Metastatik Renal Kanserde Birinci Basamak Tedavi Seçenekleri

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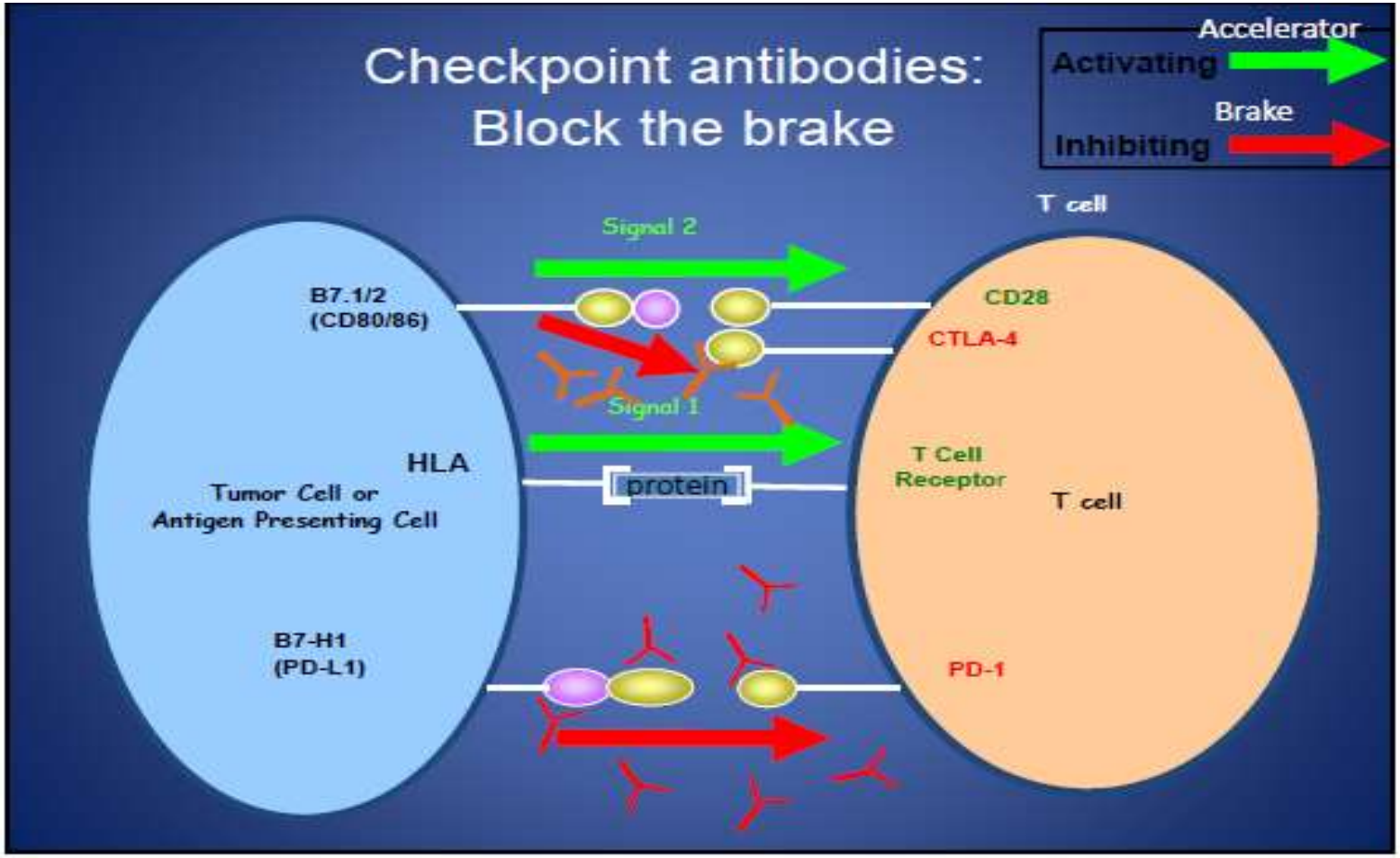
Ders Planı

- ❑ İmmünotherapi Tarihçe
- ❑ Evre IV RCC Risk Sınıflandırılması
- ❑ Nivolumab + Ipilumumab
- ❑ Pembrolizumab + Axitinib
- ❑ Nivolumab + Cabozantinib
- ❑ Lenvatinib + Pembrolizumab
- ❑ Nivolumab + Ipilumumab+Cabozantinib
- ❑ Özet

Metastatik RCC Tedavi Seçenekleri
İmmünoterapi



Metastatik RCC Tedavi Seçenekleri
İmmünoterapi

- İmmünoterapiyle ilgili ilk bilgiler New York da yaşayan cerrah William Coley 1891 yıllında 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.

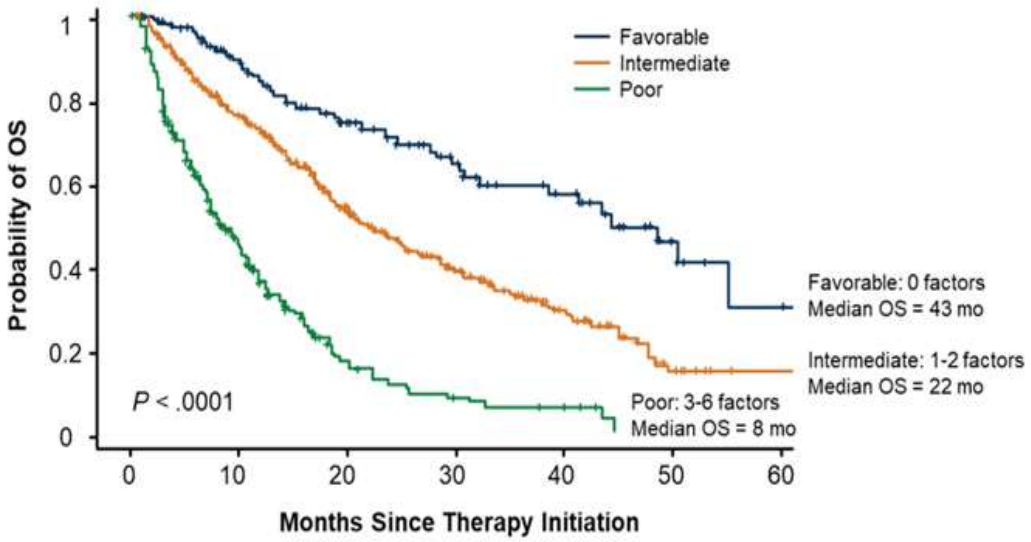
- Tüberküloz hastalığına karşı 1908 yılında Albert Calmette ve Camille Guerin BCG aşısını geliştiriyor.

- İlerleyen yıllarda tübeküloz olan hastalarda kanser oranın düşük olması bilim adamlarını araştırmalara yöneltiyor. 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.

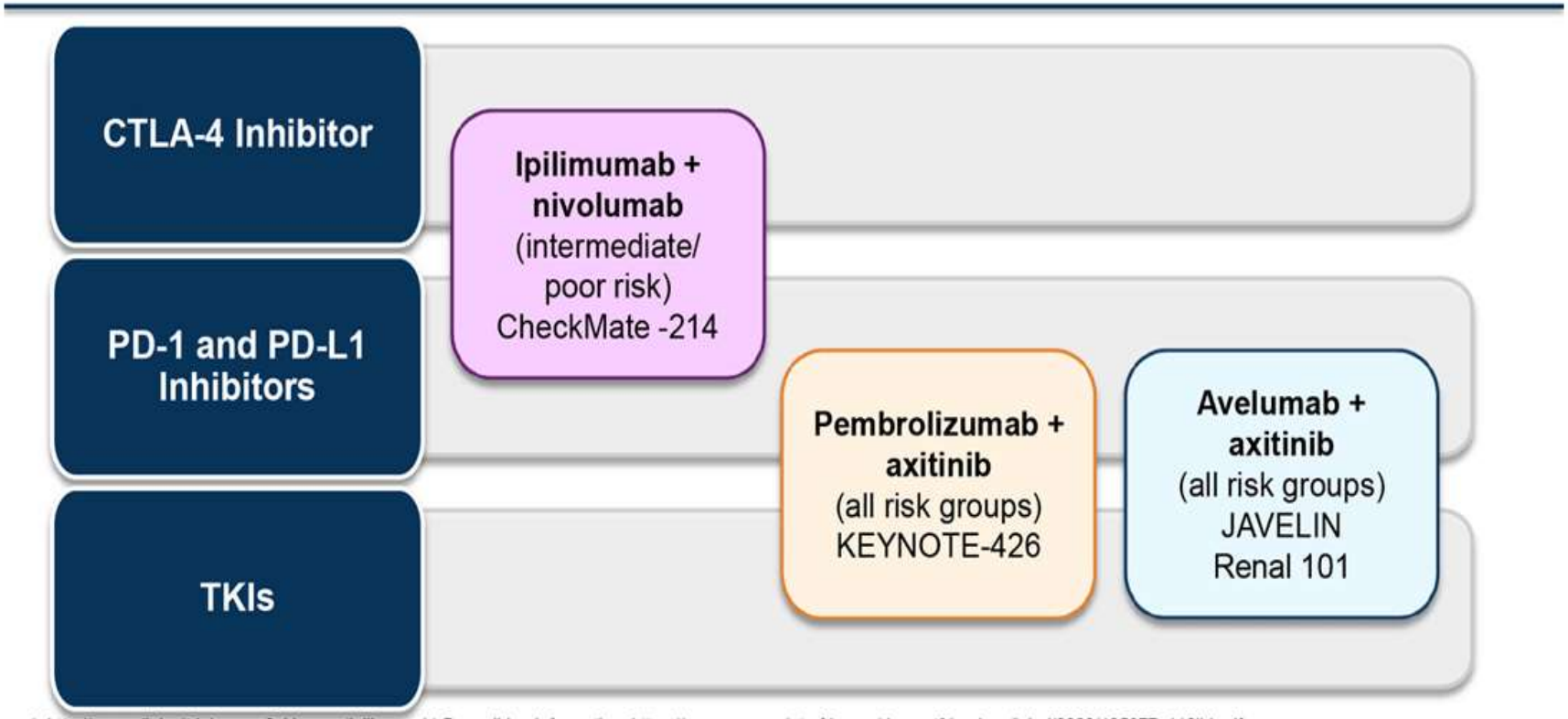
Klinik ve Laboratuvar Parametrelere Göre Risk Sınıflandırılması

IMDC Risk Scoring System Entry Criteria
KPS <80%
<1 y from time of diagnosis to systemic therapy
Hemoglobin <LLN (normal: 120 g/L or 12 g/dL)
Calcium >ULN (normal: 8.5-10.2 mg/dL)
Neutrophil >ULN (normal: 2.0-7.0 x 10^9/L)
Platelets >ULN (normal: 150,000-400,000)



1. Heng DY et al. *J Clin Oncol*. 2009;27:5794-5799. 2. Heng DY et al. *Lancet Oncol*. 2013;14:141-148.

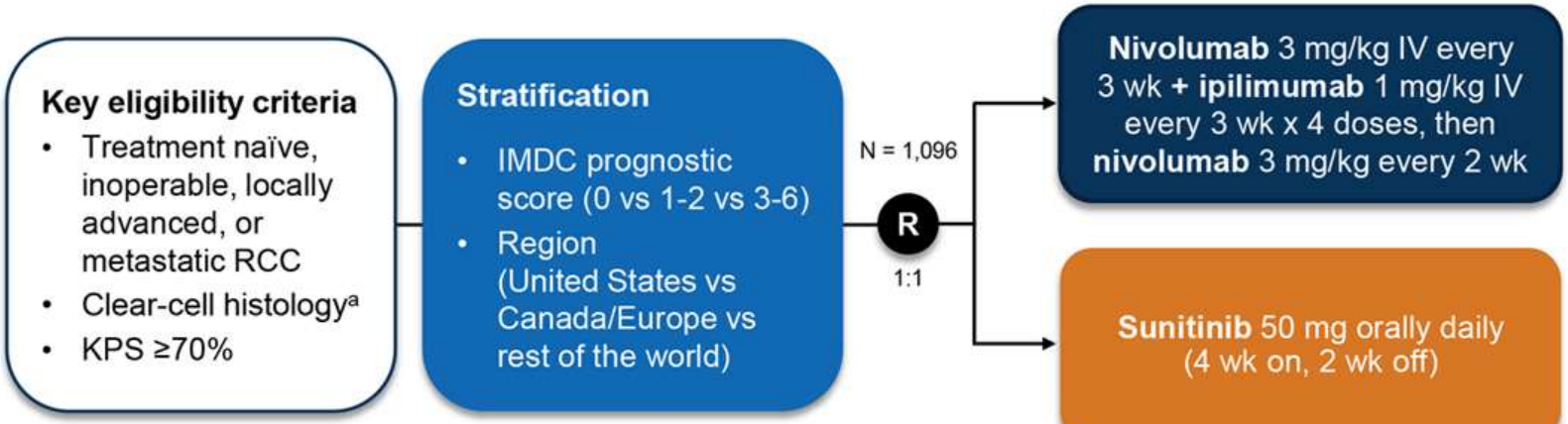
Metastatik RCC Birinci Basamak Tedavi Seçenekleri



1. http://www.clinicaltrials.gov. 2. Yervoy (ipilimumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s112lbl.pdf. 3. Opdivo (nivolumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125554s083lbl.pdf. 4. Keytruda (pembrolizumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s084lbl.pdf. 5. Inlyta (axitinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202324s011lbl.pdf. 6. Bavencio (avelumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761049s009lbl.pdf.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri

CheckMate -214: Nivolumab + Ipilimumab in Newly Diagnosed Advanced RCC[1,2]



Endpoints

- **Coprimary:** PFS, OS, ORR (intermediate/poor risk)
- **Secondary:** PFS, OS, ORR (ITT)
- **Exploratory:** PFS, OS, ORR (favorable risk)

[a] Approximately 70% of patients with RCC have this histology type.

1. https://clinicaltrials.gov/ct2/show/NCT02231749. 2. Motzer RJ et al. *Lancet Oncol*. 2019;20:1370-1385.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

CheckMate -214: Intermediate/Poor-Risk Patients

Minimum Follow-Up, mo	Median OS, mo (95% CI)		Median PFS, mo (95% CI)	
	Nivolumab + Ipilimumab (n = 425)	Sunitinib (n = 422)	Nivolumab + Ipilimumab (n = 425)	Sunitinib (n = 422)
17.5[1]	NR (28.2-NE)	26.0 (22.1-NE)	11.6 (8.7-15.5)	8.4 (7.0-10.8)
	HR (99.8% CI) 0.63 (0.44-0.89); *P* < .001		HR (99.1% CI) 0.82 (0.64-1.05); *P* = .03	
30[2]	NR (35.6-NE)	26.6 (22.1-33.4)	8.2 (6.9-10.0)	8.3 (7.0-8.8)
	HR (95% CI) 0.66 (0.54-0.80); *P* < .0001		HR (95% CI) 0.77 (0.65-0.90); *P* = .0014	
42[3]	47.0 (35.6-NE)	26.6 (22.1-33.5)	11.6 (8.4-15.5)	8.3 (7.0-10.8)
	HR (95% CI) 0.66 (0.55-0.80); *P* < .0001		HR (95% CI) 0.75 (0.62-0.90); *P* = .0015	

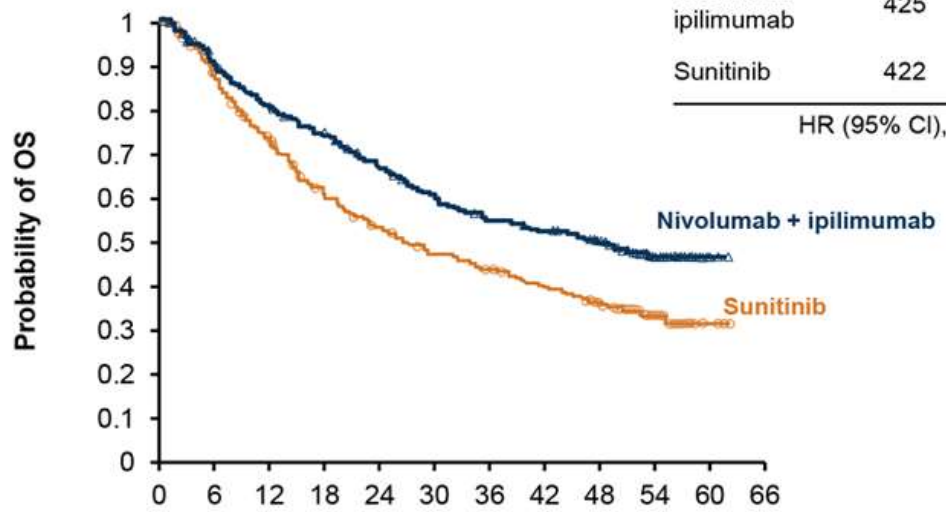
1. Motzer RJ et al *N Engl J Med*. 2018;378:1277-1290. 2. Motzer RJ et al. *Lancet Oncol*. 2019;20:1370-1385.
3. Motzer RJ et al. *J Immunother Cancer*. 2020;8:e000891.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

CheckMate -214: OS at 48 Months (Intermediate/Poor-Risk Patients)[1]

	n	Median (95% CI), mo
Nivolumab + ipilimumab	425	48.1 (35.6-NE)
Sunitinib	422	26.6 (22.1-33.5)

HR (95% CI), 0.65 (0.54-0.78)



No. at Risk												
NIVO + IPI	425	372	332	306	270	241	220	208	193	86	3	0
SUN	422	353	291	237	206	184	169	151	133	66	3	0

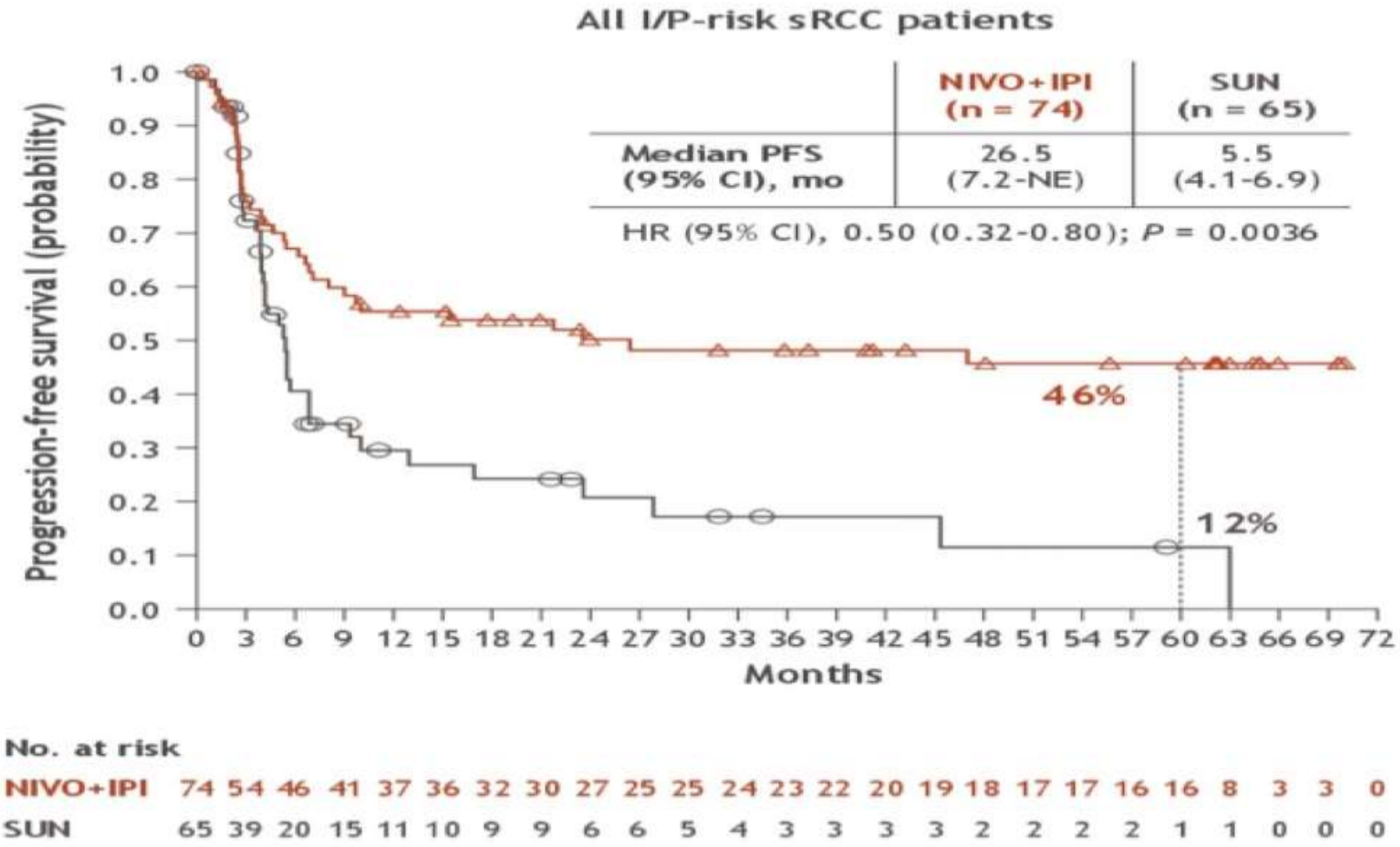
1. Albiges L et al. European Society for Medical Oncology 2020 Virtual Congress (ESMO 2020). Abstract 711P.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

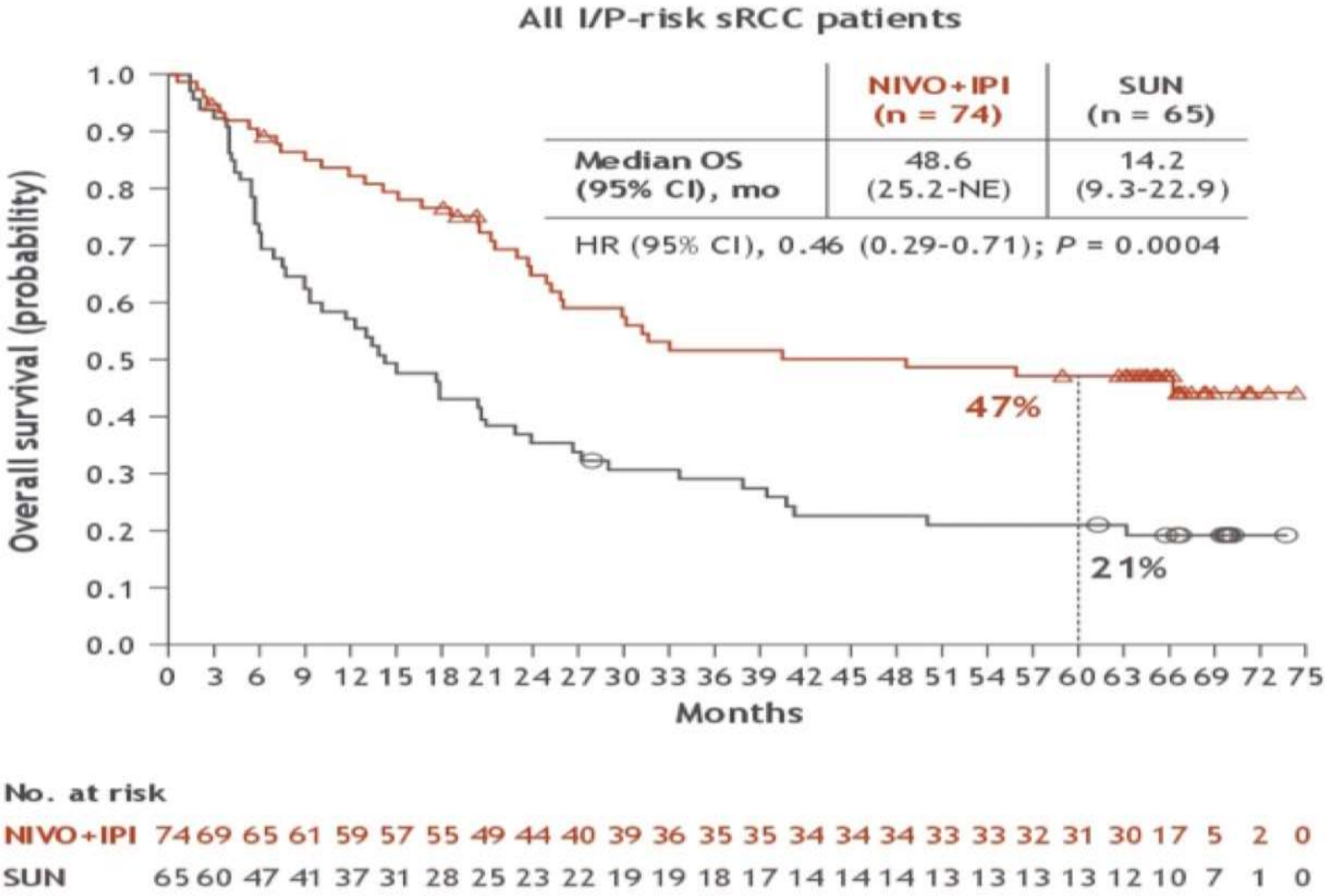
CheckMate -214: 48-Month Response

	Intermediate/Poor-Risk		ITT		Favorable-Risk	
	NIVO + IPI (n = 425)	SUN (n = 422)	NIVO + IPI (n = 550)	SUN (n = 546)	NIVO + IPI (n = 125)	SUN (n = 124)
Confirmed ORR (95% CI), %	41.9 (37-47)	26.8 (23-31)	39.1 (35-43)	32.4 (29-37)	29.6 (22-38)	51.6 (43-61)
P	< .0001		.0134		.0005	
Best overall response, n (%)						
CR	44 (10.4)	6 (1.4)	59 (10.7)	14 (2.6)	15 (12.0)	8 (6.5)
PR	134 (31.5)	107 (25.4)	156 (28.4)	163 (29.9)	22 (17.6)	56 (45.2)
SD	131 (30.8)	187 (44.3)	198 (36.0)	230 (42.1)	67 (53.6)	43 (34.7)
PD	82 (19.3)	71 (16.8)	97 (17.6)	77 (14.1)	15 (12.0)	6 (4.8)
NE	32 (7.5)	48 (11.4)	38 (6.9)	57 (10.4)	6 (4.8)	9 (7.3)
NR	2 (0.5)	3 (0.7)	2 (0.4)	5 (0.9)	0	2 (1.6)
Ongoing response, n (%)	n = 178 116 (65.2)	n = 113 56 (49.6)	n = 215 140 (65.1)	n = 177 92 (52.0)	n = 37 24 (64.9)	n = 64 34 (56.3)

Metastatik RCC /sarkomatoid Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab



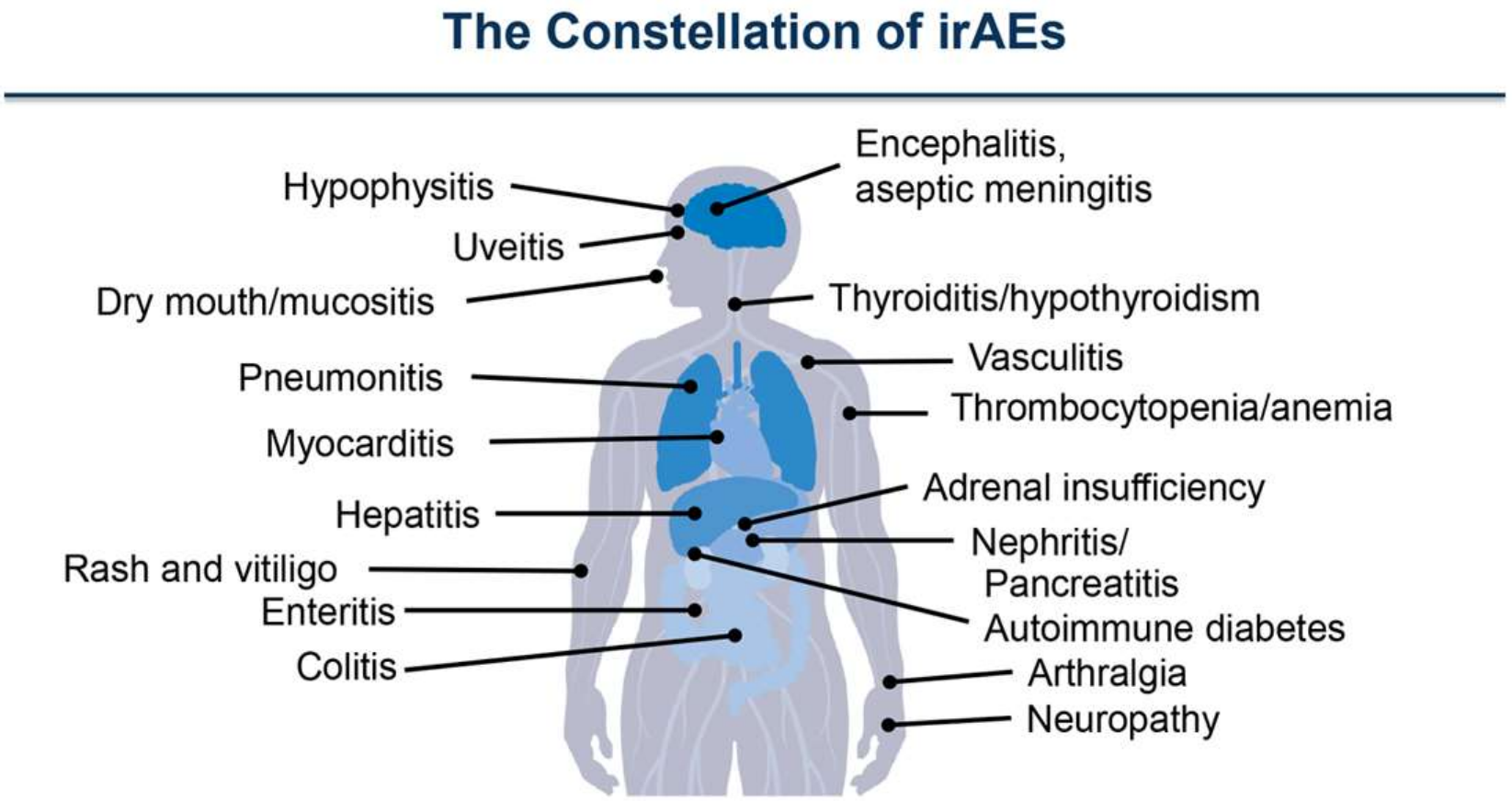
Metastatik RCC /sarkomatoid Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab



Metastatik RCC /sarkomatoid Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

	Patients with I/P risk sRCC	
	NIVO+IPI (n = 74)	SUN (n = 65)
Confirmed ORR (95% CI), %	60.8 (48.8-72.0)	23.1 (13.5-35.2)
P value	*P* < 0.0001	
Best overall response, n (%)		
Complete response	17 (23.0)	4 (6.2)
Partial response	28 (37.8)	11 (16.9)
Stable disease	8 (10.8)	28 (43.1)
Progressive disease	15 (20.3)	13 (20.0)
Unable to determine/not reported	6 (8.1)	9 (13.8)

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
İmmünoterapi/Toksisite



Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

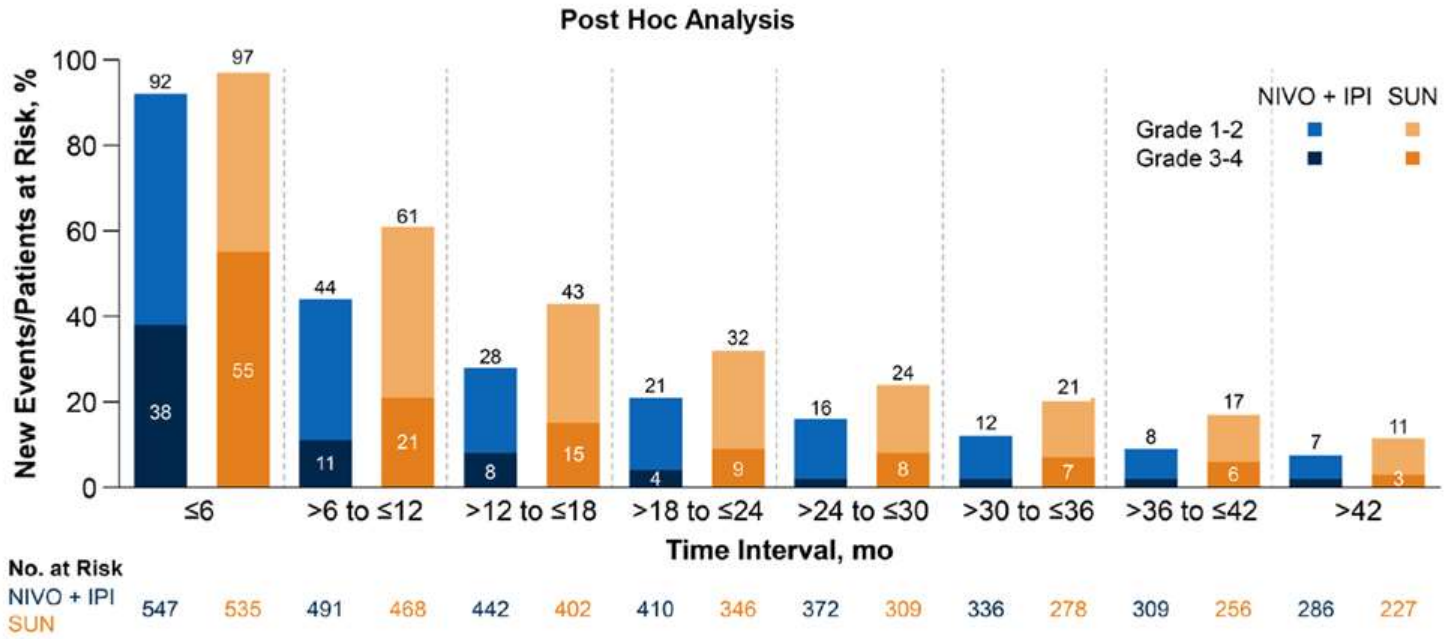
AE: Ipi + Nivo

Common	Serious
• Fatigue	• Adrenal insufficiency
• Pruritis	• Hepatitis
• Rash	• Colitis
• Diarrhea	• Pneumonitis
• Decreased appetite	• Altered thyroid function
	• Nephritis

- **Treatment-related adverse events leading to discontinuation occurred in 22% and 12% of the patients in the respective groups.**
- **Eight deaths in the nivolumab-plus ipilimumab group and four deaths in the sunitinib group were reported to be treatment-related .**
- **Immune-mediated adverse event (includes skin, endocrine, gastrointestinal, pulmonary, hepatic, and renal categories), 152 (35%) received high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent).**

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

CheckMate -214: TRAEs Over Time[1]

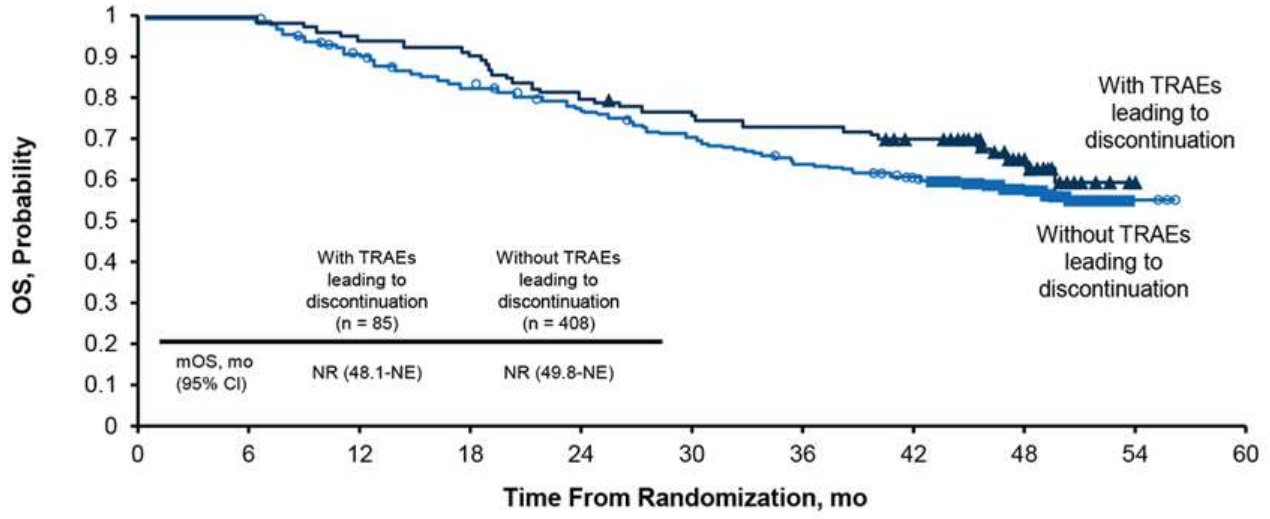


- A similar pattern over time was observed with treatment-related select AE incidence and corticosteroid use in the NIVO + IPI arm

1. Motzer RJ et al. *J Immunother Cancer*. 2020;8:e000891.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

CheckMate -214: OS in Patients Who Discontinued Because of TRAEs[1]

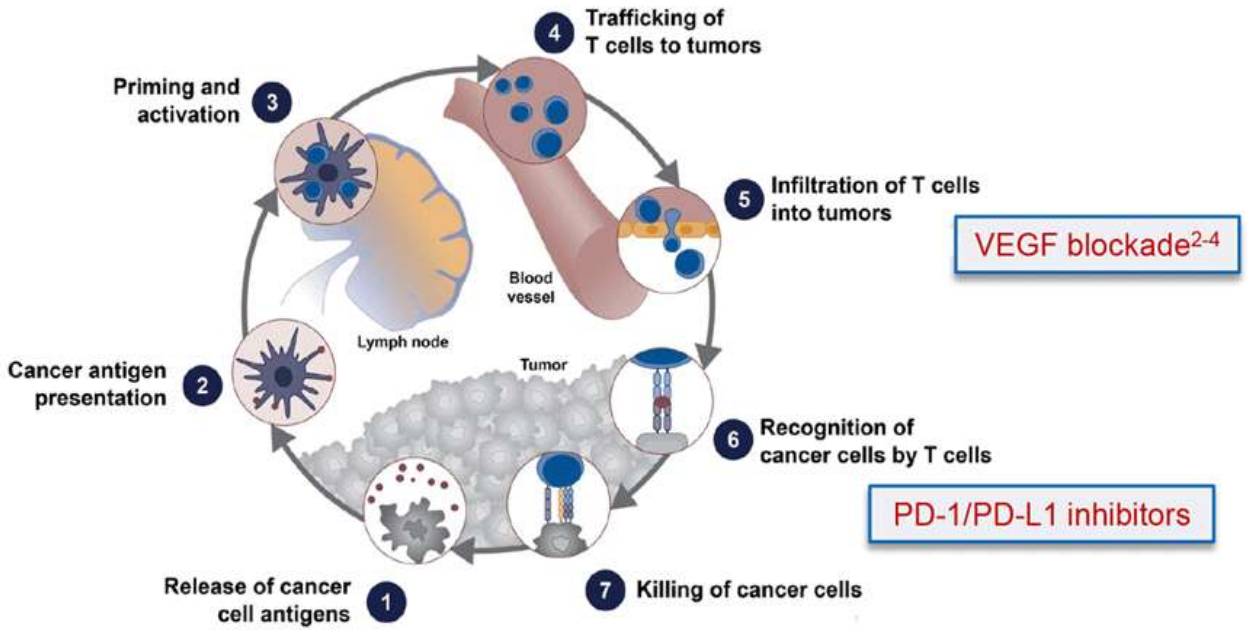


No. at Risk											
With TRAEs leading to discontinuation	85	85	80	77	68	62	61	55	27	0	0
Without TRAEs leading to discontinuation	408	408	364	334	304	275	248	231	108	3	0

1. Motzer RJ et al. *J Immunother Cancer*. 2020;8:e000891.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Pembrolizumab + Axitinib

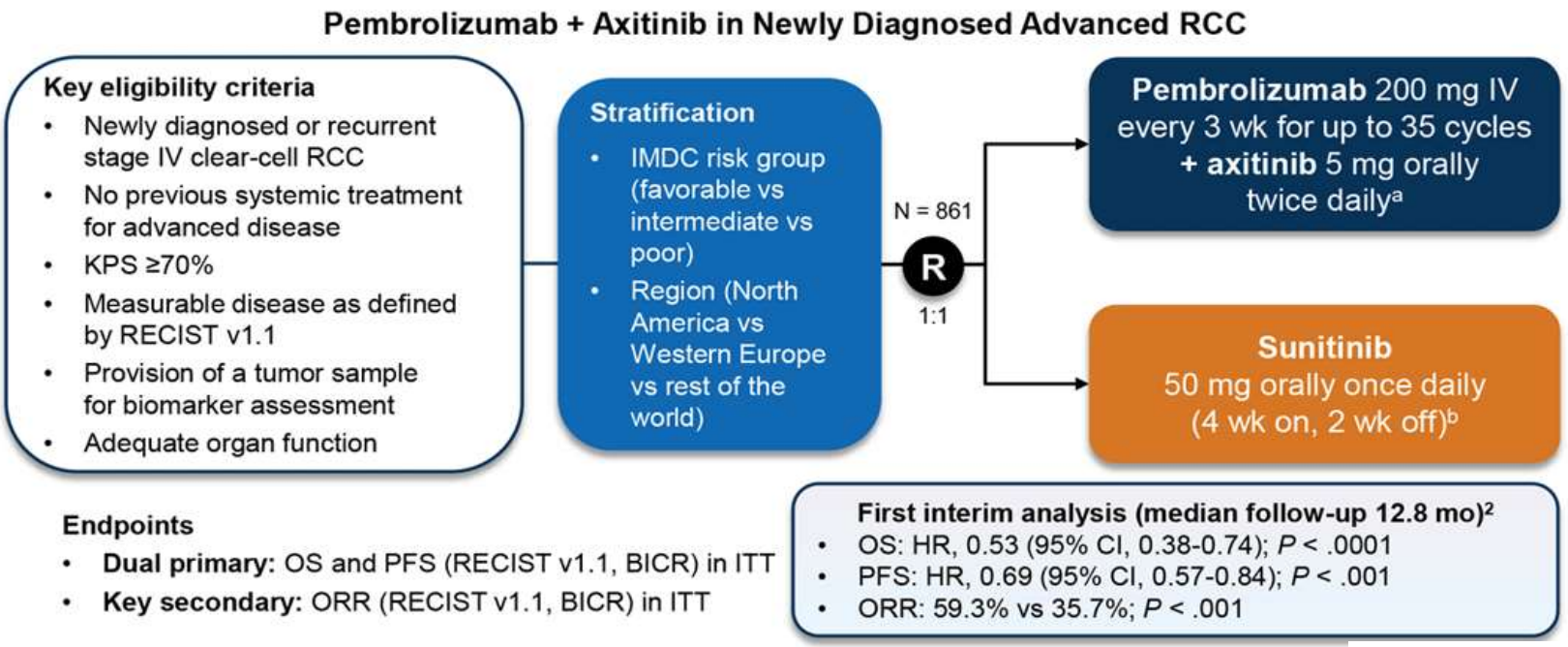
Synergy of VEGF Inhibition and PD-1/PD-L1 Blockade[1,2]



1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10. 2. Shrimali RK et al. *Can Res*. 2010;70:6171-6180. 3. Manning EA et al. *Clin Cancer Res*. 2007;13:3951-3959.
4. Motz GT et al. *Nat Med*. 2014;20:607-615.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Pembrolizumab + Axitinib

KEYNOTE-426: Phase 3 Study[1]

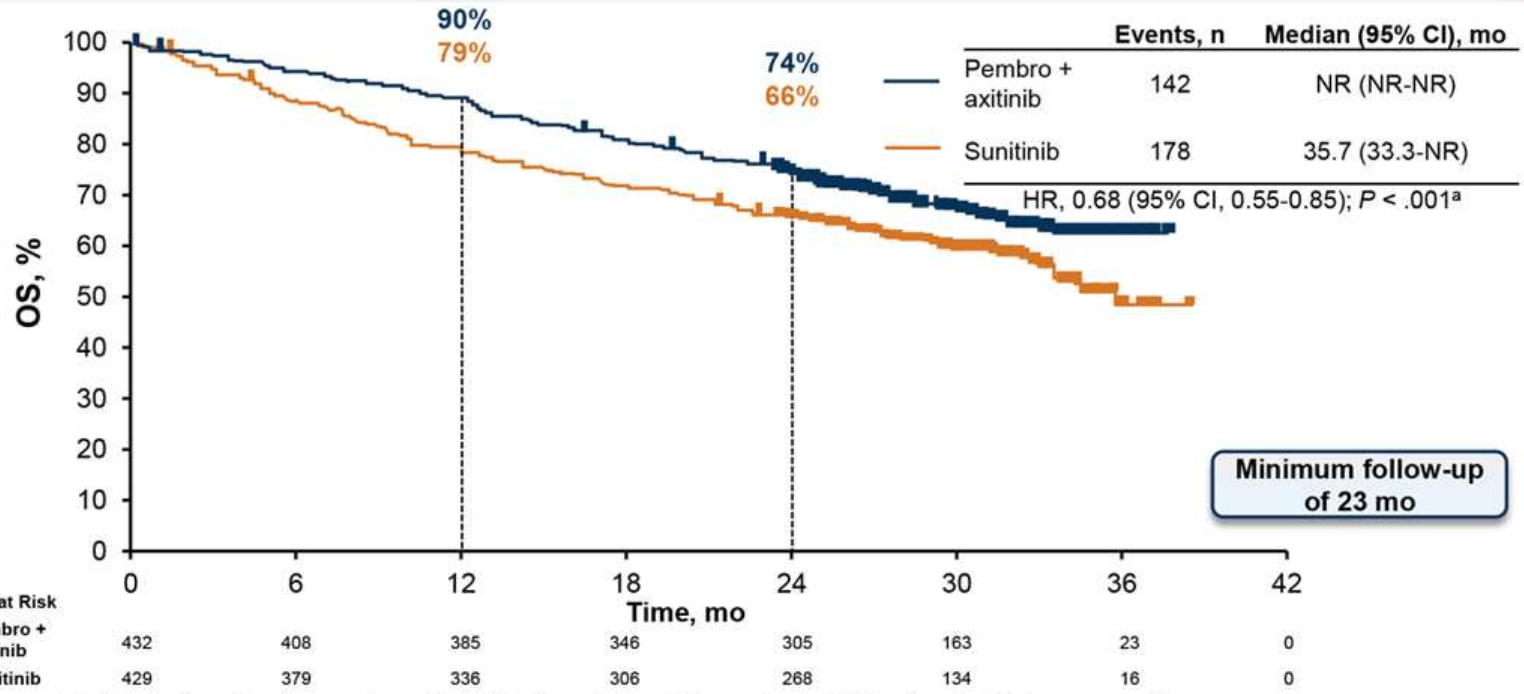


[a] Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b] Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wk of each 6-wk cycle to manage toxicity.

1. https://clinicaltrials.gov/ct2/show/NCT02853331. 2. Rini BI et al. *N Engl J Med*. 2019;380:1116-1127.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Pembrolizumab + Axitinib

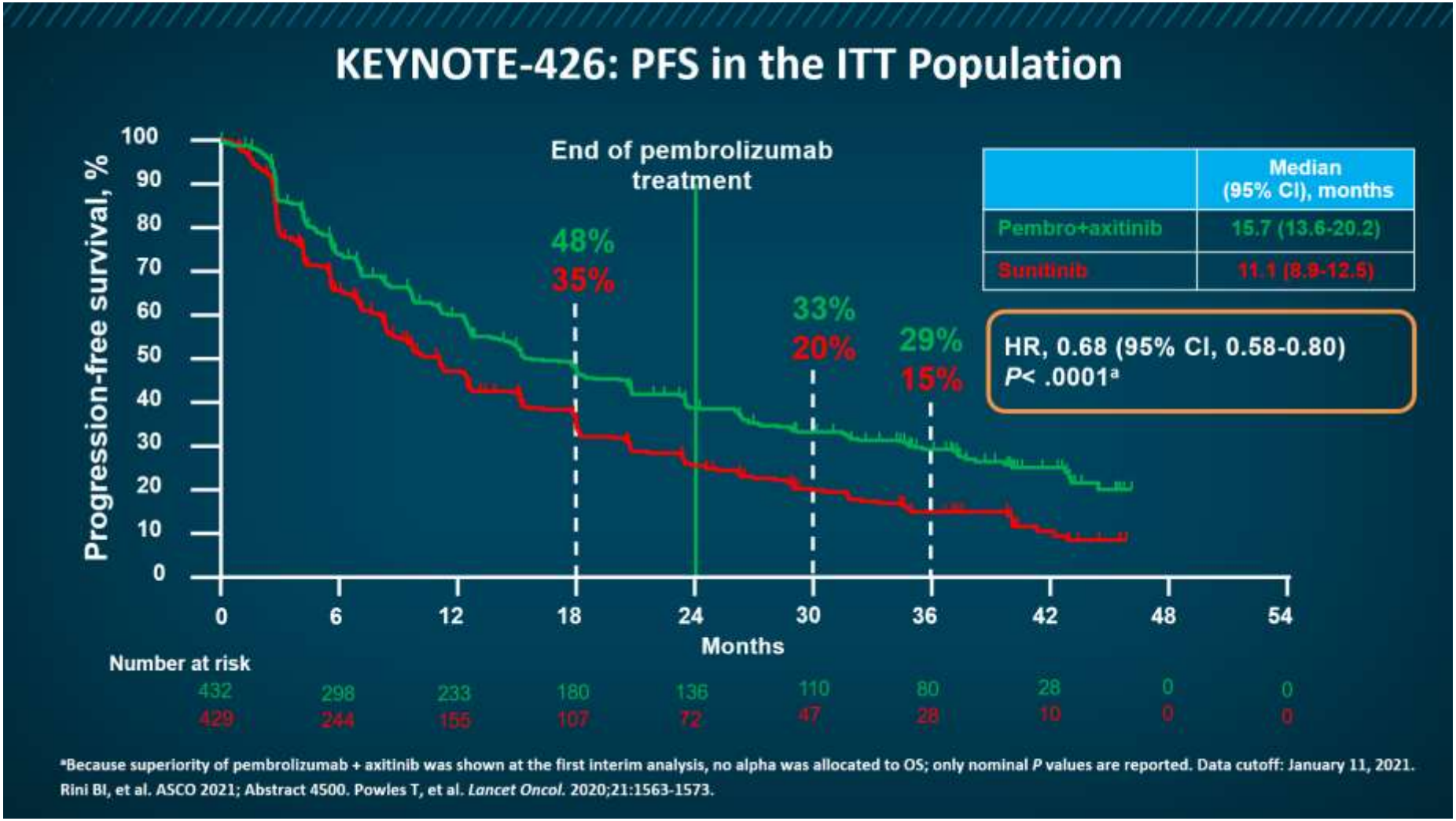
KEYNOTE-426: OS (ITT Population)[1]



[a] Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported.
Data cutoff: January 6, 2020.

1. Plimack ER et al. 2020 American Society of Clinical Oncology Virtual Scientific Program (ASCO 2020). Abstract 5001.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Pembrolizumab + Axitinib

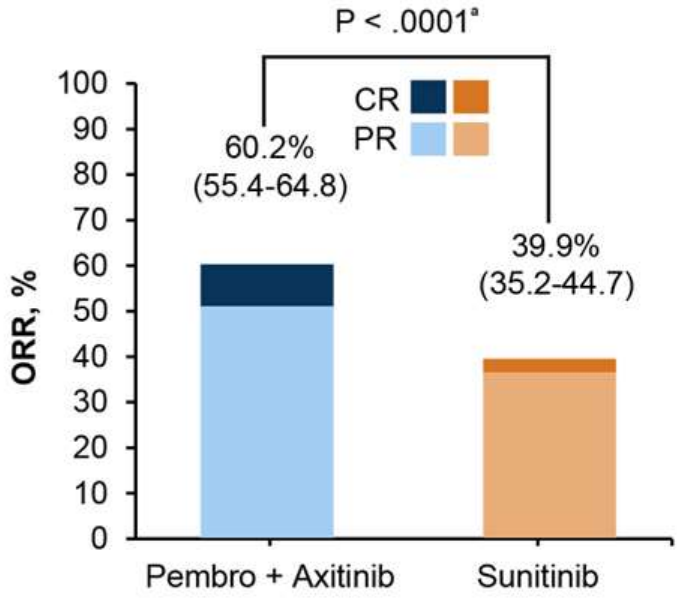


aBecause superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 11, 2021.

Rini BI, et al. ASCO 2021; Abstract 4500. Powles T, et al. *Lancet Oncol.* 2020;21:1563-1573.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Pembrolizumab + Axitinib

KEYNOTE-426: Response (ITT Population)[1]



	Pembrolizumab + Axitinib (n = 432)	Sunitinib (n = 429)
Best response, n (%)		
CR	38.8 (8.8)	13 (3.0)
PR	222 (51.4)	158 (36.8)
SD	100 (23.1)	150 (35.0)
PD	49 (11.3)	74 (17.2)
NE[b]	16 (3.7)	28 (6.5)
NA[c]	7 (1.6)	6 (1.4)
Duration of response, median (range), mo	23.5 (1.4+ to 34.5+)	15.9 (2.3 to 31.8+)

[a] Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to confirmed objective response; only nominal *P* values are reported. [b] Postbaseline assessment available but not evaluable (ie, all postbaseline assessments with insufficient data for assessment of response per RECIST v1.1 or CR/PR/SD < 6 wk from randomization). [c] No postbaseline assessment available for response evaluation; indicates an ongoing response at time of last disease assessment. Data cutoff: January 6, 2020.

1. Plimack ER et al. ASCO 2020. Abstract 5001.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Pembrolizumab + Axitinib

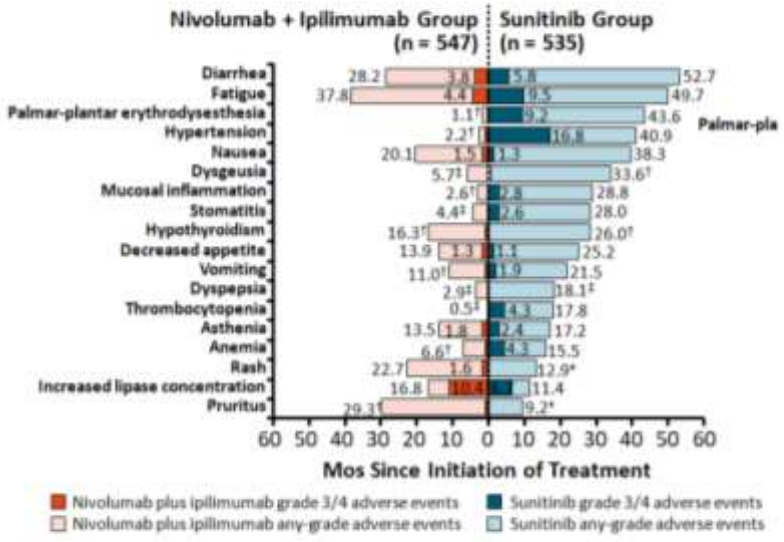
Efficacy in IMDC Subgroups

Parameter	ITT		Favorable Risk		Intermediate/Poor Risk	
	Pembro + Axitinib n = 432	Sunitinib n = 429	Pembro + Axitinib n = 138	Sunitinib n = 131	Pembro + Axitinib n = 294	Sunitinib n = 298
OS, HR (95% CI)	**0.73 (0.60-0.88)**		**1.17 (0.76-1.80)**		**0.64 (0.52-0.80)**	
42-month rate, %	57.5	48.5	72.3	73.0	50.6	37.6
PFS, HR (95% CI)	0.68 (0.58-0.80)		0.76 (0.56-1.03)		0.67 (0.55-0.81)	
Median, months	15.7	11.1	20.7	17.8	13.8	8.2
ORR, %	60.4	39.6	68.8	50.4	56.5	34.9
CR, %	10.0	3.5	11.6	6.1	9.2	2.3
PR, %	50.5	36.1	57.2	44.3	47.3	32.6

Data cutoff: January 11, 2021

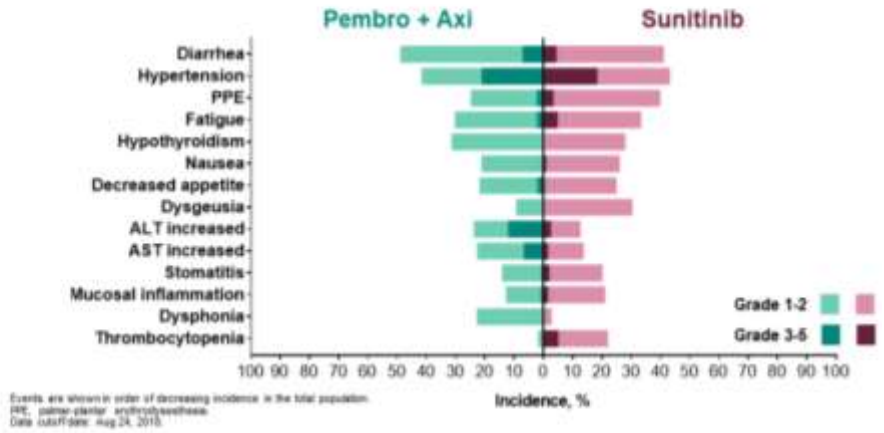
Metastatik RCC Birinci Basamak Tedavi Seçenekleri Toksisite

CheckMate 214



Motzer. Lancet Oncol. 2019;20:1370.

KEYNOTE-426



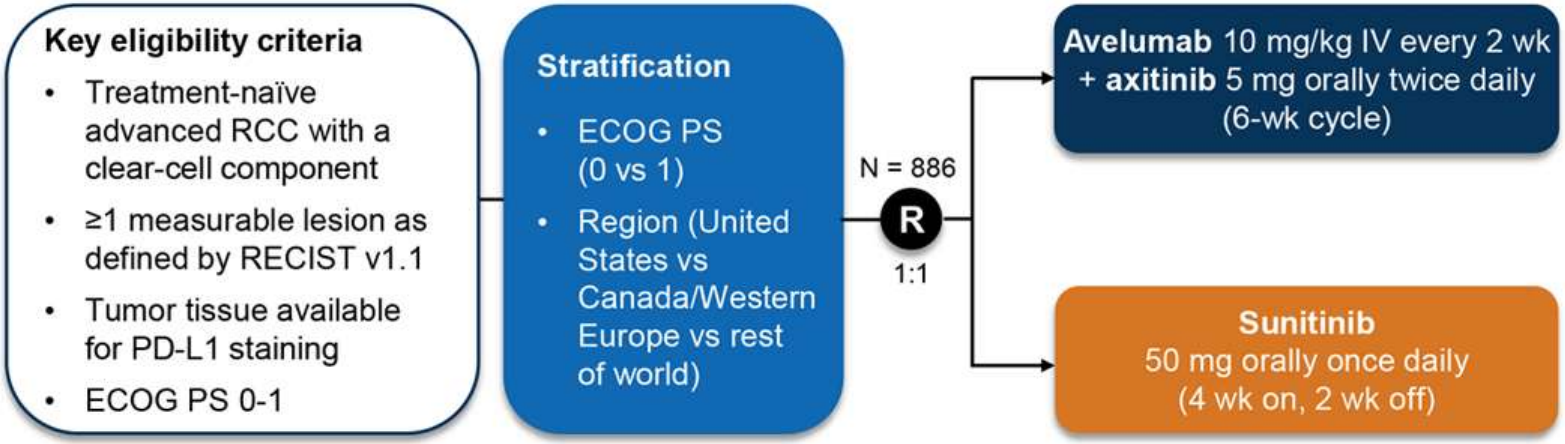
Powles. ASCO GU 2019.

- These events were of **grade 3** or higher in **75.8%** of the patients in the pembrolizumab–axitinib group and in **70.6%** of the patients in the sunitinib group
- In the pembrolizumab–axitinib group, adverse events of any cause led to **discontinuation of either drug in 30.5%** of patients, discontinuation of both drugs in **10.7%.**
- Of the **11 patients** (2.6%) in the pembrolizumab–axitinib group who died from adverse events, among the **15 patients** (3.5%) in the sunitinib group who died from adverse events

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Avelumab + Axitinib

JAVELIN Renal 101: Phase 3 Study[1]

Axitinib + Avelumab in Newly Diagnosed Advanced RCC



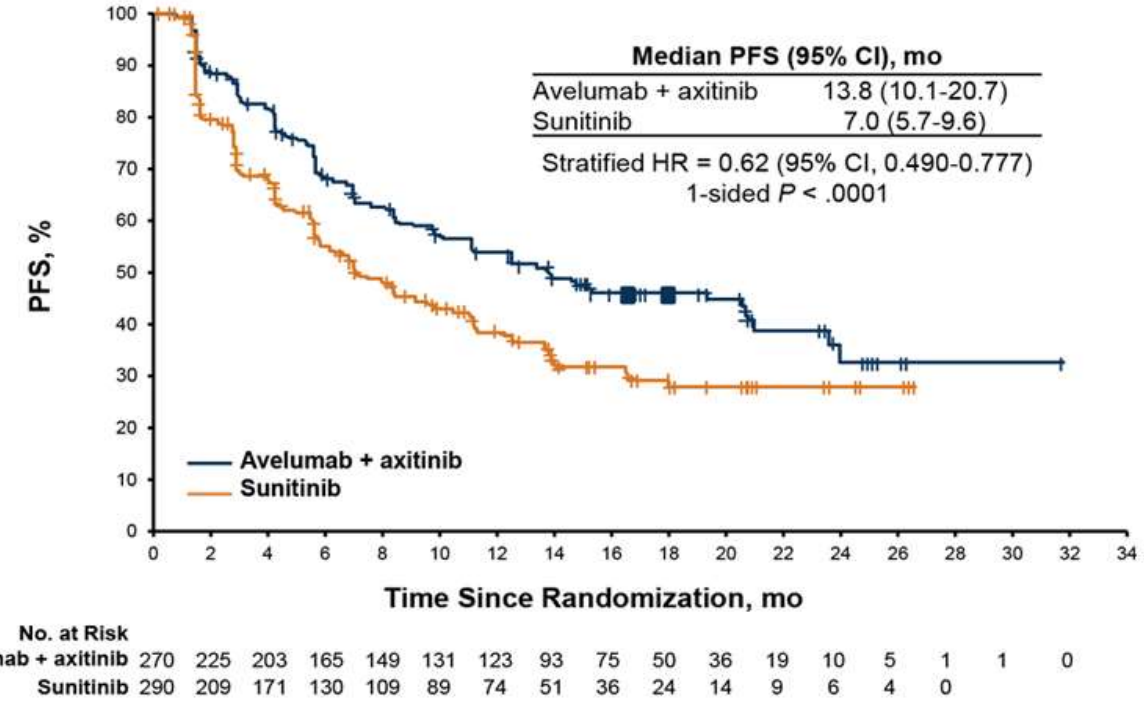
Endpoints

- **Coprimary:** PFS and OS in PD-L1–positive patients

1. https://clinicaltrials.gov/ct2/show/NCT02684006.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Avelumab + Axitinib

JAVELIN Renal 101: PFS (PD-L1+ Population)[1]



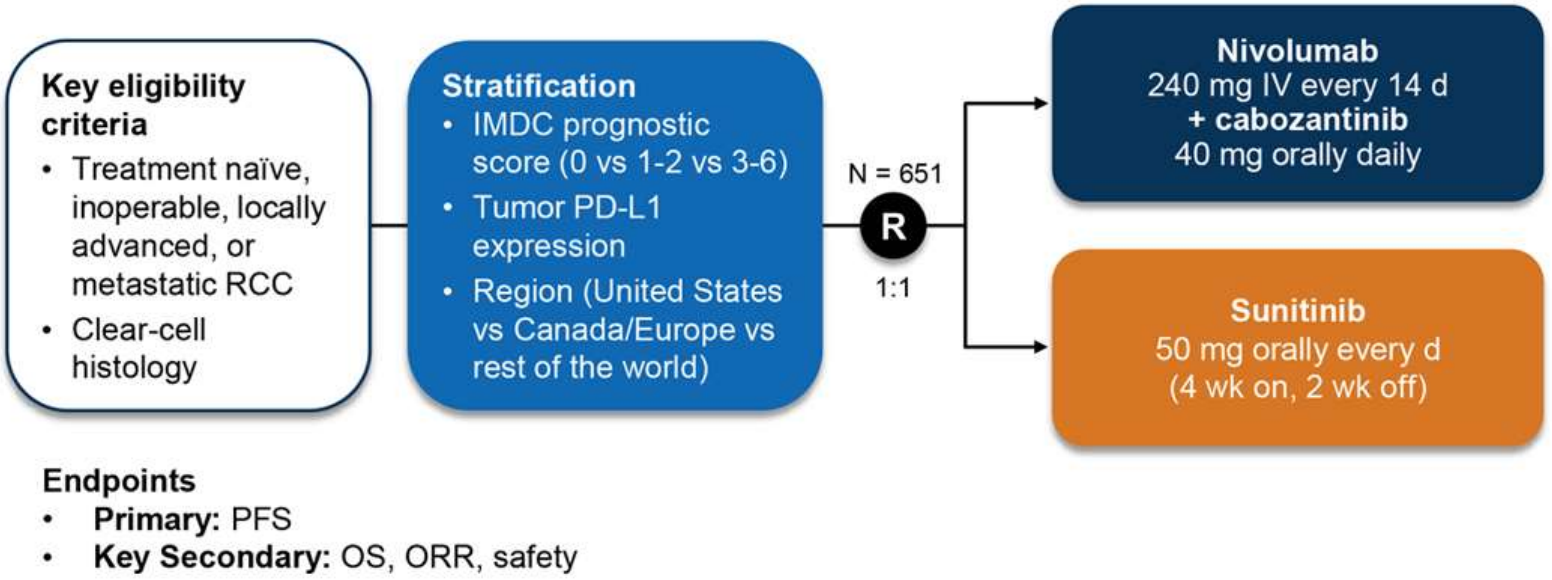
- No new safety signals
- ORR 55.9% (CR 5.6%) in the combination arm vs 27.2% (CR 2.4%) in the sunitinib arm
  - Similar response rates observed in the overall population
- OS data are still immature

1. Choueiri TK et al. *Ann Oncol*. 2020;31:1030-1039.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

CheckMate -9ER: Phase 3 Study[1,2]

Nivolumab + Cabozantinib in Newly Diagnosed Advanced RCC

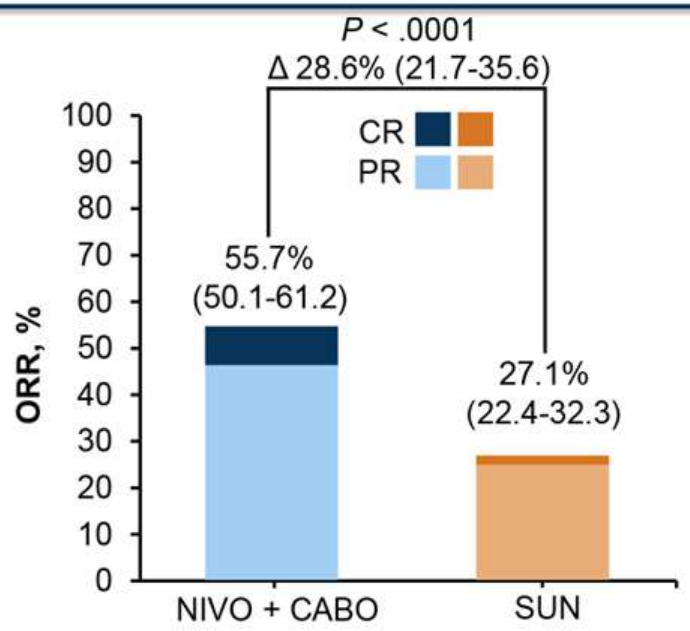


Endpoints
- **Primary:** PFS
- **Key Secondary:** OS, ORR, safety

1. https://clinicaltrials.gov/ct2/show/NCT03141177. 2. Choueiri TK et al. ESMO 2020. Abstract 696O_PR.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

CheckMate -9ER: Response[1,a]



Outcome, %	Nivolumab + Cabozantinib (n = 323)	Sunitinib (n = 328)
CR	8.0	4.6
PR	47.7	22.6
SR	32.2	42.1
PD	5.6	13.7
NE/NA[b]	6.5	17.1
Median time to response (range), mo[c]	2.8 (1.0-19.4)	4.2 (1.7-12.3)
Median duration of response (95% CI), mo[c]	20.2 (17.3-NE)	11.5 (8.3-18.4)

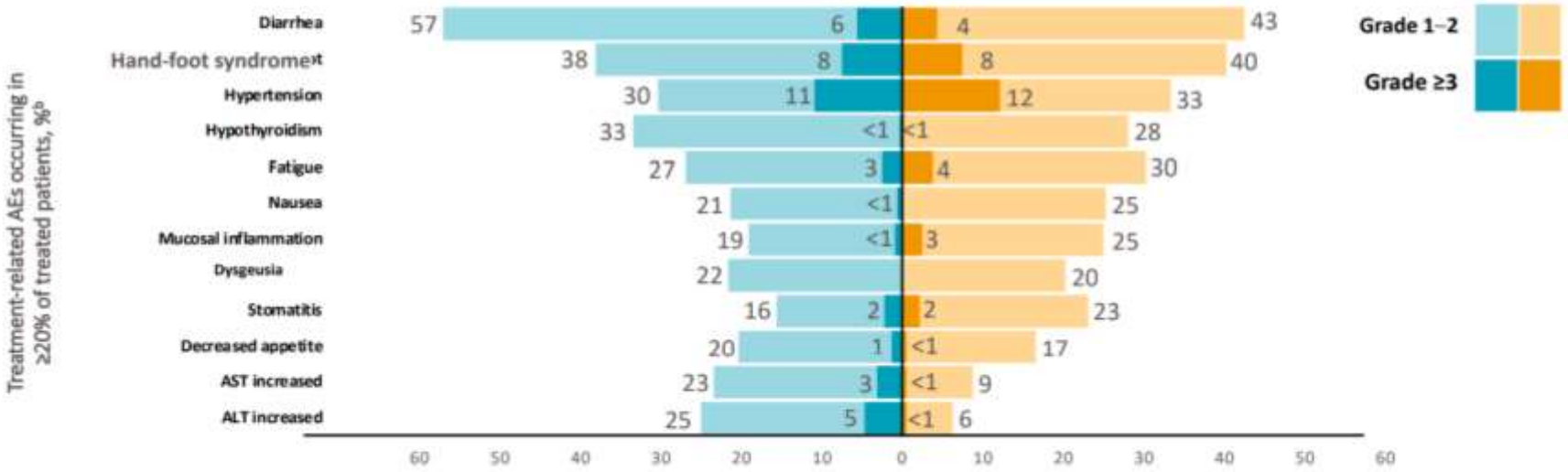
[a] BICR-assessed ORR and BOR by RECIST v1.1. [b] Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified. [c] Median time to and duration of response were calculated for patients who had a complete or partial response (n = 180 with NIVO + CABO, n = 89 patients with SUN).

1. Choueiri TK et al. ESMO 2020. Abstract 696O_PR.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

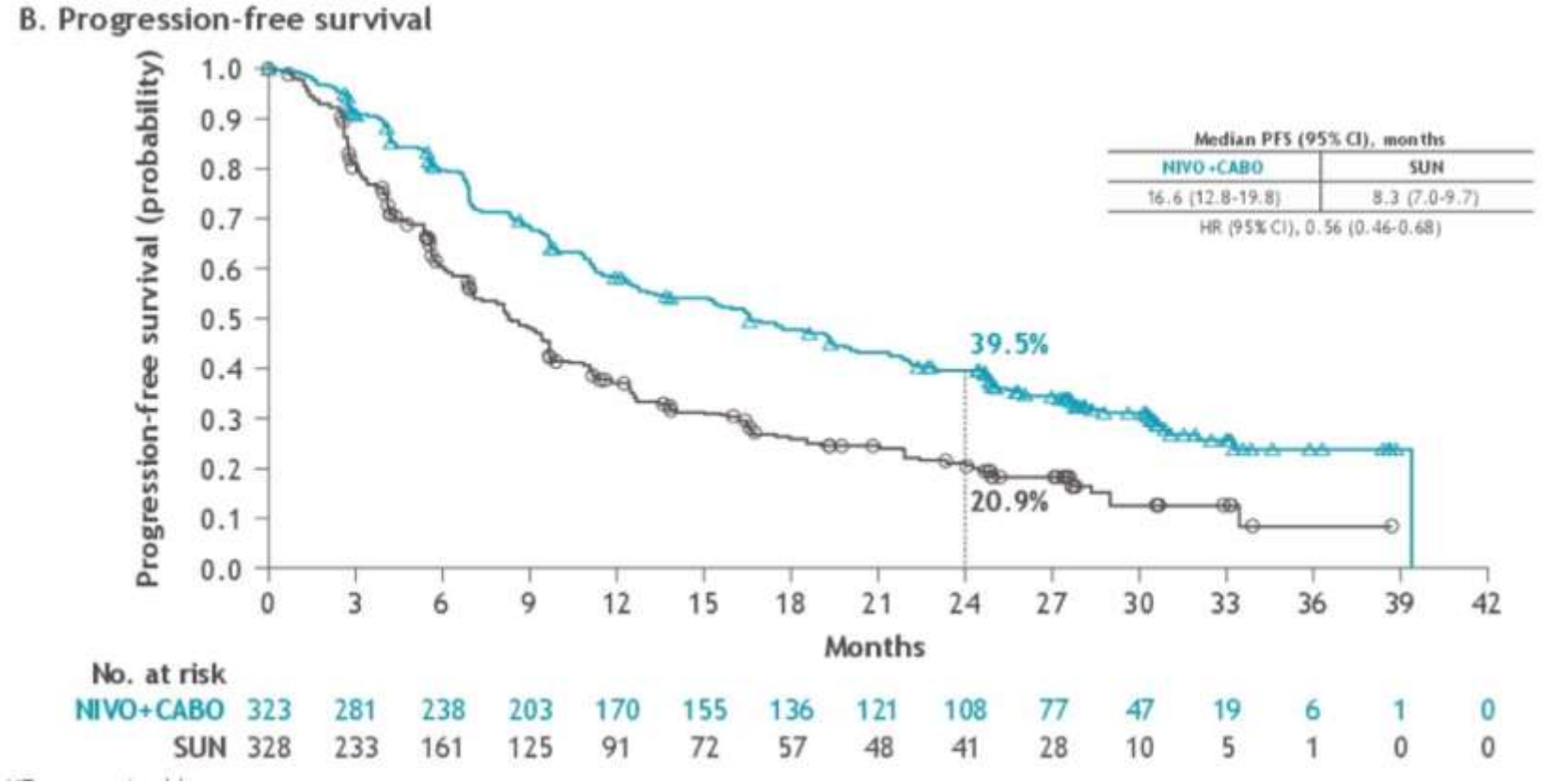
CheckMate 9ER Cabo/Nivo vs Sunitinib
Safety

Events, %[a]	NIVO+CABO, n = 320		SUN, n = 320	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
All-cause AEs	100	75	99	71
Treatment-related AEs	97	61	93	51



[a]Includes events that occurred on therapy or within 30 days after the end of the treatment period of all treated patients. Treatment-related deaths per investigator: NIVO+CABO n = 1 (small intestine perforation), SUN n = 2 (pneumonia, respiratory distress); [b]Total bar represents treatment-related AEs of any grade ≥ 20% in either treatment arm; of these events, none were grade 5.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

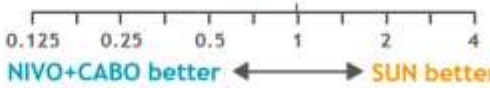


Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

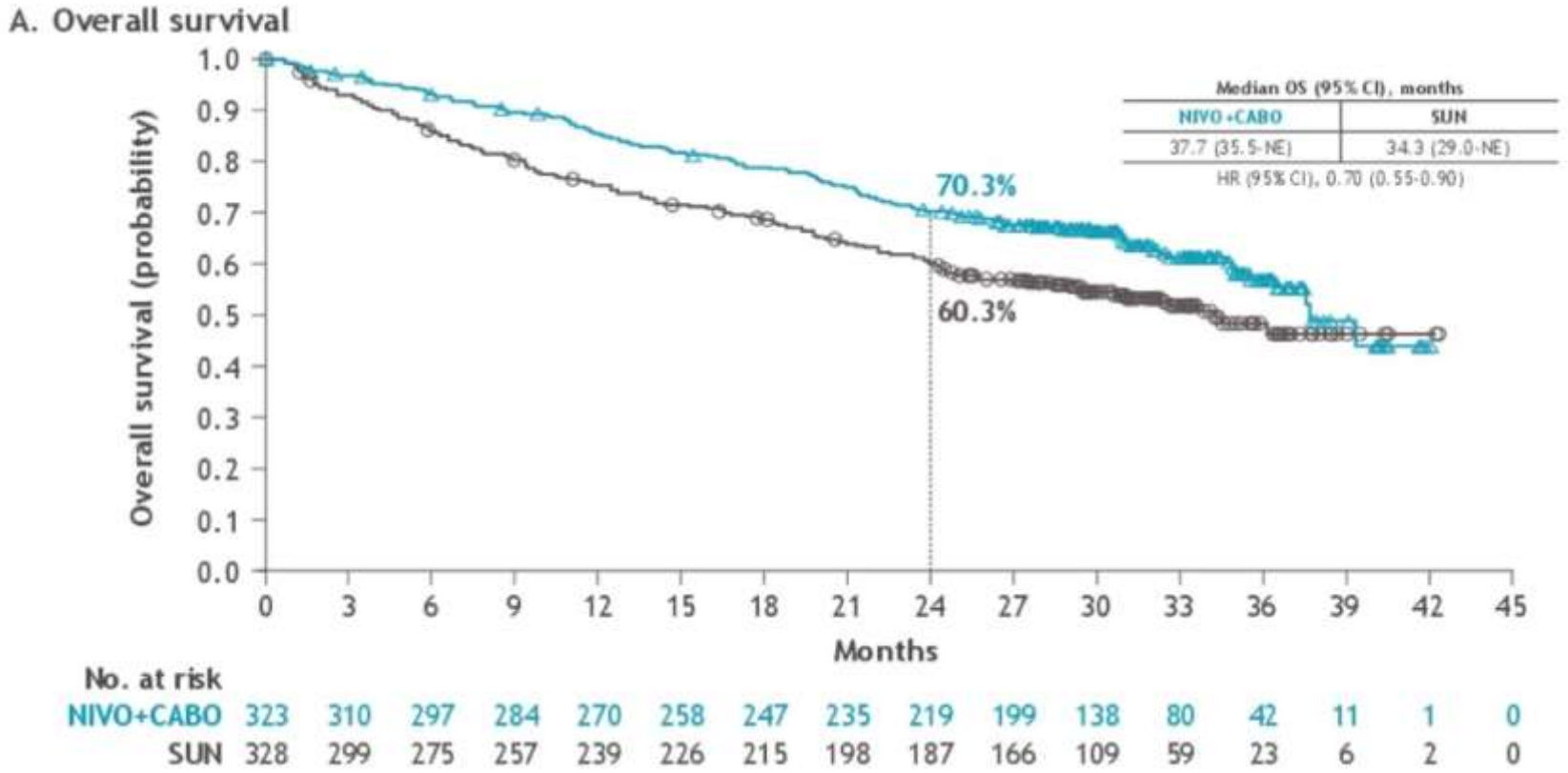
CheckMate 9ER

Progression-free survival per BICR in subgroups

Subgroup	NIVO+CABO Events/no. of patients	SUN Events/no. of patients	HR for progression or death (95% CI)
Overall	144/323	191/328	0.51 (0.41-0.64)
Region			
US/Europe	61/158	85/161	0.46 (0.33-0.64)
Rest of world	83/165	106/167	0.57 (0.42-0.76)
IMDC prognostic risk			
Favorable	30/74	35/72	0.62 (0.38-1.01)
Intermediate	82/188	108/188	0.54 (0.40-0.72)
Poor	31/61	48/68	0.37 (0.23-0.58)
PD-L1 expression			
≥ 1%	42/83	54/83	0.49 (0.32-0.73)
< 1% or indeterminate	102/240	137/245	0.52 (0.40-0.67)
Age			
< 65 years	84/191	131/210	0.44 (0.33-0.58)
≥ 65 years	60/132	60/118	0.68 (0.48-0.98)
Sex			
Male	108/249	136/232	0.48 (0.37-0.62)
Female	36/74	55/96	0.61 (0.40-0.94)
Karnofsky performance status			
90-100	109/257	129/241	0.55 (0.43-0.71)
< 80	35/66	62/85	0.44 (0.29-0.68)
Bone metastases			
Yes	33/78	45/72	0.34 (0.22-0.55)
No	111/245	146/256	0.57 (0.44-0.73)
Previous nephrectomy			
Yes	90/222	136/233	0.46 (0.35-0.60)
No	54/101	55/95	0.63 (0.43-0.92)



Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib



Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

CheckMate 9ER

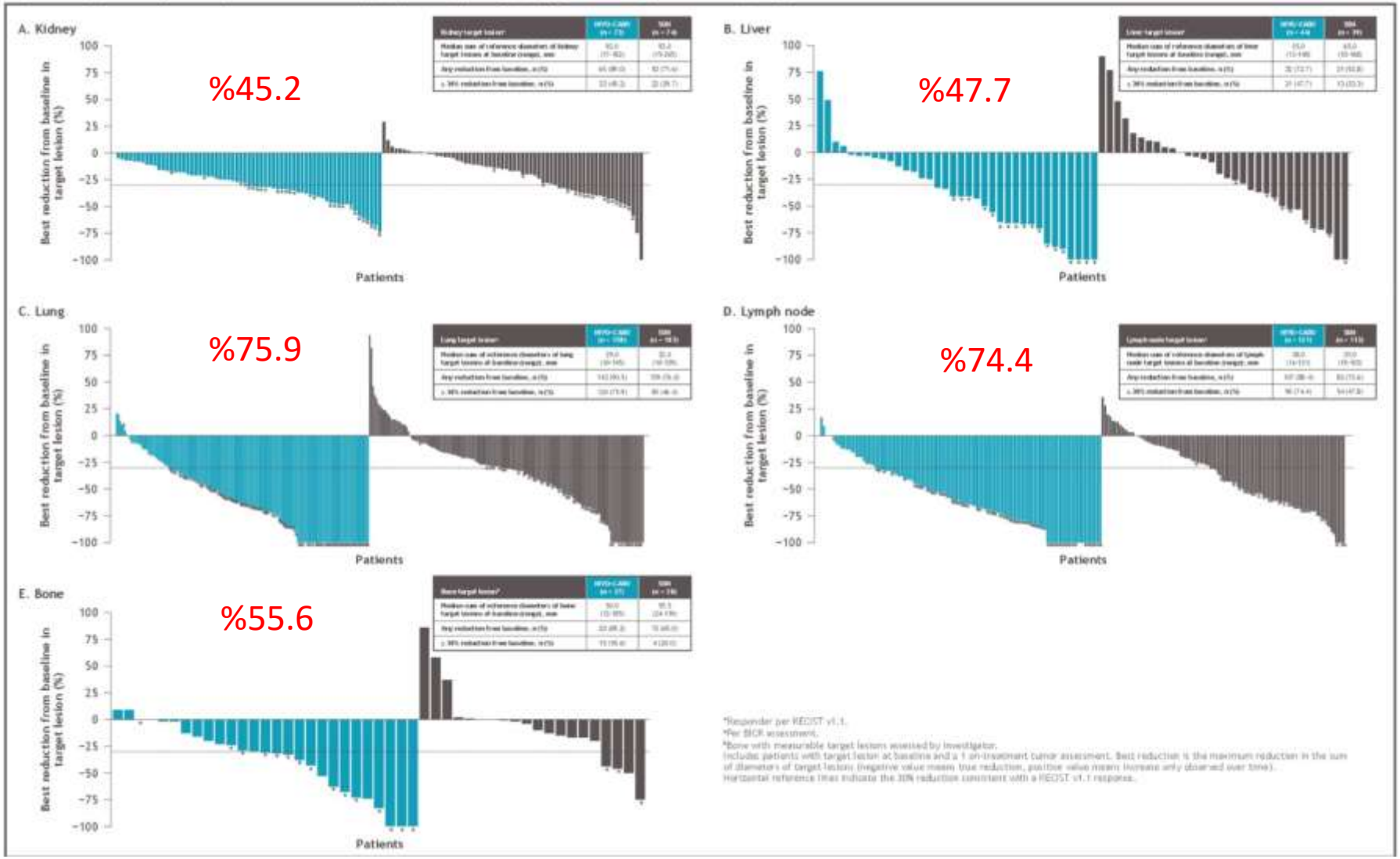
Overall survival in subgroups

Subgroup	NIVO+CABO	SUN	HR for death (95% CI)
	Events/no. of patients		
Overall	67/323	99/328	0.60 (0.44-0.82)
Region			
US/Europe	26/158	45/161	0.48 (0.30-0.79)
Rest of world	41/165	54/167	0.71 (0.48-1.07)
IMDC prognostic risk			
Favorable	10/74	11/72	0.84 (0.35-1.97)
Intermediate	40/188	51/188	0.70 (0.46-1.07)
Poor	17/61	37/68	0.37 (0.21-0.66)
PD-L1 expression			
≥ 1%	28/83	30/83	0.80 (0.48-1.34)
< 1% or indeterminate	39/240	69/245	0.51 (0.34-0.75)
Age			
< 65 years	31/191	66/210	0.44 (0.29-0.67)
≥ 65 years	36/132	33/118	0.90 (0.56-1.44)
Sex			
Male	47/249	66/232	0.59 (0.40-0.85)
Female	20/74	33/96	0.68 (0.39-1.18)
Karnofsky performance status			
90-100	45/257	56/241	0.69 (0.47-1.03)
≤ 80	22/66	43/85	0.52 (0.31-0.86)
Bone metastases			
Yes	24/78	33/72	0.54 (0.32-0.92)
No	43/245	66/256	0.61 (0.41-0.89)
Previous nephrectomy			
Yes	36/222	66/233	0.49 (0.33-0.74)
No	31/101	33/95	0.79 (0.48-1.29)

Courtesy of Thomas Powles, MBBS, MRCP, MD

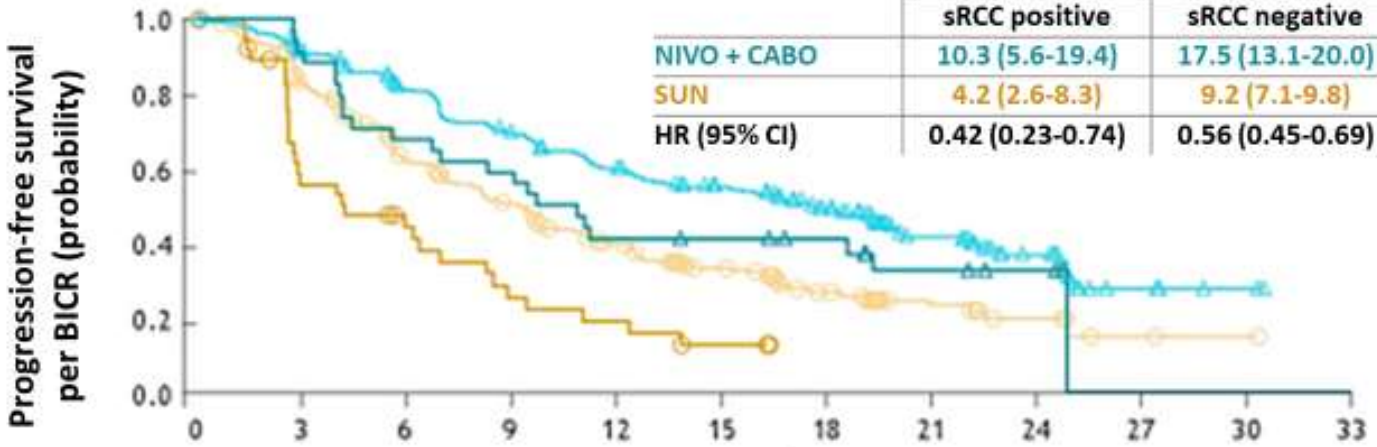
Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

Figure 2. Depth of response in patients with kidney (A), liver (B), lung (C), lymph node (D), and bone (E) target lesions at baseline



Metastatik RCC/ sarkomatoid Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

Progression-Free Survival per BICR by Sarcomatoid Histology



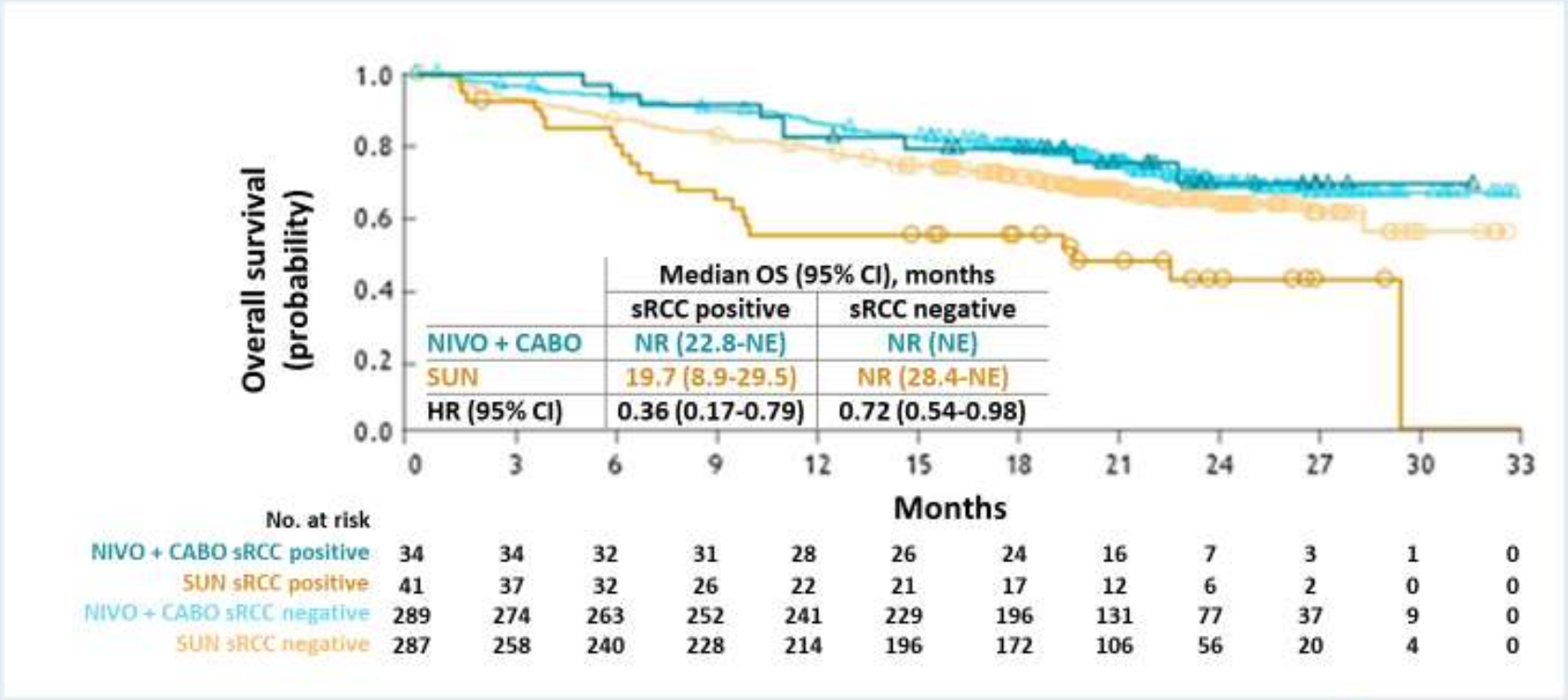
	Median PFS (95% CI), months	
	sRCC positive	sRCC negative
NIVO + CABO	10.3 (5.6-19.4)	17.5 (13.1-20.0)
SUN	4.2 (2.6-8.3)	9.2 (7.1-9.8)
HR (95% CI)	0.42 (0.23-0.74)	0.56 (0.45-0.69)

No. at risk												
NIVO + CABO sRCC positive	34	31	23	20	14	13	11	7	4	0	0	0
SUN sRCC positive	41	20	14	8	6	2	0	0	0	0	0	0
NIVO + CABO sRCC negative	289	249	213	181	152	132	91	49	22	5	2	0
SUN sRCC negative	287	210	146	114	81	59	37	17	7	2	1	0

Motzer RJ et al. Genitourinary Cancers Symposium 2021;Abstract 308.

Metastatik RCC/ sarkomatoid Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

Overall Survival by Sarcomatoid Histology

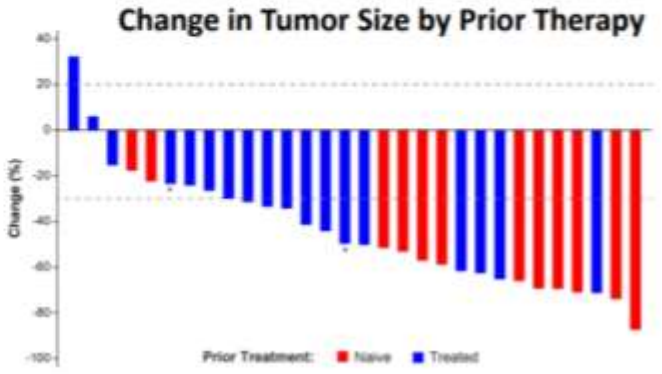


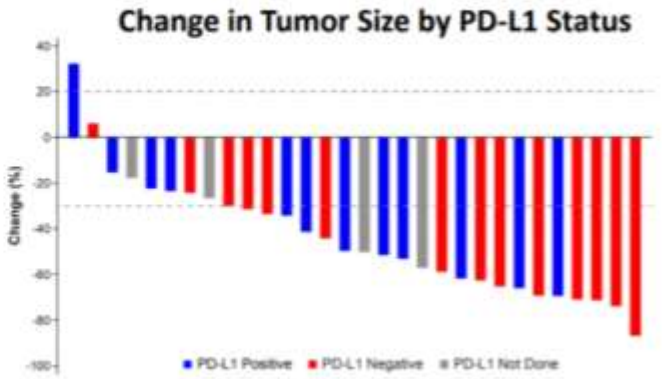
Motzer RJ et al. Genitourinary Cancers Symposium 2021;Abstract 308.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Lenvatinib + Pembrolizumab

Study 111 Lenvatinib + Pembrolizumab Phase 2
ICI Naïve — Objective Response Rate

Parameter	Total (n = 30)	Treatment Naïve (n = 12)	Previous Treatments (n=18)
$ORR_{(Week\ 24)}$, n (%)	19 (63)	10 (83)	9 (50)
95% CI	44–80	52–98	26–74
ORR, n (%)	19 (63)	10 (83)	9 (50)
95% CI	44–80	52–98	26–74
BOR, n (%)			
Partial response	19 (63)	10 (83)	9 (50)
Stable disease	10 (33)	2 (17)	8 (44)
Progression	1 (3)	0	1 (6)

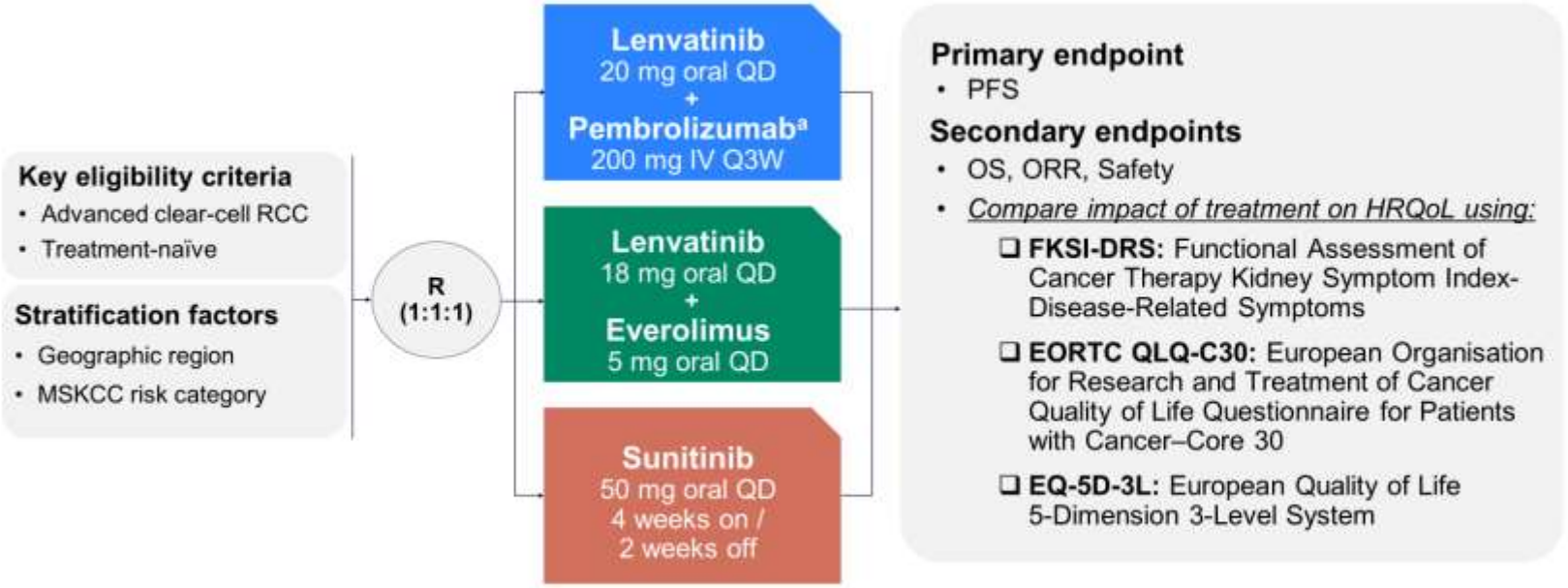




ESMO 2017

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Lenvatinib + Pembrolizumab

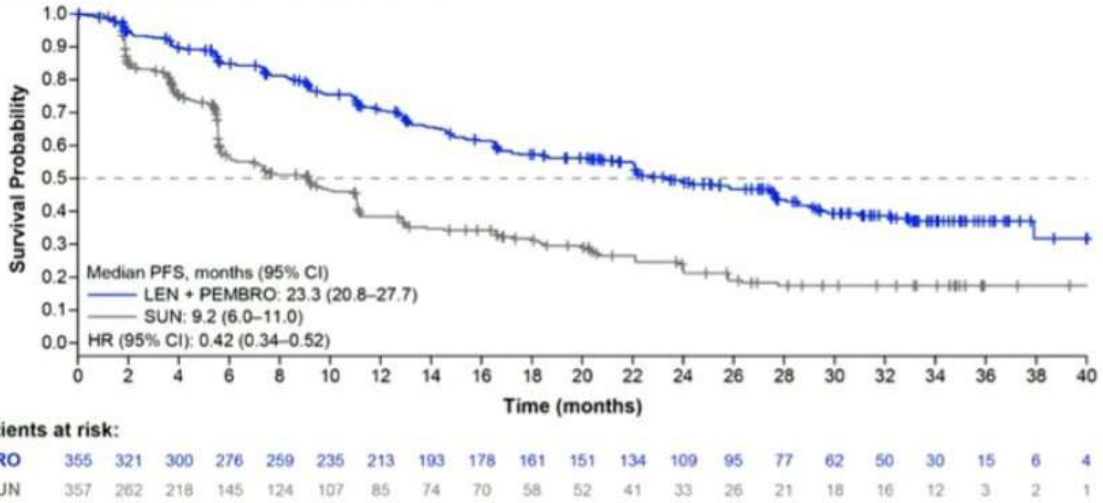
Study Design



[a]Patients could receive a maximum of 35 pembrolizumab treatments.
HRQoL, Health-related quality of life; MSKCC, Memorial Sloan Kettering Cancer Center; R, randomization.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Lenvatinib + Pembrolizumab

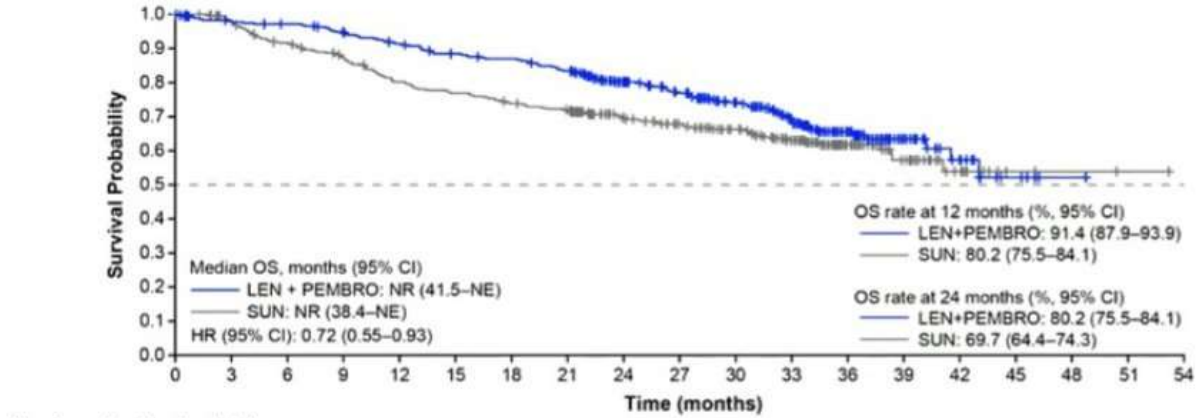
Continued improvement in PFS (by IIR per RECIST v1.1) with LEN + PEMBRO vs SUN



	MSKCC			IMDC		
	Poor risk	Intermediate risk	Favorable risk	Poor risk	Intermediate risk	Favorable risk
LEN +PEMBRO vs SUN HR (95% CI)	0.18 (0.08–0.42)	0.46 (0.35–0.60)	0.43 (0.29–0.64)	0.30 (0.14–0.62)	0.41 (0.30–0.54)	0.47 (0.32–0.69)

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Lenvatinib + Pembrolizumab

Continued improvement in OS with LEN + PEMBRO vs SUN



Number of patients at risk:

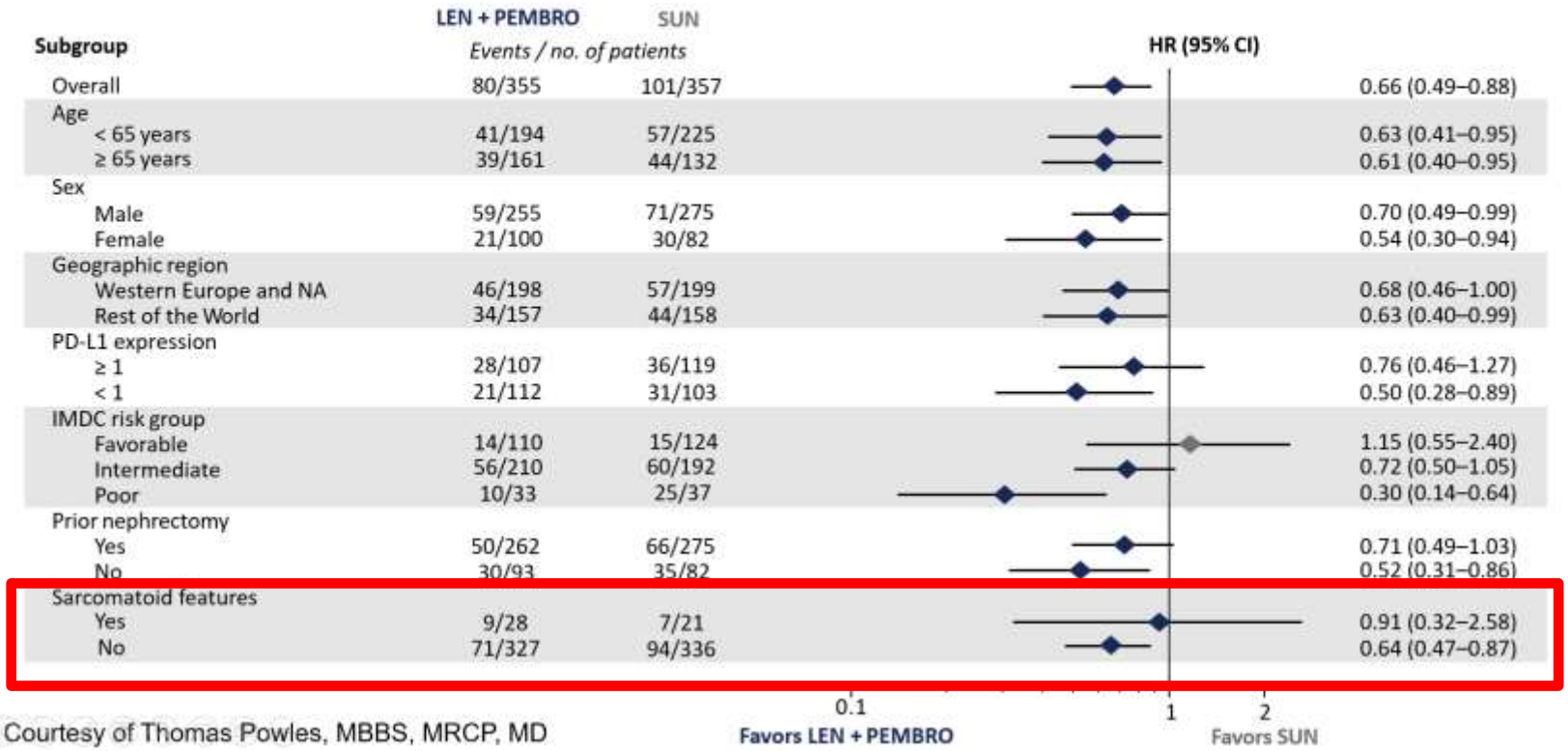
LEN + PEMBRO	355	342	338	327	313	300	294	280	232	207	174	133	75	31	15	5	1	0
SUN	357	332	307	289	264	253	242	234	195	177	153	116	66	34	14	3	2	1	0

Beyond the median duration of follow-up, there was a high rate of censoring

	MSKCC			IMDC		
	Poor risk	Intermediate risk	Favorable risk*	Poor risk	Intermediate risk	Favorable risk*
LEN +PEMBRO vs SUN HR (95% CI)	0.50 (0.25–1.02)	0.71 (0.52–0.97)	1.00 (0.51–1.96)	0.39 (0.20–0.77)	0.72 (0.52–1.00)	1.22 (0.66–2.26)*

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Lenvatinib + Pembrolizumab

Overall Survival With Lenvatinib Plus Pembrolizumab in Key Subgroups



Courtesy of Thomas Powles, MBBS, MRCP, MD

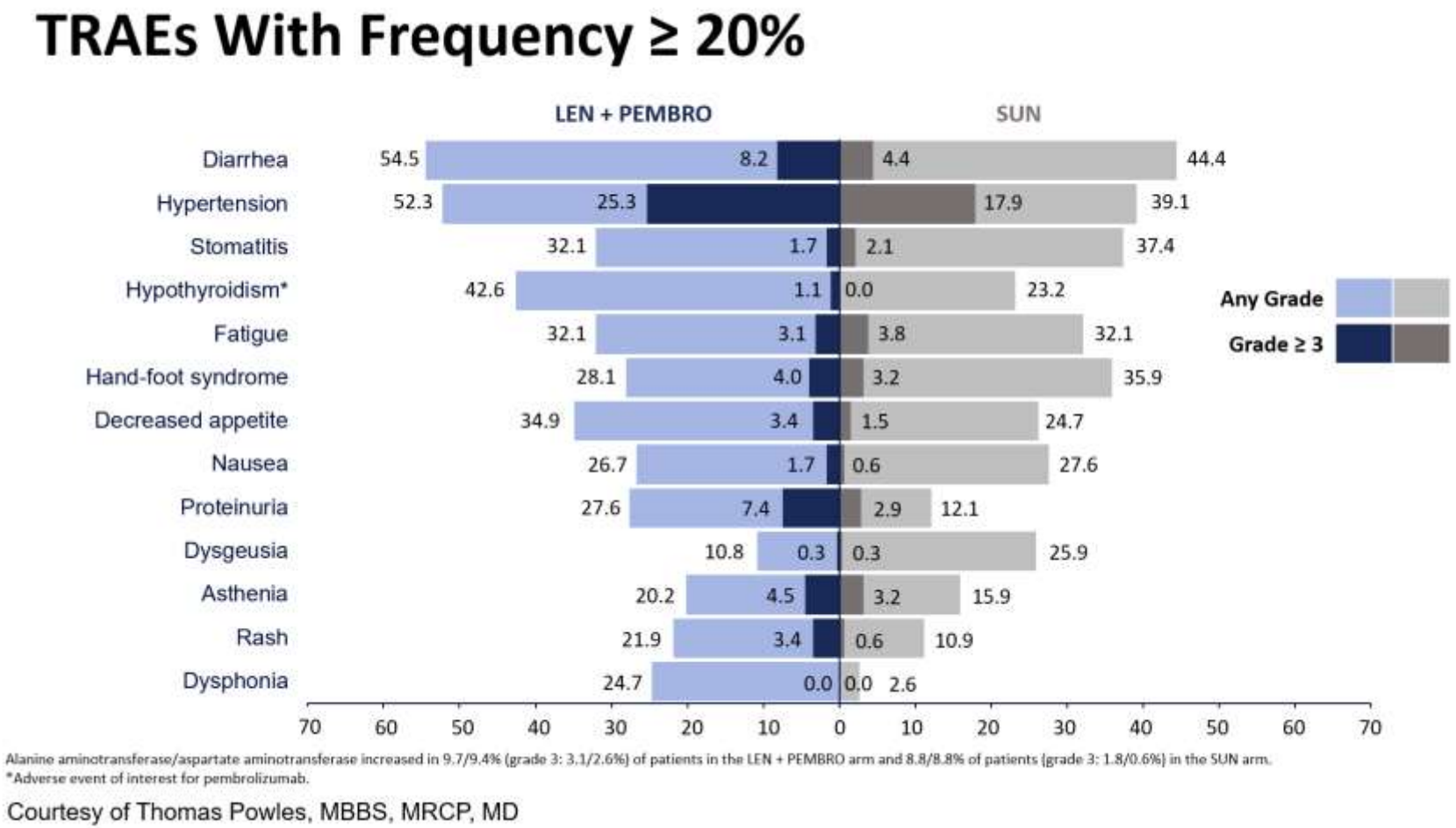
Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Lenvatinib + Pembrolizumab

Efficacy Summary

	LEN + PEMBRO n = 355	LEN + EVE n = 357	SUN n = 357
Median PFS, mo (95% CI)	23.9 (20.8–27.7)	14.7 (11.1–16.7)	9.2 (6.0–11.0)
Stratified HR (95% CI) vs SUN	**0.39 (0.32–0.49)**	**0.65 (0.53–0.80)**	--
P-value	< 0.001	< 0.001	--
Median OS, mo (95% CI)	NR (33.6–NE)	NR (NE)	NR (NE)
Stratified HR (95% CI) vs SUN	**0.66 (0.49–0.88)**	**1.15 (0.88–1.50)**	--
P-value	0.005	0.3	--
Objective response rate, %	**71.0**	**53.5**	**36.1**
Complete response, %	16.1	9.8	4.2
Median duration of treatment, mo (range)	17.0 (0.1, 39.1)	11.0 (0.1, 40.0)	7.8 (0.1, 37.0)

Motzer R et al. *N Engl J Med*. 2021;384:1289-1300.
CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reached.

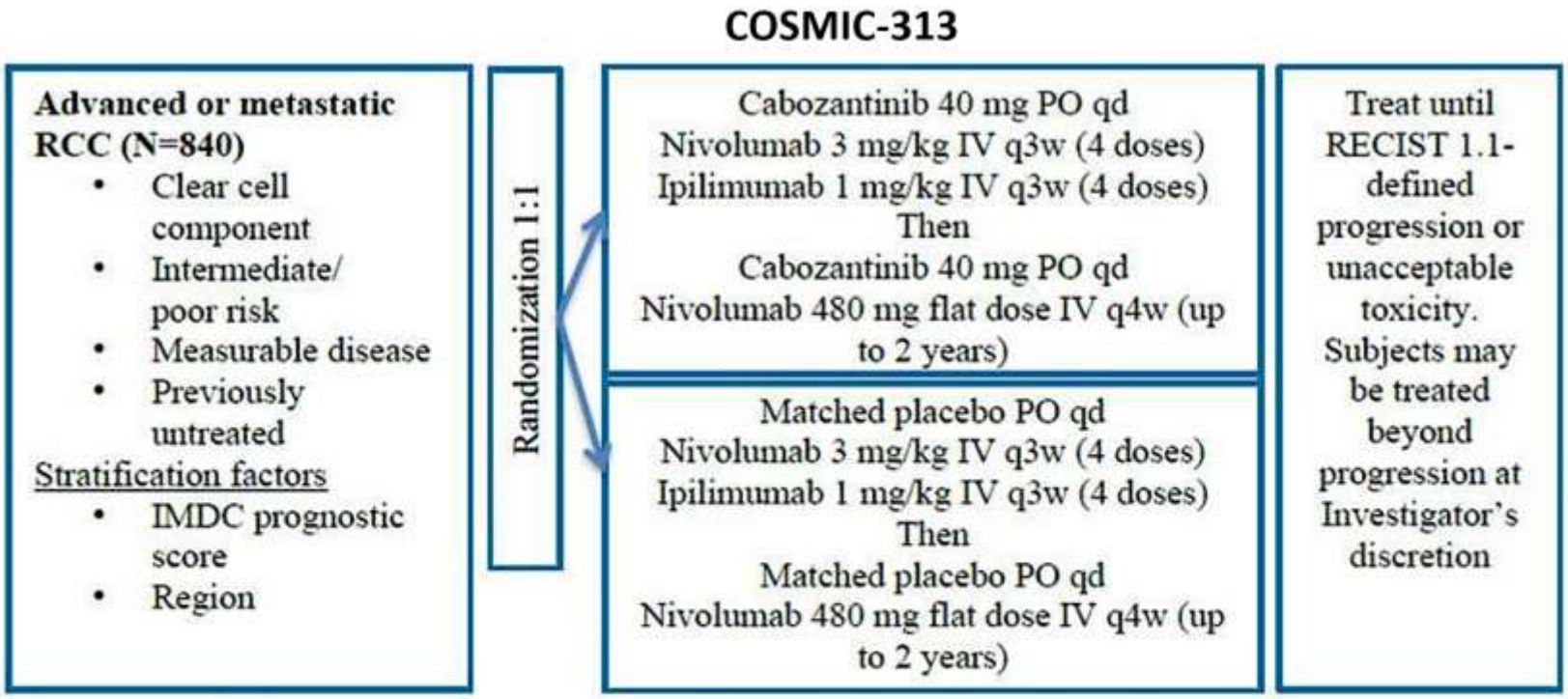
Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Lenvatinib + Pembrolizumab



Alanine aminotransferase/aspartate aminotransferase increased in 9.7/9.4% (grade 3: 3.1/2.6%) of patients in the LEN + PEMBRO arm and 8.8/8.8% of patients (grade 3: 1.8/0.6%) in the SUN arm.
*Adverse event of interest for pembrolizumab.

Courtesy of Thomas Powles, MBBS, MRCP, MD

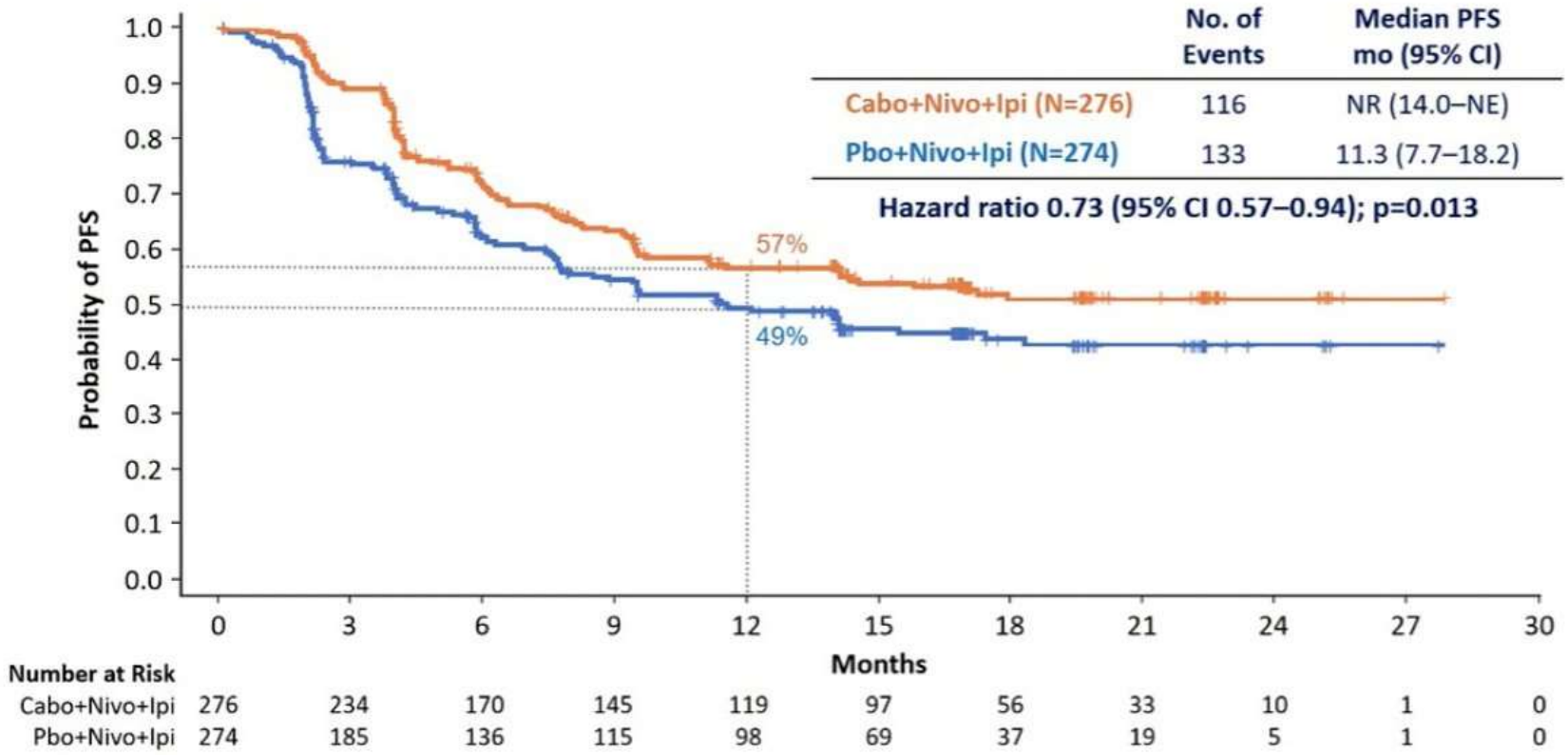
Nivolumab + Ipilumumab+Cabozantinib



IMDC, international metastatic renal cell carcinoma database consortium; IV, intravenous; PO, oral administration; qd, once daily; q3(4)w once every 3(4) weeks; RECIST, response evaluation criteria in solid tumors; RCC, renal cell carcinoma

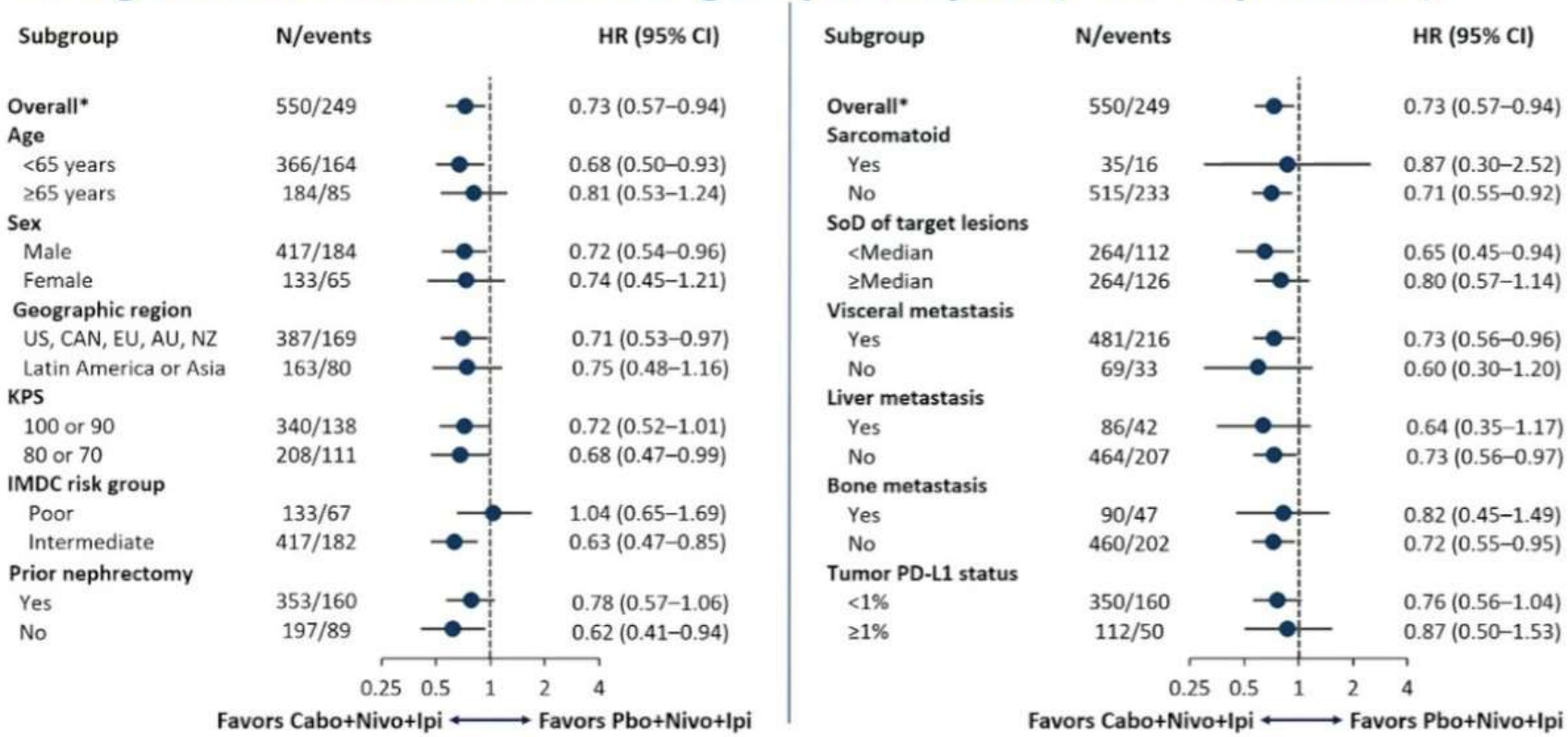
Nivolumab + Ipilumumab+Cabozantinib

Progression-Free Survival: Final Analysis (PITT Population)



Nivolumab + Ipilumumab+Cabozantinib

Progression-Free Survival Subgroup Analyses (PITT Population)

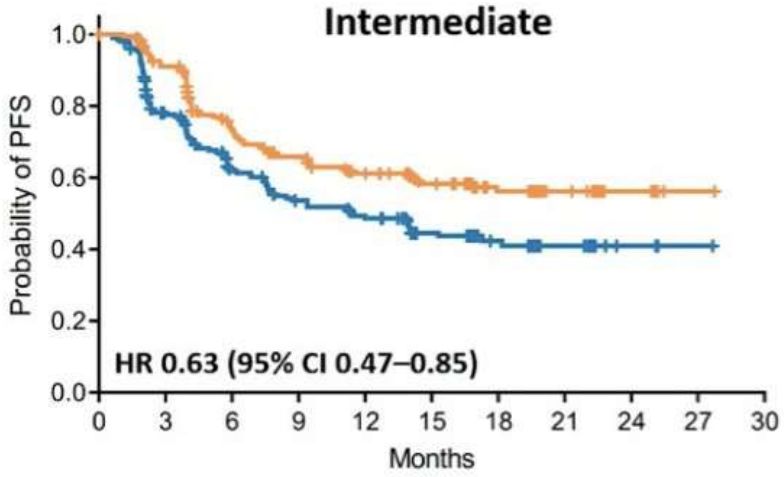


Nivolumab + Ipilumumab+Cabozantinib

	Cabo+Nivo+Ipi (N=276)	Pbo+Nivo+Ipi (N=274)
Objective response rate (95% CI), %	43 (37.2–49.2)	36 (30.1–41.8)
Best overall response, n (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Not evaluable	15 (5)	21 (8)
Disease control rate, %	86	72
Median time to objective response (range), mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI), mo	NR (20.2–NE)	NR (NE–NE)

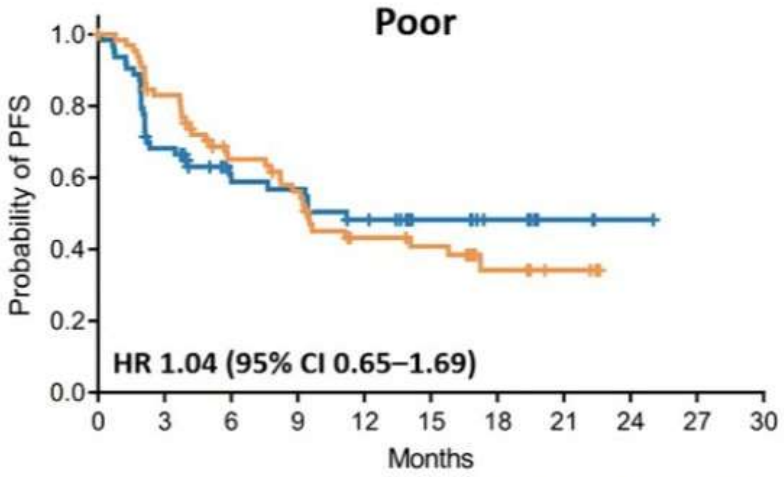
Nivolumab + Ipilumumab+Cabozantinib

PFS and ORR by IMDC Risk Group (PITT Population)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=209)	79	NR (16.9–NE)
Pbo+Nivo+Ipi (N=208)	103	11.4 (7.6–17.3)

ORR: 45% (95% CI, 38.1–52.0) for Cabo+Nivo+Ipi vs 35% (95% CI, 28.6–42.0) for Pbo+Nivo+Ipi



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=67)	37	9.5 (7.8–17.3)
Pbo+Nivo+Ipi (N=66)	30	11.2 (4.0–NE)

ORR: 37% (95% CI, 25.8–50.0) for Cabo+Nivo+Ipi vs 38% (95% CI, 26.2–50.7) for Pbo+Nivo+Ipi

Nivolumab + Ipilumumab+Cabozantinib

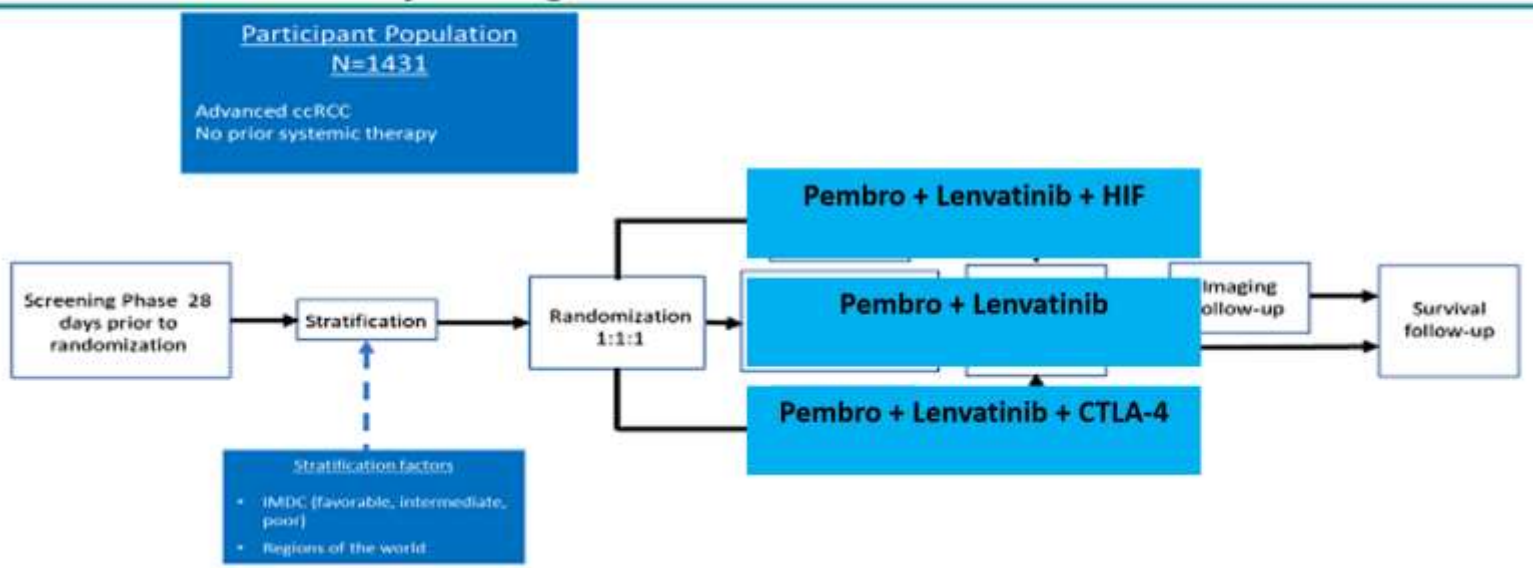
Treatment Exposure and Discontinuation (Safety Population)

	Cabo+Nivo+Ipi (N=426)	Pbo+Nivo+Ipi (N=424)
Median duration of exposure of study treatment (range), mo	10.9 (0.2–28.5)	10.3 (0.1–28.1)
Median average daily dose (range) of Cabo or Pbo, mg	23.2 (3.6–40.0)	36.1 (0.8–40.0)
Median Nivo infusions (range) received, no	10 (1–27)	9 (1–27)
Doses of Ipi received, %		
4	58	73
3	13	14
2	22	7
1	7	6
Any dose hold due to an AE, %	90	70
Any dose reduction of Cabo or Pbo due to an AE, %	54	20
Treatment-related AE leading to discontinuation, %		
Any study treatment	45	24
Cabo or Pbo	28	14
Nivo	26	18
Ipi	30	12
All treatment components (due to the same AE)	12	5

Data cut-off: Jan 31, 2022

Süren Çalışmalar

MK-6482-012 Study Design



- Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ccRCC = clear cell renal cell carcinoma.
- a. The treatment arms are the HIF triplet (MK-6482 + pembrolizumab + lenvatinib), the CTLA4 triplet (MK-1308A + lenvatinib), and the doublet (pembrolizumab + lenvatinib). Note: MK-1308A is a coformulation of pembrolizumab and MK-1308
- Global Study- ~225 sites, 33 countries

MSD

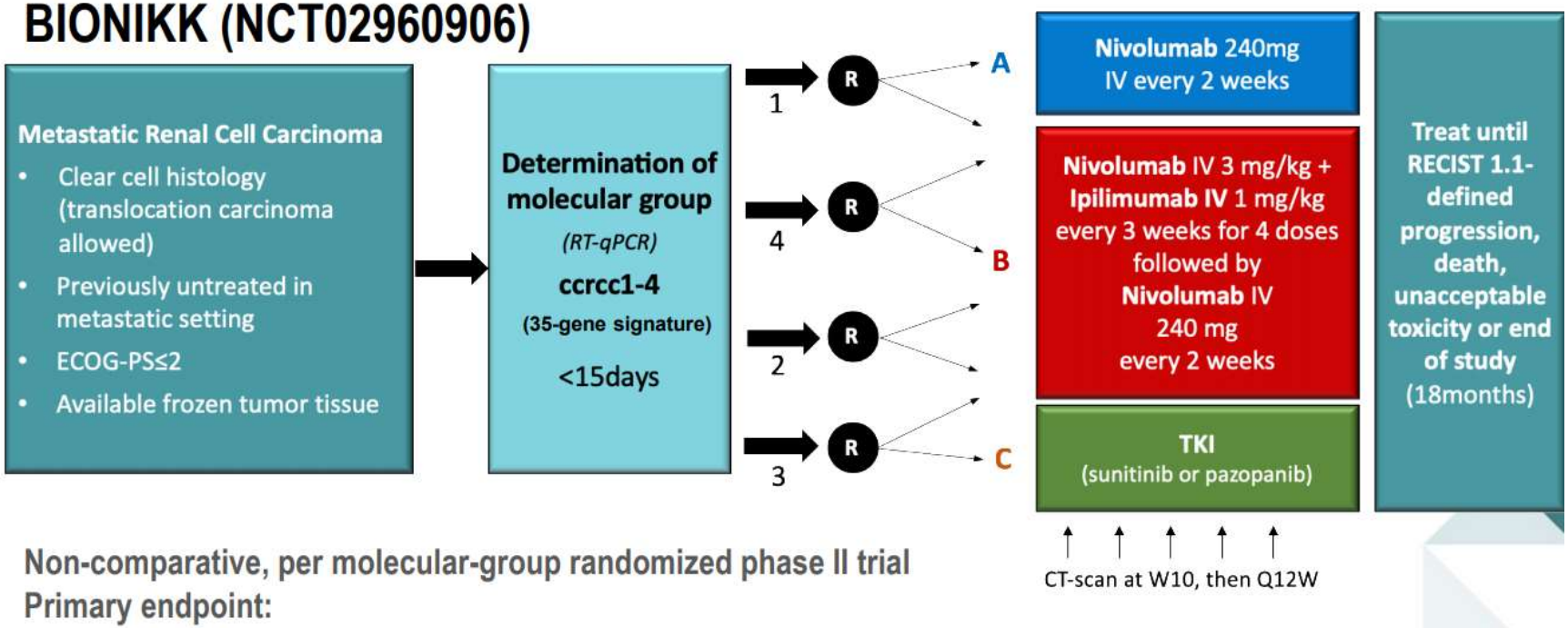
MERCK
INVENTING FOR LIFE

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif

VIRTUAL 2020 ESMO congress

METHODS: study design

BIONIKK (NCT02960906)



Non-comparative, per molecular-group randomized phase II trial

Primary endpoint:

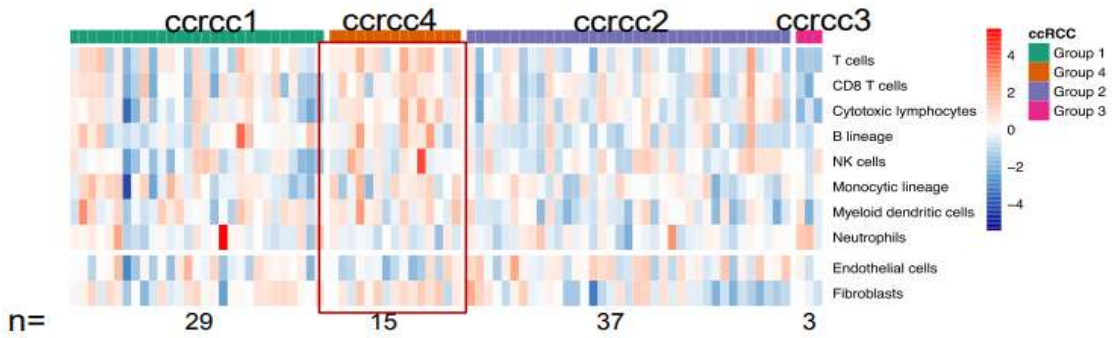
Overall response rate (ORR: CR+PR) using RECIST 1.1 per investigator

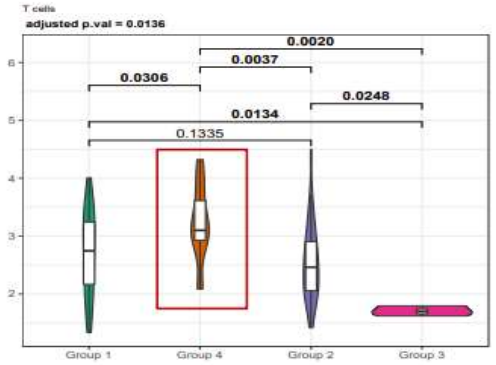
Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif

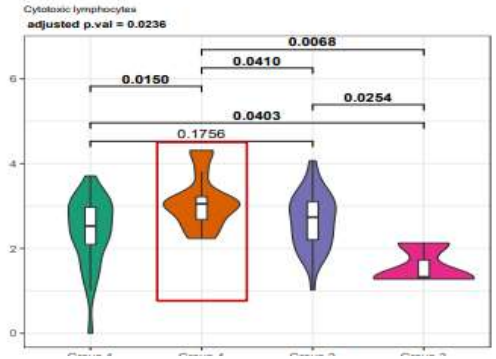
VIRTUAL 2020 ESMO congress

RESULTS: transcriptomic analysis of immune cells distribution

- We applied MCP-Counter deconvolution algorithm[1] on transcriptomic data from 84 FFPE tumor samples (3'RNAseq)
- We found that ccrcc4 tumors are the most infiltrated by immune cells, in particular cytotoxic lymphocytes







- Analysis of the correlation between TME and outcomes is ongoing

[1]Becht et al. Genome Biology 2016

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif

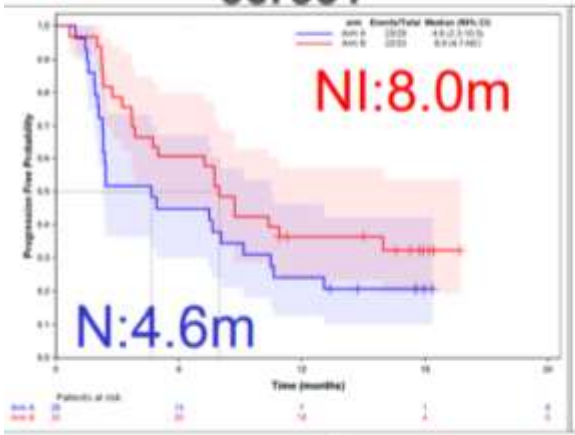
VIRTUAL 2020 ESMO congress

RESULTS: Progression Free Survival (PFS)

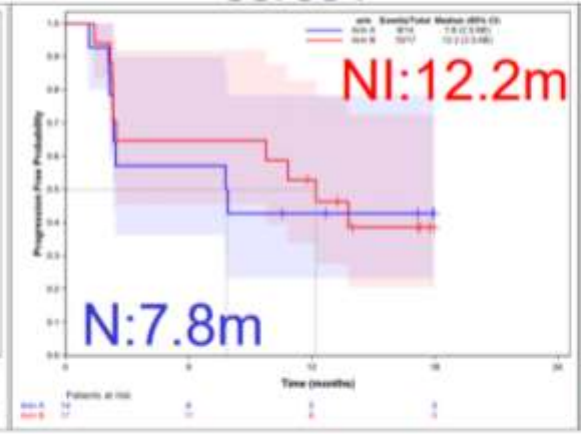
Target cohort (TCE, n=154)

Median follow-up: 16 months

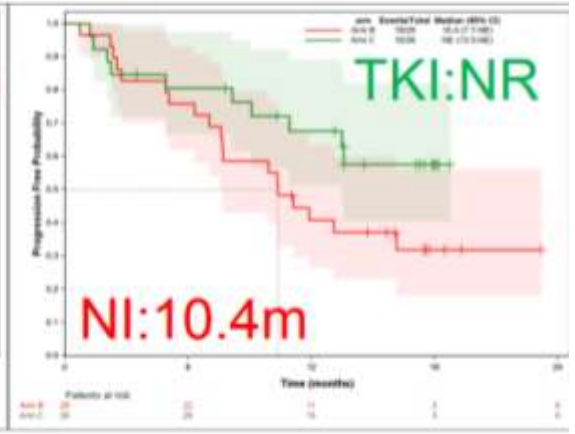
ccrcc1



ccrcc4



ccrcc2

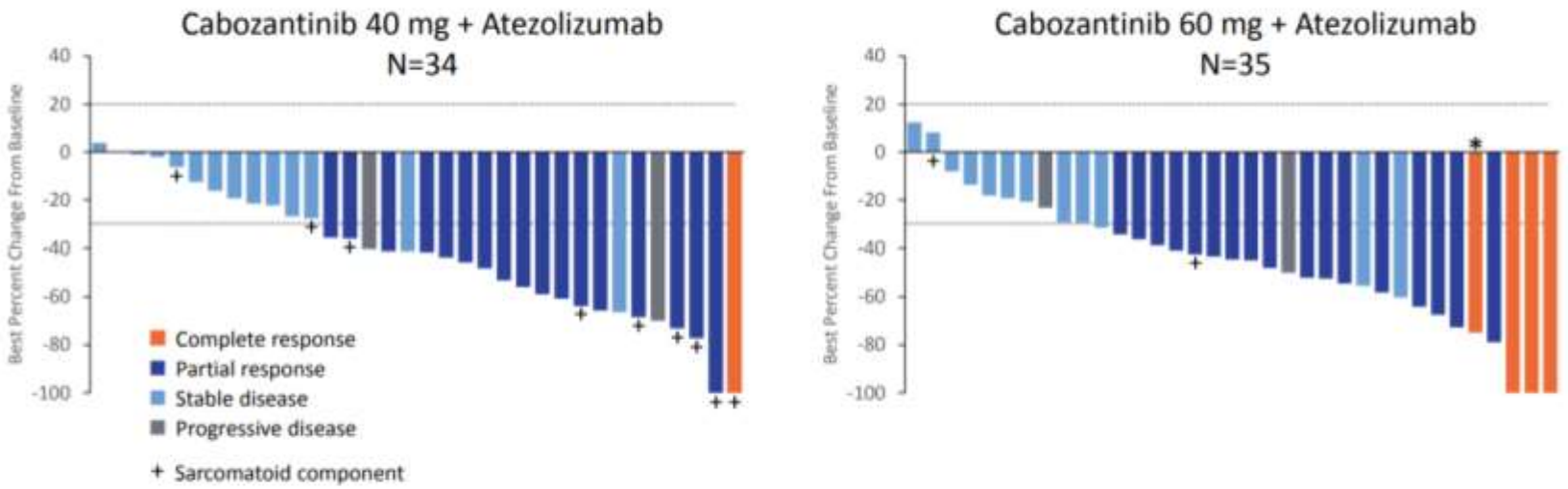


ccrcc3 No KM curve showed here because of the limited number of pts (n=6)

Overall Survival (OS) is not mature (16% of events)

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif

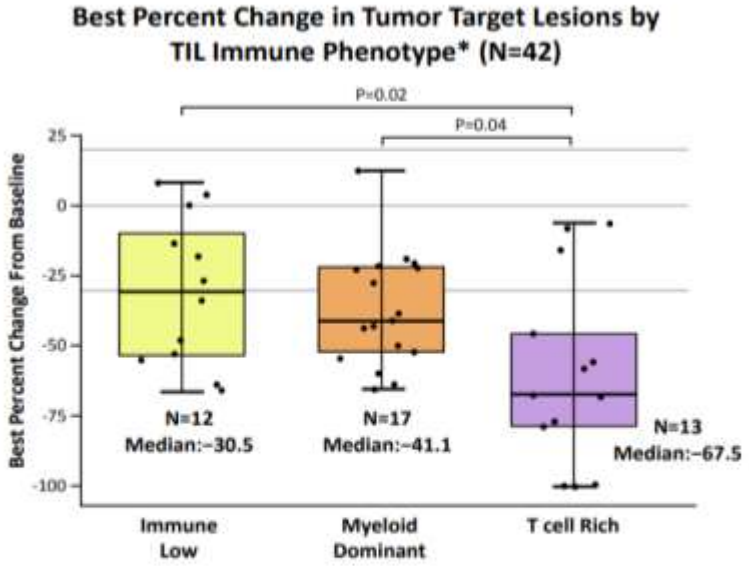
Best Change From Baseline in Sum of Target Lesions

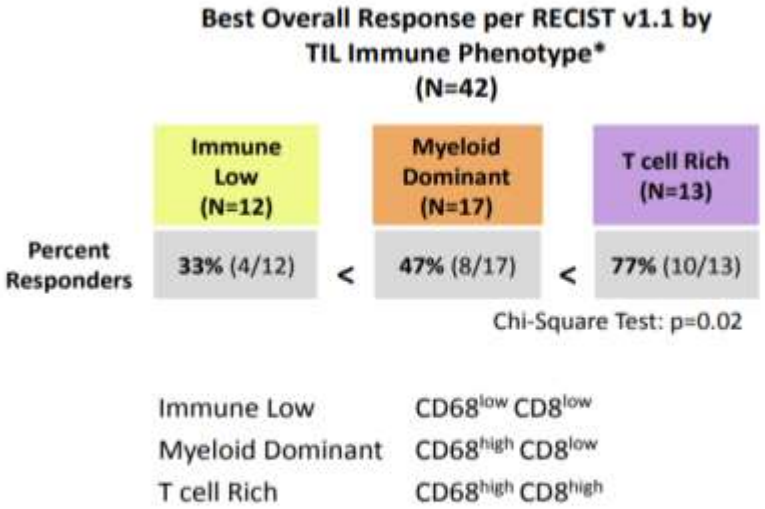


- Any reduction in tumor target lesions occurred for 94% of the 40 mg cabozantinib cohort and 92% of the 60 mg cabozantinib cohort

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif

Tumor Infiltrating Lymphocytes (TIL) at Baseline with Lesion Change and Response





- The T cell Rich tumors were associated with greater tumor shrinkage from baseline and higher overall response

*Both ccRCC dose groups are included in the analyses.
*Analyses by immunohistochemistry of CD68 (myeloid cells) and CD8 (cytotoxic T cells) with a cutoff of 20% for high vs low cell frequency showed three immune phenotypes; $CD68^{low}$ $CD8^{high}$ was not observed.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Kidney Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cabozantinib (category 1) • Lenvatinib + everolimus • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] (category 1) • Axitinib + avelumab[b] (category 3)	• Everolimus • Bevacizumab[f] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Sorafenib (category 3) • Temsirolimus[e] (category 2B) • Belzutifan (category 2B)

Evre IV RCC Birinci Basamak Tedavi Özet 1

First-line IO Combination Trials in mRCC

	CheckMate 214 (Ipi/Nivo) [1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
mOS, months HR (CI)	NR vs 38.4 **0.69** (0.59–0.81)	45.7 vs 40.1 **0.73** (0.60-0.88)	NR vs 29.5 **0.66** (0.50–0.87)	NR vs NR **0.66** (0.49-0.88)
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%	**90%** vs. 79% **74%** vs. 66%	**86%** vs. 76% **72%** vs 60% (est.)	**90%** vs 79% (est.) **79%** vs. 70%
mPFS, months HR (CI)	**12.2** vs 12.3 0.89 (0.76–1.05)	**15.7** vs 11.1 0.68 (0.58–0.80)	**17.0** vs 8.3 0.52 (0.43–0.64)	**23.9** vs 9.2 0.39 (0.32-0.49)
ORR, %	**39** vs 32	**60** vs 40	**55** vs 27	**71** vs 36
CR, %	**11** vs 3	**10** vs 4	**9** vs 4	**16** vs 4
Med f/u, months	**55**	**42.8**	**23.5**	**27**
Prognostic risk, % Favorable Intermediate Poor	 23 61 17	 32 55 13	 23 58 19	 31 59 9
Prior nephrectomy	82%	83%	69%	74%
Subsequent systemic therapies for sunitinib arm, %	Overall (69%) IO (42%)	Overall (69%) IO (48%)	Overall (40%) IO (29%)	Overall (71%) IO (53%)

1. Albiges et al. ESMO Open 2020
2. Rini et al. ASCO 2021
3. Motzer et al. ASCO GU 2021
4. Motzer et al. ASCO GU 2021.

@brian_rini and @Uromigos (podcasts: https://anchor.fm/the-Uromigos)

Evre IV RCC Birinci Basamak Tedavi
Özet 2

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
HR mOS, months	**0.72** 55.7 vs 38.4	**0.73** 45.7 vs 40.1	**0.70** 37.7 vs 34.3	**0.72** NR vs NR
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%	**90%** vs. 79% **74%** vs. 66%	**86%** vs. 76% **70%** vs 60%	**90%** vs 79% (est.) **79%** vs. 70%
HR mPFS, months	**0.86** **12.3** vs 12.3	**0.68** **15.7** vs 11.1	**0.56** **16.6** vs 8.3	**0.39** **23.9** vs 9.2
ORR, %	**39** vs 32	**60** vs 40	**56** vs 28	**71** vs 36
CR, %	**12** vs 3	**10** vs 4	**12** vs 5	**16** vs 4
Med f/u, months	**67.7**	**42.8**	**32.9**	**33.7**
Primary PD, %	**18**	**11**	**6**	**5**
Landmark PFS	30% (5 years)	29% (3 years)	39% (2 years)	

Evre IV RCC Birinci Basamak Tedavi Özet 3

The Uromigos

Front-line IO-based Trials in mRCC: 1 vs 2 vs 3 drugs in IMDC Int/Poor

	1 (IO)	2 (IO/IO)	2 (IO/TKI)			3 (IO/IO/TKI)
Comparator	None	Sunitinib				Ipi/Nivo
	KEYNOTE-427 (Pembro)[1]	CheckMate 214 (Ipi/Nivo)[2]	KEYNOTE-426 (Axi/Pembro)[3]	CheckMate 9ER (Cabo/Nivo)[4]	CLEAR (Len/Pembro)[5]	COSMIC313 (I/N/C vs I/N)[6]
OS HR	NA	0.68	0.64	I: 0.74 P: 0.44	I: 0.72 P: 0.39	NR
PFS HR	NR	0.73	0.67	I: 0.59 P: 0.36	I: 0.41 P: 0.30	0.73
mPFS, mos.	6.9	11.6	13.8	I: 17.5 P: 9.9	22.1	Not reached
Landmark PFS	24% at 2 years	31% at 5 years	NR	I: 55% P: 44% at 15 months	45% (est.) at 2 years	57% at 1 year
ORR	40%	42%	57%	51%	72%	43%
CR	4%	11%	9%	9%	14%	3%
Primary PD	37%	12%		7%	6%	8%
Med f/u, mos	35.9	67.7	42.8	32.9	33.7	20.2

1. McDermott et al. JCO 2021 2. Motzer et al. ESMO 2021/Cancer 2022 3. Rini et al. ASCO 2021 4. Motzer et al. Lancet Oncology 2022/Apollo et al ASCO 2022 5. Motzer et al. NEJM 2021/Choueiri et al. KCRS 2021/Grunwald et al. ASCO 2021/Porta et al. ESMO 2022. 6. Choueiri et al. ESMO 2022

Evre IV RCC Birinci Basamak Tedavi Özet 4

	Ipilimumab + Nivolumab	Nivolumab + Cabozantinib	Pembrolizumab + Lenvatinib	Pembrolizumab + Axitinib	Cabozantinib + Ipilimumab + Nivolumab
Population	• **Int/poor risk**	• All	• All	• All	• All
Pros	• No TKI toxicity • Maintenance with nivo only after 12 weeks, QOL benefit • Chance for durable response	• QOL benefit • Cabozantinb has activity in bone and brain mets	• Highest CR rate seen (17.2%) • 95% disease control rate	• Short TKI half life, 6 hours (easy to adjust)	• Superior PFS versus ipi/nivo, the only combo to be compared in a phase 3 trial vs another combo
Cons	• More ICI toxicity (29% high dose steroids) • 18-20% PD as best response	• Cabozantinib has long half-life (120 hours)	• 20mg lenvatinib is toxic (highest rate of grade 3 AEs, 82%)		• Toxic (58% high dose steroids), side effects can be hard to attribute • OS unknown
Consider in…	• **Sarcomatoid RCC** • **Int/poor risk pts who can "afford" risk of PD**	• **Bone mets** • **Prioritizing response + QOL**	• **Robust patients with symptomatic disease**	• **Patients who may need to stop / reduce TKI quickly**	• Role remains TBD, pending OS data

Evre IV RCC Birinci Basamak Tedavi Özet 5

İmmünoterapi-immünoterapi kombinasyonu

- Daha yüksek oranda tam yanıt
- Daha uzun takip süresi ve yanıt derinliği
- İmmün ilişkili toksisite fazla, daha çok ilaç kesme oranı

İmmünoterapi-TKI kombinasyonu

- Daha yüksek yanıt oranı ve daha uzun PSF oranı
- Daha kısa bir takip süresi, yanıt derinliği hakkında veri matür değil
- Uzun TKI toksisitesi maruziyeti
- Yaş, komorbidite, semptom, hastalık yükü tedavi seçiminde yön gösterici olabilir.
- Daha uzun takip süresi ve daha efektif prediktif belirteçler tedavi seçiminde katkı sağlayacak.