Additional Files

Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial

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

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Table S1 Demographic and baseline disease characteristics[1]

Variable[a]	IMDC Intermediate risk/ poor risk		ITT population		IMDC favorable risk	
	NIVO+IPI (N=425)	SUN (N=422)	NIVO+IPI (N=550)	SUN (N=546)	NIVO+IPI (N=125)	SUN (N=124)
Median age (range), years	62 (26–85)	61 (21–85)	62 (26–85)	62 (21–85)	62 (36–85)	63 (38–83)
Sex, n (%)						
Male	314 (74)	301 (71)	413 (75)	395 (72)	99 (79)	94 (76)
Female	111 (26)	121 (29)	137 (25)	151 (28)	26 (21)	30 (24)
IMDC prognostic score, n (%)						
Favorable (0)	0	0	125 (23)	124 (23)	125 (100)	124 (100)
Intermediate (1–2)	334 (79)	333 (79)	334 (61)	333 (61)	0	0
Poor (3–6)	91 (21)	89 (21)	91 (17)	89 (16)	0	0
Region, n (%)						
United States	112 (26)	111 (26)	154 (28)	153 (28)	42 (34)	42 (34)
Canada/Europe	148 (35)	146 (35)	201 (37)	199 (36)	53 (42)	53 (43)
Rest of the world	165 (39)	165 (39)	195 (35)	194 (36)	30 (24)	29 (23)
Prior radiotherapy, n (%)	52 (12)	52 (12)	63 (11)	70 (13)	11 (9)	18 (15)
Prior nephrectomy, n (%)	341 (80)	319 (76)	453 (82)	437 (80)	112 (90)	118 (95)
No. of sites with target/ nontarget lesions, n (%)[b]						
1	90 (21)	84 (20)	123 (22)	118 (22)	33 (26)	34 (27)
≥2	335 (79)	337 (80)	427 (78)	427 (78)	92 (74)	90 (73)
Sites of metastasis, n (%)[c]						
Lung	294 (69)	296 (70)	381 (69)	373 (68)	87 (70)	77 (62)
Lymph node	190 (45)	216 (51)	246 (45)	268 (49)	56 (45)	52 (42)
Bone[d]	95 (22)	97 (23)	112 (20)	119 (22)	17 (14)	22 (18)
Liver	88 (21)	89 (21)	99 (18)	107 (20)	11 (9)	18 (15)

Quantifiable tumor PD-L1 expression, n (%)	N=384	N=392	N=499	N=503	N=115	N=111
<1%	284 (74)	278 (71)	386 (77)	376 (75)	102 (89)	98 (88)
≥1%	100 (26)	114 (29)	113 (23)	127 (25)	13 (11)	13 (12)

[a]Information shown in the table is based on data collected with the use of an interactive voice-response system.
[b]The number of target or nontarget lesions at baseline was not reported for 1 patient in the SUN arm.
[c]Among favorable-risk patients, 21 (17%) patients in each arm had baseline pancreas lesions.
[d]Bone with and without soft-tissue component.

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ITT, intent-to-treat; NIVO+IPI, nivolumab plus ipilimumab; PD-L1, programmed death ligand 1; SUN, sunitinib.

REFERENCES

1. Motzer RJ, Tannir NM, McDermott DF, *et al. N Engl J Med* 2018;378:1277–90.

Table S2 Confirmed objective response per investigator in intermediate-risk/poor-risk patients, the intent-to-treat population, and in favorable-risk patients

Variable	**NIVO+IPI IMDC Intermediate risk/ poor risk (N=425)**	**NIVO+IPI ITT population (N=550)**	**NIVO+IPI IMDC favorable risk (N=125)**
Objective response rate, % (95% CI)	42.4 (37.6–47.2)	41.6 (37.5–45.9)	39.2 (30.6–48.3)
Best overall response, %			
Complete response	12.2	11.3	8.0
Partial response	30.1	30.4	31.2
Stable disease	25.6	29.8	44.0
Progressive disease	24.9	22.0	12.0
Unable to determine/not reported	7.1	6.5	4.8
Variable	**SUN IMDC Intermediate risk/ poor risk (N=422)**	**SUN ITT population (N=546)**	**SUN IMDC favorable risk (N=124)**
Objective response rate, % (95% CI)	29.4 (25.1–34.0)	34.1 (30.1–38.2)	50.0 (40.9–59.1)
Best overall response, %			
Complete response	1.4	2.2	4.8
Partial response	28.0	31.9	45.2
Stable disease	41.0	40.5	38.7
Progressive disease	19.2	15.9	4.8
Unable to determine/not reported	10.4	9.5	6.5

ITT, intent-to-treat; NIVO+IPI, nivolumab plus ipilimumab; SUN, sunitinib.

Table S3 Treatment-related adverse event summary

Variable[a]	N (%)			
	NIVO+IPI N=547		SUN N=535	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Overall treatment-related AEs[b]	514 (94.0)	259 (47.3)	521 (97.4)	343 (64.1)
Fatigue	208 (38.0)	24 (4.4)	266 (49.7)	52 (9.7)
Pruritis	160 (29.3)	3 (0.5)	49 (9.2)	0
Diarrhea	155 (28.3)	21 (3.8)	284 (53.1)	31 (5.8)
Rash	124 (22.7)	9 (1.6)	70 (13.1)	0
Nausea	110 (20.1)	8 (1.5)	207 (38.7)	7 (1.3)
Increased lipase	93 (17.0)	58 (10.6)	61 (11.4)	36 (6.7)
Hypothyroidism	89 (16.3)	2 (0.4)	141 (26.4)	1 (0.2)
Decreased appetite	76 (13.9)	7 (1.3)	135 (25.2)	6 (1.1)
Asthenia	74 (13.5)	10 (1.8)	93 (17.4)	13 (2.4)
Vomiting	61 (11.2)	4 (0.7)	115 (21.5)	10 (1.9)
Anemia	36 (6.6)	3 (0.5)	84 (15.7)	23 (4.3)
Dysgeusia	26 (4.8)	0	118 (22.1)	1 (0.2)
Stomatitis	25 (4.6)	0	151 (28.2)	14 (2.6)
Dyspepsia	16 (2.9)	0	97 (18.1)	0
Mucosal inflammation	15 (2.7)	1 (0.2)	154 (28.8)	15 (2.8)
Hypertension	12 (2.2)	4 (0.7)	220 (41.1)	91 (17.0)
Palmoplantar erythrodysesthesia	6 (1.1)	1 (0.2)	233 (43.6)	50 (9.3)
Thrombocytopenia	3 (0.5)	0	96 (17.9)	23 (4.3)
Treatment-related AE leading to discontinuation[c]	121 (22.1)	84 (15.4)	69 (12.9)	39 (7.3)

[a]Includes events reported between first dose and 30 days after last dose of study therapy.
[b]Listed are AEs that were reported in ≥15% of the patients in either arm.
[c]AEs of any grade that led to discontinuation in ≥5 patients in the NIVO+IPI arm were increased alanine aminotransferase (n=15), pneumonitis or diarrhea (both n=14), increased aspartate aminotransferase (n=12), colitis or hypophysitis (both n=7), and adrenal insufficiency (n=5); fatigue (n=7), and diarrhea or increased alanine aminotransferase (both n=5) led to discontinuation in ≥5 patients in the SUN arm.

AE, adverse event; NIVO+IPI, nivolumab plus ipilimumab; SUN, sunitinib.

Table S4 Select treatment-related adverse event summary

Organ class[a]	N (%)			
	NIVO+IPI N=547		SUN N=535	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Gastrointestinal	163 (29.8)	27 (4.9)	284 (53.1)	31 (5.8)
Hepatic	105 (19.2)	47 (8.6)	79 (14.8)	21 (3.9)
Skin	273 (49.9)	21 (3.8)	305 (57.0)	55 (10.3)
Endocrine	179 (32.7)	38 (6.9)	168 (31.4)	1 (0.2)
Pulmonary	37 (6.8)	6 (1.1)	2 (0.4)	0
Renal	56 (10.2)	7 (1.3)	47 (8.8)	6 (1.1)

[a]Includes potentially immune-mediated adverse events reported between first dose and 30 days after last dose of study therapy.

AE, adverse event; NIVO+IPI, nivolumab plus ipilimumab; SUN, sunitinib.

Figure S1. CONSORT diagram.

Twenty-four intermediate-risk/poor-risk patients crossed over from sunitinib to nivolumab plus ipilimumab after the primary endpoint was assessed but were not analyzed as part of the nivolumab plus ipilimumab efficacy or safety population.

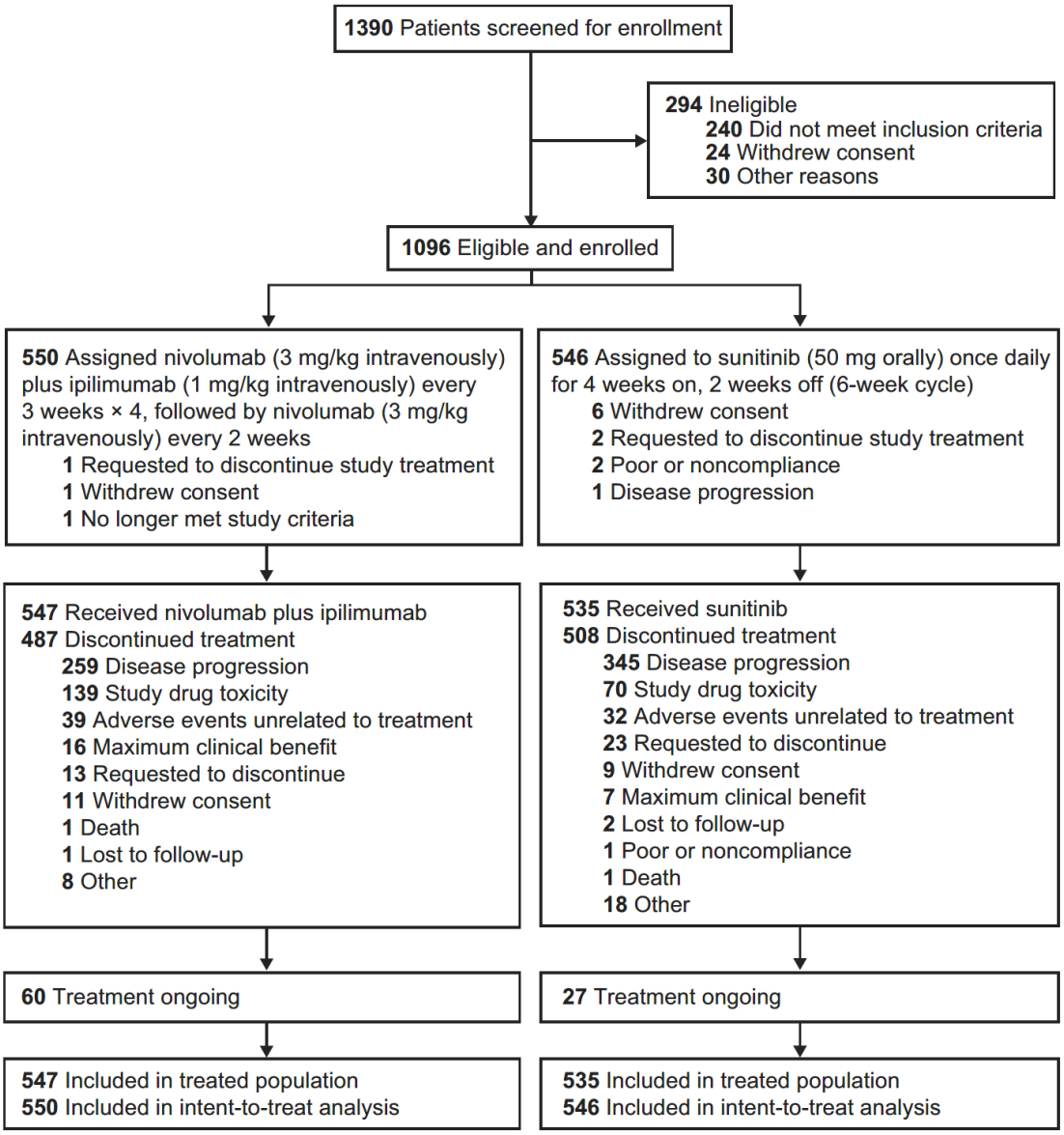
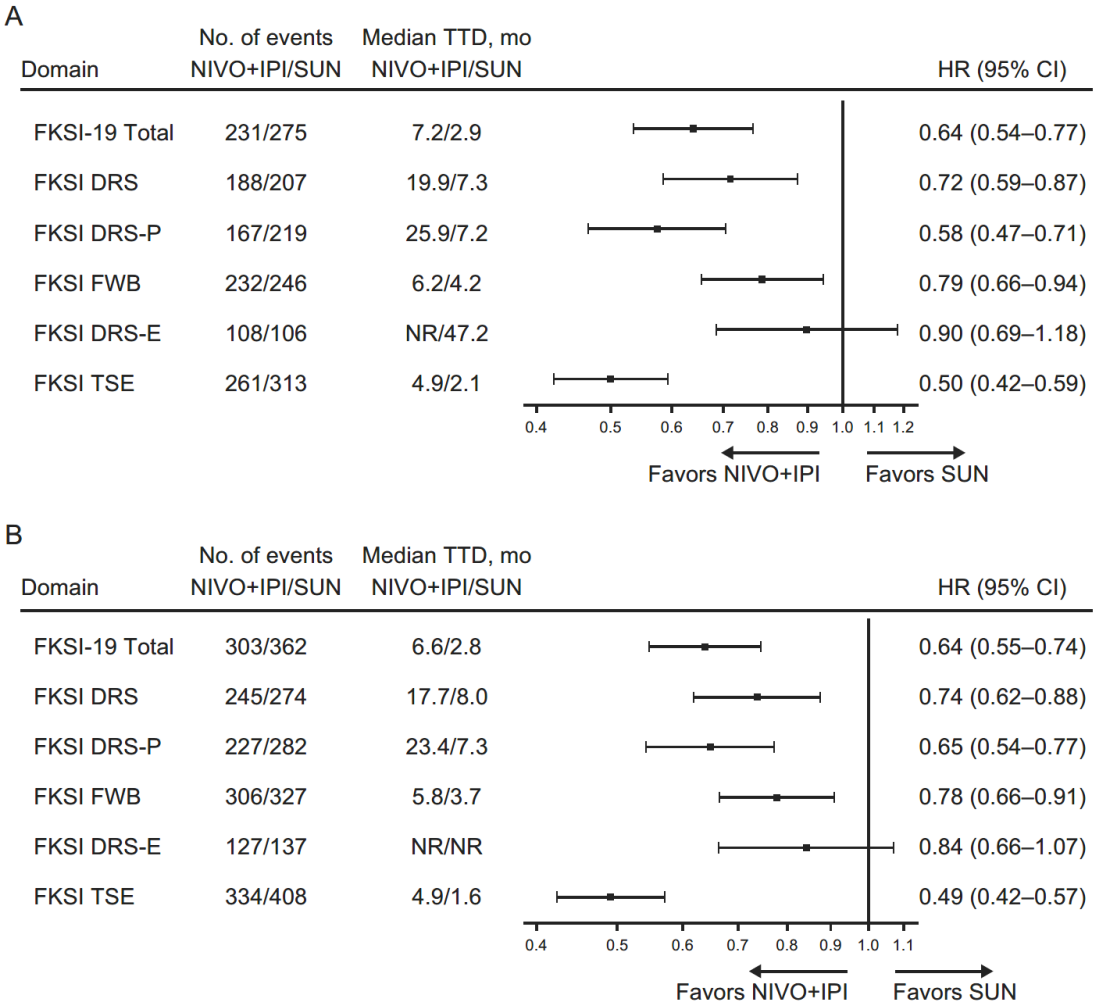


Figure S2 Time to confirmed deterioration in FKSI-19 domains.



A, In intermediate-risk/poor-risk patients. B, In ITT patients.

Data points are hazard ratios and error bars are 95% CIs. Deterioration was defined as a decrease in score of either ≥3 points (FKSI-19 and DRS), 1 point (DRS-E, TSE, FWB), or 4 points (DRS-P) compared with baseline and confirmed at the next consecutive visit.

DRS, disease-related symptoms; DRS-E, disease-related symptoms-emotional; DRS-P, disease-related symptoms-physical; FKSI-19, Functional Assessment of Cancer Therapy–Kidney Symptom Index-19; FWB, functional well-being; NIVO+IPI, nivolumab plus ipilimumab; SUN, sunitinib; TSE, treatment side effects.