Metastatik Renal Kanserde Birinci Basamak Tedavi Seçenekleri

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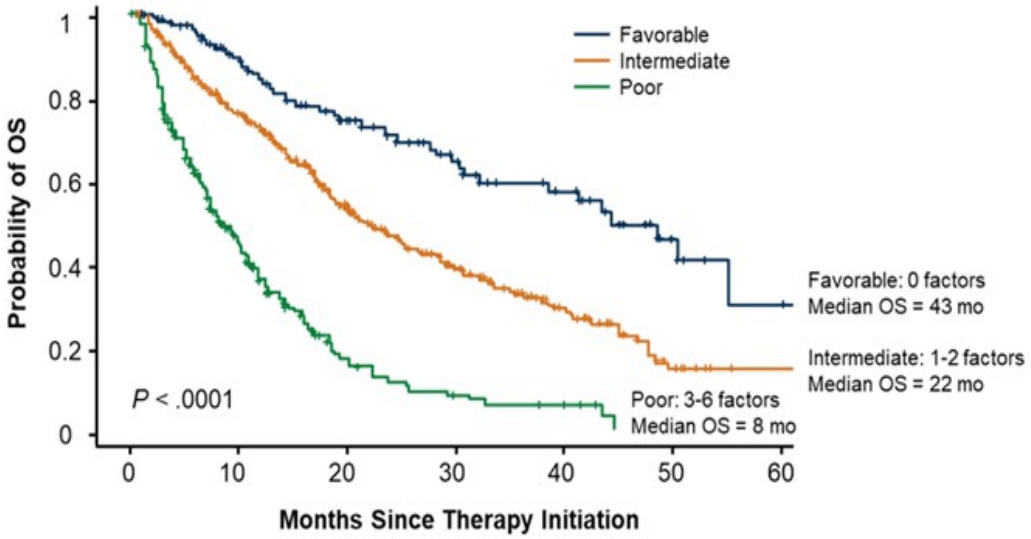
Ders Planı

- Nivolumab ipilimumab uzun dönem sonuçları
- Pembrolizumab + Axitinib
- Nivolumab + Cabozantinib
- Lenvatinib + Pembrolizumab
- Metastatik RCC Birinci Basamak Tedavi Seçenekleri
  Gelecek Perspektif
- Sonuç

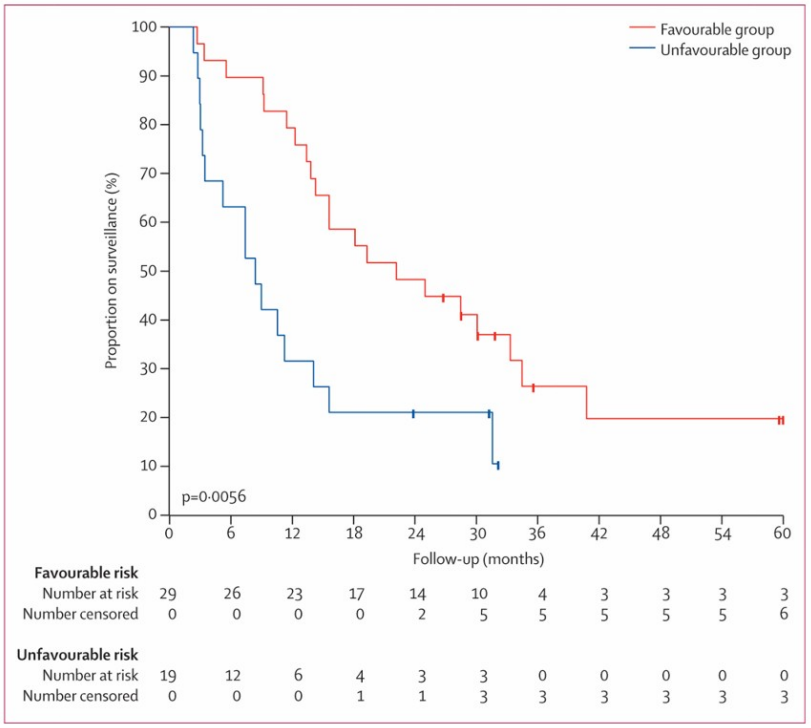
Klinik ve Laboratuvar Parametrelere Göre Risk Sınıflandırılması

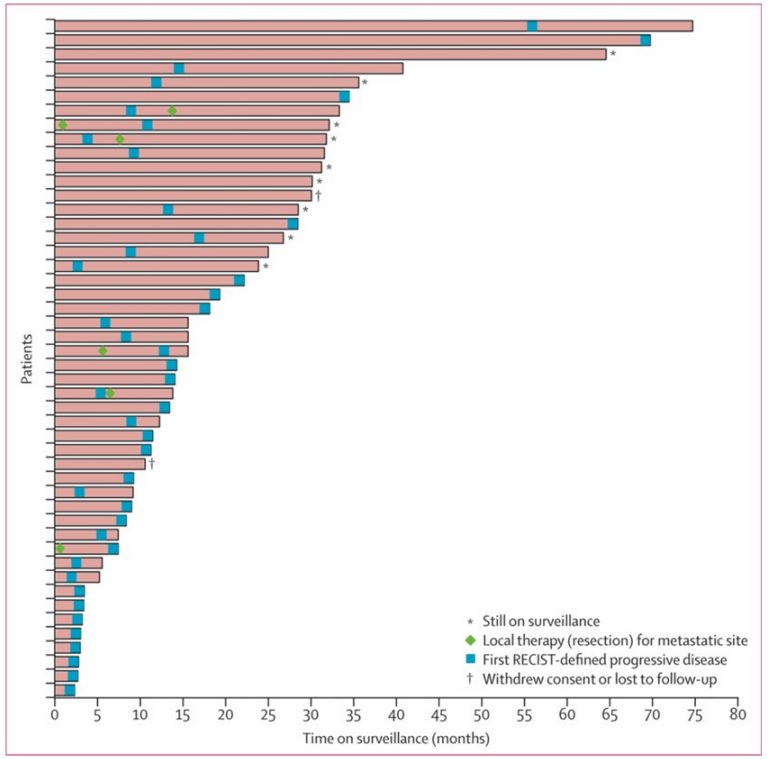
IMDC Risk Scoring System Entry Criteria
KPS <80%
<1 y from time of diagnosis to systemic therapy
Hemoglobin <LLN (normal: 120 g/L or 12 g/dL)
Calcium >ULN (normal: 8.5-10.2 mg/dL)
Neutrophil >ULN (normal: 2.0-7.0 x 10^9/L)
Platelets >ULN (normal: 150,000-400,000)



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

Metastatik renal hücreli karsinomda aktif izlem





48 hastada sistemik tedavi başlanmasına kadar geçen medyan izlem süresi 14,9 ay. **IMDC skoru** artıkça, metastaz sayısı artıkça sonuçlar ve akciğer dışı metastazlarda sonuçlar kötü.

Rini B, Lancet Oncol. 2016

Oligometastatik berrak hücreli renal hücreli karsinomda radyoterapi

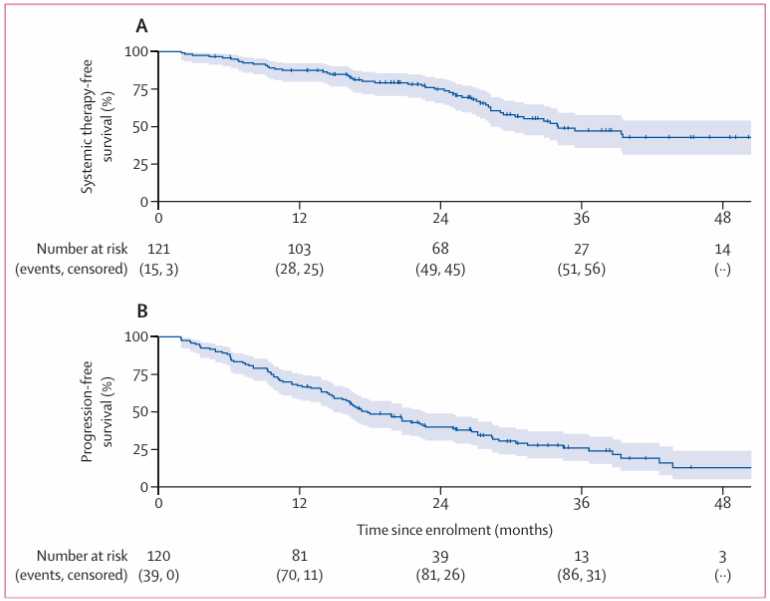


Figure 2: **Primary outcomes of systemic therapy-free survival in the intention-to-treat population (n=121; A) and progression-free survival in the per-protocol population (n=120; B)**
Vertical lines denote censored patients, and shading indicates 95% CIs.

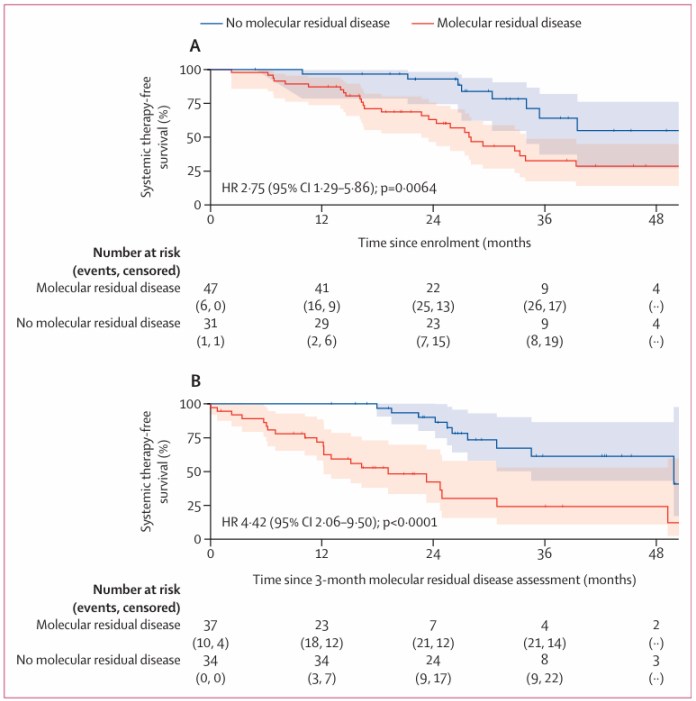


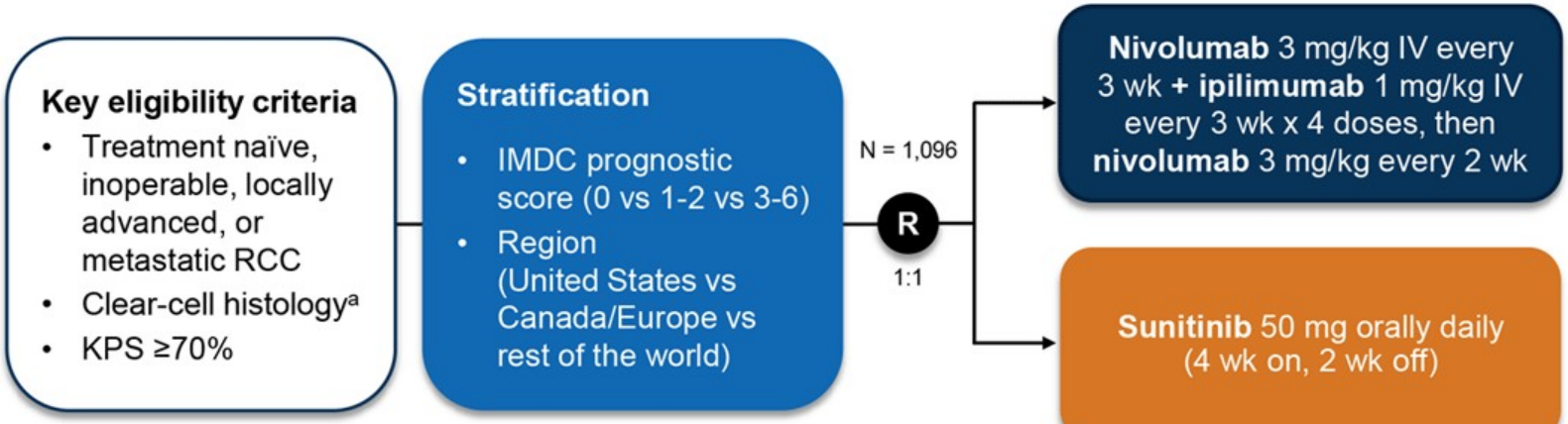
Figure 4: **Circulating tumour DNA molecular residual disease association with systemic therapy-free survival at baseline (A) and 3-month follow-up (B)**

Çalışmaya dahil edilen 121 hastanın %77 akciğer lenf nodu metastazı, medyan takip süresi 36,3 ay. Medyan progresyonsuz sağkalım 17,7 ay ve medyan sistemik tedavisiz sağkalım süresi ise 34,0 ay olarak bulundu. RT sonrası ctDNA negatif olanlar sonuçlar çok daha iyi.

Tang C, Lancet Oncol 2025

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.

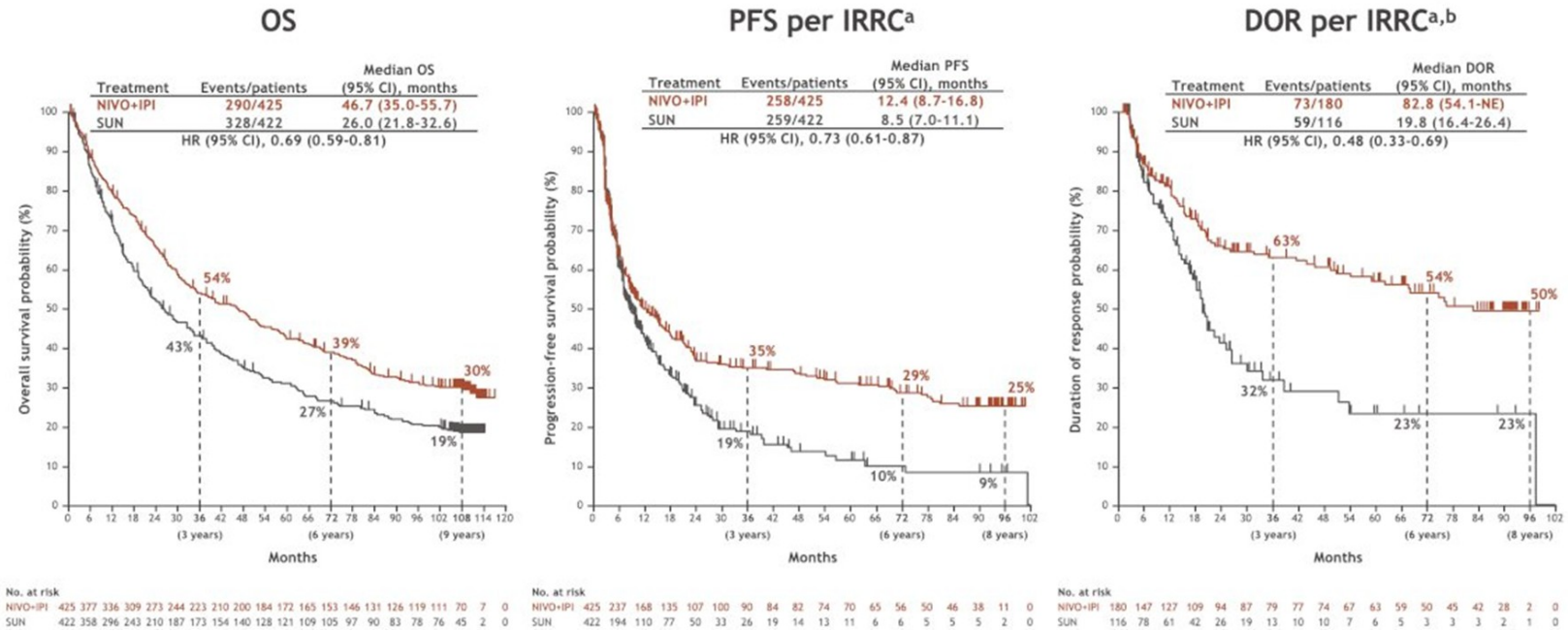
Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

Characteristic[a]	ITT patients[1,2]		Patients with IMDC intermediate/poor risk[1,2]		Patients with IMDC favorable risk[1,2]	
	NIVO+IPI (N = 550)	SUN (N = 546)	NIVO+IPI (n = 425)	SUN (n = 422)	NIVO+IPI (n = 125)	SUN (n = 124)
IMDC prognostic score, %						
Favorable (0)	23	23	0	0	100	100
Intermediate (1-2)	61	61	79	79	0	0
Poor (3-6)	17	16	21	21	0	0
Geographic region, %						
Europe and Canada	37	36	35	35	42	43
United States	28	28	26	26	34	34
Rest of the world	35	36	39	39	24	23
Sarcomatoid features, %	14	12	17	15	2	2
Selected sites of metastasis, %						
Lung	69	68	69	70	70	62
Bone[b]	20	22	22	23	14	18
Liver	18	20	21	21	9	15

CheckMate 214, ASCO 2025

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

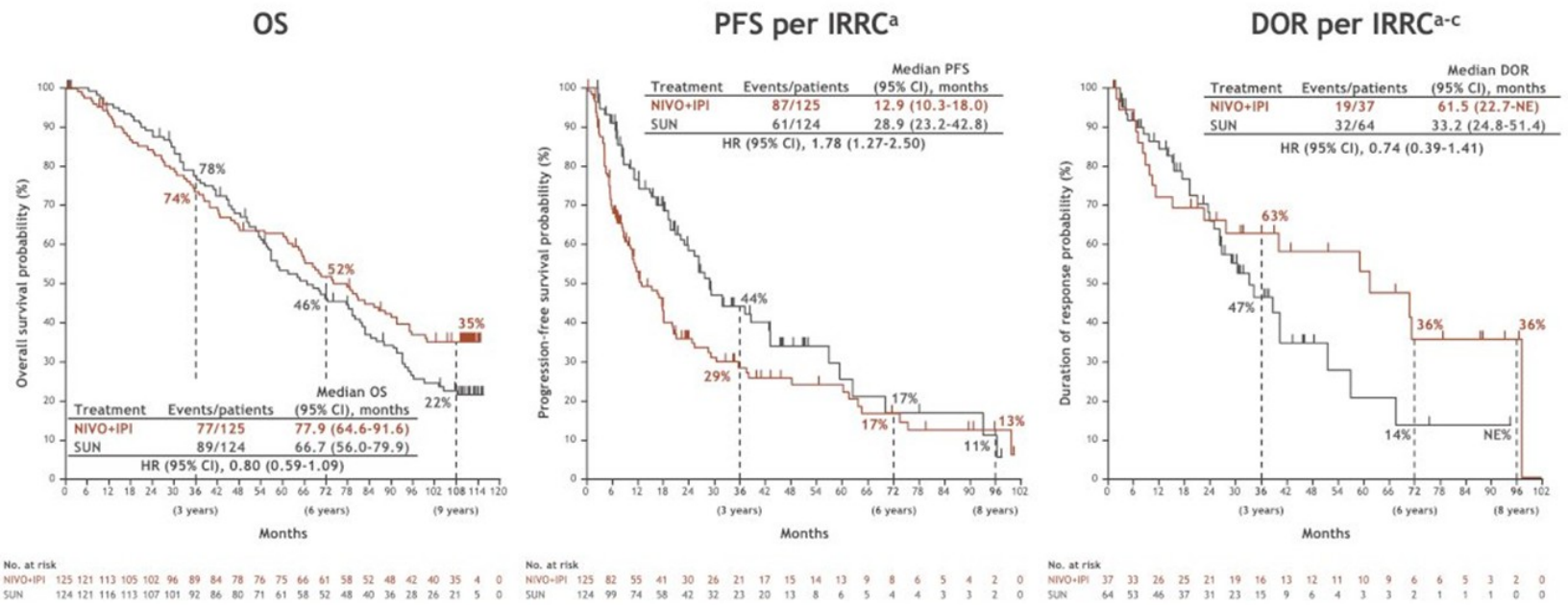
OS, PFS, and DOR in the IMDC intermediate/poor-risk population



CheckMate 214, ASCO 2025

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

OS, PFS, and DOR in the IMDC favorable-risk population



- Long-term OS results in patients with IMDC favorable risk trended in favor of NIVO+IPI over SUN, with more durable responses[d]

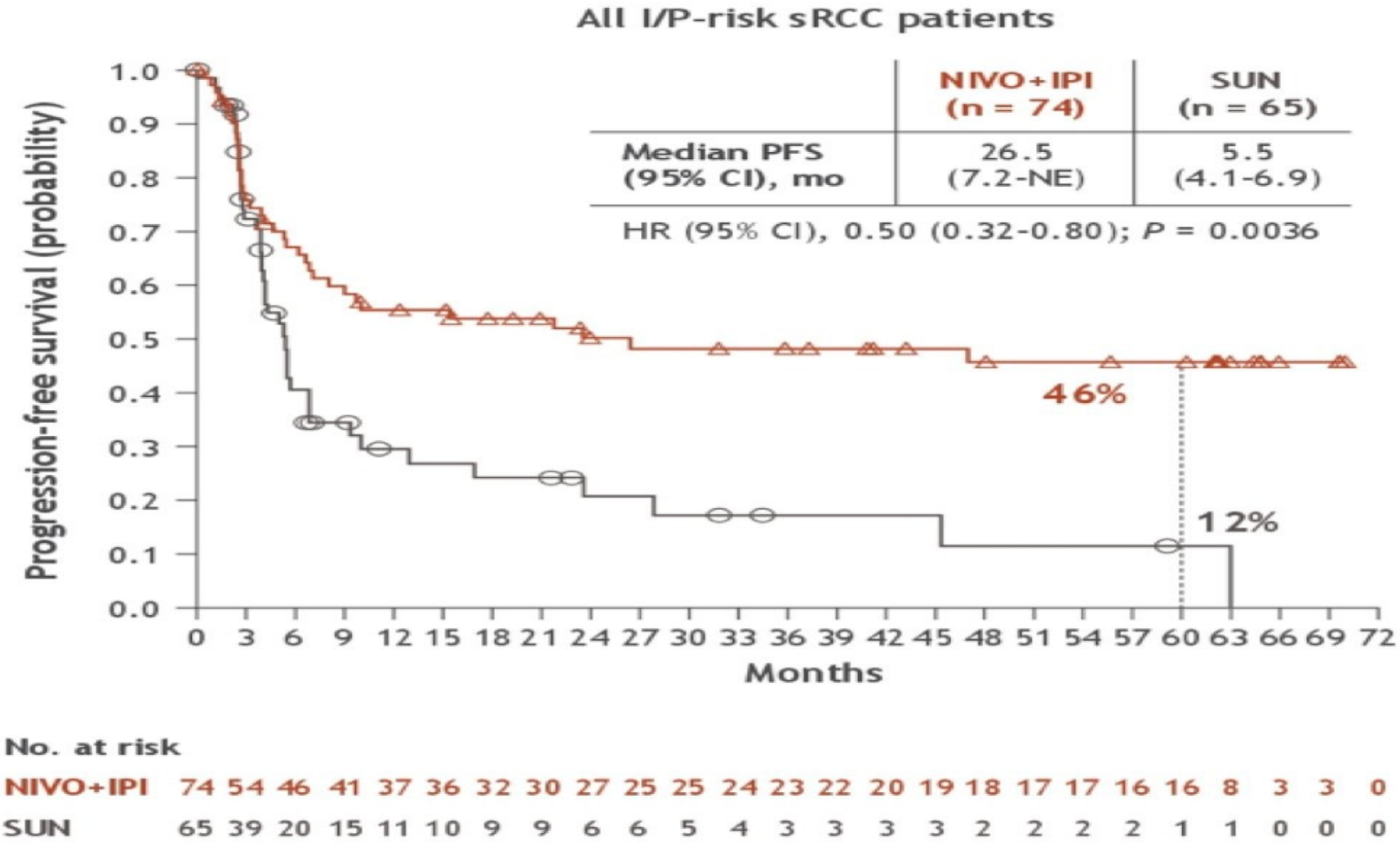
CheckMate 214, ASCO 2025

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

CheckMate -214: 48-Month Response

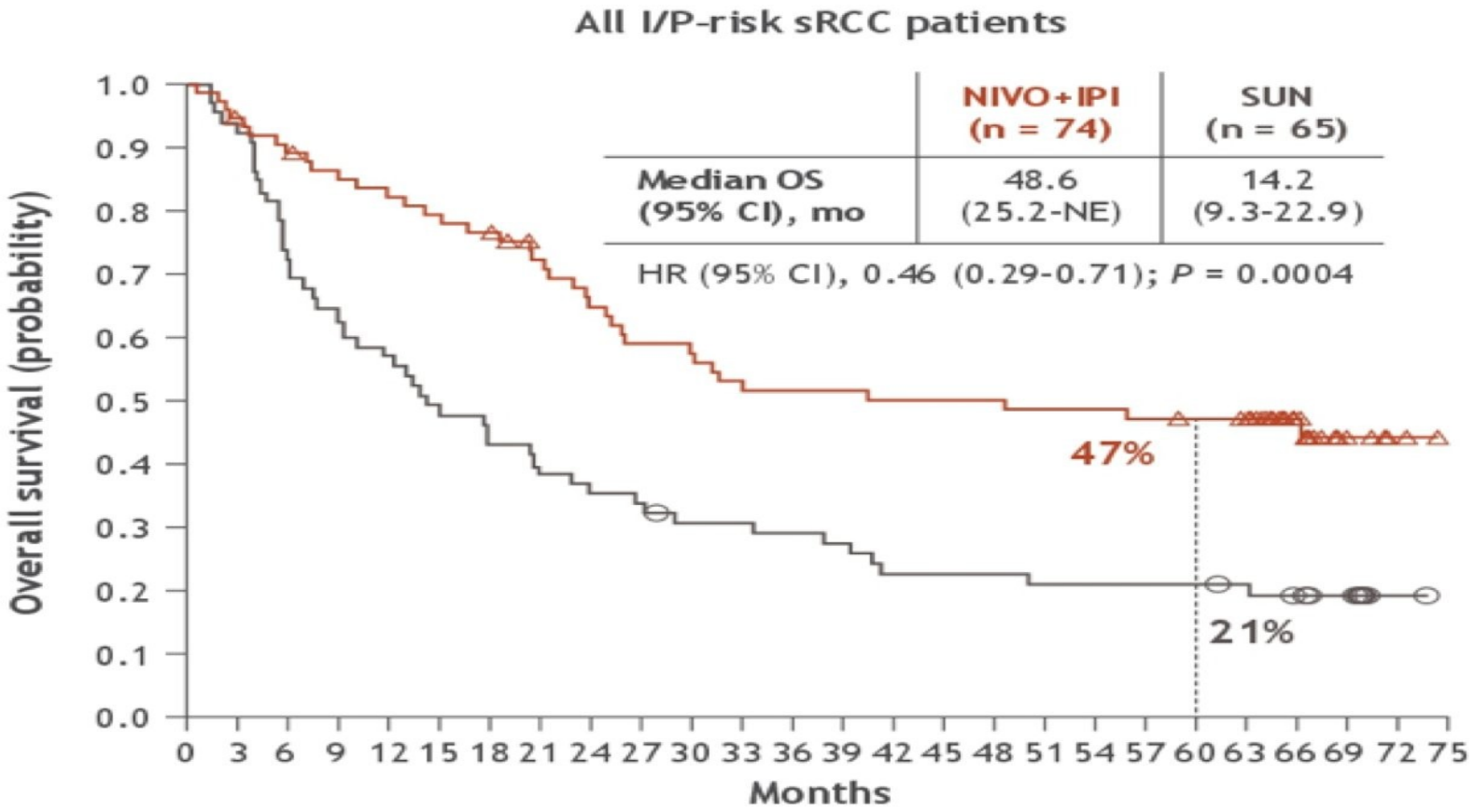
	Intermediate/Poor-Risk		ITT		Favorable-Risk	
	NIVO + IPI (n = 425)	SUN (n = 422)	NIVO + IPI (n = 550)	SUN (n = 546)	NIVO + IPI (n = 125)	SUN (n = 124)
Confirmed ORR (95% CI), %	41.9 (37-47)	26.8 (23-31)	39.1 (35-43)	32.4 (29-37)	29.6 (22-38)	51.6 (43-61)
P	< .0001		.0134		.0005	
Best overall response, 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 diferansiasyon
Nivolumab + Ipilumumab



Tannir N, Clin Cancer Res. 2021

Metastatik RCC /sarkomatoid diferansiasyon
Nivolumab + Ipilumumab



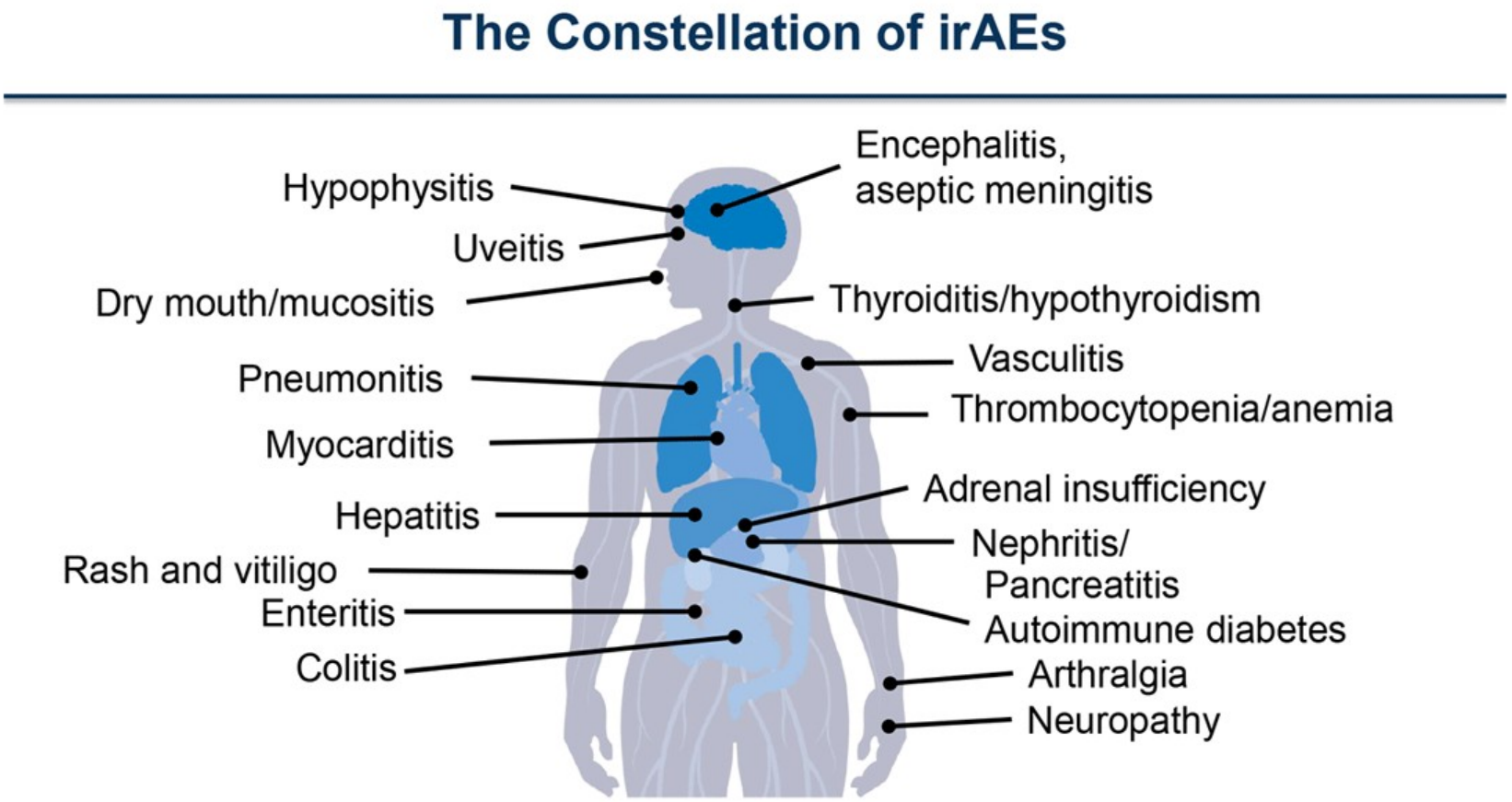
Tannir N, Clin Cancer Res. 2021

Metastatik RCC /sarkomatoid diferansiasyon
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)

Tannir N, Clin Cancer Res. 2021

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
İmmünoterapi/Toksisite



Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

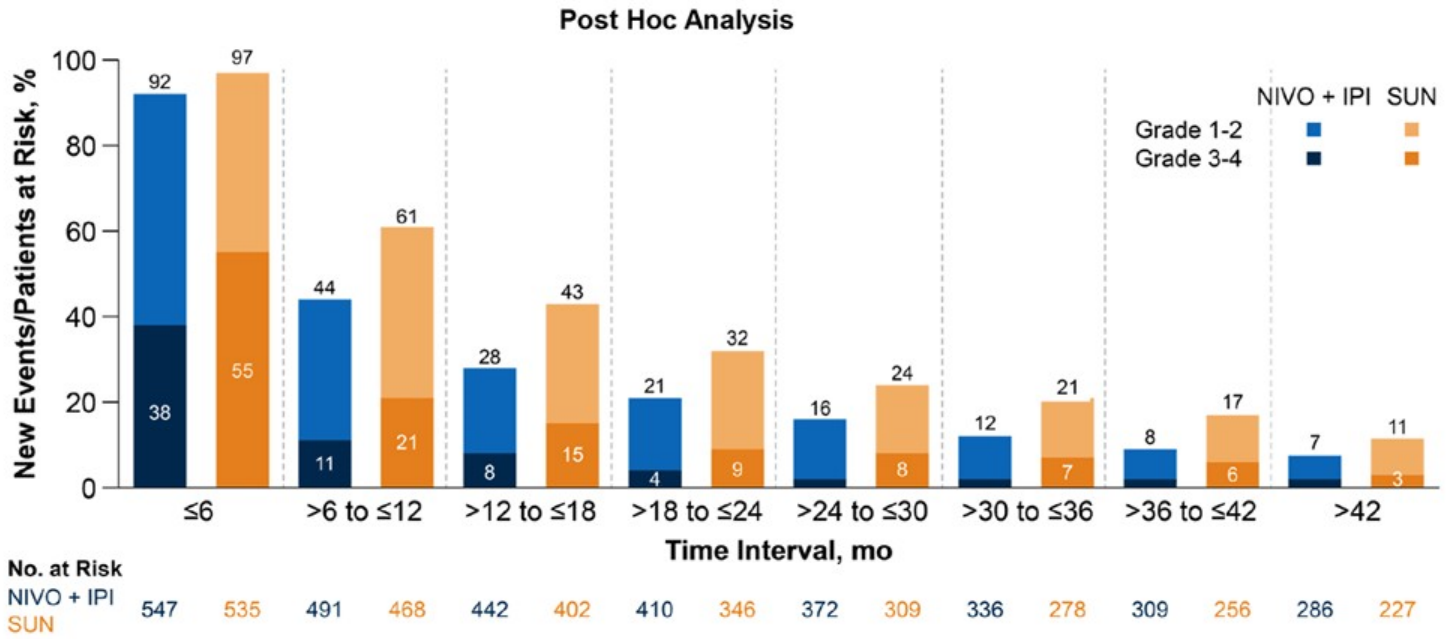
AE: Ipi + Nivo

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]

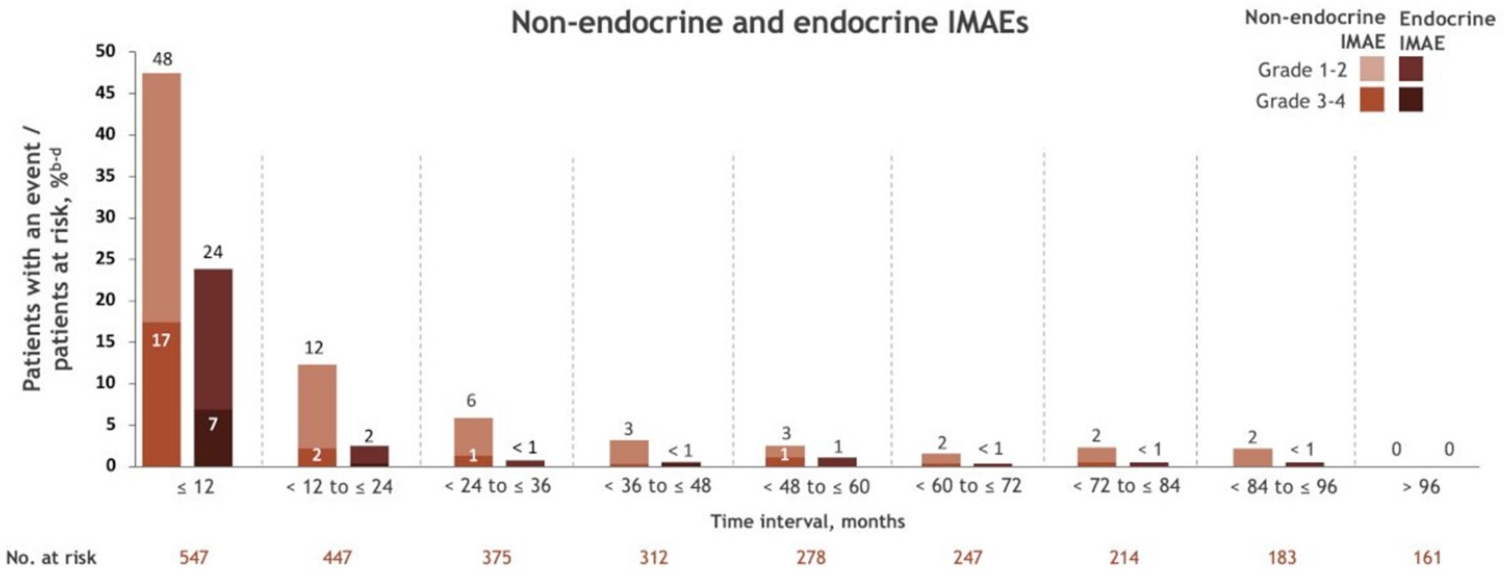


- A similar pattern over time was observed with treatment-related select AE incidence and corticosteroid use in the NIVO + IPI arm

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

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Ipilumumab

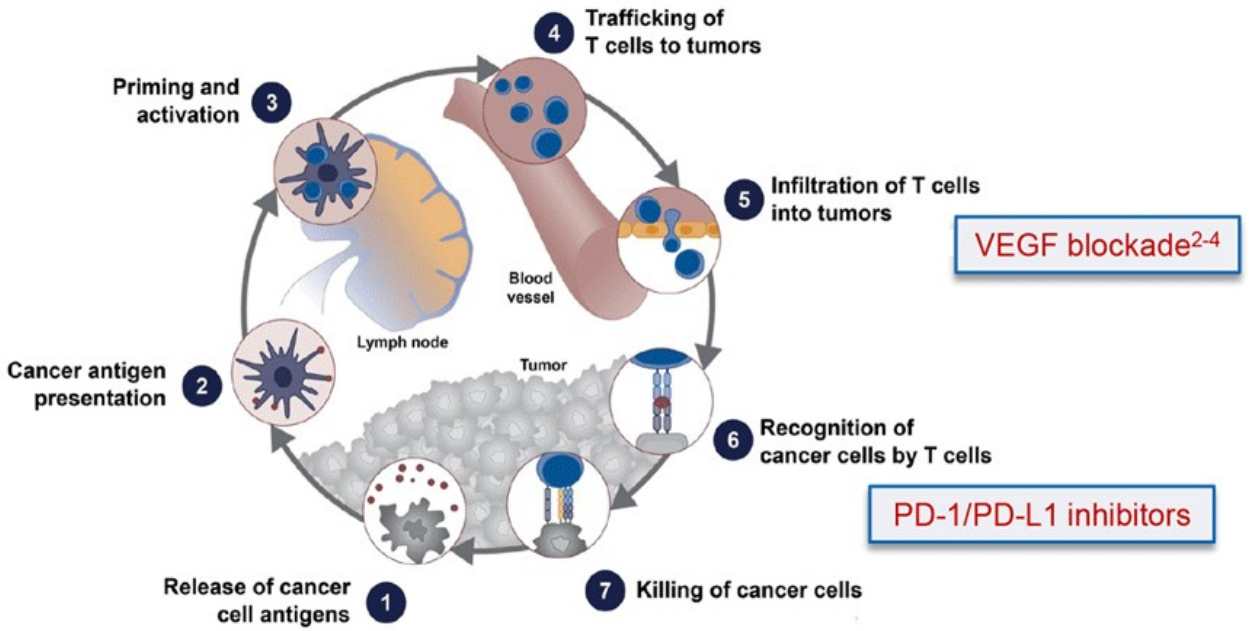
IMAEs over time with NIVO+IPI[a]



CheckMate 214, ASCO 2025

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Pembrolizumab + Axitinib

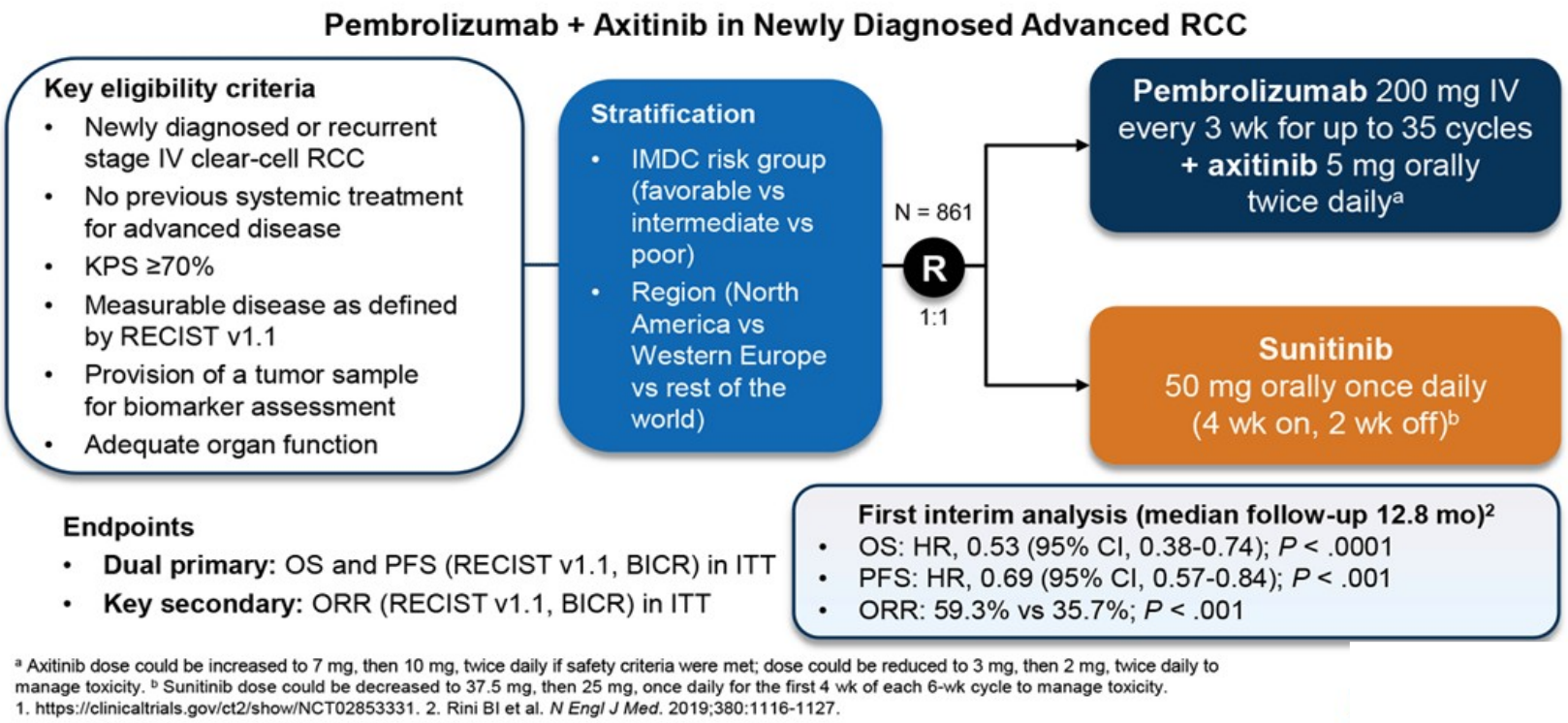
Synergy of VEGF Inhibition and PD-1/PD-L1 Blockade[1,2]



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]

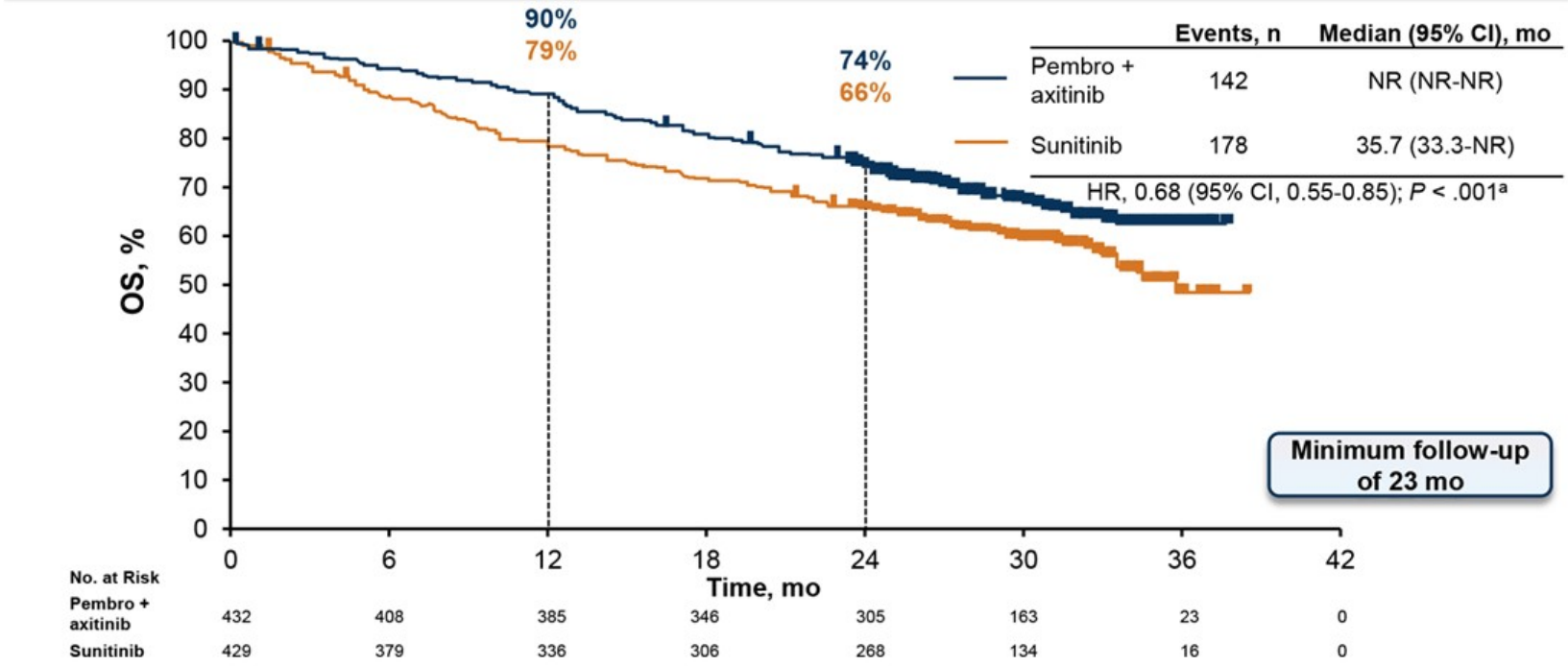


[a] Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b] Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wk of each 6-wk cycle to manage toxicity.

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

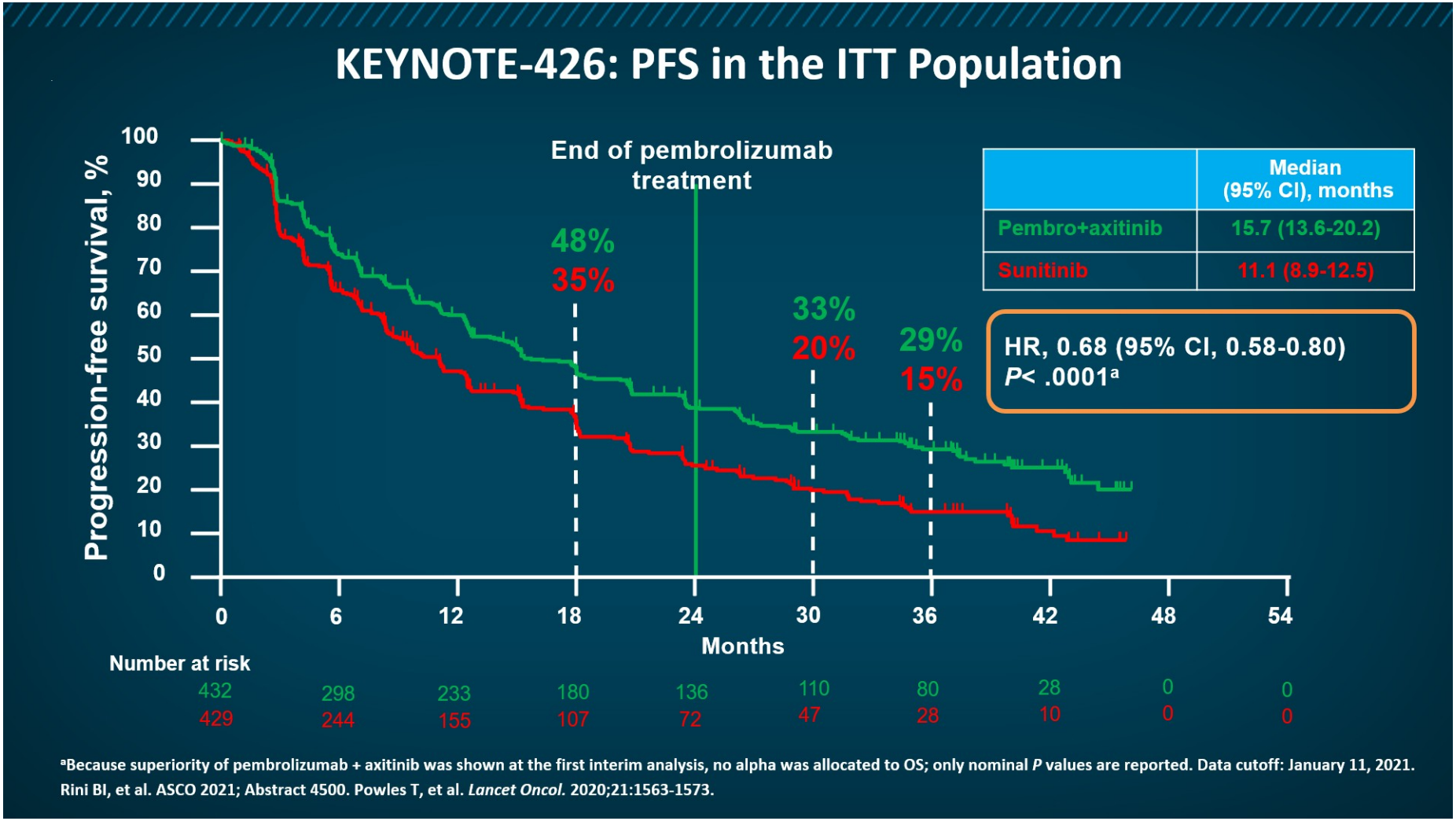
KEYNOTE-426: OS (ITT Population)[1]



[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

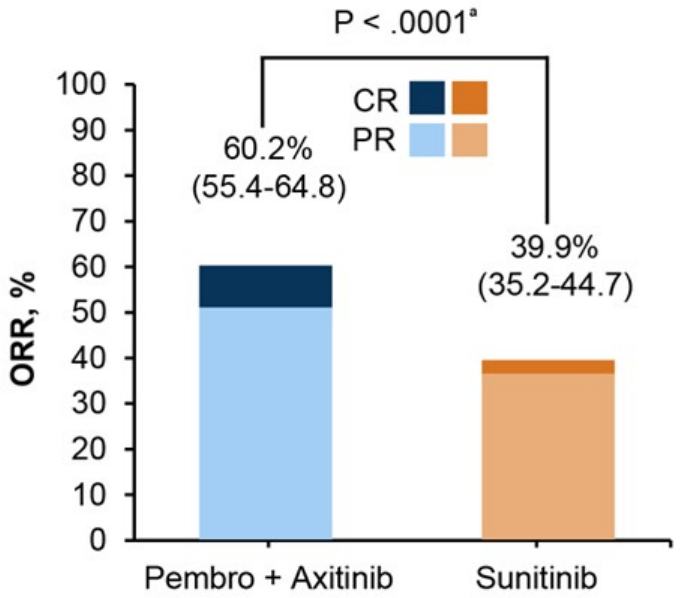


[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 11, 2021.

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]

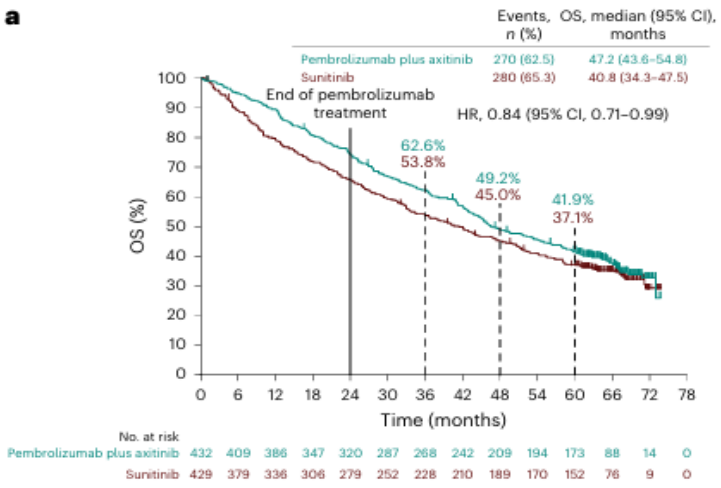


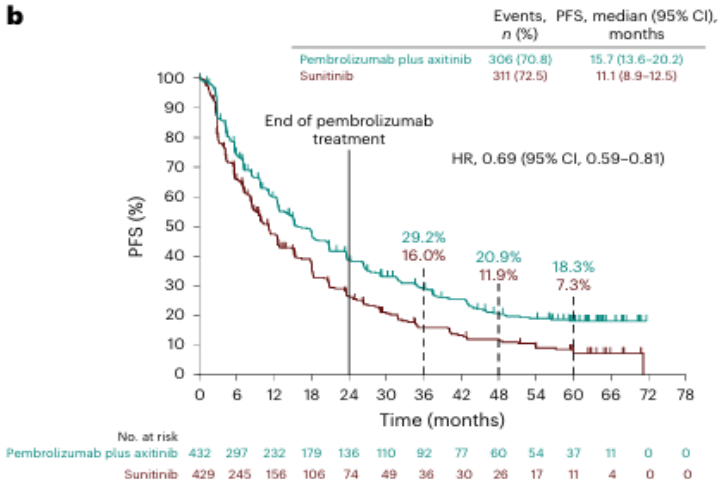
	Pembrolizumab + Axitinib (n = 432)	Sunitinib (n = 429)
Best response, n (%)		
CR	38.8 (8.8)	13 (3.0)
PR	222 (51.4)	158 (36.8)
SD	100 (23.1)	150 (35.0)
PD	49 (11.3)	74 (17.2)
NE[b]	16 (3.7)	28 (6.5)
NA[c]	7 (1.6)	6 (1.4)
Duration of response, median (range), mo	23.5 (1.4+ to 34.5+)	15.9 (2.3 to 31.8+)

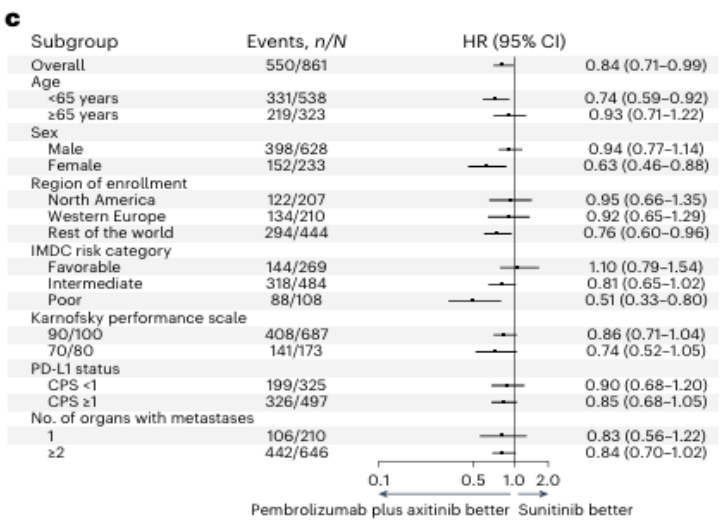
[a] Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to confirmed objective response; only nominal *P* values are reported. [b] Postbaseline assessment available but not evaluable (ie, all postbaseline assessments with insufficient data for 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.

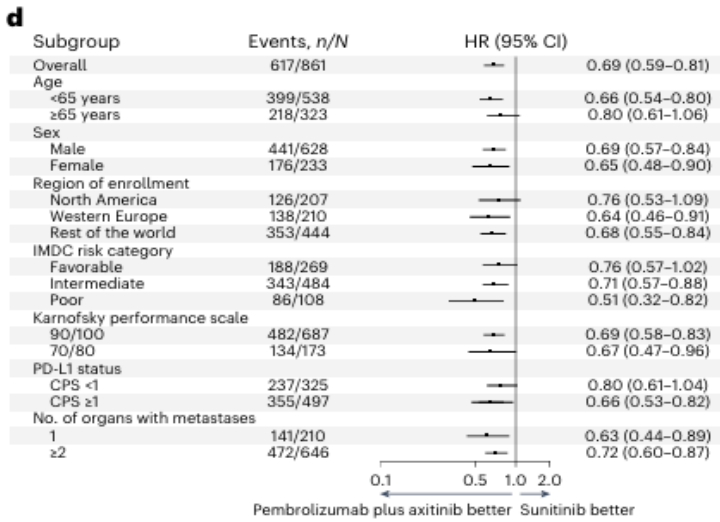
1. Plimack ER et al. ASCO 2020. Abstract 5001.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Pembrolizumab + Axitinib









Rini B, Nature medicine 2025. KEYNOTE-426 trial

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Pembrolizumab + Axitinib

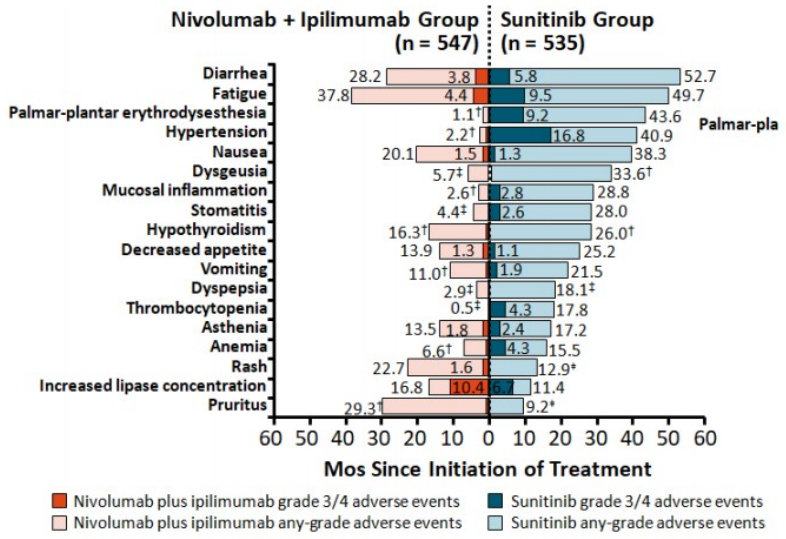
Efficacy in IMDC Subgroups

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.

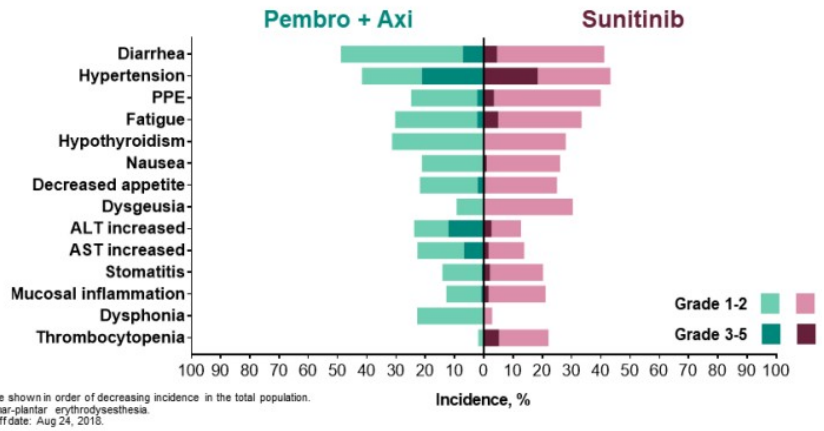
Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Toksisite

CheckMate 214



Motzer. Lancet Oncol. 2019;20:1370.

KEYNOTE-426



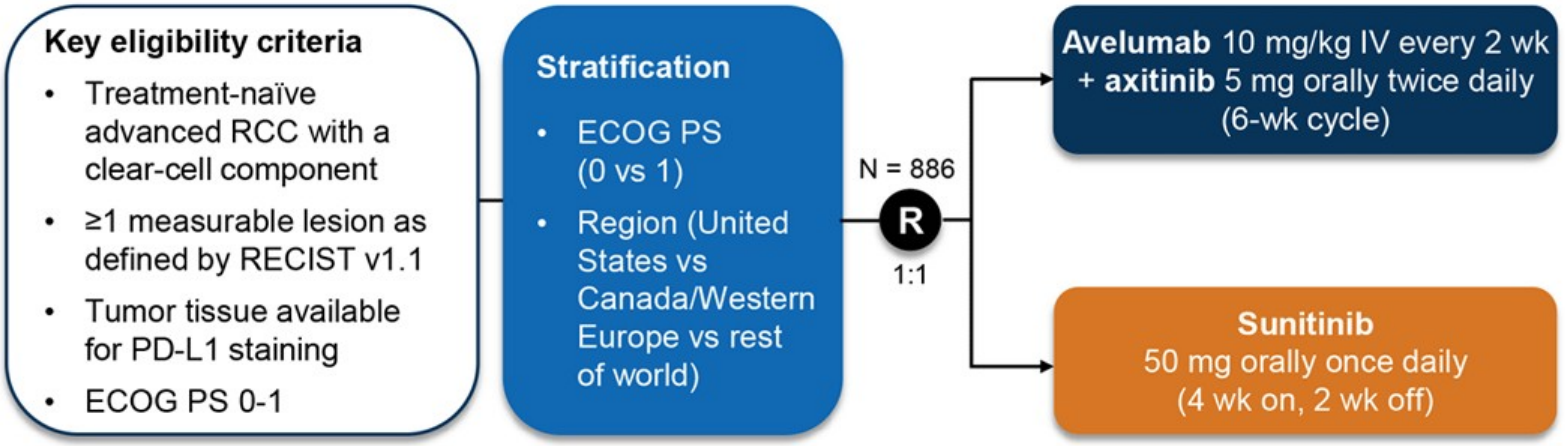
Powles. ASCO GU 2019.

- 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



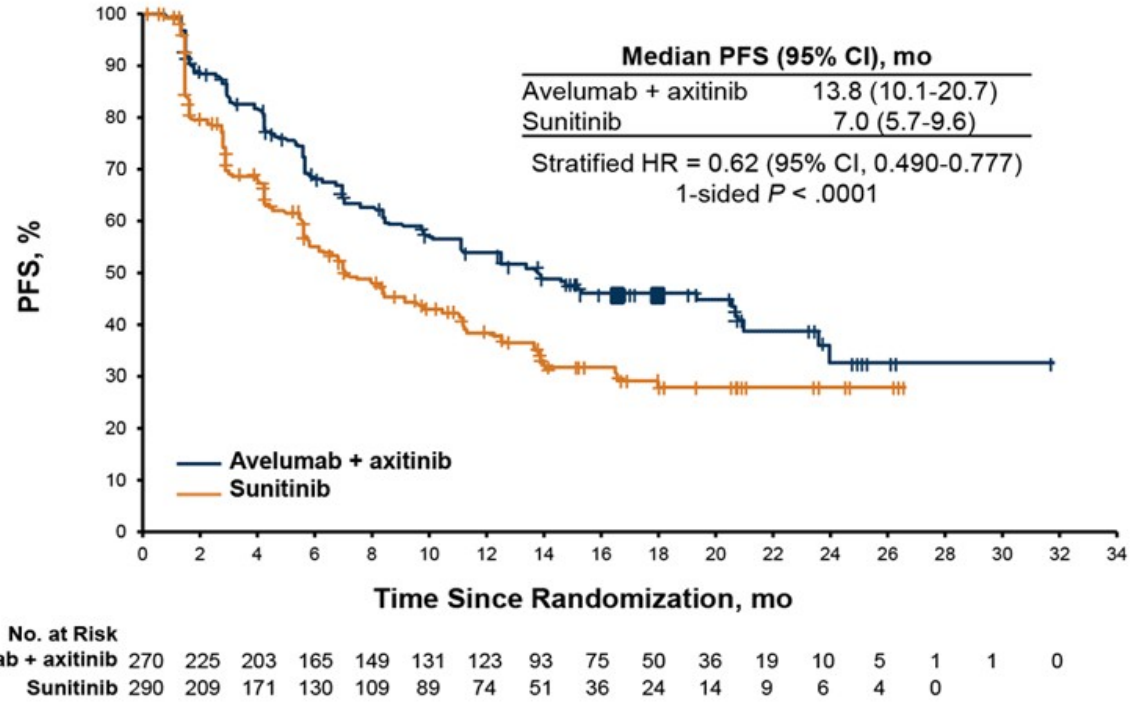
Endpoints

- **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]



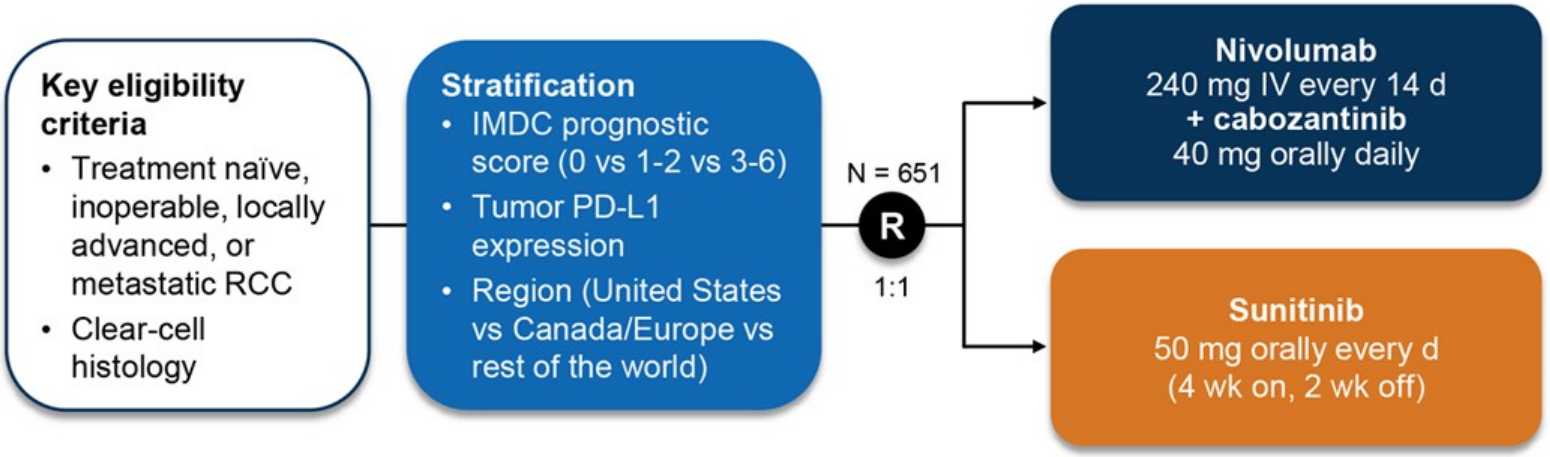
- No new safety signals
- ORR 55.9% (CR 5.6%) in the combination arm vs 27.2% (CR 2.4%) in the sunitinib arm
  - Similar response rates observed in the overall population
- OS data are still immature

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

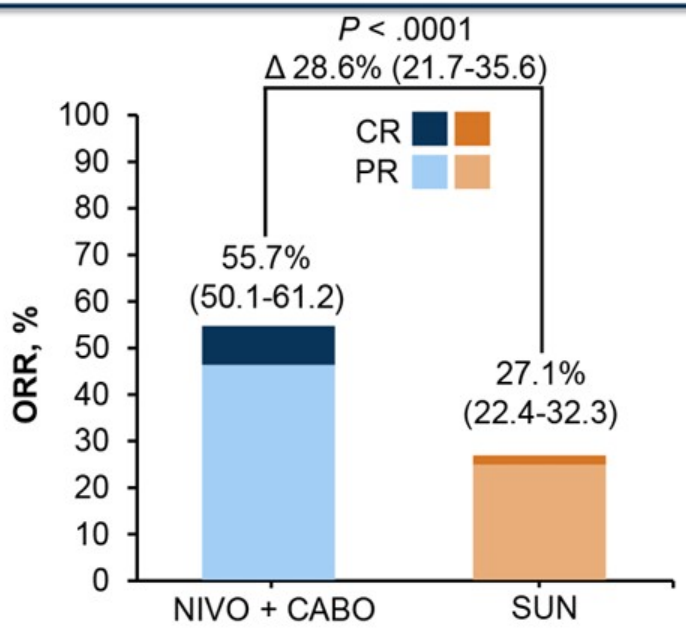


Endpoints
- **Primary:** PFS
- **Key Secondary:** OS, ORR, safety

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)

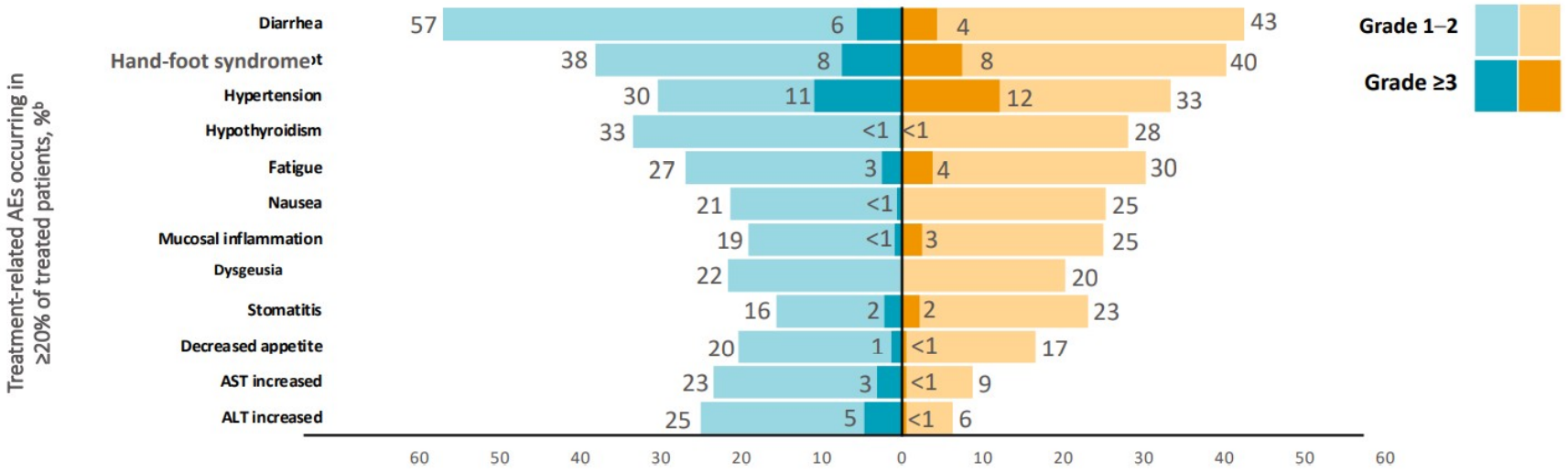
[a] BICR-assessed ORR and BOR by RECIST v1.1. [b] Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified. [c] Median time to and duration of response were calculated 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

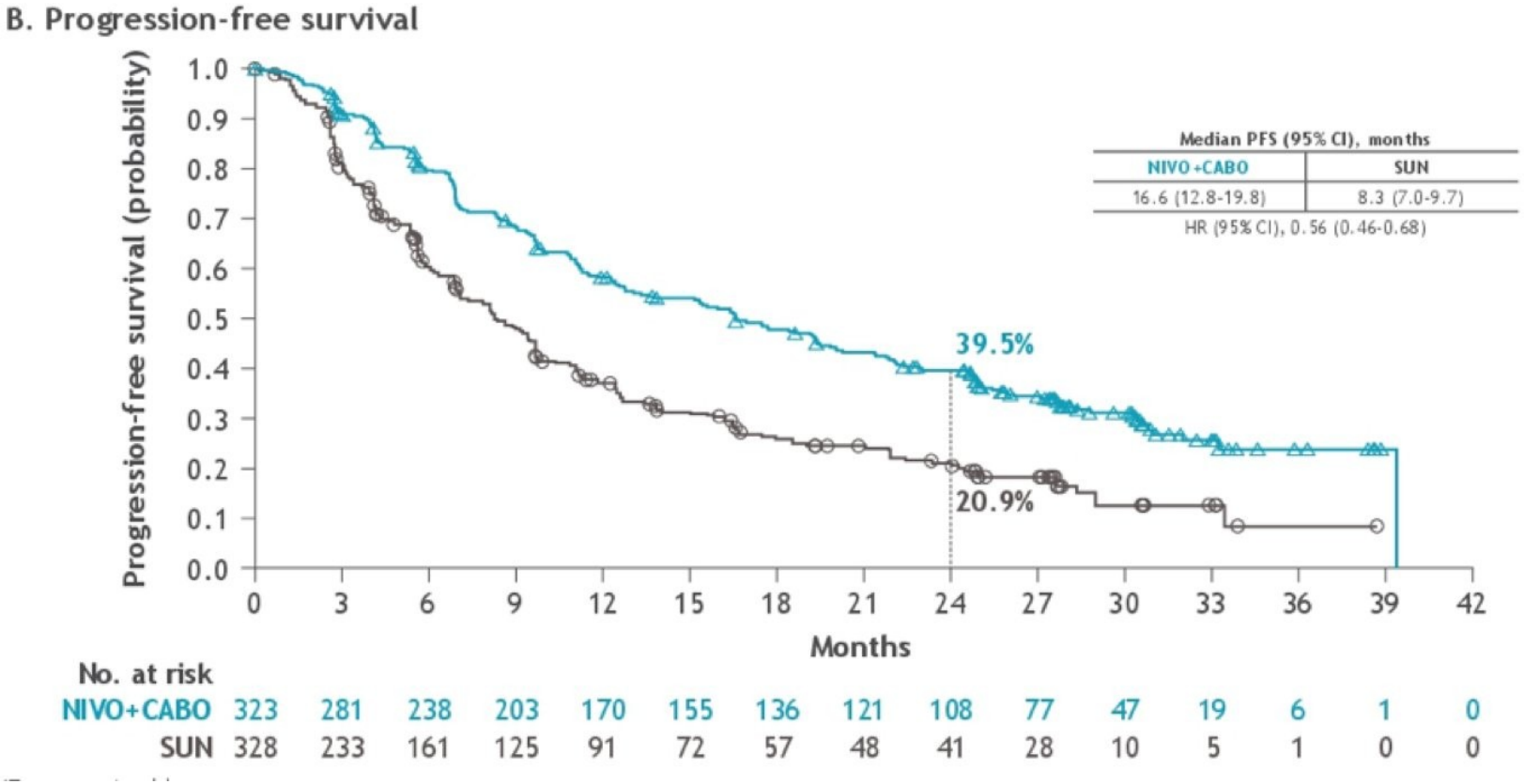
CheckMate 9ER Cabo/Nivo vs Sunitinib
Safety

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



CheckMate 9ER clinical trial

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

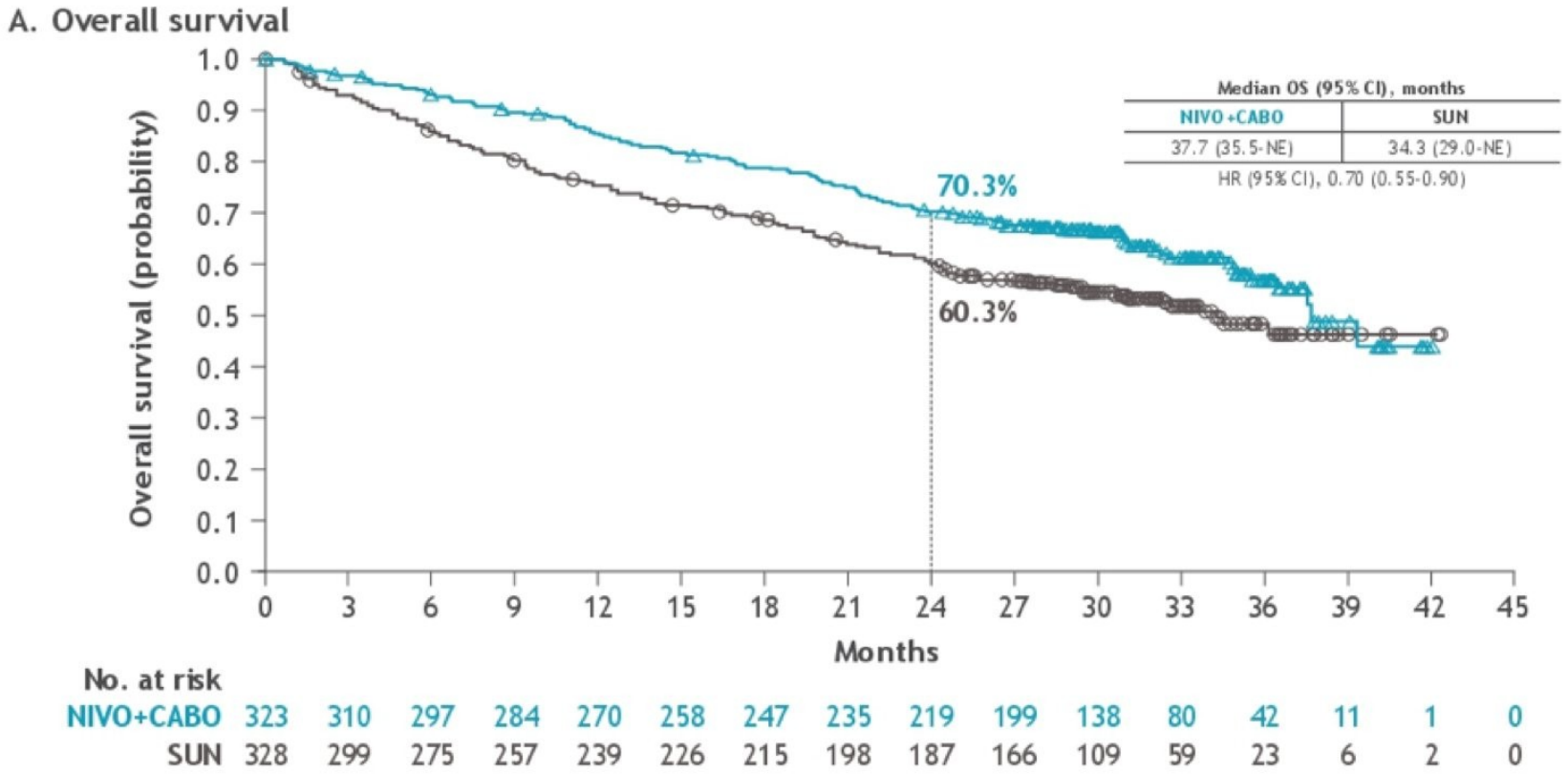
CheckMate 9ER

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)

CheckMate 9ER clinical trial

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib



CheckMate 9ER clinical trial

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

• CheckMate 9ER

Overall survival in subgroups

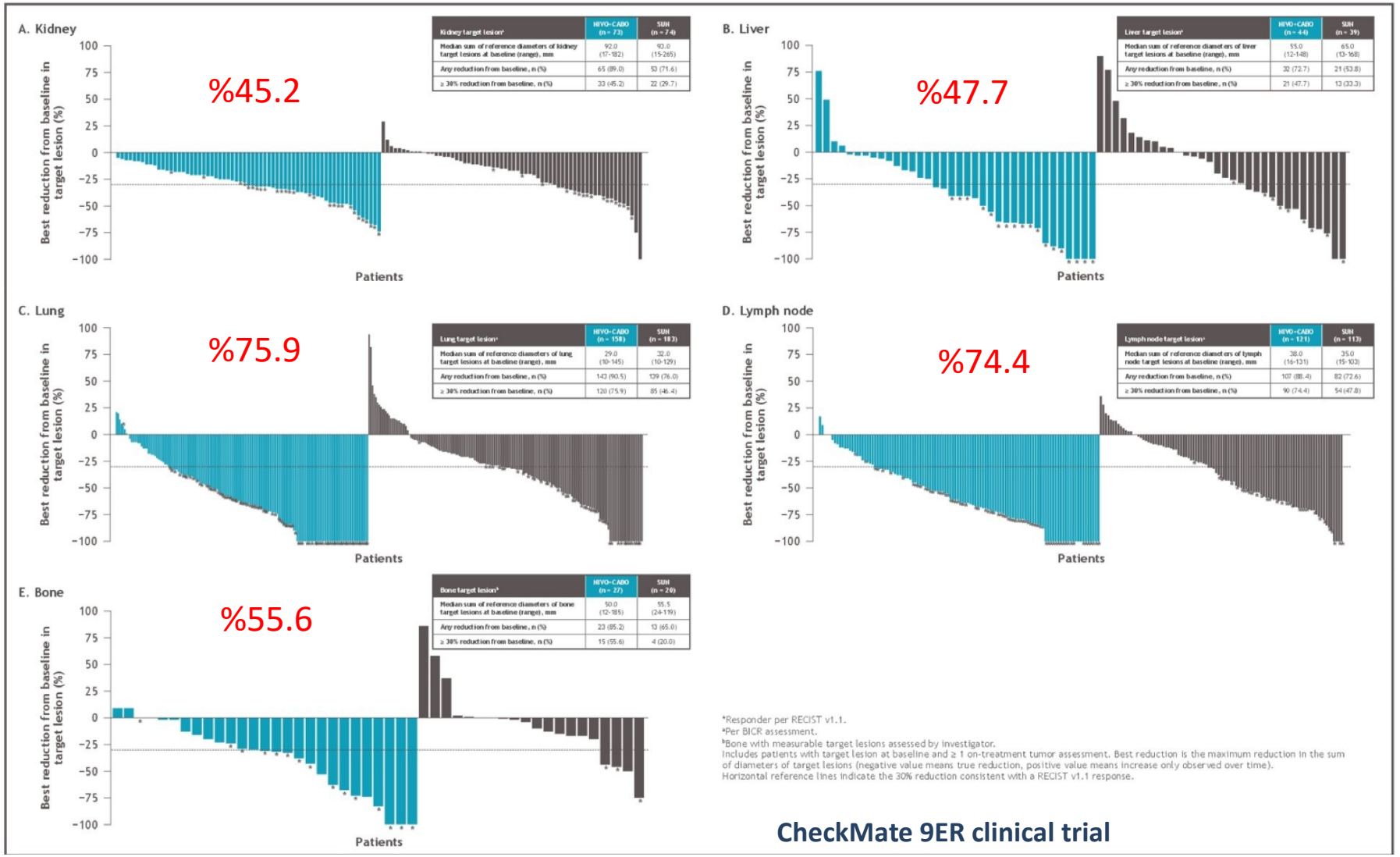
Subgroup	NIVO+CABO	SUN	HR for death (95% CI)
	Events/no. of patients		
Overall	67/323	99/328	0.60 (0.44-0.82)
Region			
US/Europe	26/158	45/161	0.48 (0.30-0.79)
Rest of world	41/165	54/167	0.71 (0.48-1.07)
IMDC prognostic risk			
Favorable	10/74	11/72	0.84 (0.35-1.97)
Intermediate	40/188	51/188	0.70 (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

CheckMate 9ER clinical trial

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



Kidney target lesion*	HIVO-CABO (n = 73)	SUN (n = 74)
Median sum of reference diameters of kidney target lesions at baseline (range), mm	92.0 (17-182)	93.0 (15-265)
Any reduction from baseline, n (%)	65 (89.0)	53 (71.6)
≥ 30% reduction from baseline, n (%)	33 (45.2)	22 (29.7)

Liver target lesion*	HIVO-CABO (n = 44)	SUN (n = 39)
Median sum of reference diameters of liver target lesions at baseline (range), mm	55.0 (12-148)	65.0 (13-168)
Any reduction from baseline, n (%)	32 (72.7)	21 (53.8)
≥ 30% reduction from baseline, n (%)	21 (47.7)	13 (33.3)

Lung target lesion*	HIVO-CABO (n = 158)	SUN (n = 183)
Median sum of reference diameters of lung target lesions at baseline (range), mm	29.0 (10-145)	32.0 (10-129)
Any reduction from baseline, n (%)	143 (90.5)	139 (76.0)
≥ 30% reduction from baseline, n (%)	120 (75.9)	85 (46.4)

Lymph node target lesion*	HIVO-CABO (n = 121)	SUN (n = 113)
Median sum of reference diameters of lymph node target lesions at baseline (range), mm	38.0 (16-131)	35.0 (15-103)
Any reduction from baseline, n (%)	107 (88.4)	82 (72.6)
≥ 30% reduction from baseline, n (%)	90 (74.4)	54 (47.8)

Bone target lesion*	HIVO-CABO (n = 27)	SUN (n = 20)
Median sum of reference diameters of bone target lesions at baseline (range), mm	50.0 (12-185)	55.5 (24-119)
Any reduction from baseline, n (%)	23 (85.2)	13 (65.0)
≥ 30% reduction from baseline, n (%)	15 (55.6)	4 (20.0)

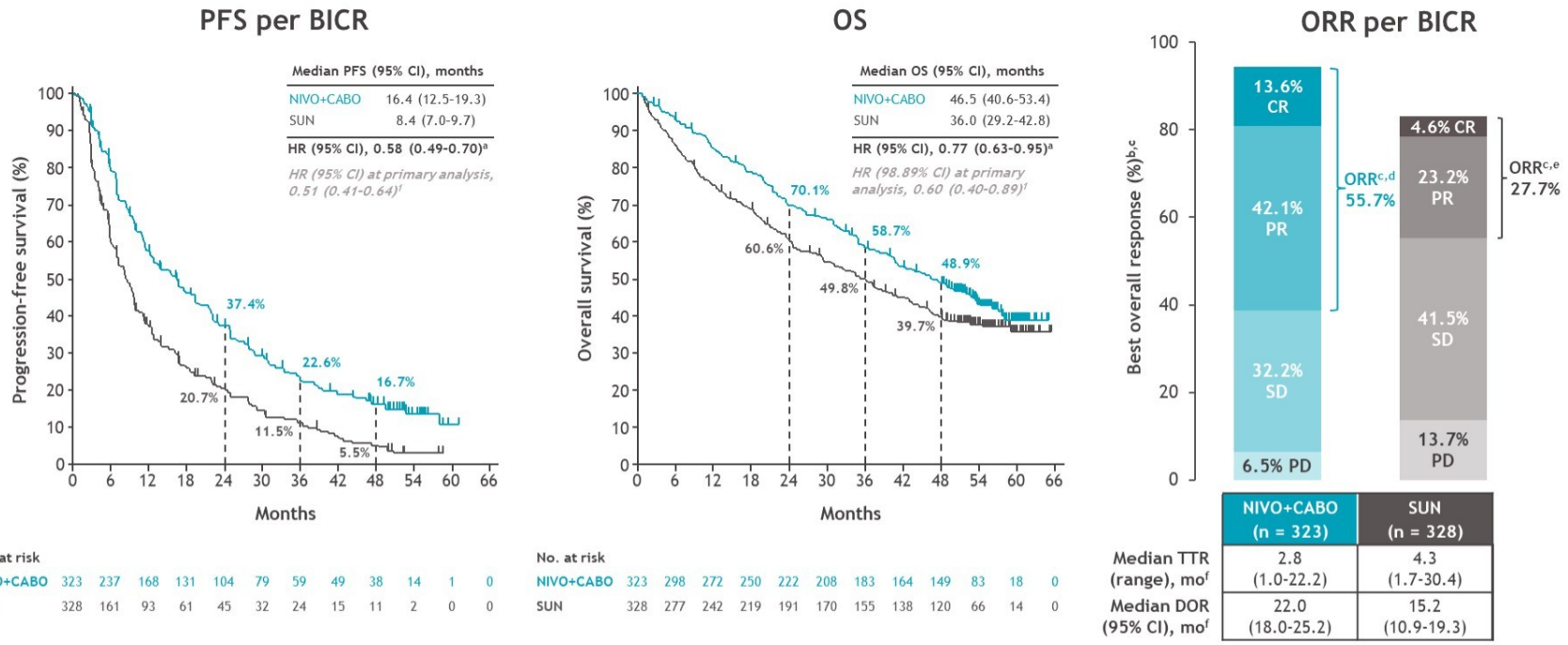
*Responder per RECIST v1.1.
*Per BICR assessment.
*Bone with measurable target lesions assessed by investigator.
Includes patients with target lesion at baseline and ≥ 1 on-treatment tumor assessment. Best reduction is the maximum reduction in the sum of diameters of target lesions (negative value means true reduction, positive value means increase only observed over time).
Horizontal reference lines indicate the 30% reduction consistent with a RECIST v1.1 response.

CheckMate 9ER clinical trial

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

CheckMate 9ER

PFS per BICR, OS, ORR per BICR in *ITT population*



	NIVO+CABO (n = 323)	SUN (n = 328)
Median TTR (range), mo[f]	2.8 (1.0-22.2)	4.3 (1.7-30.4)
Median DOR (95% CI), mo[f]	22.0 (18.0-25.2)	15.2 (10.9-19.3)

Median (range) follow-up for OS, 55.6 (48.1-68.1) months (ITT population).
[a]Stratified Cox proportional hazards model used for HR. [b]Unable to determine/not reported: 5.6% for NIVO+CABO; 17.1% for SUN. [c]No. of patients with ORR and BOR in NIVO+CABO arm: ORR, n = 180; CR, n = 44; PR, n = 136; SD, n = 104; PD, n = 21. No. of patients with ORR and BOR in SUN arm: ORR, n = 91; CR, n = 15; PR, n = 76; SD, n = 136; PD, n = 45. [d]95% CI, 50.1-61.2. [e]95% CI, 23.0-32.9. [f]TTR and DOR were calculated only for patients who had a CR or PR.

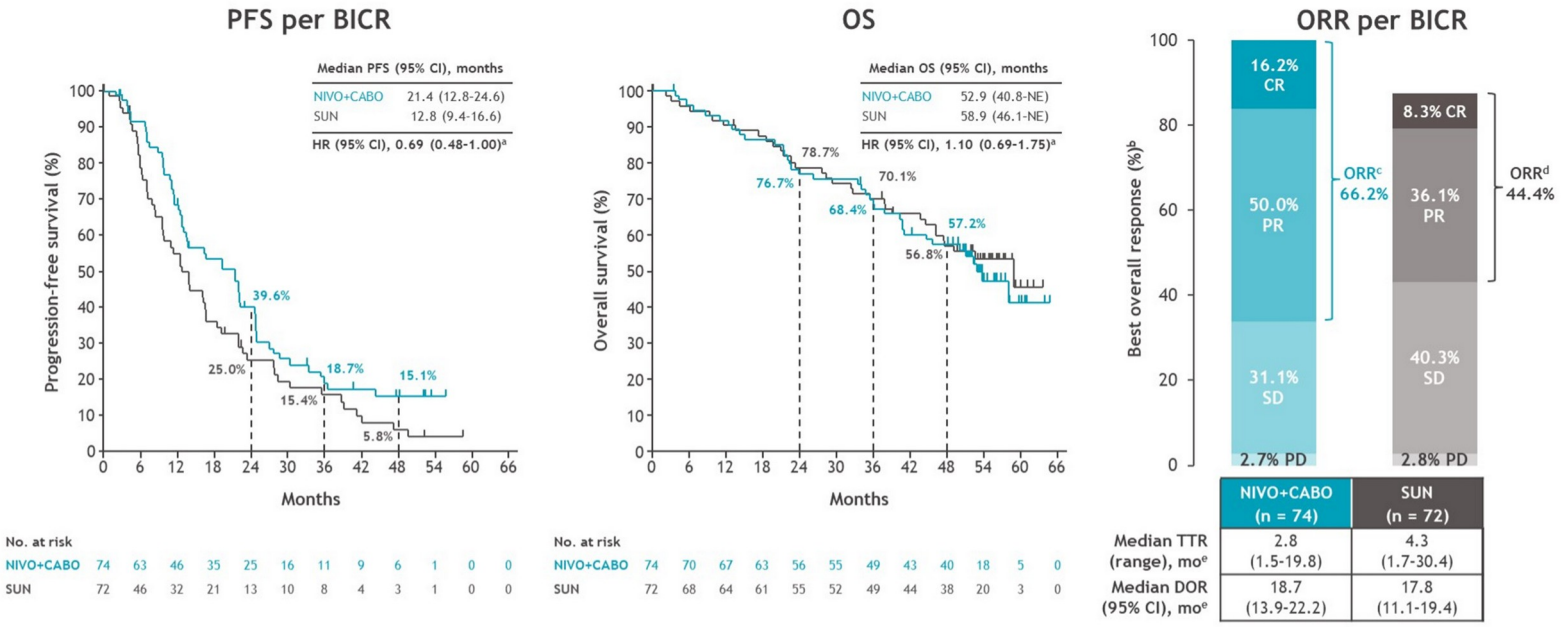
1. Choueiri TK, et al. *N Engl J Med* 2021;384:829-841.

CheckMate 9ER clinical trial, ASCO GO2025

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

CheckMate 9ER

PFS per BICR, OS, ORR per BICR in *IMDC favorable-risk population*



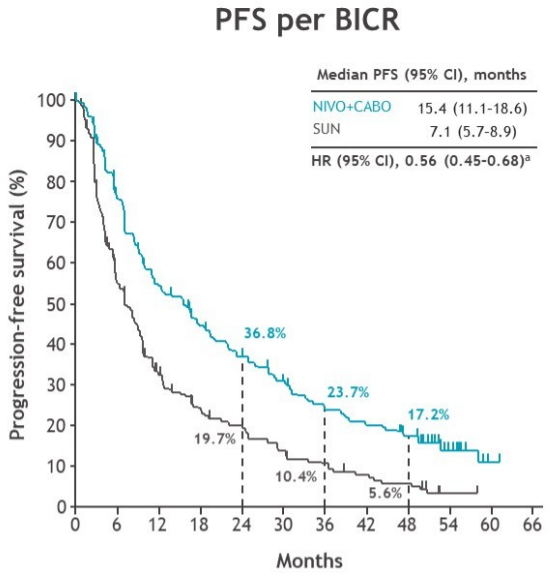
	NIVO+CABO (n = 74)	SUN (n = 72)
Median TTR (range), mo[e]	2.8 (1.5-19.8)	4.3 (1.7-30.4)
Median DOR (95% CI), mo[e]	18.7 (13.9-22.2)	17.8 (11.1-19.4)

Median (range) follow-up for OS, 55.6 (48.1-68.1) months (ITT population).
[a]Unstratified Cox proportional hazards model used for HR. [b]Unable to determine/not reported: 0.0% for NIVO+CABO; 12.5% for SUN. [c]95% CI, 54.3-76.8. [d]95% CI, 32.7-56.6. [e]TTR and DOR were calculated only for patients who had a CR or PR.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

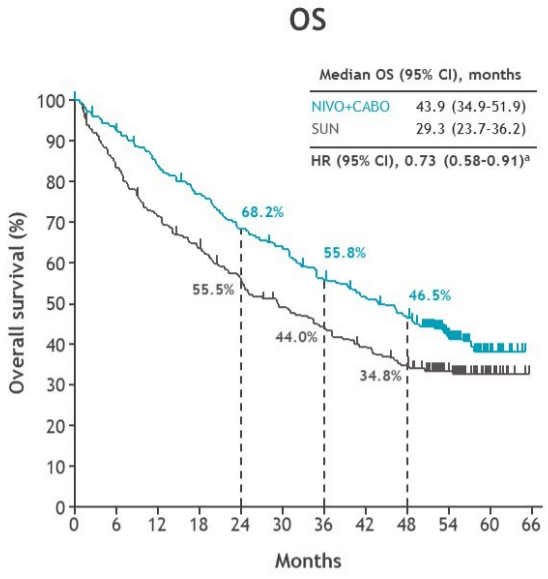
CheckMate 9ER

PFS per BICR, OS, ORR per BICR in *IMDC intermediate/poor-risk population*



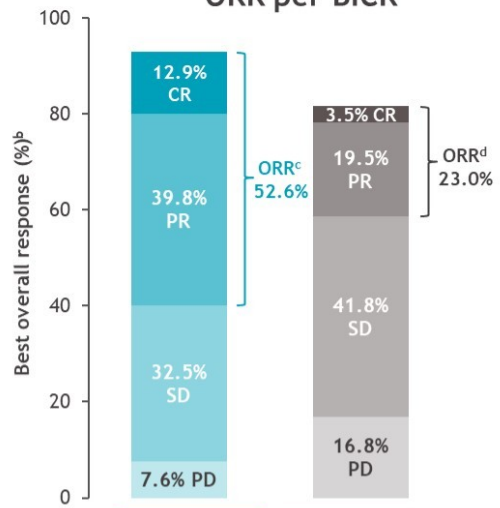
No. at risk

NIVO+CABO	249	174	122	96	79	63	48	40	32	13	1	0
SUN	256	115	61	40	32	22	16	11	8	1	0	0



No. at risk

NIVO+CABO	249	228	205	187	166	153	134	121	109	65	13	0
SUN	256	209	178	158	136	118	106	94	82	46	11	0



	NIVO+CABO (n = 249)	SUN (n = 256)
Median TTR (range), mo[e]	2.8 (1.0-22.2)	4.4 (1.7-18.1)
Median DOR (95% CI), mo[e]	23.1 (17.3-30.5)	13.8 (7.1-23.5)

Median (range) follow-up for OS, 55.6 (48.1-68.1) months (ITT population).
[a]Unstratified Cox proportional hazards model used for HR. [b]Unable to determine/not reported: 7.2% for NIVO+CABO; 18.4% for SUN. [c]95% CI, 46.2-58.9. [d]95% CI, 18.0-28.7. [e]TTR and DOR were calculated only for patients who had a CR or PR.

CheckMate 9ER clinical trial

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

CheckMate 9ER

Efficacy by baseline organ sites of metastases

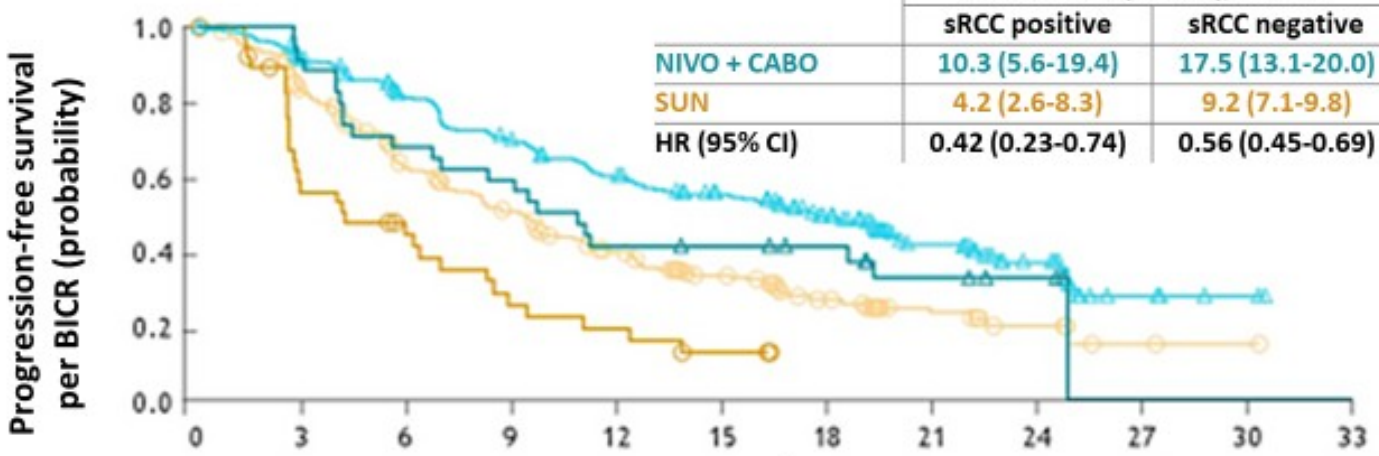
- PFS, OS, and ORR favored NIVO+CABO versus SUN in subgroups by baseline organ sites of metastases shown here

Outcome	Liver[a,b]		Bone[a,b]		Lung[a,b]	
	NIVO+CABO (n = 73)	SUN (n = 55)	NIVO+CABO (n = 79)	SUN (n = 73)	NIVO+CABO (n = 241)	SUN (n = 251)
Median PFS (95% CI), mo	10.9 (7.0-15.2)	6.2 (2.9-8.3)	13.8 (8.3-20.1)	4.4 (3.8-8.2)	16.4 (12.3-21.4)	8.3 (6.9-9.7)
HR (95% CI)[c]	0.54 (0.36-0.81)		0.45 (0.30-0.66)		0.56 (0.46-0.69)	
Median OS (95% CI), mo	37.6 (23.5-49.9)	22.1 (9.8-29.3)	34.8 (21.4-NE)	20.7 (12.5-25.7)	47.5 (40.6-56.1)	32.6 (24.9-39.7)
HR (95% CI)[c]	0.62 (0.41-0.95)		0.57 (0.38-0.84)		0.73 (0.58-0.92)	
ORR (95% CI), %	52.1 (40.0-63.9)	21.8 (11.8-35.0)	49.4 (37.9-60.9)	9.6 (3.9-18.8)	57.3 (50.8-63.6)	28.3 (22.8-34.3)

[a]An exploratory analysis of efficacy outcomes by baseline organ sites of metastases was conducted in the ITT population (prespecified for bone; post hoc for liver and lung). [b]Within each subgroup, all patients had metastasis within the specified site but may have had lesions in more than 1 site. [c]Unstratified Cox proportional hazards model used for HR.

Metastatik RCC/ sarkomatoid Birinci Basamak Tedavi Seçenekleri
Nivolumab + Cabozantinib

Progression-Free Survival per BICR by Sarcomatoid Histology



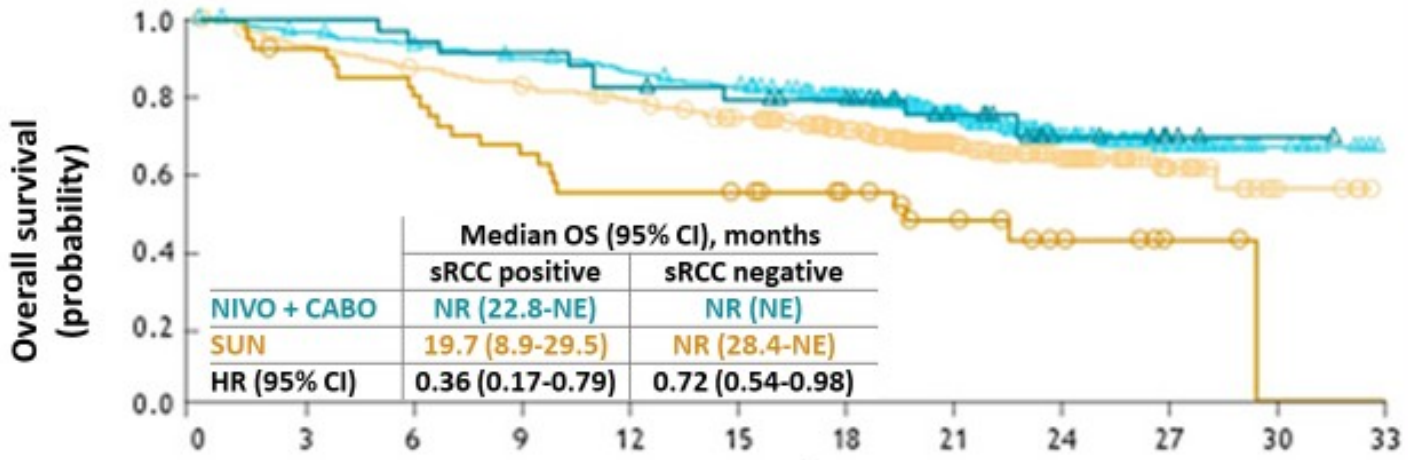
	Median PFS (95% CI), months	
	sRCC positive	sRCC negative
NIVO + CABO	10.3 (5.6-19.4)	17.5 (13.1-20.0)
SUN	4.2 (2.6-8.3)	9.2 (7.1-9.8)
HR (95% CI)	0.42 (0.23-0.74)	0.56 (0.45-0.69)

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



	Median OS (95% CI), months	
	sRCC positive	sRCC negative
NIVO + CABO	NR (22.8-NE)	NR (NE)
SUN	19.7 (8.9-29.5)	NR (28.4-NE)
HR (95% CI)	0.36 (0.17-0.79)	0.72 (0.54-0.98)

No. at risk												
NIVO + CABO sRCC positive	34	34	32	31	28	26	24	16	7	3	1	0
SUN sRCC positive	41	37	32	26	22	21	17	12	6	2	0	0
NIVO + CABO sRCC negative	289	274	263	252	241	229	196	131	77	37	9	0
SUN sRCC negative	287	258	240	228	214	196	172	106	56	20	4	0

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

Metastatik RCC /sarkomatoid diferansiasyon
Tirozin kinaz inhibitörü+Immune checkpoint inhibitörü

IO-VEGF Combinations for Sarcomatoid RCC

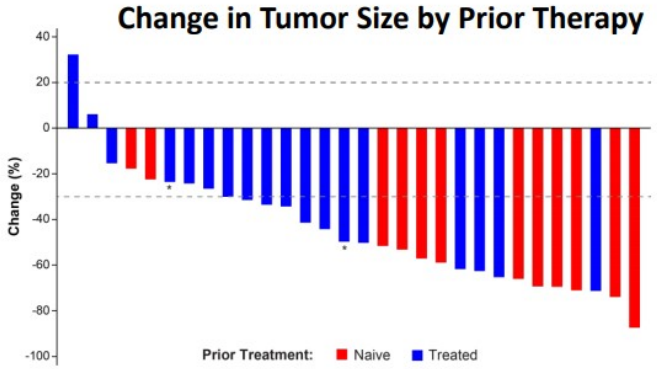
Trial	Phase	Histology	Sarcomatoid	ORR	PFS	OS
IMmotion-151 – Atezo + Bevacizumab	III	cc	142/915 (15.5%)	49%	8.3 months	21.7 months
Javelin 101 – Avelumab + Axitinib	III	cc	108/886 (12.2%)	46.8%	7.0 months	NR
Keynote-426 – Pembro + Axitinib	III	cc	105/861 (12.2%)	58.8%	Not reached	Not reached
Checkmate-9ER – Nivo + Cabozantinib	III	cc	75/651 (11.5%)	55.9%	10.9 months	Not reached
Clear – Pembrolizumab + Lenvatinib	III	cc	49/712 (6.8%)	60.7%	11 months	Not reached
Atezo + Bevacizumab	II	cc + ncc	26/60 (43%)	cc 50%/ncc 38%	NR	NR

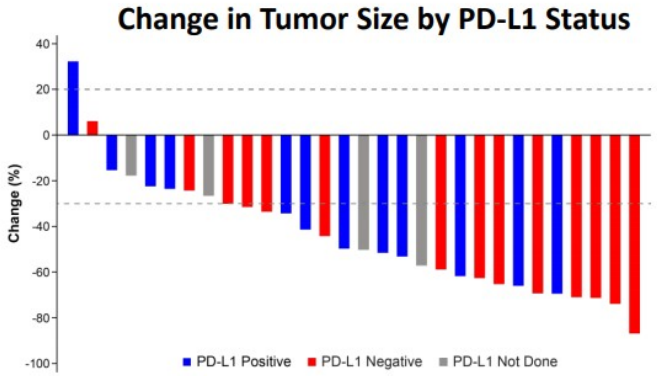
Ncc=Non-clear cell; cc=Clear cell; ORR=Objective response rate; PFS=Progression free survival; OS=Overall survival; NR=Not recorded.

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)

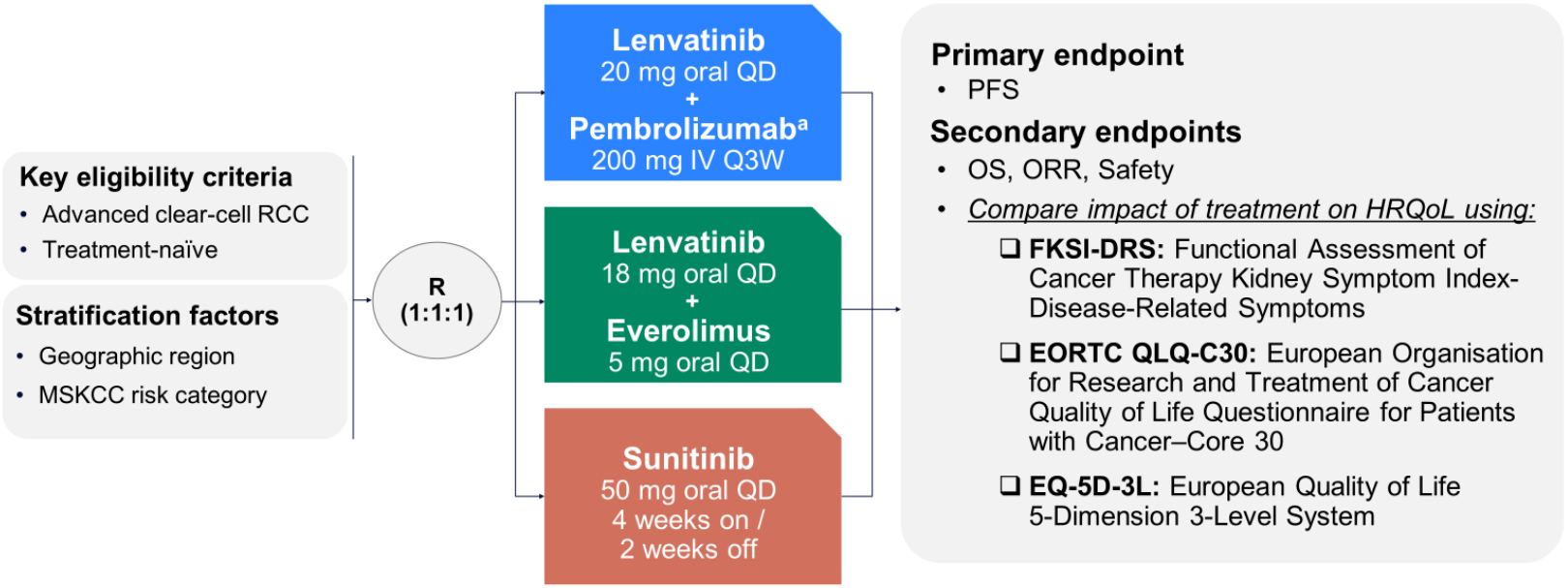




ESMO 2017

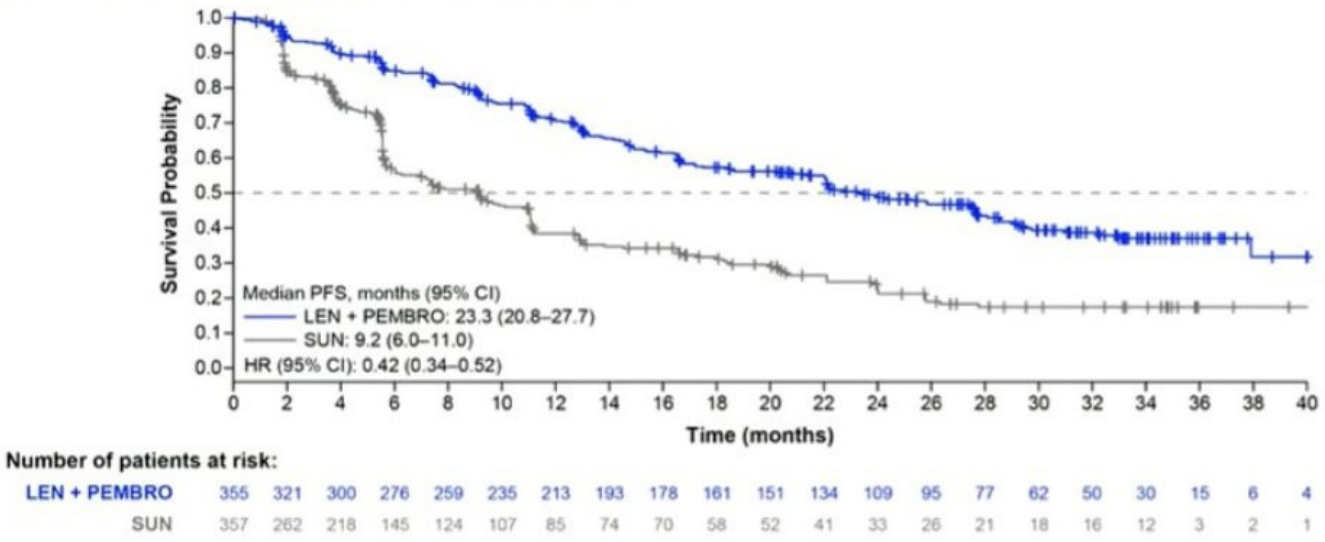
Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Lenvatinib + Pembrolizumab

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.

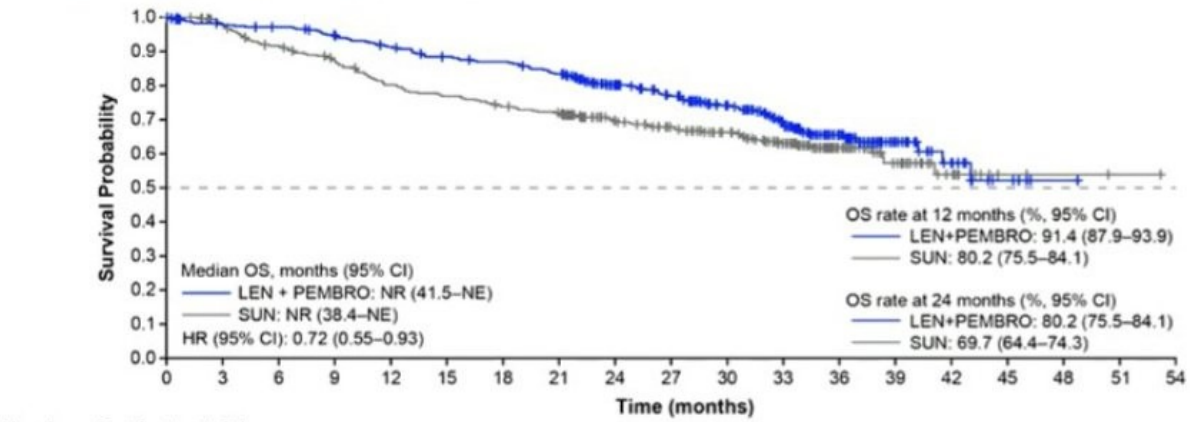
Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Lenvatinib + Pembrolizumab



	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)

CLEAR Trial

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Lenvatinib + Pembrolizumab



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

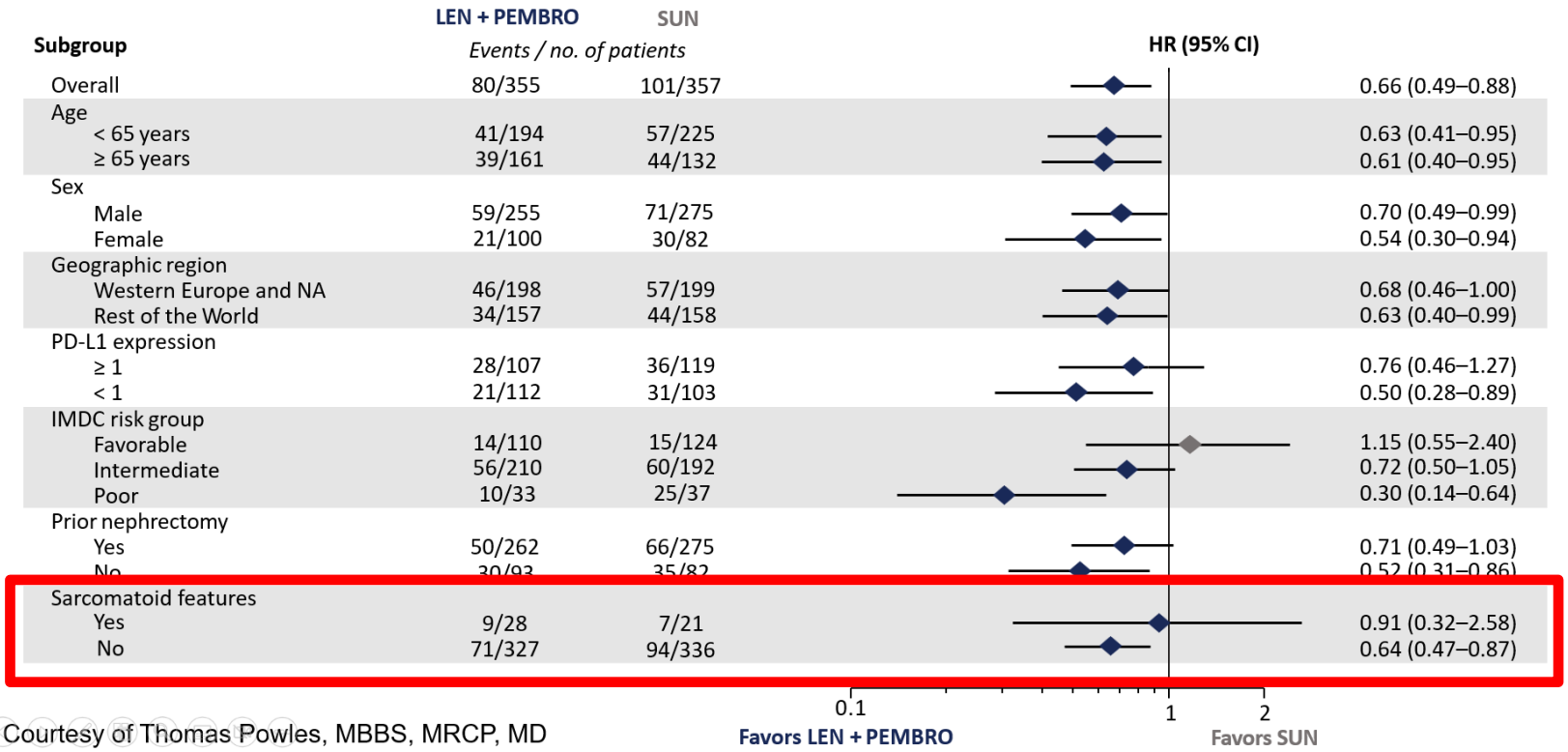
Beyond the median duration of follow-up, there was a high rate of censoring

	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)*

CLEAR Trial

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

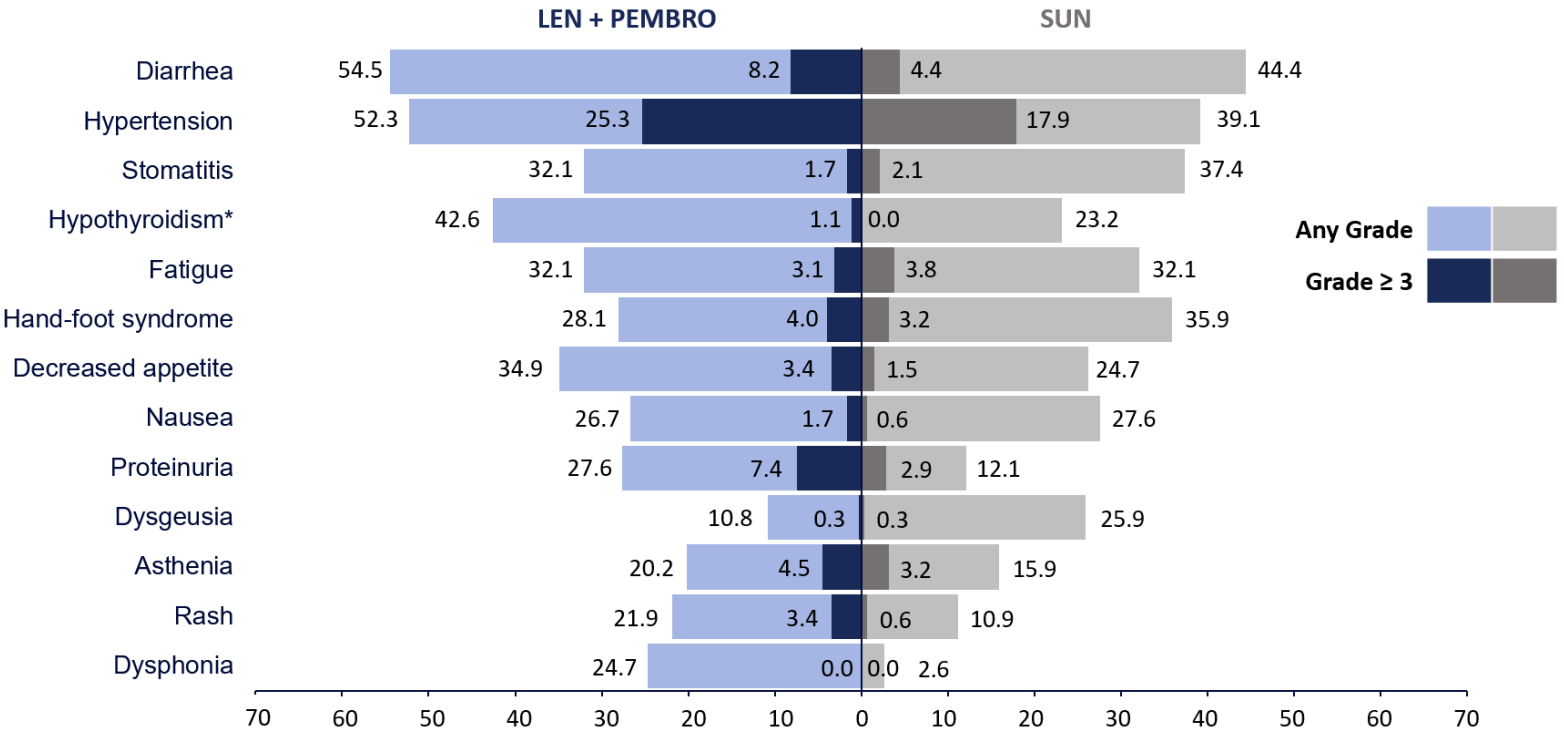
Efficacy Summary

	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 *P*-value	**0.39 (0.32–0.49)** < 0.001	**0.65 (0.53–0.80)** < 0.001	-- --
Median OS, mo (95% CI)	NR (33.6–NE)	NR (NE)	NR (NE)
Stratified HR (95% CI) vs SUN *P*-value	**0.66 (0.49–0.88)** 0.005	**1.15 (0.88–1.50)** 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

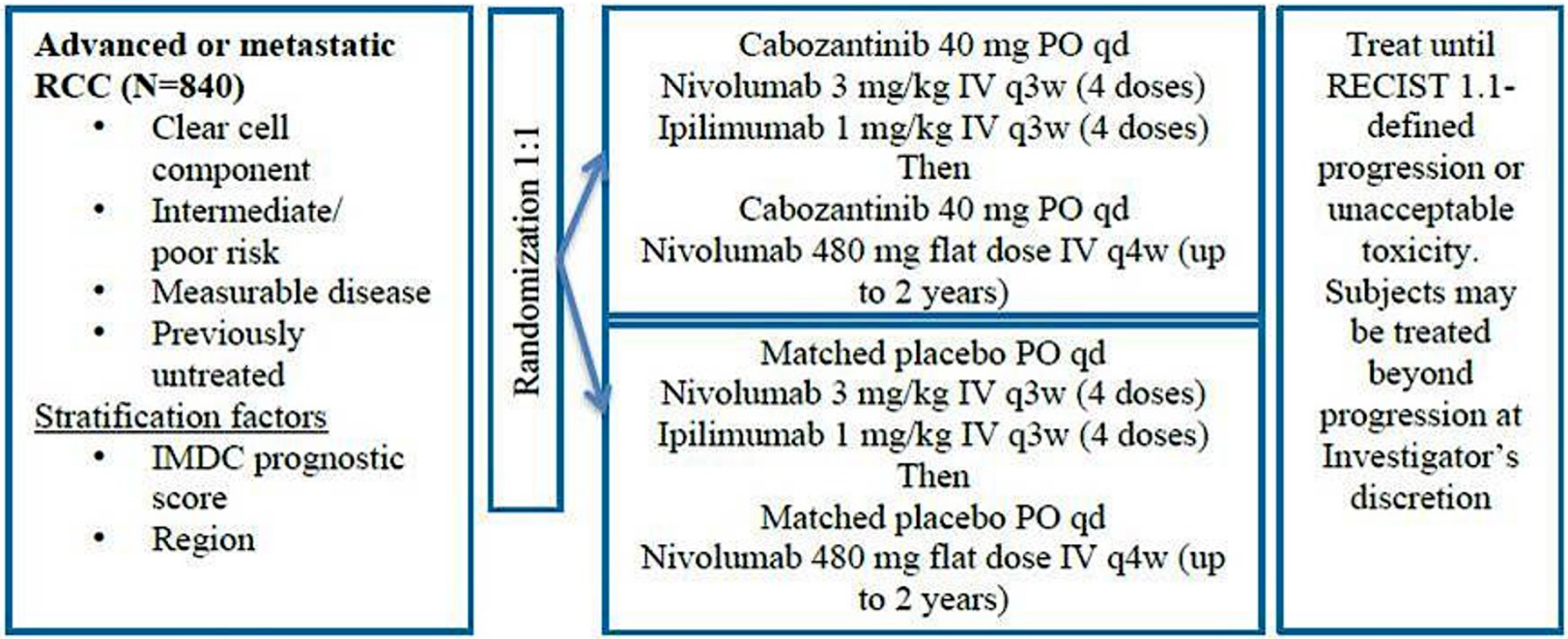
TRAEs With Frequency ≥ 20%



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.

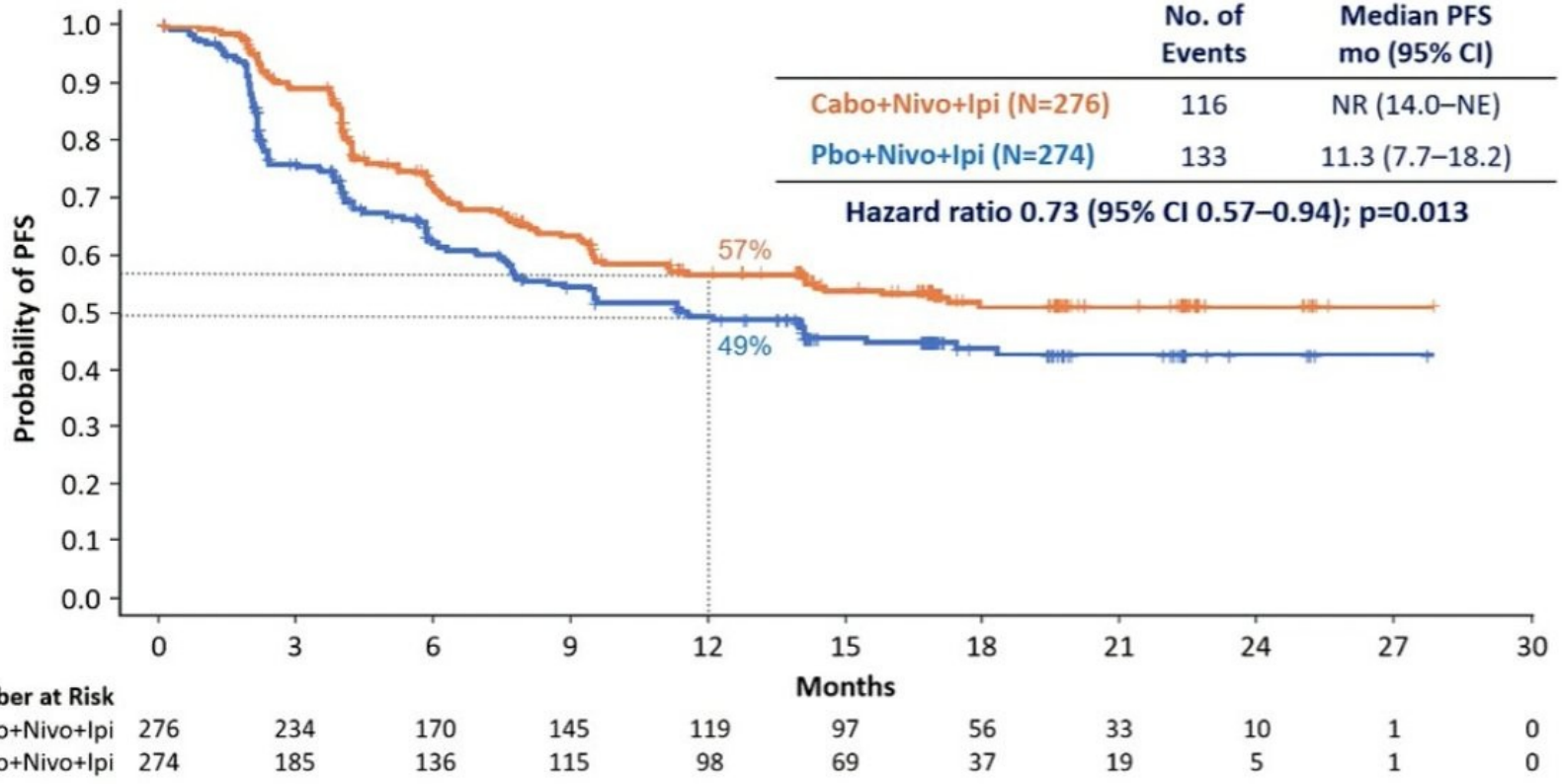
Courtesy of Thomas Powles, MBBS, MRCP, MD

COSMIC-313



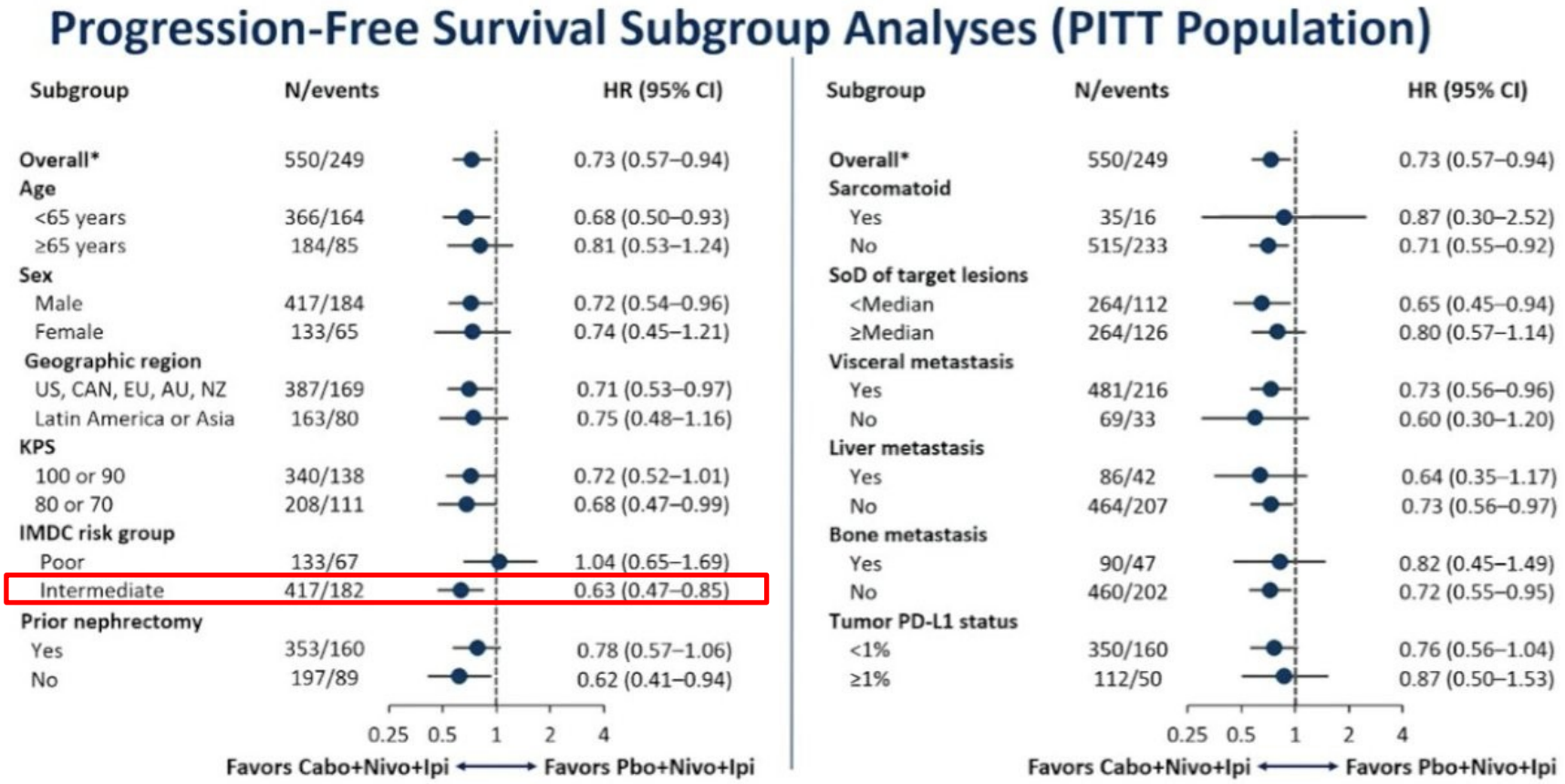
IMDC, international metastatic renal cell carcinoma database consortium; IV, intravenous; PO, oral administration; qd, once daily; q3(4)w once every 3(4) weeks; RECIST, response evaluation criteria in solid tumors; RCC, renal cell carcinoma

Progression-Free Survival: Final Analysis (PITT Population)



Cosmic 313 clinical trial

Metastatik RCC Birinci Basamak Tedavi
Nivolumab + Ipilumumab+Cabozantinib



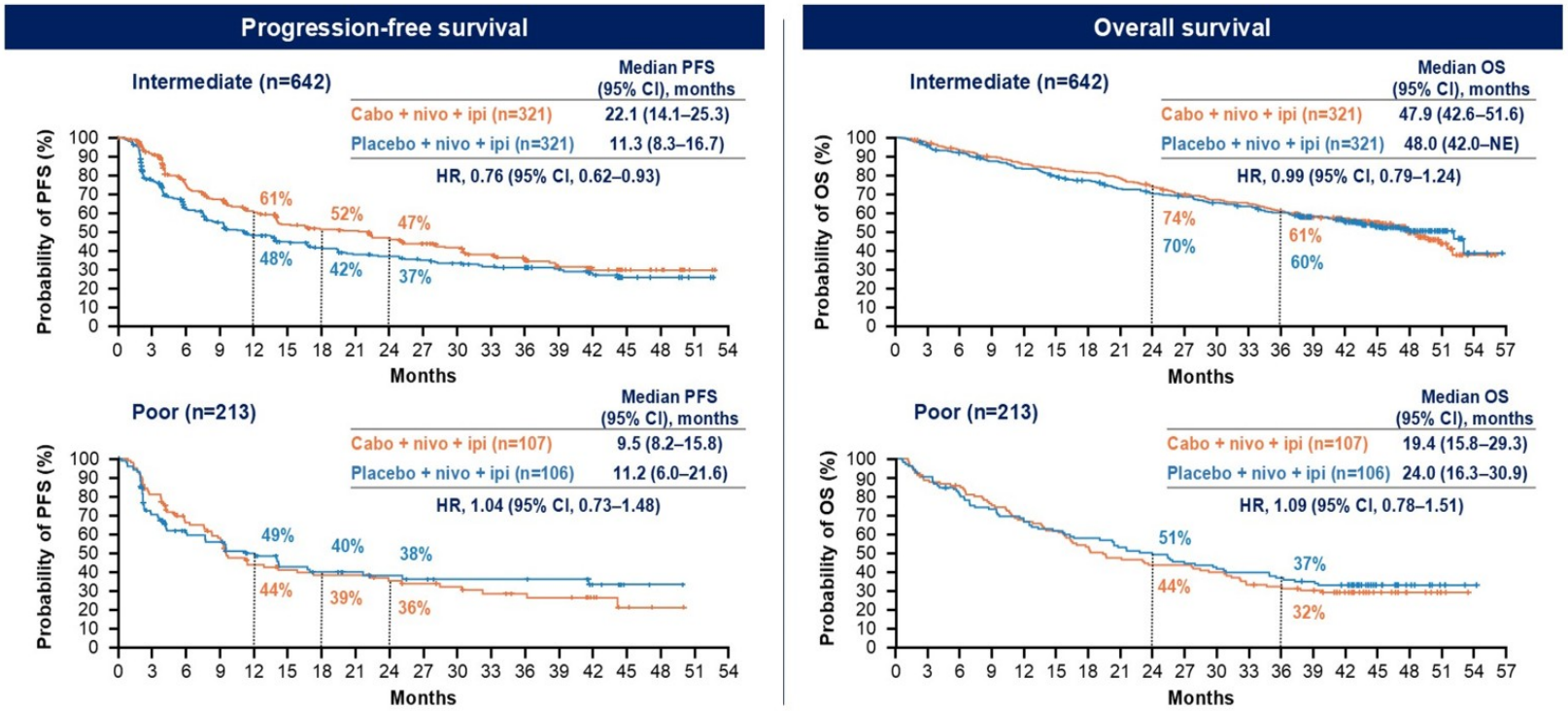
Cosmic 313 clinical trial

Metastatik RCC Birinci Basamak Tedavi
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)

Cosmic 313 clinical trial

Metastatik RCC Birinci Basamak Tedavi
Nivolumab + Ipilumumab+Cabozantinib



Median follow-up of 45.0 months.
NE, not estimable.

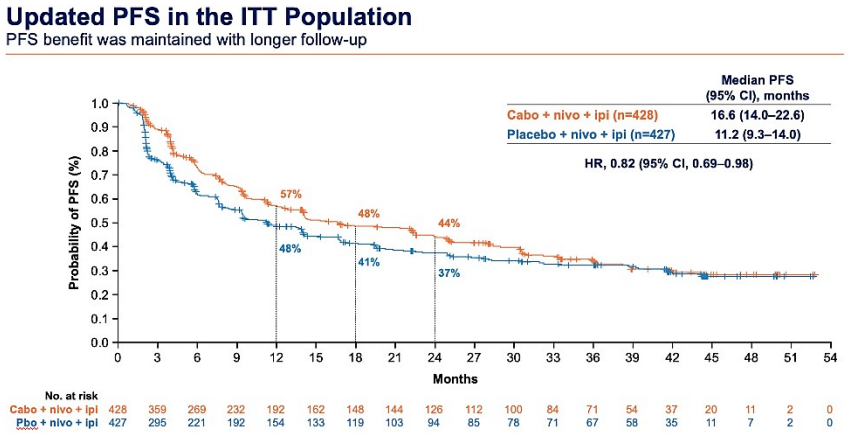
Metastatik RCC Birinci Basamak Tedavi
Nivolumab + Ipilumumab+Cabozantinib

Treatment Exposure and Discontinuation (Safety Population)

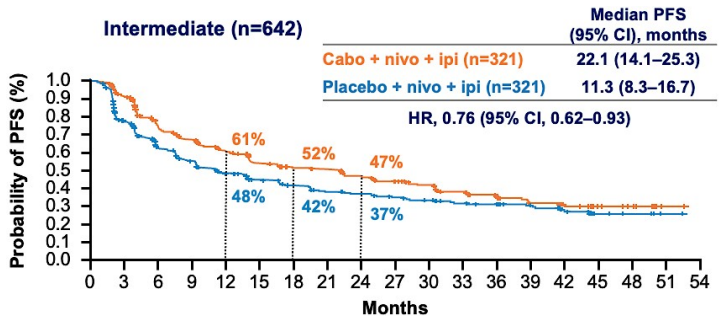
	Cabo+Nivo+Ipi (N=426)	Pbo+Nivo+Ipi (N=424)
Median duration of exposure of study treatment (range), mo	10.9 (0.2–28.5)	10.3 (0.1–28.1)
Median average daily dose (range) of Cabo or Pbo, mg	23.2 (3.6–40.0)	36.1 (0.8–40.0)
Median Nivo infusions (range) received, no	10 (1–27)	9 (1–27)
Doses of Ipi received, %		
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

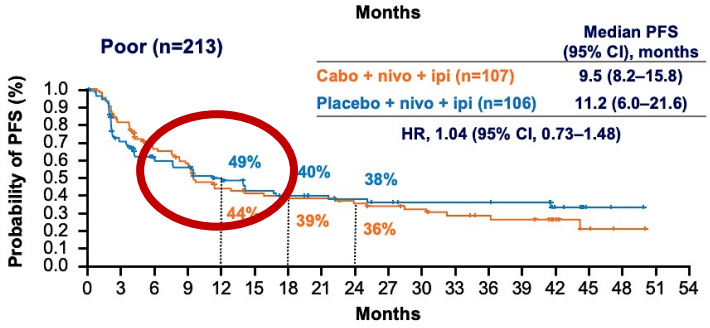
Data cut-off: Jan 31, 2022

Metastatik RCC Birinci Basamak Tedavi
Nivolumab + Ipilumumab+Cabozantinib



No overall survival benefit for cabo-ipi-nivo





UT Southwestern Medical Center

Albiges et al, GU ASCO 2025

Metastatik RCC Birinci Basamak Tedavi
Nivolumab + Ipilumumab+Cabozantinib

	Cabo + nivo + ipi (n=426)	Placebo + nivo + ipi (n=423)
Median duration of exposure of study treatment, months (range)	13.7 (0.2–53.4)	10.3 (0.1–55.3)
Median average daily dose of cabo/placebo, mg (range)	22.4 (3.6–40.0)	35.2 (0.8–40.0)
Median nivo infusions per patient, n (range)	11.0 (1–52)	9.0 (1–48)
1 / 2 / 3 / 4 cycles of ipi administered, %	7 / 22 / 13 / 58	6 / 7 / 13 / 74
Dose modification (any treatment component) due to AE, %	92	76
Treatment-related AE leading to discontinuation of ≥1 component, %	49	26

Triplet therapy:

- Less average daily dose of cabozantinib
- Fewer received 4 cycles of ipilimumab
- Almost all patients had dose modification & half discontinued at least 1 study treatment

Albiges et al, GU ASCO 2025

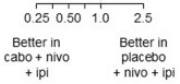
Metastatik RCC Birinci Basamak Tedavi
Nivolumab + Ipilumumab+Cabozantinib

Association of Molecular Clusters With PFS and OS

- No clear association between molecular clusters and clinical outcomes was observed; however, the sample sizes in each cluster were small

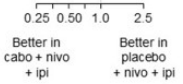
Progression-free survival

Subgroup	HR [95% CI]	Cabo + nivo + ipi (n)	Placebo + nivo + ipi (n)	*P*
Molecular subsets				
1 – Angiogenic/stromal	1.8 [0.73–4.3]	9.4 (21)	24.9 (18)	0.21
2 – Angiogenic	0.72 [0.42–1.2]	22.3 (40)	13.9 (43)	0.24
3 – Complement/Ω oxidation	0.95 [0.42–2.1]	NR (27)	NR (31)	0.89
4 – T-effector/proliferative	0.52 [0.27–0.98]	32.2 (30)	11.2 (36)	0.004
5 – Proliferative	0.68 [0.39–1.2]	11.2 (40)	7.6 (36)	0.17
6 – Stromal/proliferative	0.81 [0.39–1.7]	9.5 (23)	5.9 (19)	0.59
7 – snoRNA	0.51 [0.18–1.5]	NR (16)	27.7 (18)	0.22



Overall survival

Subgroup	HR [95% CI]	Cabo + nivo + ipi (n)	Placebo + nivo + ipi (n)	*P*
Molecular subsets				
1 – Angiogenic/stromal	1.5 [0.59–3.9]	29 (21)	NR (18)	0.38
2 – Angiogenic	1.3 [0.7–2.5]	34.8 (40)	NR (43)	0.38
3 – Complement/Ω oxidation	1.1 [0.43–2.8]	52.1 (27)	53.1 (31)	0.84
4 – T-effector/proliferative	0.86 [0.46–1.6]	41.9 (30)	28.7 (36)	0.63
5 – Proliferative	0.56 [0.3–1.1]	47.9 (40)	26.8 (36)	0.081
6 – Stromal/proliferative	0.83 [0.4–1.7]	34.5 (23)	25.4 (19)	0.62
7 – snoRNA	1.4 [0.43–4.7]	NR (16)	NR (18)	0.56



Median follow-up of 45.0 months.

Metastatik RCC Birinci Basamak Tedavi
Nivolumab + Ipilumumab+Cabozantinib

M2-like Macrophage-Mediated Immune Suppression

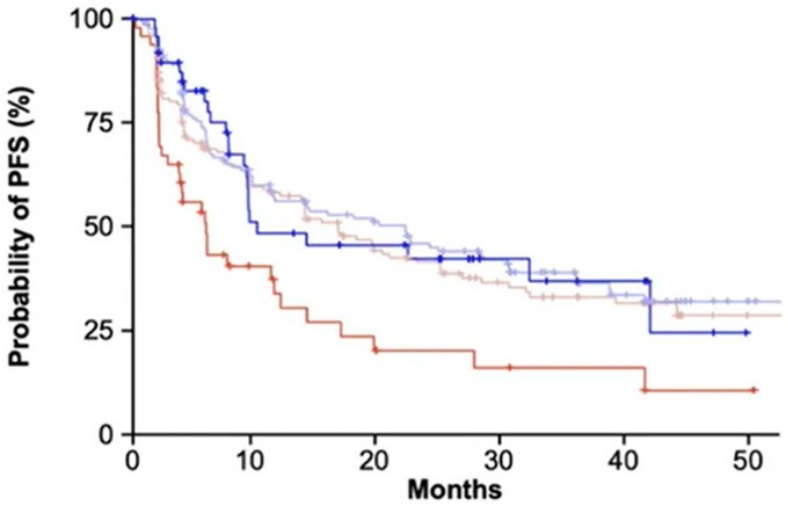
Progression-free survival

M2-like low	Median PFS (95% CI), months
Cabo + nivo + ipi (n=147)	22.1 (11.4–30.6)
Placebo + nivo + ipi (n=151)	16.7 (12–25)

HR, 0.89 (95% CI, 0.66–1.2), *P*=0.44

M2-like high	Median PFS (95% CI), months
Cabo + nivo + ipi (n=50)	10.1 (9.23–NE)
Placebo + nivo + ipi (n=50)	5.95 (3.81–12)

HR, 0.48 (95% CI, 0.29–0.81), *P*=0.0058



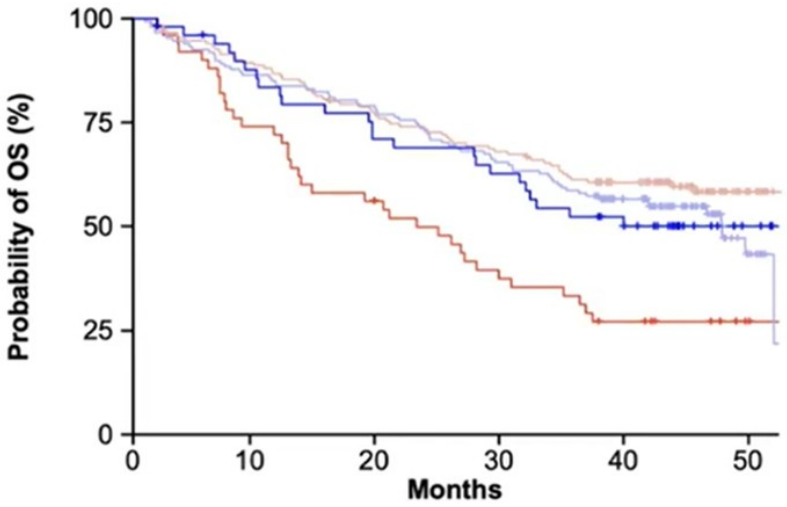
Overall survival

M2-like low	Median OS (95% CI), months
Cabo + nivo + ipi (n=147)	47.8 (36.8–NE)
Placebo + nivo + ipi (n=151)	NE (NE–NE)

HR, 1.2 (95% CI, 0.88–1.7), *P*=0.23

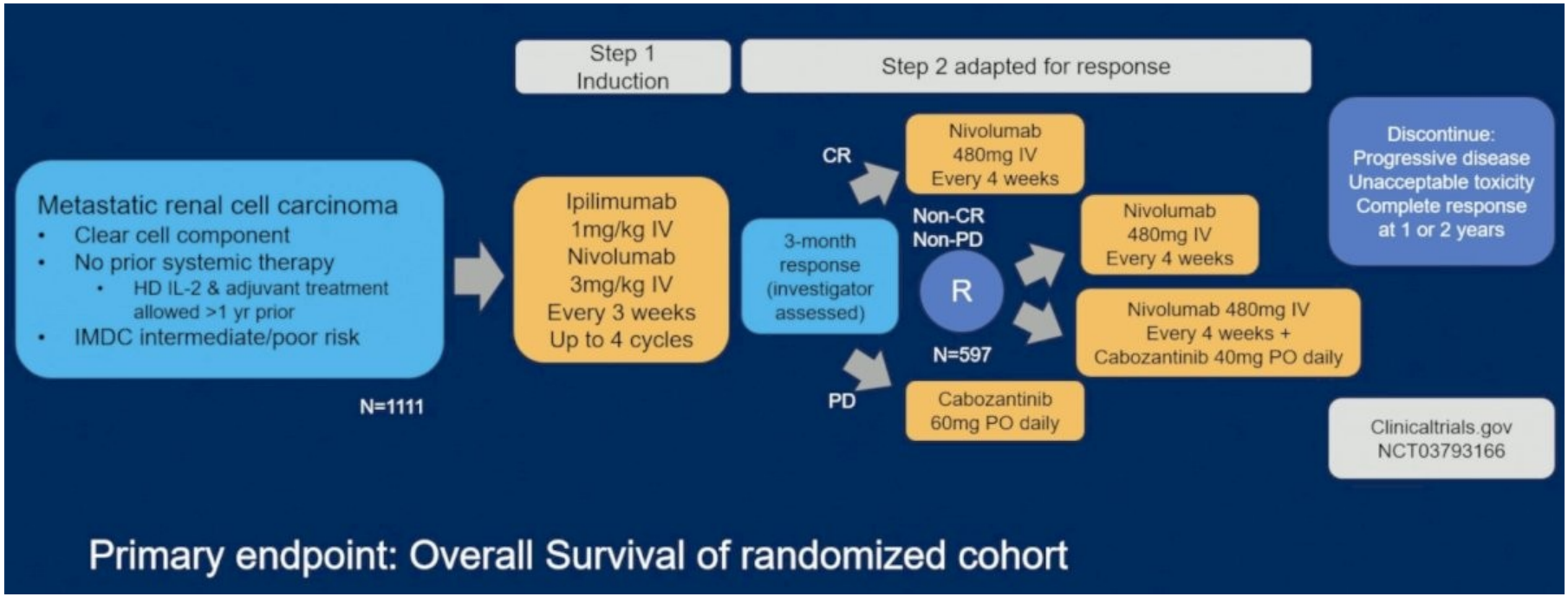
M2-like high	Median OS (95% CI), months
Cabo + nivo + ipi (n=50)	39.9 (31.4–NE)
Placebo + nivo + ipi (n=50)	23 (13.4–35)

HR, 0.51 (95% CI, 0.31–0.86), *P*=0.012



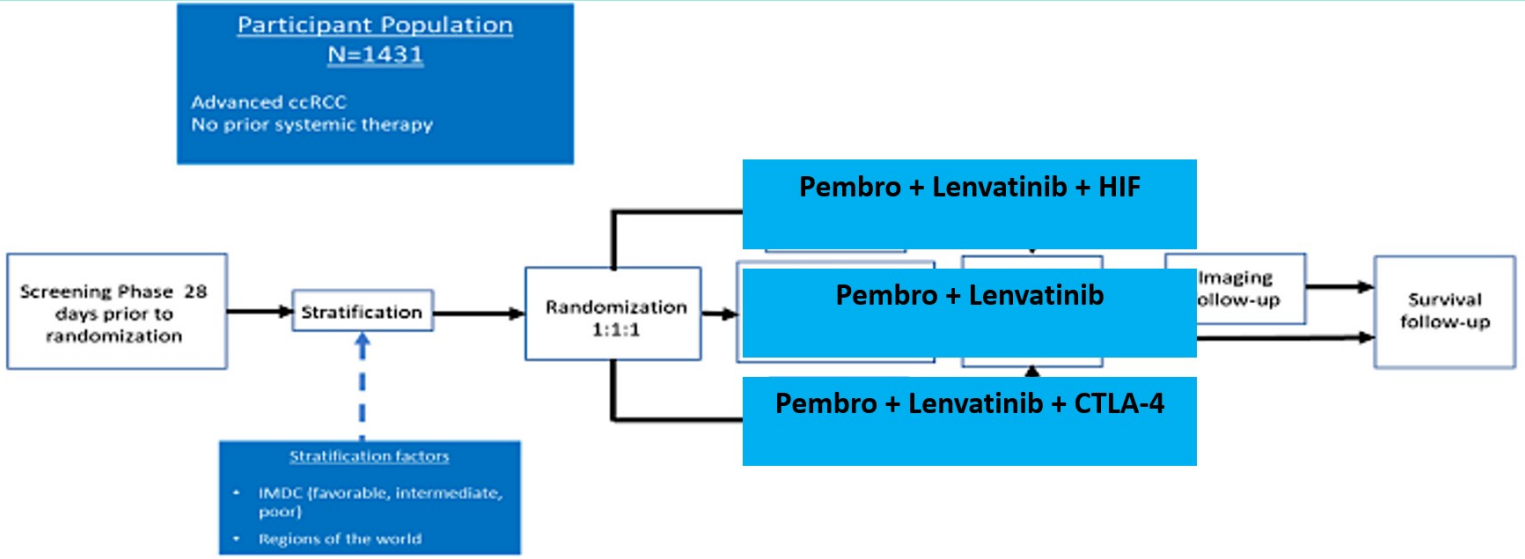
Median follow-up of 45.0 months.
A cox univariate model with different quantiles of M2-like macrophage level was used to determine the cutoff with the minimum hazard ratio. Patients with M2-like macrophage level in the top 25% were classified as M2-like high.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif



Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif

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

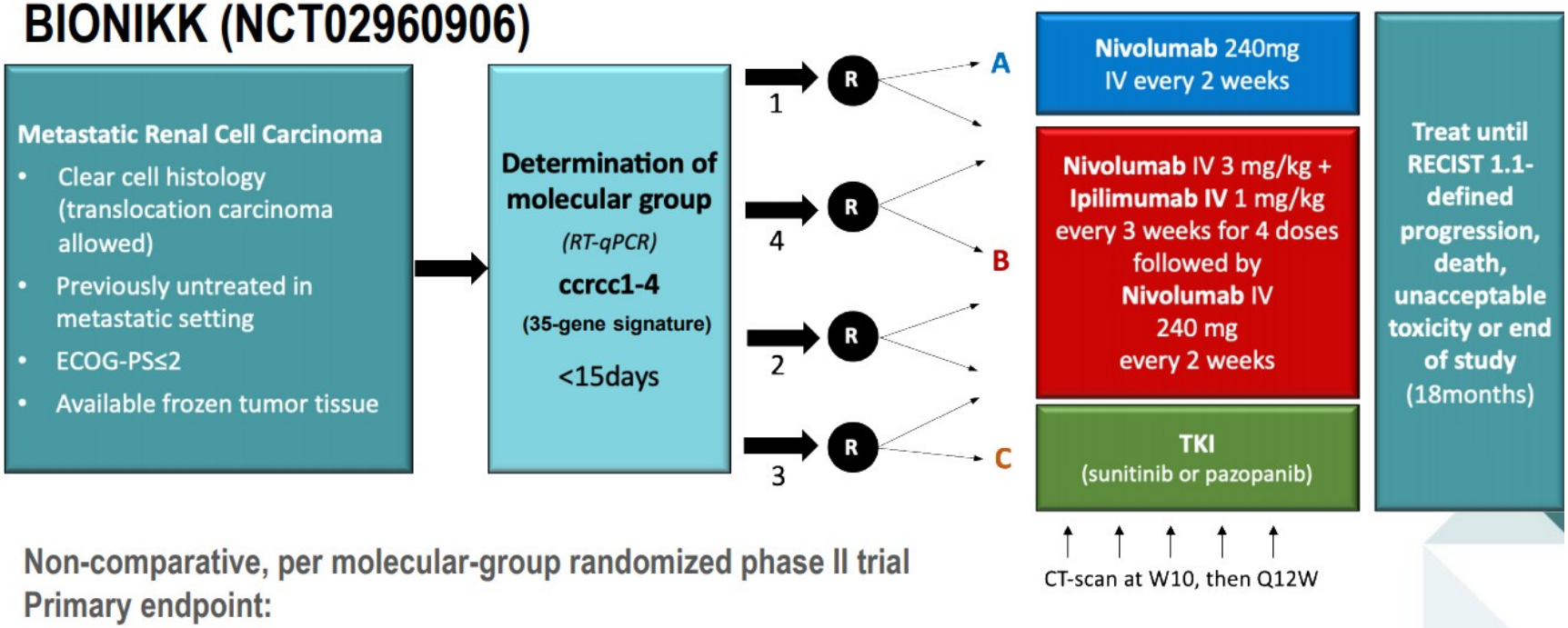
MERCK
INVENTING FOR LIFE

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif

VIRTUAL 2020 ESMO congress

METHODS: study design

BIONIKK (NCT02960906)



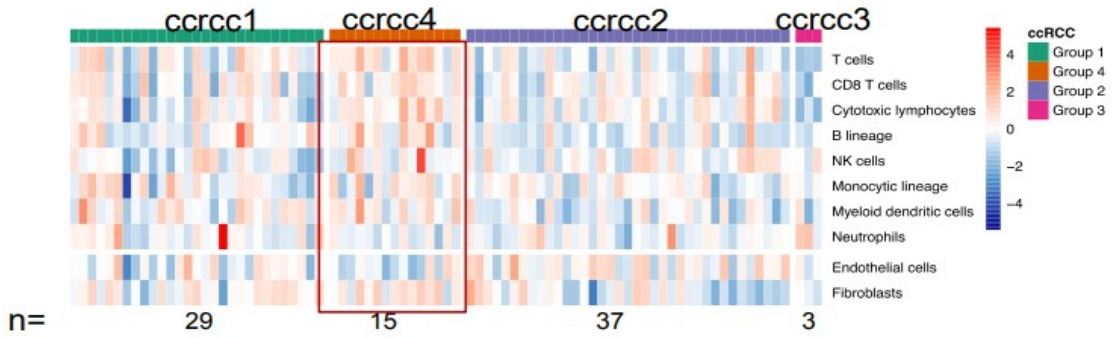
Non-comparative, per molecular-group randomized phase II trial
Primary endpoint:
Overall response rate (ORR: CR+PR) using RECIST 1.1 per investigator

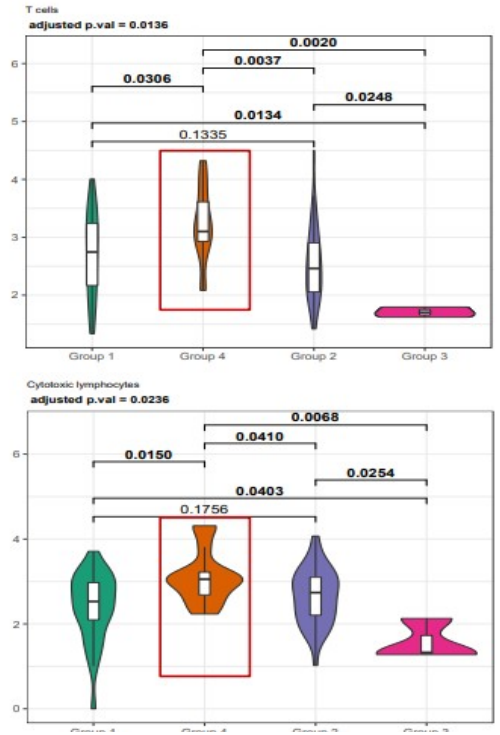
Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif

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

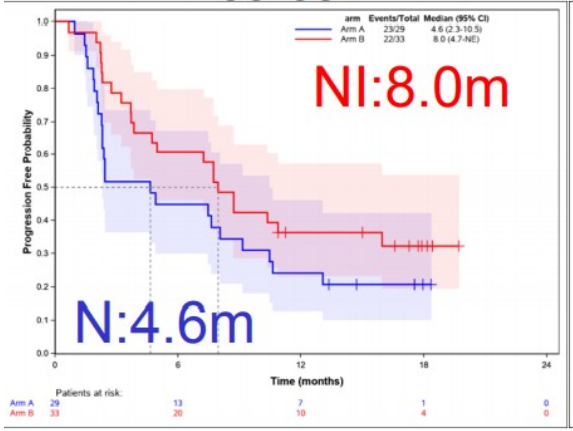
VIRTUAL 2020 ESMO congress

RESULTS: Progression Free Survival (PFS)

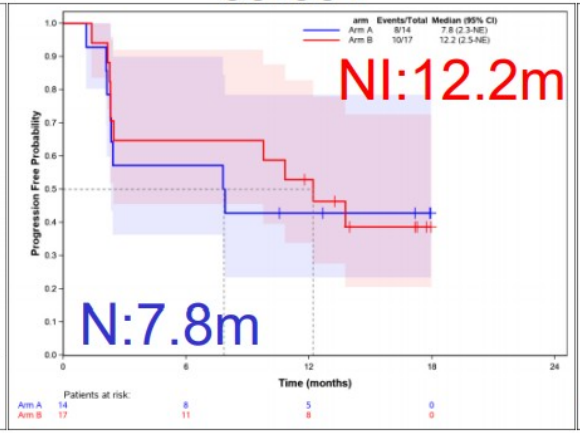
Target cohort (TCE, n=154)

Median follow-up: 16 months

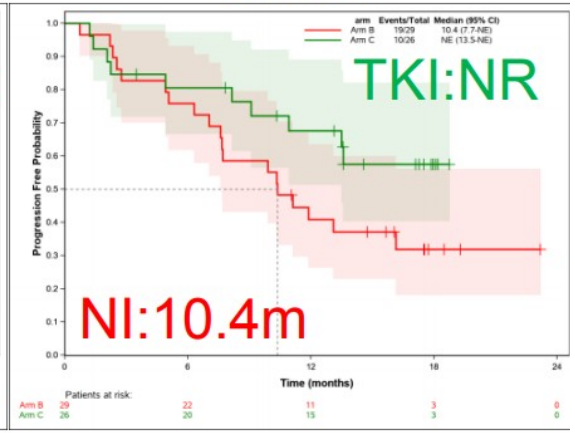
ccrcc1



ccrcc4



ccrcc2

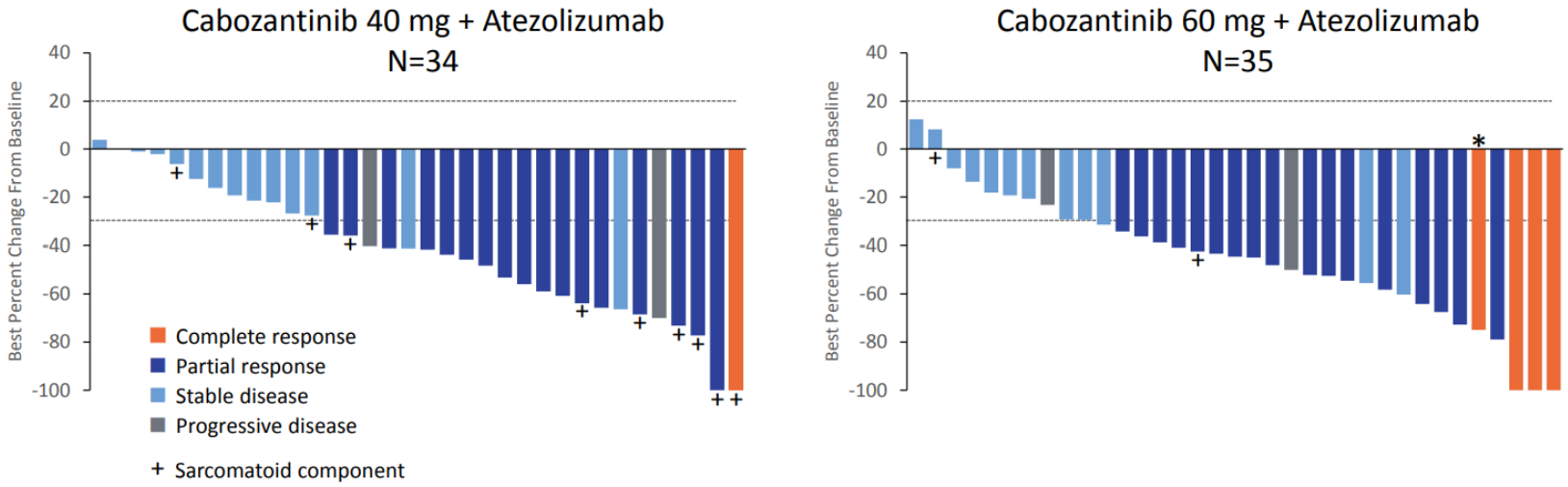


ccrcc3 No KM curve showed here because of the limited number of pts (n=6)

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

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif

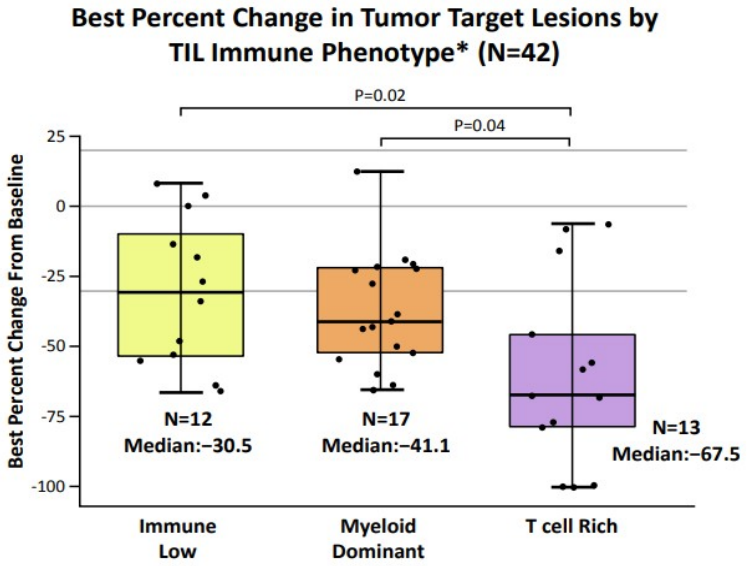
Best Change From Baseline in Sum of Target Lesions

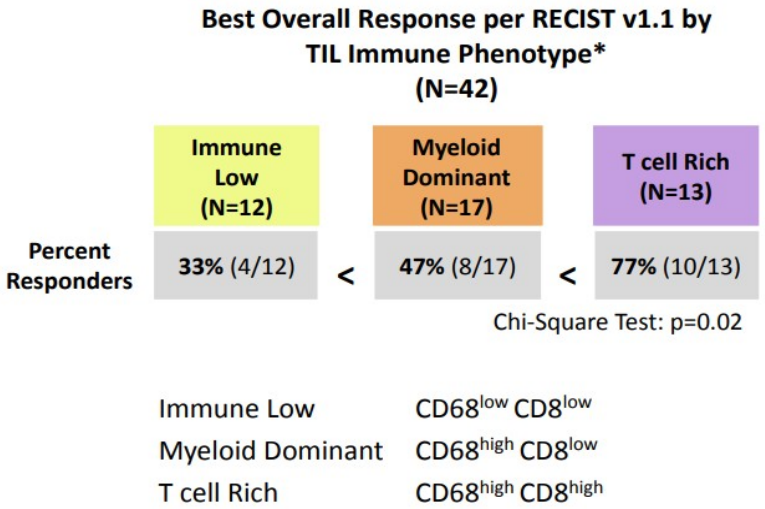


- Any reduction in tumor target lesions occurred for 94% of the 40 mg cabozantinib cohort and 92% of the 60 mg cabozantinib cohort

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 Gelecek Perspektif

STELLAR-002 (NCT05176483): 1L ccRCC Expansion Cohort

Patient Population

- Aged ≥18 years
- Unresectable advanced or metastatic RCC with a clear cell component (sarcomatoid features allowed)
- All IMDC risk groups
- No prior systemic anticancer therapy for RCC
  - Prior non-VEGF(R)–targeted adjuvant or neoadjuvant therapy allowed if disease recurrence occurred 6 months after the last dose

Non-randomized

Sequential assignment

→ **Zanzalintinib 100 mg PO QD + Nivo 480 mg IV Q4W (n=40)[a]**

→ **Zanzalintinib 100 mg PO QD + Nivo/Rela 480/480 mg IV Q4W (fixed-dose combination) (n=40)[a]**

Endpoints

Primary:	Incidence and severity of AEs
	ORR per RECIST v1.1
Secondary:	PFS per RECIST v1.1

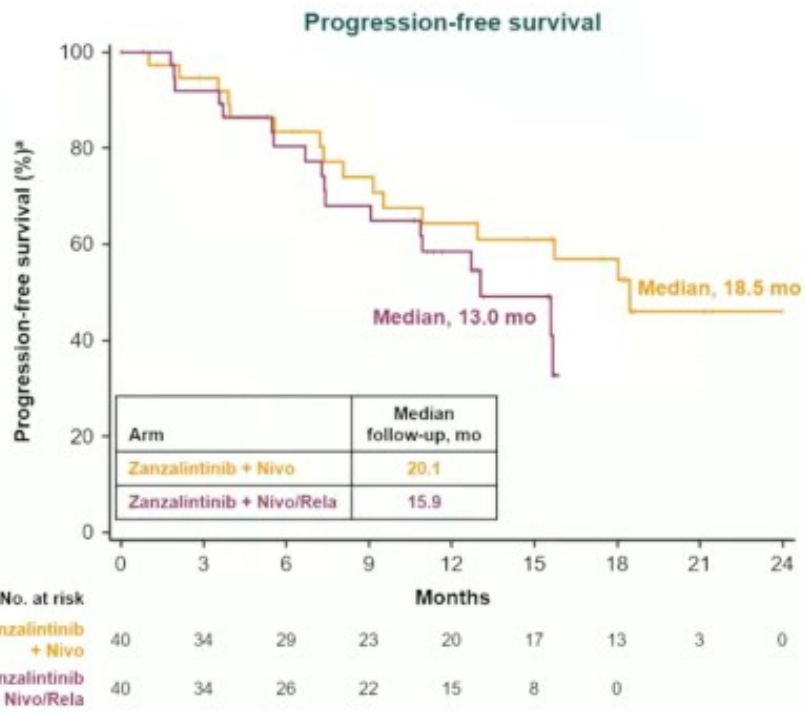
[a]Patients were allowed to receive treatment beyond radiographic progression if the investigator believed they were receiving clinical benefit.

1L, first-line; AE, adverse event; IMDC, International Metastatic RCC Database Consortium; IV, intravenously; Nivo, nivolumab; ORR, objective response rate; PFS, progression-free survival; PO, orally; Q4W, every 4 weeks; QD, once daily; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Rela, relatlimab.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri
Gelecek Perspektif

Antitumor Activity Summary

	Zanzalintinib + Nivo (n=40)	Zanzalintinib + Nivo/Rela (n=40)
ORR (95% CI), %	**63 (46–77)**	**40 (25–57)**
Confirmed CR, n (%)	3 (8)	1 (3)
Confirmed PR, n (%)	22 (55)	15 (38)
SD, n (%)	11 (28)	20 (50)
PD, n (%)	2 (5)	3 (8)
DCR (95% CI), %	90 (76–97)	90 (76–97)
Median DOR (95% CI), months	NE (11.1–NE)	NE (4.0–NE)
12-month DOR (95% CI), %	73.4 (50.0–87.1)	74.1 (39.1–90.9)
Median TTR (range), months	2.1 (1.7–11.0)	3.6 (1.7–12.8)
Median PFS (95% CI), months	**18.5 (9.5–NE)**	**13.0 (7.4–NE)**
6-month PFS (95% CI), %	83.4 (66.8–92.2)	80.4 (63.1–90.2)
12-month PFS (95% CI), %	64.4 (45.7–78.1)	58.4 (39.9–73.0)



Per RECIST v1.1. [a]Kaplan-Meier estimate.
CI, confidence interval; DCR, disease control rate; DOR, duration of response; mo, months; NE, not estimable; TTR, time to objective response.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif

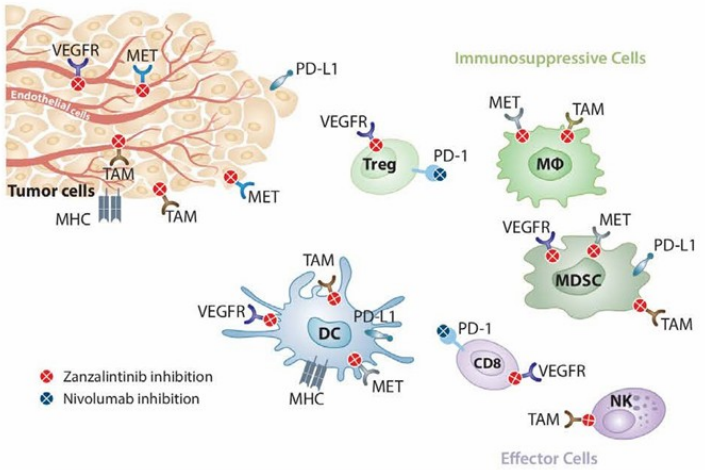
Phase III STELLAR-304 Trial: Zanzalintinib with Nivolumab

Previously untreated advanced nccRCC (papillary, unclassified, and translocation-associated)
N≈291

R2:1

- **Zanzalintinib + Nivolumab**
- **Sunitinib**

- **Dual primary endpoints:** PFS and ORR per RECIST v1.1 by BIRC
- **Secondary endpoint:** OS
- **Other endpoints:** safety, including incidence and severity of AEs



VEGFR, MET, and TAM kinases promote tumorigenesis and angiogenesis in tumor cells

- Promote proliferation and survival of tumor cells
- Promote epithelial–mesenchymal transition leading to increased invasion and metastasis
- Promote endothelial proliferation, migration, and survival
- TAM and MET may act as compensatory mechanisms of VEGFR inhibition

VEGFR, MET, and TAM kinases promote an immunosuppressive tumor microenvironment

- Promote activity of Tregs, MDSCs, and MΦs
- Increase M2/M1 ratio of Mϕ
- Inhibit antigen presentation
- Inhibit T cell activation and limit anti-tumor T cell responses

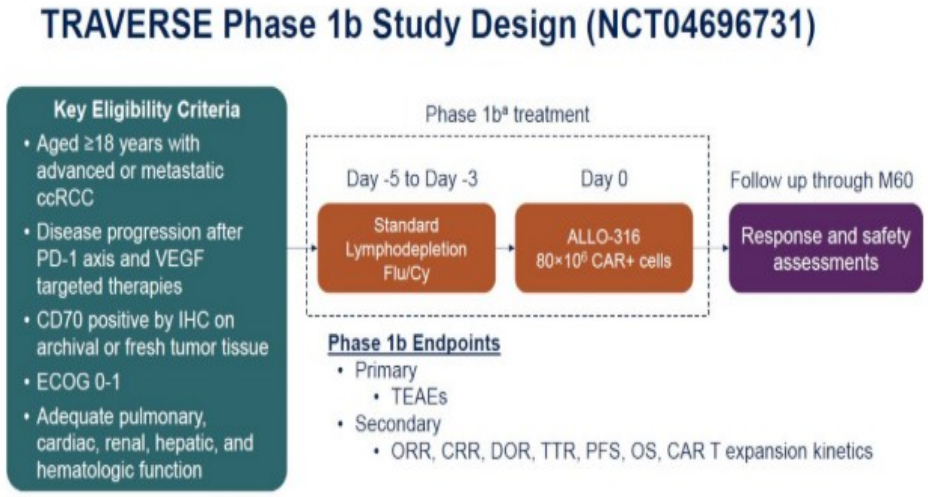
Zanzalintinib and nivolumab combination

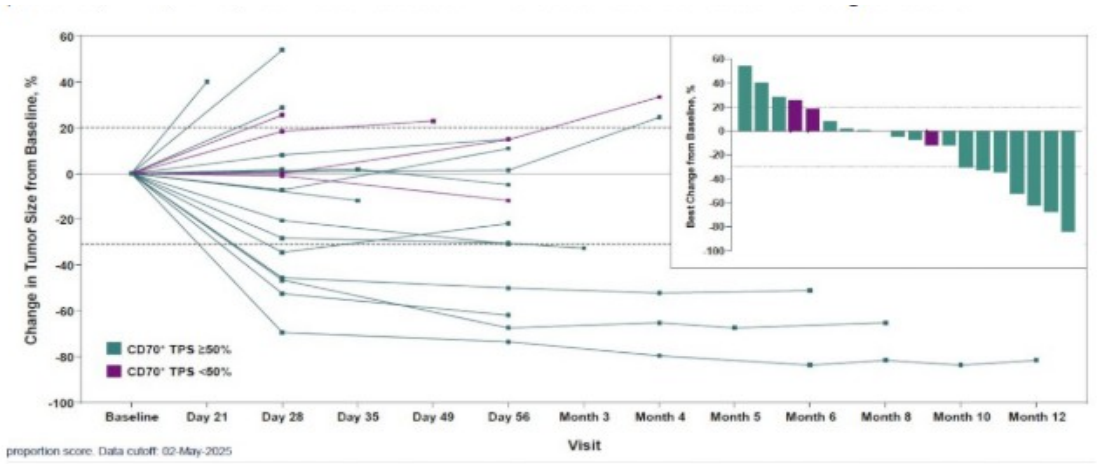
- Zanzalintinib inhibits VEGFR, MET, and TAM kinases and may enhance the activity of nivolumab by promoting an immune-permissive tumor microenvironment
- Nivolumab binds to the PD-1 receptor on immune cells and blocks interactions with ligands, such as PD-L1, which restores T-cell activation and increases antitumor effects

RTP RESEARCH TO PRACTICE

Pal SK et al. ASCO 2024;Abstract TPS4611.

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Gelecek Perspektif





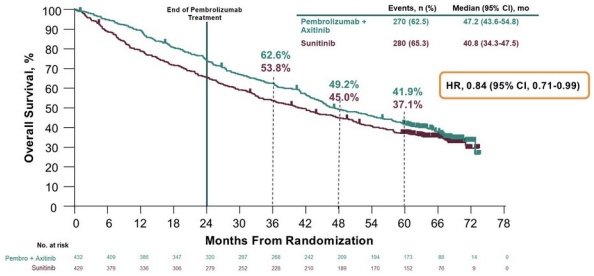
Tümör yanıtları erken dönemde ortaya çıktı ve ALLO-316'nın tek seferlik infüzyonunu takiben devam etti.

CD70+ TPS ≥%50 olan hastaların %44'ünde (7/16), başlangıçtaki hedef lezyonların çaplarında %30'dan fazla azalma görüldü

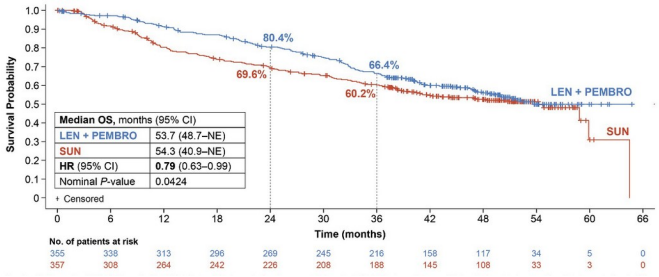
Pal S, ASCO 2025

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Karşılaştırmalar

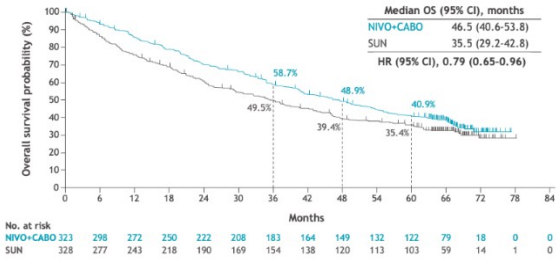
Keynote 426: OS (5yr follow up)



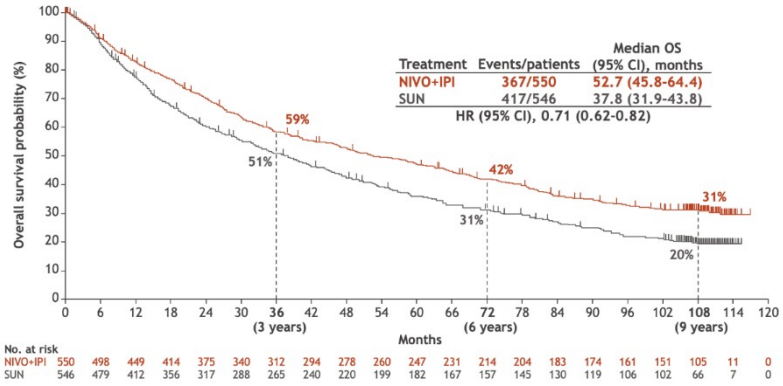
CLEAR/Keynote 581: OS (4yr follow up)



Checkmate 9ER OS (5yr follow up)



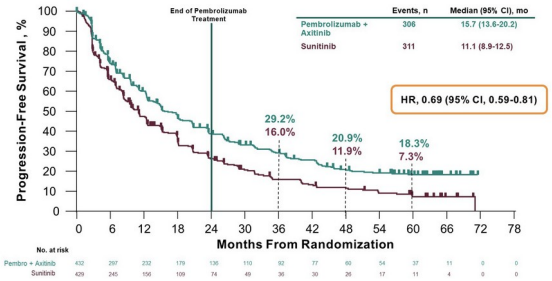
Checkmate 214 – 9yr follow up OS



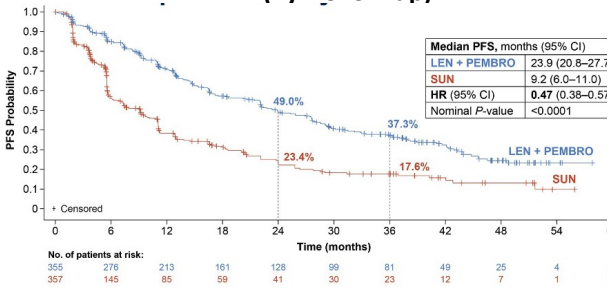
Choueiri TK et al, ASCO 2025
Rini BI et al, ASCO 2023
Motzer RJ, Porta C, Eto M, et al. *J Clin Oncol*. 2024.
Motzer RJ et al, *NEJM*, 2021
Motzer RJ et al, GU ASCO, 2025

Metastatik RCC Birinci Basamak Tedavi Seçenekleri Karşılaştırmalar

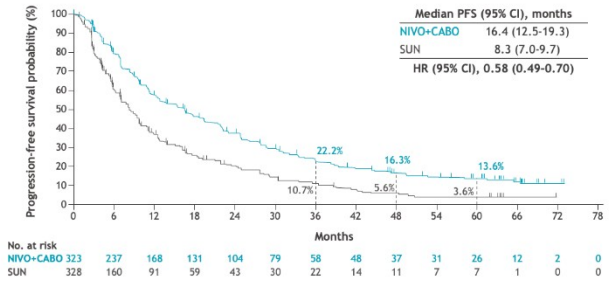
Keynote 426: PFS
ITT (5yr follow up)



CLEAR/Keynote 581: PFS
(4yr follow up)

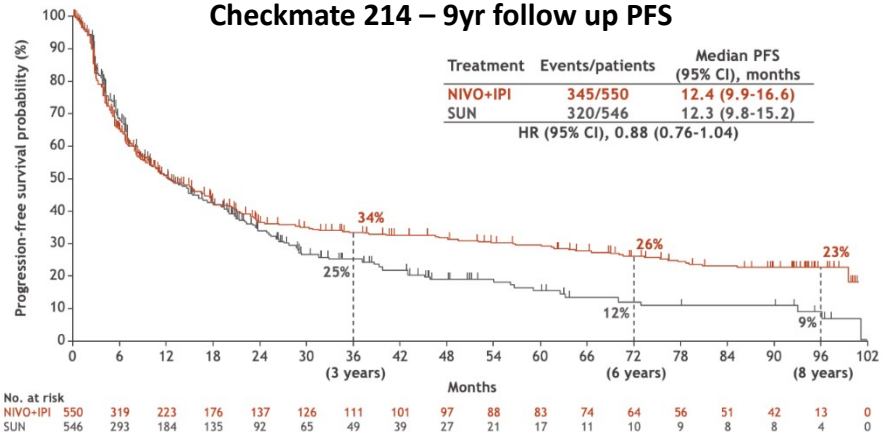


Checkmate 9ER PFS:
67mo follow up



Abstract 4505

Checkmate 214 – 9yr follow up PFS



Choueiri TK et al, ASCO 2025
Rini BI et al, ASCO 2023
Motzer RJ et al, *NEJM*, 2021
Motzer RJ et al, GU ASCO, 2025

Metastatik RCC Birinci Basamak Tedavi Seçenekleri

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Kidney Cancer

NCCN Guidelines Index
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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)

Metastatik RCC Birinci Basamak Tedavi Seçenekleri

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

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)			
Risk	**Preferred**	**Other Recommended**	**Useful in Certain Circumstances**
Favorable[a]	• Axitinib + Pembrolizumab[b] (category 1) • Cabozantinib + Nivolumab[b,c] (category 1) • Ipilimumab + Nivolumab[b,d] (category 1) • Lenvatinib + Pembrolizumab[b] (category 1)	• Axitinib + Avelumab[b] • Pazopanib • Sunitinib • Cabozantinib (category 2B)	• Active surveillance[1,2,3] • Axitinib (category 2B)
Poor/ intermediate[a]	• Axitinib + Pembrolizumab[b] (category 1) • Cabozantinib + Nivolumab[b,c] (category 1) • Ipilimumab + Nivolumab[b,d] (category 1) • Lenvatinib + Pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + Avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B)

Evre IV RCC Birinci Basamak Tedavi
Özet 1

Final Results of First-line IO Combination Trials in mRCC (ITT population)

	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)
OS HR mOS, months	**0.71** 52.7 vs 37.8	**0.84** 47.2 vs 40.8	**0.79** 46.5 vs 35.5	**0.79** 53.7 v. 54.3
Landmark OS	**42%** at 6 years **31%** at 9 years	**42%** at 5 years	**41%** at 5 years	**66%** at 3 years
PFS HR mPFS, months	**0.88** **12.4** vs 12.3	**0.69** **15.7** vs 11.1	**0.58** **16.4** vs 8.3	**0.47** **23.9** vs 9.2
Landmark PFS	**26%** at 6 years **23%** at 8 years	**18%** at 5 years	**14%** at 5 years	**37%** at 3 years
ORR, %	**40** vs 33	**61** vs 40	**56** vs 27	**71** vs 37
CR, %	**12** vs 3	**12** vs 4	**14** vs 5	**18** vs 4
Median f/u	**9.3 years**	**5.6 years**	**5.6 years**	**4.2 years**
Primary PD	**18%**	**12%**	**7%**	**5%**

1. Choueiri et al. ASCO 2025
2. Rini et al. Nature Medicne (submitted)
3. Motzer et al ASCO GU 2025
4. Motzer et al. JCO 2024

@brian_rini and @Uromigos (podcasts: https://podcasters.spotify.com/pod/show/the-uromigos)

Evre IV RCC Birinci Basamak Tedavi Özet 2

	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 3

İmmünoterapi-immünoterapi kombinasyonu

- Daha düşük yanıt oranı ve yüksek PD riski
- 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 giderek netleşiyor
- Uzun TKI toksisitesi maruziyeti
- Yaş, komorbidite, semptom, hastalık yükü ve metastaz bölgesi tedavi seçiminde yön gösterici olabilir.
- Daha efektif prediktif belirteçler tedavi seçiminde katkı sağlayacak.