Non clear cell RCC:
Bridging Translational Data to the clinic

Papillary RCC

Laurence Albiges

Gustave Roussy, Villejuif, France

Sixteenth International Kidney Cancer Symposium

November 3-4, 2017
National Doral, Miami, Florida

KidneyCancer.org

www.kidneycancersymposium.com

Disclosures

- Consulting & Advisory role to:
  - Novartis
  - Pfizer
  - BMS
  - Roche
  - Ipsen
  - Astellas
  - Janssen

Bridging Translational Data to the clinic in non ccRCC

Papillary RCC

- A decade of non bridging!
- Translational Data
- Clinical impact

Bridging Translational Data to the clinic in non ccRCC

Papillary RCC

- A decade of non bridging!
- Translational Data
- Clinical impact

pRCC a decade

		pRCC	Type I	Type II
N		**466**	30	165
Median PFS (months)		**4.7**	7.7	4.3
Median OS (months)		**13.8**	20.0	12.6
Median OS by IMDC risk group (months)	Good	**34.1**		
	Intermediate	**17.0**		
	Poor	**6.0**		

IMDC 2017: 466 pRCC treated with targeted therapy (out of >5200pts)
NO improvement in outcome over the last decade

JC Wells et al. Cancer medecine 2017

pRCC : NON Bridging translational data

Treatment	n	Ref	ORR (%)	Median PFS (months)	Median OS (months)
Erlotinib SWOG 0317	45	Gordon JCO 2009	11	NA	NA
Sunitinib (SUPAP)	61	Ravaud Ann Oncol 2015	12	5.6	12.5
	Type 1 (n=15)		13	6.6	17.8
	Type 2 (n=46)		11	5.5	12.4
Everolimus (RAPTOR)	92 PP: 46	Escudier EJC 2016	NA	3.7	21
	Type 1 (n=14)		NA	7.6	28.0
	Type 2 (n=50)		NA	3.7	20.3

Bridging Translational Data to the clinic in non ccRCC

Papillary RCC

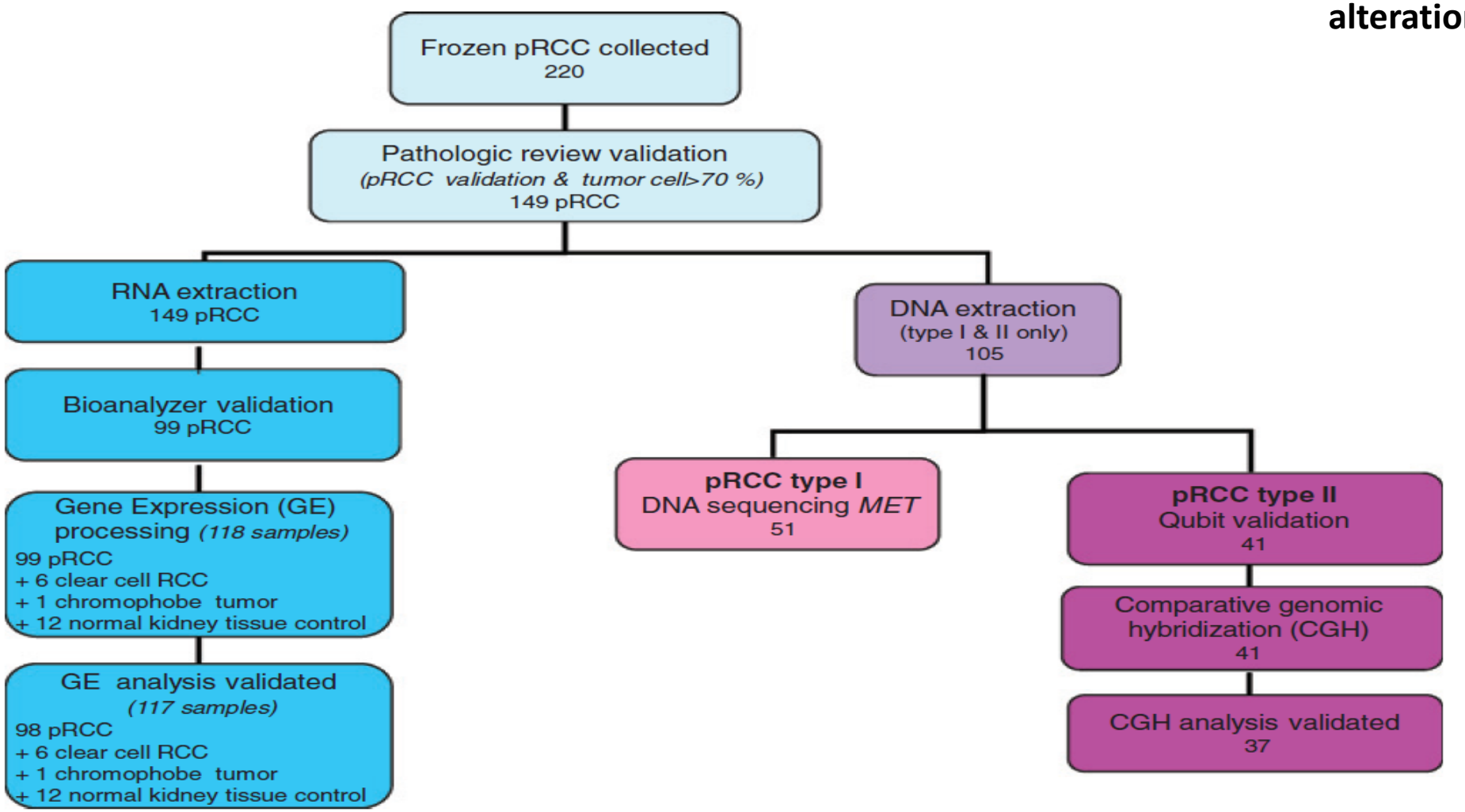
- A decade of non bridging!
- Translational Data
- Clinical impact

Clinical Cancer Research

MET Is a Potential Target across All Papillary Renal Cell Carcinomas: Result from a Large Molecular Study of pRCC with CGH Array and Matching Gene Expression Array

Objective:

Characterise *c-MET* distinct alteration across pRCC subtypes

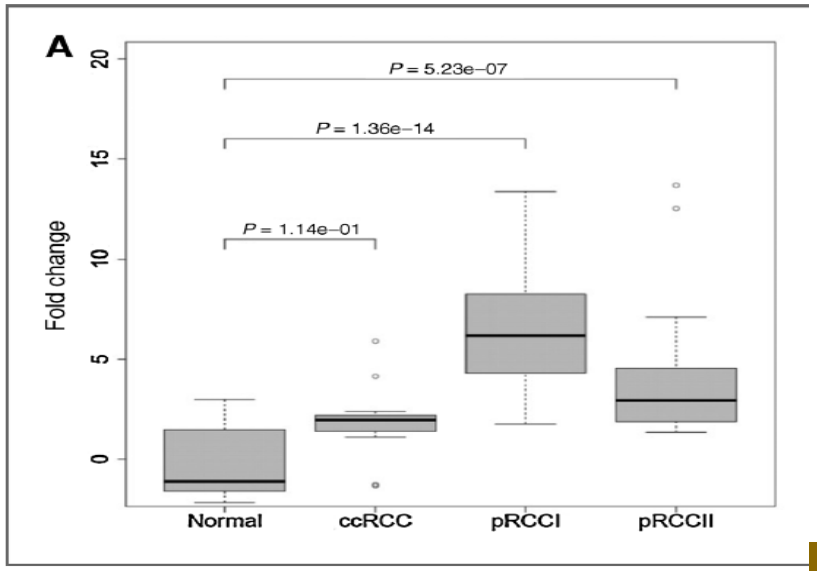


Albiges, CCR 2014

1- expression level of MET

- Protein over expression in pRCC *(Choi2006, Gibney, 2012)*
- *MET* germline and somatic mutation *(Smith, 2000)*

- c-MET mRNA expression level was high across all pRCC when compared to clear cell carcinomas when compared to normal kidney expression
- Gene expression results were confirmed by RT-q-PCR



Albiges, CCR 2014

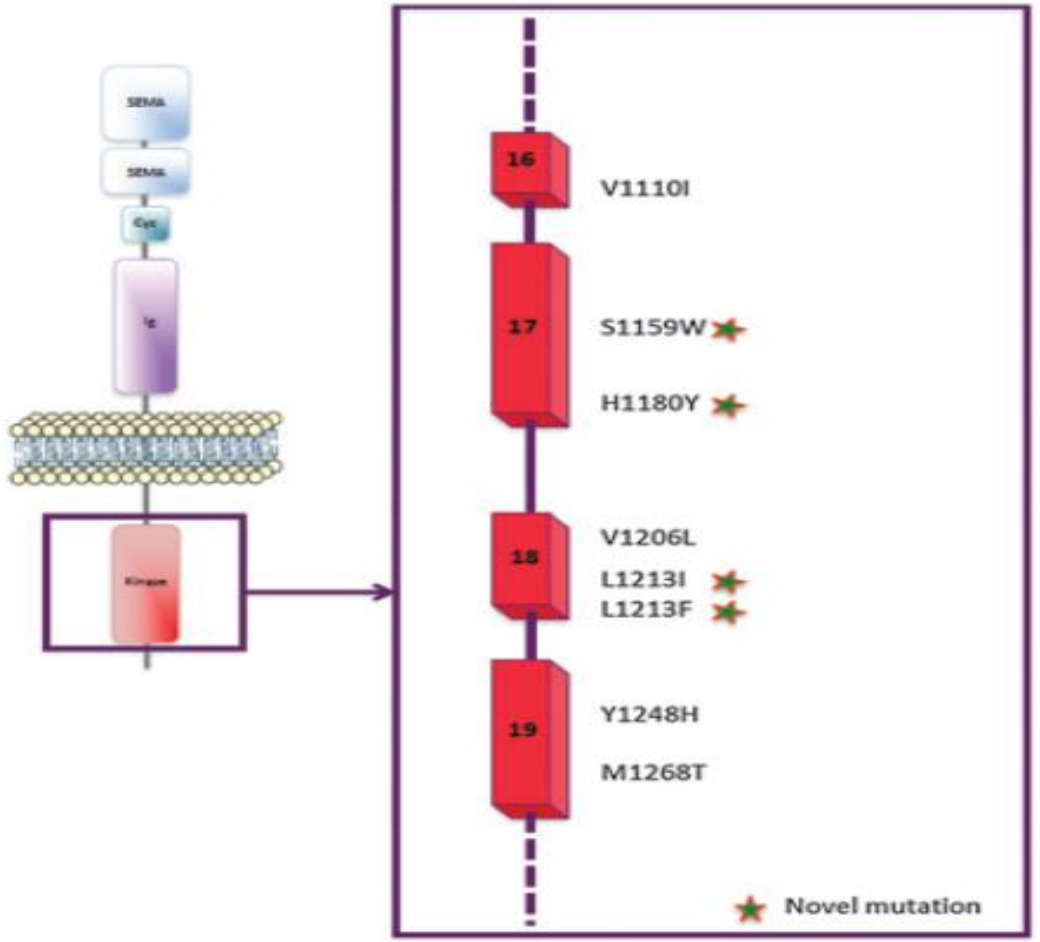
2- Mutation analysis

11 mutations in exons 16-19 of the MET gene were identified amongst 51 type I pRCC (21.5%) :

- •7 previously reported, including 4 times de same M1268T mutation
- •2 mutations on known sites with new AA substitution
- •2 new mutations strongly predicted to be damaging

4 new mutations:

- ✓ In silico prediction models: damaging
- ✓ Pathway analysis

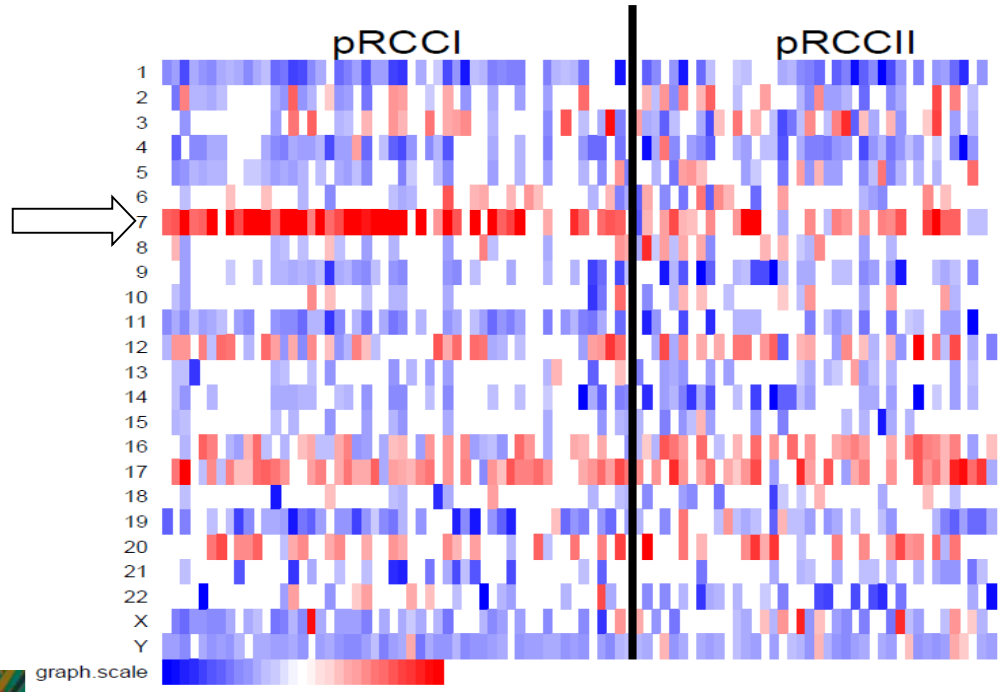


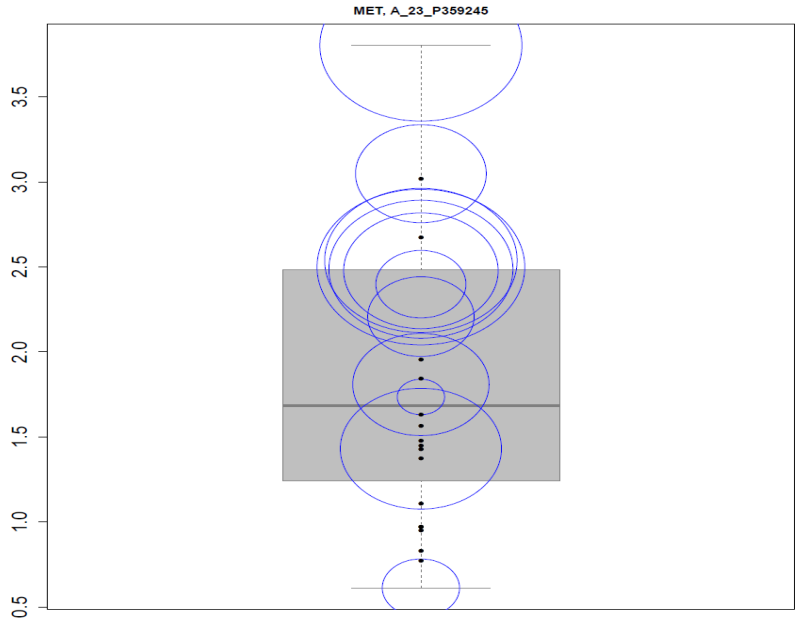
3- Copy Number alteration and expression correlation

Copy Number Alterations (partial gain or Kr 7 polysomy) were identified

- •by CGHa in 46 % of type II pRCC
- •by CGMA in 81% of type I pRCC

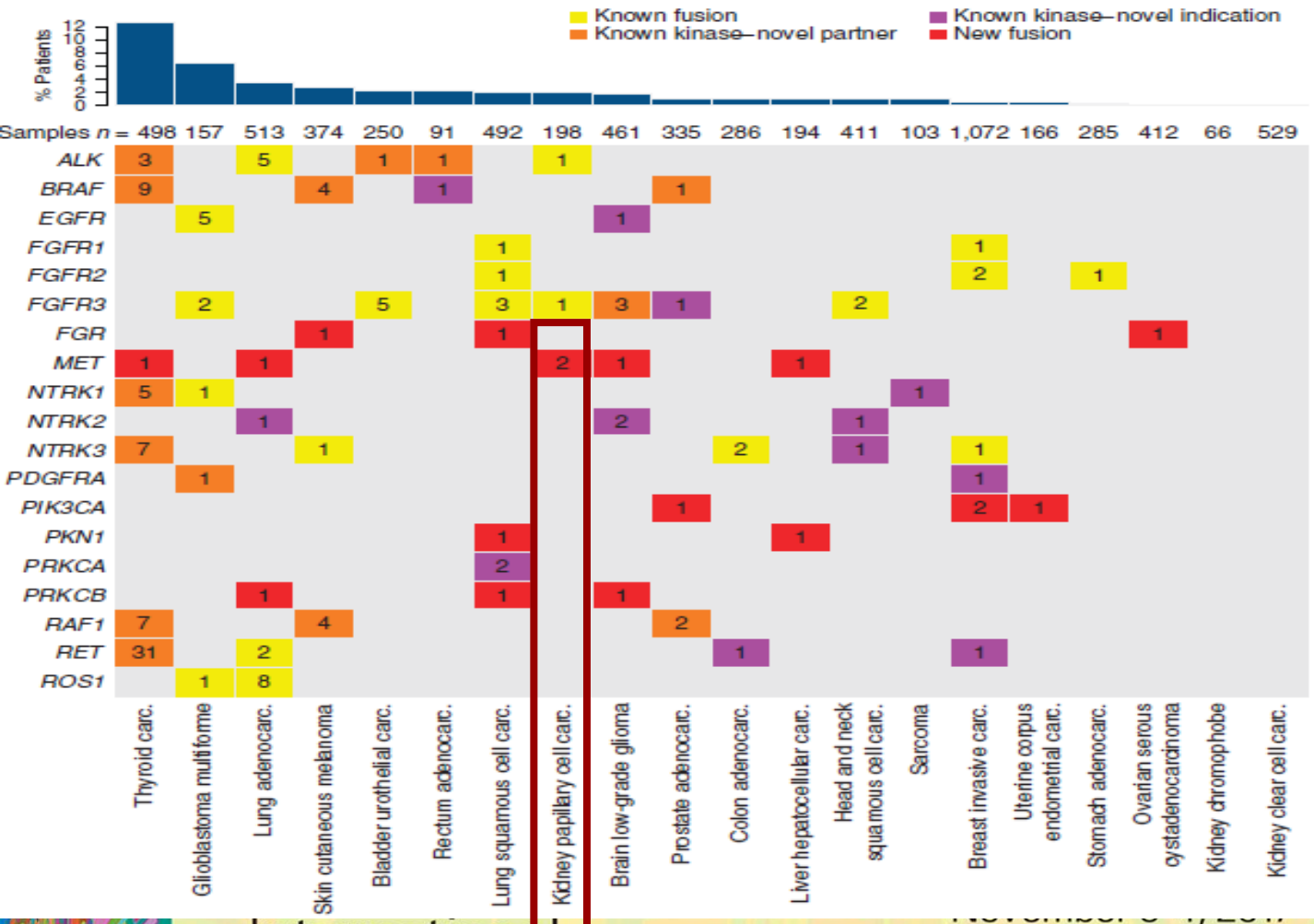
Correlation between DNA copy number alterations (CGH) and mRNA expression level was highly significant

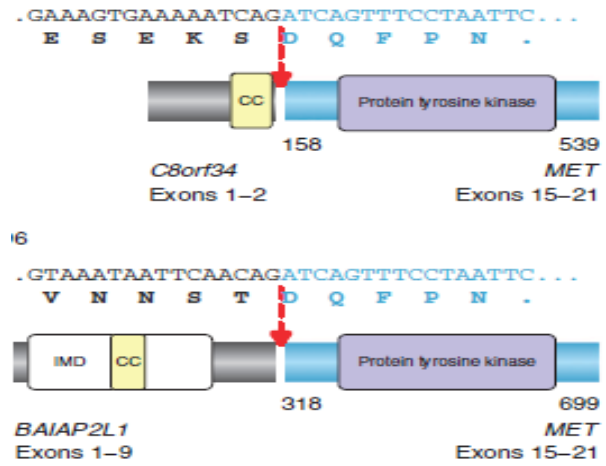




Albiges, CCR 2014

MET gene fusion identification





- Two in-frame MET fusions:
  - BAIAP2L1–MET
  - C8orf34–MET

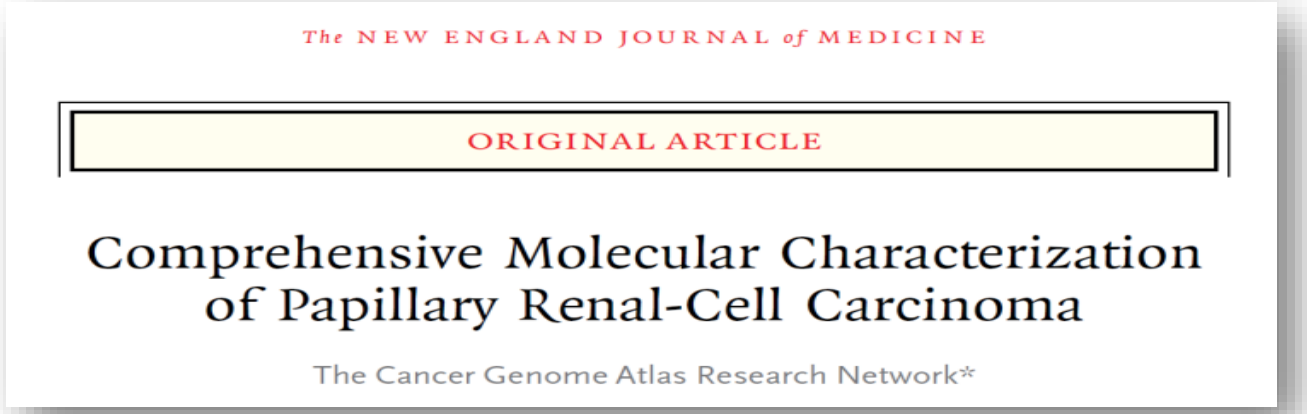
- act as dimerization motifs => potentially activates MET TK activity

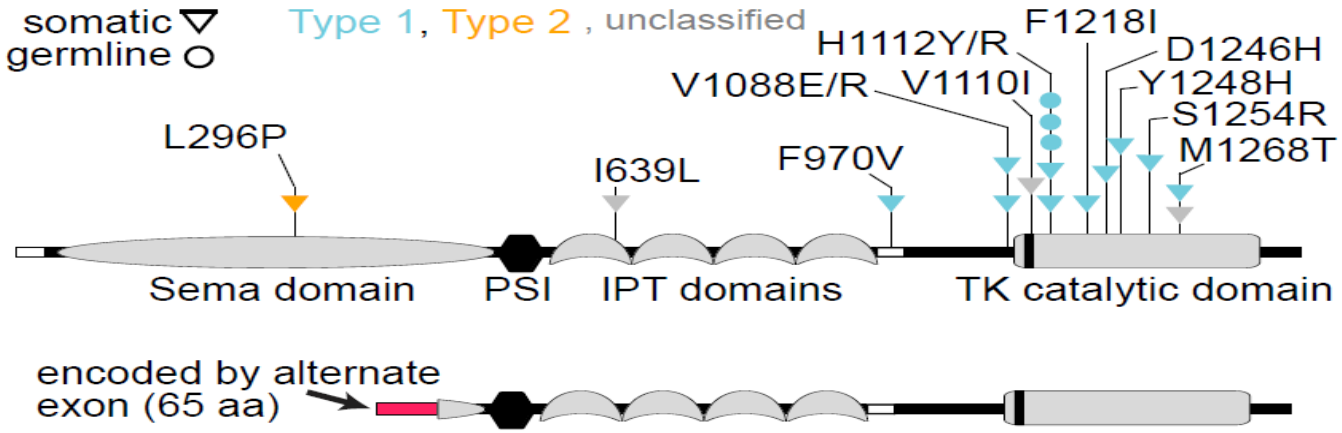
Stransky N, et al . The landscape of kinase fusions in cancer. Nat Commun. 2014

Refining MET receptor role in pRCC

MET alterations in papillary RCC

- Germline mutation TK domain
- Somatic mutation TK domain
- Mutation outside the TK domain
- **Copy Number Alteration**
- **Fusion**
- **Transcript variant**





Sixteenth International Kidney Cancer Symposium
November 3-4, 2017
National Doral, Miami, Florida
KidneyCancer.org
www.kidneycancersymposium.com

The NEW ENGLAND JOURNAL of MEDICINE

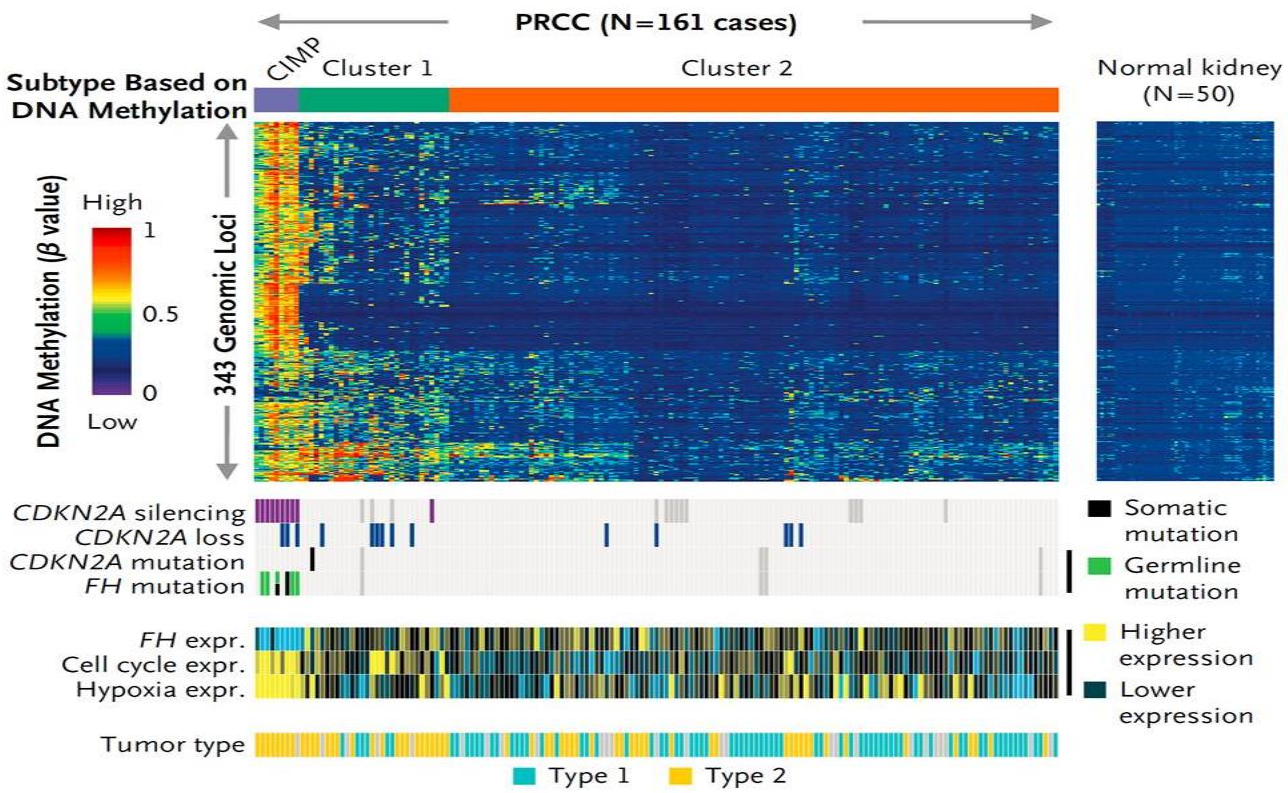
ORIGINAL ARTICLE

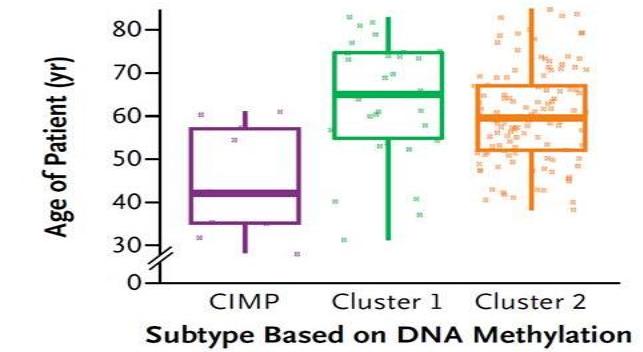
Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma

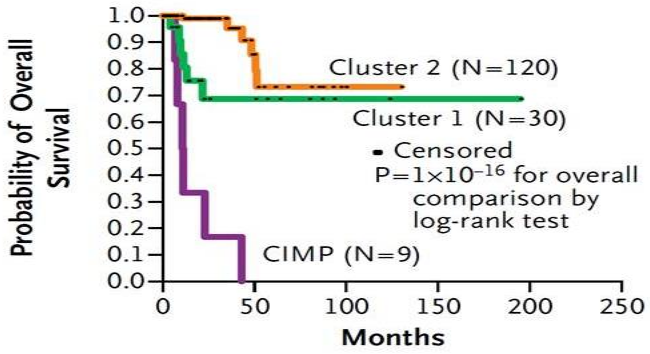
The Cancer Genome Atlas Research Network*

Identification of 3 subgroups

- Type I
- Type II
- CIMP sugroup (CpG Island Methylator Phenotype) matching with FH mutations







Linehan WM et al. NEJM, 2015

Refining MET receptor role in advanced pRCC

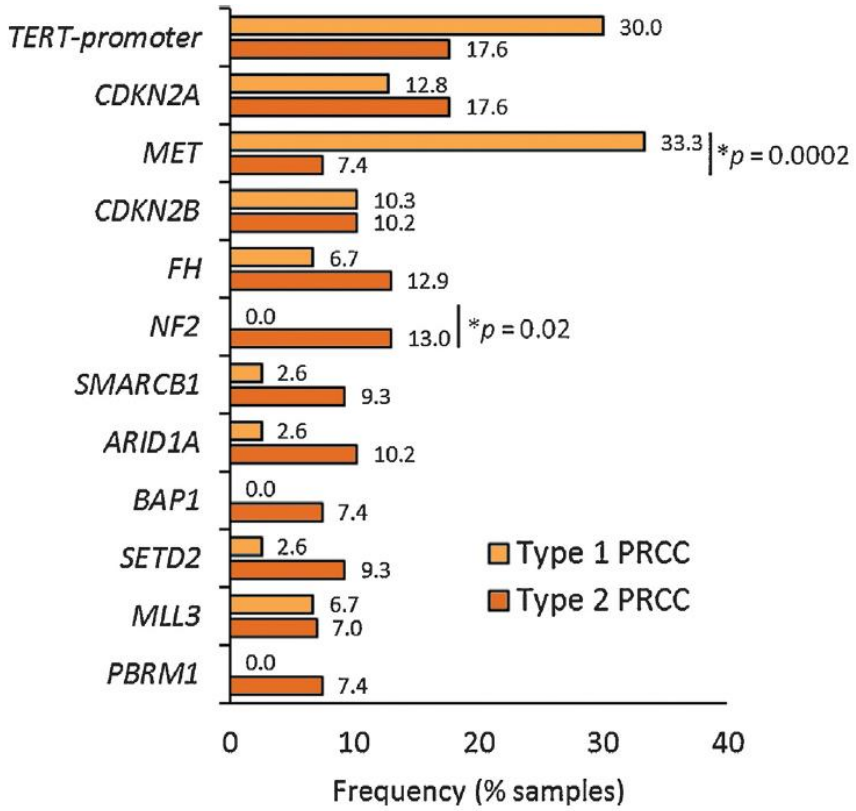


Fig. 3 – Frequency of selected alterations in type 1 versus type 2 papillary renal cell carcinoma (PRCC).

169 patients with advanced pRCC
comprehensive genomic profiling (CGP) performed in the context of routine clinical care

type 1 PRCC:

- MET (33%; 8 activating mutations, 5 amplifications at >6 copies),
- TERT (30%),
- CDKN2A/B (13%)
- EGFR (8%)

type 2 PRCC:

- CDKN2A/B (18%),
- TERT (18%),
- NF2 (13%),
- FH (13%);
- MET GAs (5 mutations, 3 amplifications) were observed in 7%

Notable differences from TCGA data including higher frequencies of MET, NF2, and CDKN2A/B GAs

Pal SK, et al. Eur Urol. 2017

Sixteenth International Kidney Cancer Symposium
November 3-4, 2017
National Doral, Miami, Florida
KidneyCancer.org
www.kidneycancersymposium.com

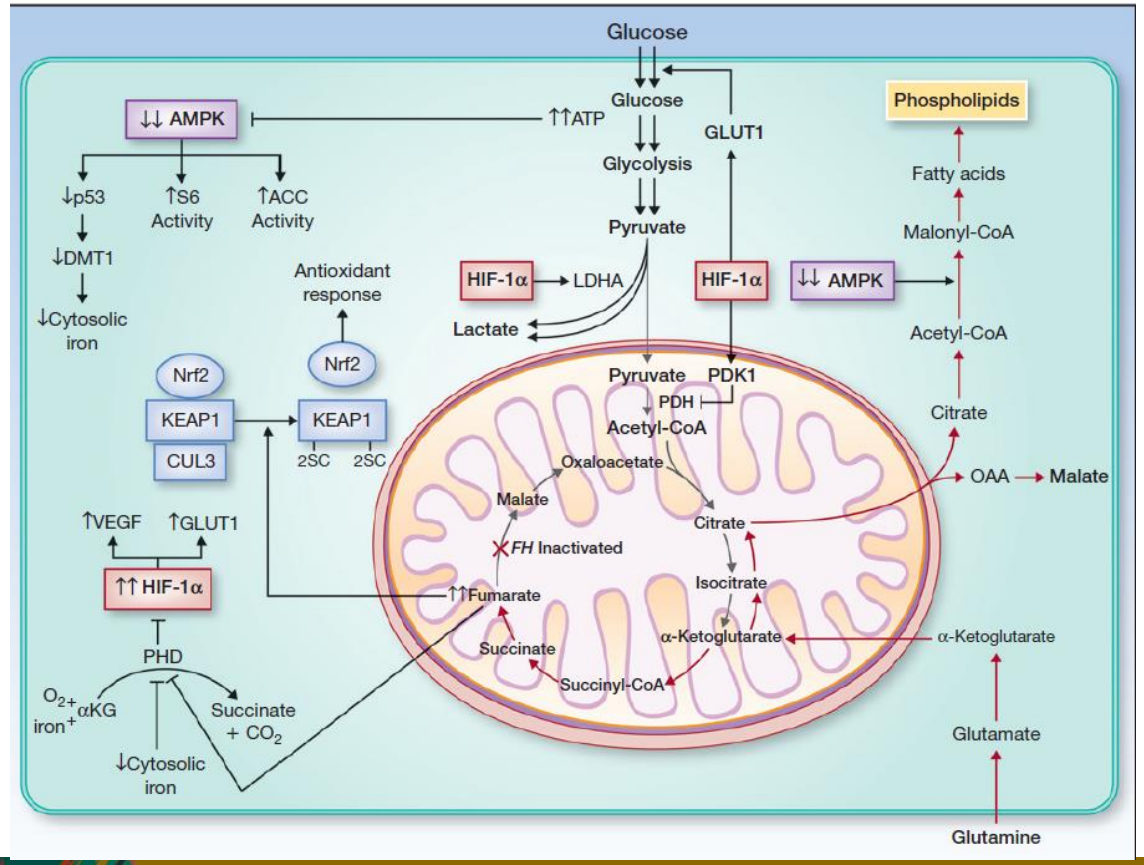
Bridging Translational Data to the clinic in non ccRCC

Papillary RCC

- A decade of non bridging!
- Translational Data
- Clinical impact

Targeting the metabolic switch?

HLRCC& sporadic pRCC : bevacizumab and erlotinib



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

Srinivasan R, et al:.EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. Abstract 5. Presented November 19, 2014

Sixteenth International Kidney Cancer Symposium

November 3-4, 2017
National Doral, Miami, Florida

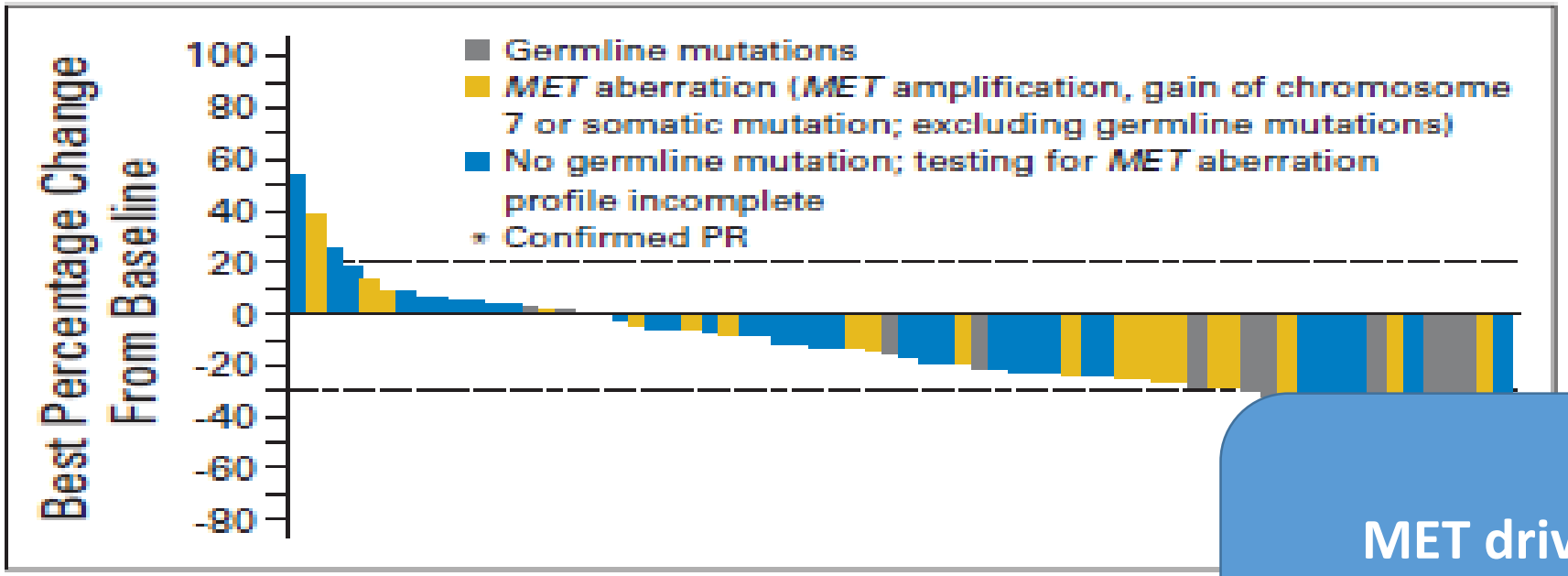
KidneyCancer.org

www.kidneycancersymposium.com

MET inhibition in pRCC (I): FORETINIB

Foretinib (VEGFR2 & MET TKI) trial

- Population : 65 metastatic pRCC type I & II
- Median PFS >9 months in pretreated patients, OS : 70% at 1 year
- Germline MET mutation predictive of response



MET driven tumors

- Germline mutation

MET inhibition in pRCC (II)

CRIZOTINIB in type 1 PRCC1 EORTC 90101- CREATE

P. Schöffski, et al. EJC 2017 , in press

Screened pts
PRCC1 per local pathology
N=41

Other (ineligible) diagnoses:
- 4 translocation carcinomas
- 2 PRCC2
- 1 clear cell RCC
- 1 adenoid-cystic carcinoma or metanephric adenoma
- 1 non-specified malignancy

4 patients not enrolled due to brain metastasis, rapid clinical deterioration, no measurable lesion or lost-to-follow up

PRCC1 analysis set

Centrally confirmed PRCC1 and enrolled
N=23
(all started crizotinib)

MET+
N=4

MET-
N=16

MET?
N=3

***MET+* analysis set**

***MET-* analysis set**

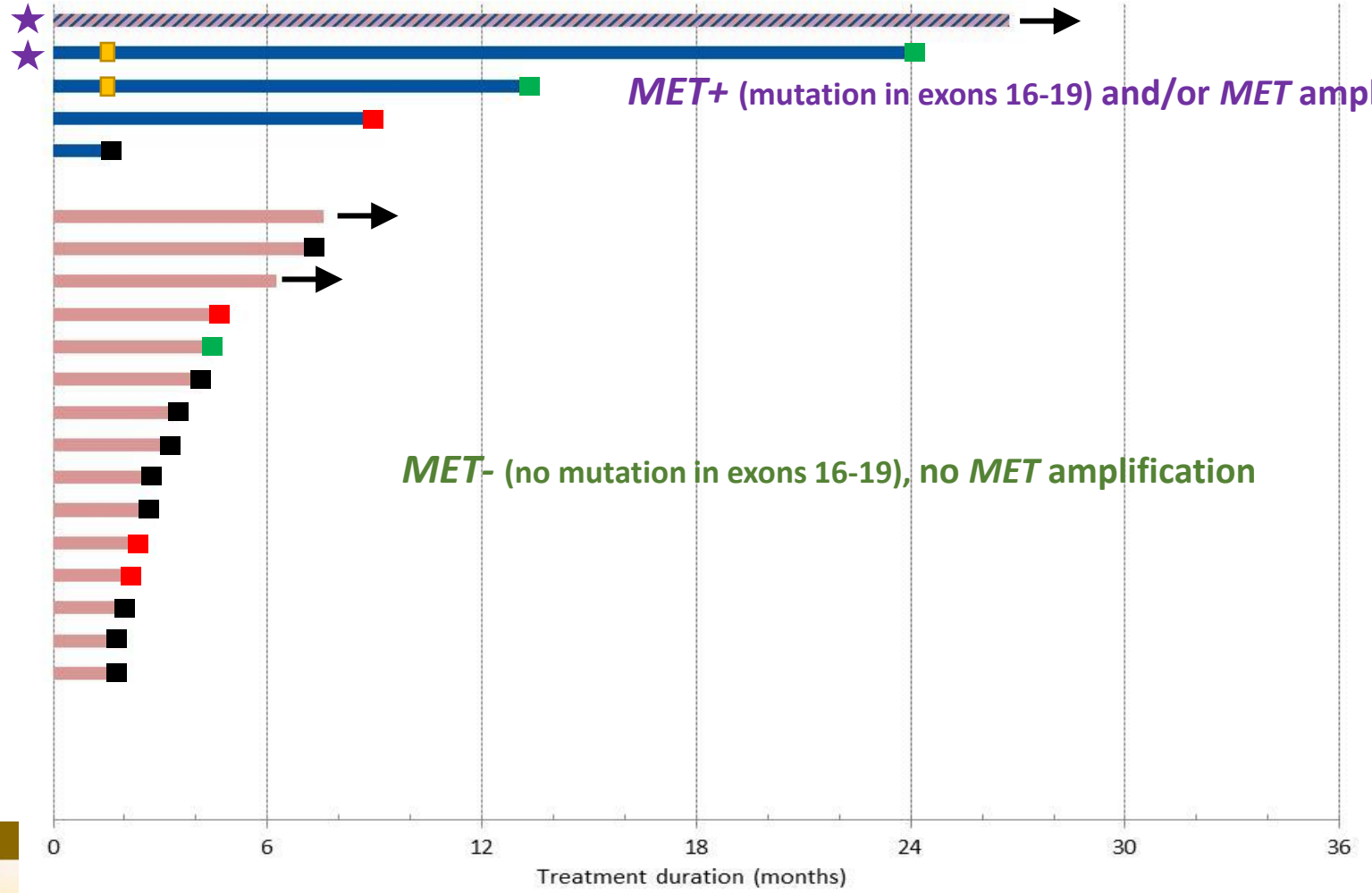
Eligible and evaluable
N=4
(incl. 1 *MET* amplified)

Eligible and evaluable
N=16
(incl. 1 *MET* amplified)

Eligible and evaluable
N=3

MET?: Technical failure, mutational analysis could not be done

CREATE Treatment duration



★ *MET* amplification (exploratory)
RECIST PR first documented
→ Treatment ongoing

Treatment stopped due to
- Adverse event
- Progression
- Patient's decision or other reason

MET driven tumors

- Mutation in the TK domain
- Amplification (exploratory)

MET inhibition in pRCC (III)

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

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

Table 1. Patient Demographic and Baseline Clinical Characteristics

Characteristic	No. (%) MET Driven (n = 44)	MET Independent (n = 46)	MET Unknown (n = 19)	Total (N = 109)
Age, years				
Median	64	64	58	64
Range	23-87	29-75	37-80	23-87
Sex				
Female	12 (27)	11 (24)	8 (42)	31 (28)
Male	32 (73)	35 (76)	11 (58)	78 (72)
Race				
White	38 (86)	40 (87)	18 (95)	96 (88)
Black or African American	5 (11)	2 (4)	1 (5)	8 (7)
Asian	0 (0)	1 (2)	0 (0)	1 (1)
Other	1 (2)	3 (7)	0 (0)	4 (4)
ECOG performance status				
0	18 (41)	25 (54)	8 (42)	51 (47)
1	26 (59)	21 (46)	11 (58)	58 (53)
PRCC confirmation*				
Yes	35 (80)	39 (85)	10 (53)	84 (77)
No	9 (21)	7 (15)	9 (47)	25 (23)
Renal cell classification*				
Type 1 PRCC	12 (27)	2 (4)	2 (11)	16 (15)
Type 2 PRCC	23 (52)	37 (80)	8 (42)	68 (62)
Subtype unclassifiable	9 (21)	7 (15)	9 (47)	25 (23)

Any of the following molecular alterations or combination of these alterations detected in tumor tissue using the targeted MET NGS test

MET driven tumors

- Chromosome 7 gain/trisomy
- *MET* amplification
- *MET* kinase domain mutations
- *HGF* amplification

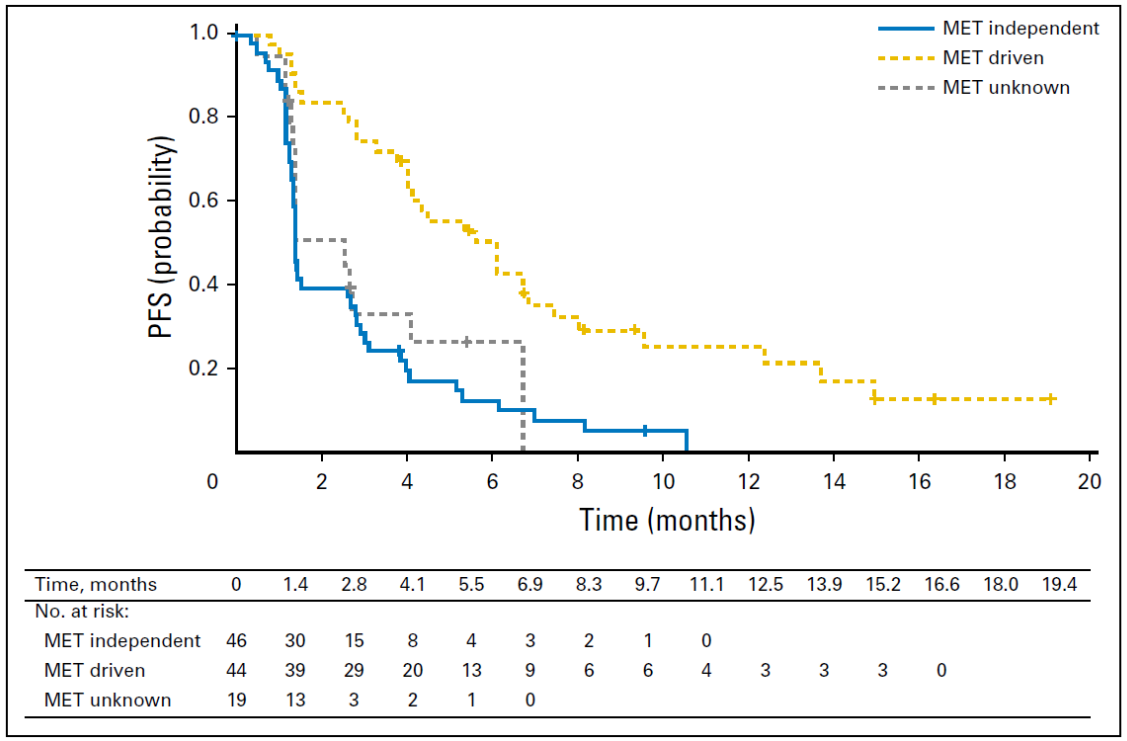
J Clin Oncol. 2017 Sep 10;35(26):2993-3001.

MET inhibition in pRCC (III)

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

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



Time, months	0	1.4	2.8	4.1	5.5	6.9	8.3	9.7	11.1	12.5	13.9	15.2	16.6	18.0	19.4
No. at risk:															
MET independent	46	30	15	8	4	3	2	1	0						
MET driven	44	39	29	20	13	9	6	6	4	3	3	3	0		
MET unknown	19	13	3	2	1	0									

MET-driven pRCC had significantly longer median PFS than those with MET-independent disease: 6.2 mo (95% CI, 4.1–7.0) vs 1.4 mo (95% CI, 1.4–2.7), **HR, 0.33** [95% CI, 0.20–0.52]; *P* < .0001)

J Clin Oncol. 2017 Sep 10;35(26):2993-3001.

MET inhibition in pRCC (III): SAVOLITINIB

Table 2. Tumor Responses in Overall Treatment Population and by MET Status

RECIST Response	No. (%) MET Driven (n = 44)	MET Independent (n = 46)	MET Unknown (n = 19)	Total (N = 109)
PR*	8 (18)†	0 (0)	0 (0)	8 (7)
SD	22 (50)	11 (24)	5 (26)	38 (35)
PD	11 (25)	28 (61)	9 (47)	48 (44)
NE	3 (7)	7 (15)	5 (26)	15 (14)

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.
*Unconfirmed responses excluded.
†$P = .002$ versus MET-independent subgroup (Fisher's exact test). Responses assessed according to RECIST (version 1.1).

MET driven tumors

- Chromosome 7 gain/trisomy
- *MET* amplification
- *MET* kinase domain mutations
- *HGF* amplification

PREDICTIVE ROLE

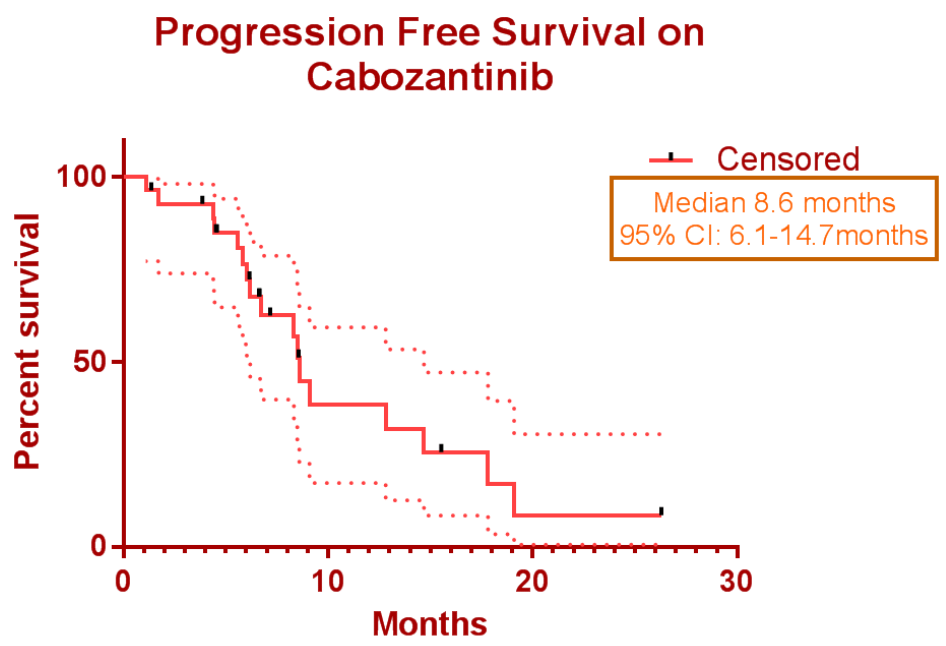
J Clin Oncol. 2017 Sep 10;35(26):2993-3001.

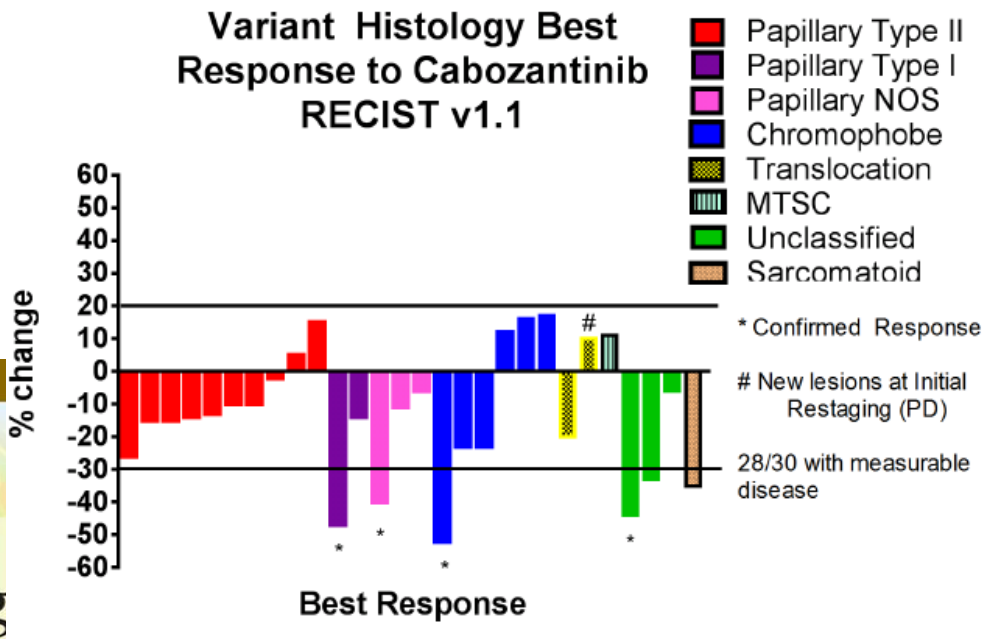
MET inhibition in pRCC (IV)

Cabozantinib

Baseline Characteristics	N = 30	
Gender	Male = 26 (86.7%)	
Age, median (range)	58.4 years (range 25-81)	
Prior Nephrectomy	27 (90%)	
Histology	Papillary	17 (57%)
	Papillary type I	3 (10%)
	Papillary type II	11 (36.7%)
	Papillary NOS	3 (10%)
Number of Prior Therapies		
0	3 (10%)	
1	7 (23.3%)	
>1	20 (66.7%)	
Median (range)	2 (range 0-5)	
Previous VEGFR TKI	26 (86.7%)	
Sunitinib	22 (73.3%)	

- 17 pRCC (retrospective cohort in nonccRCC)
- Activity beyond sunitinib





Sixteenth International Kidney Cancer Symposium
November 3-4, 2017
National Doral, Miami, Florida
KidneyCancer.org

MET inhibition in pRCC- Open questions

- Best agent amongst MET inhibitors?
- Seeking for MET or MET+VEGFR inhibition?
- Optimal definition of the MET driven population?

SAVOIR
Savolitinib pRCC Phase III

Screening

Part 1

- Any line pRCC
- Unresectable locally advanced or metastatic
- No prior sunitinib or MET inhibitor

TAT 10 business days →

Part 2

- MET-driven with no *FH* or *VHL* mutation

N = 180

Open- label

R 1:1

- **Savolitinib 600 mg po qd**
- **Sunitinib 50 mg po 4 w on/2 w off**

Primary Endpoint: PFS by BICR RECIST v1.1
Key Secondary Endpoints: DOR, OS, ORR, PRO; Safety

BICR, blinded independent central review; DOR, duration of response; FH, family history; po, oral; PRO, patient-reported outcome; qd, once daily; TAT, turnaround time; w, weeks.
ClinicalTrials.gov. NCT03091192.
PI: Choueiri T.

S1500: PAPMET Trial
Randomised phase II

mPRCC
- Histologically confirmed diagnosis of PRCC
- Measurable disease
- 0-1 prior lines of therapy
- No prior therapy with sunitinib
- ECOG 0-1

1:1:1:1 Randomization

180 pts

- Sunitinib
- Cabozantinib
- Crizotinib
- Savolitinib

Primary Endpoint:
- Progression-free survival

Secondary Endpoints:
- Overall survival
- Response rate
- Adverse events
- Exploratory evaluation of:
  - MET mutational status
  - MET expression

Funding granted for Biomarker, Imaging and QoL studies
ClinicalTrials.gov. NCT02761057
PI Sumanta Pal Southwest Oncology Group

Bridging Translational Data to the clinic in non ccRCC

Papillary RCC

- A decade of non bridging!
- Translational Data
- Clinical impact
- What is next?

Perspective for pRCC treatment: A Role for IO?

	Brandao Moreira et al. ASCO GU 2017	Koshkin et al. ASCO 2017
N (all non ccRCC) N pRCC	44 14	23 10
Io Agent	PD-1/PD-L1 inhibitors (including combo with VEGF/VEGFRi)	nivolumab
ORR (all histologies) ORR pRCC	18% **28%**	28.5% NA
Median follow up	11.2 months	6.5 months
TTF/PFS (mo) TTF pRCC	4.1 **5.5**	4.2 NA
OS (mo)	12.9	Not Reached

IO trials for pRCC

Agent	ClinicalTrials.gov Nb	Brief Description
Nivolumab/ Ipilimumab	NCT03075423 NCT02982954	Phase II randomized study Phase II single-arm study
Pembrolizumab	NCT02853344	Phase II study with nccRCC cohort
Atezolizumab/ Bevacizumab	NCT02724878	Phase II single-arm study
Nivolumab	NCT02596035	Checkmate374: Phase IIIb/IV safety trial of ccRCC and non-ccRCC
Durvalumab	NCT02819596	Phase I/II trial of ccRCC and pRCC (pRCC patients receive durvalumab + savolitinib)

Conclusion

- Yes, Translationnal Research has improved our knowledge of pRCC
- Dedicated trials on pRCC have moved from single arm phase II to randomised studies
- We are integrating genomic screens in prospective trials
- MET driven definition and benefit with TT: an open question
- For all the non-MET driven pRCC patients: recommendation should remain : “clinical trial investigation”
- Only collaborative effort can address these rare tumors management