Berrak Hücre Dışı Böbrek Kanserinde Tedavi Seçenekleri

Dr. Deniz Tural
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi-Tıbbi Onkoloji

Ders Planı

- ❑ **WHO göre sınıflandırma**
- ❑ **Görülme sıklığı ve sağkalım sonuçları**
- ❑ **nccRCC sarkomatoid ve rabdoid diferansiasyon**
- ❑ **mTOR ve TKI etkinliği**
- ❑ **Histolojik alt tiplere göre tedavi seçeneği**
- ❑ **VEGF+TKI kombinasyonları**
- ❑ **İmmüne checkpoint inhibitörleri**
- ❑ **İmmüne checkpoint inhibitörleri+TKI/VEGF**
- ❑ **Devam eden çalışmalar**
- ❑ **Sonuç**

Berrak Hücre Dışı Böbrek Kanserinde(nccRCC) Sınıflandırma

Evolving Renal Tumor Classification

2016 Edition

Renal cell tumors
Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of low malignant potential
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Collecting duct carcinoma
Renal medullary carcinoma
Mucinous tubular and spindle cell carcinoma
MiTF family translocation renal cell carcinomas
Hereditary leiomyomatosis and renal cell carcinoma-associated RCC
Tubulocystic renal cell carcinoma
Clear cell papillary renal cell carcinoma
Succinate dehydrogenase-deficient renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Oncocytoma

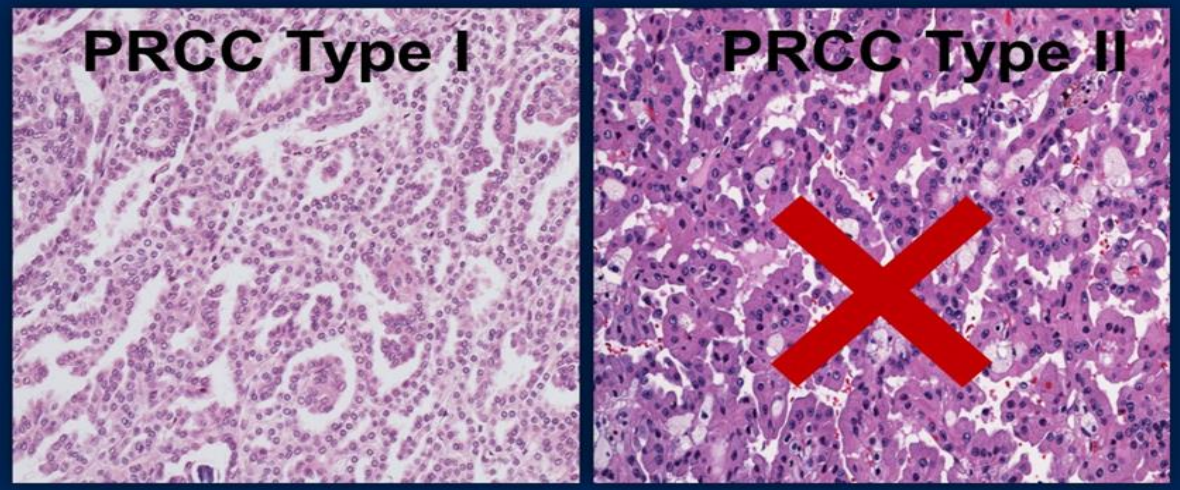
2022 Edition

Renal cell tumors
Clear cell renal tumours
Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of low malignant potential
Papillary renal tumours
Papillary adenoma
Papillary renal cell carcinoma
Oncocytic and chromophobe renal tumours
Oncocytoma of the kidney
Chromophobe renal cell carcinoma
Other oncocytic tumours of the kidney
Collecting duct tumours
Collecting duct carcinoma
Other renal tumours
Clear cell papillary renal cell tumour
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Eosinophilic solid and cystic renal cell carcinoma
Renal cell carcinoma NOS
Molecularly defined renal carcinomas
TFE3-rearranged renal cell carcinomas
TFEB-altered renal cell carcinomas
ELOC (formerly *TCEB1*)-mutated renal cell carcinoma
Fumarate hydratase-deficient renal cell carcinoma
Succinate dehydrogenase-deficient renal cell carcinoma
ALK-rearranged renal cell carcinomas
SMARCB1-deficient renal medullary carcinoma

Berrak Hücre Dışı Böbrek Kanserinde(nccRCC) Sınıflandırma

Organizational and Nomenclature changes in 2022 WHO Classification

2022 Edition
Clear cell renal tumours
Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of low malignant potential
Papillary renal tumours
Papillary adenoma
Papillary renal cell carcinoma



Subclassification into type 1 and type 2 PRCC no longer recommended

Network TCGAR, et al., NEJM 2016

nccRCC Sınıflandırma

Evolving Renal Tumor Classification

Nomenclature changes

Original name	2022 WHO Terminology
PRCC subtyping Type I & Type II	Type I
Clear cell papillary RCC	Clear cell papillary renal tumor
MiT family translocation RCC	TFE3-rearranged RCC TFEB- altered RCC
Renal medullary carcinoma	SMARCB1 (INI1)- deficient renal medullary carcinoma
HLRCC	Fumarate hydratase (FH)-deficient RCC

Newly recognized entities

Novel entities
Eosinophilic solid and cystic (ESC) RCC
Low grade oncocytic tumor (LOT)
Eosinophilic vacuolated tumor (EVT)
ELOC (TCEB1)- mutated RCC
Anaplastic lymphoma kinase (ALK)-rearranged RCC
Hybrid oncocytic tumors (syndrome) vs. Oncocytic renal neoplasm, NOS (sporadic)

nccRCC ve Herediter sendromlar

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Hereditary Renal Cell Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

HEREDITARY RCC SYNDROMES OVERVIEW

Syndrome/Gene	Common Histologies	Inheritance Pattern Major Clinical Manifestations	Other Specialists Involved in Screening
von Hippel-Lindau (VHL)/ *VHL* gene	Clear cell	• Autosomal dominant • See Table 2	• Neurosurgery • Ophthalmology • Audiology • Endocrinology • Endocrine surgery
Hereditary papillary renal carcinoma (HPRC)/*MET* gene	Type 1 papillary	• Autosomal dominant • Multifocal, bilateral renal cell tumors	• Nephrology
Birt-Hogg-Dubé syndrome (BHDS)/*FLCN* gene[1,2]	Chromophobe, hybrid oncocytic tumors, papillary RCC	• Autosomal dominant • Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, and spontaneous pneumothorax	• Pulmonology • Dermatology
Tuberous sclerosis complex (TSC)/*TSC1*, *TSC2* genes	Angiomyolipoma, clear cell	• Autosomal dominant • See Table 1	• Neurology • Dermatology
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)/*FH* gene	HLRCC or FH-associated RCC/ type 2 papillary	• Autosomal dominant • Leiomyomas of skin and uterus, unilateral, solitary, and aggressive renal cell tumors. PET-positive adrenal adenomas	• Gynecology • Dermatology
BAP1 tumor predisposition syndrome (TPDS)/*BAP1* gene[3,4]	Clear cell, chromophobe	• Autosomal dominant • Melanoma (uveal and cutaneous), kidney cancer, mesothelioma	• Dermatology • Ophthalmology • Thoracic oncology
Hereditary paraganglioma/ pheochromocytoma (PGL/ PCC) syndrome/*SDHA/B/ C/D* genes	Clear cell (not usually *SDHB*), chromophobe, papillary type 2, renal oncocytoma, oncocytic neoplasm	• Autosomal dominant • Head and neck PGL and adrenal or extra-adrenal PCCs, gastrointestinal stromal tumors (GISTs)	• Endocrine • Endocrine surgery

See GENE-1

[1] Schmidt LS, Nickerson ML, Warren MB, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. Am J Hum Genet 2005;76:1023-1033.
[2] Sattler EC, Steinlein OK. Birt-Hogg-Dubé Syndrome. 2006 Feb 27 [Updated 2020 Jan 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle;1993-2020.
[3] Peña-Llopis S, Vega-Rubín-de-Celis S, Liao A. BAP1 loss defines a new class of renal cell carcinoma. Nat Genet 2012;44:751-759.
[4] Hakimi AA, Ostrovnaya I, Reva B. Adverse outcomes in clear cell renal cell carcinoma with mutations of 3p21 epigenetic regulators BAP1 and SETD2: a report by MSKCC and the KIRC TCGA Research Network. Clin Cancer Res 2013;19:3259-3267.

nccRCC %5 oranında herediter görülür

Lopez-Beltran at al, Eur. Urol.2006

Berrak Hücre Dışı Böbrek Kanseri(nccRCC) Heterojene Bir Grup

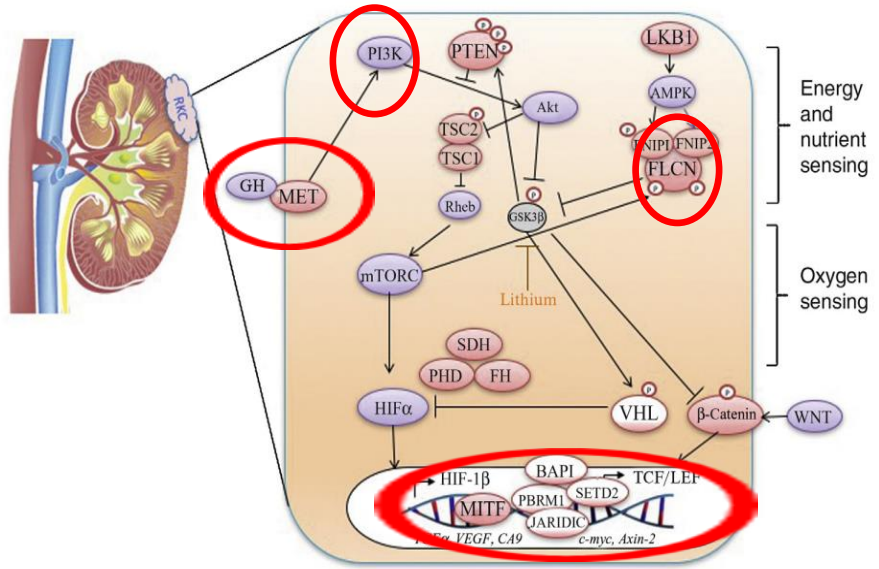
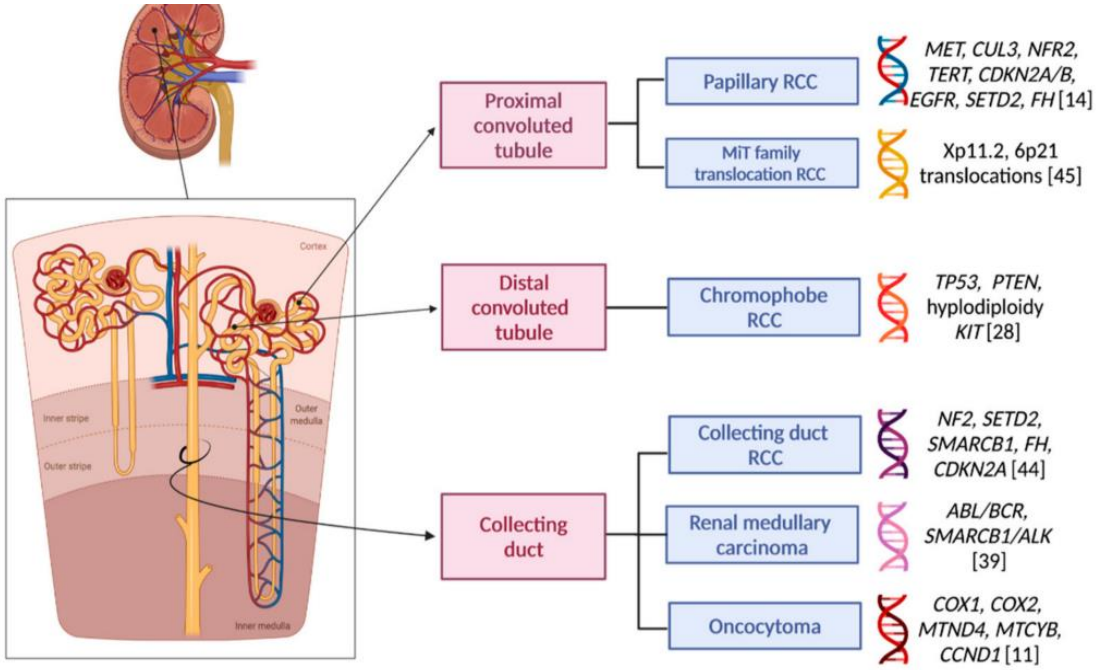


Fig. 1 – Pathways driving most subtypes of RCCs converge on nutrient- and/or oxygen-sensing pathways in the renal cell. Pink circles indicate proteins whose genes are mutated in rare kidney cancers (RKCs), and clear circles indicate genes mutated in clear-cell RCCs. RCC = renal cell carcinoma.

Rachel H. Giles at al, E U R O P E A N U R O L O G Y 2017



Andrea Marchetti at al, Int. J. Mol. Sci. 2021

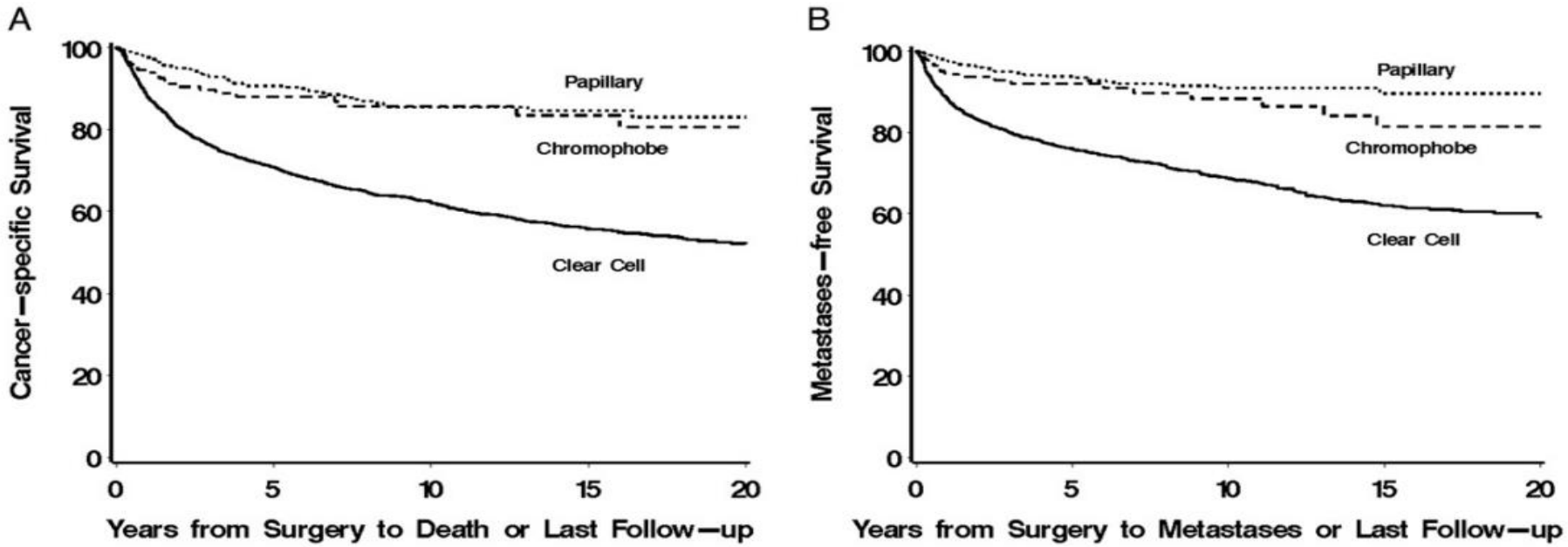
ccRCC ve nccRCC Görülme Sıklığı

Subtype	% of all RCC
Papillary RCC (Types 1 and 2)	10–15
Chromophobe RCC	5
Collecting duct RCC	1
MiT family translocation RCC	1
Multilocular cystic renal neoplasm of low malignant potential	1
Medullary RCC	<1%
Tubulocystic RCC	<1%
Acquired cystic kidney disease-associated RCC	<1%
Hereditary leiomyomatosis with RCC	<1%
Succinate dehydrogenase deficient RCC	<1%
Unclassified	<1%

RCC hastaların yaklaşık olarak %80 ccRCC ve %20 nccRCC

John A at al, Curr. Oncol. 2023

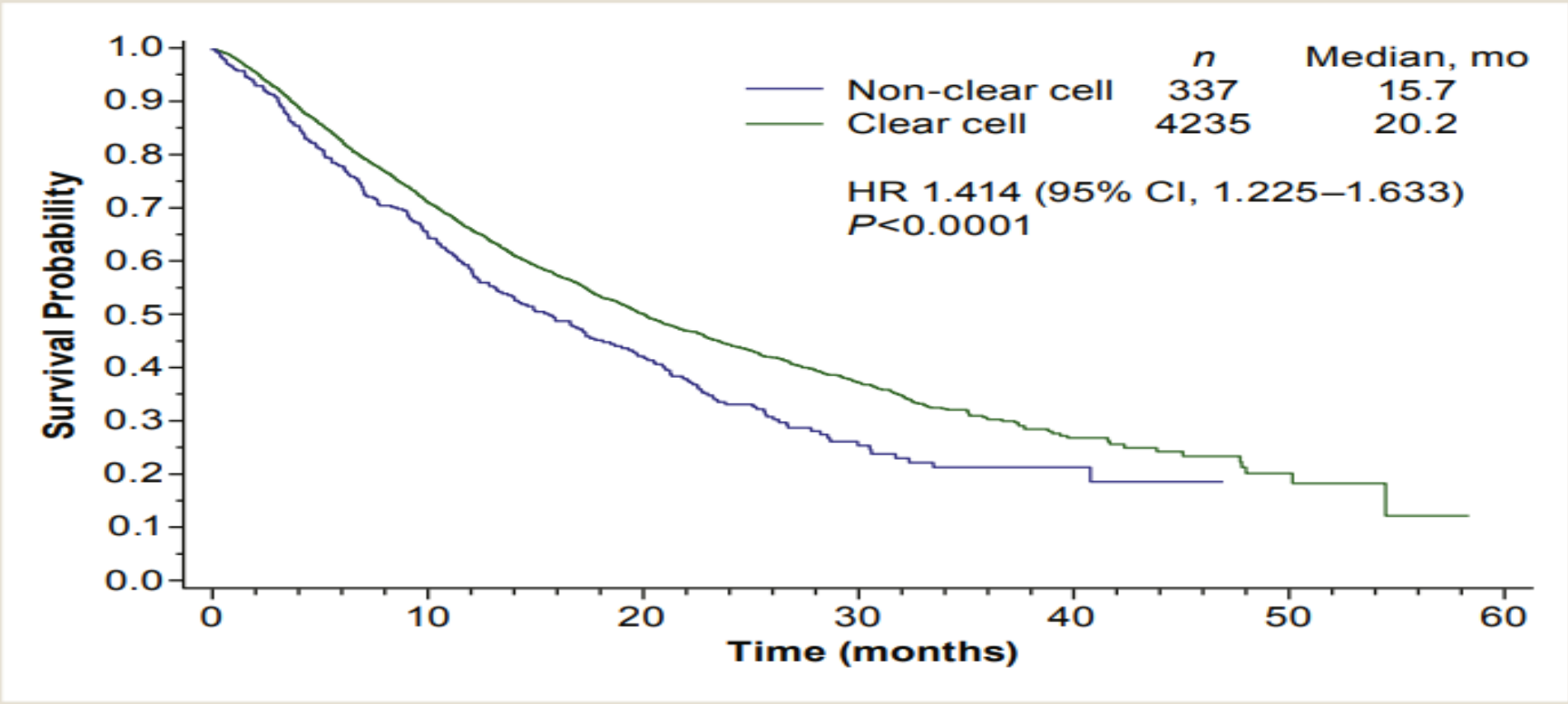
Metastatik olmayan RCC histolojik alt tipe göre sağkalım



RCC histological subtype and survival. *A*, cancer specific survival in 2,466 patients with clear cell, 438 with papillary and 158 with chromophobe RCC. *B*, distant metastasis-free survival in 2,088 patients with clear cell, 423 with papillary and 151 with chromophobe RCC who underwent nephrectomy for clinical M0 disease.

Bradley C at al, JOURNAL OF UROLOGY 2010

Metastatik RCC histolojik alt tipe göre sağkalım

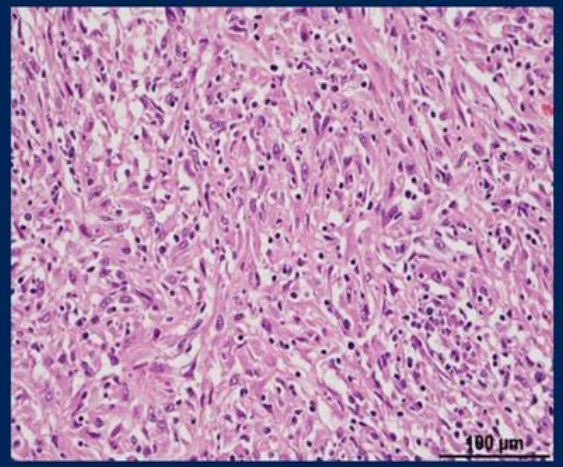


Guillermo de Velasco at al, Clinical Genitourinary Cancer 2017

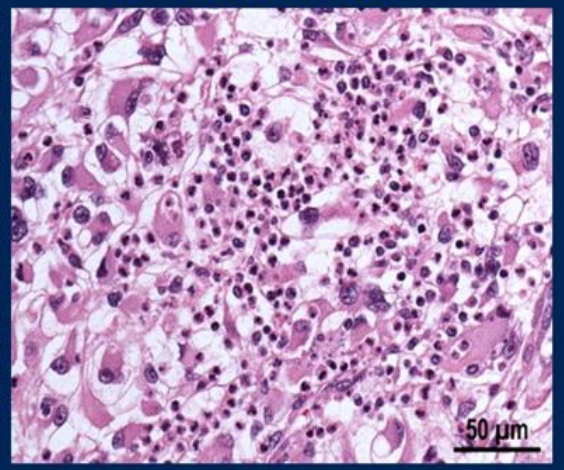
ccRCC ve nccRCC sarkomatoid ve rabdoid diferansiasyon

- Represent dedifferentiated form of RCC (any subtype)
- 10-15% of metastatic RCC
- Highly responsive to immune checkpoint inhibitors (ICI) & refractory to Targeted therapies
- Enriched for *BAP1* and *CDKN2A* deletions
- Display an immune-inflamed and angio-poor phenotype

Sarcomatoid RCC



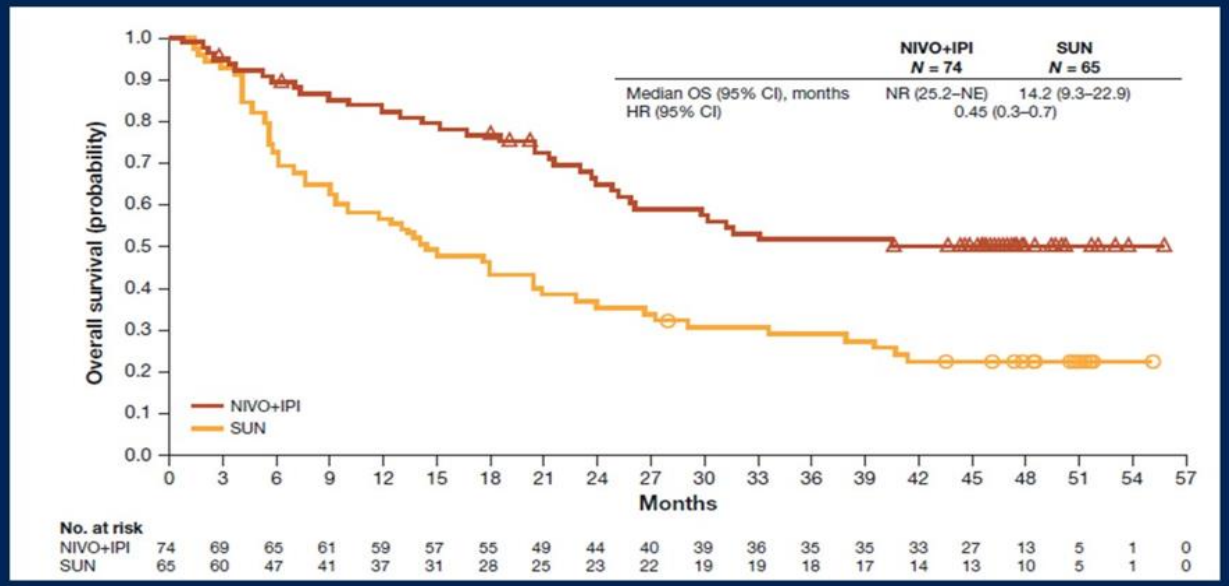
Rhabdoid RCC



Motzer J et al., *Cancer Cell* 2020
Bakouny Z et al., *Nat Commun* 2021

ccRCC ve nccRCC sarkomatoid ve rabdoid diferansiasyon

Clear cell with Sarcomatoid differentiation



I/P mRCC	Nivo/Ipi (n=74)	Sunitinib (N=65)	HR
mOS	NR	14.2m	0.45
mPFS	26.5m	5.1m	0.56
CR	19%	3%	

5 year followup

OS- 49 vs 14 months; HR 0.46
95% CI [0.29, 0.71]; *P* = .0004)
CR rate 23% and median DOR not reached

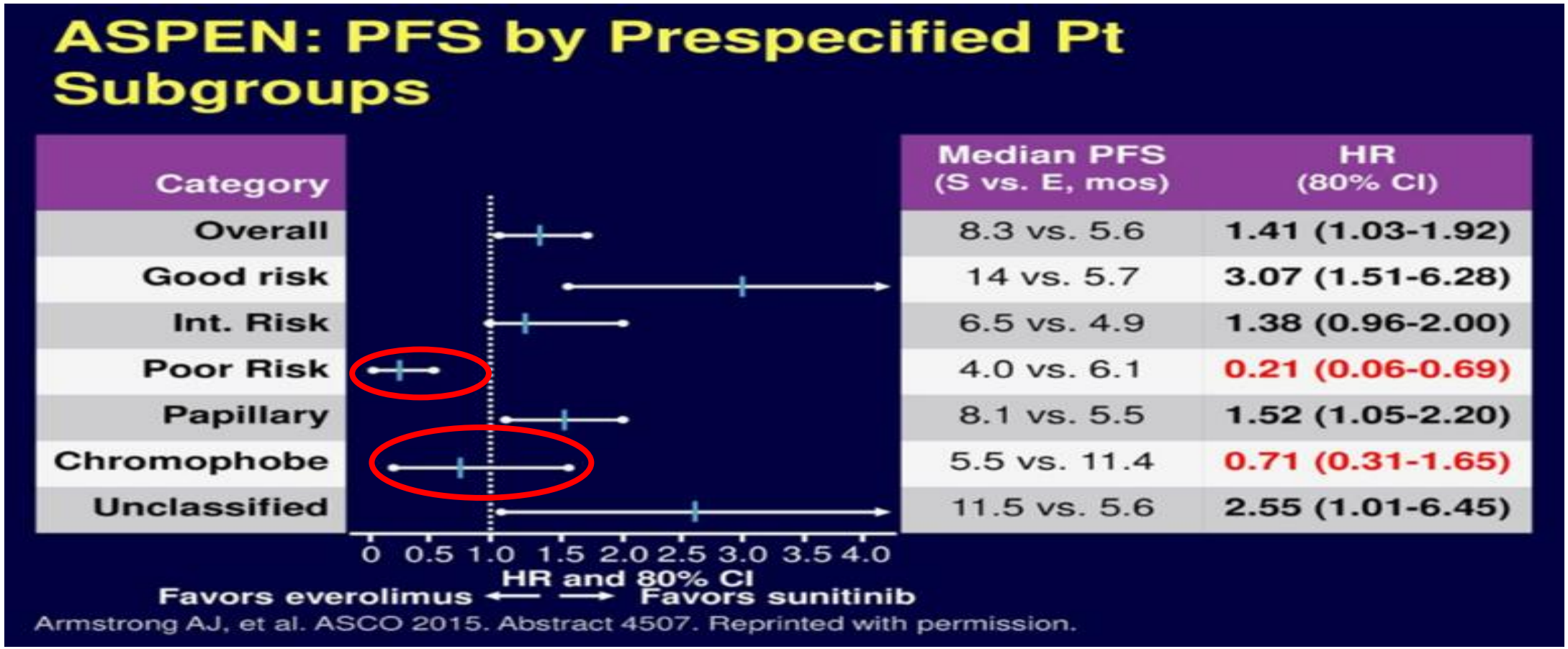
Tannir et al, CCR 2021, GUCS 2022

Evre IV nccRCC TKI ve mTOR inhibitörleri

Trial	Treatment	Randomized?	Number Enrolled	Histology Type	Overall Response Rate	Progression-Free Survival	Overall Survival
ESPN	Sunitinib vs. everolimus	Yes	68 patients	All non-clear cell	9% vs. 3%	6.1 vs. 4.1 months	16.2 vs. 14.9 months
ASPEN	Sunitinib vs. everolimus	Yes	108 patients	All non-clear cell	18% vs. 9%	8.3 vs. 5.6 months	31.5 vs. 13.2 months
RECORD-3	Sunitinib vs. everolimus	Yes	66 patients	All non-clear cell	N/A	7.2 vs 5.1 months	N/A
SUPAP	Sunitinib	No	61 patients	Papillary	13% (type I) and 11% (type II)	6.6 months (type I) and 5.5 months (type II)	17.8 months (type I) and 12.4 months (type II)

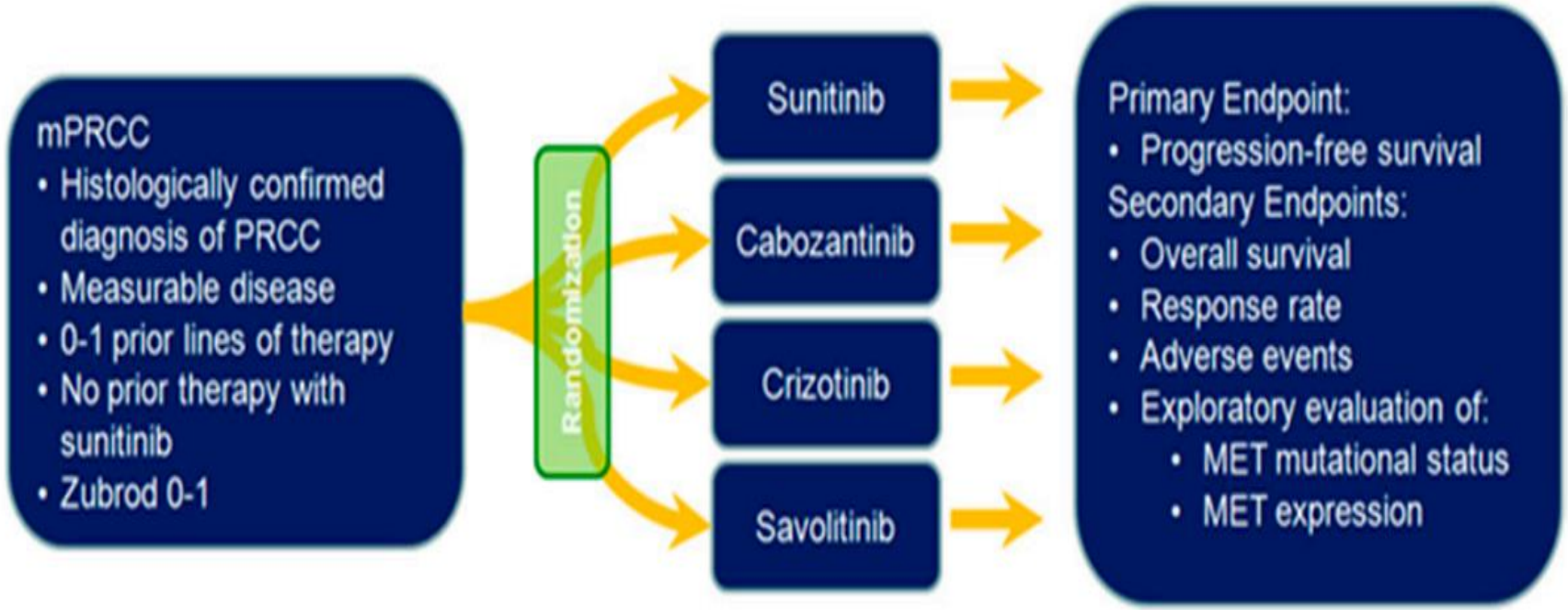
Tian Zhang, 2017 ASCO EDUCATIONAL BOOK

Evre IV nccRCC TKI ve mTOR inhibitörleri



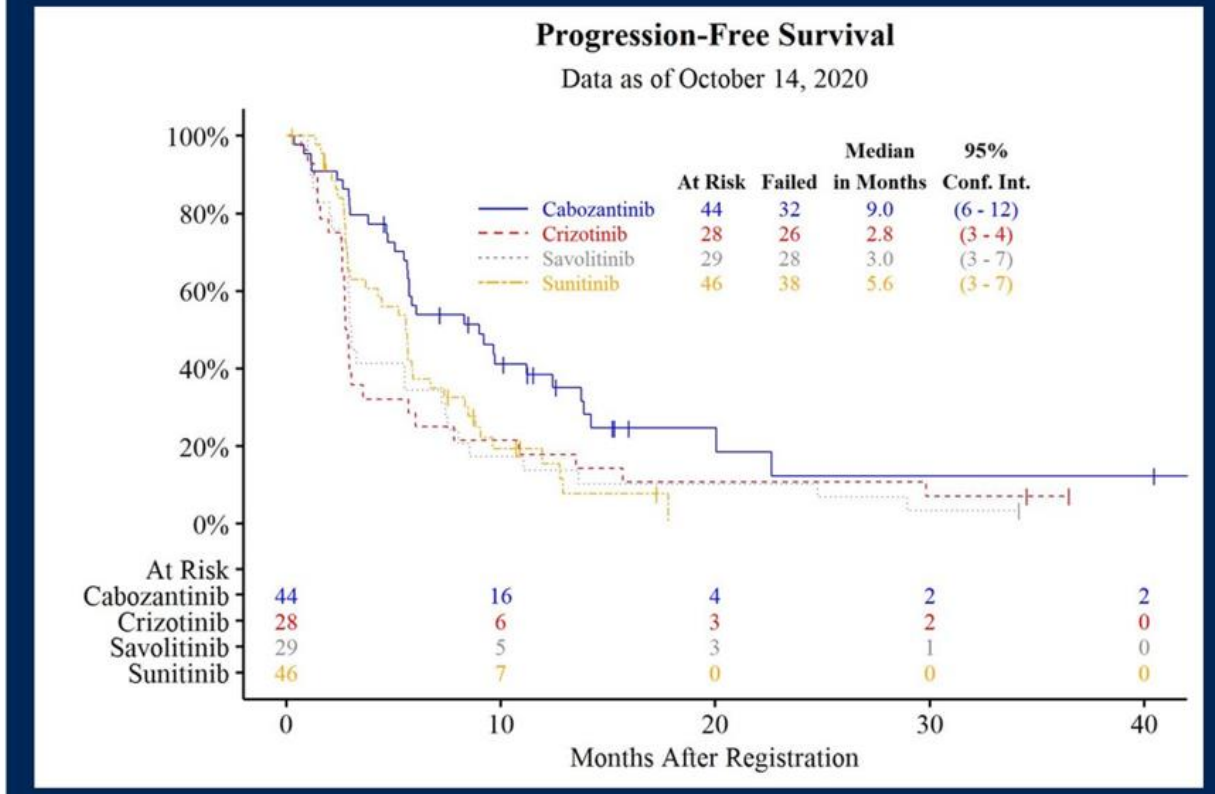
Evre IV nccRCC Histolojik alt tipe göre tedavi seçenekleri

FIGURE 1. Schema for SWOG 1500: A Randomized, Phase II Study Comparing Sunitinib, Cabozantinib, Crizotinib, and Savolitinib in Patients With Metastatic Papillary Renal Cell Carcinoma



Pal at al, GU ASCO 2021

Evre IV nccRCC Histolojik alt tipe göre tedavi seçenekleri



	Cabozantinib	Sunitinib	HR/P-value
Median PFS	9 months	5.6 months	0.6 (95% CI 0.37-0.97) P=0.019
ORR	23%	4%	P=0.01
OS	20 months	16.4 months	0.84 (95% CI 0.47-1.51)

Pal et al GU ASCO 2021, Lancet 2021

Evre IV nccRCC TKI+mTOR kombinasyonu

Lenvatinib +Everolimus phase II study in non-clear cell RCC

- Similar efficacy outcomes were observed by both investigator assessment and IIR (**Table 2**).
- The median duration of response was not estimable (NE).

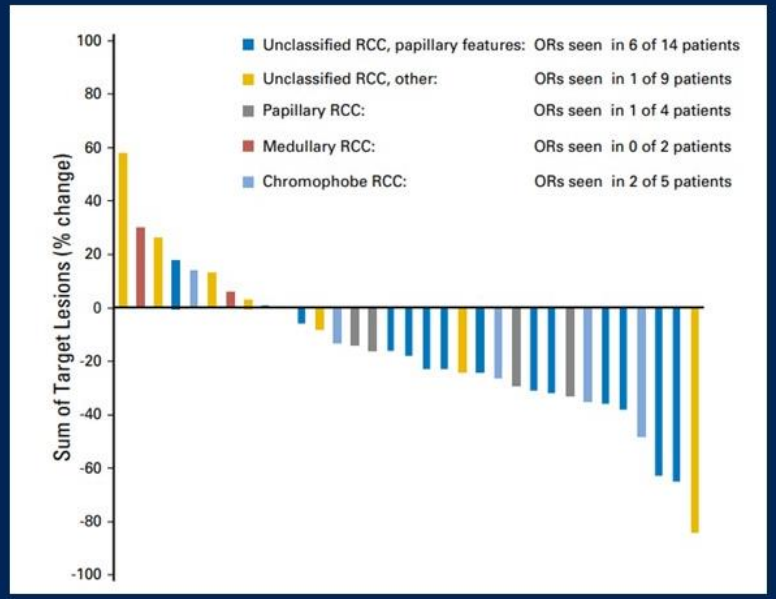
Table 2. Summary of Efficacy Outcomes by Histological Subtype

Parameter, n (%)[a]	By Investigator Assessment				By IIR
	Papillary (n = 20)	Chromophobe (n = 9)	Unclassified (n = 2)	Total (N = 31)	Total (N = 31)
Objective response rate (95% CI)[b]	3 (15.0) (3.2–37.9)	4 (44.4) (13.7–78.8)	1 (50.0) (1.3–98.7)	8 (25.8) (11.9–44.6)	8 (25.8) (11.9–44.6)
Best overall response					
Complete response	0	0	0	0	0
Partial response	3 (15.0)	4 (44.4)	1 (50.0)	8 (25.8)	8 (25.8)
Stable disease	14 (70.0)	3 (33.3)	1 (50.0)	18 (58.1)	14 (45.2)
Durable stable disease[c]	7 (35.0)	3 (33.3)	1 (50.0)	11 (35.5)	8 (25.8)
Progressive disease	2 (10.0)	1 (11.1)	0	3 (9.7)	6 (19.4)
Not evaluable / unknown	1 (5.0)	1 (11.1)	0	2 (6.5)	3 (9.7)
Clinical benefit rate[d] (95% CI)[b]	10 (50.0) (27.2–72.8)	7 (77.8) (40.0–97.2)	2 (100.0) (15.8–100.0)	19 (61.3) (42.2–78.2)	16 (51.6) (33.1–69.8)
Disease control rate[e] (95% CI)[b]	17 (85.0) (62.1–96.8)	7 (77.8) (40.0–97.2)	2 (100.0) (15.8–100.0)	26 (83.9) (66.3–94.5)	22 (71.0) (52.0–85.8)

[a]Percentages for the histological subtypes (ie, papillary, chromophobe, and unclassified) are based on the number of patients with that subtype.
[b]The 95% CI was calculated using the 2-sided Clopper–Pearson method.
[c]Durable stable disease = duration ≥ 23 weeks.
[d]Clinical benefit rate = complete response + partial response + durable stable disease.
[e]Disease control rate = complete response + partial response + stable disease.
CI, confidence interval; IIR, independent imaging review.

Hutson et al, GU ASCO 2020 and European Urol 2021

Evre IV nccRCC VEGF+mTOR kombinasyonu



Bevacizumab +Everolimus phase II study in non-clear cell RCC

Table 2. Summary Efficacy Analysis

Group	PR	CR	SD	PD	Median PFS (months)	95% CI	6-Month PFS* (%)
Full cohort (n = 34)†	9	1	15	8	11.0	3.8 to 19.3	60
Unclassified RCC with papillary features (n = 14)	6	0	8	0	12.9	10.9 to NA	92
Unclassified RCC without papillary features (n = 9)†	0	1	3	4	1.9	1.6 to NA	11
Chromophobe RCC (n = 5)	2	0	2	1	NR	1.9 to NA	75
Papillary RCC (n = 4)	1	0	2	1	13.8	1.4 to NA	75
Medullary RCC (n = 2)	0	0	0	2	1.7	1.6 to NA	0

Voss et al JCO 2016

Evre IV nccRCC immüne checkpoint inhibitörleri

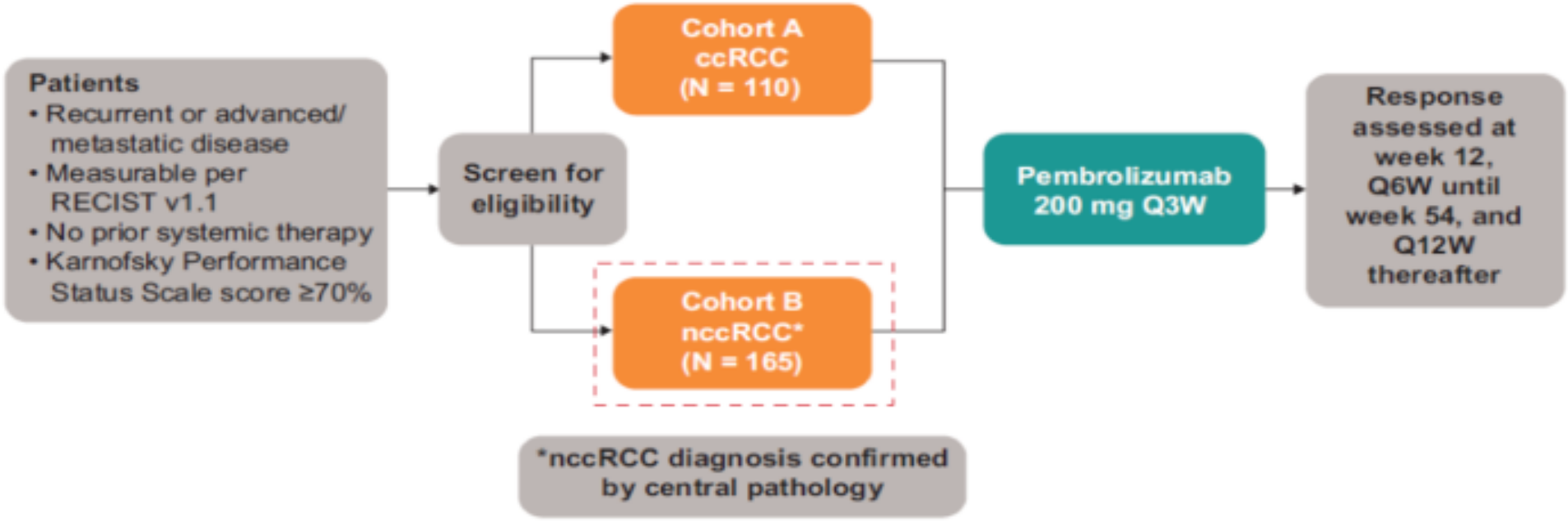
		ORR	Papillary	Chromophobe	Unclassified/ Other	DOR (months)	Toxicites (≧Grade 3)
Pembrolizumab[1]	Phase 2	44/165 26.7%	34/118 28.8%	2/21 9.5%	8/26 39.8%	29	17%
Nivolumab[2]	Phase 2	5/36 14%	1/19 5.3%	1/6 16.7%	3/10 30%	NA	20%
Nivolumab and Ipilimumab[3]	Phase 3b/4	9/52 17.3%	5/18 28%	0/7 0%	4/27 15%	NR	37%

1. McDermott et al JCO 2021. 2. Atkins et al ASCO 2021 3. Tykodi et al, J Immunother Cancer 2022

Evre IV nccRCC immüne checkpoint inhibitörleri

2. Cohort B – Assessed single agent pembrolizumab in previously untreated nccRCC patients.

Figure 1. Study Design



ccRCC, clear cell renal cell carcinoma; nccRCC, non–clear cell renal cell carcinoma; Q3W, every 3 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks.

The objective of this study was to evaluate the efficacy, safety, and tolerability of pembrolizumab monotherapy in patients with nccRCC (cohort B) over one year of follow-up.

KEYNOTE-427 Kohort-B

Evre IV nccRCC immüne checkpoint inhibitörleri

Table 2. Confirmed ORR in the Overall Population and in Patient Subgroups per RECIST v1.1 by BICR

	Overall N = 165	RCC Histology			IMDC Category		PD-L1 Status[a]		Sarcomatoid Features n = 38
		Papillary n = 118	Chromophobe n = 21	Unclassified n = 26	Favorable n = 53	Intermediate/Poor n = 112	CPS <1 n = 58	CPS ≥1 n = 102	
ORR, % (95% CI)	26.1 (19.5-33.5)	28.0 (20.1-37.0)	9.5 (1.2-30.4)	30.8 (14.3-51.8)	32.1 (19.9-46.3)	23.2 (15.8-32.1)	10.3 (3.9-21.2)	35.3 (26.1-45.4)	42.1 (26.3-59.2)
DCR, % (95% CI)[b]	40.6 (33.0-48.5)	44.1 (34.9-53.5)	33.3 (14.6-57.0)	30.8 (14.3-51.8)	43.4 (29.8-57.7)	39.3 (30.2-49.0)	25.9 (15.3-39.0)	49.0 (39.0-59.1)	52.6 (35.8-69.0)
Best objective response	%								
CR	6.1	5.9	4.8	7.7	11.3	3.6	5.2	6.9	7.9
PR	20.0	22.0	4.8	23.1	20.8	19.6	5.2	28.4	34.2
SD	30.9	33.1	47.6	7.7	32.1	30.4	41.4	24.5	18.4
PD	37.0	33.1	42.9	50.0	34.0	38.4	43.1	33.3	31.6
NE[c]	1.2	0.8	0.0	3.8	1.9	0.9	0.0	2.0	2.6
NA[d]	4.8	5.1	0.0	7.7	0.0	7.1	5.2	4.9	5.3

BICR, blinded independent central review; CPS, combined positive score; CR, complete response; DCR, disease control rate; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NA, no assessment; NE, nonevaluable; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; RCC, renal cell carcinoma; SD, stable disease.

[a]5 patients had missing PD-L1 status.
[b]DCR = CR + PR + SD ≥6 months.
[c]Includes patients with insufficient data for response assessment.
[d]Includes patients who discontinued or died before first postbaseline imaging.

KEYNOTE-427 Kohort-B

Evre IV nccRCC immüne checkpoint inhibitörleri

Safety and Efficacy of Nivolumab in Patients With Advanced Non—Clear Cell Renal Cell Carcinoma: Results From the Phase IIIb/IV CheckMate 374 Study

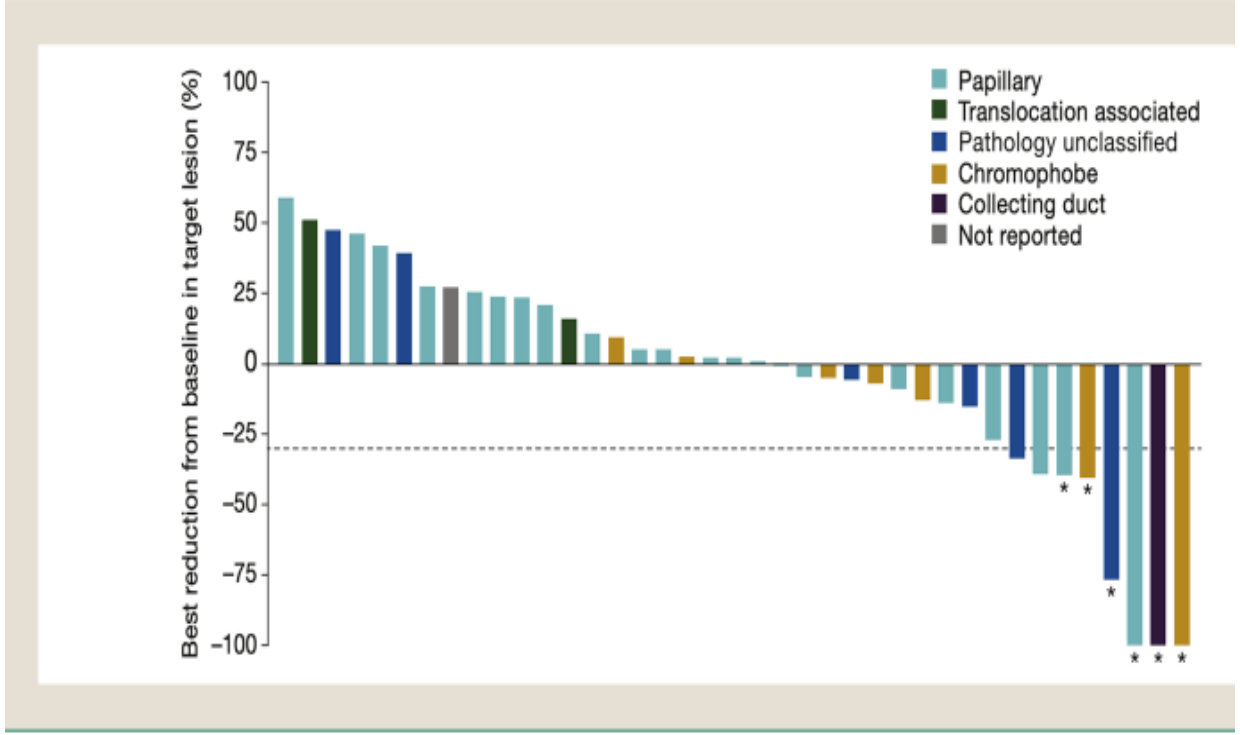
Nicholas J. Vogelzang,[1] Mark R. Olsen,[2] Joshua J. McFarlane,[3] Edward Arrowsmith,[4] Todd M. Bauer,[5] Rohit K. Jain,[6] Bradley Somer,[7] Elaine T. Lam,[8] Mark D. Kochenderfer,[9] Ana Molina,[10] Gurjyot Doshi,[11] Brian Lingerfelt,[12] Ralph J. Hauke,[13] Vijay Gunuganti,[14] Ian Schnadig,[15] Peter Van Veldhuizen,[16] Mark Fleming,[17] Robert Galamaga,[18,a] Mukul Gupta,[19] Hugo Hool,[20] Thomas Hutson,[21] Joshua Zhang,[22] M. Brent McHenry,[22] Jennifer L. Johansen,[22] Scott S. Tykodi[23]

Abstract

Promising antitumor activity of nivolumab monotherapy was observed in patients with advanced non—clear cell renal cell carcinoma (nccRCC) from CheckMate 374, with a manageable safety profile. These results establish nivolumab monotherapy at a flat dose of 240 mg every 2 weeks as a treatment option for patients with advanced nccRCC, a patient population with high unmet need.

Background: The open-label phase IIIb/IV CheckMate 374 study (NCT02596035) was conducted to validate the safety and efficacy of flat-dose nivolumab 240 mg every 2 weeks (Q2W) in previously treated advanced/metastatic renal cell carcinoma. Three cohorts included patients with predominantly clear cell histology, non—clear cell histologies, or brain metastases. We report safety and efficacy from the advanced non—clear cell RCC (nccRCC) cohort of CheckMate 374. **Methods:** Eligible patients received 0 to 3 prior systemic therapies. Patients received nivolumab 240 mg Q2W for ≤24 months or until confirmed progression or unacceptable toxicity. The primary endpoint was incidence of high-grade (grade 3-5) immune-mediated adverse events (IMAEs). Exploratory endpoints included objective

Evre IV nccRCC immüne checkpoint inhibitörleri



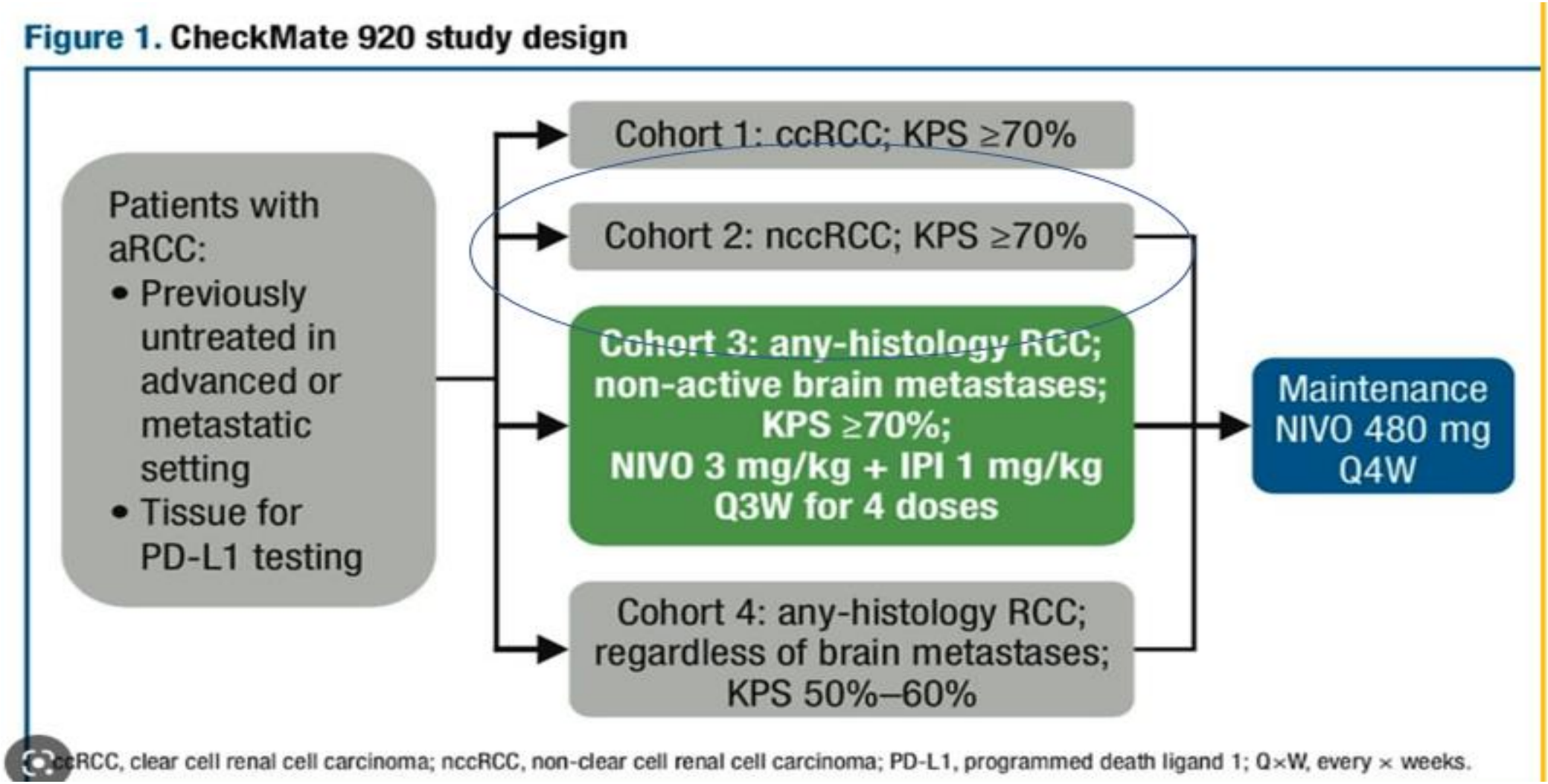
*Responder per RECIST v1.1 criteria, confirmation of response required. Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1.

Outcome	Non–Clear Cell RCC, No. of Patients (%); N = 44
ORR, % (95% CI)	13.6 (5.2-27.4)
Best overall response, n (%)	
Complete response	1 (2.3)[a]
Partial response	5 (11.4)[b]
Stable disease	16 (36.4)[c]
Progressive disease	18 (40.9)[d]
Unable to determine	4 (9.1)

Abbreviations: CI = confidence interval; ORR = objective response rate; RCC = renal cell carcinoma.
[a]This patient had chromophobe histology.
[b]Two patients with papillary and 1 each with chromophobe, collecting duct, and unclassified histology.
[c]Nine patients with papillary, 4 with chromophobe, 1 with medullary, and 2 with unclassified histology.
[d]Eleven patients with papillary, 2 with translocation associated, 1 with chromophobe histology, 3 with unclassified pathology, and 1 with nonreported histology.

CheckMate 374

Evre IV nccRCC immüne checkpoint inhibitörleri



Evre IV nccRCC immüne checkpoint inhibitörleri

	All treated patients (N=52)
Age, median (range), years	64 (23–86)
Male, n (%)	36 (69.2)
IMDC risk group, n (%)	
Favorable	9 (17.3)
Intermediate	27 (51.9)
Poor	16 (30.8)
Karnofsky performance score, n (%)	
100	15 (28.8)
90	25 (48.1)
80	9 (17.3)
70	3 (5.8)
Prior nephrectomy, n (%)	35 (67.3)
Prior radiotherapy, n (%)	4 (7.7)
Histological subtype, n (%)	
Non-clear cell	52 (100)
Unclassified	22 (42.3)
Papillary	18 (34.6)
Chromophobe	7 (13.5)
Translocation-associated	2 (3.8)
Collecting duct	2 (3.8)
Renal medullary	1 (1.9)
Sarcomatoid features, n (%)	
Yes	15 (28.8)
No	37 (71.2)
Tumor PD-L1 expression, n (%)	n=39
<1%	24 (61.5)
≥1%	15 (38.5)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PD-L1, programmed death ligand 1.

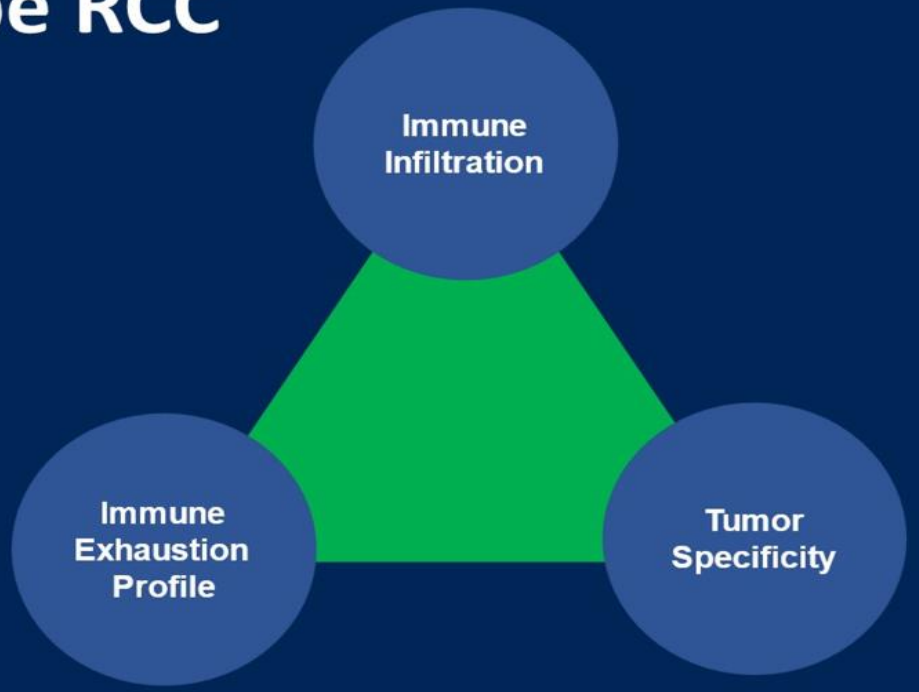
Outcome	Response-evaluable patients (N=46)
Investigator-assessed confirmed ORR per RECIST V.1.1 (95% CI), %	19.6 (9.4 to 33.9)
BOR, n (%)	
Complete response	2 (4.3)*
Partial response	7 (15.2)†
Stable disease	17 (37.0)
Progressive disease	19 (41.3)
Unable to determine	1 (2.2)
Investigator-assessed confirmed ORR per RECIST V.1.1 among subgroups (95% CI), %	
Baseline tumor PD-L1 expression <1% (n=21)	14.3 (3.0 to 36.3)
Baseline tumor PD-L1 expression ≥1% (n=13)	30.8 (9.1 to 61.4)
Presence of sarcomatoid features (n=14)	35.7 (12.8 to 64.9)
Absence of sarcomatoid features (n=32)	12.5 (3.5 to 29.0)
IMDC favorable risk (0; n=8)	12.5 (0.3 to 52.7)
IMDC intermediate risk (1–2; n=25)	20.0 (6.8 to 40.7)
IMDC poor risk (3–6; n=13)	23.1 (5.0 to 53.8)
Median TTR (range), months	2.8 (2.1–14.8)
Median DOR (range), months	NR (0.0+–27.8+)

CheckMate 920

Evre IV nccRCC immüne checkpoint inhibitörleri

Chromophobe RCC

- Poor response among patients with ChRCC to IO-based regimens (vs. ccRCC)
- Characteristics of the TME in renal oncocytic neoplasms:
  1. Low infiltration of immune cells
  2. Poor exhaustion profile
  3. Low tumor specificity (T-cells)



Potential implications for therapy: reinvigoration of the immune landscape in ChRCC (i.e. targeted cancer vaccines) to elicit IO response?

Adapted from Labaki

Labaki, KCRS 2022

Evre IV nccRCC TKI-VEGF+immüne checkpoint inhibitörleri

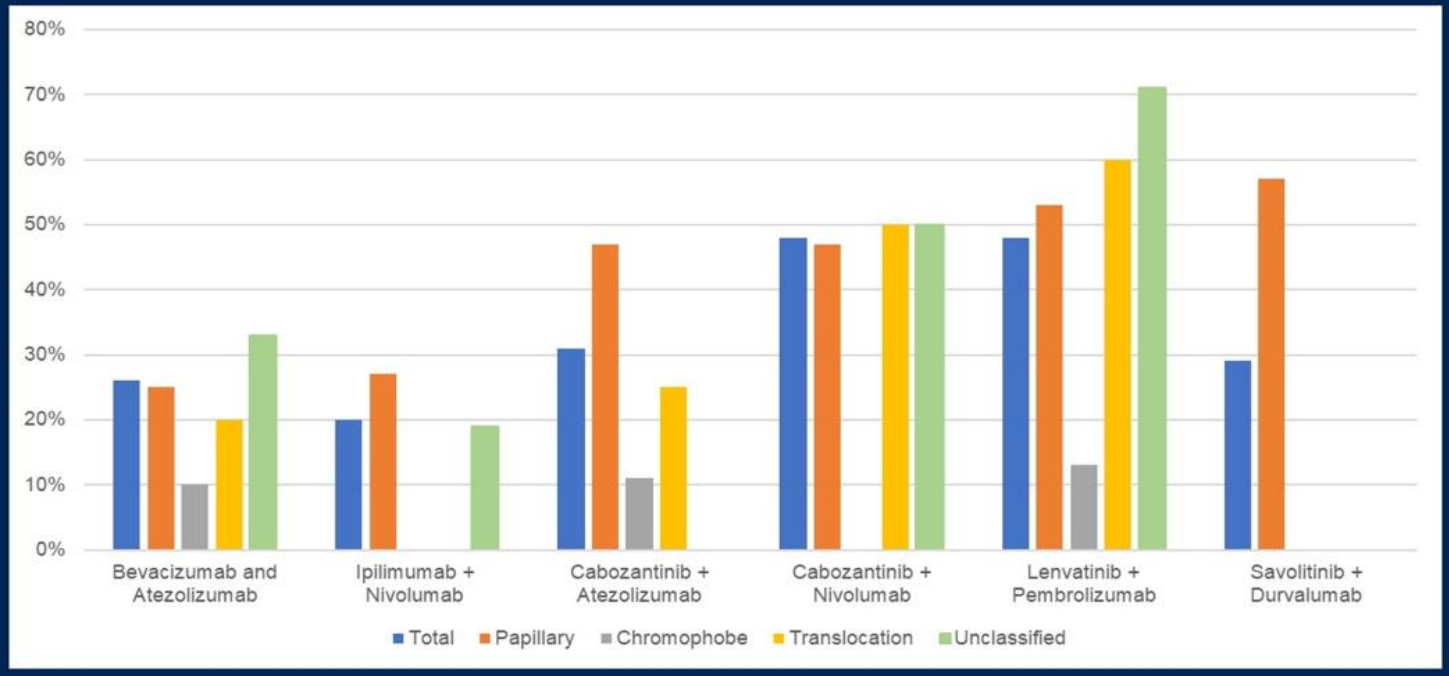
VEGF/IO (Single arm Phase 2 trials)

	Total	Papillary	Chromophobe	Translocation	Unclassified/ Other	Prior VEGF Therapy?
Atezolizumab Bevacizumab[1]	42	12	10	5	15	Y (35%)
Cabozantinib Nivolumab[2]	47	32	7	2	6	Y (29%)
Cabozantinib Atezolzumab[3]	32	15	9	-	7	Y (22%)
Lenvatinib Pembrolizumab[4]	147	87	26	6	28	N

1. McGregor et al, JCO 2020, 2. Lee et al, JCO 2022. 3. Pal et al, JCO 2021 4. Albiges et al ESMO 2022

Evre IV nccRCC TKI-VEGF+immüne checkpoint inhibitörleri

Combination Therapy Efficacy



McGregor et al, JCO 2020; Tykodi et al, J Immunother Cancer 2022 , Pal et al, JCO 2021, Lee et al, JCO 2022, Albiges et al ESMO 2022, C Suarez Rodriguez et al, ASCO 2021

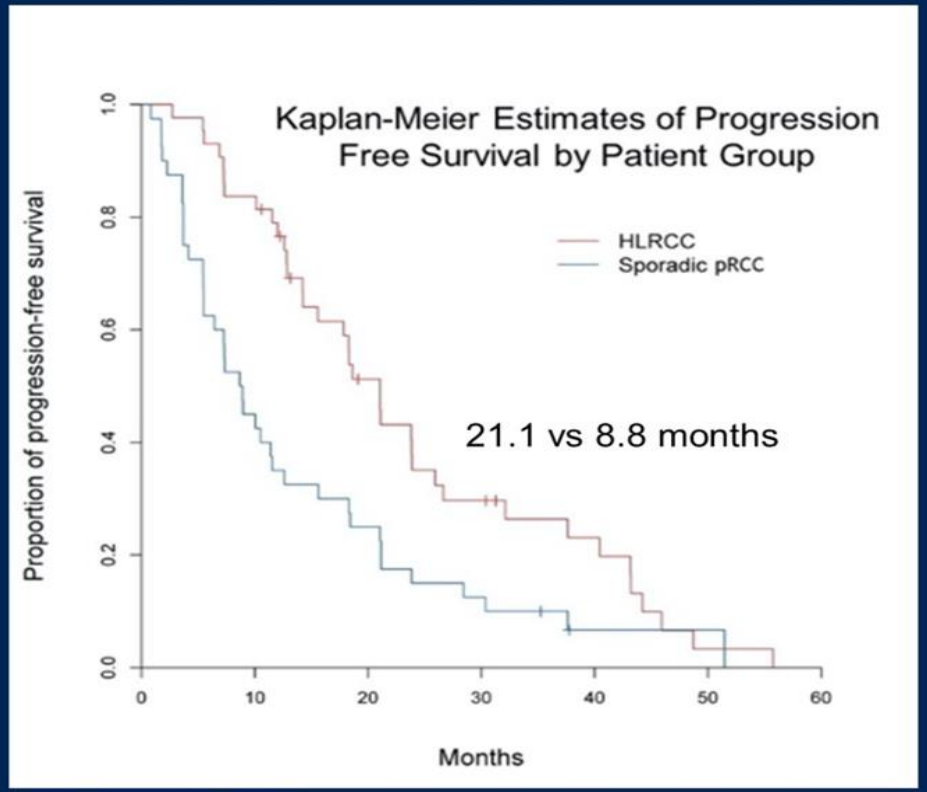
Evre IV nccRCC TKI-VEGF+immüne checkpoint inhibitörleri

Trial	Phase	Treatment	Sample Size	Efficacy
NCT02724878 [81]	II	Atezolizumab/ Bevacizumab	$n = 60$ Papillary: $n = 12$ Chromophobe: $n = 10$ Unclassified: $n = 9$ Collecting duct: $n = 5$ Medullary: $n = 1$	ORR: 33% Papillary: 25% Chromophobe: 10% Unclassified: 33% Collecting duct: 40% Medullary: 100%
COSMIC-021 [82]	Ib/II	Atezolizumab/ Cabozantinib	$n = 32$ (nccRCC cohort) Papillary: $n = 15$ Chromophobe: $n = 9$ Other: $n = 7$	mPFS: 9.5mths ORR 31% (80% CI: 20-44) Papillary: 40% Chromophobe: 14% Other: 60%
CALYPSO [79]	I/II	Durvalumab/ Savolitinib	$n = 41$ Papillary: $n = 40$	ORR 27% mOS: 12.3mths mPFS: 4.9mths
NCT03635892 [78]	II	Nivolumab/ Cabozantinib	$n = 47$ Cohort 1 (papillary, unclassified, translocation associated RCC): $n = 40$ Cohort 2 (chromophobe): $n = 7$	Cohort 1: ORR 47.5%, mPFS 12.5mths, mOS: 28mths Cohort 2: ORR 0%

Herediter leyomiyomatozise bağlı-nccRCC

Bevacizumab + Erlotinib

Confirmed Best Response	HLRCC, n (%) (N = 43)	Sporadic, n (%) (N = 40)
Complete Response	2 (4.7)	0 (0)
Partial Response	29 (67)	14 (35)
Stable Disease	12 (28)	21 (53)
Unconfirmed Partial Response	0 (0)	1 (2.5)
Progressive Disease	0 (0)	4 (10)
ORR	72%	35%

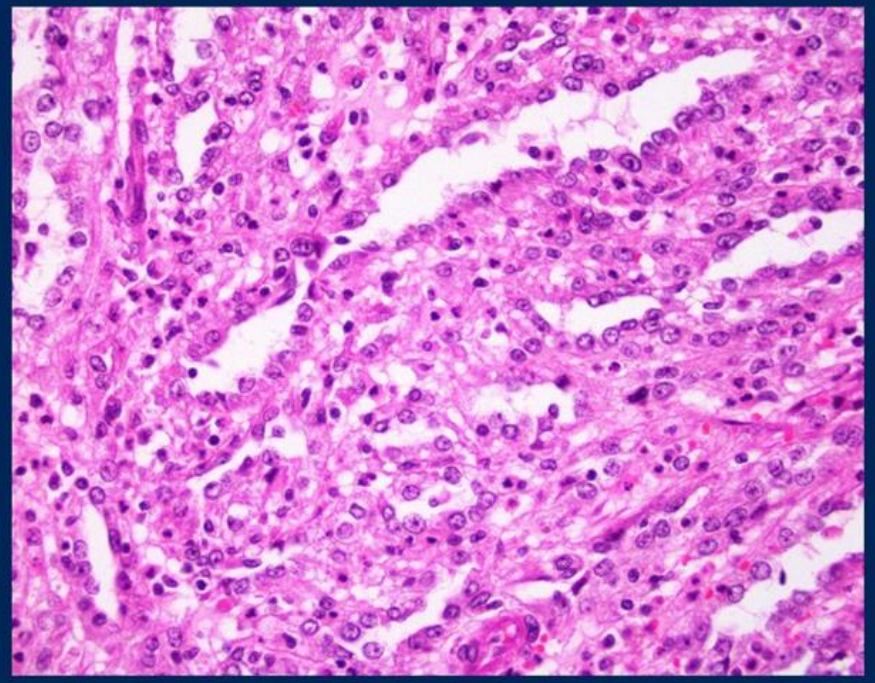


Add Atezolizumab?
NCT04981509

Srinivasan, ASCO 2020

Toplayıcı kanal ve renal medüller karsinom

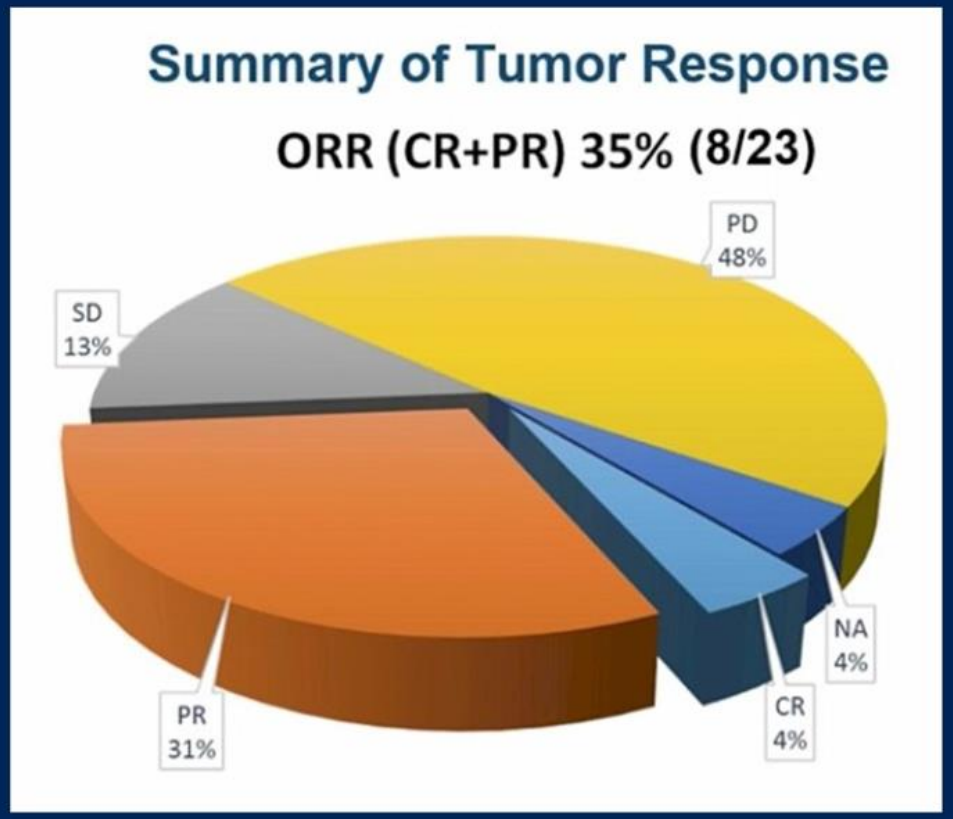
- Collecting Duct[1]
  - Cisplatin/Gemcitabine phase II GETUG:
    - ORR 26%, PFS 7.1 months
- Renal Medullary Carcinoma[2]
  - Sickle cell trait → SMARCB1 loss
  - No sickle cell trait → RCCU-MP
  - Platinum-based chemo even in localized disease



1. Oudard et al, J Urol 2007 2. Msaouel et al, Clin Genitourin Cancer, 2019

Toplayıcı kanal-nccRCC

Cabozantinib for Collecting Duct Carcinoma



- DNA sequencing (n=21 (91%))
  - All tumors microsatellite stable
  - No association between tumor mutational burden and response
- PFS > 6 months associated with mutations affecting deubiquitination, cell-cell communication, and TGF-b signaling
- Non-responders frequently mutated in chromatin remodeling, transcriptional regulation and WNT pathways

Median PFS was 6 months

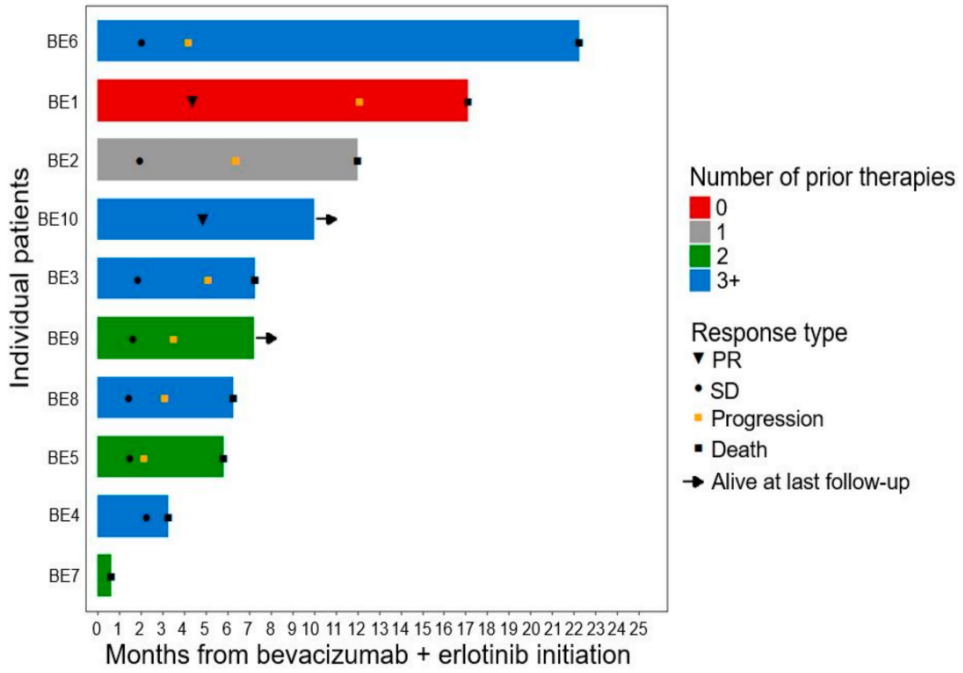
Procopio et al Jam Oncol 2022

Renal medüller karsinom-Gemsitabin+Doksorubisin

Median Age – yr. (range)	29 (20-47)
Male Gender – no. (%)	7 (44%)
African American – no. (%)	15 (94%)
Right Kidney Primary RMC – no. (%)	13 (81%)
ECOG Performance Status ≤ 1 – no. (%)	12 (75%)
Cytoreductive Nephrectomy – no. (%)	12 (75%)
Prior Platinum-based therapy – no. (%)	15 (94%)
0-1 Prior Lines of Therapy – no. (%)	11 (69%)
2-3 Prior Lines of Therapy – no. (%)	5 (31%)

- Hastaların %94 daha önce platin bazlı kemoterapi almış
- OR oranı=21.4%
- Satabil hastalık oranı=71.4%
- progression-free survival= 3.0 ay
- OS=9.8 mo ay

Renal medüller karsinom-Bevacizumab + Erlotinib



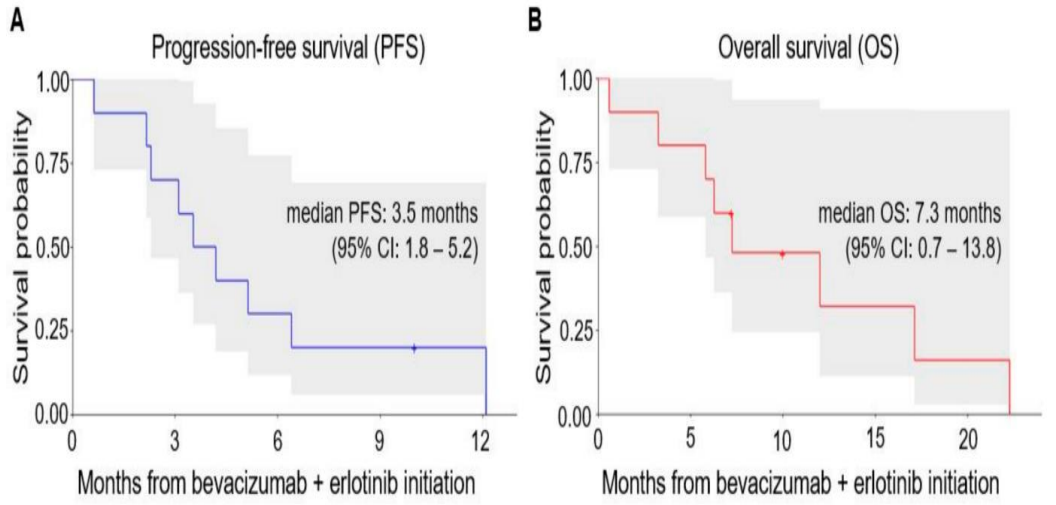
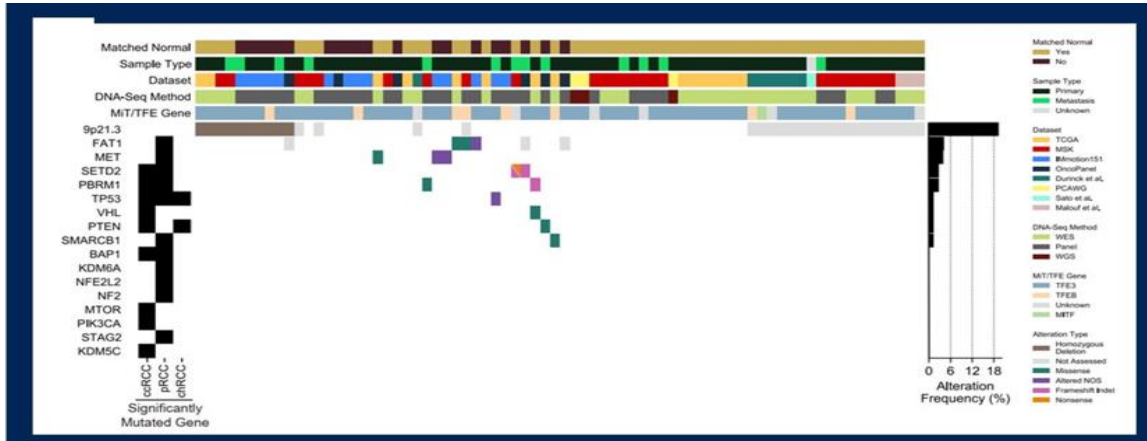


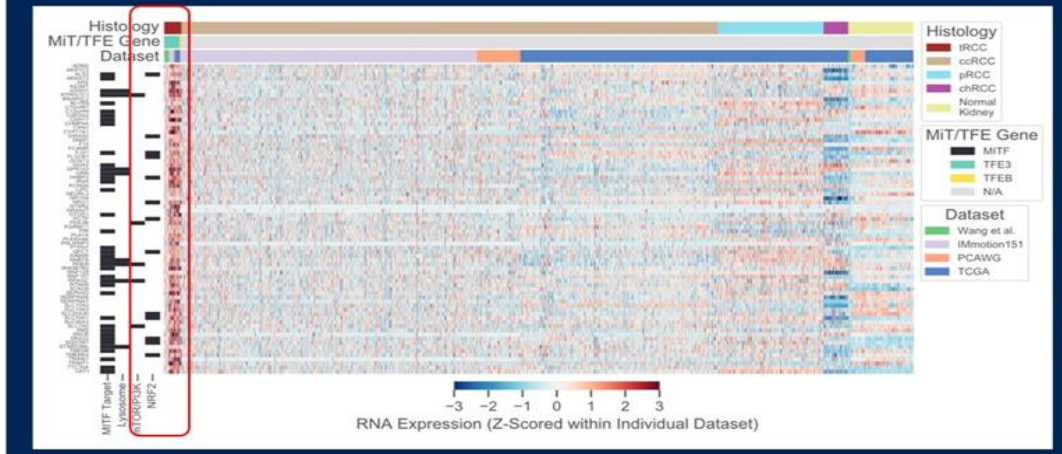
Figure 3. (**A**) Progression-free survival and (**B**) overall survival from treatment initiation with bevacizumab plus erlotinib. The shaded areas represent the 95% confidence bands for each curve. CI, Confidence interval.

- ❑ OR=%20
- ❑ Stabil hastalık=%70
- ❑ Hastaların %90'nı daha önce platin bazlı kemoterapi almış
- ❑ Hastaların %60 oranında ≥3 sistemik tedavi almış

Andrew J. Wiele at al, Cancers 2021

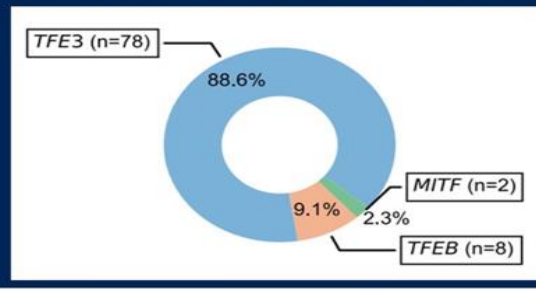
Translokasyon Renal Hücreli Karsinom

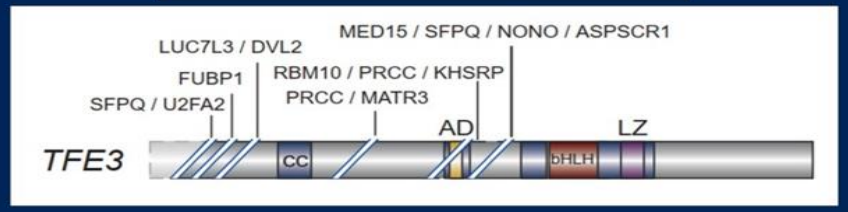




Adapted from Viswanathan

Genomic Features of tRCC





- Few genomic alterations in tRCC aside from *MiT/TFE* fusion
- *TFE3* is most involved in the fusion
- Activation of NRF2 pathway a defining feature
- TGFβ, MET, and metabolic/proliferative signaling represent other downstream pathways.

Bakouny et al., *Cell Reports*, 2022; Sun et al., *Nature Communications*, 2021; Marcon et al., *CCR*, 2020; Malouf et al., *CCR*, 2013, 2014; Kauffman et al., *Nature Rev Urol*, 2014

Translokasyon Renal Hücreli Karsinom TKI/VEGF

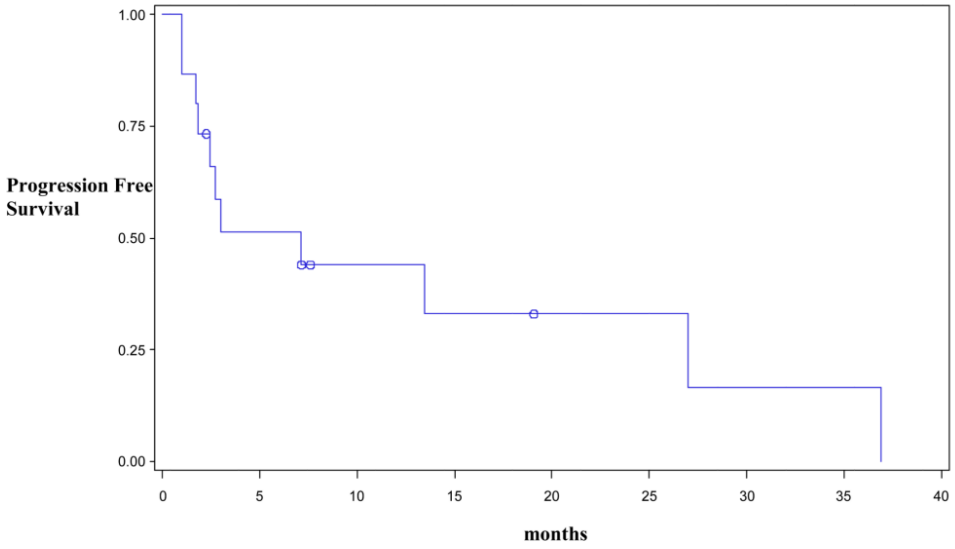


Figure 2a. Progression Free Survival of 7.1 months for 15 patients with advanced Xp11 translocation renal cell carcinoma treated with VEGF-targeted therapy

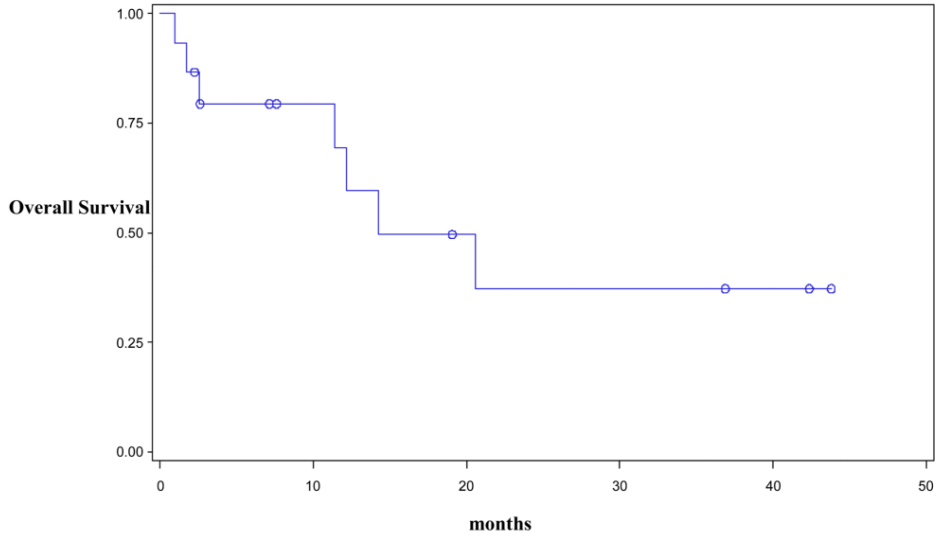
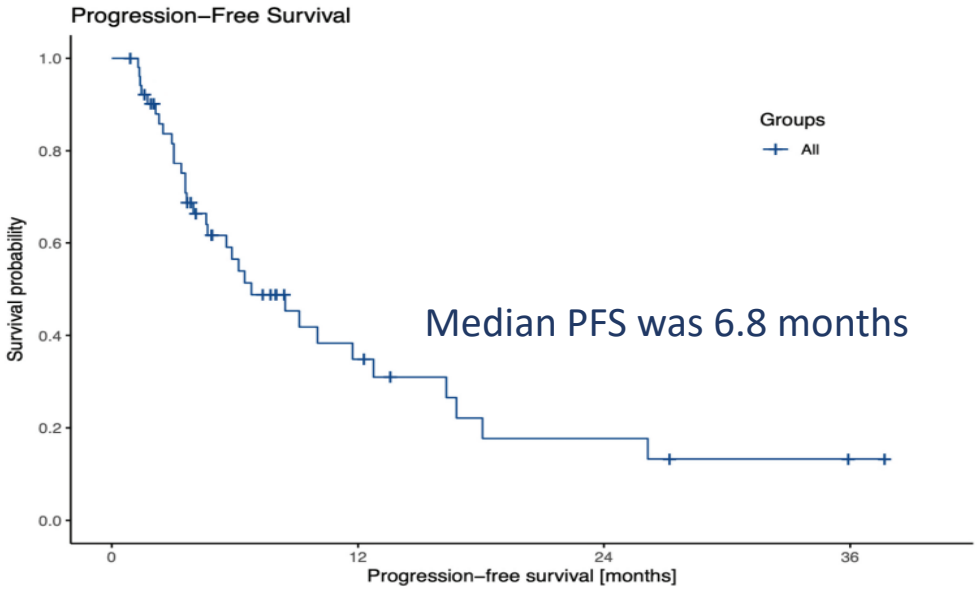


Figure 2b. Overall Survival of 14.3 months for 15 patients with advanced Xp11 translocation renal cell carcinoma treated with VEGF-targeted therapy

By RECIST, 3 patients had an objective response, for an overall response rate of 20%. All responders who were treated with sunitinib (N=1), sorafenib (N=1) and ramucirumab (N=1) had partial responses (PR). The duration of response was 7, 13 and 27 months, respectively.
Seven patients achieved stable disease (SD)

Choueiri T at al, Cancer 2010

Translokasyon Renal Hücreli Karsinom -Kabozantinib



Outcomes	Objective response rate, *n* (%)
Best overall response	9 (17.3%)
Complete response	2 (3.8%)
Partial response	7 (13.5%)
Stable disease	26 (50%)
>6 months	15 (29%)
<6 months	11 (21%)
Progressive disease	17 (32.7%)
Clinical benefit	24 (46%)

	Median progression-free survival, months (95%CI)	Hazard ratio, (95%CI)	*P*-value
IMDC (favorable vs intermediate/poor)	6.2 (5.8-not reached) vs 6.8 (4.6-16.8)	0.89 (0.33-2.4)	.82
Line of cabozantinib (1 vs ≥2)	11.7 (4.7-not reached) vs 6.5 (3.6-16.3)	0.59 (0.23-1.5)	.28
Prior nephrectomy (yes vs no)	6.5 (3.6-26.1) vs 4.7 (4.0–not reached)	0.62 (0.27-1.4)	.26
Bone metastasis (yes vs no)	6.8 (4-not reached) vs 6.5 (4.6-16.8)	0.78 (0.38–1.6)	.5
Brain metastasis (yes vs no)	3.8 (2.1-not reached) vs 9.1 (5.6-16.8)	3.1 (1.1-9.3)	.03

Thouvenin J at al, The Oncologist 2022

Translokasyon Renal Hücreli Karsinom
TKI-VEGF+immüne checkpoint inhibitörleri

Line of therapy	ICT + VEGF TT (*N* = 11)	Objective response rate (%)	Dual ICT (*N* = 18)	Objective response rate (%)
1L	Pembrolizumab + axitinib (*N* = 2) Avelumab + axitinib (*N* = 2) Atezolizumab + bevacizumab (*N* = 1)	3/5 (60%)	Nivolumab + ipilimumab (*N* = 12)	1/12 (8%)
2L	Nivolumab + cabozantinib (*N* = 2) Nivolumab + axitinib (*N* = 1) Atezolizumab + bevacizumab (*N* = 1)	0/4 (0%)	Nivolumab + ipilimumab (*N* = 3)	0/3 (0%)
≥3L	Nivolumab + cabozantinib (*N* = 2)	1/2 (50%)	Nivolumab + ipilimumab (*N* = 2) Durvalumab + tremelimumab (*N* = 1)	0/3 (0%)

Abbreviations: ICT, immune checkpoint therapy; VEGF, vascular endothelial growth factor; TT, targeted therapy; 1L, first line; 2L, second line; ≥3L, third line or beyond.

Alhalabi O at al, The Oncologist 2023

Evre IV nccRCC sistemik tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Kidney Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[h]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Clinical trial • Cabozantinib • Sunitinib	• Lenvatinib + everolimus • Nivolumab[b] • Nivolumab + cabozantinib • Pembrolizumab[b]	• Axitinib • Bevacizumab[g] • Bevacizumab[g] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC (See HERED-RCC-D) • Bevacizumab[f] + everolimus • Erlotinib • Everolimus • Nivolumab + ipilimumab (category 2B) • Pazopanib • Temsirolimus[e] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

Evre IV nccRCC devam eden çalışmalar

	NCT	Interventions	Trial type	n
SUNIFORECAST	NCT03075423	Sun vs Nivo/Ipi	Phase 2	306
SAMETA	NCT05043090	Salvo/Durva vs Sun vs Durva (MET driven)	Phase 3	300
LENKYN	NCT04267120	Len/Pembro	Phase 2	34
INDIGO	NCT04644432	Genomics based approach	phase 2	30
ANZUP	NCT03177239	Nivo → nivo/ipi	Phase 2	85
CANI	NCT04413123	Cabo/nivo/ipi	Phase 2	40
PAPMET2	NCT05411081	Cabo vs Cabo/Atezo	Phase 2	200
ICONIC	NCT03866382	Cabo/nivo/ipi	Phase 2	224

Sonuç 1

nccRCC heterojen bir grup

- nccRCC sarkomatoid ve rabdoid diferansiasyon

  Nivolumab+ipilimumab, Cabozantinib+Nivolumab, Axitinib+Pemrolizumab

- Papiler alt tip için tedavi seçeneği

  Cabozantinib, Cabozantinib+Nivolumab, lenvatinib+Pemrolizumab, Sunitinib

  Savolitinib+Durvalumab (MET alterasyonu olanlarda)

- Unklasifiye nccRCC

  Cabozantinib, Cabozantinib+Nivolumab, lenvatinib+Pemrolizumab, Sunitinib

Sonuç 2

- Kromofob nccRCC

  Genel olarak immüne checkpoint inhibitörlerine dirençli

  Everolimus+Lenvatinib, Bevacizumab+Everolimus, Kabozantinib, sunitinib

- Toplayıcı kanal

  Platin bazlı kemoterapi, kabozantinib

- Renal medüller karsinom

  Platin bazlı kemoterapi, Gemsitabin+Doksorubisin, Bevacizumab + Erlotinib

Sonuç 3

- Herediter leiomyomatozis bağlı-ncc RCC

  Bevacizumab+Erlotinib

  Somatik mutasyonda etkinlik daha az olmak ile beraber

  Bevacizumab+Erlotinib

- Translokasyon Renal Hücreli Karsinom : TFE3, TFEB and MIT

  Lenvatinib+pemrolizumab, Axitinib+Pemrolizumab,kabozantinib+Nivulumab, kabozantinib, Sunitinib