Non-Clear Cell Updates in RCC

MaTOS GU

3/22/2025

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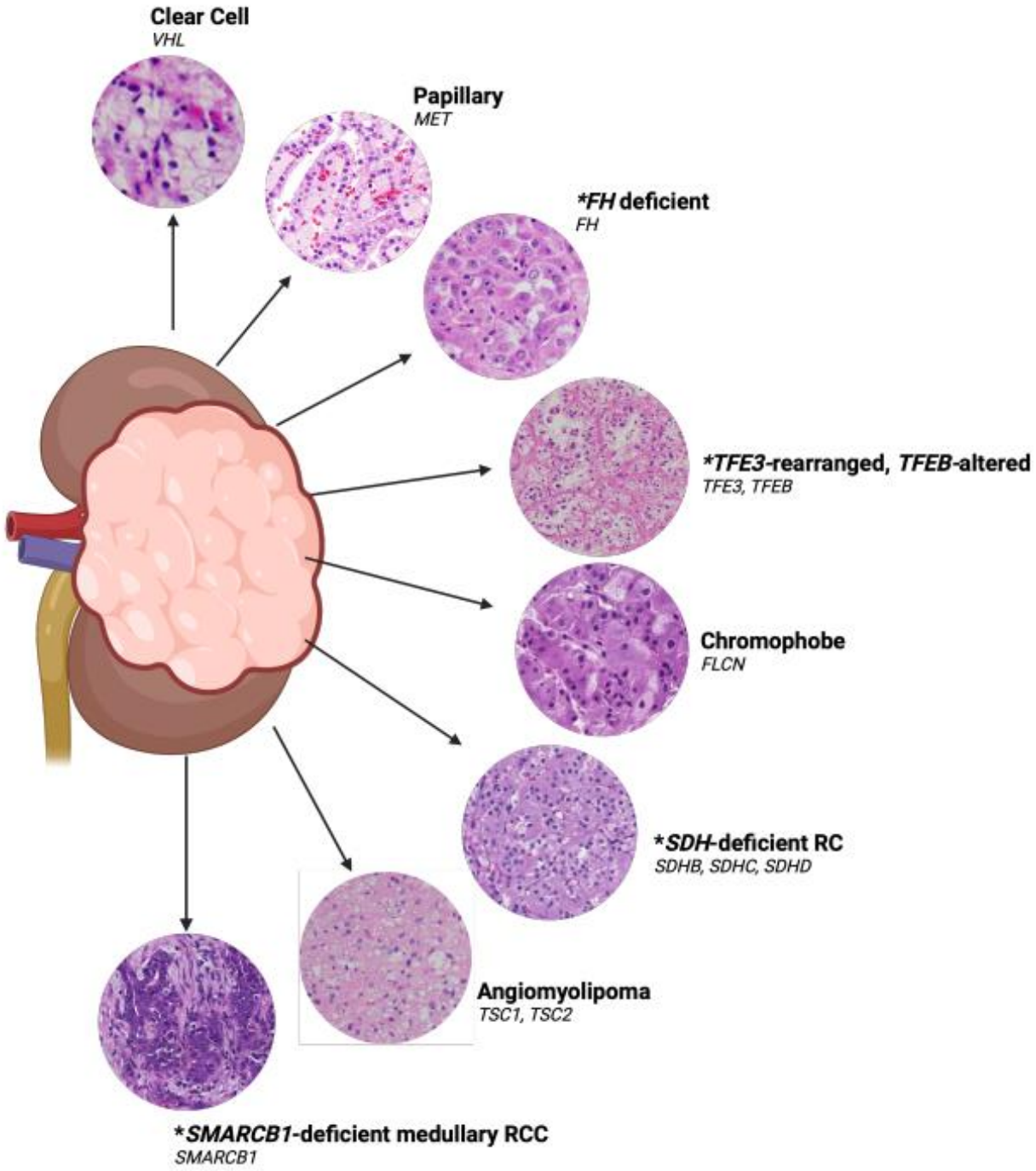


Kidney cancer consists of multiple histologic subtypes

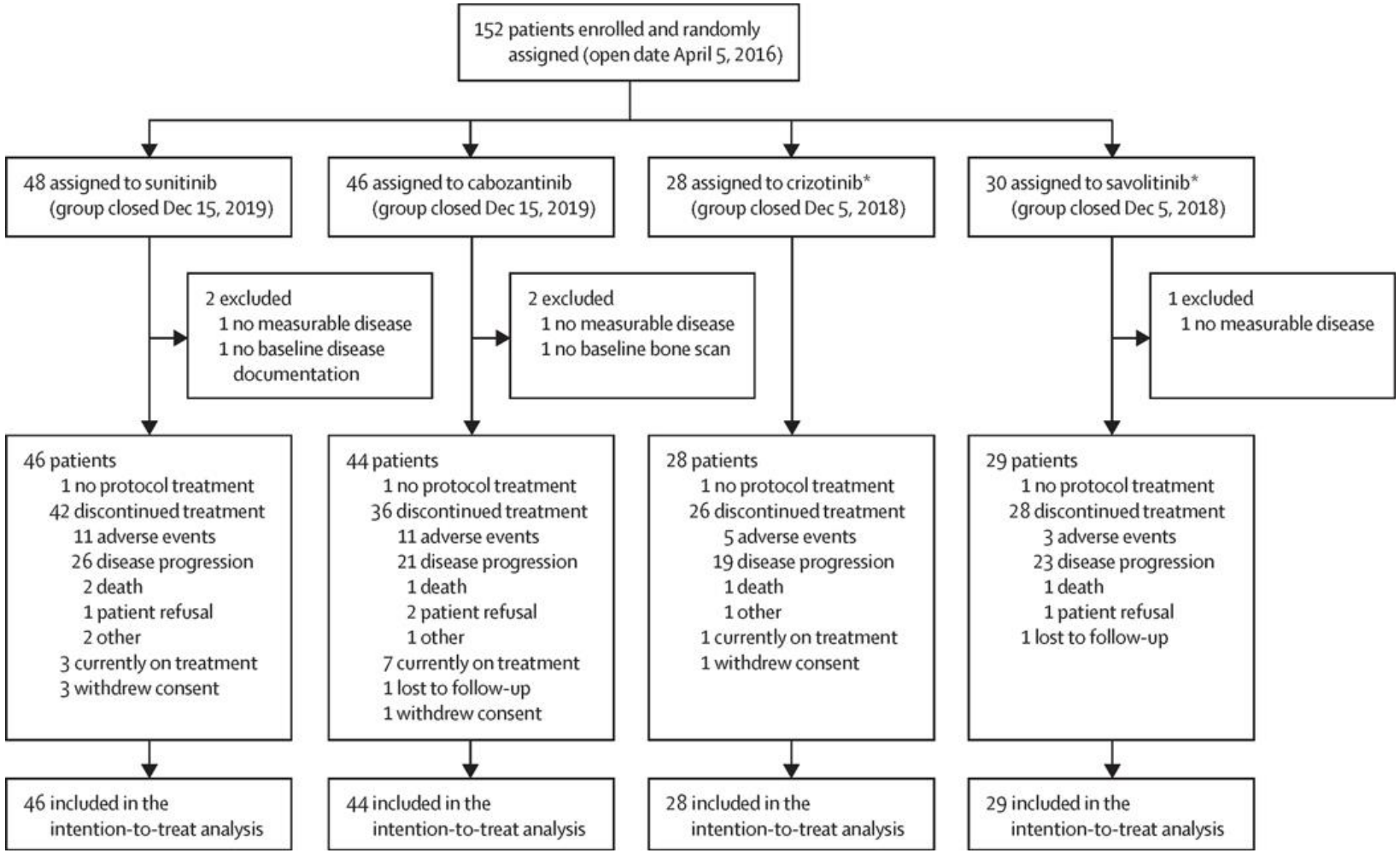
- Clear cell renal cell carcinoma is the most common type of kidney cancer and the most well studied
- Characteristic mutations are found across subtypes
- FH deficient, TFE-rearranged SDH-deficient and SMARCB1 deficient are molecularly defined

Courtesy of Tracy Rose

PAPMET examined TKI monotherapy for pRCC

Phase II, open label trial

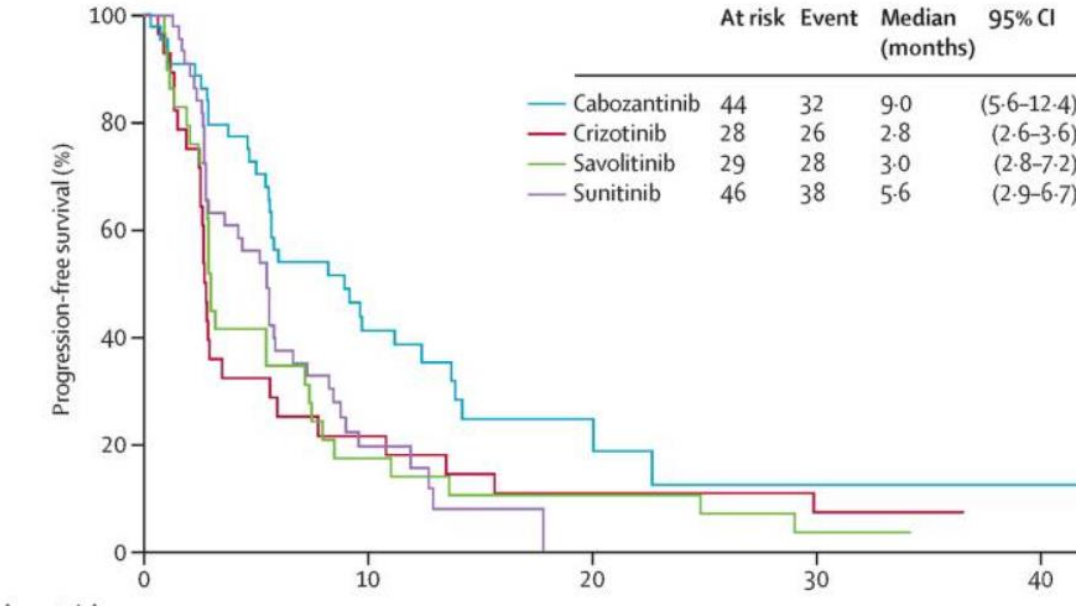
Primary Endpoint: PFS



Pal et al, Lancet 2021. PMID 33592176

Cabozantinib had improved PFS and ORR

- Savolitinib and crizotinib arms halted at futility analysis
- Cabozantinib demonstrated:
  - longer PFS (9.0 months *v* 5.6 months; HR, 0.60, *P* value: .019)
  - higher ORR (23% *v* 4%)



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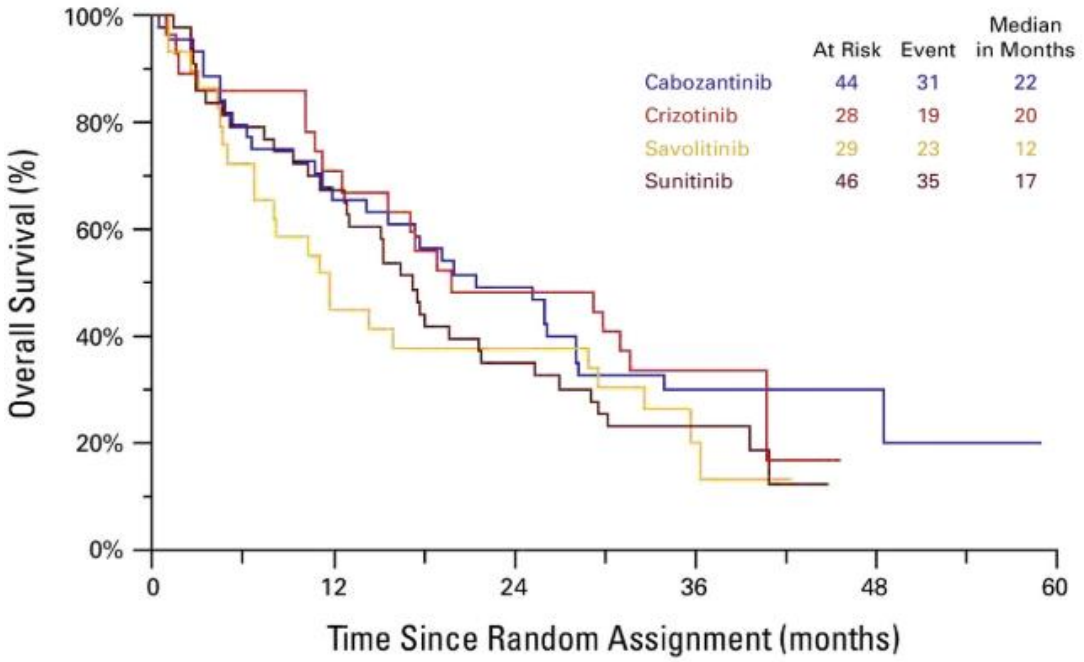
  - higher ORR (23% *v* 4%)
- Median OS not significantly different between cabozantinib and sunitinib
  - 21.5 months v 17.3 months



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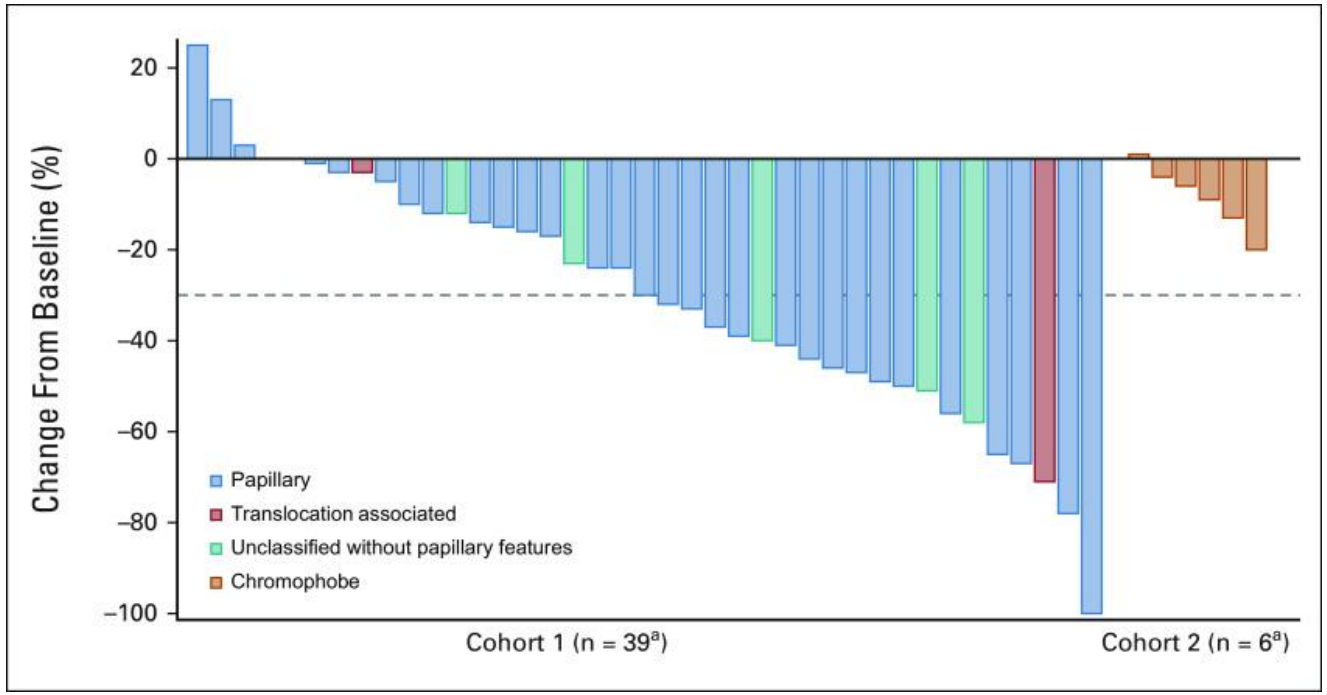
Immunotherapy has modest activity in nccRCC

- Nivolumab monotherapy was investigated in CheckMate 374 and HCRN GU 160-260 Cohort B
  - CM-374 – 44 patients: 24 pRCC, 7 chRCC, 8 unclassified, 5 other
    - 34% previously treated
    - ORR 13.6%
  - HCRN GU – 35 patients: 19 pRCC, 6 chRCC, 10 unclassified
    - ORR 14.3%
    - Trial included option to receive salvage ipi/nivo, only 17 patients did, with 1 PR
  - PD rate ~40% in both studies
- Pembrolizumab was studied in KEYNOTE-427
  - 165 patients, 118 pRCC, 21 chRCC, 26 unclassified
  - ORR 27% - 28.8% for papillary, 9.5% for chromophobe, and 30.8% for unclassified
  - 34% PD

McDermott et al, JCO 2021. PMID: 33529058
Vogelzang et al, Clin Genitourin Cancer 2020. PMID: 32718906
Atkins et al, J Immunother Cancer 2023. PMID 36948504

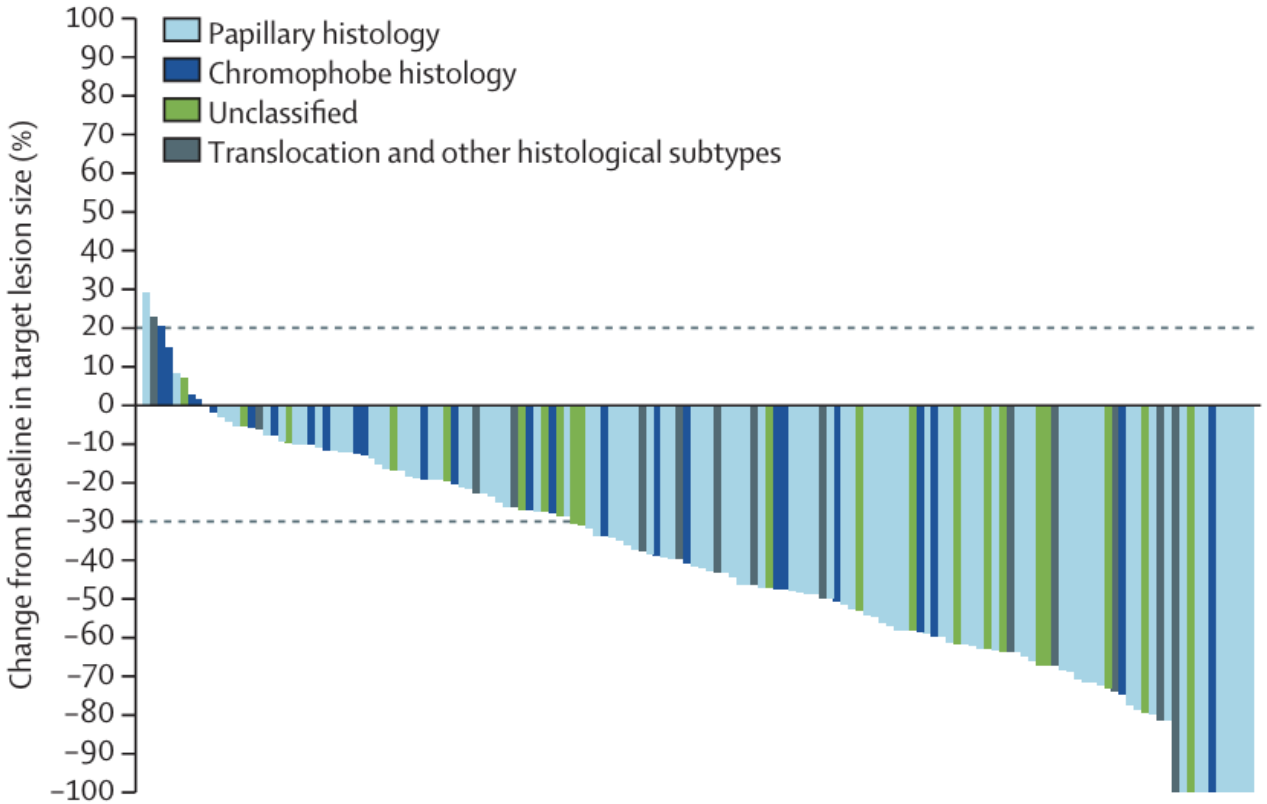
Nivolumab + Cabozantinib in nccRCC

- Phase 2 trials for patients with 0-1 prior treatments
- 47 patients enrolled
  - 32 pRCC
  - 6 unclassified
  - 2 translocation
  - 7 chromophobe (cohort 2)
- 34% prior treatment
- mPFS 12.5 months
- ORR 48%



Lee et al, JCO 2022. PMID 35298296

KEYNOTE-B61 – single arm trial of pembrolizumab + Lenvatinib in nccRCC



- 158 pts with non-ccRCC
  - 93 pRCC, 29 chRCc, 21 unclassified, 6 translocation
- ORR 49% (6% CR)
- mPFS 18 months
- 12 mo OS 82%

Albiges et al, Lancet Oncol 2023. PMID 37451291

SUNNIFORECAST – Study design

BARCELONA 2024 ESMO congress

Key Inclusion Criteria (KIC)

- Metastatic or locally advanced nccRCC (>50% ncc component):

  nccRCC subtypes: papillary, chromophobe, collecting duct carcinoma (CDC), renal medullary carcinoma (RMC), unclassified, etc., or sarcomatoid*
- No prior systemic therapy for RCC
- Tumor material available
- Measurable disease as per RECIST v1.1
- Karnofski performance status ≥ 70%
- No active CNS metastases

**sarcomatoid is defined for lesions with at least 20% sarcomatoid component*

Follow-up (median, range):
22.3 mos (0.5 – 70.2)

Principal Investigator and Coordinator:
Prof. Dr. L. Bergmann, Med. Klin. II, Goethe University, Frankfurt, Germany

R
1:1

Arm A

Nivolumab 3 mg/kg IV
+ Ipilimumab 1 mg/kg IV q3w
4 times

Followed by
Nivolumab
240 mg flat IV q2w or 480 mg flat q4w

Arm B

Standard of Care agent(s)

- until progression, unacceptable toxicity, or withdrawal of consent
- pts. may be treated beyond progression under protocol-defined circumstances

Stratification

- Histology (papillary vs non-papillary)
- IMDC score

Central pathological review

N=306 pts. (planned)

Primary Endpoint: OS rate at 12 months

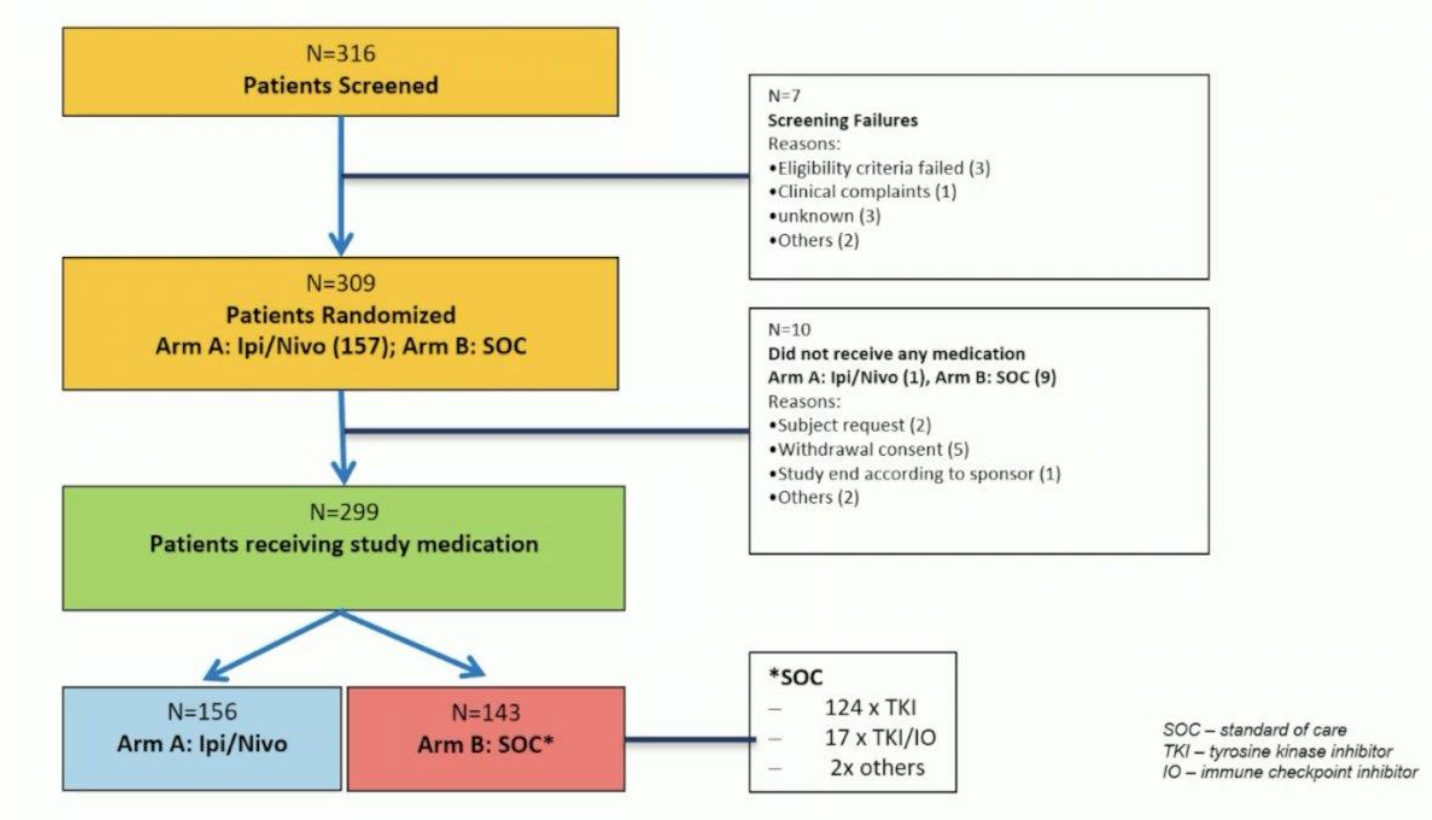
Key Secondary Endpoints: OS, OS-rate at 6 and 18 months; PFS, ORR, TTP, Safety, QoL

Exploratory Endpoints: predictive biomarkers (e.g.PD-L1 expression)

Bergmann et al, ESMO Congress 2024 abstract LBA75

SUNNIFORECAST trial of ipi/nivo

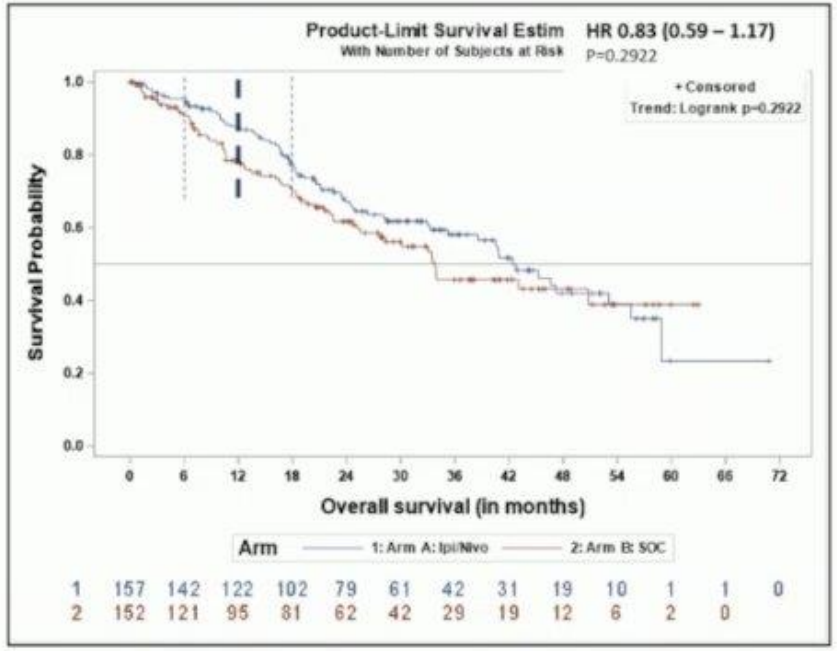
- 309 patients enrolled
  - 178 pRCC
  - 60 chRCC
  - 12 MIT
  - 9 collecting duct
  - 50 other



Bergmann et al, ESMO Congress 2024 abstract LBA75

Ipi/Nivo showed improved OS at 12 months

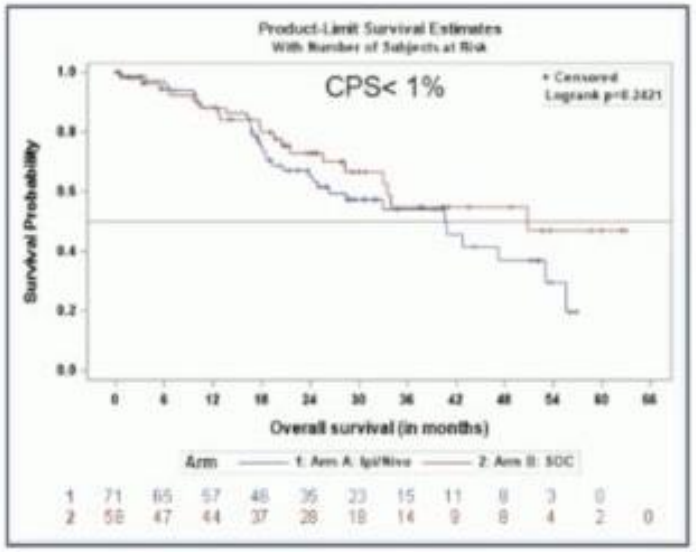
	Total N=309	Ipilimumab/ Nivolumab N=157	Standard of Care (SOC) N=152	*p-value*
OS rate at 12 mos (95%-CI)	**82.5%** (77.46% - 86.46%)	**86.9%** (80.24% - 91.46%)	**76.8%** (68.62% - 83.09%)	***p=0.0141***
OS rate at 6 mos (95%-CI)	92.8% (95.27% - 2.83%)	94.7% (89.72% - 97.32%)	90.0% (83.75% - 93.98%)	*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*

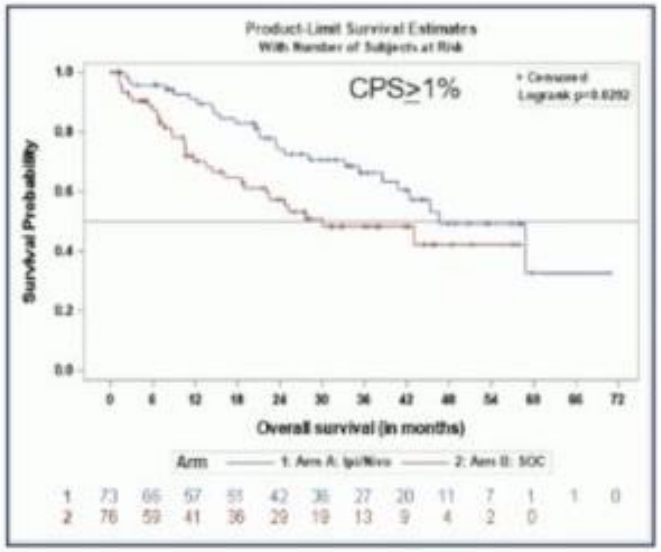


Median follow-up: 24.3 mos (0.5 -70.2)

Bergmann et al, ESMO Congress 2024 abstract LBA75

PD-L1 CPS is a biomarker of response to ipi/nivo





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*

Bergmann et al, ESMO Congress 2024 abstract LBA75

Response rate varies with histology

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%)
	p=0.001					
papillary (N=148)	Nivo/Ipi	7 (9.7%)	14 (19.4%)	21 (29.2%)	27 (37.5%)	24 (33.3%)
	SOC	2 (2.6%)	14 (18.4%)	16 (21.0%)	46 (60.5%)	14 (18.4%)
non-papillary (N=97)	Nivo/Ipi	3 (5.7%)	17 (32.1%)	20 (37.7%)	14 (18.4%)	19 (27.1%)
	SOC	0 (0.0%)	8 (18.2%)	8 (18.2%)	27 (61.4%)	9 (20.5%)
chromophobe (N=54)	Nivo/Ipi	0 (0.0%)	7 (25.9%)	7 (25.9%)	12 (44.4%)	8(29.6%)
	SOC	0 (0.0%)	3 (11.1%)	3 (11.1%)	21 (77.8%)	4 (14.8%)

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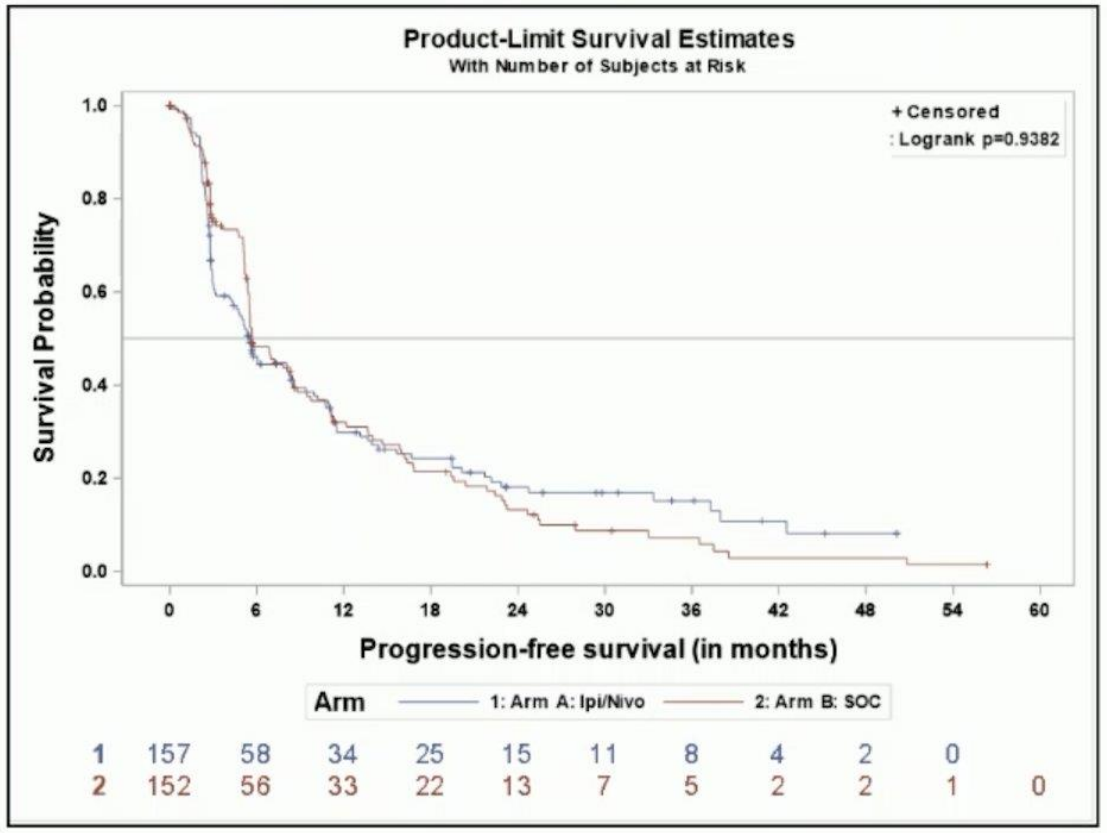
PFS is not significantly different for ipi/nivo or SOC in nccRCC



	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)	

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Multiple ICI based combinations can be considered in nccRCC

Trial/Treatment	ORR	Best response = PD	mPFS	mOS
Keynote-B61 (1L) Pembrolizumab + Lenvatinib (n=158)	49% ORR 6% CR	11%	18 months (63% at 12 mos)	NR (82% at 12 mos)
Lee et al (1 or 2L) Nivolumab + cabozantinib (n=40)	48% ORR	4%	13 months (51% at 12 mos)	28 mos (70% at 18 mos)
SUNNIFORECAST (1L) Ipilimumab + nivolumab (n= 156)	33% ORR	34%	5.5 months	42 mos (87% at 12 mos)
SUNNIFORECAST (1L) SOC (n= 143) (mostly TKI)	20% ORR	19%	5.7 months	34 mos (77% at 12 mos)

Albiges et al, Lancet Oncol 2023. PMID 37451291
Lee et al, JCO 2022. PMID 35298296
Bergmann et al, ESMO Congress 2024 abstract LBA75

Take Home Points

- nccRCC consists of multiple histologies that have variable responses to treatment
- ICI combination therapies have data showing benefit
- SUNNIFORECAST is a randomized trial that shows an OS benefit at 12 months for ipilimumab + nivolumab for nccRCC
- Randomized trials for this rarer subtype can be completed with collaboration