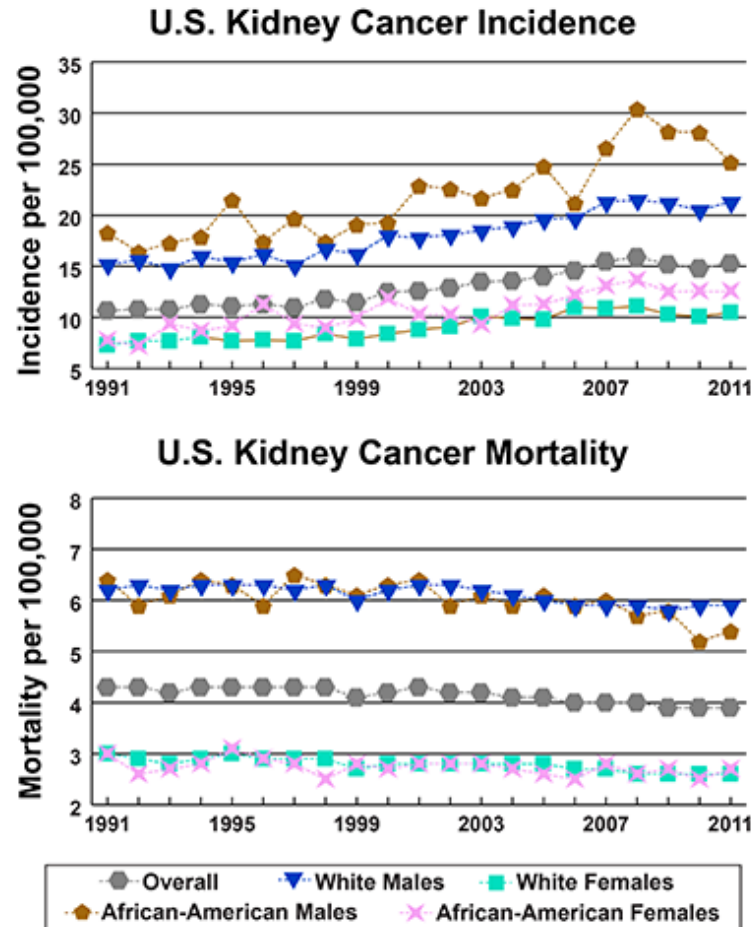


Metastatik Renal Kanserlerinde Tedavi Seçenekleri

Dr. Deniz Tural

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

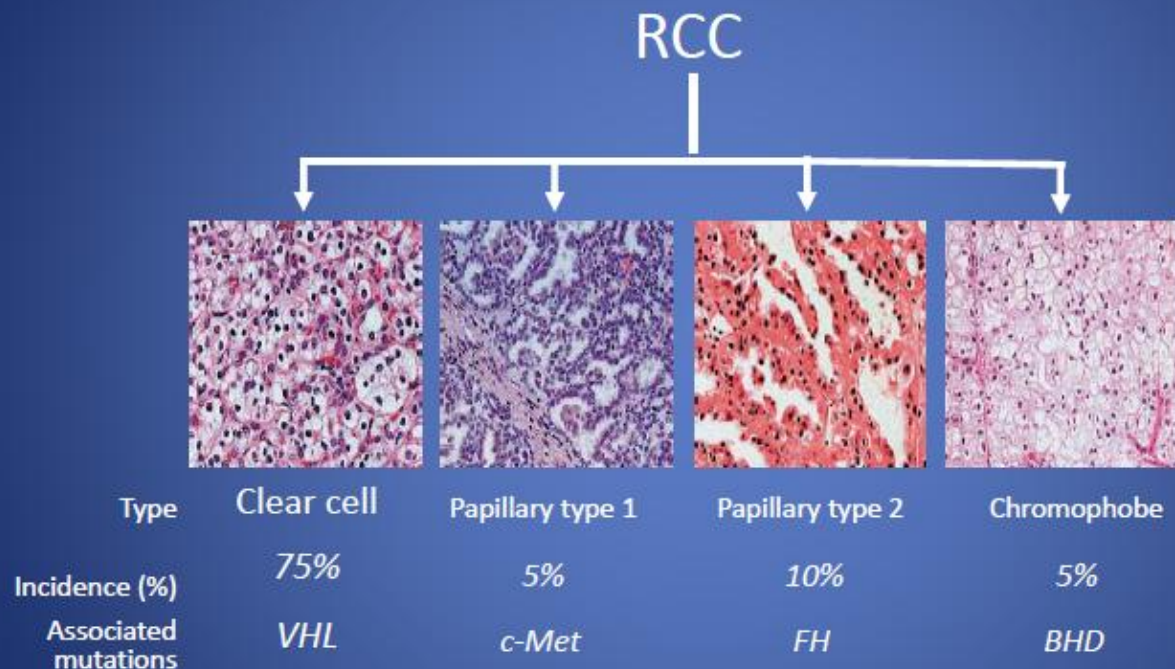
İnsidans ve Epidemiyoloji



Source: Surveillance, Epidemiology, and End Results (SEER) Program and the National Center for Health Statistics. Additional statistics and charts are available at the SEER Web site.

Histolojik Alt Gruplar

Histological Classification of Human Renal Epithelial Neoplasms



VHL= von Hippel-Lindau; FH=fumarate hydratase; BHD=Birt-Hogg-Dubé.

Modified from Linehan WM et al. *J Urol*. 2003;170:2163-2172.

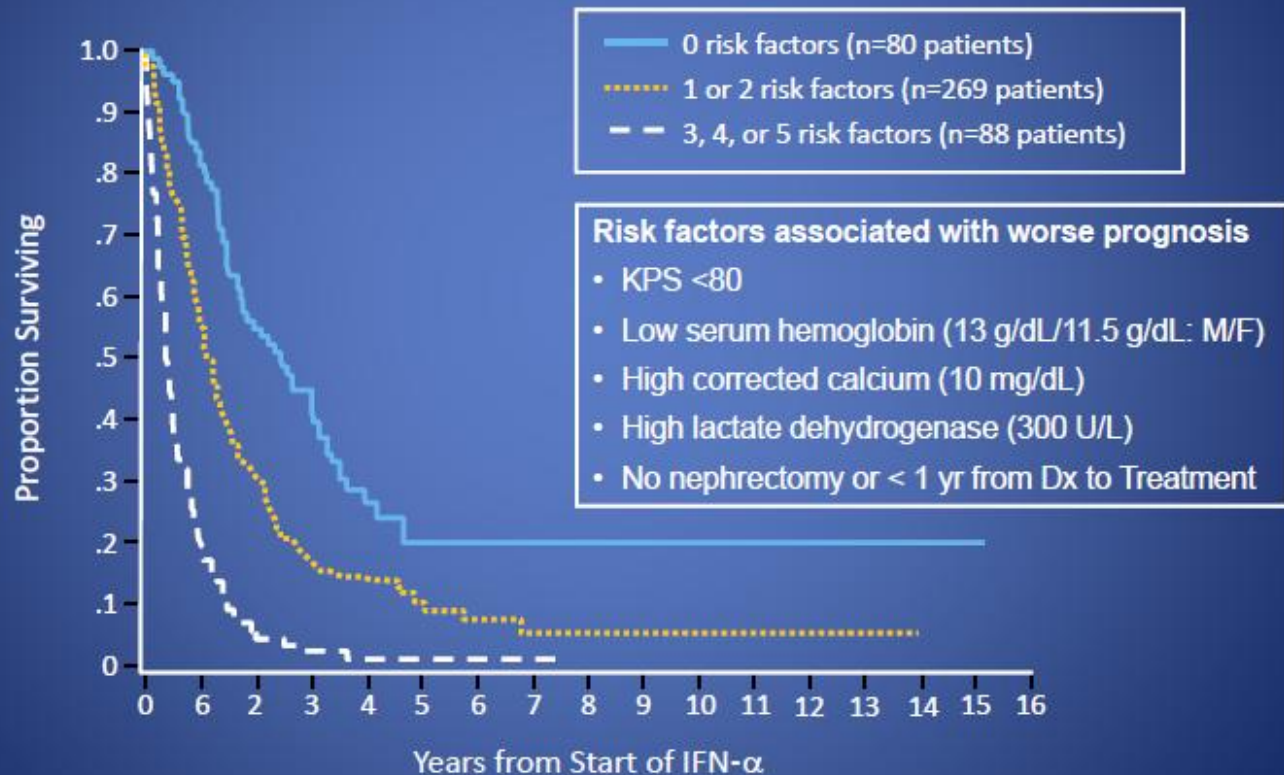
Evreyeye Göre Sağkalım

American Joint Committee on Cancer (AJCC) 2010 Clinical Staging System

Stage	Description	5-Year Survival (%)
Stage I	T1, N0, M0	95
Stage II	T2, N0, M0	88
Stage III	T1-2, N1 or T3, N0-1	59
Stage IV	T4 (any N or M) or N2 (any T or M) or M1	20

Risk Faktörlerine Göre Sağkalım

MSKCC Risk Factor Model in mRCC



Risk Faktörlerine Göre Sağkalım

VOLUME 27 • NUMBER 34 • DECEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prognostic Factors for Overall Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Vascular Endothelial Growth Factor–Targeted Agents: Results From a Large, Multicenter Study

Daniel Y.C. Heng, Wanling Xie, Meredith M. Regan, Mark A. Warren, Ali Reza Golshayan, Chakshu Sahi, Bernhard J. Eigel, J. Dean Ruether, Tina Cheng, Scott North, Peter Venner, Jennifer J. Knox, Kim N. Chi, Christian Kollmannsberger, David F. McDermott, William K. Oh, Michael B. Atkins, Ronald M. Bukowski, Brian I. Rini, and Toni K. Choueiri

From the Tom Baker Cancer Center, Calgary; Cross Cancer Institute, Edmonton, Alberta; Princess Margaret Hospital, Toronto, Ontario; British Columbia Cancer Agency, Vancouver, British Columbia, Canada; Harvard School of Public Health; Dana-Farber/Harvard Cancer Center Renal Cancer Program, Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Boston, MA; Medical University of South Carolina, Charleston, SC; and Cleveland Clinic Taussig Cancer Institute, Cleveland, OH.

Submitted December 9, 2008; accepted June 18, 2009; published online ahead of print at www.jco.org on October 13, 2009.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Daniel Y.C. Heng, MD, MPH, FRCPC, Department of Medical Oncology, Tom Baker Cancer Center, University of Calgary, 1331 29th St NW, Calgary, Alberta, Canada T2N 4N2; e-mail: daniel.heng@cancerboard.ab.ca.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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A B S T R A C T

Purpose

There are no robust data on prognostic factors for overall survival (OS) in patients with metastatic renal cell carcinoma (RCC) treated with vascular endothelial growth factor (VEGF)–targeted therapy.

Methods

Baseline characteristics and outcomes on 645 patients with anti-VEGF therapy–naïve metastatic RCC were collected from three US and four Canadian cancer centers. Cox proportional hazards regression, followed by bootstrap validation, was used to identify independent prognostic factors for OS.

Results

The median OS for the whole cohort was 22 months (95% CI, 20.2 to 26.5 months), and the median follow-up was 24.5 months. Overall, 396, 200, and 49 patients were treated with sunitinib, sorafenib, and bevacizumab, respectively. Four of the five adverse prognostic factors according to the Memorial Sloan-Kettering Cancer Center (MSKCC) were independent predictors of short survival: hemoglobin less than the lower limit of normal ($P < .0001$), corrected calcium greater than the upper limit of normal (ULN; $P = .0006$), Karnofsky performance status less than 80% ($P < .0001$), and time from diagnosis to treatment of less than 1 year ($P = .01$). In addition, neutrophils greater than the ULN ($P < .0001$) and platelets greater than the ULN ($P = .01$) were independent adverse prognostic factors. Patients were segregated into three risk categories: the favorable-risk group (no prognostic factors; $n = 133$), in which median OS (mOS) was not reached and 2-year OS (2y OS) was 75%; the intermediate-risk group (one or two prognostic factors; $n = 301$), in which mOS was 27 months and 2y OS was 53%; and the poor-risk group (three to six prognostic factors; $n = 152$), in which mOS was 8.8 months and 2y OS was 7% (log-rank $P < .0001$). The C-index was 0.73.

Conclusion

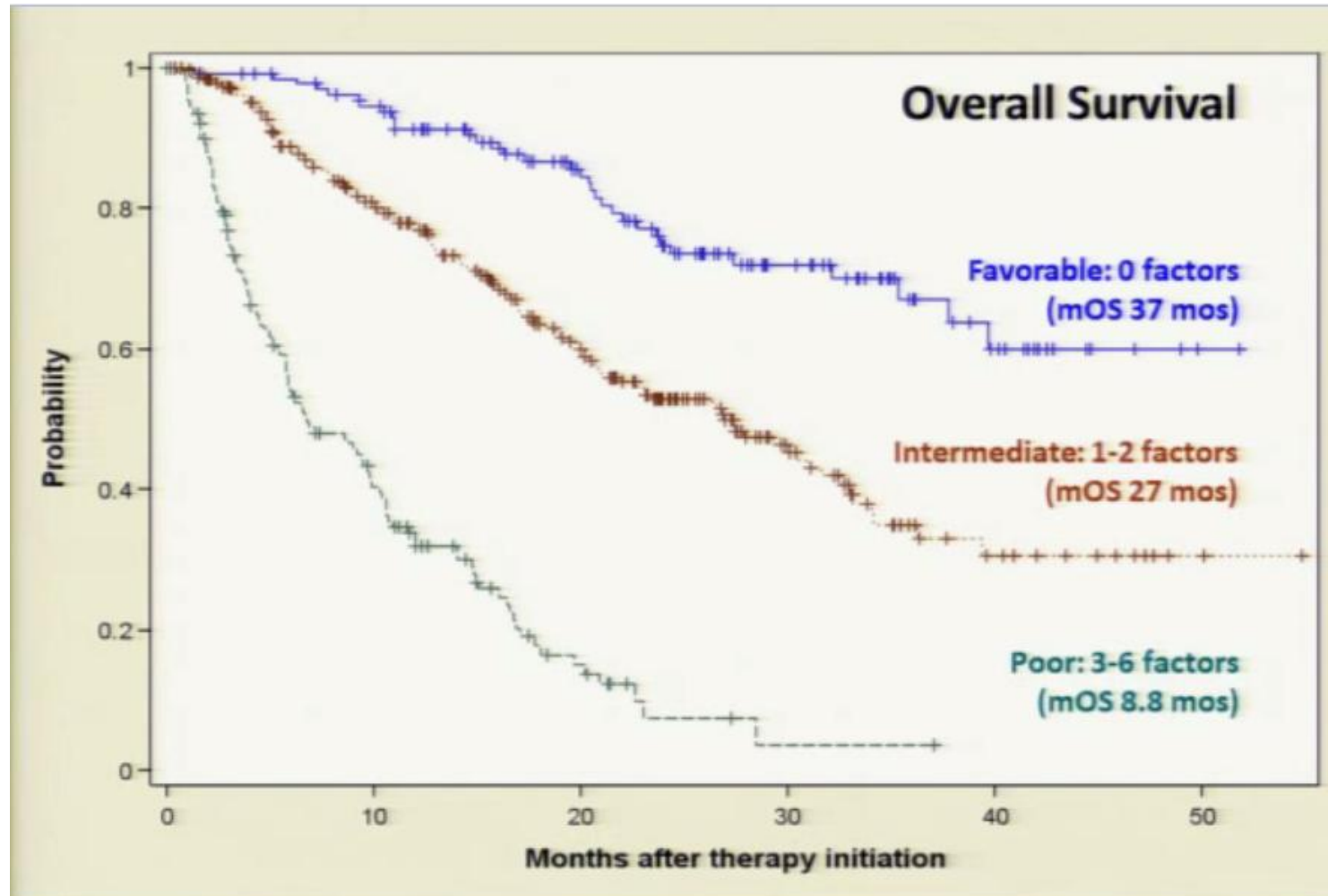
This model validates components of the MSKCC model with the addition of platelet and neutrophil counts and can be incorporated into patient care and into clinical trials that use VEGF-targeted agents.

Risk Faktörlerine Göre Sağkalım

Heng Criteria for Prognosis in TKI Treated Patients

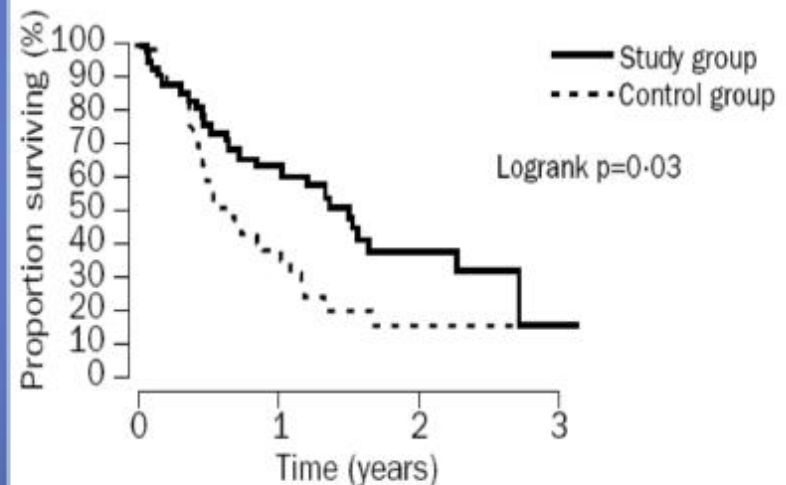
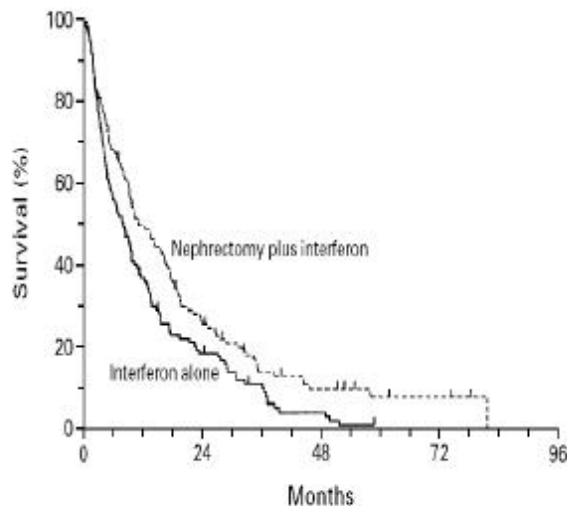
1. KPS < 80
2. Diagnosis to treatment less than 1 year
3. Anemia
4. Hypercalcemia
5. Thrombocytosis
6. Leukocytosis

Risk Faktörlerine Göre Sağkalım



Metastatik RCC, Nefrektomi?

Nephrectomy Followed by Interferon Alpha Improves Survival



Flanigan *et al*, NEJM 345, 23: 1655-9.

Mickisch *et al*, Lancet 2001; 358: 966-70

Metastatik RCC, Nefrektomi?

Absolute Benefit Diminishes in Poor Risk Groups

TABLE 2. SURVIVAL IN SUBGROUPS DEFINED ACCORDING TO STRATIFICATION FACTORS.

CATEGORY	MEDIAN SURVIVAL		1-YR SURVIVAL		P VALUE*
	INTERFERON ALONE	NEPHREC-TOMY PLUS INTERFERON	INTERFERON ALONE	NEPHREC-TOMY PLUS INTERFERON	
	mo		%		
Not stratified	8.1	11.1	36.8	49.7	0.012
Stratification factor					
Measurable disease					0.010
Yes	7.8	10.3	34.7	46.6	
No	11.2	16.4	43.1	63.6	
Performance status†					0.080
0	11.7	17.4	49.2	63.6	
1	4.8	6.9	28.2	32.5	
Type of metastases					0.008
Lung only	10.3	14.3	41.5	58.5	
Other	6.3	10.2	34.6	45.1	

*P values for the comparison of median survival between groups were derived with the log-rank test.

Metastatik RCC, Nefrektomi?

Table 1 Phase III trials of IFN- α with nephrectomy

Trial	No. patients	Median survival (months)			Response to therapy (%)			Unable to receive post-surgery immunotherapy <i>n</i> (%)	Operative Mortality no. (%)
		IFN alone	Surgery + IFN	<i>P</i>	IFN alone	Surgery + IFN	<i>P</i>		
SWOG 8949 ⁶	241	8.1	11.1	0.05	3.3	3.6	NS	NR	1 (0.8)
EORTC 30957 ⁷	85	7	17	0.03	12	19	0.38	NR	1 (2.4)
Combined analysis ²⁶	331	7.8	13.6	0.002	5.7	6.9	0.60	9 (5.6)	2 (1.4)

EORTC, European Organization for the Research and Treatment of Cancer; IFN, Interferon; NR, not reported; NS, not significant; SWOG, Southwest Oncology Group.

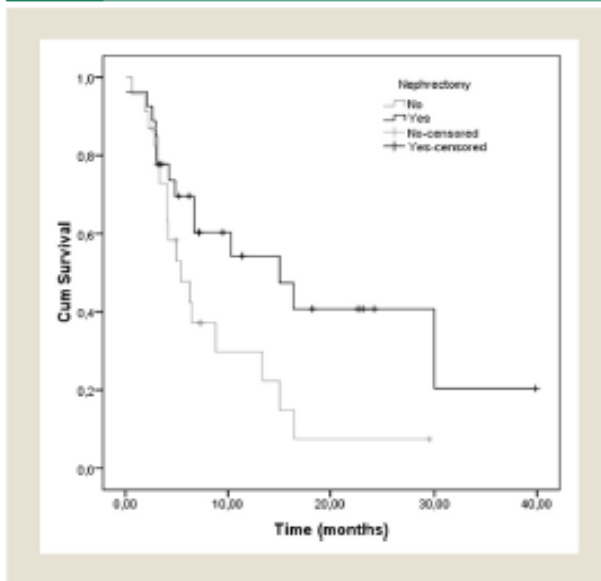
Anthony J Polcari , et al, International Journal of Urology 2009

Metastatik RCC, Nefrektomi?

Original Study

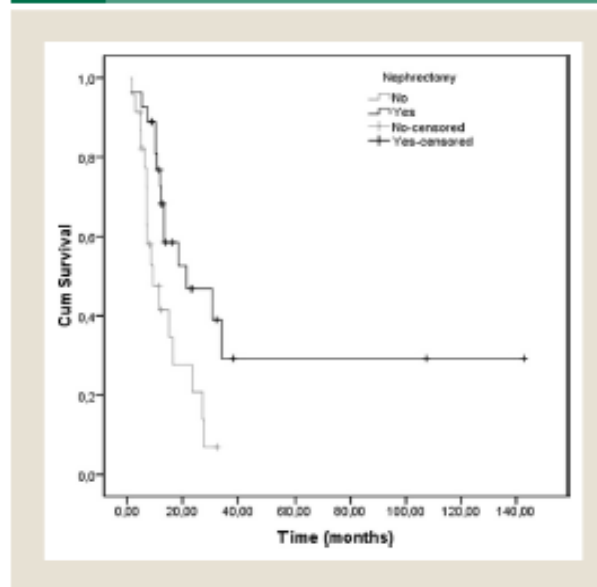
The Necessity of Cytoreductive Nephrectomy in Patients With Metastatic Renal Cell Carcinoma Using Antiangiogenic Targeted Therapy After Interferon Alfa-2b

Figure 2 Overall Survival Curves From the Date of Starting TKI for CRN (+) and (-) Groups ($P = .034$)



Abbreviations: CRN — Cytoreductive Nephrectomy; Cum — Cumulative; TKI — Tyrosine Kinase Inhibitors.

Figure 4 Overall Survival Curves From Diagnosis for CRN (+) and (-) Groups ($P = .008$)



Abbreviations: CRN — Cytoreductive nephrectomy; Cum — Cumulative.

Metastatik RCC, Nefrektomi?

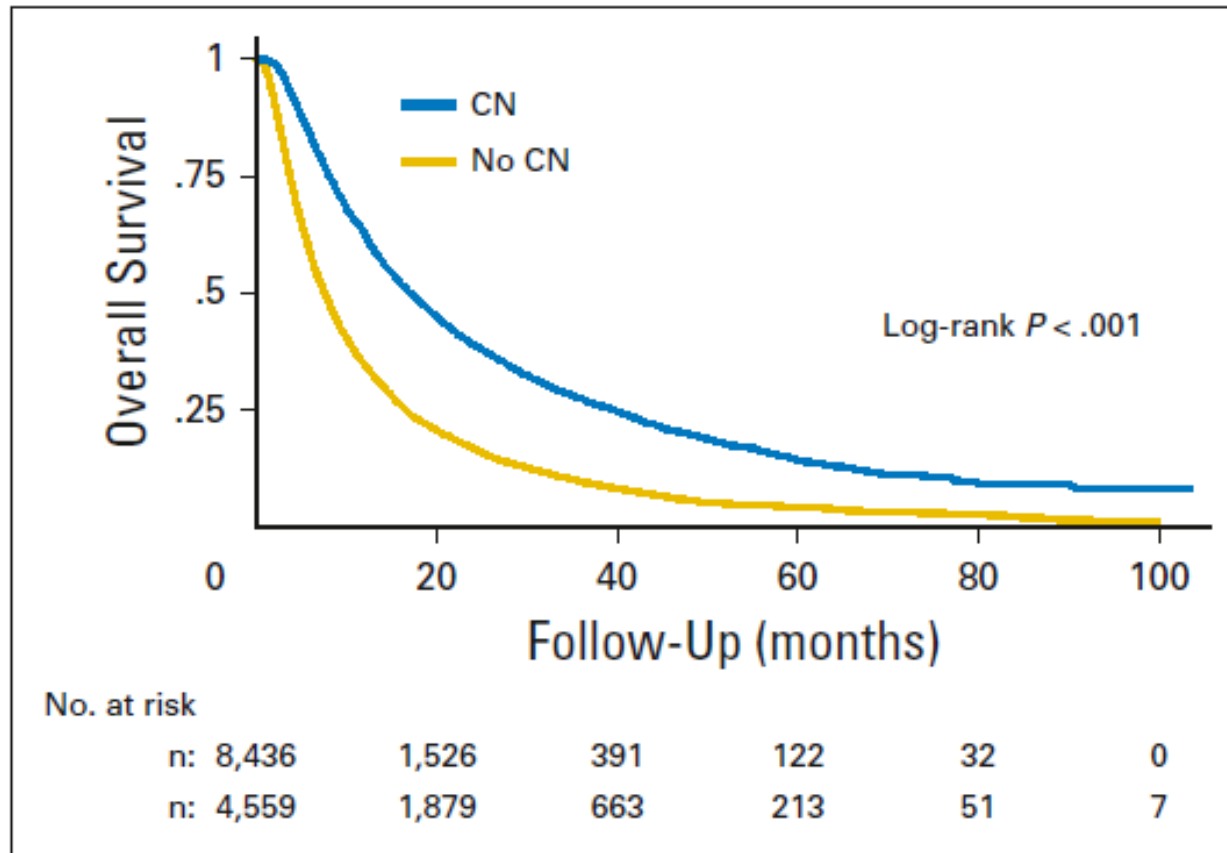


Fig 2. Kaplan-Meier survival analyses of patients with metastatic renal cell carcinoma treated with targeted therapy stratified according to cytoreductive nephrectomy (CN) status (yes or no), National Cancer Data Base, 2006 to 2012. Data were restricted to 12,995 patients with no missing information on vital status or follow-up time.

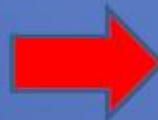
Metastatik RCC, Nefrektomi?

Good Performance Status
Readily Resectable Primary
Tumor



Upfront Nephrectomy

Poor Performance Status
Unresectable Primary Tumor



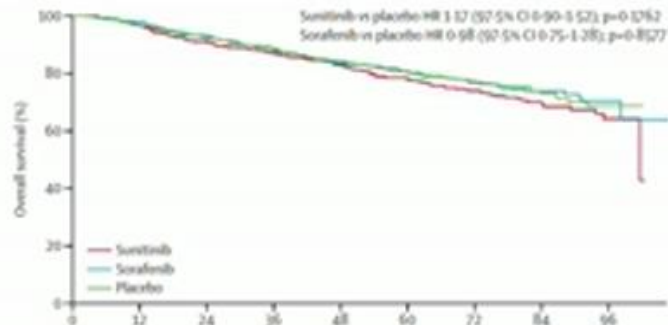
Upfront Systemic Therapy

Nefrektomi (Metastatik olmayan) Sonrası Adjuvan Tedavi?

Ongoing/Recently Completed Adjuvant Trials

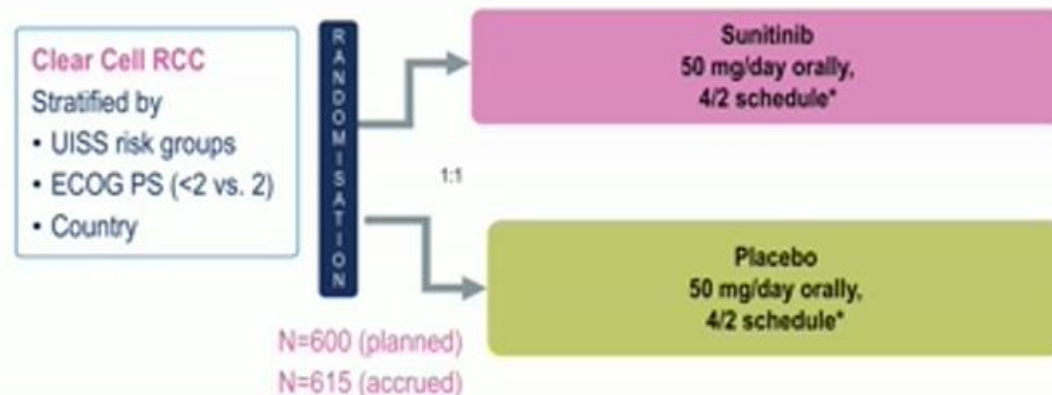
Study Name	Sponsor	N	Design	Outcome Measure	Status
ASSURE	ECOG/NCI	1941	1 yr sorafenib vs 1 yr sunitinib vs placebo	Relapse free survival	Accrual complete
SORCE	MRC(UK)	1656	3 yrs sorafenib vs 1 yr sorafenib vs placebo	Relapse free survival	Ongoing
STAR	Pfizer	720	1 yr sunitinib vs 1 yr placebo	Relapse free survival	Ongoing
PROTECT	GSK	1500	1 yr pazopanib vs 1 yr placebo	Relapse free survival	Ongoing
EVEREST	SWOG	1218	1 yr everolimus vs 1 yr placebo	Relapse free survival	Ongoing

Nefrektomi (Metastatik olmayan) Sonrası Adjuvan Tedavi?



ASSURE Study:
pT1b G3-4 N0 (or pNX where clinically N0) M0
to T(any) G(any) N + (fully resected) M0

Haas NB, Lancet 2016



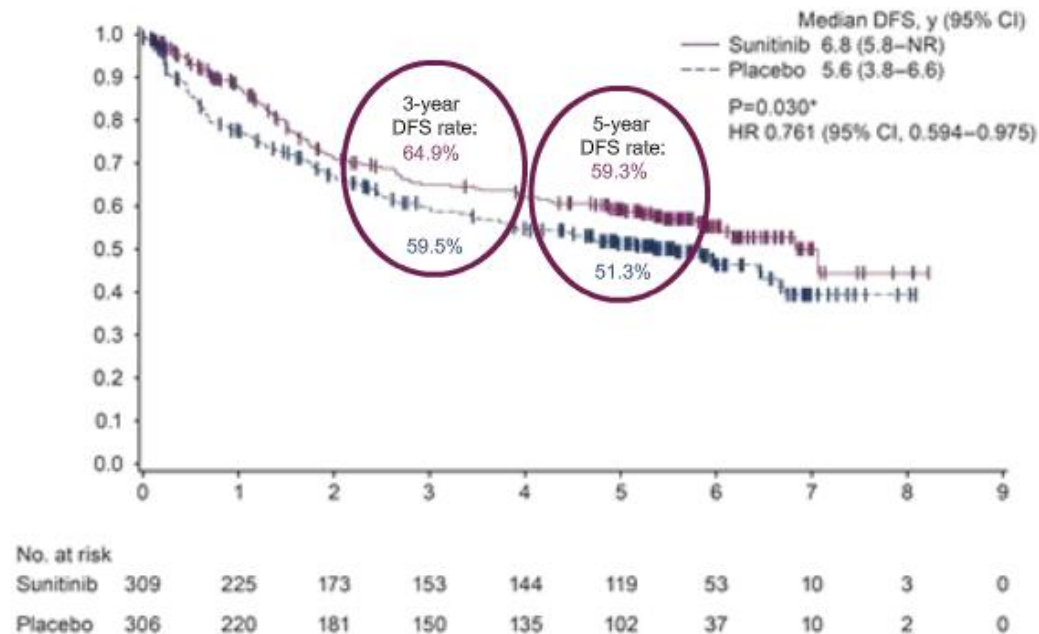
High-risk population selected based on modified UISS Criteria:

- T3 N0 or Nx, M0, any Fuhrman's grade and any ECOG status
- T4 N0 or Nx, M0, any Fuhrman's grade and any ECOG status
- Any T, N1-2, M0, any Fuhrman's grade and any ECOG status

Primary endpoint: DFS

Nefrektomi (Metastatik olmayan) Sonrası Adjuvan Tedavi?

S-TRAC study: DFS results (Independent Centralized Review)



Treatment completion (1y):
55.6% (S) vs 69.4% (P)

Incidence of any G3-4 AEs:
60.5% vs 19.4%

PRA: ↑ appetite loss and diarrhea with Sunitinib

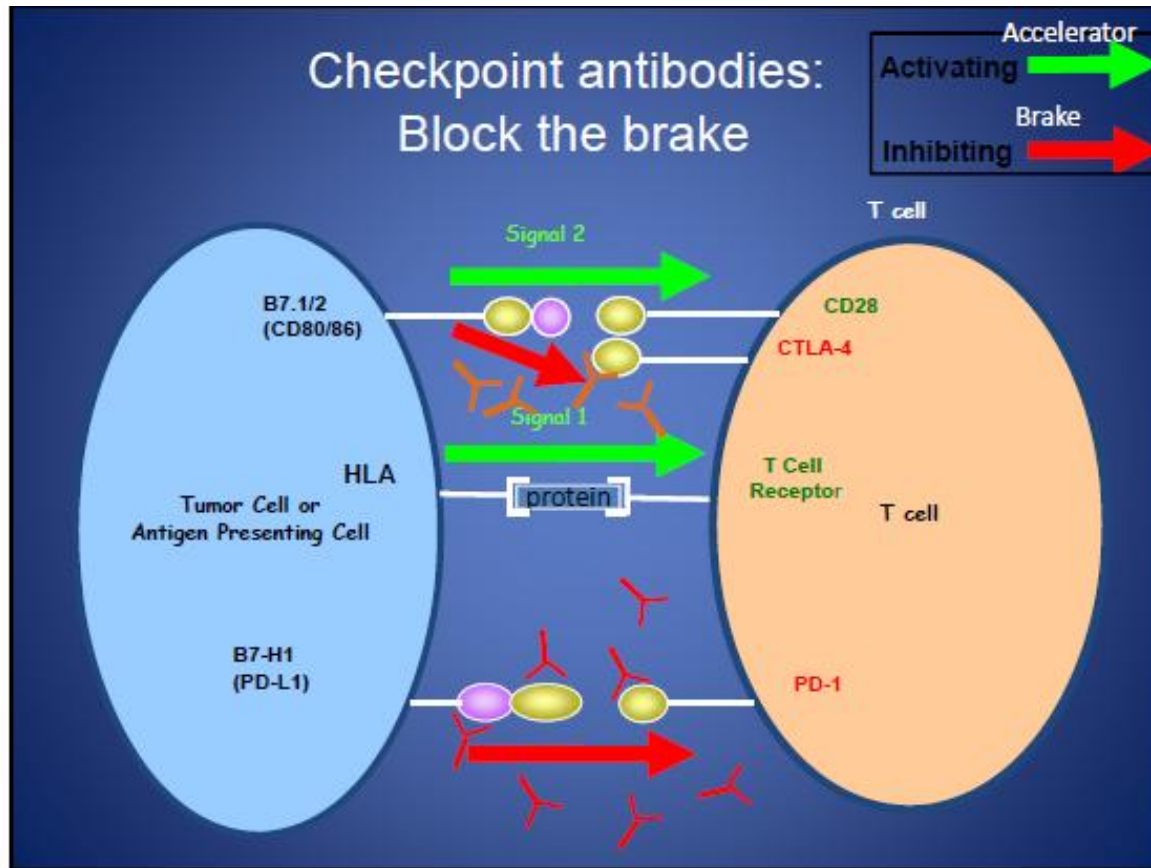
Metastatik RCC Tedavi Seçenekleri

İmmünoterapi

- ❑ immünoterapiyle ilgili ilk bilgiler New York da yaşayan cerrah William Coley 1891 yılında veriyor. Dr coley enfeksiyon sonrası hastasının yüzünde ki kanserin (sarkom) gerilediğini belirtmiş.
- ❑ İlerleyen zamanda bağışıklık sistemini aktive eden Streptococcus pyogenes and Serratia marcescens bakterilerinin antijenik yapılarının immün sistemi aktivite ettiği saptanıyor.
- ❑ Tüberküloz hastalığına karşı 1908 yılında Albert Calmette ve Camille Guerin BCG aşısını geliştiriyor.
- ❑ İlerleyen yıllarda tüberküloz olan hastalarda kanser oranının düşük olması bilim adamlarını araştırmalara yönlendiriyor. Bu çalışmalar sonrası tüberküloz bakterilerinin antijenlerinde elde edilen BCG aşısı erken evre mesane kanserinde günümüze halen kullanılmaktadır.
- ❑ Modern immünoterapi 1985 yılında İnterleukin 2 metastatik melanomda kullanılmasıyla başlıyor.



Metastatik RCC, Tedavi Seçenekleri İmmünoterapi



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Metastatik RCC, Tedavi Seçenekleri

İmmünoterapi

FDA approved

1. High dose IL-2
2. Nivolumab

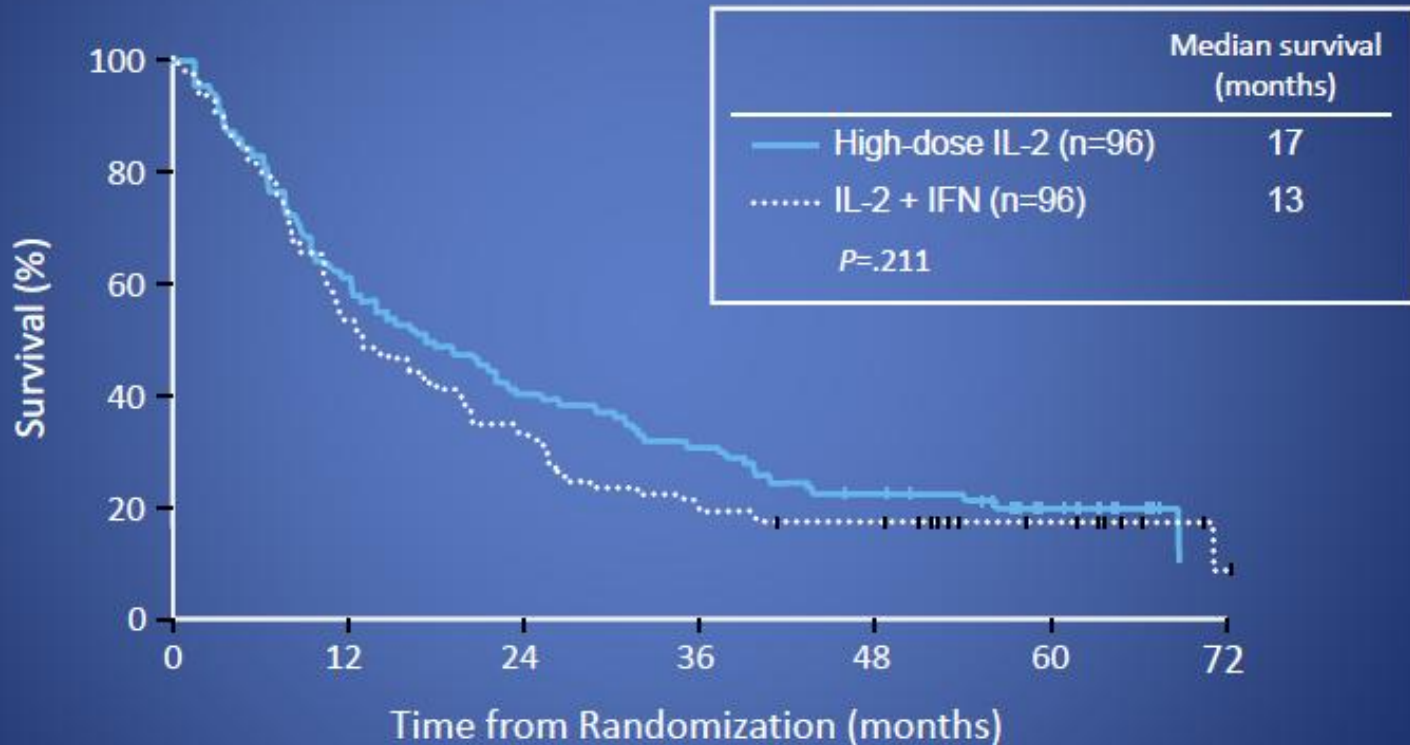
Metastatik RCC, Tedavi Seçenekleri

Yüksek Doz İL-2

	HD IL-2 (720,000 IU/kg)	LD IL-2 (72,000 IU/kg)	SC IL-2 (250,000 IU/kg d1-5, 125,000 IU/kg 5x/wk)
Evaluable (n)	155	149	93
CR	6%	1%	2%
PR	14%	9%	8%
Major RR	21%	13%	10%

Metastatik RCC Tedavi Seçenekleri

Yüksek Doz İL-2



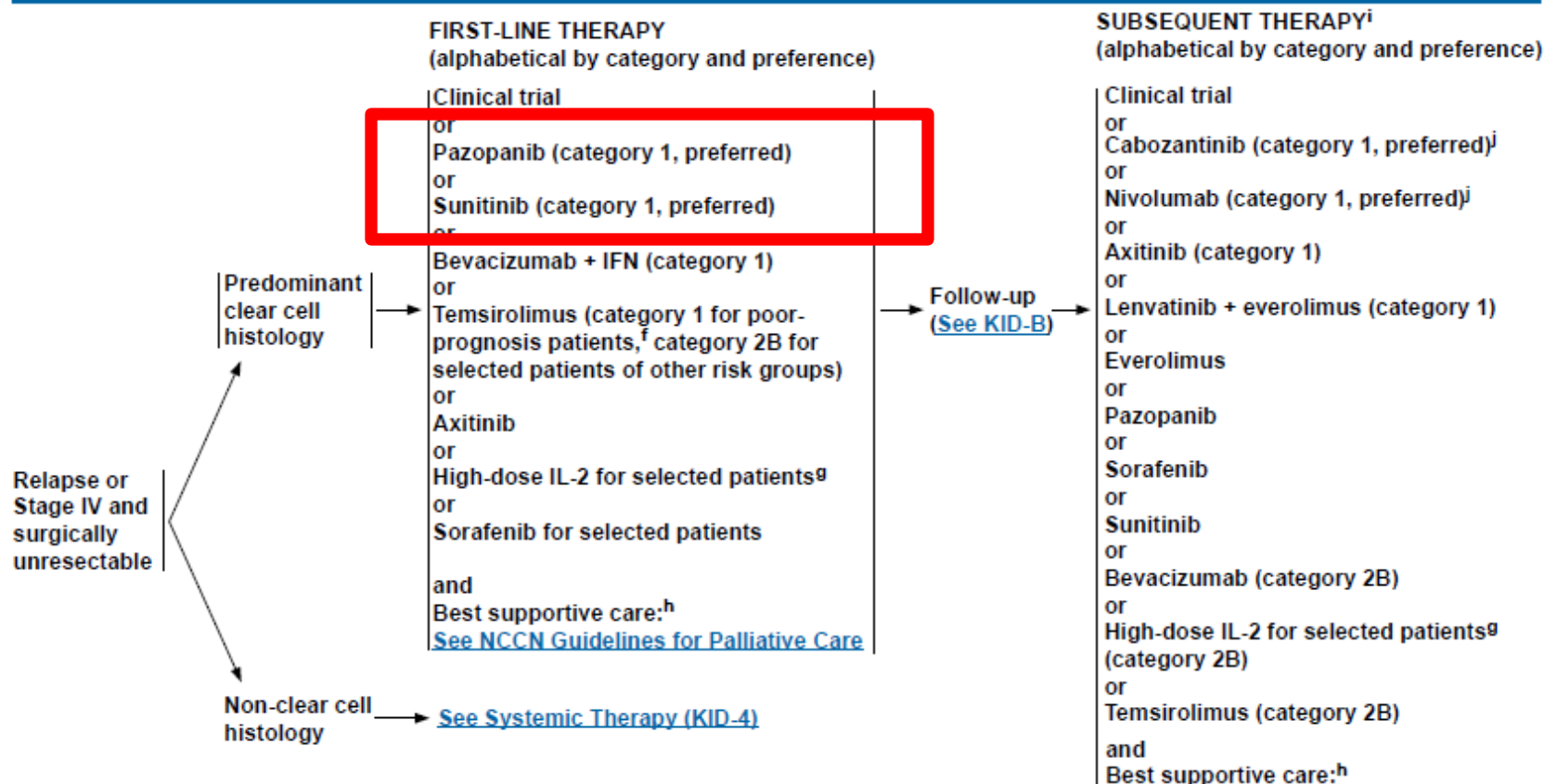
Metastatik RCC Tedavi Seçenekleri

Antianjiojenik Ajanlar

FDA Approved

1. Sunitinib
2. Pazopanib
3. Bevacizumab + IFN
4. Sorafenib
5. Axitinib
6. Cabozantinib
7. Lenvatinib + everolimus

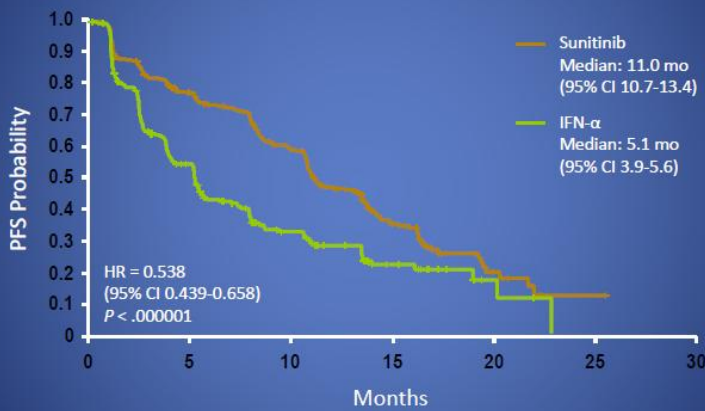
Metastatik RCC, Tedavi Seçenekleri



Metastatik RCC Tedavi Seçenekleri

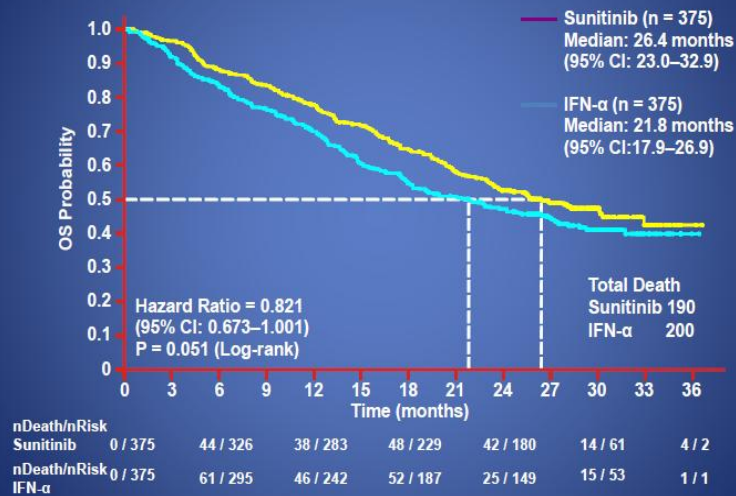
Antianjiojenik Ajanlar-Sunitinib

Phase 3 Trial of Sunitinib vs IFN- α in Patients With Metastatic RCC



Motzer et al NEJM 2007

Sunitinib vs. IFN- α Final OS



Motzer RJ, et al. *J Clin Oncol.* 2009;27:3584–3590.

Metastatik RCC Tedavi Seçenekleri

Antianjiojenik Ajanlar

Table 3. Results of an Analysis of OS by Individual Baseline Factors

Factor	OS		P
	HR	95% CI	
Treatment (sunitinib v IFN- α)	0.764	0.623 to 0.936	.0096
ECOG PS (0 v 1)	0.515	0.417 to 0.636	< .0001
Hemoglobin (\geq v < LLN)	0.504	0.401 to 0.634	< .0001
Time from diagnosis to treatment (\geq v < 1 year)	0.574	0.461 to 0.715	< .0001
Corrected calcium (\leq v > 10 mg/dL)	0.466	0.327 to 0.664	< .0001
Alkaline phosphatase (\leq v > ULN)	0.676	0.542 to 0.844	.0005
Lactate dehydrogenase (\leq v > 1.5 \times ULN)	0.500	0.337 to 0.742	.0006
No. of metastatic sites (1 v \geq 2)	0.664	0.503 to 0.876	.0037

Abbreviations: OS, overall survival; HR, hazard ratio; IFN- α , interferon alfa; ECOG PS, Eastern Cooperative Oncology Group performance status; LLN, lower limit of normal; ULN, upper limit of normal.

Table 4. Poststudy Cancer Treatment

Treatment	Sunitinib (n = 323)		IFN- α (n = 359)*	
	No. of Patients	%	No. of Patients	%
Any poststudy treatment	182	56	213	59
Sunitinib†	36	11	117	33
Other VEGF inhibitors	106	33	115	32
Cytokines	63	20	47	13
mTOR inhibitors	28	9	16	4
Chemotherapy	21	6	20	6

Abbreviations: IFN- α , interferon alfa; VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin.

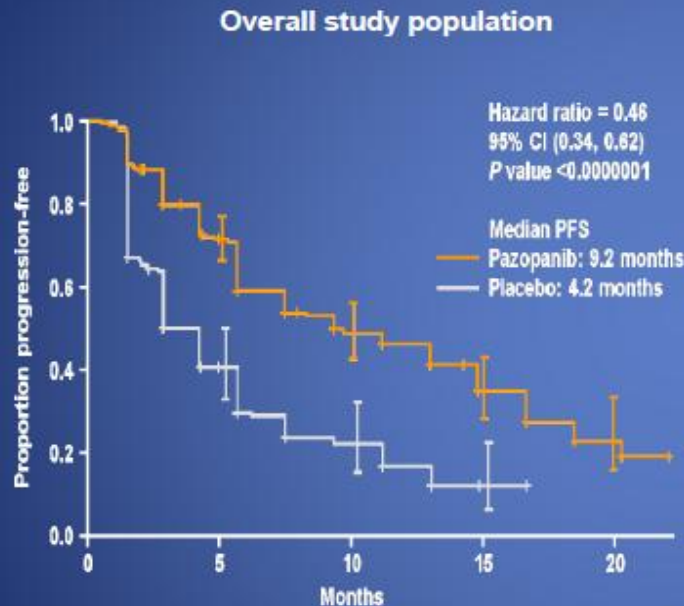
*Includes patients who crossed over to sunitinib on study before discontinuation.
†P < .001 for the comparison between the sunitinib group and the IFN- α group.

Robert J. Motzer, et al, JCO 2009

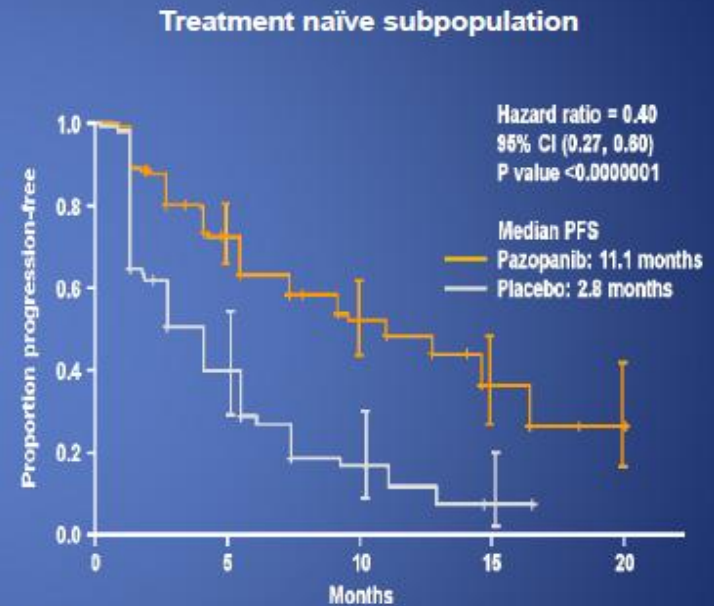
Metastatik RCC Tedavi Seçenekleri

Antianjiojenik Ajanlar-Pazopanib

PFS in Overall Study Population and Treatment-naïve Subpopulation



Patients at risk	0	5	10	15	20
Pazopanib	290	159	76	29	6
Placebo	145	38	14	2	

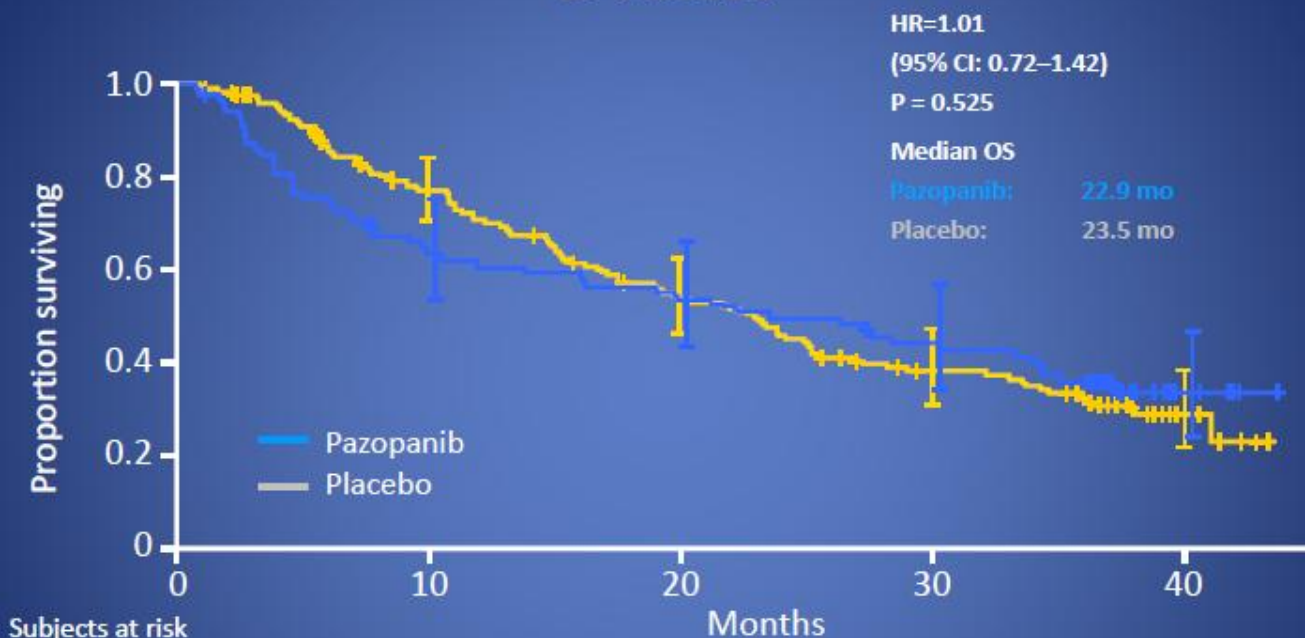


Patients at risk	0	5	10	15	20
Pazopanib	155	34	39	11	1
Placebo	78	22	7	2	

Metastatik RCC Tedavi Seçenekleri

Antianjiojenik Ajanlar-Pazopanib

Overall Survival in Treatment-naïve Patients Receiving Pazopanib or Placebo



Subjects at risk	
Pazopanib	155
Placebo	78

	10	20	30	40
Pazopanib	110	74	46	7
Placebo	47	40	32	5

	Overall Population	Treatment-Naïve
ORR	= 30% vs. 3% by central review Not updated	= 32% vs. 4% by central review Not updated

Metastatik RCC Tedavi Seçenekleri Antianjiojenik Ajanlar-Sunitinib

COMPARZ

COMParing the, s**A**fety and tole**R**ability
of
pa**Z**opanib vs sunitinib

22 Ağustos 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

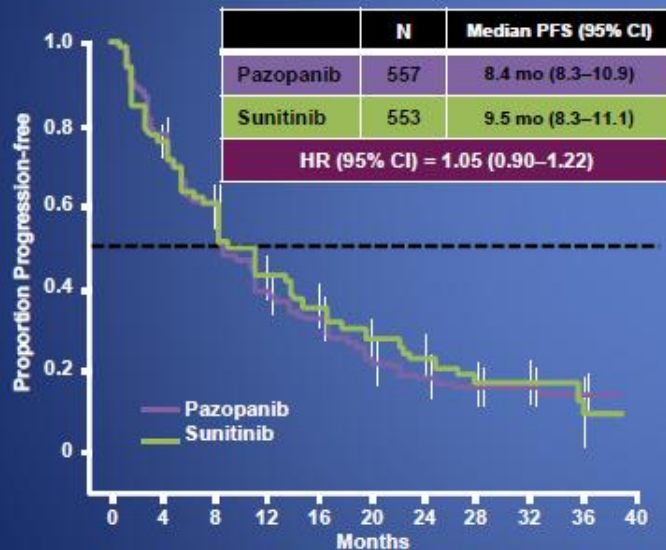
Robert J. Motzer, M.D., Thomas E. Hutson, D.O., David Cella, Ph.D.,
James Reeves, M.D., Robert Hawkins, M.B., B.S., Ph.D., Jun Guo, Ph.D.,
Paul Nathan, M.B., B.S., Ph.D., Michael Staehler, M.D., Paul de Souza, M.B., B.S., Ph.D.,
Jaime R. Merchan, M.D., Ekaterini Boleti, M.D., Ph.D., Kate Fife, M.D.,
Jie Jin, M.D., Robert Jones, Ph.D., Hirotosugu Uemura, M.D., Ph.D., Ugo De Giorgi, M.D.,

Metastatik RCC Tedavi Seçenekleri

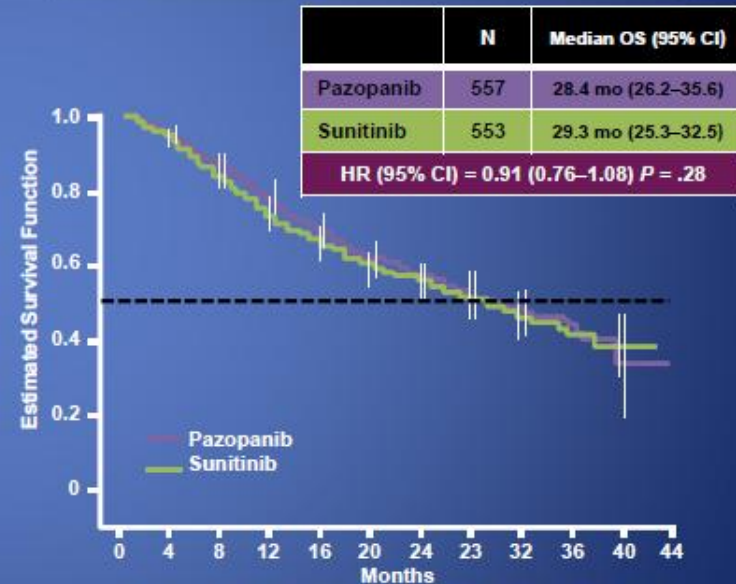
Antianjiojenik Ajanlar-Sunitinib/Pazopanib

COMPARZ: Efficacy of Pazopanib is Non-inferior to Sunitinib

PFS*,1



OS†,1,2



*Independent review
†Interim analysis

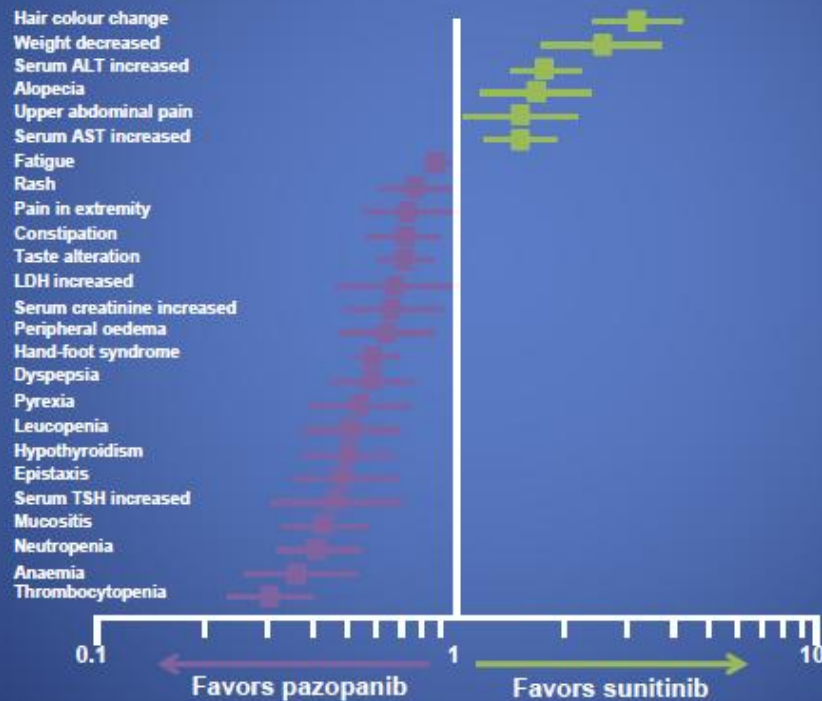
1. Motzer RJ et al. *N Engl J Med.* 2013;369:722-31.

Metastatik RCC Tedavi Seçenekleri

Antianjiojenik Ajanlar-Sunitinib/Pazopanib

COMPARZ: Relative Risk of AEs

AE occurrence $\geq 10\%$ in either arm; 95% CI for RR does not cross 1



Metastatik RCC Tedavi Seçenekleri

Antianjiojenik Ajanlar-IFN+Bevacizumab

Phase III CALGB 90206 trial of first-line interferon alpha +/- bevacizumab in patients with metastatic renal cell carcinoma: Efficacy

	IFN (n=363)	IFN+bev (n=369)	HR	P Value
ORR (%)	13 (n = 314)	25.5 (n = 325)	NR	<.0001
Median PFS (months)	4.9	8.4	0.71	<.0001
Median OS (months)	17.4	18.3	NR	.069
Median OS by MSKCC risk group (months)				
Favorable	33.5	32.5	0.89	.524
Intermediate	16.1	17.7	0.87	.174
Poor	5.7	6.6	0.76	.25
Median OS based on receiving 2nd line therapy				
Yes (n = 408)	26.8	31.4	0.80	.055
No (n = 324)	9.1	13.1	0.82	.108

Metastatik RCC Tedavi Seçenekleri Pratik Nasıl Değişecek

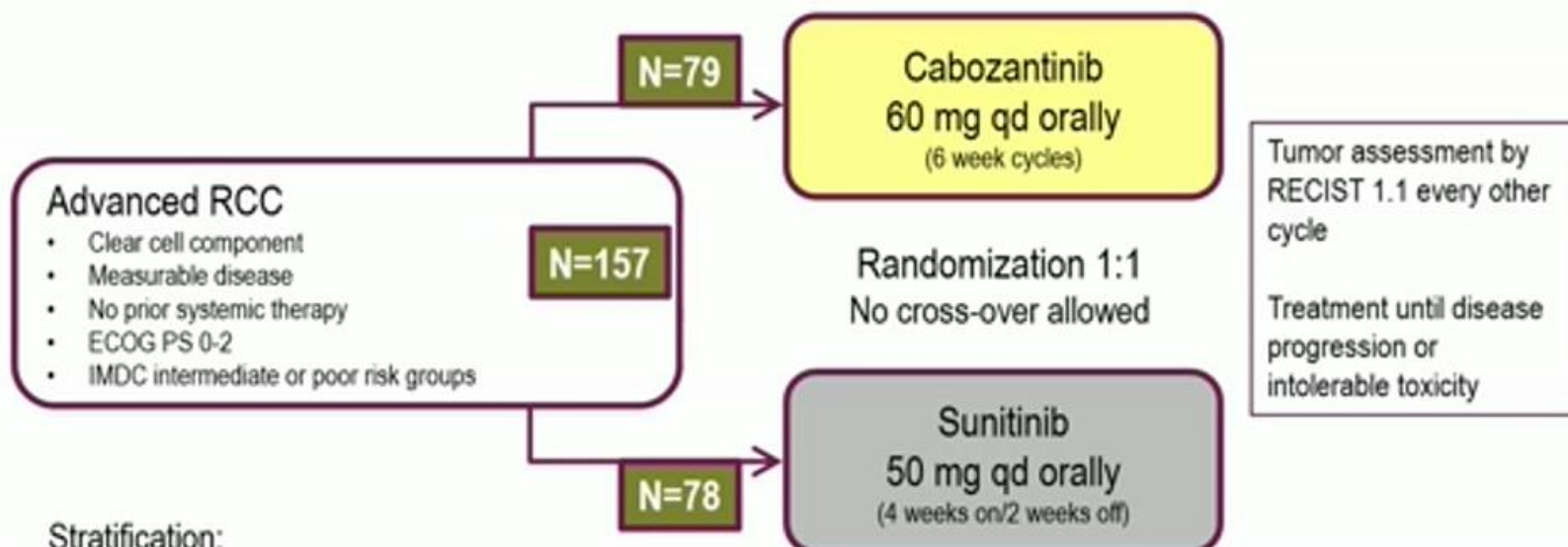
CABOzantinib versus SUNitinib (CABOSUN) as initial targeted therapy for patients with metastatic renal cell carcinoma (mRCC) of poor and intermediate risk groups

ALLIANCE A031203 Trial

Toni K. Choueiri MD, Susan Halabi PhD, Ben Sanford MS,
Olwen Hahn MD, M. Dror Michaelson MD, Meghara Walsh RN,
Thomas Olencki MD, Joel Picus MD, Eric Small MD, Shaker Dakhil MD,
Daniel George MD, and Michael J. Morris MD

Metastatik RCC Tedavi Seçenekleri Pratik Nasıl Değişecek

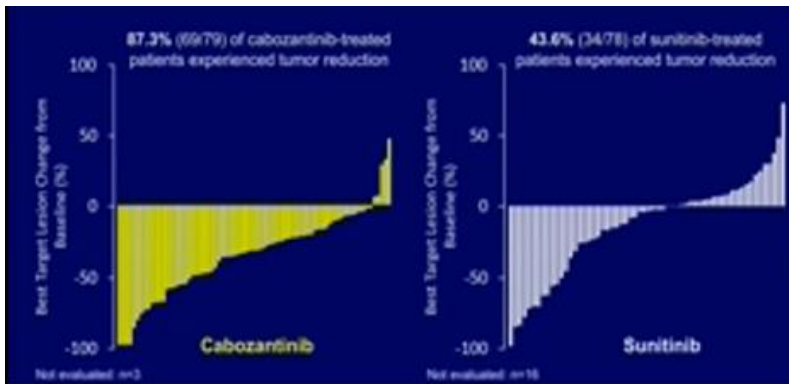
CABOSUN Randomized Ph2 study design



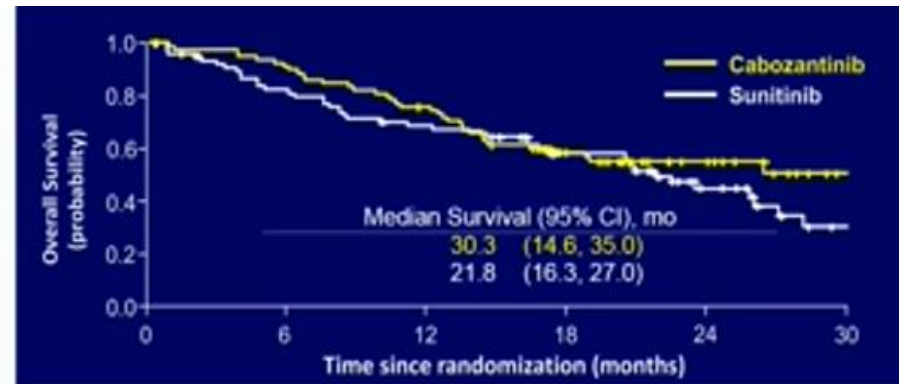
Stratification:

- IMDC risk group: intermediate, poor
- Bone metastases: yes, no

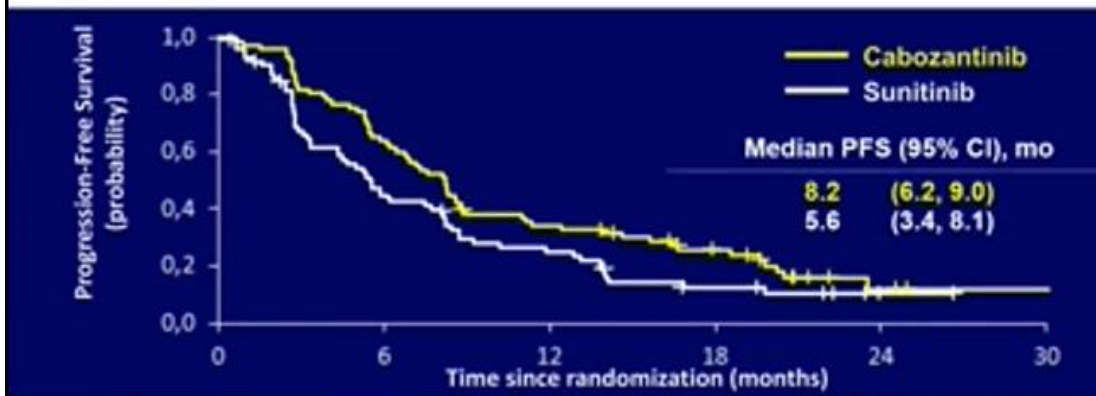
Metastatik RCC Tedavi Seçenekleri Pratik Nasıl Değişecek



Inv-assessed ORR



Δ OS: NS



Δ PFS:

HR: 0.69 (95%CI: 0.48-0.99)

Improvement across subgroups

Metastatik RCC Tedavi Seçenekleri mTOR Yollađı İnhibitörleri

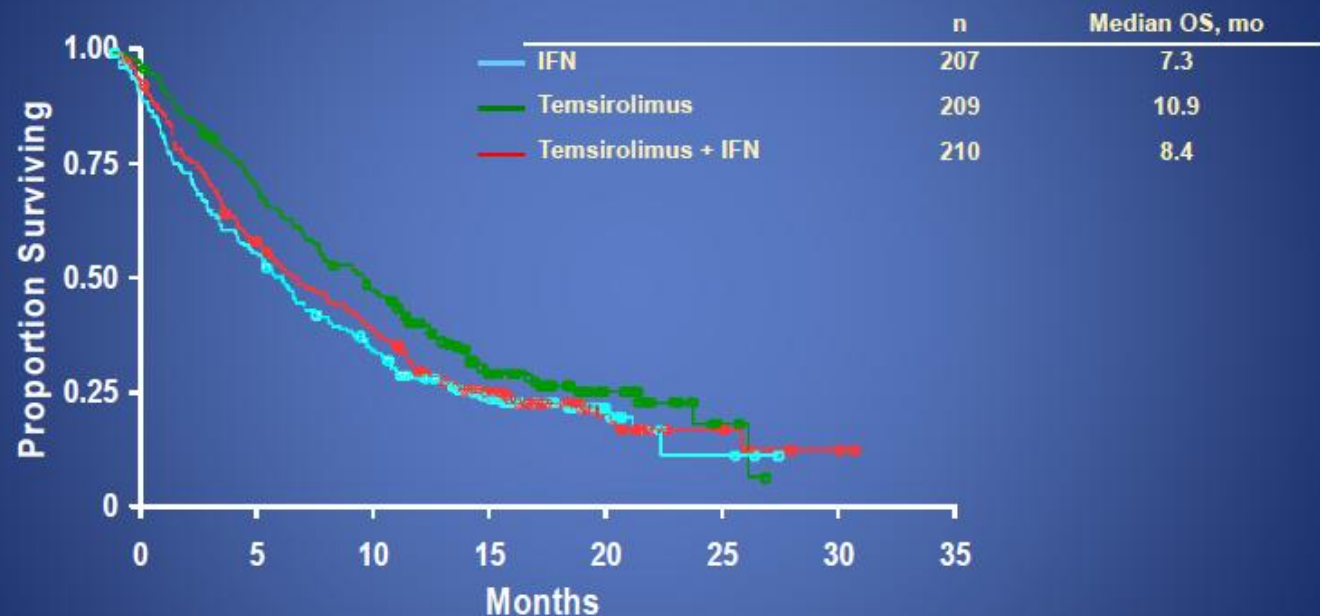
Mammalian Target of Rapamycin Inhibitors (mTORi)

FDA approved

1. Temsirolimus
2. Everolimus

Metastatik RCC Tedavi Seçenekleri mTOR Yolağı İnhibitörleri-Temsirolimus

Phase 3 Study of Temsirolimus and IFN in Advanced RCC: OS by Treatment Arm



Metastatik RCC Tedavi Seçenekleri

2.Basamak Tedaviler

Nivolumab

Cabozantinib

Lenvatinib+Everolimus

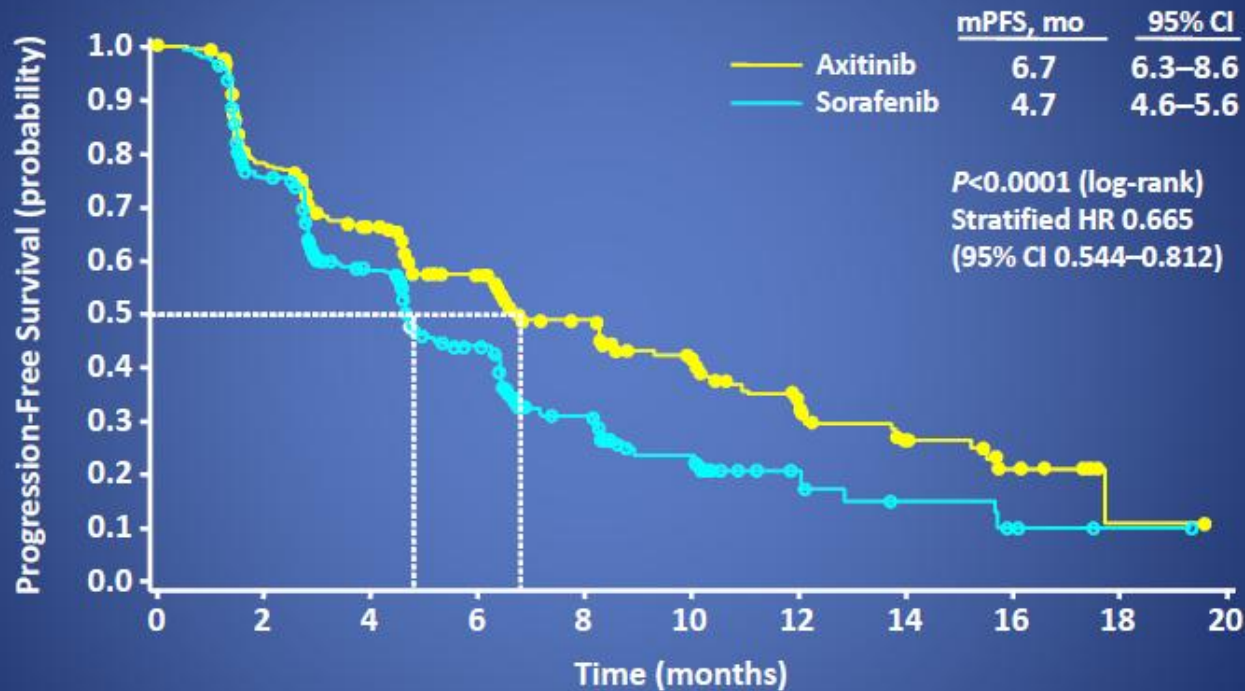
Axitinib

Everolimus

Metastatik RCC Tedavi Seçenekleri

2.Basamak Tedaviler-Axitinib

Progression-free Survival (IRC Assessment)



Subjects at risk, n

Axitinib	361	256	202	145	96	64	38	20	10	1	0
Sorafenib	362	224	157	100	51	28	12	6	3	1	0

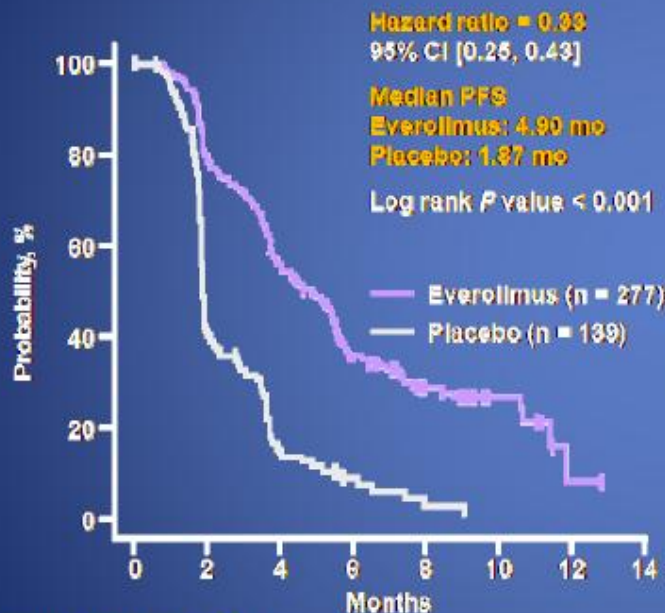
IRC = Independent Review Committee

Metastatik RCC Tedavi Seçenekleri

2. Basamak Tedaviler-Everolimus

Everolimus vs. Placebo Phase 3 Trial: Key Data from RECORD-1

**Progression-free Survival
Central Radiology Review**

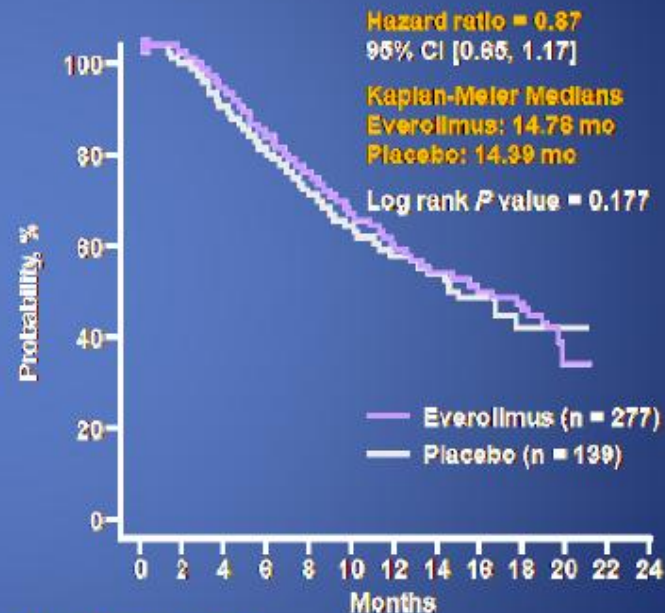


Number of patients at risk

Everolimus	277	192	115	51	26	10	1	0
Placebo	139	47	16	6	2	0	0	0

Analysis on Feb 2008 Data Cut-Off.

Overall Survival



Number of patients at risk

Everolimus	277	267	240	204	164	155	131	101	61	30	6	0	0
Placebo	139	131	117	100	86	74	66	43	27	13	3	0	0

Analysis on Nov 2008 Data Cut-Off.

Metastatik RCC Tedavi Seçenekleri

2.Basamak Tedaviler-Nivolumab

Nivolumab

- PD-1 checkpoint antibody
- Administered 3mg/kg IV every two weeks
- FDA approved for TKI failures Nov 2015

Metastatik RCC Tedavi Seçenekleri

2.Basamak Tedaviler-Nivolumab

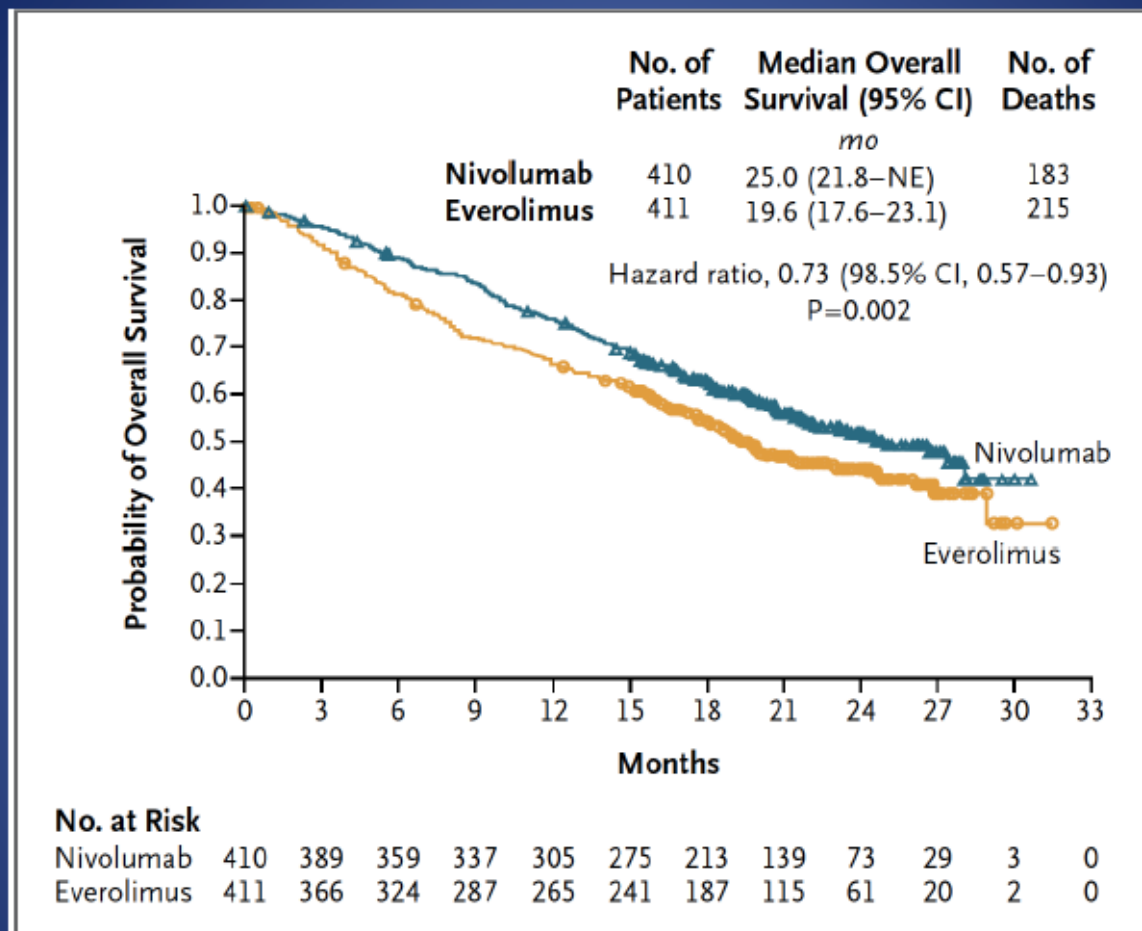


Figure 1. Kaplan–Meier Curve for Overall Survival.

CI denotes confidence interval, and NE not estimable.

Metastatik RCC Tedavi Seçenekleri

2.Basamak Tedaviler-Nivolumab

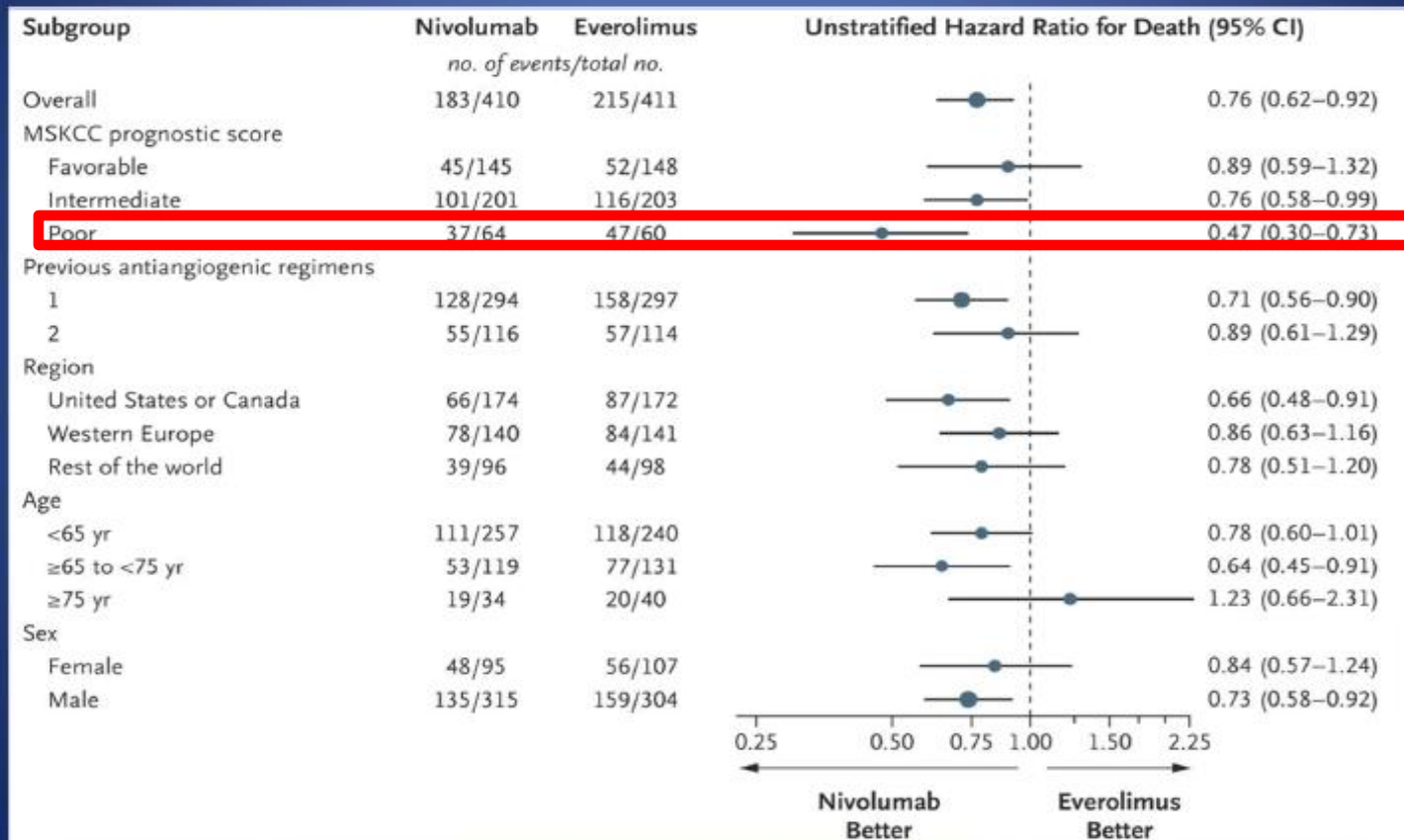
Objective Response Rate

	Nivolumab N=410	Everolimus N=411
Objective Response Rate n (%)	103 (25) P<0.001	22 (5)
Odds ratio (95% CI)	5.98 (3.68-9.72)	
Best Overall Response		
CR	4 (1)	2 (<1)
PR	99 (24)	20 (5)
SD	141 (34)	227 (55)
PD	143 (35)	114 (28)
Not evaluated	23 (6)	48 (12)
Median time to response, months (range)	3.5 (1.4-24.8)	3.7 (1.5-11.2)
Median duration of response, months (range)	12.0 (0-27.6)	12.0 (0-22.2)
Median Duration of Treatment, months (range)	5.5 (<1 to 29.6)	3.7 (0.2 to 25.7)

Metastatik RCC Tedavi Seçenekleri

2.Basamak Tedaviler-Nivolumab

Nivolumab Phase III: OS by subgroup analysis



Metastatik RCC Tedavi Seçenekleri

2.Basamak Tedaviler-Cabozantinib

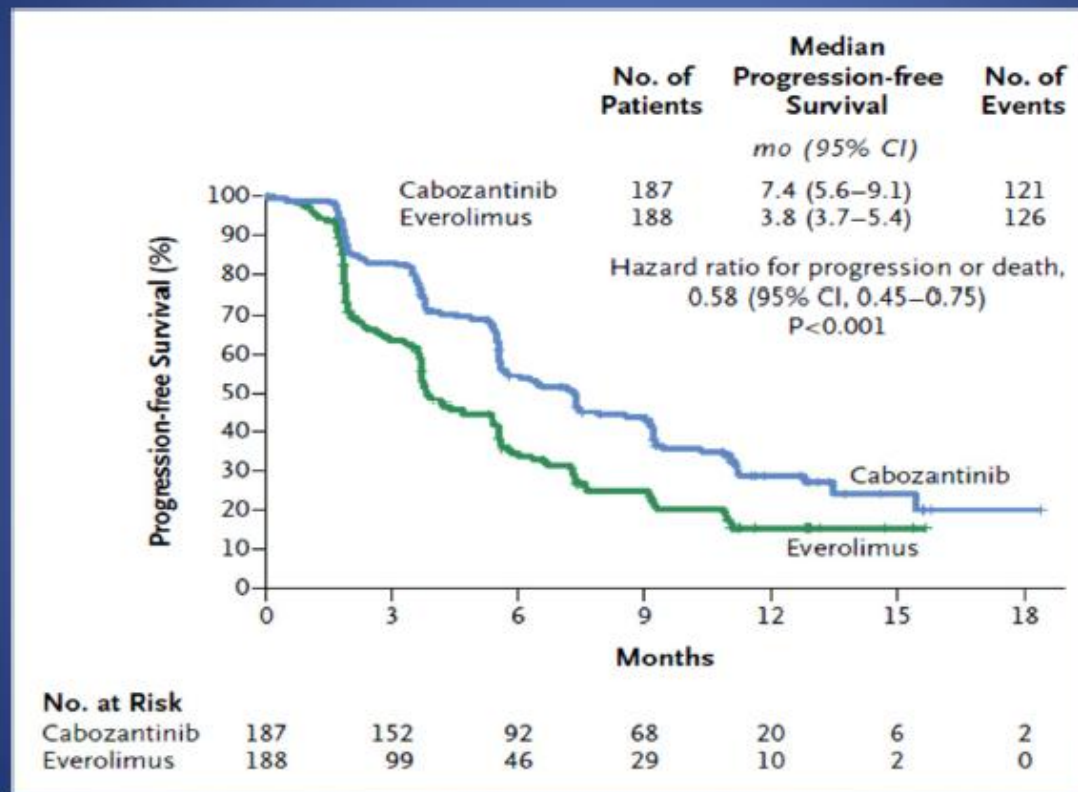
Cabozantinib

- Oral small molecule inhibitor of VEGFRs, AXL, MET.
- Administered 60mg PO daily
- FDA approved March 2016 for RCC patients who progressed after TKI therapy

Metastatik RCC Tedavi Seçenekleri

2.Basamak Tedaviler-Cabozantinib

Cabozantinib Phase III: PFS*



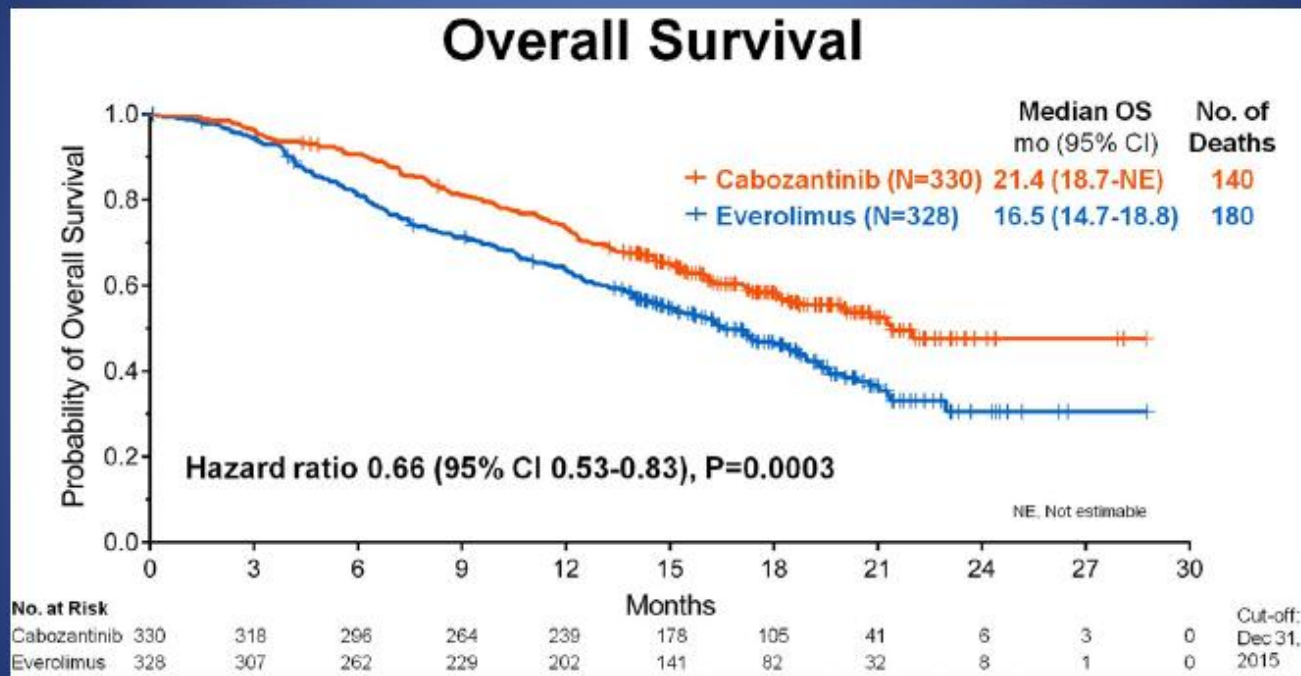
*IRC

Choueiri et al. N Engl J Med 2015

Metastatik RCC Tedavi Seçenekleri

2.Basamak Tedaviler-Cabozantinib

Cabozantinib Phase III: Survival

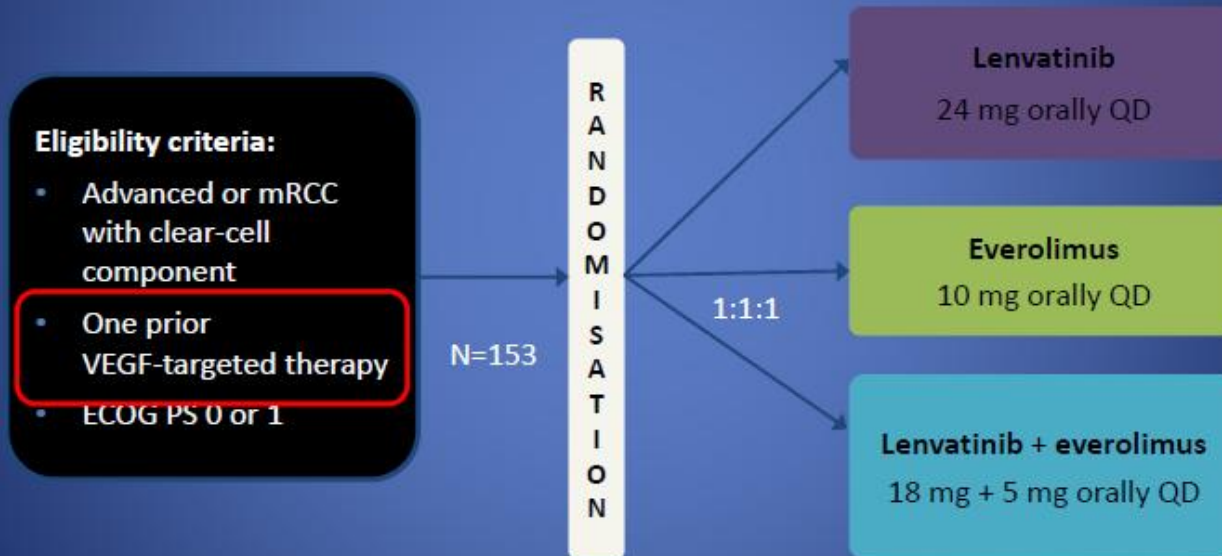


Metastatik RCC Tedavi Seçenekleri

2. Basamak Tedaviler-Lenvatinib

Phase II study of lenvatinib versus everolimus versus lenvatinib + everolimus in mRCC^{1,2}

- Targets: VEGFR, FGFR, PDGFR, RET and KIT



- Primary endpoint: PFS of LEN+EVE or LEN versus EVE
- Secondary endpoints: OS, ORR and safety

1. www.clinicaltrials.gov (NCT01136733);

2. Motzer *et al.* *J Clin Oncol* 2015

Metastatik RCC Tedavi Seçenekleri

2.Basamak Tedaviler-Lenvatinib

Phase II study of lenvatinib versus everolimus versus lenvatinib + everolimus in mRCC

Primary analysis	LEN+EVE (n=51)	LEN (n=52)	EVE (n=50)
Median survival, months (95% CI)			
mPFS ¹	12.8 (7.4–17.5)*	9.0 (5.6–10.2) [†]	5.6 (3.6–9.3)
OS ²	25.5 (20.8–25.5)	18.4 (13.3–NE)	17.5 (11.8–NE)
ORR, n (%) ¹	18 (35) [‡]	20 (39) [‡]	0 (0)

*p=0.0029 compared with everolimus alone; [†]p=0.12 compared with everolimus alone; [‡]p<0.0001 compared with everolimus alone; NE, not evaluable

1. Motzer *et al. Lancet Oncol* 2016; 2. Motzer *et al. J Clin Oncol* 2015

Metastatik RCC Tedavi Seçenekleri Pratik Nasıl Değişecek

Axitinib in Combination With Pembrolizumab in Patients With Advanced Renal Cell Carcinoma: Preliminary Safety and Efficacy Results

Michael B Atkins¹, Elizabeth R Plimack², Igor Puzanov³, Mayer N Fishman⁴, David F McDermott⁵, Daniel C Cho⁶, Ulka Vaishampayan⁷, Saby George⁸, Thomas Olencki⁹, Jamal C Tawbi¹⁰, Brad Rosbrook¹¹, Kathrine Fernandez¹², Stephen Keefe¹³, Toni K Choueiri¹⁴
¹Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; ²Fox Chase Cancer Center, Philadelphia, PA, USA; ³Vanderbilt University Medical Center, Nashville, TN, USA; ⁴Roswell Park Cancer Institute, Buffalo, NY; ⁵Moffitt Cancer Center, Tampa, FL, USA; ⁶Brigham Young University Medical Center, Boston, MA, USA; ⁷NYU Langone Medical Center, New York, NY, USA; ⁸Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; ⁹The Ohio State University, Wexner Medical Center, Columbus, OH, USA; ¹⁰Pfizer Oncology, San Diego, CA, USA; ¹¹Pfizer Oncology, Cambridge, MA, USA; ¹²Merck & Co., Inc., Kenilworth, NJ, USA; ¹³Dana-Farber Cancer Institute, Boston, MA, USA

Best Overall Response

N=52	Axitinib + PEM
Pts with baseline assessment	52 (100)
Pts with measurable disease at BL	52 (100)
Best overall response, n (%)	
Complete response (CR)	3 (5.8)
Partial response (PR)	34 (65.4)
Stable disease	10 (19.2)
Progressive disease	2 (3.8)
Indeterminate*	3 (5.8)
Objective response rate (CR+PR)	37 (71.2)
95% Exact CI	56.9–82.9

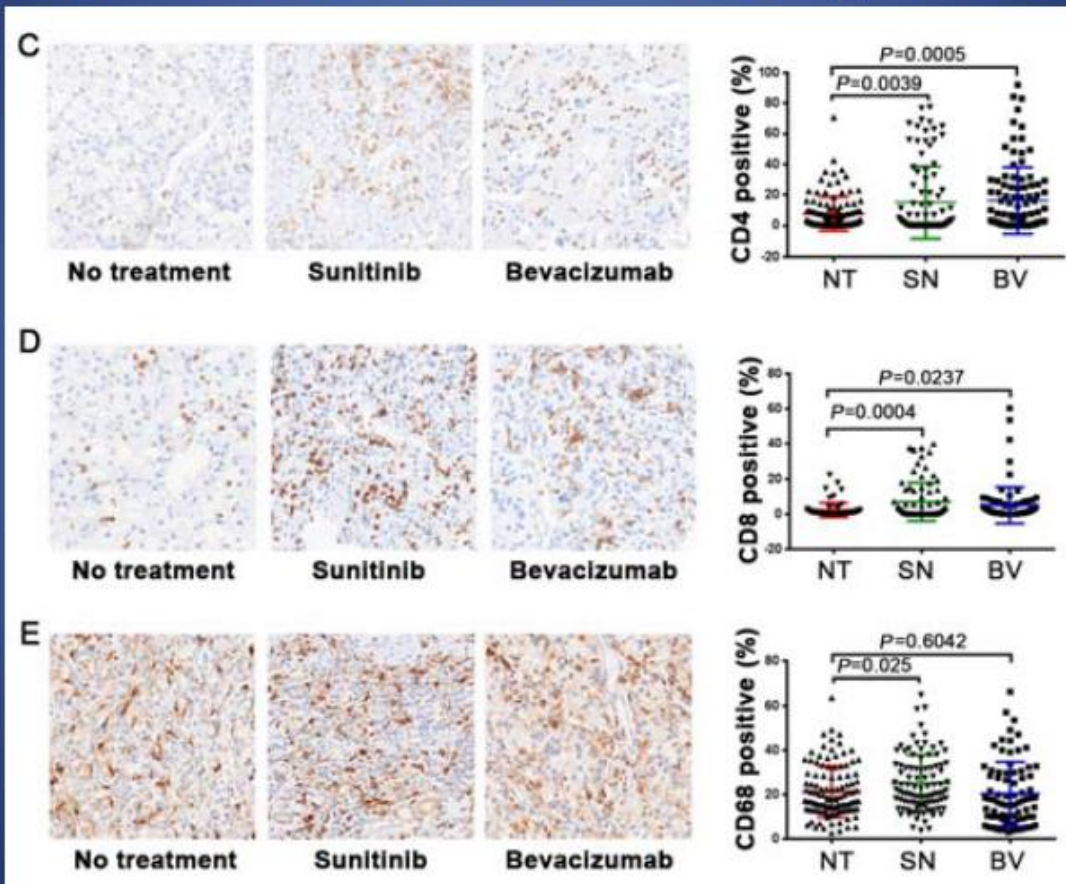
Treatment-naïve patients with advanced RCC.

- ▶▶ Ongoing, open-label, phase Ib, multicenter study (NCT02133742)
- ▶▶ Interim safety and efficacy results from both phases is reported
- ▶▶ Axitinib 5mg BID + Pembrolizumab 2 mg/Kg q3wks

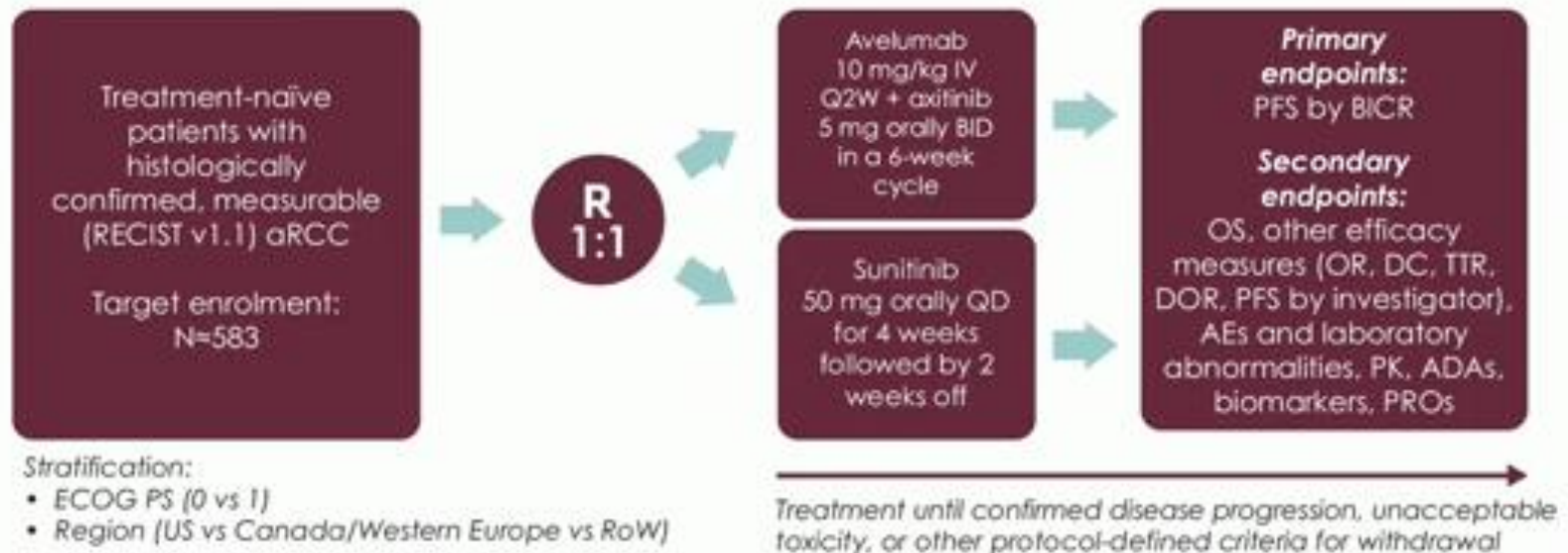
- PFS data are immature; only 14 (26.9%) events for the overall analysis.
- Acceptable toxicity profile - no new or unusual toxicities were observed.
- There were a few treatment discontinuations due to hepatotoxicity.
- PD-L1 status did not predict tumor response.

Metastatik RCC Tedavi Seçenekleri Pratik Nasıl Değişecek

Antiangiogenic treated tissues are associated with increased tumor infiltrating T cells



Renal Cell Ca Gelecekteki Tedavi Algoritmaları



Metastatik RCC Tedavi Seçenekleri Pratik Nasıl Değişecek

Monotherapy studies of additional PD-1 inhibitors in RCC

Agent	Phase	Study name	Intervention	Line of therapy	Primary endpoints	Status
Anti-PD-1						
Pembrolizumab	I	NCT02212730	Monotherapy	1st	Safety Intratatumoural lymphocytic infiltration	Recruiting
Anti-PD-L1						
Atezolizumab	II	RAPID NCT01984242	Monotherapy or + bevacizumab vs sunitinib	1st	PFS	Ongoing but not recruiting
Avelumab	I	JAVELIN NCT01772004	Monotherapy	1st	Safety	Recruiting
MDX-1105	I	NCT00729664	Monotherapy	1st+	Safety MTD/DLT	Completed

DLT, dose-limiting toxicity; MTD, maximum tolerated dose
www.clinicaltrials.gov

Metastatik RCC Tedavi Seçenekleri

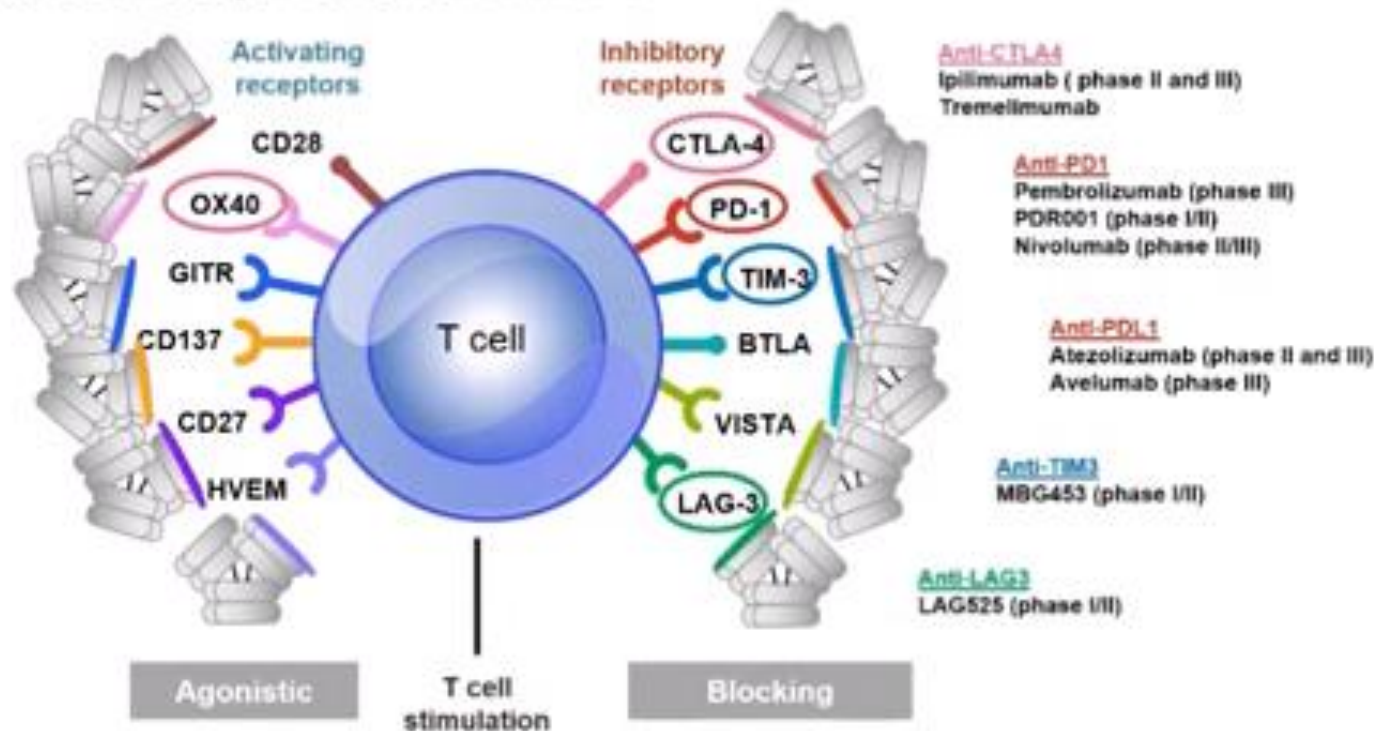
Lines of Treatment in Advanced RCC

Setting		Approved Agents	Alternative
1st-Line Therapy	Good or intermediate risk*	Sunitinib Pazopanib Bevacizumab + IFN α	HD IL-2
	Poor risk*	Temsirolimus	Sunitinib Pazopanib
2nd-Line Therapy	Prior VEGFR inhibitor	Nivolumab Cabozantinib Lenvatinib+Everolimus Axitinib Everolimus	Sunitinib Pazopanib
	Prior mTOR inhibitor	Clinical trial; other approved agents	

*MSKCC risk status.

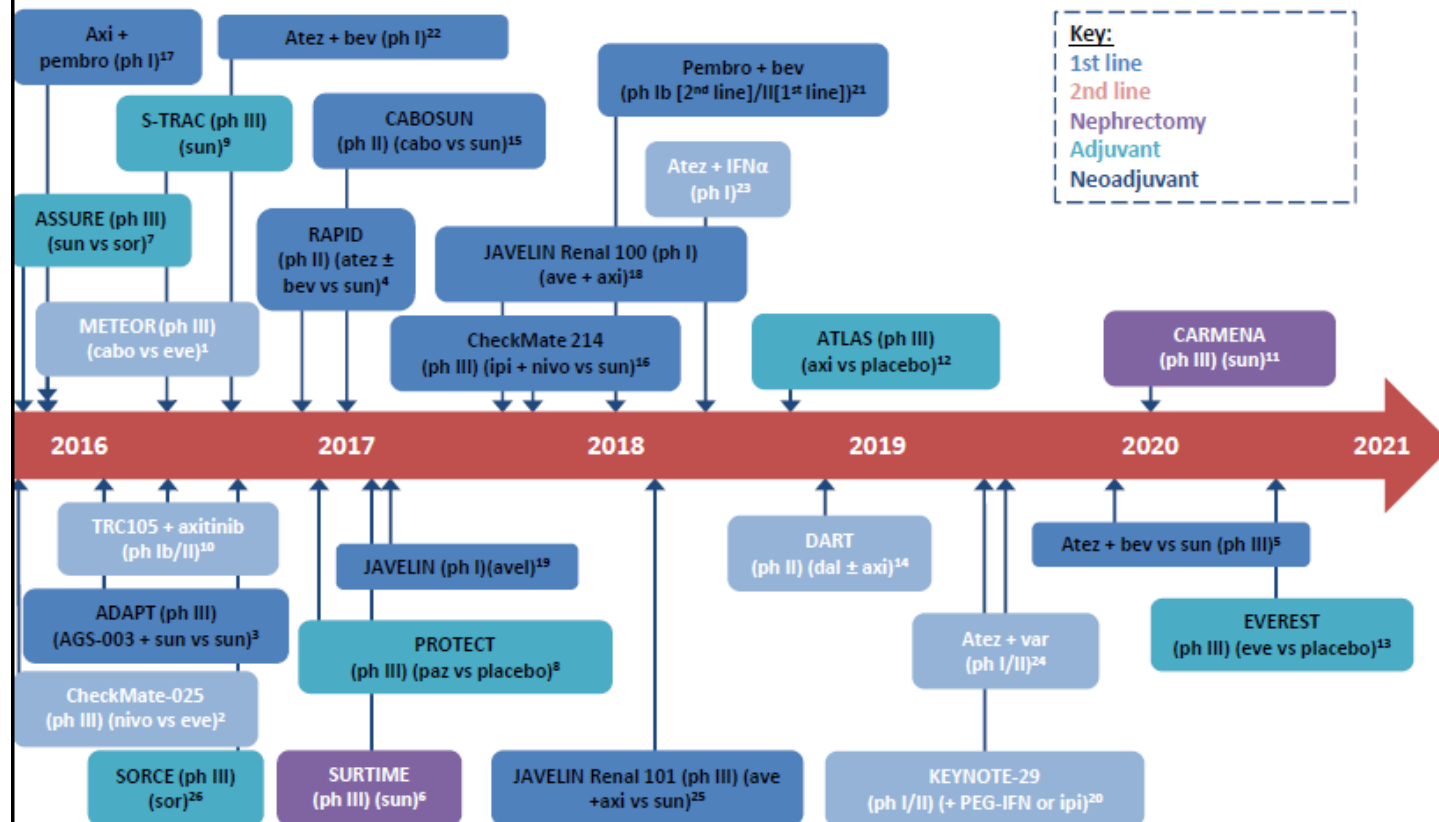
Metastatik RCC Tedavi Seçenekleri Pratik Nasıl Değişecek

Multiple targets for checkpoint inhibitor in clinical development for mRCC



Metastatik RCC Tedavi Seçenekleri Pratik Nasıl Değişecek

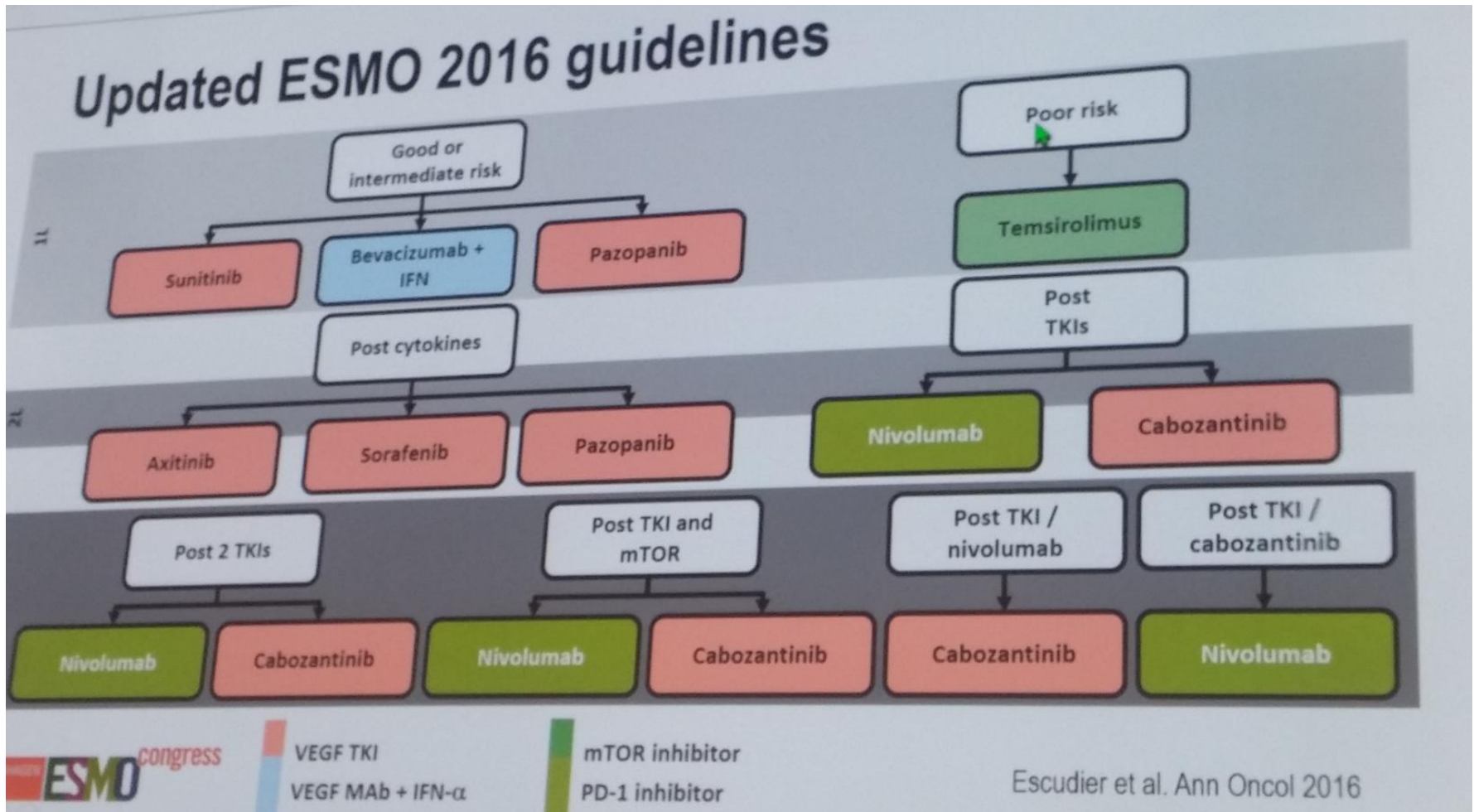
Many ongoing or planned trials to be reported



*Estimated study completion dates are taken from www.clinicaltrials.gov

The following references are available from www.clinicaltrials.gov: 1. NCT01865747; 2. NCT01668784; 3. NCT01582672; 4. NCT01984242; 5. NCT02410821; 6. NCT01099423; 7. NCT00226890; 8. NCT01235962; 9. NCT00975674; 10. NCT01806064; 11. NCT00930033; 12. NCT01599754; 13. NCT01120249; 14. NCT01727316; 15. NCT01835158; 16. NCT02231749; 17. NCT02153742; 18. NCT02483751; 19. NCT01772006; 20. NCT02089685; 21. NCT02348008; 22. NCT01613970; 23. NCT02174172; 24. NCT02543645; 25. NCT02684006; 26. NCT00492258

Renal Cell Ca Gelecekteki Tedavi Algoritmaları



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