IV GO NORTE INTERNATIONAL GU DEBATES
OCTOBER 2nd - 3rd 2025
#GonorteGUDebates

ADVANCED NON-CLEAR CELL RCC MANAGEMENT IN 2025: IS ANYTHING CLEAR FOR THE CLINICIAN?

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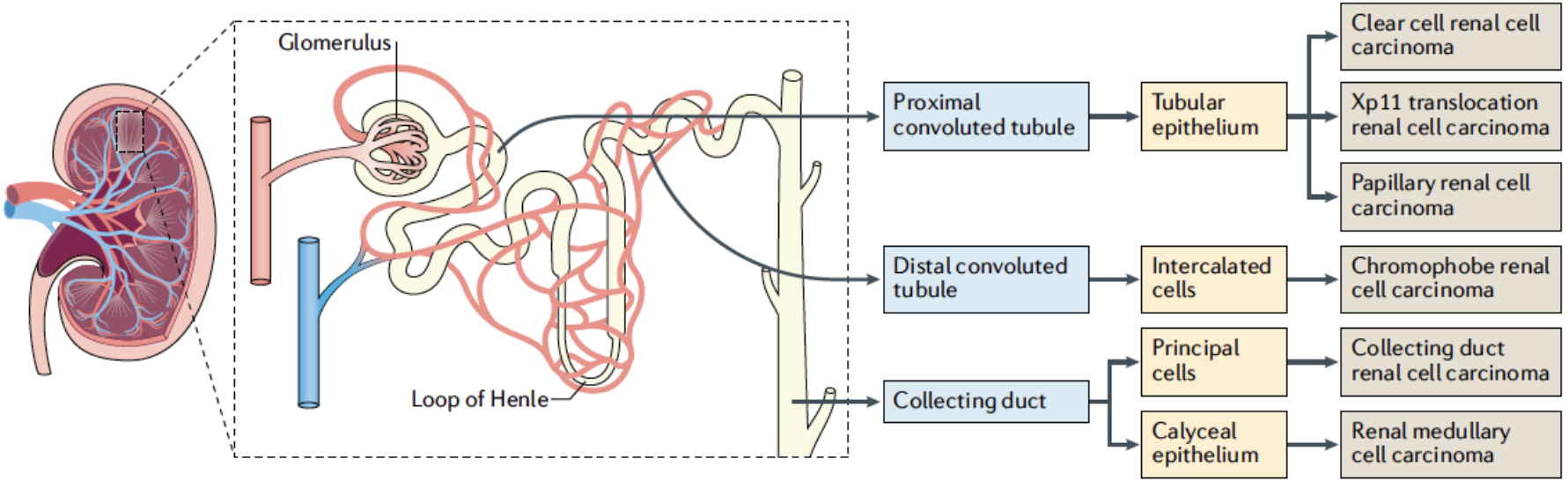
Hospital Universitari Vall d'Hebron – Vall d'Hebron Institute of Oncology,

Disclosures

- Employment: None
- Consultant or Advisory Role: BMS, Pfizer, IPSEN, MSD, Pharma, EISAI, Recordati,Tellix
- Stock Ownership: None
- Research Funding: IPSEN. BMS, Pfizer
- Speaking: Ipsen, EISAI, MSD, Tellix
- Travel/acommodation expenses: Ipsen, MSD, Bayer

Location and cell of origin of RCC histological subtypes



Dizman N, *et al*. Genomic profiling in renal cell carcinoma. Nat Rev Nephrol 2020;16(8):435–51.

NON-CLEAR RCC IS A HETEROGENOUS DISEASE

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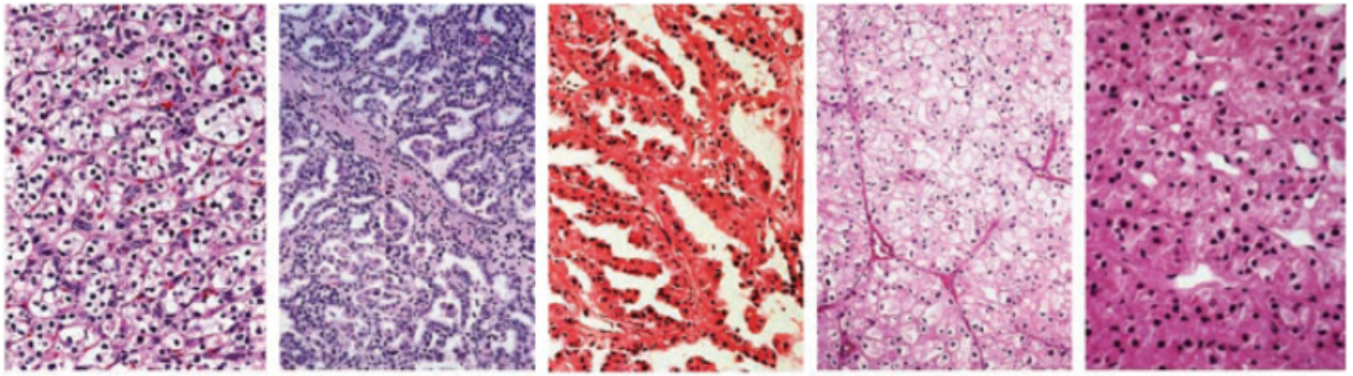

Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
Frequency	80%	5%	10%	<5%	<5%
Gene	*VHL*	*c-Met*	*FH*	*BHD*	*BHD*
Locus	3p25	7q31	1q42	17p11	17p11

Modified from Linehan WM, *et al.* J Urol 2003;170:2163–72; Kim WY, Kaelin WG. J Clin Oncol 2004;22:4991-5004; American Cancer Society.

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	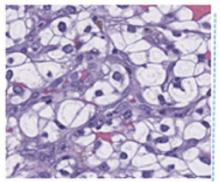	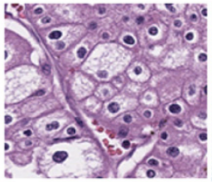	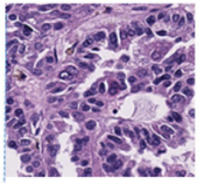	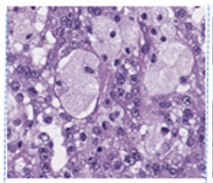	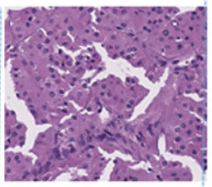	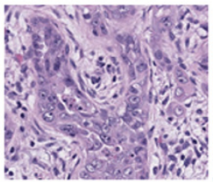	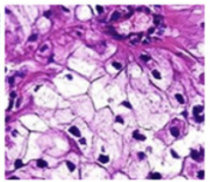	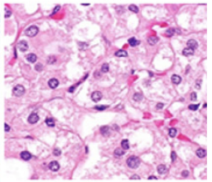
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	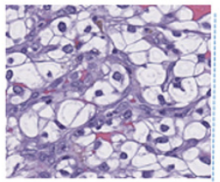	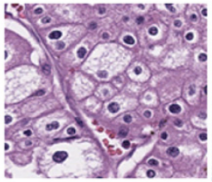	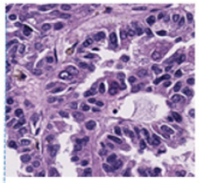	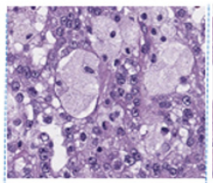	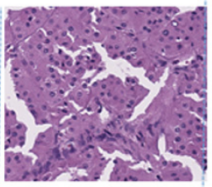	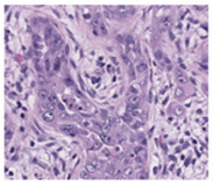	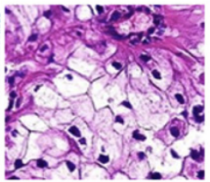	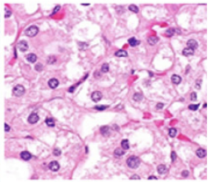
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	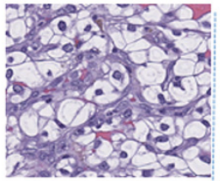	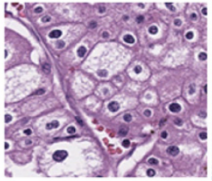	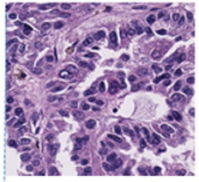	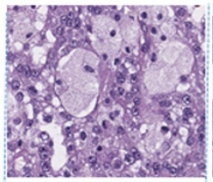	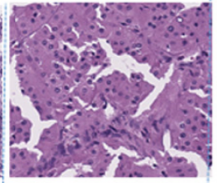	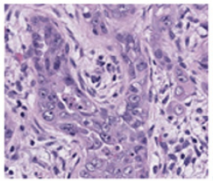	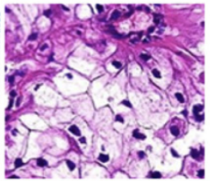	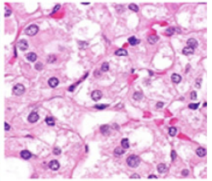
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	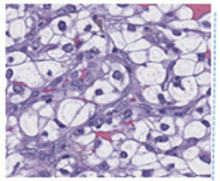	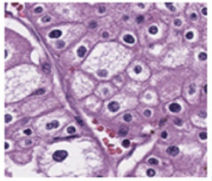	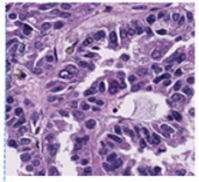	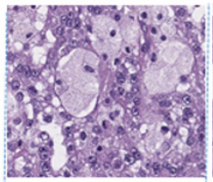	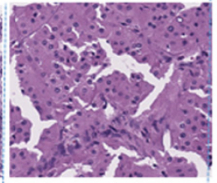	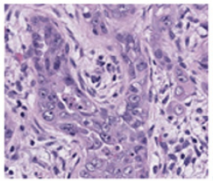	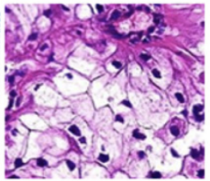	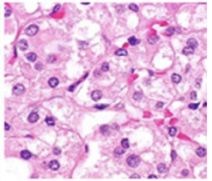
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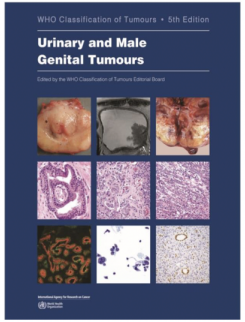

WHO 2004

Clear cell renal cell carcinoma
Multi-locular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinoma
Carcinoma associated with neuroblastoma
Mucinous, tubular, and spindle cell carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Oncocytoma

WHO 2016

Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of LMP
Papillary renal cell carcinoma
Hereditary leiomyomatosis and RCC associated
Chromophobe renal cell carcinoma
Collecting duct carcinoma of the kidney
Renal medullary carcinoma
MiT Family translocation carcinomas
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease associated renal cell carcinoma
Clear cell papillary renal cell carcinoma
Succinate dehydrogenase (SDH) deficient renal carcinoma
Renal cell carcinoma, unclassified

WHO 2022

Clear cell
Multilocular cystic renal neoplasm of low m.p
ELOC Mutation
Papillary RCC
Fumarate H deficient
Mucinous tubular spindle RCC
Tubulocystic
Clear cell papillary RC tumour
Chromophobe
Oncocytoma
SDH deficient
Other oncocytic tumours
TFE3- rearranged
TFEB- altered
Collecting duct carcinoma
SMARCB1 deficient renal medullary carcinoma
ALK rearranged renal cell carcinomas
Eosinophilic solid and cystic RCC
Acquired cystic disease associatedRCC
RCC NOS

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TKI and mTOR INHIBITORS

MET INHIBITORS

IMMUNOTHERAPY

COMBINATIONS

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MET INHIBITORS

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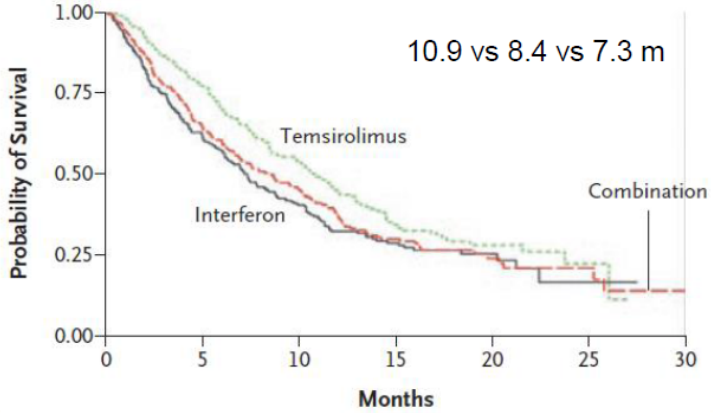
COMBINATIONS

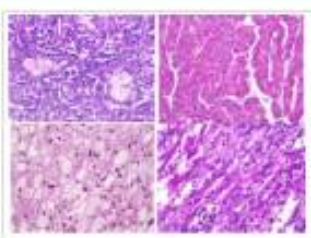
A little bit of history…
mtor inhibitors: TEMSIROLIMUS (intorsect)



Tumor histologic type — no. (%)				
Clear-cell	170 (82)	169 (81)	163 (78)	502 (80)
Other	37 (18)	40 (19)	47 (22)	124 (20)

N Engl J Med, Hudes G, *et al.* Temsirolimus, Interferon Alfa, or Both for Advanced Renal-Cell Carcinoma, 356 (22): 2271–81

NCCN GUIDELINES 2015…



Relapse or Stage IV and surgically unresectable → Non-clear cell histology →

Clinical trial (preferred)
or
Temsirolimus (category 1 for poor-prognosis patients;[f] category 2A for other risk groups)
or
Sorafenib
or
Sunitinib
or
Pazopanib
or
Axitinib
or
Everolimus
or
Bevacizumab
or
Erlotinib

and
Best supportive care:[h]
See NCCN Guidelines for Palliative Care

→ Follow-up (See KID-B)

NCCN Guidelines® Insights. Kidney Cancer, Version 3.2015

SUNITINIB vs EVEROLIMUS

	Median PFS (months)	Median OS (months)	Overall Response Rate (ORR)
Sunitinib (SUPAP) N=61	6.6 (Type 1) vs 5.5 (Type 2)	17.8 (Type 1) vs 12.4 (Type 2)	13% (Type 1) vs 11% (Type 2)
Sunitinib N=31	6.4	25.6	36%
Everolimus (RAPTOR) N=92	4.1	21.4	0%
Everolimus N=49	5.2	14	10%
Sunitinib vs everolimus (ESPN) N=68	6.1 vs 4.1	NR vs 10.5	9% vs 3%
Sunitinib vs everolimus (ASPEN) N=108	8.3 vs 5.6	32 vs 13	18% vs 9%

Ravaud A, *et al* Ann Oncol 2015;26(6):1123-1128; Lee J-L, *et al.* Ann Oncol 2012;23(8):2108-211; Escudier B, *et al.* Eur J Cancer 2016:69:226-235; Koh Y, *et al.* Ann Oncol 2013;24(4):1026-31; Tannir NM, *et al.* Eur Urol 2016;69(5):866-74; Armstrong AJ, *et al.* Lancet Oncol 201617(3):378-388.

TKI: AXITINIB IN PAPILLARY RCC (AXIPAP)

Axitinib in first-line for patients with metastatic papillary renal cell carcinoma: Results of the multicentre, open-label, single-arm, Phase 2 AXIPAP trial

Endpoints	Global PRCC population (N=42)[a,b]	Type 1 subgroup (N=13)	Type 2 subgroup (N=28)
Best response			
PR	12 (28.6%)	1 (7.7%)	10 (35.7%)
SD	26 (61.9%)	10 (76.9%)	16 (57.1%)
PD	4 (9.5%)	2 (15.4%)	2 (7.1%)
Median PFS (months)	6.6 (95% CI: 5.5, 9.2)	6.7 (95% CI: 2.9, 14.0)	6.2 (95% CI: 5.4, 9.2)
24 wk-PFR	45.2 (95% CI: 32.6 to +∞)	46.2 (95% CI: 23.4 to +∞)	42.9 (95% CI: 27.5 to +∞)
Median OS (months)	18.9 (95% CI: 12.8, NR)	NR	17.4 (95% CI: 11.4, NR)

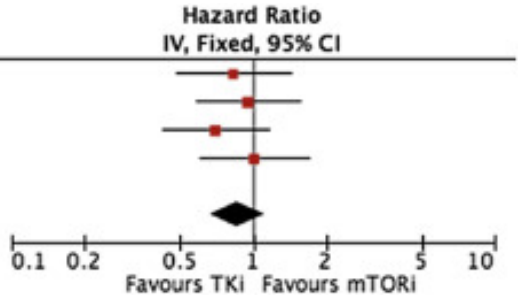
Negrier S, et al. Eur J Cancer 2014;50(10):1766-1771.

TKI vs mTOR INHIBITORS

Addressing the best treatment for non-clear cell renal cell carcinoma: A meta-analysis of randomised clinical trials comparing VEGFR-TKis versus mTORi-targeted therapies

Study or Subgroup	log[Hazard Ratio]	SE	TKi Total	mTORi Total	Weight	Hazard Ratio IV, Fixed, 95% CI
ASPEN	-0.1881	0.2785	51	57	22.4%	0.83 [0.48, 1.43]
ESPN	-0.05	0.2524	33	35	27.2%	0.95 [0.58, 1.56]
INTORSECT	-0.3595	0.2592	45	45	25.8%	0.70 [0.42, 1.16]
RECORD-3	0.0099	0.2657	35	31	24.6%	1.01 [0.60, 1.70]
Total (95% CI)			**164**	**168**	**100.0%**	**0.86 [0.67, 1.12]**

Heterogeneity: $Chi^2 = 1.19$, $df = 3$ ($P = 0.76$); $I^2 = 0\%$
Test for overall effect: $Z = 1.11$ ($P = 0.27$)



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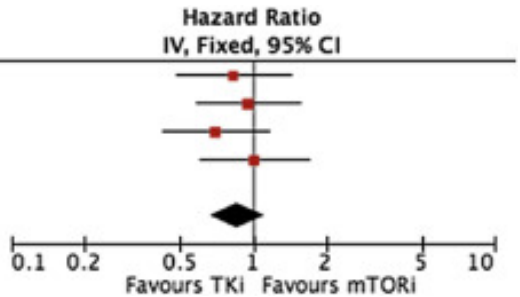
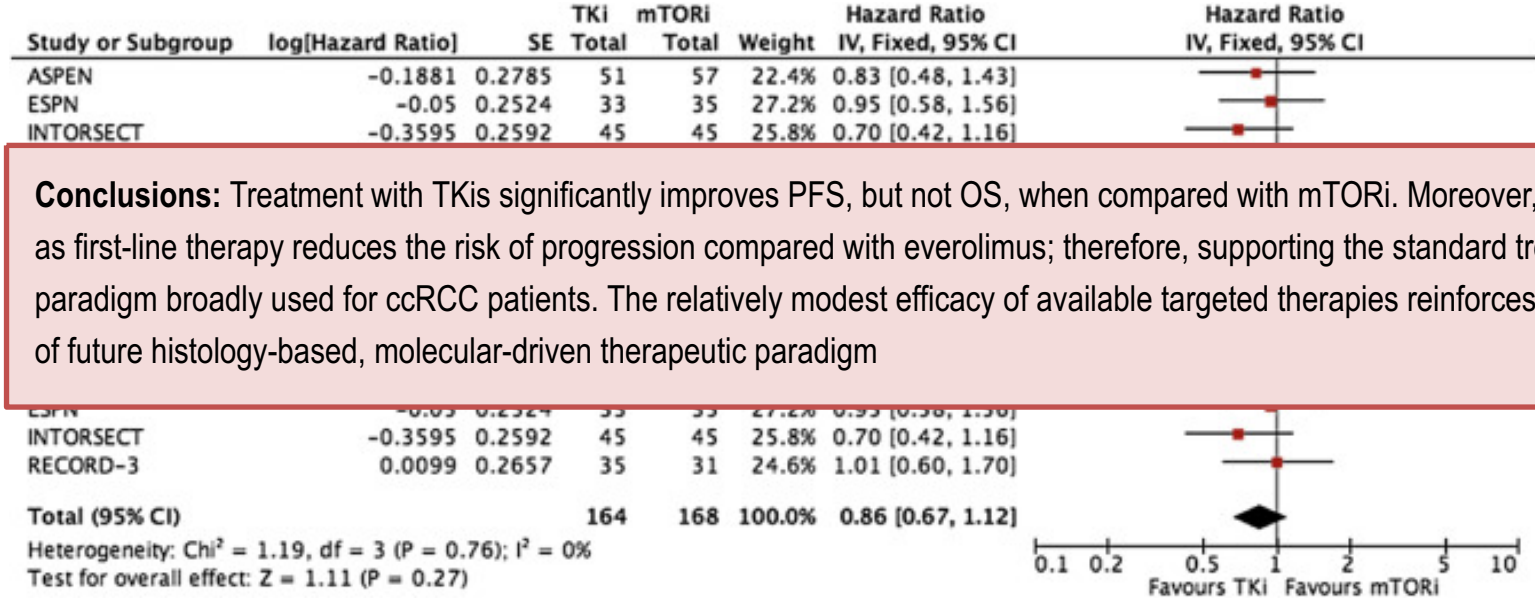


Eur J Cancer, 83, Ciccarese C, *et al.* Addressing the best treatment for non-clear cell renal cell carcinoma: A meta-analysis of randomised clinical trials comparing VEGFR-TKis versus mTORi-targeted therapies, 237–46..

TKI vs mTOR INHIBITORS

Addressing the best treatment for non-clear cell renal cell carcinoma: A meta-analysis of randomised clinical trials comparing VEGFR-TKis versus mTORi-targeted therapies



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Hazard Ratio IV, Fixed, 95% CI

0.1 0.2 0.5 1 2 5 10
Favours TKi Favours mTORi

Conclusions: Treatment with TKis significantly improves PFS, but not OS, when compared with mTORi. Moreover, sunitinib as first-line therapy reduces the risk of progression compared with everolimus; therefore, supporting the standard treatment paradigm broadly used for ccRCC patients. The relatively modest efficacy of available targeted therapies reinforces the need of future histology-based, molecular-driven therapeutic paradigm

Eur J Cancer, 83, Ciccarese C, *et al.* Addressing the best treatment for non-clear cell renal cell carcinoma: A meta-analysis of randomised clinical trials comparing VEGFR-TKis versus mTORi-targeted therapies, 237–46..

GUIDELINES IN 2019…

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Kidney Cancer

RELAPSE OR STAGE IV: SYSTEMIC THERAPY NON-CLEAR CELL HISTOLOGY[n,o]

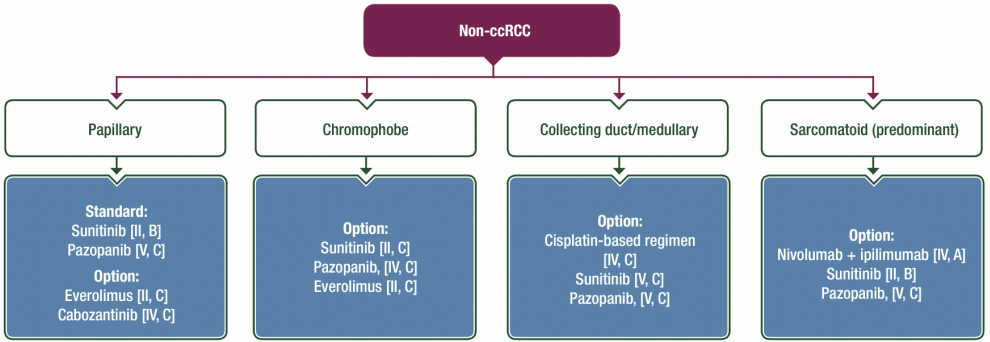
Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Clinical trial • Sunitinib	• Cabozantinib • Everolimus	• Axitinib • Bevacizumab • Erlotinib • Lenvatinib + everolimus • Nivolumab • Pazopanib • Bevacizumab + erlotinib for selected patients with advanced papillary RCC including HLRCC • Bevacizumab + everolimus • Temsirolimus (category 1 for poor-prognosis risk group;[m] category 2A for other risk groups)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 706–720, 2019
doi:10.1093/annonc/mdz056
Published online 21 February 2019

SPECIAL ARTICLE

Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†



Escudier B, *et al*. Ann Oncol 2019;30(5): 706–720.

TKI and mTOR INHIBITORS

MET INHIBITORS

IMMUNOTHERAPY

COMBINATIONS

Comprehensive Molecular Characterisation of Papillary Renal-Cell Carcinoma

The Cancer Genome Atlas Research Network. N Engl J Med 2016;374(2):135-45

Characterisation of clinical cases of advanced papillary renal cell carcinoma via comprehensive genomic profiling

Pal SK, *et al.* European Urology 2018;73:71-78

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

Albiges L, *et al.* Clin Cancer Res 2014;20(13):3411-21

MET INHIBITORS: PHASE 2 TRIALS

	Histology	MET Status	PFS (m)	ORR
Foretinib (N=74) 1st and 2nd line	All papillary	MET +: 10 MET −: 57 NA: 7	9.3	MET +: **50%** MET −: 9%
Savolitinib (N=109) 1st–3rd line	All papillary	MET +: 44 MET −: 46 NA: 19	MET +: 6.2 MET −: 1.4	MET +: 18% MET −: 0%
Crizotinib (N=109) 1st–3rd line	Type 1 Papillary	MET +: 4 MET −: 16 NA: 3	5.8 MET +: 30.5 MET −: 3	MET +: **50%** MET −: 25%

Choueiri TK, *et al.* J Clin Oncol 2013; Choueiri TK, *et al.* J Clin Oncol 2017; Schöffski P, *et al.* ASCO GU 2018.

WHAT DOES *MET* ALTERATION MEAN?

***MET* alterations in papillary RCC**

Germline mutations in *MET* are the hallmark of hereditary papillary renal cancer but are relatively uncommon

Definitions vary on what constitutes "*MET* altered"

- ❑ Activating *MET* mutations of the protein kinase domain or germline *MET*
- ❑ Gain of chromosome 7
- ❑ *MET* amplification
- ❑ HGF amplification

MET INHIBITORS: SAVOIR

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[‡] until objective progressive disease

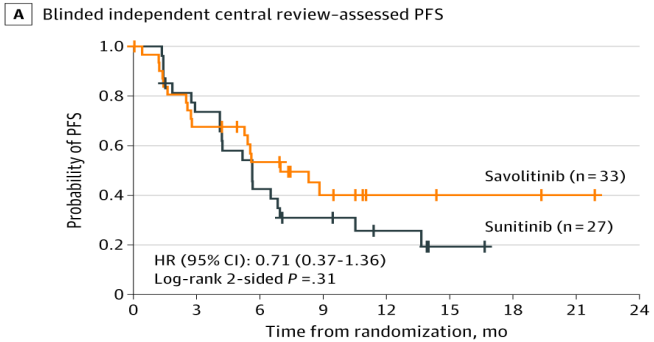
Approximately 360–450 patients were planned to be screened, in order to randomize ~180 patients

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

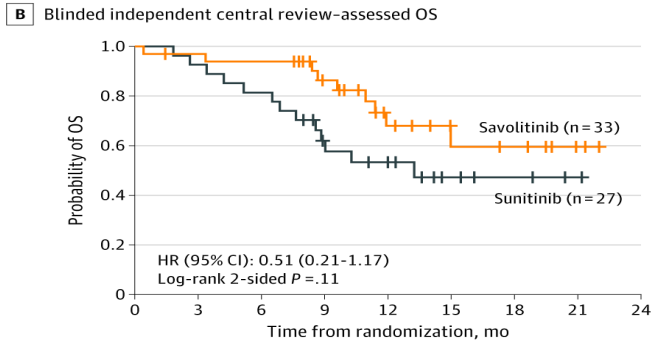
- **Primary endpoints:** PFS by BICR
- **Secondary endpoints**: OS and ORR by BICR, safety and HRQoL

Choueiri TK, *et al.* Presented at ASCO 2020;; Choueiri TK, *et al.* JAMA Oncol 2020;6(8):1247–55.

MET INHIBITORS: SAVOIR



	Number Randomized	Number of Events	Median PFS in months (95% CI)
Savolitinib	33	17	7.0 (2.8-NC)
Sunitinib	27	20	5.6 (4.1-6.9)

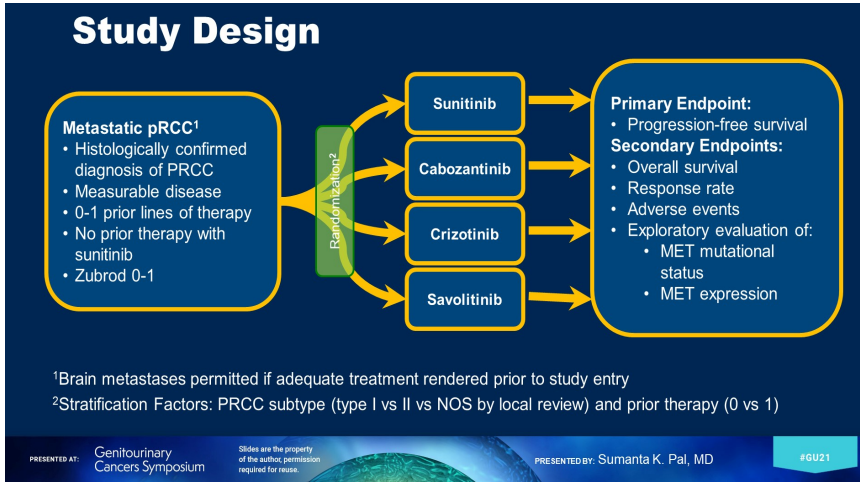


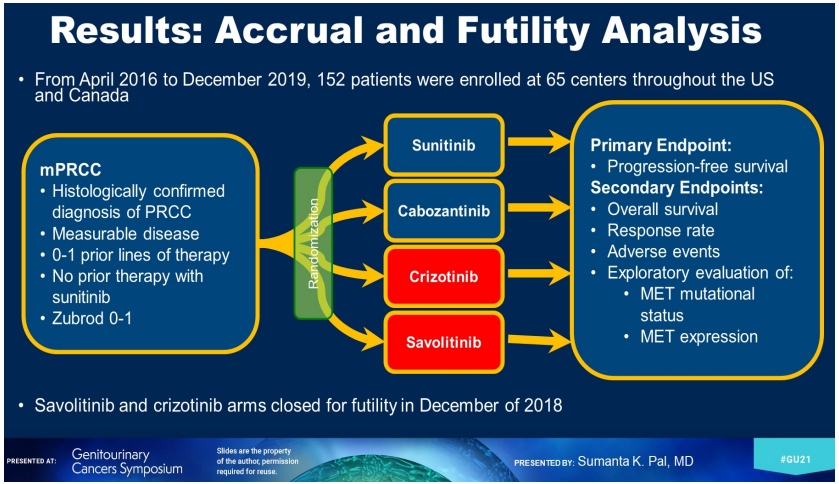
	Number Randomized	Number of Events	Median OS in months (95% CI)
Savolitinib	33	9	NC (11.9-NC)
Sunitinib	27	13	13.2 (7.6-NC)

Outcome	Savolitinib (n=33)	Sunitinib (n=27)
ORR* by BICR, % (95 % CI)	27 (13.3-45.5)	7 (0.9-24.3)
DCR by BICR,% (95% CI)		
6 months	48 (30.8-66.5)	37 (19.4-57.6)
12 months	30 (15.6-48.7)	22 (8.6-42.3)
Any tumour shrinkage, %	67	71

Choueiri TK, *et al.* Presented at ASCO 2020;; Choueiri TK, *et al.* JAMA Oncol 2020;6(8):1247–55.

MET INHIBITORS: PAPMET

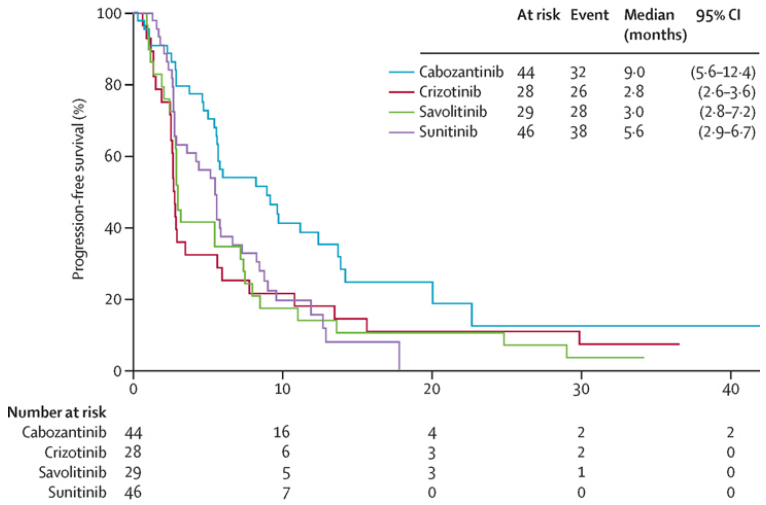




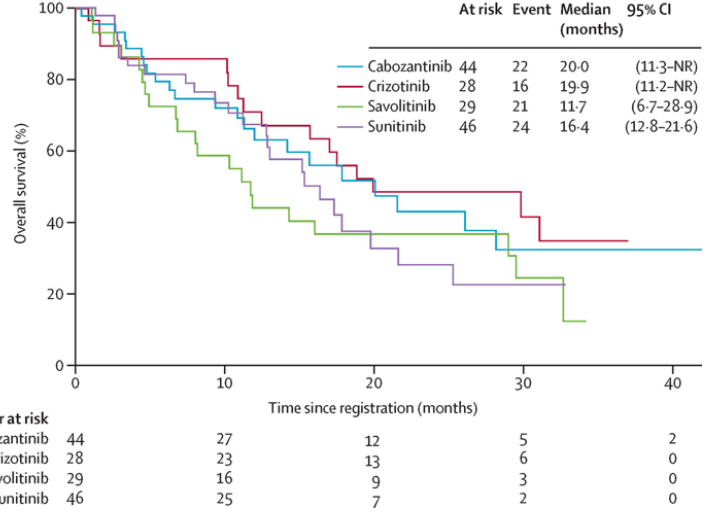
Pal S. Presented at the 2021 Genitourinary Cancers Symposium. By permission of Prof S.K. Pal; Pal S, *et al.* Lancet 2021;397(10275):695–703.

MET INHIBITORS: PAPMET

Progression-free survival



Overall survival



	Cabozantinib	Sunitinib	HR/P-value
Median PFS, mo	9	5.6	0.6 (95% CI 0.37-0.97)
ORR, %	23	4	P=0.01
Median OS, mo	20	16.4	0.84 (95% CI 0.47-1.51)

Pal S. Presented at the 2021 Genitourinary Cancers Symposium. By permission of Prof S.K. Pal; Pal S, *et al.* Lancet 2021;397(10275):695–703.

MET INHIBITORS: CABOZANTINIB in Collecting Duct Carcinoma (BONSAI)

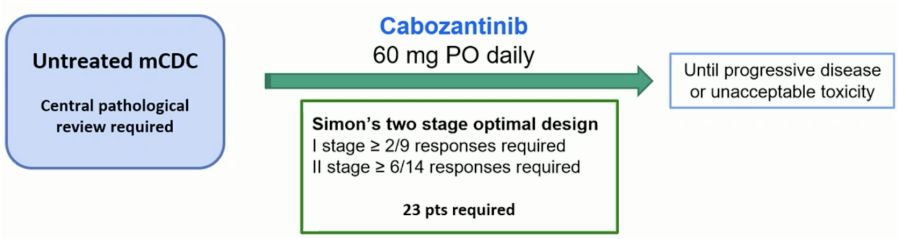
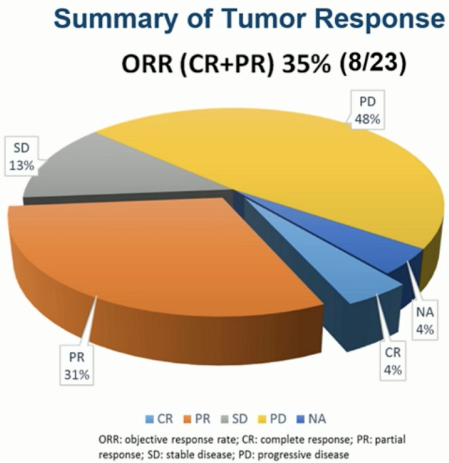
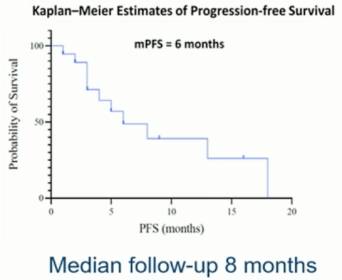


Table 1. baseline Characteristics of Patients

Patients - n	23
Age	
Median - years	66
Gender – n (%)	
M	19 (83)
F	4(17)
Nefrectomy – n (%)	19 (83)
Number of Metastatic sites – n of pts (%)	
1	9(39)
2	8(35)
>2	6(26)
Disease Locations - n of pts (%)	
Nodes	15(65)
bone	13(56)
Lung	10(43)
Liver	4(17)





Median follow-up 8 months

Procopio G. Presented at ESMO 2021.

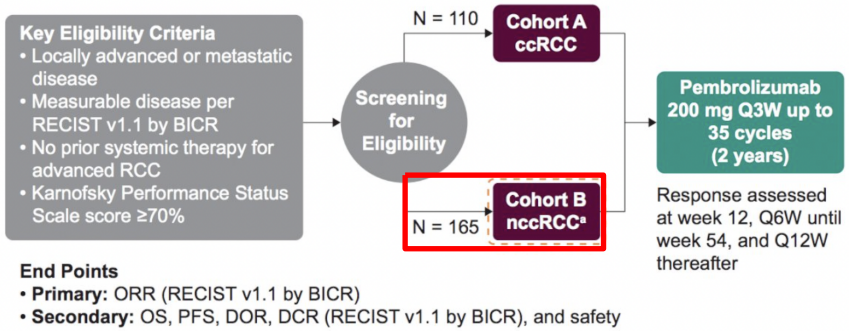
TKI and mTOR INHIBITORS

MET INHIBITORS

IMMUNOTHERAPY

COMBINATIONS

IMMUNOTHERAPY: PEMBROLIZUMAB (KEYNOTE 427)



		IMDC Category		Histology		
	Overall N = 165	Favorable n = 53	Intermediate/ Poor n = 112	Papillary RCC n = 118	Chromophobe RCC n = 21	Unclassified RCC n = 26
ORR,[a] % (95% CI)	26.7 (20.1-34.1)	32.1 (19.9-46.3)	24.1 (16.5-33.1)	28.8 (20.8-37.9)	9.5 (1.2-30.4)	30.8 (14.3-51.8)
DCR,[b] % (95% CI)	43.0 (35.4-51.0)	43.4 (29.8-57.7)	42.9 (33.5-52.6)	47.5 (38.2-56.9)	33.3 (14.6-57.0)	30.8 (14.3-51.8)
Best response, n (%)						
CR	11 (6.7)	7 (13.2)	4 (3.6)	7 (5.9)	1 (4.8)	3 (11.5)
PR	33 (20.0)	10 (18.9)	23 (20.5)	27 (22.9)	1 (4.8)	5 (19.2)
SD	51 (30.9)	17 (32.1)	34 (30.4)	39 (33.1)	10 (47.6)	2 (7.7)
PD	60 (36.4)	18 (34.0)	42 (37.5)	38 (32.2)	9 (42.9)	13 (50.0)
NE[c]	2 (1.2)	1 (1.9)	1 (0.9)	1 (0.8)	0 (0)	1 (3.8)
No assessment[d]	8 (4.8)	0 (0)	8 (7.1)	6 (5.1)	0 (0)	2 (7.7)

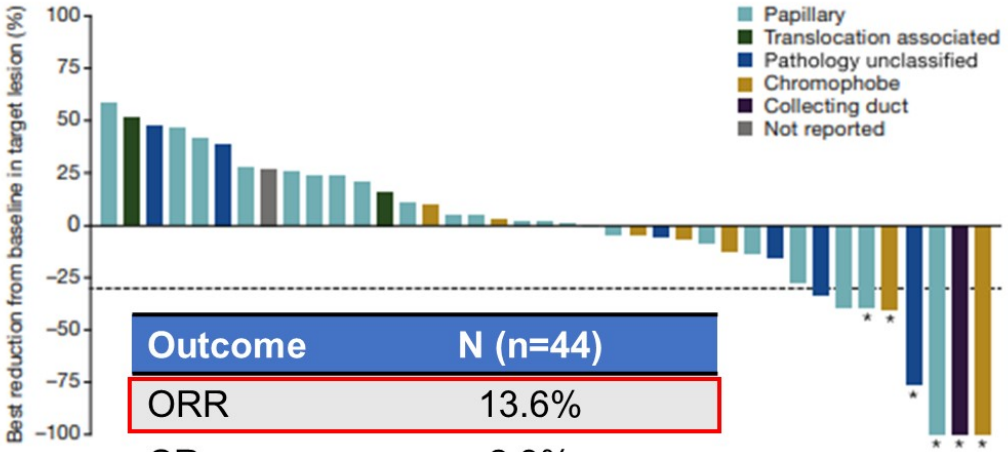
Characteristics	N (n=165)	ORR
Papillary	71.5%	28.8%
Chromophobe	12.7%	9.5%
Unclassified	15.8%	30.8%
Sarcomatoid	23.0%	42.1%
Prior treatment	0%	26.7%
PD-L1+	61.8%	35.3% (12.1%)

Median PFS 4.2 m
Median OS 30 m

McDermott D, J Clin Onc 2020; Lee DL, *et al.* presented at ESMO 2021

IMMUNOTHERAPY: Nivolumab (CHeCKMATE-374)

Characteristics	N (n=44)	ORR
Papillary	54.5%	8.3%
Chromophobe	15.9%	28.6%
Unclassified	18.2%	12.5%
Translocation	5%	0%
Collecting duct	2%	100%
Medullary	2%	0%
Not reported	2%	-
Sarcomatoid	9.1%	50%
Prior treatment	34.1%	-



Outcome	N (n=44)
ORR	13.6%
CR	2.3%
PD	40.9%
PFS	2.2 months
OS	16.3 months

Vogelzang NJ, *et al.* Clin Genitourin Cancer 2020

IMMUNOTHERAPY: nivolumab-IPILIMUMAB (CHECKMATE-920)

N=200

Key inclusion criteria

- Advanced or metastatic RCC (ccRCC and nccRCC)
- No prior systemic therapy for advanced/ metastatic RCC
- Any IMDC risk
- Brain metastases allowed if asymptomatic and not on CS or receiving radiation (enrolled to cohort 3 or 4)
- KPS 70% (cohorts 1-3) or 50-60% (cohort 4)

Cohort 1: predominantly ccRCC KPS ≥ 70% (n = 100)
NIVO 6 mg/kg + IPI 1 mg/kg Q8W alternating with NIVO 480 mg Q8W, staggered Q4W

Cohort 2: nccRCC KPS ≥ 70% (n = 50)
NIVO 3 mg/kg + IPI 1 mg/kg Q3W x 4 doses

Cohort 3: cc/nccRCC with non-active brain metastases KPS > 70% (n = 25) NIVO 3 mg/kg + IPI 1 mg/kg Q3W x 4 doses

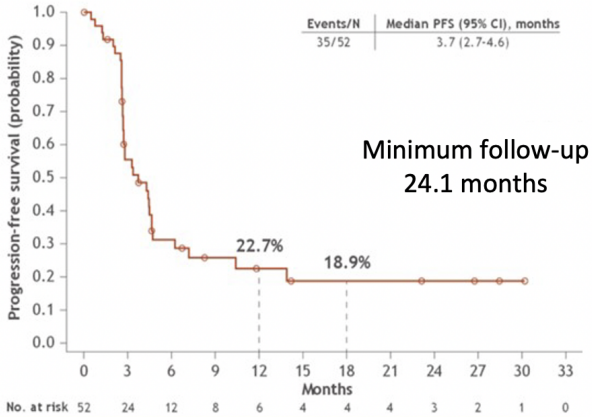
Cohort 4: cc/nccRCC KPS 50% -60% (n = 25) NIVO 3 mg/kg + IPI 1 mg/kg Q3W x 4 doses

NIVO 480 mg Q4W

Treat for ≤ 2 years or until RECIST v1.1-defined progression, unacceptable toxicity, or withdrawal of consent

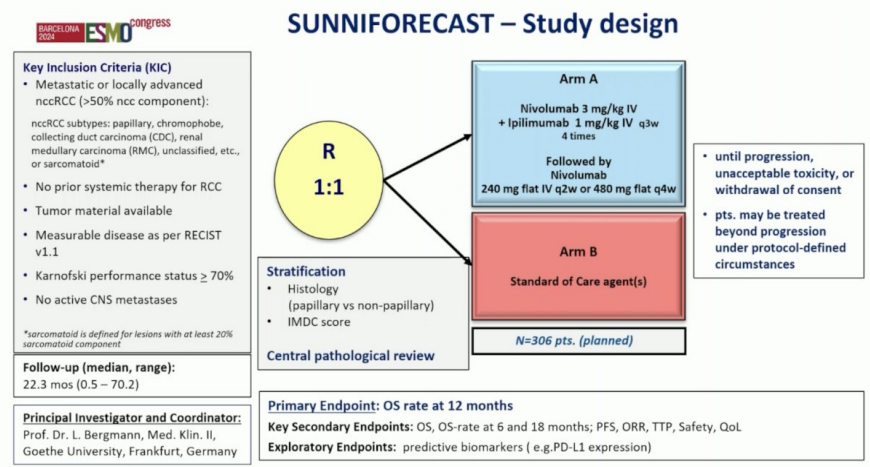
Characteristics	N (n=44)	ORR
Unclassified	42.3%	-
Papillary	34.6%	-
Chromophobe	13.5%	-
Translocation	3.8%	-
Collecting duct	3.8%	-
Medullary	1.9%	-
Sarcomatoid	28.8%	35.7%
Prior treatment	0%	19.6%
PD-L1+	38.5%	30.8%

Outcome	
ORR/CR	19.6%/4.3%
PD	41.3%
PFS	3.7 months
OS	21.2 months



Tykodi SS, *et al.* J Immunother Cancer 2022

IMMUNOTHERAPY: NIVOLUMAB-IPILIMUMAB SUNNIFORECAST



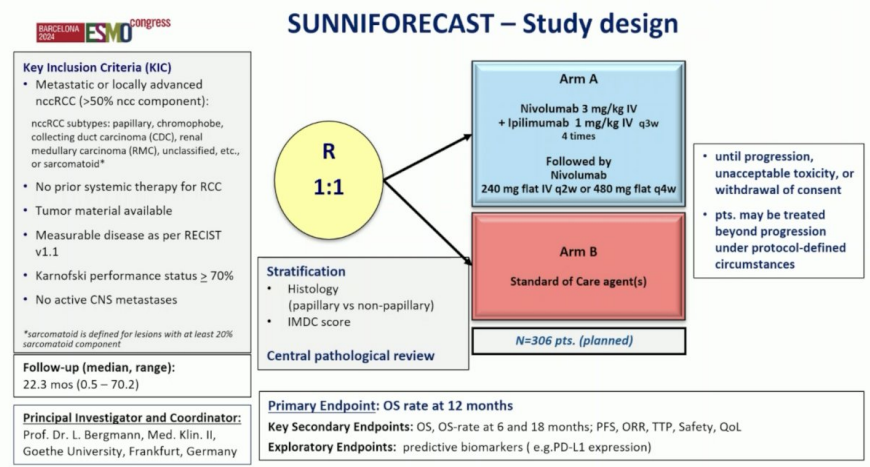
	Ipilimumab/ nivolumab *N* = 157	Standard of Care *N* = 152	*P* value
OS rate at 12 months (95%CI)	**78%** (71%-84%)	**68%** (60%-75%)	**0.026**
OS rate at 6 months (95%CI)	91% (85%-95%)	85% (79%-90%)	0.064
OS rate at 18 months (95%CI)	67% (59%-73%)	60% (52%-68%)	0.124
Median OS, months (95%CI)	33.2 (23.4-40.8)	25.2 (18.8-33.0)	0.163

Table 3. Response according to RECIST v1.1 and ORR by study treatment and by histology strata. The analysis is restricted to 248 patients with a valid tumor response assessment during therapy

	All		Papillary nccRCC		Non-papillary nccRCC	
	Ipilimumab/ nivolumab (*N* = 125)	SOC (*N* = 123)	Ipilimumab/ nivolumab (*N* = 72)	SOC (*N* = 77)	Ipilimumab/ nivolumab (*N* = 53)	SOC (*N* = 46)
Objective response rate, *n* (%)	41 (33)	24 (20)	21 (29)	16 (21)	20 (38)	8 (17)
Best overall response, *n* (%)						
Complete response	10 (8)	2 (2)	7 (10)	2 (3)	3 (6)	0
Partial response	31 (25)	22 (18)	14 (20)	14 (18)	17 (32)	8 (17)
Stable disease	41 (33)	76 (62)	27 (38)	47 (61)	14 (26)	29 (63)
Progressive disease	43 (34)	23 (19)	24 (33)	14 (18)	19 (36)	9 (20)

Bergmann L, *et al.* ESMO 2024;; Bergmann L, Ann Onc 2025

IMMUNOTHERAPY: NIVOLUMAB-IPILIMUMAB SUNNIFORECAST



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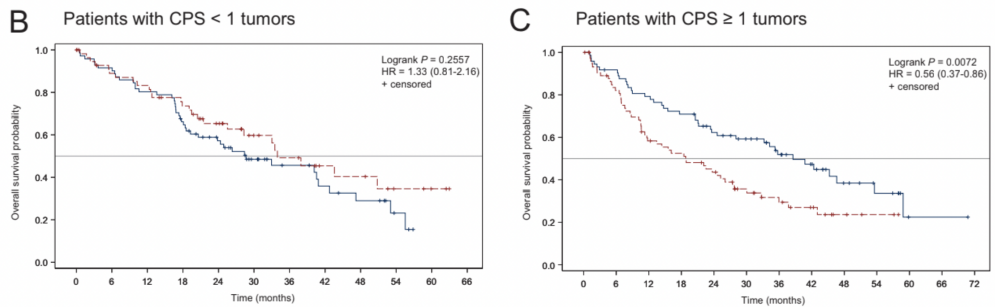


Bergmann L, *et al.* ESMO 2024;; Bergmann L, Ann Onc 2025

TKI and mTOR INHIBITORS

MET INHIBITORS

IMMUNOTHERAPY

COMBINATIONS

COMBOS:
NIVOLUMAB+CABOZANTINIB IN NON-CLEAR RCC

Key inclusion criteria
- Advanced or metastatic ncRCC
- Measurable disease per RECIST v1.1
- 0-1 prior lines of systemic therapy

→ **Cabozantinib** 40 mg PO daily
+
Nivolumab 240 mg IV every 2 weeks (or 480 mg IV 4 weeks)

→ **Primary endpoint**
- ORR by RECIST

Secondary endpoints
- PFS by RECIST
- PFS by irRECIST
- OS
- Safety and tolerability

Cohort 1: papillary[2], unclassified, or translocation-associated RCC (N=40)

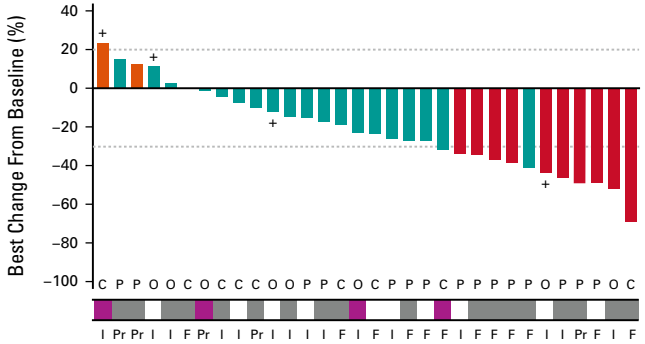
Cohort 2: chromophobe RCC (N=7)

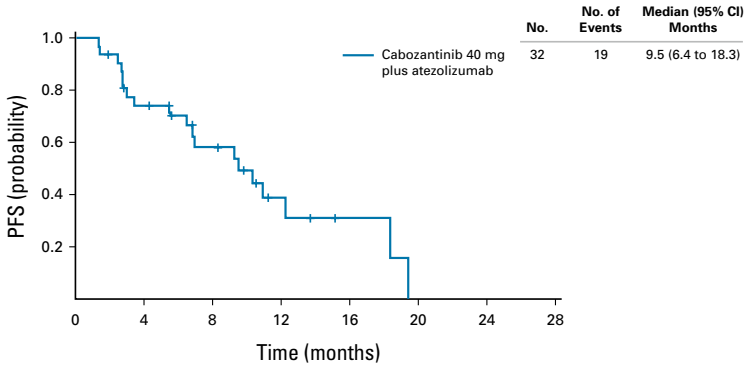
Parameter	Line of treatment		Renal cell carcinoma histology		
	1st line (n=26)	2nd line (n=14)	Papillary (n=32)	UCP (n=6)	TA-RCC (n=2)
ORR,% (95% CI)	54 (33-73)	36 (13-65)	47 (30-64)	50 (12-88)	50 (1-99)
Complete response, n (%)	1 (3.8)	0 (0)	1 (3.1)	0 (0)	0 (0)
Partial response, n (%)	13 (50)	5 (36)	14 (44)	3 (50)	1 (50)
Stable disease, n (%)	12 (46)	7 (50)	16 (50)	2 (33)	1 (50)
Progressive disease, n (%)	0 (0)	2 (14)	1 (3.1)	1 (17)	0 (0)
Median PFS, mo (95% CI)	11 (7-19)	13 (5-16)	13 (7-16)	8 (1-NE)	14 (5-23)

Fitzgerald KN, *et al.* Eur Urol 2024;86(2):90-94; Lee CH. Presented at ASCO 2021.

COMBOS: ATEZOLIZUMAB+CABOZANTINIB IN NON-CLEAR RCC (COSMIC 021)

Response	ncRCC Cabozantinib 40 mg plus atezolizumab (n=32)
Objective response rate, % (80% CI)	31 (20 to 44)
Best overall response, n (%)	
Complete response	0
Partial response	10 (31)
Stable disease	20 (63)
Progressive disease	2 (6)
Not evaluable or missing	0
Disease control, n (%)	30 (94)
Time to response, median (range), months	2.7 (1-7)
Duration of response, median (95% CI), months	8.3 (2.4 to NE)
Patients with ongoing response at cutoff, n (%)	4 (13)





Pal SK, *et al.* J Clin Oncol 2021;39(33:3725–36.

COMBOS: LENVATINIB-PEMBROLIZUMAB IN NON-CLEAR RCC (KEYNOTE B61)

Key eligibility criteria
- Histologically confirmed diagnosis of nccRCC (per investigator)
- Locally advanced/metastatic disease
- No prior systemic therapy
- Measurable disease per RECIST v1.1
- Tumour tissue sample available
- KPS ≥70%

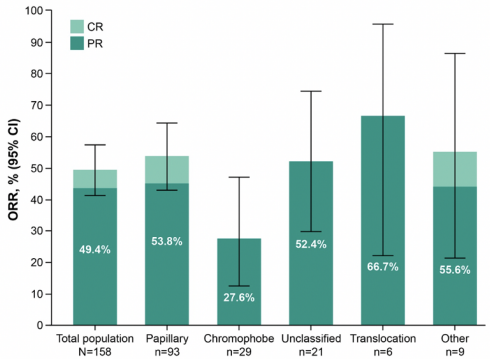
N=158

Pembrolizumab
400 mg IV Q6W for ≤18 cycles (~2 years)
+
Lenvatinib
20 mg PO QD

Tumour assessments
12 weeks from allocation then Q6W for 54 weeks then Q12W thereafter

Endpoints
- Primary: ORR per RECIST v1.1 by BICR
- Secondary: CBR, DCR, DOR, and PFS per RECIST v1.1 by BICR; OS, safety and tolerability

	Pembrolizumab + Lenvatinib N=158
ORR (CR + PR), % (95% CI)	49.4 (41.3-57.4)
DCR (CR+PR+SD), % (95% CI)	82.3 (75.4-87.9)
CBR (CR, PR, or SD for ≥6 months), % (95% CI)	71.5 (63.8-78.4)
Best response, n (%)	
CR	9 (5.7)
PR	69 (43.7)
SD	52 (32.9)
PD	17 (10.8)
NE	1 (0.6)
NA[b]	10 (6.3)



Albiges L, *et al.* Lancet Oncol 2023;24(8):881-891; Voss M. Presented at ASCO GU Meeting 2024.

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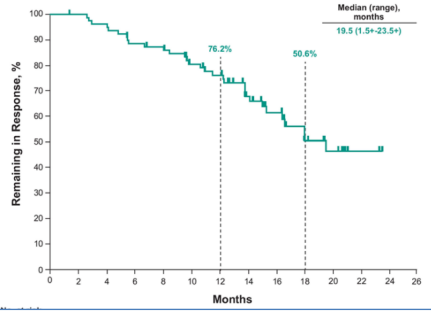
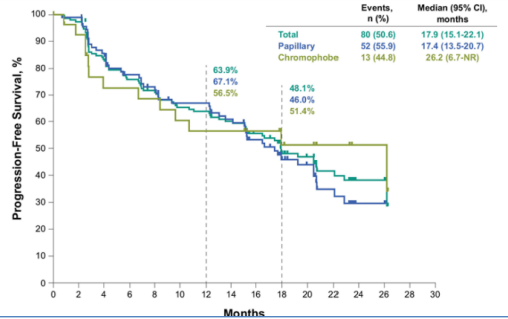
Kaplan-Meier Estimates of DOR in All Patients With a Confirmed Objective Response Per RECIST v1.1 by BICR



Kaplan-Meier Estimates of PFS Per RECIST v1.1 by BICR in the Total Population, Papillary Histology, and Chromophobe Histology Subgroups



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COMBOS: ATEZOLIZUMAB+ERLOTINIB IN PAPILLARY RCC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bevacizumab and Erlotinib in Hereditary and Sporadic Papillary Kidney Cancer

Ramaprasad Srinivasan, M.D., Ph.D.,[1] Sandeep Gurram, M.D.,[1] Eric A. Singer, M.D.,[2] Abhinav Sidana, M.D., M.P.H.,[1] Munjid Al Harthy, M.D.,[1] Mark W. Ball, M.D.,[1] Julia C. Friend, M.P.H., P.A.-C.,[1] Lisa Mac, M.P.H., P.A.-C.,[1,2] Erin Purcell, B.S.N., R.N.,[1] Cathy D. Vocke, Ph.D.,[1] Christopher J. Ricketts, Ph.D.,[1] Heidi H. Kong, M.D., M.H.Sc.,[3] Edward W. Cowen, M.D., M.H.Sc.,[3] Ashkan A. Malayeri, M.D.,[4] Joanna H. Shih, Ph.D.,[5] Maria J. Merino, M.D.,[6] and W. Marston Linehan, M.D.[1]

Patients
- Advanced/ metastatic papillary RCC
- Measurable disease
- ECOG PS 0-2
- No more than 2 prior regimens targeting VEGF pathway
- No prior bevacizumab

HLRCC Group*
N=43

Sporadic Papillary Group*
N=40

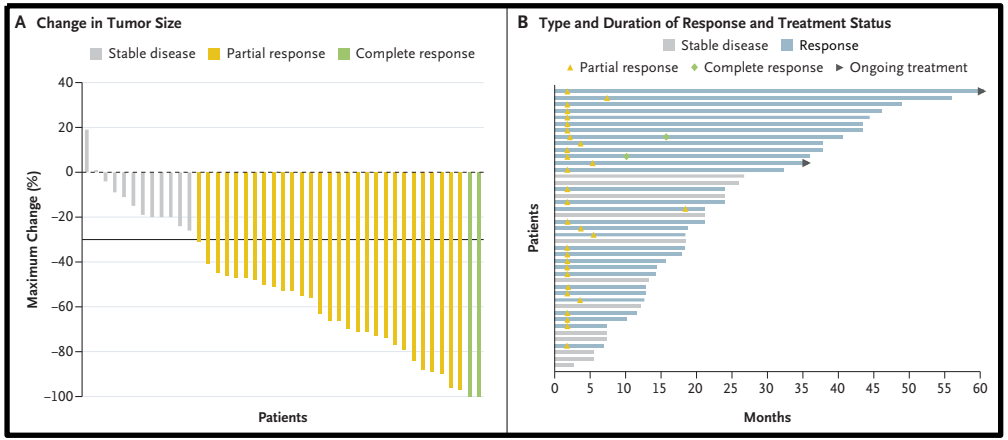
Treatment

Bevacizumab
10 mg/kg IV q2w
+
Erlotinib
150 mg PO daily

Primary endpoint
Overall Response Rate per RECIST 1.1
Secondary endpoints
PFS and duration of response

Table 2. Best Response in Papillary Renal-Cell Carcinoma.*

Variable	HLRCC-Associated Papillary RCC (N=43)	Sporadic Papillary RCC (N=40)
Objective response†		
No. with response	31	14
Percent (95% CI)	72 (57–83)	35 (22–51)
Best response — no. (%)		
Complete response	2 (5)	0
Partial response	29 (67)	14 (35)
Stable disease	12 (28)	21 (52)
Unconfirmed partial response‡	0	1 (2)
Progressive disease	0	4 (10)
Median time to response (range) — mo	1.8 (1.7–18.3)	1.8 (1.7–7.3)
Median duration of response (95% CI) — mo	19.3 (12.9–35.9)	18.4 (13.8–49.7)



Srinivasan R. Presented at ASCO 2020; Srinivasan R. NEJM 2025

COMBOS: ATEZOLIZUMAB+ERLOTINIB IN PAPILLARY RCC

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Overall Response Rate per RECIST 1.1
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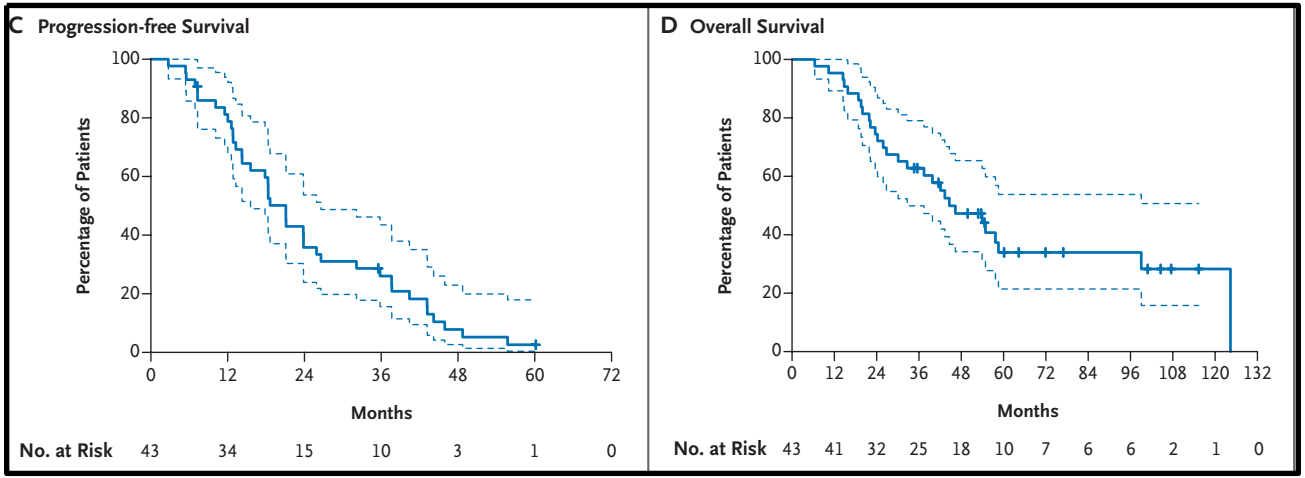
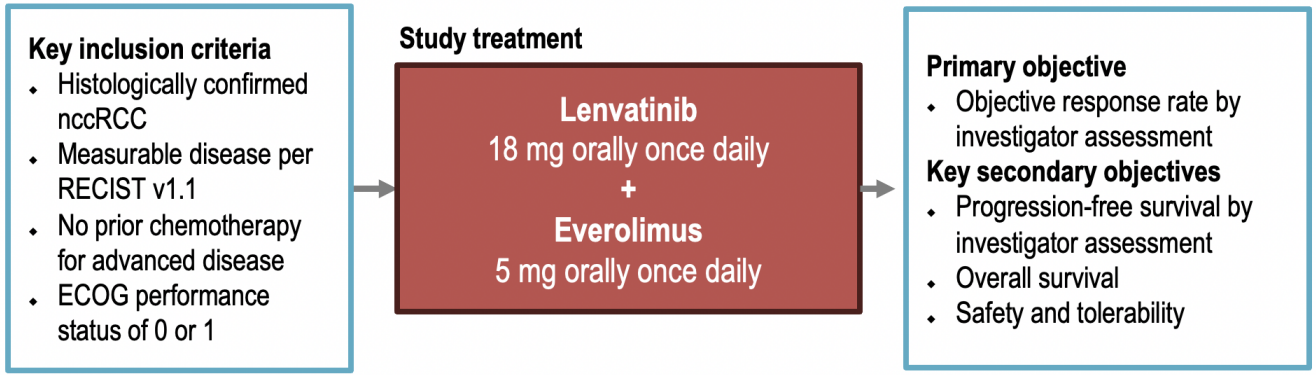


Srinivasan R. Presented at ASCO 2020; Srinivasan R. NEJM 2025

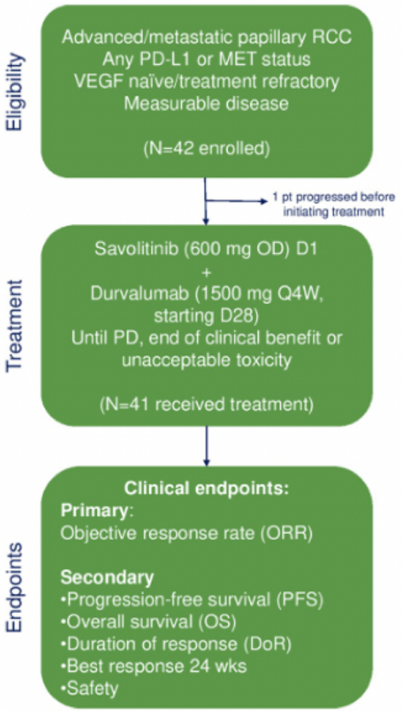
COMBOS: LENVATINIB-EVEROLIMUS IN NON-CLEAR RCC



	pRCC (n=20)	ChRCC (n=9)	Unclassified (n=2)	Total (n=31)
ORR, % (95% CI)	15.0 (3.2-37.9)	**44.4 (13.7-78.8)**	50.0 (1.3-98.7)	25.8 (11.9-44.6)
Clinical benefit rate, % (95% CI)	50 (27.2-72.8)	77.8 (40.0-97.2)	100 (15.8-100)	61.3 (66.3-94.5)

Hutson TE, *et al.* Eur Urol 2021;80:162-170.

COMBOS: DURVALUMAB+SAVOLITINIB IN PAPILLARY RCC (CALYPSO)

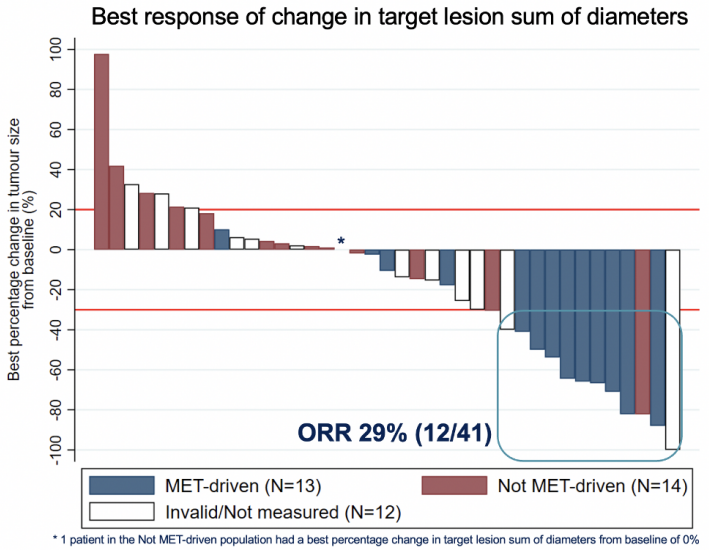


14/41 (34%) patients in the PRC cohort were MET-driven defined as

- ❑ Chromosome 7 gain
- ❑ *MET* amplification
- ❑ MET kinase domain variations
- ❑ HGF amplification

Response in MET-driven papillary RCC patients

- ✓ Confirmed response rate in MET-driven patients was 57% (8/14)
- ✓ Median duration of response was 9.4 months



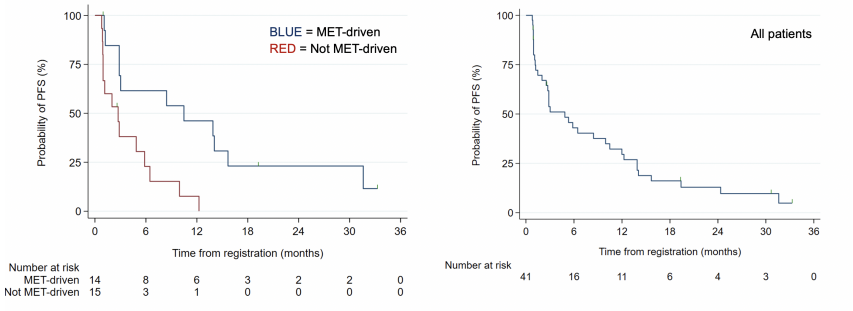
Suarez C, ASCO 2021, Suarez C JCO 2023

COMBOS: DURVALUMAB+SAVOLITINIB IN PAPILLARY RCC (CALYPSO)

Progression-Free Survival

	MET-driven (N=14)	All patients (N=41)
PFS rate at 12 months, % (95% CI)	46.2 (19.2 – 69.6)	29.6 (16.1 – 44.3)
Median PFS, months (95% CI)	10.5 (2.9 – 15.7)	4.9 (2.5 – 10.0)

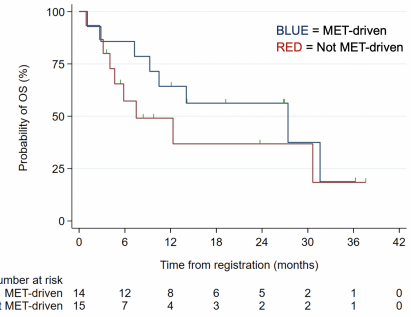
NR = Not reached

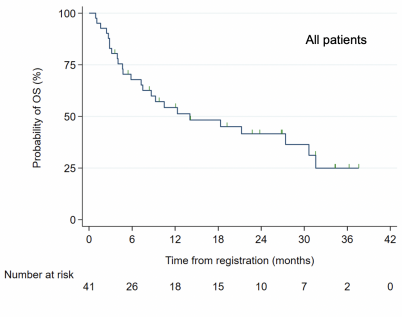


Overall Survival

	MET-driven (N=14)	All patients (N=41)
OS rate at 12 months, % (95% CI)	64.3 (34.3 – 83.3)	54.3 (37.5 – 68.4)
Median OS, months (95% CI)	27.4 (7.3 – NR)	14.1 (7.3 – 30.7)

NR = Not reached





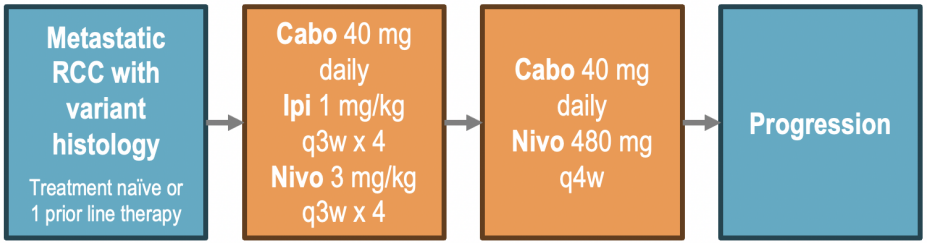
Median OS MET-driven vs all patients: 27.4 vs 14.1 months

Median PFS MET-driven vs all patients: 10.5 vs 4.9 months

Suarez C, ASCO 2021, Suarez C JCO 2023

COMBOS: CABO+NIVO+IPI (CaNI)

CaNI schema



	n (%)
Any grade of AE	39 (100)
Any grade of treatment-related AE	38 (97)
Grade 5 Lethal toxicity	0
Grade 3-4 of treatment-related AE	29 (74)
Grade 3-4 elevation in AST or ALT	14 (36)
Required high dose steroids (prednisone 240 mg daily or equivalent)	17 (44)
Discontinued treatments due to toxicity	8 (21)

Primary endpoint – ORR per RECIST 1.1

Secondary endpoints – PFS, OS, safety

	Total N	Objective response, n (%)		
		PR	SD	PD
Overall	39	7 (18)	23 (59)	9 (23)
Histology				
Papillary	20	5 (25)	11 (55)	4 (20)
Chromophobe	11	1 (9)	5 (45)	5 (45)
Translocation	5	-	5 (100)	-
Other	2	-	2 (100)	-
Unclassified RCC	1	1 (100)	-	-
Sarcomatoid diff				
No	30	5 (17)	19 (63)	6 (20)
Yes	9	2 (22)	4 (44)	3 (33)
Prior therapy				
No	34	7 (21)	20 (59)	7 (21)
Yes	5	-	3 (60)	2 (40)

McGregor BA, *et al.* ASCO 2023.

Ongoing trials for non-clear cell RCC

PAPMET 2
N=200

Key Inclusion Criteria:
Metastatic pRCC (type 1 & 2)
0-1 Previous systemic therapies

Key Exclusion Criteria:
Previous cabozantinib therapy
Previous aPD-1/PD-L1 checkpoint inhibitor therapy (incl. adjuvant)

Randomization 1:1

- Cabozantinib + atezolizumab
- Cabozantinib

Primary end point: PFS
Secondary end points: OS, ORR, adverse events

SAMETA
N=220

Key Inclusion Criteria:
Met-driven metastatic/locally advanced pRCC
No previous systemic therapies

Randomization 2:1:1

- Durvalumab + savolitinib
- Savolitinib
- Sunitinib

Primary end point: PFS (durvalumab + savolitinib vs sunitinib)
Secondary end points: OS, ORR, DCR, DoR, HRQoL

STELLAR 304
N=291

Key Inclusion Criteria:
Metastatic/advanced non-clear cell RCC
No previous systemic therapies (one previous adjuvant therapy allowed)

Randomization 2:1

- Zanzalitinib + nivolumab
- Sunitinib

Primary end point: PFS, ORR
Secondary end points: OS

CONCLUSIONS

- Non clear cell RCC is a heterogeneous disease
- We should stop doing “non-clear RCC trials”
  - Clinical trials by subtypes are essential
- Biomarkers are REALLY needed
- IO-TKI combinations (lenva-pembro/cabo-nivo) showed the best ORR
- *MET* alterations appear to be a good biomarker for MET inhibitors.

Muchas gracias por vuestra atención