Precision Oncology and Landmark Advances in GU Malignancies

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GU Cancer Therapy: 1994

Standard of Care

Prostate Cancer
- "Hormone sensitive" vs "hormone refractory"
- Medical oncologist as bone pain doctor
- LHRH agonists rather than orchiectomy

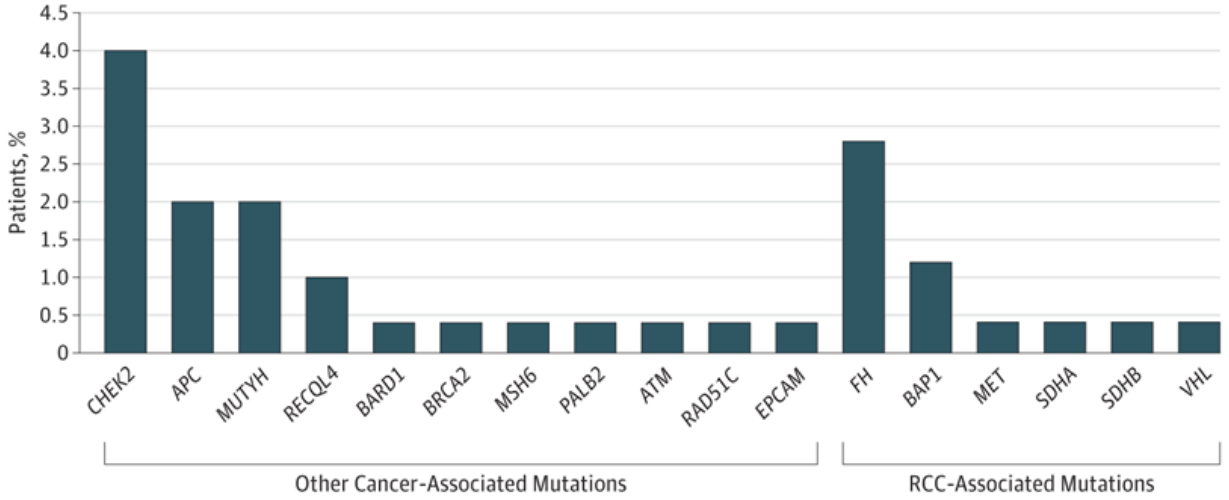
Renal Cancer
- "Hypernephroma" as one disease
- Very few academic oncologists focused on this disease
- High dose IL2/(Interferon-α)

Bladder Cancer
- A "chemotherapy sensitive" disease
- MVAC (1980's)

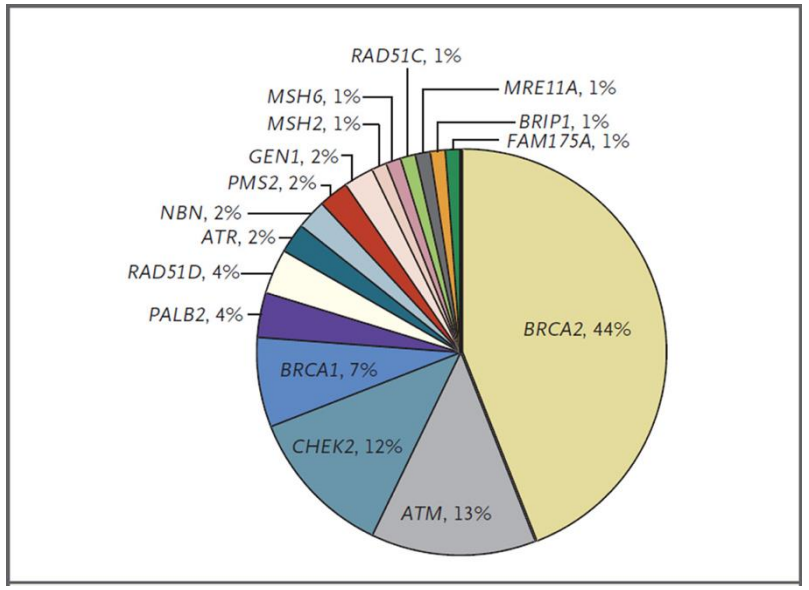
Data in Context

Recognition of Genomic Predisposition

Renal Cancer: 16%



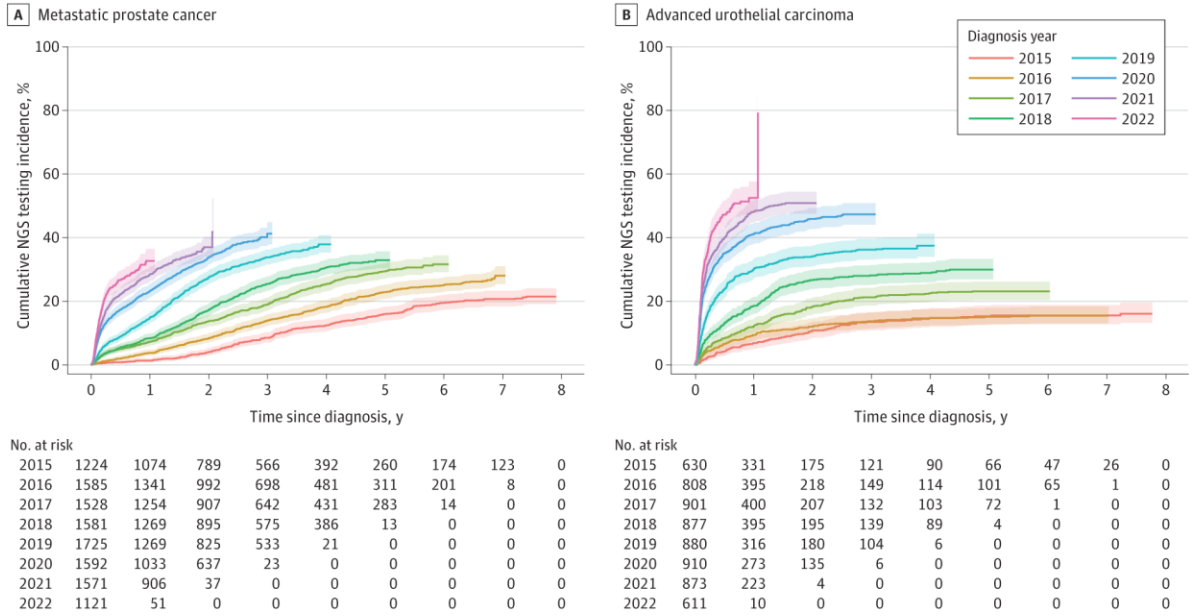
Prostate Cancer: 11%

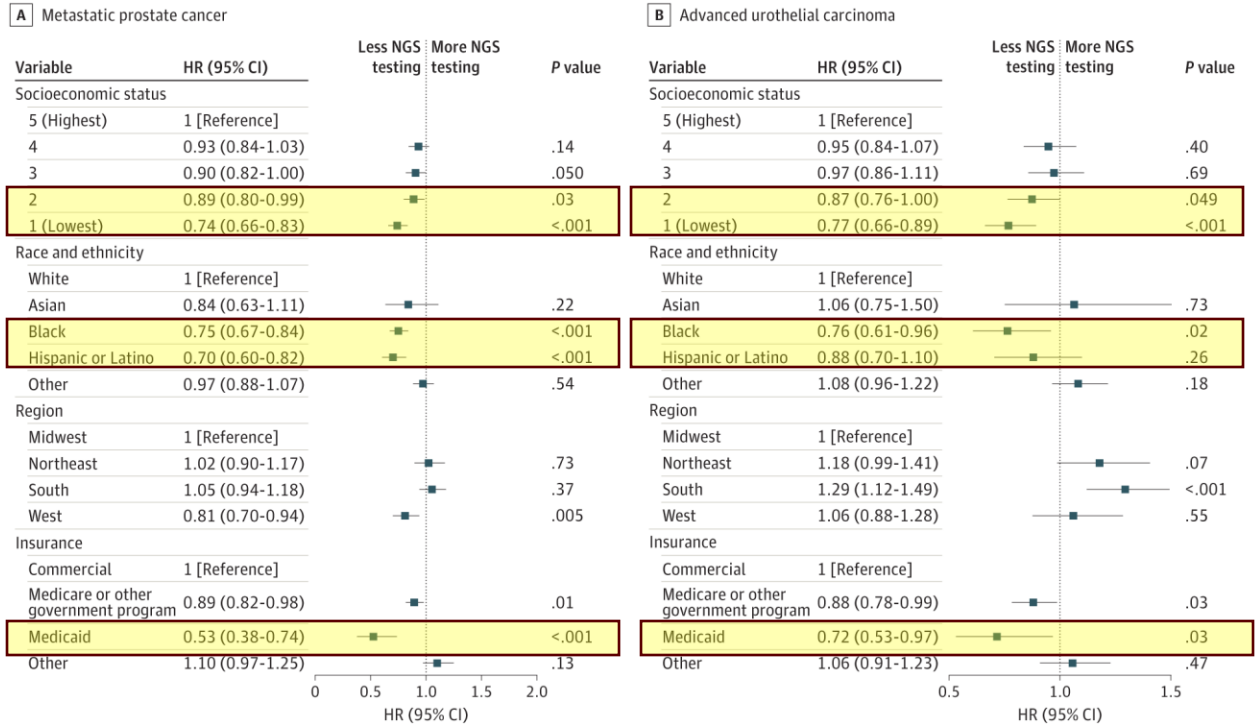


- Fraction of patients getting germline testing: <20% (of those meeting guidelines)
- Not enough genetic counselors
- Treating MD's will have to take testing responsibility

Carlo, et al. JAMA Oncol. 2018 Sep 1;4(9):1228-1235.
Pritachard, et al. N Engl J Med. 2016 Aug 4;375(5):443-53.

Any NGS Test in Metastatic Prostate & Bladder Cancer





JAMA Netw Open. 2024;7(7):e2423186. doi:10.1001/jamanetworkopen.2024.23186

Tumor Based Genomic Testing

- Primary tumor
- Biopsy of metastatic site
- CTC
- ctDNA

Tumor Based Genomic Testing

- Primary tumor
  - Differences between biopsy & surgical specimen
  - Genomic evolution over time
  - Age of specimen
  - Location of specimen

Tumor Based Genomic Testing

- Biopsy of metastatic site
  - Bone biopsy successful in ~70% (experienced hands)
  - Bone biopsy decalcification affects NGS
  - Sampling error, intra-patient heterogeneity

Tumor Based Genomic Testing

- CTC
  - Multiple platforms
    - Epic Biosciences
    - Cell Search
    - Various other technologies
  - CTC incidence low in early stage disease
  - Sample sufficiency for sequencing
  - Falling out of favor due to logistical difficulties

Tumor Based Genomic Testing

- ctDNA
  - Rapidly emerging and changing technology
  - Distinguishing clonal hematopoiesis of indeterminate potential (CHIP)
  - ctDNA incidence low in early stage disease
  - Sample sufficiency for sequencing

University of Chicago and Targeted Therapy

Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

(Received for publication March 22, 1941)

Charles B. Huggins
Facts

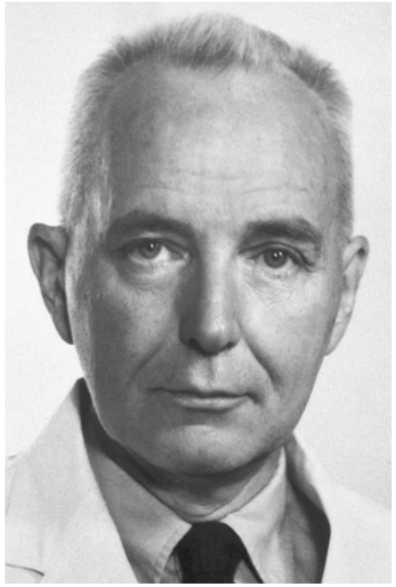


Photo from the Nobel Foundation archive.

Charles Brenton Huggins
The Nobel Prize in Physiology or Medicine 1966

Born: 22 September 1901, Halifax, Nova Scotia, Canada

Died: 12 January 1997, Chicago, IL, USA

Affiliation at the time of the award: University of Chicago, Ben May Laboratory for Cancer Research, Chicago, IL, USA

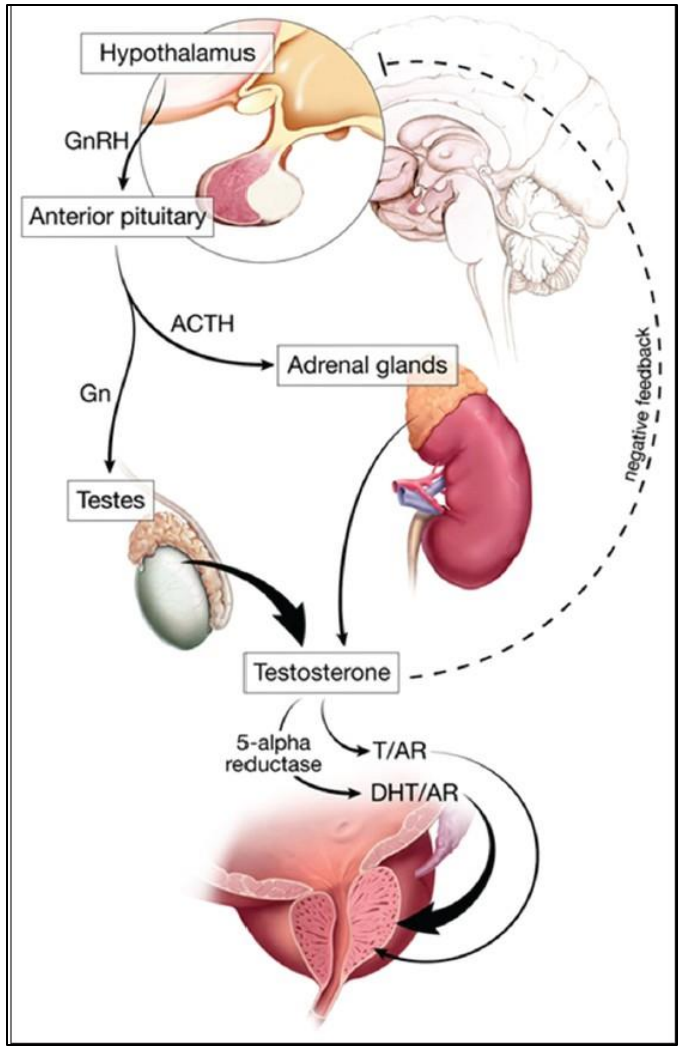
Prize motivation: “for his discoveries concerning hormonal treatment of prostatic cancer”

Prize share: 1/2

The Prostatologist's Endocrine Axis

Orchiectomy

Antiandrogens



GnRH agonist, antagonist

Tumor/Adrenal Androgen Synthesis Block

AR Targeted Therapy Toxicity

- **Financial**:
  - Orchiectomy vs chemical castration
  - Brand name vs generic vs pharmacology guided dosing
- **Fatigue**
- **Neuropsychiatric**
  - Depression vs neurocognitive vs fatigue/activation
  - Rare seizures (enzalutamide, apalutamide)
  - Benefit with low-brain penetration? (darolutomide)
- **Libido/sexual function** (we are ignoring the partner)
- **Osteopenia/Osteoporosis**
  - Role of exercise, calcium, Vitamin D
  - Role for denosumab, zoledronate
- **Sarcopenia**
  - Part of fatigue syndrome
  - Role of exercise
- **Frailty**
- **Metabolic syndrome**
  - Diabetes
  - Hyperlipidemia

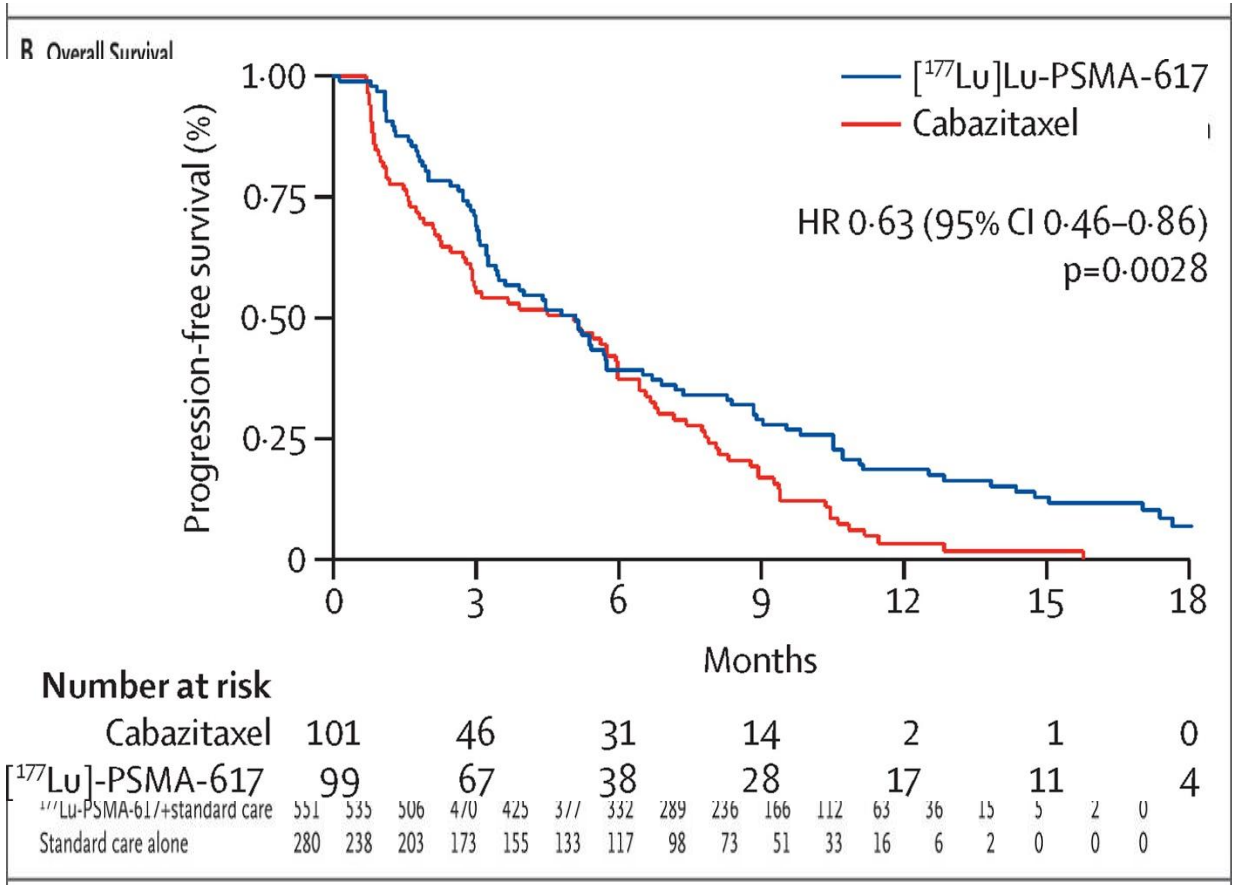
Phase 3 Trials in Metastatic “Castrate Sensitive” PCa

TRIAL	ARSI	Docetaxel	PFS	OS
LATITUDE	abiraterone	No	HR = 0.47; p < 0.001	HR = 0.66; p < 0.0001
TITAN	apalutamide	11%	HR = 0.48; p < 0.001	HR = 0.65; p < 0.0001
ARCHES	enzalutamide	18%	HR = 0.39; p < 0.001	HR = 0.66; p < 0.0001
STAMPEDE	abiraterone	No	HR = 0.29; p < 0.001	HR = 0.63; p < 0.0001
ARASENS	darolutamide	100%	HR = 0.36; p < 0.001	HR = 0.68; p < 0.001
CHAARTED	None	50% (exptl arm)	HR = 0.61; p < 0.001	HR = 0.72; p = .0018

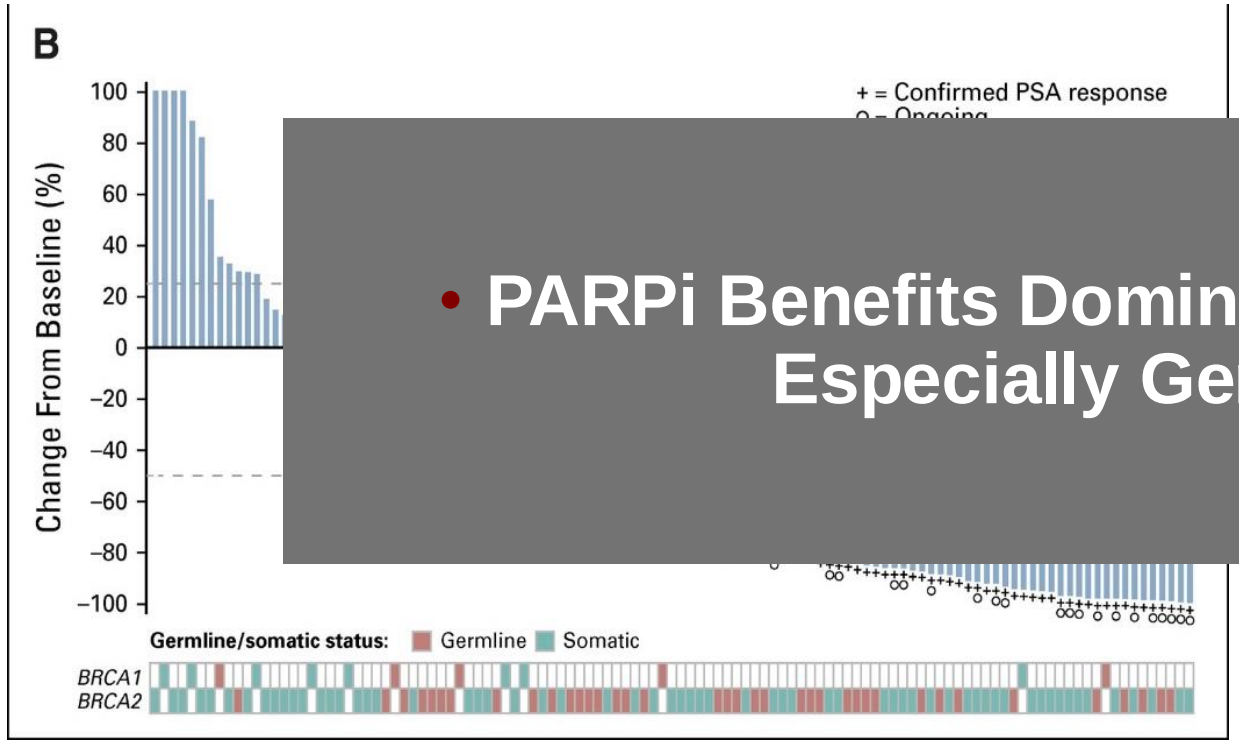
- **Docetaxel vs 2nd generation AR pathway inhibitor?**
  - Docetaxel only for high risk (> 4 bone mets/visceral disease)
  - Based on ARASENS should not be used w/o ARSI
  - No level 1 data for triplet therapy
- **Which AR pathway inhibitor?**
  - Outcomes data very similar
  - Abiraterone + AR antagonist offers no advantage
  - Differences can be explained by study design and enrollment period
  - Darolutamide vs enzalutmide study in progress
- **Similar data for biochemical recurrence/non-metastatic disease**
  - How define?
  - Who should get only ADT?

Lu-PSMA Therapy

- Eligibility
  - PSMA-positivity with ^{68}Ga-PSMA-11
  - Prior ARSI and at least 1 taxane (only 40% with 2 taxanes)
- Treatment
  - Up to 6 doses, every 4 weeks
  - Control = no taxane
- Issues
  - Coordination with Nuclear Medicine
  - Supply chain
  - Other PSMA targeted therapies emerging



PARPi Therapy: The Rucaparib Example



- **PARPi Benefits Dominated By BRCA2 Mutations, Especially Germ-Line Mutations**

Response by DDR gene alteration.

	By DDR gene group		
	ATM (*n* = 49)	*CDK12* (*n* = 15)	*CHEK2* (*n* = 12)
Confirmed investigator-assessed objective response[b]	2/19 (10.5)	0/10 (0)	1/9 (11.1)
Confirmed PSA response[e]	2/49 (4.1)	1/15 (6.7)	2/12 (16.7)
Median time to PSA progression, mo (95% CI)	3.1 (2.8–4.6)	3.2 (2.8–4.6)	7.4 (2.8–7.4)

THE UNIVERSITY OF CHICAGO | Biological Sciences Division

- Journal of Clinical Oncology 2020 2020 Aug 14:JCO2001035
- Clin Cancer Res 2020 Jun 1;26(11):2487-2496.

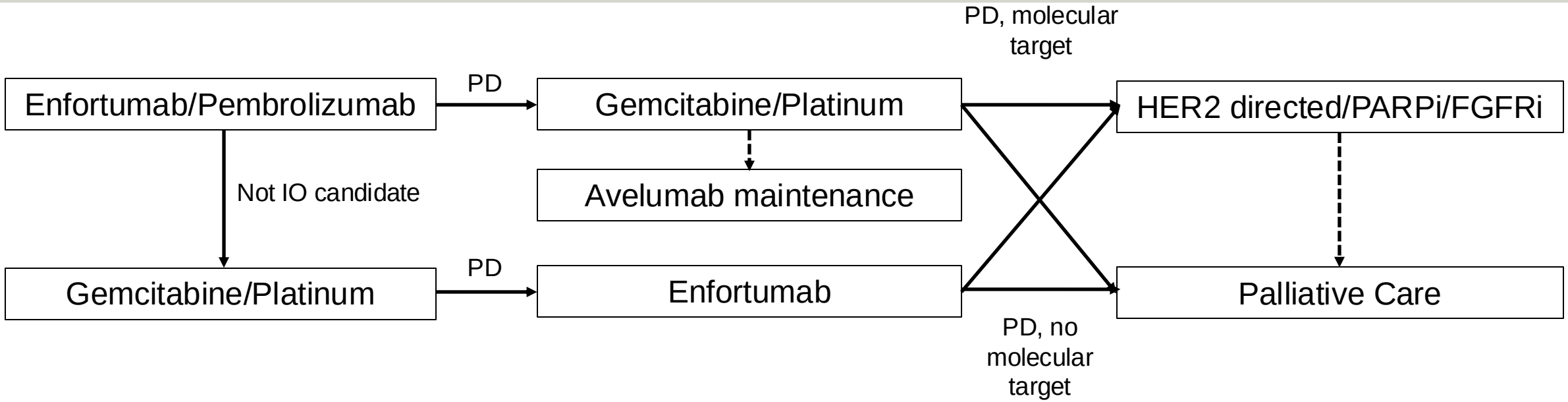
Prostate Cancer Conclusions

- Prostate cancer is an androgen receptor driven cancer and AR directed therapies will remain key
  - Combination androgen ablation and an ARSI is standard for most castrate sensitive patients
  - No differences between methods to suppress testicular androgens & orchiectomy is cheapest
  - No significant difference between androgen synthesis inhibitor (abiraterone) & potent AR antagonists (enzalutamide, apalutamide, darolutamide)
- Hormonal therapy toxicity
  - Not significantly different between ADT and combination therapy (in good prognosis patients)
  - Short term LHRH agonist may not be so short
  - Needs better management
- The term “CRPC” needs to be retired
- “M0” is confusing and depends on imaging modality
- Taxanes play a role
  - No significant differences between docetaxel & cabazitaxel
  - Docetaxel is cheaper and cabazitaxel has a role post docetaxel
- Lu-PSMA now standard, but relative timing versus taxanes unclear
- PARPi plays a role, but mainly for BRCA2 mutations
- Other molecular targets and immunotherapy remain a promising tease

Bladder Cancer since 1994

- Treatment of high grade non-muscle invasive disease is undergoing a revolution
  - But mostly the purview of urologists
  - Will not be covered here
- For muscle invasive disease
  - Both chemo/RT and surgery are appropriate
  - Neoadjuvant CDDP based chemo remains the standard (for now)
  - In the absence of neo-adjuvant therapy, adjuvant pembrolizumab is the standard (for now)
- For metastatic disease
  - MVAC is (almost) dead
  - Enfortumab/pembrolizumab is the new standard of care
  - Gemcitabine/platinum still plays a role
  - Molecular targeted therapies available for FGFR & ERBB2/3 alterations

Pragmatic Guideline for Metastatic Bladder Cancer



Major emerging issue:

- Multiple agents in same class (PD1i, PARPi, Nectin 4, Trop 2, HER2, etc)
- Extremely expensive meds
- -> How select in absence of definitive comparison data.

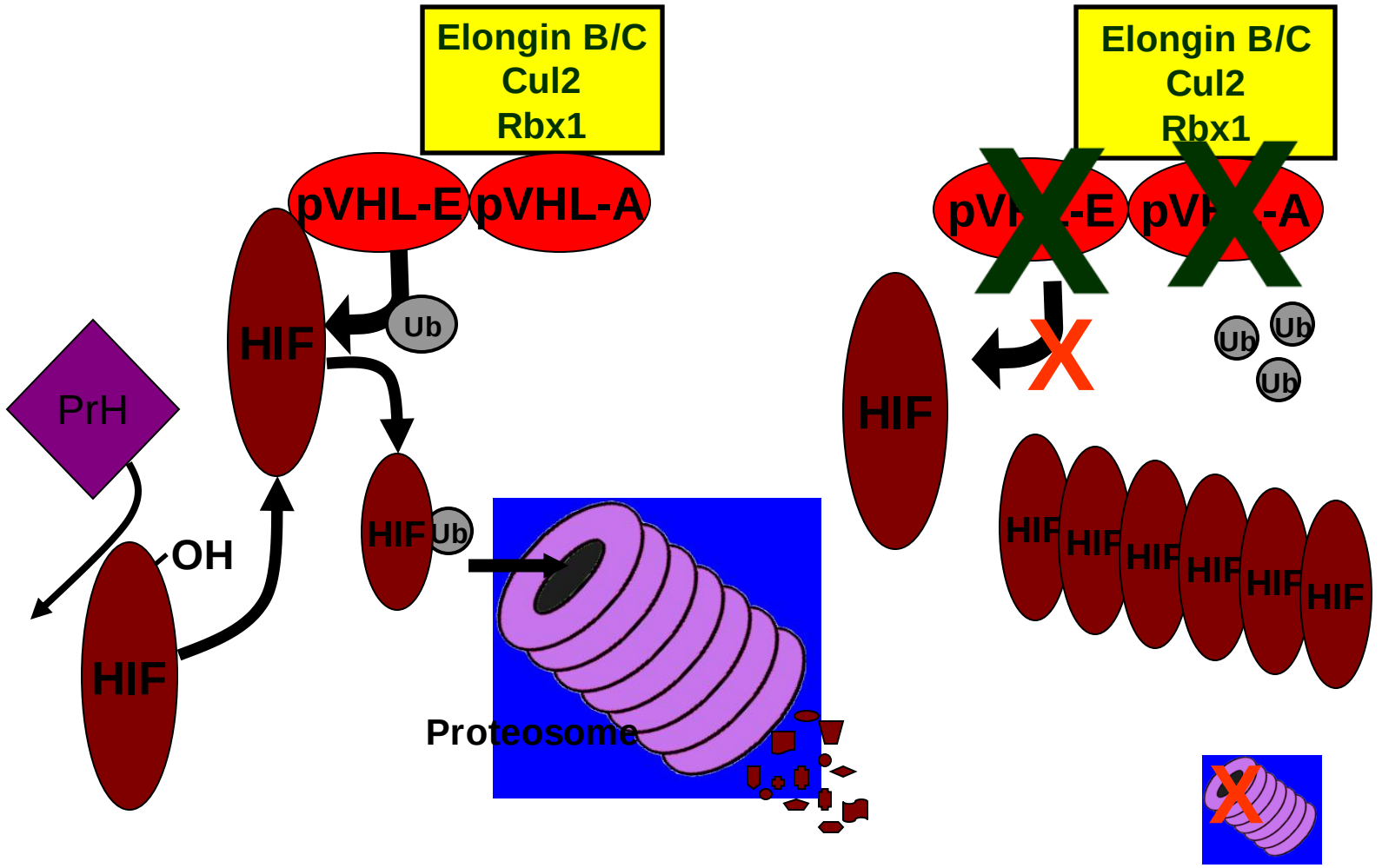
Somatic Genomic Alterations with Potential Therapies

- FGFR mutations and alterations
  - Erdafitinib (FDA approved)
- ERBB2/3 alterations
  - Trastuzumab deruxtecan-nxki (FDA approved)
  - Afatinib
- BRCA2 alterations
  - PARPi???
- ERCC2 alterations
  - CDDP??

WHO Renal Cancer Classification

- Clear cell renal cell carcinoma
- Papillary renal cell carcinoma
- Oncocytoma
- Chromophobe renal cell carcinoma
- Collecting duct carcinoma
- Renal medullary carcinoma
- MiT family translocation renal cell carcinomas
- Mucinous tubular and spindle cell carcinoma
- Clear cell papillary renal cell carcinoma
- Succinate dehydrogenase deficient renal cell carcinoma
- Hereditary leiomyomatosis and renal cell carcinoma associated renal cell carcinoma
- Tubulocystic renal cell carcinoma
- Multilocular cystic renal neoplasm of low malignant potential
- Acquired cystic disease-associated renal cell carcinoma
- Renal cell carcinoma, unclassified
- Papillary adenoma

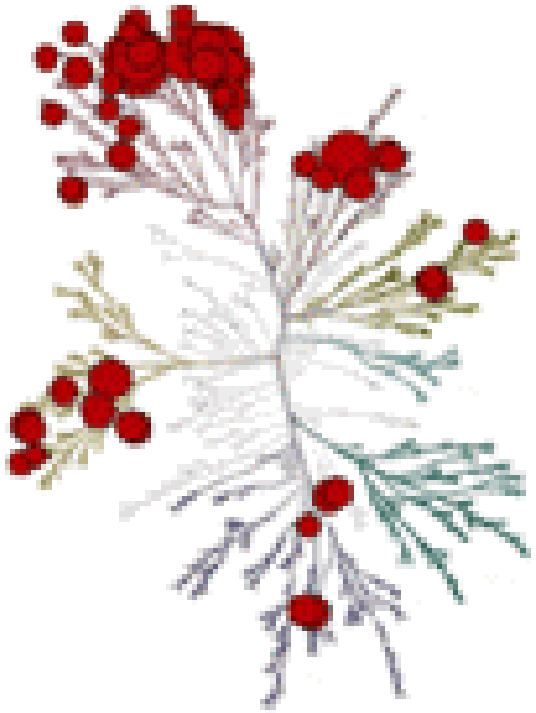
Normal Oxygen Clear cell renal cancer



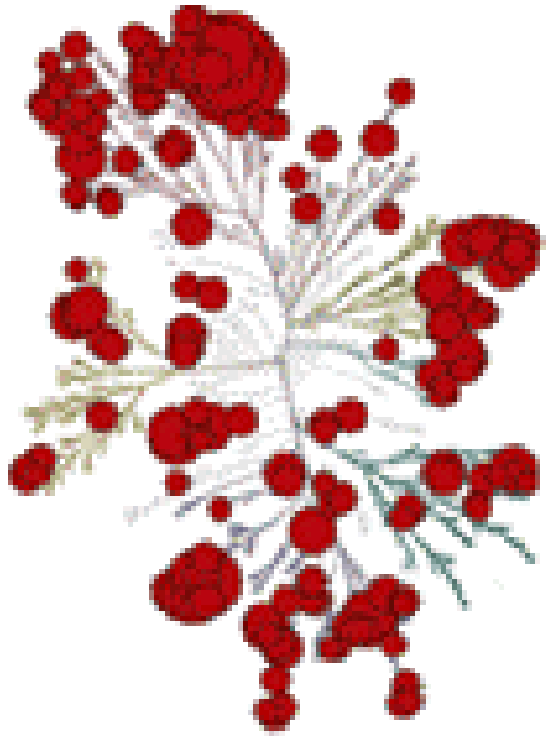
It's Not Quite That Simple

- VHL targets other proteins than just HIF
- There's more than one prolyl hydroxylase
- HIF is really a complex
  - Stable HIF-β
  - Labile HIF-α
    - HIF-1α OR HIF-2α (HIF-3α)
    - HIF-1α acts as tumor suppressor in renal cancer
- Not all clear cell cancers have VHL inactivation

Kinase Interaction Map



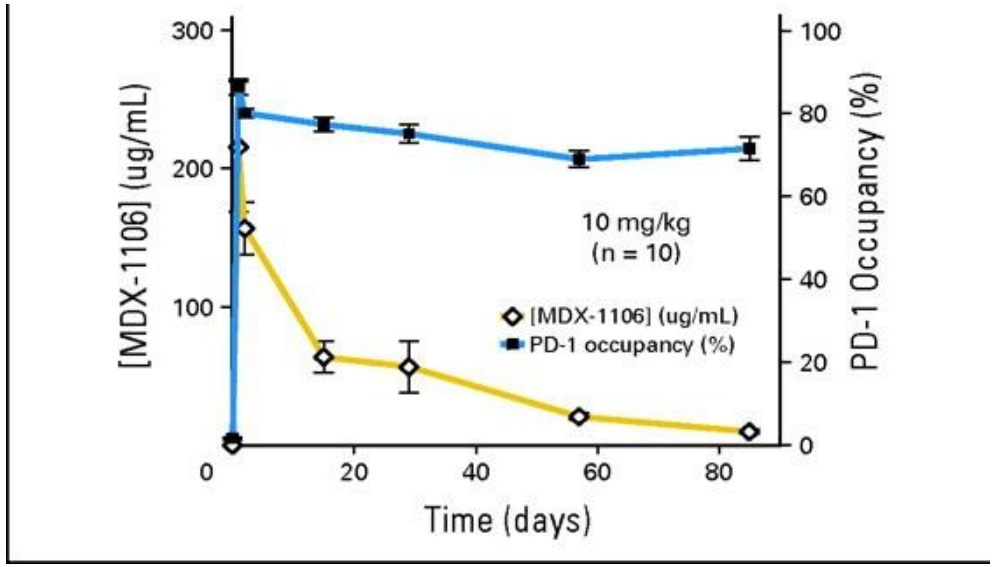
Sorafenib

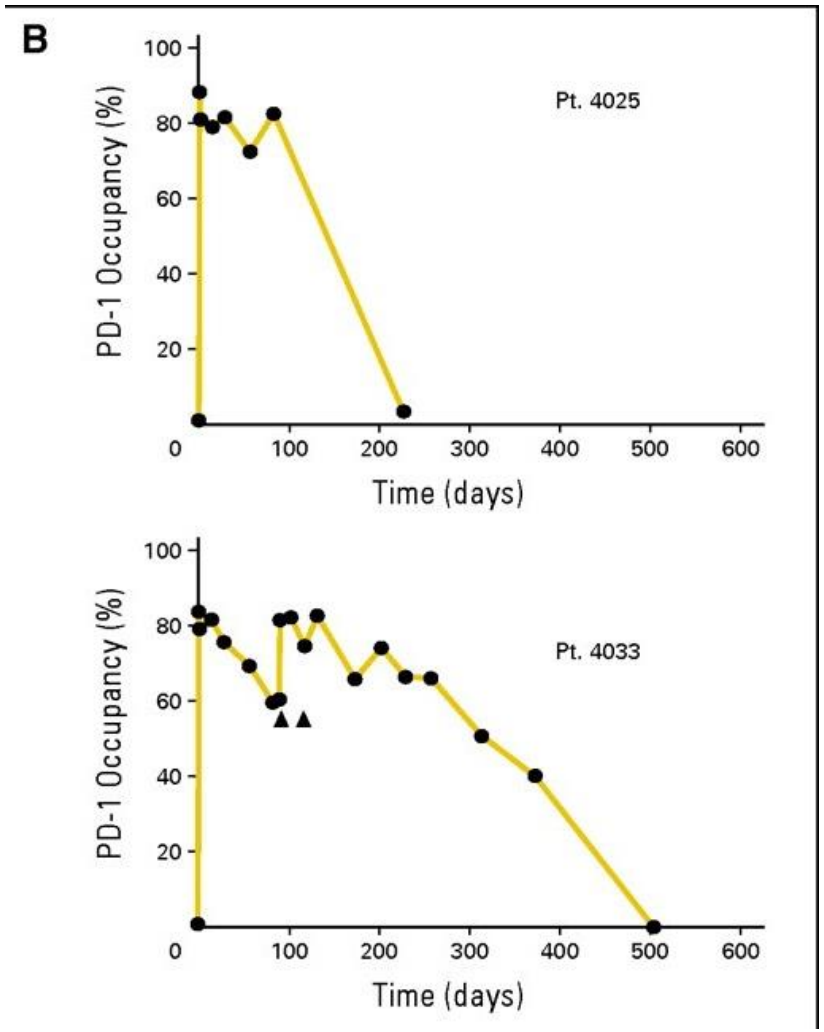


Sunitinib

Karaman, et al Nature Biotech. 26:127, 2008

Nivolumab CD3 T-Cell PD1 Occupancy



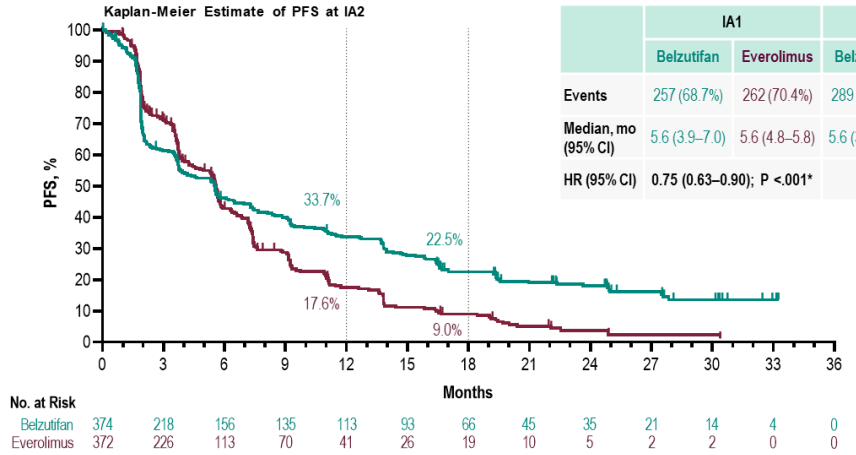


Ongoing studies evaluating dose and schedule

HIF Inhibitor Belzutifan Ph 3 Study

Albiges LS005 ESMO 2023

Primary Endpoint: PFS per RECIST 1.1 by BICR

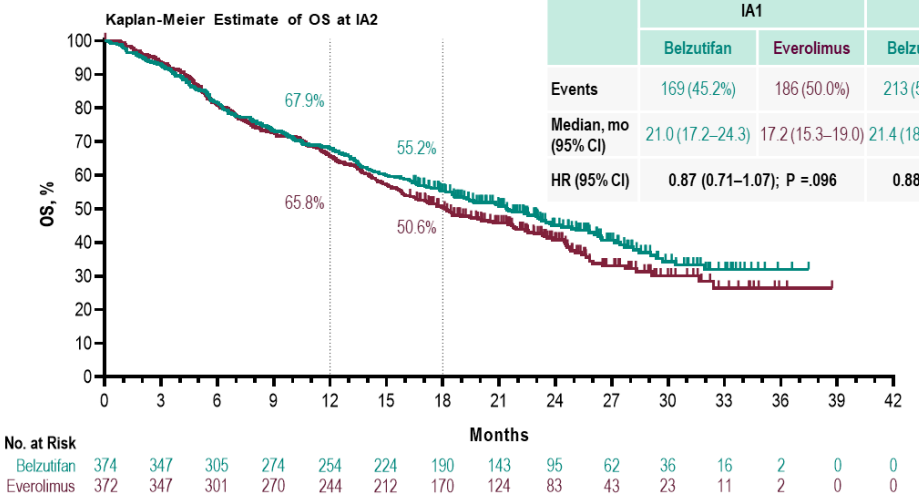


	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*		0.74 (0.63–0.88)	

* denotes statistical significance. Primary PFS endpoint was met at IA1 and was not formally statistically tested at IA2. Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

Albiges LS005 ESMO 2023

Primary Endpoint: OS



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	169 (45.2%)	186 (50.0%)	213 (57.0%)	228 (61.3%)
Median, mo (95% CI)	21.0 (17.2–24.3)	17.2 (15.3–19.0)	21.4 (18.2–24.3)	18.1 (15.8–21.8)
HR (95% CI)	0.87 (0.71–1.07); P =.096		0.88 (0.73–1.07); *P* =.099	

Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

Non-Clear Cell Renal Cancer

- Typically follow Clear Cell due to lack of definitive data
- “Sarcomatoid”: Ipilimumab/Nivolumab
- Medullary: platinum based therapy
- Papillary Type 1: Cabozantinib
- “Papillary Type 2”: Pembrolizumab/lenvatinib
- FH germline mutation: Bevacizumab/erlotinib
- Chromophobe: everolimus w/wo lenvatinib
- Translocation associated: Pembrolizumab/lenvatinib

RCC Conclusions

- Nephrectomy in metastatic patients should only be considered in very good risk patients
  - Perioperative therapy is not standard
- Ipilimumab/Nivolumab OR pembro/axitinib OR nivo/cabozantinib OR pembrol/lenvatinib are a first line standard
  - Surveillance, oligometastatic directed therapy, and single agent therapy appropriate for good prognosis pts
  - Sequential use of VEGFRi is appropriate
- Belzutifan is a 2nd/3rd line standard
- mTOR inhibitors have a minimal role
- Multiple combinations are being tested
- Therapy sequencing is very confusing
- Therapy for non-clear cell renal cancer is unclear

“Precision Oncology” for GU Cancers

- The AR is the target for prostate cancer
- ~~All refractory prostate cancer patients should get somatic testing~~
- “Every” advanced GU cancer patient should get testing for a germline predisposition syndrome
  - Easy, cheap, available
  - Treatment as well as family implications
  - Exceptions should be justified
- Non-clear cell, undifferentiated cancer should get somatic testing
  - May not have treatment implications (yet)
- All 2nd line urothelial cancer patients should get somatic testing

The patient is more than their molecular data

- Medical comorbidities
- Functional status
- Family support
- Education
- Wishes, desires, and goals
- Social determinants of health

Precision Oncology

The right therapy for the right patient at the right time

Thanks to:

My home base colleagues:

- Peter O'Donnell
- Randy Sweiss
- Russ Szmulewitz
- Akash Patnaik
- Mohammad Atiq
- Jonathon Trujillo

My nurses and support staff

My GU community colleagues

My patients