Renal Cell Carcinoma of Variant Histology (The Rare and Very Rare): Have We Made Progress?

Nizar M. Tannir, MD, FACP

Ransom Horne, Jr. Professor for Cancer Research

Professor and Chair *ad interim*

Department of Genitourinary Medical Oncology

MD Anderson Cancer Center

Making Cancer History®

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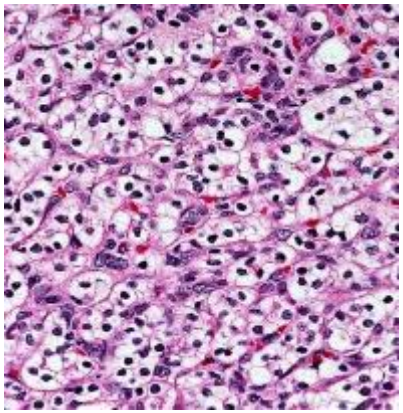
Personal Disclosures

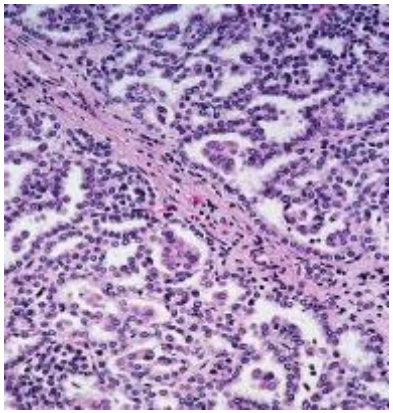
Nizar M. Tannir, MD, FACP, has a financial interest/relationship or affiliation in the form of:
Consultant and/or Advisor for Bristol-Myers Squibb; Eli Lilly and Company; Exelixis, Inc. and Nektar.
Other financial interest/relationship Clinical trial grant for Exelixis, Inc., Calithera Biosciences, and Nektar. Strategic Council meeting with Eisai Inc. Steering Committee Meeting with Pfizer, Inc. Ono Pharmaceutical CO., Ltd. for seminar presentations.

Nizar M. Tannir, MD, does intend to discuss either non–FDA-approved or investigational use for the following products/devices: various combination strategies with targeted agents and immunotherapies for renal cell carcinoma.

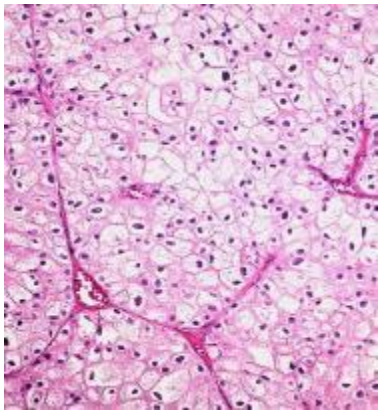
In the beginning…
Kidney Tumors were simple…



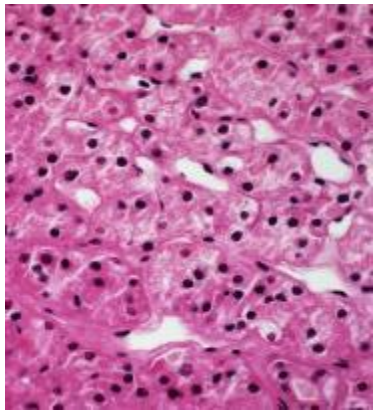
Clear cell



Papillary type

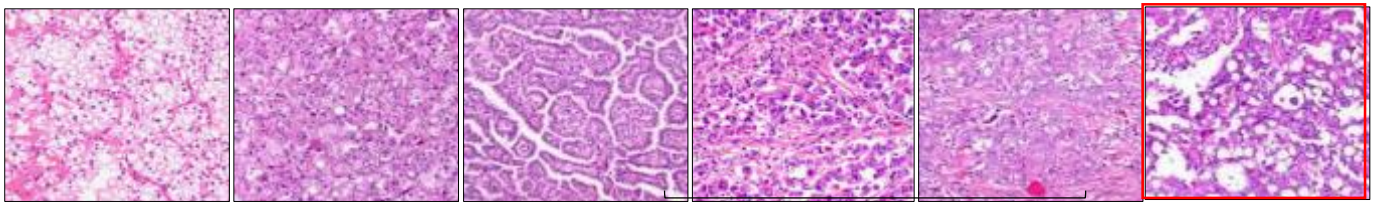


Chromophobe



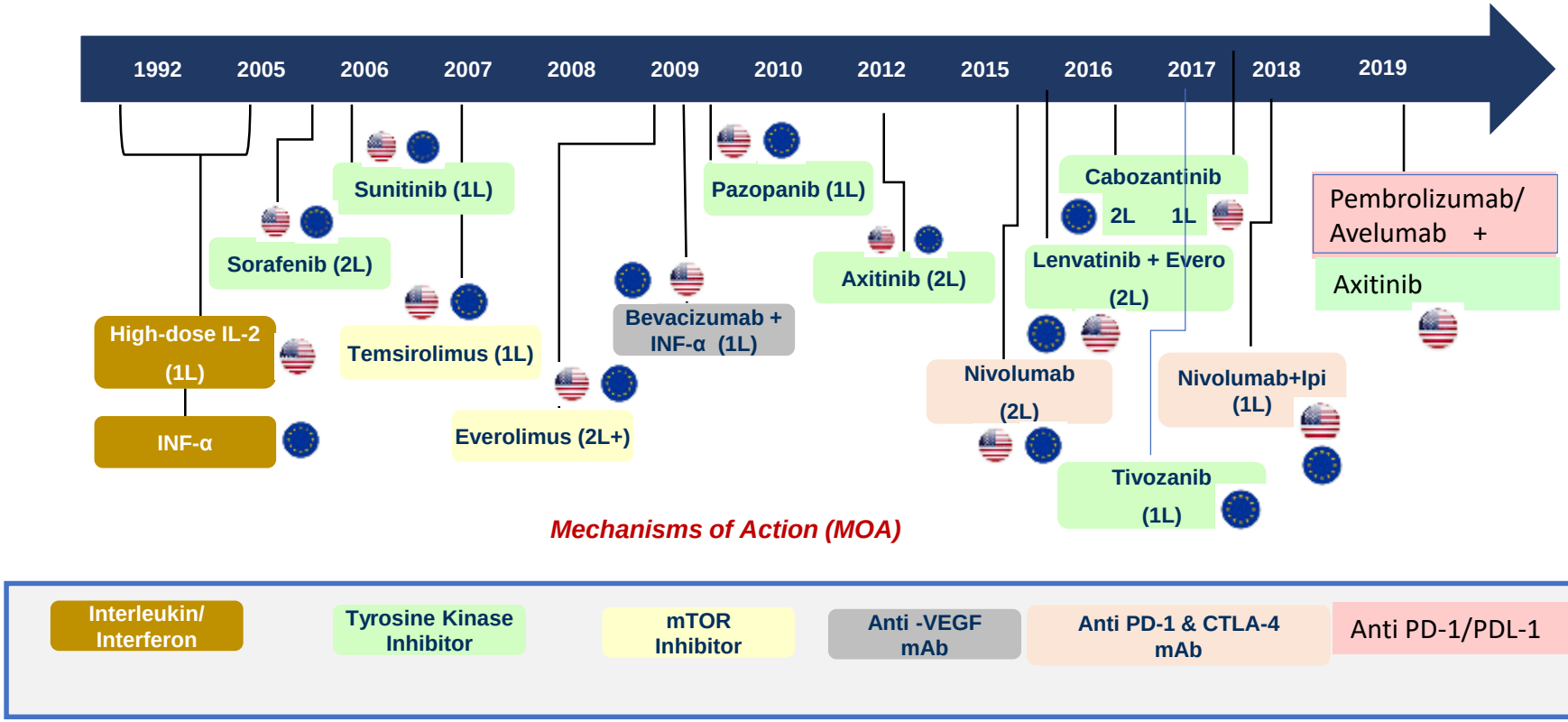
Oncocytoma

RCC Subtypes by Pathology/Genetics



	ccRCC	chRCC	Type I pRCC	Type II pRCC/CDC/Unclassified		RMC/MRT
Incidence:	**75%**	**5%**	**5%**	**~15%**		**<1%**
Median Age:	**62**	**58**	**62**	**62**	**50-55**	**20's**
Prognosis:	**Good**	**Very good**	**Good**	**Poor**	**Very poor**	**Dismal**
Genetics:	***VHL*, 3p loss**	***BHD* Aneuploidy**	***c-MET***	***FH*, *NF2*, 9p loss**	***NF2*, *SETD2* BAP1, 9p loss**	***SMARCB1* 22q loss**
Therapeutic targets:	**HIF, VEGF, RTKs, mTOR**	**PTEN, mTOR, TSC1, TSC2**	**c-MET**			

Timeline of Approvals of Therapies for Renal Cell Carcinoma



IMDC Prognostic Model for Non-Clear Cell RCC

- International Metastatic RCC Database Consortium prognostic model was used to evaluate patients with nccRCC treated with 1st-line VEGF or mTOR targeted therapies
- N = 2215 (1963 ccRCC / 252 nccRCC)
- nccRCC patients:
  - Younger ($P < .0001$)
  - Low HGB ($P = .014$)
  - Elevated neutrophils ($P = .0001$)
  - Significantly worse outcomes
    - OS 22.3 vs 12.8 mo ($P < .0001$)
    - TTF 7.8 vs 4.2 mo ($P < .0001$)

TTF, time to treatment failure.

Kroeger N, et al. *Cancer*. 2013;119:2999-3006.

Non-clear cell RCC vs. clear cell RCC

- Non-clear cell RCC is typically treated with agents developed based on studies in ccRCC, such as vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI) or mammalian targets of rapamycin (mTOR) inhibitors

- Clinical trials commonly exclude non-clear cell histology, or lump all non-ccRCC together, making conclusions based on specific histologies difficult

Recent first-line trials demonstrate only modest activity of VEGFR TKI and mTOR inhibition in non-ccRCC

Trial	Treatment	No of Patients	Response Rate	PFS (mos)	OS (mos)
ASPEN	Sunitinib	51	18%	8.3	31.5
	Everolimus	57	10%	5.6	13.2
ESPN	Sunitinib	33	9%	6.1	16.2
	Everolimus	35	3%	4.1	14.9
RECORD-3 (nccRCC subset)	Sunitinib	35	?	7.2	16.8
	Everolimus	31	?	5.1	16.2

Abbreviations: No, number; PFS, progression free survival; mos, months; OS, overall survival

Armstrong et al, Lancet Oncol 2016, 17:378; Tannir et al, Euro Urol 2016, 69:866; Motzer et al, JCO 2014, 32:2765; Knox et al, Ann Oncol 2017, 28:1339

ASPEN and ESPN trials demonstrate a slight advantage of sunitinib over everolimus, and sunitinib represents current standard of care for first-line non-ccRCC

ASPEN

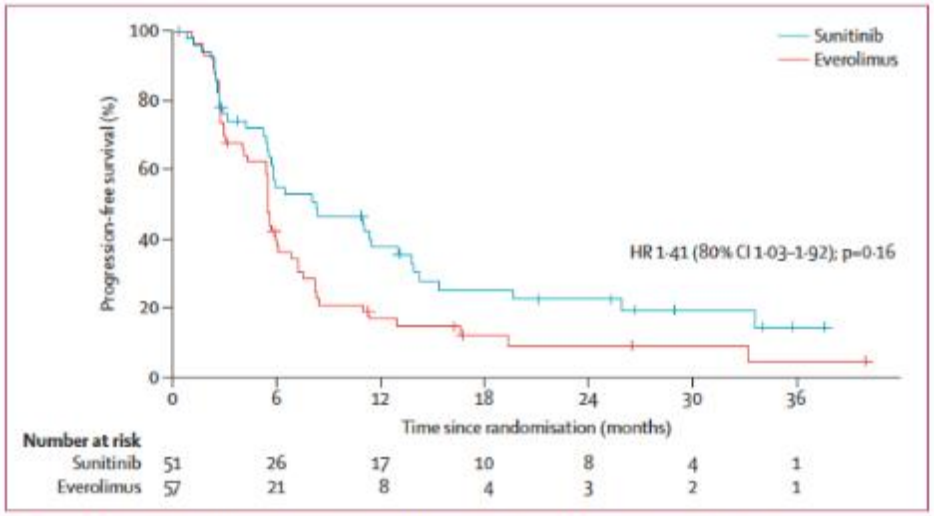
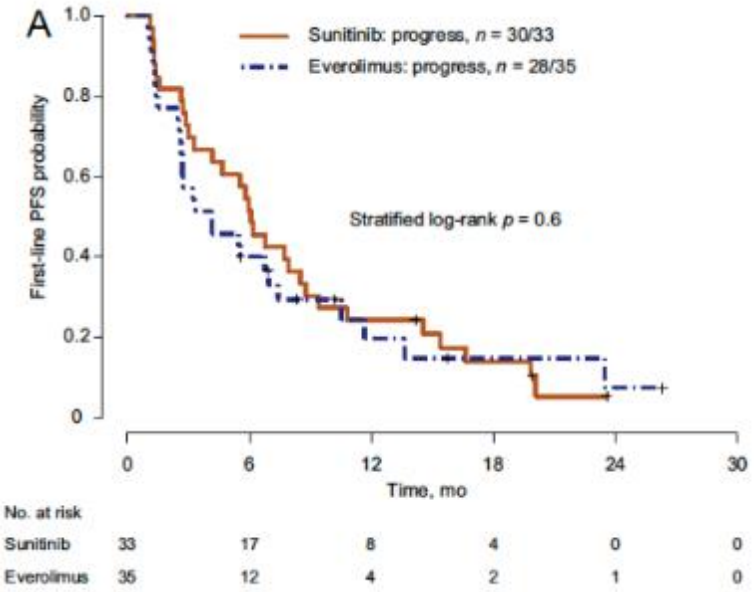


Figure 2: Kaplan-Meier estimates of progression-free survival according to treatment group

Armstrong et al, Lancet Oncol 2016, 17:378

ESPN



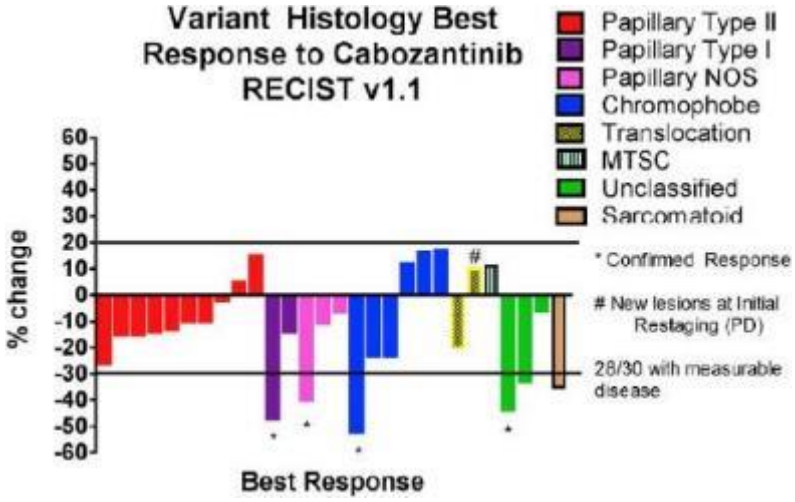
Tannir et al, Euro Urol 2016, 69(5):866

Original Research

Cabozantinib for the treatment of patients with metastatic non-clear cell renal cell carcinoma: A retrospective analysis

Matthew T. Campbell [a,*], Mehmet A. Bilen [b], Amishi Y. Shah [a], Emily Lemke [a], E. Jonasch [a], A.M. Venkatesan [d], E. Altinmakas [d], C. Duran [d], Pavlos Msaouel [c], N.M. Tannir [a]

Campbell et al. Eur J Cancer, 2018



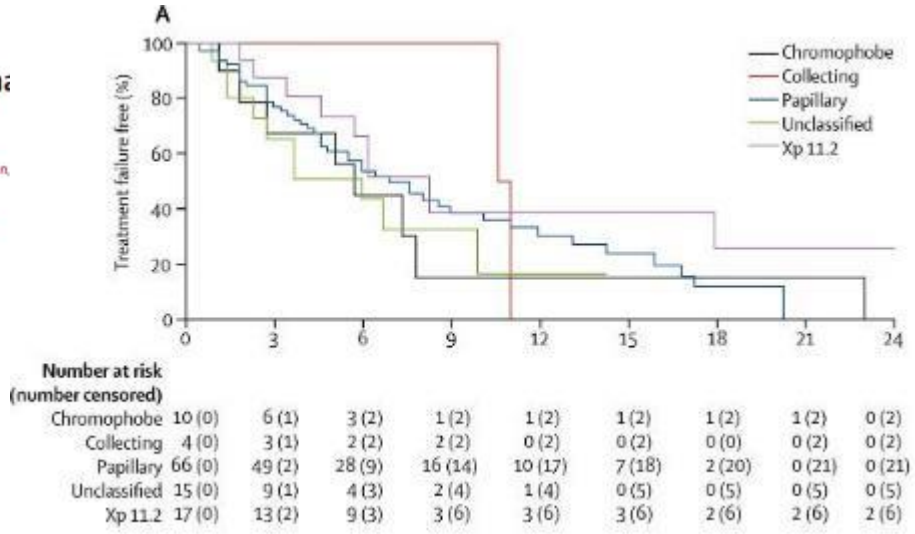
- Retrospective data (n=30 pts):
  - Disease control in 22/28 pts (78.6%); most had previous PD on other targeted therapies
  - ORR 4/28 pts (14.3%; 2 papillary, 1 chromophobe and 1 unclassified)
  - Two papillary RCC pts with PD on savolitinib had partial response and stable disease with cabozantinib
  - Conclusions: cabozantinib can achieve disease control in pretreated pts regardless of histology

- **CABOSUN II**: ongoing phase II RCT of cabozantinib vs sunitinib in non-clear cell RCC: NCT03541902

Cabozantinib in advanced non-clear-cell renal cell carcinoma: a multicentre, retrospective, cohort study

Nieves Martínez Chanzá, Wanling Xie, Mehmet Asim Bilen, Hannah Dzimitrowicz, Jarred Burkart, Daniel M Geynisman, Archana Balakrishnan, J Alex Bowman, Rohit Jain, Walter Stadler, Yousef Zakharia, Vivek Narayan, Benoit Beuselinck, Rana R McKay, Abhishek Tripathi, Russell Pachynski, Andrew W Hahn, JoAnn Hsu, Sumit A Shah, Elaine T Lam, Tracy L Rose, Anthony E Mega, Nicholas Vogelzang, Michael R Harrison, Amir Mortazavi, Elizabeth R Plimack, Ulka Vaishampayan, Hans Hammers, Saby George, Naomi Haas, Neeraj Agarwal, Sumanta K Pal, Sandy Srinivas, Benedito A Carneiro, Daniel Y C Heng, Dominick Bosse, Toni K Choueiri, Lauren C Harshman

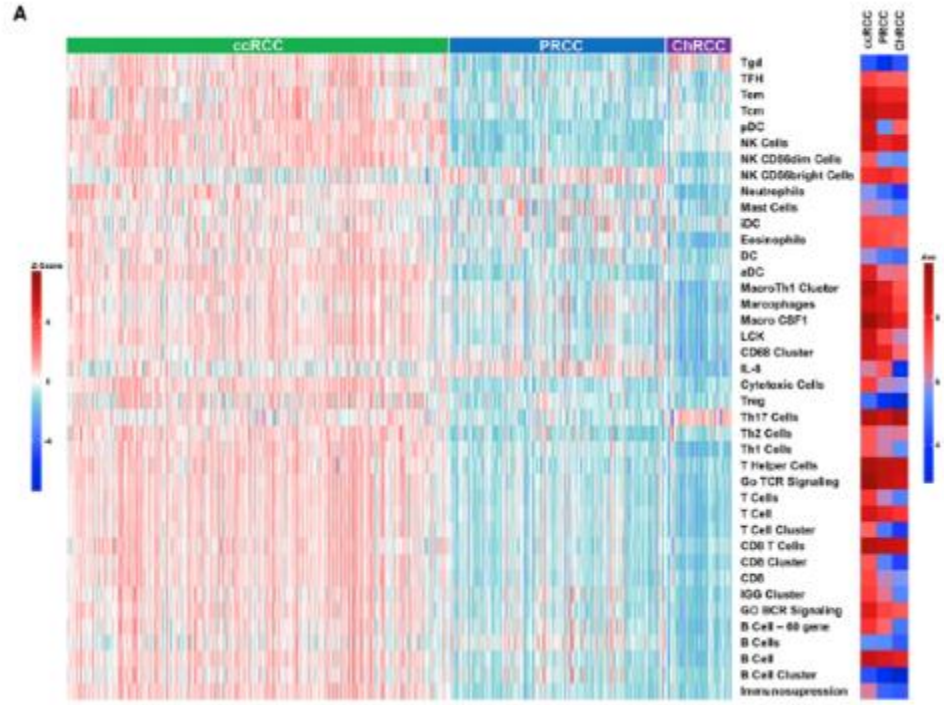
Martínez Chanzá et al. Lancet Oncol, 2019

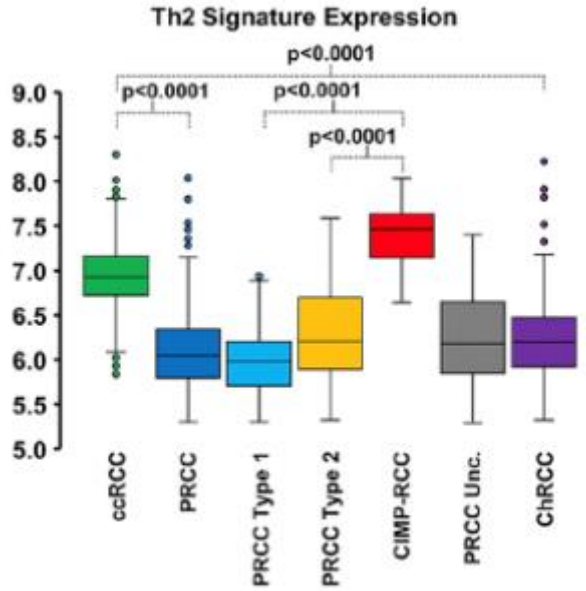


Time to treatment Failure

- Retrospective data (n=112 pts):
  - 66/112 (59%) papillary, 10/112 (9%) chromophobe, 17/112 (15%) Xp11.2 translocation, 15/112 (13%) unclassified, 4/112 (4%) collecting duct
  - ORR 27% (30/112 pts; 95% CI 19-36%)
    - Papillary ORR 27%
    - Chromophobe ORR 30%
    - Xp11.2 translocation ORR 29%
    - Collecting duct carcinoma ORR 50%
    - Unclassified ORR 13%
  - Most common somatic gene mutations: CDKN2A (22%), MET (20%)
    - Responses seen regardless of mutational status

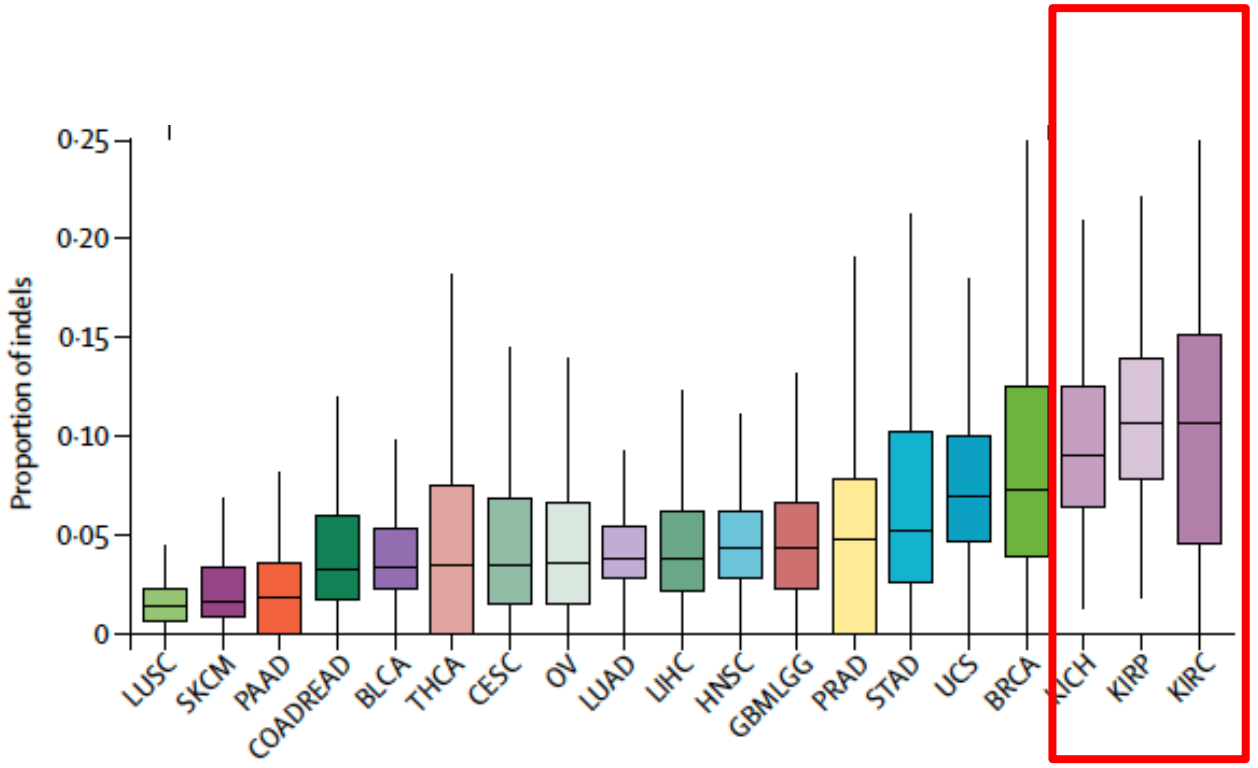
There is near universal upregulation of immune gene signatures in ccRCC compared with non-ccRCC





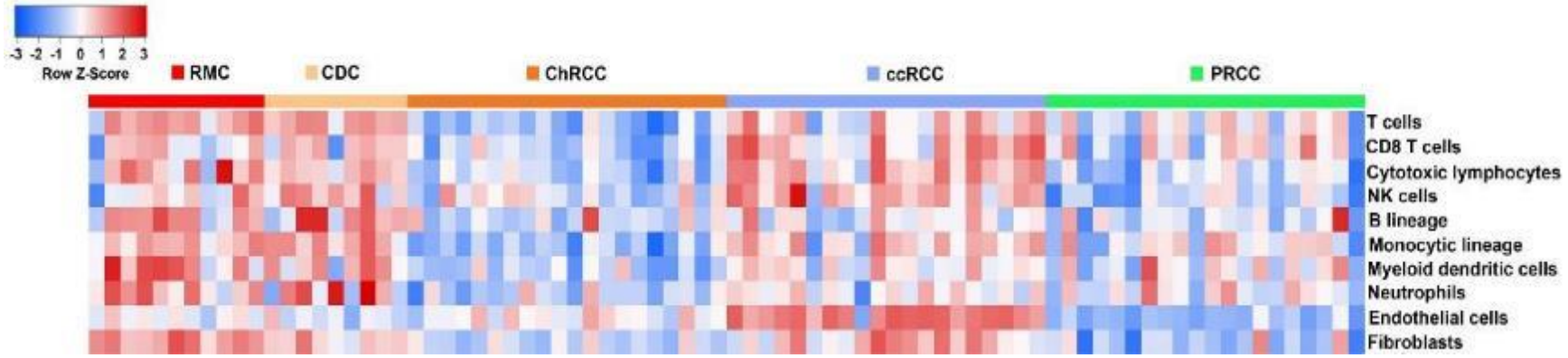
Rickets et al, Cell Reports 2018, 23:313

Indel burden may suggest a source of neoantigens across histologic subtypes of kidney cancer



Turajlic et al, Lancet Oncol 2017; 18:1009.

The Immune Microenvironment of Non-Clear Cell RCC



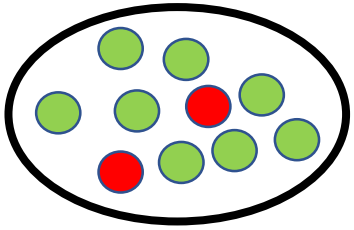
Legend:

- RMC: renal medullary carcinoma
- CDC: collecting duct carcinoma
- ChRCC: chromophobe renal cell carcinoma
- ccRCC: clear cell renal cell carcinoma
- PRCC: papillary renal cell carcinoma

- Clear cell RCC, renal medullary carcinoma (RMC) and collecting duct carcinoma (CDC): immunologically **"hot"** tumors
  - However, RMC and CDC contain a **large number of potentially immunosuppressive cells**
- Papillary RCC: **intermediate** number of immune infiltrates
- Chromophobe RCC: immunologically "**cold**" tumor

Msaouel et al. (unpublished data)

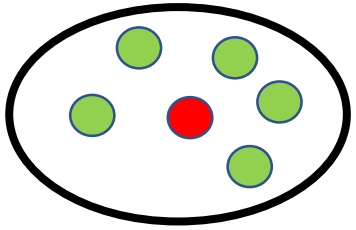
Immune Cells in Non-Clear Cell Tumors



Clear cell renal cell carcinoma

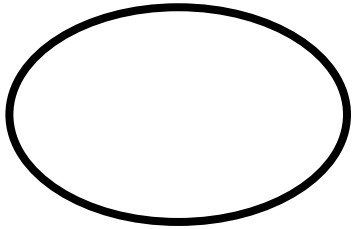
Goal:

activate the antitumor Immune cells



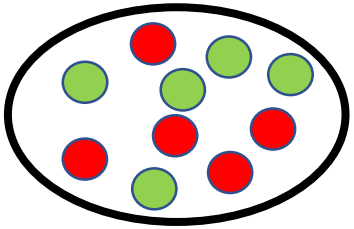
Papillary renal cell carcinoma

activate & bring more antitumor immune cells



Chromophobe renal cell carcinoma

Bring antitumor immune cells (and then activate them)



Collecting duct carcinoma

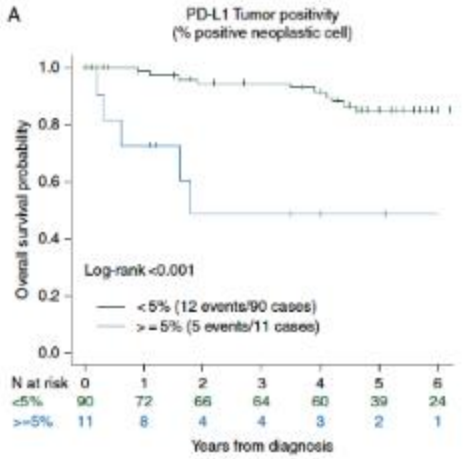
Remove the immunosuppressive cells and activate the antitumor immune cells

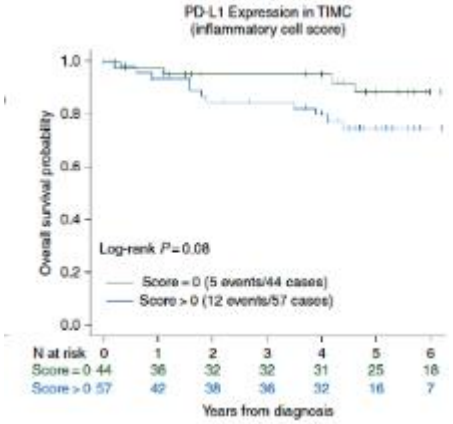
Antitumor immune cells (CTLs etc.)

Immunosuppressive cells (Tregs, MDSCs etc.)

Non-ccRCC tumors/tumor immune cells variably express programmed death ligand-1 (PD-L1)

Histology	Number Analyzed	PD-L1 staining of tumor*	PD-L1 staining of TIMC*
Chromophobe	36	6%	36%
Collecting Duct	5	20%	100%
Papillary	50	10%	60%
Translocation	10	30%	90%





* Defined as >=5% positive on tumor cell membrane or >0 (% TIMC positive x extent of mononuclear cell infiltration) on tumor-infiltrating mononuclear cells staining by mouse anti-PD-L1 antibody from DFCI

Choueiri et al, Annal Oncol 2014; 25:2178

Responses of Non-Clear Cell RCC to IO

Best response to nivolumab (RECIST v 1.1) based on RCC histology

Histology	*N*	PR	SD	PD	Non-evaluable
Papillary	16	2 (14%)	3 (21%)	9 (64%)	2
Unclassified	14	4 (36%)	3 (27%)	4 (36%)	3
Chromophobe	5	0 (0%)	3 (75%)	1 (25%)	1
Collecting Duct	4	1 (25%)	0 (0%)	3 (75%)	0
MTSCC	1	0 (0%)	1 (100%)	0 (0%)	0
Translocation	1	0 (0%)	0 (0%)	1 (100%)	0
All Histologies	41	7 (20%)	10 (29%)	18 (51%)	6

No complete responses (CRs) were observed in this study

For some histologies total percentages do not add up to 100% due to rounding

Koshkin et al. J Immunother Cancer. 2018

Total

Papillary RCC:

- CR: 1/30 (3.3%)
- PR: 5/30 (16.7%)

} **ORR 20%**

- SD: 7/30 (23.3%)
- **PD: 15/30 (50%)**

Chromophobe RCC:

- CR/PR: **0/15 (0%)**
- SD: 7/15 (46.7%)
- **PD: 8/15 (53.3%)**

Translocation RCC:

- CR: 0/4 (0%)
- PR: 1/4 (25%)
- SD: 1/4 (25%)
- **PD: 2/4 (50%)**

		CR		PR		SD		PD	
	Total *N*	*N*	%	*N*	%	*N*	%	*N*	%
All	43	1	2	7	16	14	33	21	49
Histology									
Papillary	14	1	7	3	21	4	29	6	43
Chromophobe	10	—	—	—	—	4	40	6	60
Unclassified	9	—	—	—	—	3	33	6	67
Clear cell with sarcomatoid and/or rhabdoid differentiation >20%	7	—	—	3	43	2	29	2	29
Translocation	3	—	—	1	33	1	33	1	33
Sarcomatoid and/or rhabdoid differentiation									
No	32	1	3	4	13	11	34	16	50
Yes[a]	11	—	—	3	27	3	27	5	45
Type of checkpoint blockade									
Monotherapy	30	—	—	4	13	11	37	15	50
Combination therapy	13	1	8	3	23	3	23	4	46
PD-1/PD-L1 + CTLA-4 inhibitor	4	1	25	1	25	1	25	1	25
PD-1/PD-L1 + VEGF-targeted therapy	9	—	—	2	22	2	22	5	56

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; IMDC, International Metastatic RCC Database Consortium.
[a]Clear cell ($n = 7$), chromophobe ($n = 3$), and unclassified ($n = 1$).

McKay et al. Cancer Immunol Res. 2018

The Oncologist®

Genitourinary Cancer

Nivolumab for the Treatment of Patients with Metastatic Non-Clear Cell Renal Cell Carcinoma (nccRCC): A Single-Institutional Experience and Literature Meta-Analysis

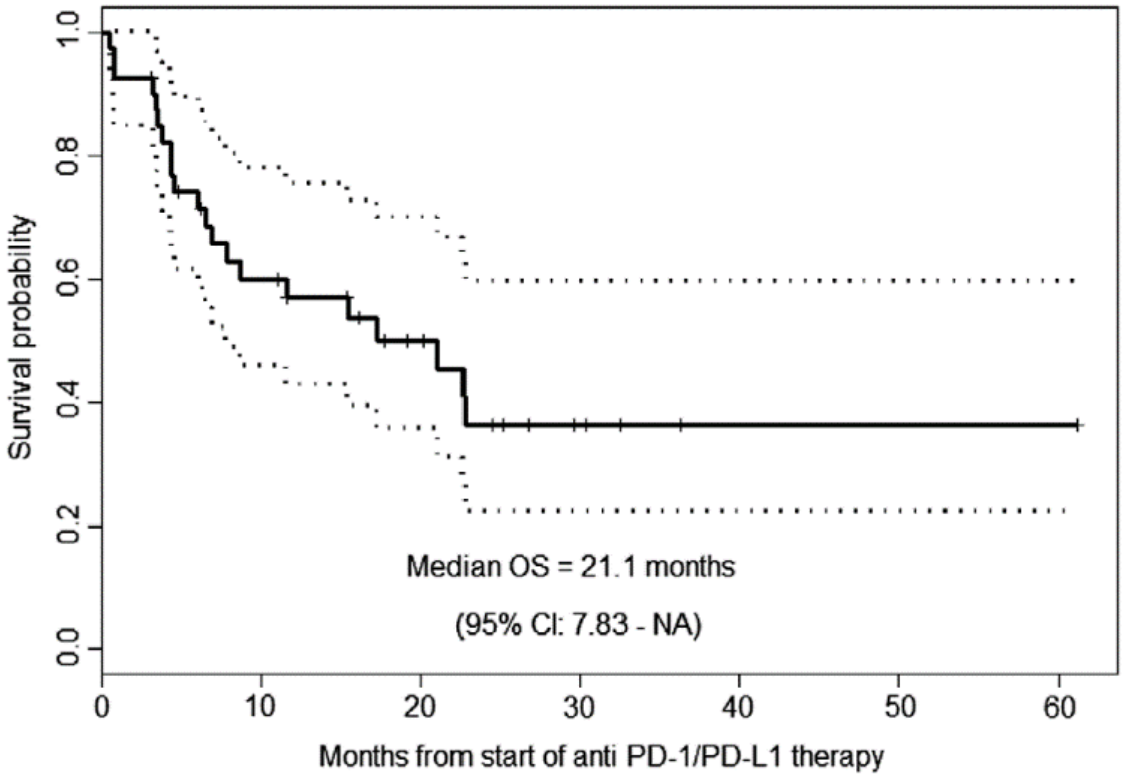
Jad Chahoud,[a] Pavlos Msaouel,[b] Matthew T. Campbell,[b] Tharakeswara Bathala,[b] Lianchun Xiao,[b] Jianjun Gao,[b] Amado J. Zurita,[b] Amishi Yogesh Shah,[b] Eric Jonasch,[b] Padmanee Sharma,[b] Nizar M. Tannir[b]

[a]Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, Florida, USA; [b]The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Best Overall Response

Variable	Total *n*	CR, *n* (%)	PR, *n* (%)
All	40	3 (8.8)	4 (11.8)
Histology			
Papillary type 1	6	0 (0)	1 (25)
Papillary type 2	6	0 (0)	0 (0)
Chromophobe	5	0 (0)	0 (0)
Unclassified	11	2 (22.2)	2 (22.2)
Translocation	3	0 (0)	0 (0)
Mucinous tubular and spindle cell carcinoma	1	0 (0)	0 (0)
ccRCC with rhabdoid >20%	8	1 (14.3)	1 (14.3)
IMDC risk group			
Favorable	3	0 (0)	0 (0)
Intermediate	29	3 (11.1)	4 (14.8)
Poor	8	0 (0	0 (0)
Line of systemic therapy			
1	6	2 (33.3)	1 (16.7)
2	14	1 (9)	2 (18.3)
≥3	20	0 (0)	1 (5.9)
Type of checkpoint blockade			
Monotherapy	31	2 (8)	1 (4)
Combination therapy (nivolumab with ipilimumab or nivolumab with VEGFR-TKI)	9	1 (11.1)	3 (33.4)

Chahoud, et al., The Oncologist, 2019



Chahoud, et al., The Oncologist, 2019

Ipilimumab + Nivolumab: Retrospective Experience CCF / UT Southwestern

N = 18 pts nccRCC, 78% no prior Rx

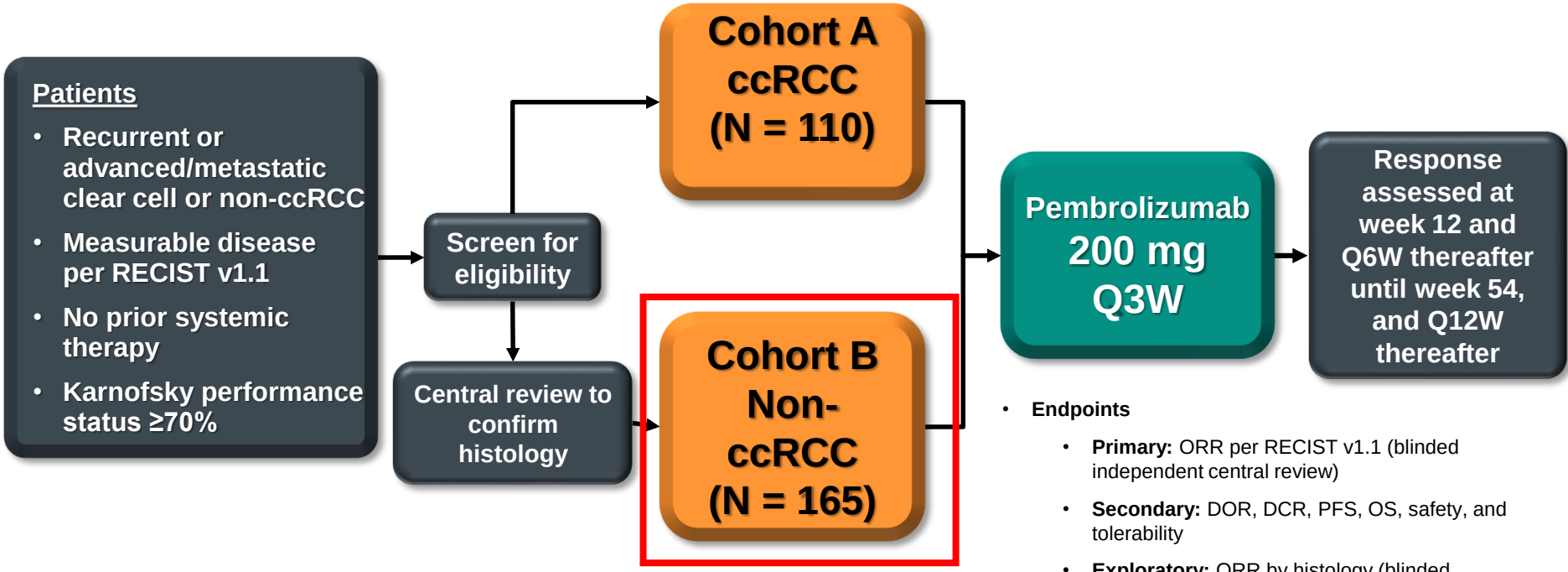
Histology	N. pts	PR	SD	PD
Total	18	4 (28%)	2 (14%)	8 (58%)
Papillary	6	2 (33%)	1 (17%)	3 (50%)
Chromophobe	5	0 (0%)	0 (0%)	3 (60%)
Adc renal origin	2	1 (50%)	0 (0%)	1 (50%)
Unclassified	3	1 (33%)	0 (0%)	0 (0%)
Translocation	1	0 (0%)	1 (100%)	0 (0%)
Medullary	1	0 (0%)	0 (0%)	1 (100%)

	Freq.	Grade irAE
Colitis	4 (28%)	3
Hepatotoxicity	3 (17%)	3
Hypophysitis	1 (7%)	3
Fatigue	1 (7%)	2
Rash	1 (7%)	2
Encephalitis	1 (7%)	3

- 50% received Ipi x 4
- 60% required high-dos steroids for irAEs

Gupta et al, ASCO GU 2019

KEYNOTE-427: (NCT02853344)



- **Endpoints**
  - **Primary:** ORR per RECIST v1.1 (blinded independent central review)
  - **Secondary:** DOR, DCR, PFS, OS, safety, and tolerability
  - **Exploratory:** ORR by histology (blinded independent central review) and PD-L1 expression;[a] tissue-based biomarkers (e.g. IHC, RNA sequencing)

[a]PD-L1 positive defined as combined positive score [CPS] ≥1.

Confirmed ORR by Blinded Independent Central Review

	N = 165		
	n	%	95% CI
ORR	**41**	**24.8**	**18.5-32.2**
DCR (CR + PR + SD ≥6 months)	**67**	**40.6**	**33.0-48.5**
Best overall response			
CR	8	4.8	
PR	33	20.0	
SD	53	32.1	
PD	61	37.0	
No assessment[a]	8	4.8	
Not evaluable[b]	2	1.2	

[a]Includes patients who discontinued or died before their first post-baseline scan. [b]Includes patients with insufficient data for response assessment. Database cutoff: September 7, 2018.

Clinical Trials Identifier: NCT02853344

ORR by IMDC

	Favorable n = 53	Intermediate/Poor n =112
Confirmed ORR, % (95%CI)	**28.3 (16.8-42.3)**	**23.2 (15.8-32.1)**
DCR, % (95%CI)[a]	**41.5 (28.1-55.9)**	**40.2 (31.0-49.9)**
Confirmed BOR, %		
CR	9.4	2.7
PR	18.9	20.5
SD	34.0	31.3
PD	35.8	37.5
No assessment[b]	0.0	7.1
Not evaluable[c]	1.9	0.9

[a]DCR = CR + PR + SD ≥6 months; [b]Includes patients who discontinued or died before their first post-baseline scan. [c]Includes patients with insufficient data for response assessment.
Database cutoff: September 7, 2018.

Clinical Trials Identifier: NCT02853344

ORR by Confirmed RCC Histology per Blinded Independent Central Review

	Papillary n = 118	Chromophobe n =21	Unclassified n = 26
Confirmed ORR, % (95%CI)	**25.4 (17.9-34.3)**	**9.5 (1.2-30.4)**	**34.6 (17.2-55.7)**
DCR, % (95%CI)[a]	**43.2 (34.1-52.7)**	**33.3 (14.6-57.0)**	**34.6 (17.2-55.7)**
Confirmed BOR, %			
CR	4.2	4.8	7.7
PR	21.2	4.8	26.9
SD	34.7	47.6	7.7
PD	33.9	42.9	46.2
No assessment[b]	5.1	0.0	7.7
Not evaluable[c]	0.8	0.0	3.8

[a]DCR = CR + PR + SD ≥6 months; [b]Includes patients who discontinued or died before their first post-baseline scan. [c]Includes patients with insufficient data for response assessment.
Database cutoff: September 7, 2018.

Clinical Trials Identifier: NCT02853344

ORR by PD-L1 Expression

	CPS ≥1 n = 102	CPS <1 n =58
Confirmed ORR, % (95%CI)	**33.3 (24.3-43.4)**	**10.3 (3.9-21.2)**
DCR, % (95%CI)[a]	**49.0 (39.0-59.1)**	**25.9 (15.3-39.0)**
Confirmed BOR, %		
CR	5.9	3.4
PR	27.5	6.9
SD	26.5	41.4
PD	33.3	43.1
No assessment[b]	4.9	5.2
Not evaluable[c]	2.0	0.0

[a]DCR = CR + PR + SD ≥6 months; [b]Includes patients who discontinued or died before their first post-baseline scan. [c]Includes patients with insufficient data for response assessment.
Database cutoff: September 7, 2018.

Clinical Trials Identifier: NCT02853344

KEYNOTE-427 Conclusions

- This is the first prospective data of immune checkpoint inhibition in non-clear cell RCC
- Pembrolizumab has activity in non-clear cell RCC with durable responses and is certainly worthy of further study
  - An option for first-line treatment
- Response rates remain inferior to that seen in ccRCC
- Randomized studies are needed
- PD-L1 staining of TILs may be predictive, as may subtype, although cannot use either to dictate therapy at this point

Clinical Trials Identifier: NCT02853344

Study Design

Multicenter, Open-Label, Single Arm Phase II

Patients

-Non-clear cell RCC OR clear cell RCC with >20% sarcomatoid differentiation

-Measurable disease

-ECOG 0-2

-Any number of lines

-No prior CPI

N=65 enrolled

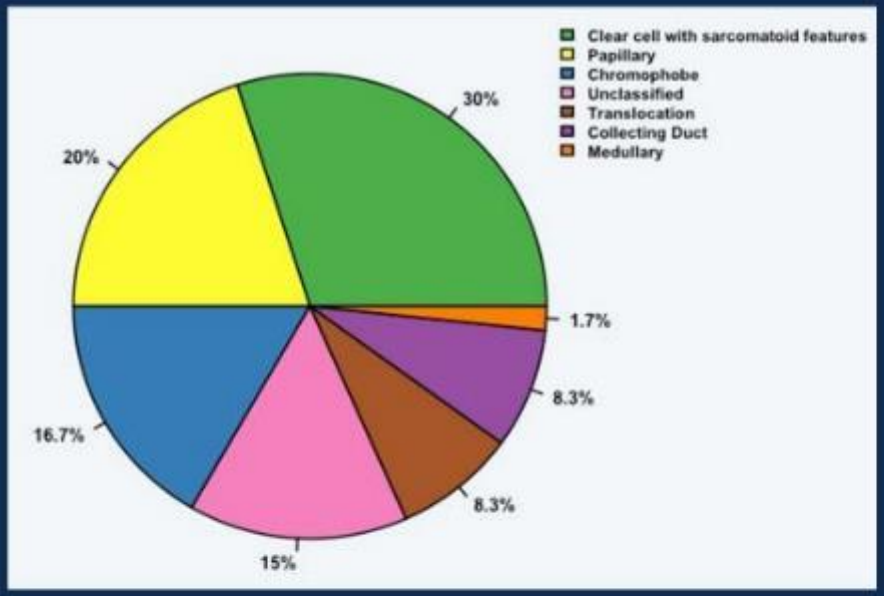
Primary Endpoint: ORR

Secondary Endpoints: DOR, PFS, OS, irORR, toxicity, QOL, tissue/blood based biomarkers of response

RCC=Renal cell carcinoma; ECOG=Eastern Cooperative Oncology Group; CPI=Checkpoint Inhibition; ORR=Objective response rate; DOR=Duration of response; PFS=Progression-free survival, OS=Overall survival, irORR=Immune related objective response rate; QOL=Quality of life.

Presented by: Rana R. McKay

Histology



Presence of Sarcomatoid Differentiation, % (n)	
Non-Clear Cell	17% (n=7/42)
Clear Cell	100% (n=18/18)
Total	42% (n=21/60)

Objective Response Rate

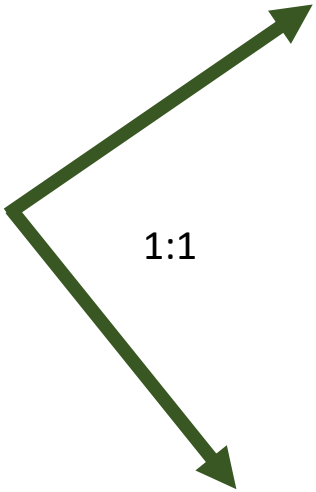
	ORR
Overall	34% (n=19/56)*
Prior Treatment	
Treatment Naïve	31% (n=11/36)
Previously Treated	40% (n=8/20)
IMDC Risk Group	
IMDC Favorable Risk	33% (n=3/9)
IMDC Intermediate Risk	42% (n=14/33)
IMDC Poor Risk	14% (n=2/14)

	ORR
Clear Cell SD	53% (n=9/17)
Non-Clear	26% (n=10/39)
Sarcomatoid Present	44% (n=11/25)
Sarcomatoid Absent	26% (n=8/31)
Papillary	25% (n=3/12)
Chromophobe	10% (n=1/10)
Unclassified	29% (n=2/7)
Other#	30% (n=3/10)

Analytical cohort includes patient with at least 1 scan assessment. *Confirmed 23% (n=13/56). Complete response=2 (3.6%). #Translocation, Collecting Duct, Medullary. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; SD=Sarcomatoid Differentiation.

Phase 2 Trial of Nivolumab and Ipilimumab in Non-Clear Cell RCC (SUNIFORECAST)

- N= 306
- KPS >70%
- No previous therapy
- Primary Endpoint: OS rate at 12 mos
- Secondary endpoints: OS at 6, 18 mos, PFS, OS, ORR
- No active brain mets
- Location: Frankfurt, Germany

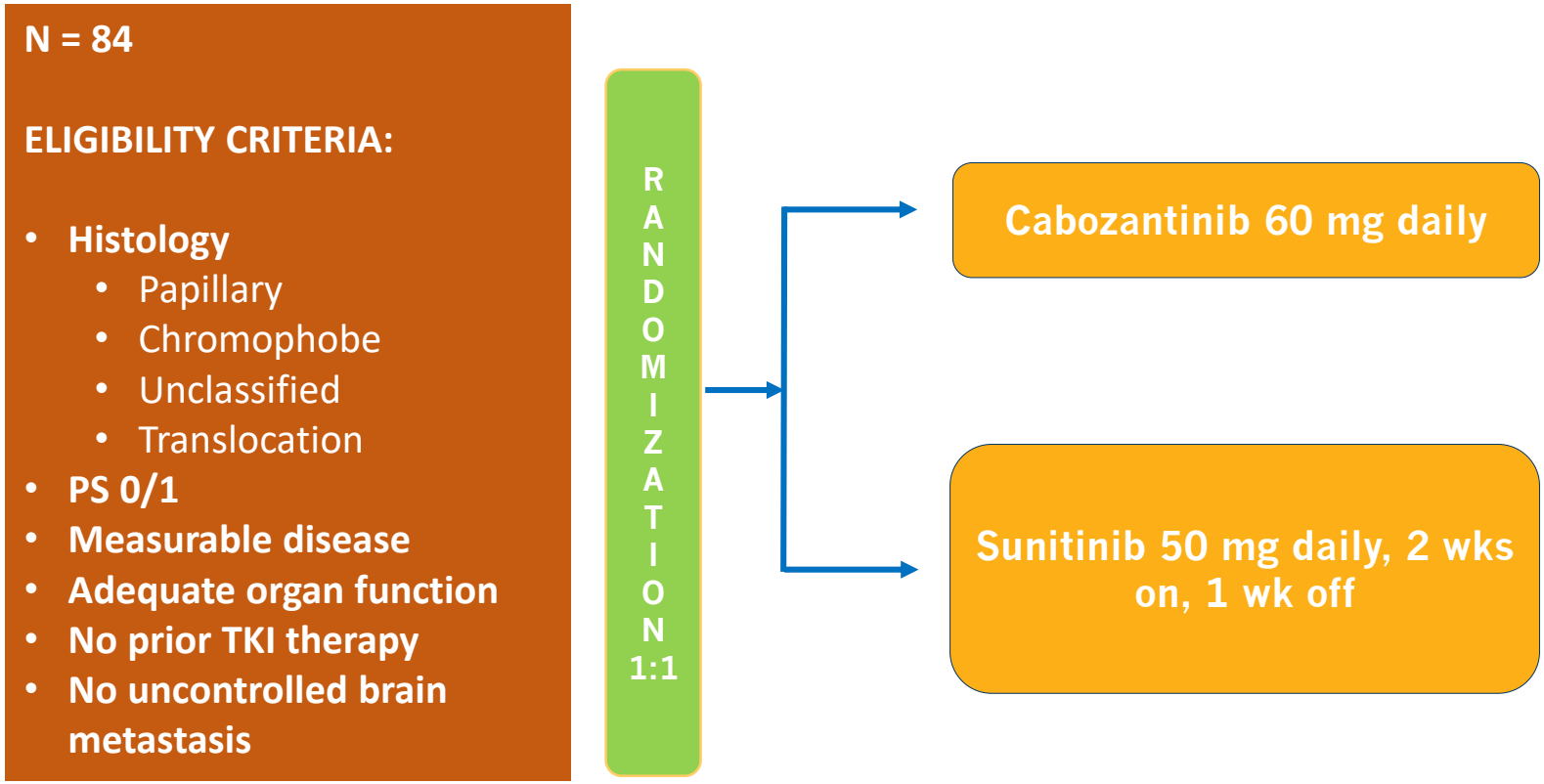


Ipi (1 mg/kg) + Nivo (3mg/kg)
Q 3weeks x 4,
then Nivo 240 mg IV Q 2 weeks

Sunitinib 50 mg
4 weeks on / 2 weeks off

NCT 03075423

CaboSun 2 Trial Schema



Stratification:
1. **IMDC risk group**
2. **Papillary vs other**

NCT03541902

Selected MET inhibitor papillary RCC trials

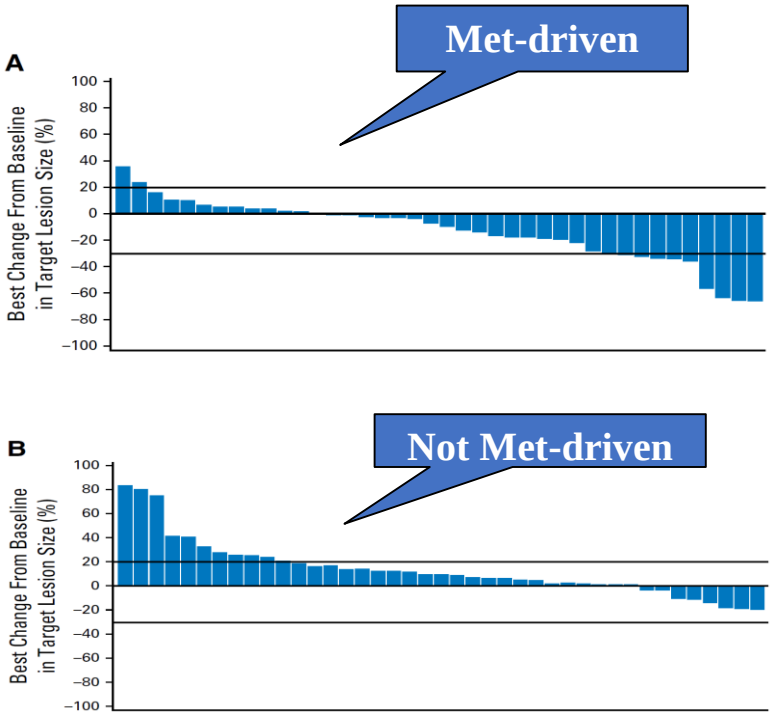
Treatment	Trial	Setting	MET-altered definition	No of Patients	ORR
Crizotinib	EORTC 90101/ CREATE	Type 1 pRCC Any line	Mutation in exon 16-19	23	15% overall 50% MET+ (2/4) 6% MET- (1/16)
Foretinib	Choueiri et al JCO 2013	pRCC Any line	MET germline mutation	74	13.5% overall 50% MET+ (5/10) 9% MET-
Savolitinib	Choueiri et al JCO 2017	pRCC Any line	Chr7 copy gain Focal MET or HGF amp MET kinase domain mutations	119	7% overall 18% MET+ 0% MET-

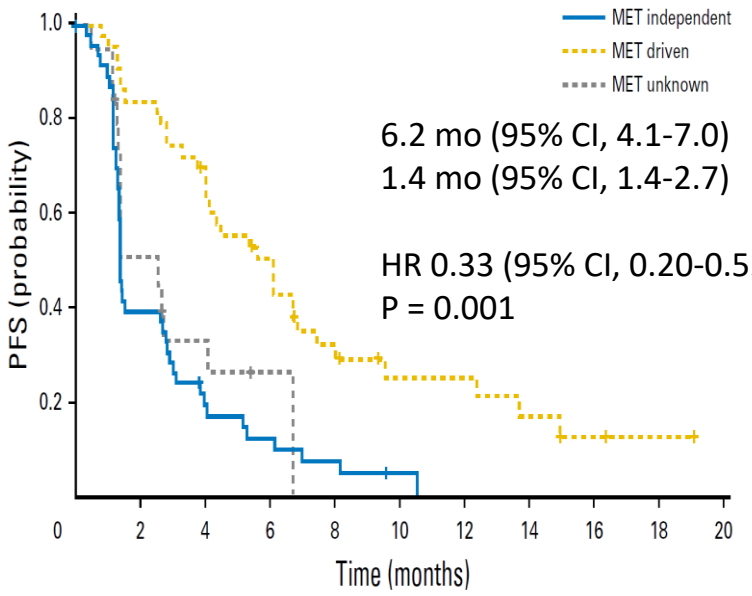
Biomarker-Based Phase II Trial of Savolitinib in Patients With Advanced Papillary Renal Cell Cancer

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

JCO 35:2993-3001, 2017

N=109

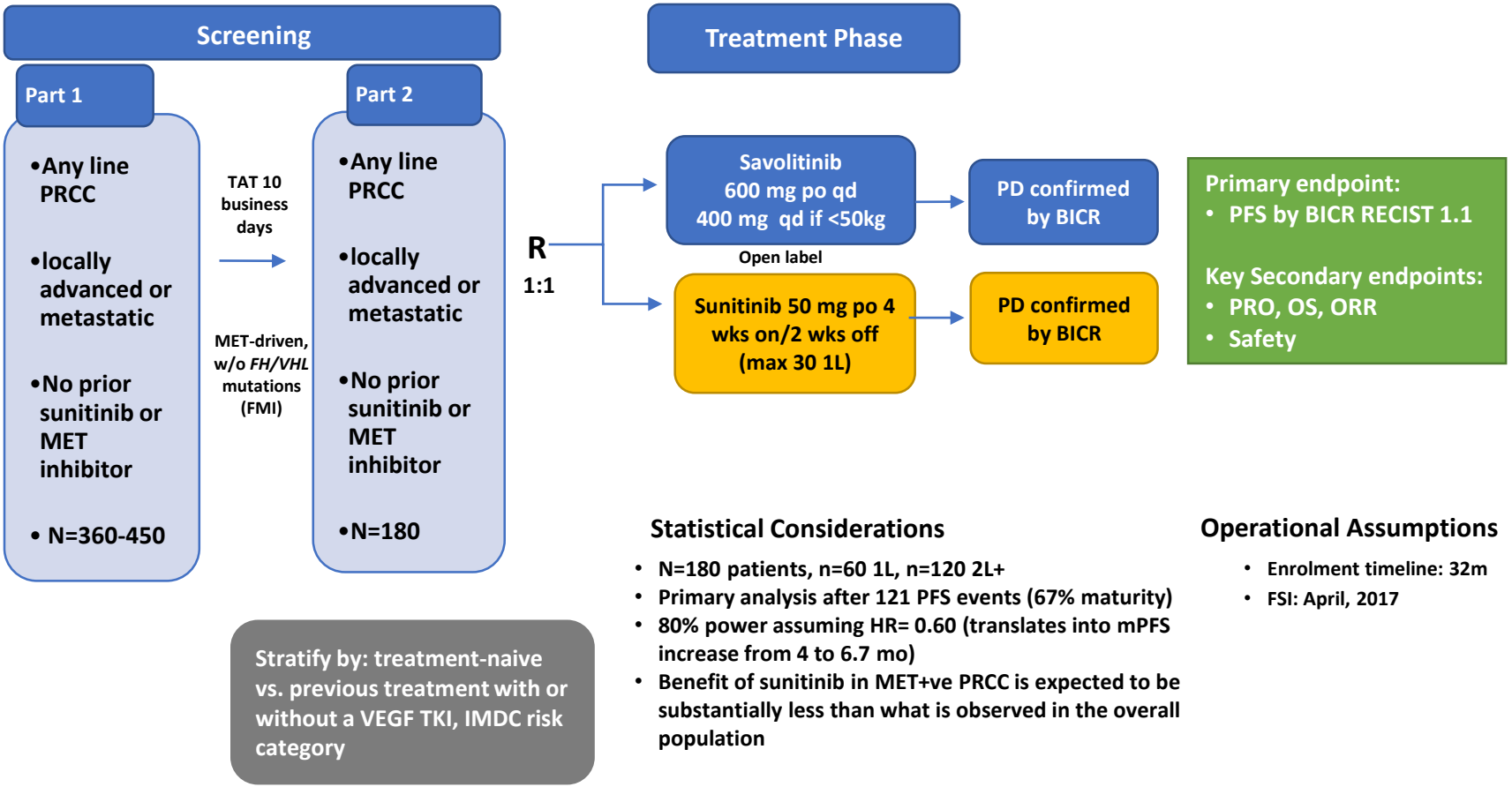




6.2 mo (95% CI, 4.1-7.0)
1.4 mo (95% CI, 1.4-2.7)

HR 0.33 (95% CI, 0.20-0.52)
P = 0.001

Savolitinib PRCC Phase III Study Design (SAVOIR)



Statistical Considerations

- N=180 patients, n=60 1L, n=120 2L+
- Primary analysis after 121 PFS events (67% maturity)
- 80% power assuming HR= 0.60 (translates into mPFS increase from 4 to 6.7 mo)
- Benefit of sunitinib in MET+ve PRCC is expected to be substantially less than what is observed in the overall population

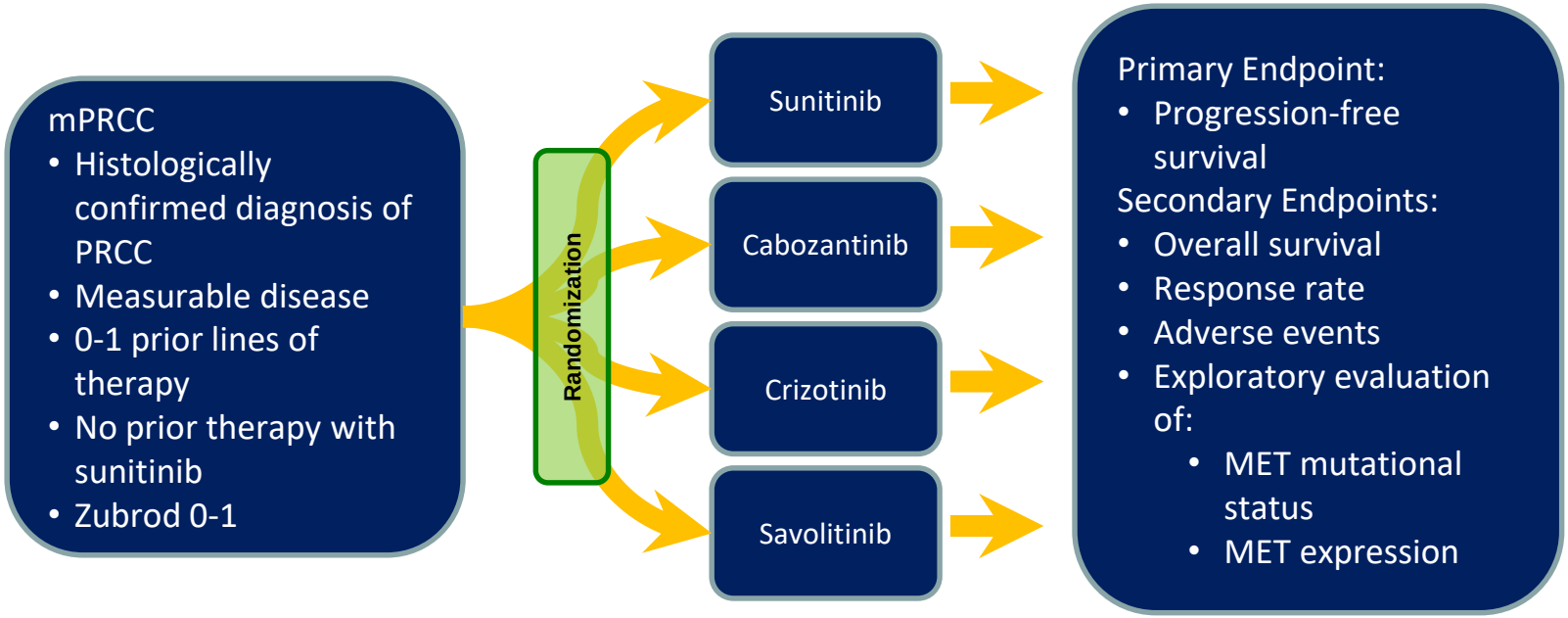
Operational Assumptions

- Enrolment timeline: 32m
- FSI: April, 2017

SAVOIR Study Press Release

- Randomized phase III registration study of savolitinib vs sunitinib in MET-driven papillary RCC
- Suspended due to [yet unreleased] molecular epidemiology study demonstrating MET positive PRCC lower than previously thought

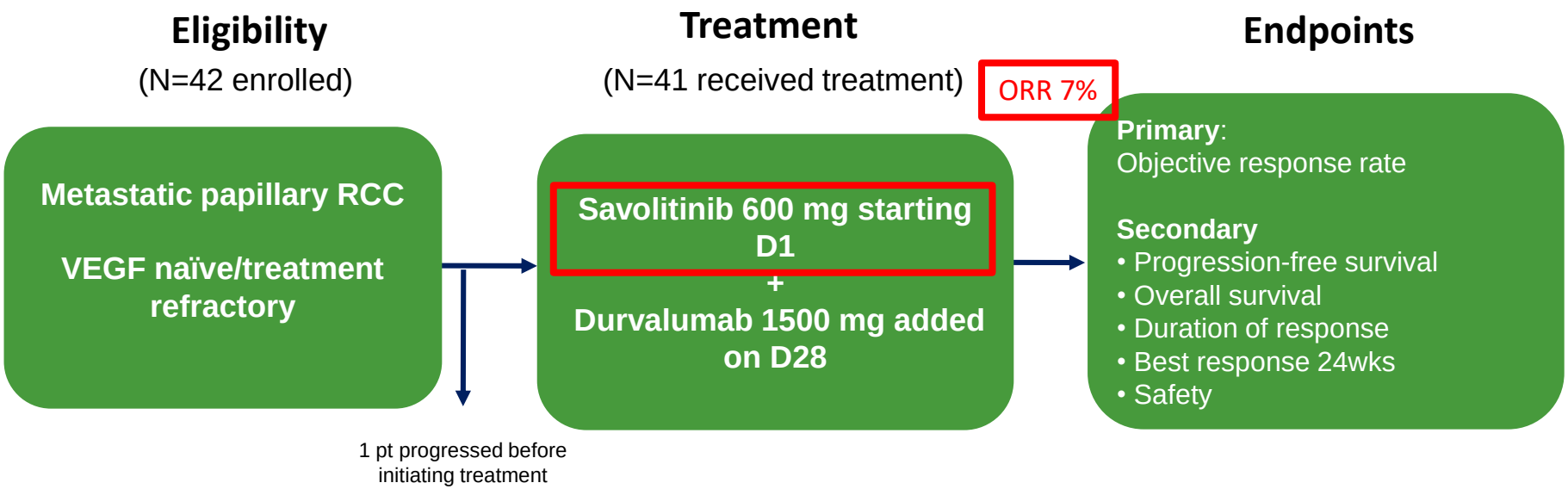
S1500 (PAPMET)



- **BISQFP funding awarded for correlative studies**
- ***MET* alterations**
- **Broader genomic profiling**

CALYPSO Study Design: Papillary Cohort

Trial Sponsor: Queen Mary University of London

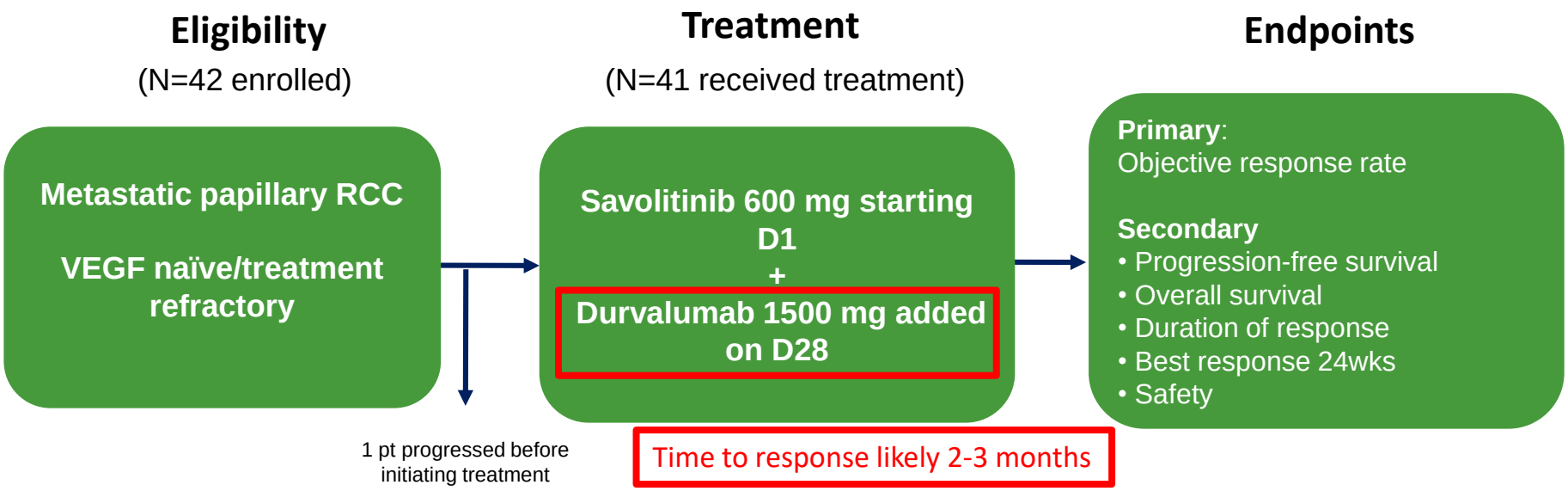


- Treatment until progression or loss of clinical benefit
- **Median follow-up: 6.9 months** (95% CI: 4.7 – 10.0) as of 25Sep2018

Statistical considerations:
RR≤30% not worthy of further investigation
RR≥50% treatment developed further
80% power at 5% significance
17 responses / 39 patients to further study drugs

CALYPSO Study Design: Papillary Cohort

Trial Sponsor: Queen Mary University of London



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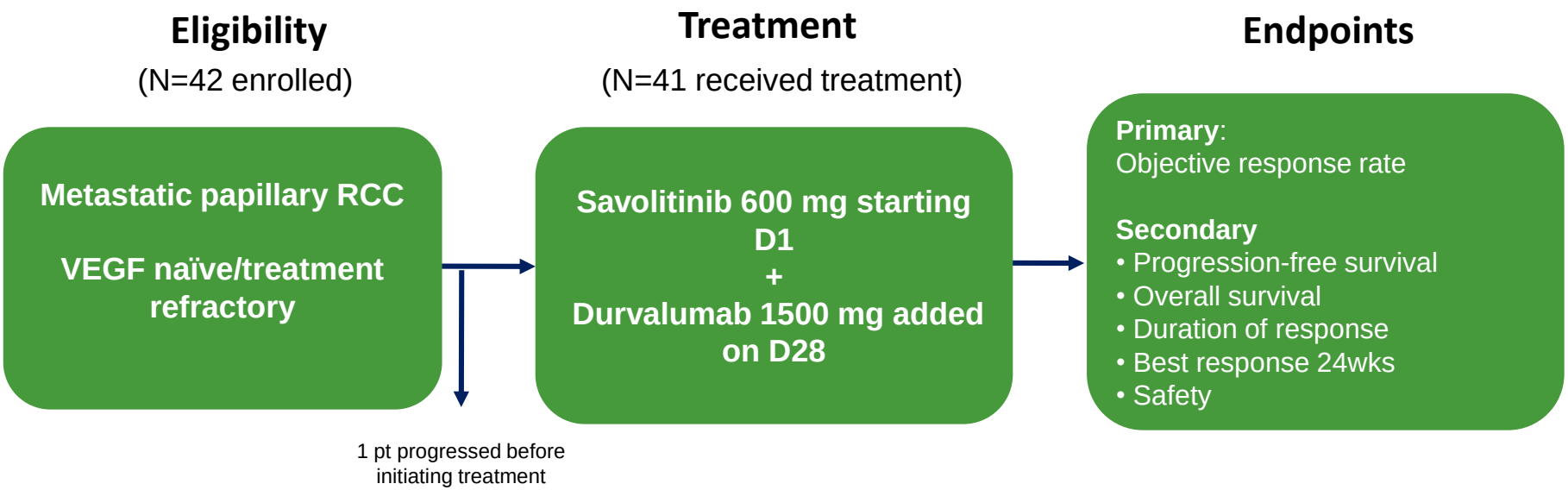

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RR≤30% not worthy of further investigation
RR≥50% treatment developed further
80% power at 5% significance
17 responses / 39 patients to further study drugs

Best Overall Response Rate

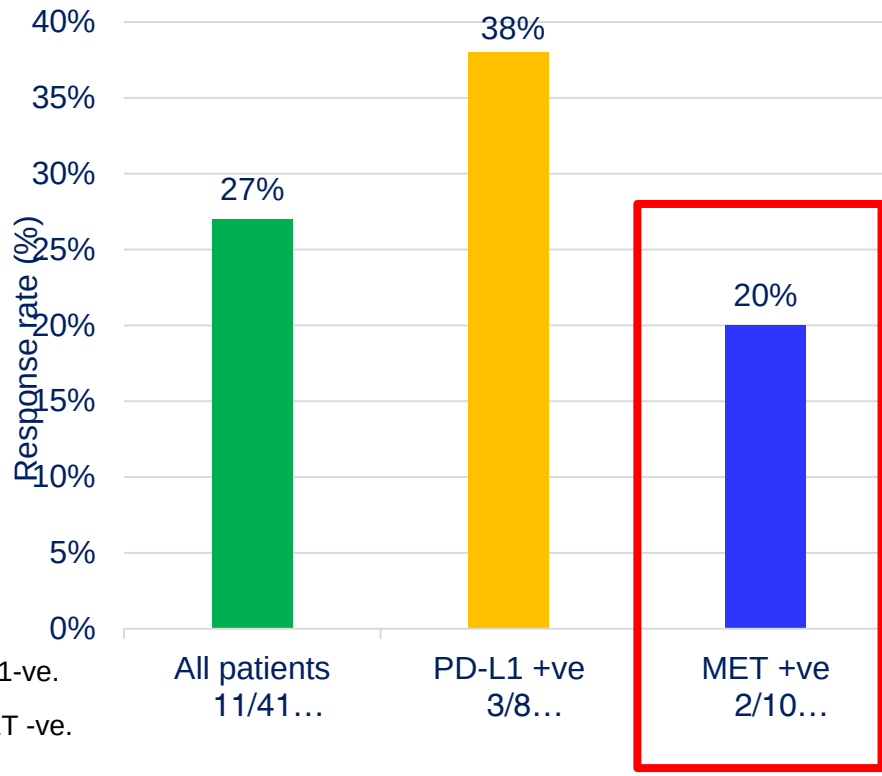
Best overall response	All patients (N=41)		Previously untreated (N=28)	
	n (%)	95% CI for %	n (%)	95% CI for %
PR	11 (27)	(14 - 43)	9 (32)	(16 - 52)
SD	16 (39)	(24 - 55)	12 (43)	(24 - 63)
PD	11 (27)	(14 - 43)	5 (18)	(6 – 37)
NA*	3 (7)	(2 – 20)	2 (7)	(1 – 24)

*Only baseline scan available.

ClinicalTrials.gov Identifier: NCT02819596

Best Overall Response Rate by PD-L1 & MET Status

Best overall response	PD-L1+ (N=8) n (%)	MET+ (N=10) n (%)
PR	3 (38)	2 (20)
SD	1 (13)	5 (50)
PD	3 (38)	2 (20)
NA*	1 (13)	1 (10)



*Only baseline scan available.

8/41 PD-L1 +ve (>25% immune component with SP263 Ab). 27 PD-L1-ve.

10/41 patients MET +ve (≥ 3+ in ≥ 50% tumour cells with IHC). 25 MET -ve.

6 patients not assessable/available for both biomarkers

ClinicalTrials.gov Identifier: NCT02819596

CALYPSO Conclusions

- Savolitinib and durvalumab has activity in non-clear cell RCC and toxicity is manageable
- Did not reach prespecified endpoint for further study of savolitinib and durvalumab in combination
- 4 week lead-in of savolitinib (likely the less active partner) may have diminished ORR
- Unclear that combination treatment is better than sequential given no signal of synergy and toxicity appears additive

ClinicalTrials.gov Identifier: NCT02819596

Phase 2 Trial of Bevacizumab plus Erlotinib in Papillary RCC

N = 41 patients Papillary RCC
N = 19 w/ +1 prior treatment

Table 1. Summary of results

	Cohort 1 [HLRCC] (%)	Cohort 2 [Non-HLRCC] (%)	Total (%)
Best Response by *RECIST*			
Complete response (CR)	0	0	0
Confirmed Partial response (PR)	12 (60%)	6 (29%)	18 (44%)
Overall Response Rate	**60%**	**29%**	**44%**
Stable disease (SD)	8 (40%)	12 (57%)	20 (49%)
Progressive disease (PD)	0	3 (14%)	3 (7%)
Disease Control Rate (SD+PR)	**100%**	**86%**	**93%**
Median Progression Free Survival – months	**24.2**	**7.4**	**12.8**

NCT01130519, N=85 ONGOING!

Srinivasan et al, EORTC-AACR-NCI 2014

Front-Line Combinatorial IO Trials in Variant Histology RCC

Treatment	Histology	No Patients	Phase	PI
Ipilimumab + Nivolumab	SMARCB1-def*	30	II	P. Msaouel/N. Tannir, MDACC
Nivolumab + salvage Ipilimumab	metRCC	120	II	M. Atkins, HCRN
Ipilimumab + Nivolumab + Cabozantinb	Rare GU tumors (med.; sarc RCC)	186	II	A. Apolo, Alliance
Pembrolizumab + cabozantinib		55	I/II	E. Lam, Colorado Univ.
Nivolumab + Cabozantinib	nccRCC (dif. cohorts)	57	II	CH. Lee, MSKCC
Atezolizumab + bevacizumab	nccRCC ccRCC >20% sarc.	42 nccRCC	II	T. Choueiri, DFCI
Savolitinib + Durvalumab	Papillary RCC	42	II	T. Powles, BCI

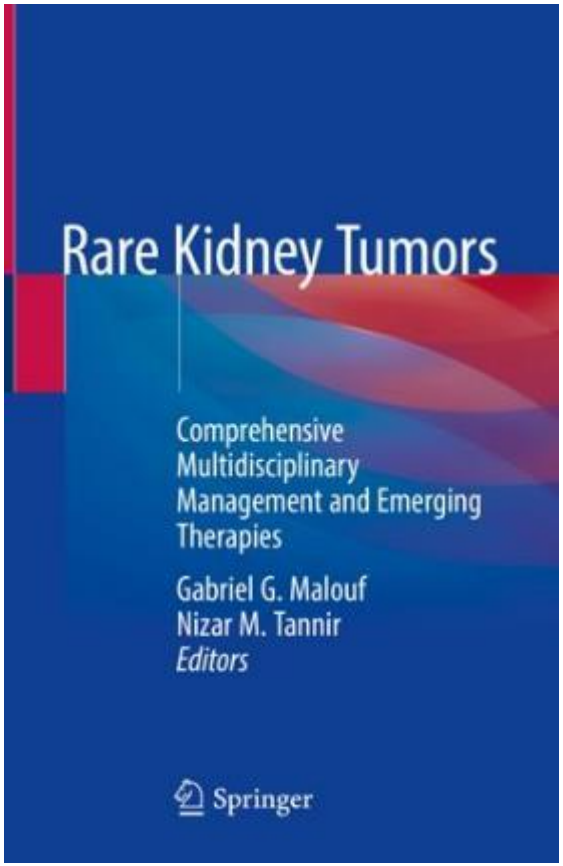
NR: not reported
*medullary RCC, unclassified RCC, most malignant rhabdoid tumors (young > old age)

Ongoing Trials of Targeted Therapies in Variant Histology RCC

	Mechanism of action	Histology	Setting and number of patients	Trial
Lenvatinib + everolimus	VEGFR/BFGFR + mTOR inhibition	nccRCC	First line, Phase II, 31 patients	NCT02915783
Everolimus + bevacizumab	mTOR + VEGF-A inhibition	nccRCC	First line, phase II, 55 patients	NCT01399918
Everolimus	mTOR inhibition	BHD-associated and chromophobe RCC	All lines, phase II, 18 patients	NCT02504892

Conclusions

- There is no established standard of care for nccRCC
- Participation in clinical trials is preferred
- Efficacy of pembrolizumab in a large single-arm study is encouraging
- Interesting results were observed with cabozantinib in retrospective collaborative studies
- Biology-driven, target specific trials are needed and necessary to advance the field in rare RCC types



Questions?

Email: ntannir@mdanderson.org

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PATIENTS

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