Adjuvant Nivolumab for Localized Renal Cell Carcinoma at High Risk of Recurrence After Nephrectomy: Part B of the Randomized, Placebo-Controlled, Phase III CheckMate 914 Trial

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ABSTRACT

PURPOSE CheckMate 914 is a two-part, randomized phase III trial evaluating adjuvant nivolumab plus ipilimumab (part A) or adjuvant nivolumab monotherapy (part B) versus placebo in mutually exclusive populations of patients with localized renal cell carcinoma (RCC) at high risk of postnephrectomy recurrence. Part A showed no disease-free survival (DFS) benefit for adjuvant nivolumab plus ipilimumab versus placebo. We report results from part B.

METHODS Patients were randomly assigned (2:1:1) to nivolumab (240 mg once every 2 weeks for up to 12 doses), placebo, or nivolumab (240 mg once every 2 weeks for up to 12 doses) plus ipilimumab (1 mg/kg once every 6 weeks for up to four doses). The planned treatment duration was 24 weeks (approximately 5.5 months). The primary end point was DFS per blinded independent central review (BICR) for nivolumab versus placebo; safety was a secondary end point.

RESULTS Overall, 825 patients were randomly assigned to nivolumab (n = 411), placebo (n = 208), or nivolumab plus ipilimumab (n = 206). With a median follow-up of 27.0 months (range, 18.0-42.4), the primary end point of improved DFS per BICR with nivolumab versus placebo was not met (hazard ratio [HR], 0.87 [95% CI, 0.62 to 1.21]; $P = .40$); the median DFS was not reached in either arm, and 18-month DFS rates were 78.4% versus 75.4%. The HR for DFS per investigator was 0.80 (95% CI, 0.58 to 1.12; $P = .19$). Grade 3-4 all-cause adverse events (AEs) occurred in 17.2%, 15.0%, and 28.9% of patients with nivolumab, placebo, and nivolumab plus ipilimumab, respectively. Any-grade treatment-related AEs led to discontinuation in 9.6%, 1.0%, and 28.4%, respectively.

CONCLUSION Part B of CheckMate 914 did not meet the primary end point of improved DFS for nivolumab versus placebo in patients with localized RCC at high risk of postnephrectomy recurrence.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Current international guidelines recommend partial or radical nephrectomy as the primary therapeutic approach for patients with localized (stage I-III) clear cell renal cell carcinoma (RCC).[1,2] However, although the postnephrectomy prognosis of patients with stage I tumors is generally favorable, patients with stage II and III tumors have a relatively high risk of disease recurrence.[3-6] Although patients with clear cell RCC at high risk of disease recurrence can currently receive approved adjuvant therapy with pembrolizumab (a PD-1 inhibitor; Europe and the United States) or sunitinib (a small-molecule multikinase inhibitor; United States only),[1,7] there remains a need for additional efficacious and well-tolerated adjuvant options in this setting.

Investigations into the potential benefits of adjuvant therapy for patients with localized RCC have been ongoing for decades, with studies showing generally mixed results. Early trials of adjuvant radiotherapy and cytokines failed to show benefits,[8-11] and those evaluating vaccine-based regimens or multikinase inhibitors (including sunitinib) showed varying

CONTEXT

Key Objective

To determine whether an approximate 5.5-month regimen of adjuvant nivolumab can improve disease-free survival (DFS) versus placebo in a population of patients with localized renal cell carcinoma (RCC) who are at high risk of disease recurrence after nephrectomy.

Knowledge Generated

As was observed in part A of CheckMate 914, where nivolumab plus ipilimumab did not improve DFS versus placebo, part B of the trial showed that nivolumab monotherapy also did not improve DFS. Preliminary results from exploratory subgroup analyses provided insights into possible subpopulations of patients with localized RCC who may benefit from treatment with nivolumab with or without ipilimumab following nephrectomy.

Relevance *(M.A. Carducci)*

CheckMate 914 (parts A and B) is important for its negative results and consistent with results of EA8143 (PROSPER), all demonstrating no DFS benefit with nivolumab alone or in combination with ipilumimab.*

*Relevance section written by *JCO* Associate Editor Michael A. Carducci, MD, FACP, FASCO.

outcomes.[3-5,12,13] Similarly, recent phase III trials investigating adjuvant therapy with immune checkpoint inhibitors have reported inconsistent results. In the KEYNOTE-564 trial, approximately 12 months of adjuvant pembrolizumab showed significant disease-free survival (DFS) and overall survival (OS) benefits versus placebo among patients with an intermediate-to-high risk of disease recurrence or M1 stage with no evidence of disease status, leading to regulatory approvals and updated guideline recommendations.[1,14-16] In contrast, the IMmotion010 trial of approximately 12 months of adjuvant atezolizumab (a PD-L1 inhibitor) versus placebo and the PROSPER RCC trial of perioperative (including 9 months of adjuvant) nivolumab (a PD-1 inhibitor) versus surveillance, both conducted in patients at increased or high risk of postnephrectomy recurrence, showed no significant improvement in DFS.[17,18]

Nivolumab combined with ipilimumab (a cytotoxic T-lymphocyte–associated protein 4 inhibitor) is an established standard of care for untreated patients with advanced RCC,[19,20] and previous studies have demonstrated the efficacy of adjuvant nivolumab in non-RCC tumor types.[21-23] As such, part A of the phase III CheckMate 914 trial (ClinicalTrials.gov identifier: NCT03138512) was designed to evaluate approximately 5.5 months of adjuvant nivolumab plus ipilimumab versus placebo in patients with surgically resected stage II/III clear cell RCC with a high risk of disease recurrence.[24] Part B of CheckMate 914 was later added by protocol amendment and was designed to support part A by (1) allowing evaluation of potential benefits of approximately 5.5 months of adjuvant nivolumab monotherapy versus placebo, albeit with a relatively limited statistical power of 60%, and (2) facilitating a contribution of components analysis (via assessment of both adjuvant nivolumab plus ipilimumab and nivolumab), should the primary end point be met in part A of the trial. As previously reported, after a median follow-up of 37.0 months, the primary end point of improved DFS with adjuvant nivolumab plus ipilimumab versus placebo was not met in part A of CheckMate 914.[24] Here, we report results from part B of the trial, as well as from ad hoc analyses in select patient subgroups of clinical interest, performed using pooled data from parts A and B.

METHODS

Patients

Patient eligibility criteria were the same for parts A and B of CheckMate 914 and have been described previously.[24] In brief, eligible patients had to undergo radical or partial nephrectomy with negative surgical margins 4-12 weeks before random assignment; had predominantly clear cell histology (with or without sarcomatoid features); pathological TNM stage pT2a, grade 3/4 (N0M0), pT2b-T4, any grade (N0M0), or any pT, any grade (N1M0); and no evidence of residual disease or distant metastases (M0) after nephrectomy. Exclusion criteria included autoimmune disease, conditions requiring systemic corticosteroid treatment (>10 mg of prednisone equivalent per day) or other immunosuppressive medication within 14 days before first dose of study drug, and previous systemic RCC therapy. Full inclusion/exclusion criteria are provided in the protocol (online only).

Study Design

In part B of CheckMate 914, patients were randomly assigned 2:1:1 to the nivolumab arm (intravenous [IV] nivolumab 240 mg once every 2 weeks for up to 12 doses plus IV placebo administered at the same frequency as the ipilimumab

infusions), placebo arm (IV placebo infusions administered at the same frequency as the nivolumab and ipilimumab infusions), or nivolumab plus ipilimumab arm (IV nivolumab 240 mg once every 2 weeks for up to 12 doses plus IV ipilimumab 1 mg/kg once every 6 weeks for up to four doses). Random assignment between arms was stratified according to pathological TNM stage (pT2a, grade ≥3 or pT2b, any grade [N0M0] *v* pT3, any grade [N0M0] *v* pT4, any grade [N0M0] or any pT, any grade [N1M0]) and type of nephrectomy (partial *v* radical). Treatments were administered until completion of twelve 2-week cycles (12 nivolumab or equivalent placebo doses; four ipilimumab or equivalent placebo doses), week 36 (extended treatment up to 36 weeks was allowed for dose delays), unacceptable toxicity, disease recurrence (confirmed by blinded independent central review [BICR]), or withdrawal of consent, whichever occurred first.

No dose modifications were allowed. Dose delays were allowed for all study drugs; to maintain blinding, if one drug was delayed or discontinued, both drugs were delayed or discontinued. Discontinuation criteria are detailed in the protocol.

The trial was approved by relevant site-specific institutional review boards or independent ethics committees and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

End Points and Assessments

The primary end point of part B was DFS per BICR in the nivolumab arm versus placebo arm. Secondary end points were OS in the nivolumab arm versus placebo arm, assessment of DFS and OS in the nivolumab plus ipilimumab and nivolumab arms, and safety. DFS was defined as time from random assignment to development of local disease recurrence (ie, recurrence of primary tumor in situ or occurrence of a secondary primary RCC), distant metastasis, or death, whichever occurred first. Details of DFS censoring rules are provided in the Data Supplement (online only). Prespecified exploratory end points included changes in health-related quality of life measures—the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19) and the EQ-5D-3L.

Additional ad hoc analyses were conducted using pooled data from parts A and B of the trial to assess DFS per BICR with immunotherapy (nivolumab plus ipilimumab or nivolumab) and placebo in select patient subgroups of clinical interest, as described in the Data Supplement. Subgroups were selected due to observed trends of DFS favoring both nivolumab plus ipilimumab versus placebo in part A[24,25] and nivolumab versus placebo in part B.

The tumor assessment schedule was the same as described for part A of the trial.[24] Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (v4.0). All-cause and treatment-related AEs are reported within 30 days of last dose of study drug; immune-mediated AEs are reported within 100 days of last dose. Immune-mediated AEs were defined as events consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out.

Statistical Analysis

The sample size for part B of CheckMate 914 was driven by the primary end point comparison of DFS per BICR in the nivolumab arm versus placebo arm. For this end point, approximately 149 DFS events were expected among approximately 600 patients randomly assigned to nivolumab or placebo, providing 60% power to detect a hazard ratio (HR) of 0.68 with an overall type I error of 0.05 (two-sided). The trial was not powered to show differences between treatment arms for secondary end points. The secondary end point of OS was to be tested hierarchically, that is, only if the primary end point of DFS was significant. The secondary end point of assessing DFS and OS in the nivolumab plus ipilimumab and nivolumab arms (ie, the contribution of components analysis) was only applicable if DFS was improved with nivolumab plus ipilimumab versus placebo in part A.

A two-sided log-rank test stratified by the randomization stratification factors was used for between-arm DFS comparisons. A Cox proportional-hazards model with treatment arm as the sole covariate, and stratified by the randomization stratification factors, was used to estimate the HR and CI. Median DFS, corresponding 95% CIs, and DFS rates were estimated using Kaplan-Meier methodology. All statistical analyses were consistent across the main part B analyses and ad hoc pooled analyses, and were done with SAS (v9.4).

RESULTS

Patients

In part B of CheckMate 914, 825 patients were randomly assigned between March 2020 and March 2022 at 151 sites across 24 countries. The intention-to-treat (ITT) population comprised 411 patients randomly assigned to nivolumab, 208 to placebo, and 206 to nivolumab plus ipilimumab. The safety/exposure population comprised 408 patients in the nivolumab arm, 207 in the placebo arm, and 204 in the nivolumab plus ipilimumab arm who received at least one dose of study drug (Fig 1).

Baseline demographic and clinical characteristics for the ITT population were generally similar across treatment arms, albeit the nivolumab arm included a lower proportion of women versus the placebo arm (25.8% *v* 32.2%) and a lower proportion of patients from the United States, Canada, or

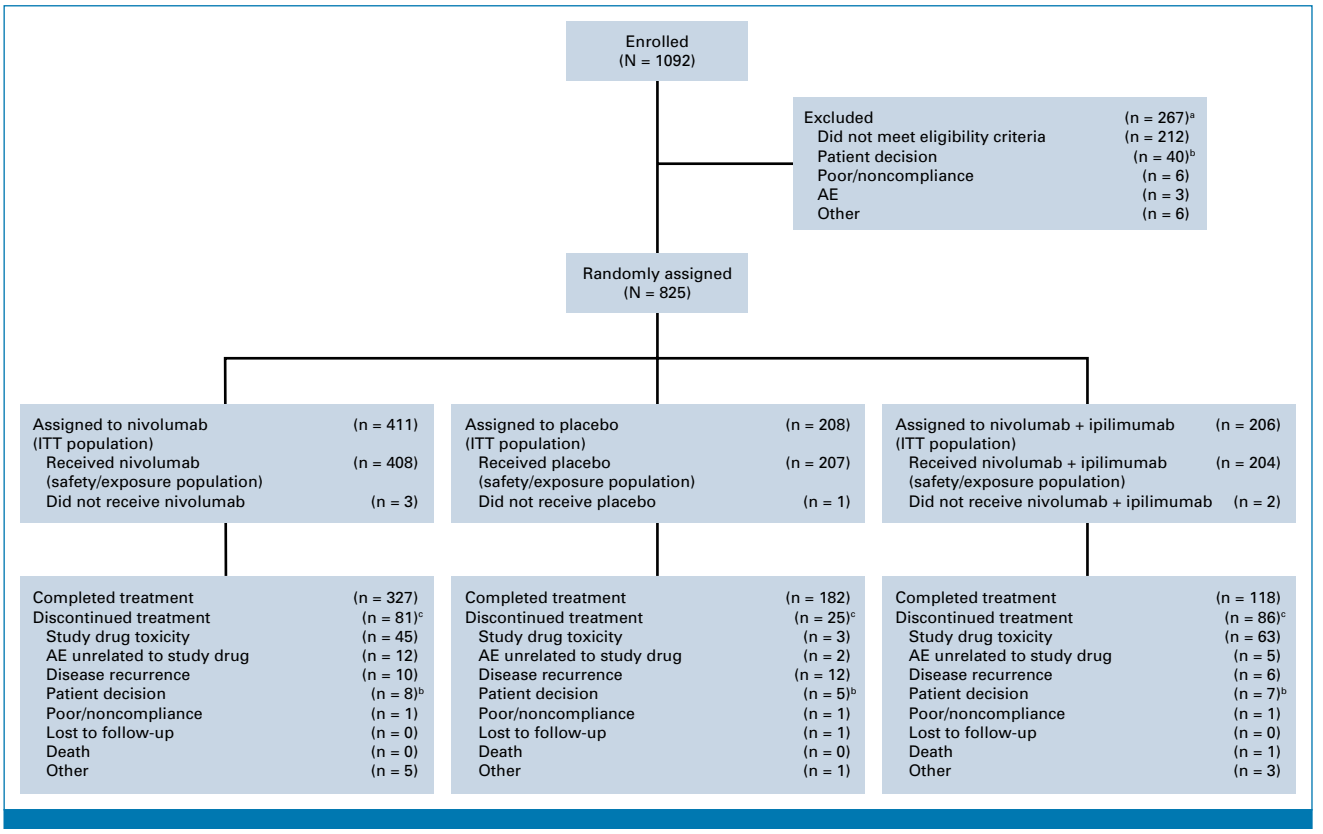

FIG 1. CONSORT diagram. AE, adverse event; ITT, intention-to-treat. [a]Three patients were excluded before random assignment due to COVID-19 disease. [b]Includes patients who withdrew consent or requested to discontinue study treatment. [c]Four patients in the nivolumab arm, two in the placebo arm, and two in the nivolumab plus ipilimumab arm discontinued treatment due to COVID-19 disease.

Europe versus the nivolumab plus ipilimumab arm (54.7% *v* 60.2%; Table 1).

The proportion of patients in the ITT population receiving at least one subsequent systemic anticancer therapy was 13.1% in the nivolumab arm, 19.7% in the placebo arm, and 13.6% in the nivolumab plus ipilimumab arm (Data Supplement, Table S1). The most common subsequent therapies were VEGF-targeted therapies in the nivolumab (11.2%) and nivolumab plus ipilimumab (12.6%) arms and anti-PD-1/PD-L1 antibodies in the placebo arm (13.9%; Data Supplement, Table S1).

Efficacy

At clinical data cutoff (September 28, 2023), the median (range) duration of follow-up for the ITT population was 27.0 (18.0-42.4) months. In the primary end point analysis, the median DFS per BICR was not reached with either nivolumab or placebo, and there was no statistically significant reduction in risk of disease recurrence or death with active treatment (HR, 0.87 [95% CI, 0.62 to 1.21]; P = .40; Fig 2); 18-month DFS rates were 78.4% with nivolumab versus 75.4% with placebo. Corresponding median DFS per investigator was also not reached with either nivolumab or placebo, and there was no statistically significant risk reduction with active treatment (HR, 0.80 [95% CI, 0.58 to 1.12]; P = .19; Data Supplement, Fig S1); 18-month DFS rates were 81.1% with nivolumab versus 75.0% with placebo.

In prespecified exploratory analyses of DFS per BICR in subgroups based on stratification factors and other select characteristics, there were no differences between nivolumab and placebo for most subgroups (Fig 3). However, DFS favored nivolumab over placebo in a subgroup of patients with hemoglobin below the lower limit of normal (HR, 0.49 [95% CI, 0.25 to 0.95]), and there was a trend toward DFS favoring nivolumab over placebo in subgroups of patients with sarcomatoid features (HR, 0.42 [95% CI, 0.17 to 1.07]), PD-L1 expression ≥1% (HR, 0.53 [95% CI, 0.22 to 1.29]), and pT4, any grade (N0M0) or any pT, any grade (N1M0) staging (HR, 0.46 [95% CI, 0.15 to 1.43]; Fig 3).

At clinical data cutoff, only 35 of the 825 patients in the ITT population had died (19 of 411 in the nivolumab arm, eight of 208 in the placebo arm, and eight of 206 in the nivolumab plus ipilimumab arm). Due to the immaturity of these OS data, the median OS was not estimable for any of the treatment arms.

TABLE 1. Baseline Demographic and Clinical Characteristics (ITT population)

Characteristic	Nivolumab (n = 411)	Placebo (n = 208)	Nivolumab + Ipilimumab (n = 206)
Age, years, median (range)	59 (25-86)	59 (25-80)	60 (29-81)
<65, No. (%)	279 (67.9)	137 (65.9)	132 (64.1)
≥65, No. (%)	132 (32.1)	71 (34.1)	74 (35.9)
Sex, No. (%)			
Male	305 (74.2)	141 (67.8)	147 (71.4)
Female	106 (25.8)	67 (32.2)	59 (28.6)
Race, No. (%)			
White	331 (80.5)	169 (81.3)	173 (84.0)
Asian	50 (12.2)	26 (12.5)	20 (9.7)
American Indian or Alaska native	14 (3.4)	3 (1.4)	5 (2.4)
Black or African American	4 (1.0)	1 (0.5)	0
Other	9 (2.2)	6 (2.9)	5 (2.4)
Not reported	3 (0.7)	3 (1.4)	3 (1.5)
Region, No. (%)			
United States/Canada/W. Europe/N. Europe	225 (54.7)	111 (53.4)	124 (60.2)
Rest of the world	186 (45.3)	97 (46.6)	82 (39.8)
ECOG performance status, No. (%)			
0	360 (87.6)	185 (88.9)	183 (88.8)
1	51 (12.4)	23 (11.1)	23 (11.2)
Type of nephrectomy, No. (%)[a]			
Radical	383 (93.2)	193 (92.8)	193 (93.7)
Partial	28 (6.8)	15 (7.2)	13 (6.3)
Pathological TNM staging, No. (%)[a]			
pT2a, G3 or G4 (N0M0)/pT2b, G any (N0M0)	47 (11.4)	24 (11.5)	24 (11.7)
pT3, G any (N0M0)	337 (82.0)	169 (81.3)	168 (81.6)
pT4, G any (N0M0)/pT any, G any (N1M0)	27 (6.6)	15 (7.2)	14 (6.8)
Disease risk category, No. (%)[b,c]			
High	252 (61.3)	129 (62.0)	116 (56.3)
Moderate	158 (38.4)	79 (38.0)	88 (42.7)
Other	1 (0.2)	0	2 (1.0)
Fuhrman grade, No. (%)[b]			
Grade 1-2	136 (33.1)	68 (32.7)	75 (36.4)
Grade 2	127 (30.9)	64 (30.8)	67 (32.5)
Grade 3	187 (45.5)	86 (41.3)	86 (41.7)
Grade 4	88 (21.4)	54 (26.0)	45 (21.8)
Sarcomatoid features, No. (%)			
Yes	32 (7.8)	14 (6.7)	10 (4.9)
No	379 (92.2)	194 (93.3)	196 (95.1)
PD-L1 expression, No. (%)[d]			
≥1%	47 (11.4)	16 (7.7)	22 (10.7)
<1%	322 (78.3)	174 (83.7)	167 (81.1)
Not evaluable	28 (6.8)	12 (5.8)	10 (4.9)
Not reported	14 (3.4)	6 (2.9)	7 (3.4)
Time from initial disease diagnosis to random assignment, No. (%)			
<1 year	411 (100.0)	208 (100.0)	205 (99.5)
LDH level, No. (%)			
≤1.5 × ULN	409 (99.5)	207 (99.5)	205 (99.5)
>1.5 × ULN	1 (0.2)	0	0
Not reported	1 (0.2)	1 (0.5)	1 (0.5)

(continued on following page)

TABLE 1. Baseline Demographic and Clinical Characteristics (ITT population) (continued)

Characteristic	Nivolumab (n = 411)	Placebo (n = 208)	Nivolumab + Ipilimumab (n = 206)
Hemoglobin, No. (%)			
<LLN	98 (23.8)	40 (19.2)	53 (25.7)
≥LLN	313 (76.2)	167 (80.3)	152 (73.8)
Not reported	0	1 (0.5)	1 (0.5)
Corrected calcium, No. (%)			
≤10 mg/dL	384 (93.4)	192 (92.3)	194 (94.2)
>10 mg/dL	19 (4.6)	10 (4.8)	8 (3.9)
Not reported	8 (1.9)	6 (2.9)	4 (1.9)
Alkaline phosphatase, No. (%)			
<ULN	371 (90.3)	186 (89.4)	183 (88.8)
≥ULN	38 (9.2)	21 (10.1)	22 (10.7)
Not reported	2 (0.5)	1 (0.5)	1 (0.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; G, grade; ITT, intention-to-treat; LDH, lactate dehydrogenase; LLN, lower limit of normal; ULN, upper limit of normal.
[a]Data were determined from an interactive response system.
[b]Data were determined from case report forms.
[c]Disease risk categories were defined as follows: high risk (pT3, G3 or G4 [N0M0]; pT4, G any [N0M0]; pT any, G any [N1M0]) and moderate risk (pT2a, G3 or G4 [N0M0]; pT2b, G any [N0M0]; pT3, G1 and G2 [N0M0]).
[d]PD-L1 testing was performed locally (Labcorp, Burlington, NC) using a validated tumor proportion score–based PD-L1 immunohistochemical assay (Dako PD-L1 IHC 28-8 pharmDx).

Because the primary end point of improved DFS with nivolumab plus ipilimumab versus placebo was not met in part A of the trial,[24] a contribution of components analysis was no longer relevant. DFS outcomes per BICR for the nivolumab plus ipilimumab arm of part B are shown in the Data Supplement (Fig S2), with the placebo arm as

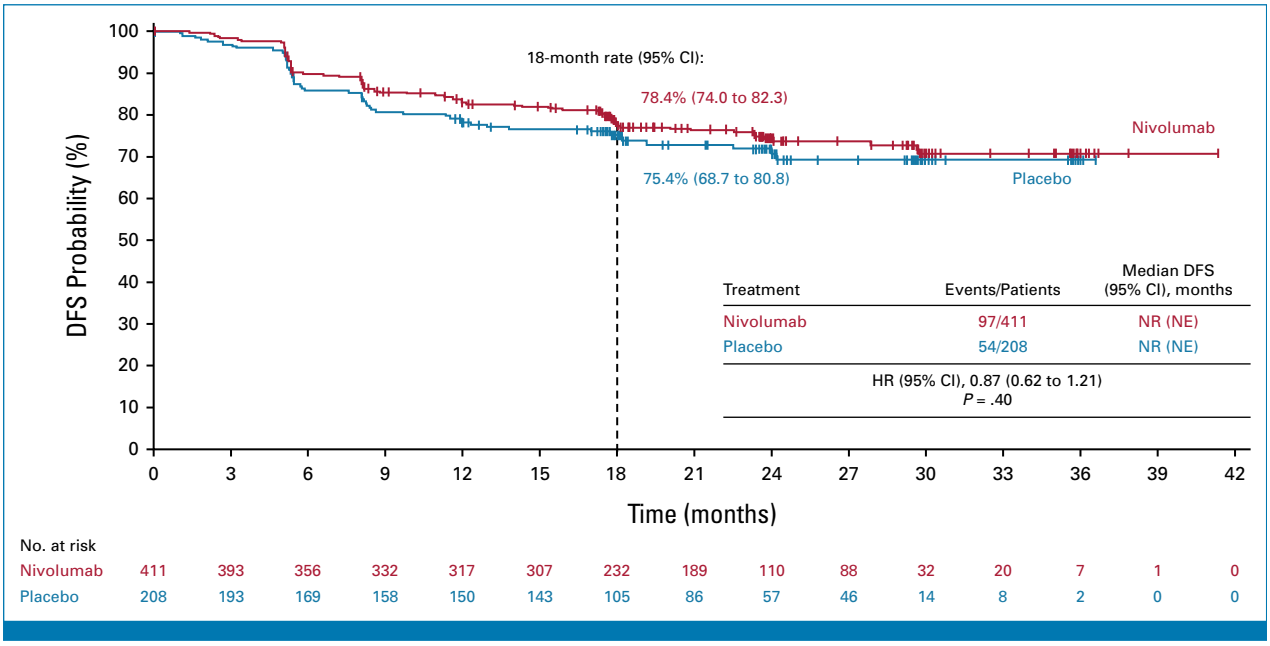

FIG 2. DFS per BICR in the overall ITT population for nivolumab versus placebo. DFS was estimated in all randomly assigned patients and defined as the time from random assignment to the development of local disease recurrence, distant metastasis, or death, whichever came first. BICR, blinded independent central review; DFS, disease-free survival; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; NR, not reached.

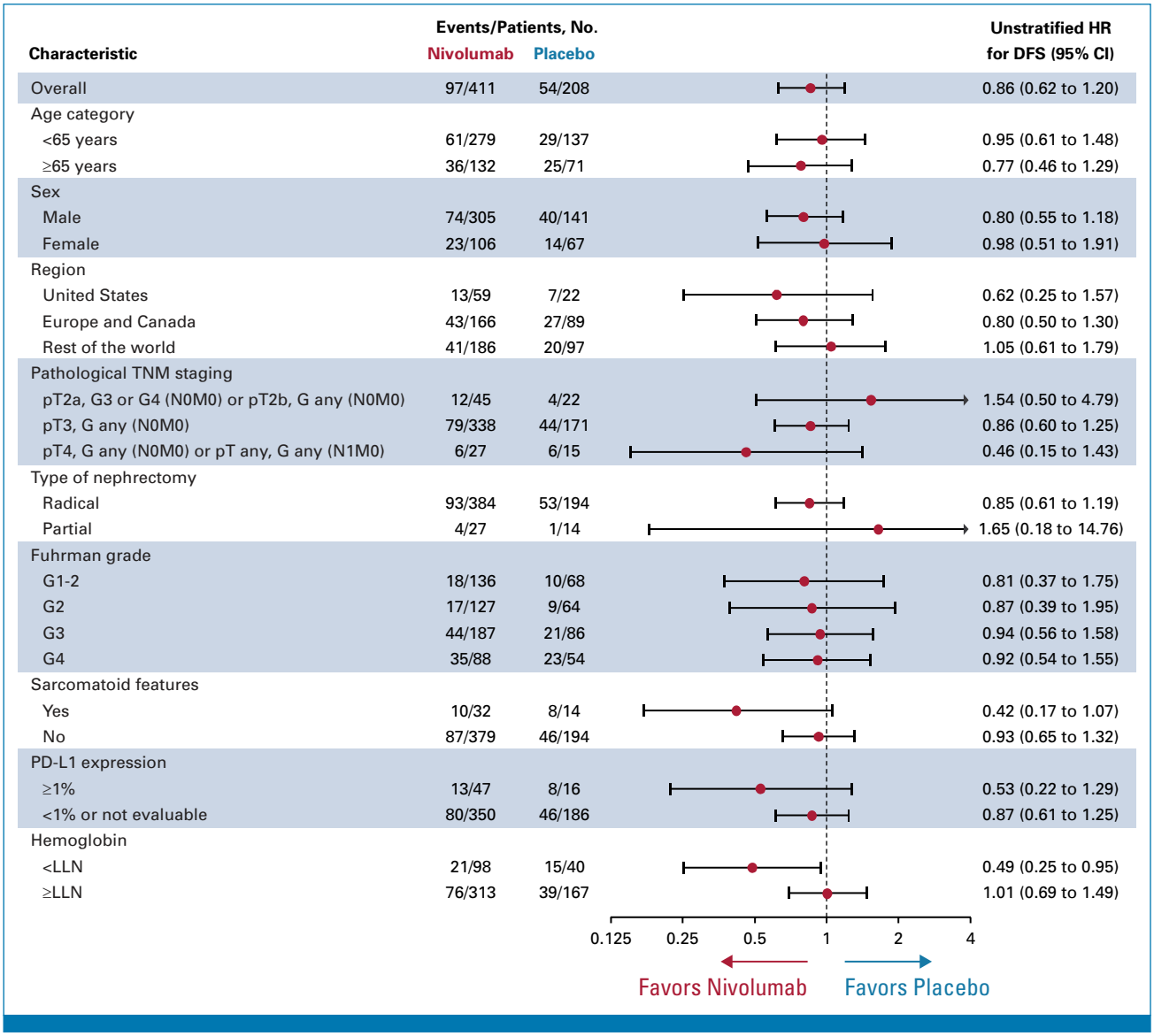

FIG 3. DFS per BICR in key subgroups for nivolumab versus placebo. DFS was estimated in all randomly assigned patients and defined as the time from random assignment to the development of local disease recurrence, distant metastasis, or death, whichever came first. The influence of demographic and baseline clinical characteristics on DFS among randomly assigned patients was assessed via exploratory subgroup analyses. HRs were not computed for subgroups with <11 patients per treatment arm (except for age, region, and sex). The statistical analysis plan prespecified that subgroup analyses for stratification factors (TNM staging and type of nephrectomy) would be based on case report form data. BICR, blinded independent central review; DFS, disease-free survival; HR, hazard ratio; ITT, intention-to-treat; LLN, lower limit of normal.

reference; the median DFS per BICR was not reached with nivolumab plus ipilimumab, and the 18-month DFS rate was 72.3%.

Safety

Treatment exposure is summarized in the Data Supplement (Table S2). The median treatment duration was 5.1 months in all three arms, with an IQR of 5.1-5.3 in the nivolumab arm, 5.1-5.2 in the placebo arm, and 2.9-5.2 in the nivolumab plus ipilimumab arm; the respective median number of received doses was 12 (IQR, 12-12), 12 (IQR, 12-12), and 12 (IQR, 6.5-12) for nivolumab or equivalent placebo and 4 (IQR, 4-4), 4 (IQR, 4-4), and 4 (IQR, 2.5-4) for ipilimumab or equivalent placebo. The proportion of patients requiring at least one nivolumab or equivalent placebo dose delay was 28.9% in the nivolumab arm, 27.5% in the placebo arm, and 36.3% in the nivolumab plus ipilimumab arm. The proportion of patients with a relative nivolumab dose intensity ≥90% was 90.4% in the nivolumab arm and 81.4% in the nivolumab plus ipilimumab arm (Data Supplement, Table S2).

In the safety/exposure population, the incidence of any-grade all-cause AEs was 88.7% with nivolumab, 87.9%

TABLE 2. All-Cause AEs and Immune-Mediated AEs (safety/exposure population)

	Nivolumab (n = 408), No. (%)		Placebo (n = 207), No. (%)		Nivolumab + Ipilimumab (n = 204), No. (%)	
AE[a]	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
All-cause AEs						
Patients with any event	292 (71.6)	70 (17.2)	150 (72.5)	31 (15.0)[b]	133 (65.2)	59 (28.9)[c]
Pruritus	98 (24.0)	2 (0.5)	33 (15.9)	0	79 (38.7)	1 (0.5)
Fatigue	97 (23.8)	0	47 (22.7)	0	58 (28.4)	0
Diarrhea	71 (17.4)	2 (0.5)	33 (15.9)	1 (0.5)	59 (28.9)	0
Arthralgia	54 (13.2)	0	34 (16.4)	0	31 (15.2)	1 (0.5)
Headache	49 (12.0)	1 (0.2)	25 (12.1)	0	30 (14.7)	0
Nausea	48 (11.8)	0	21 (10.1)	0	30 (14.7)	0
Hyperthyroidism	47 (11.5)	0	2 (1.0)	0	33 (16.2)	0
Hypothyroidism	47 (11.5)	0	6 (2.9)	0	45 (22.1)	0
Asthenia	44 (10.8)	2 (0.5)	23 (11.1)	0	22 (10.8)	1 (0.5)
Rash	45 (11.0)	1 (0.2)	15 (7.2)	0	36 (17.6)	1 (0.5)
Back pain	42 (10.3)	0	22 (10.6)	2 (1.0)	15 (7.4)	0
Increased blood creatinine	40 (9.8)	0	19 (9.2)	0	33 (16.2)	0
Myalgia	38 (9.3)	0	16 (7.7)	0	25 (12.3)	0
Increased ALT	23 (5.6)	3 (0.7)	5 (2.4)	1 (0.5)	20 (9.8)	3 (1.5)
Pyrexia	13 (3.2)	0	6 (2.9)	0	22 (10.8)	0
Adrenal insufficiency	6 (1.5)	2 (0.5)	2 (1.0)	0	14 (6.9)	8 (3.9)
Event leading to study treatment discontinuation[d]	24 (5.9)	25 (6.1)	1 (0.5)	4 (1.9)[b]	27 (13.2)	36 (17.6)

	Nivolumab (n = 408), No. (%)		Placebo (n = 207), No. (%)		Nivolumab + Ipilimumab (n = 204), No. (%)	
Immune-Mediated AE[e]	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Category						
Hypothyroidism	52 (12.7)	0	6 (2.9)	0	49 (24.0)	0
Hyperthyroidism	45 (11.0)	0	2 (1.0)	0	30 (14.7)	0
Rash	27 (6.6)	3 (0.7)	5 (2.4)	0	22 (10.8)	4 (2.0)
Adrenal insufficiency	10 (2.5)	3 (0.7)	2 (1.0)	0	14 (6.9)	10 (4.9)
Thyroiditis	10 (2.5)	0	0	0	9 (4.4)	0
Diarrhea/colitis	9 (2.2)	1 (0.2)	0	1 (0.5)	8 (3.9)	6 (2.9)
Hepatitis	3 (0.7)	5 (1.2)	1 (0.5)	3 (1.4)	7 (3.4)	4 (2.0)
Pneumonitis	4 (1.0)	2 (0.5)	0	0	0	2 (1.0)
Diabetes mellitus	1 (0.2)	3 (0.7)	1 (0.5)	0	1 (0.5)	1 (0.5)
Nephritis/renal dysfunction	1 (0.2)	2 (0.5)	0	0	4 (2.0)	1 (0.5)
Hypersensitivity	2 (0.5)	0	0	0	0	1 (0.5)
Hypophysitis	1 (0.2)	0	0	0	9 (4.4)	5 (2.5)

Abbreviation: AE, adverse event.

[a]Includes all-cause AEs reported between first dose and 30 days after last dose of study drug. Individual AEs are listed in descending order of frequency in the nivolumab arm and represent events that were reported at any grade in ≥10% of patients in any treatment arm.

[b]A grade 5 all-cause AE of disease recurrence was reported in one patient in the placebo arm, which led to treatment discontinuation.

[c]A grade 5 all-cause AE of sudden death was reported in one patient in the nivolumab plus ipilimumab arm.

[d]Includes all-cause AEs reported between first dose and 30 days after last dose of study drug and leading to discontinuation.

[e]Includes all immune-mediated AEs reported between first dose and 100 days after last dose of study drug. Immune-mediated AEs are events consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out. Endocrine events (hypothyroidism, hyperthyroidism, adrenal insufficiency, thyroiditis, diabetes mellitus, and hypophysitis) were considered immune-mediated regardless of use of immune-modulating medication. Nonendocrine events (rash, diarrhea/colitis, hepatitis, pneumonitis, nephritis/renal dysfunction, and hypersensitivity) were considered immune-mediated if they were associated with initiation of immune-modulating medication.

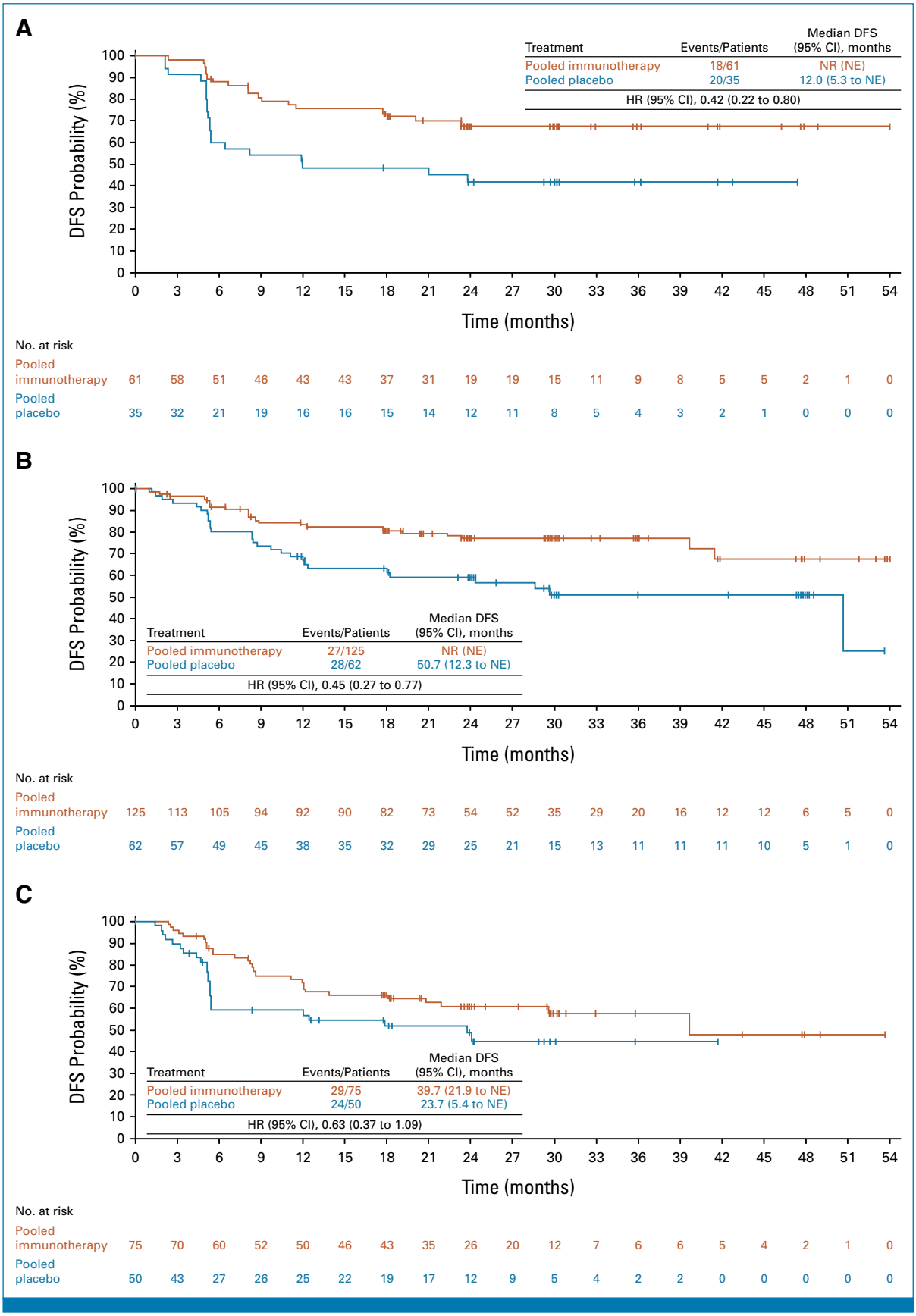

FIG 4. DFS per BICR in pooled subgroups of interest with sarcomatoid features (A), PD-L1 expression ≥1% (B), or pT4, any grade (N0M0) or any pT, any grade (N1M0) staging (C). Ad hoc analyses were conducted using pooled data from parts A and B of the study to compare DFS per BICR with immunotherapy (nivolumab plus ipilimumab in part A and (continued on following page)

FIG 4. (Continued). either nivolumab or nivolumab plus ipilimumab in part B) versus placebo (from parts A and B) in select subgroups of patients. DFS was estimated in all randomly assigned patients and defined as the time from random assignment to the development of local disease recurrence, distant metastasis, or death, whichever came first. PD-L1 testing was performed locally (Labcorp) using a validated tumor proportion score–based PD-L1 immunohistochemical assay (Dako PD-L1 IHC 28-8 pharmDx). BICR, blinded independent central review; DFS, disease-free survival; HR, hazard ratio; NE, not estimable; NR, not reached.

with placebo, and 94.6% with nivolumab plus ipilimumab; the incidence of grade 3-4 all-cause events was 17.2%, 15.0%, and 28.9%, respectively (Table 2). Treatment-related AEs are summarized in the Data Supplement (Table S3). Treatment-related AEs of any grade led to discontinuation in 9.6% of patients with nivolumab, 1.0% of patients with placebo, and 28.4% of patients with nivolumab plus ipilimumab (Data Supplement, Table S3). The most common treatment-related AEs of any grade leading to discontinuation were hyperthyroidism and pneumonitis (1.0% each) with nivolumab, and adrenal insufficiency (4.4%) and hypophysitis (2.9%) with nivolumab plus ipilimumab. Immune-mediated AEs are summarized in Table 2. High-dose corticosteroids (≥40 mg of prednisone per day or equivalent) to manage immune-mediated AEs were received for any duration by 5.9% of patients in the nivolumab arm, 1.9% of patients in the placebo arm, and 19.1% of patients in the nivolumab plus ipilimumab arm; respective proportions receiving high-dose corticosteroids for ≥14 days were 3.2%, 1.0%, and 10.3% and for ≥30 days were 2.0%, 0.5%, and 4.9%. In total, 4.7% of patients in the nivolumab arm, 3.9% of patients in the placebo arm, and 3.9% of patients in the nivolumab plus ipilimumab arm died; no deaths were attributed to study drug toxicity.

Health-Related Quality of Life

Mean changes from baseline through week 23 (all declines) for the FKSI-19 total and disease-related symptom subscale scores and for the EQ-5D-3L utility index were relatively comparable across the nivolumab and placebo arms and did not reach respective meaningful change thresholds (Data Supplement, Figs S3 and S4). Mean changes from baseline through week 23 for the EQ-5D-3L visual analog scale (increases) were similar with nivolumab and placebo and did not reach the meaningful change threshold (Data Supplement, Fig S4).

Pooled Analyses

In ad hoc pooled analyses conducted across parts A and B of CheckMate 914 in patient subgroups of interest, DFS favored treatment with nivolumab with or without ipilimumab over placebo in patients with sarcomatoid features (HR, 0.42 [95% CI, 0.22 to 0.80]; Fig 4A) and PD-L1 expression ≥1% (HR, 0.45 [95% CI, 0.27 to 0.77]; Fig 4B). In the pooled subgroup of patients with pT4, any grade (N0M0) or any pT, any grade (N1M0) staging, there was a trend toward DFS favoring nivolumab with or without ipilimumab over placebo (HR, 0.63 [95% CI, 0.37 to 1.09]; Fig 4C).

DISCUSSION

In part B of the phase III CheckMate 914 trial, the primary end point of improved DFS per BICR for an approximate 5.5-month regimen of nivolumab versus placebo was not met. Safety of nivolumab in the localized RCC patient population was as anticipated and appeared aligned with the published profile in patients with advanced RCC.[26,27] These results, along with those from part A of the trial,[24] do not support use of nivolumab, alone or combined with ipilimumab, as adjuvant treatment for this population of patients with localized RCC at high risk of postnephrectomy disease recurrence.

Potential reasons for differing outcomes between part A of CheckMate 914, showing no improvement in DFS with adjuvant nivolumab plus ipilimumab, and KEYNOTE-564, showing improved DFS and OS with adjuvant pembrolizumab,[14,16] have been discussed previously in the reporting of part A.[24] Many of the suggested reasons, including those related to different screening methods, patient populations, stratification factors, and end points,[24] would also apply to part B of the trial. Furthermore, the expected treatment duration in both parts A and B of CheckMate 914 was 24 weeks (or approximately 5.5 months) with actual median durations of 5.1 months in all active treatment arms, whereas the planned treatment duration in KEYNOTE-564 was 51 weeks (or approximately 12 months) with an actual median duration of 11.1 months in the pembrolizumab arm.[14] Results from part B also appear to lend support to the hypothesis that the lack of clinical activity seen with adjuvant nivolumab plus ipilimumab in part A might have resulted from suboptimal drug exposure due to early tolerability-related discontinuations in the localized RCC patient population.[24,25] In part A, 43% of patients did not complete their nivolumab plus ipilimumab treatment, and overall, 33% discontinued nivolumab plus ipilimumab due to study drug toxicity[24]; in part B, 42% of patients did not complete nivolumab plus ipilimumab treatment, and overall, 31% discontinued nivolumab plus ipilimumab due to study drug toxicity. Evidence from previous studies suggests that patients receiving adjuvant therapy may be less tolerant of treatment-related AEs than patients receiving the same therapy for advanced disease, increasing the proportion discontinuing treatment due to an AE in the earlier setting.[28]

Published data from part A,[24,25] along with results reported here, suggest that certain clinical or tumor-specific characteristics favor or show a trend toward favoring a DFS benefit with adjuvant nivolumab plus ipilimumab

(sarcomatoid features and more advanced pathological TNM staging or Fuhrman grading) and/or nivolumab (sarcomatoid features, higher PD-L1 expression, more advanced pathological TNM staging, and low baseline hemoglobin) over placebo. Although these represent preliminary results from exploratory analyses, they provide insights into patient subpopulations who could potentially benefit from treatment with nivolumab with or without ipilimumab. Larger prospective studies would be required to validate these observations.

General limitations of the CheckMate 914 trial related to methods of population selection and overlap with the COVID-19 pandemic have been discussed previously.[24] In addition, the results from part B should be interpreted in consideration of the relatively limited statistical power for the primary end point, meaning that there was only a 60% probability of detecting an effect if present (ie, improved DFS with nivolumab *v* placebo). A higher statistical power was deemed unnecessary for part B since it was not designed as a standalone study of nivolumab versus placebo, but was intended to support part A on the basis of the hypothesis that nivolumab plus ipilimumab would show a significant DFS benefit over placebo in that part of the trial.

In conclusion, adjuvant nivolumab did not improve DFS versus placebo in this population of patients with localized RCC at high risk of postnephrectomy recurrence. Preliminary evidence of DFS benefits with nivolumab, with or without ipilimumab, in patient subpopulations with certain clinical or tumor-specific characteristics warrants further investigation.

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Stock and Other Ownership Interests: MSD, Bristol Myers Squibb, AstraZeneca, Genmab, Bicycle Therapeutics
Honoraria: Bristol Myers Squibb, Pfizer, Ipsen, Eisai, MSD Oncology, Merck Serono, AstraZeneca, Janssen-Cilag, Advanced Accelerator Applications/Novartis, Apogepha, Ono Pharmaceutical, Astellas Pharma, Amgen
Consulting or Advisory Role: Bristol Myers Squibb, Pfizer, Novartis, MSD Oncology, Ipsen, Janssen-Cilag, Eisai, Debiopharm Group, PCI Biotech, Gilead Sciences, Cureteq, Oncorena, Synthekine
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Travel, Accommodations, Expenses: Pfizer, AstraZeneca, Janssen, Merck Serono, Ipsen

No other potential conflicts of interest were reported.