

Therapeutische Realität beim nicht-klarzelligen Nierenzellkarzinom (ncc-RCC)

Jahrestagung DGHO, ÖGHO, SGHO
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Deklaration meiner möglichen Interessenskonflikte

Gewährung von Reisekosten, Advisory Boards, Studien- und/ oder Forschungsunterstützung

- Bayer
- BMS
- MSD
- Roche
- IPSEN

Überblick der Nierenzellkarzinome (klar + *nicht*-klarzellige)

Neue ICD-O-3.2. nennt 52 Untergruppen

8310/3 Clear cell renal cell carcinoma

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8260/3 Papillary renal cell carcinoma

..

8319/3 Collecting duct carcinoma

..

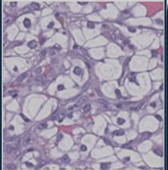
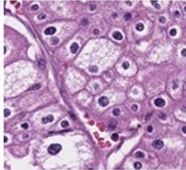
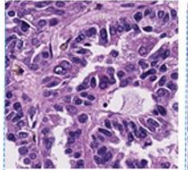
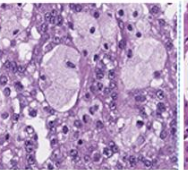
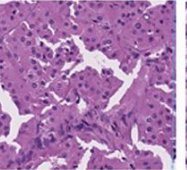
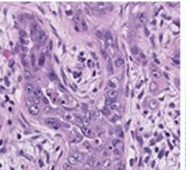
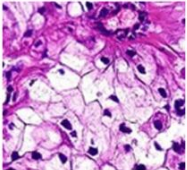
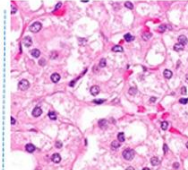
8960/3 Nephroblastoma

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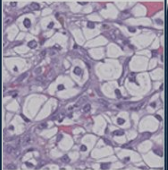
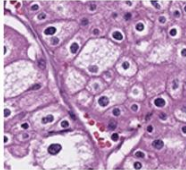
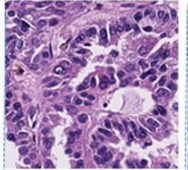
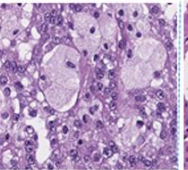
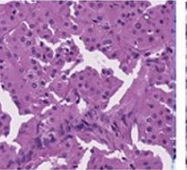
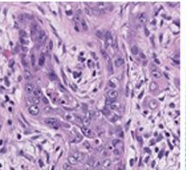
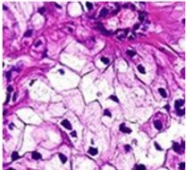
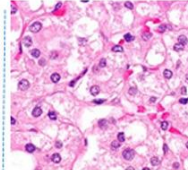
Überblick der Nierenzellkarzinome (klar + *nicht*-klarzellige)

<i>Molecularly defined renal carcinomas</i>	
8311/3	<i>TFE3</i> -rearranged renal cell carcinomas
8311/3	<i>TFEB</i> -altered renal cell carcinomas
8311/3	<i>ELOC</i> (formerly <i>TCEB1</i>)-mutated renal cell carcinoma
8311/3	Fumarate hydratase-deficient renal cell carcinoma
8311/3	Hereditary leiomyomatosis and renal cell carcinoma syndrome-associated renal cell carcinoma
8311/3	Succinate dehydrogenase-deficient renal cell carcinoma
8311/3	<i>ALK</i> -rearranged renal cell carcinomas
8510/3	Medullary carcinoma, NOS
8510/3	SMARCB1-deficient medullary-like renal cell carcinoma
8510/3	SMARCB1-deficient undifferentiated renal cell carcinoma, NOS
8510/3	SMARCB1-deficient dedifferentiated renal cell carcinomas of other specific subtypes

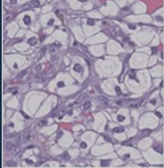
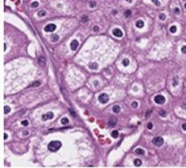
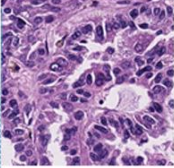
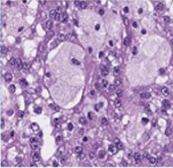
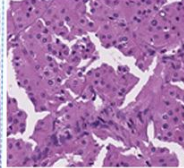
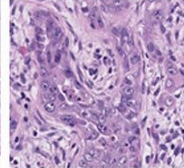
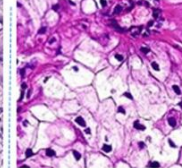
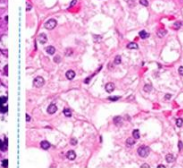
Überblick der Nierenzellkarzinome (klar + *nicht*-klarzellige)

	Clear Cell RCC	Chromophobe RCC	Type I Papillary RCC	Type 2 Papillary RCC/FH-RCC/HLRCC	Unclassified RCC	Renal Medullary Carcinoma	MIT family Translocation RCC	SDH-Deficient RCC
								
Incidence:	75%	5%	5%-10%	5%-10%	< 5%	< 1%	~ 1%	< 1%
Median Age:	62	58	62	Type 2 pRCC: 62 HLRCC: 39-45	50-55	27	31-49	38
Prognosis:	Variable	Very good	Good	Poor	Variable (often poor)	Dismal	Often poor	Variable (often good)
Molecular Alterations:	3p loss, VHL	PTEN, TP53, mTOR, TSC1/2	MET	FH, NF2, 9p loss	NF2, SETD2, BAP1, KMT2C, 9p loss	SMARCB1 loss, 8q gain	TFE3/TFEB translocation	SDHA, SDHB, SDHC, or SDHD
Therapeutic Targets:	HIF, VEGF, mTOR	c-KIT, mTOR	MET	Metabolism	Hippo-YAP, EGFR & mTOR if NF2 loss	c-MYC, replication and proteotoxic stress, Notch2	TFE3/PI3K/AKT/ mTOR	Metabolism

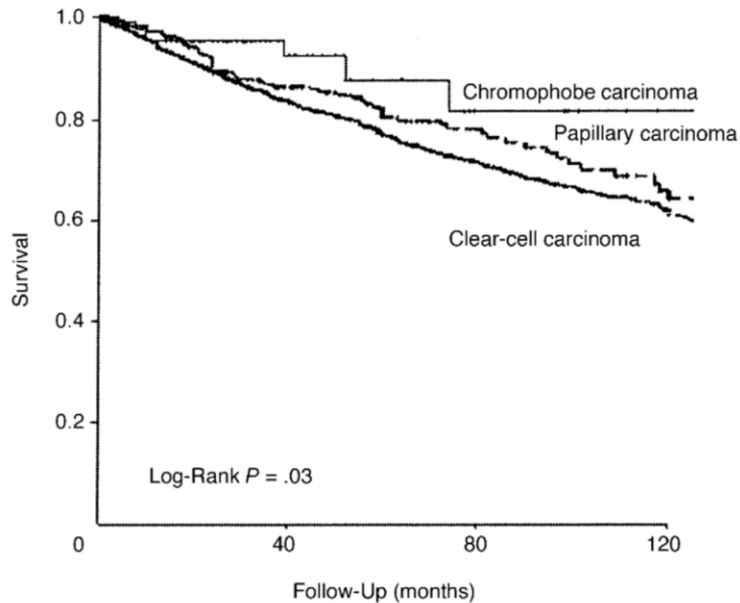
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Überblick der Nierenzellkarzinome (klar + *nicht*-klarzellige)

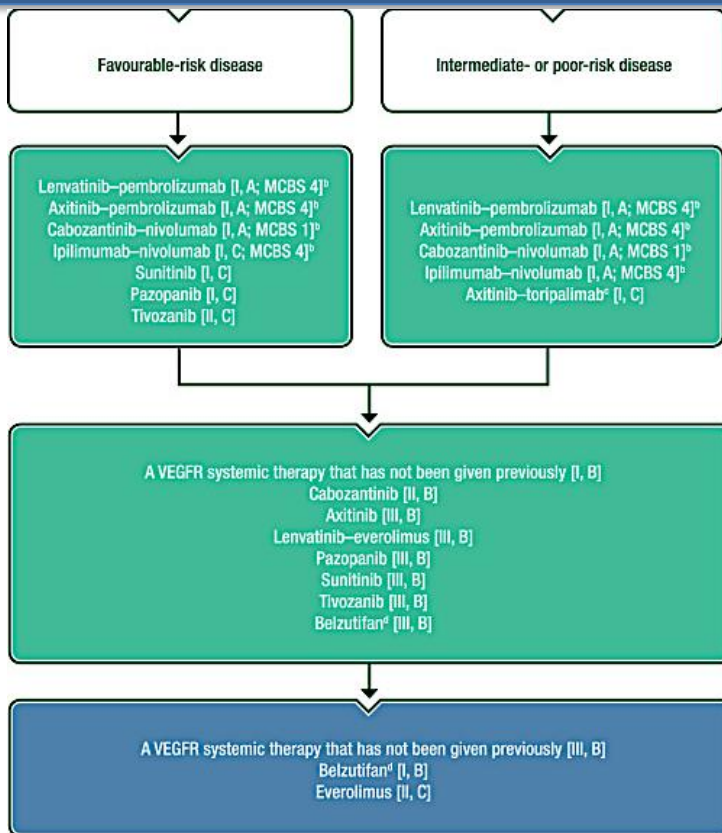
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Prognose – RCC (cc-/ ncc-RCC)

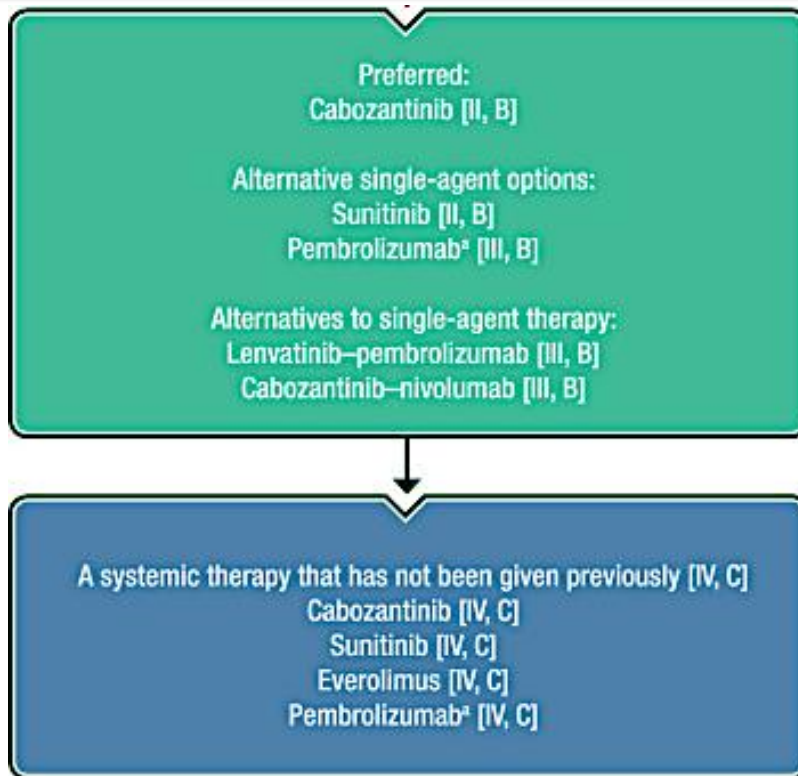


n=4063
50% T1-T2
50% T3-T4
25% metastatic

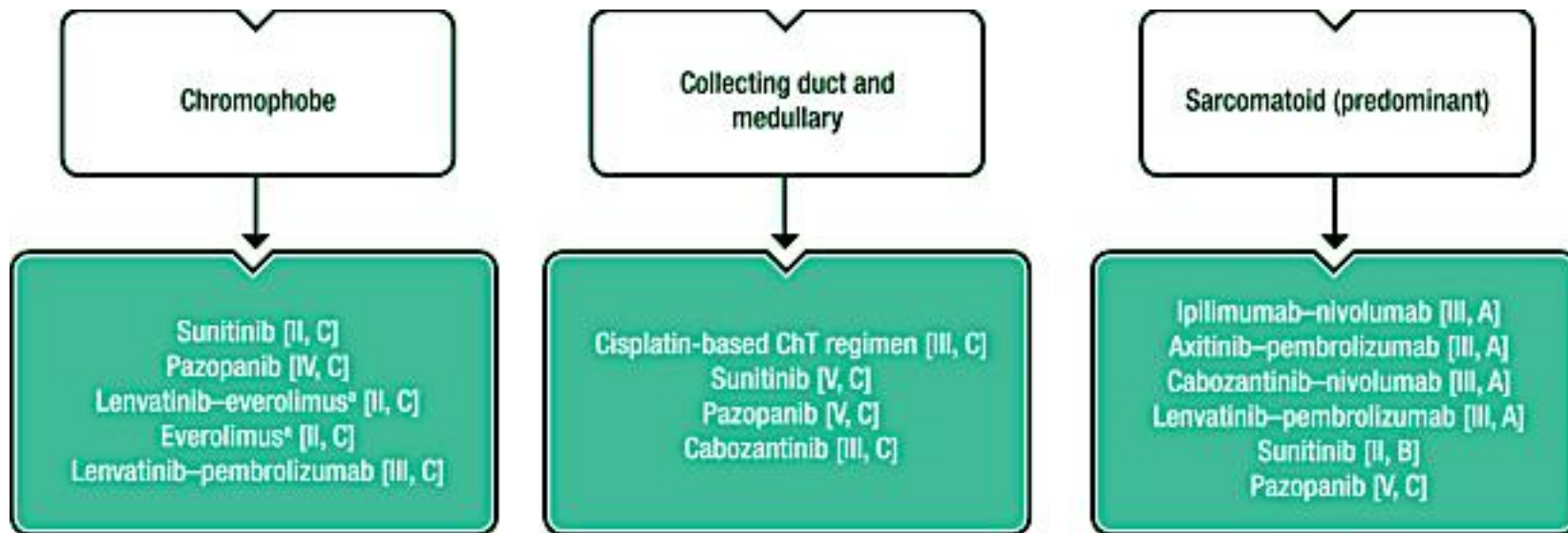
Therapieoptionen beim cc-RCC



Therapie der papillären RCC (pRCC)



Therapie der nicht-papillären nicht-klarzelligen RCC (np ncc RCC)



TKI als SOC für ncc-RCC

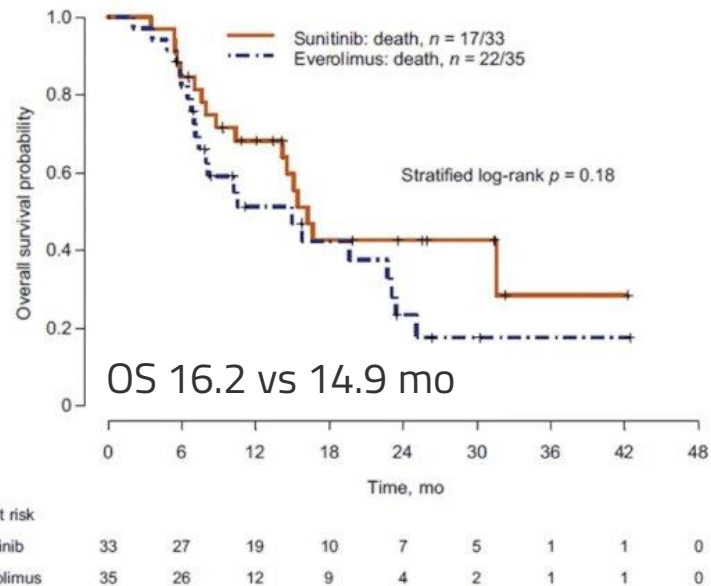
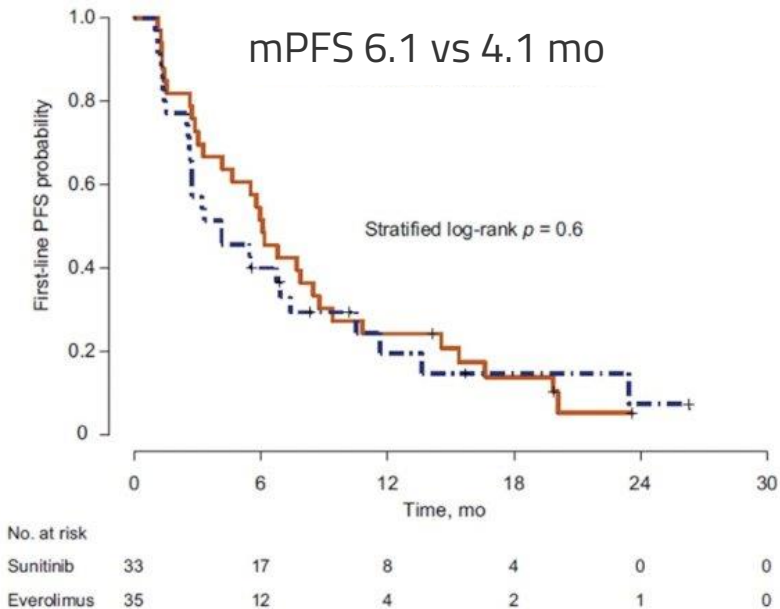
Sunitinib ⁵	61 pts.	13% ^a 11% ^b RR	6.6 mos ^a 5.5 mos ^b PFS	<ul style="list-style-type: none"> • Prospective analysis • Included both type I (n=15) and type II (n=46) papillary <p><i>Ravaud A et al Annal Oncol 2012,23 (Suppl 9) #707PD</i></p>
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Sunitinib als langjähriger Therapiestandard für ncc-RCC:

SUPAP¹ (n=61), ASPEN^{2*} (n=81), ESPN^{3*} (n=73) und RECORD-3^{4*} (n=66)

*Sun vs EVe

TKI für ncc-RCC



ORR 9% (Sun) versus 3% (Eve)

Therapie der metastasierten papillären RCC (pRCC)

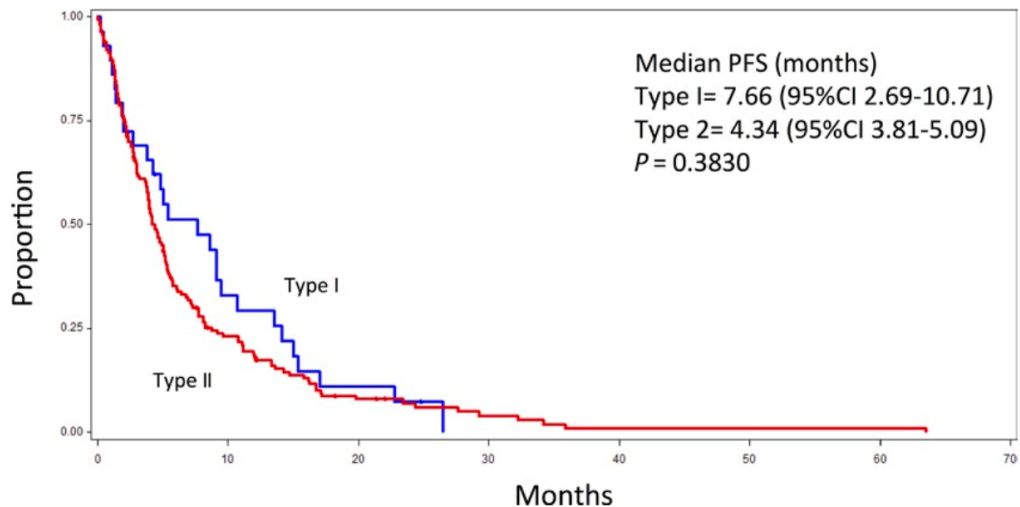


Figure 2. Kaplan–Meier curve depicting the progression-free survival of type I ($n = 30$) and type II ($n = 165$) metastatic papillary renal cell carcinoma patients treated with targeted therapy.

Therapie der metastasierten papillären RCC (pRCC)

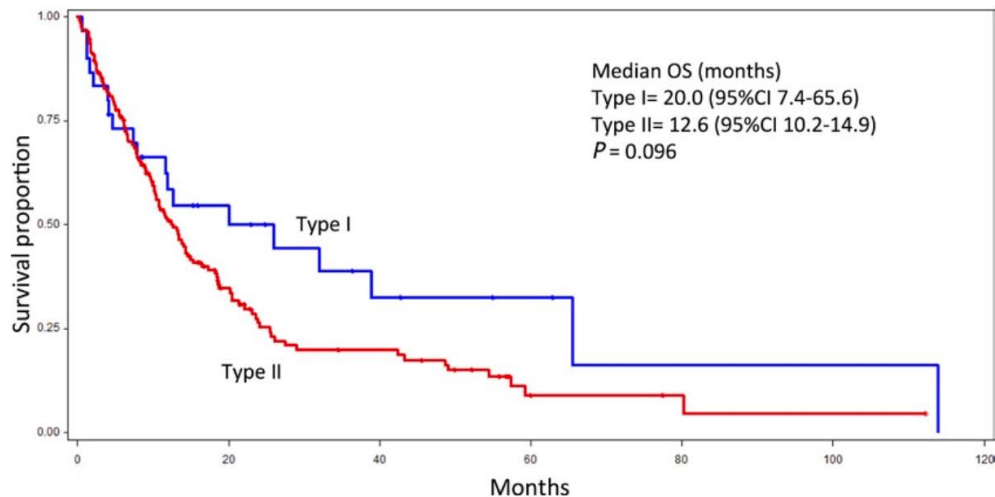
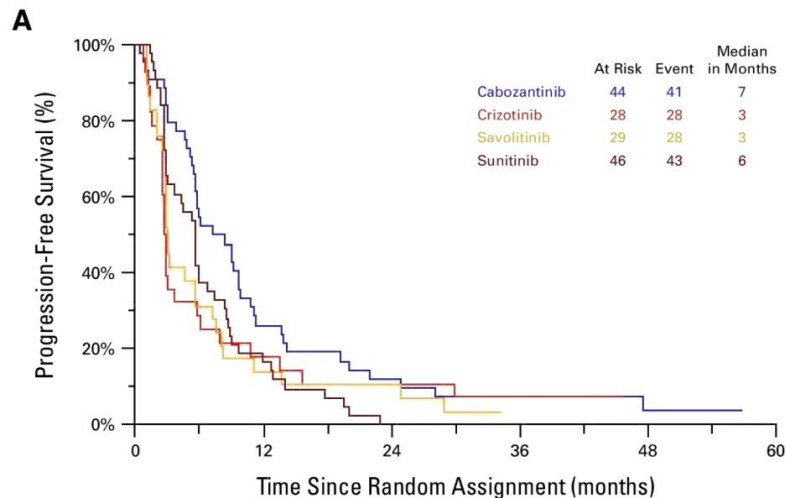
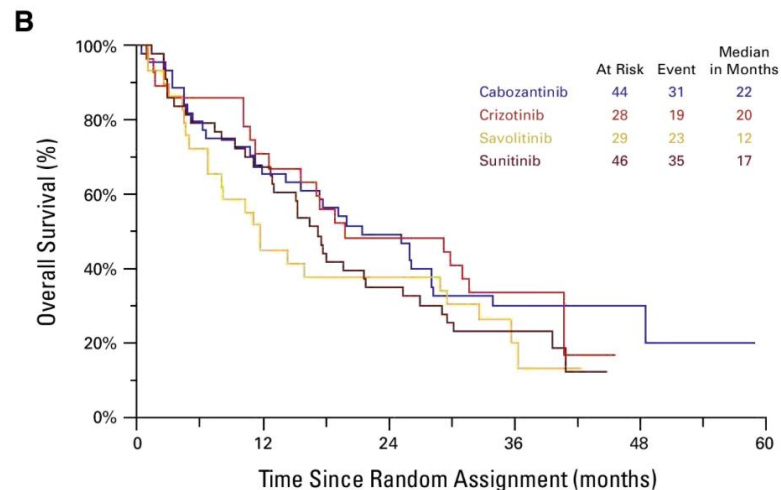


Figure 1. Kaplan–Meier curve depicting the overall survival of type I ($n = 30$) and type II ($n = 165$) metastatic papillary renal cell carcinoma patients treated with targeted therapy.

Cabozantinib für ncc-RCC



No. at risk:	0	12	24	36	48	60
Cabozantinib	44	11	5	3	1	0
Crizotinib	28	5	3	2	0	0
Savolitinib	29	4	3	0	0	0
Sunitinib	46	7	0	0	0	0



No. at risk:	0	12	24	36	48	60
Cabozantinib	44	28	21	9	3	0
Crizotinib	28	19	13	5	0	0
Savolitinib	29	13	11	3	0	0
Sunitinib	46	29	15	5	0	0

ORR 23% (Cabo) vs. 4% (Sun) $p=0.01$

Real World Outcome ccRCC vs. pRCC

Metastatic Papillary Renal Cell Carcinoma Outcomes

J. Connor Wells et al.

Table 2. Outcomes in response to targeted therapy for ccRCC (clear cell renal cell carcinoma) and papillary renal cell carcinoma (pRCC).

	ccRCC (n = 5008)	pRCC (n = 466)	P-value
OS (months; 95% CI)	21.9 (20.9–22.9)	13.8 (12.5–16.1)	0.0001
PFS (months; 95% CI)	7.3 (6.9–7.7)	4.7 (4.1–5.2)	0.0001
RR to 1st Line TT	n (%)	n (%)	<0.0001
Complete response	110/4389 (2.5%)	3/391 (0.8%)	
Partial response	1234/4389 (28.1%)	37/391 (9.5%)	
Stable disease	1950/4389 (44.4%)	217/391 (55.5%)	
Progressive disease	1095/4389 (24.9%)	134/391 (34.3%)	
OS by IMDC prognostic group (months; 95% CI)			
Favorable	41.9 (38.0–44.8) (n = 783)	34.1 (18.6–49.1) (n = 43)	0.40
Intermediate	24.0 (22.8–25.1) (n = 2165)	17.0 (13.4–18.7) (n = 200)	0.0001
Poor	7.1 (6.5–8.0) (n = 971)	6.0 (4.1–7.9) (n = 116)	0.03

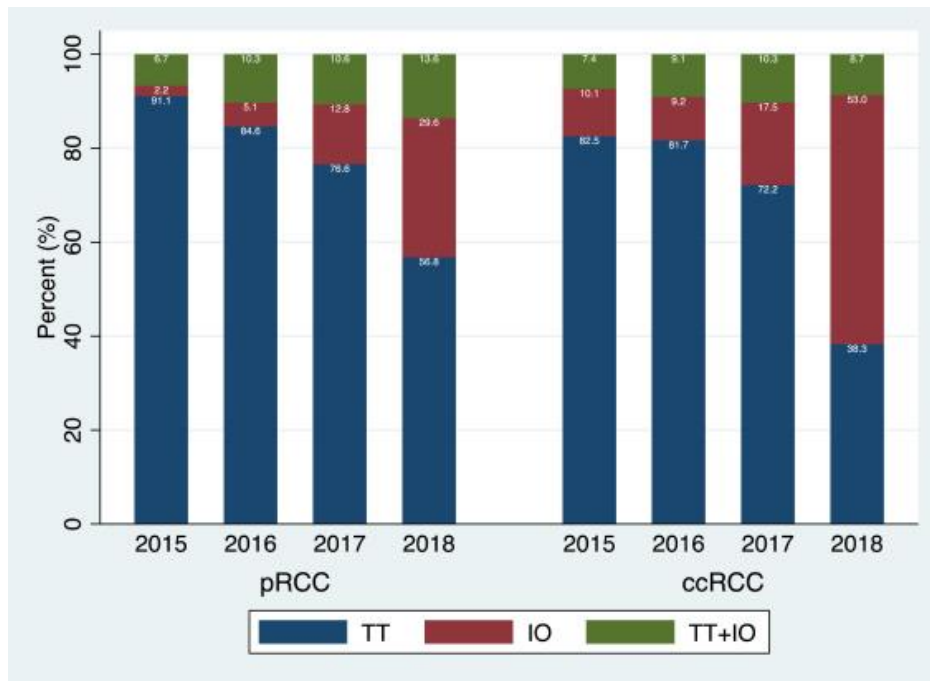
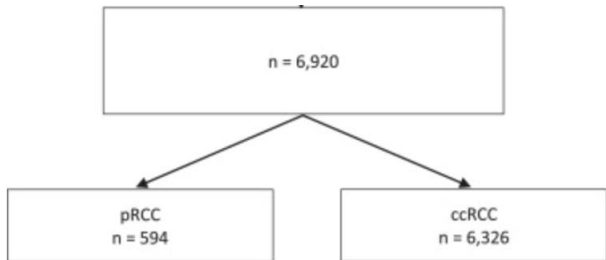
OS, overall survival; PFS, progression-free survival; RR, response rate; TT, targeted therapy; IMDC, International mRCC database consortium; CI, Confidence interval.

Therapie der ncc-RCC mit TKI

“If all you have is a hammer, everything looks like a nail.”

Abraham Maslow

„Real World“ Therapie des pRCC vs. ccRCC



Real World Outcome pRCC vs. ccRCC

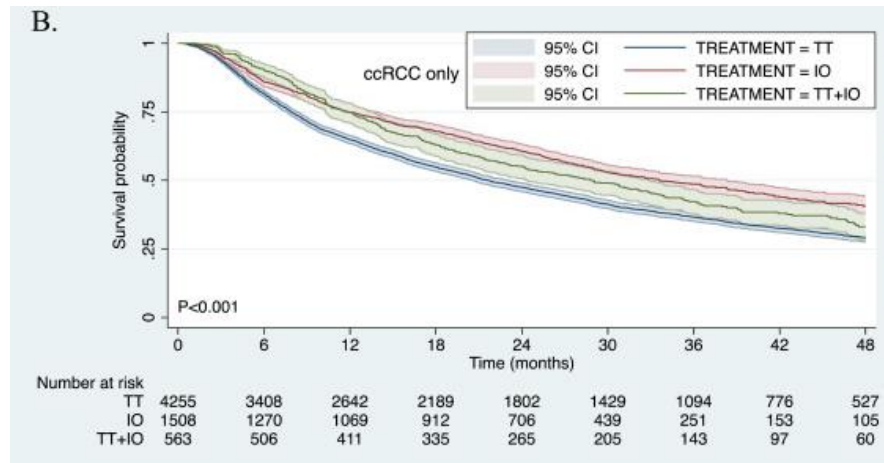
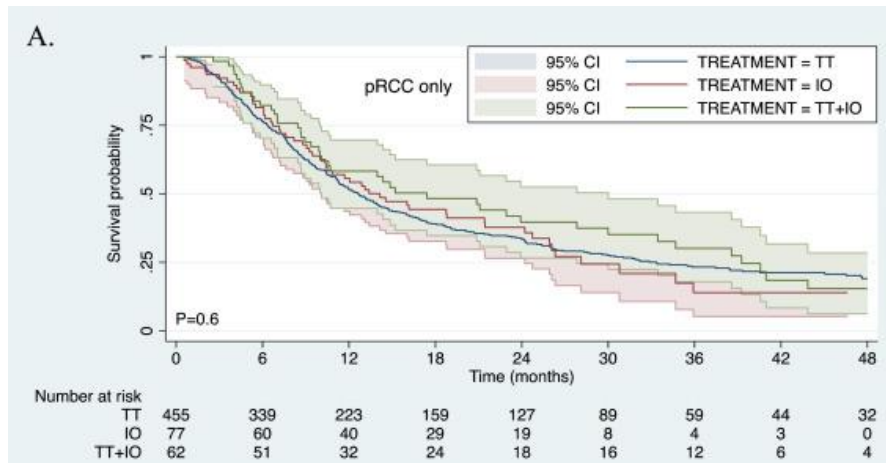
Table 2. Multivariable Cox regression for overall survival grouped by histology.

			aHR (95% CI) ^a	P value
pRCC	Treatment	TT	1.00 (reference)	
		IO	1.03 (0.75–1.42)	0.9
		TT+IO	0.90 (0.63–1.28)	0.6
	Cytoreductive nephrectomy	No	1.00 (reference)	
		Yes	0.59 (0.46–0.77)	<0.001
ccRCC	Treatment	TT	1.00 (reference)	
		IO	0.75 (0.68–0.82)	<0.001
		TT+IO	0.82 (0.72–0.93)	0.002
	Cytoreductive nephrectomy	No	1.00 (reference)	
		Yes	0.54 (0.50–0.58)	<0.001

ccRCC = clear-cell renal cell carcinoma; CI = confidence interval; HR = hazard ratio;

IO = immunotherapy; pRCC = papillary renal cell carcinoma; TT = targeted therapy.

Real World Outcome pRCC vs. ccRCC



SUNNIFORECAST: IPI – Nivo für ncc-RCC



Prospective Randomised Phase-II Trial of Ipilimumab/Nivolumab versus Standard of Care in *non-clear* Renal Cell Cancer

Results of the SUNNIFORECAST Trial

Lothar Bergmann, Frankfurt, Germany

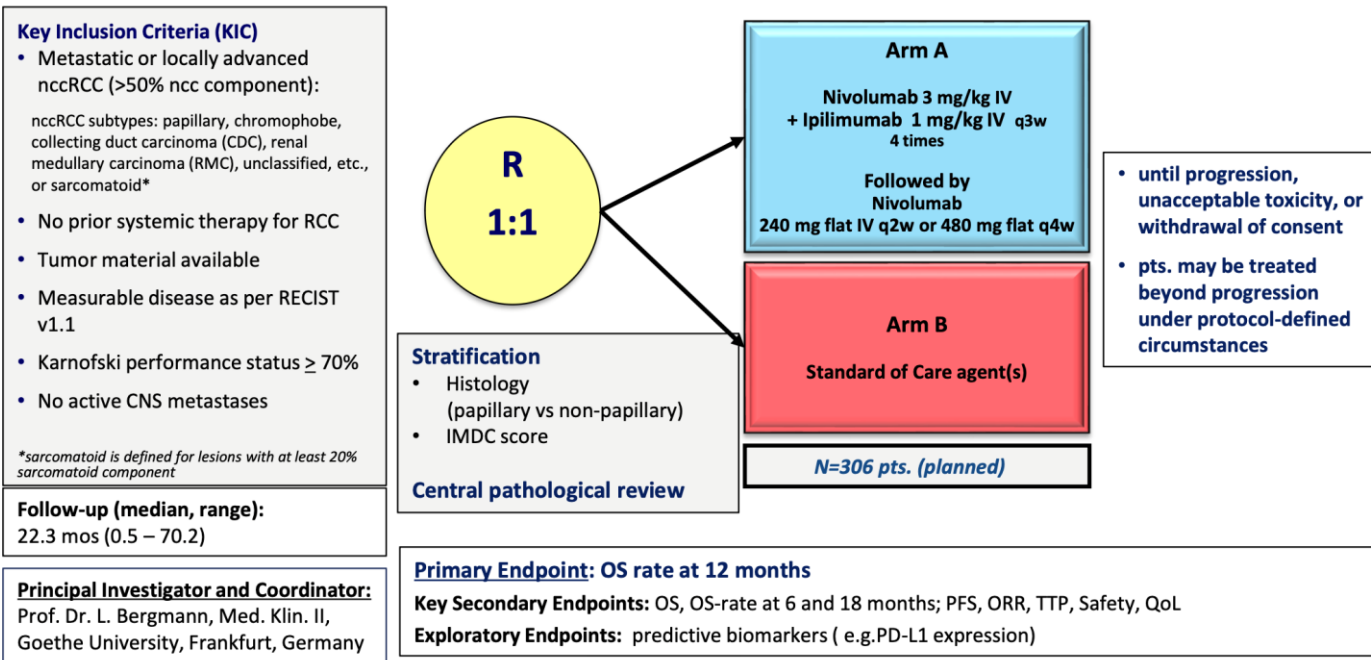
Marit Ahrens, Laurence Albiges, Marine Gross-Goupil, Ektarini Boleti, Gwenaelle Gravis, Aude Flechon, Marc-Oliver Grimm, Jens Bedke, Philippe Barthelemy, Daniel Castellano, Begona Mellado, Philipp Ivanyi, Anne Flörcken, Cristina Suarez, Pablo Maroto, Viktor Grünwald, Iris Burkholder, Arndt Hartmann, John Haanen



SUNNIFORECAST: IPI – Nivo für ncc-RCC

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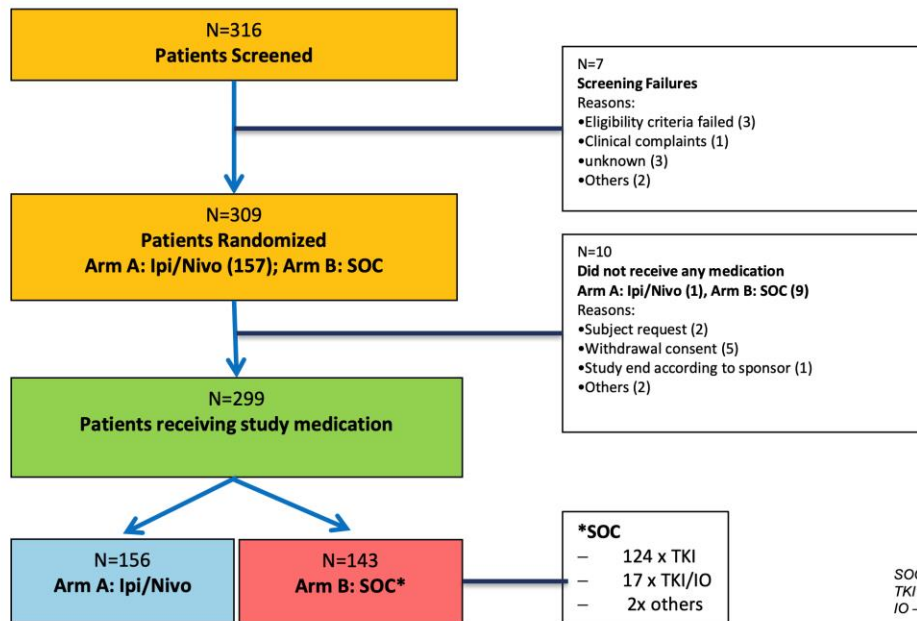
SUNNIFORECAST – Study design



SUNNIFORECAST: IPI – Nivo für ncc-RCC



Consort Diagram



SOC – standard of care
TKI – tyrosine kinase inhibitor
IO – immune checkpoint inhibitor

SUNNIFORECAST: IPI – Nivo für ncc-RCC



Histological subtypes

According to WHO classification 2022*

Subtypes of nccRCC (central pathological review)	Total N=309	Ipilimumab/Nivolumab N=157	Standard of Care (SOC) N=152	p-value
Papillary RCC	178 (57.6 %)	89 (56.7%)	89 (58.6%)	p=0.17
Chromophobe RCC	60 (19.4 %)	28 (17.8%)	32 (21.2%)	
Renal medullary carcinoma	3 (1.0 %)	0 (0.0%)	3 (2.0%)	
Translocation RCC (TFE, TEFEB)	17 (5.5%)	12 (7.6%)	5 (3.3%)	
Tubulocystic RCC	3 (1.0 %)	3 (1.9%)	0 (0.0%)	
Mucinous tubular and spindle cell carcinoma	1 (0.3 %)	1 (0.6%)	0 (0.0%)	
Sarcomatoid	14 (4.5 %)	8 (5.1%)	6 (3.9%)	
Ductus Bellini carcinoma	3 (1.0%)	0 (0.0%)	3 (2.0%)	
Others	21 (6.7 %)	11 (7.0%)	10 (6.6%)	

* Moch H, Amin MB, Berney DM, et al. The 2022 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. Eur Urol. 2022 Nov;82(5):458-468.

SUNNIFORECAST: IPI – Nivo für ncc-RCC

BARCELONA 2024 

Patient characteristics

	Total (N=309)	Ipilimumab/ Nivolumab (N=157)	Standard of care (SOC) (N=152)	p-value
Age (median, range)	62.3 (18.8 - 86.2)	61.4 (18.8 - 81.8)	64 (19.4 - 86.2)	<i>p</i> =0.69
Sex no. (%)				<i>p</i> =0.83
male	219 (70.9)	112 (71.3)	107 (70.4)	
female	90 (29.1)	45 (28.7)	45 (29.6)	
Karnofsky score no. (%)				<i>p</i> =0.20
100	162 (52.4)	80 (51.0)	82 (53.9)	
90	76 (24.6)	34 (21.7)	42 (27.6)	
80	51 (16.5)	27 (17.2)	24 (15.8)	
70	16 (5.2)	12 (7.6)	4 (2.6)	
≤60	1 (0.3)	1 (0.6)		
missing	3 (1.0)	3 (1.9)		
IMDC prognostic risk score no. (%)				<i>p</i> =0.87
favorable: 0	74 (23.9)	39 (24.8)	35 (23.0)	
intermediate: 1-2	160 (51.8)	79 (50.3)	81 (53.3)	
poor: 3-6	75 (24.3)	39 (24.8)	36 (23.7)	
Prior therapies no. (%)				<i>p</i> =0.33
any surgery	237 (76.7)	124 (79.0)	113 (74.3)	
nephrectomy/partial nephrectomy	213 (68.9)	109 (69.4)	104 (68.4)	
any radiotherapy	29 (9.4)	14 (8.9)	15 (9.9)	
Most common sites of metastases no. (%)				<i>p</i> =0.01
lung	299 (22.0)	161 (23.9)	138 (20.1)	
liver	137 (10.1)	55 (8.2)	82 (12.0)	
bone	68 (5.1)	32 (4.8)	37 (5.4)	
lymph node	418 (30.8)	210 (31.1)	208 (30.4)	
others	276 (20.3)	139 (20.6)	137 (20.0)	
Time since initial diagnosis mos (median, range)	30.9 (1.3 - 1416.6)	33.6 (1.9 - 1416.6)	25.4 (1.3 - 1097.7)	<i>p</i> =0.30



SUNNIFORECAST: IPI – Nivo für ncc-RCC

Overall Response

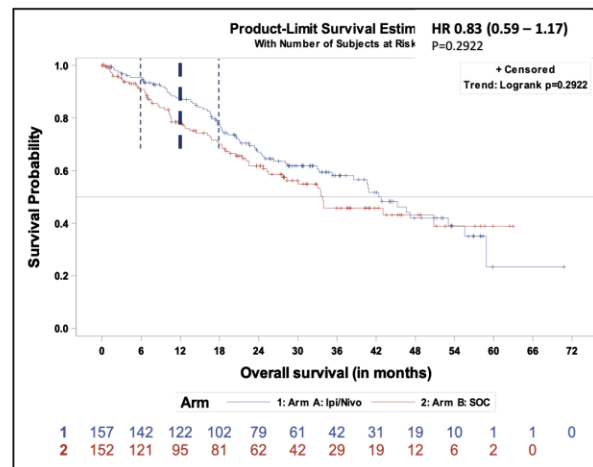
Histology	Treatment	CR	PR	ORR	SD	PD
all nccRCC (N=247*)	Nivo/Ipi	10 (8.0%)	31 (24.8%)	41 (32.8%)	41 (32.8%)	43 (34.4%)
	SOC	2 (1.6%)	22 (18.0%)	124 (19.6%)	75 (61.5%)	23 (18.9%)
	<i>p=0.001</i>					

SUNNIFORECAST: IPI – Nivo für ncc-RCC



Overall survival rate and OS

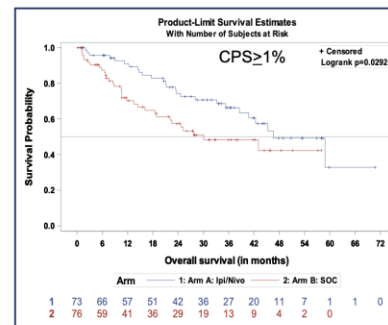
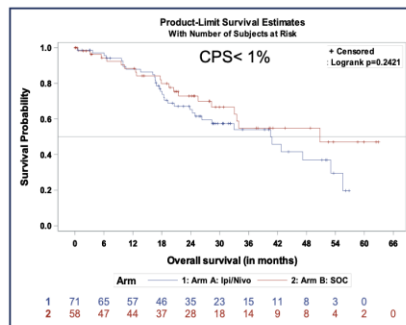
	Total N=309	Ipilimumab/ Nivolumab N=157	Standard of Care (SOC) N=152	p-value
OS rate at 12 mos (95%-CI)	82.5% (77.46% - 86.46%)	86.9% (80.24% - 91.46%)	76.8% (68.62% - 83.09%)	p=0.0141
OS rate at 6 mos (95%-CI)	92.8% (95.27% - 2.83%)	94.7% (89.72% - 97.32%)	90.0% (83.75% - 93.98%)	p=0.067
OS rate at 18 mos (95%-CI)	73.4% (67.67% - 78.28%)	76.6% (68.69% - 82.79%)	69.1% (60.25% - 76.34%)	p=0.084
OS mos (median, 95%-CI)	40.8 (33.2 - 47.21)	42.4 (35.24 - 55.54)	33.9 (25.52 - *)	p=0.292



Median follow-up: 24.3 mos (0.5 - 70.2)

SUNNIFORECAST: IPI – Nivo für ncc-RCC

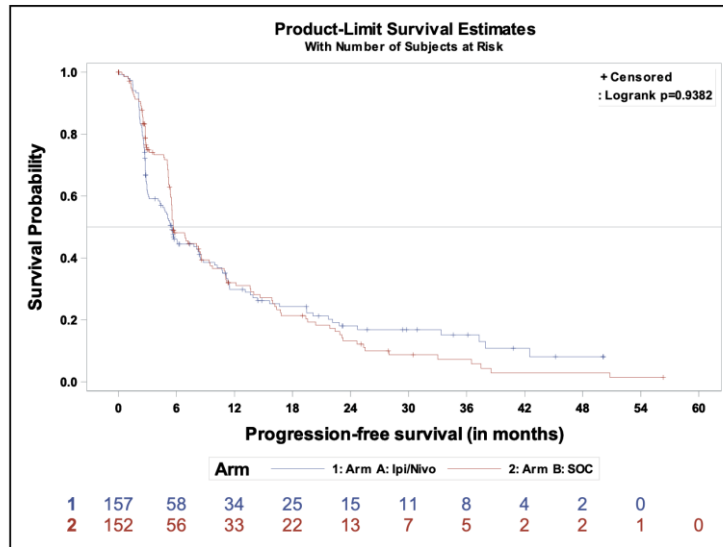
PDL1 and OS



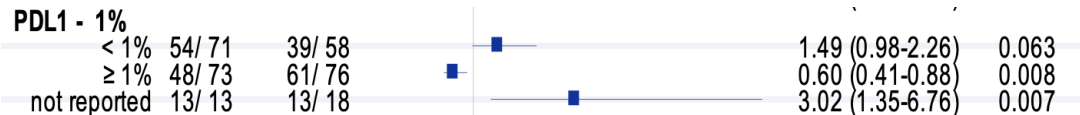
Baseline PDL1 CPS (OS – Univariate Cox regression)	NIVO/IPI	SOC	HR	p-value
< 1%	33/ 71	19/ 58	1.40 (0.79-2.46)	p=0.244
≥ 1%	26/ 73	32/ 76	0.56 (0.33-0.95)	p=0.031
not reported	7/ 13	11/ 18	1.07 (0.41-2.81)	p=0.884

SUNNIFORECAST: IPI – Nivo für ncc-RCC

PFS



	IPI/Nivo	SOC
PFS mos.	5.52	5.65
(median, range)	4.30 – 8.23	5.49 – 8.46
HR 0.99 (0.76-1.18)		



SUNNIFORECAST: IPI – Nivo für ncc-RCC



Most frequent AEs

	IPI/Nivo		SOC		P-value
	All AEs (%)	Grad 3/4 (%)	All AEs (%)	Grad 3/4 (%)	
Skin reactions	48.4	3.1	74.2	2.1	<0.001
Fatigue	42.9	3.8	63.7	8.4	<0.001
Diarrhea	21.0	3.2	45.1	4.9	<0.001
Nausea	20.6	1.3	31.5	1.4	0.008
Mucositis	3.2	0.0	36.4	4.2	<0.001
Hypothyroidism	12.8	0.6	21.7	0.0	0.046
Hypertension	5.7	0.6	38.5	16.8	<0.001
Dysgeusia	3.8	0.0	28.7	0.0	<0.001
Pruritus	25.0	0.0	2.8	1.4	<0.001
Anorexia	7.7	0.0	20.3	0.7	0.002
ALT	14.1	5.7	12.6	0.0	0.736

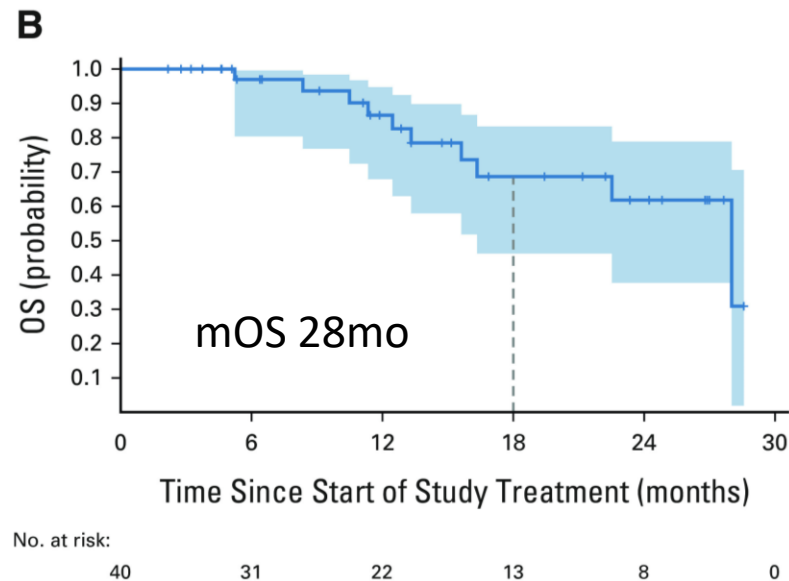
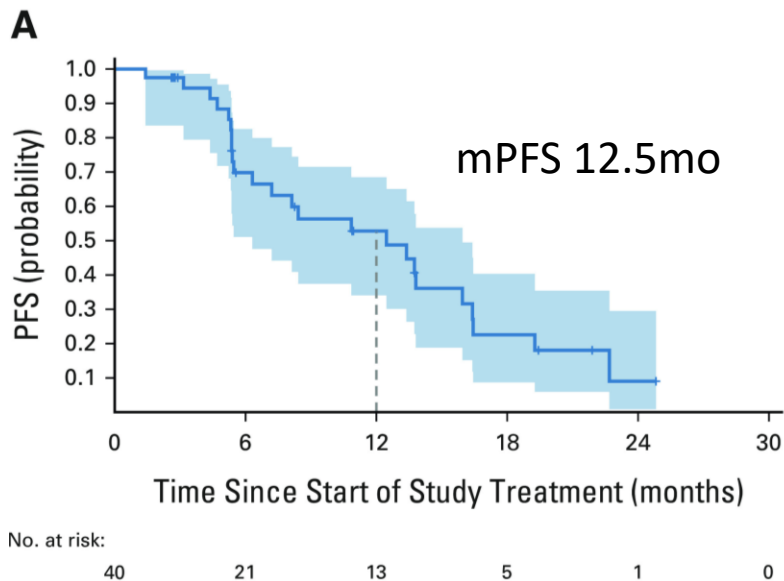
«Therapieansprechen» ncc-/cc-RCC

Studie	Sunniforecast		CM-214	KN426	CLEAR ^{i/p*}
Regime	IPI+NIVO	SOC	IPI+NIVO	PEM+AXI	PEM + LEN
ORR %	33	20	42	59	72
CR %	8	1.6	10.5	5.8	14
PR %	25	18	31	54	59
SD %	33	62	30	25	17
PD %	34	18	22	11	6
NE %	2	6	7	4	5

i/p intermediate/poor

Nichtklarzellige RCC Histologien Klarzellige RCC Histologien

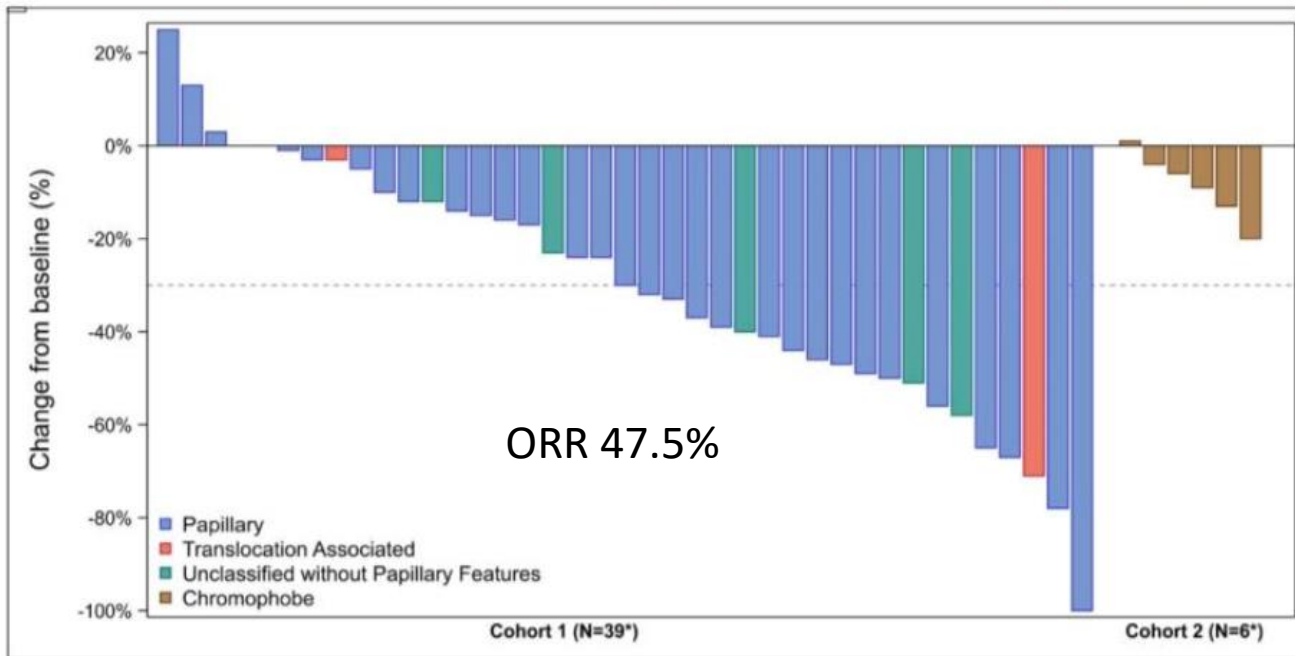
TKI + I/O für ncc-RCC: Cabozantinib + Nivolumab



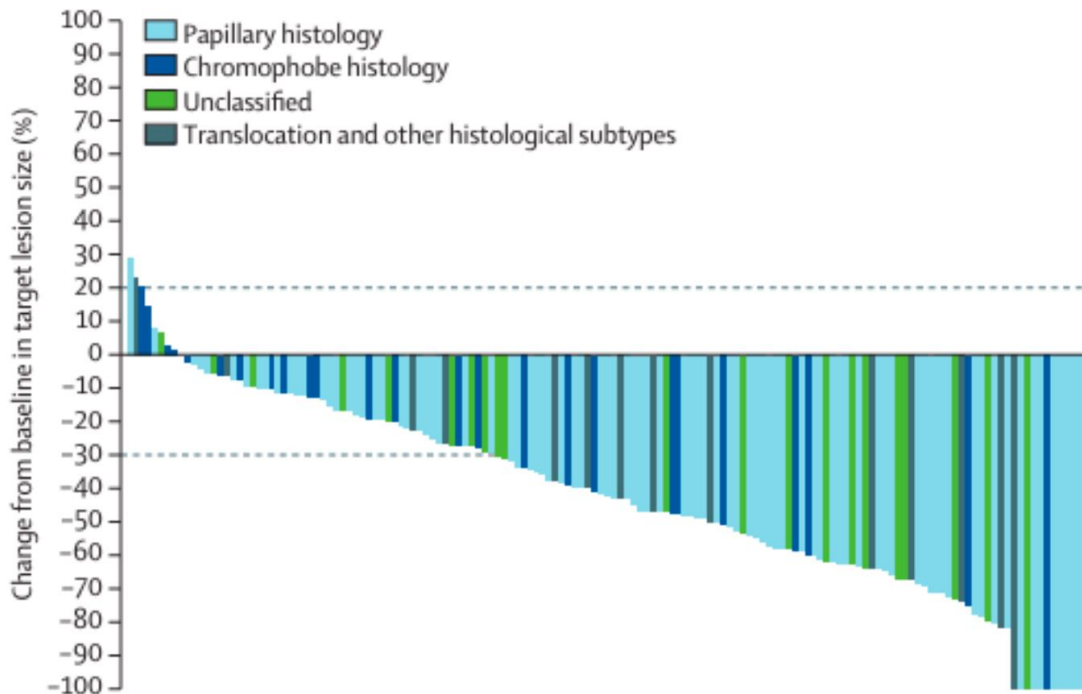
ORR 47.5%

TKI + I/O ncc-RCC: Cabozantinib + Nivolumab

Maximum Change in Target Lesions by Histology

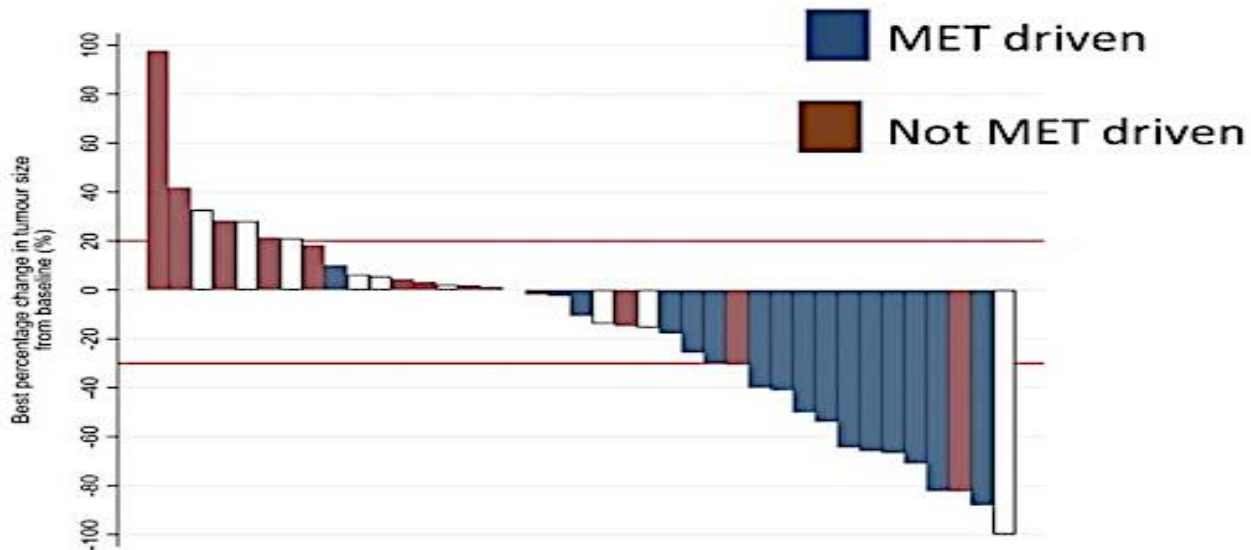


TKI + I/O für ncc-RCC: Len+Pembro



Papillary
ORR 53%

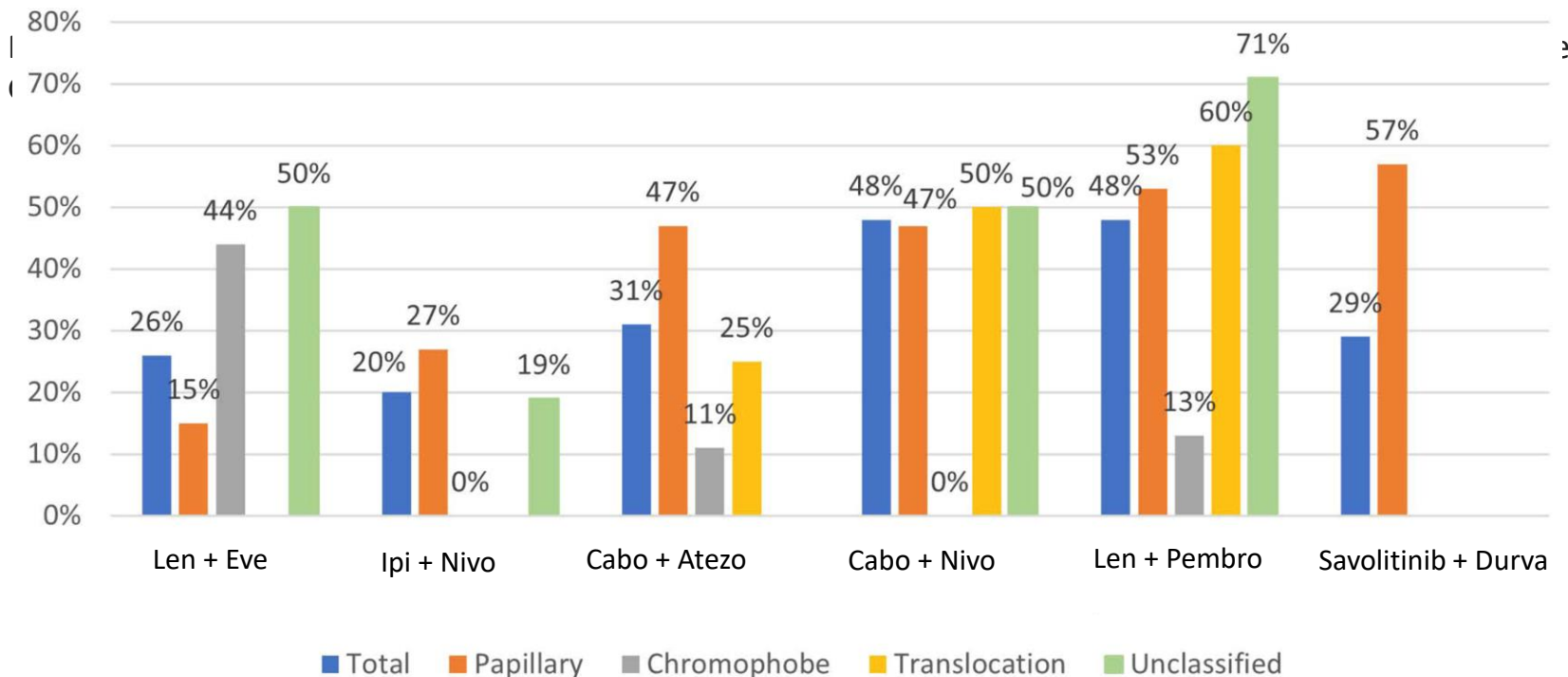
MET getriebene pRCC - Savolitinib-Durvalumab



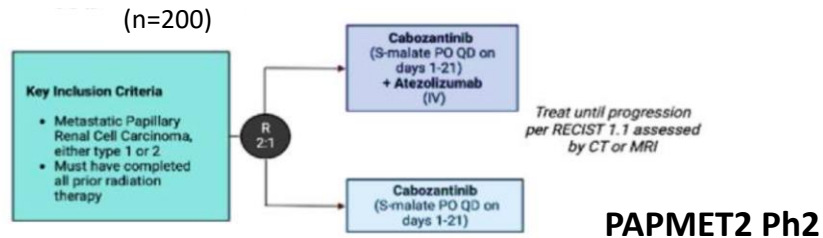
ORR 53%

MET driven papillary RCC n=17

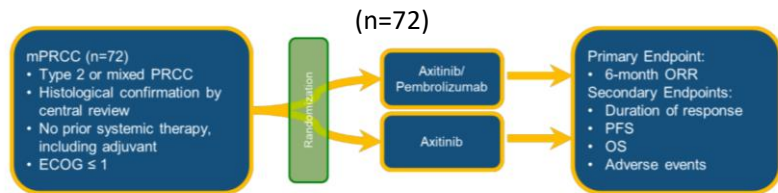
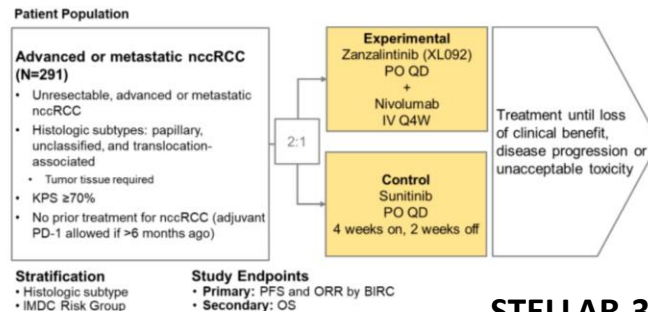
Kombinationstherapien: Variante Histologien ORR%



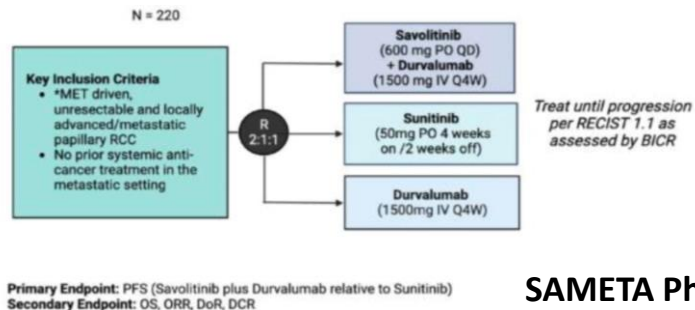
Laufende Studien zum ncc-RCC



Primary Endpoint: Compare PFS with metastatic papillary renal cell carcinoma to cabozantinib S-malate with atezolizumab versus cabozantinib alone
Secondary Endpoint: OS, RECIST, ORR, quantitative and qualitative adverse events in each arm

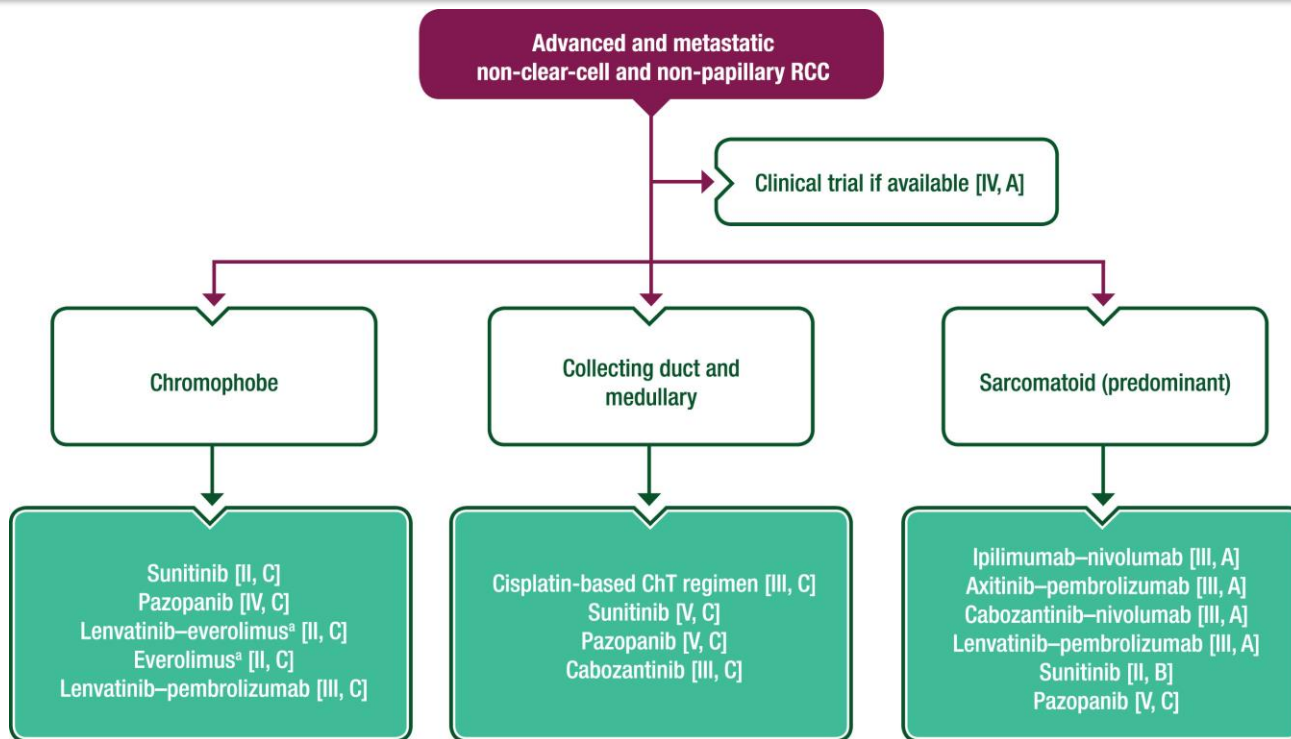


PAXIPEM Ph2



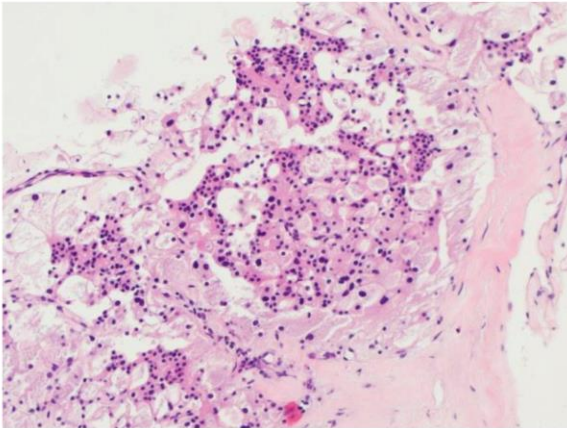
CAN-I (NCT04413123): (n=60) alle ncc-RCC > Cabo-Ipi-Nivo 1.EP: ORR (Dez 2025)

Therapie der übrigen nicht-klarzelligen RCC



Sarkomatoide RCCs – eine eigene Entität?

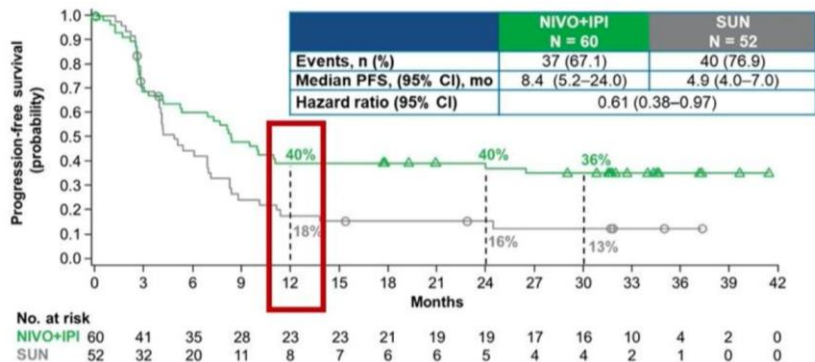
initial biopsy:
chromophobes RCC



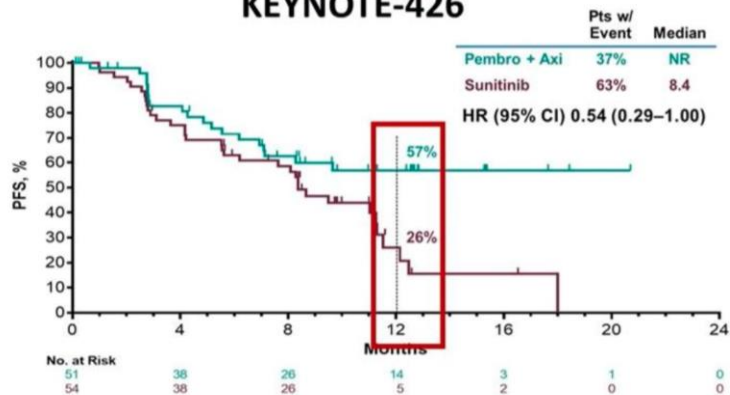
Courtesy of Prof. L. Bubendorf, Pathology Dept. of University Hospital Basel

Sarkomatoide RCCs → I/O + I/O oder TKI

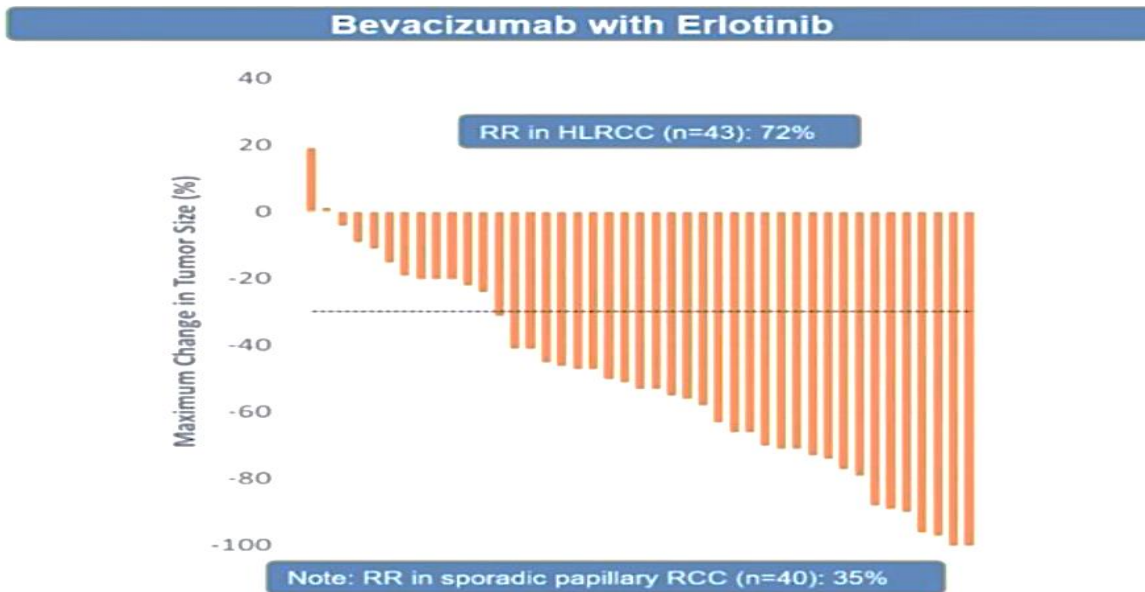
CheckMate 214



KEYNOTE-426



Hereditäre Leiomyomatose und RCC (HLRCC)



und die übrigen ncc-RCC

- Sammelrohrkarzinome (Ductus-Bellini-Karzinom) und SMARCB1-deficient RCC
Therapie?: Platinbasierte Chemotherapie (RR:26%) oder Cabozantinib (RR:35%)
- FH-deficient RCC sind rar, aggressiv und oft mit Hereditäre Lyomyomatose und RCC (HLRCC) assoziiert
Therapieoption Erlotinib + Bev
- ALK-rearranged RCC sind rar, aber einen Versuch mit einem ALK-Inhibitor wert (80%PR, 20% SD)
- Medulläre RCC: Gemcitabine+Doxorubicin oder Erlotinib + Bevacizumab RR: \approx 20%

Therapeutische Realität beim nicht-klarzelligen Nierenzellkarzinom

- Prognose der ncc-RCC bleibt schlechter als die der cc-RCC
- Erweiterung der Therapieoptionen ncc-RCC (I/O+I/O !)
- Beste Evidenz für pRCC
- Therapiesequenzen bleiben unklar
- In Zukunft eher tumoragnostische Ansätze für ncc-RCC

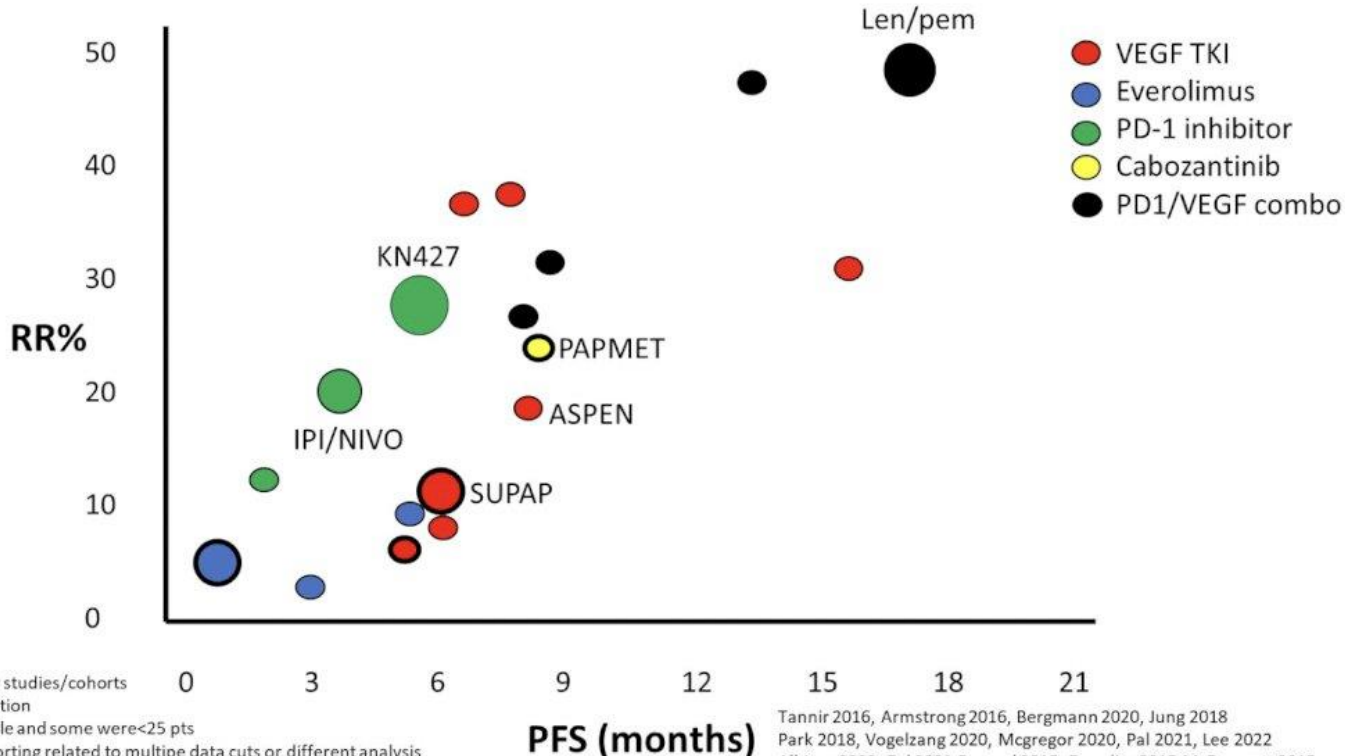
Vielen Dank !

frank.stenner@usb.ch



Backup slides

Effektivität von Kombinationstherapien bei ncc-RCC



Black ring around circle = papillary only studies/cohorts
 Cross trial comparison-handle with caution
 Not all trials had all data points available and some were <25 pts
 Some studies had inconsistency in reporting related to multiple data cuts or different analysis

Tannir 2016, Armstrong 2016, Bergmann 2020, Jung 2018
 Park 2018, Vogelzang 2020, McGregor 2020, Pal 2021, Lee 2022
 Albiges 2023, Pal 2021 Ravaud 2015, Escudier 2015 McDermott 2015

Effektivität von Kombinationstherapien bei ncc-RCC

