Non Clear Cell RCC Sistemik Tedavi Seçenekleri

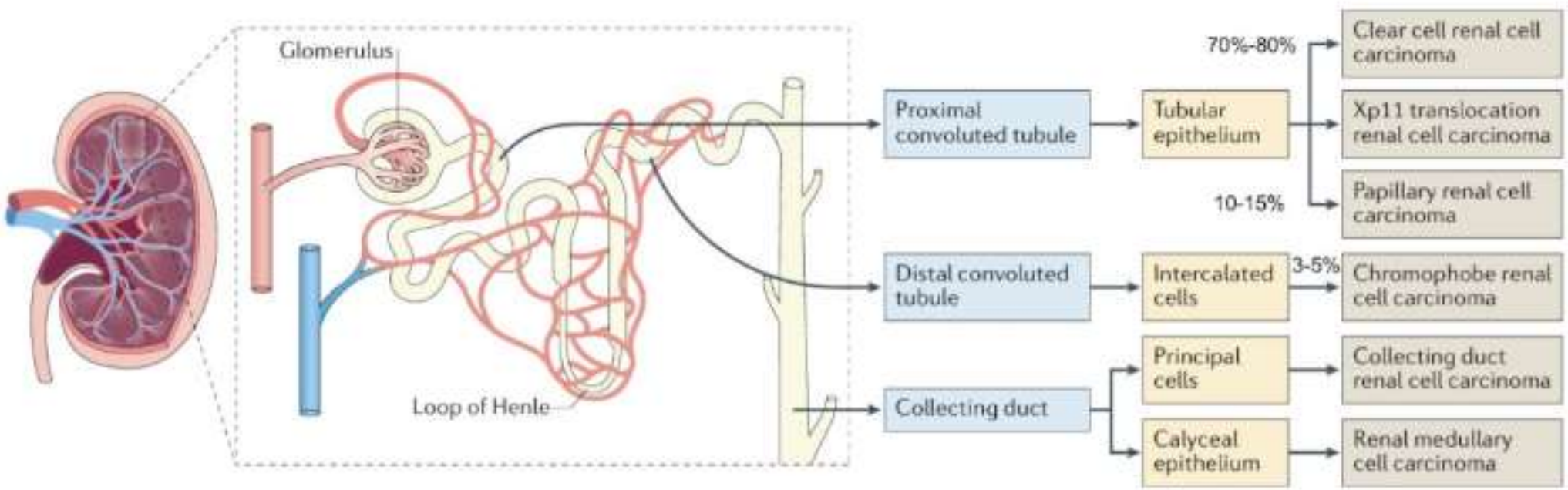
Dr. Deniz Tural

Koç Üniversitesi Hastanesi Medikal Onkoloji

Ders Planı

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

Böbrek Tümörleri Lokalizasyona Göre Alt Tipleri



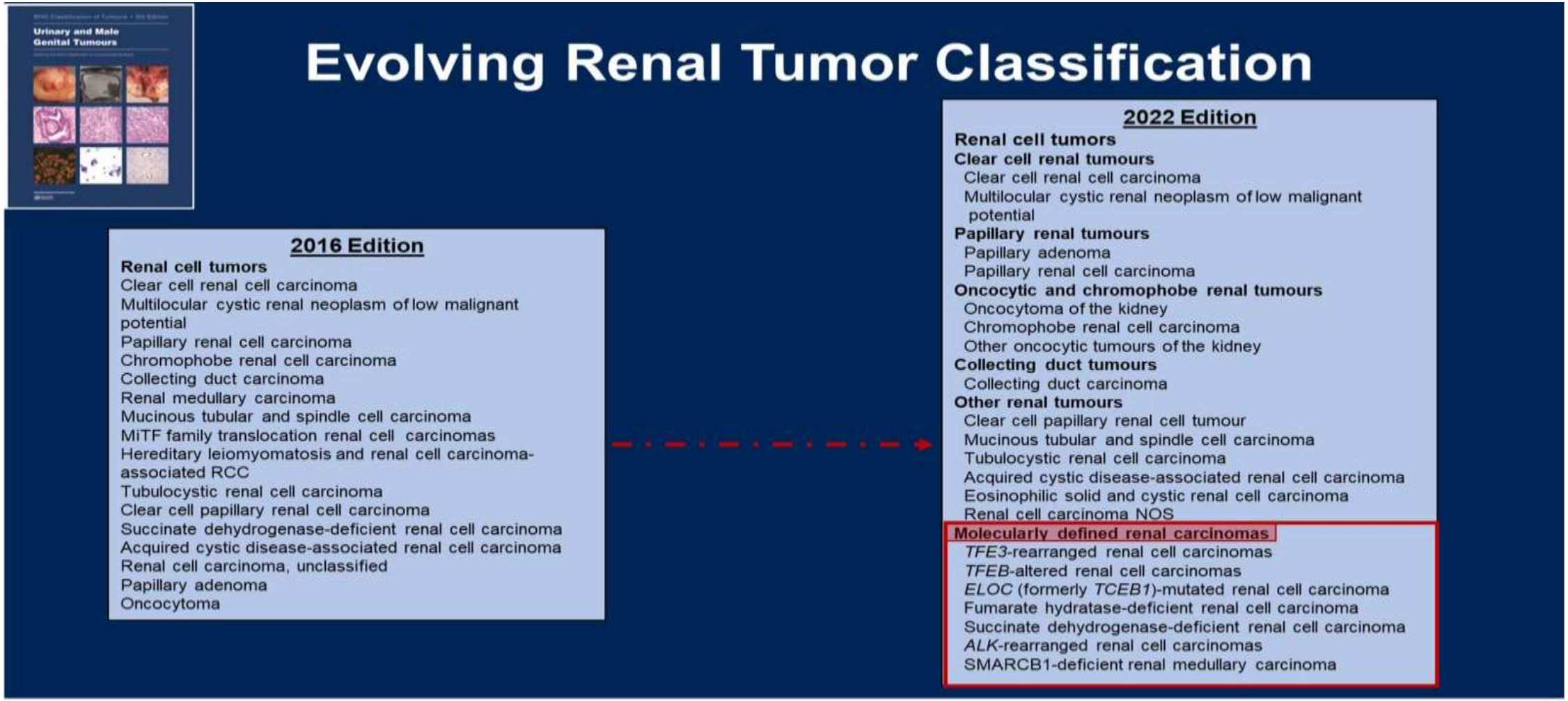
Böbrek hücreli kanserin en yaygın alt tipi, vakaların %70–80'ini oluşturan berrak hücreli tiptir. Berrak olmayan tipler içinde en sık görüleni ise %10–15 ile papiller tiptir.

Berrak Hücre Dışı Böbrek Kanserleri(nccRCC) Heterojen Bir Grup

Hücre döngüsü, yağ asidi oksidasyonu ve sentezi gibi gen skorlar nccRCC alt tiplerinde yüksekti

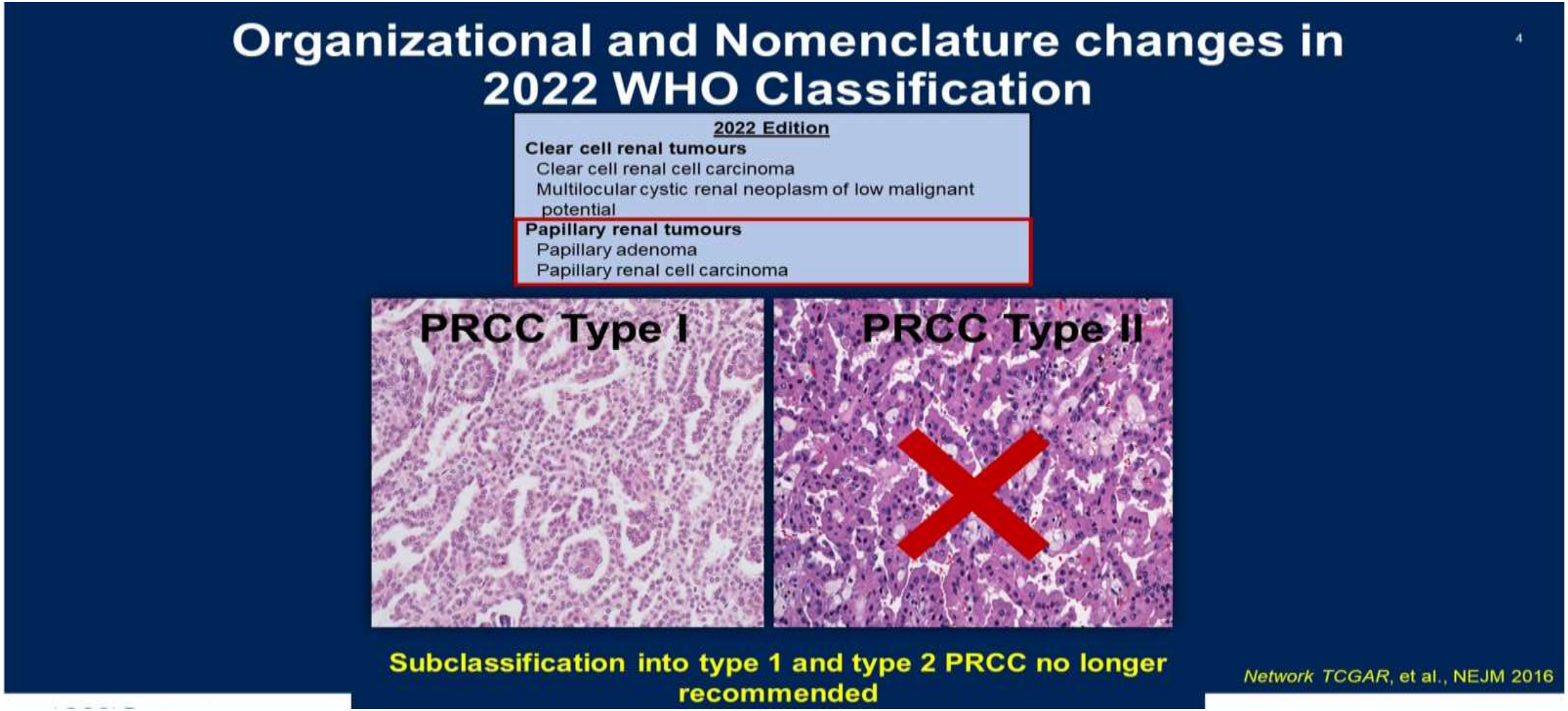
Berrak hücreli böbrek kanseri (ccRCC), anjiyogenez gen ifadesi ve immün inflamasyon yüksek

Berrak Hücre Dışı Böbrek Kanserinde(nccRCC) Sınıflandırma



Kapur P, ASCO GU23

Berrak Hücre Dışı Böbrek Kanserinde(nccRCC) Sınıflandırma



Kapur P, ASCO GU23

nccRCC moleküler 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)

Kapur P, ASCO GU23

nccRCC moleküler sınıflandırma

Table 1. New molecular-defined RCC entities defined by the WHO[6]

RCC subtype (WHO)	Genetic alteration	Comments
Eosinophilic solid and cystic RCC	*TSC* mutation and activation of mTOR pathway	Typically clinically indolent Responses with use of mTOR inhibitors have been reported
ELOC-mutated RCC	*ELOC* (*TCEB1*) mutation	Clear cells with abundant cytoplasm and presence of fibromuscular bands Based on limited data, seem to behave indolently and are associated with good prognosis
ALK-rearranged RCC	*ALK* rearrangements	Typically morphologically very heterogeneous Responses with use of ALK inhibitors have been reported
SMARCB1-deficient medullary RCC	*SMARCB1* loss	Highly aggressive subtype Frequently occurs in young patients with sickle cell trait (although not required for diagnosis)
TFEB-altered RCC	*TFEB* translocation and *TFEB* amplification	*TFEB*-translocated RCC is typically clinically indolent *TFEB*-amplified RCC is typically highly aggressive, tends to occur in older patients
FH-deficient RCC	*FH* loss or mutation	May be associated with HLRCC

ALK, anaplastic lymphoma kinase; FH, fumarate hydratase; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; mTOR, mammalian target of rapamycin; RCC, renal cell carcinoma; WHO, World Health Organization.

Powles T, et al, Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up 2024.

nccRCC moleküler sınıflandırma

***ALK* fusions noted across a database of 2214 cases of advanced renal cell carcinoma**

Patient	Subtype	Sequenced specimen site	Gender	Age	Fusion	5′ partner exons	ALK exons	Concurrent GAs
1	RCC-NOS	Kidney	M	3	*STRN-ALK*	Exons 1–3	Exons 20–29	None
2	RCC-NOS	Kidney	M	62	*EML4-ALK* (variant 5a/b)	Exons 1–2	Exons 20–29	*TERT* promoter -146C > T
3	RCC-NOS	Left flank, soft tissue	M	18	*EML4-ALK* (variant 3)	Exons 1–6	Exons 20–29	*BCORL1* W1468*, *MCL1* amplification, *TP53* R248Q

GA = genomic alteration; M = male; NOS = not otherwise specified; RCC = renal cell carcinoma.

The Cancer Genome Atlas (TCGA) veritabanına göre
Papiller renal hücreli karsinom (PRCC) tanısı olan 292 hastanın 9'unda (**%2,86**) **ALK geninde değişiklik** saptanmıştır.
Bu hastalarda ALK genine ait şu değişiklikler görülmüştür:

1.Üç nokta mutasyonu (point mutation):

1. I801T
2. R1253T
3. Q1336H

2.üç genomik amplifikasyon (gen düzeyinde artış)
3.İki delesyon (gen kaybı/silinmesi)
4.Bir hastada ALK genine ait mRNA ekspresyonunda artış (yükselmiş gen ifadesi)

Clinical Laboratory Improvement Amendments (CLIA)-certified targeted sequencing platform

Pal S et al European Urology 2018. Cerami E et al. Cancer Discov 2012.

nccRCC ve Herediter sendromlar

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
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 • Table 2	• Neurosurgery • Ophthalmology • Audiology • Endocrinology • Endocrine surgery
Hereditary papillary renal carcinoma (HPRC)/*MET* gene	Papillary	• Autosomal dominant • Multifocal, bilateral renal cell tumors	• Nephrology
Birt-Hogg-Dubé syndrome (BHDS)/*FLCN* gene[1,2]	Chromophobe, hybrid oncocytic tumors, clear cell, oncocytomas, angiomyolipomas, papillary RCC	• Autosomal dominant • Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, and spontaneous pneumothorax	• Pulmonology • Dermatology
Tuberous sclerosis complex (TSC)/*TSC1, TSC2* genes	Angiomyolipoma (and other PEComas), renal cysts, eosinophilic solid and cystic RCC, RCC with fibromyomatous stroma, eosinophilic vacuolated tumor, low-grade oncocytic tumor, clear cell	• Autosomal dominant • Table 1	• Neurology • Dermatology
Hereditary leiomyomatosis and renal cell cancer (HLRCC)/*FH* gene	HLRCC-associated RCC or FH-deficient RCC	• 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	• Autosomal dominant • Melanoma (uveal and cutaneous), kidney cancer, mesothelioma	• Dermatology • Ophthalmology • Thoracic oncology
Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome/*SDHA/ B/C/D* genes	SDH-deficient RCC	• Autosomal dominant • Head and neck PGL and adrenal or extra-adrenal PCCs, gastrointestinal stromal tumors (GIST)	• Endocrine • Endocrine surgery

[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-Ruweather bín-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 sendromlar şeklinde görülür

Lopez-Beltran at al, Eur. Urol.2006

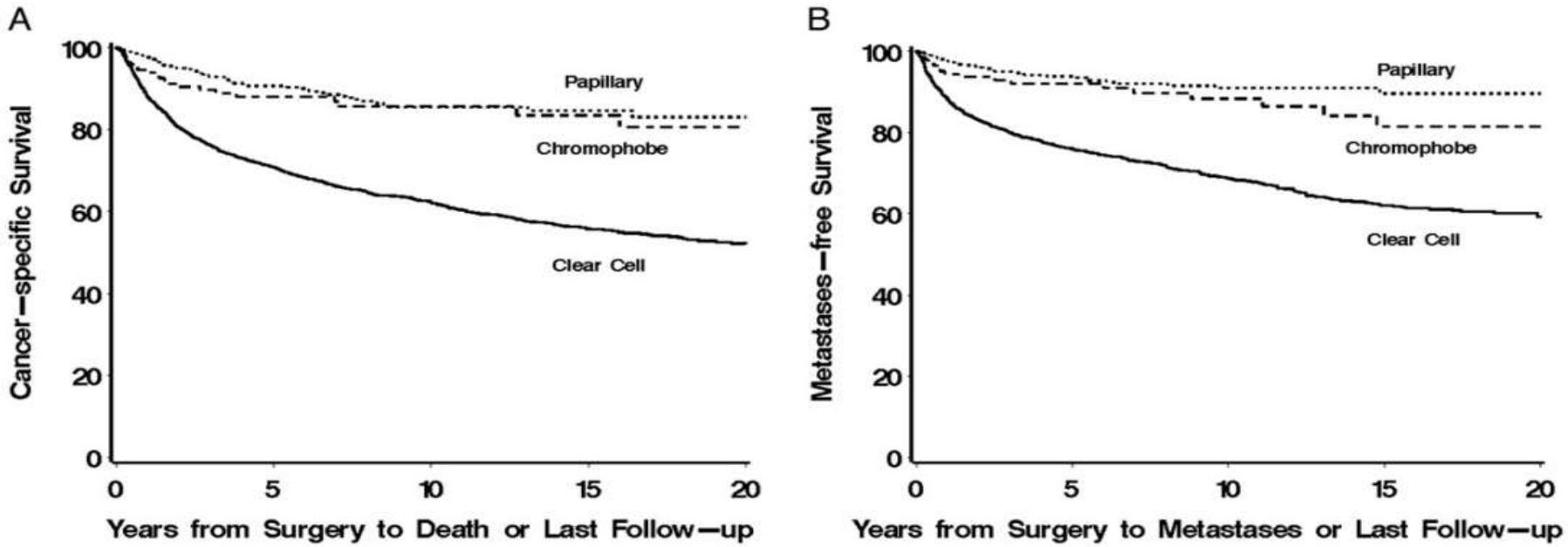
ccRCC ve nccRCC Görülme Sıklığı

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

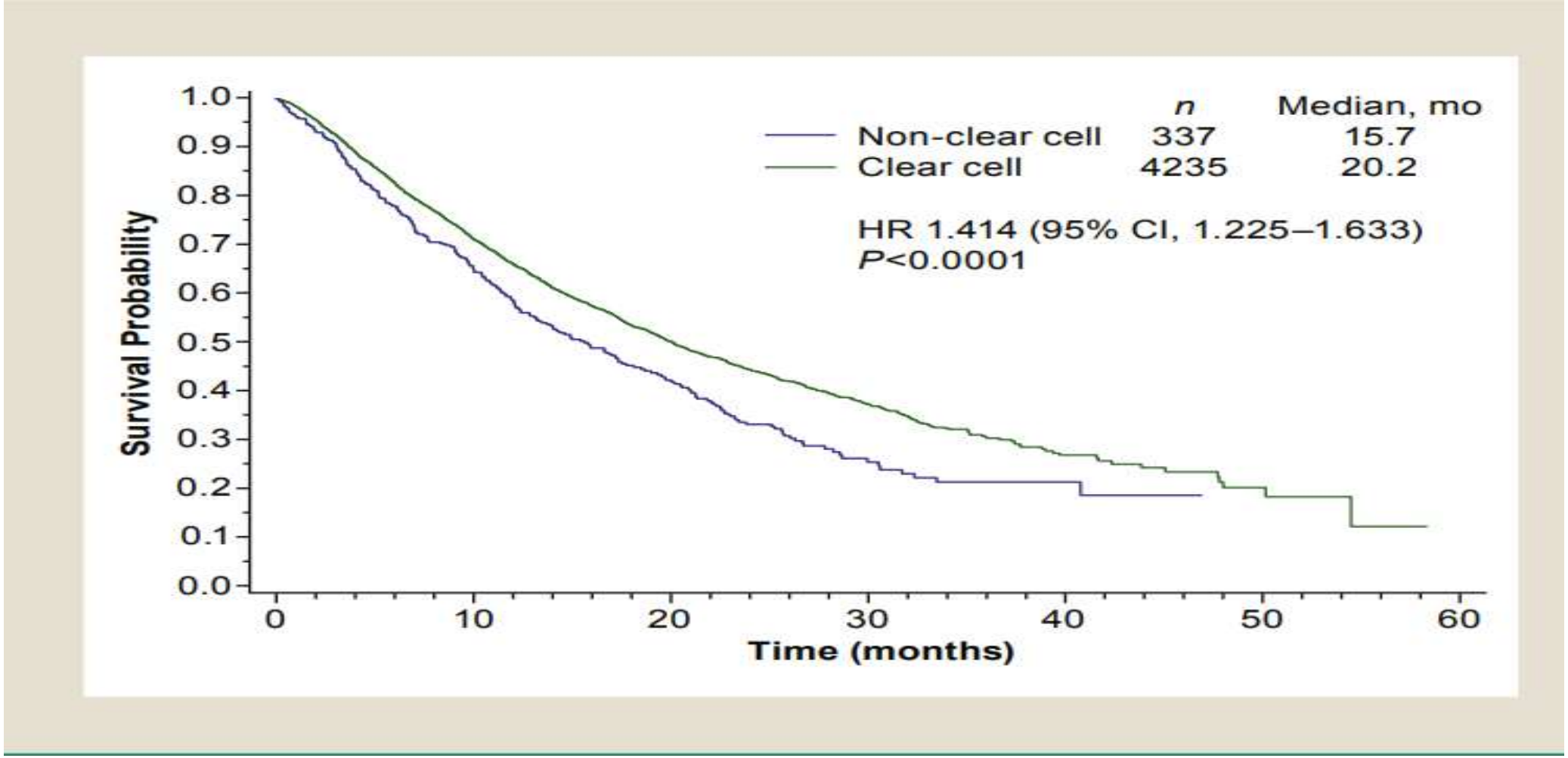
Metastatik olmayan RCC histolojik alt tipe göre sağkalım



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.

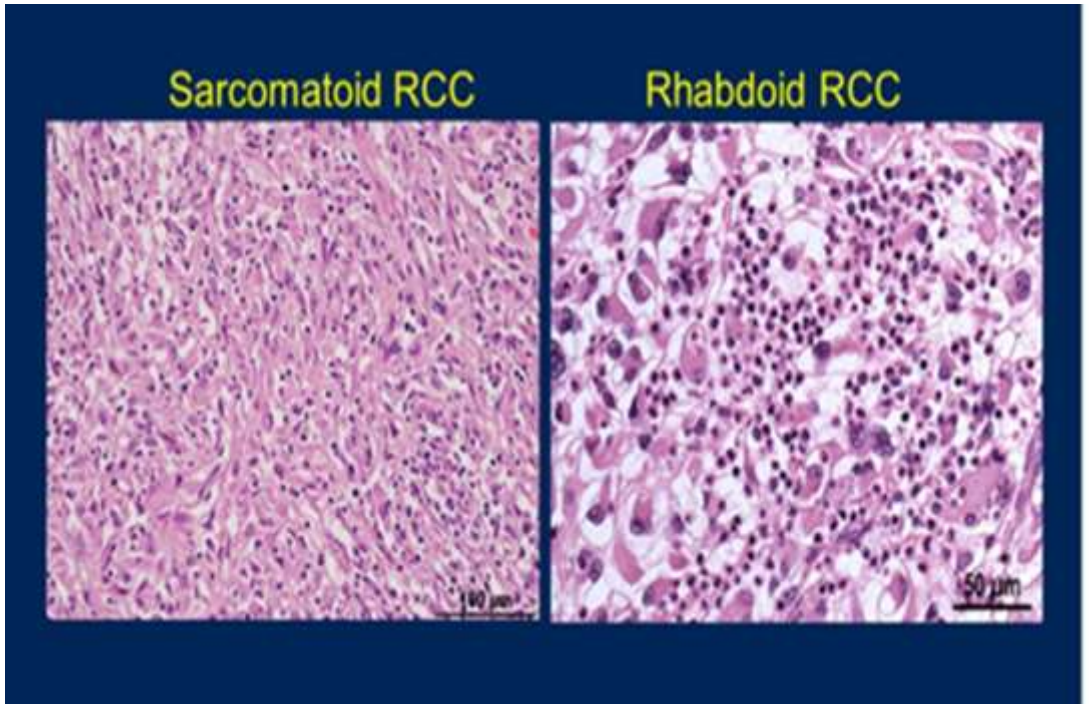
Bradley C et al, JOURNAL OF UROLOGY 2010

Metastatik RCC histolojik alt tipe göre sağkalım



Guillermo de Velasco et al, Clinical Genitourinary Cancer 2017

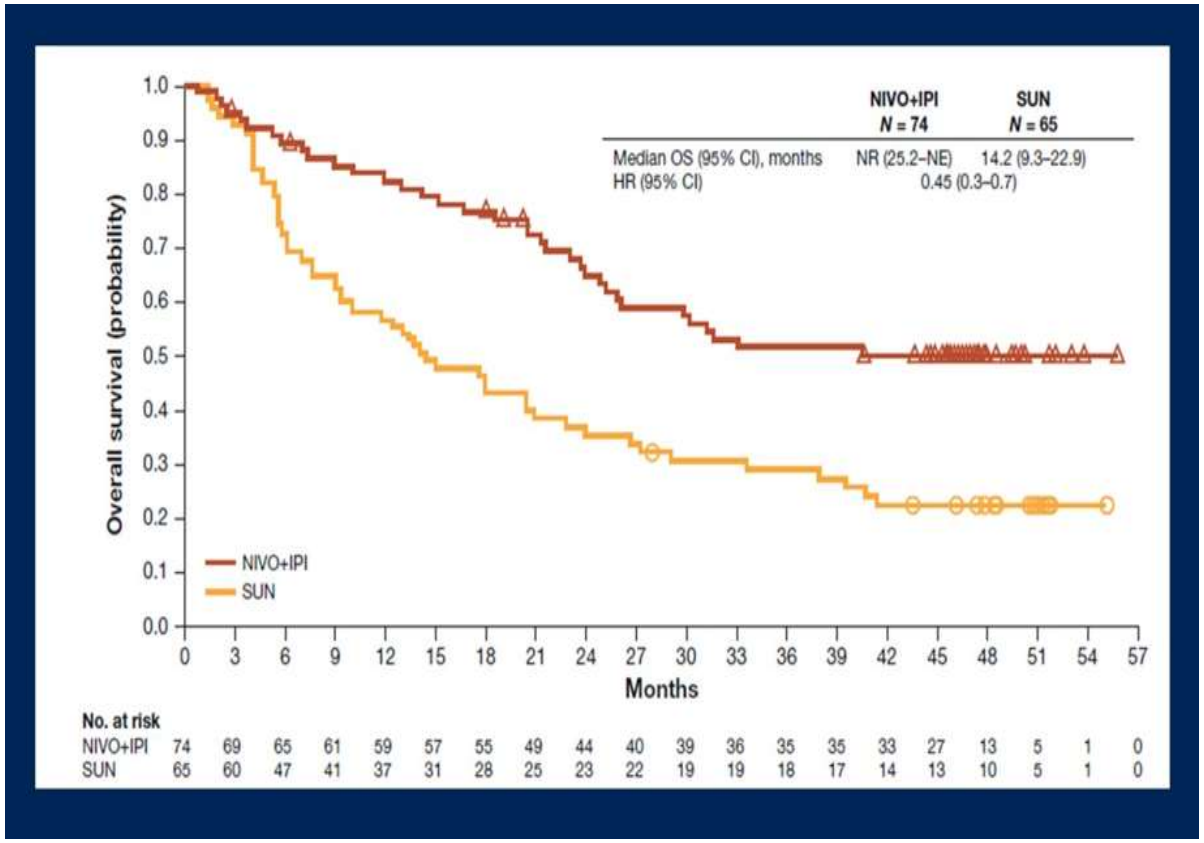
ccRCC ve nccRCC sarkomatoid ve rabdoid dediferansiasyon



- ❑ ccRCC ve nccRCC dediferansiye formda görülür
- ❑ %10-15 oranında ccRCC ve nccRCC görülür
- ❑ BAP1 ve CDKN2A mutasyonu yüksek
- ❑ TKI ve mTOR yanıt düşük
- ❑ İmmüne inflamasyon oranı yüksek ve anjiyogeneziz düşük
- ❑ İmmüne checkpoint yanıt iyi

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

ccRCC ve nccRCC sarkomatoid ve rabdoid dediferansiasyon



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%	

Medyan takip süresi 42 ay

CheckMate 214 çalışmasında 145(%13) hastada sarkomatoid ve rabdoid

ORR 60.8% NIVO+IPI vs 23.1% SUN

Tannir N et al, Clin Cancer Res. 2021.

ccRCC ve nccRCC sarkomatoid ve rabdoid dediferansiasyon

Trial	Arms	No. of Patients with Sarcomatoid RCC	ORR	CR Rate	PFS	OS
CheckMate-214 (ClinicalTrials.gov identifier: NCT02231749)	Nivolumab + ipilimumab *v* sunitinib	139[a]	60.8% *v* 23.1%	23.0% *v* 6.2%	26.5 months *v* 5.5 months (HR = 0.50)	48.6 months *v* 14.2 months (HR = 0.46)
JAVELIN 101 (ClinicalTrials.gov identifier: NCT02684006)	Avelumab + axitinib *v* sunitinib	108	46.8% *v* 21.3%	4.3% *v* 0%	7.0 months *v* 4.0 months (HR = 0.57)	12-month OS rate: 83.0% *v* 67.0%
IMmotion151 (ClinicalTrials.gov identifier: NCT02420821)	Atezolizumab + bevacizumab *v* sunitinib	142	49% *v* 14%	10% *v* 3%	8.3 months *v* 5.3 months (HR = 0.52)	21.7 months *v* 15.4 months (HR = 0.64)
KEYNOTE-426 (ClinicalTrials.gov identifier: NCT02853331)	Pembrolizumab + axitinib *v* sunitinib	105	58.8% *v* 31.5%	11.8% *v* 0%	NR *v* 8.4 months (HR = 0.54)	12-month OS rate: 83.4% *v* 79.5% (HR = 0.58)
CLEAR (ClinicalTrials.gov identifier: NCT02811861)	Pembrolizumab + lenvatinib *v* sunitinib	49	60.7% *v* 23.8%	0.8% *v* 0%	11.1 months *v* 5.5 months (HR = 0.39)	NR *v* NR (HR = 0.91)
CheckMate-9ER (ClinicalTrials.gov identifier: NCT03141177)	Nivolumab + cabozantinib *v* sunitinib	75	58.8% *v* 22.0%	Not reported	13.8 months *v* 4.2 months (HR = 0.34)	37.6 months *v* 22.1 months (HR = 0.38)

Nivolumab+İpilimumab, takip süresi, tam yanıt oranı ve PFS yönünden daha iyi sonuçlara sahip

Salgia J et al, asco.org/edbook 2025

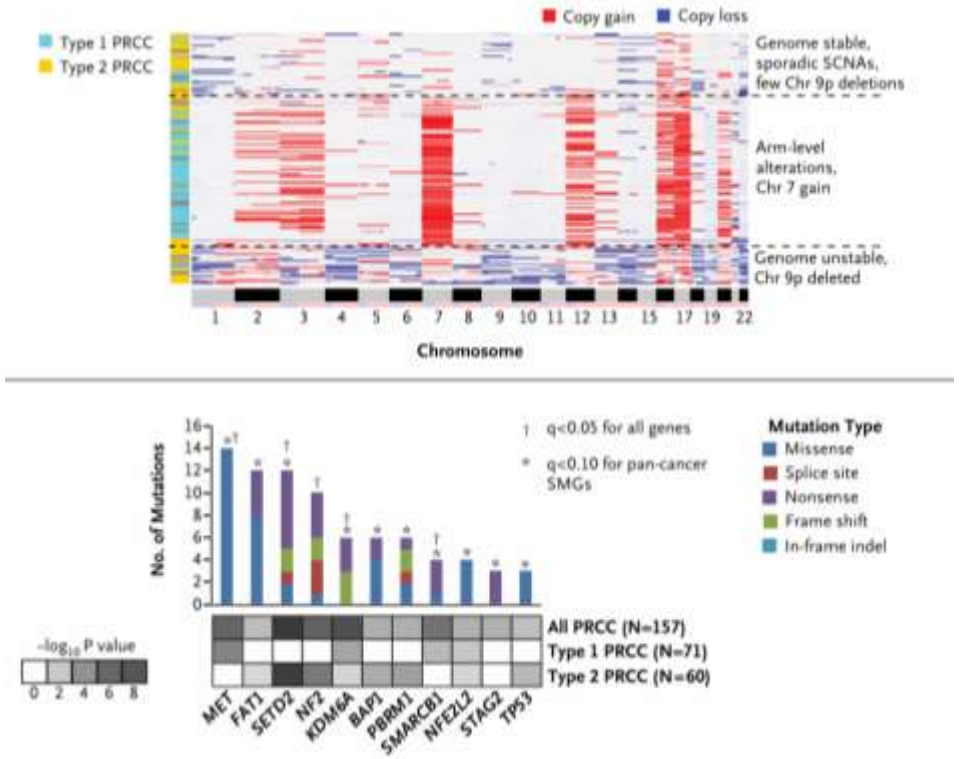
nccRCC TKI ve mTOR inhibitörleri

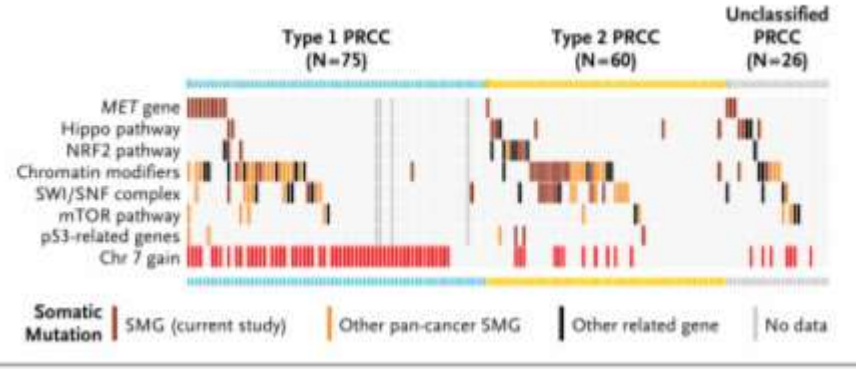
Trial	Treatment	Randomized?	Number Enrolled	Histology Type	Overall Response Rate	Progression-Free Survival	Overall Survival
ESPN	Sunitinib vs. everolimus	Yes	68 patients	All non-clear cell	9% vs. 3%	6.1 vs. 4.1 months	16.2 vs. 14.9 months
ASPEN	Sunitinib vs. everolimus	Yes	108 patients	All non-clear 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)

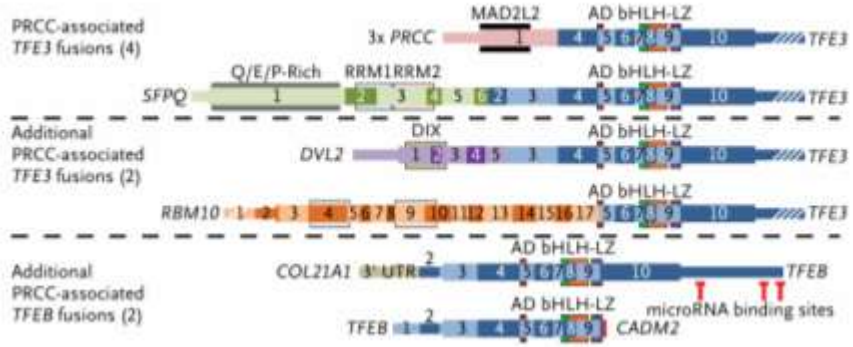
Sunitinib nccRCC tedavisinde 6-8 ay PFS, daha iyi RR ve OS değerleri ile everolimus tedavisine göre daha avantajlı

Tian Zhang et al, ASCO Educational Book 2017.

nccRCC papiller histolojiye göre tedavi seçenekleri







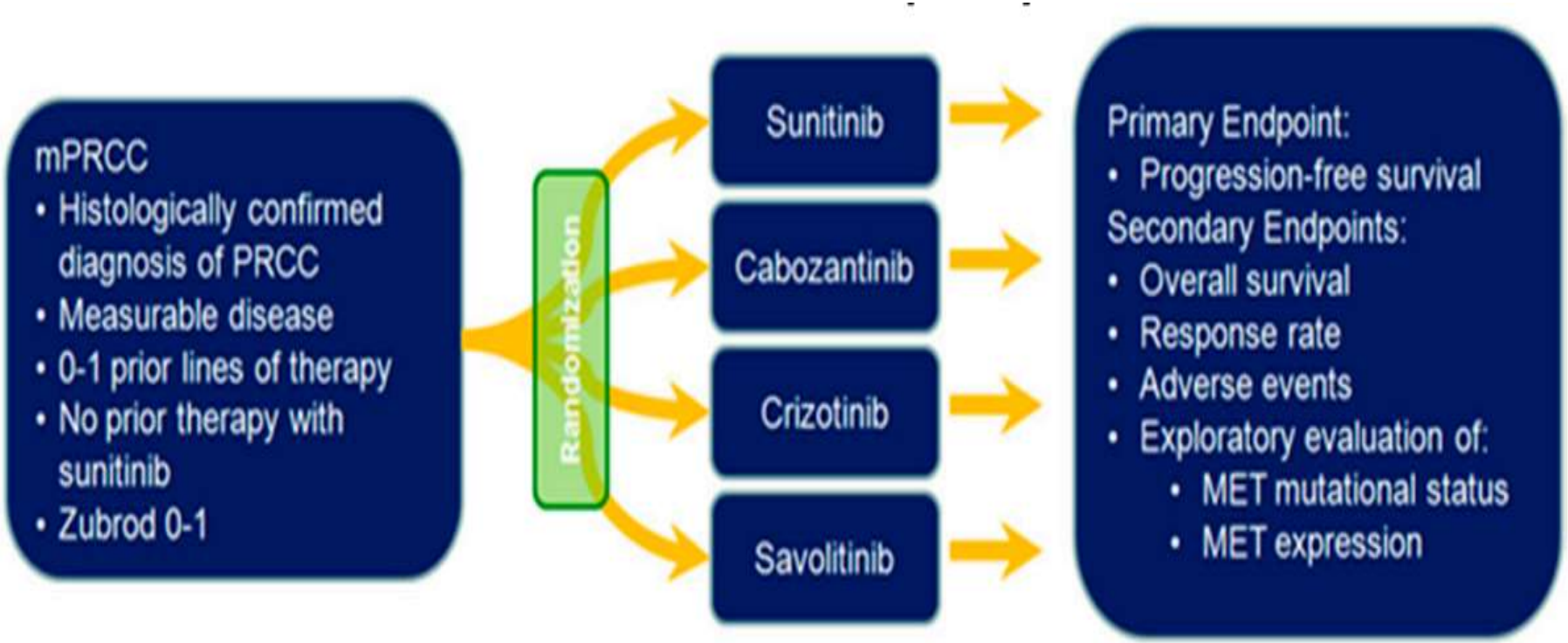
Papiller renal hücreli karsinomlar klinik ve biyolojik olarak farklıdır

- **Tip 1**, genellikle **MET yolu aktivasyonu** ile ilişkilidir
- **Tip 2**, **NRF2-ARE yolu aktivasyonu**, **CDKN2A kaybı** ve CpG Island Methylator Phenotype(**CIMP)** ile ilişkilidir; bu değişiklikler **kötü prognoz** göstergesidir
- Ayrıca **Tip 2**, moleküler ve fenotipik özelliklere göre **en az üç alt tipe** ayrılır

DeVolk, B.A et al, N Engl J Med 2016

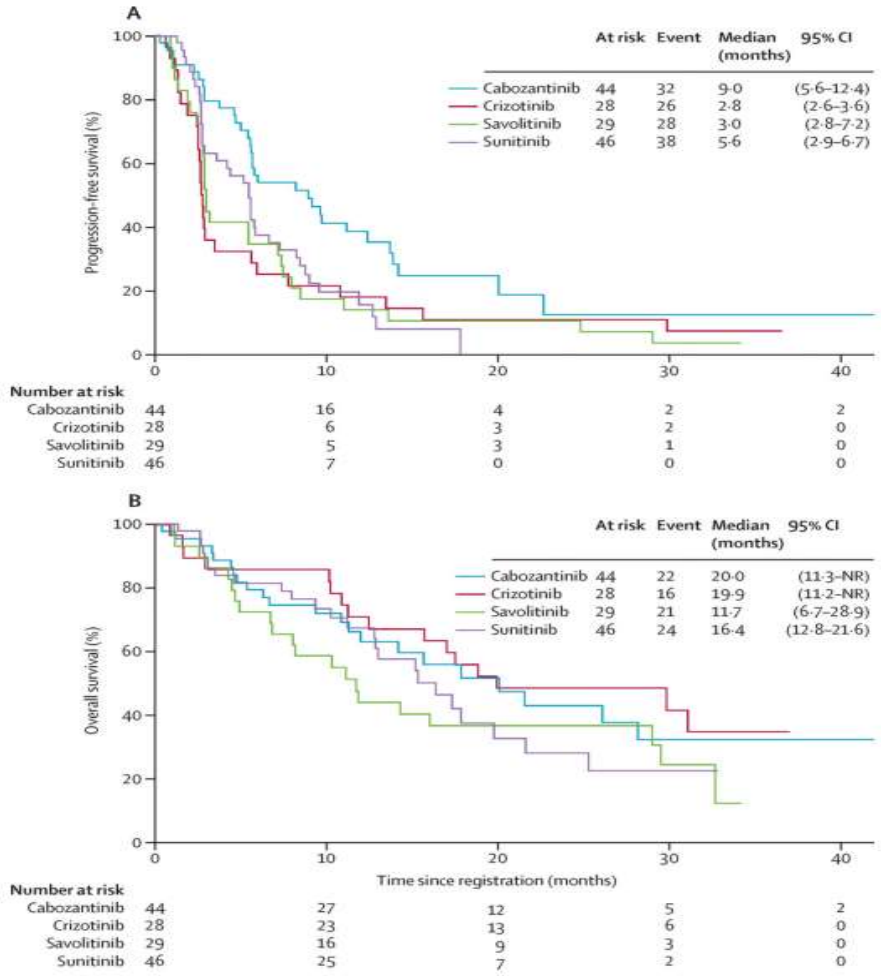
nccRCC papiller histolojiye göre tedavi seçenekleri

SWOG 1500 Faz II çalışması



Pal at al, GU ASCO 2021

nccRCC papiller histolojide göre tedavi seçenekleri

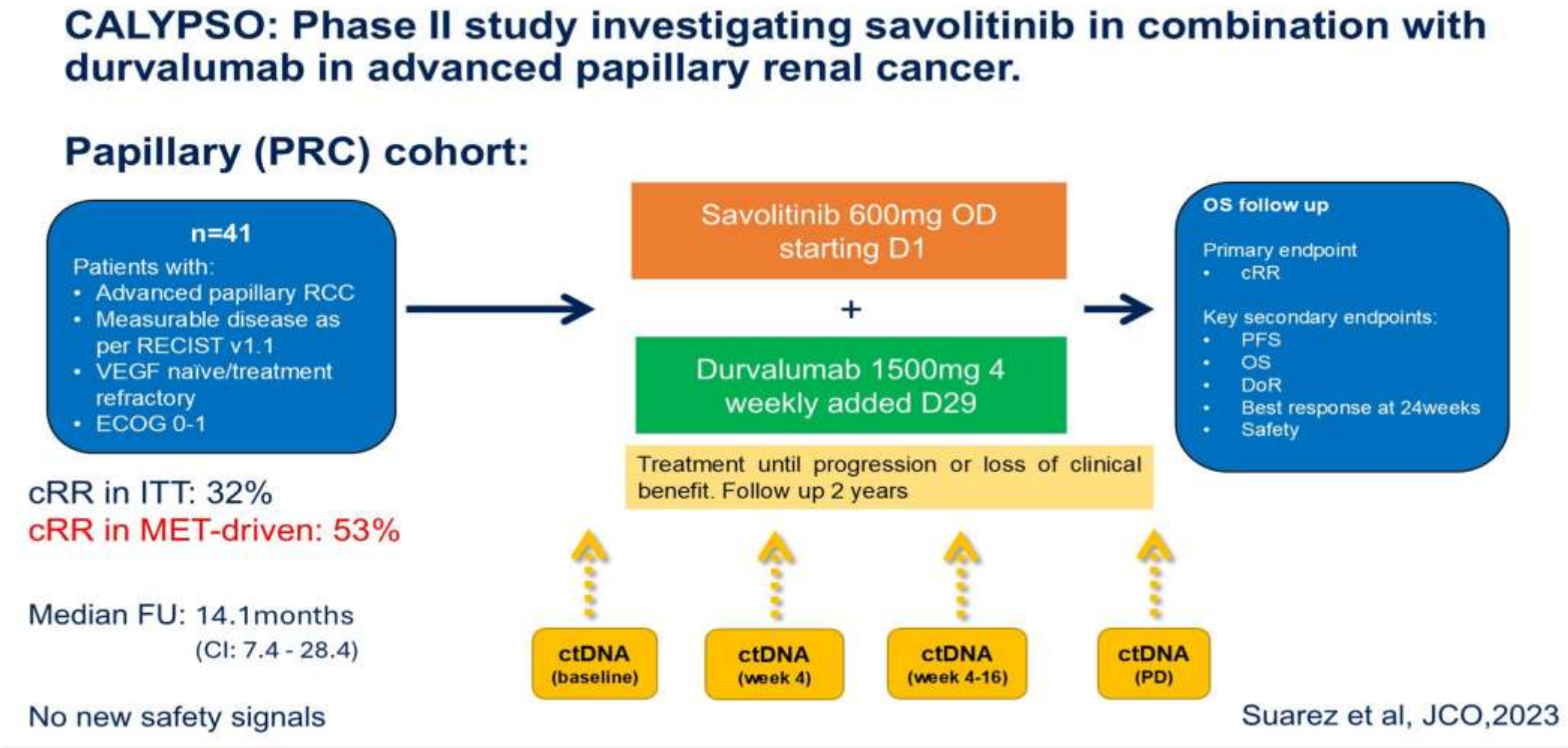


	Cabozantinib	Sunitinib	HR/P-value
Median PFS	9 months	5.6 months	0.6 (95% CI 0.37-0.97) P=0.019
ORR	23%	4%	P=0.01
OS	20 months	16.4 months	0.84 (95% CI 0.47-1.51)

- **152 hasta çalışmaya dahil edildi**
- **Savolitinib=29, crizotinib=28, sunitinib=46 ve cabozantinib n=44**

Pal S et al, Lancet 2021

nccRCC papiller histolojide göre tedavi seçenekleri



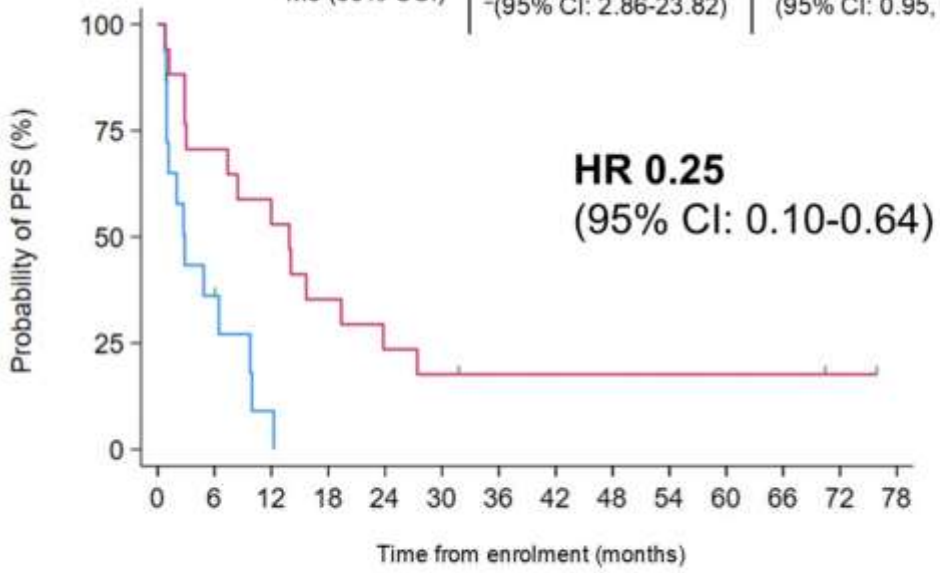
Spence F, ASCO GU25

nccRCC papiller histolojide göre tedavi seçenekleri

Final PFS and OS in MET-driven population

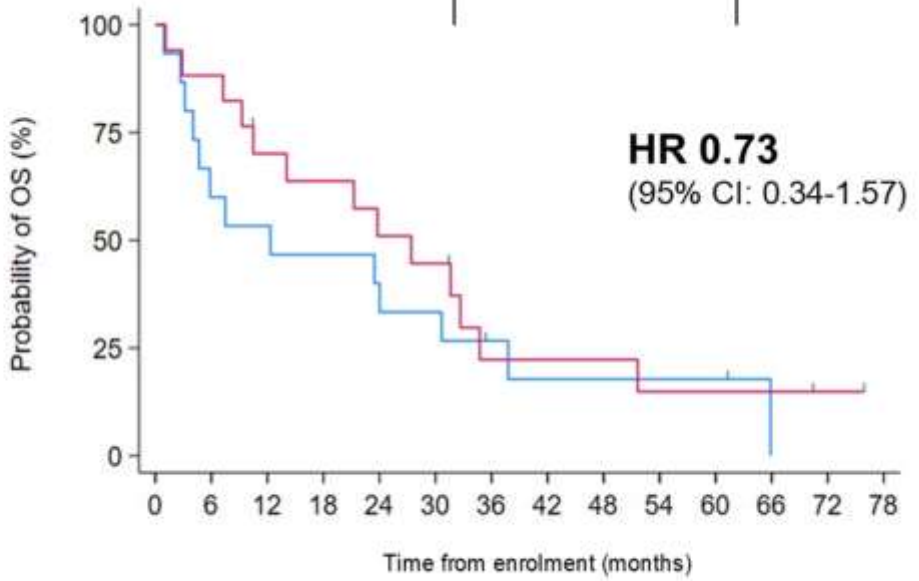
MET-driven Progression-Free Survival

	MET-driven (n=17)	Non-MET-driven (n=15)
Median PFS Mo (95% CCI)	**13.9** (95% CI: 2.86-23.82)	2.9 (95% CI: 0.95, 9.7)



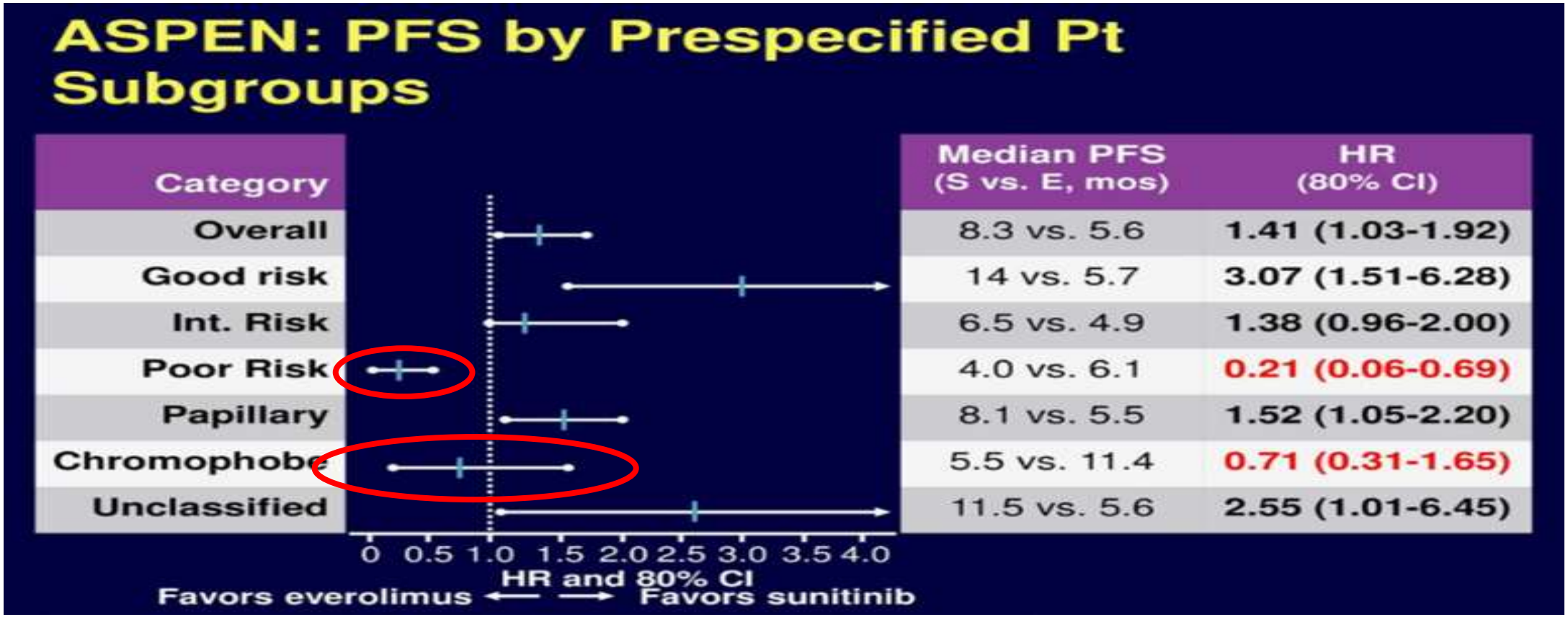
MET-driven Overall Survival

	MET-driven (n=17)	Non-MET-driven (n=15)
Median OS Mo (95% CCI)	**27.4** (95% CI: 9.27-34.73)	12.3 (95% CI:3.15-30.65)



Spence F, ASCO GU2025

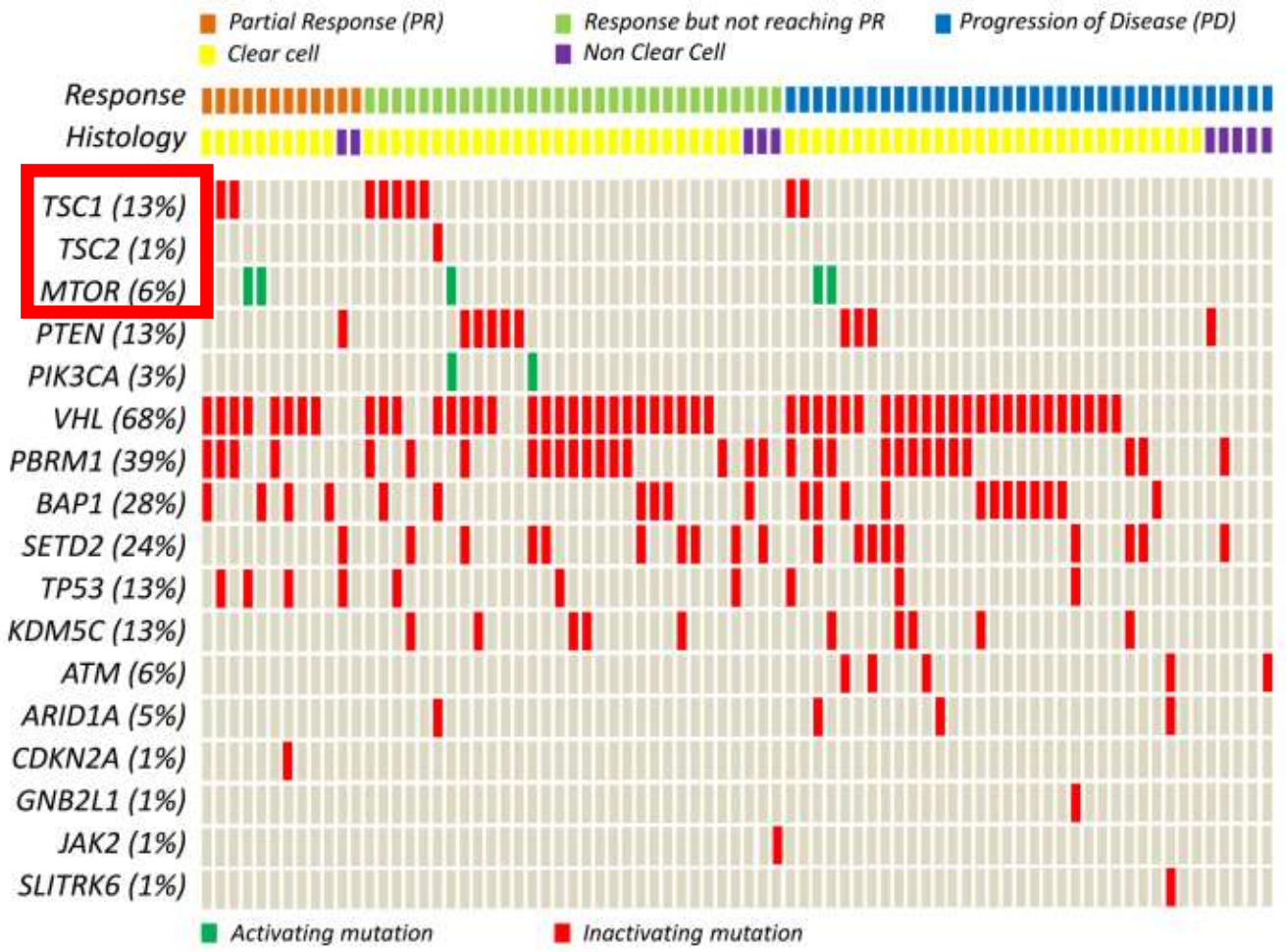
nccRCC TKI ve mTOR inhibitörleri



nccRCC chromophobe histolojide mTOR etkinliği daha belirgin

Armstrong AJ et al, ASCO 2015.

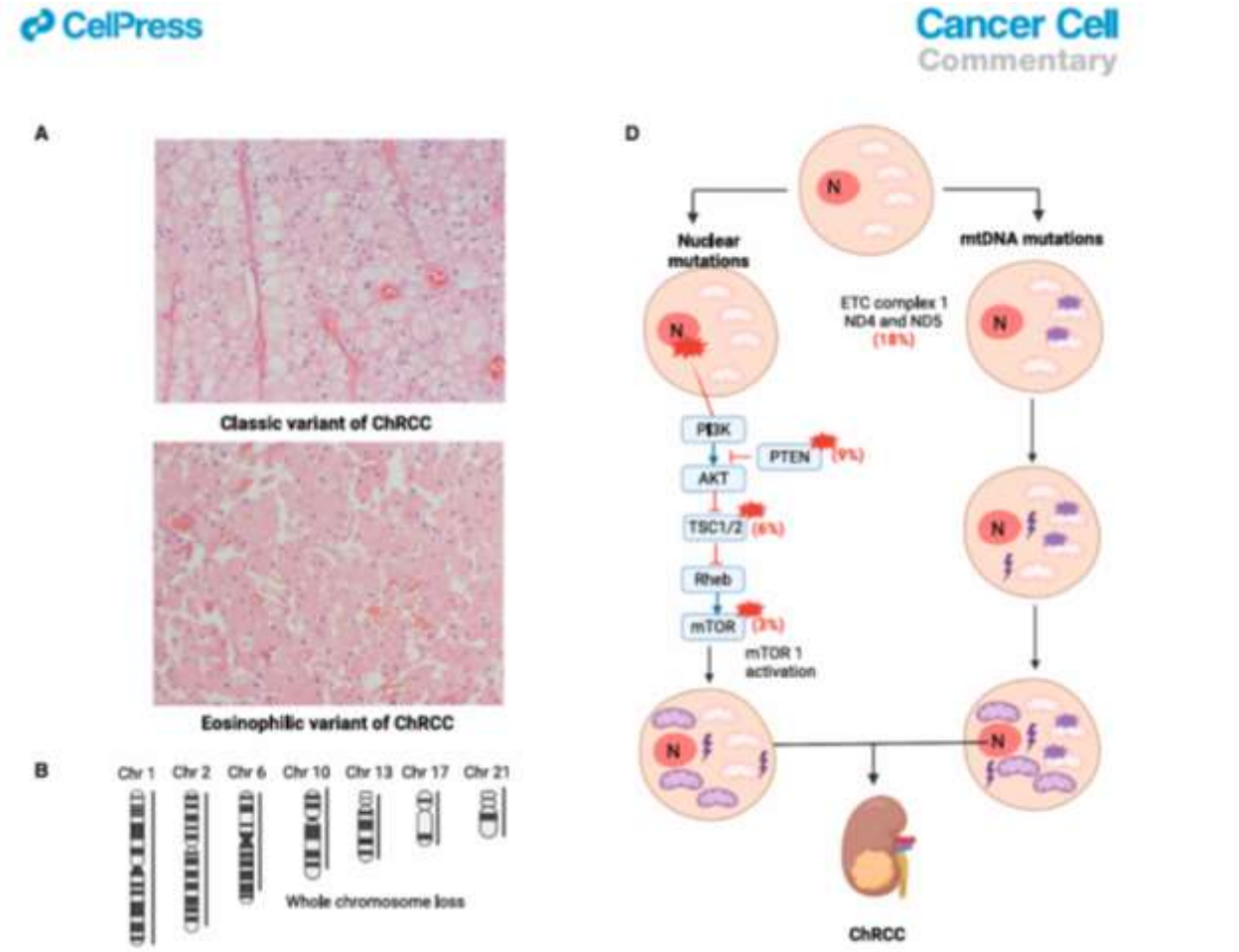
Tuberous sclerosis gen kompleksi mutasyonlarında mTOR inhibitörlerinin etkinliği



- TSC1 ve TSC2 tümör baskılayıcı gen ve mutasyonunda mTOR yolunun aşırı aktivasyonu ile ilişkilidir
- Anjiyomiyolipomlar ve böbrek kistleri, en sık görülen böbrek bulgularıdır. Ayrıca papiller, berrak hücreli ve kromofob böbrek tümörleriyle de ilişkili olabilir
- Temsirolimus, everolimus alan hastalarda, mTOR, TSC1 veya TSC2 genlerinde mutasyon olanların tedaviye daha iyi yanıt verdiği gösterilmiştir
- TSC1 veya TSC2 mutasyonu, yanıt veren hastaların %21'inde; yanıt vermeyenlerin ise %6'sında bulunmuştur
- Ayrıca, kısmi tedavi yanıtı gösteren hastaların %42 mTOR, TSC1 veya TSC2 mutasyonu saptanırken, yanıt vermeyen hastanın yalnızca %11 bu mutasyonlar bulunmuştur

Kwiatkowski DJ et al, Clin Cancer Res 2016.

nccRCC chromophobe histolojiye göre tedavi seçenekleri



- **ChRCC, en sık ikinci görülen non-clear cell RCC alt tipidir.**
- **ChRCC, böbrekteki α-interkale hücrelerden köken alır.**
- **ccRCC'den genetik ve metabolik olarak farklıdır.**
- **Patogenez:**
  - PTEN mutasyonları → mTORC1 aktivasyonu
  - Mitokondriyal disfonksiyon → oksidatif stres
  - MHC sınıf I genlerinin downregülasyonu, immün checkpoint terapilere zayıf yanıtla ilişkilidir.
- **Spesifik tedavisi yoktur.**
  - TKI ve mTOR inhibitörlerine kısmi yanıt
  - İmmünoterapiye düşük yanıt
  - HSP70 genlerinin baskılanması, ChRCC'nin ferroptozise duyarlılığını artırabilir
- **Yeni hedefler: IL-15 yolu, ferroptozis**

Henske E et al, Cancer Cell 2023. Labaki C et al, The Oncologist 2023.

nccRCC chromophobe histolojiye göre tedavi seçenekleri

Lenvatinib+Everolimus Faz II çalışması

Table 2. Summary of Efficacy Outcomes by Histological Subtype

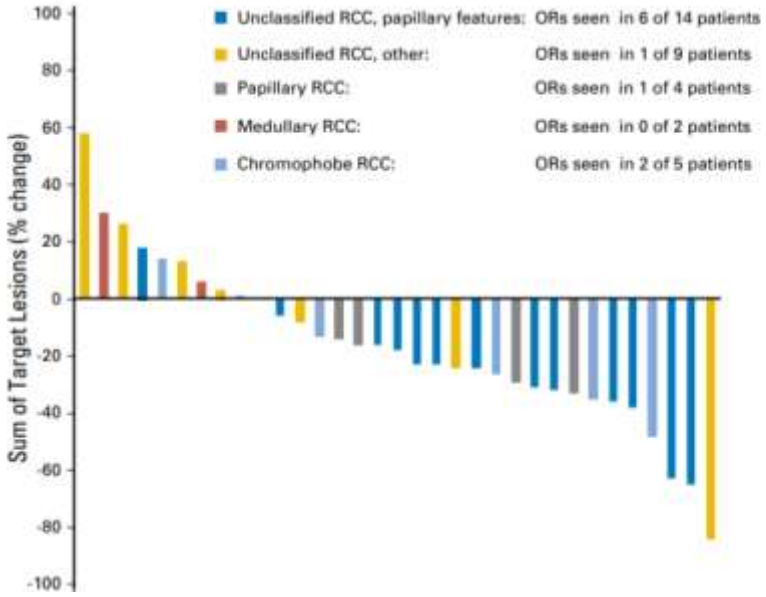
Parameter, n (%)[a]	By Investigator Assessment				By IIR
	Papillary (n = 20)	Chromophobe (n = 9)	Unclassified (n = 2)	Total (N = 31)	Total (N = 31)
Objective response rate	3 (15.0)	4 (44.4)	1 (50.0)	8 (25.8)	8 (25.8)
(95% CI)[b]	(3.2–37.9)	(13.7–78.8)	(1.3–98.7)	(11.9–44.6)	(11.9–44.6)
Best overall response					
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]	10 (50.0)	7 (77.8)	2 (100.0)	19 (61.3)	16 (51.6)
(95% CI)[b]	(27.2–72.8)	(40.0–97.2)	(15.8–100.0)	(42.2–78.2)	(33.1–69.8)
Disease control rate[e]	17 (85.0)	7 (77.8)	2 (100.0)	26 (83.9)	22 (71.0)
(95% CI)[b]	(62.1–96.8)	(40.0–97.2)	(15.8–100.0)	(66.3–94.5)	(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

Everolimus + Bevacizumab Faz II



Sınıflandırılamayan nccRCC hastalarında, tümörde belirgin papiler özelik bulunması (n = 14) veya bulunmaması (n = 9), tedavi yanıtı ile ilişkili

- **Objektif yanıt oranı (ORR**
  - **Papiller özelik varsa: %43**
  - **Yoksa: %11**
- **Ortalama PFS**
  - **Papiller özelik varsa: 12,9 ay**
  - **Yoksa: 1,9 ay**
- **Ortalama OS**
  - **Papiller özelik varsa: 28,2 ay**
  - **Yoksa: 9,3 ay**

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

Abbreviations: CR, complete response; NA, not applicable; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; SD, stable disease.
*Kaplan-Meier estimates.
†One patient with unclassified RCC experienced clinical disease progression and death related to cancer before radiographic disease reassessment during the trial could be obtained. Although the patient is evaluable for PFS analysis (per time of clinical progression/death), radiographic response assessment was not performed.

Voss M et al, J Clin Oncol 2016.

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

nccRCC immüne checkpoint inhibitörleri

Birinci basamak evre IV nccRCC tek kolu Faz II Pemrolizumab monoterapi

Key eligibility criteria
- Locally advanced or metastatic disease
- Measurable disease per RECIST v1.1 by BICR
- No prior systemic therapy for advanced RCC
- Karnofsky Performance Status score ≥70%

Screening for Eligibility

Cohort A CCRCC N=110

Cohort B nccRCC N=165

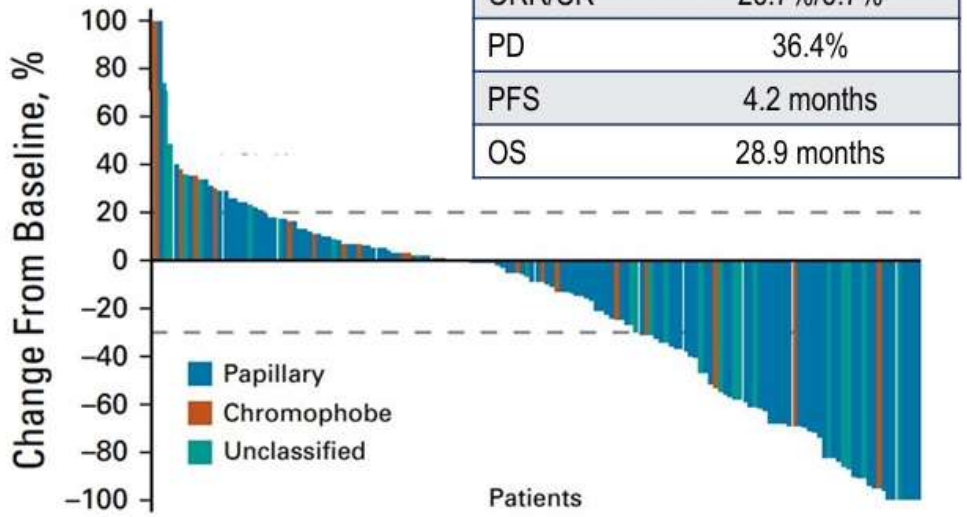
Response assessed at Week 12, Q6W until Week 54, and Q12W thereafter

Pembrolizumab 200 mg Q3W up to 35 cycles (2 years)

Endpoints
- Primary: ORR (RECIST v1.1 by BICR)
- Secondary: OS, PFS, DOR, DCR (RECIST v1.1 by BICR), safety

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%)

Outcome	(n=165)
ORR/CR	26.7%/6.7%
PD	36.4%
PFS	4.2 months
OS	28.9 months



McDermott D et al, JCO 201.

nccRCC immüne checkpoint inhibitörleri

Birinci basamak evre IV nccRCC tek kolu Faz 3b/4 Nivolumab monoterapi

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=44)
ORR	13.6%
CR	2.3%
PD	40.9%
PFS	2.2 months
OS	16.3 months

Vogelzang N et al, Clinical Genitourinary Cancer 202

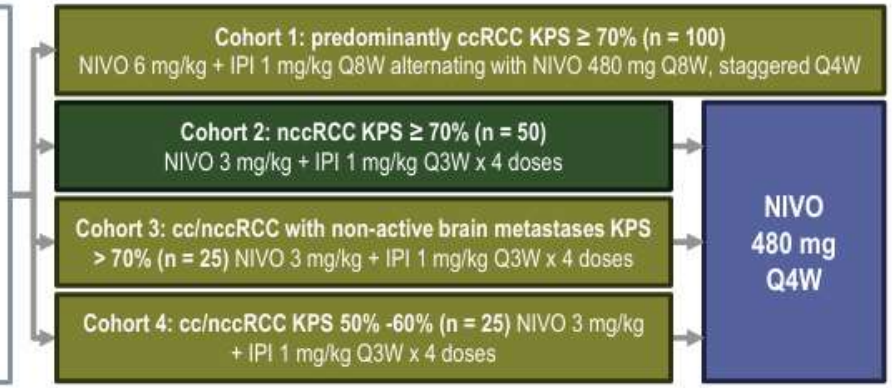
nccRCC immüne checkpoint inhibitörleri

Birinci basamak evre IV nccRCC tek kolu Faz 3b/4 Nivolumab+İpilimumab

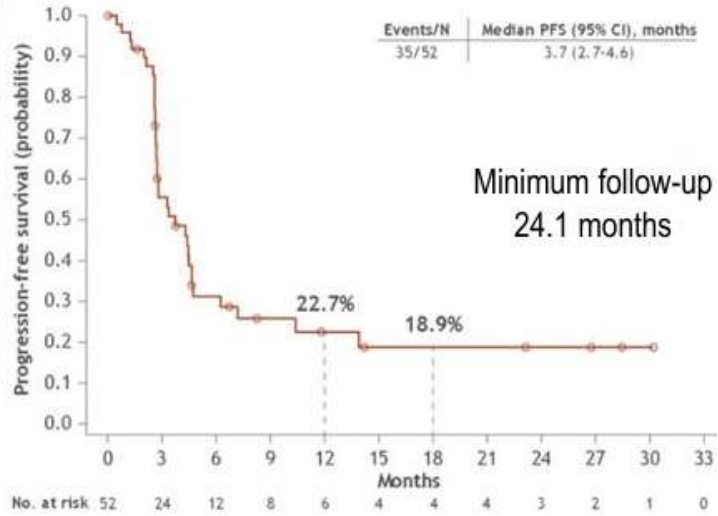
Key inclusion criteria

- 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)

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%



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



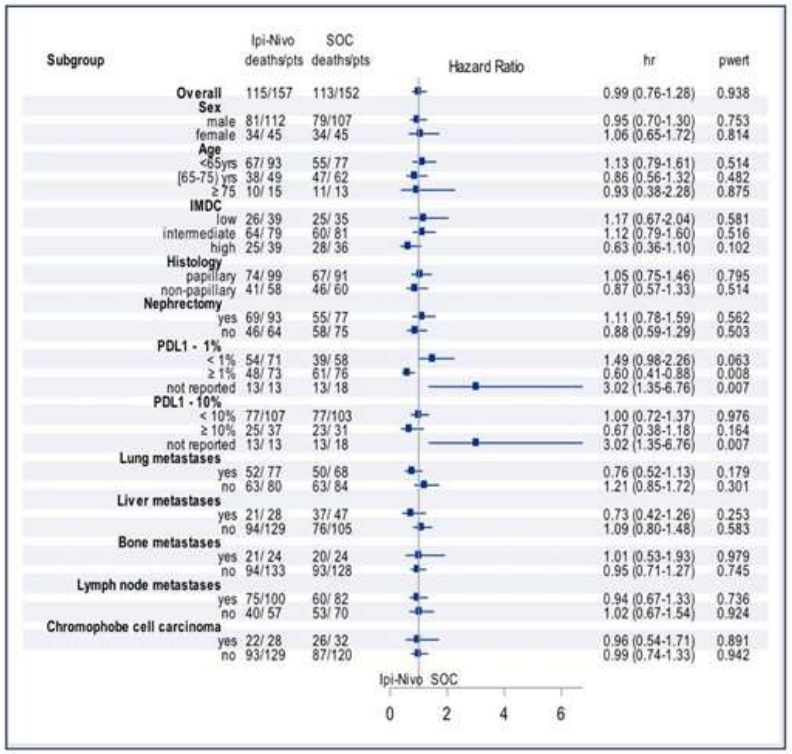
Outcome	
ORR/CR	19.6%/4.3%
PD	41.3%
PFS	3.7 months
OS	21.2 months

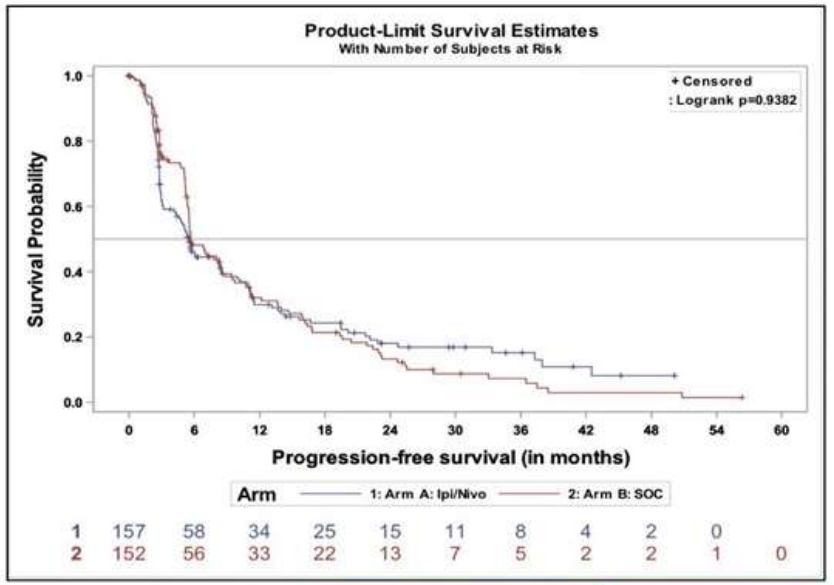
Tykodi SS, et al, J Immunother Cancer 2022.

nccRCC immüne checkpoint inhibitörleri

Birinci basamak evre IV nccRCC tek kolu Faz 2 Nivolumab+İpilimumab vs. Standart tedavi

Forest Plot for 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)	

Bergmann L, et al, ESMO 2024.

nccRCC TKI-VEGF+immüne checkpoint inhibitörleri

	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

nccRCC TKI-VEGF+immüne checkpoint inhibitörleri

Birinci basamak evre IV nccRCC tek kolu Faz 2 Nivolumab+Cabozantinib

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)

PFS: 13 ay ve OS: 28 ay

Fitzgerald KN, et al, Eur Urol 2024.

nccRCC TKI-VEGF+immüne checkpoint inhibitörleri

Birinci basamak evre IV nccRCC tek kolu Faz 2 Pemrolizumab+Lenvatinib

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%

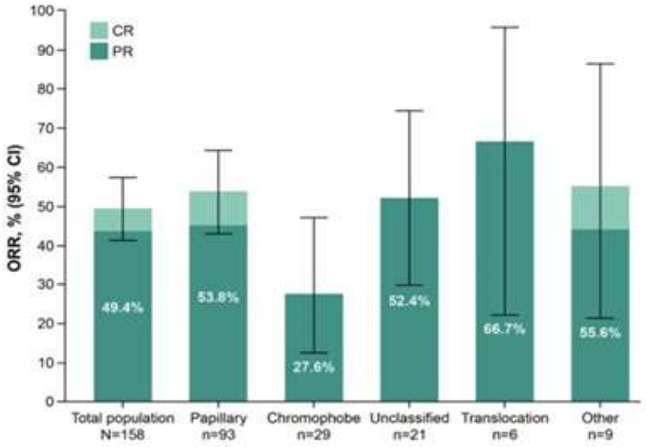
N=158

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

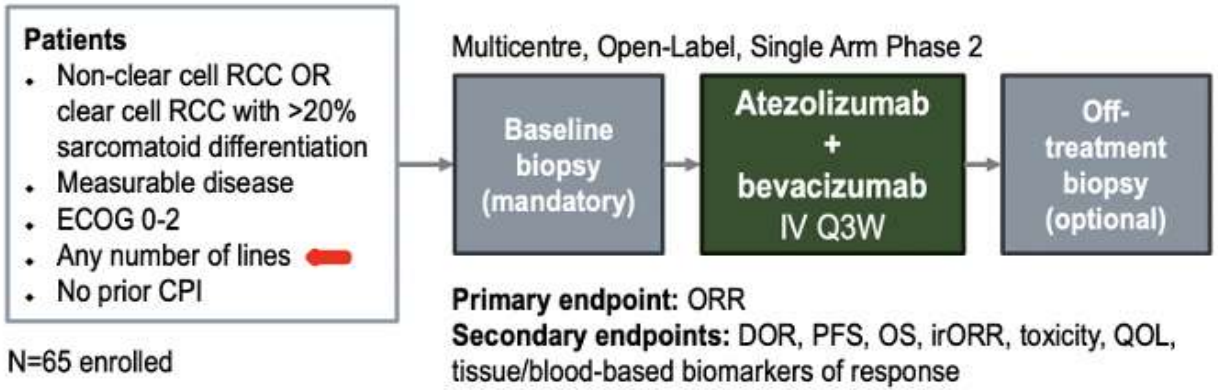
	Pembrolizumab + Lenvatinib N=158
ORR (CR + PR), % (95% CI)	49.4 (41.3-57.4)
DCR (CR+PR+SD), % (95% CI)	82.3 (75.4-87.9)
CBR (CR, PR, or SD for ≥6 months), % (95% CI)	71.5 (63.8-78.4)
Best response, n (%)	
CR	9 (5.7)
PR	69 (43.7)
SD	52 (32.9)
PD	17 (10.8)
NE	1 (0.6)
NA[b]	10 (6.3)



Albiges L, et al, Lancet Oncol 2023.

nccRCC TKI-VEGF+immüne checkpoint inhibitörleri

evre IV nccRCC tek kolu Faz 2 Atezolizumab+Bevacizumab



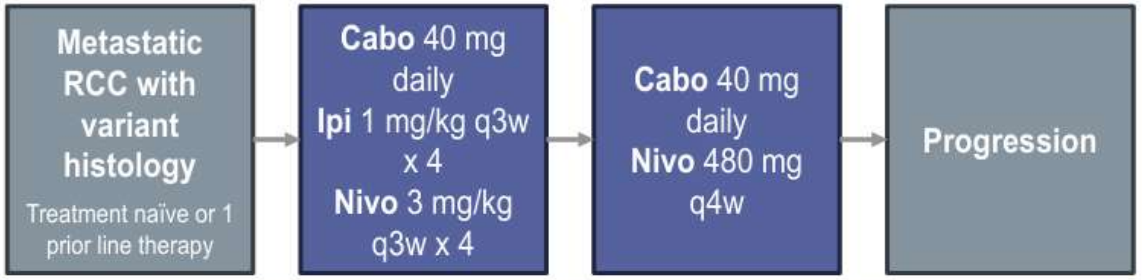
Group	N	ORR, n (%)
Overall	60	20 (33)
Variant histology RCC	42	11 (26)
Papillary	12	3 (25)
Chromophobe	10	1 (10)
Unclassified	9	3 (33)
TFE3 translocation	5	1 (20)
Collecting duct	5	2 (40)
Medullary	1	1 (100)
Sarcomatoid differentiation		
None	34	9 (26)
Clear cell RCC	18	9 (50)
Variant histology RCC	8	3 (38)
IMDC risk group		
Favourable	9	3 (33)
Intermediate	33	15 (45)
Poor	18	2 (11)
Prior systemic therapy		
Yes	21	12 (31)
No	39	8 (38)

McGregor BA et al, J Clin Oncol 2020.

nccRCC TKI-VEGF+immüne checkpoint inhibitörleri

Birinci basamak evre IV nccRCC tek kolu Faz 2 Nivolumab+İpilimumab+Cabozantinib

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)

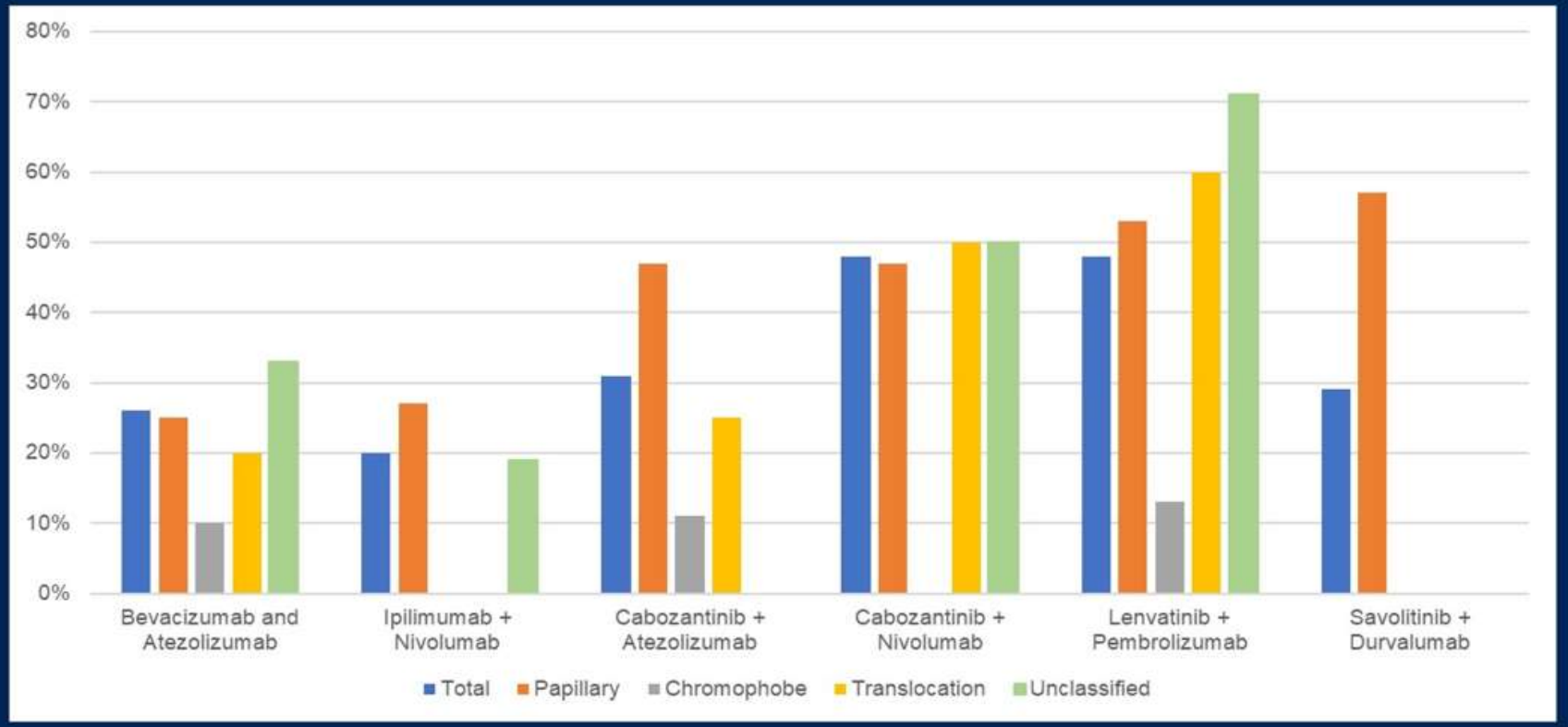
Primary endpoint – ORR per RECIST 1.1

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.

nccRCC TKI-VEGF+immüne checkpoint inhibitörleri



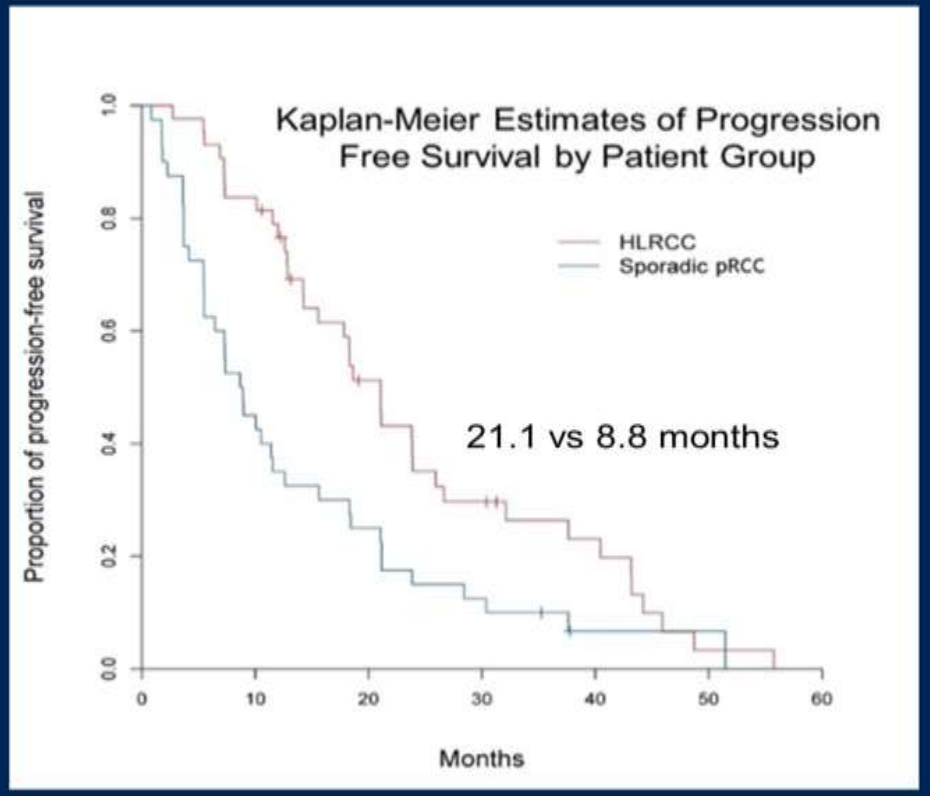
McGregor et al, JCO 2020; Tykodi et al, J Immunother Cancer 2022 , Pal et al, JCO 2021, Lee et al, JCO 2022, Albiges et al ESMO 2022, C Suarez Rodriguez et al, ASCO 2021

McGregor BA, ASCO GU23

Herediter leiomyomatozis-ilişkili 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%**



Srinivasan R, ASCO 2020; abstract 5004.

Herediter leiomyomatozis-ilişkili nccRCC

	N	Median DoT (mo)	Best overall response, n (%) PR or CR	SD	PD	DCR by line of therapy (n/N) 1st	2nd	3rd	4rd
Bevacizumab + erlotinib	20	8	6 (30)	9 (45)	5 (25)	8/12	5/6	2/2	NA
TKI monotherapy	34	11.5	3 (8.8)	16(47)	15(44)	18/29	1/5	NA	NA
Pazopanib	6	9.5	1 (17)	2 (33)	3 (50)	3/5	0/1	NA	NA
Sunitinib	15	12	0 (0)	9 (60)	6 (40)	9/14	0/1	NA	NA
Cabozantinib	4	13	0 (0)	2 (50)	2 (50)	1/2	1/2	NA	NA
Axitinib	7	10	1 (14)	3 (43)	3 (43)	4/6	0/1	NA	NA
Sorafenib	1	24	1 (100)	0 (0)	0 (0)	1/1	NA	NA	NA
Lenvatinib	1	3	0 (0)	0 (0)	1 (100)	0/1	NA	NA	NA
TKI/mTORi combination									
Everolimus + lenvatinib	2	5.5	0 (0)	2 (100)	0 (0)	NA	1/1	NA	1/1
ICI/TKI combination	48	12	16 (33)	25 (52)	7 (15)	22/26	13/14	5/7	1/1
Anti-PD1 + pazopanib	5	12	2 (40)	2 (40)	1(20)	2/2	1/2	1/1	NA
Anti-PD1 + cabozantinib	15	12	6 (40)	8 (53)	1 (6)	5/6	6/6	2/2	1/1
Anti-PD1 + lenvatinib	4	9.5	2 (50)	1 (25)	1 (25)	NA	2/2	1/2	NA
Anti-PD1 + axitinib	24	11	6 (25)	14 (58)	4 (17)	15/18	4/4	1/2	NA

PR = partial response; CR = complete response; SD = stable disease; PD = progressive disease; DCR = disease control rate (CR + PR + SD); DoT = duration of treatment; TKI = tyrosine kinase inhibitor; mTORi = mTOR inhibitor; ICI = immune checkpoint inhibitor; NA = not applicable.

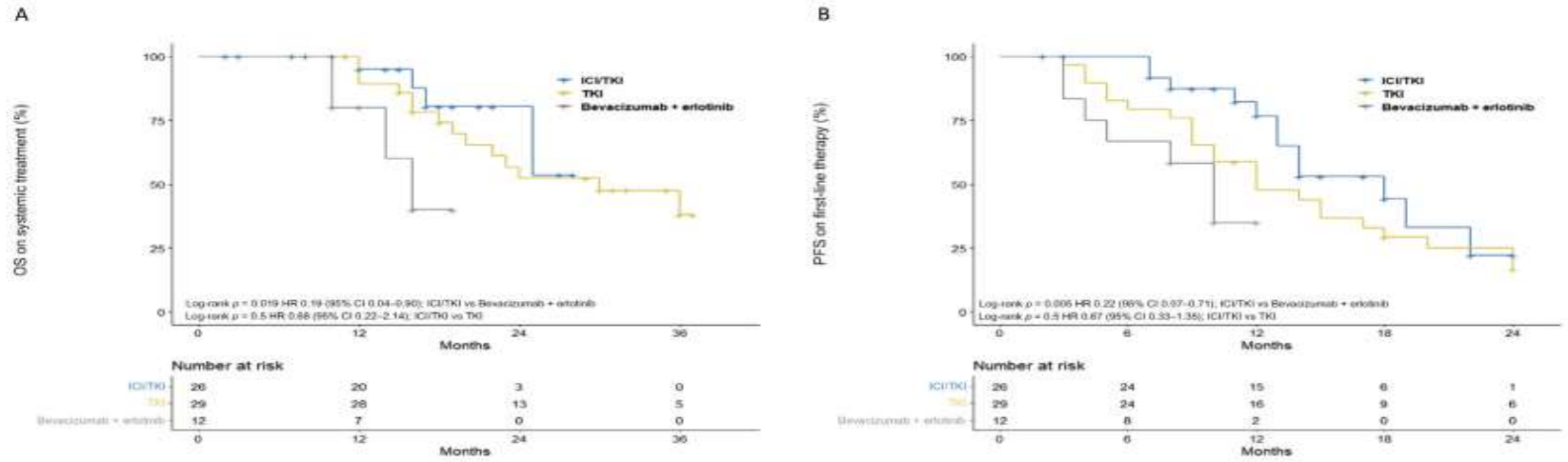


Fig. 3 – Kaplan-Meier estimates by treatment group of (A) OS on systemic treatment and (B) PFS on first-line therapy. TKI = tyrosine kinase inhibitor; ICI = immune checkpoint inhibitor; OS = overall survival; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval.

Xu Y, et al, Eur Urol.2023.

Herediter leiomyomatozis-ilişkili nccRCC

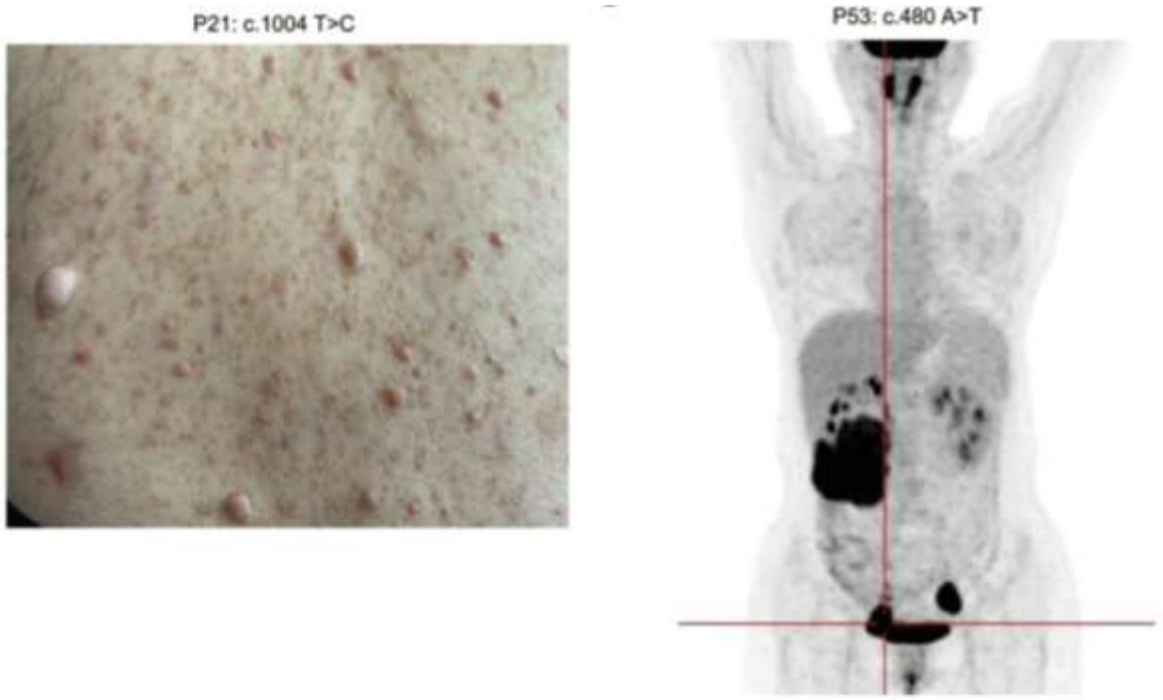
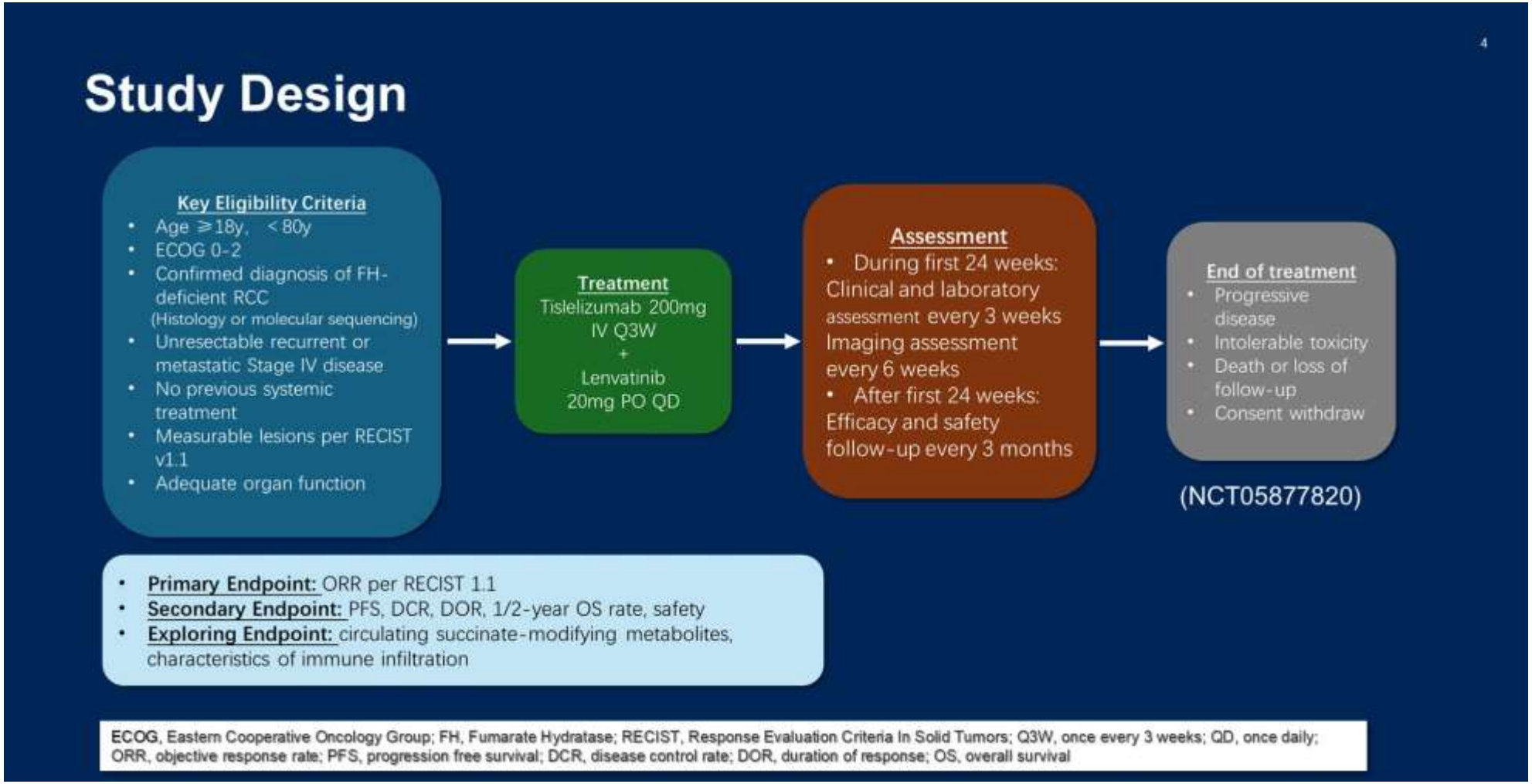


Fig. 1 – Characteristics and genomic alterations in FH-deficient RCC. (A) Oncoprint showing patient and tumor characteristics, germline and somatic *FH* alterations, histologic results, and co-occurring gene alterations. (B) Median overall survival for 77 patients with FH-deficient RCC was 66 mo (95% confidence interval 32.1–99.9). (C) Median recurrence-free survival for 54 patients with localized FH-deficient RCC was 9 mo (95% confidence interval 5.5–12.5). (D) A female patient with HLRCC carrying a germline *FH* alteration presented with skin leiomyomas (patient 21). (E) A female patient with HLRCC carrying a germline *FH* alteration presented with uterine leiomyomas (patient 53). RCC = renal cell carcinoma; HLRCC = hereditary leiomyomatosis RCC syndrome.

Xu Y, et al, Eur Urol.2023.

Herediter leyomiyomatozise nccRCC



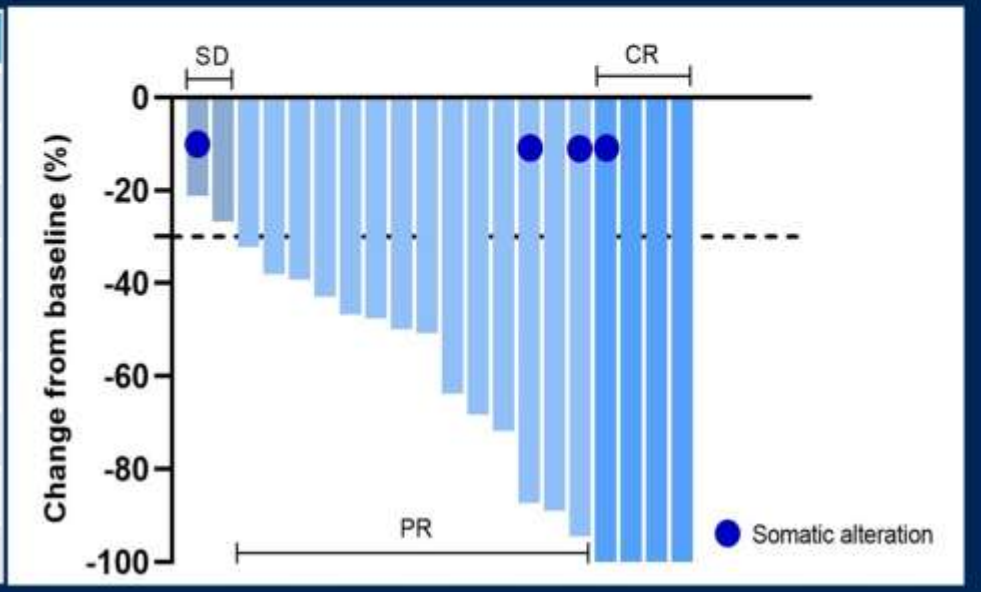
Kong W, ASCO GU25

Herediter leyomiyomatozise nccRCC

Results: efficacy

- The median follow up was 9.7 (1.4-15.2) months.
- ORR：90% (18/20); DCR: 100%.
- Both hereditary and sporadic FH-RCC benefited from the treatment.

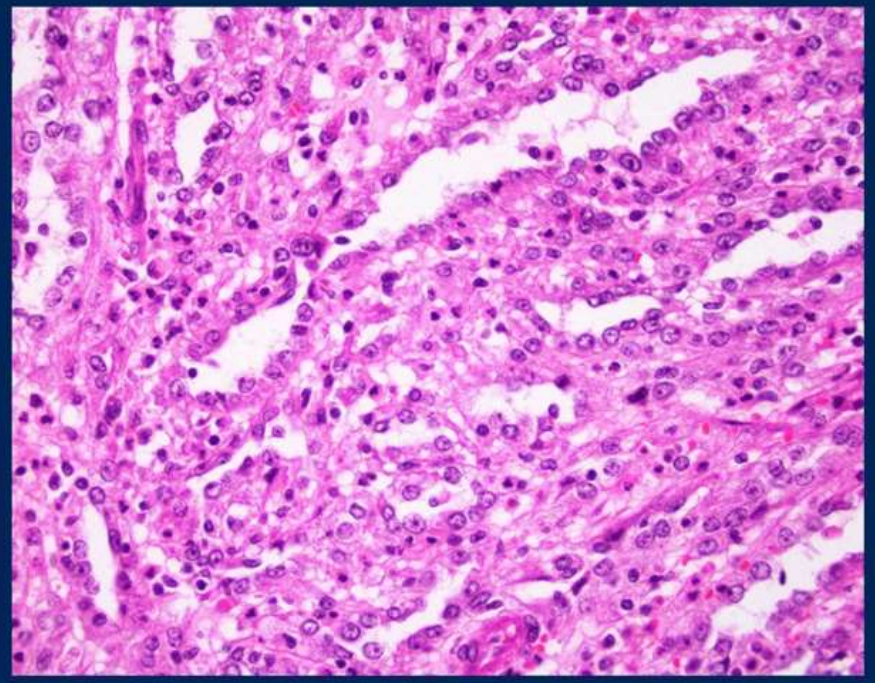
Response	Cohort (n=20)
ORR, % (95% CI)	90 (66.9-98.3)
Best response, No. (%)	
CR	4 (20)
PR	14 (70)
SD	2 (10)
PD	0 (0)
Disease control rate, % (95% CI)	100 (80.0-100)
Clinical benefit rate, % (95% CI)	85 (61.1-96.0)
Median PFS, months	NR



Kong W, ASCO GU25

Toplayıcı kanal ve renal medüller karsinom

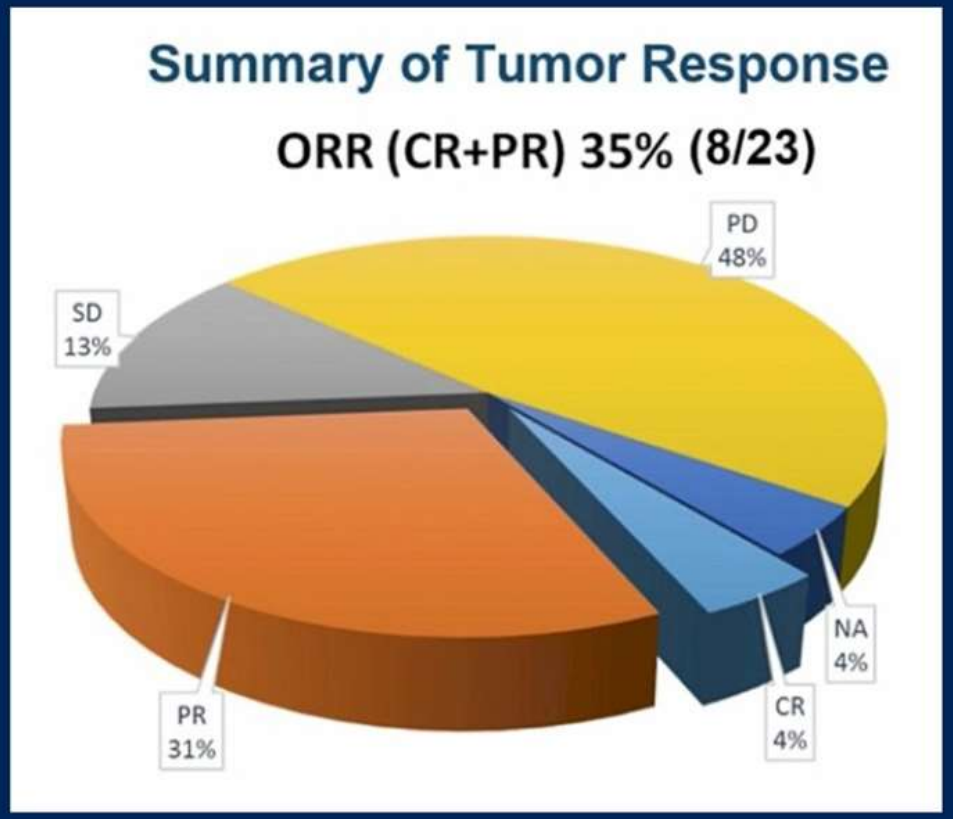
- Collecting Duct[1]
  - Cisplatin/Gemcitabine phase II GETUG:
    - ORR 26%, PFS 7.1 months
- Renal Medullary Carcinoma[2]
  - Sickle cell trait → SMARCB1 loss
  - No sickle cell trait → RCCU-MP
  - Platinum-based chemo even in localized disease



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

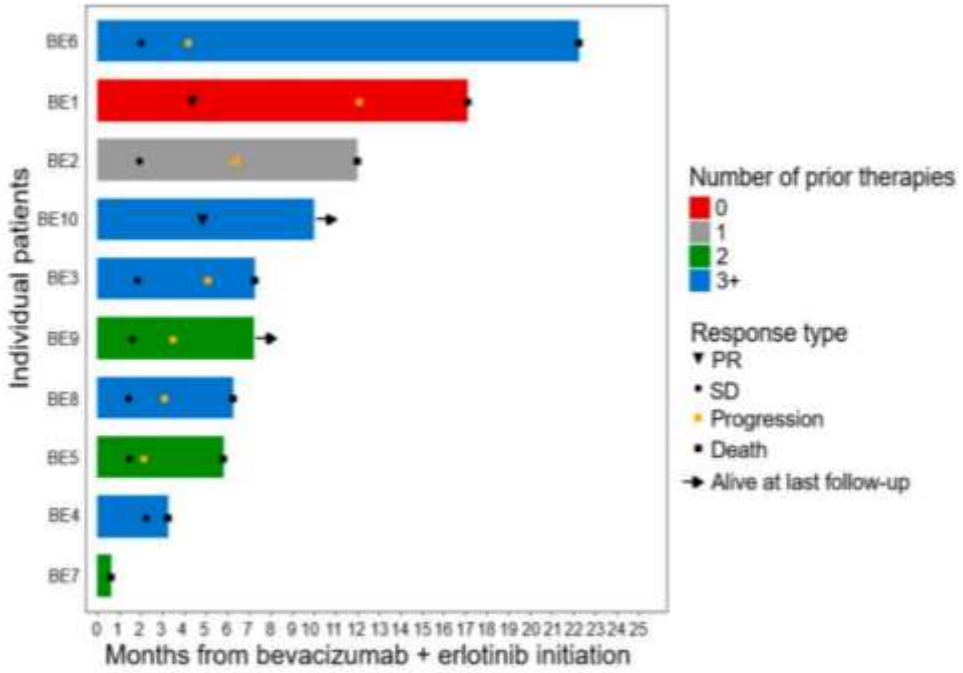
Procopio et al Jam Oncol 2022

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



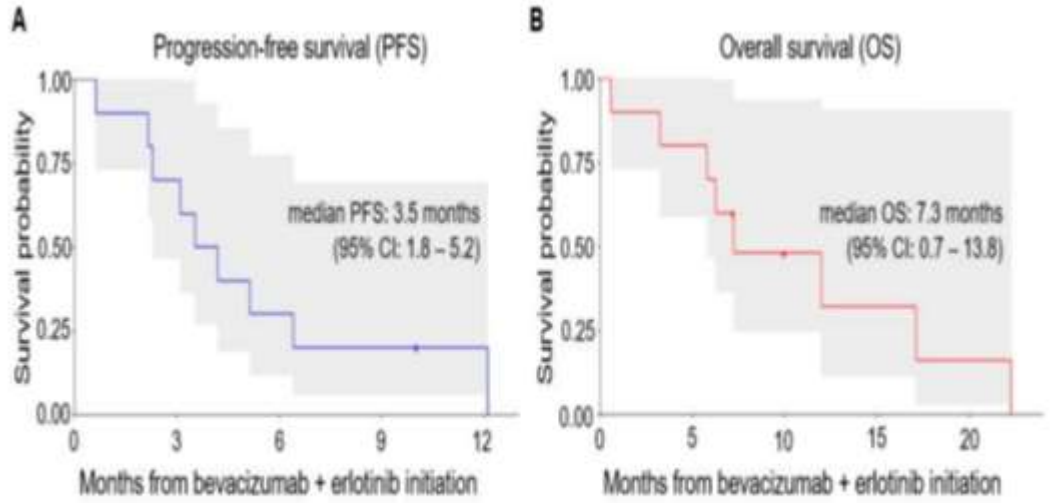
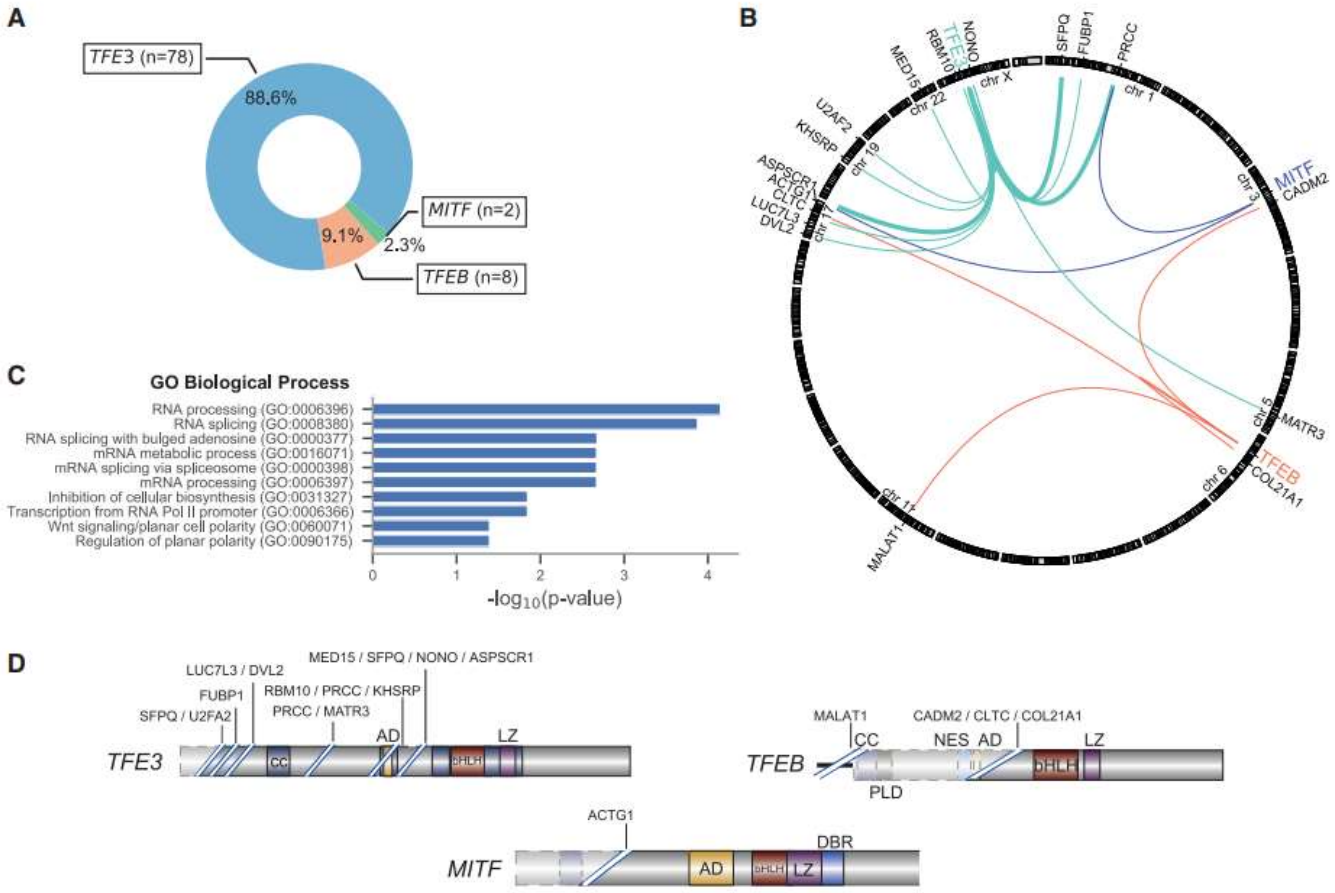


Figure 3. (**A**) Progression-free survival and (**B**) overall survival from treatment initiation with bevacizumab plus erlotinib. The shaded areas represent the 95% confidence bands for each curve. CI, Confidence interval.

- ❑ 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



- Pozitif TFE3 floresan in situ hibridizasyon (FISH) testi veya immünohistokimya pozitif
- tRCC nccRCC agresif bir alt tipidir.
- Erişkinlerde nccRCC yaklaşık %5'ini, çocuklarda ise %50'sini oluşturur
- Daha genç yaşta tanı konur, tanı anında hastalık ileri evrededir ve kadınlarda daha sık görülür.
- tRCC, histolojik olarak çok çeşitli görünümler sergileyebilir ve neredeyse tüm diğer RCC alt tiplerini taklit edebilir.
- Translokasyon renal hücreli karsinomlar (tRCC), genellikle MiT/TFE füzyonları ve 9p21.3 delesyonları dışında belirgin genetik değişiklik göstermez.
- Bu tümörler, yüksek NRF2 aracılı antioksidan yanıt nedeniyle hedefe yönelik tedavilere dirençlidir.
- VEGFR-TKI alan hastalarda sonuçlar, immün kontrol noktası inhibitörleri alanlara kıyasla daha kötüdür.
- Tümörlerde CD8+ T hücresi infiltrasyonu mevcuttur, ancak bu hücreler farklı bir tükenmişlik fenotipi gösterir.

Bakouny et al., 2022, Cell Reports 38, 110190

Translokasyon Renal Hücreli Karsinom TKI/VEGF

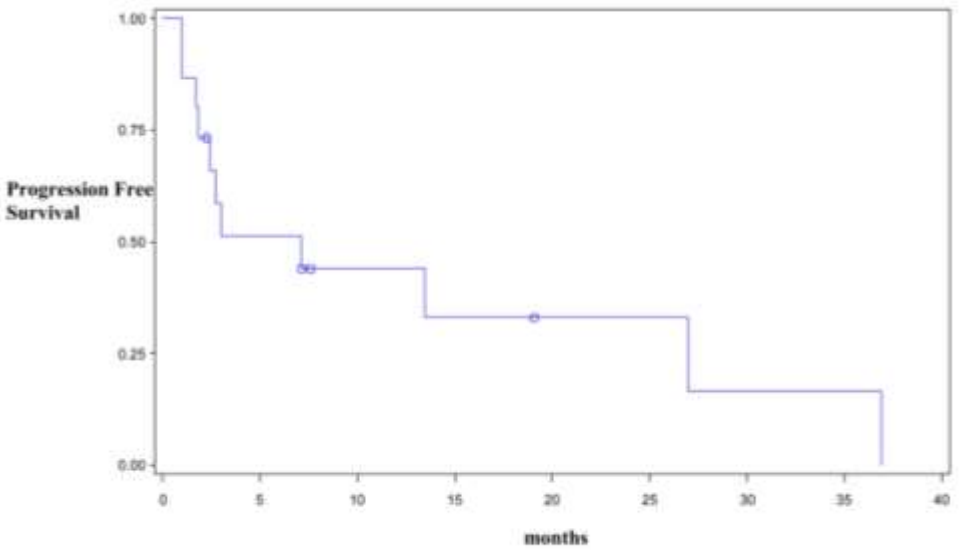


Figure 2a. Progression Free Survival of 7.1 months for 15 patients with advanced Xp11 translocation renal cell carcinoma treated with VEGF-targeted therapy

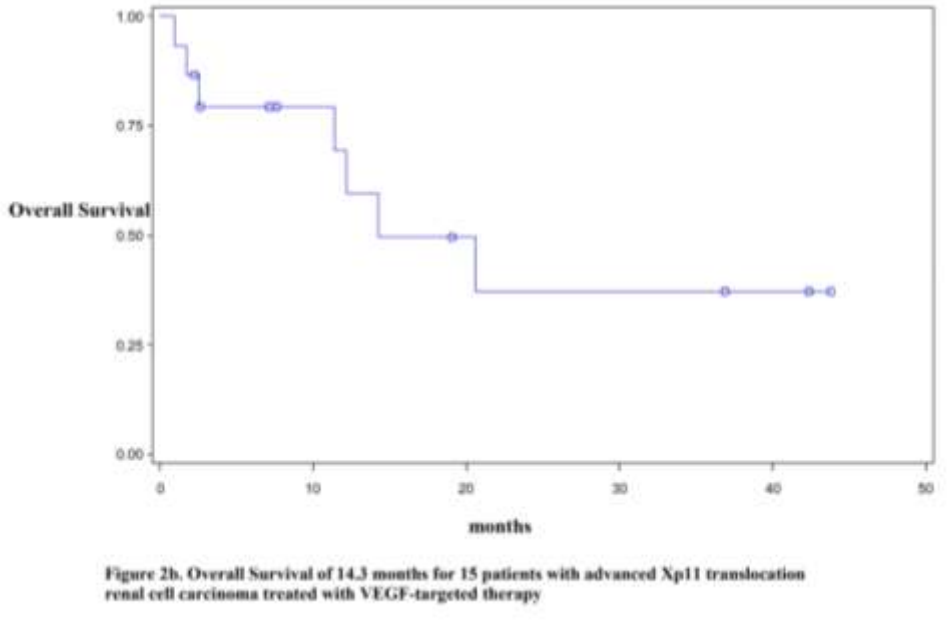


Figure 2b. Overall Survival of 14.3 months for 15 patients with advanced Xp11 translocation renal cell carcinoma treated with VEGF-targeted therapy

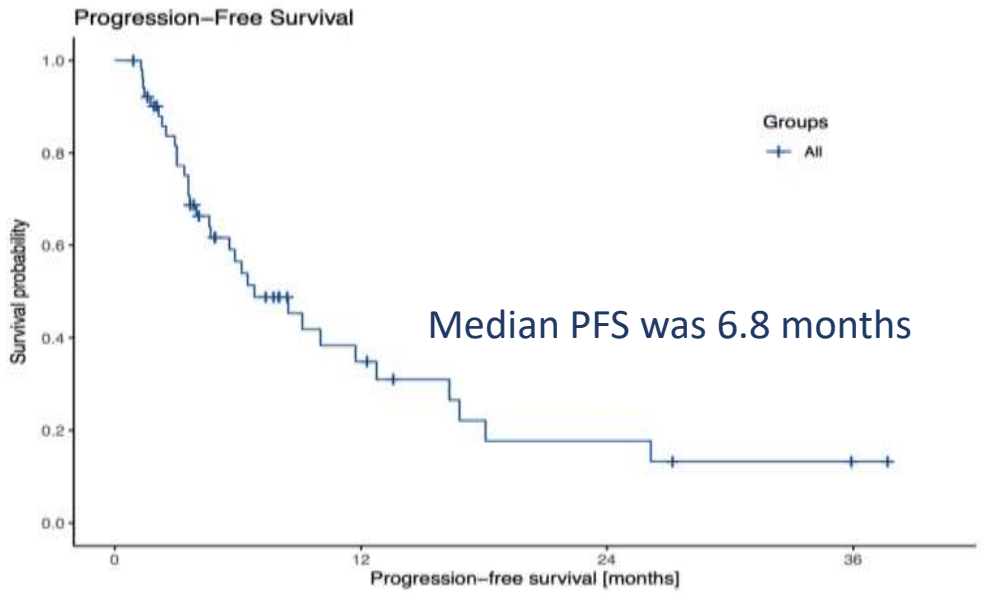
RECIST kriterlerine göre, 3 hastada **objektif yanıt** gözlendi; **toplam yanıt oranı %20** idi. Yanıt veren hastaların tümü **parsiyel yanıt (PR)** elde etti ve tedavi aldıkları ajanlar şunlardı:

- **Sunitinib** (n=1),
- **Sorafenib** (n=1),
- **Ramucirumab** (n=1).

Yanıt süreleri sırasıyla **7, 13 ve 27 ay** olarak bildirildi.
Ayrıca, **7 hastada stabil hastalık (SD)** elde edildi.

Choueiri T at al, Cancer 2010

Translokasyon Renal Hücreli Karsinom -Cabozantinib



Median PFS was 6.8 months

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 3.2025
Kidney Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0)[h] OR RELAPSED DISEASE

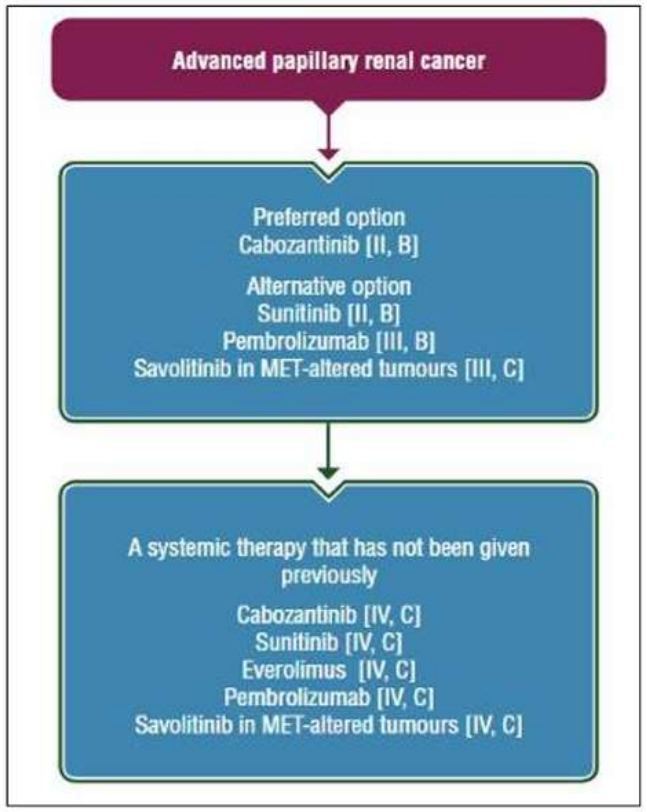
SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[i]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Clinical trial • Cabozantinib • Cabozantinib + nivolumab[b,c] • Lenvatinib + pembrolizumab[b]	• Erlotinib + bevacizumab[g] + for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (HERED-RCC-D) • Everolimus + lenvatinib • Nivolumab[b,c] • Pembrolizumab[b] • Sunitinib	• Axitinib • Everolimus + bevacizumab[g] • Everolimus • Ipilimumab[b] + nivolumab[b,d] (category 2B)

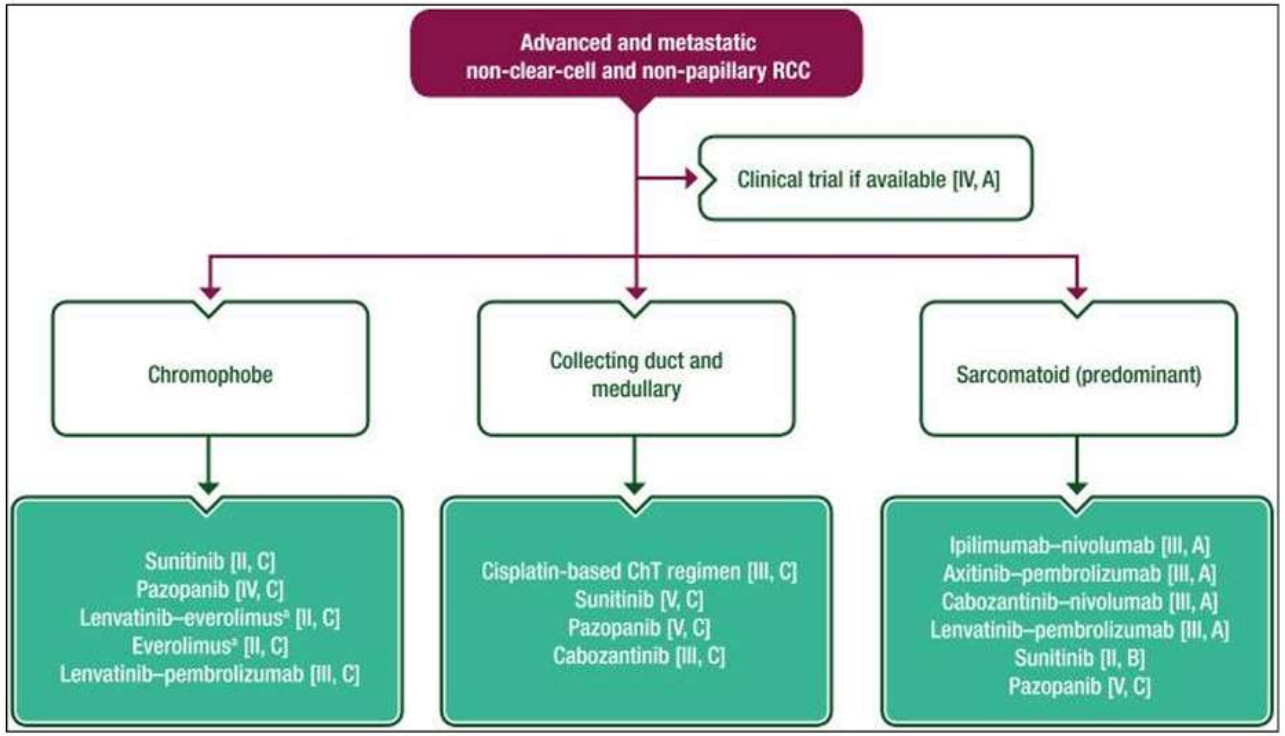
[b] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[c] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[d] Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[g] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[h] For first-line only.
[i] For collecting duct or medullary subtypes, partial responses have been observed with cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) and other platinum-based chemotherapies currently used for urothelial carcinomas. Gemcitabine + doxorubicin can also produce responses in renal medullary carcinoma (RMC) (Wilson NR, et al. Clin Genitourin Cancer 2021;19:e401-e408). Oral targeted therapies generally do not produce responses in patients with RMC; erlotinib + bevacizumab can produce responses even in heavily pretreated patients with RMC. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred first-line therapy for RMC.

Note: All recommendations are category 2A unless otherwise indicated.

Evre IV nccRCC sistemik tedavi

ESMO GUIDELINES





Powles T, *et al.* ESMO Guidelines Committee. Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2024:S0923-7534(24)00676-8. doi: 10.1016/j.annonc.2024.05.537.

nccRCC devam eden çalışmalar

NCT identifier	Phase	Treatment	Histology	Enrollment	Primary endpoints	Estimated completion date
NCT05678673	3	XL092 + nivolumab vs sunitinib	nccRCC	291	PFS, ORR	06/2028
NCT04413123	2	Cabozantinib + ipilimumab + nivolumab	nccRCC	60	ORR	12/2025
NCT05831891	2	Fruquintinib + serplulimab	nccRCC	39	PFS	07/2026
NCT06302569 (REPRINT)	2	Pembrolizumab + enfortumab vedotin	Collecting duct RCC	23	ORR	05/2026
			RMC			
NCT03587662	2	Ixazomib + gemcitabine + doxorubicin	RMC, RCC unclassified with medullary phenotype	30	ORR, DCR	01/2025
NCT03595124	2	Axitinib + nivolumab	*TFE3*-rearranged RCC	40	PFS	09/2027
NCT04146831	2	Sintilimab	FH-deficient mRCC	37	PFS	Unknown
NCT05877820	2	Tislelizumab + lenvatinib	FH-deficient mRCC	10	ORR	12/2025
NCT05347212	2	Nivolumab + relatlimab	RMC	30	ORR	07/2026
NCT05286801	1/2	Tiragolumab + atezolizumab	RMC	86	Safety, ORR	09/2025
NCT05678673 (STELLAR-304)	3	XL092 + nivolumab vs sunitinib	nccRCC (excludes RMC, collecting duct, chromophobe)	291	PFS, ORR	06/2028
NCT05411081 (PAPMET-2)	2	Cabozantinib +/– atezolizumab	pRCC	200	PFS	07/2027
NCT05043090 (SAMETA)	3	Savolitinib + durvalumab vs sunitinib vs durvalumab	MET-driven pRCC	200	PFS	09/2026

Sonuç 1

nccRCC heterojen bir grup

- **nccRCC sarkomatoid ve rabdoid diferansiasyon**

  Nivolumab+ipilimumab, Cabozantinib+Nivolumab, Lenvatinib + Pemrolizumab

- **Papiller alt tip için tedavi seçeneği**

  Cabozantinib+Nivolumab, lenvatinib+Pemrolizumab, Savolitinib+Durvalumab (MET alterasyonu olanlarda), Cabozantinib, Sunitinib

- **Unklasifiye nccRCC**

  Cabozantinib+Nivolumab, lenvatinib+Pemrolizumab, Cabozantinib, Sunitinib

Sonuç 2

- **Kromofob nccRCC**

  Genel olarak immüne checkpoint inhibitörlerine dirençli

  Everolimus+Lenvatinib, Bevacizumab+Everolimus, Cabozantinib, sunitinib

- **Toplayıcı kanal**

  Sisplatin+Gemsitabin, kabozantinib

- **Renal medüller karsinom**

  Sisplatin+Gemsitabin, Gemsitabin+Doksorubisin, Bevacizumab + Erlotinib

Sonuç 3

❑Herediter leiomyomatozis bağlı nccRCC

Germline mutasyon*;Tiselizumab+Lenvatinib, Bevacizumab+Erlotinib*

Somatik mutasyonda: *Tiselizumab+Lenvatinib ilk seçenek, sonraki basamaklarda* etkinlik daha az olmak ile beraber *Bevacizumab+Erlotinib*

❑Translokasyon Renal Hücreli Karsinom : TFE3, TFEB and MIT

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