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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

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ABSTRACT

Background CheckMate 920 (NCT02982954) is a multicohort, phase 3b/4 clinical trial of nivolumab plus ipilimumab treatment in predominantly US community-based patients with previously untreated advanced renal cell carcinoma (RCC) and clinical features mostly excluded from phase 3 trials. We report safety and efficacy results from the advanced non-clear cell RCC (nccRCC) cohort of CheckMate 920.

Methods Patients with previously untreated advanced/metastatic nccRCC, Karnofsky performance status ≥70%, and any International Metastatic Renal Cell Carcinoma Database Consortium risk received up to four doses of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks followed by nivolumab 480 mg every 4 weeks for ≤2 years or until disease progression/unacceptable toxicity. The primary endpoint was incidence of grade ≥3 immune-mediated adverse events (AEs) within 100 days of last dose of study drug. Key secondary endpoints included objective response rate (ORR), progression-free survival (PFS; both investigator-assessed), time to response (TTR), and duration of response (DOR), all using RECIST V.1.1. Overall survival (OS) was exploratory.

Results Fifty-two patients with nccRCC (unclassified histology, 42.3%; papillary, 34.6%; chromophobe, 13.5%; translocation-associated, 3.8%; collecting duct, 3.8%; renal medullary, 1.9%) received treatment. With 24.1 months minimum study follow-up, median duration of therapy (range) was 3.5 (0.0–25.8) months for nivolumab and 2.1 (0.0–3.9) months for ipilimumab. Median (range) number of doses received was 4.5 (1–28) for nivolumab and 4.0 (1–4) for ipilimumab. Grade 3–4 immune-mediated AEs were diarrhea/colitis (7.7%), rash (5.8%), nephritis and renal dysfunction (3.8%), hepatitis (1.9%), adrenal insufficiency (1.9%), and hypophysitis (1.9%). No grade 5 immune-mediated AEs occurred. ORR (n=46) was 19.6% (95% CI 9.4 to 33.9). Two patients achieved complete response (papillary, n=1; unclassified, n=1), seven achieved partial response (papillary, n=4; unclassified, n=3), and 17 had stable disease. Median TTR was 2.8 (range 2.1–14.8) months. Median DOR was not reached (range 0.0+–27.8+); eight of nine responders remain without reported progression. Median PFS (n=52) was 3.7 (95% CI 2.7 to 4.6) months. Median OS (n=52) was 21.2 (95% CI 16.6 to not estimable) months.

Conclusions Nivolumab plus ipilimumab for previously untreated advanced nccRCC showed no new safety signals and encouraging antitumor activity.

Trial registration number NCT02982954.

INTRODUCTION

Collectively, non-clear cell renal cell carcinoma (nccRCC) represents approximately 20%–30% of RCC tumors, with the remaining cases having a clear cell histology (ccRCC).[1–3] A number of histological subtypes comprise nccRCC, including papillary, chromophobe, collecting duct, medullary, microphthalmia-associated transcription factor family translocation, and unclassified.[4] Because of the heterogeneity and rarity of nccRCC, most prospective RCC clinical trials have included only patients with ccRCC-predominant histology, or a small proportion of patients with nccRCC.[5] As such, systemic therapy options for nccRCC tend to be based on ccRCC trials and retrospective studies.[5 6] However, when compared with ccRCC, systemic therapies for nccRCC are less effective with lower response rates and worse survival outcomes.[7–9] In treatment guidelines, preferred regimens for metastatic nccRCC currently include enrolment in clinical trials or use of cabozantinib or sunitinib.[8] Other recommended treatment options include lenvatinib plus everolimus, which has shown encouraging antitumor efficacy in a recent prospective phase 2 trial, as well as nivolumab and pembrolizumab.[8 10]

Retrospective studies and, more recently, prospective clinical trials have evaluated the antitumor activity of immune checkpoint inhibitors (ICIs) for nccRCC, either as a monotherapy (nivolumab,[11 12] pembrolizumab[13]) or in combination with a targeted agent (atezolizumab plus vascular endothelial growth factor (VEGF) inhibitor bevacizumab,[14] durvalumab plus mesenchymal-epithelial transition inhibitor savolitinib[15]). Despite differences between studies in the proportion of each histologic subtype and line of therapy, objective responses have been reported in patients treated with single-agent ICIs (objective response rate (ORR) 14%–27%) and ICI-targeted agent combinations (ORR 26%–27%).[11–15]

The long-term efficacy and tolerability of nivolumab plus ipilimumab for previously untreated advanced RCC demonstrated in the registrational CheckMate 214 clinical trial were described based on results in patients with advanced RCC and a predominantly clear cell component.[16–18] Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks was subsequently approved by the US Food and Drug Administration and the European Medicines Agency for previously untreated International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor-risk advanced RCC.[19 20] Limited available retrospective data of the clinical activity of nivolumab plus ipilimumab in nccRCC have shown promising antitumor responses.[21 22] However, prospective data are needed to inform the use of nivolumab plus ipilimumab in the previously untreated advanced nccRCC setting.

CheckMate 920 is a prospective, multicohort clinical trial conducted largely in a US community practice setting and designed to assess the safety profile of nivolumab plus ipilimumab treatment for patients with previously untreated advanced RCC and clinical features mostly excluded from phase 3 trials (eg, nccRCC, brain metastases, and low Karnofsky performance status (KPS)).[23] We hypothesized that the safety profile of nivolumab plus ipilimumab in these select patients, treated predominantly within a community-based setting, would be similar to those with untreated advanced RCC and a predominantly clear cell component treated in an international academic center-based setting. Here, we report the safety and efficacy results for patients with advanced nccRCC from CheckMate 920 in cohort 2.

METHODS

Study design and patients

Methods have been described in detail previously.[23] CheckMate 920 (NCT02982954) is a non-randomized, open-label, multicohort, phase 3b/4 clinical trial of nivolumab plus ipilimumab treatment in patients with previously untreated advanced or metastatic RCC. Enrolled patients were assigned to one of four cohorts based on RCC histology, the presence of brain metastases, and KPS: predominantly ccRCC with KPS of at least 70% (cohort 1); nccRCC with KPS of at least 70% (cohort 2); cc/nccRCC with non-active brain metastases and KPS of at least 70% (cohort 3); and cc/nccRCC with KPS of 50%–60% (cohort 4).

In cohort 2, patients were included with advanced or metastatic histologically confirmed previously untreated nccRCC, no prior systemic therapy for RCC, KPS of at least 70%, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1, any IMDC risk, and available fresh or archival tumor tissue. One prior adjuvant or neoadjuvant therapy for completely resected RCC was allowed if it did not include ICIs and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy. Patients with autoimmune disease or a condition requiring systemic corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of study drug were excluded. Patients received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for up to four doses followed by nivolumab 480 mg every 4 weeks for up to 2 years or until disease progression, unacceptable toxicity, withdrawal of consent, or end of trial, whichever occurred first. Patients were permitted to continue treatment beyond progressive disease (per RECIST V.1.1) providing there was an investigator-assessed clinical benefit, tolerance of study drug, stable performance status, no delay to an imminent intervention to prevent serious complications of disease progression, and written informed consent. Patients who discontinued combination treatment early due to an adverse event (AE) may have been eligible to receive nivolumab 480 mg every 4 weeks, contingent on discussion with and approval by the medical monitor. The study will continue until the last enrolled patient completes 5 years of survival follow-up from the time of first visit.

Endpoints and assessments

As described in detail previously,[23] the primary endpoint of CheckMate 920 was the incidence of high-grade (grade 3–4 and grade 5) immune-mediated AEs (specific events that occurred within 100 days of the last dose of study drug; were of any causality; had no clear alternate etiology based on investigator assessment, or with an immune-mediated component; and treated with immune-modulating medication (with the exception of endocrine events)). Secondary endpoints included characterization of high-grade immune-mediated AEs (including the percentage of patients who received immune-modulating medication (or hormonal replacement therapy), length of immune-modulating medication administration, percentage of patients who received corticosteroids ≥40 mg prednisone or equivalent, time to onset, and time to resolution), and, using RECIST V.1.1, investigator-assessed ORR, time to response (TTR), duration of response (DOR), and investigator-assessed progression-free survival (PFS). Exploratory endpoints included the incidence of treatment-related AEs; investigator-assessed PFS-2 for patients treated beyond initial RECIST V.1.1-defined

progression (the time from first-dose baseline to the imaging-confirmed second progression (defined as an additional 20% increase in tumor volume from time of initial progression, including the sum of all target lesions and/or the development of new measurable lesions) or death from any cause, whichever occurred first); overall survival (OS); and clinical response by baseline tumor programmed death ligand 1 (PD-L1) expression. An analysis of ORR was also performed post hoc in patients with or without sarcomatoid features; and in patients with either IMDC favorable, intermediate, or poor risk. PD-L1 expression was evaluated using the validated Dako PD-L1 immunohistochemistry 28–8 pharmDx assay.

AEs were collected continuously during the treatment period and for at least 100 days after discontinuation of study treatment. Imaging assessments in cohort 2 were performed by CT/MRI during the screening period before the first dose, at 12 weeks (±1 week) after the first dose, every 8 weeks (±1 week) up to the first 13 months, then every 12 weeks (±1 week) until disease progression or treatment discontinuation.[23] Objective responses and progressive disease were confirmed by repeat scans per RECIST V.1.1.

Statistical analyses

The planned sample size was determined largely by the feasibility concern and based on the incidence of high-grade immune-mediated AEs with nivolumab plus ipilimumab from phase 1 studies of advanced or metastatic RCC and non-small cell lung cancer. The estimated half-width of the 95% CI of high-grade immune-mediated AE rates was considered to be within an acceptable degree of precision.

Safety and efficacy analyses were conducted on the treated population (all patients who received any nivolumab). Objective response analyses were conducted on the response-evaluable population (all treated patients who had baseline and at least one on-study evaluable tumor measurement).[23]

As described previously,[23] immune-mediated AEs were summarized per National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0. ORR was summarized using binomial response rates and two-sided 95% exact CIs using the Clopper-Pearson method.[24] TTR and DOR were summarized using Kaplan-Meier methodology; median values were calculated with two-sided 95% CIs using the Brookmeyer and Crowley method.[25] PFS, PFS-2 for patients treated beyond initial RECIST V.1.1-defined progression, and OS were summarized by Kaplan-Meier method; median values were calculated with two-sided 95% CI using the Brookmeyer and Crowley method.[25 26]

RESULTS

Patients

In a cohort of 52 patients with nccRCC who were treated (all treated patients), median age was 64 (range 23–86) years, 69.2% were male, 100% had a KPS of at least 70%, 82.7% had IMDC intermediate/poor risk, and 28.8% had sarcomatoid features (table 1).

Table 1 Patient demographics and characteristics at baseline for all treated patients

	All treated patients (N=52)
Age, median (range), years	64 (23–86)
Male, n (%)	36 (69.2)
IMDC risk group, n (%)	
Favorable	9 (17.3)
Intermediate	27 (51.9)
Poor	16 (30.8)
Karnofsky performance score, n (%)	
100	15 (28.8)
90	25 (48.1)
80	9 (17.3)
70	3 (5.8)
Prior nephrectomy, n (%)	35 (67.3)
Prior radiotherapy, n (%)	4 (7.7)
Histological subtype, n (%)	
Non-clear cell	52 (100)
Unclassified	22 (42.3)
Papillary	18 (34.6)
Chromophobe	7 (13.5)
Translocation-associated	2 (3.8)
Collecting duct	2 (3.8)
Renal medullary	1 (1.9)
Sarcomatoid features, n (%)	
Yes	15 (28.8)
No	37 (71.2)
Tumor PD-L1 expression, n (%)	n=39
<1%	24 (61.5)
≥1%	15 (38.5)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PD-L1, programmed death ligand 1.

Most patients had a histological subtype of unclassified (42.3%) or papillary nccRCC (34.6%). Of the 15 patients with sarcomatoid features at baseline, eight had unclassified histology, three had papillary, three had chromophobe, and one had collecting duct. After a minimum study follow-up (the time from last patient first treatment in cohort two to last patient last visit) of 24.1 months, all patients had discontinued treatment and 55.8% received subsequent anticancer therapy. Of all treated patients, the most common reasons for treatment discontinuation were disease progression (50.0%) and study drug toxicity (19.2%) (online supplemental figure S1).

Exposure

The median (range) duration of therapy was 3.5 (0.0–25.8) months for nivolumab and 2.1 (0.0–3.9) months

Table 2 Incidence of immune-mediated AEs and corticosteroid use for grade 3–4 immune-mediated AEs

Immune-mediated AE* category, n (%)	All treated patients (N=52)		
	Any grade	Grade 3–4	Corticosteroid use† for grade 3–4
Rash	12 (23.1)	3 (5.8)	2 (3.8)
Diarrhea/colitis	7 (13.5)	4 (7.7)	3 (5.8)
Hypothyroidism/thyroiditis‡	5 (9.6)	0	–
Nephritis and renal dysfunction	2 (3.8)	2 (3.8)	2 (3.8)
Adrenal insufficiency‡	2 (3.8)	1 (1.9)	0
Hepatitis	2 (3.8)	1 (1.9)	1 (1.9)
Hypophysitis‡	2 (3.8)	1 (1.9)	1 (1.9)
Hyperthyroidism‡	2 (3.8)	0	–
Hypersensitivity	1 (1.9)	0	–
Pneumonitis	1 (1.9)	0	–

*Specific events that occurred within 100 days of the last dose of study drug; were of any causality; had no clear alternate etiology based on investigator assessment, or with an immune-mediated component; and treated with immune-modulating medication (with the exception of endocrine events).
†≥40 mg prednisone or equivalent.
‡Considered endocrine immune-mediated AEs.
AE, adverse event.

for ipilimumab (patients received up to four doses of nivolumab plus ipilimumab before receiving nivolumab monotherapy; online supplemental figure S1). Most patients (86.5%) received a dose intensity of 90% to <110% for nivolumab and ipilimumab (as patient weight was used to calculate relative dose intensities, fluctuations in an individual patient's weight could result in a dose intensity above 100%). Overall, 28.8% received ≤3 nivolumab doses, 21.2% received 4 nivolumab doses, and 50.0% received ≥5 nivolumab doses; 30.8% received ≤3 ipilimumab doses and 69.2% received 4 ipilimumab doses. The median (range) number of doses received was 4.5 (1–28) for nivolumab and 4.0 (1–4) for ipilimumab. In total, 19 (36.5%) patients experienced at least one dose delay, most commonly due to AEs (22/43 total dose delays).

Safety

The most frequent any-grade immune-mediated AEs were rash (23.1%), diarrhea/colitis (13.5%), and hypothyroidism/thyroiditis (9.6%; table 2). No grade 5 immune-mediated AEs were reported. Grade 3–4 immune-mediated AEs were diarrhea/colitis (7.7%), rash (5.8%), nephritis and renal dysfunction (3.8%), and adrenal insufficiency, hepatitis, and hypophysitis (1.9% each; table 2).

The percentage of patients receiving immune-modulating medication for each grade 3–4 immune-mediated AE (data not shown) was the same as the incidence of each respective grade 3–4 immune-mediated AE. Grade 3–4 immune-mediated AEs were managed with systemic corticosteroids, dermatological corticosteroids, and the immunosuppressive agents infliximab and mycophenolic acid. The median length of immune-modulating medication administration for grade 3–4 immune-mediated AEs ranged from 3.0 weeks (nephritis and renal dysfunction) to 120.1 weeks (hepatitis). Overall, 30.8% of all treated patients received continuous corticosteroid (≥40 mg prednisone or equivalent) for any-grade immune-mediated AEs occurring within 100 days of the last dose of study drug (does not include patients who required adrenal replacement or corticosteroid ≥40 mg prednisone or equivalent for brain edema); 25.0% of patients received continuous corticosteroid for ≥14 days and 11.5% of patients received continuous corticosteroid for ≥30 days. Corticosteroid (≥40 mg prednisone or equivalent) use for grade 3–4 immune-mediated AEs is shown in table 2.

Median time to onset of grade 3–4 immune-mediated AEs ranged from 6.1 (range 2.3–13.7; rash) weeks to 18.7 (range 18.7–18.7; hypophysitis) weeks (table 3).

Median time to resolution of grade 3–4 immune-mediated AEs ranged from 5.9 (range 0.9–16.9; diarrhea/colitis) weeks to 8.0 (range 3.1–69.9+; rash) weeks. Patients with grade 3–4 immune-mediated AEs resolved in most cases, with the exception of one case each of hepatitis, rash, and adrenal insufficiency. The case of grade 3 hepatitis was managed with prednisone, methylprednisolone, and mycophenolic acid; the case of grade 3 rash was managed with triamcinolone, desonide, and hydrocortisone; and the case of grade 3 adrenal insufficiency was managed with lactated Ringer's, prednisone, fludrocortisone, and hydrocortisone, and was downgraded to grade 2 (unresolved), which was managed with fludrocortisone and hydrocortisone.

Any-grade treatment-related AEs were reported by 92.3% of all treated patients, with the most frequent being fatigue (48.1%), diarrhea (30.8%) and nausea (26.9%; table 4).

There were no treatment-related deaths. Grade 3–4 treatment-related AEs occurred in 36.5% of all treated patients with the most common being lipase increased (7.7%) and rash maculo-papular (5.8%). Any-grade and grade 3–4 AEs leading to discontinuation occurred in 26.9% and 21.2% of all treated patients, respectively, with the most frequent being diarrhea (3.8% for both any-grade and grade 3–4 AEs) and malignant neoplasm progression reported as an AE (3.8% for both any-grade and grade 3–4 AEs).

Efficacy

Median follow-up for survival (the time between first treatment date and last known date alive or death) was 19.0 months. Any reduction in the sum of the diameter of target lesions was observed in >50% of response-evaluable patients (online supplemental figure S2). Investigator-assessed confirmed ORR per RECIST V.1.1 in response-evaluable patients (n=46) was 19.6% (95% CI 9.4% to 33.9%; table 5).

Table 3 Time to onset and resolution of immune-mediated AEs

Immune-mediated AE category	Median (range) time to onset, weeks		Median (range) time to resolution,* weeks	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Pneumonitis	n=1; 2.9 (2.9–2.9)	–	n=1; 0.4 (0.4–0.4)	–
Hepatitis	n=2; 6.1 (2.9–9.4)	n=1; 9.4 (9.4–9.4)	–	–
Nephritis/renal dysfunction	n=2; 9.4 (1.4–17.4)	n=2; 9.4 (1.4–17.4)	n=2; 7.8 (1.1–14.4)	n=2; 7.8 (1.1–14.4)
Rash	n=12; 6.1 (1.1–14.9)	n=3; 6.1 (2.3–13.7)	n=9; 4.4 (2.9–128.1+)	n=2; 8.0 (3.1–69.9+)
Diarrhea/colitis	n=7; 9.4 (0.7–44.4)	n=4; 10.4 (4.4–20.1)	n=5; 10.9 (1.7–113.0+)	n=4; 5.9 (0.9–16.9)
Hypersensitivity	n=1; 3.9 (3.9–3.9)	–	n=1; 0.1 (0.1–0.1)	–
Adrenal insufficiency†	n=2; 54.1 (12.7–95.4)	n=1; 12.7 (12.7–12.7)	–	–
Hyperthyroidism†	n=2; 20.6 (2.1–39.1)	–	n=2; 4.0 (3.9–4.1)	–
Hypophysitis†	n=2; 12.7 (6.7–18.7)	n=1; 18.7 (18.7–18.7)	n=2; 17.1 (7.6–26.6)	n=1; 7.6 (7.6–7.6)
Hypothyroidism/thyroiditis†	n=5; 6.1 (3.6–15.1)	–	n=1; NR (12.0+–134.1+)	–

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

Two patients (4.3%) achieved complete response (papillary, n=1; unclassified, n=1), seven patients (15.2%) achieved partial response (papillary, n=4; unclassified, n=3), and 17 patients (37.0%) had stable disease. Investigator-assessed confirmed ORR per RECIST V.1.1 in patients with baseline tumor PD-L1 expression <1% or ≥1% was 14.3% (95% CI 3.0% to 36.3%) and 30.8% (95% CI 9.1% to 61.4%), respectively (table 5). Among subgroups in a post hoc analysis, investigator-assessed confirmed ORR per RECIST V.1.1 in patients with the presence or absence of sarcomatoid features was 35.7% (95% CI 12.8% to 64.9%) and 12.5% (95% CI 3.5% to 29.0%), respectively, and in IMDC favorable-risk, intermediate-risk, and poor-risk patients was 12.5% (95% CI 0.3% to 52.7%), 20.0% (95% CI 6.8% to 40.7%), and 23.1% (95% CI 5.0% to 53.8%), respectively (table 5). Median TTR in all treated patients was 2.8 (range 2.1–14.8) months and median DOR was not reached (range 0.0+–27.8+); eight of nine responders remained without reported progression at the time of database lock, even though treatment had been discontinued. Of the two responders who received subsequent systemic anticancer therapy, both received nivolumab.

Table 4 Treatment-related AEs reported in ≥10% of all treated patients

	All treated patients (N=52)	
	Any grade	Grade 3–4
Total patients with a treatment-related AE, n (%)	48 (92.3)	19 (36.5)
Treatment-related AEs in ≥10% of all treated patients, n (%)		
Fatigue	25 (48.1)	2 (3.8)
Diarrhea	16 (30.8)	2 (3.8)
Nausea	14 (26.9)	0
Vomiting	10 (19.2)	0
Rash maculo-papular	9 (17.3)	3 (5.8)
Pruritus	9 (17.3)	0
Decreased appetite	9 (17.3)	0
Lipase increased	6 (11.5)	4 (7.7)
Muscular weakness	6 (11.5)	1 (1.9)
Pyrexia	6 (11.5)	0

Includes events reported between first dose and 100 days after last dose of study therapy.
AE, adverse event.

Median PFS in all treated patients was 3.7 (95% CI 2.7 to 4.6) months (figure 1), and in IMDC favorable-risk, intermediate-risk, and poor-risk patients was 3.6 (95% CI 2.6 to NE; n=9) months, 4.3 (95% CI 2.6 to 10.4; n=27) months, and 2.8 (95% CI 1.3 to 4.7; n=16) months, respectively. Median PFS-2 for 12 patients treated beyond initial RECIST V.1.1-defined progression was 16.6 (95% CI 7.7 to 27.9) months (online supplemental figure S3).

Median OS (N=52) was 21.2 (95% CI 16.6 to not estimable (NE)) months; the probability of survival at 12 and 18 months was 72.6% (95% CI 58.1% to 82.8%) and 64.5% (95% CI 49.7% to 76.0%), respectively (figure 2). Median OS among IMDC favorable-risk, intermediate-risk, and poor-risk patients was not reached (95% CI 4.1 to NE; n=9), 22.7 (95% CI 16.6 to NE; n=27) months, and 16.6 (95% CI 4.5 to 27.9; n=16) months, respectively.

DISCUSSION

The non-randomized, open-label, multicohort, phase 3b/4 CheckMate 920 clinical trial was conducted largely in US community-based practices to evaluate nivolumab

Table 5 Investigator-assessed objective response per RECIST V.1.1 in response-evaluable patients

Outcome	Response-evaluable patients (N=46)
Investigator-assessed confirmed ORR per RECIST V.1.1 (95% CI), %	19.6 (9.4 to 33.9)
BOR, n (%)	
Complete response	2 (4.3)*
Partial response	7 (15.2)†
Stable disease	17 (37.0)
Progressive disease	19 (41.3)
Unable to determine	1 (2.2)
Investigator-assessed confirmed ORR per RECIST V.1.1 among subgroups (95% CI), %	
Baseline tumor PD-L1 expression <1% (n=21)	14.3 (3.0 to 36.3)
Baseline tumor PD-L1 expression ≥1% (n=13)	30.8 (9.1 to 61.4)
Presence of sarcomatoid features (n=14)	35.7 (12.8 to 64.9)
Absence of sarcomatoid features (n=32)	12.5 (3.5 to 29.0)
IMDC favorable risk (0; n=8)	12.5 (0.3 to 52.7)
IMDC intermediate risk (1–2; n=25)	20.0 (6.8 to 40.7)
IMDC poor risk (3–6; n=13)	23.1 (5.0 to 53.8)
Median TTR (range), months	2.8 (2.1–14.8)
Median DOR (range), months	NR (0.0+–27.8+)

*One patient with papillary and one patient with unclassified histology.
†Four patients with papillary and three patients with unclassified histology.
+, censored value; BOR, best overall response; DOR, duration of response; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NR, not reached; ORR, objective response rate; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

plus ipilimumab in patients with previously untreated advanced RCC with clinical features mostly excluded from phase 3 trials. To our knowledge, the cohort of patients with previously untreated advanced nccRCC from CheckMate 920 is the first prospective study of nivolumab plus ipilimumab in this setting to date. Overall, the safety profile of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for up to four doses followed by nivolumab 480 mg every 4 weeks for previously untreated advanced nccRCC was as expected, and no new safety signals were identified. The dosing used in this cohort is currently approved by the US Food and Drug Administration and the European Medicines Agency for patients with previously untreated RCC, regardless of histology.[19 20] Few patients reported grade 3–4 immune-mediated AEs and no grade 5 immune-mediated AEs occurred. The safety profile and incidence of immune-mediated AEs in this trial were generally consistent with nivolumab plus ipilimumab for patients with previously untreated advanced RCC and a predominantly clear cell component in the registrational CheckMate 214 trial.[17 27] In total, 69.2% of patients received the maximum four doses of ipilimumab, which is comparable with the level reported in CheckMate 214 (79%), in which patients were required to have received all four doses of ipilimumab before receiving nivolumab monotherapy.[16] The incidence and type of the most frequent grade 3–4 immune-mediated AEs after 24.1 months minimum study follow-up (diarrhea/colitis, 7.7%; rash, 5.8%) were mostly similar with those reported in CheckMate 214 after 17.5 months minimum follow-up (diarrhea/colitis, 5%; rash, 3%) and from data pooled across 666 patients with RCC or metastatic colorectal cancer receiving nivolumab plus ipilimumab (grade 3 immune-mediated colitis, 4.4%; grade 3 immune-mediated rash, 3.5%).[19 27]

Encouraging antitumor activity and survival was observed; ORR tended to be higher in patients with sarcomatoid features, which is consistent with the efficacy benefit of nivolumab plus ipilimumab or ICI-VEGF-targeted agent combinations over sunitinib in this setting,[28] and durable responses were seen in patients with papillary and unclassified histology. Notably, the proportion of patients with unclassified histology in this largely US community center-based trial (42.3%) is higher than reported previously in other prospective clinical trials (~6%–20%)[10 11 13 29 30] and retrospective studies (~7%–34%) of nccRCC.[9 12 21 22 31 32] However, cases of unclassified and other histologic subtypes determined at each site were not confirmed by central laboratory testing in this study.

Although reported separately in this trial (unlike CheckMate 214), efficacy measures were not significantly different between IMDC intermediate-risk and poor-risk groups, suggesting that neither of these subgroups have contributed disproportionately to the efficacy outcomes in this cohort of CheckMate 920. PFS-2 showed a clinical benefit of nivolumab plus ipilimumab in some patients treated beyond initial RECIST V.1.1-defined progression. The observed antitumor activity in this trial appears to be lower across most efficacy measures relative to that reported in patients with advanced RCC with a predominantly clear cell component from CheckMate 214 after 30 months minimum follow-up.[17] Notably, however, in both CheckMate 920 and CheckMate 214 (30 months minimum follow-up, intention-to-treat population) the median TTR and median DOR were 2.8 months and not reached, respectively.[33]

The limited existing retrospective data of nivolumab plus ipilimumab clinical activity in nccRCC have also reported promising antitumor responses. In a retrospective study of 18 patients with nccRCC who received nivolumab plus ipilimumab, of whom 13 (72%) were untreated, ORR was 33.3%, 17% of patients had stable disease, median DOR was 4.3 months, and of six patients with a response, three had an ongoing response after a

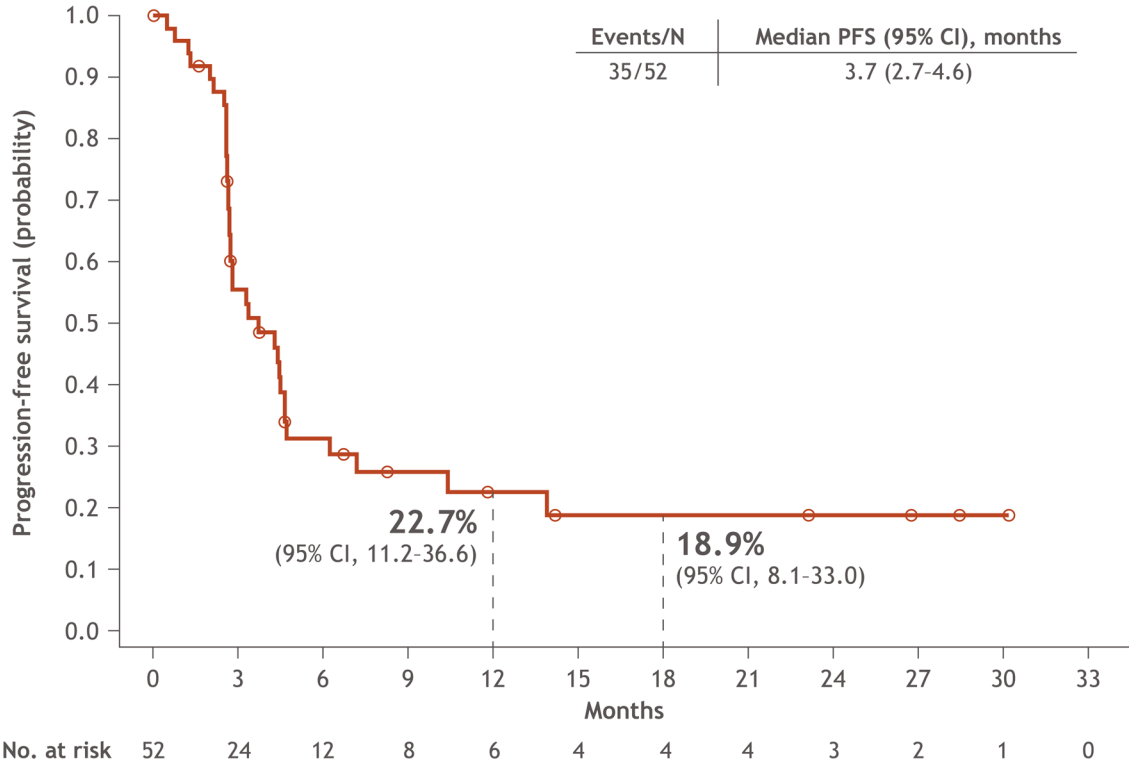

Figure 1 Kaplan-Meier plot of PFS per investigator assessment in all treated patients. PFS, progression-free survival.

median follow-up of 6.8 months.[22] Median PFS was 7.1 months; two patients were treated beyond progression and experienced further progression without radiographic tumor shrinkage.[22] In contrast, a lower ORR was observed in CheckMate 920 but a greater proportion of patients had stable disease (37.0%).

Two separate retrospective analyses included patients receiving nivolumab plus ipilimumab among patients

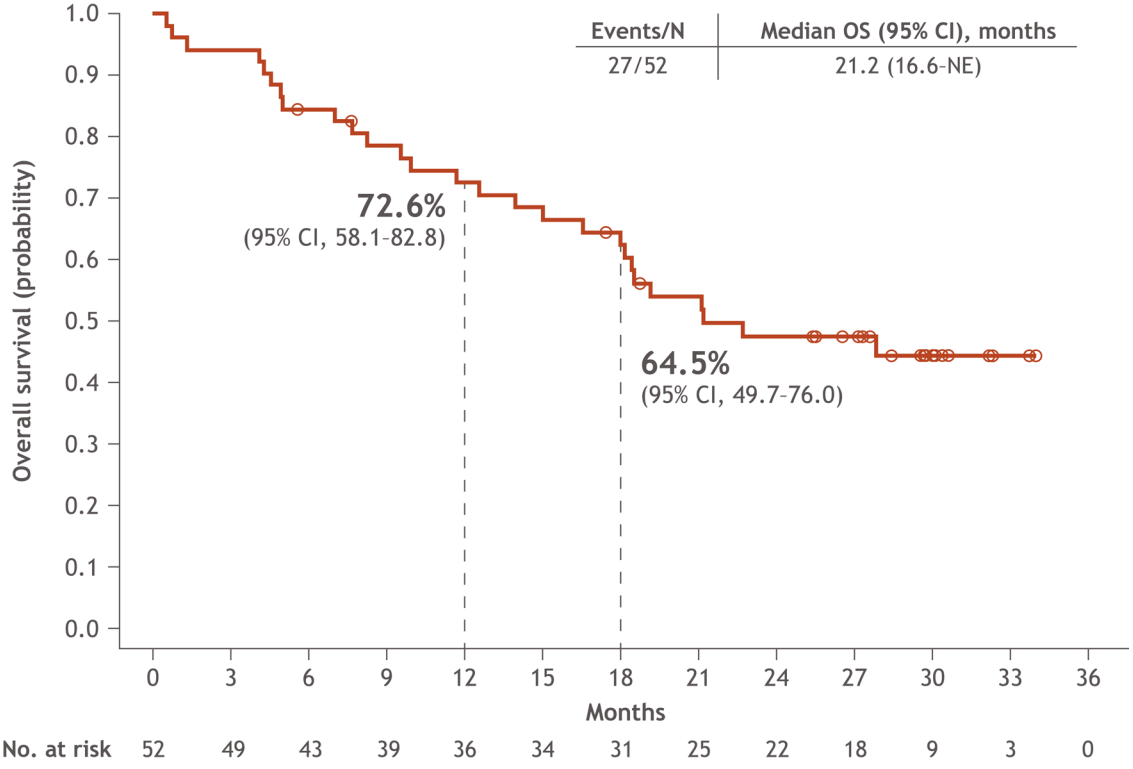

Figure 2 Kaplan-Meier plot of OS in all treated patients. NE, not estimable; OS, overall survival.

receiving other immune-oncology regimens.[21 32] McKay *et al* reported outcomes from an analysis of largely previously treated patients with nccRCC, or ccRCC with sarcomatoid differentiation, who received programmed death-1/PD-L1 monotherapy or in combination with ipilimumab or a VEGF-targeted therapy. After a median follow-up of 11.4 months, ORR was 19%, 33% of patients had stable disease, and median OS was 12.9 months.[21] Separately, Chahoud *et al* reported outcomes from 40 predominantly previously treated patients with nccRCC, of whom 31 received nivolumab monotherapy, and nine received nivolumab in combination with ipilimumab or VEGF-targeted therapy.[32] For the total cohort, ORR was 20.6% (44.4% for the nine patients receiving combination therapy), median PFS was 4.9 months (~45 months for patients receiving combination therapy), and median OS was 21.7 months (NR for patients receiving combination therapy) after a median follow-up of 24.5 months.[32] Although differences in the proportion of tumor histologic subtypes, the number of prior systemic therapies, and available follow-up preclude direct comparison, our prospective data from CheckMate 920 add to the existing retrospective clinical evidence for nivolumab plus ipilimumab antitumor activity and durable responses seen in patients with advanced nccRCC.

Current treatment guidelines for advanced nccRCC are based on limited evidence from phase 2 trials, retrospective studies, and a meta-analysis; our study adds much-needed prospective data to inform clinical practice. The efficacy data for nivolumab plus ipilimumab reported here are comparable with prospective nccRCC data used to support the National Comprehensive Cancer Network preferred regimens cabozantinib (ORR, 23%; median PFS, 9.0 months; median OS, 20.0 months)[34] and sunitinib (ORR, 6%–18%; median PFS, 6.1–8.3 months; median OS, 16.2–31.5 months)[29 30]; as well as the other recommended treatment options lenvatinib plus everolimus (ORR, 26%; PFS, 9.2 months; OS, 15.6 months)[10] and pembrolizumab (ORR, 27%; median PFS, 4.2 months; median OS, 28.9 months).[13] Nivolumab as a recommended treatment option is currently supported by retrospective data,[12 21] however, prospective data are available (ORR, 13.6%; median PFS, 2.2 months; median OS, 16.3 months).[11]

This large prospective cohort of previously untreated patients with nccRCC undergoing dual ICI treatment was not without limitations. Due to a small number of patients with advanced nccRCC, efficacy analyses by baseline tumor PD-L1 expression level, in patients with sarcomatoid features, and by IMDC risk should be interpreted with caution. Other limitations include the non-randomized nature of the trial, the lack of a standard-of-care comparator arm, and absence of central laboratory testing to confirm nccRCC histology. The ongoing large phase 2 SUNNIFORECAST trial of nivolumab plus ipilimumab versus standard of care for previously untreated advanced/metastatic nccRCC will provide additional prospective comparative data in this population with high unmet medical need (NCT03075423).

In conclusion, the safety profile of the approved nivolumab plus ipilimumab dosing regimen for predominantly clear cell advanced RCC given in the previously untreated advanced nccRCC setting did not identify any new safety signals. These data support the safe administration of nivolumab plus ipilimumab for a heterogenous and difficult-to-treat patient population. Encouraging antitumor activity and survival were observed; durable responses were seen in patients with papillary and unclassified histology. Taken together, data from the CheckMate 920 trial support nivolumab plus ipilimumab as a first-line treatment option for select patients with advanced/metastatic nccRCC.

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