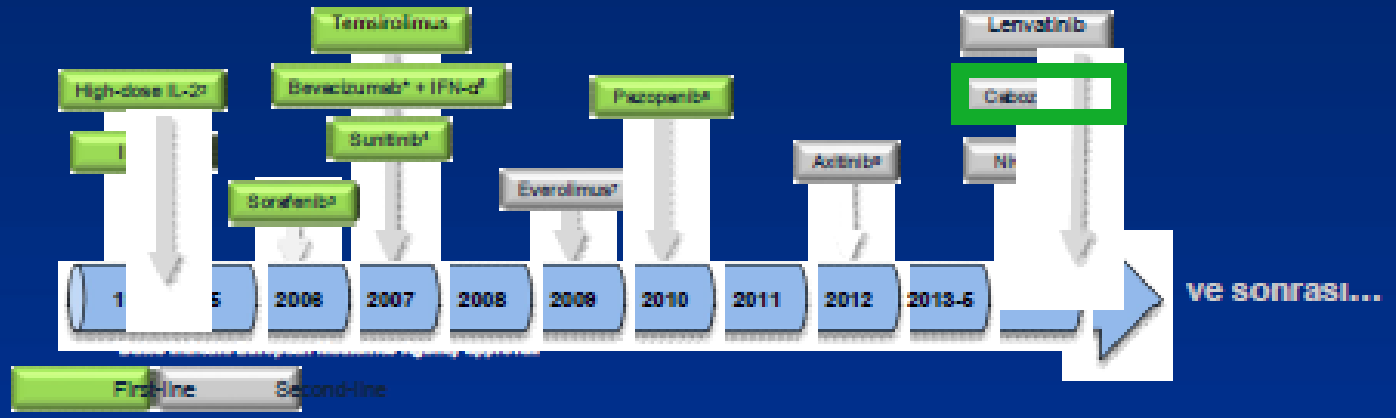
İleri evre berrak hücreli böbrek kanseri tedavisinde immünoterapi

Dr.Serkan Değirmencioğlu

mRCC Tedavisinde 2006 – 2016 Arasında 10 Yeni Tedavi Ajanı

- **Medyan Sağkalım: 7-9 ay → 28 - 30 ay**



1. Ljungberg B *et al. EAU Guidelines on RCC* 2013
2. Fyfe G *et al. J Clin Oncol* 1995;13:688–696
3. Escudier B *et al. N Engl J Med* 2007;356:125–134
4. Motzer RJ *et al. N Engl J Med* 2007;356:115–124
5. Rudas G *et al. N Engl J Med* 2007;356:2271–2281
6. Escudier B *et al. Lancet* 2007;370:2103–2111
7. Motzer RJ *et al. Cancer* 2010;116:4256–4265
8. Sternberg CN *et al. J Clin Oncol*
9. Rini BI *et al. Lancet* 2011;378:1931–1939.

IFN, interferon; IL, interleukin; mRCC, metastatic renal cell carcinoma.

RISK MODELS TO DIRECT TREATMENT

Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model[a]

Prognostic factors
- Interval from diagnosis to treatment of less than 1 year
- Karnofsky performance status less than 80%
- Serum lactate dehydrogenase (LDH) greater than 1.5 times the upper limit of normal (ULN)
- Corrected serum calcium greater than the ULN
- Serum hemoglobin less than the lower limit of normal (LLN)

Prognostic risk groups
- Low-risk group: no prognostic factors
- Intermediate-risk group: one or two prognostic factors
- Poor-risk group: three or more prognostic factors

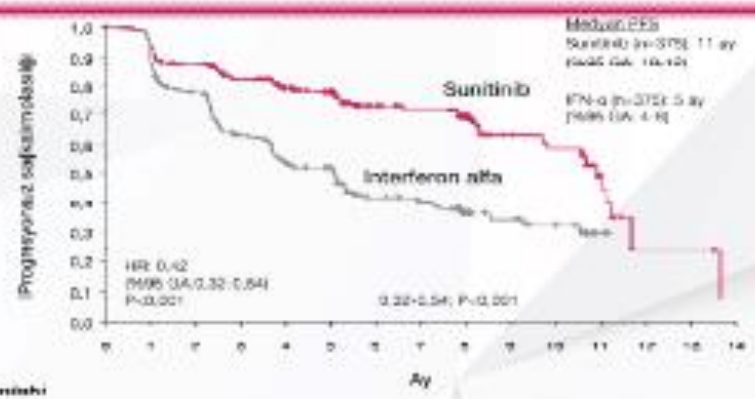
International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria[b]

Prognostic factors
- Less than one year from time of diagnosis to systemic therapy
- Performance status <80% (Karnofsky)
- Hemoglobin < lower limit of normal (Normal: 120 g/L or 12 g/dL)
- Calcium > upper limit of normal (Normal: 8.5–10.2 mg/dL)
- Neutrophil > upper limit of normal (Normal: 2.0–7.0×10^3/L)
- Platelets > upper limit of normal (Normal: 150,000–400,000)

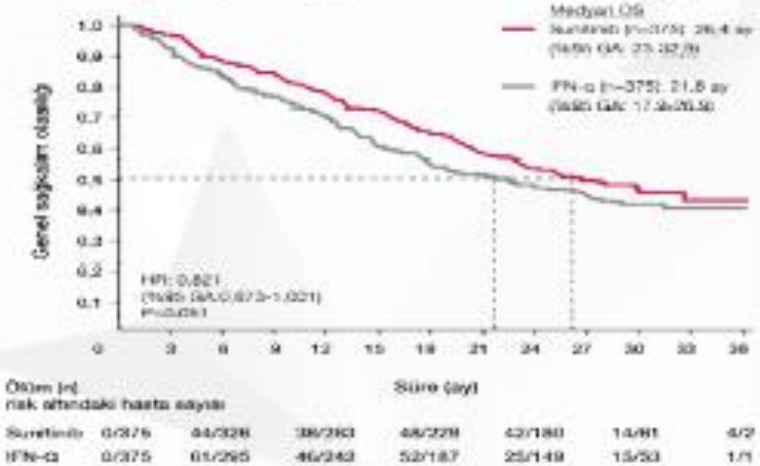
Prognostic risk groups
- Favorable-risk group: no prognostic factors
- Intermediate-risk group: one or two prognostic factors
- Poor-risk group: three to six prognostic factors

Sunitinib pivotal çalışma: Etkinlik

Medyan progresyonsuz sağkalım[1]

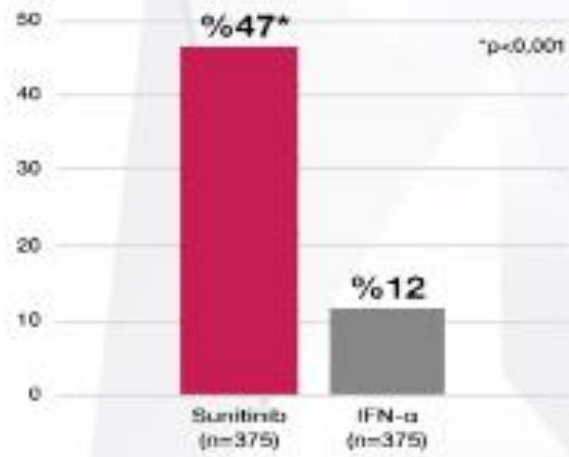


Medyan genel sağkalım[2]



Risk altındaki hasta sayısı					
Sunitinib	375	235	90	32	2
IFN-α	375	152	42	18	0

Objektif yanıt oranı[2]

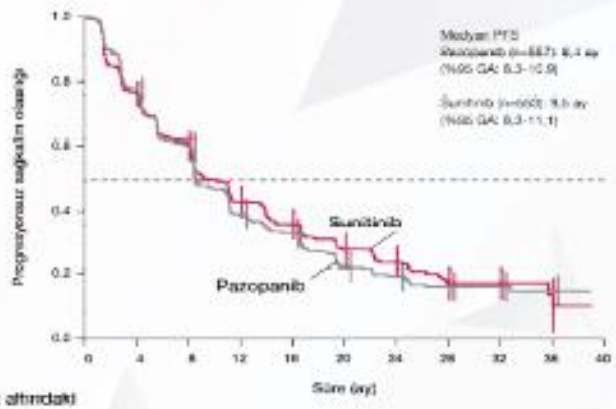


Metastatik renal hücreli karsinomu olan 750 hastada, 4/2 doz şeması ile kullanılan sunitinib 50 mg/gün tedavisinin, IFN-alfa ile karşılaştırıldığı randomize, çok merkezli, faz III çalışma.[1]

1. Motzer RJ, et al. N Engl J Med 2007;356:115–124. 2. Motzer RJ, et al. J Clin Oncol 2009;27:3584–3590.

COMPARZ: Pazopanib vs Sunitinib

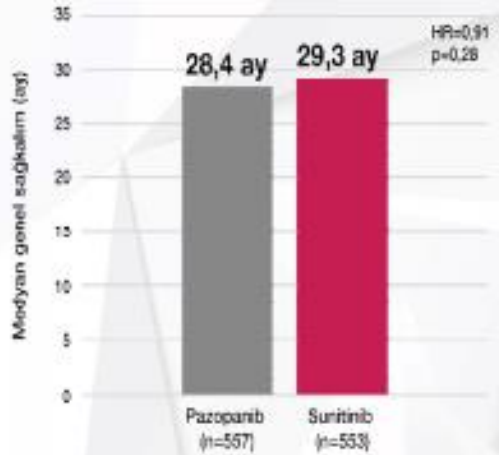
Medyan progresyonsuz sağkalım[1]



Risk altındaki hasta sayısı

Pazopanib	557	361	245	136	105	61	46	19	13	1
Sunitinib	553	351	249	147	111	69	48	18	10	3

Medyan genel sağkalım[1]



Metastatik renal hücreli karsinomu olan 1.100 hastada birinci basamak tedavi olarak sunitinib ve pazopanibin karşılaştırıldığı randomize, faz III çalışma.[1]

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

Birinci basamak çalışmalarda TKI Etkinliği

Ajan	n	Medyan PFS (ay)	Medyan OS (ay)	ORR (%)
Sunitinib vs IFN-α[1]	750	11 vs 5 p<0,001	26,4 vs 21,8 p=0,051	47 vs 12 p<0,001
Pazopanib vs plasebo[2,3]	435	11,1 vs 2,8 p<0,0001	22,9 vs 20,5 p=0,224	30 vs 3 p<0,001
Pazopanib vs sunitinib[4]	1.110	8,4 vs 9,5 NA	28,4 vs 29,3 p=0,28	31 vs 25 p=0,03
Sorafenib vs plasebo[5]	905	5,5 vs 2,8 p<0,01	19,3 vs 15,9 p=0,02*	10 vs 2 p<0,001

1. Motzer RJ, et al. J Clin Oncol 2009;27:3584–3590. 2. Sternberg CN, et al. J Clin Oncol 2010;28:1061-1068. 3. Sternberg CN, et al. Eur J Cancer. 2013;49(6):1287-96.
4. Motzer RJ, et al. N Engl J Med 2013;369:722-31. 5. Gore ME, et al. Br J Cancer. 2015;113(1):12-9.

Pembrolizumab Monotherapy as First-Line Therapy in Advanced Clear Cell Renal Cell Carcinoma: Results From Cohort A of KEYNOTE-427

D. F. McDermott[1] ; J-L. Lee[2]; C. Szczylik[3]; F. Donskov[4]; J. Malik[5]; B. Y. Alekseev[6]; J. M. G. Larkin[7]; V. B. Matveev[8]; R. A. Gafanov[9]; P. Tomczak[10]; S. S. Tykodi[11]; P. F. Geertsen[12]; P. Wiechno[13]; S. J. Shin[14]; F. Pouliot[15]; T. A. Gordoa[16]; W. Li[17]; R. F. Perini[18]; C. Schloss[18]; M. B. Atkins[19]

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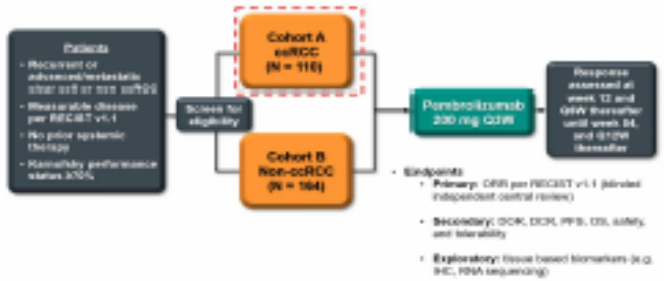
mRCC: 1. Basamakta Pembrolizumab Monoterapi

ASCO 2018

KEYNOTE-427: (NCT02853344)



Characteristic, n (%)	N = 110
IMDC risk categories	
Favorable	41 (37.3)
Intermediate	52 (47.3)
Poor	17 (15.5)
Geographic region of enrolling site	
North America	45 (40.9)
Western Europe	37 (33.6)
Rest of the world	28 (25.5)
PD-L1 status[a]	
CPS ≥1	46 (41.8)
CPS <1	53 (48.2)
Missing	11 (10.0)

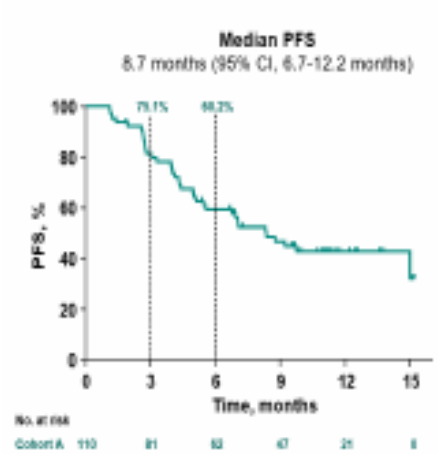
Yanıt Oranları

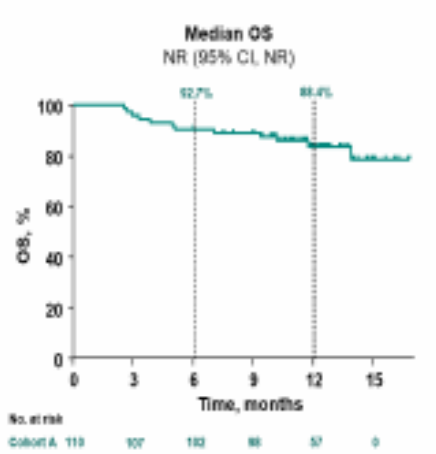
	N = 110		
	n	%	95% CI
ORR	42	38.2	29.1-47.9
DOR (CR + PR + SD ≥6 months)	66	59.1	49.2-68.4
Best overall response			
CR	3	2.7	
PR	39	35.5	
SD	35	31.8	
PD	31	28.2	
No assessment	2	1.8	

Yanıt Oranları: PD-L1 Ekpresyonuna Göre

	CPS ≥1 n = 46	CPS <1 n = 53	Missing n = 11
Confirmed ORR, % (95%CI)	50.0 (34.9-65.1)	26.4 (15.3-40.3)	45.5 (16.7-76.6)
DCR, % (95%CI)[b]	67.4 (52.0-80.5)	49.1 (35.1-63.2)	72.7 (39.0-94.0)
Confirmed BOR, %			
CR	6.5	0	0
PR	43.5	26.4	45.5
SD	26.1	35.8	36.4
PD	23.9	34.0	18.2
NA	0	3.8	0

1. Basamak Tedavide Pembrolizumab: OS-PFS-Toksisite





Toksisite

n (%) N = 110	Grade 3/4 (≥2 pts)
Any	20 (30.2)
Diarrhea	4 (3.6)
Colitis	3 (2.7)
Asthenia	2 (1.8)
Hepatitis	2 (1.8)
AST increased	2 (1.8)
Hyponatremia	2 (1.8)
Hypophosphatemia	2 (1.8)

- Discontinuation because of a treatment-related AE was reported in 12 (10.9%) patients
- High dose steroids[a] were administered in 14 patients (12.7%)
- 1 patient had grade 5 treatment-related pneumonitis

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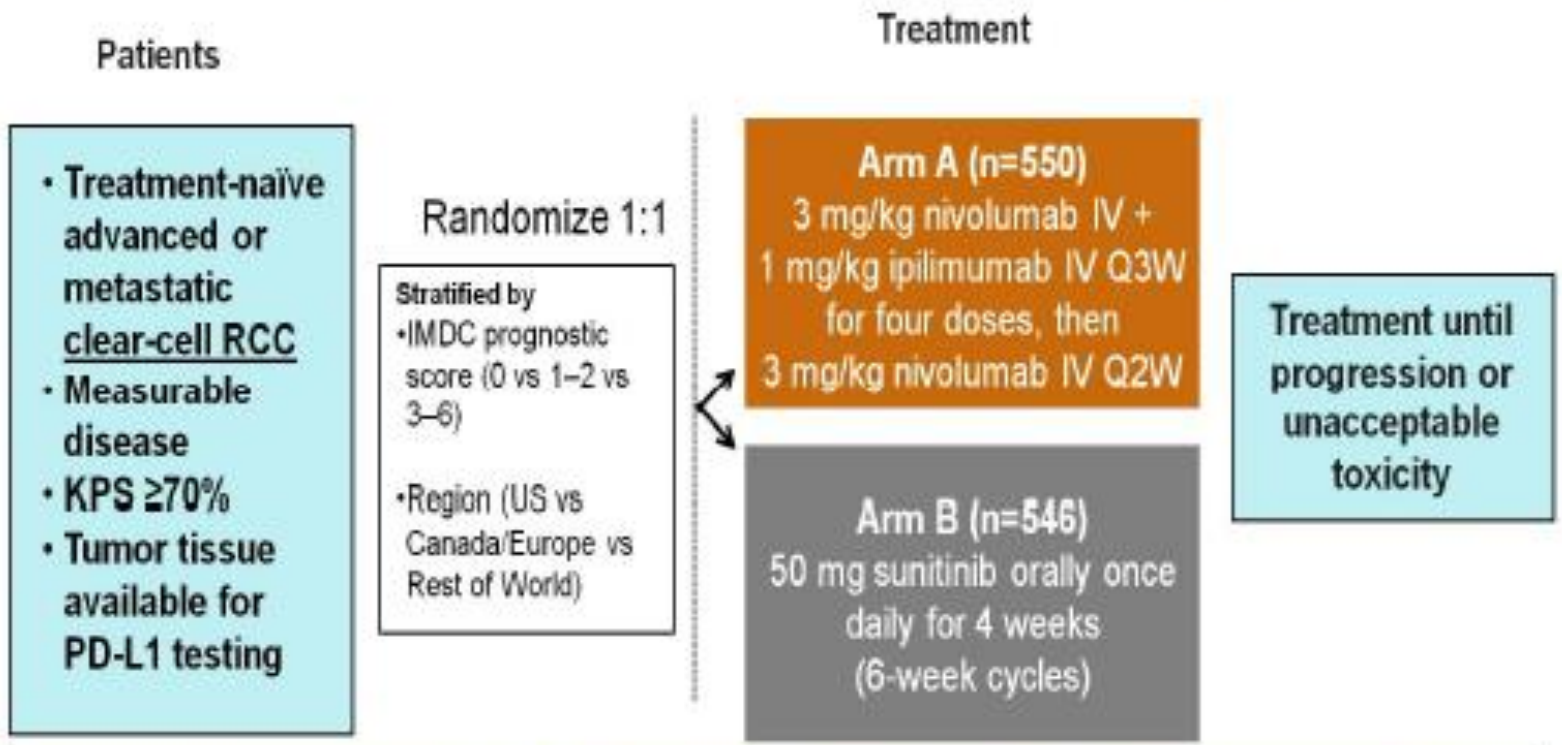
Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*

CheckMate 214:Phase III Study design (n=1096)



Co- primary endpoints were OS (α=0.04), ORR (α=0.001), and PFS (α=0.009) in Int and Poor Risk
Overall alpha is 0.05, split among the three co-primary endpoints

IMDC, International Metastatic RCC Database Consortium

Escudier B et al, LBA 5, ESMO 2017

Baseline characteristics

Characteristic	IMDC intermediate/poor risk		Intention to treat	
	NIVO + IPI N = 425	SUN N = 422	NIVO + IPI N = 550	SUN N = 546
Median age, years	62	61	62	62
Male, %	74	71	75	72
IMDC prognostic score (IVRS), %				
Favorable (0)	0	0	23	23
Intermediate (1–2)	79	79	61	61
Poor (3–6)	21	21	17	16
Region (IVRS), %				
USA	26	26	28	28
Canada/Europe	35	35	37	36
Rest of the world	39	39	35	36
Quantifiable tumor PD-L1 expression, %	n = 384	n = 392	n = 499	n = 503
<1%	74	71	77	75
≥1%	26	29	23	25

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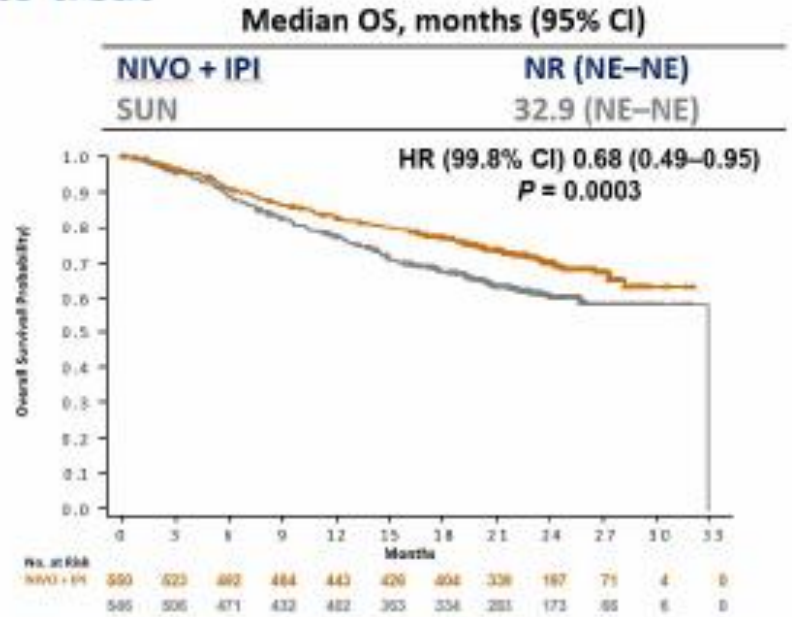
Baseline characteristics in favorable-risk patients were similar, except tumor PD-L1 expression baseline PD-L1 expression was lower among favorable-risk patients

CheckMate 214; Tüm Hastalarda Sonuçlar

ORR, PFS, and OS: Intention to treat

Outcome	N = 1,096[a]	
	NIVO + IPI N = 550	SUN N = 546
Confirmed ORR,[b] % (95% CI)	39 (35–43)	32 (28–36)
	P = 0.0191	
PFS,[c] median (95% CI), months	12.4 (9.9–16.5)	12.3 (9.8–15.2)
	HR (99.1% CI) 0.98 (0.79–1.23) *P* = 0.8498	



[a]23% of patients in the NIVO + IPI arm and 25% of patients in the SUN arm had tumor PD-L1 expression ≥1%
[b]IRRC-assessed by RECIST v1.1
[c]IRRC-assessed

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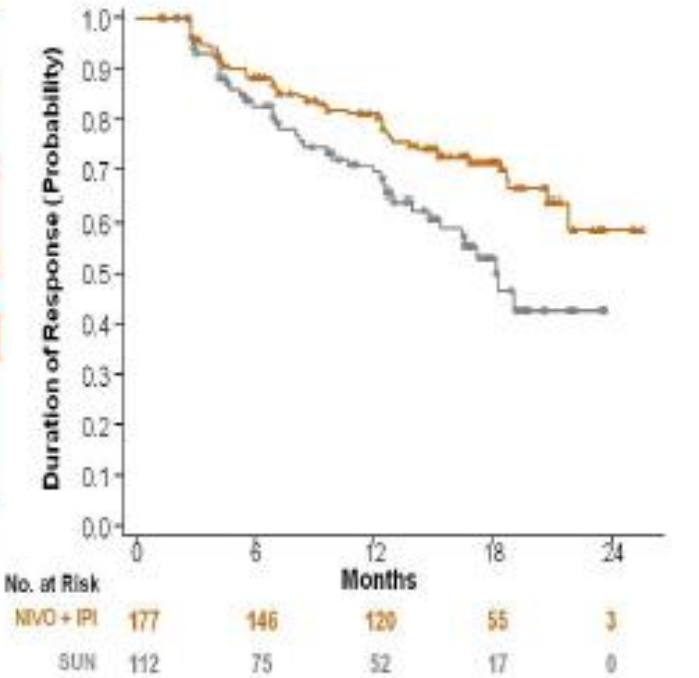
Co-primary endpoint: ORR

ORR and DOR: IMDC intermediate/poor risk

Outcome	N = 847	
	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	42 (37–47)	27 (22–31)
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	9[b]	1[b]
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine/not reported	8	12

	Median duration of response, months (95% CI)	Patients with ongoing response, %
NIVO + IPI	NR (21.8–NE)	72
SUN	18.2 (14.8–NE)	63



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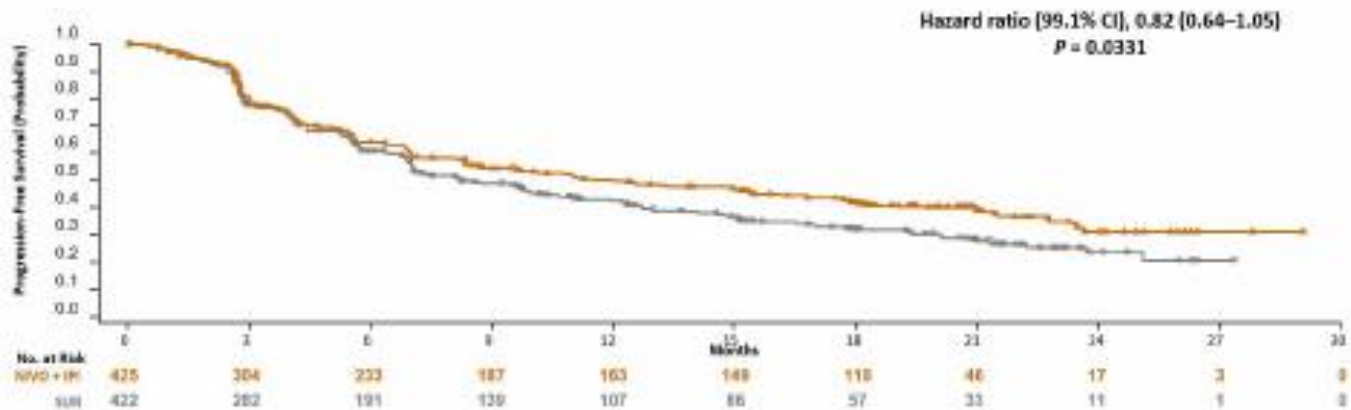
[a]IRRC-assessed ORR and BOR by RECIST v1.1; [b]P < 0.0001

Metastatik RCC'de; Nivolumab + Ipilimumab; Faz III - CheckMate 214

Intermediate/poor risk hastalar

	Median PFS, months (95% CI)
NIVO + IPI	11.6 (8.7–15.5)
SUN	8.4 (7.0–10.8)



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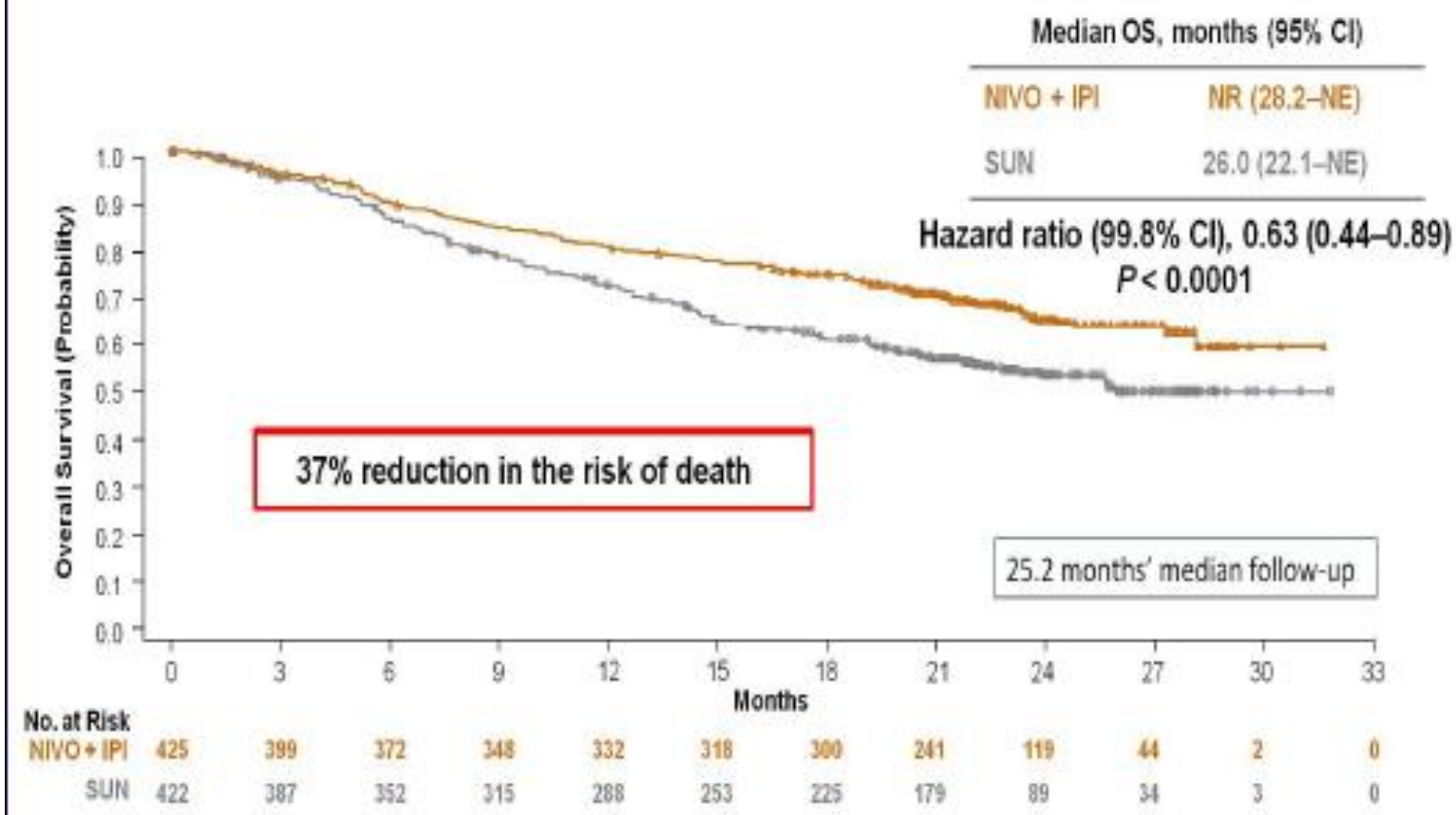
Co-primary endpoint

OS: IMDC intermediate/poor risk



Exploratory endpoint

ORR and PFS: IMDC favorable risk

Outcome	N = 249[a]	
	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	29 (21–38)	52 (43–61)
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) *P* < 0.0001	

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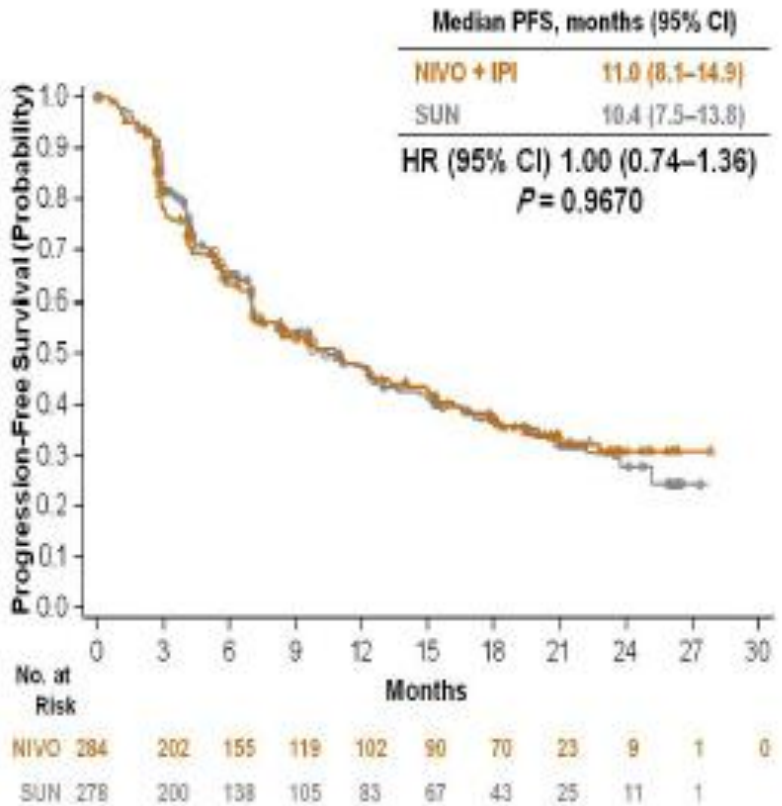
[a]11% of patients in both arms had tumor PD-L1 expression ≥1%
[b]IRRC-assessed by RECIST v1.1
[c]IRRC-assessed

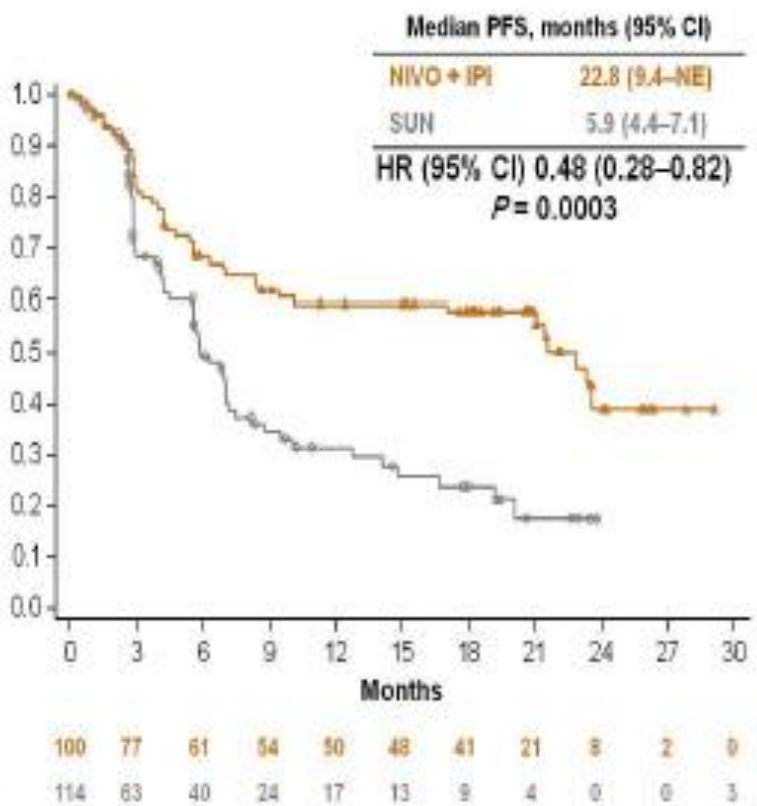
Exploratory endpoint

PFS by PD-L1 expression: IMDC intermediate/poor risk

PD-L1 <1% (n = 562)

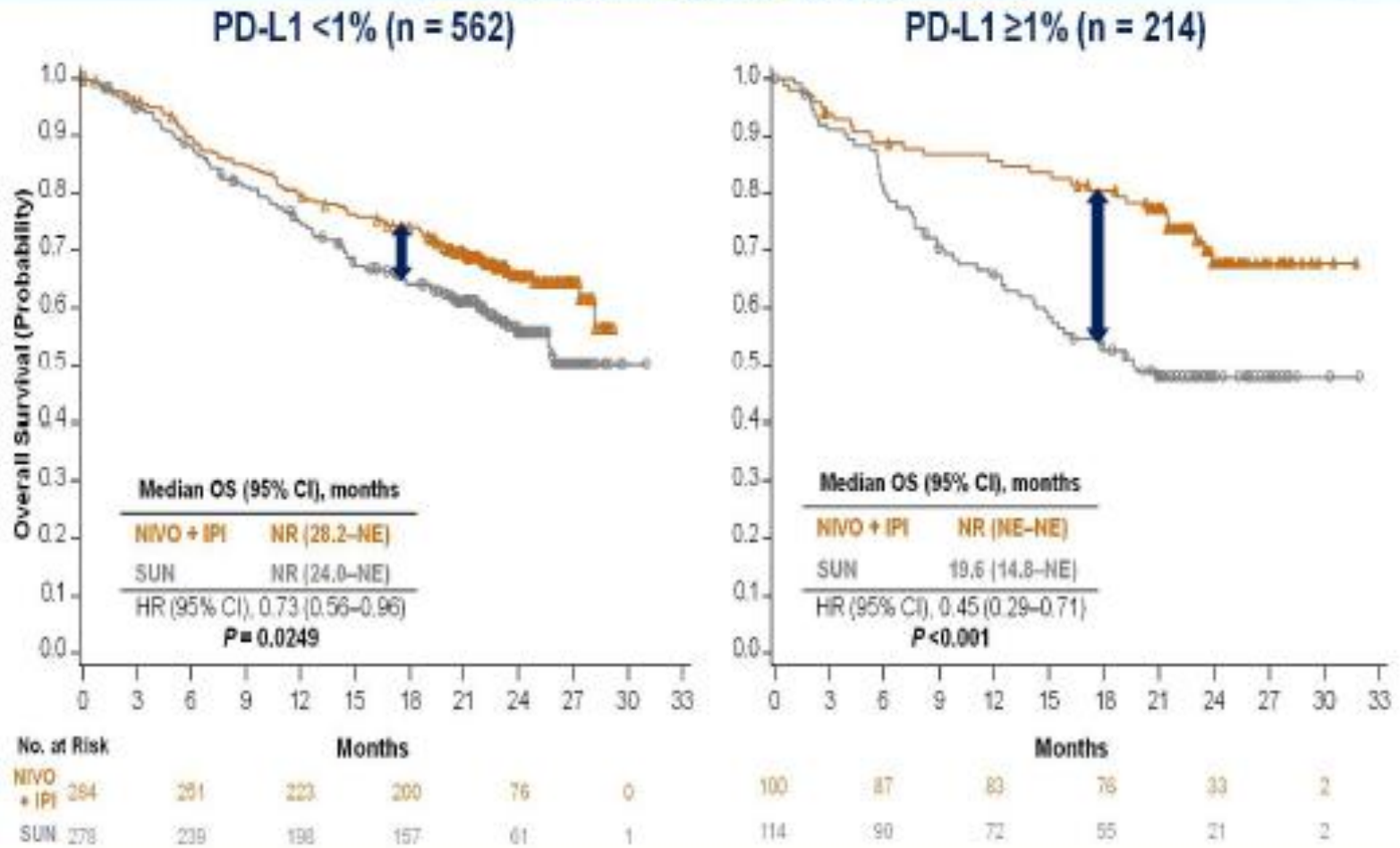


PD-L1 ≥1% (n = 214)



Motzer et al SITC 2017

OS by tumor PD-L1 expression: IMDC intermediate/poor risk



CheckMate 214: Güvenlik

TRAE, %	Nivo + Ipi (n = 547)		Sun (n = 535)	
	Any	Gr 3-5	Any	Gr 3-5
TRAE in ≥ 25% of pts	93	46	97	63
▪ Fatigue	37	4	49	9
▪ Pruritus	28	< 1	9	0
▪ Diarrhea	27	4	52	5
▪ Nausea	20	2	38	1
▪ Hypothyroidism	16	< 1	25	< 1
▪ Decreased appetite	14	1	25	1
▪ Dysgeusia	6	0	33	< 1
▪ Stomatitis	4	0	28	3
▪ Hypertension	2	< 1	40	16
▪ Mucosal inflammation	2	0	28	3
▪ Hand–foot syndrome	1	0	43	9

irAE,* %	Nivo + Ipi (n = 547)	
	Any	Gr 3-4
Rash	17	3
Diarrhea/colitis	10	5
Hepatitis	7	6
Nephritis & renal dysfunction	5	2
Pneumonitis	4	2
Hypersensitivity/infusion rx	1	0
Hypothyroidism	19	< 1
Hyperthyroidism	12	< 1
Adrenal insufficiency	8	3

*Additional irAE in ≤ 5% of pts: hypophysitis, thyroiditis, diabetes mellitus.

- Tx-related deaths: nivo + ipi, n = 7; sun, n = 4
- TRAE leading to d/c: nivo + ipi, 22%; sun, 12%

Escudier B, et al. ESMO 2017. Abstract LBA5.

CheckMate 214: ÖZET

- **Tüm hasta grubunda: GS, ORR açısından;** NIVO+IPI > SUN
- **IMDC intermediate/poor risk grubunda**
- Genel sağkalım NIVO + IPI kolunda daha iyi; ölüm riskinde %37 azalma
- Genel yanıt oranı: NIVO + IPI > SUN, (CR: 9.4%; uzun süreli yanıt)
- PFS: NIVO + IPI > SUN (>3 ay)
- **İyi risk grubundaki hastalarda;** SUN kolunda ORR ve PFS daha iyi

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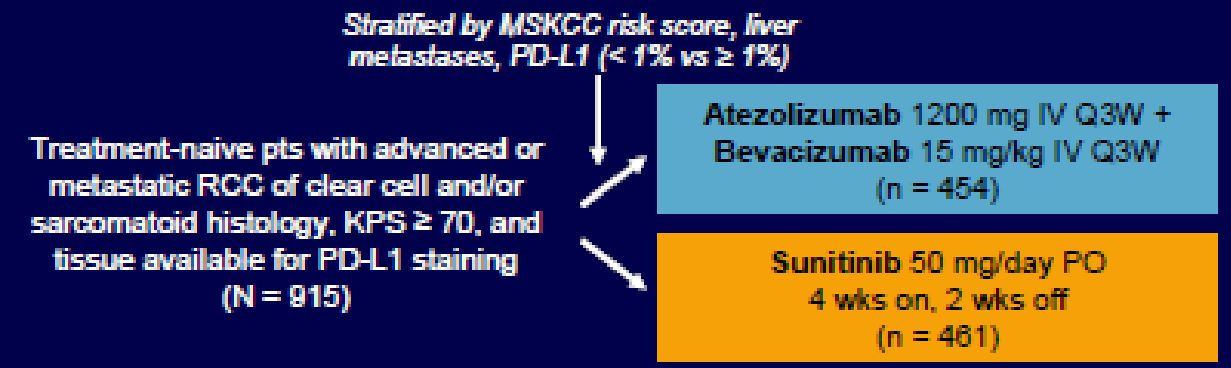
Atezolizumab + Bevacizumab vs Sunitinib: 1. basamak RCC (IMmotion151)

- Randomized, open-label phase III study



- Primary endpoints: PFS (investigator assessed) in PD-L1+ pts, OS in ITT pts
  - PD-L1+ defined as ≥ 1% staining on tumor-infiltrating immune cells by IHC
- Secondary endpoints: PFS in ITT pts, OS in PD-L1+ pts, ORR, DoR, PFS and ORR (IRC assessed), pt-reported outcomes, safety

Motzer RJ, et al. ASCO GU 2018. Abstract 578.

IMmotion 151: Hasta Özellikleri

Characteristic	PD-L1+		ITT	
	Atezo + Bev (n = 178)	Sunitinib (n = 184)	Atezo + Bev (n = 454)	Sunitinib (n = 461)
Median age, yrs (range)	62 (33-84)	59 (23-80)	62 (24-88)	60 (18-84)
Male, %	67	79	70	76
KPS ≥ 80, %	95	95	91	92
Liver metastasis, %	17	18	17	18
Prior nephrectomy, %	84	83	74	72
Predominant clear cell histology, %	92	87	93	92
Sarcomatoid component, %	20	27	15	16
≥ 1% PD-L1+ immune cells, %	--	--	39	40
MSKCC risk category, % •Favorable (0) •Intermediate (1/2) •Poor (≥ 3)	 17 74 8	 18 73 9	 20 71 10	 20 70 10

Motzer RJ, et al. ASCO GU 2018. Abstract 578.

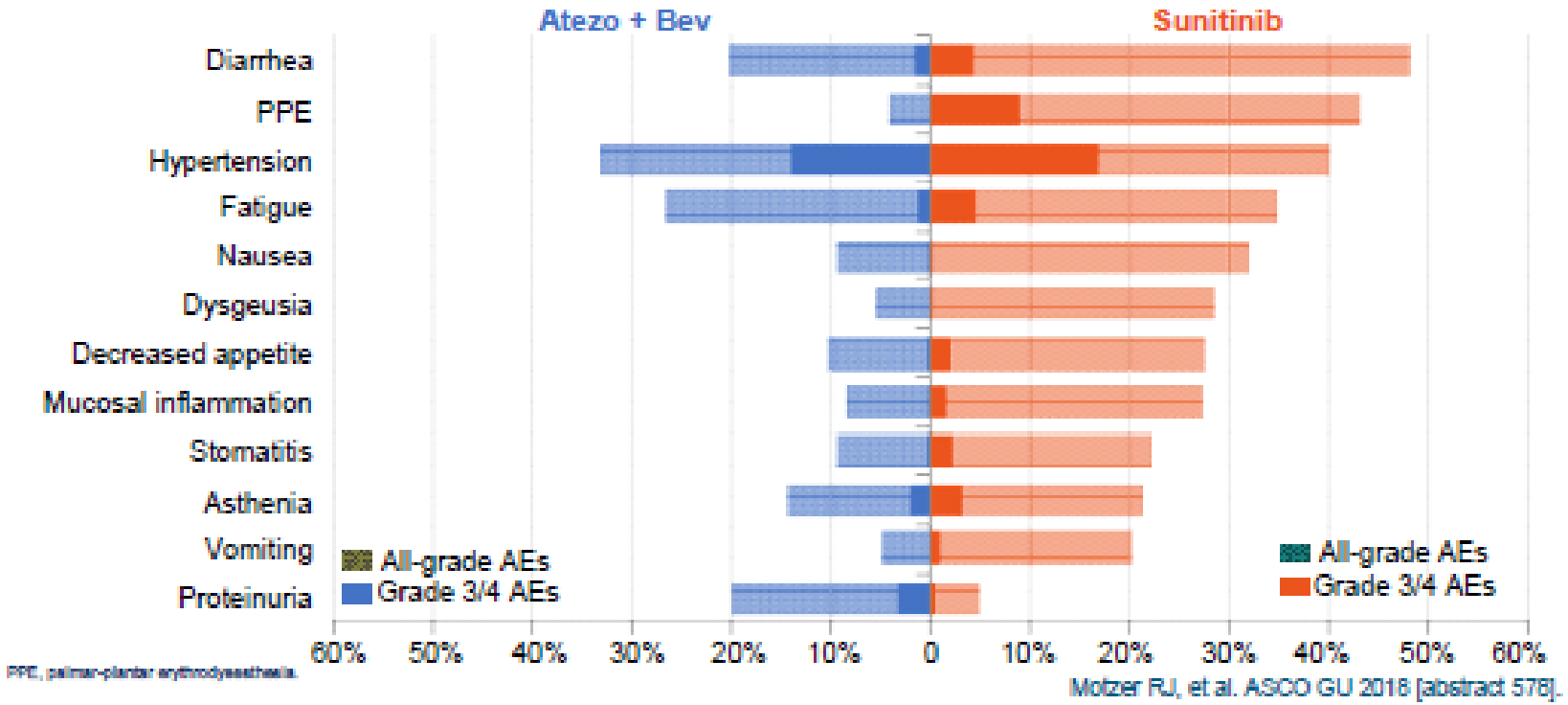
Immotion 151: Etkinlik Özeti

	PD-L1+		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 454	Sunitinib n = 461[a]
Median PFS, mo (95% CI)	11.2 (8.9, 15.0)	7.7 (6.8, 9.7)	11.2 (9.6, 13.3)	8.4 (7.5, 9.7)
Stratified HR, (95% CI)	0.74 (0.57, 0.96)		0.83 (0.70, 0.97)	
Overall survival, mo *Interim analysis*[b]	Not reached	23.3 (21.3, NR)	Not reached	Not reached
Stratified HR, (95% CI)	0.68 (0.46, 1.00)		0.81 (0.63, 1.03)[c]	
Confirmed ORR, % (95% CI)	43% (35, 50)	35% (28, 42)	37% (32, 41)	33% (29, 38)
Complete response	9%	4%	5%	2%

[a] n = 460 for ORR analysis.
[b] Event/patient ratio: PD-L1+, atezo + bev, 25% and sunitinib, 30%; ITT, atezo + bev, 23% and sunitinib, 31%.
[c] *P* = 0.03. The OS analysis did not pass the *P* value boundary of α = 0.0009 at the first interim analysis.
Response and progression assessed by investigator; minimum follow-up, 12 months. Median follow-up, 15 months.

Motzer RJ, et al. ASCO GU 2018 [abstract 578].

Tedavi İlişkili Yanetkiler: *Sıklık ≥ 20% ve kollar arasında > 5% fark*



PPE, palmar-plantar erythrodysesthesia.

Motzer RJ, et al. ASCO GU 2016 [abstract 578].

MUNICH 2018 ESMO Congress

JAVELIN Renal 101: Randomized Phase 3 Trial of Avelumab + Axitinib vs Sunitinib as First-Line Treatment of Advanced Renal Cell Carcinoma

Robert J. Motzer,[1] Konstantin Penkov,[2] John Haanen,[3] Brian Rini,[4] Laurence Albiges,[5] Matthew T. Campbell,[6] Christian Kollmannsberger,[7] Sylvie Negrier,[8] Motohide Uemura,[9] Jae Lyun Lee,[10] Howard Gurney,[11] Raanan Berger,[12] Manuela Schmidinger,[13] James Larkin,[14] Michael B. Atkins,[15] Jing Wang,[16] Paul B. Robbins,[17] Aleksander Chudnovsky,[16] Alessandra di Pietro,[18] and Toni K. Choueiri[19]

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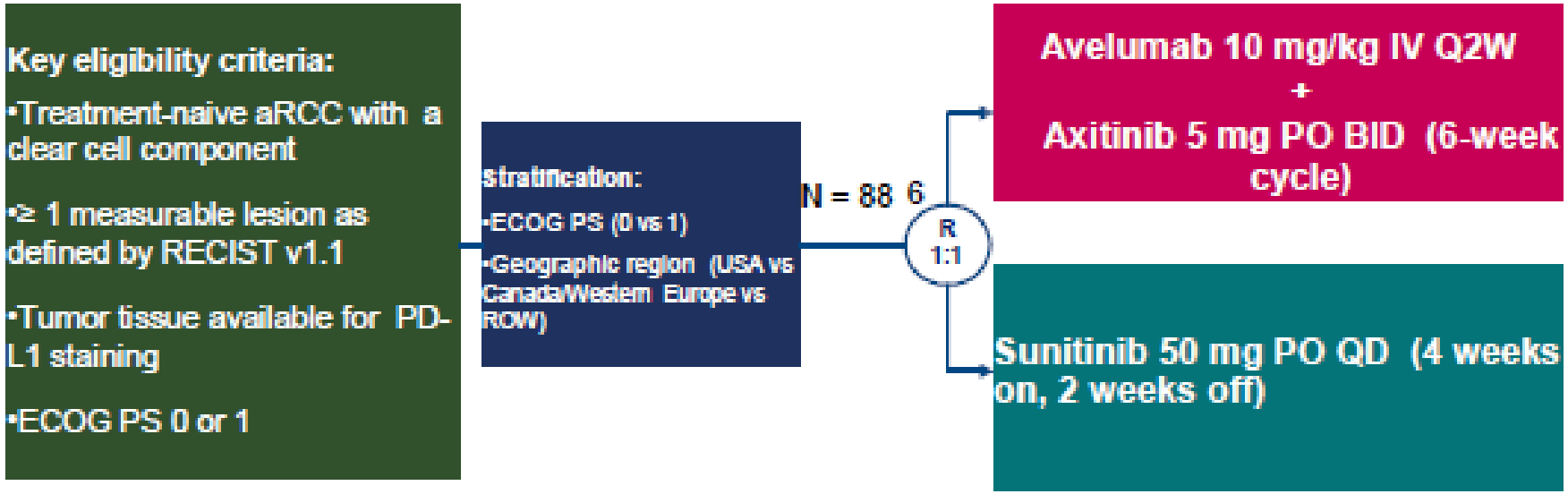
Abstract No. LBA6_PR

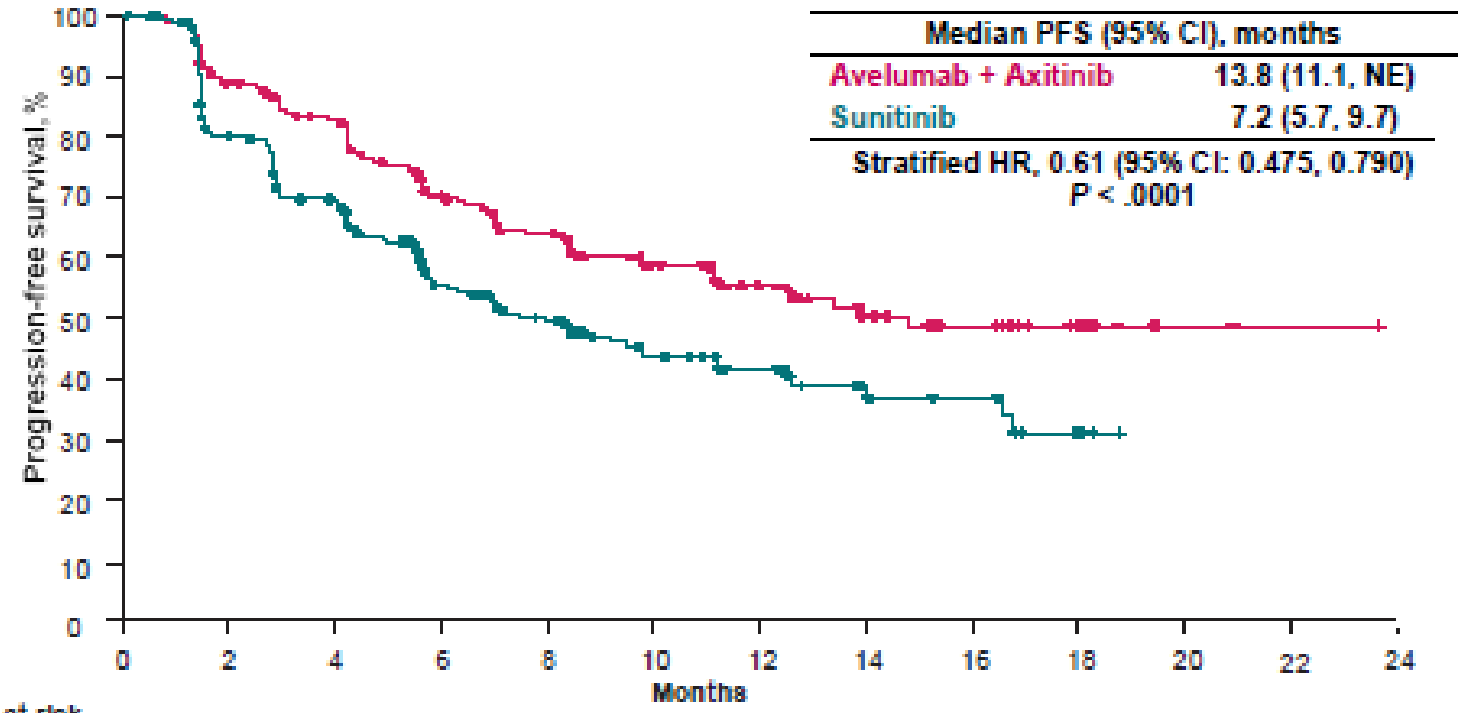
JAVELIN RENAL 101: STUDY DESIGN



BID, twice per day; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PO, orally; Q2W, every 2 weeks; QD, once per day; ROW, rest of the world.

PFS: PD-L1+ Hastalar (IRC)

Primary endpoint



Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function ($P = .001$).

NE, not estimable.

Yanıt Oranları

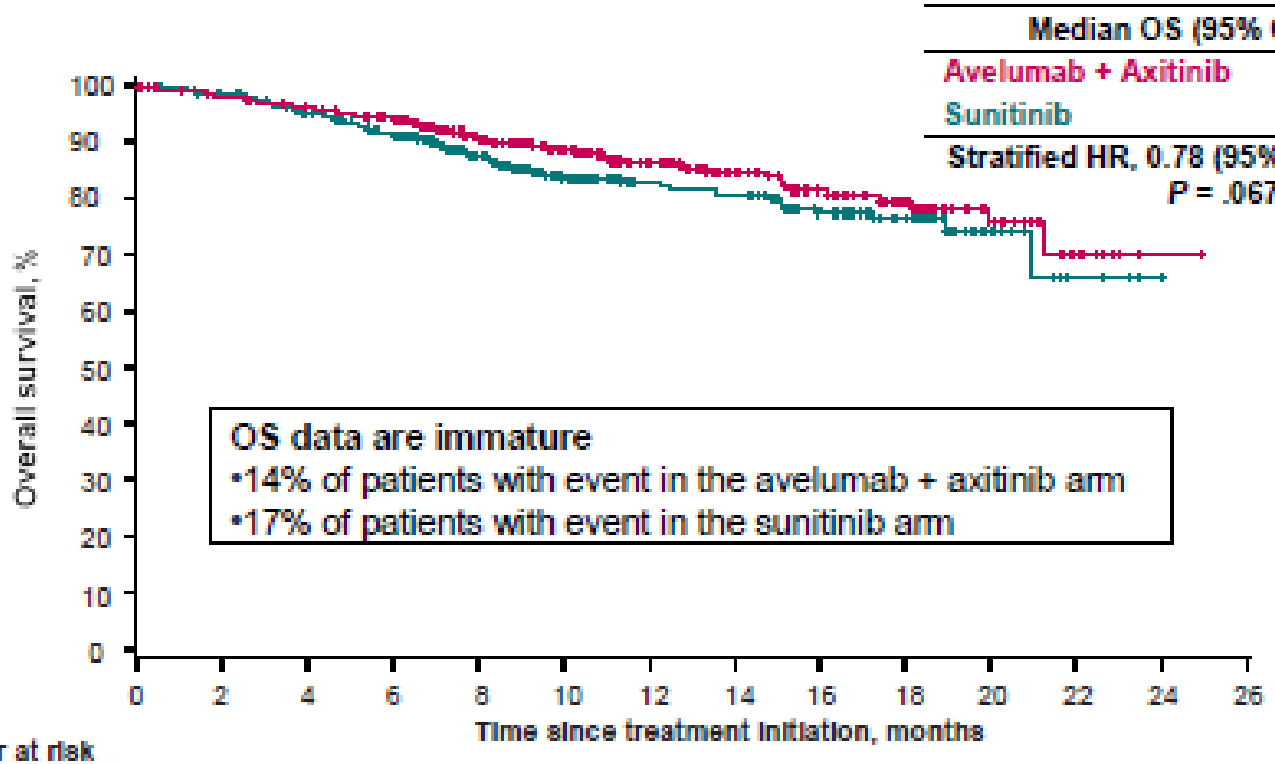
Secondary endpoint

Per IRC	PD-L1+ group (N = 560)		Overall population (N = 886)	
	Avelumab + Axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + Axitinib (N = 442)	Sunitinib (N = 444)
Objective response rate (95% CI), %	**55 (49.0, 61.2)**	**26 (20.6, 30.9)**	**51 (46.6, 56.1)**	**26 (21.7, 30.0)**
Best overall response, %*				
Complete response	4	2	3	2
Partial response	51	23	48	24
Stable disease	27	43	30	46
Progressive disease	11	22	12	19
Not evaluable†	4	7	6	8
Patients with ongoing response, %‡	73	65	70	71
Per investigator assessment				
Objective response rate (95% CI), %	**62 (55.8, 67.7)**	**30 (24.5, 35.3)**	**56 (51.1, 60.6)**	**30 (25.9, 34.7)**
Best overall response, %				
Complete response	4	3	3	2
Partial response	58	27	53	28

Median duration of response was not yet reached in either treatment arm in either population.

* Patients without target lesions at baseline per IRC who achieved non-complete response/non-progressive disease: 3% (avelumab + axitinib) and 2% (sunitinib) in the PD-L1+ group; 2% (avelumab + axitinib) and 2% (sunitinib) in the overall population. † Including patients with no postbaseline assessments. ‡ In patients with confirmed complete or partial response.

OS: Tüm Hastalar



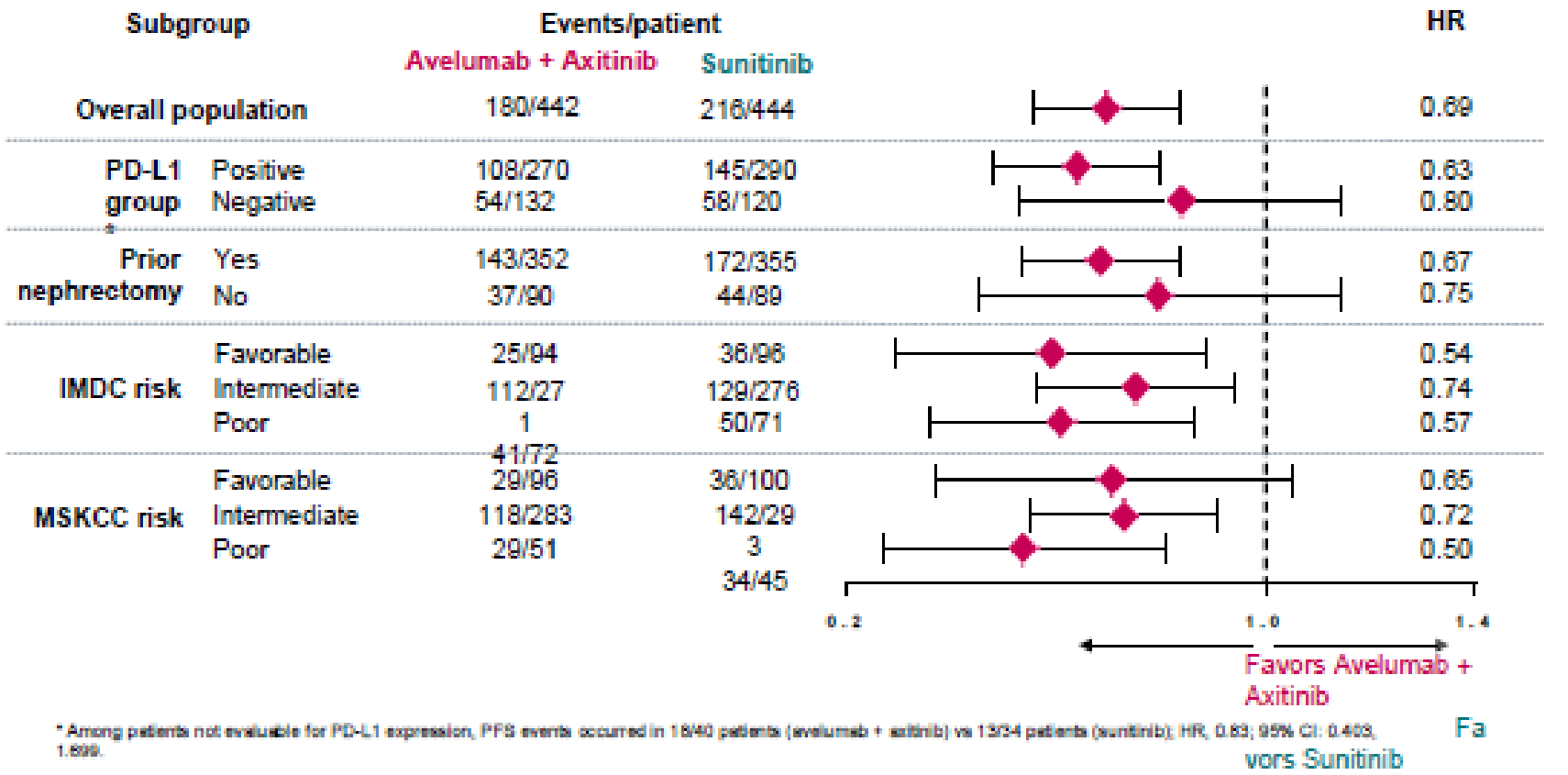
Number at risk

Avel + Axit:	442	426	412	396	319	252	187	121	93	70	27	8	1	0
Sunitinib:	444	426	401	373	295	224	175	113	84	59	17	5	1	0

Median follow-up, 12.0 months (avelumab + axitinib) and 11.5 months (sunitinib).

PFS: Alt grup Analizi

Subgroup analysis



* Among patients not evaluable for PD-L1 expression, PFS events occurred in 18/40 patients (avelumab + axitinib) vs 13/34 patients (sunitinib); HR, 0.83; 95% CI: 0.403, 1.699.

The ASCO Post

ABOUT NEWS MEETINGS TOPICS VIDEOS CME

2019 GU Cancers Symposium: KEYNOTE-426: Pembrolizumab Plus Axitinib vs Sunitinib in Advanced Renal Cell Carcinoma

Posted: 2/12/2019 3:30:22 PM
Last Updated: 2/12/2019 5:00:47 PM

Key Points

- At a median follow-up of 12.8 months, combination therapy was associated with a 47% reduction in the risk of

Results from the randomized, phase III KEYNOTE-426 clinical trial show that first-line therapy with a combination of pembrolizumab and axitinib extended both overall survival (OS) and

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Brian I. Rini, M.D., Elizabeth R. Plimack, M.D., Viktor Stus, M.D., Ph.D., Rustem Gafanov, M.D., Robert Hawkins, M.B., B.S., Ph.D., Dmitry Nosov, M.D., D.Sci., Frédéric Pouliot, M.D., Ph.D., Boris Alekseev, M.D., Denis Soulières, M.D., Bohuslav Melichar, M.D., Ph.D., Ihor Vynnychenko, M.D., Ph.D., Anna Kryzhanivska, M.D., et al., for the KEYNOTE-426 Investigators*

March 21, 2019
N Engl J Med 2019; 380:1116-1127
DOI: 10.1056/NEJMoa1816714

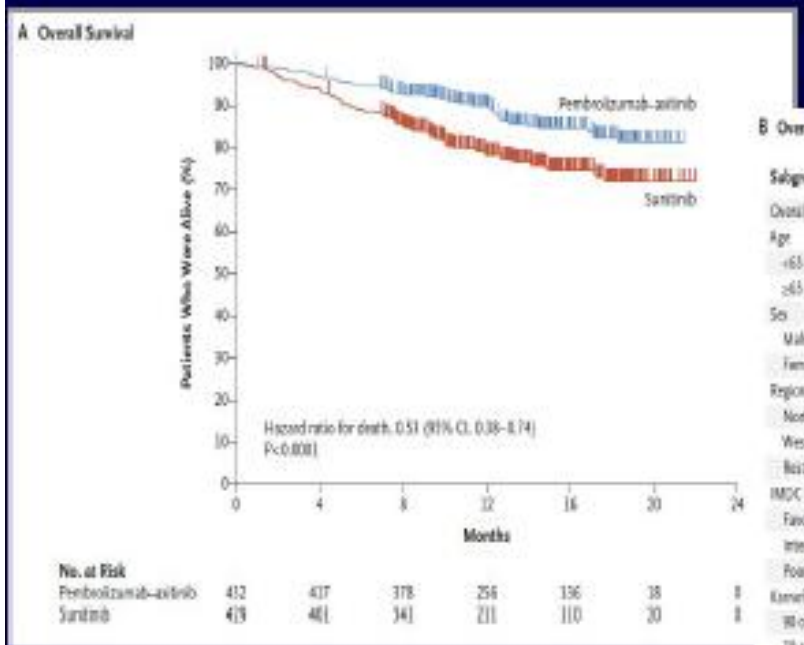
Abstract

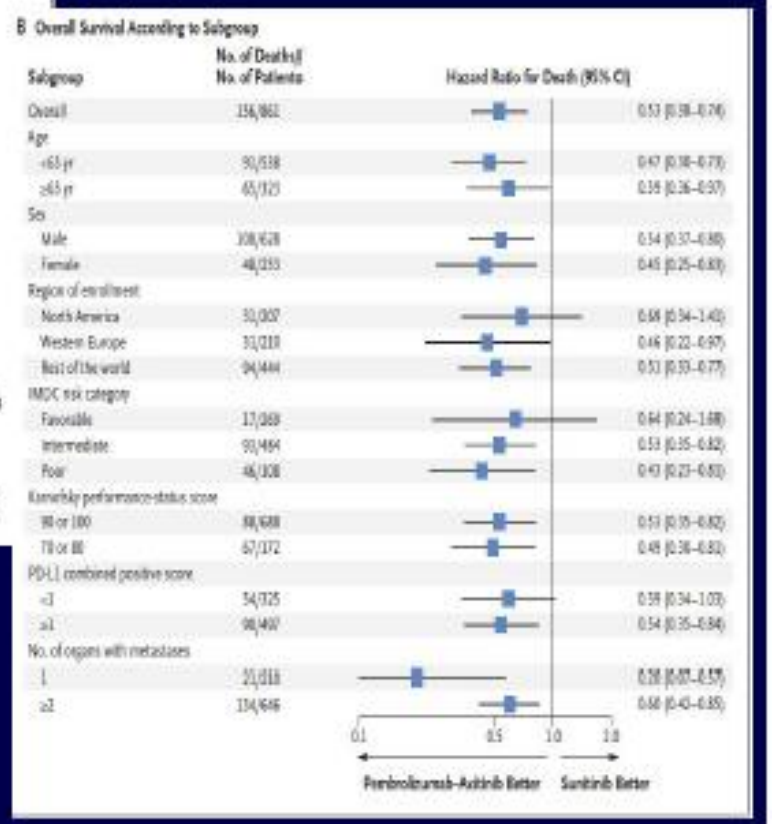

U.S. FOOD & DRUG
FDA approves pembrolizumab plus axitinib for advanced renal cell carcinoma
On April 19, 2019, the Food and Drug Administration approved pembrolizumab (KEYTRUDA, Merck & Co., Inc.) plus axitinib for the first-line treatment of patients with advanced renal cell carcinoma (RCC).
Approval was based on KEYNOTE-426 (NCT02853331), a randomized, multicenter, open-
KEYNOTE-426
Sunitinib
50 mg/day 4/2
R
N = 840
Axitinib + pembro
5 mg BID + 200 mg (IV) every 3 weeks

Keynote 426: Hasta Özellikleri

Characteristic	Pembrolizumab–Axitinib (N = 432)	Sunitinib (N = 429)
Age		
Median (range) — yr	62 (30–89)	61 (26–90)
<65 yr — no. (%)	260 (60.2)	278 (64.8)
Male sex — no. (%)	308 (71.3)	320 (74.6)
Region of enrollment — no. (%)		
North America	104 (24.1)	103 (24.0)
Western Europe	106 (24.5)	104 (24.2)
Rest of the world	222 (51.4)	222 (51.7)
IMDC prognostic risk — no. (%)†		
Favorable	138 (31.9)	131 (30.5)
Intermediate	238 (55.1)	246 (57.3)
Poor	56 (13.0)	52 (12.1)
Sarcomatoid features — no./total no. with known status (%)	51/285 (17.9)	54/293 (18.4)
PD-L1 combined positive score — no./total no. with data (%)‡		
≥1	243/410 (59.3)	254/412 (61.7)
<1	167/410 (40.7)	158/412 (38.3)
No. of organs with metastases — no. (%)§		
1	114 (26.4)	96 (22.4)
≥2	315 (72.9)	331 (77.2)
Most common sites of metastasis — no. (%)¶		
Lung	312 (72.2)	309 (72.0)
Lymph node	199 (46.1)	197 (45.9)
Bone	103 (23.8)	103 (24.0)
Adrenal gland	67 (15.5)	76 (17.7)
Liver	66 (15.3)	71 (16.6)
Previous radiotherapy — no. (%)	41 (9.5)	40 (9.3)
Previous nephrectomy — no. (%)	357 (82.6)	358 (83.4)

Keynote 426: OS ve Alt grup Analizi



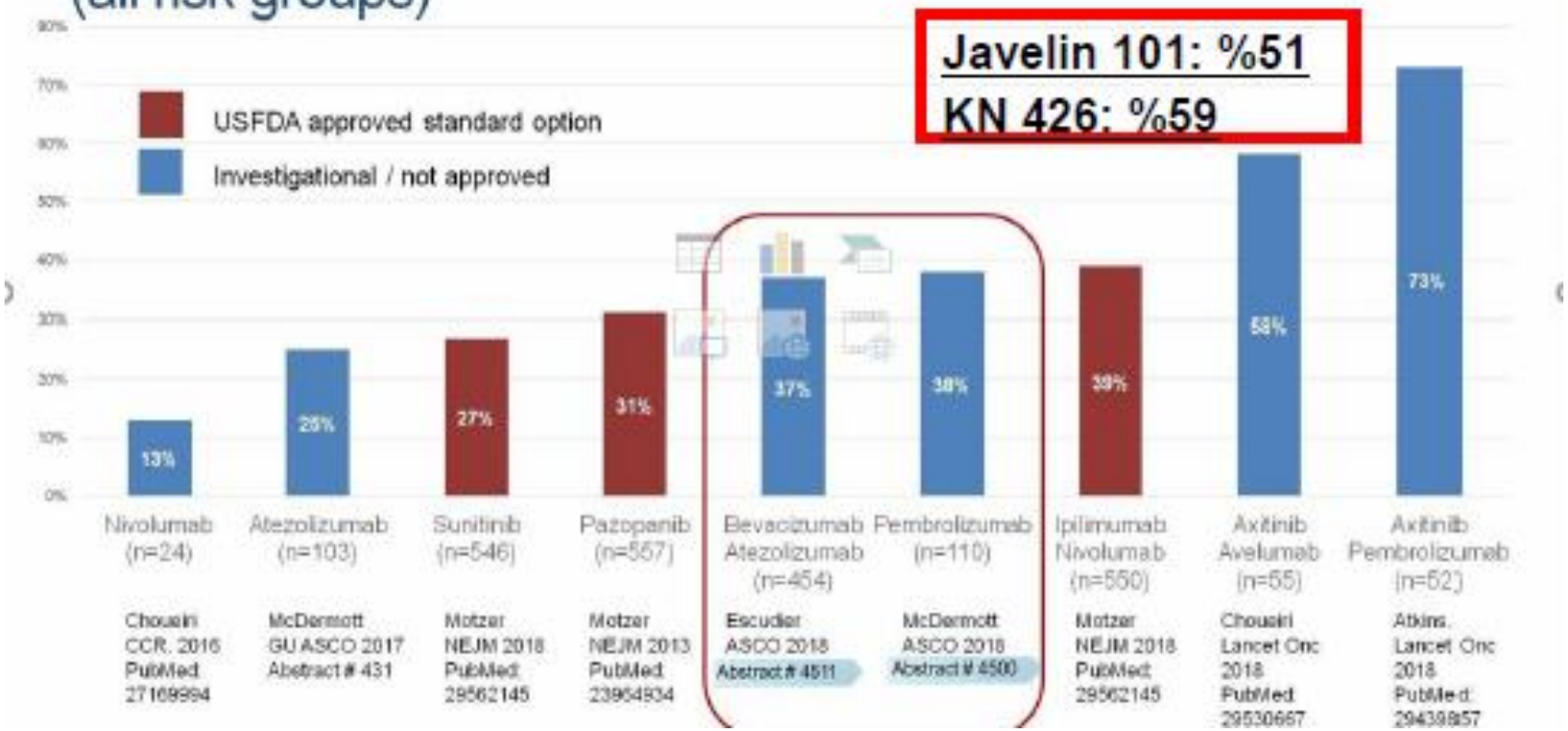


Keynote 426: Sonuçlar

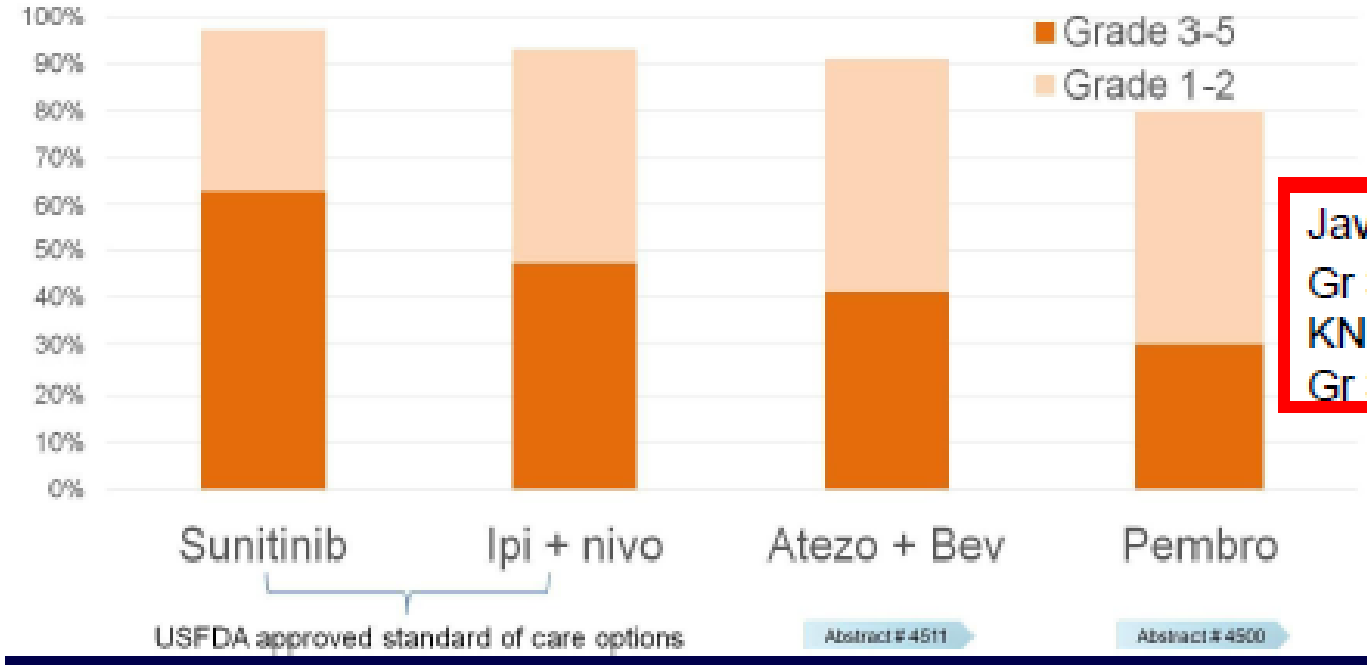
- **Axitinib + pembrolizumab** vs **sunitinib**
- N: 840, Medyan takip; 12.8 ay
- 12 ay OS oranı %89.9 vs % 78.3 (RR: %47); PDL-1'den bağımsız
- PFS: 15.1 vs 11.1 ay
- ORR: %59.3 vs %35.7
- Yanıt süresi: NR vs 15.2 ay
- Grad 3-4 toks: %62.9 vs %58.1
- Tedaviyi bırakma: %8.2 vs %10.1

B. Rini et al; N Engl J Med March 2019

Response Rates in Front Line metastatic ccRCC (all risk groups)



Treatment Related Adverse Events in Front Line metastatic ccRCC



Javelin:
Gr 3-5: %51
KN 426:
Gr 3-5: %63

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 (category 1) • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] • 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)

Teşekkür ederim…