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Nivolumab plus ipilimumab versus sunitinib in previously untreated advanced renal-cell carcinoma: analysis of Japanese patients in CheckMate 214 with extended follow-up

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Y.T. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Motzer, McHenry. Provision of study materials or patients: Tomita, Kondo, Kimura, Inoue, Wakumoto, Yao, Sugiyama, Oya, Fujii, Obara, Motzer, Uemura. Collection and assembly of data: Motzer, McHenry, Tomita. Data analysis and interpretation: All authors. Drafting of the manuscript: Tomita. Critical revision of the manuscript for important intellectual content: All authors. Final approval of manuscript: All authors.

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Abstract

Background: Nivolumab plus ipilimumab (NIVO+IPI) demonstrated superior efficacy over sunitinib (SUN) for previously untreated advanced renal cell carcinoma (aRCC) in CheckMate 214, with a manageable safety profile. We report efficacy and safety with extended follow-up amongst Japanese patients.

Methods: CheckMate 214 patients received NIVO (3 mg/kg) plus IPI (1 mg/kg) every 3 weeks for four doses, then NIVO (3 mg/kg) every 2 weeks; or SUN (50 mg) once daily for 4 weeks (6-week cycle). This subgroup analysis assessed overall survival (OS), objective response rate (ORR) and progression-free survival (PFS) per investigator in International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor-risk and intent-to-treat (ITT) patients and safety (ITT patients).

Results: Of 550 and 546 patients randomized to NIVO+IPI and SUN, 38 and 34, respectively, were Japanese. Of these, 31 (NIVO+IPI) and 29 (SUN) patients were IMDC intermediate/poor-risk.

In IMDC intermediate/poor-risk patients with 30 months' minimum follow-up, there was a delayed trend in OS benefit with NIVO+IPI (hazard ratio [HR] 0.56; 95% confidence interval [CI]: 0.19–1.59; $P = 0.2670$), and 24-month OS probability favoured NIVO+IPI (84%) versus SUN (76%). The ORR was 39% with NIVO+IPI and 31% with SUN ($P = 0.6968$). PFS was similar in both treatment arms (HR 1.17; 95% CI: 0.62–2.20; $P = 0.6220$). Efficacy in ITT patients was similar to IMDC intermediate/poor-risk patients. Grade 3–4 treatment-related adverse event incidence was lower with NIVO+IPI versus SUN (58 versus 91%).

Conclusions: Japanese patients with untreated aRCC in the NIVO+IPI arm had a numerically higher ORR and improved safety profile versus patients in the SUN arm. A delayed OS benefit appears to be emerging with NIVO+IPI. Longer follow-up is needed.

https://clinicaltrials.gov/ct2/show/NCT02231749?term=NCT02231749&rank=1 identifier: NCT02231749.

Key words: advanced renal cell carcinoma, first-line treatment, nivolumab, ipilimumab, Japanese

Introduction

Sunitinib (SUN), a vascular endothelial growth factor receptor tyrosine kinase inhibitor, is one of the standard-of-care therapies for first-line treatment of advanced renal-cell carcinoma (aRCC) in Japan (1). An earlier Phase II open-label trial of SUN in previously untreated Japanese patients reported an objective response rate (ORR) of 48% and a median progression-free survival (PFS) of 46.0 weeks. There was a high rate of haematological toxic effects associated with SUN treatment (2).

The combination of nivolumab plus ipilimumab (NIVO+IPI) has been approved by the US Food and Drug Administration (3,4), the European Medicines Agency (5) and the Japanese Ministry of Health, Labor and Welfare (6) for the first-line treatment of patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor-risk aRCC, based on superior overall survival (OS) and ORR over SUN in the randomized, Phase III CheckMate 214 trial (7). Recently, extended follow-up and expanded efficacy and safety analyses of the global population of CheckMate 214 were published (8). At a median follow-up of 32.4 months (minimum [range] follow-up, 30 [0–44] months) in IMDC intermediate/poor-risk patients, OS benefit was observed with NIVO+IPI versus SUN (hazard ratio [HR] 0.66; 95% confidence interval [CI]: 0.54–0.80; $P < 0.0001$); median OS (95% CI) was not reached (35.6–not estimable [NE]) with NIVO+IPI and 26.6 months (22.1–33.4) with SUN. The ORR (95% CI) was 42% (37–47) versus 29% (25–34) with NIVO+IPI and SUN, respectively ($P = 0.0001$). PFS benefit in the NIVO+IPI arm was apparent after the median PFS was reached (HR 0.77; 95% CI: 0.65–0.90; $P = 0.0014$); the median (95% CI) PFS was similar for both arms (8.2 [6.9–10.0] months in the NIVO+IPI arm versus 8.3 [7.0–8.8] in the SUN arm) (8). Similar efficacy benefits were observed in the intent-to-treat (ITT) population. Treatment-related adverse events (AEs) occurred in 94% of all patients treated with NIVO+IPI, and in 97% of all patients treated with SUN. Grade 3/4 AEs occurred in 47 and 64% of patients treated with NIVO+IPI and SUN, respectively. As there have been differences in efficacy and safety of renal cell carcinoma treatments in Asian patients compared with global clinical trial populations (9–12), NIVO+IPI treatment should be analyzed in Japanese patients in CheckMate 214.

Here, we present the efficacy and safety data from Japanese patients treated with NIVO+IPI or SUN in CheckMate 214 at a median follow-up of 32.4 months.

Patients and methods

Study design and treatment

The design of CheckMate 214, a Phase III, randomized, open-label study of NIVO+IPI followed by NIVO monotherapy versus SUN monotherapy in patients with previously untreated aRCC, was reported previously (7). Patients were randomized 1:1 to receive NIVO+IPI at a dose of 3 mg/kg intravenously for 60 minutes and 1 mg/kg for 30 minutes, respectively, every 3 weeks for four doses (induction phase), followed by NIVO monotherapy at a dose of 3 mg/kg every 2 weeks (maintenance phase); or SUN at a dose of 50 mg orally once daily for 4 weeks of each 6-week cycle. Randomization was stratified according to IMDC risk score (0 [favourable] versus 1–2 [intermediate] versus 3–6 [poor]) and geographic region (United States versus Canada and Europe versus the rest of the world). Japanese patients were included as part of the "rest of the world" stratification group.

Patients

Adult patients (≥18 years) with previously untreated, clear-cell component aRCC with a Karnofsky performance status (KPS) ≥70 were eligible for the study. Patients with central nervous system metastases, autoimmune disease, or glucocorticoid or immunosuppressant use were excluded from the study.

Endpoints and assessments

The co-primary endpoints of CheckMate 214 were OS, ORR per independent radiology review committee (IRRC) and PFS per IRRC amongst IMDC intermediate/poor-risk patients; secondary endpoints included efficacy in ITT patients and the incidence of AEs in all treated patients; exploratory endpoints included efficacy in favourable-risk patients—all of which were reported previously (7). In the present subgroup analysis with longer follow-up after coprimary endpoints were met, OS was analyzed as reported previously; however, progression and ORR (including time to response and duration of response) were assessed per investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 instead of IRRC. Disease assessments (per RECIST v1.1) were performed with computed tomography or magnetic resonance imaging at baseline and 12 weeks after randomization and continued every 6 weeks for the first 13 months, and then every 12 weeks until progression or treatment discontinuation. Patients

were allowed to continue therapy after initial investigator-assessed, RECIST-defined progression if they had investigator-assessed clinical benefit and were tolerating the study treatment. Patients were followed for safety and survival after progression or treatment discontinuation. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0 (13) and reported between first dose and 30 days after last dose of study therapy. Treatment-related select AEs—those deemed to be related to the checkpoint inhibitor's mechanism of action (11)—were defined using the following criteria: AEs that may differ in type, frequency or severity from those caused by agents not targeting the immune system, AEs that may require immunosuppressants (e.g. corticosteroids) as part of their management, AEs whose early recognition and management may mitigate severe toxicity and AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization. Treatment-related select AEs were reported between first dose and 30 days after last dose of study therapy.

Study oversight

CheckMate 214 was approved by the institutional review board or independent ethics committee at each centre and conducted in accordance with Good Clinical Practice guidelines defined by the International Conference on Harmonisation. All patients provided written informed consent to participate based on the principles of the Declaration of Helsinki.

Statistical analyses

OS, PFS, duration of therapy, time to response, duration of response and time to resolution of treatment-related select AEs were estimated using Kaplan–Meier methodology (14). The two treatment arms were compared with stratified log-rank tests. The estimated HRs and associated 95% CIs obtained for OS and PFS of NIVO+IPI versus SUN were calculated using a stratified Cox proportional hazards model with the treatment as a single covariate. ORR and the corresponding 95% CIs were calculated based on the Clopper and Pearson method (15). Baseline demographics and safety were reported using descriptive statistics. CheckMate 214 was not prospectively designed to detect differences between treatment arms among Japanese patients, and therefore, no statistical comparison between arms was possible due to low patient numbers.

Results

Patients

As reported previously, 550 and 546 patients in CheckMate 214 were randomized to NIVO+IPI and SUN, respectively. Of these, 425 and 422 were IMDC intermediate/poor-risk patients (7). Overall, 195 patients in the NIVO+IPI arm and 194 patients in the SUN arm were stratified by the "rest of the world" region, which included Japanese patients (7). There were 38 and 34 Japanese patients randomized to NIVO+IPI and SUN in the ITT population of the study; most were classified as IMDC intermediate/poor-risk (31 and 29 in the NIVO+IPI and SUN arms, respectively).

The demographic and baseline characteristics of the Japanese patients were relatively balanced between arms in the ITT and IMDC intermediate/poor-risk groups. However, there were greater proportions of patients with IMDC poor risk, higher disease burden, liver metastases and without previous nephrectomy in the NIVO+IPI arm compared with the SUN arm, but low patient numbers precluded a statistical comparison between arms (Table 1). Amongst all treated Japanese patients, with a median follow-up of 32.4 months (minimum [range] follow-up, 30 [0–44] months), 5 of 38 (13%) patients in the NIVO+IPI arm and 6 of 34 (18%) in the SUN arm continued to receive treatment. The primary reason for discontinuation in both arms was disease progression (50% in the NIVO+IPI arm and 53% in the SUN arm).

The median (interquartile range [IQR]) duration of treatment for all Japanese patients treated with NIVO+IPI was 9.6 (2.1–26.3) months; patients treated with SUN had a median (IQR) duration of therapy of 11.7 (3.8–30.1) months. Patients received a median (range) of 4 (1–4) IPI doses and 20 (1–71) NIVO doses. The median (range) average daily dose of SUN received was 18.3 (7.8–50.0) mg/day over the 42-day cycle.

Efficacy

IMDC intermediate/poor-risk patients. The Japanese patients treated with NIVO+IPI had a trend towards a late OS benefit compared with patients treated with SUN (HR 0.56; 95% CI: 0.19–1.59; $P = 0.2670$). The median OS (95% CI) was not reached (33.5–NE) with NIVO+IPI and was 33.4 (32.4–NE) months with SUN (Fig. 1). The 24-month OS probability (95% CI) favoured NIVO+IPI (84% [66–93]) versus SUN (76% [56–88]).

Investigator-assessed confirmed ORR (95% CI) was 39% (22–58) with NIVO+IPI and 31% (15–51) with SUN ($P = 0.6968$). Two patients in the NIVO+IPI arm had a complete response, versus one patient in the SUN arm (Table 2). Amongst responders, the median time to response was shorter with NIVO+IPI versus SUN (2.8 [IQR 2.7–3.4] months with NIVO+IPI and 4.2 [IQR 2.8–6.9] months with SUN). The median duration of response was similar between treatment arms (26.5 [95% CI: 12.5–NE] months with NIVO+IPI and 23.6 [11.0–31.8] months with SUN). Five (42%) and four (44%) patients in the NIVO+IPI and SUN arms, respectively, had an ongoing response. Response to NIVO+IPI treatment was durable amongst Japanese patients (Fig. 2).

PFS was similar in both treatment arms (HR 1.17; 95% CI: 0.62–2.20; $P = 0.6220$). The median PFS (95% CI) was 12.5 (5.2–22.2) months versus 15.2 (5.3–26.3) months for NIVO+IPI versus SUN, respectively (Fig. 3).

Intent-to-treat patients. The OS was similar in the NIVO+IPI and SUN treatment arms (HR 0.65; 95% CI: 0.24–1.76; $P = 0.3885$). The median OS (95% CI) was not reached (33.5–NE) with NIVO+IPI and not reached (32.4–NE) with SUN (see Supplemental Fig. 1). The 24-month OS probability (95% CI) was 87% (71–94) with NIVO+IPI versus 79% (62–90) with SUN.

Investigator-assessed confirmed ORR (95% CI) was 34% (20–51) with NIVO+IPI and 38% (22–56) with SUN ($P = 0.6195$). Two patients in the NIVO+IPI arm had a complete response, versus one patient in the SUN arm (Supplemental Table 1). Amongst responders, the median time to response was shorter with NIVO+IPI versus SUN (2.8 [IQR 2.8–4.0] months with NIVO+IPI and 4.2 [IQR 2.8–5.7] months with SUN). Furthermore, the median duration of response was similar amongst both treatment arms (23.0 [95% CI: 11.1–NE] months with NIVO+IPI and 25.1 [11.0–31.8] months with SUN). Five (38%) and six (46%) patients in the NIVO+IPI and SUN arms, respectively, had an ongoing response.

PFS was similar in both treatment arms (HR 1.33; 95% CI: 0.74–2.38; $P = 0.3406$). The median PFS (95% CI) was 12.5 (8.1–20.8) months versus 17.9 (7.1–27.9) months for NIVO+IPI versus SUN, respectively (see Supplemental Fig. 2).

Table 1. Baseline demographic and clinical characteristics of Japanese patients

Characteristic	IMDC intermediate/poor-risk patients		Intent-to-treat patients	
	NIVO+IPI (*N* = 31)	SUN (*N* = 29)	NIVO+IPI (*N* = 38)	SUN (*N* = 34)
Median age (range), years	65 (44–81)	68 (48–85)	65 (44–81)	68 (48–85)
Sex, *n* (%)				
Male	26 (84)	21 (72)	32 (84)	25 (74)
Female	5 (16)	8 (28)	6 (16)	9 (26)
IMDC prognostic risk, *n* (%)				
Favourable	0	0	7 (18)	5 (15)
Intermediate	25 (81)	27 (93)	25 (66)	27 (79)
Poor	6 (19)	2 (7)	6 (16)	2 (6)
Quantifiable tumour PD-L1 expression, *n*/total evaluable (%)				
<1%	22/29 (76)	23/28 (82)	29/36 (81)	27/33 (82)
≥1%	7/29 (24)	5/28 (18)	7/36 (19)	6/33 (18)
Previous radiotherapy, *n* (%)	1 (3)	0	1 (3)	0
Previous nephrectomy, *n* (%)	23 (74)	23 (79)	28 (74)	28 (82)
Sites with target or non-target lesions, *n* (%)				
1	7 (23)	11 (38)	12 (32)	13 (38)
≥2	24 (77)	18 (62)	26 (68)	21 (62)
Most common site of metastasis, *n* (%)				
Lung	22 (71)	19 (66)	23 (61)	22 (65)
Lymph node	13 (42)	12 (41)	14 (37)	15 (44)
Bone[a]	9 (29)	7 (24)	9 (24)	7 (21)
Liver	4 (13)	2 (7)	5 (13)	2 (6)

[a]Patients who had bone metastases with or without a soft-tissue component.

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

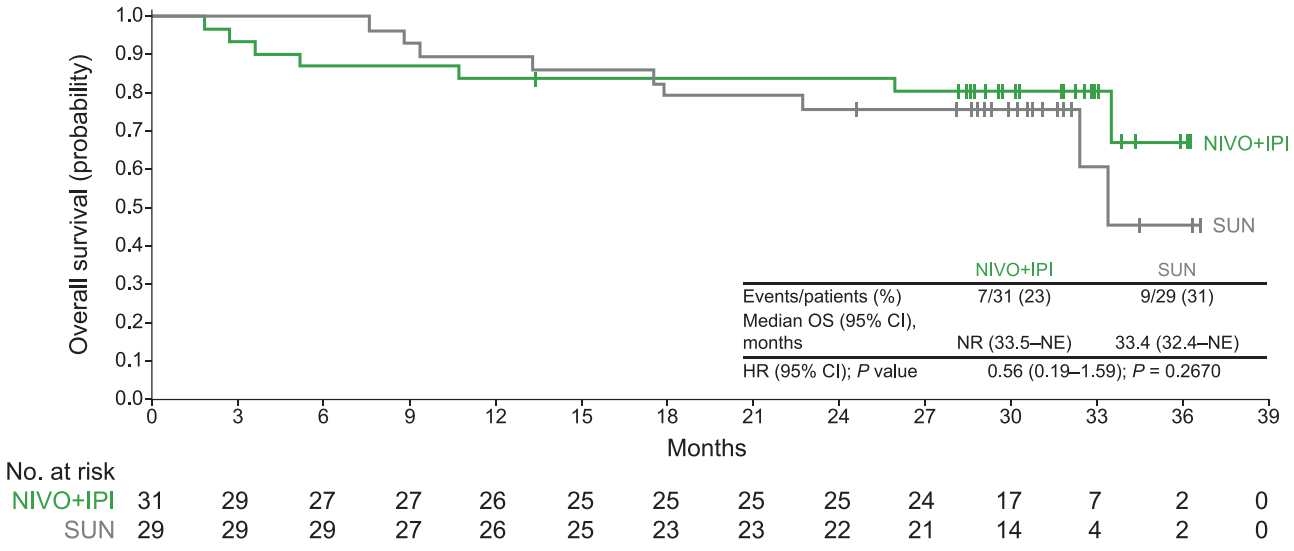

Figure 1. Overall survival amongst Japanese IMDC intermediate/poor-risk patients. CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IPI, ipilimumab; NE, not estimable; NIVO, nivolumab; OS, overall survival; SUN, sunitinib.

Safety

Treatment-related AEs of any grade occurred in 34 (89%) patients treated with NIVO+IPI and 34 (100%) patients treated with SUN. The most common any-grade treatment-related AEs in patients treated with NIVO+IPI were pruritus (26%), increased lipase (21%), pyrexia (16%) and rash (16%); the most common treatment-related AEs in patients treated with SUN were decreased platelet count (85%), palmar-plantar erythrodysaesthesia syndrome (68%) and decreased white blood cell count (68%). Grade 3/4 treatment-related AEs occurred in 22 (58%) and 31 (91%) patients treated with NIVO+IPI and SUN, respectively. The most common grade 3/4 treatment-related AE in patients treated with NIVO+IPI was increased lipase (16%); the most common treatment-related AE in patients treated with SUN was decreased platelet count (56%) (Table 3). Treatment-related AEs leading to discontinuation occurred in 12 (32%) and 8 (24%) patients treated with NIVO+IPI and SUN,

Table 2. Antitumour activity in Japanese IMDC intermediate/poor-risk patients

Response	NIVO+IPI (*N* = 31)	SUN (*N* = 29)
Confirmed ORR per investigator[a], *n* (%)	12 (39)	9 (31)
95% CI	22–58	15–51
Best overall response per investigator, *n* (%)		
Complete response	2 (6)	1 (3)
Partial response	10 (32)	8 (28)
Stable disease	13 (42)	14 (48)
Progressive disease	5 (16)	5 (17)
Not determined	1 (3)	1 (3)

[a]Per Response Evaluation Criteria in Solid Tumors v1.1.
CI, confidence interval; ORR, objective response rate.

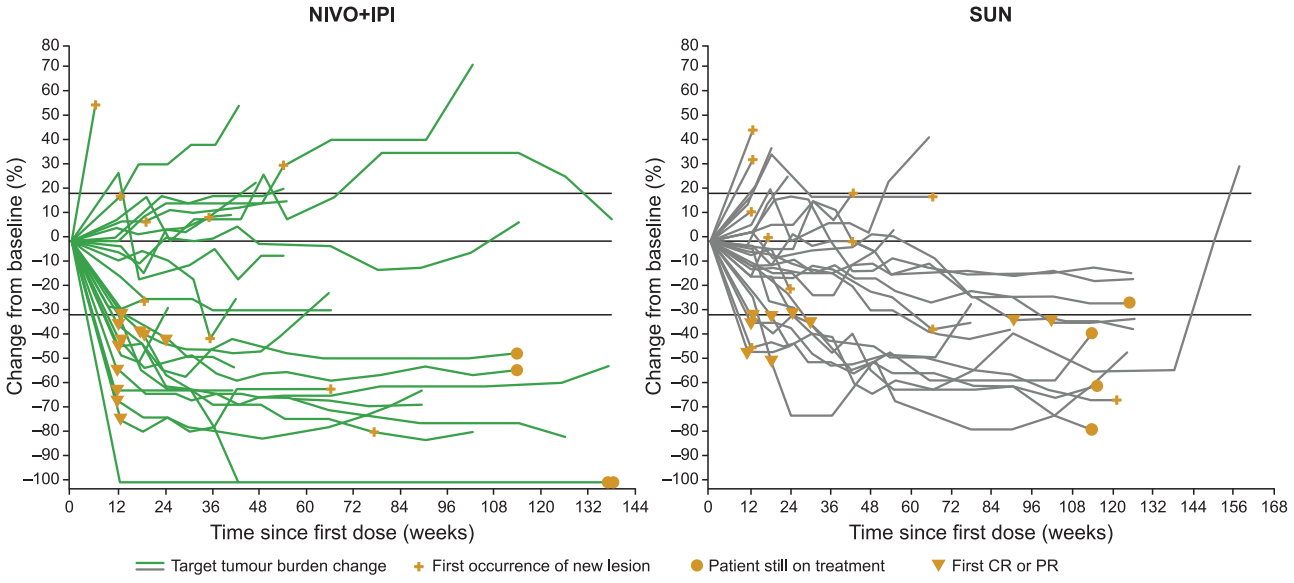

Figure 2. Change in target tumour burden over time in IMDC intermediate/poor-risk Japanese patients treated with nivolumab plus ipilimumab. CR, complete response; PR, partial response.

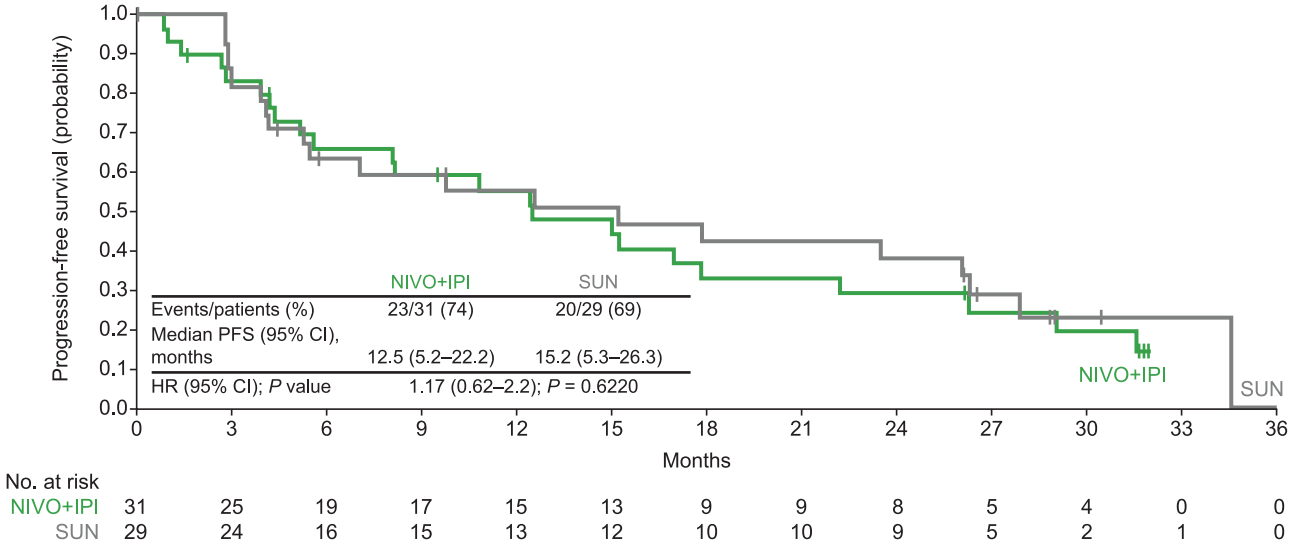

Figure 3. Progression-free survival per investigator amongst Japanese IMDC intermediate/poor-risk patients. PFS, progression-free survival.

Table 3. Treatment-related adverse events in ITT Japanese patients

Event, *n* (%)	NIVO+IPI (*N* = 38)		SUN (*N* = 34)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AEs	34 (89)	22 (58)	34 (100)	31 (91)
Treatment-related AEs in ≥15% of patients in either arm				
Pruritus	10 (26)	0	0	0
Increased lipase	8 (21)	6 (16)	12 (35)	8 (24)
Pyrexia	6 (16)	0	11 (32)	1 (3)
Rash	6 (16)	0	8 (24)	0
Diarrhoea	5 (13)	1 (3)	11 (32)	1 (3)
Increased aspartate aminotransferase	5 (13)	1 (3)	8 (24)	1 (3)
Increased amylase	4 (11)	2 (5)	5 (15)	5 (15)
Decreased lymphocyte count	3 (8)	1 (3)	12 (35)	8 (24)
Fatigue	3 (8)	0	8 (24)	6 (18)
Increased alanine aminotransferase	3 (8)	2 (5)	7 (21)	1 (3)
Abnormal hepatic function	2 (5)	2 (5)	7 (21)	0
Decreased appetite	2 (5)	1 (3)	15 (44)	1 (3)
Decreased platelet count	2 (5)	0	29 (85)	19 (56)
Decreased white blood cell count	2 (5)	0	23 (68)	6 (18)
Dysgeusia	2 (5)	0	12 (35)	0
Hypothyroidism	2 (5)	0	12 (35)	0
Increased blood creatinine	2 (5)	0	8 (24)	0
Malaise	2 (5)	0	17 (50)	0
Anaemia	1 (3)	0	10 (29)	3 (9)
Decreased neutrophil count	1 (3)	1 (3)	15 (44)	12 (35)
Hyponatraemia	1 (3)	0	6 (18)	2 (6)
Stomatitis	1 (3)	0	14 (41)	1 (3)
Vomiting	1 (3)	0	10 (29)	0
Epistaxis	0	0	6 (18)	0
Hyperkalaemia	0	0	5 (15)	0
Hypertension	0	0	17 (50)	8 (24)
Increase in blood thyroid-stimulating hormone	0	0	7 (21)	0
Nausea	0	0	11 (32)	1 (3)
PPE syndrome	0	0	23 (68)	3 (9)

AE, adverse event; ITT, intent-to-treat; PPE, palmar-plantar erythrodysaesthesia.

respectively. Eight (21%) and nine (26%) deaths were reported in the NIVO+IPI and SUN arms, respectively; one death (haemophagocytic syndrome) in the NIVO+IPI arm was considered treatment-related.

Treatment-related any-grade select AEs in patients treated with NIVO+IPI were observed as follows: skin (58%), endocrine (24%), hepatic (16%), pulmonary (16%), gastrointestinal (13%) and renal (5%). Grade 3/4 treatment-related select AEs were endocrine (11%), skin (8%), hepatic (8%) and gastrointestinal (5%). No grade 3/4 renal or pulmonary treatment-related select AEs were observed (Table 4). The median time to onset of treatment-related select AEs mostly occurred during the induction phase: skin and gastrointestinal events developed between weeks 3 and 4, followed by hepatic (10 weeks) and endocrine (12 weeks). Renal and pulmonary treatment-related select AEs generally occurred after the induction phase (median of approximately 17 and 36 weeks, respectively) (Table 4). The majority of treatment-related select AEs resolved within 15 weeks from onset, with the exception of select endocrine treatment-related AEs, which were managed with appropriate hormonal therapies (Table 4).

Subsequent therapy

Subsequent systemic therapy was received by 21 (55%) patients in the NIVO+IPI arm; the most common of these were axitinib (*n* = 14, 37%) and pazopanib (*n* = 8, 21%). In the SUN arm, 20 (59%) patients received subsequent systemic therapy; the most common therapies were axitinib (*n* = 15, 44%) and nivolumab (*n* = 10, 29%).

Discussion

The primary results in the IMDC intermediate/poor-risk global population of CheckMate 214 established a superior efficacy of NIVO+IPI versus SUN in the first-line treatment of aRCC (7). With extended follow-up, improved OS, PFS and ORR per investigator were maintained with NIVO+IPI versus SUN in both the ITT and the IMDC intermediate/poor-risk populations (8).

The present analysis examined the efficacy and safety of NIVO+IPI versus SUN in the Japanese patients of CheckMate 214. With 30 months of minimum follow-up, a delayed trend in OS benefit (HR 0.56, 95% CI: 0.19–1.59; 24-month OS probabilities of 84% with NIVO+IPI versus 76% with SUN) became apparent with NIVO+IPI versus SUN, and the IMDC intermediate/poor-risk Japanese patients treated with NIVO+IPI had a numerically higher ORR compared with patients treated with SUN. In addition, the median time to response was shorter in Japanese patients treated with NIVO+IPI versus SUN. PFS was statistically similar between treatment arms. The efficacy results in ITT patients were similar

Table 4. Incidence, time to onset, time to resolution and resolution rate of treatment-related select adverse events in Japanese patients

Organ category	NIVO+IPI (*N* = 38)				
	Incidence of treatment-related select AEs, *n* (%)		Median time to onset of all grades (IQR), weeks	Median time to resolution of all grades (95% CI), weeks	Overall resolution rate of all grades, *n/N* (%)
	Any grade	Grade 3/4			
Skin	22 (58)	3 (8)	3.1 (0.9–6.7)	13.1 (6.7–42.0)	16/22 (73)
Endocrine	9 (24)	4 (11)	12.0 (7.1–14.7)	NR (1.1–NE)	4/9 (44)
Hepatic	6 (16)	3 (8)	10.0 (3.1–11.1)	2.0 (0.9–4.1)	5/6 (83)
Pulmonary	6 (16)	0	16.6 (7.0–30.1)	14.6 (1.3–NE)	5/6 (83)
Gastrointestinal	5 (13)	2 (5)	3.6 (1.1–5.1)	2.7 (0.6–14.7)	5/5 (100)
Renal	2 (5)	0	36.4 (2.7–70.1)	1.6 (1.0–2.1)	2/2 (100)

IQR, interquartile range; NR, not reached.

to the results in IMDC intermediate/poor-risk patients. Additional follow-up is needed to determine if efficacy trends with NIVO+IPI continue to show benefit over SUN treatment in Japanese patients.

The demographic and baseline characteristics of the Japanese patients in the ITT and IMDC intermediate/poor-risk groups were generally similar to the global population of CheckMate 214 (7). However, in the Japanese patient population, a lower proportion of patients had received prior radiotherapy or had high disease burden compared with the global population; in the SUN treatment arm, lower proportions had liver metastases or were IMDC poor-risk compared with the global population (7). These differences in baseline characteristics influencing prognosis may have contributed to the differences in efficacy results seen between the global and Japanese patients.

The incidence of any-grade and grade 3/4 treatment-related AEs with NIVO+IPI was lower than that with SUN in Japanese patients. Most treatment-related select AEs with NIVO+IPI were low-grade, with low incidence of grade 3/4 select AEs. The median time to onset of skin, endocrine, hepatic and gastrointestinal select AEs was early, during the induction period. Most select AEs resolved. These results point to a manageable safety profile of NIVO+IPI in Japanese patients.

This analysis of the Japanese patients in CheckMate 214 is limited by the small sample size in each treatment arm, reducing the confidence level and increasing the margin of error compared with the global analysis. Furthermore, the Japanese patients were part of the "rest of the world" stratification, and the study was not designed with the statistical power to detect significant differences in such a small subset of patients. However, the results observed in Japanese patients are consistent with the results observed in the global population, and further follow-up of the Japanese population may show a late significant clinical benefit of NIVO+IPI versus SUN in the first-line treatment of aRCC.

In conclusion, Japanese patients with untreated aRCC in the NIVO+IPI arm had a numerically higher ORR and improved safety profile compared with patients in the SUN arm. A delayed trend in OS benefit became apparent with NIVO+IPI versus SUN, although further follow-up is needed.

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

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Conflict of interest statement

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Data sharing

Bristol-Myers Squibb's policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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Appendix

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