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Nivolumab + Ipilimumab vs Sunitinib for Treatment-Naïve Advanced or Metastatic Renal Cell Carcinoma (RCC): Results From CheckMate 214, Including Overall Survival by Subgroups

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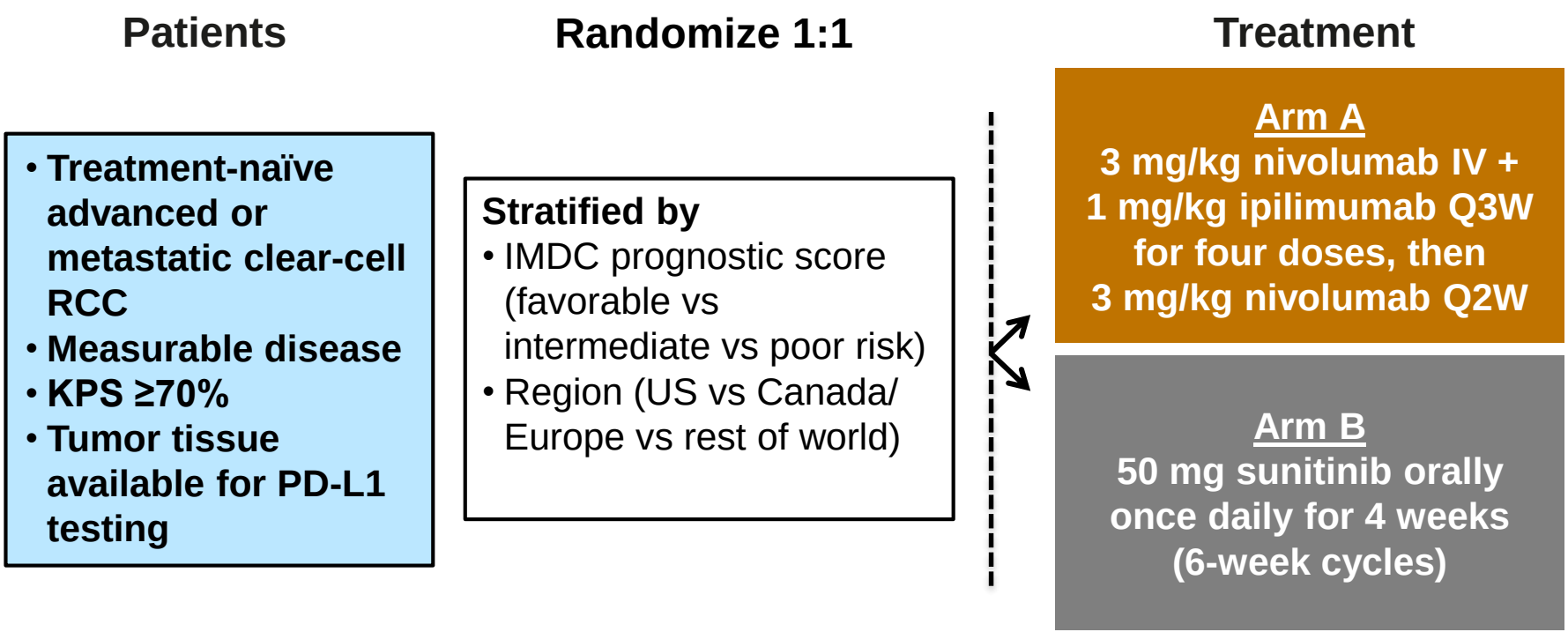
Introduction

- Nivolumab is a PD-1 inhibitor approved for previously treated aRCC
  - OS benefit with nivolumab compared with everolimus has been observed irrespective of PD-L1 expression level[1]
- Nivolumab + ipilimumab (CTLA-4 antibody) combination therapy (NIVO + IPI) has shown antitumor activity in aRCC in a phase Ib study[2]
- Here we report results from the phase III CheckMate 214 study of NIVO + IPI versus sunitinib (SUN) for treatment-naïve aRCC, including OS by subgroups

1. Motzer RJ et al. *N Engl J Med* 2015;373:1803–13. 2. Hammers HJ et al. *J Clin Oncol* 2017. doi:JCO2016721985.
aRCC, advanced RCC; CTLA-4, cytotoxic T-lymphocyte antigen-4

CheckMate 214: Study design



IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; Q2W, every 2 weeks; Q3W, every 3 weeks

IMDC risk categories for RCC

IMDC risk factors	IMDC risk categories[1]	Median OS in patients treated with anti-VEGF therapy[1]
• KPS of 70 • <1 year from diagnosis to randomization • Hemoglobin <LLN • Corrected calcium concentration >10 mg/dL • Absolute neutrophil count >ULN • Absolute platelet count >ULN	0 factors = favorable	43 months
	1–2 factors = intermediate	23 months
	3–6 = poor	8 months

1. Heng DYC et al. *Lancet Oncol* 2013; 14:141–48.

IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal

Endpoints

- **Co-primary endpoints: In IMDC intermediate- and poor-risk patients:**
  - ORR (per independent radiology review committee, IRRC)
  - PFS (per IRRC)
  - OS
  - Alpha was 0.001 for ORR, 0.009 for PFS, and 0.04 for OS
- **Key secondary endpoints:** ORR, PFS, OS in the intention-to-treat patients and adverse event incidence rate in all treated patients
- **Key exploratory endpoints:** Outcomes by tumor PD-L1 expression level[a] and quality of life based on NCCN FACT-Kidney Symptom Index

[a]Tumor PD-L1 membrane expression (≥1% vs <1%) was assessed in sections with ≥100 evaluable tumor cells using Dako PD-L1 IHC 28-8 pharmDx test
FACT, Functional Assessment of Cancer Therapy; IHC, immunohistochemical

Key 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 (CRF), %				
Favorable (0)[a]	2	2	23	23
Intermediate (1–2)	74	75	61	61
Poor (3–6)	24	23	17	16
Region, %				
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

[a]The 2% of patients in each arm who were reported as favorable risk per the case report form (CRF) were reported as intermediate risk per the interactive voice response system and were categorized as such for efficacy

Patient disposition and exposure

	All treated patients	
	NIVO + IPI N = 547	SUN N = 535
Treatment discontinuation, %	77	82
Reasons for treatment discontinuation, %		
Disease progression	42	55
Study drug toxicity	24	12
Adverse event unrelated to study drug	6	6
Other	4	9
Median duration of therapy (95% CI), months	7.9 (6.5–8.4)	7.8 (6.4–8.5)
Median doses received (range)		
Nivolumab	14 (1–63)	NA
Ipilimumab	4 (1–4)	NA
Median daily dose (range), mg/day	NA	31 (14–50)

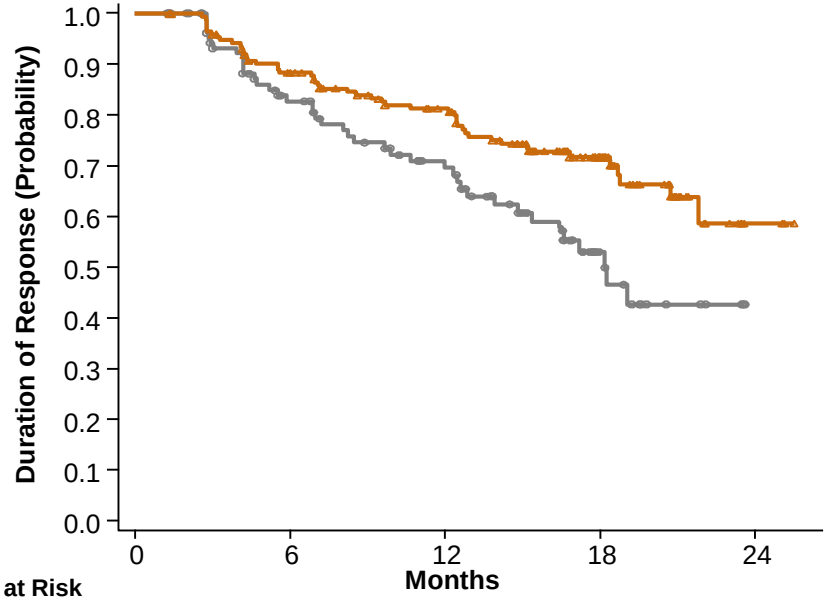
- In the NIVO + IPI arm, 79% of patients received all four doses of IPI
- Median follow-up was 25.2 months

ORR and DoR: IMDC intermediate/poor risk

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

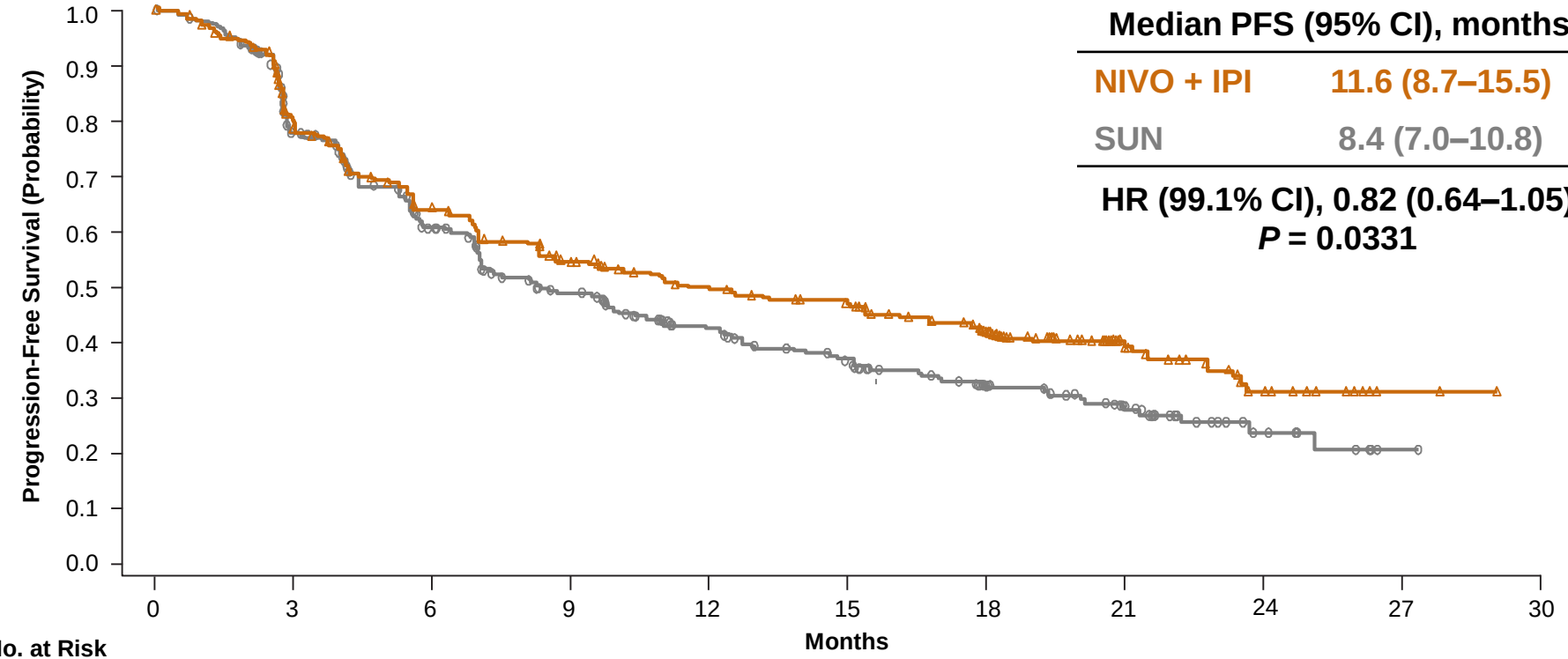
[a]IRRC-assessed confirmed ORR and BOR by RECIST v1.1; [b]*P* < 0.0001
BOR, best overall response; DoR, duration of response; NE, not estimable; NR, not reached

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



No. at Risk					
NIVO + IPI	177	146	120	55	3
SUN	112	75	52	17	0

PFS per IRRC: IMDC intermediate/poor risk

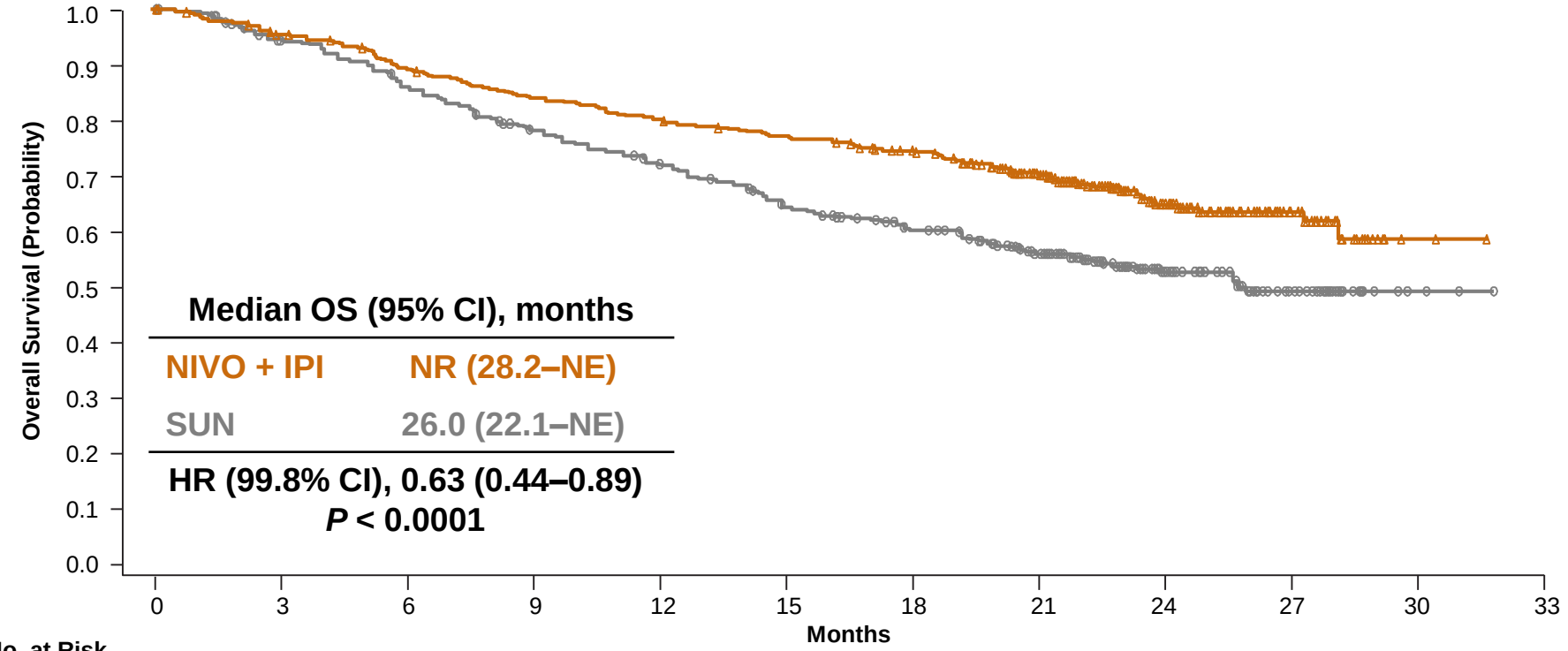


Median PFS (95% CI), months	
NIVO + IPI	11.6 (8.7–15.5)
SUN	8.4 (7.0–10.8)

HR (99.1% CI), 0.82 (0.64–1.05)
***P* = 0.0331**

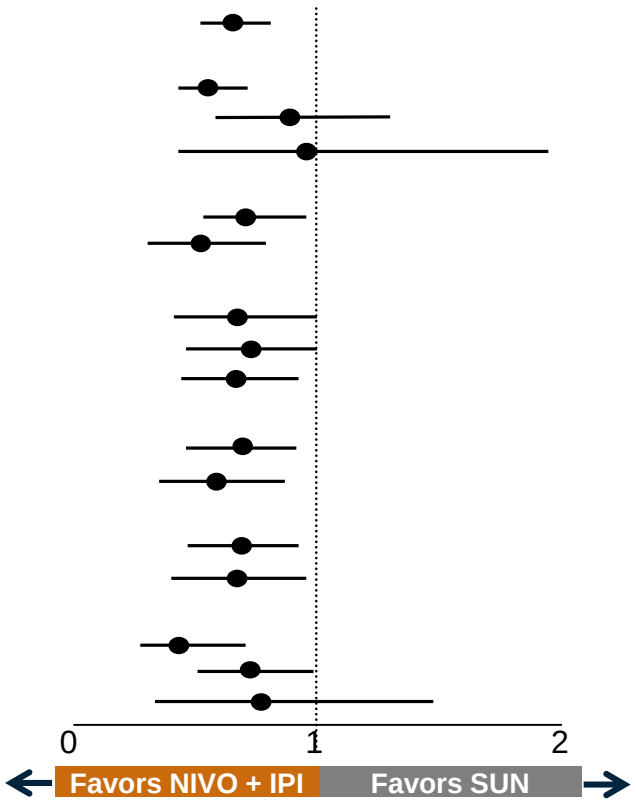
No. at Risk											
NIVO + IPI	425	304	233	187	163	149	118	46	17	3	0
SUN	422	282	191	139	107	86	57	33	11	1	0

OS: IMDC intermediate/poor risk



OS subgroup analysis: IMDC intermediate/poor risk

Subgroup	NIVO + IPI No. of patients	SUN No. of patients
Overall	**425**	**422**
Age, years		
<65	265	259
≥65 and <75	125	133
≥75	35	30
Sex		
Male	314	301
Female	111	121
Region		
USA	112	110
Canada/Europe	148	147
Rest of the world	165	165
Baseline IMDC prognostic score (CRF)		
1–2	314	317
3–6	102	97
Prior nephrectomy		
Yes	341	319
No	84	103
Baseline PD-L1 expression		
≥1%	100	114
<1%	284	278
Not reported	41	30



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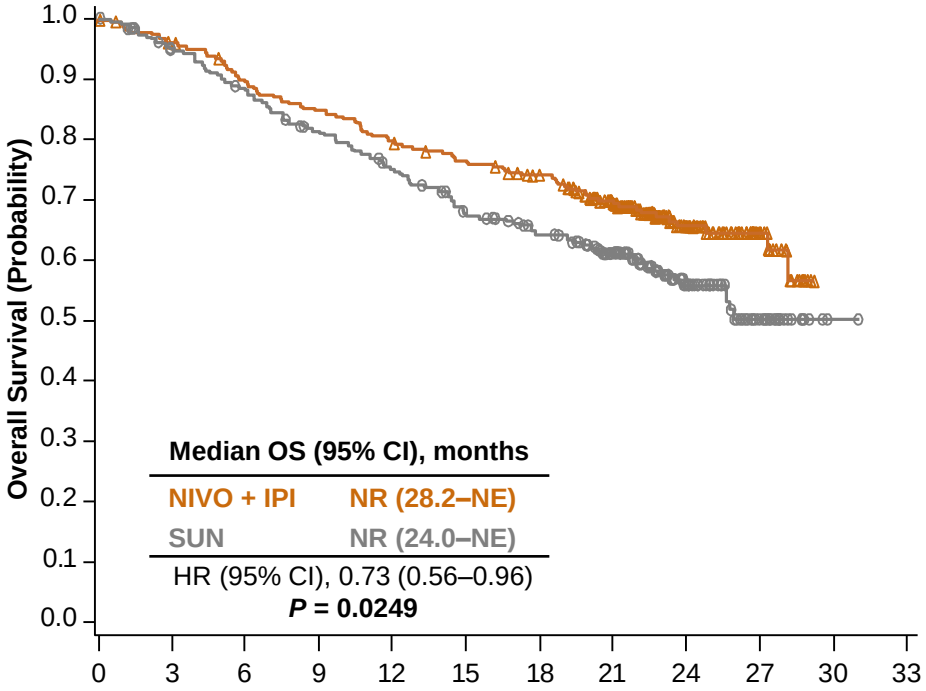
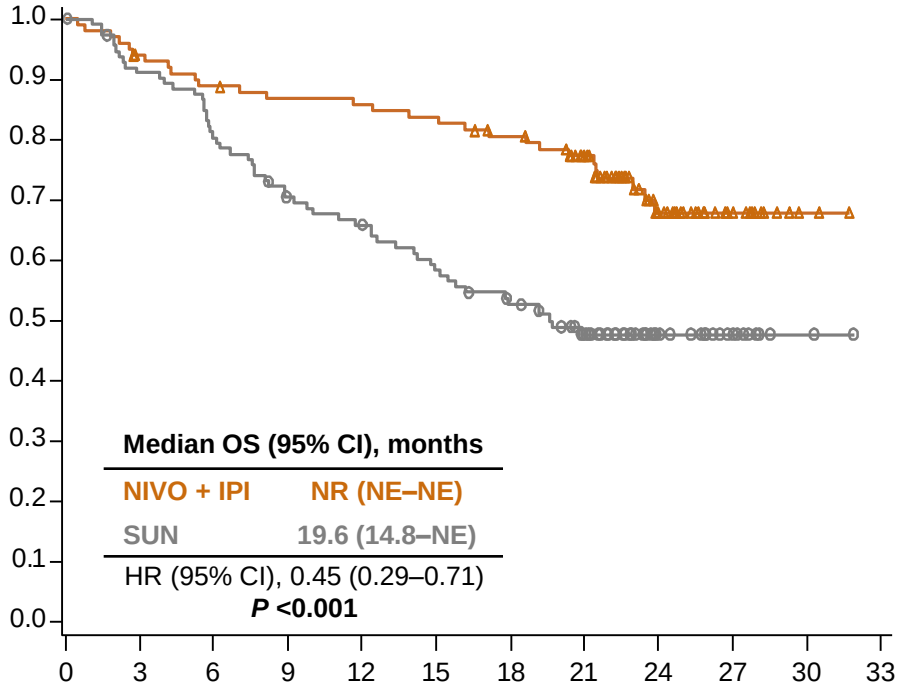
OS by tumor PD-L1 expression: IMDC intermediate/poor risk

PD-L1 <1% (n = 562)



No. at Risk	Months					
NIVO + IPI	284	251	223	200	76	0
SUN	278	239	198	157	61	1

PD-L1 ≥1% (n = 214)

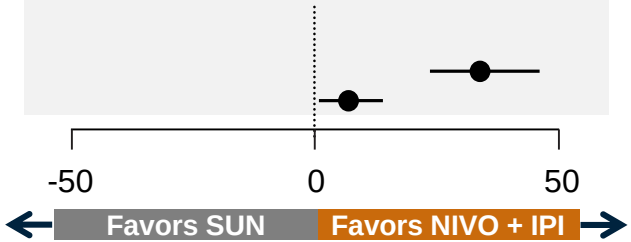


Months					
100	87	83	76	33	2
114	90	72	55	21	2

CheckMate 214, Motzer et al.

Efficacy by baseline PD-L1 expression: IMDC intermediate/poor risk

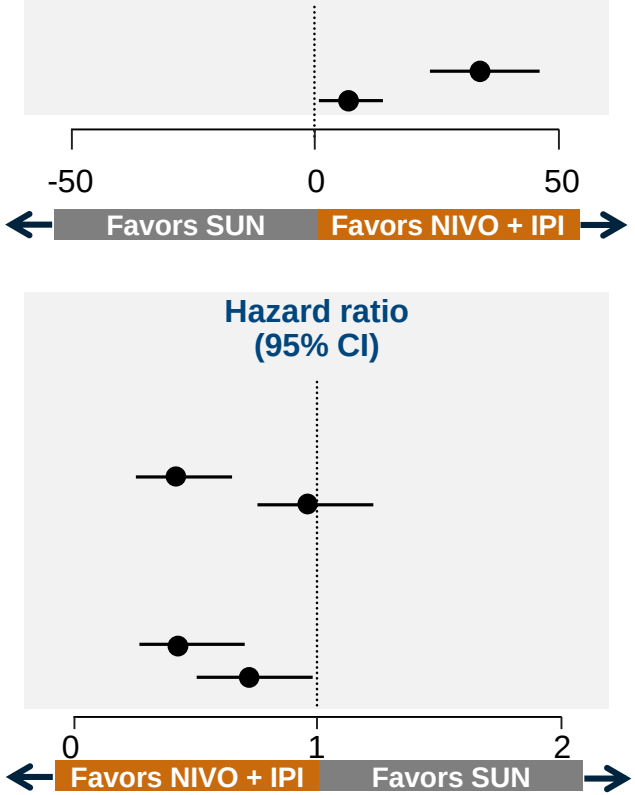
Subgroup	NIVO + IPI No. of patients	SUN No. of patients	ORR difference (95% CI)	*P* value
ORR				
Baseline PD-L1 expression				
≥1%	100	114		< 0.0001
<1%	284	278		0.0252



CheckMate 214, Motzer et al.

Efficacy by baseline PD-L1 expression: IMDC intermediate/poor risk

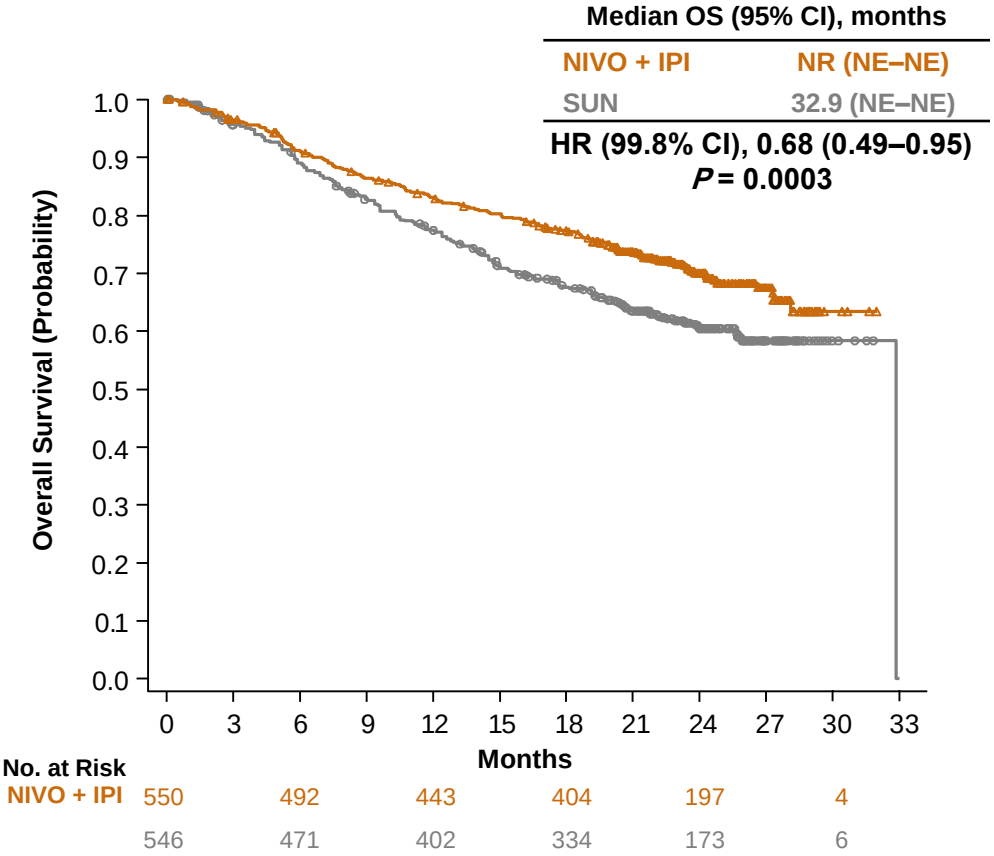
Subgroup	NIVO + IPI No. of patients	SUN No. of patients	ORR difference (95% CI)	*P* value
ORR				
Baseline PD-L1 expression				
≥1%	100	114		< 0.0001
<1%	284	278		0.0252
PFS			Hazard ratio (95% CI)	
Baseline PD-L1 expression				
≥1%	100	114		0.0003
<1%	284	278		0.9670
OS				
Baseline PD-L1 expression				
≥1%	100	114		<0.001
<1%	284	278		0.0249



ORR, PFS, and OS: Intention to treat

Outcome	N = 1,096[a]	
	NIVO + IPI N = 550	SUN N = 546
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 confirmed ORR by RECIST v1.1
[c]IRRC-assessed

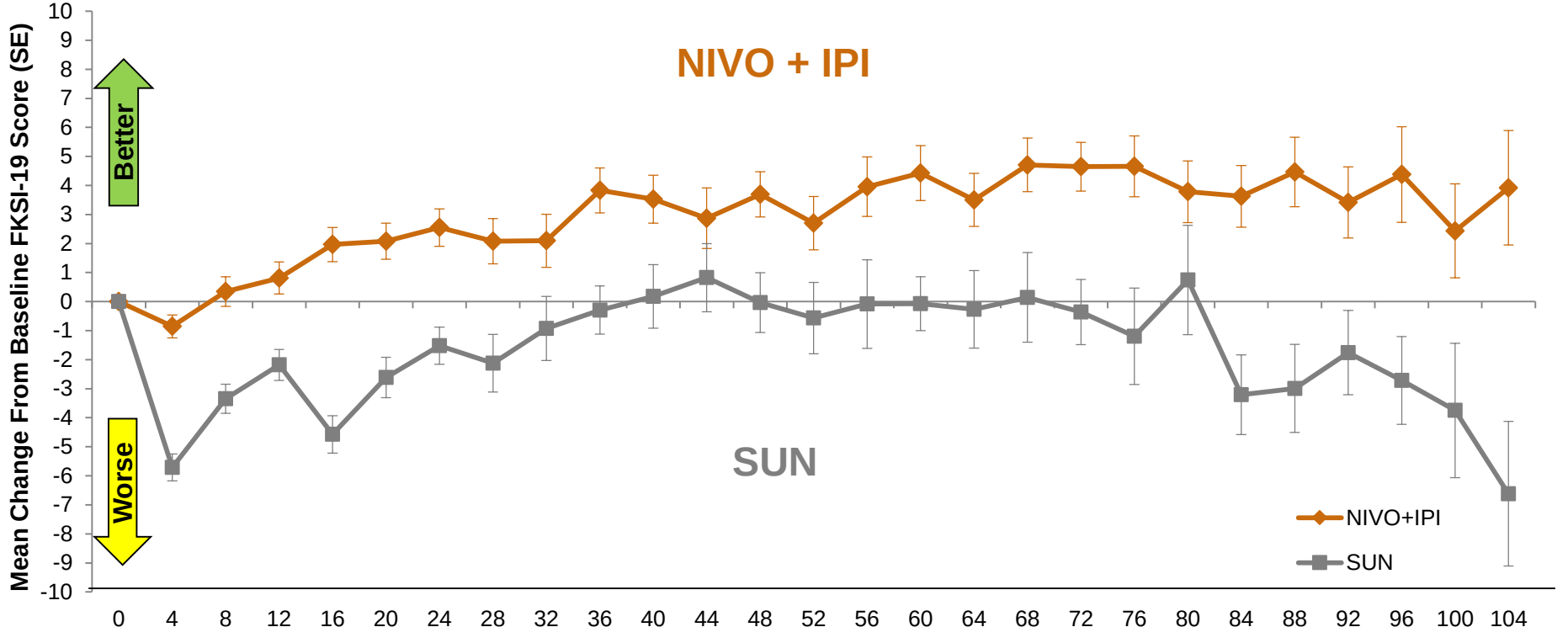


Treatment-related adverse events: All treated patients

Treatment-related event, %	NIVO + IPI N = 547		SUN N = 535	
	Any grade	Grade 3–4	Any grade	Grade 3–4[a]
AEs in ≥25% of patients	**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**
AEs leading to discontinuation, %	**22**		**12**	
Deaths	**n = 7[b]**		**n = 4[c]**	

[a]Two patients had grade 5 cardiac arrest. [b]Pneumonitis, immune mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c]Cardiac arrest (n = 2), heart failure, multiple organ failure

Patient-reported kidney cancer symptom index: IMDC intermediate/poor risk



No. at Risk														
NIVO + IPI	425	347	281	239	212	180	166	152	143	139	125	108	76	44
SUN	422	371	284	221	184	147	127	113	104	93	80	64	43	26

Conclusions

- CheckMate 214 met two primary endpoints, demonstrating superior OS and ORR with NIVO + IPI versus SUN in intermediate/poor-risk treatment-naïve aRCC
- OS benefit with NIVO + IPI was observed across PD-L1 expression levels and other subgroups
- The safety profile of NIVO + IPI was manageable with patients reporting better quality of life compared with SUN
- These results support the use of NIVO + IPI as a new first-line standard of care option for patients with intermediate/poor-risk aRCC

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