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Safety and efficacy of first-line nivolumab plus ipilimumab alternating with nivolumab monotherapy in patients with advanced renal cell carcinoma: the non-randomised, open-label, phase IIIb/IV CheckMate 920 trial

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ABSTRACT

Objectives The non-randomised, open-label, phase IIIb/IV multicohort CheckMate 920 trial explored the safety and efficacy with a less frequent, but continual nivolumab plus ipilimumab (NIVO+IPI) dosing regimen (cohort 1) to determine whether this modification could potentially retain efficacy benefits while improving on the manageable safety profile previously observed with this combination in patients with advanced renal cell carcinoma (aRCC).

Setting Patients were enrolled from 48 largely community-based sites in the USA.

Participants 106 patients with previously untreated, predominantly clear cell aRCC received treatment.

Interventions Patients received NIVO 6 mg/kg plus IPI 1 mg/kg on day 1 of the first week of each 8-week cycle; the combination alternated with NIVO 480 mg monotherapy on day 1 of the fifth week of each 8-week cycle. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or study end. The maximum treatment duration was 2 years. The primary endpoint was the incidence of high-grade (grade 3/4 and grade 5) immune-mediated adverse events (IMAEs) within 100 days of the last dose. Select secondary endpoints included time to onset and resolution of high-grade IMAEs, progression-free survival (PFS) and objective response rate (ORR). The incidence of treatment-related adverse events and the overall survival (OS) were the exploratory endpoints.

Results The most common grade 3/4 IMAEs were diarrhoea/colitis (7.5%) and rash (6.6%) and no grade 5 IMAEs occurred, with a minimum follow-up of 28.5 months. The median PFS was 4.8 (95% CI 3.0 to 8.3) months, the ORR in evaluable patients (n=96) was 34.4% (95% CI 25.0 to 44.8), and the median OS was not reached (95% CI 24.8 months to not estimable).

Conclusions While no new safety signals were reported with less frequent, but continual NIVO+IPI dosing in CheckMate 920, the modified regimen was not associated with clinical benefits relative to the approved NIVO+IPI dose. These results support the continued use of the currently approved NIVO+IPI combination dosing schedule for patients with aRCC.

Trial registration number NCT02982954.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The non-randomised, open-label, phase IIIb/IV multicohort trial explored the safety and efficacy with a less frequent, but continual nivolumab plus ipilimumab dosing regimen to determine whether this modification could potentially retain the efficacy benefits while further improving on the manageable safety profile previously observed with this combination in patients with advanced renal cell carcinoma, helping to answer an important clinical question.

⇒ The trial was purposely conducted in a large community-based setting in order to better understand the tolerability of this alternative dosing regimen in a real-world context.

⇒ Direct cross-trial comparisons are not possible as there are a number of notable differences in the study design and research setting in this trial versus randomised clinical trials.

BACKGROUND

The combination of nivolumab (NIVO; anti-programmed death-1 antibody) with ipilimumab (IPI; anticytotoxic T lymphocyte antigen-4 antibody) is a standard option for the first-line treatment of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)[1 2] intermediate-risk or poor-risk patients with advanced or metastatic renal cell carcinoma (aRCC) based on the efficacy and safety results of the phase

III CheckMate 214 trial.[3–9] Patients in CheckMate 214 received NIVO (3 mg/kg) plus IPI (1 mg/kg) every 3 weeks for four doses followed by NIVO monotherapy (3 mg/kg) every 2 weeks (later modified to 240 mg every 2 weeks or 480 mg every 4 weeks per protocol amendment).[3] The combination dosing schedule approved by the US Food Drug Administration (FDA) and the European Medicines Agency (EMA) is NIVO (3 mg/kg) plus IPI (1 mg/kg) every 3 weeks for four doses followed by NIVO monotherapy (either 240 mg every 2 weeks or 480 mg every 4 weeks).[8–11] Overall survival (OS) and objective response rate (ORR) benefits were observed with NIVO+IPI versus sunitinib (SUN) in both IMDC intermediate-risk/poor-risk and intent-to-treat (ITT) patients.[3] Treatment-related adverse events (AEs) occurred in 93% of patients in the NIVO+IPI arm and 97% in the SUN arm; grade 3 or 4 events occurred in 46% and 63% of patients, respectively.[3] Looking at safety events by 6-month interval with extended follow-up in CheckMate 214, the incidence of both treatment-related AEs and treatment-related select (potentially immune-mediated) AEs was highest within the first 6 months of treatment with NIVO+IPI before decreasing substantially over time.[5]

The phase IIIb/IV CheckMate 920 trial (NCT02982954) explored the safety and efficacy outcomes with a less frequent, but continual NIVO+IPI dosing regimen to determine if this modification could potentially retain the efficacy benefits while further improving on the manageable safety profile previously observed with this combination in patients with aRCC.

METHODS

CheckMate 920 is a largely community-based, multicohort, open-label, phase IIIb/IV trial. Phase IIIb/IV trials typically are conducted at or after the time of approval, and are intended to increase patient exposure and are driven by the needs of the industry (ie, evaluation of new indications, new comparators, different efficacy endpoints or different patient subpopulations). Modified NIVO+IPI dosing was evaluated in cohort 1 and is reported here (figure 1). Outcomes with standard NIVO+IPI dosing in patients with aRCC with clinical features mostly excluded from phase III studies were assessed in cohorts 2, 3 and 4 (data not reported here). Adults with previously untreated predominantly clear cell aRCC (advanced: not amenable to curative surgery or radiation therapy; or metastatic: American Joint Committee on Cancer stage IV disease) were included in cohort 1. Patients had histologically confirmed and measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST V.1.1) and Karnofsky performance status of at least 70%, and any IMDC risk score was permitted.

Patients were treated with NIVO 6 mg/kg plus IPI 1 mg/kg on day 1 of the first week of each 8-week cycle; the combination alternated with NIVO 480 mg monotherapy on day 1 of the fifth week of each 8-week cycle. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or end of study. The maximum treatment duration was 2 years. Patients were permitted to continue treatment beyond RECIST v.1.1-defined progression under protocol-defined circumstances. No dose modifications were allowed for either NIVO or IPI. Patients who discontinued treatment due to an AE were eligible to receive NIVO monotherapy (480 mg every 4 weeks), contingent on medical monitor approval.

The primary objective for cohort 1 was to assess the incidence of high-grade (grade 3/4 and grade 5; National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.0) immune-mediated adverse events (IMAEs) in all treated patients. The secondary safety objective was to characterise the outcome of high-grade IMAEs (endpoints included median time to onset and median time to resolution of IMAEs, and high-grade IMAE management inclusive of the percentage of patients who received immune-modulating medication). Select secondary efficacy objectives included progression-free survival (PFS), ORR (complete response [CR] +

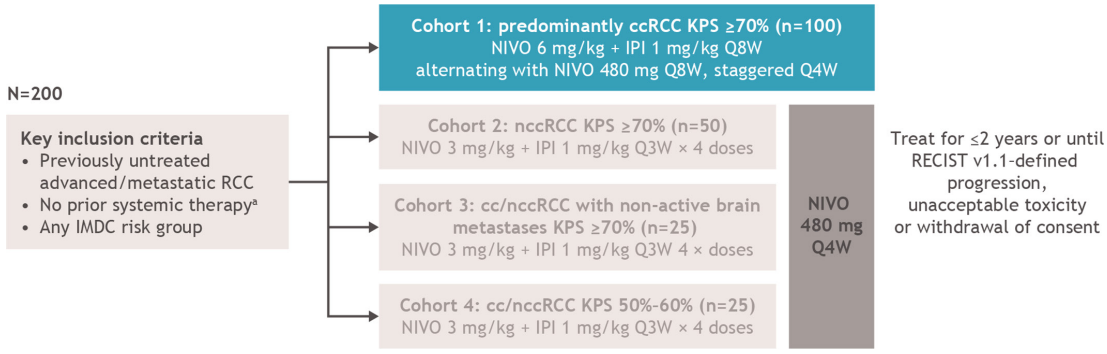

Figure 1 CheckMate 920 study design. [a]One prior adjuvant or neoadjuvant therapy for completely resectable RCC was allowed if it did not include checkpoint inhibitors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy. ccRCC, clear cell renal cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IPI, ipilimumab; KPS, Karnofsky performance status; nccRCC, non-clear cell carcinoma; NIVO, nivolumab; OS, overall survival; Q3W, every 3 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 1 Select baseline characteristics

Baseline characteristics	All treated patients (n=106)
Median age (range), years	64.5 (40–84)
Sex, n (%)	
Male	86 (81.1)
Female	20 (18.9)
IMDC risk group, n (%)	
Favourable	21 (19.8)
Intermediate	65 (61.3)
Poor	20 (18.9)
Race, n (%)	
White	104 (98.1)
Black or African American	1 (0.9)
Other	1 (0.9)
KPS, n (%)	
100	36 (34.0)
90	45 (42.5)
80	24 (22.6)
70	1 (0.9)
Sarcomatoid features, n (%)	
Yes	12 (11.3)
No	93 (87.7)
Not reported	1 (0.9)
Disease stage at study entry, n (%)	
III	2 (1.9)
IV	104 (98.1)
Number of disease sites, n (%)	
1	5 (4.7)
≥2	101 (95.3)
Most common sites of disease, n (%)*	
Visceral lung	56 (52.8)
Lymph node	43 (40.6)
Kidney	41 (38.7)
Visceral liver	26 (24.5)
Visceral adrenal	16 (15.1)
Quantifiable tumour PD-L1 expression, n (%)	n=96
<1%	83 (86.5)
≥1%	13 (13.5)

Information shown in the table is based on data collected using electronic case report forms.
*Patients may have more than one site.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance status; PD-L1, programmed death ligand 1.

partial response [PR] rate), time to response (TTR) and duration of response (DOR) using RECIST v.1.1. ORR was defined as the number of patients with a best overall response of CR or PR divided by the number of response-evaluable patients. TTR was defined as time from the date of first dose to the first documented CR or PR, and patients who did not have CR or PR were censored at the maximum time of response plus 1 day. DOR was computed for patients who achieved PR or CR only. Clinical benefit rate (CR+PR+stable disease rate) was included as a secondary efficacy endpoint. Exploratory objectives included the assessment of all treatment-related AEs and OS outcomes.

IMAEs were defined as specific events (or groups of preferred terms describing specific events) that occurred regardless of causality within 100 days of the last dose and included pneumonitis, diarrhoea/colitis, hepatitis, nephritis and renal dysfunction, rash, hypersensitivity, and endocrine events (adrenal insufficiency, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, hypophysitis). Other events considered by the investigator to be potential IMAEs were those that occurred within 100 days of the last dose, and regardless of causality, with no clear alternate aetiology or with an immune-mediated component, and were treated with immune-modulating medication. IMAE analyses were limited to patients who received immune-modulating medication for treatment of the event, with the exception of endocrine IMAEs, which were included regardless of treatment. PFS was defined as the time from the first dose to the date of the first documented progression as determined by the investigator (per RECIST v.1.1) or death from any cause, whichever occurred first. ORR was also assessed per investigator using RECIST v.1.1. Safety, PFS and OS outcomes were assessed in all treated patients; ORR and related outcomes were assessed in response-evaluable patients. The number and percentage of patients who experienced high-grade IMAEs were summarised. High-grade IMAEs were tabulated using worst grade per NCI CTCAE by system organ class and the Medical Dictionary for Regulatory Affairs preferred term. Additional descriptive statistics for high-grade IMAEs included median time to onset and median time to resolution. PFS, TTR, DOR and OS were calculated by the Kaplan-Meier product-limit method.[12] Two-sided 95% CIs for PFS and OS probabilities were calculated using the Greenwood formula.[13] Median PFS, median OS, median TTR and median DOR were calculated along with two-sided 95% CIs using the Brookmeyer and Crowley method. The ORR and clinical benefit rate were summarised by binomial response rates, and their corresponding two-sided 95% exact CIs were calculated using the Clopper-Pearson method.

The planned sample size was determined largely by the feasibility concern and based on the incidence of high-grade IMAEs with NIVO+IPI from other trials in patients with aRCC and non-small cell lung cancer. Given the values reported in the selected trials of combination treatment of approximately 40%–60% high-grade IMAEs, the estimated half-width of the 95% CI of high-grade IMAE rates between 9.3% and 9.8% for 100 participants was considered to be within an acceptable degree of precision.[14 15]

Table 2 Immune-mediated adverse events and safety summary

IMAEs*† by category	All treated patients (n=106)	
	Any grade, n (%)‡	Grade 3/4, n (%)
Rash	27 (25.5)	7 (6.6)§
Hypothyroidism and thyroiditis	21 (19.8)	0
Diarrhoea/colitis	15 (14.2)	8 (7.5)¶
Adrenal insufficiency	9 (8.5)	3 (2.8)
Hyperthyroidism	8 (7.5)	0
Hepatitis	7 (6.6)	3 (2.8)**
Diabetes mellitus	6 (5.7)	4 (3.8)
Hypersensitivity	6 (5.7)	0
Pneumonitis	3 (2.8)	1 (0.9)
Hypophysitis	3 (2.8)	0
Nephritis and renal dysfunction	2 (1.9)	0
Treatment-related AEs*		
Total	94 (88.7)	46 (43.4)
Treatment-related AEs (any grade) in ≥10% of all treated patients		
Fatigue	49 (46.2)	4 (3.8)
Diarrhoea	31 (29.2)	4 (3.8)
Nausea	24 (22.6)	3 (2.8)
Pruritus	23 (21.7)	1 (0.9)
Lipase increased	21 (19.8)	15 (14.2)
Hypothyroidism	18 (17.0)	0 (0)
Decreased appetite	17 (16.0)	1 (0.9)
Amylase increased	13 (12.3)	5 (4.7)
Blood creatinine increased	12 (11.3)	2 (1.9)
Rash maculopapular	11 (10.4)	3 (2.8)
AST increased	11 (10.4)	2 (1.9)
AEs leading to discontinuation*		
Total	30 (28.3)	21 (19.8)
AEs leading to discontinuation in >1% of patients		
Colitis	4 (3.8)	4 (3.8)
Malignant neoplasm progression	4 (3.8)	4 (3.8)
Pneumonitis	4 (3.8)	2 (1.9)
Diarrhoea	4 (3.8)	1 (0.9)
Blood bilirubin increased	2 (1.9)	2 (1.9)
Nausea	2 (1.9)	1 (0.9)
AST increased	2 (1.9)	1 (0.9)
ALT increased	2 (1.9)	1 (0.9)
Pancreatitis	2 (1.9)	0

Continued

Table 2 Continued

IMAEs*† by category	All treated patients (n=106)	
	Any grade, n (%)‡	Grade 3/4, n (%)

*Reported between first dose and 100 days after last dose of study drug.
†Adrenal insufficiency, hypothyroidism and thyroiditis, diabetes mellitus, hyperthyroidism, and hypophysitis were considered endocrine IMAEs.
‡No grade 5 IMAEs were reported.
§Included maculopapular rash in four patients (3.8%), pruritic rash in two patients (1.9%) and erythematous rash in one patient (0.9%).
¶Included diarrhoea in two patients (1.9%) and colitis in six patients (5.7%).
**Included blood bilirubin increased and autoimmune hepatitis (both in a single patient; 0.9%), AST increased in one patient (0.9%) and drug-induced liver injury in one patient (0.9%).
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IMAE, immune-mediated adverse event.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Overall, 124 patients were enrolled in cohort 1, and 106 patients with predominantly clear cell aRCC received treatment. The enrolment period lasted from January 2017 to March 2018, and the last patient was enrolled on 9 February 2018; the results presented here are based on a cut-off date of 3 March 2020, with a minimum follow-up for OS of 28.5 months. The median age was 64.5 (range, 40–84) years, 81.1% of patients were male, 98.1% were white, 98.1% had stage IV disease at study entry, 11.3% had sarcomatoid features, and 19.8% had IMDC favourable-risk, 61.3% had intermediate-risk and 18.9% had poor-risk disease (table 1).

No patients continued treatment as of the cut-off date; the most common reasons for discontinuation were disease progression (58.5%) and study drug toxicity (18.9%). The median (range) duration of treatment was 5.1 (0–26.1) months for NIVO and 4.0 (0–25.7) months for IPI; overall, patients received a median (range) of 6.0 (1–26) doses of NIVO and 3.0 (1–13) doses of IPI. Unlike the approved dosing for NIVO+IPI in first-line aRCC, IPI was not limited to four doses in this trial and 40.6% of patients received more than four doses of IPI (online supplemental table S1).

The incidence of grade 3/4 IMAEs was low for each organ category and no grade 5 IMAEs were reported (table 2).

The most common grade 3/4 IMAEs reported in at least 5% of patients were diarrhoea/colitis (7.5%)

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Table 3 Time to onset and resolution of immune-mediated adverse events

	All treated patients who experienced at least 1 IMAE*			
	Median (range) time to onset, weeks		Median (range) time to resolution, weeks	
IMAE by category	Any grade	Grade 3/4	Any grade	Grade 3/4
Rash	n=27 5.3 (0.3–80.4)	n=7 4.0 (1.1–80.4)	n=17 12.6 (1.9–156.1)	n=2 NR (5.3–126.9+)
Hypothyroidism and thyroiditis†	n=21 12.1 (2.3–25.1)	n=0 –	n=5 NR (3.7–156.7+)	n=0 –
Diarrhoea/colitis	n=15 26.1 (1.4–115.7)	n=8 21.8 (1.7–115.7)	n=11 5.9 (0.9–141.7+)	n=7 2.7 (0.7–117.0+)
Adrenal insufficiency†	n=9 33.9 (16.1–54.0)	n=3 51.4 (21.0–54.0)	n=4 NR (0.4–130.6+)	n=2 0.7 (0.4–89.0+)
Hyperthyroidism†	n=8 6.3 (4.0–39.1)	n=0 –	n=8 12.1 (5.1–134.7+)	n=0 –
Hepatitis	n=7 37.1 (2.0–80.7)	n=3 8.4 (2.0–82.1)	n=1 3.0 (NC)	n=1 3.0 (NC)
Diabetes mellitus†	n=6 29.1 (4.3–58.6)	n=4 13.6 (4.3–39.1)	n=2 NR (0.4–141.3+)	n=2 NR (0.4–141.3+)
Hypersensitivity	n=6 4.8 (4.0–8.1)	n=0 –	n=6 0.1 (0.1–0.1)	n=0 –
Pneumonitis	n=3 12.7 (11.1–64.0)	n=1 12.7 (NC)	n=3 14.9 (0.9–17.3)	n=1 0.9 (NC)
Hypophysitis†	n=3 33.9 (25.9–52.7)	n=0 –	n=0 –	n=0 –
Nephritis and renal dysfunction	n=2 16.4 (3.7–29.1)	n=0 –	n=2 6.0 (4.7–7.3)	n=0 –

*Includes events reported between the first dose and 100 days after last dose of study therapy. Time to onset was calculated from the first dosing date to the IMAE event onset date. Time to resolution was calculated from the IMAE onset date to IMAE end date. If an IMAE was ongoing at the time of analysis, the time to resolution was censored at the last contact date. Patients who experienced an IMAE without worsening from baseline grade were excluded from time to resolution analysis. Events without a stop date or with a stop date equal to the date of death were considered unresolved. For each patient, the longest duration of IMAEs where immune-modulating medication was initiated is considered.
†Considered endocrine IMAEs.
+, censored value; IMAE, immune-mediated adverse event; NC, not calculated; NR, not reached.

and rash (6.6%). Time to onset and time to resolution of IMAEs are summarised in table 3. Overall, 33.0% of patients received corticosteroid treatment (≥40 mg prednisone or equivalent) to manage IMAEs; 21.7% of patients were treated for ≥14 days and 6.6% of patients were treated for ≥30 days. The median duration of corticosteroid treatment (≥40 mg prednisone or equivalent) to manage IMAEs was 3.0 weeks. Non-endocrine IMAEs that required the use of corticosteroid treatment (≥40 mg prednisone or equivalent) included pneumonitis in 2 patients, diarrhoea/colitis in 14 patients, hepatitis in 7 patients, nephritis/renal dysfunction in 2 patients, hypersensitivity in 4 patients and rash in 13 patients. Endocrine IMAEs that required corticosteroid treatment (≥40 mg prednisone or equivalent) for management included adrenal insufficiency in five patients, thyroiditis in one patient and hypophysitis in three patients.

Most of the any-grade IMAEs reported were treatment-related, non-serious, and did not result in discontinuation of NIVO+IPI. Treatment-related AEs of any grade occurred in 94 patients (88.7%); grade 3/4 treatment-related AEs occurred in 46 patients (43.3%; table 2). Fatigue (46.2%) was the most frequently reported any-grade treatment-related event. Treatment-related AEs of any grade leading to discontinuation were reported in 30 patients (28.3%; table 2).

A total of 44 patients (41.5%) died, of whom 4 (3.8%) died within 30 days after the last dose. The most common cause of death was disease progression, and one patient died from study drug toxicity (myasthenia gravis was cited as the cause of death; complete heart block and refractory hypotension were cited as potential causes).

PFS probabilities in all treated patients (n=106) were 28.7% (95% CI 20.0 to 37.9) at 12 months and 15.9% (95% CI 9.2 to 24.2) at 24 months, and the median PFS was 4.8 (95% CI 3.0 to 8.3) months (figure 2A). The ORR was 34.4% (95% CI 25.0 to 44.8) and the CR rate was 5.2% in evaluable patients (n=96; figure 2B); the clinical benefit rate was 63.5% (95% CI 53.1 to 73.1). The median TTR was 2.9 (range, 2.5–36.9) months, the median DOR was 9.2 (95% CI 6.0 to 22.9) months, and 14 of 33 responders (42.4%) had an ongoing response. The median OS was

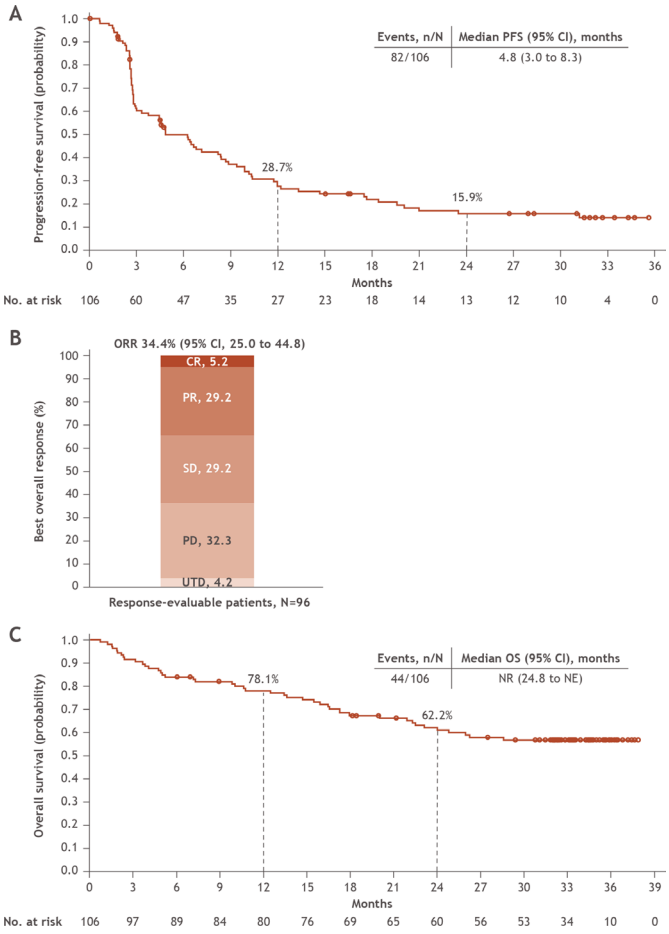

Figure 2 Progression-free survival per investigator (A), investigator-assessed objective response per RECIST V.1.1 (B) and overall survival (C). CR, complete response; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UTD, unable to determine.

not reached (95% CI 24.8 months to not evaluable) in all treated patients (n=106), and OS probabilities were 78.1% (95% CI 68.9 to 84.9) at 12 months and 62.2% (95% CI 52.1 to 70.8) at 24 months (figure 2C).

DISCUSSION

A modified, continual, less frequent NIVO+IPI dosing regimen was explored in CheckMate 920 cohort 1 to describe the safety and efficacy outcomes relative to the approved NIVO+IPI dosing regimen established in CheckMate 214 to determine whether this modification could potentially retain the efficacy benefits while further improving on the manageable safety profile previously observed with this combination. The modified NIVO dosing regimen (6 mg/kg every 8 weeks, alternating with a 480 mg dose every 8 weeks, staggered by 4 weeks) was anticipated to provide a similar average steady-state plasma concentration exposure compared with the NIVO dose (3 mg/kg every 2 weeks) administered in CheckMate 214. The modified IPI dosing regimen (1 mg/kg every 8 weeks) was administered with prolonged intervals to allow for a lower probability of cumulative safety events versus the IPI schedule in CheckMate 214 (1 mg/kg every 3 weeks). Patients received a maximum of four doses of IPI in CheckMate 214, whereas patients were able to continue IPI beyond four doses, as tolerated, in CheckMate 920. Finally, patients who discontinued IPI due to an AE were permitted to continue NIVO treatment as a monotherapy in CheckMate 920, unlike CheckMate 214.

The modified NIVO+IPI regimen was similarly tolerable to the standard regimen. Grade 3/4 IMAEs were infrequent (0%–7.5% for each category) and were manageable in the present study using established guidelines. Any-grade treatment-related AEs were reported in 89% of patients in the present study; 43% had grade 3/4 treatment-related AEs and 28% discontinued due to treatment-related AEs. For reference, any-grade treatment-related AEs were reported in 94% of patients in the NIVO+IPI arm; 47% had grade 3/4 treatment-related AEs and 22% discontinued due to treatment-related AEs after a comparable 30-month minimum follow-up in CheckMate 214.[4] Overall, the modified regimen was not associated with safety benefits relative to the approved NIVO+IPI dose based on the safety profile observed in the CheckMate 214 trial.[4]

In regard to efficacy, we observed a median PFS of 4.8 months (24-month PFS probability was 16%) with the modified NIVO+IPI regimen, ORR was 34% (5% achieved CR) and the median OS was not reached (24-month OS probability was 62%). For context, in CheckMate 214, the median PFS was 9.7 months (24-month PFS probability was 31%), ORR was 41% (11% achieved CR) and the median OS was not reached (24-month OS probability was 71%) with NIVO+IPI in ITT patients after a comparable 30-month minimum follow-up.[4]

Cross-trial comparisons should be made with caution and there are some inherent limitations associated with the CheckMate 920 study design and research setting versus randomised clinical trials. Unlike CheckMate 214, CheckMate 920 was purposely conducted in a large community-based setting in order to better understand the tolerability of this alternative dosing regimen in a real-world context. This distinction cannot be overstated as we have seen a wide disparity in outcomes associated with vascular endothelial growth factor receptor tyrosine kinase inhibitor use in prospective real-world settings compared with historical clinical trial data.[16] Additional differences between this trial and CheckMate 214 include the study phase (IIIb/IV vs III), randomisation (no vs yes), arm (single vs comparative) and population size (106 vs 550).

There are currently several other ongoing phase II trials of NIVO+IPI in renal cell carcinoma (RCC) that are evaluating alternative dosing regimens.[17–19] The phase II response-adaptive trial, Optimized Management of Nivolumab and Ipilimumab in Advanced Renal Cell Carcinoma (OMNIVORE) (NCT03203473), enrolled patients

with metastatic RCC with no prior checkpoint inhibitor exposure (n=83). All patients received NIVO alone with subsequent arm allocation based on response, and either discontinued NIVO and were observed or received two doses of IPI. This study found that NIVO followed by two doses of IPI in patients without an objective response to NIVO monotherapy results in no complete responses and a low response conversion rate. The data did not support a response-adaptive strategy for checkpoint blockade in aRCC, and upfront dual checkpoint blockade was still recommended in patients eligible to receive this treatment.[18] Another ongoing, prospective, single-stage, single-arm, multicentre phase II trial (NCT03297593) is evaluating the outcomes associated with reducing IPI in the combination treatment of metastatic RCC (mRCC). Patients begin treatment with NIVO (240 mg every 2 weeks until week 20, then 480 mg every 4 weeks thereafter). After 2 weeks, IPI 1 mg/kg every 6 weeks is initiated. As soon as a radiographic CR or PR is observed, IPI is discontinued and NIVO is continued for a maximum of 2 years. Preliminary data suggest that this approach is non-inferior to the regimen evaluated in CheckMate 214.[19] An additional phase II randomised study is evaluating multiple administration regimens for NIVO+IPI in patients with aRCC (CheckMate 800; NCT03029780). Patients are treated with either NIVO+IPI combination therapy or NIVO and IPI sequentially. Results have not yet been published.[17]

Overall, the modified NIVO+IPI regimen evaluated in CheckMate 920 cohort 1 was associated with a similar safety profile relative to the approved dosing schedule, with a clinical benefit rate of 63.5%, suggesting that NIVO+IPI can benefit a broad selection of patients in real-world settings. Taken together, these results support the continued use of the NIVO+IPI standard dosing schedule approved by the FDA and EMA for patients with aRCC based on the CheckMate 214 trial results.[3 8–11]

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REFERENCES

1 Heng DYC, Xie W, Regan MM, *et al*. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009;27:5794–9.
2 Heng DYC, Xie W, Regan MM, *et al*. External validation and comparison with other models of the International metastatic renal-cell carcinoma database Consortium prognostic model: a population-based study. *Lancet Oncol* 2013;14:141–8.
3 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.
4 Motzer RJ, Rini BI, McDermott DF, *et al*. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol* 2019;20:1370–85.
5 Motzer RJ, Escudier B, McDermott DF, *et al*. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. *J Immunother Cancer* 2020;8:e000891.
6 Albiges L, Tannir NM, Burotto M, *et al*. 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. *ESMO Open* 2020;5:e001079.
7 Sheng IY, Ornstein MC. Ipilimumab and nivolumab as first-line treatment of patients with renal cell carcinoma: the evidence to date. *Cancer Manag Res* 2020;12:4871–81.
8 US Food and Drug Administration. Fda approves nivolumab plus ipilimumab combination for intermediate or poor-risk advanced renal cell carcinoma. Available: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-plus-ipilimumab-combination-intermediate-or-poor-risk-advanced-renal-cell [Accessed 14 Jun 2021].
9 OPDIVO (nivolumab) [package insert]. Princeton, NJ Bristol Myers Squibb; 2021. https://packageinserts.bms.com/pi/pi_opdivo.pdf [Accessed 26 May 2021].
10 European Medicines Agency. Opdivo: EPAR - Product information. Annex I - Summary of product characteristics. Available: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf [Accessed 27 Jul 2021].
11 Bristol Myers Squibb. European Commission approves Opdivo (nivolumab) plus low-dose Yervoy (ipilimumab) for first-line treatment of patients with intermediate- and poor-risk advanced renal cell carcinoma. Available: https://news.bms.com/news/corporate-financial/2019/European-Commission-Approves-Opdivo-nivolumab-Plus-Low-Dose-Yervoy-ipilimumab-for-First-Line-Treatment-of-Patients-with-Intermediate-and-Poor-Risk-Advanced-Renal-Cell-Carcinoma/default.aspx [Accessed 27 Jul 2021].
12 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
13 Greenwood M. The natural duration of cancer. *Rep Public Health Med Subj* 1926:1–36.
14 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.
15 Tykodi SS, Gordan LN, Alter RS, *et al*. Safety and efficacy of nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 CheckMate 920 trial. *J Immunother Cancer* 2022;10:e003844.
16 Costello BA, Bhavsar NA, Zakharia Y. A prospective multicenter evaluation of initial treatment choice in metastatic renal cell carcinoma prior to the immunotherapy era: the MaRCC registry experience. *Clin Genitourin Cancer* 2021.
17 Clinical Trials.gov. NCT03029780. An investigational immuno-therapy safety and efficacy study of multiple administration regimens for nivolumab plus ipilimumab in subjects with renal cell carcinoma (CheckMate 800). Available: https://clinicaltrials.gov/ct2/show/NCT03029780
18 McKay RR, McGregor BA, Xie W, *et al*. Optimized management of nivolumab and ipilimumab in advanced renal cell carcinoma: a response-based phase II study (OMNIVORE). *J Clin Oncol* 2020;38:4240–8.
19 Stenner-Liewen F, Cathomas R, Rothermundt CA, *et al*. 716P optimizing ipilimumab in metastatic renal cell carcinoma: SAKK 07/17 study. *Ann Oncol* 2020;31:S563.