



Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial



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ABSTRACT

Purpose To report updated analyses of the phase III CheckMate 214 trial with extended minimum follow-up assessing long-term outcomes with first-line nivolumab plus ipilimumab (NIVO+IPI) versus (vs) sunitinib (SUN) in patients with advanced renal cell carcinoma (aRCC).
Methods Patients with aRCC with a clear cell component were stratified by International Metastatic Renal Cell Carcinoma Database Consortium risk and randomised to NIVO (3 mg/kg) plus IPI (1 mg/kg) every three weeks ×4 doses, followed by NIVO (3 mg/kg) every two weeks; or SUN (50 mg) once per day ×4 weeks (6-week cycle). Efficacy endpoints included overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) per independent radiology review committee in patients with intermediate/poor-risk disease (I/P; primary), intent-to-treat patients (ITT; secondary) and in patients with favourable-risk disease (FAV; exploratory).
Results Overall, 1096 patients were randomised (ITT: NIVO+IPI, n=550, SUN, n=546; I/P: NIVO+IPI, n=425, SUN, n=422; FAV: NIVO+IPI, n=125, SUN, n=124). After 4 years minimum follow-up, OS (HR; 95% CI) remained superior with NIVO+IPI vs SUN in ITT (0.69; 0.59 to 0.81) and I/P patients (0.65; 0.54 to 0.78). Four-year PFS probabilities were 31.0% vs 17.3% (ITT) and 32.7% vs 12.3% (I/P), with NIVO+IPI vs SUN. ORR remained higher with NIVO+IPI vs SUN in ITT (39.1% vs 32.4%) and I/P (41.9% vs 26.8%) patients. In FAV patients, the HRs (95% CI) for OS and PFS were 0.93 (0.62 to 1.40) and 1.84 (1.29 to 2.62); ORR was lower with NIVO+IPI vs SUN. However, more patients in all risk groups achieved complete responses with NIVO+IPI: ITT (10.7% vs 2.6%), I/P (10.4% vs 1.4%) and FAV (12.0% vs 6.5%). Probability (95% CI) of response ≥4 years was higher with NIVO+IPI vs SUN (ITT, 59% (0.51 to 0.66) vs 30% (0.21 to 0.39); I/P, 59% (0.50 to 0.67) vs 24% (0.14 to 0.36); and FAV, 60% (0.41 to 0.75) vs 38% (0.22 to 0.54)) regardless of risk category. Safety remained favourable with NIVO+IPI vs SUN.

Key questions

What is already known about this subject?

- Nivolumab plus ipilimumab (NIVO+IPI) combination immunotherapy was the first to demonstrate superiority over sunitinib (SUN) in the first-line treatment of patients with advanced renal cell carcinoma (aRCC).
- NIVO+IPI is currently approved for clinical use in patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor-risk disease based on results from the randomised phase III CheckMate 214 trial (NCT02231749).

What does this study add?

- Here, we report durable efficacy benefits after long-term follow-up with NIVO+IPI over SUN in patients with aRCC in CheckMate 214.
- With over 4 years of minimum follow-up, overall survival benefits with NIVO+IPI were maintained. Progression-free survival probabilities reached a plateau above 30% with NIVO+IPI in intent-to-treat and intermediate/poor-risk patient populations.
- Objective response rates were consistent, with a complete response rate per independent radiology review committee over 10% as well as more ongoing responses and longer duration of response with NIVO+IPI regardless of IMDC risk group.

How might this impact on clinical practice?

- These results continue to support the use of first-line NIVO+IPI to achieve meaningful and durable clinical outcomes in patients with aRCC.

Conclusion After long-term follow-up, NIVO+IPI continues to demonstrate durable efficacy benefits vs SUN, with manageable safety.

Trial registration details ClinicalTrials.gov identifier: NCT02231749.

INTRODUCTION

Many patients experience lasting benefits from immunology-based therapy due to improved efficacy together with favourable safety and quality-of-life outcomes. This new potential for prolonged survival underscores the importance of long-term updates to assess the durability of clinical benefits with first-line therapies for patients with advanced renal cell carcinoma (aRCC).^{1–3}

Dual checkpoint inhibition with nivolumab plus ipilimumab (NIVO+IPI) is currently approved for the first-line treatment of patients with aRCC and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor (I/P)-risk disease, on the basis of results from the randomised phase III CheckMate 214 trial (NCT02231749). In the primary analysis of the CheckMate 214 trial (minimum follow-up, 17.5 months) in patients with I/P risk, overall survival (OS) was significantly superior (HR, 0.63; $p < 0.001$) and confirmed objective response rate (ORR) was higher (42% versus (vs) 27%; $p < 0.001$ per independent radiology review committee (IRRC)) with NIVO+IPI over sunitinib (SUN).⁴ Comparable OS benefits (HR 0.68; $p < 0.001$) and improved ORR (39% vs 32%) were also observed with NIVO+IPI in intent-to-treat (ITT) patients.⁴ NIVO+IPI continued to demonstrate improved efficacy outcomes over SUN in both ITT and I/P-risk patients, including OS benefits and durable responses with additional follow-up.^{1,2,4} In IMDC favourable (FAV)-risk patients, ORR and progression-free survival (PFS) benefits were observed with SUN, yet the difference in OS outcomes between treatment arms was inconclusive.^{1,2,4}

Here, we report extended 4-year minimum follow-up from the CheckMate 214 trial in ITT, I/P-risk and FAV-risk patients with aRCC. Survival outcomes, response per IRRC, durability of response and safety were assessed, providing the longest follow-up to date of an approved first-line checkpoint inhibitor-based therapy in aRCC.

METHODS

Patients and treatment

The CheckMate 214 study design and statistical analyses details have been published previously.^{2,4} Briefly, adults with treatment-naïve aRCC with a clear cell component were randomised 1:1 to the NIVO+IPI or SUN arms and stratified by region and IMDC risk status (favourable, intermediate or poor).^{4–6} Combination NIVO 3 mg/kg and IPI 1 mg/kg was administered intravenously every 3 weeks for four doses, followed by NIVO 3 mg/kg monotherapy every 2 weeks. Patients were required to receive all four doses of NIVO+IPI before beginning NIVO monotherapy. SUN 50 mg was administered orally once daily for 4 weeks on and 2 weeks off in each 6-week cycle. Treatment continued until disease progression or unacceptable toxicity. A total of two dose reductions were permitted for SUN in 12.5 mg increments per day (for daily dose ≥ 25 mg); no dose reductions were allowed in the NIVO+IPI arm. The trial was stopped when NIVO+IPI

demonstrated OS superiority over SUN in the primary efficacy population (database lock, 7 August 2017). A subsequent protocol amendment on 13 November 2017 permitted modifications to the NIVO+IPI arm, including the following: patients could discontinue after 2 years of study treatment even in the absence of disease progression or unacceptable toxicity; patients receiving NIVO maintenance therapy were permitted to switch to NIVO 240 mg every 2 weeks; and I/P-risk patients could cross over from SUN to NIVO+IPI.

Assessments

Primary endpoints included OS, PFS per IRRC and ORR per IRRC in the I/P-risk population. Secondary endpoints included OS, PFS and ORR in the ITT population, and the incidence rate of adverse events (AEs) among all treated patients. Exploratory endpoints included OS, PFS and ORR in FAV-risk patients. Response outcomes were confirmed and reported per IRRC using Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1.⁷ Safety was assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.0.⁸ Treatment-related select AEs were prespecified, and defined as events that might be immune-mediated, differ from those caused by non-immunotherapeutic drugs, might require immunosuppression for management and whose early recognition might mitigate severe toxicity (including events in the skin, gastrointestinal, endocrine, hepatic, pulmonary or renal systems). A detailed characterisation of all responders, including durability of response, treatment-free interval and subsequent therapy outcomes, were conducted as post hoc analyses. Treatment-free interval was defined as the time between protocol therapy discontinuation until subsequent therapy initiation or last known date alive.¹

Trial oversight

CheckMate 214 was approved by the institutional review board or ethics committee at each site and was conducted according to Good Clinical Practice guidelines, defined by the International Conference on Harmonisation. All patients provided written informed consent that was based on the Declaration of Helsinki principles. A data and safety monitoring committee reviewed efficacy and safety. The trial was designed by the authors in collaboration with the sponsors (Bristol Myers Squibb and ONO Pharmaceutical). Bristol Myers Squibb collected and analysed the data with the authors. A data confidentiality agreement was in place between Bristol Myers Squibb and the investigators. The authors vouch for the completeness and accuracy of the data and analyses and for the adherence of the trial to the protocol.

Statistical analysis

After the planned interim analysis met the prespecified boundary of statistical significance for OS, it was considered the final primary analysis per protocol.⁴ Descriptive p values were included in the present analyses to confirm

consistency with the primary analysis as appropriate. Here, OS, PFS and duration of response were estimated using Kaplan-Meier methods.⁹ Stratified Cox proportional HRs and 95% CIs were calculated between treatment arms for OS and PFS (NIVO+IPI over SUN). ORR and the exact two-sided 95% CI were computed by Clopper-Pearson method; the two-sided p values were calculated per DerSimonian and Laird.^{10,11} Treatment-related AEs of interest were calculated in all treated patients. The incidence of corticosteroid use (≥ 40 mg prednisone daily or equivalent (PDE)) for management of treatment-related select AEs over time was analysed retrospectively for patients in the NIVO+IPI arm. The univariate Cox model was used to

calculate the HR with 95% CI. All statistical analyses were done with SAS V.8.2 or East V.5.4.

RESULTS

Patients

Among 1096 patients randomised, 550 patients in the ITT population were randomised to NIVO+IPI (425 I/P risk; 125 FAV risk) and 546 patients were randomised to SUN (422 I/P risk; 124 FAV risk; online supplemental figure 1). Efficacy analyses were conducted in ITT patients and are presented in all-risk, I/P-risk and FAV-risk groups. Overall, 547 patients in the NIVO+IPI arm and 535

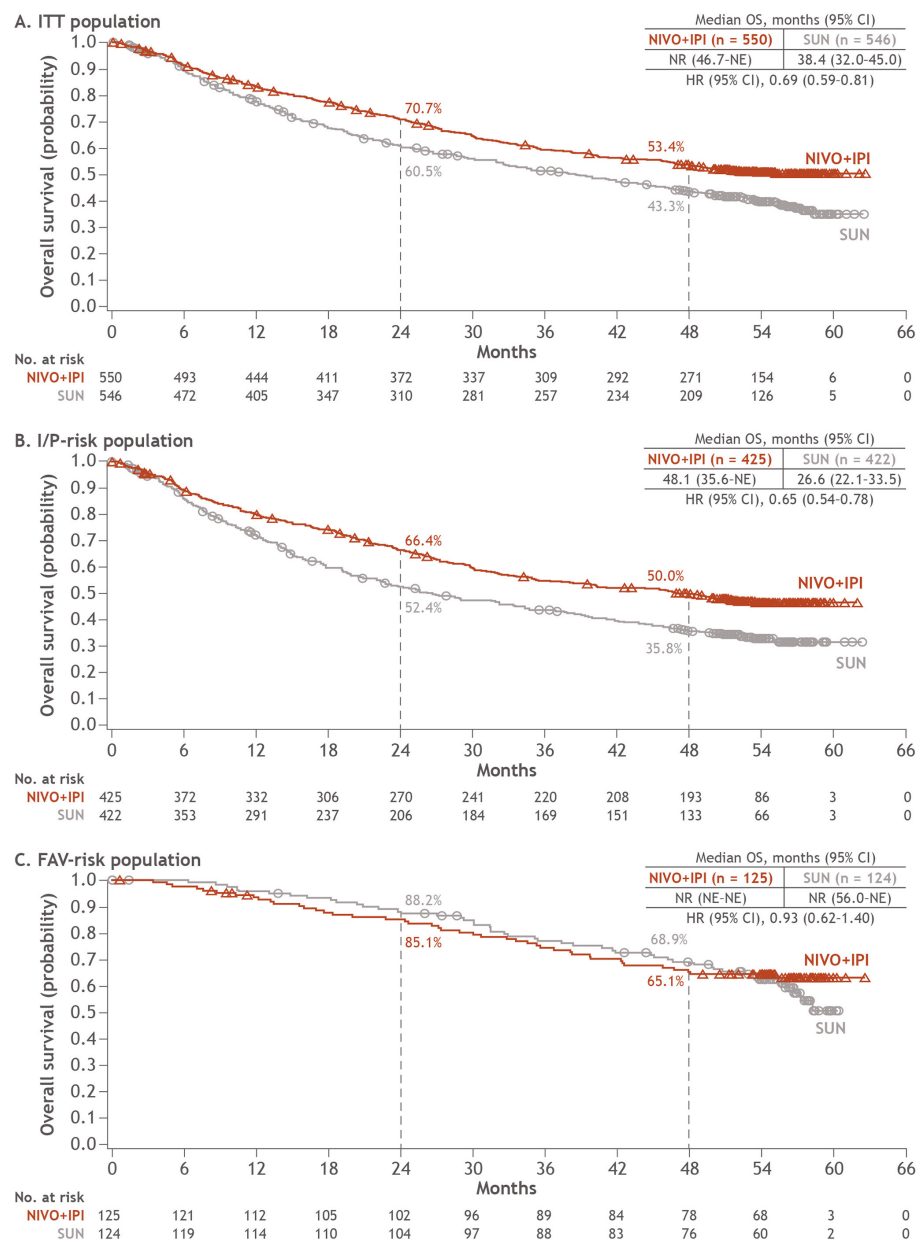


Figure 1 OS in ITT, I/P-risk and FAV-risk patients. FAV, favourable; I/P, intermediate/poor; ITT, intent-to-treat; NE, not estimable; NIVO+IPI, nivolumab plus ipilimumab; NR, not reached; OS, overall survival; SUN, sunitinib.

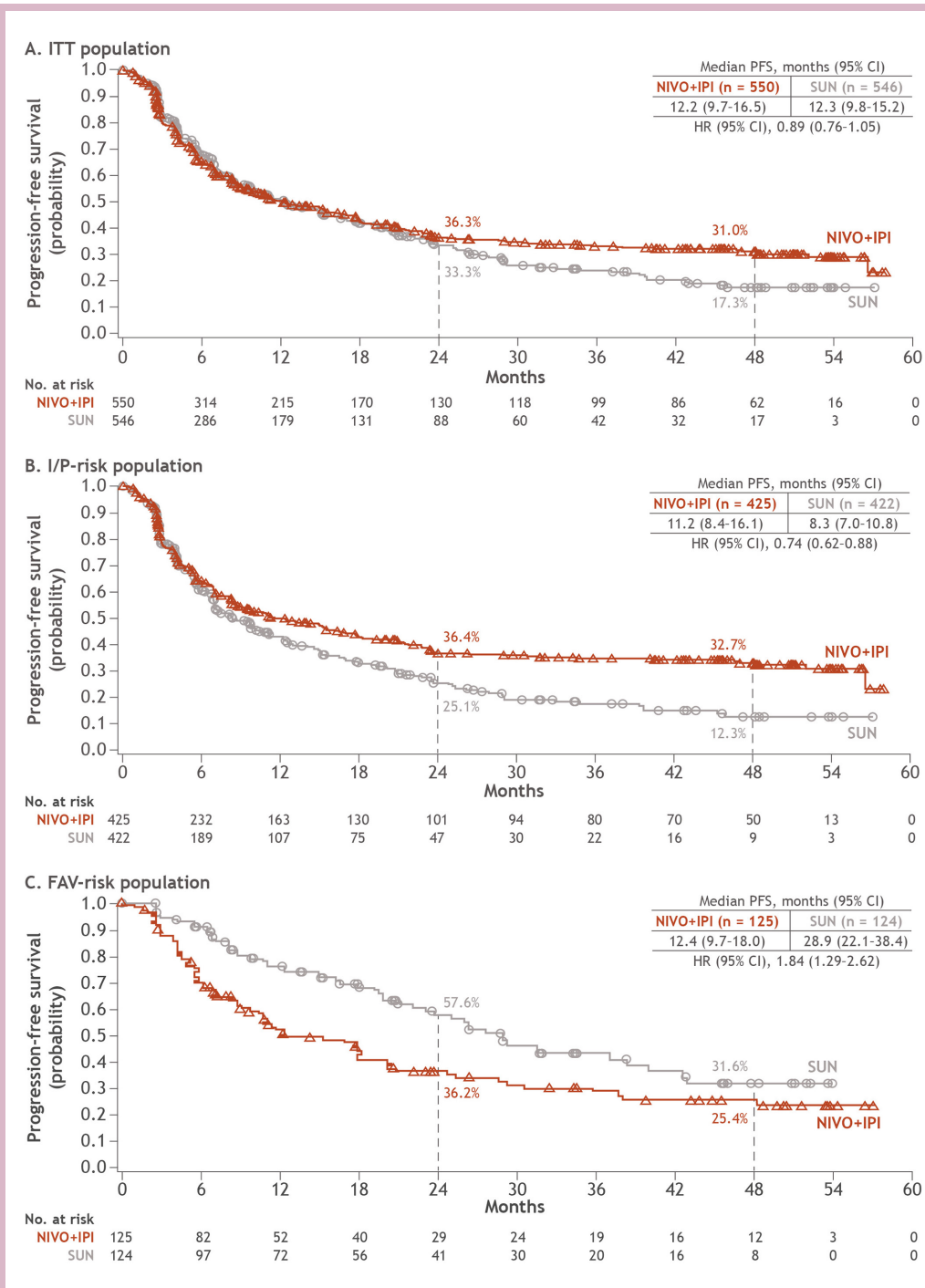


Figure 2 PFS per IRRC in ITT, I/P-risk and FAV-risk patients. FAV, favourable; I/P, intermediate/poor; IRRC, independent radiology review committee; ITT, intent-to-treat; NIVO+IPI, nivolumab plus ipilimumab; PFS, progression-free survival; SUN, sunitinib.

patients in the SUN arm received treatment and were included in the safety analyses. Patients were enrolled from 16 October 2014 through 23 February 2016 (database lock, 25 February 2020). The minimum follow-up was 4 years (median follow-up=55 months), and 53 (10%) of 547 patients in the NIVO+IPI arm and 15 (3%) of 535 patients in the SUN arm continued therapy.

Key baseline characteristics were similar between treatment arms and across risk groups, as previously reported

(online supplemental table 1).^{2 4} Among all treated patients in the NIVO+IPI arm, a median (range) of 14.0 doses (1 to 128) of NIVO and 4.0 doses (1 to 4) of IPI were received. The median duration of therapy (IQR) in all treated patients was 7.9 months (2.1 to 21.8) for patients treated with NIVO+IPI and 7.8 months (3.5 to 19.6) with SUN. Of all ITT patients, fewer treated with NIVO+IPI (53.5%; 294/550) received subsequent systemic therapy compared with patients treated with SUN

Table 1 ORR and BOR per IRRC at 4 years minimum follow-up in ITT, I/P-risk and FAV-risk patients

	Intent-to-treat		Intermediate/poor risk		Favourable risk	
	NIVO+IPI (n=550)	SUN (n=546)	NIVO+IPI (n=425)	SUN (n=422)	NIVO+IPI (n=125)	SUN (n=124)
Confirmed ORR (95% CI), %	39.1 (35 to 43)	32.4 (29 to 37)	41.9 (37 to 47)	26.8 (23 to 31)	29.6 (22 to 38)	51.6 (43 to 61)
p value	0.0134		<0.0001		0.0005	
Best overall response, n (%)						
Complete response	59 (10.7)	14 (2.6)	44 (10.4)	6 (1.4)	15 (12.0)	8 (6.5)
Partial response	156 (28.4)	163 (29.9)	134 (31.5)	107 (25.4)	22 (17.6)	56 (45.2)
Stable disease	198 (36.0)	230 (42.1)	131 (30.8)	187 (44.3)	67 (53.6)	43 (34.7)
Progressive disease	97 (17.6)	77 (14.1)	82 (19.3)	71 (16.8)	15 (12.0)	6 (4.8)
Unable to determine	38 (6.9)	57 (10.4)	32 (7.5)	48 (11.4)	6 (4.8)	9 (7.3)
Not reported	2 (0.4)	5 (0.9)	2 (0.5)	3 (0.7)	0	2 (1.6)
Ongoing response, n (%)	n=215 140 (65.1)	n=177 92 (52.0)	n=178 116 (65.2)	n=113 56 (49.6)	n=37 24 (64.9)	n=64 36 (56.3)

BOR, best overall response; FAV, favourable-risk disease; I/P, intermediate/poor-risk disease; IRRC, independent radiology review committee; ITT, intent-to-treat; NIVO+IPI, nivolumab plus ipilimumab; ORR, objective response rate; SUN, sunitinib.

(66.5%; 363/546; online supplemental table 2). In the NIVO+IPI arm, the most common subsequent systemic therapies included SUN (23.5%; 129/550), pazopanib (19.3%; 106/550) and axitinib (18.0%; 99/550). In the SUN arm, the most common subsequent systemic therapies included NIVO (40.1%; 219/546), axitinib (24.9%; 136/546) and cabozantinib (16.3%; 89/546).

Efficacy

Superior OS with NIVO+IPI vs SUN was sustained in the ITT population (HR 0.69; 95% CI 0.59 to 0.81) as well as in patients with I/P risk (HR 0.65; 95% CI 0.54 to 0.78). Median OS with NIVO+IPI was not reached vs 38.4 months with SUN in the ITT population and 48.1 vs 26.6 months in patients with I/P risk. OS probabilities at 4 years were 53.4% with NIVO+IPI vs 43.3% with SUN in ITT patients and 50.0% vs 35.8% in patients with I/P risk. In patients with FAV risk, the difference in OS was not statistically significant (HR 0.93; 95% CI 0.62 to 1.4) and median OS was not reached in either arm (figure 1). OS probabilities at 4 years were similar between arms at 65.1% vs 68.9% with NIVO+IPI vs SUN.

PFS outcomes favoured NIVO+IPI vs SUN and remained consistent with previous reports in ITT (HR 0.89; 95% CI 0.76 to 1.05) and I/P-risk patients (HR 0.74; 95% CI 0.62 to 0.88); PFS probabilities remained above 30% with NIVO+IPI in both patient groupings (figure 2). Median (95% CI) PFS with NIVO+IPI vs SUN was 12.2 months (9.7 to 16.5) vs 12.3 months (9.8 to 15.2) in ITT patients and 11.2 months (8.4 to 16.1) vs 8.3 months (7.0 to 10.8) in patients with I/P risk. The 4-year PFS probabilities were 31.0% vs 17.3% and 32.7% vs 12.3%, with NIVO+IPI vs SUN, in ITT and I/P risk patients, respectively. In

patients with FAV risk, PFS outcomes favoured SUN (HR 1.84; 95% CI 1.29 to 2.62), with 4-year PFS probabilities of 25.4% with NIVO+IPI vs 31.6% with SUN. However, the difference in PFS probabilities across arms has decreased over time.

ORR (95% CI) per IRRC for patients in the ITT group was 39.1% (35.0 to 43.3) with NIVO+IPI vs 32.4% (28.5 to 36.5) with SUN and 41.9% (37.1 to 46.7) vs 26.8% (22.6 to 31.3) in patients with I/P risk (table 1). In patients with FAV risk, ORR was lower with NIVO+IPI vs SUN (29.6% vs 51.6%); however, the complete response rate was greater with NIVO+IPI over SUN regardless of baseline risk assessment: ITT (10.7% vs 2.6%), I/P risk (10.4% vs 1.4%) and FAV risk (12.0% vs 6.5%; table 1). Median (range) time to response with NIVO+IPI was 2.8 months (0.9 to 35.0) vs 4.0 months (0.6 to 23.6) with SUN among ITT patients. Across IMDC risk groups, median duration of response with NIVO+IPI has not yet been reached in any group vs 23.7, 19.7 and 33.2 months with SUN (ITT, I/P-risk and FAV-risk groups, respectively; figure 3). Additionally, the probability of response (95% CI) lasting at least 4 years was higher with NIVO+IPI vs SUN (ITT, 59% (0.51 to 0.66) vs 30% (0.21 to 0.39); I/P risk, 59% (0.50 to 0.67) vs 24% (0.14 to 0.36); and FAV risk, 60% (0.41 to 0.75) vs 38% (0.22 to 0.54)). More patients had ongoing responses with NIVO+IPI vs SUN regardless of risk group (table 1).

Additional analyses were conducted to assess long-term outcomes in complete and partial responders, including treatment discontinuation, subsequent systemic therapy and treatment-free interval outcomes. Treatment-free interval was assessed in patients with I/P and FAV risk

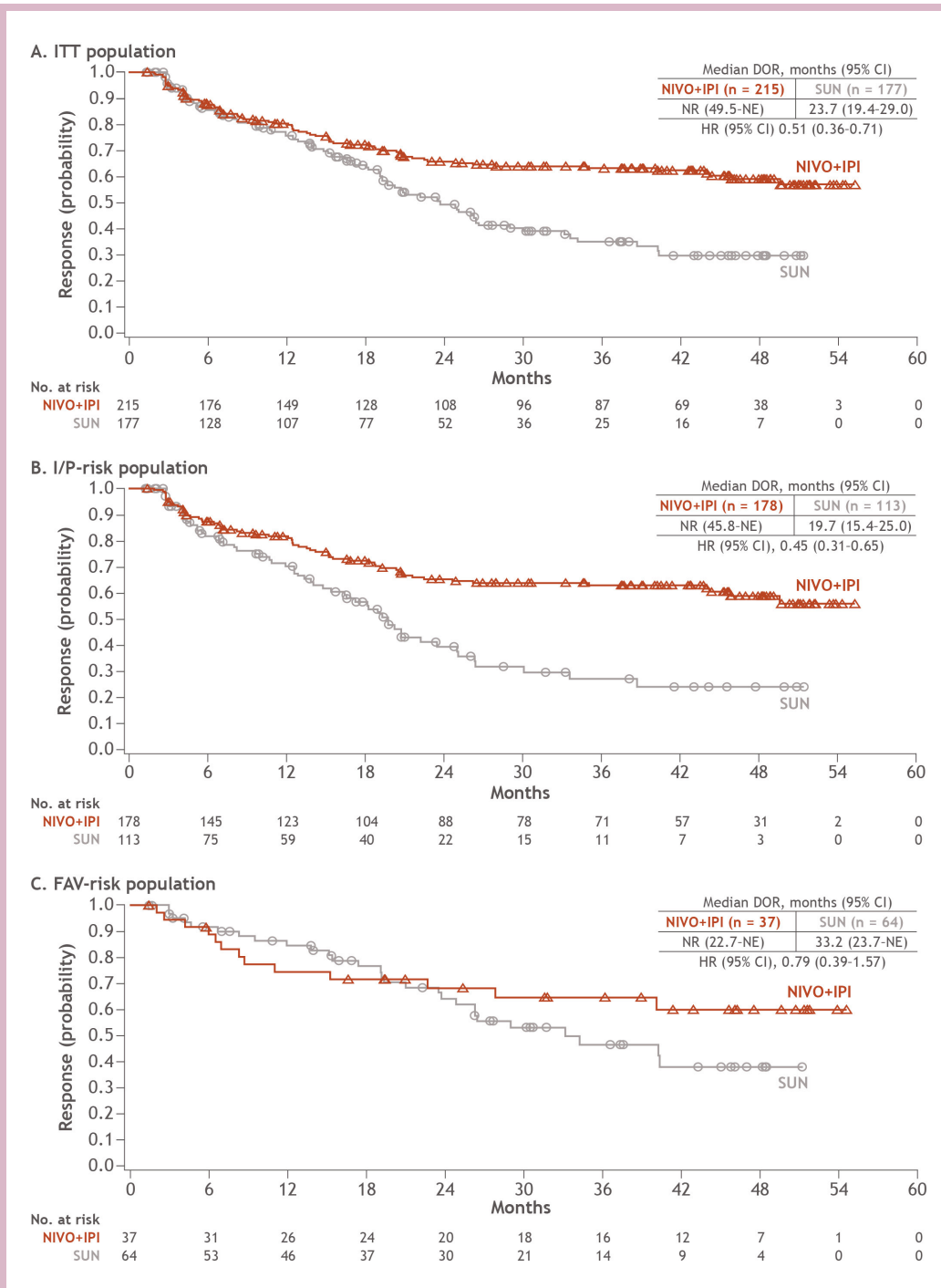


Figure 3 DOR per IRRc in ITT, I/P-risk and FAV-risk patients. DOR, duration of response; FAV, favourable; I/P, intermediate/poor; IRRc, independent radiology review committee; ITT, intent-to-treat; NE, not estimable; NIVO+IPI, nivolumab plus ipilimumab; NR, not reached; SUN, sunitinib.

in both arms (figure 4a, figure 4b). Of all 59 patients who achieved complete responses with NIVO+IPI, 19 (32.2%) were still on therapy, 27 (45.8%) discontinued therapy and did not require subsequent systemic therapy and 13 (22.0%) received subsequent systemic therapy after discontinuation. With SUN, of the 14 patients who achieved complete responses, 3 (21.4%) were still on therapy, 3 (21.4%) discontinued therapy and did not require subsequent systemic therapy and 8 (57.1%)

received subsequent systemic therapy after discontinuation. In the 156 patients who achieved partial responses with NIVO+IPI, 28 (17.9%) were still on therapy, 67 (42.9%) discontinued therapy and did not require subsequent systemic therapy and 61 (39.1%) received subsequent systemic therapy after discontinuation. Among the 163 patients with partial responses treated with SUN, 9 (5.5%) were still on therapy, 39 (23.9%) discontinued therapy and did not require subsequent systemic therapy

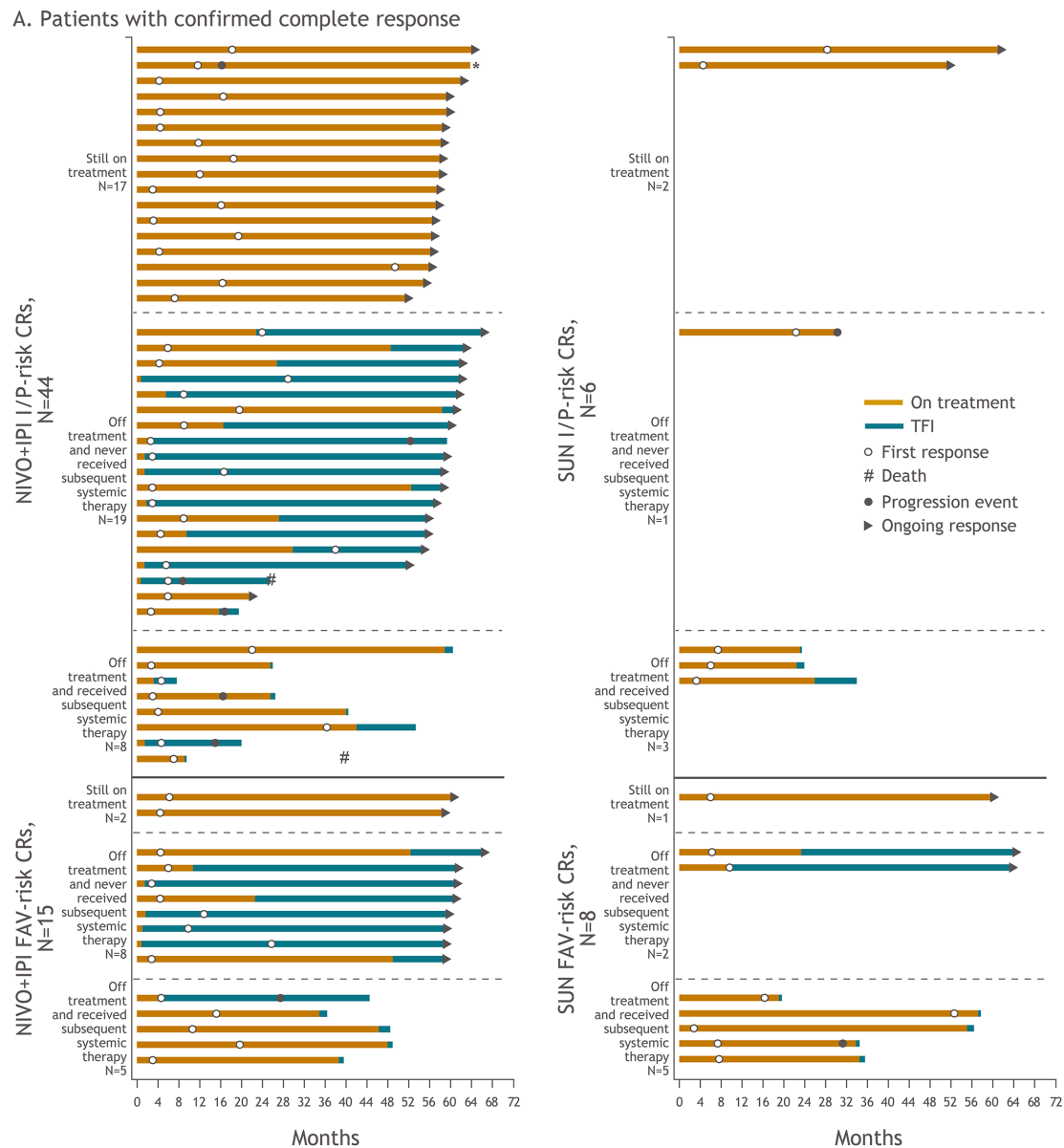


Figure 4A

and 115 (70.6%) received subsequent systemic therapy after discontinuation.

Safety

Consistent with previous reports,^{2,4} similar overall rates of treatment-related AEs of any grade occurred in the NIVO+IPI and SUN arms with extended follow-up (514/547 (94.0%) vs 521/535 (97.4%) patients), and there were fewer grade 3 to 4 treatment-related AEs with NIVO+IPI vs SUN (47.9% vs 64.1%; online supplemental table 3). Treatment-related AEs leading to discontinuation within 30 days of the last dose occurred in 124 (22.7%) patients in the NIVO+IPI arm and in 70 (13.1%) patients in the SUN arm. No additional treatment-related deaths were reported since the primary analysis. The overall incidence of treatment-related select AEs with

NIVO+IPI was similar to previous reports (online supplemental table 3).^{2,4} In total, 159 (29.1%) of 547 patients treated with NIVO+IPI received corticosteroids (≥ 40 mg PDE) to manage any-grade treatment-related select AEs, 106 (19.4%) patients received ≥ 40 mg PDE continuously for ≥ 2 weeks and 54 (9.9%) received ≥ 40 mg PDE continuously for ≥ 30 days.

DISCUSSION

With an extended minimum follow-up of 4 years, the longest in a phase III trial of a checkpoint inhibitor-based combination regimen for first-line treatment of patients with aRCC, NIVO+IPI continues to demonstrate superior long-term survival benefits in both ITT patients and in patients with I/P risk. The HR for OS with NIVO+IPI

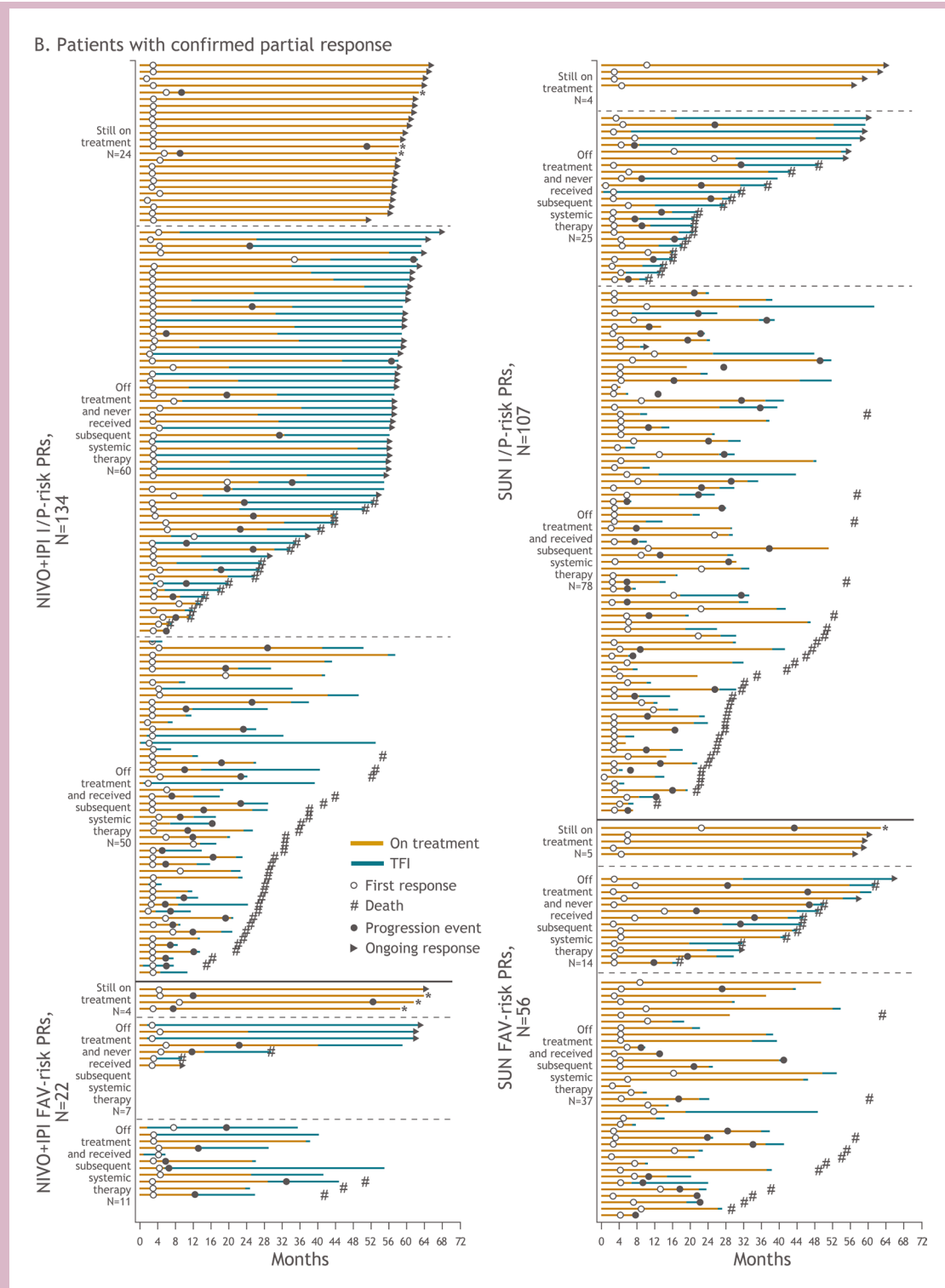


Figure 4B Treatment-free interval and response outcomes in patients with confirmed complete response (A) and confirmed partial response (B) in I/P-risk and FAV-risk patients. Of all-risk patients with confirmed complete response, 13 versus 8 received subsequent systemic therapy with NIVO+IPI versus SUN. Of all-risk patients with confirmed partial response, 61 versus 115 received subsequent systemic therapy with NIVO+IPI versus SUN. These patients may have stopped therapy due to investigator-assessed progression or other protocol-specified reason such as toxicity (data not shown). The decision to start subsequent systemic therapy in either arm was made by the investigator based on expert opinion and treatment guidelines, and these data were not formally collected. *Denotes patients who were treated beyond confirmed blinded independent central review–assessed progression. CR, complete response; FAV, favourable; I/P, intermediate/poor; NIVO+IPI, nivolumab plus ipilimumab; PR, partial response; SUN, sunitinib.

vs SUN has remained stable over time in ITT and I/P-risk patients, ranging from 0.68 and 0.63 at 17.5 months follow-up to 0.69 and 0.65 at 48 months follow-up, respectively. Moreover, after 4 years, $\geq 50\%$ of patients in the ITT and I/P-risk populations were alive, with median OS not reached in ITT patients. ORR remained consistent and significantly in favour of NIVO+IPI over SUN. In addition, more responses were complete, more responses were ongoing and duration of response was longer with NIVO+IPI, with median duration of response not reached at 4 years minimum follow-up with the combination immunotherapy regimen in any IMDC risk group. Interestingly, of patients achieving partial or complete responses, a greater proportion of patients treated with NIVO+IPI discontinued therapy without progression and did not receive subsequent systemic therapy. Furthermore, no new safety signals were observed with longer follow-up. The overall incidence of treatment-related events, those leading to discontinuation and select (potentially immune-mediated) AEs (including the proportion of patients who required prednisone or equivalent to manage these events) was similar to previous reports.^{1 2 4}

In patients with FAV risk, an OS benefit for either treatment arm remains inconclusive with 4 years minimum follow-up. Median PFS was longer and ORR was higher with SUN, yet the complete response rate was double with NIVO+IPI with more ongoing responses, compared with SUN. Although no significant benefit with NIVO+IPI has emerged in this exploratory cohort, the difference in OS between arms continues to evolve with long-term follow-up. The HR for OS with NIVO+IPI vs SUN has decreased over time from 1.45 at 17.5 months minimum follow-up to 0.93 at 4 years minimum follow-up.⁴ Additionally, a recent separate analysis suggests that while OS has appeared similar among FAV-risk patients between treatment arms, the way these patients experienced OS was notably different: SUN patients spent more time on protocol treatment with toxicity, whereas NIVO+IPI patients spent more time off treatment without toxicity.¹²

IMDC risk assessment was specifically derived from patients treated with vascular endothelial growth factor-targeted therapies, but it is now routinely applied to all patients with aRCC including those treated with immuno-oncology-based therapy.^{5 13} Identifying patients who will survive longer or develop a long-term response with immuno-oncology-based regimens via additional markers of response is a clear unmet need.^{14 15} The ongoing demonstration of survival and response benefits with NIVO+IPI vs SUN through 4 years of follow-up in both the primary I/P-risk population and the secondary ITT population suggests that a range of patients with aRCC across the spectrum of IMDC risk may derive long-term clinical benefit with NIVO+IPI.

Extended follow-up reported in this study provides further evidence for the clinically meaningful, durable benefits of first-line NIVO+IPI in patients with aRCC and continues to support NIVO+IPI as a first-line treatment option for patients with aRCC.

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