Dana-Farber/Harvard Cancer Center Kidney Cancer SPORE
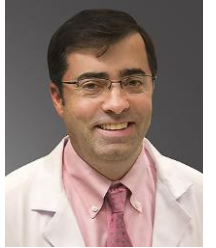
A brief overview

2014-2019
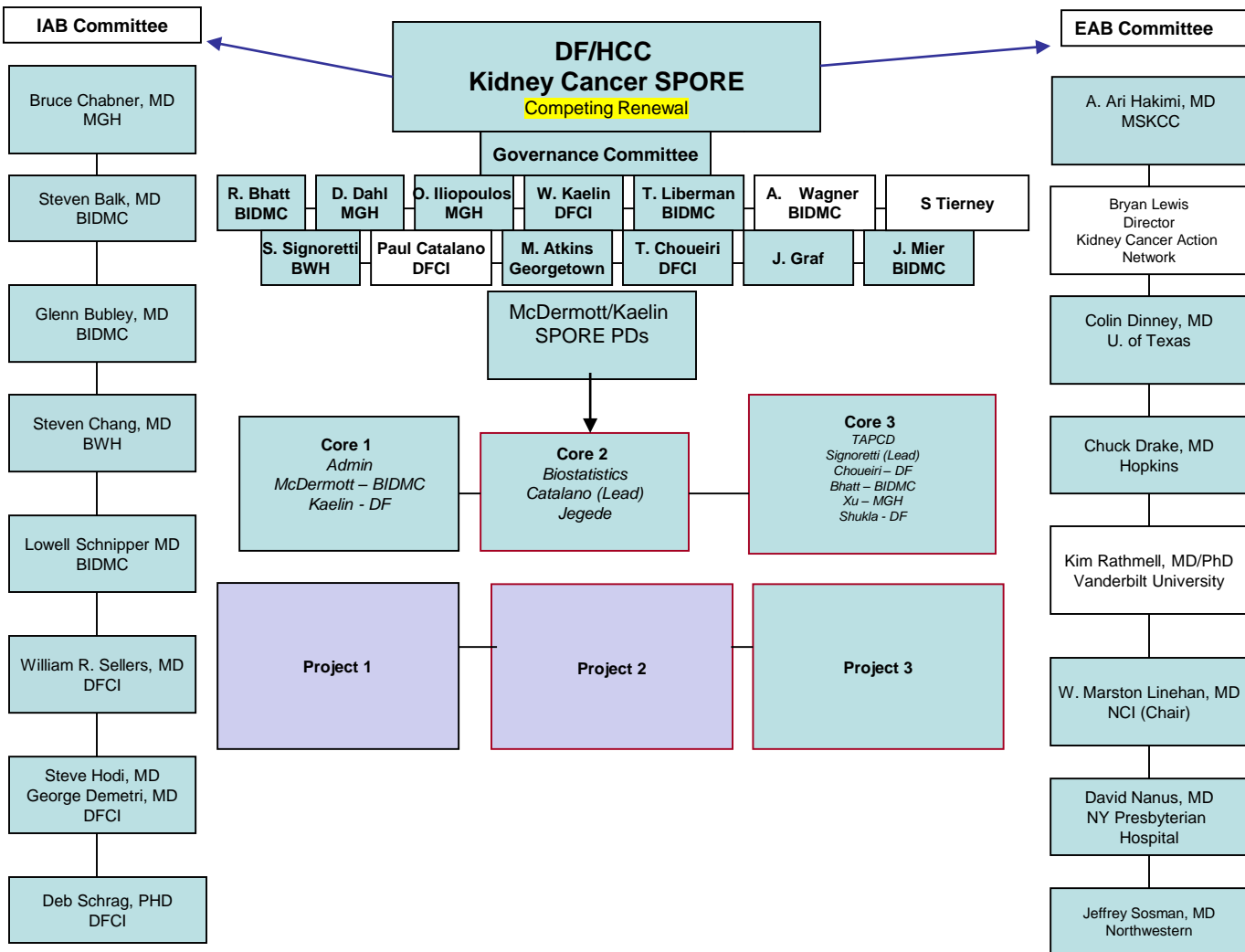
Toni K. Choueiri, MD

On Behalf of DF/HCC SPORE leadership

PI: McDermott and Kaelin

@DrChoueiri

KidneyCAN

**DF/HCC
Kidney Cancer SPORE**
Competing Renewal

Bruce Chabner, MD
MGH

A. Ari Hakimi, MD
MSKCC

Governance Committee

| R. Bhatt BIDMC | D. Dahl MGH | O. Iliopoulos MGH | W. Kaelin DFCI | T. Liberman BIDMC | A. Wagner BIDMC | S Tierney |

| S. Signoretti BWH | Paul Catalano DFCI | M. Atkins Georgetown | T. Choueiri DFCI | J. Graf | J. Mier BIDMC |

Steven Balk, MD
BIDMC

Bryan Lewis
Director
Kidney Cancer Action
Network

McDermott/Kaelin
SPORE PDs

Glenn Bubley, MD
BIDMC

Colin Dinney, MD
U. of Texas

Core 3
*TAPCD
Signoretti (Lead)
Choueiri – DF
Bhatt – BIDMC
Xu – MGH
Shukla - DF*

Core 1
*Admin
McDermott – BIDMC
Kaelin - DF*

Core 2
*Biostatistics
Catalano (Lead)
Jegede*

Steven Chang, MD
BWH

Chuck Drake, MD
Hopkins

Lowell Schnipper MD
BIDMC

Kim Rathmell, MD/PhD
Vanderbilt University

Project 1

Project 2

Project 3

William R. Sellers, MD
DFCI

W. Marston Linehan, MD
NCI (Chair)

Steve Hodi, MD
George Demetri, MD
DFCI

David Nanus, MD
NY Presbyterian
Hospital

Deb Schrag, PHD
DFCI

Jeffrey Sosman, MD
Northwestern

SPORE Related Clinical Research (2014-2019)

Discovery → **Translation** → **Impact**

Project	Agent	Target	Phase	Status
Angiogenic Escape	X4P-001	CXCR-4	1/2	Completed x 2
mTOR Targeting	TAK-228	mTOR kinase	2	Enrolling
PD-1 Targeting	Nivo then Ipi	PD-1, CTLA-4	2	Enrolling x 2
HIF2 Inhibition	PT-2385 PT-2977	HIF-2α	1/2	Completed P1 (x2) Enrolling P1/2 Combinations

Beside Projects and Cores

- Career Development Awards (CDAs)

- Development Research Projects (DRPs)

- Director Choice Awards

- Patients and caregivers symposium (every year)

- E-Newsletters

- Integration within the DF/Harvard Kidney Cancer Program
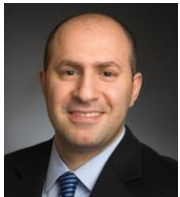
Efficacy of Novel HIF2a Inhibitor

nature
2016

Kaelin[DFCI]

CMV-Luc 786-O Tumors

Day 0

Day 30

Placebo

Drug
(PT2399)

Relative Value

Week post treatment

V1
V2
V3
V4
V5
V6
V7
V8
V9
V10
PT1
PT2
PT3
PT4
PT5
PT6
PT7
PT8
PT9
PT10

DF/HCC
DANA-FARBER / HARVARD CANCER CENTER
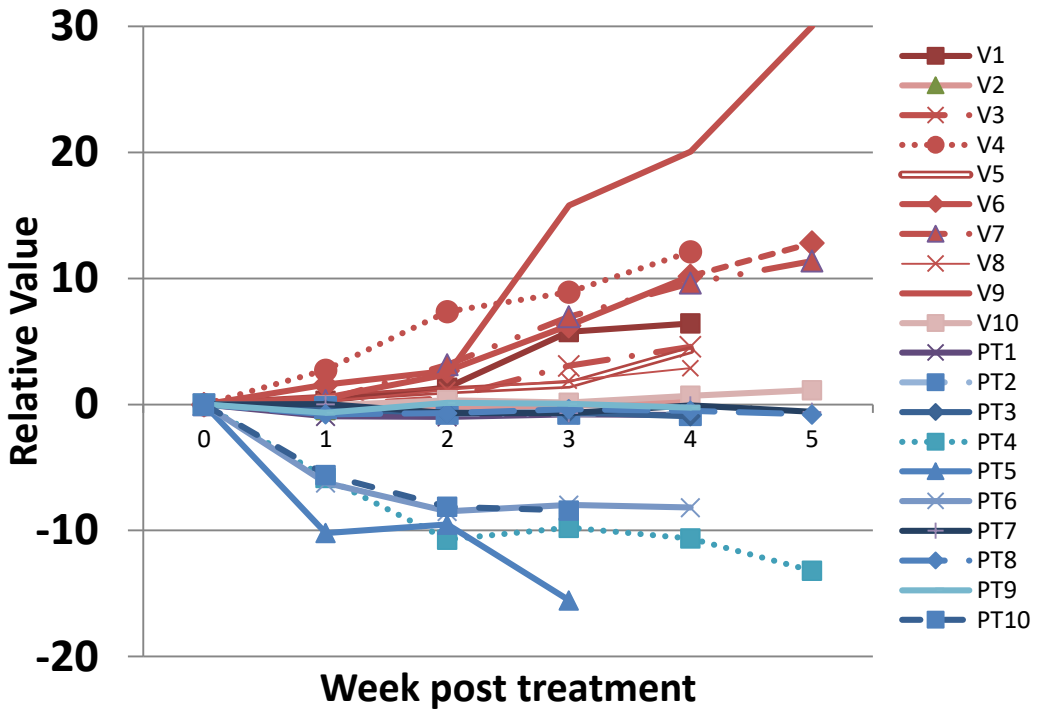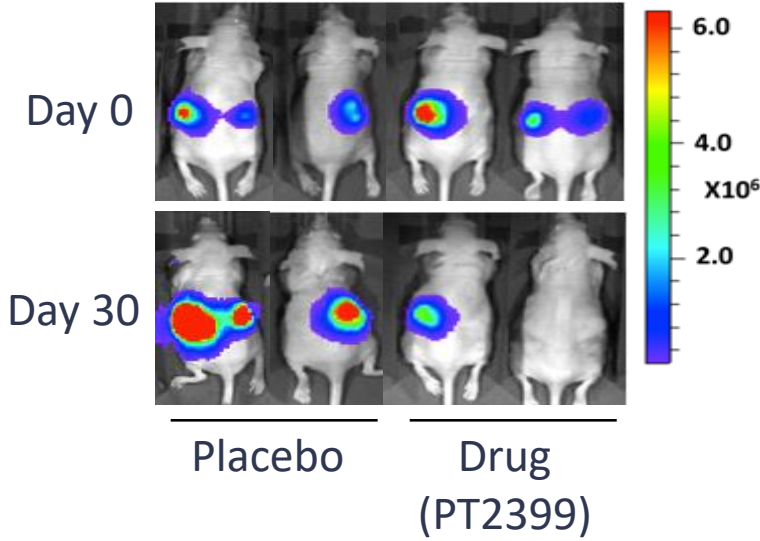
Proof of Principle - HIF2a Inhibition: P1 PT-2977
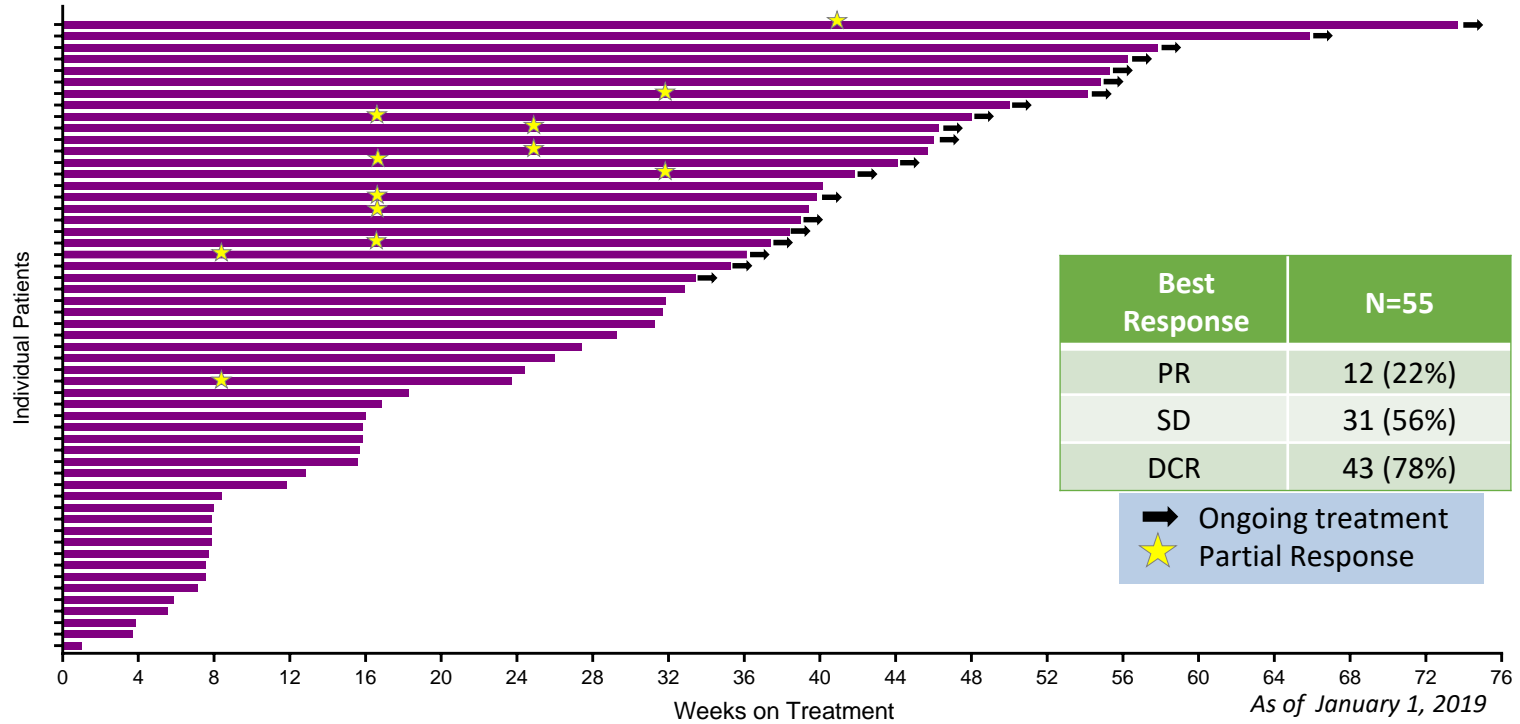
Best Response	N=55
PR	12 (22%)
SD	31 (56%)
DCR	43 (78%)

➡ Ongoing treatment
⭐ Partial Response

As of January 1, 2019

Individual Patients

Weeks on Treatment

Choueiri[DFCI]

Beyond PD-L1 expression

- Quantification of tumor infiltrating CD8-positive T cells

- Expression of multiple immune checkpoints on CD8-positive T cells

Combined model (TC PD-L1 expression plus % of CD8+ cells that are PD-1+TIM-3-LAG-3-) identifies 3 groups of patients with distinct outcomes
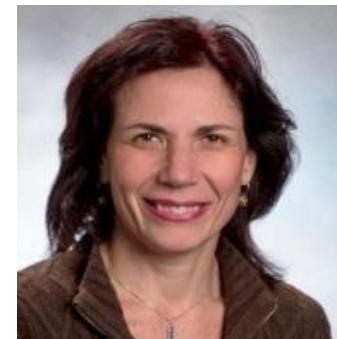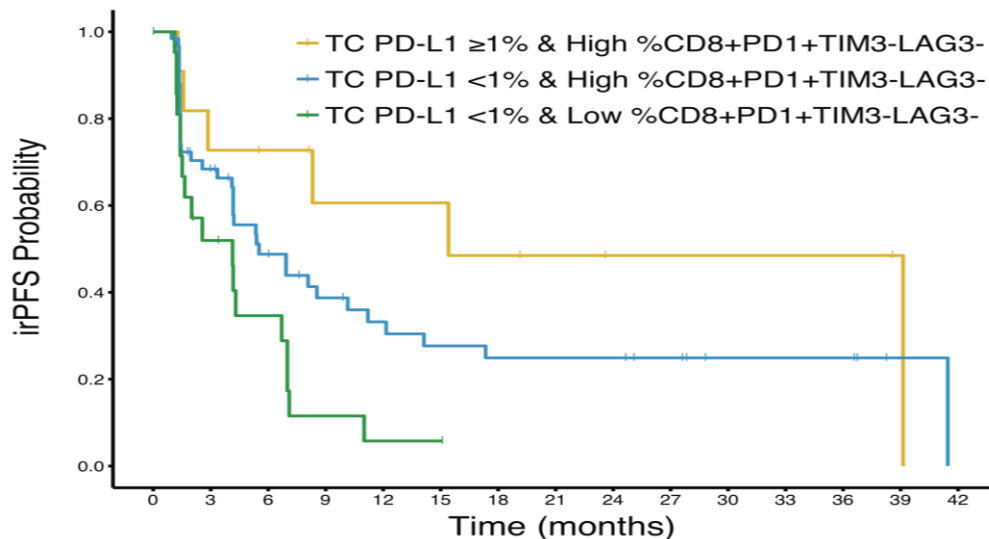
	TC PD-L1 expression ≥1% and high % of CD8+ PD-1+TIM-3-LAG-3- TIC (n = 11)		TC PD-L1 expression <1% and high % of CD8+PD-1+TIM-3-LAG-3- TIC (n = 63[a])		TC PD-L1 expression <1% and low % of CD8+PD-1+TIM-3-LAG-3- TIC (n = 23)		
Endpoints	n	%	n	%	n	%	*p*-value
irORR	6	54.5	15	24.2	0	0.0	0.001
95% CI, %	23.4 - 83.3		14.2 - 36.7		0.0 - 15.4		
Median **irPFS**, months	15.4		5.5		4.1		0.013
95% CI	1.6 - 39.1		4.1 - 10.2		1.4 - 6.7		

[a] irORR data for 2 patients were missing.

Pignon et al, Clin Cancer Res 2019
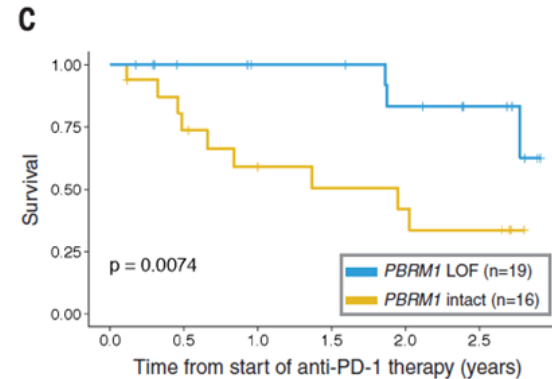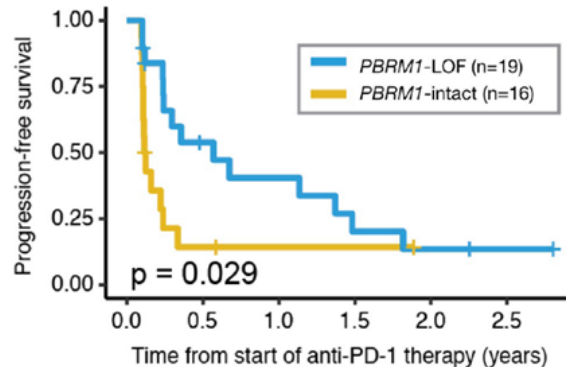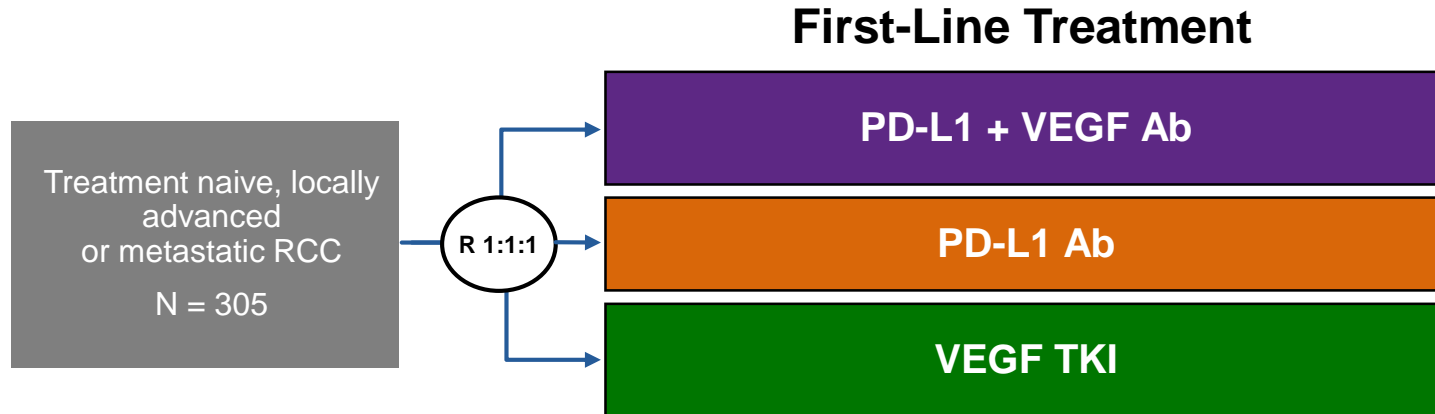
Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma

Diana Miao, Claire A. Margolis, Wenhua Gao, Martin H. Voss, Wei Li, Dylan J. Martini, Craig Norton, Dominick Bossé, Stephanie M. Wankowicz, Dana Cullen, Christine Horak, Megan Wind-Rotolo, Adam Tracy, Marios Giannakis, Frank Stephen Hodi, Charles G. Drake, Mark W. Ball, Mohamad E. Allaf, Alexandra Snyder, Matthew D. Hellmann, Thai Ho, Robert J. Motzer, Sabina Signoretti, William G. Kaelin Jr., Toni K. Choueiri, Eliezer M. Van Allen

PBRM1 LOF enriched PFS and OS in Checkmate-009

# IMmotion150 Trial Design: Randomized P2

First-Line Treatment

Treatment naive, locally advanced or metastatic RCC

N = 305

R 1:1:1

PD-L1 + VEGF Ab

PD-L1 Ab

VEGF TKI

- 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

McDermott D, et al. Nature Med 2018

Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mKC
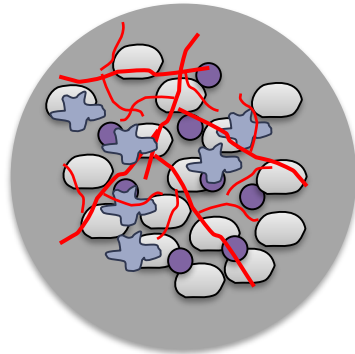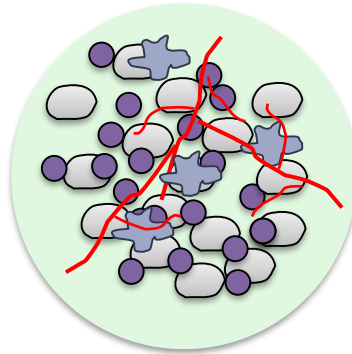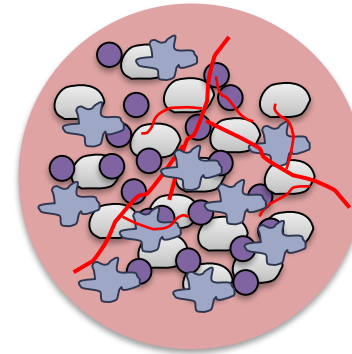
McDermott D, et al. IMmotion150 biomarkers: AACR 2017
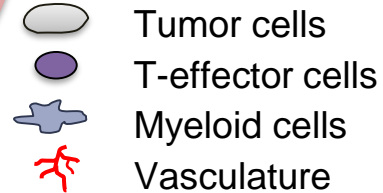
First-Line Phase 3 Trials in Advanced RCC

Control	Experimental Arm
Sunitinib	Axitinib + avelumab
Sunitinib	Bevacizumab + atezolizumab
Sunitinib	Nivolumab + cabozantinib
Sunitinib	Lenvatinib + everolimus or lenvatinib + pembrolizumab
Sunitinib	Axitinib + pembrolizumab
Sunitinib	Nivolumab + ipilimumab
Nivo/ipi	Nivolumab+ipilimumab
Adaptive	Nivolumab+ipilimumab followed by cabozantinib (Alliance)

All above with DF/HCC leadership or SC membership

**Should these approaches be applied to all patients?**

DF/HCC KCP Immunotherapy Trials: Investigator Initiated

| Trial	N	DF/HCC PI	Status
HCRN	200	McDermott	Enrolling
Omnivore	83	Harshman Choueiri	Enrolled
PROSPER	766	Harshman	Enrolling
Atezo/Bev *(non-clear cell)*	60	Choueiri	Enrolled

Close involvement with correlatives DF/HCC Lab- based colleagues:

- Signoretti Lab
- Wu lab
- Van Allen Lab
- Sharpe Lab
- Freeman Lab

Biomarker Model
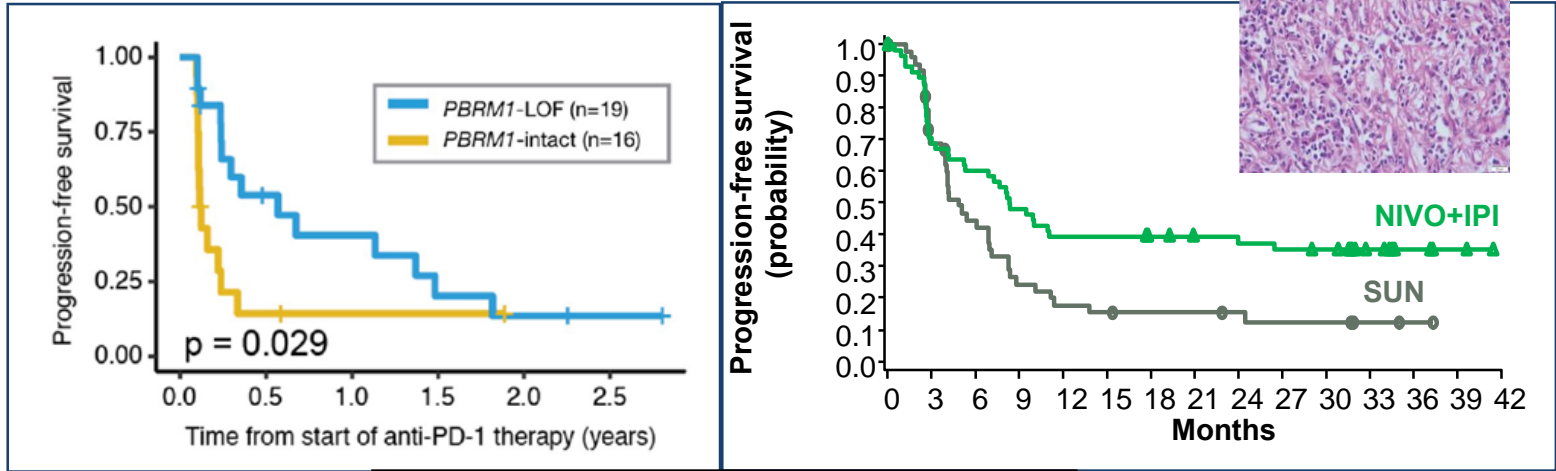
- All inter-related

- Some tumors may have a larger sweet spot
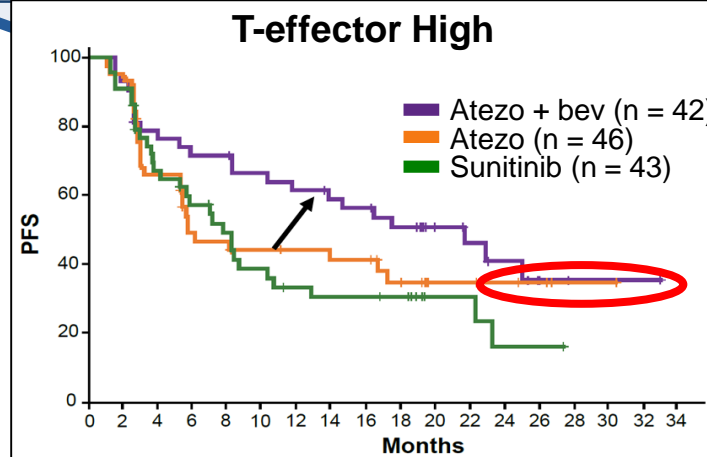
Program Accomplishments 2016-present

Awards

Lasker Basic Medical Research Award 2016
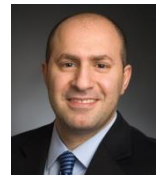
Bill Kaelin[DFCI]

Large Grants

UO1 Grant – 4/19

(PI: McDermott/Linehan)

Developing a Translational Pipeline for VHL Mutant Malignancies

SPORE Pathology Core Supports Collaborative Efforts

Sabina Signoretti[BWH]

Director

SPORE TAPCD Core

Toni Choueiri[DFCI]

Co-PI

International mRCC Data Base Consortium

Future Plans (DF/HCC Kidney SPORE)

- Competitive Renewal (2019-
- Promote the rationale application of therapies:
  - Integrative Biomarkers
  - Novel targets (e.g.: HIF-2, neoantigens)
  - Novel trials design (e.g. HCRN, OMNIVORE, PROSPER, Neovax)

- External funding (e.g. DOD)
- Continue to liaise with advocacy groups
- Mentor **and sponsor** the next-generation of Kidney Cancer researchers