Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277-90. DOI: 10.1056/NEJMoa1712126

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Statistical methods: Intention-to-treat patients

A two-sided 95% confidence interval for the difference of objective response rate between treatment arms was computed for all randomized patients by the method of DerSimonian and Laird,[1] using a fixed-effects model (setting Δ^2 equal to zero), adjusting for the stratification factors. Progression-free survival and overall survival secondary efficacy endpoints were subject to hierarchical testing, first testing in intermediate/poor-risk patients, and if significant, followed by testing in the intention-to-treat patients. If for each endpoint the statistical test is not significant in intermediate/poor-risk patients, that efficacy endpoint in the intention-to-treat patients was only for qualitative purposes.

Discontinuation criteria

Nivolumab plus ipilimumab

Patients who developed grade 2 drug-related uveitis or eye pain or blurred vision that did not respond to topical therapy and did not improve to grade 1 severity within the re-treatment period or required systemic treatment were required to discontinue. Patients who developed a non-skin grade 3 or higher nivolumab-related or ipilimumab-related adverse event that remained grade 3 or higher for more than 7 days were required to discontinue both drugs, except for grade 3 uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, and hypersensitivity reactions, which required discontinuation regardless of duration. Patients who developed drug-related aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 8× the upper limit of normal (ULN); total bilirubin > 5× ULN; concurrent AST or ALT > 3× ULN and total bilirubin > 2× ULN; and any drug-related Grade 4 laboratory abnormality (excluding asymptomatic Grade 4 amylase or lipase elevations) were also required to discontinue study treatment. Patients with adverse events necessitating treatment discontinuation during the nivolumab plus ipilimumab induction phase had to discontinue both drugs irrespective of the attribution of the adverse event, and could not continue on to nivolumab maintenance therapy.

Sunitinib

Patients were required to permanently discontinue sunitinib if more than two sunitinib dose reductions occurred. Discontinuation was also required for any-grade drug-related arterial thrombosis, as well as any grade 4 drug-related symptomatic venous thrombosis, cardiac toxicity, hemorrhage, or recurrent grade 3 hemorrhage after dose reduction; two or more symptomatic episodes of hypertension despite modification of antihypertensive medication(s) and reduction of sunitinib dose; any drug-related liver function test abnormality that met the following criteria: AST or ALT > 8× the ULN or concurrent AST or ALT > 3× ULN and total bilirubin >2× ULN.

Health-related quality of life functional assessment of cancer therapy-kidney symptom index (FKSI-19)

The FKSI-19 uses five Likert-type response categories that range from "not at all" to "very much." Patients are asked to circle the response category that best characterizes their response over the past 7 days on 19 items that include symptoms such as lack of energy, fatigue, appetite, coughing, shortness of breath, pain, nausea, and ability to work. FKSI-19 scores range from 0 to 76, with higher scores indicating fewer symptoms.

Figure S1. CONSORT Diagram for Patient Disposition.

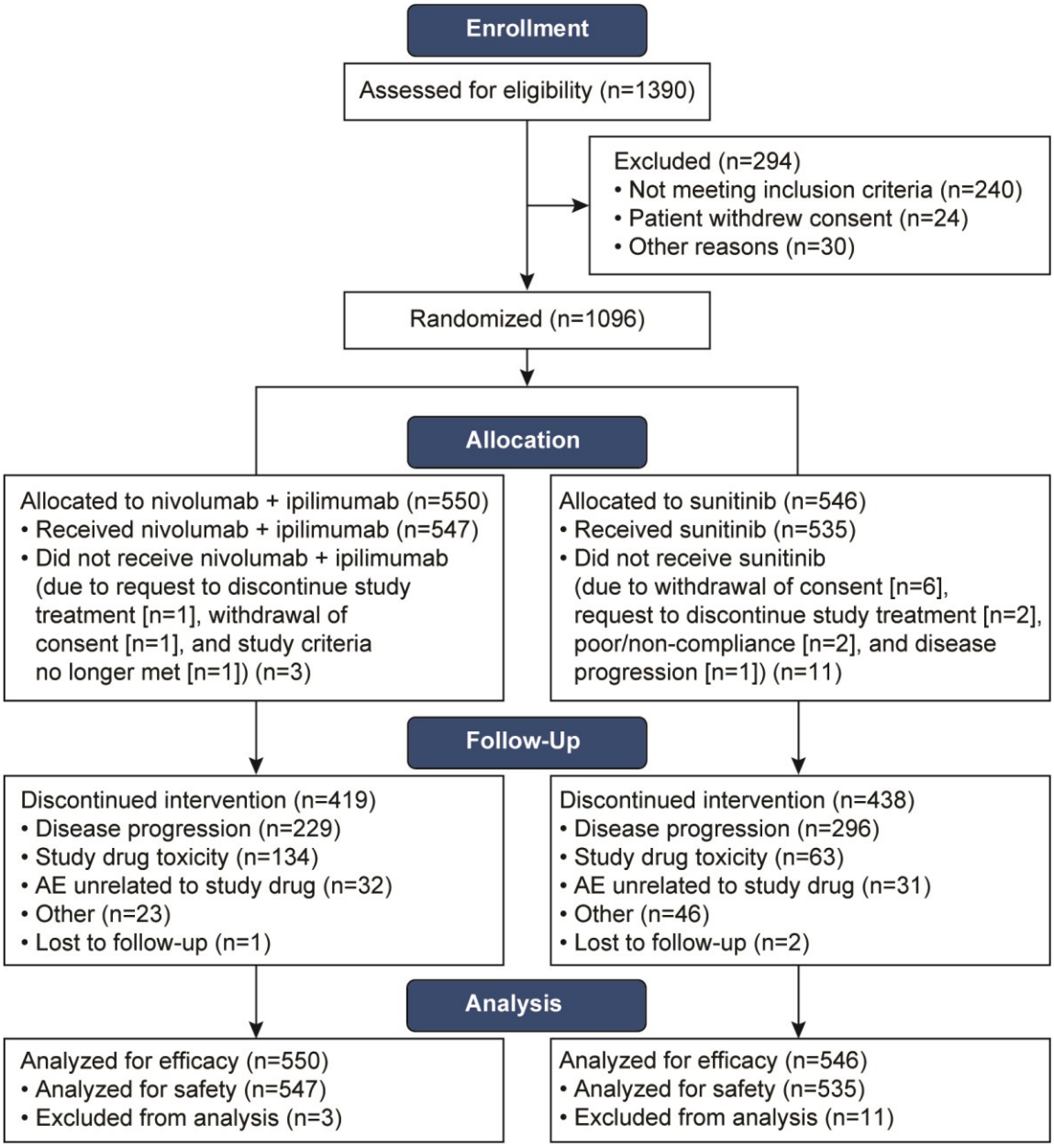
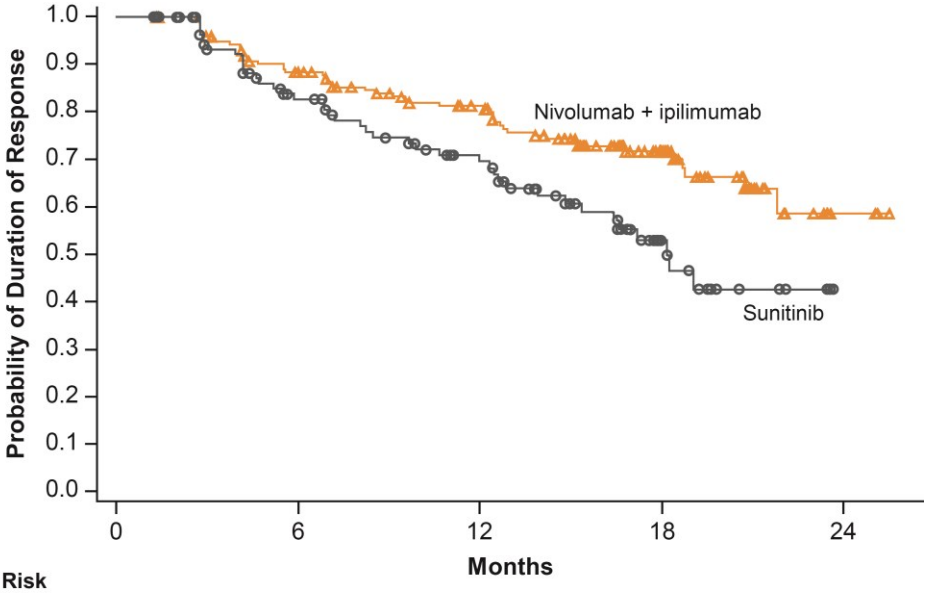


Figure S2. Duration of Response in IMDC Intermediate- and Poor-risk Patients. IPI denotes ipilimumab; NIVO, nivolumab; SUN, sunitinib



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

Figure S3. Subgroup Analysis of Objective Response Rate in IMDC Intermediate/Poor-risk Patients.

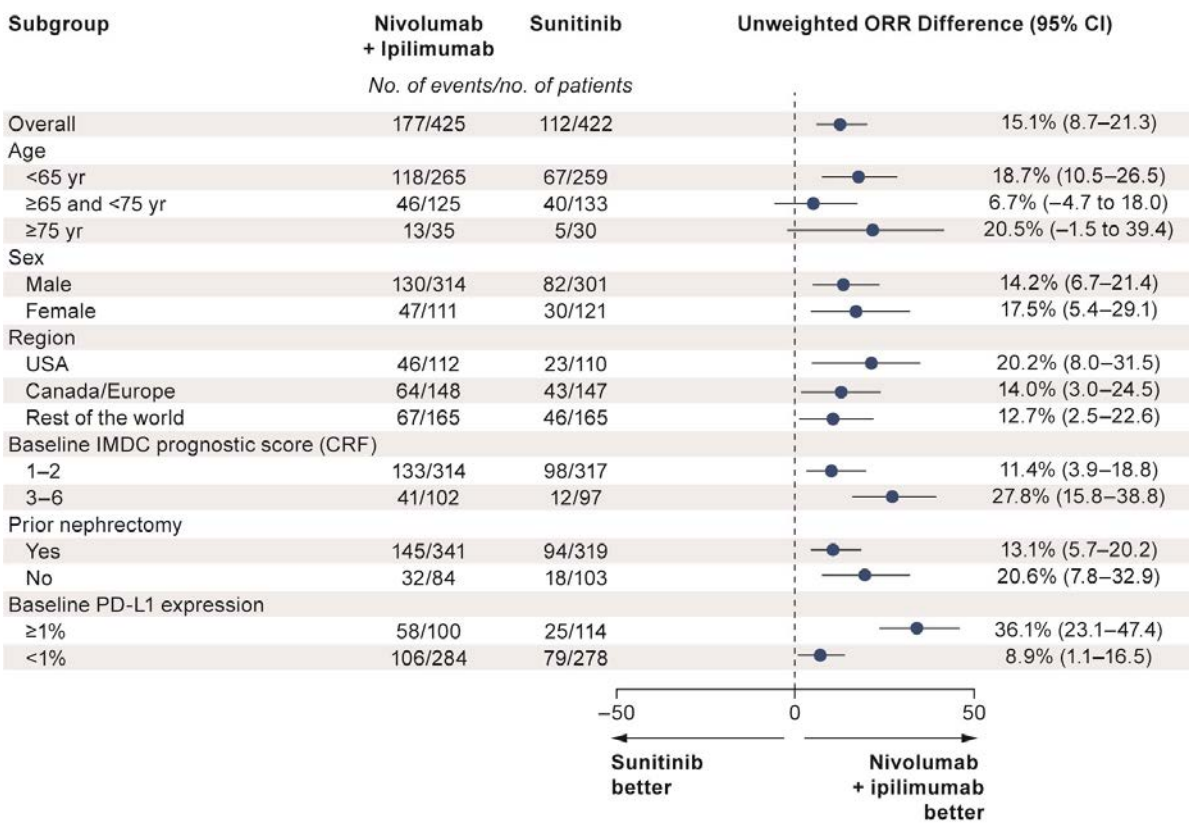
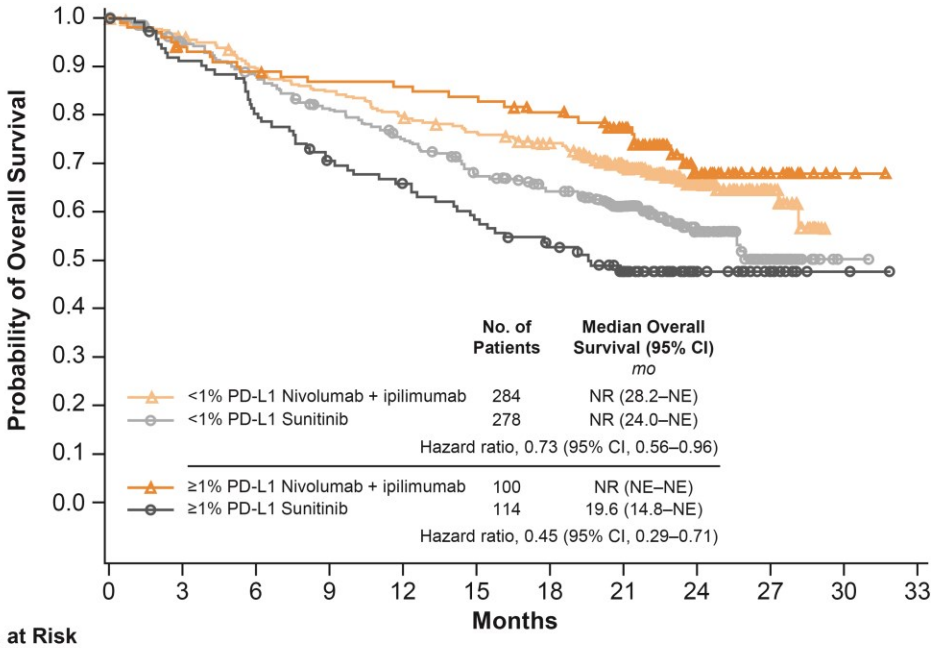


Figure S4. Kaplan–Meier Curves for Overall Survival According to PD-L1 Expression Level in IMDC Intermediate- and Poor-risk Patients



No. at Risk						
NIVO + IPI <1% PD-L1	284	251	223	200	76	0
SUN <1% PD-L1	278	239	198	157	61	1
NIVO + IPI ≥1% PD-L1	100	87	83	76	33	2
SUN ≥1% PD-L1	114	90	72	55	21	2

Table S1. IRRC-assessed and Investigator-assessed Objective Response Rates in IMDC Intermediate/Poor-risk Patients.

	IRRC-assessed*		**Investigator-assessed***	
Variable	**Nivolumab + Ipilimumab** (N=425)	**Sunitinib** (N=422)	**Nivolumab + Ipilimumab** (N=425)	**Sunitinib** (N=422)
Confirmed objective response rate, % (95% CI)	42 (37–47)	27 (22–31)	41 (36–46)	28 (24–33)
	P<0.001		P<0.001	
Confirmed best overall response — no. (%)				
Complete response	40 (9†)	5 (1†)	45 (11)	5 (1)
Partial response	137 (32)	107 (25)	129 (30)	114 (27)
Stable disease	133 (31)	188 (45)	113 (27)	179 (42)
Progressive disease	83 (20)	72 (17)	107 (25)	80 (19)
Unable to determine/not reported	32 (8)	50 (12)	31 (7)	44 (10)

* Assessed by RECIST v1.1.
† P < 0.001 per exploratory analysis.

Table S2. Demographic and Baseline Disease Characteristics of IMDC Favorable-risk Patients.

Characteristic*	**Nivolumab + Ipilimumab** (N=125)	**Sunitinib** (N=124)
Median age (range) — yr	62 (36–85)	63 (38–83)
Sex — no. (%)		
Male	99 (79)	94 (76)
Female	26 (21)	30 (24)
Region — no. (%)		
USA	42 (34)	42 (34)
Canada/Europe	53 (42)	53 (43)
Rest of the world	30 (24)	29 (23)
Quantifiable tumor PD-L1 expression† — no. (%)	N=115	N=111
<1%	102 (89)	98 (88)
≥1%	13 (11)	13 (12)
Prior radiotherapy — no. (%)	11 (9)	18 (15)
Prior nephrectomy — no. (%)	112 (90)	118 (95)
No. of sites with target/non-target lesions — no. (%)		
1	33 (26)	34 (27)
≥2	92 (74)	90 (73)
Sites of metastasis — no. (%)		

Lung	87 (70)	77 (62)
Lymph node	56 (45)	52 (42)
Pancreas	21 (17)	21 (17)
Bone‡	17 (14)	22 (18)
Liver	11 (9)	18 (15)

* Information shown in the table is based on data collected from the interactive voice response system.

† PD-L1 expression was not reported in 10 patients in the nivolumab plus ipilimumab arm and 13 patients in the sunitinib arm.

‡ Bone with and without soft-tissue component.

Table S3. Antitumor Activity by PD-L1 Expression Level in Intermediate/Poor-risk Patients.

	PD-L1 <1%		**PD-L1 ≥1%**	
Outcome	**Nivolumab + Ipilimumab N=284**	**Sunitinib N=278**	**Nivolumab + Ipilimumab N=100**	**Sunitinib N=114**
Objective response rate,* % (95% CI)	37 (32–43)	28 (23–34)	58 (48–68)	22 (15–31)
	P=0.0252†		P<0.001†	
Best overall response,* %				
Complete response	7	1	16	1
Partial response	30	27	42	21
Stable disease	36	47	19	40
Progressive disease	20	13	14	25
NA	7	12	9	13

* IRRC-assessed.
† Exploratory analyses.

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2. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14:141-48.