Long-term outcomes with nivolumab plus ipilimumab versus sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma

Brian I Rini [1], Sabina Signoretti,[2,3] Toni K Choueiri [4], David F McDermott,[5,6] Robert J Motzer [7], Saby George,[8] Thomas Powles,[9] Frede Donskov,[10] Scott S Tykodi,[11] Sumanta K Pal [12], Saurabh Gupta,[13] Chung-Wei Lee,[14] Ruiyun Jiang,[15] Nizar M Tannir[16]

For numbered affiliations see end of article.

Correspondence to
Dr Brian I Rini;
brian.rini@vumc.org

ABSTRACT

Background Patients with advanced renal cell carcinoma with sarcomatoid features (sRCC) have a poor prognosis and limited therapeutic options. First-line nivolumab plus ipilimumab (NIVO+IPI) provided efficacy benefits over sunitinib (SUN) in patients with intermediate/poor-risk sRCC at 42 months minimum follow-up in the phase 3 CheckMate 214 trial. In this exploratory post hoc analysis, we report clinical efficacy of NIVO+IPI in sRCC after a minimum follow-up of 5 years.

Methods In CheckMate 214, patients with clear cell advanced RCC were randomized to NIVO 3 mg/kg plus IPI 1 mg/kg every 3 weeks (four doses), then NIVO 3 mg/kg every 2 weeks versus SUN 50 mg once daily (4 weeks; 6-week cycles). Randomized patients with sRCC were identified via independent central pathology review of archival tumor tissue or histological classification per local pathology report. Overall survival (OS), as well as progression-free survival (PFS) and objective response rate (ORR) per independent radiology review using Response Evaluation Criteria in Solid Tumors V.1.1, were evaluated in all International Metastatic Renal Cell Carcinoma Database Consortium intermediate/poor-risk sRCC patients and by baseline tumor PD-L1 expression level (≥1% vs <1%). Safety outcomes are reported using descriptive statistics.

Results In total, 139 patients with intermediate/poor-risk sRCC were identified (NIVO+IPI, n=74; SUN, n=65). At 5 years minimum follow-up, more patients remained on treatment with NIVO+IPI versus SUN (12% vs zero). Efficacy benefits with NIVO+IPI versus SUN were maintained with median OS of 48.6 vs 14.2 months (HR 0.46), median PFS of 26.5 vs 5.5 months (HR 0.50), and ORR 60.8% vs 23.1%. In addition, median duration of response was longer (not reached vs 25.1 months), and more patients had complete responses (23.0% vs 6.2%) with NIVO+IPI versus SUN, respectively. Efficacy was better with NIVO+IPI versus SUN regardless of tumor PD-L1 expression, but the magnitude of OS, PFS, and ORR benefits with NIVO+IPI was greater for sRCC patients with tumor PD-L1 ≥1%. No new safety signals emerged in either arm with longer follow-up.

Conclusions Among patients with intermediate/poor-risk sRCC, NIVO+IPI maintained long-term survival benefits and demonstrated durable and deep responses over SUN at minimum follow-up of 5 years, supporting NIVO+IPI as a preferred first-line therapy in this population.

Trial registration number NCT02231749.

INTRODUCTION

Sarcomatoid differentiation is an aggressive histological growth pattern that is detected in 5% of renal cell carcinomas (RCCs), including 15%–20% of advanced disease.[1] Patients with sarcomatoid RCC (sRCC) have poor prognosis and a longstanding unmet medical need for safe and effective therapeutic options.[2 3] Recently, progress has been made to improve treatment modalities for sRCC with the introduction of immune checkpoint therapy.[4] The use of anti-programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) agents alone or in combination with anti-vascular endothelial growth factor (VEGF) or anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) agents has led to improved efficacy and survival outcomes in sRCC, reporting objective response rates (ORRs) ranging from 47% to 61% with combination regimens.[5–9] Such outcomes are a significant improvement from cytotoxic chemotherapies and molecular targeted agents (eg, VEGF signaling inhibitors, mTOR inhibitors), with historical ORRs ranging from 11% to 26% and very few complete responses (CRs).[10] However, there are limited data on long-term outcomes in patients with sRCC treated with immune checkpoint therapy.[5–8 11]

In the phase 3 CheckMate 214 trial, nivolumab plus ipilimumab (NIVO+IPI) showed substantial long-term survival benefits and antitumor activity over sunitinib (SUN) in patients with sRCC and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor

(I/P)-risk disease. With minimum follow-up of 42 months, patients treated with NIVO+IPI had an ORR of 60.8% vs 23.1% with SUN; CRs were observed in 18.9% vs 3.1%, respectively.[9] On the basis of these results, the Society for Immunotherapy of Cancer recommended NIVO+IPI combination immunotherapy as a first-line treatment option for patients with sRCC.[12] Here, we present long-term results in patients with sRCC from CheckMate 214 after minimum follow-up of 5 years.

METHODS

CheckMate 214 was a global, multicenter, open-label, randomized phase 3 trial. Study design details were published previously.[9 13] Briefly, adults with treatment-naïve advanced RCC (aRCC) with a clear cell component were randomized 1:1 to intravenous NIVO 3 mg/kg and IPI 1 mg/kg every 3 weeks (four doses), followed by NIVO 3 mg/kg every 2 weeks or oral SUN 50 mg once daily (4 weeks on and 2 weeks off; 6-week cycles). Randomized patients were stratified by geographical region and IMDC risk (favorable (0); intermediate (1-2); poor (3-6)). This post hoc, exploratory analysis reports long-term, 5-year minimum follow-up in the subpopulation of patients with IMDC I/P-risk sRCC. Patients with favorable-risk sRCC were not included in this analysis as CheckMate 214 focused primarily on I/P-risk disease and only six favorable-risk sRCC patients were identified within the intention-to-treat population.

This analysis identified aRCC patients with sarcomatoid histology via two distinct methodologies: central pathology review, which allowed for analysis of archived patient tissue samples, and local pathology reports, which

Table 1 Select baseline demographic and disease characteristics

Characteristic*	All patients with I/P risk[13]		Patients with I/P-risk sRCC[9]	
	NIVO+IPI	SUN	NIVO+IPI	SUN
	(N=425)	(N=422)	(n=74)	(n=65)
Median age (range), years	62 (26–85)	61 (21–85)	58 (35–84)	61 (39–79)
Sex, n (%)				
Male	314 (74)	301 (71)	55 (74)	48 (74)
Female	111 (26)	121 (29)	19 (26)	17 (26)
IMDC prognostic score, n (%)				
Intermediate (1–2)	334 (79)	333 (79)	54 (73)	48 (74)
Poor (3–6)	91 (21)	89 (21)	20 (27)	17 (26)
Region, n (%)				
USA	112 (26)	111 (26)	34 (46)	19 (29)
Canada/Europe	148 (35)	146 (35)	20 (27)	29 (45)
Rest of the world	165 (39)	165 (39)	20 (27)	17 (26)
Prior nephrectomy, n (%)	341 (80)	319 (76)	66 (89)	54 (83)
No of sites with target/nontarget lesions,† n (%)				
1	90 (21)	84 (20)	15 (20)	16 (25)
≥2	335 (79)	337 (80)	59 (80)	49 (75)
Most common sites of metastasis,‡§ n (%)				
Lung	294 (69)	296 (70)	58 (78)	50 (77)
Lymph node	190 (45)	216 (51)	36 (49)	36 (55)
Bone¶	95 (22)	97 (23)	16 (22)	13 (20)
Liver	88 (21)	89 (21)	10 (14)	8 (12)
Quantifiable tumor PD-L1 expression, n (%)	n=384	n=392	n=71	n=62
<1%	284 (74)	278 (71)	35 (49)	29 (47)
≥1%	100 (26)	114 (29)	36 (51)	33 (53)

*Information shown in the table is based on data collected with the use of an interactive voice-response system.
†The number of target or nontarget lesions at baseline was not reported for one patient in the SUN group.
‡Patients may have lesions at more than one site.
§Includes both target and nontarget lesions.
¶Includes bone with and without a soft-tissue component.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; I/P, intermediate/poor; NIVO+IPI, nivolumab plus ipilimumab; PD-L1, programmed death ligand 1; sRCC, sarcomatoid renal cell carcinoma; SUN, sunitinib.

reduced the risk of identifying false negatives due to limited tissue availability for central review (online supplemental figure S1). The percent of tumor area with sarcomatoid differentiation was independently assessed by three pathologists blinded to patient outcomes; discrepancies were resolved by consensus review. Sarcomatoid differentiation per independent central review was defined by criteria discussed at the International Society of Urological Pathology 2012 Consensus Conference.[14] Randomized patients who demonstrated any percent of sarcomatoid histology by either method were identified as sRCC.

Outcomes in patients with IMDC I/P-risk sRCC were exploratory, and not prespecified in the trial protocol. Overall survival (OS), as well as progression-free survival (PFS) and ORR by independent radiology review committee using Response Evaluation Criteria in Solid Tumors V.1.1, were evaluated. Outcomes were also assessed according to baseline tumor PD-L1 expression level (≥1% vs <1%) in IMDC I/P-risk sRCC patients. Baseline tumor PD-L1 expression was determined at a central laboratory using the Dako PD-L1 IHC 28-8 pharmDx assay. Safety was assessed in all treated IMDC I/P-risk sRCC patients. Treatment-free interval (TFI) was defined as the time between protocol therapy discontinuation and subsequent therapy initiation or last known date alive. Statistical analysis for this exploratory subgroup follows the overall trial methodology, as described.[9 13]

RESULTS

Patients

In total, 1096 patients with aRCC were randomized in CheckMate 214 (NIVO+IPI, n=550; SUN, n=546).[13] Of the 847 randomized patients with I/P-risk disease (NIVO+IPI, n=425; SUN, n=422), 139 (16.4%) were identified with sarcomatoid histology (74 in the NIVO+IPI arm and 65 in the SUN arm) and included in this analysis. Among all the 139 I/P-risk sRCC patients, 73 (98.6%) out of 74 patients in the NIVO+IPI group and all 65 (100%) in the SUN group received treatment. Baseline demographic and disease characteristics in the subgroup of patients with I/P-risk sRCC were largely similar between treatment arms and in comparison with the general I/P–risk study population in the NIVO+IPI arm (table 1); of note, a higher proportion of I/P-risk sRCC patients in the NIVO+IPI arm had baseline tumor PD-L1 expression ≥1% versus all patients with I/P-risk disease (50.7% vs 26.0%). In addition, a greater proportion of patients with sRCC had lung metastases at baseline and a smaller proportion had liver metastases compared with the general study population with I/P-risk disease.

At time of the database lock (February 24, 2021), the minimum study follow-up was 5 years for the subpopulation of patients in CheckMate 214 with I/P-risk sRCC (median, 5.6 years). The median duration of therapy (quartile (Q) Q1–Q3) in patients with I/P-risk sRCC was
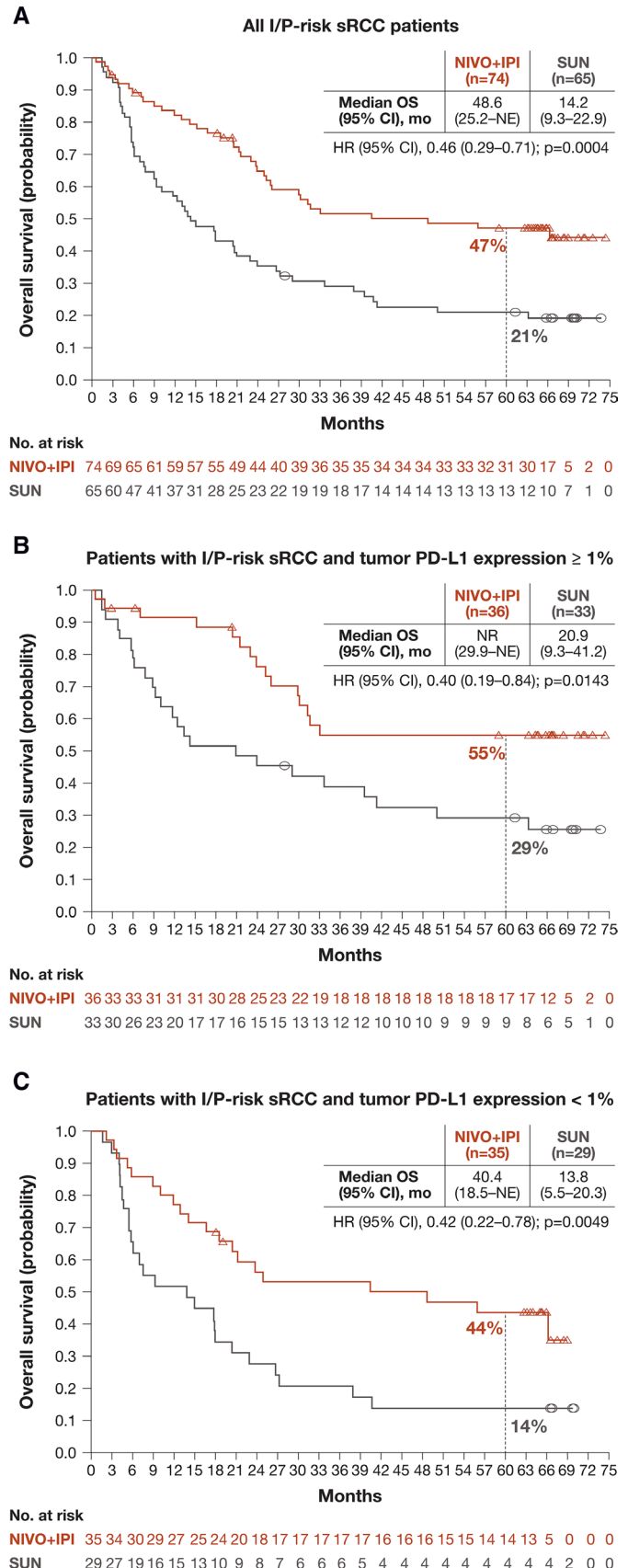

Figure 1 Kaplan-Meier plot of OS in (A) all patients with I/P risk and by tumor PD-L1 expression (B) ≥1% or (C) <1%. Symbols represent censored observations.
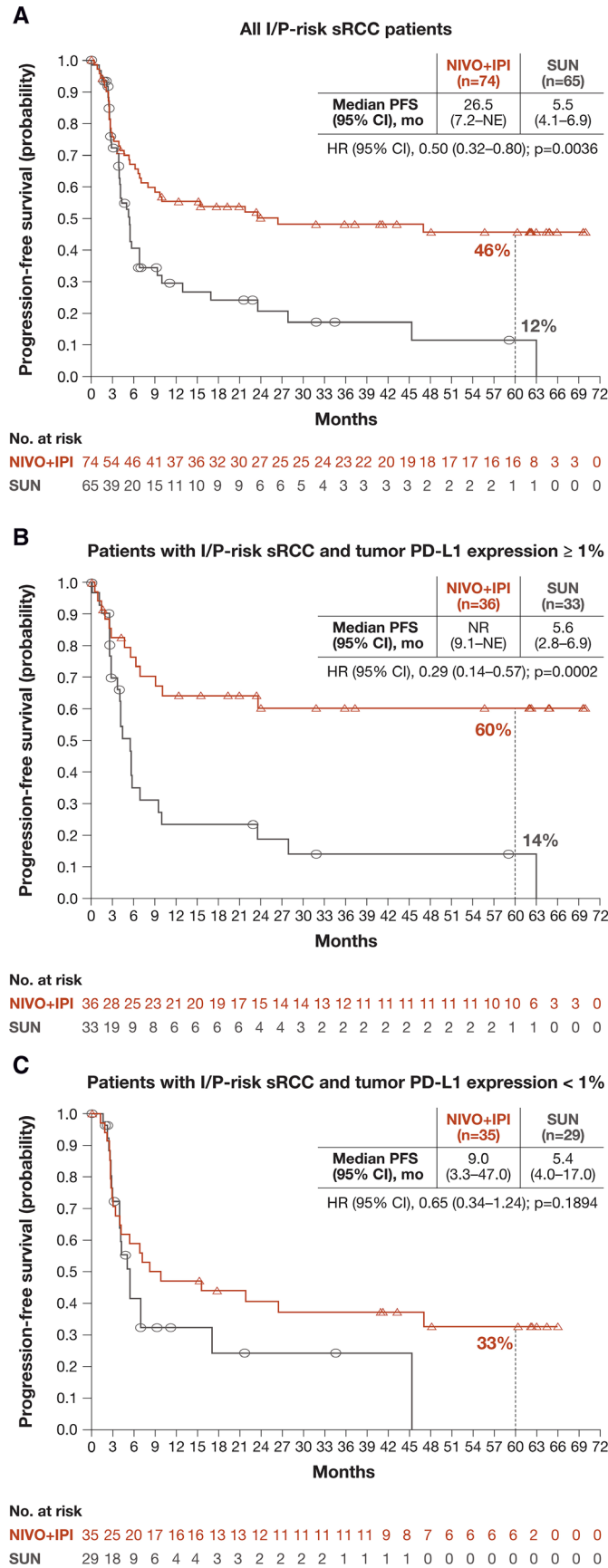
A

All I/P-risk sRCC patients

	NIVO+IPI (n=74)	SUN (n=65)
Median PFS (95% CI), mo	26.5 (7.2–NE)	5.5 (4.1–6.9)
HR (95% CI), 0.50 (0.32–0.80); p=0.0036		

No. at risk

NIVO+IPI 74 54 46 41 37 36 32 30 27 25 25 24 23 22 20 19 18 17 17 16 16 8 3 3 0

SUN 65 39 20 15 11 10 9 9 6 6 5 4 3 3 3 3 2 2 2 2 1 1 0 0 0

B

Patients with I/P-risk sRCC and tumor PD-L1 expression ≥ 1%

	NIVO+IPI (n=36)	SUN (n=33)
Median PFS (95% CI), mo	NR (9.1–NE)	5.6 (2.8–6.9)
HR (95% CI), 0.29 (0.14–0.57); p=0.0002		

No. at risk

NIVO+IPI 36 28 25 23 21 20 19 17 15 14 14 13 12 11 11 11 11 11 11 10 10 6 3 3 0

SUN 33 19 9 8 6 6 6 6 4 4 3 2 2 2 2 2 2 2 2 1 1 0 0 0

C

Patients with I/P-risk sRCC and tumor PD-L1 expression < 1%

	NIVO+IPI (n=35)	SUN (n=29)
Median PFS (95% CI), mo	9.0 (3.3–47.0)	5.4 (4.0–17.0)
HR (95% CI), 0.65 (0.34–1.24); p=0.1894		

No. at risk

NIVO+IPI 35 25 20 17 16 16 13 13 12 11 11 11 11 11 9 8 7 6 6 6 6 2 0 0 0

SUN 29 18 9 6 4 4 3 3 2 2 2 2 1 1 1 1 0 0 0 0 0 0 0 0 0

Figure 2 Kaplan-Meier plot of PFS per independent radiology review committee in (A) all patients with I/P risk and by tumor PD-L1 expression (B) ≥1% or (C) <1%. Symbols represent censored observations. PFS, progression-free survival.

Table 2 Best overall confirmed response per RECIST V.1.1 in all patients with IMDC I/P-risk sRCC and by tumor PD-L1 expression levels

	Patients with I/P risk sRCC		Patients with I/P risk sRCC and PD-L1 ≥1		Patients with I/P risk sRCC and PD-L1 <1%	
	NIVO+IPI (n=74)	SUN (n=65)	NIVO+IPI (n=36)	SUN (n=33)	NIVO+IPI (n=35)	SUN (n=29)
Confirmed ORR (95% CI), %	60.8 (48.8 to 72.0)	23.1 (13.5 to 35.2)	69.4 (51.9 to 83.7)	24.2 (11.1 to 42.3)	54.3 (36.6 to 71.2)	20.7 (8.0 to 39.7)
P value	<0.0001		–		–	
Best overall response, n (%)						
Complete response	17 (23.0)	4 (6.2)	9 (25.0)	3 (9.1)	8 (22.9)	1 (3.4)
Partial response	28 (37.8)	11 (16.9)	16 (44.4)	5 (15.2)	11 (31.4)	5 (17.2)
Stable disease	8 (10.8)	28 (43.1)	4 (11.1)	13 (39.4)	4 (11.4)	13 (44.8)
Progressive disease	15 (20.3)	13 (20.0)	5 (13.9)	9 (27.3)	9 (25.7)	4 (13.8)
Unable to determine/not reported	6 (8.1)	9 (13.8)	2 (5.6)	3 (9.1)	3 (8.6)	6 (20.7)

I/P, intermediate/poor; NIVO+IPI, nivolumab plus ipilimumab; ORR, objective response rate; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; sRCC, sarcomatoid renal cell carcinoma; SUN, sunitinib.

7.9 (2.1–28.1) months in the NIVO+IPI arm and 4.7 (2.3–8.5) months in the SUN arm. Of all treated patients, 9 of 73 (12%) in the NIVO+IPI arm versus zero of 65 in the SUN arm remained on treatment. The primary reason for discontinuation was disease progression, observed in 27 of 73 (37.0%) treated patients in the NIVO+IPI arm and 46 of 65 (70.8%) in the SUN arm (online supplemental figure S2).

Efficacy in patients with IMDC I/P-risk sRCC

Survival benefit with NIVO+IPI versus SUN was maintained in patients with I/P-risk sRCC with minimum follow-up of 5 years. Median OS (95% CI) was 48.6 (25.2 to not estimable (NE)) months with NIVO+IPI vs 14.2 (9.3 to 22.9) months with SUN; HR for death was 0.46 (95% CI 0.29 to 71; p=0.0004; figure 1A). Median PFS (95% CI) was also longer with NIVO+IPI versus SUN: 26.5 (7.2-NE) months vs 5.5 (4.1 to 6.9) months; HR for disease progression or death was 0.50 (95% CI 0.32 to 0.80; p=0.0036; figure 2A). In addition, patients had higher ORR (95% CI) with NIVO+IPI versus SUN (60.8% (48.8% to 72.0%)) vs 23.1% (95% CI 13.5% to 35.2%); p<0.0001), with more ongoing responses (66.7% vs 40.0%) and CRs (23.0% vs 6.2%), respectively (table 2). Median duration of response (95% CI) was longer with NIVO+IPI versus SUN (not reached (22.5 to NE) months vs 25.1 (7.2 to 60.4) months). The probability of response at 5 years was 63% with NIVO+IPI vs 19% with SUN.

Outcomes in patients with IMDC I/P-risk sRCC by baseline tumor PD-L1 expression level

NIVO+IPI continued to demonstrate efficacy benefits over SUN, regardless of tumor PD-L1 expression level at this long-term follow-up. In all patients with sRCC and evaluable baseline tumor PD-L1 expression ≥1% (NIVO+IPI, n=36; SUN, n=33), median OS (95% CI) was not reached (29.9 to NE) months with NIVO+IPI vs 20.9 (9.3 to 41.2) months with SUN; HR for death was 0.40 (0.19 to 0.84; p=0.0143; figure 1B). Median OS among patients with sRCC and evaluable baseline tumor PD-L1 expression <1% (NIVO+IPI, n=35; SUN, n=29) was 40.4 (18.5 to NE) months with NIVO+IPI vs 13.8 (5.5 to 20.3) months with SUN; HR for death was 0.42 (0.22 to 0.78; p=0.0049; figure 1C). Median PFS (95% CI) in patients with baseline tumor PD-L1 expression ≥1% with NIVO+IPI versus SUN was not reached (9.1 to NE) months vs 5.6 (2.8 to 6.9) months (figure 2B), and the median PFS among patients with baseline tumor PD-L1 expression <1% was 9.0 (3.3 to 47.0) months with NIVO+IPI vs 5.4 (4.0 to 17.0) months with SUN (figure 2C). Furthermore, the ORR among patients with tumor PD-L1 expression ≥1% was 69.4% with NIVO+IPI vs 24.2% with SUN; of these, 25.0% (9 of 36) vs 9.1% (3 of 33) of patients had CRs, respectively. For patients with baseline tumor PD-L1 expression <1%, the ORR for NIVO+IPI versus SUN was 54.3% vs 20.7%. Of these patients, 22.9% (8 of 35) treated with NIVO+IPI and 3.4% (1 of 29) treated with SUN had CRs (table 2).

Safety

Any-grade treatment-related adverse events (AEs) occurred in 71 of 73 (97.3%) vs 63 of 65 (96.9%) patients treated with NIVO+IPI versus SUN, respectively (online supplemental table S1). Grades 3–4 treatment-related AEs occurred in 36 of 73 (49.3%) vs 29 of 65 (44.6%) patients, respectively. Treatment-related AEs leading to discontinuation occurred in 16 (21.9%) patients in the NIVO+IPI arm and eight (12.3%) patients in the SUN arm. Treatment-related select AEs (potentially immune-mediated) were less frequent in the pulmonary (NIVO+IPI, 9.6%; SUN, 0%) and renal (NIVO+IPI, 12.3%; SUN, 6.2%) categories, yet more common with regard to any-grade skin-related events (NIVO+IPI, 53.4%; SUN, 41.5%), any-grade gastrointestinal-related events (NIVO+IPI, 24.7%; SUN, 36.9%), any-grade hepatic-related events (NIVO+IPI, 21.9%; SUN, 10.8%), and any-grade endocrine-related events (NIVO+IPI, 37.0%; SUN, 18.5%). One treatment-related death, reported previously, occurred in a patient with I/P-risk sRCC treated with NIVO+IPI[9]; no deaths were reported among patients with I/P-risk sRCC treated with SUN.

TFI in treated patients with IMDC I/P-risk sRCC

Overall, median TFI (range) was 2.9 (0.0–68.2) months with NIVO+IPI and 1.4 (0.1–65.8) months with SUN. In all patients who discontinued therapy due to treatment-related AEs, median TFI (range) was 12.3 (1.0–66.0) months with NIVO+IPI and 3.1 (0.7–65.8) months with SUN. Among all patients with an objective response, 22 of 45 (48.9%) responders treated with NIVO+IPI vs 6 of 15 (40.0%) treated with SUN discontinued therapy and never received subsequent therapy; median TFI (range) was 26.5 (0.0–68.2) months vs 15.9 (0.5–51.6) months with NIVO+IPI versus SUN in this group of patients, respectively (online supplemental figure S2). In addition, 15 of 45 (33.3%) responders in the NIVO+IPI arm compared with nine of 15 (60.0%) responders in the SUN arm discontinued therapy and received subsequent therapy; median TFI (range) was 2.8 (0.5–48.8) months with NIVO+IPI vs 2.5 (0.4–31.1) months with SUN.

DISCUSSION

Before the introduction of immune checkpoint therapy, clinical trials in patients with sRCC treated with traditional therapies reported median OS of <1 year from the time of diagnosis.[2–4 10] The results from this extended 5-year follow-up in the subgroup of patients with sRCC from the CheckMate 214 trial provide compelling data in long-term efficacy outcomes with the combination of NIVO+IPI.

With long-term follow-up of 5 years, dual checkpoint inhibition with NIVO+IPI showed enduring clinical benefit in patients with sRCC. Consistent with data reported at 42 months of follow-up,[9] ORR was considerably higher, with greater depth of response, and long-term OS and PFS benefits favored treatment with NIVO+IPI over SUN.

Since 42 months of follow-up, three additional CRs were observed by independent radiology review with NIVO+IPI treatment versus two additional CRs with SUN, and two additional responders in the NIVO+IPI arm experienced a TFI without subsequent therapy versus one additional responder in the SUN arm. This analysis showed particularly impressive CR rates of 23.0% with NIVO+IPI vs 6.2% with SUN among all patients with IMDC I/P-risk sRCC. The improvements in OS, PFS, and ORR were observed in patients treated with NIVO+IPI over SUN regardless of tumor PD-L1 expression. The similar clinical results in sRCC patients with or without PD-L1 expression highlight that the presence of sarcomatoid histology better differentiates clinical response to NIVO+IPI than does PD-L1 expression.

Outcomes in the overall I/P-risk population treated with NIVO+IPI in CheckMate 214 have been reported previously (n=425; median OS, 47.0 months; median PFS, 11.6 months; ORR, 42.1%; CR, 11.3%).[15] Of note, the median duration of therapy among patients with I/P–risk sRCC was 7.9 months while that of the overall I/P–risk population was 7.4 months at 5 years follow-up. In addition, the median TFI among I/P-risk sRCC patients in the NIVO+IPI arm (2.9 months) was relatively short, whereas the median TFI among responders in the overall I/P-risk population was 33.2 months for NIVO+IPI and 8.1 months for SUN, suggesting a differential response in immunotherapy by sarcomatoid histology. However, it is important to note that TFI was only defined in patients who were off study treatment for I/P-risk sRCC patients, and in patients who were off study treatment and never received subsequent therapy for responders in the overall I/P-risk population. Further studies maybe helpful to understand these differences, as at present there are no data available from other sRCC trials for context.

The growing body of evidence supporting the use of immune checkpoint blockade therapies in RCC has generated a desire to further explore their role in various subpopulations, including patients with RCC and a sarcomatoid component.[5–7] To our knowledge, this is the first trial in the sRCC population to demonstrate long-term efficacy that was maintained at extended follow-up of 5 years. The durability of responses with NIVO+IPI beyond 5 years in patients with sRCC underscores the key role of early CTLA-4 blockade when combined with PD-1 blockade, especially in an aggressive tumor such as sRCC with a clear cell component. The phase 2 HCRN GU16-260 study in patients with tumors (both sRCC and non-sRCC tumors) resistant to NIVO monotherapy (n=35/123) demonstrated low overall response and CR rates with salvage NIVO+IPI (ORR, 11.4%; CR, 2.9%; partial response, 8.6%).[16] Contemporary data have shown that sRCC has a high expression of PD-1/PD-L1 and increased infiltration of T-regulatory cells in comparison with RCC without a sarcomatoid component.[17 18] CTLA-4 is constitutively expressed on CD25+CD4+ T-regulatory cells and contributes to T-cell–mediated immunosuppression.[19] In addition, increased expression of PD-1/

PD-L1 and increased T-cell infiltration are associated with poor prognosis in RCC and sarcomatoid dedifferentiation.[17 18] Thus, the addition of CTLA-4 blockade provides deep and durable responses in conjunction with PD-1 blockade in this population. Previous phase 3 clinical trials have reported favorable data from immunotherapy combinations with VEGF tyrosine kinase inhibitors (KEYNOTE-426, pembrolizumab plus axitinib; JAVELIN Renal 101, avelumab plus axitinib) and anti-VEGF antibodies (IMmotion151; atezolizumab plus bevacizumab).[6–8 11] Most recently, the phase 3 CheckMate 9ER trial assessed NIVO plus cabozantinib (TKI) versus SUN in 75 patients with untreated sRCC, reporting a median PFS of 10.3 vs 4.2 months (HR 0.42; 95% CI 0.23 to 0.74), an ORR of 55.9% vs 22.0%, and CR rates of 8.8% vs 2.4%, respectively (minimum follow-up, 16 months).[20] However, long-term benefits in patients with sRCC with these regimens have not been evaluated.

Although CheckMate 214 enrolled patients with predominantly clear cell RCC, favorable outcomes have also been reported in trials including patients with sRCC who were treated with NIVO+IPI.[21] The phase 3b/4 CheckMate 920 trial (N=211) evaluated NIVO+IPI treatment in a subpopulation of patients with advanced RCC with brain metastases (n=28), and reported an objective response in two of three patients with sarcomatoid features.[21 22] In addition, results from the subpopulation of patients with predominantly clear cell RCC treated with modified NIVO+IPI dosing (n=106) showed no differences in responses or safety compared with standard NIVO+IPI dosing, including those with sarcomatoid histology (n=12).[23] NIVO-based treatment strategies and other combination therapies are currently being evaluated in ongoing, prospective trials that will include patients with sRCC.[24–26]

As described previously, the limitations of the current analysis include its non-prespecified, post hoc nature and small patient subgroups, although the distribution of patients with IMDC I/P-risk sRCC was well balanced between treatment arms. In addition, this analysis identified aRCC patients with sarcomatoid histology via two distinct methodologies: central pathology review and local pathology reports. However, sensitivity analyses of sRCC patients identified by these differing methodologies still showed similar efficacy outcomes, with the exception of CR rate at an earlier follow-up.[9] The reason for this difference, which reflects only a small number of patients, remains unclear.

In conclusion, the results from this long-term analysis of patients with IMDC I/P-risk sRCC who were treated with NIVO+IPI versus SUN extend those previously reported and provide compelling support for the use of NIVO+IPI as the standard of care therapy in patients with IMDC I/P–risk sRCC.

Author affiliations

[1]Department of Medicine, Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, USA
[2]Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts, USA
[3]Department of Oncologic Pathology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA
[4]Lank Center for Genitourinary Oncology, Dana Farber Cancer Institute, Boston, MA, USA
[5]Division of Medical Oncology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA
[6]Dana-Farber/Harvard Cancer Center, Boston, Massachusetts, USA
[7]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA
[8]Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York, USA
[9]Department of Urology, Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, UK
[10]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
[11]Department of Medicine, University of Washington and Fred Hutchinson Cancer Center, Seattle, Washington, USA
[12]Department of Medical Oncology and Therapeutics Research, City of Hope, Duarte, California, USA
[13]Department of Translational Medicine, Bristol Myers Squibb, Princeton, New Jersey, USA
[14]Department of Clinical Trials, Bristol Myers Squibb, Princeton, New Jersey, USA
[15]Division of Biostatistics, Bristol Myers Squibb, Princeton, New Jersey, USA
[16]Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Twitter Brian I Rini @brian_rini and Toni K Choueiri @DrChoueiri

Nuscan, Novartis, Pfizer, Roche, Sanofi/Aventis, Surface Oncology, Takeda, Tempest, and UpToDate; leadership role from NCCN, GU Steering Committee, ASCO, and ESMO; stock ownership in Pionyr, Tempest, Osel, and NuscanDx; institutional patents filed on molecular mutations and immunotherapy response, and ctDNA; medical writing and editorial assistance support funded by communications companies; mentored several non-US citizens on research projects with potential funding (in part) from non-US sources/Foreign Components; and independent funding (institutional) of drug companies or/and royalties potentially involved in research around the subject matter. DFM reports consulting or advisory role from BMS, Merck, Genentech/Roche, Pfizer, Exelixis, Novartis, Array BioPharma, Peloton Therapeutics, EMD Serono, Jounce Therapeutics, Alkermes, Lilly, Eisai, Calithera Biosciences, and Iovance Biotherapeutics; other fees from Beth Israel Deaconess Medical Center; research funding (institutional) from Prometheus, BMS, Merck, Genentech, Novartis, Alkermes, and Peloton Therapeutics; and uncompensated relationships with X4 Pharmaceuticals and AVEO. RJM reports consulting or advisory role from Novartis, Eisai, Exelixis, Merck, Genentech/Roche, Incyte, Lilly, Pfizer, AstraZeneca, EMD Serono, and Calithera Biosciences, travel accommodations and expenses from BMS; and research funding (institutional) from Pfizer, BMS, Eisai, Novartis, Genentech/Roche, Exelixis, and Merck. S George reports consultant or advisory role from AVEO, Bayer, BMS, Eisai, EMD Serono, Exelixis, Merck, Pfizer, QED Therapeutics, Sanofi/Genzyme, and Seattle Genetics; and local PI fees (institutional) from Agensys, Aravive, AVEO, Bayer, BMS, Calithera, Corvus, Eisai, Exelixis, Gilead, Merck, Novartis, Pfizer, Seattle Genetics, and Surface Oncology. TP reports research grants from AstraZeneca, Roche, BMS, Exelixis, Ipsen, Merck, MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas Pharma, Johnson & Johnson, and Eisai; consulting fees from BMS, Merck, AstraZeneca, Ipsen, Pfizer, Novartis, Incyte, Seattle Genetics, Roche, Exelixis, MSD, Merck Serono, Astellas Pharma, Johnson & Johnson, and Eisai; and travel accommodations and expenses from Pfizer, MSD, AstraZeneca, Roche, and Ipsen. FD reports research funding (institutional) from MSD Oncology. SST reports consulting or advisory role from Merck, Intellisphere, Natera, BMS, and Exelixis; research funding (institutional) from Genentech, BMS, MSD, Calithera Biosciences, Pfizer, Jounce Therapeutics, Nektar, Exelixis, and Clinigen Group; and Patent pending (institutional). SKP reports consultant or advisory role from F. Hoffmann LaRoche; travel accommodations and expenses; and research funding from Eisai, Genentech, Roche, and Pfizer. S Gupta, C–WL, and RJ are employed by and have stock ownership in BMS. NMT reports consulting or advisory role from Novartis, Exelixis, BMS, Nektar, Pfizer, Eisai, Ono Pharmaceutical, Oncorena, Surface Oncology, Neoleukin Therapeutics, Ipsen, MSD, Calithera Biosciences, and Lilly; travel accommodations and expenses from Pfizer, Nektar, BMS, Eisai, Surface Oncology, Lilly, Ipsen, and Calithera Biosciences; honoraria from Pfizer, Novartis, BMS, Exelixis, Nektar, Eisai, Ono Pharmaceutical, Lilly, Oncorena, Ipsen, Surface Oncology, Neoleukin Therapeutics, MSD, and Calithera Biosciences; and research funding from BMS, Exelixis, Pfizer, Nektar, Calithera Biosciences, Lilly, Mirati Therapeutics, Arrowhead Pharmaceuticals, Takeda, Epizyme, and Eisai.

Patient consent for publication Not applicable.

Ethics approval The CheckMate 214 study involves human participants and was approved by the institutional review board or ethics committee at each site and conducted in accordance with Good Clinical Practice guidelines per the International Conference on Harmonisation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. Bristol Myers Squibb's policy on data sharing may be found online at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Brian I Rini http://orcid.org/0000-0002-2212-080X
Toni K Choueiri http://orcid.org/0000-0002-9201-3217
Robert J Motzer http://orcid.org/0000-0001-6925-2327
Sumanta K Pal http://orcid.org/0000-0002-1712-0848

REFERENCES

1 Keskin SK, Msaouel P, Hess KR, *et al*. Outcomes of patients with renal cell carcinoma and sarcomatoid dedifferentiation treated with nephrectomy and systemic therapies: comparison between the cytokine and targeted therapy eras. *J Urol* 2017;198:530–7.

2 Mian BM, Bhadkamkar N, Slaton JW, *et al*. Prognostic factors and survival of patients with sarcomatoid renal cell carcinoma. *J Urol* 2002;167:65–70.

3 Shuch B, Bratslavsky G, Linehan WM, *et al*. Sarcomatoid renal cell carcinoma: a comprehensive review of the biology and current treatment strategies. *Oncologist* 2012;17:46–54.

4 Iacovelli R, Ciccarese C, Bria E, *et al*. Patients with sarcomatoid renal cell carcinoma - re-defining the first-line of treatment: a meta-analysis of randomised clinical trials with immune checkpoint inhibitors. *Eur J Cancer* 2020;136:195–203.

5 McKay RR, Bossé D, Xie W, *et al*. The clinical activity of PD-1/PD-L1 inhibitors in metastatic non-clear cell renal cell carcinoma. *Cancer Immunol Res* 2018;6:758–65.

6 Choueiri TK, Larkin JMG, Pal SK. Efficacy and biomarker analysis of patients with advanced renal cell carcinoma with sarcomatoid histology: subgroup analysis from the phase III javelin renal 101 trial of first-line avelumab plus axitinib vs sunitinib. *European Society for Medical Oncology Congress*; September 27-October 1, Barcelona, Spain, 2019:Poster 910PD.

7 Soulieres D, Plimack ER, Rini BI. Pembrolizumab plus axitinib versus sunitinib as first-line therapy for metastatic renal cell carcinoma: outcomes by IMDC risk and sarcomatoid subgroups of the phase 3 KEYNOTE-426 study. *The 18th International Kidney Cancer Symposium*; 15-16 November, Miami, FL, USA, 2019.

8 Rini BI, Motzer RJ, Powles T, *et al*. Atezolizumab plus bevacizumab versus sunitinib for patients with untreated metastatic renal cell carcinoma and sarcomatoid features: a prespecified subgroup analysis of the IMmotion151 clinical trial. *Eur Urol* 2021;79:659–62.

9 Tannir NM, Signoretti S, Choueiri TK, *et al*. Efficacy and safety of nivolumab plus ipilimumab versus sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma. *Clin Cancer Res* 2021;27:78–86.

10 Mouallem NE, Smith SC, Paul AK. Sarcomatoid renal cell carcinoma: biology and treatment advances. *Urol Oncol* 2018;36:265–71.

11 Rini BI, Plimack ER, Stus V, *et al*. Pembrolizumab plus sunitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380:1116–27.

12 Rini BI, Battle D, Figlin RA, *et al*. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of advanced renal cell carcinoma (RCC). *J Immunother Cancer* 2019;7:354.

13 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.

14 Delahunt B, Cheville JC, Martignoni G, *et al*. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol* 2013;37:1490–504.

15 Motzer RJ, McDermott DF, Escudier B, *et al*. Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. *Cancer* 2022;128:2085–97.

16 Atkins MB, Jegede OA, Haas NB, *et al*. Phase II study of nivolumab and salvage Nivolumab/Ipilimumab in treatment-naive patients with advanced clear cell renal cell carcinoma (HCRN GU16-260-Cohort A). *J Clin Oncol* 2022;40:2913–23.

17 Joseph RW, Millis SZ, Carballido EM, *et al*. PD-1 and PD-L1 expression in renal cell carcinoma with sarcomatoid differentiation. *Cancer Immunol Res* 2015;3:1303–7.

18 Kawakami F, Sircar K, Rodriguez-Canales J, *et al*. Programmed cell death ligand 1 and tumor-infiltrating lymphocyte status in patients with renal cell carcinoma and sarcomatoid dedifferentiation. *Cancer* 2017;123:4823–31.

19 Takahashi T, Tagami T, Yamazaki S, *et al*. Immunologic self-tolerance maintained by CD25(+)CD4(+) regulatory T cells constitutively expressing cytotoxic T lymphocyte-associated antigen 4. *J Exp Med* 2000;192:303–10.

20 Motzer RJ, Choueiri TK, Powles T. Nivolumab plus cabozantinib versus sunitinib for advanced renal cell carcinoma: outcomes by sarcomatoid histology and updated trial results with extended follow-up of CheckMate 9ER. In: *Genitourinary Cancers Symposium*. Chicago, IL, 2021.

21 Emamekhoo H, Olsen MR, Carthon BC, *et al*. Safety and efficacy of nivolumab plus ipilimumab in patients with advanced renal cell carcinoma with brain metastases: CheckMate 920. *Cancer* 2022;128:966–74.

22 ClinicalTrials.gov. A study to evaluate the safety of nivolumab and ipilimumab in subjects with previously untreated advanced or metastatic renal cell cancer. Available: https://ClinicalTrials.gov/show/NCT02982954 [Accessed 23 Mar 2022].

23 Bendell JC, Hutson T, Gordan LN. Nivolumab 6 mg/kg plus ipilimumab 1 mg/kg (N6I1) every 8 weeks (Q8W) alternating with nivolumab 480 Mg Q8W for first-line (1L) advanced renal cell carcinoma (aRCC): safety and efficacy from CheckMate 920. *The 19th Annual Meeting of the International Kidney Cancer Symposium*; 6–7 November, Virtual, 2020.

24 ClinicalTrials.gov. Phase II sequential treatment trial of single agent nivolumab, then combination ipilimumab + nivolumab in metastatic or unresectable non-clear cell renal cell carcinoma (ANZUP1602) (UNISoN). Available: https://ClinicalTrials.gov/show/NCT03177239 [Accessed 22 Mar 2022].

25 ClinicalTrials.gov. Immunotherapy with nivolumab and ipilimumab followed by nivolumab or nivolumab with cabozantinib for patients with advanced kidney cancer, the PDIGREE study. Available: https://ClinicalTrials.gov/show/NCT03793166 [Accessed 07 Apr 2022].

26 Powles T, Albiges L, Bex A, *et al*. ESMO clinical practice guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. *Ann Oncol* 2021;32:1511–9.