


Safety and efficacy of nivolumab plus ipilimumab in patients with advanced renal cell carcinoma with brain metastases: CheckMate 920

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Background: Nivolumab plus ipilimumab (NIVO + IPI) has demonstrated long-term efficacy and safety in patients with previously untreated, advanced renal cell carcinoma (aRCC). Although most phase 3 clinical trials exclude patients with brain metastases, the ongoing, multicohort phase 3b/4 CheckMate 920 trial (ClinicalTrials.gov identifier NCT02982954) evaluated the safety and efficacy of NIVO + IPI in a cohort that included patients with aRCC and brain metastases, as reported here. **Methods:** Patients with previously untreated aRCC and asymptomatic brain metastases received NIVO 3 mg/kg plus IPI 1 mg/kg every 3 weeks × 4 followed by NIVO 480 mg every 4 weeks. The primary end point was the incidence of grade ≥3 immune-mediated adverse events (imAEs) within 100 days of the last dose of study drug. Key secondary end points were progression-free survival and the objective response rate according to Response Evaluation Criteria in Solid Tumors, version 1.1 (both determined by the investigator). Exploratory end points included overall survival, among others. **Results:** After a minimum follow-up of 24.5 months (N = 28), no grade 5 imAEs occurred. The most common grade 3 and 4 imAEs were diarrhea/colitis (n = 2; 7%) and hypophysitis, rash, hepatitis, and diabetes mellitus (n = 1 each; 4%). The objective response rate was 32% (95% CI, 14.9%-53.5%) with a median duration of response of 24.0 months; 4 of 8 responders remained without reported progression. Seven patients (25%) had intracranial progression. The median progression-free survival was 9.0 months (95% CI, 2.9-12.0 months), and the median overall survival was not reached (95% CI, 14.1 months to not estimable). **Conclusions:** In patients who had previously untreated aRCC and brain metastases—a population with a high unmet medical need that often is underrepresented in clinical trials—the approved regimen of NIVO + IPI followed by NIVO showed encouraging antitumor activity and no new safety signals. **Cancer 2022;128:966-974.** © 2021 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: aRCC, brain metastases, intracranial, ipilimumab, nivolumab, renal cell carcinoma, unmet need.

INTRODUCTION

Many patients with renal cell carcinoma (RCC) present with de novo metastatic disease, and a considerable proportion initially diagnosed with localized disease subsequently develop advanced RCC (aRCC).¹⁻³ The incidence of brain metastases in RCC is generally reported as 10%, but asymptomatic brain lesions in patients with widespread metastatic disease could mask a higher incidence.⁴⁻⁶

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Patients with untreated brain metastases have a poor prognosis, short median overall survival (OS), and short progression-free survival (PFS).^{2,3,7} With the approval of targeted therapy for RCC, median survival has improved for patients with brain metastases (80% symptomatic) to 14.4 months after first-line treatment versus 19.0 months for patients without brain metastases.^{3,8,9} Of the limited available data in patients who have RCC and focally treated, asymptomatic brain metastases, a median OS of 10.3 months has been reported, suggesting that, even when diagnosed in the occult setting, the presence of brain metastasis alone may correlate with a relatively poor prognosis.¹⁰ Immune checkpoint inhibitor combination therapy has superseded targeted monotherapy as the preferred treatment for patients with aRCC, resulting in significantly improved clinical outcomes, including response and survival.¹¹ In the pivotal CheckMate 214 (CM214) trial (ClinicalTrials.gov identifier NCT02231749), treatment with the combination immuno-oncology (IO)-IO therapy nivolumab plus ipilimumab (NIVO + IPI) yielded an objective response rate (ORR) of 41% versus 34% with sunitinib monotherapy in the intent-to-treat population and a 29% reduction in the risk of death.¹² After the advent of combination IO-IO therapies, additional trials evaluated IO-tyrosine kinase inhibitor combination therapies, which reported ORRs ranging from 53% to 59% versus 27% to 36% for tyrosine kinase inhibitor monotherapy with sunitinib and reductions in mortality risk ranging from 20% to 47%.¹³⁻¹⁵ However, the effects of immune checkpoint inhibitors and other targeted therapies on metastatic lesions in the brain (either symptomatic or asymptomatic) are an area of needed research and reflect an unmet clinical need,^{2,6,11} and the optimal systemic treatment of RCC that has metastasized to the brain is not defined.³

Patients who have evidence of intracranial metastases are generally excluded from registrational trials, typically because the presence of brain metastases is considered a marker of poor prognosis and a potential complicating factor in assessing the toxicity of novel treatments.^{2,16-19} Poor prognoses may result from the relative resistance of brain metastases to radiotherapy and poor central nervous system (CNS) penetration by targeted therapies.^{2,3} However, stereotactic radiosurgery provides durable local control for patients with RCC and brain metastases; further investigation is needed to determine whether outcomes are improved with the addition of targeted agents or immunotherapies.^{3,20,21}

The long-term efficacy and tolerability of NIVO + IPI for patients with previously untreated aRCC

demonstrated in CM214 was based on outcomes in patients who had aRCC and a predominantly clear cell component.^{12,18} Data evaluating NIVO + IPI in patients with aRCC and brain metastases are limited, although antitumor activity has been observed in patients with other cancers and brain metastases.^{22,23}

CheckMate 920 (ClinicalTrials.gov identifier NCT 02982954) is a prospective, multicohort clinical trial of NIVO + IPI in patients with previously untreated aRCC and clinical features mostly excluded from phase 3 trials (ie, nonclear cell RCC [nccRCC], brain metastases, and low Karnofsky performance status [KPS]). Here, we report the safety and efficacy results for the cohort of patients with brain metastases and KPS $\geq 70\%$ from CheckMate 920.

MATERIALS AND METHODS

Study Design and Patients

CheckMate 920²⁴ is a prospective, nonrandomized, open-label, multicohort, phase 3b/4 clinical trial of NIVO + IPI treatment for patients in the United States with previously untreated aRCC or metastatic RCC and clinical features typically excluded from phase 3 trials. Patients were assigned to 1 of 4 cohorts: predominantly clear cell RCC (ccRCC) with KPS $\geq 70\%$ (cohort 1), nccRCC with KPS $\geq 70\%$ (cohort 2), cc/nccRCC with nonactive brain metastases and KPS $\geq 70\%$ (cohort 3), and cc/nccRCC with KPS from 50% to 60% (cohort 4). This report focuses on cohort 3.

Patients in cohort 3 had previously untreated aRCC of any histology; no prior systemic therapy for RCC (1 prior adjuvant or neoadjuvant therapy for completely resectable RCC was permitted if it did not include immune checkpoint inhibitors and if recurrence occurred ≥ 6 months after the last dose of adjuvant or neoadjuvant therapy); measurable disease (extracranial metastasis required) according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1); KPS $\geq 70\%$; any International Metastatic RCC Database Consortium (IMDC) prognostic risk; and available tumor tissue. Enrolled patients had asymptomatic brain metastases and had received no systemic corticosteroid or radiation treatment within 14 days before beginning study therapy. According to RECIST v1.1, brain lesions < 10 mm or previously irradiated brain lesions were only assessed as nontarget lesions, and brain lesions ≥ 10 mm and not previously irradiated were assessed as target lesions. Patients with known or suspected autoimmune disease or those who required systemic corticosteroids (> 10 mg/day prednisone or equivalent) or

other immunosuppressive medications within 14 days of the first dose of study drug were excluded.

Patients in cohort 3 received NIVO 3 mg/kg plus IPI 1 mg/kg every 3 weeks for up to 4 doses intravenously followed by NIVO 480 mg every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the trial, whichever occurred first, or up to a maximum of 2 years. Patients could continue treatment beyond RECIST v1.1-defined progressive disease under protocol-defined circumstances. The study will continue until the last enrolled patient completes 5 years of survival follow-up from the time of their first visit.

The study was conducted in accordance with Good Clinical Practice, as defined by the International Council on Harmonisation based on the ethical principles underlying the European Union Directive, the US Code of Federal Regulations, and applicable local requirements.

End Points and Assessments

The primary end point was the incidence of high-grade (grade 3-4 and grade 5) immune-mediated adverse events (imAEs) (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 had an immune-mediated component, and were treated with immune-modulating medication [IMM], with the exception of endocrine events). Secondary end points included the characterization of high-grade imAEs (including time to onset, time to resolution, percentage of patients who received IMM, percentage of patients who received corticosteroids ≥ 40 mg/day prednisone or equivalent); duration of treatment with IMM; PFS and ORR according to RECIST v1.1 (both investigator-assessed); duration of response (DOR); and time to response (TTR). Exploratory end points included the incidence of treatment-related adverse events (AEs), OS, ORR according to PD-L1 expression, and CNS tumor assessments (the number of brain metastases at initial diagnosis, prior therapies for brain metastases, intracranial progression, and treatment discontinuation at the time of intracranial progression).

AEs were collected throughout the treatment period and for at least 100 days after discontinuation of study treatment. Imaging assessments were performed by computed tomography/magnetic resonance imaging during screening 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. Objective responses and progressive disease were confirmed by repeat scans.

Statistical Analyses

The planned sample size was determined according to the incidence of high-grade imAEs with NIVO + IPI for nonsmall cell lung cancer in CheckMate 012 (approximately 35% in both combined therapy arms; ClinicalTrials.gov identifier NCT01454102) and for RCC in the CheckMate 016 study (approximately 40%-60% in both combination therapy arms; ClinicalTrials.gov identifier NCT01472081). The planned enrollment was 200 patients, with approximately 100 patients in cohort 1, 50 in cohort 2, and 25 each in cohorts 3 and 4 (there were approximately 100 patients in cohort 1 and 100 patients in cohorts 2-4 combined).

Safety and efficacy analyses were performed in the treated population (all patients who received any NIVO). Objective response analyses were assessed in the response-evaluable population (all treated patients who had baseline tumor measurements and ≥ 1 on-study evaluable tumor measurement).

imAEs were characterized according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0). The ORR was assessed with binomial response rates and 2-sided 95% exact confidence intervals (CIs) using the Clopper-Pearson method.²⁵ TTR and DOR were summarized using Kaplan-Meier methodology, and the median DOR was calculated with 2-sided 95% exact CIs using the Brookmeyer and Crowley method.²⁶ PFS and OS were summarized using the Kaplan-Meier product-limit method, and median values were calculated with 2-sided 95% CIs using the Brookmeyer and Crowley method.^{26,27}

RESULTS

Patients

Twenty-eight patients with brain metastases received treatment with NIVO (all treated patients) in cohort 3. The median age of patients was 60 years (range, 38-87 years), 86% ($n = 24$) were men, 100% ($n = 28$) had KPS $\geq 70\%$, 93% ($n = 26$) had a clear cell component, 14% ($n = 4$) had sarcomatoid features, 64% ($n = 18$) had an intermediate IMDC risk score, and 26% ($n = 7$) of patients with evaluable tumor PD-L1 expression had PD-L1 expression $\geq 1\%$ (see Supporting Table 1); none had received prior systemic anticancer therapy.

At initial diagnosis, 68% (n = 19) of all treated patients in cohort 3 (N = 28; all of whom were evaluable for CNS tumor assessments) had 1 brain metastatic lesion/disease site, 29% (n = 8) had between 2 and 5 brain metastatic lesions/disease sites, and 4% (n = 1) had between 6 and 10 brain metastatic lesions/disease sites. Prior therapy for brain metastases was reported by disease site (percentages are out of all patients who had disease sites at enrollment, where 1 disease site from a patient may be counted in >1 prior therapy but it is counted only once in the number of sites) and by patient (percentages are out of all treated patients, where patients who received >1 treatment are counted once). Most patients (n = 25; 89%) had received prior therapy for brain metastasis; by disease site, most had received stereotactic radiosurgery (n = 12; 43%), whole-brain radiation (n = 10; 36%), or surgical resection (n = 10; 36%). Considering nondrug prior treatment by patient, 7 patients (25%) received >1 prior therapy, 8 (29%) received stereotactic radiosurgery, 7 (25%) received whole-brain radiation, 3 (11%) received surgical resection, and 3 (11%) received no prior therapies.

After a minimum study follow-up of 24.5 months, all patients had discontinued treatment. Of all treated patients (N = 28), the most common reasons for discontinuation were disease progression (n = 12; 43%) and study drug toxicity (n = 8; 29%).

Exposure

The median duration of therapy was 3.4 months (range, 0.03-23.3 months) for NIVO and 2.1 months (range, 0.03-3.3 months) for IPI (see Supporting Table 2). Of all treated patients, 36% (n = 10) received ≤ 3 NIVO doses, 14% (n = 4) received 4 NIVO doses, and 50% (n = 14) received ≥ 5 NIVO doses; 46% (n = 13) received ≤ 3 IPI doses, and 54% (n = 15) received 4 IPI doses. The median number of doses received was 4.5 (range, 1-25 doses) for NIVO and 4 (range, 1-4 doses) for IPI.

Safety

No grade 5 imAEs (deaths) were reported. Grade 3 and 4 imAEs by category in all treated patients (N = 28) were diarrhea/colitis (n = 2; 7%) and hypophysitis, rash, hepatitis, and diabetes mellitus (n = 1 each; 4%) (Table 1). The median time to onset of grade 3 and 4 imAEs ranged from 2.0 weeks (diabetes mellitus) to 11.6 weeks (hepatitis), and the median time to resolution of grade 3 and 4 imAEs ranged from 1.1 weeks (diabetes mellitus and diarrhea/colitis) to 5.3 weeks (rash) (Table 2). Grade

TABLE 1. Incidence of Immune-Mediated Adverse Events and Corticosteroid Use in All Treated Patients, N = 28

Immune-Mediated AE Category ^a	All Treated Patients: No. (%)		
	Any Grade	Grade 3-4	Corticosteroid Use for Grade 3-4 ^b
Hypothyroidism/thyroiditis ^c	9 (32)	0 (0)	0 (0)
Rash	6 (21)	1 (4)	1 (4)
Diarrhea/colitis	5 (18)	2 (7)	2 (7)
Hyperthyroidism ^c	3 (11)	0 (0)	0 (0)
Diabetes mellitus ^c	2 (7)	1 (4)	1 (4)
Hypophysitis ^c	2 (7)	1 (4)	0 (0)
Adrenal insufficiency ^c	1 (4)	0 (0)	0 (0)
Hepatitis	1 (4)	1 (4)	1 (4)
Nephritis/renal dysfunction	1 (4)	0 (0)	0 (0)

Abbreviation: AE, adverse event.

^aImmune-mediated AEs included 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 had an immune-mediated component, and were treated with immune-modulating medication (with the exception of endocrine events).

^bThe corticosteroid dose was ≥ 40 mg/day prednisone or equivalent.

^cThese were considered endocrine immune-mediated AEs.

3 and 4 imAEs resolved in most cases, with the exception of 1 case of hypophysitis, which was managed with hydrocortisone.

The most frequent any-grade imAEs were hypothyroidism/thyroiditis (n = 9; 32%), rash (n = 6; 21%), and diarrhea/colitis (n = 5; 18%) (Table 1). Overall, 36% (n = 10) of all treated patients received corticosteroid treatment (≥ 40 mg/day prednisone or equivalent) for any-grade imAE (does not include patients who required adrenal replacement or required treatment with corticosteroids ≥ 40 mg/day prednisone or equivalent for brain edema); 25% (n = 7) for ≥ 14 days and 14% (n = 4) for ≥ 30 days. The median duration of IMM use for grade 3 and 4 imAEs ranged from 0.1 week for diabetes mellitus to 20.4 weeks for hepatitis.

Any-grade treatment-related AEs were reported by 93% (n = 26) of all treated patients, and grade 3 and 4 treatment-related AEs occurred in 54% of all treated patients (see Supporting Table 3). No neurotoxicities occurred in $\geq 10\%$ of patients. Grade 3 or 4 myasthenia gravis occurred in 1 patient; and any-grade headache, peripheral sensory neuropathy, and tremor occurred in 1 patient each. Any-grade and grade 3 and 4 AEs leading to discontinuation occurred in 36% (n = 10) and 32% (n = 9) of all treated patients, respectively. All other any-grade AEs leading to discontinuation occurred in 1 patient each (see Supporting Table 4). There were no treatment-related deaths.

TABLE 2. Time to Onset and Resolution of Immune-Mediated Adverse Events^a

Immune-Mediated AE Category	Time to Onset		Time to Resolution ^b	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Adrenal insufficiency ^c	n = 1	—	—	—
Median (range), wk	21.0 (21.0-21.0)	—	—	—
Hypothyroidism/thyroiditis ^c	n = 9	—	n = 1	—
Median (range), wk	9.3 (1.9-44.3)	—	NR (2.3+ to 141.0+)	—
Diabetes mellitus ^c	n = 2	n = 1	n = 1	n = 1
Median (range), wk	21.3 (2.0-40.6)	2.0 (2.0-2.0)	NR (1.1 to 114.6+)	1.1 (1.1-1.1)
Hyperthyroidism ^c	n = 3	—	n = 2	—
Median (range), wk	6.6 (5.7-15.1)	—	12.1 (3.1 to 93.3+)	—
Hypophysitis ^c	n = 2	n = 1	—	—
Median (range), wk	7.8 (7.1-8.4)	8.4 (8.4-8.4)	—	—
Diarrhea/colitis	n = 5	n = 2	n = 5	n = 3
Median (range), wk	4.9 (3.7-6.4)	11.0 (10.1-11.9) ^d	4.9 (0.6-6.6)	1.1 (1.1-4.9) ^d
Hepatitis	n = 1	n = 1	n = 1	n = 1
Median (range), wk	11.6 (11.6-11.6)	11.6 (11.6-11.6)	3.0 (3.0-3.0)	3.0 (3.0-3.0)
Nephritis/renal dysfunction	n = 1	—	—	—
Median (range), wk	8.9 (8.9-8.9)	—	—	—
Rash	n = 6	n = 1	n = 3	n = 1
Median (range), wk	4.8 (1.0-51.6)	8.3 (8.3-8.3)	NR (1.9 to 142.0+)	5.3 (5.3-5.3)

Abbreviations: +, Censored value; AEs, adverse events; NR, not reached.

^aImmune-mediated AEs included 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 had an immune-mediated component, and were treated with immune-modulating medication (with the exception of endocrine events).

^bPatients who experienced immune-mediated AEs without worsening from baseline grade are 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 for which immune-modulating medication was initiated is considered.

^cThese were considered endocrine immune-mediated AEs.

^dThe number of patients may be lower for the time to onset than for the time to resolution because the time to onset accounts for AE records that indicate an AE was treated with immune-modulating medication. One patient who had grade 4 diarrhea/colitis was not treated with immune-modulating medication and is not included in the analysis of the time to onset for diarrhea/colitis.

Efficacy

The median follow-up for survival (the time between the first treatment date and the date last known alive or the date of death) was 26.3 months. The investigator-assessed, confirmed ORR according to RECIST v1.1 in response-evaluable patients (n = 25) was 32% (95% CI, 15%-54%) (Table 3). No patients achieved a complete response, 8 (32%) achieved a partial response, 10 (40%) had stable disease, and 6 (24%) had progressive disease. The median TTR was 2.8 months (range, 2.4-3.0 months). The median DOR was 24.0 (range, 3.9 to 32.7+ months), and 4 of 8 responders remained without reported progression at the time of database lock. The investigator-assessed, confirmed ORR according to RECIST v1.1 in patients with the presence or absence of sarcomatoid features was 67% (95% CI, 9%-99%) and 27% (95% CI, 11%-50%), respectively (Table 3). The investigator-assessed, confirmed ORR according to RECIST v1.1 in patients with baseline tumor PD-L1 expression <1% or ≥1% was 37% (95% CI, 16%-62%) and 20% (95% CI, 1%-72%), respectively (Table 3).

Seven of 28 patients (25%) in the overall cohort experienced intracranial progression; 5 (18%) had only

TABLE 3. Investigator-Assessed Objective Response According to Response Evaluation Criteria in Solid Tumors, Version 1.1, in Response-Evaluable Patients, N = 25

Outcome	Response-Evaluable Patients
Best overall response, no. (%) ^a	
Complete response	0 (0)
Partial response	8 (32)
Stable disease	10 (40)
Progressive disease	6 (24)
Unable to determine	1 (4)
Investigator-assessed confirmed ORR per RECIST v1.1: (95% CI), %	32 (15-54)
Presence of sarcomatoid features, n = 3	67 (9-99)
Absence of sarcomatoid features, n = 22	27 (11-50)
Baseline tumor PD-L1 expression <1%, n = 19 ^b	37 (16-62)
Baseline tumor PD-L1 expression ≥1%, n = 5 ^b	20 (1-72) ^c
Median TTR (range), mo	2.8 (2.4-3.0)
Median DOR (range), mo	24.0 (3.9 to 32.7+)

Abbreviations: +, Censored value; DOR, duration of response; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TTR, time to response.

^aOf the 2 patients with nonclear cell renal cell carcinoma, 1 had unclassified pathology and a best overall response of stable disease, and the other had unclassified pathology but was not evaluable for response.

^bThis was assessed using the PD-L1 IHC 28-8 pharmDx assay (Dako, an Agilent Technologies, Inc. company, Santa Clara, CA).

^cSeven patients in cohort 3 had tumor PD-L1 expression ≥1%.

TABLE 4. Intracranial Progression in All Treated Patients, N = 28

	All Treated Patients: No. (%)
Patients with intracranial progression	7 (25)
Type of progression	
Only intracranial progression	5 (18)
Intracranial and systemic progression ^a	2 (7)
Type of intracranial progression ^b	
Appearance of new lesions	5 (71)
Previously existing irradiated lesions	2 (29)
Intervention for intracranial progression	
Study drug continued ^a	5 (18)
Discontinue treatment within window ^c	1 (4)
Last dose date was before intracranial progression	1 (4)

^aThe 2 patients who had both intracranial progression and systemic progression continued the study drug.

^bPercentages are out of those patients who had intracranial progression.

^cIf the date the decision was made to discontinue treatment occurred within 4 weeks after the intracranial progression date.

intracranial progression, and 2 (7%) had both intracranial and systemic progression (Table 4). Of the 7 patients with intracranial progression, 5 (71%) progressed beyond intracranial progression because of the appearance of new lesions, of whom 3 of 5 patients continued study drug beyond intracranial disease progression. Patient-level descriptions are provided in Supporting Table 5.

The median PFS in all treated patients (N = 28) was 9.0 months (95% CI, 2.9-12.0) (Fig. 1). The median OS (N = 28) was not reached (95% CI, 14.1 months to not estimable) (Fig. 2). The probability of survival was 85.6% (95% CI, 66.0%-94.3%) at 12 months, 67.0% (95% CI, 46.1%-81.3%) at 18 months, and 63.2% (95% CI, 42.4%-78.3%) at 24 months (Fig. 2).

DISCUSSION

The nonrandomized, open-label, multicohort, phase 3b/4 CheckMate 920 clinical trial was designed to evaluate NIVO + IPI in patients who had previously untreated aRCC with clinical features mostly excluded from phase 3 trials. Although prospective trial data evaluating NIVO + IPI in patients with aRCC and brain metastases were limited before CheckMate 920, the combination has shown efficacy in other tumor types. The addition of IPI to NIVO significantly increased the intracranial response in patients who had brain metastases from melanoma or lung cancer in several phase 2 studies.^{23,28} In the current study, the safety profile of this dosing regimen of NIVO + IPI for previously untreated aRCC was as expected, with no new safety signals noted. Few grade 3 and 4

imAEs were reported, and no grade 5 imAEs occurred. Corticosteroid use was consistent with prior experience in patients without CNS involvement, suggesting no increased risk of imAEs requiring corticosteroids for management in this population. Encouraging antitumor activity, OS, and durable responses were observed.

The overall safety profile and incidence of imAEs, including grade 3 and 4 imAEs, in this cohort of patients with brain metastases were generally consistent with observations for NIVO + IPI in patients with previously untreated aRCC in the CM214 trial at a similar minimal length of study follow-up (30 months).¹²

The antitumor activity for most efficacy measures in this study was similar relative to the overall population of patients in CM214 after a comparable length of minimum follow-up.¹² In the current study, the investigator-assessed, confirmed ORR according to RECIST v1.1 was higher for patients with PD-L1 tumor expression <1% versus ≥1%, which may be attributable to the small number (n = 7) of patients with tumor PD-L1 expression ≥1%. The ORR was also higher for patients who had sarcomatoid features compared with patients without sarcomatoid histology, although the small number (n = 3) of patients who had sarcomatoid features limits interpretation. Direct cross-trial comparisons are not possible, and there are several notable differences in the study designs and research settings of CM214 and CheckMate 920, including the exclusion of patients with brain metastases from CM214.¹⁸ The results of the analysis in this cohort of patients suggests that patients with asymptomatic, predominantly pretreated CNS metastases may be biologically similar in their response to immunotherapy to patients with non-CNS disease.

The results from CheckMate 920 add to the limited evidence and relative dearth of prospective or retrospective analyses that have evaluated outcomes in patients with RCC and brain metastases. To our knowledge, this is the first and only phase 3b/4 trial to prospectively evaluate the safety and efficacy of immunotherapy in this population. Currently, 4 phase 2 trials are evaluating immunotherapy in patients with RCC and brain metastases, including sunitinib for untreated brain metastases, cabozantinib for untreated brain metastases (CABRAMET; ClinicalTrials.gov identifier NCT03967522), NIVO monotherapy after failure of angiogenic therapy (GETUG-AFU 26 NIVOREN; ClinicalTrials.gov identifier NCT03013335), and NIVO plus stereotactic radiosurgery (ClinicalTrials.gov identifier NCT02978404).^{21,29-31}

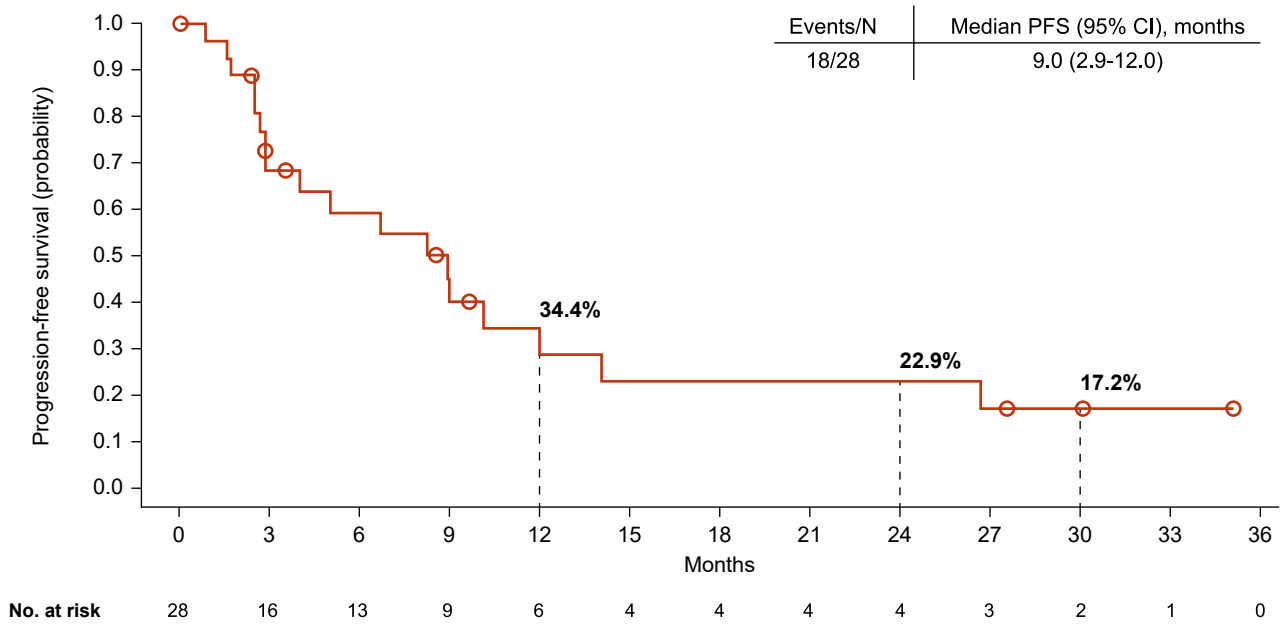


Figure 1. Progression-free survival (PFS) is illustrated according to investigator assessment in all treated patients. CI indicates confidence interval.

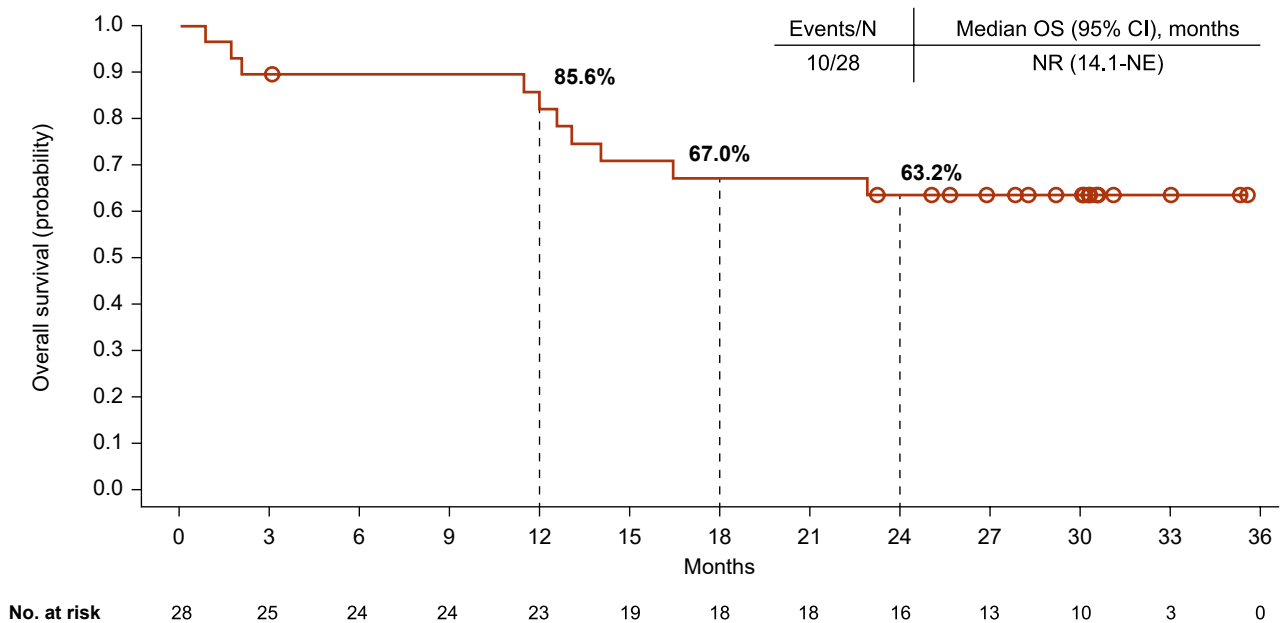


Figure 2. Overall survival (OS) is illustrated in all treated patients. CI indicates confidence interval; NE, not estimable; NR, not reached.

Because of the small number of patients with aRCC and brain metastases included in the current study, efficacy outcomes should be interpreted with caution. Other limitations in CheckMate 920 include the lack of

randomization and of a standard-of-care, active comparator arm; however, the intent of this study is signal-finding.

In summary, the safety profile of the approved dosing regimen of NIVO 3 mg/kg plus IPI 1 mg/kg every 3 weeks

for 4 doses followed by NIVO 480 mg every 4 weeks for patients with previously untreated aRCC and asymptomatic brain metastases was as expected, with no new safety signals identified, suggesting that this combination can be safely administered in this population. Three-quarters of all treated patients were without intracranial progression. CheckMate 920 is the first prospective trial of NIVO + IPI as first-line therapy for patients who have aRCC with metastasis to the brain, a population with a poor prognosis and a high unmet medical need; and, although promising efficacy was observed, further study of NIVO + IPI in untreated brain metastases is needed.

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CONFLICT OF INTEREST DISCLOSURES

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Hamid Enamekhoo and **Scott S. Tykodi**: Conceptualization, investigation, validation, and writing—review and editing. **Mark R. Olsen, Bradley C. Carthon, Alexandra Drakaki, Ivor J. Percent, Ana M. Molina, Daniel C. Cho, Johanna C. Bendell, Lucio N. Gordan, Arash Rezazadeh Kalebasty, Daniel J. George, Thomas E. Hutson,** and **Edward R. Arrowsmith**: Investigation, validation, and writing—review and editing. **Joshua Zhang, Jesus Zoco, and David K. Leung**: Conceptualization, data curation, formal analysis, methodology, project administration, resources, software, supervision, and validation. **Jennifer L. Johansen**: Conceptualization, methodology, validation, and writing—review and editing.

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