Original Article

Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma

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BACKGROUND: Conditional survival estimates provide critical prognostic information for patients with advanced renal cell carcinoma (aRCC). Efficacy, safety, and conditional survival outcomes were assessed in CheckMate 214 (ClinicalTrials.gov identifier NCT02231749) with a minimum follow-up of 5 years. **METHODS:** Patients with untreated aRCC were randomized to receive nivolumab (NIVO) (3 mg/kg) plus ipilimumab (IPI) (1 mg/kg) every 3 weeks for 4 cycles, then either NIVO monotherapy or sunitinib (SUN) (50 mg) daily (four 6-week cycles). Efficacy was assessed in intent-to-treat, International Metastatic Renal Cell Carcinoma Database Consortium intermediate-risk/poor-risk, and favorable-risk populations. Conditional survival outcomes (the probability of remaining alive, progression free, or in response 2 years beyond a specified landmark) were analyzed. **RESULTS:** The median follow-up was 67.7 months; overall survival (median, 55.7 vs 38.4 months; hazard ratio, 0.72), progression-free survival (median, 12.3 vs 12.3 months; hazard ratio, 0.86), and objective response (39.3% vs 32.4%) benefits were maintained with NIVO+IPI versus SUN, respectively, in intent-to-treat patients (N = 550 vs 546). Point estimates for 2-year conditional overall survival beyond the 3-year landmark were higher with NIVO+IPI versus SUN (intent-to-treat patients, 81% vs 72%; intermediate-risk/poor-risk patients, 79% vs 72%; favorable-risk patients, 85% vs 72%). Conditional progression-free survival and response point estimates were also higher beyond 3 years with NIVO+IPI. Point estimates for conditional overall survival were higher or remained steady at each subsequent year of survival with NIVO+IPI in patients stratified by tumor programmed death ligand 1 expression, grade ≥3 immune-mediated adverse event experience, body mass index, and age. **CONCLUSIONS:** Durable clinical benefits were observed with NIVO+IPI versus SUN at 5 years, the longest phase 3 follow-up for a first-line checkpoint inhibitor-based combination in patients with aRCC. Conditional estimates indicate that most patients who remained alive or in response with NIVO+IPI at 3 years remained so at 5 years. *Cancer* 2022;128:2085-2097. © 2022 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: advanced renal cell carcinoma, CheckMate 214, dual checkpoint inhibition, durable response, long-term follow-up, nivolumab plus ipilimumab, phase 3.

INTRODUCTION

Survival outcomes for patients with advanced or metastatic renal cell carcinoma (aRCC) have improved significantly in recent years, with immunotherapy-based combination regimens further prolonging survival over single-agent, targeted therapies.[1-4] However, because limited follow-up is available for most phase 3 trials of newer first-line aRCC treatments, additional analyses that comprehensively assess long-term clinical benefits in this setting remain of critical importance. Nivolumab (NIVO) plus ipilimumab (IPI) (NIVO+IPI) is approved for patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate-risk/poor-risk disease based on the primary phase 3 CheckMate 214 trial results.[2]

Traditional prognostic risk models like the IMDC classification are routinely used to inform upfront prognosis and treatment decisions to help predict patient outcomes in aRCC.[5] However, such prognostic estimates based on baseline risk factors were established in the era of single-agent tyrosine kinase inhibitors and cytokines, and do not adequately address outcomes for patients with aRCC who achieve a durable response and survival benefits with immunotherapy.[6,7] As the aRCC treatment landscape evolves and long-term outcomes continue to improve, an updated prognostic framework is needed. Although clinical response and survival projections at diagnosis using standard prognostic models can help individualize therapy regimens, prognoses may change over time, particularly among patients with a poor outlook according to baseline assessments.[8,9] *Conditional survival* has since emerged as a clinically relevant measure of prognosis that estimates survival probability for patients as the length of survival increases in response to treatment.[9,10] Conditional survival assessments may account for the time alive since randomization or treatment initiation and can help provide critical long-term prognostic information as prespecified survival milestones are reached. Previous conditional survival analyses in patients with aRCC who received VEGF-targeted therapy demonstrated improved outcomes over time with length of survivorship.[8,11] However, limited conditional survival data exist in patients with aRCC who received NIVO monotherapy or first-line immunotherapy combinations.[11]

With a minimum follow-up of 5 years, we report the longest phase 3 follow-up for a checkpoint inhibitor combination therapy in aRCC together with the first long-term conditional survival analyses of patients in CheckMate 214.

MATERIALS AND METHODS

Patients and Treatment

CheckMate 214 is a global, open-label, randomized, phase 3 trial. Study design and statistical analyses details have been described previously, and additional details are included in the online Supporting Information.[12] CheckMate 214 was approved by institutional review boards or ethics committees at each site and was conducted following Good Clinical Practice Guidelines according to the International Conference for Harmonisation. All patients provided written informed consent in accordance with Declaration of Helsinki principles. This study is registered with ClinicalTrials.gov (ClinicalTrials.gov identifier NCT02231749).

Assessments

The co-primary trial end points were overall survival (OS), progression-free survival (PFS) according to an independent radiology review committee, and the objective response rate (ORR) according to the independent radiology review committee (with duration of response [DOR]) in intermediate-risk/poor-risk patients (primary), intent-to-treat (ITT) patients (secondary), and favorable-risk patients (exploratory). Conditional OS, conditional PFS, and conditional response estimates, together with an evaluation of patients who had durable clinical benefits and an assessment of treatment-free interval in responders, were analyzed post hoc. Additional assessment details are included in the Supporting Methods.

Statistical Analysis

Conditional survival was analyzed using a landmark approach based on Kaplan-Meier estimates and was calculated for patients who were either alive, progression free, or in response at 1-year increments from time zero. Conditional OS, conditional PFS (time zero was the date of randomization for both), and conditional response (time zero was the date of first confirmed response) were assessed until death or censoring at the date of last follow-up. Data from patients who died before the landmark timepoint or whose follow-up interval was less than the landmark time were excluded. Statistical analysis details for OS, PFS, ORR, and health-related quality of life (HRQoL) were previously reported, and additional information is included in the Supporting Information.

RESULTS

Patients and Treatment Outcomes

In total, 1096 patients were randomized to NIVO+IPI (ITT patients, n = 550; intermediate-risk/poor-risk patients, n = 425; favorable-risk patients, n = 125) or

sunitinib (SUN) (ITT patients, n = 546; intermediate-risk/poor-risk patients, n = 422; favorable-risk patients, n = 124). Overall, 547 patients in the NIVO+IPI arm and 535 in the SUN arm received treatment and were included in the safety analyses. The database lock for this analysis was February 24, 2021. At a minimum 5-year study follow-up (median follow-up, 67.7 months), 34 of 547 (6%) treated patients in the NIVO+IPI arm and 9 of 535 (2%) treated patients in the SUN arm continued therapy (see Supporting Fig. 1). Key baseline characteristics were generally similar between treatment arms in ITT patients, as previously reported (see Supporting Table 1).[2,12-14] The median duration of therapy was 7.9 months (quartile 1 [Q1]-Q3, 2.1-21.8 months) in the NIVO+IPI arm and 7.8 months (Q1-Q3, 3.5-19.6 months) in the SUN arm. Subsequent systemic therapy was received by 305 of 550 (55%) ITT patients in the NIVO+IPI arm and by 372 of 546 (68%) ITT patients in the SUN arm (see Supporting Table 2).

OS, PFS, and ORR in ITT, Intermediate-Risk/Poor-Risk, and Favorable-Risk Patients

With a minimum follow-up of 5 years, OS superiority was maintained with NIVO+IPI versus SUN in the ITT population (hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.62-0.85). The median OS was 55.7 versus 38.4 months with NIVO+IPI versus SUN, respectively, and the 5-year OS probability was greater with NIVO+IPI (48% vs 37%) (Fig. 1A). In intermediate-risk/poor-risk patients, OS also remained superior with NIVO+IPI versus SUN, with a median OS of 47.0 versus 26.6 months, respectively (HR, 0.68; 95% CI, 0.58-0.81), and 5-year OS probabilities of 43% versus 31%, respectively (Fig. 2A). In favorable-risk patients, the HR for OS was 0.94 (95% CI, 0.65-1.37). The median OS was 74.1 months with NIVO+IPI versus 68.4 months with SUN, and the 5-year OS probability was 63% with NIVO+IPI versus 55% with SUN (Fig. 3A). OS benefits were observed with NIVO+IPI versus SUN in both intermediate-risk patients (HR, 0.74) and poor-risk patients (HR, 0.58) and in ITT patients regardless of tumor programmed death ligand 1 (PD-L1) expression status (<1%: HR, 0.77; ≥1%: HR, 0.57) (Fig. 4).

The HR for PFS with NIVO+IPI versus SUN was 0.86 (95% CI, 0.73-1.01) in ITT patients and 0.73 (95% CI, 0.61-0.87) (Fig. 2B) in patients with intermediate-risk/poor-risk disease. PFS benefits were observed in these patients, as demonstrated by greater 5-year PFS probabilities with NIVO+IPI versus SUN in both populations (ITT, 30% vs 14%; intermediate-risk/poor-risk, 31% vs 11%) (Figs. 1B and 2B). In patients with favorable-risk disease, the HR for PFS favored SUN (HR, 1.60; 95% CI, 1.13-2.26), yet the 5-year PFS probability was 26% with NIVO+IPI versus 21% with SUN (Fig. 3B).

The ORR was greater with NIVO+IPI versus SUN both in ITT patients (39% vs 32%) and in intermediate-risk/poor-risk patients (42% vs 27%) (see Supporting Table 3). Among favorable-risk patients, the ORR was lower with NIVO+IPI versus SUN (30% vs 52%); however, a higher proportion of patients achieved a complete response (CR) with NIVO+IPI regardless of risk group (ITT population, 12% vs 3%; intermediate-risk/poor-risk population, 11% vs 2%; favorable-risk population, 13% vs 6%) (see Supporting Table 3). The median time to response was shorter with NIVO+IPI versus SUN (2.8 months [Q1-Q3, 2.7-4.0 months] vs 4.0 months [Q1-Q3, 2.8-5.6 months]), and the median DOR was longer (not reached vs 24.8 months) in the ITT population, with more ongoing responses at 5 years in those who received NIVO+IPI across risk groups (ITT population, 63% vs 50%; intermediate-risk/poor-risk population, 64% vs 50%; favorable-risk population, 59% vs 52%) (Figs. 1C, 2C, and 3C; see Supporting Table 3). More ITT responders experienced a treatment-free interval without requiring subsequent systemic therapy with NIVO+IPI (103 of 216 patients; 48%) versus SUN (43 of 177 patients; 24%).

Conditional Survival in ITT, Intermediate-Risk/Poor-Risk, and Favorable-Risk Patients

In the NIVO+IPI arm, point estimates for the probability of remaining alive for an additional 2 years (conditional OS) were higher or stable at each subsequent year of survival after time zero (randomization) in ITT patients (randomization, 71%; year 1, 71%; year 2, 76%; year 3, 81%) and in intermediate-risk/poor-risk patients (randomization, 66%; year 1, 68%; year 2, 75%; year 3, 79%), and remained high in favorable-risk patients (randomization, 85%; year 1, 80%; year 2, 77%; year 3, 85%) (Fig. 5; see Supporting Table 4). Point estimates for 2-year conditional OS were also higher with NIVO+IPI versus SUN from the 3-year landmark regardless of IMDC risk group (ITT patients, 81% vs 72%; intermediate-risk/poor-risk patients, 79% vs 72%; favorable-risk patients, 85% vs 72%).

With NIVO+IPI, point estimates for 2-year conditional PFS were higher or remained stable from time zero (randomization) at each subsequent year of survival in ITT (randomization, 37%; year 1, 66%; year 2, 87%; year 3, 89%), intermediate-risk/poor-risk
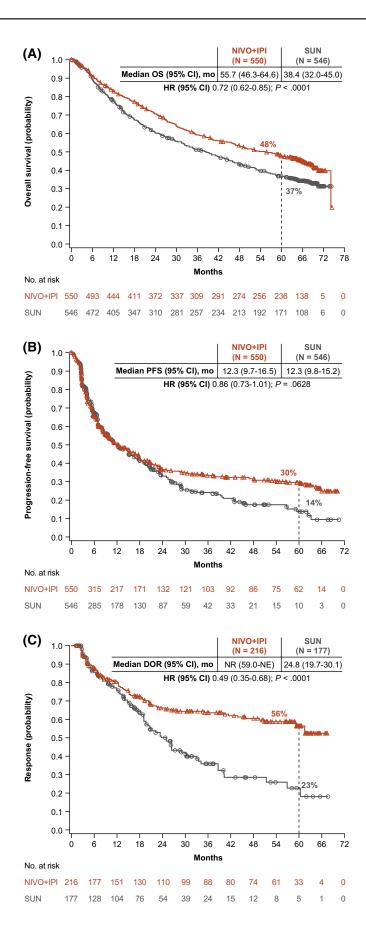
(A)

	NIVO+IPI (N = 550)	SUN (N = 546)
Median OS (95% CI), mo	55.7 (46.3-64.6)	38.4 (32.0-45.0)
HR (95% CI)	0.72 (0.62-0.85); *P* < .0001	

Overall survival (probability)

48%

37%

Months

No. at risk

NIVO+IPI	550	493	444	411	372	337	309	291	274	256	236	138	5	0
SUN	546	472	405	347	310	281	257	234	213	192	171	108	6	0

(B)

	NIVO+IPI (N = 550)	SUN (N = 546)
Median PFS (95% CI), mo	12.3 (9.7-16.5)	12.3 (9.8-15.2)
HR (95% CI)	0.86 (0.73-1.01); *P* = .0628	

Progression-free survival (probability)

30%

14%

Months

No. at risk

NIVO+IPI	550	315	217	171	132	121	103	92	86	75	62	14	0
SUN	546	285	178	130	87	59	42	33	21	15	10	3	0

(C)

	NIVO+IPI (N = 216)	SUN (N = 177)
Median DOR (95% CI), mo	NR (59.0-NE)	24.8 (19.7-30.1)
HR (95% CI)	0.49 (0.35-0.68); *P* < .0001	

Response (probability)

56%

23%

Months

No. at risk

NIVO+IPI	216	177	151	130	110	99	88	80	74	61	33	4	0
SUN	177	128	104	76	54	39	24	15	12	8	5	1	0

FIGURE 1. (A) Overall survival (OS), (B) progression-free survival (PFS), and (C) duration of response (DOR) are illustrated according to an independent radiology review committee using Response Evaluation Criteria in Solid Tumors, version 1.1, among patients in the intent-to-treat group. CI indicates confidence interval; HR, hazard ratio; NE, not estimable; NIVO+IPI, nivolumab plus ipilimumab; NR, not reached; SUN, sunitinib.

(randomization, 36%; year 1, 69%; year 2, 91%; year 3, 90%), and favorable-risk (randomization, 38%; year 1, 58%; year 2, 73%; year 3, 85%) patients (Fig. 5; see Supporting Table 4). At the 3-year landmark, point estimates for conditional PFS were higher with NIVO+IPI versus SUN in ITT (89% vs 57%), intermediate-risk/poor-risk (90% vs 62%), and favorable-risk (85% vs 50%) patients. The probability of remaining in response with NIVO+IPI for an additional 2 years (conditional response) was also higher or remained stable from time zero (first response) according to point estimates at each subsequent year of survival in ITT (first response, 66%; year 1, 79%; year 2, 91%; year 3, 89%), intermediate-risk/poor-risk (first response, 65%; year 1, 76%; year 2, 92%; year 3, 90%), and favorable-risk (first response, 71%; year 1, 91%; year 2, 89%; year 3, 85%) patients (Fig. 5; see Supporting Table 4). Point estimates for 2-year conditional response from the 3-year landmark were higher with NIVO+IPI versus SUN regardless of IMDC risk group (ITT patients, 89% vs 63%; intermediate-risk/poor-risk patients, 90% vs 88%; favorable-risk patients, 85% vs 45%).

Conditional OS in Subgroups
Point estimates for conditional OS with NIVO+IPI varied to some extent across age groups in ITT patients at time zero yet were stable or consistently higher with NIVO+IPI at each subsequent year of conditional survival regardless of IMDC risk group, except for favorable-risk patients younger than 65 years (Fig. 6A; see Supporting Table 5). Point estimates for conditional OS with NIVO+IPI in ITT patients were similar regardless of body mass index (BMI), grade ≥3 immune-mediated adverse event (AE) experience, or tumor PD-L1 expression and were either higher or stable at each subsequent year of survival in each subgroup (Fig. 6B-D; see Supporting Table 5). Point estimates for conditional OS with NIVO+IPI in intermediate-risk/poor-risk patients were also higher or stable from time zero at each subsequent year of survival regardless of BMI, grade ≥3 immune-mediated AEs, or tumor PD-L1 expression and generally remained high (approximately ≥80%) at 3 years in favorable-risk patients (see Supporting Table 5). Point estimates for conditional OS with NIVO+IPI remained high (>96%) in ITT patients who had a CR from all

landmark timepoints assessed (Fig. 6E; see Supporting Table 5); similar trends were observed in patients who had a CR regardless of IMDC risk group (see Supporting Table 5). Point estimates for conditional OS with SUN were higher or remained stable at each subsequent year of survival from time zero across all subgroups among ITT and intermediate-risk/poor-risk patients, except for patients aged 75 years and older (see Supporting Table 6). Interestingly, point estimates for conditional OS with SUN decreased with subsequent years of survival across almost all subgroups in favorable-risk patients, except for those with tumor PD-L1 expression ≥1% and those who achieved a CR.

Durable Clinical Benefit
More patients achieved a CR and did not progress with NIVO+IPI (n = 53 of 550; 9.6%) versus SUN (n = 13 of 546; 2.4%). Among complete responders without progression, baseline characteristics were largely similar to those of ITT patients in the NIVO+IPI arm. However, a higher proportion of complete responders without progression in the SUN arm had just 1 site with target/nontarget lesions at baseline (5 of 13 patients [38%] vs 118 of 546 patients [22%]), and more had favorable-risk disease (6 of 13 patients [46%] vs 124 of 546 patients [23%]) compared with ITT patients; none of the complete responders without progression had poor-risk disease in the SUN arm (see Supporting Table 1).

Few patients discontinued treatment because of maximum clinical benefit in either treatment arm (NIVO+IPI, n = 18; SUN, n = 7) (see Supporting Fig. 1). Among this small subgroup, all 18 patients in the NIVO+IPI arm, versus 4 patients in the SUN arm, achieved an objective response: 5 versus 2 patients had CRs, respectively; 13 versus 2 patients had a partial response, respectively; and zero versus 3 patients had stable disease, respectively. The median duration of study therapy among these patients was 32.8 months (Q1-Q3, 24.2-45.1 months) in the NIVO+IPI arm and 7.8 months (Q1-Q3, 6.5-19.1 months) in the SUN arm.

Safety and HRQoL
Comparable overall rates of treatment-related AEs of any grade occurred with NIVO+IPI (515 of 547 patients; 94%) versus SUN (522 of 535 patients; 98%) with
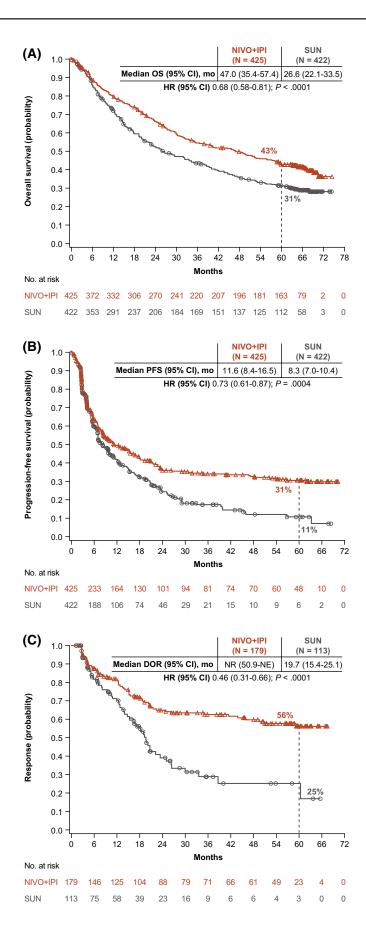
(A)

	NIVO+IPI (N = 425)	SUN (N = 422)
Median OS (95% CI), mo	47.0 (35.4-57.4)	26.6 (22.1-33.5)
HR (95% CI) 0.68 (0.58-0.81); *P* < .0001		

Overall survival (probability)

43%

31%

Months

No. at risk

NIVO+IPI	425	372	332	306	270	241	220	207	196	181	163	79	2	0
SUN	422	353	291	237	206	184	169	151	137	125	112	58	3	0

(B)

	NIVO+IPI (N = 425)	SUN (N = 422)
Median PFS (95% CI), mo	11.6 (8.4-16.5)	8.3 (7.0-10.4)
HR (95% CI) 0.73 (0.61-0.87); *P* = .0004		

Progression-free survival (probability)

31%

11%

Months

No. at risk

NIVO+IPI	425	233	164	130	101	94	81	74	70	60	48	10	0
SUN	422	188	106	74	46	29	21	15	10	9	6	2	0

(C)

	NIVO+IPI (N = 179)	SUN (N = 113)
Median DOR (95% CI), mo	NR (50.9-NE)	19.7 (15.4-25.1)
HR (95% CI) 0.46 (0.31-0.66); *P* < .0001		

Response (probability)

56%

25%

Months

No. at risk

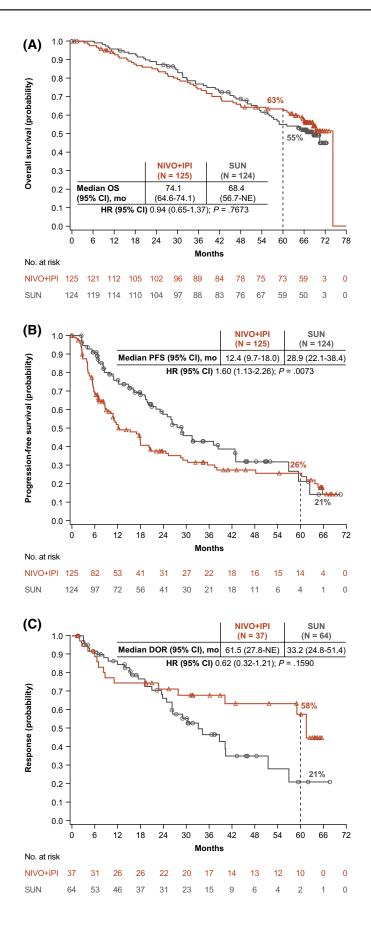|													
NIVO+IPI	179	146	125	104	88	79	71	66	61	49	23	4	0
SUN	113	75	58	39	23	16	9	6	6	4	3	0	0

FIGURE 2. (A) Overall survival (OS), (B) progression-free survival (PFS), and (C) duration of response (DOR) are illustrated according to an independent radiology review committee using Response Evaluation Criteria in Solid Tumors, version 1.1, in patients with intermediate-risk/poor-risk renal cell carcinoma according to the International Metastatic Renal Cell Carcinoma Database Consortium. CI indicates confidence interval; HR, hazard ratio; NE, not estimable; NIVO+IPI, nivolumab plus ipilimumab; NR, not reached; SUN, sunitinib.

extended follow-up (see Supporting Table 7). However, fewer grade 3 and 4 treatment-related AEs were reported in patients who received NIVO+IPI versus SUN (48% vs 64%). Treatment-related AEs leading to discontinuation occurred in 127 patients (23%) in the NIVO+IPI arm and 70 patients (13%) in the SUN arm. The overall incidence of treatment-related, select (potentially immune-mediated) AEs with NIVO+IPI (see Supporting Table 7) was similar to previous reports.[12] In total, 162 of 547 patients (30%) treated with NIVO+IPI received corticosteroids (≥40 mg prednisone daily or equivalent [PDE]) to manage any-grade, treatment-related, select AEs, as reported within 30 days of the last dose of NIVO+IPI; 108 patients (20%) received ≥40 mg PDE continuously for ≥2 weeks, and 56 (10%) received ≥40 mg PDE continuously for ≥30 days.

With 5 years of follow-up, the overall difference in the mean change from baseline between treatment arms was statistically significant in favor of NIVO+IPI according to the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy-Kidney Symptom Index total and disease-related symptoms subscale scores ($P < .05$) in both ITT patients and intermediate-risk/poor-risk patients (see Supporting Table 8).

DISCUSSION

With a minimum 5 years of follow-up in CheckMate 214, NIVO+IPI demonstrated long-term efficacy benefits versus SUN in ITT patients, establishing new benchmarks for the magnitude and durability of benefits possible using first-line, immunotherapy-based combinations for patients with aRCC. Notably, OS benefits with NIVO+IPI versus SUN were observed in the ITT population and in both IMDC intermediate-risk and poor-risk subgroups. Median OS was reached with NIVO+IPI in ITT patients for the first time and was numerically longer for the NIVO+IPI arm versus the SUN arm regardless of IMDC risk group. In addition, the ORR was higher in ITT patients, and the DOR was notably longer with NIVO+IPI versus SUN regardless of IMDC risk group. PFS probabilities appeared to stabilize above approximately 30% for both ITT patients and intermediate-risk/poor-risk

patients after 3 years. Although the ORR was higher with SUN among favorable-risk patients, 5-year OS, PFS, and CR rates and DOR probabilities were all numerically higher with NIVO+IPI versus SUN in this subgroup. The proportion of patients who maintained a CR with NIVO+IPI was also relatively high versus SUN, yet responses were durable in those who had a CR in both treatment arms. In addition, approximately one-half of all responders experienced a treatment-free interval without initiating subsequent therapy in the NIVO+IPI arm. The overall incidence of treatment-related AEs remained consistent with previous reports, and no new safety signals emerged.[2,12] Together with improved efficacy and safety benefits, NIVO+IPI treatment led to fewer symptoms and better HRQoL outcomes compared with SUN, further substantiating the long-term benefits of NIVO+IPI for patients with aRCC. Of note, 75% of treated patients in the NIVO+IPI arm discontinued therapy by approximately 22 months, in alignment with the protocol amendment allowing for optional discontinuation of study treatment after 2 years; this approach has become common in clinical practice. However, the optimal duration of immunotherapy remains an important clinical question and continues to be investigated.

Conditional survival analyses estimate the probability of remaining event free (ie, remaining alive, progression free, or in response) for a defined period of time beyond reaching a landmark study milestone. These analyses are a novel, clinically relevant method to predict continued survival and response benefits as patients reach or exceed annual landmarks, thus providing meaningful insights for clinicians and patients.[10] In our analysis, point estimates for conditional OS with NIVO+IPI were higher or remained stable at each subsequent year of survival between randomization and the 3-year landmark in ITT and intermediate-risk/poor-risk patients, and point estimates for conditional OS were higher for NIVO+IPI versus SUN at 3 years regardless of IMDC risk group. In favorable-risk patients, conditional OS in those who received NIVO+IPI remained high over time, whereas conditional point estimates mostly declined with subsequent years of survival in those who received SUN. These data highlight that

FIGURE 3. (A) Overall survival (OS), (B) progression-free survival (PFS), and (C) duration of response (DOR) are illustrated according to an independent radiology review committee using Response Evaluation Criteria in Solid Tumors, version 1.1, in patients with favorable-risk renal cell carcinoma according to the International Metastatic Renal Cell Carcinoma Database Consortium. CI indicates confidence interval; HR, hazard ratio; NE, not estimable; NIVO+IPI, nivolumab plus ipilimumab; SUN, sunitinib.

survival benefits with NIVO+IPI are largely durable with extended follow-up, regardless of IMDC risk group. Furthermore, point estimates for conditional OS were higher or remained steady at each subsequent year of survival with NIVO+IPI in ITT patients stratified by age, BMI, grade ≥3 immune-mediated AEs, and tumor PD-L1 expression and remained consistently high in patients who achieved a CR, indicating that none of these baseline characteristics precluded patients from achieving durable survival benefits with NIVO+IPI.

The conditional survival analyses presented here only considered patients who were alive, progression free, or in response at a certain landmark timepoint, thus excluding those who died or were censored before

the landmark time. In addition, these analyses were post hoc and descriptive and were intended to provide relevant information for possible scenarios that physicians and patients face, but not for inferential purposes. Limitations of the conditional survival analyses reported in this study include the increasingly small ITT patient numbers as the 3-year landmarks were reached in the SUN arm and at later timepoints within some subgroups in both arms. Furthermore, because the conditional survival analyses were exploratory in nature, additional findings from other phase 3 prospective studies are needed to confirm the treatment effects reported in this analysis. Further investigation of long-term efficacy in patients with aRCC treated with a first-line tyrosine

Baseline Characteristic	NIVO+IPI Events/patients	NIVO+IPI mOS (95% CI)	SUN Events/patients	SUN mOS (95% CI)	HR for Death (95% CI)
Age, years					
< 65 (n = 668)	169/340	64.6 (52.1-NE)	201/328	34.4 (27.0-42.2)	0.65 (0.53-0.80)
≥ 65 and < 75 (n = 342)	102/164	46.7 (32.3-58.4)	110/178	44.4 (32.9-52.8)	0.96 (0.73-1.25)
≥ 75 (n = 86)	26/46	28.9 (10.6-NE)	28/40	34.8 (13.3-53.5)	0.89 (0.52-1.51)
Sex					
Male (n = 808)	231/413	49.7 (41.2-63.1)	246/395	40.1 (33.4-46.6)	0.81 (0.68-0.97)
Female (n = 288)	66/137	66.8 (48.9-NE)	93/151	29.4 (19.5-47.2)	0.62 (0.45-0.84)
Region					
United States (n = 306)	76/154	63.1 (42.3-NE)	87/152	43.6 (30.1-52.8)	0.72 (0.53-0.97)
Canada/W Europe/ N Europe (n = 401)	107/201	58.1 (42.6-67.3)	123/200	46.6 (31.9-58.3)	0.81 (0.63-1.05)
Rest of world (n = 389)	114/195	47.0 (35.2-60.3)	129/194	29.6 (22.7-39.3)	0.73 (0.57-0.94)
IMDC score					
0 (n = 232)	50/120	74.1 (65.5-74.1)	50/112	70.4 (56.0-NE)	0.92 (0.62-1.36)
1-2 (n = 665)	174/329	59.2 (49.2-67.3)	205/336	38.5 (29.4-45.1)	0.74 (0.61-0.91)
3-6 (n = 198)	73/101	21.5 (15.1-26.5)	83/97	9.7 (6.7-14.3)	0.58 (0.42-0.80)
Prior nephrectomy					
Yes (n = 894)	234/455	59.7 (48.6-68.5)	257/439	45.0 (38.5-52.3)	0.79 (0.67-0.95)
No (n = 202)	63/95	31.9 (21.3-52.4)	82/107	15.5 (12.9-25.8)	0.64 (0.46-0.88)
Tumor PD-L1 expression					
≥ 1% (n = 240)	55/113	66.8 (36.5-NE)	82/127	23.9 (15.8-35.3)	0.57 (0.40-0.80)
< 1% (n = 762)	206/386	59.2 (46.7-66.2)	230/376	41.9 (35.2-49.5)	0.77 (0.64-0.93)
Not reported (n = 94)	36/51	26.1 (17.0-46.8)	27/43	32.7 (15.7-57.3)	1.22 (0.73-2.01)
Body mass index, kg/m²					
< 30 (n = 755)	207/382	53.7 (42.6-66.8)	235/373	35.3 (28.7-42.2)	0.74 (0.61-0.89)
≥ 30 (n = 333)	88/165	55.1 (40.3-NE)	100/168	44.7 (32.7-56.0)	0.82 (0.61-1.09)

0   1   2   3
NIVO+IPI   SUN

FIGURE 4. Subgroup analysis of overall survival is illustrated in intent-to-treat patients. Note that hazard ratios (HRs) were not computed for subset categories that included <21 patients per treatment group. CI indicates confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mOS, median overall survival; N Europe, northern Europe; NE, not estimable; NIVO+IPI, nivolumab plus ipilimumab; PD-L1, programmed death ligand 1; SUN, sunitinib; W Europe, western Europe.

FIGURE 5. (A) Conditional overall survival (OS), (B) conditional progression-free survival (PFS), and (C) and conditional responses are illustrated among patients in the intent-to-treat (ITT) group, patients who had International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate-risk/poor-risk disease, and patients who had IMDC favorable-risk disease. X-axes indicate the landmark time from randomization (conditional OS and PFS) or the landmark time from the first confirmed response (conditional response). Error bars indicate 95% confidence intervals. OS, PFS, and response probabilities were conditioned on the time alive, the time progression-free, or the time in response after time zero. NIVO+IPI indicates nivolumab plus ipilimumab; SUN, sunitinib.

kinase inhibitor who subsequently receive either immunotherapy or antiangiogenic therapy in the refractory setting would help to shed light on which patient populations are likely to experience durable outcomes. Finally, it is important to point out that although baseline characteristics for this patient subgroup were largely balanced at the start of the trial, there may be imbalances in some clinical characteristics for those patients who remained alive at the landmark timepoints assessed, potentially affecting outcomes in the conditional survival

analyses. Along these lines, the natural history of disease for patients with aRCC may vary considerably, depending on the biology of individual disease and the behavior of the tumor (aggressive vs indolent), both underlying the patient's response to therapy and also potentially affecting conditional survival outcomes.[15]

In summary, the current results establish the durability of clinical benefit observed with NIVO+IPI over SUN in patients who have aRCC after a minimum follow-up of 5 years. In addition, results from the first

FIGURE 6. Conditional overall survival (OS) is illustrated according to baseline clinical subgroups and complete responses among patients in the intent-to-treat group from the nivolumab plus ipilimumab arm. X-axes indicate the landmark time from randomization. Error bars are 95% confidence intervals. OS probabilities were conditioned on the time survived after time zero and were stratified by (A) age (<65, 65-75, or ≥75 years), (B) body mass index (BMI) (<30 or ≥30 kg/m^2), (C) grade ≥3 immune-mediated adverse event (IMAE) experience (yes or no), (D) tumor programmed death ligand 1 (PD-L1) expression (<1% or ≥1%), and (E) and among patients who had a complete response (CR) as their best overall response (BOR).

long-term conditional survival analyses in CheckMate 214 show that most patients who remain alive or in response at the 3-year landmark will remain alive or in response at 5 years with NIVO+IPI. These data provide a new prognostic framework critical to the improved clinical management of patients with aRCC in the current era.

CONFLICT OF INTEREST DISCLOSURES

Robert J. Motzer reports institutional grants or contracts from Aveo Pharmaceuticals, Bristol Myers Squibb (BMS), Eisai, Exelixis Inc, Genentech/Roche, Merck, Pfizer; and personal fees for advisory board participation from AstraZeneca, Aveo Pharmaceuticals, Eisai, EMD Serono, Exelixis Inc, Genentech/Roche, Incyte, Lilly Oncology, Merck, Novartis, and Pfizer, all outside the submitted work. David F. McDermott reports institutional research grants from Alkermes Inc, BMS, Genentech/Roche, Merck, Novartis, Peloton Therapeutics, and Prometheus Laboratories; consulting or advisory fees from Alkermes Inc, Array BioPharma, Aveo Pharmaceuticals, BMS, Calithera Biosciences, Checkmate Pharmaceuticals, CRISPR Therapeutics, Eisai, Eli Lilly and Company, EMD Serono, Exelixis Inc, Genentech/Roche, Iovance, Johnson & Johnson, Jounce Therapeutics, Merck, Novartis, Peloton Therapeutics, Pfizer, Synthekine, Werewolf Therapeutics, and X4 Pharma; and other fees from the Beth Israel Deaconess Medical Center, all outside the submitted work. Bernard Escudier reports personal fees from Aveo Pharmaceuticals, BMS, Eisai, Ipsen, Oncorena, and Pfizer; honoraria from BMS, Ipsen, Oncorena, and Pfizer; and support for meetings and/or travel accommodations/expenses from BMS, Ipsen, and MSD, all outside the submitted work. Mauricio Burotto reports honoraria from AstraZeneca, BMS, Merck, Novartis, and Roche; and participation on a data safety monitoring board at AstraZeneca, BMS, Merck, and Roche, all outside the submitted work. Toni K. Choueiri reports support in part by grants from the National Cancer Institute to the Dana-Farber/Harvard Specialized Program of Research Excellence (2P50CA101942-16) and Program 5P30CA006516-56, the Kohlberg Chair at Harvard Medical School, and the Trust Family, Michael

AUTHOR CONTRIBUTIONS

Robert J. Motzer had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Robert J. Motzer** and **Nizar M. Tannir** contributed to the conception and design of the study. All authors provided study materials or patients. **M. Brent McHenry** completed the statistical analyses. **Chung-Wei Lee** reviewed the clinical data. All authors contributed to the data analysis and interpretation, drafting, and revising of the article and provided final approval to submit the article for publication.

DATA AVAILABILITY

Bristol Myers Squibb's policy on data sharing may be found online (see https://www.bms.com/researchers-and-partners/independent-research/data-sharingrequest-process.html).

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