96	NR (NE)	0.22 (0.13–0.38)
Q4	17/107	NR (NE)	0.18 (0.11–0.32)

[a]When compared with Q0 in the NIVO+IPI arm



No. at risk

Q0	94	90	72	60	45	36	30	25	23	23	23	18	5	0	0	0
Q1	137	136	127	114	104	91	84	79	73	69	65	52	32	10	1	0
Q2	109	109	108	104	100	92	89	86	84	78	74	62	36	14	1	0
Q3	73	73	73	72	72	69	67	63	60	57	50	46	34	14	2	0
Q4	46	46	46	46	46	45	45	43	42	41	37	34	25	12	0	0

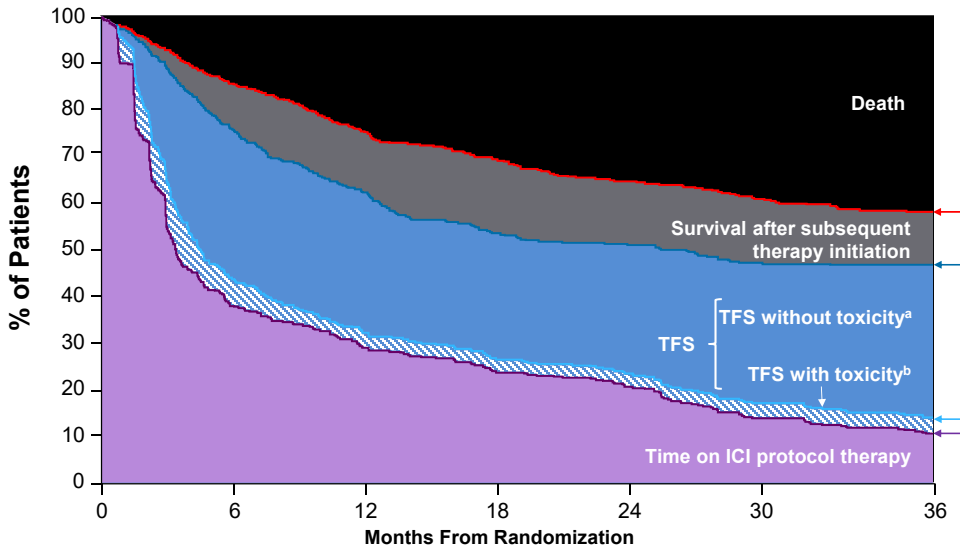
Quartile	Events	Median OS, mo (95%CI)	HR (95% CI) [a]
Q0	69/94	12.4 (9.5–15.0)	–
Q1	78/137	31.9 (22.1–37.8)	0.48 (0.35–0.67)
Q2	35/109	NR (NE)	0.21 (0.14–0.32)
Q3	21/73	NR (NE)	0.18 (0.11–0.29)
Q4	6/46	NR (NE)	0.08 (0.03–0.17)

[a]When compared with Q0 in the SUN arm

Grünwald V et al. Poster presentation at ESMO 2019. Abstract 2368.

OTAC ONCOLOGY TUMOR ADVISORY COUNCIL

Treatment-free Survival (TFS)



Time-to-Event Endpoints

Overall survival: From randomization until death, or censored at date last known alive

Time to subsequent therapy initiation or death: From randomization until subsequent systemic anticancer therapy initiation or death, whichever occurred first, or censored at date last known alive and free of subsequent therapy

Time to cessation of both ICI protocol therapy and toxicity[c]: From randomization until cessation of ICI protocol therapy plus duration of time with toxicity[c] (or censored if alive on protocol therapy or treatment-free with toxicity)

Time to ICI protocol therapy cessation: From randomization until cessation of ICI protocol therapy (or censored at date last known alive on ICI protocol therapy)

[a]Time after cessation of ICI protocol therapy without toxicity, before initiation of subsequent systemic anticancer therapy or death
[b]Time after cessation of ICI protocol therapy with toxicity while treatment-free
[c]Includes toxicity persisting since protocol therapy and toxicity newly presenting after protocol therapy cessation

Regan et al, JCO 2019

Standard Therapy for mRCC: 2030

Setting	NCCN	Alternative
1st-Line Therapy	Treatment based on TME Profile	
2nd-Line Therapy	**Not Necessary**	

TME indicates tumor microenvironment.
Smyth MJ, et al. *Nat Rev Clin Oncol*. 2016;13(3):143-158.

HOW WILL YOU SEQUENCE NOW?
Personalizing Care Along the RCC Treatment Continuum When There Are Many Options

IPER® Physicians' Education Resource, LLC

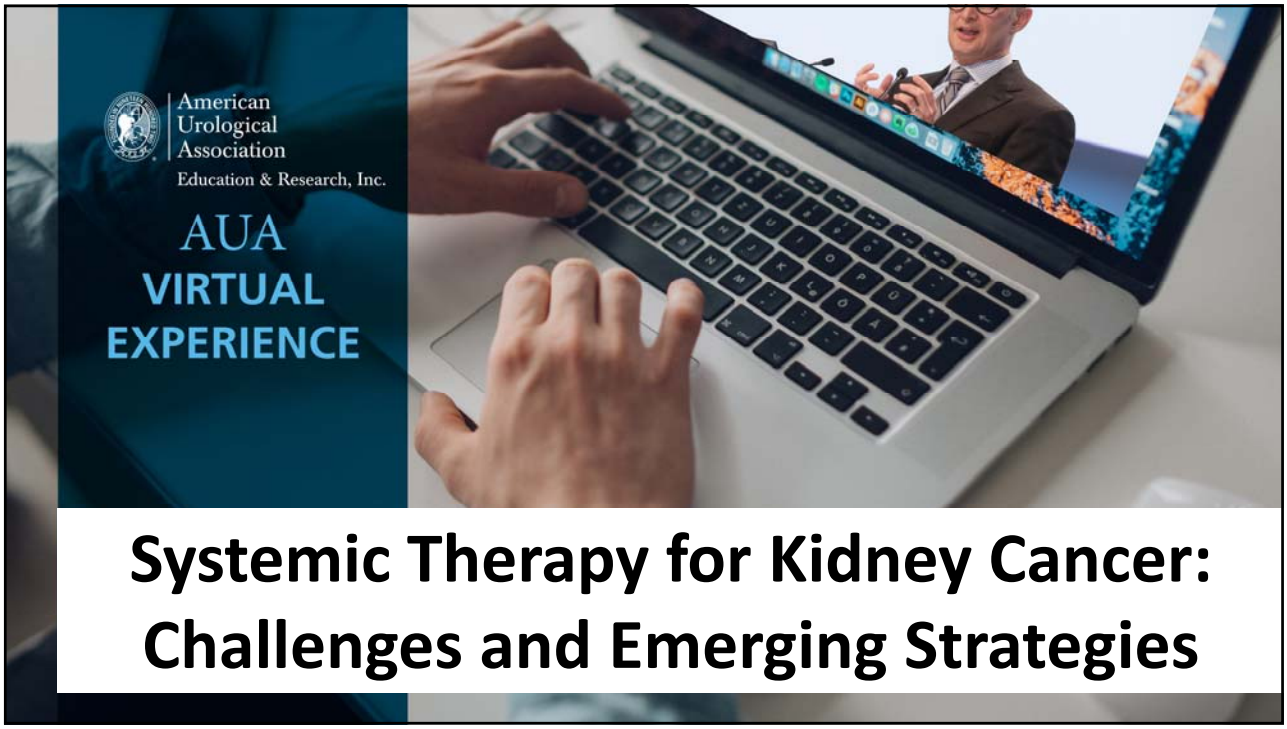
Making Remissions More Common in Kidney Cancer

- Patient Selection
- Trial Design
- Novel Endpoints
- Novel Targets

Acknowledgements

- DFHCC Collaborators
  - Kidney Cancer
    - Toni Choueiri
    - Sabina Signoretti
    - Bill Kaelin (SPORE co-PI)
    - Gordon Freeman
    - Dror Michaelson
    - Cathy Wu
  - Melanoma
    - Steve Hodi
    - Ryan Sullivan
    - Beth Buchbinder
    - Keith Flaherty
- GLCCC – Mike Atkins, Dick Schegel
- MIT – David Sabatini
- HMS – Arlene Sharpe
- Funding
  - Kidney Cancer SPORE - P50-CA101942
  - DFHCC Kidney Cancer Program - P30-CA006516
  - Department of Defense - KC170036
  - BIDMC Development Office
- Research Administration
  - Tara Johnston
  - Mary Mahoney, Ramesh Gunawardena
  - Stephanie Wasserman, Denise Graham

NIH NATIONAL CANCER INSTITUTE



American Urological Association
Education & Research, Inc.

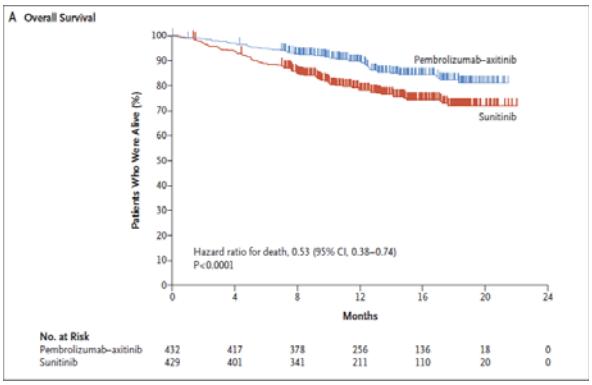
AUA VIRTUAL EXPERIENCE

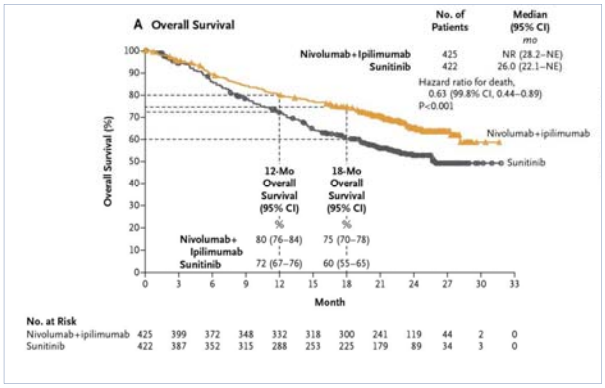
Systemic Therapy for Kidney Cancer: Challenges and Emerging Strategies

Ramaprasad Srinivasan, M.D., Ph.D.
Investigator and Head, Molecular Cancer Section
Urologic Oncology Branch, Center for Cancer Research
National Cancer Institute

NIH NATIONAL CANCER INSTITUTE

Front Line Therapy: Advanced Clear Cell RCC





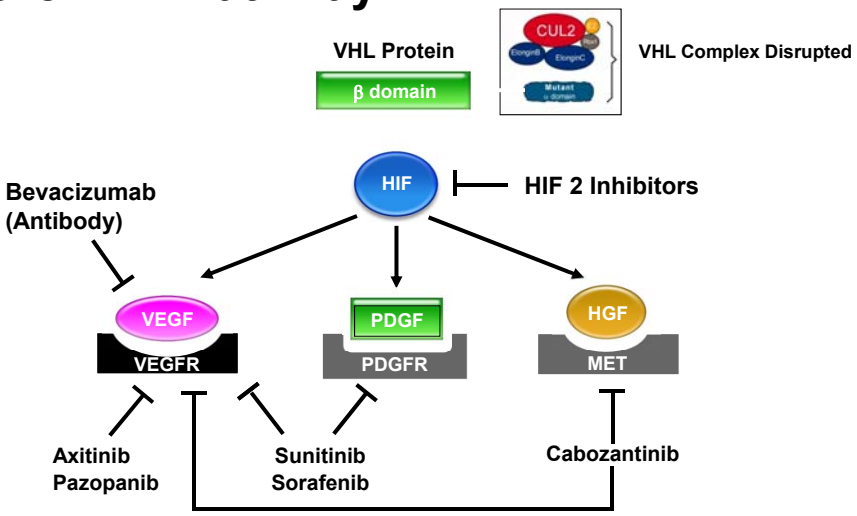
Motzer et al, NEJM 2109
Motzer et al NEJM, 2018

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Advanced Clear Cell RCC: Options Beyond ICI and VEGFR TKIs

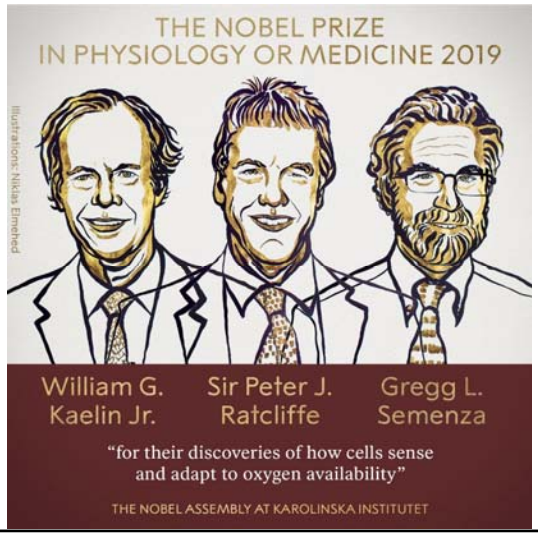
- Cabozantinib, Lenvatinib plus Everolimus
- Other VEGFR TKIs/ICI/Combinations not previously used
- Choices based on studies in patients who had failed antiangiogenic therapy
- No phase 3 randomized studies in patients who have progressed on ICI/ICI-based combinations
- Novel approaches needed

Targeting the VHL Pathway



American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Targeting HIF 2-α in Clear Cell RCC



Targeting HIF 2-α in Clear Cell RCC

ARTICLE

The contribution of VHL substrate binding and HIF1-α to the phenotype of VHL loss in renal cell carcinoma

Jodi K. Maranchie,[1] James R. Vasselli,[1] Joseph Riss,[2] Juan S. Bonifacino,[3] W. Marston Linehan,[1,4] and Richard D. Klausner[2]

[1]Urologic Oncology Branch
[2]Laboratory of Biosystems and Cancer, Center for Cancer Research, National Cancer Institute
[3]Cell Biology and Metabolism Branch, National Institute of Child Health and Development
National Institutes of Health, Bethesda, Maryland 20892
[4]Correspondence: uob@mail.nih.gov

ARTICLE

Inhibition of HIF is necessary for tumor suppression by the von Hippel-Lindau protein

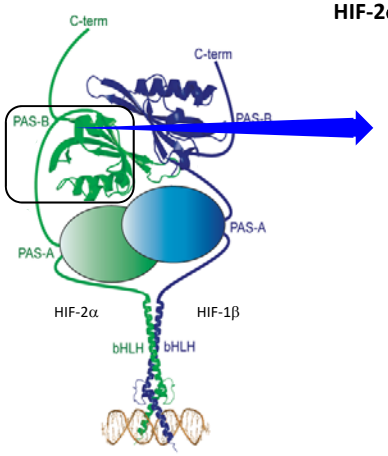
Kelichi Kondo,[1] Jeff Kim,[1] Eijiro Nakamura,[1] Mirna Lechpammer,[1] and William G. Kaelin, Jr.[1,2,3]

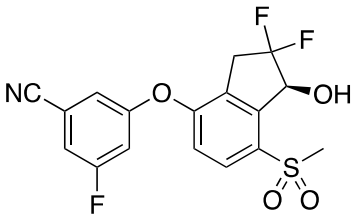
[1]Department of Adult Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115
[2]Howard Hughes Medical Institute, Chevy Chase, Maryland
[3]Correspondence: william_kaelin@dfci.harvard.edu

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Development of Small Molecule HIF2-α Inhibitor

HIF-2α antagonist bound to HIF-2α PAS-B* domain





PT2385

Wallace *et al. Cancer Res* **2016**, *76*:5491
Cho *et al. Nature* **2016**, *539*:107
Chen *et al. Nature* **2016**, *539*:112
Courtney *et al. J Clin Oncol* **2018**

Slide courtesy of Naseem Zojwalla, Peloton

HIF2α Inhibitor- PT2385: 1st Generation HIF-2α Inhibitor

- N = 26 in dose escalation at doses of 100-1800 mg PO BID
- N = 25 in expansion at 800 mg PO BID
- Median prior therapies: 4
- Anemia most common adverse event
- ORR: CR 2%; PR 12%; SD 52%
- **High variability in drug levels among patients**

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

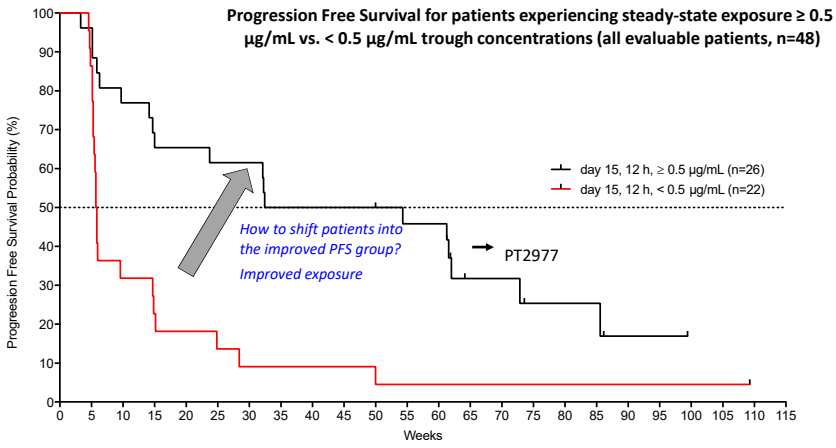
Phase I Dose-Escalation Trial of PT2385, a First-in-Class Hypoxia-Inducible Factor-2α Antagonist in Patients With Previously Treated Advanced Clear Cell Renal Cell Carcinoma

Kevin D. Courtney, Jeffrey R. Infante, Elaine T. Lam, Robert A. Figlin, Brian I. Rini, James Brugarolas, Naseem J. Zojwalla, Ann M. Lowe, Keshi Wang, Eli M. Wallace, John A. Josey, and Toni K. Choueiri

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

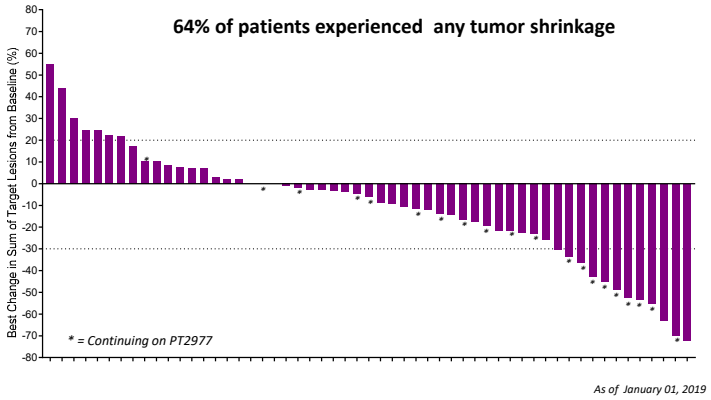
HIF2α Inhibitor- PT2385: 1st Generation HIF-2α Inhibitor

Sustained HIF-2α target engagement is necessary to achieve clinically meaningful benefit



Slide courtesy of Naseem Zojwalla, Peloton

HIF2α Inhibitor- PT2977/MK-6482: Phase 1/2 study in RCC- Best Change in Tumor Size

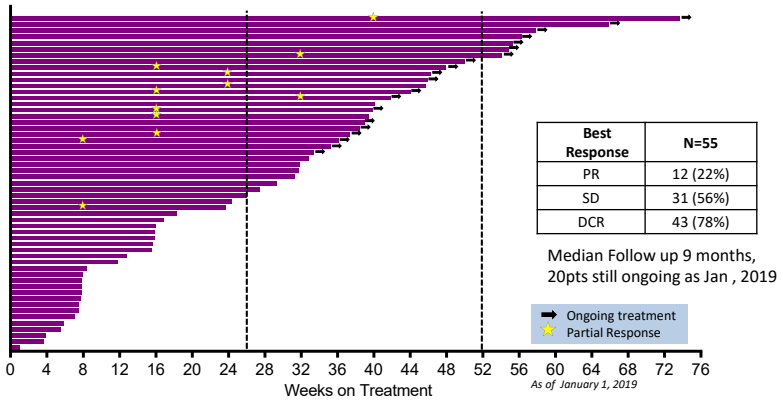


As of January 01, 2019

Choueiri et al., KCA; Slide courtesy of Naseem Zojwalla, Peloton

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

HIF2α- PT2977/MK-6482: Duration of Treatment



Best Response	N=55
PR	12 (22%)
SD	31 (56%)
DCR	43 (78%)

Median Follow up 9 months,
20pts still ongoing as Jan , 2019

Ongoing treatment
Partial Response

Choueiri et al., KCA; Slide courtesy of Naseem Zojwalla, Peloton

HIF2α- PT2977/MK-6482: Safety

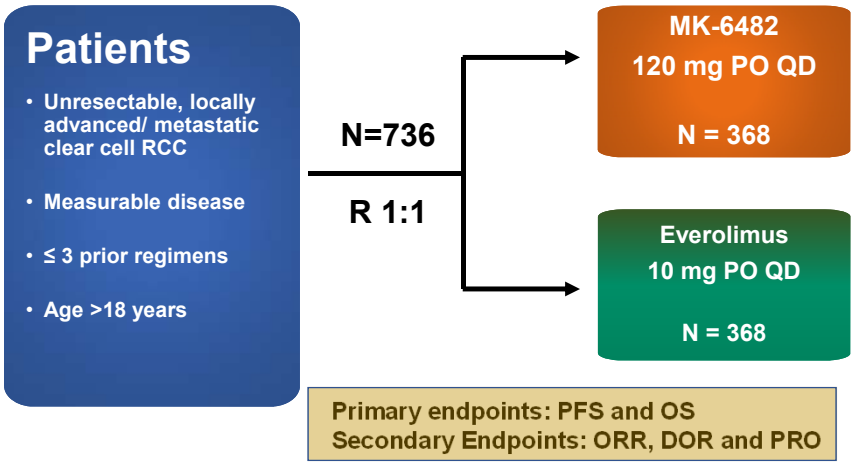
- **Anemia**
  - Most common AE
  - Expected AE due to Regulation of EPO with HIF2α inhibitors
  - Managed well with EPO replacement as clinically indicated (EPO therapy initiated on average 6-8 weeks)
- **Hypoxia**
  - Average time of onset is after 3-4 weeks of therapy
  - Majority of cases triggered by an acute event
- No cardiovascular toxicities reported with treatment with HIF2α inhibitors (no Hypertension, no CHF…)

Safety profile compares well with current VEGFR TKI

Choueiri et al., KCA; Slide courtesy of Naseem Zojwalla, Peloton

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Phase 3 MK 6482 vs Everolimus in clear cell RCC



Choueiri et al, ASCO 2020

VHL Associated Tumors: Principles of Management

Local Control: Surgery/Ablation

- Minimize the risk of metastases (RCC, PNET, pheochromocytoma)
- Control of local symptoms (CNS, retinal, ELST) or systemic complications (pheochromocytoma)

Metastatic Disease: Systemic Therapy

- No dedicated/VHL-specific studies
- Management derived from standard of care for sporadic tumors

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Why Should We Explore Alternative Treatment Strategies?

- **Current therapy associated with significant morbidity**
  - Multiple surgeries during a patient's lifetime
  - Perioperative complications from surgery
  - Gradual loss of renal function, pancreatic or adrenal insufficiency
  - Neurologic deficits
- **Lifelong risk of developing new lesions**

Systemic Therapy as an Alternative to Surgery

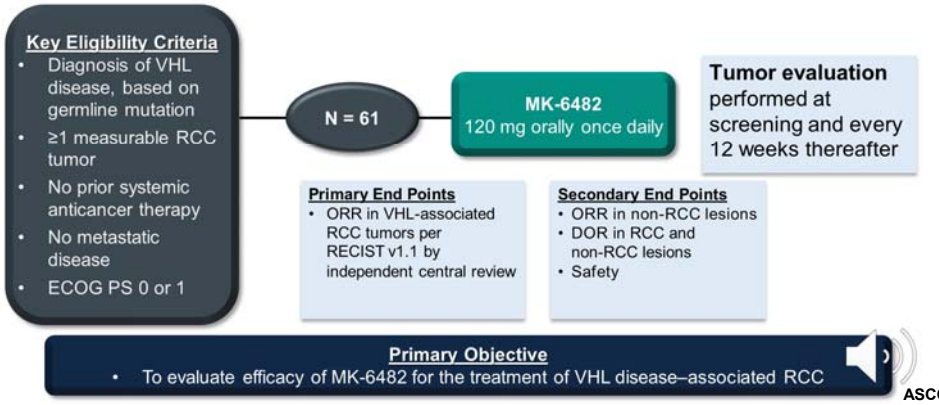
Goals of Therapy

- Delay or avoid surgery
  - Prevent tumor growth/reduce tumor size
  - Prevent new tumors
- Prevent distant spread/metastasis
- Improve quality of life
- Preserve function
- Acceptable short and long term side effects

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

HIF 2-α Inhibition as a Therapeutic Strategy in VHL

Phase 2 Study: MK-6482 for VHL-Associated RCC (NCT03401788)



ASCO Annual Meeting 2020

Confirmed ORR in RCC Lesions by Independent Central Review

	All Patients N = 61
ORR, % (95% CI)	27.9 (17.1-40.8)
Best response, n (%)	
CR	0
PR	17 (27.9)
SD	43 (70.5)
Unconfirmed PRs[a]	8 (13.1)
PD	0
Not Evaluable	1 (1.6)

[a]Documented at 1 time point and to be confirmed at subsequent time point. Data cutoff: December 6, 2019.

ASCO Annual Meeting 2020

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Maximum Change From Baseline in Target RCC Lesions by Independent Central Review

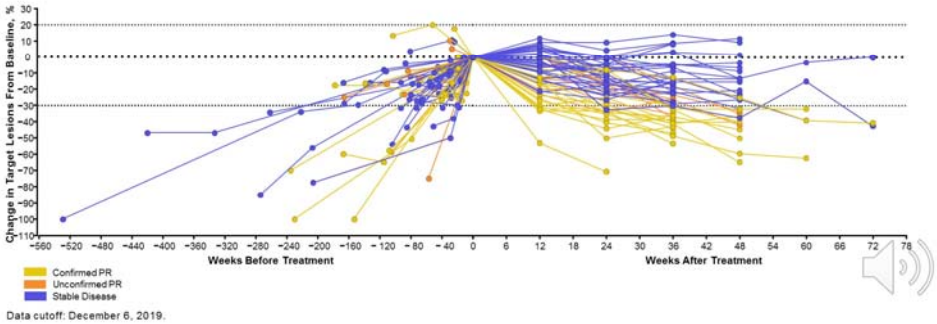
- 86.9% (53/61) of patients had decrease in size of target lesions

[a]Documented at 1 time point and to be confirmed at subsequent time point. Data cutoff: December 6, 2019.

ASCO Annual Meeting 2020

Longitudinal Change From Baseline in Target RCC Lesions by Independent Central Review

- Median linear growth rate
  - +3.63 mm/year (range, 3.06-10.91) before treatment
  - -6.40 mm/year (range 23.32-4.48) after treatment



Data cutoff: December 6, 2019.

ASCO Annual Meeting 2020

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

All-Cause Adverse Events ≥10%

AE, n (%)	All Patients N = 61			
	Any Grade	Grade 1/2	Grade 3[a]	Grade 4/5[b,c]
Anemia	53 (86.9)	51 (83.6)	2 (3.3)	0
Fatigue	35 (57.4)	32 (52.5)	3 (4.9)	0
Headache	22 (36.1)	22 (36.1)	0	0
Dizziness	19 (31.1)	19 (31.1)	0	0
Nausea	15 (24.6)	15 (24.6)	0	0
Dyspnea	12 (19.7)	11 (18.0)	1 (1.6)	0
Arthralgia	10 (16.4)	10 (16.4)	0	0
Alanine aminotransferase increased	10 (16.4)	10 (16.4)	0	0
Myalgia	9 (14.8)	9 (14.8)	0	0
Vision blurred	9 (14.8)	9 (14.8)	0	0
Constipation	8 (13.1)	8 (13.1)	0	0
Aspartate aminotransferase increased	7 (11.5)	7 (11.5)	0	0
Upper respiratory tract infection	7 (11.5)	7 (11.5)	0	0
Weight increased	7 (11.5)	6 (9.8)	1 (1.6)	0

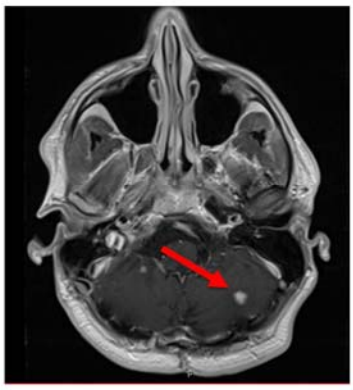
[a]1 patient was recorded as having hypoxia (grade 3).[b]1 patient was recorded with retinal detachment (grade 4). [c]1 patient died from toxicity of various agents (grade 5).
Data cutoff: December 6, 2019.

Presented By Eric Jonasch at TBD

American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

Response in Non-RCC Tumors



Baseline

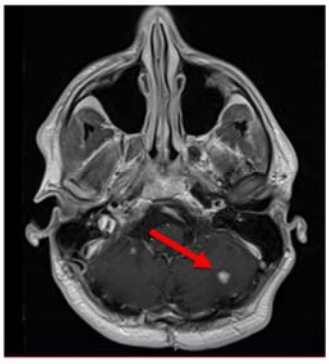
Images courtesy of Ramaprasad Srinivasan. Used with permission.
Data cutoff: December 6, 2019.

ASCO Annual Meeting 2020

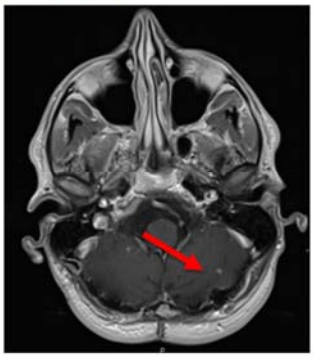
American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

Response in Non-RCC Tumors



Baseline



Week 24

Images courtesy of Ramaprasad Srinivasan. Used with permission.
Data cutoff: December 6, 2019.

ASCO Annual Meeting 2020

American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

Response in Non-RCC Tumors

Baseline

Images courtesy of Ramaprasad Srinivasan. Used with permission.
Data cutoff: December 6, 2019.

ASCO Annual Meeting 2020

American Urological Association Education & Research, Inc.

AUA VIRTUAL EXPERIENCE

Response in Non-RCC Tumors

Baseline

Week 24

Images courtesy of Ramaprasad Srinivasan. Used with permission.
Data cutoff: December 6, 2019.

Presented By Eric Jonasch at TBD

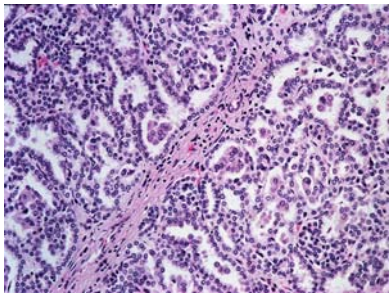
Papillary RCC

- Papillary RCC is the second most common histological subtype of RCC and occurs in both familial and sporadic forms
- Patients with advanced pRCC exhibit poorer survival outcomes compared to clear cell RCC[1]
- Phase II studies of first line VEGFR TKIs, mTOR inhibitors, and MET inhibitors in papillary RCC demonstrate a median PFS of 5-8 months[2-5]
- IO monotherapy and combination therapy has shown promise in pRCC with a 25-27% ORR[6-8]

1. Roseillo, *World J. Urol* 2020; 2. Tannir, *Eur Urol* 2016; 3. Armstrong, *Lancet Oncol*. 2016; 4. Escudier, *Eur J Cancer* 2016; 5. Choueiri, *J Clin Oncol* 2017; 6. McGregor, *J Cl Oncol* 2020; 7. McDermott, *J Clin Oncol* 2019; 8. Powles *J Clin Oncol* 2020

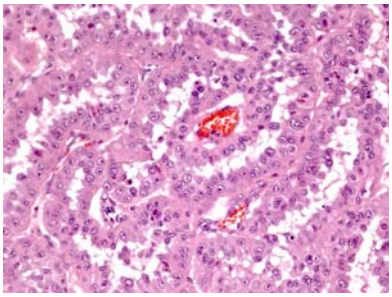
American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Papillary RCC: Histologic Subtypes



Type 1

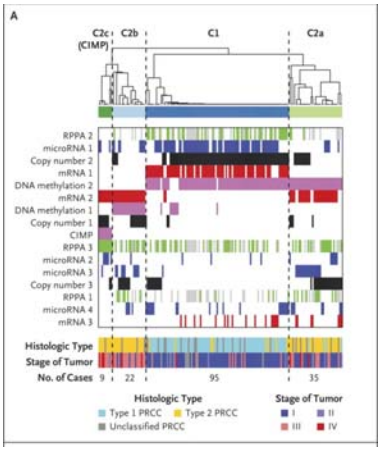
MET
Gain of Ch 7 and 17

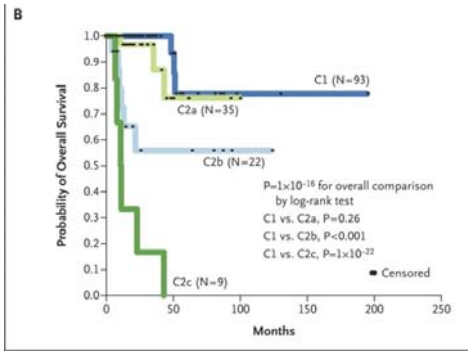


Type 2 (Non Type 1)

FH
***NRF2* Pathway**
CDKN2A
Chromatin Remodeling

Type 2 Papillary RCC: 4 Distinct Subgroups



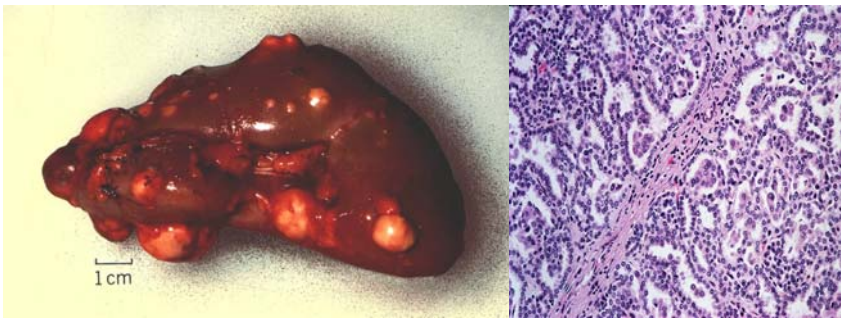


TCGA, NEJM 2015

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

Hereditary Papillary Renal Cancer (HPRC)

- Familial form of type I papillary RCC
- Affected individuals present with bilateral multifocal papillary RCC
- Characterized by activating mutations in *MET*



Met Activation in Papillary Renal Cancer

- **Activating Mutations in *MET***
  - Germline mutations in tyrosine kinase domain (HPRC)
  - Somatic activating mutations seen in ~15% of sporadic papillary RCC
  - *MET* fusion or splice variants~ 5%
- **Duplication of chromosome 7**
  - ~ 50% - 70% of all papillary RCC
  - Both *MET* and its activating ligand *HGF* located on Ch 7
- **MET and Ch7 alterations seen predominantly in type 1 papillary RCC**

Nat Genet 1997; Am J Path 1999;
TCGA, NEJM 2015;

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

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

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%**

SAVOIR study design

Open-label, randomized, Phase III trial (NCT03091192)

Patients with locally advanced or metastatic PRCC

Key inclusion criteria
- ≥18 years
- Central confirmation of a *MET*-driven tumor (chromosome 7 gain / *MET* or *HGF* amplification / *MET* kinase domain mutations)*
- Measurable disease
- Karnofsky Performance Status ≥80%
- Patients could have received prior systemic treatment in the advanced setting or be treatment-naive#

Savolitinib 600 mg QD (or 400 mg if <50 kg)

Randomized 1:1

Sunitinib 50 mg QD in 6-week cycles of 4 weeks on / 2 weeks off

RECIST 1.1 assessment every 6 weeks[1] until objective progressive disease

Approximately 360–450 patients were planned to be screened, in order to randomize ~180 patients

After external data on predicted PFS with sunitinib in patients with *MET*-driven disease became available, study enrollment was closed early[1]

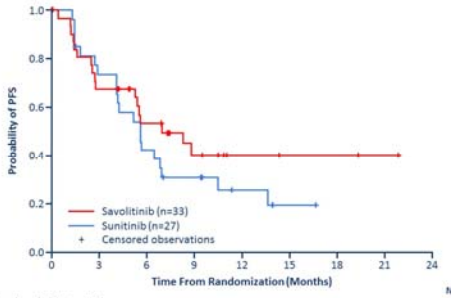
- **Primary endpoints:** PFS by BICR
- **Secondary endpoints**: OS and ORR by BICR, safety and HRQoL

1. Albiges et al. ASCO; May 29–31, 2020; presented here: abstract e19321; 2. Frigault et al. AACR 2018;78:4541–4541.
*In the absence of co-occurring *FH* or *VHL* mutations. #Patients were excluded if they had previously received sunitinib or a MET inhibitor. †Follow-up every 12 weeks after first year. BICR, blinded independent central review; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRCC, papillary renal cell carcinoma; QD, once daily; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors

Toni Choueiri, ASCO, 2020

American Urological Association Education & Research, Inc.
AUA VIRTUAL EXPERIENCE

SAVOIR progression-free survival



Number of Patients at Risk										Number Randomized/ Number of Events
Savolitinib	33	21	15	8	4	3	3	1	0	33/17
Sunitinib	27	19	11	7	4	1	0	0	0	27/20

Median PFS by BICR in months (95% CI)
Savolitinib 7.0 (2.8, NC)
Sunitinib 5.6 (4.1, 6.9)

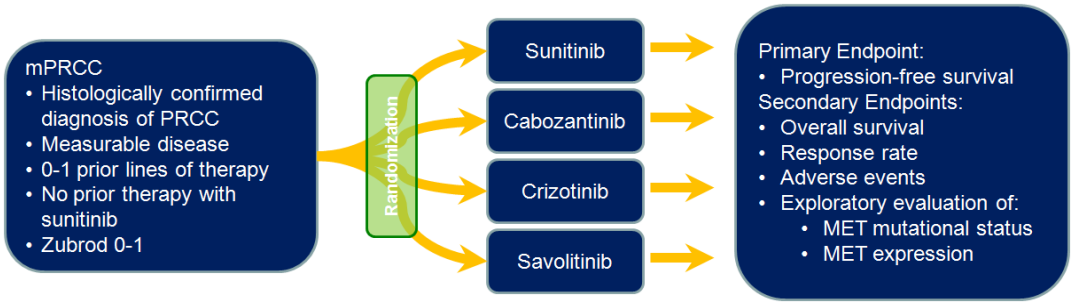
HR (95% CI): 0.71 (0.37, 1.36)
Log-rank two-sided *P*-value: 0.313

PFS reported for sunitinib was in range with previous studies[1,2]

Data cut-off August 19, 2019.
1. Albiges et al. J Clin Oncol 2018;36:3624–3631; 2. Ravaud et al. Ann Oncol 2015;26:1123–1128. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculated; PFS, progression-free survival

Toni Choueiri, ACO 2020

SWOG 1500 for mPRCC



- PI: S. Pal (City of Hope)
- Translational PI: B. Shuch (Yale)
  - BISQFP funding for genomic characterization
- Requires 41 pts/arm → 164 pts total
- Assuming 10% ineligibility → 180 pts total

NCT02761057: A Randomized, Phase II Efficacy Assessment of Multiple MET Kinase Inhibitors (Cabozantinib [NSC #761968], Crizotinib [NSC #749005], Savolitinib [NSC #785348], and Sunitinib [NSC #736511]) in Metastatic Papillary Renal Carcinoma (PAPMET)

City of Hope

Hereditary Leiomyomatosis Renal Cell Carcinoma: HLRCC

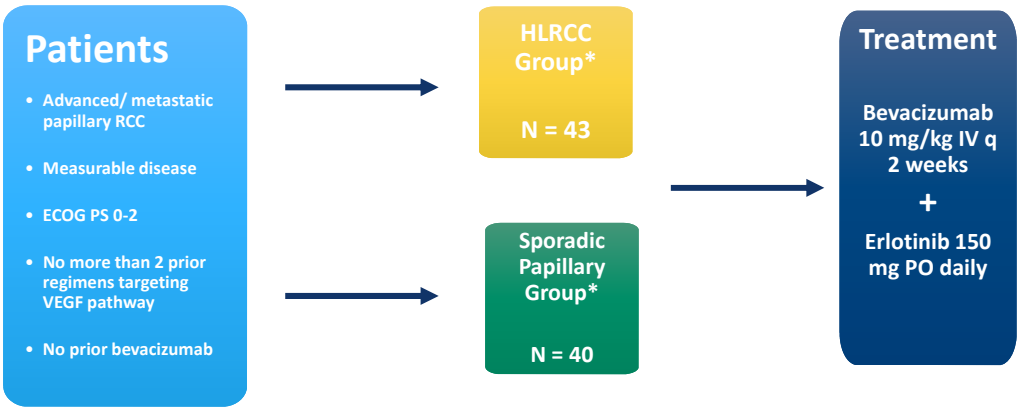
- **Cutaneous leiomyomas**
- **Uterine leiomyomas (fibroids)**
- **Renal cell carcinoma (Type 2 papillary RCC)**

HLRCC

- HLRCC is a familial disorder characterized by germline loss of function alterations in the *fumarate hydratase* (*FH)* gene
- HLRCC predisposes patients to early onset, aggressive papillary RCC[9-12]
- There are currently no data from prospective systemic therapy trials and no established standard of care for this patient population

9. Forde, *Eur Urol* 2019; 10. Grubb, *J. Urol* 2007; 11. Lehtonen, *J. Med Genet* 2006; 12. Muller, *Clin Genet* 2017;

Study Design



ECOG PS, Eastern Cooperative Oncology Group performance status. **VEGF**, Vascular Endothelial Growth Factor. **IV**, intravenous, **PO**, per oral, **PFS**, progression free survival

Primary Endpoint: Overall Response Rate per RECIST 1.1

Secondary Endpoints: PFS and Duration of Response

* Each group is comprised of an initial cohort of `20 patients and an expansion cohort

Primary Outcome

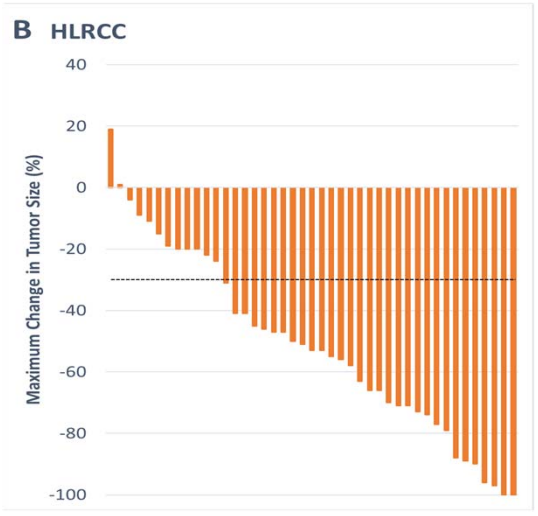
Overall Response by Group

- HLRCC
  - 31/43 patients had a confirmed response
  - ORR: 72.1% (95% CI 57.2 – 83.4)
- Sporadic
  - 14/40 patients had an overall response
  - ORR: 35% (95% CI 22.1 – 50.6)

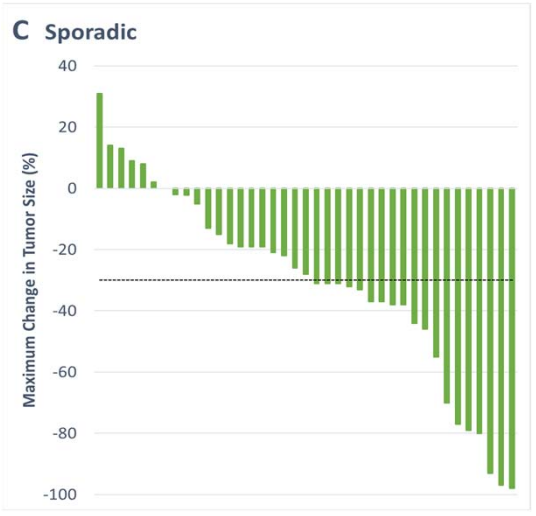
Confirmed Best Response	HLRCC, n (%) (N = 43)	Sporadic, n (%) (N = 40)
Complete Response	2 (4.7)	0 (0)
Partial Response	29 (67)	14 (35)
Stable Disease	12 (28)	21 (53)
Unconfirmed Partial Response	0 (0)	1 (2.5)
Progressive Disease	0 (0)	4 (10)
ORR	72%	35%

Ramaprasad Srinivasan, ASCO 2020

Maximum Change in Sum of Longest Dimensions



41/43 (95%) had decrease in tumor burden



32/40 (80%) had decrease in tumor burden

Ramaprasad Srinivasan

Evolving Strategies in the Management of Kidney Cancer

- **VHL Deficient RCC**
  - HIF 2-α a promising target in advanced sporadic clear cell RCC
  - HIF 2-α being explored as a systemic therapy alternatives to standard of care surgical management in VHL patients-Potential paradigm shift
- **Papillary RCC**
  - Heterogeneous group of malignancies
  - Immunotherapy effective in a proportion of patients
  - Mechanism based targeted therapy approaches effective in specific subsets

Acknowledgements

Urologic Oncology
Marston Linehan, M.D.
Mark Ball, M.D..
Gennady Bratslavsky, M.D

Clinical Team
Lisa Mac, PA-C
Julia Friend, PA-C
Martha Ninos, RN
Cheryl Royce, NP
Erin Purcell, RN
Geri Hawks, RN
Andy Gillespie, RN
Caitlin Drew, RN
Debbie Nielsen, RN

Berton Zbar, Ph.D
Len Neckers, Ph.D.
Don Bottaro, Ph.D.

UOB laboratories
Christopher Ricketts, Ph.D.
Roma Pahwa, Ph.D.
Cathy Vocke, Ph.D.
Carole Sourbier, Ph.D.
Youfeng Yang, M.S.
Robert Worrell, Ph.D

Laboratory of Pathology
Maria Merino, M.D.
Vanessa Moreno, M.D.
Sara Gil Hernandez, M.D.

Ophthalmology
Emily Chew, M.D
Henry Wiley, M.D.

Neurosurgery
Kareem Zaghloul, M.D.
Prashant Chittiboina, M.D.

Dermatology
Ed Cowan, M.D.
Heidi Kong, M.D.

Radiology/Nuc Med
Peter Choyke, M.D.
Ashkan Malayeri, M.D.
Clara Chen, M.D.
Mark Ahlman, M.D.
Brad Wood, M.D.
Venkatesh Krishnaswamy, M.D.

UOB Staff
Rabindra Gautam
Donna Drake
Kristin Choo
James Peterson
Gabby Coello
Cristiane Leite
Janet Gichonge

UOB Fellows
Eric Singer, M.D
Brian Shuch, M.D.
Abhinav Sidana, M.D.
Mark Ball, M.D.
Vladimir Valera, M.D.
Sandeep Gurram, M.D.

Pharma Collaborators
Peloton/Merck
Genentech