original reports

Optimized Management of Nivolumab and Ipilimumab in Advanced Renal Cell Carcinoma: A Response-Based Phase II Study (OMNIVORE)

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abstract

PURPOSE In this phase II response-adaptive trial, we investigated the rational application of immune checkpoint blockade in renal cell carcinoma (RCC; ClinicalTrials.gov identifier: NCT03203473).

METHODS We enrolled patients with metastatic RCC with no prior checkpoint inhibitor exposure. All patients received nivolumab alone with subsequent arm allocation based on response. Patients with a confirmed partial response (PR) or complete response (CR) within 6 months discontinued nivolumab and were observed (arm A). Patients with stable disease or progressive disease (PD) after no more than 6 months of nivolumab received two doses of ipilimumab (arm B). The primary endpoints were the proportion of patients with PR/CR at 1 year after nivolumab discontinuation (arm A) and proportion of nivolumab nonresponders who converted to PR/CR after ipilimumab (arm B).

RESULTS Overall, 83 patients initiated treatment, of whom 96% had clear-cell histology, 51% were treatment naïve, and 67% had intermediate/poor-risk disease. Median follow-up was 19.5 months. Within 6 months, induction nivolumab resulted in a confirmed PR in 12% of patients (n = 10). Fourteen patients were not allocated to a study arm (seven because of toxicity, seven because of PD). Twelve patients (14%) were allocated to arm A and discontinued nivolumab, of whom five (42%; 90% CI, 18% to 68%) remained off nivolumab at ≥ 1 year. Of 57 patients (69%) allocated to arm B, two patients converted to a confirmed PR (4%; 90% CI, 1% to 11%), and no CRs were observed.

CONCLUSION In this study, nivolumab followed by two doses of ipilimumab resulted in no CRs and a low PR/CR conversion. The number of patients evaluated for nivolumab discontinuation was too small to assess the value of this approach. Currently, our data do not support a response-adaptive strategy for checkpoint blockade in advanced RCC.

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INTRODUCTION

The efficacy of immune checkpoint inhibitors has dramatically revolutionized the treatment paradigm for patients with advanced renal cell carcinoma (RCC). The phase III CheckMate-025 trial (ClinicalTrials.gov identifier: NCT01668784) demonstrated the efficacy of nivolumab, a programmed cell death-protein 1 (PD-1) inhibitor, in patients with advanced RCC having received prior vascular endothelial growth factor (VEGF) targeted therapy.[1] In the frontline setting, the phase III CheckMate-214 study (ClinicalTrials.gov identifier: NCT02231749) evaluated the role of combination nivolumab and ipilimumab, a cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor, compared with sunitinib.[2] The immunotherapy combination resulted in improved objective responses (39%), including 11% of patients experiencing a complete response (CR) and prolonged overall survival.[3] Currently, frontline treatment options for patients with advanced RCC include immunotherapy combinations of either nivolumab plus ipilimumab,[2] pembrolizumab plus axitinib,[4] or avelumab plus axitinib,[4] and in some scenarios, single-agent VEGF inhibition.

Despite the marked efficacy observed with immune checkpoint blockade, immune-related adverse events (irAEs) are common and can be life-threatening.[5] Unlike adverse events with conventional VEGF targeted therapy, which have a predictable dose-dependent pattern and tend to be reversible, irAEs tend to be variable in onset, presentation, and severity, often require steroids and other immunosuppressive agents for management, and may not be easily reversible.[2] With nivolumab monotherapy, grade 3-4 treatment-related adverse events (TRAEs) were observed in 21% of patients, with 8% discontinuing treatment because of toxicity.[6] With combination nivolumab and ipilimumab, 47% of patients experienced grade 3-4 TRAEs, with one in five patients requiring treatment discontinuation.[3]

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Is it possible to rationally escalate or discontinue treatment with immune checkpoint blockade in patients with metastatic renal cell carcinoma?

Knowledge Generated

Nivolumab followed the addition of two doses of ipilimumab in patients without an objective response to nivolumab monotherapy results in no complete responses and a low response conversion rate. Patients with a complete or partial response to nivolumab monotherapy were eligible to discontinue treatment; however, the number of patients evaluable for maintenance of response after nivolumab discontinuation was too small to assess the value of this approach.

Relevance

A response-based adaptive strategy for nivolumab and ipilimumab is currently not recommended, and upfront dual checkpoint blockade is suggested in patients eligible to receive this treatment.

Immune checkpoint inhibitors, which engage T cells with inherent capacity for memory, have caused us to redefine traditional clinical trial endpoints. Treatment-free survival characterizes antitumor activity and toxicity of the period after cessation of immunotherapy treatment. In patients who discontinued treatment in the CheckMate-214 trial, treatment-free survival was 21% at 24 months since treatment discontinuation, suggesting that a subset of patients may have a durable time off therapy after treatment discontinuation.[7]

As we optimize therapeutic paradigms for patients with advanced RCC, we questioned whether benefits could be maintained with less intensive treatment. Additionally, at the time our study was launched, there remained uncertainty about the benefit of adding ipilimumab to nivolumab in the frontline setting, given the lack of data on frontline nivolumab. Our trial was designed to shed light on these questions. We specifically hypothesized that an adaptive strategy of treatment intensification and discontinuation based on response would maximize efficacy and limit toxicity for patients with metastatic RCC. We thus designed a multicenter, phase II, response-adaptive trial to investigate the sequential addition of ipilimumab to nivolumab nonresponders and discontinuation of nivolumab in responding patients.

METHODS

Patient Population

This study enrolled patients with histologically confirmed advanced RCC of any histologic subtype. Advanced disease was defined as unresectable, locally recurrent, or metastatic by American Joint Committee on Cancer 7th edition staging. Patients could have received prior therapy, excluding PD-1 pathway or CTLA-4 inhibitors. Other key inclusion criteria included presence of measurable disease per RECIST version 1.1,[8] Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2, and adequate organ function. Patients with a history of autoimmune disease requiring $\geq$ 10 mg per day of prednisone or equivalent were excluded. The study was approved by the institutional review board at each institution. All patients provided written informed consent.

Study Design

This was a phase II adaptive trial (Appendix Fig A1, online only). Before therapy initiation, patients underwent a baseline tumor biopsy unless not medically feasible. All eligible patients initially received induction nivolumab with subsequent arm allocation based on RECIST version 1.1 response within 6 months of treatment initiation.[8] Nivolumab was administered at 240 mg intravenously every 2 weeks until the protocol was amended, converting nivolumab monotherapy dosing to 480 mg intravenously every 4 weeks. Patients underwent imaging assessments at 8, 16, and 24 weeks. Patients with a partial response (PR) or CR within 6 months of treatment discontinued nivolumab and were observed (arm A). Response confirmation was required before arm allocation. Arm A patients reinitiated nivolumab if they developed progressive disease (PD); two doses of ipilimumab were added to nivolumab if PD persisted or recurred in arm A patients. Once patients were allocated to arm A, they remained in arm A for all analyses. Patients with confirmed stable disease (SD) or PD after a minimum of 2 but no more than 6 months of nivolumab received two doses of ipilimumab with nivolumab continuation (arm B). In combination therapy, patients received nivolumab 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for two doses. Dose modifications were not permitted; however, dose delays were allowed. After arm allocation, arm A patients underwent imaging assessments every 8 weeks, and arm B patients underwent imaging after the first 12 weeks and then every 8 weeks.

Primary and Secondary Endpoints

The primary endpoints were the proportion of patients with durable CR/PR at 1 year after nivolumab discontinuation (arm A) and proportion with SD/PD receiving nivolumab who converted to PR/CR after the addition of ipilimumab (arm B). Secondary endpoints included overall survival, treatment-free interval, duration of disease control, progression-free survival (PFS), and toxicity (Appendix Table A1, online only).

Statistical Design

The planned accrual was 83 patients, assuming 23 patients would have a confirmed PR or CR transitioning to arm A, 57 patients with PD or confirmed SD transitioning to arm B, and three patients ineligible or withdrawing (Appendix, online only). With 23 patients in arm A, there would be 94% power to distinguish a true durable PR/CR rate of 35% from 10% for an exact one-sample binomial test (one-sided alpha of .07). With 57 patients in arm B, there would be 92% power for a true PR/CR conversion rate of 20% versus 5% (one-sided alpha of .05) under a Simon's two-stage design (ie, suspension of arm B if less than or equal to one PR/CR in the first 20 response-evaluable patients). The treatment strategy would be deemed effective if five or more of 23 patients in arm A (observed rate of 22%) had persistent PR/CR at 1 year off nivolumab, and six or more of 57 patients in arm B (observed rate of 11%) converted to PR/CR when ipilimumab was added. Response rates are presented with 90% two-sided exact binomial CIs. Kaplan-Meier methodology was used to assess time-to-event endpoints (Appendix Table A1).

RESULTS

Baseline Characteristics

Eighty-five patients were enrolled between October 2017 and July 2019 at 10 centers in the United States. Two patients never initiated treatment, resulting in 83 patients for analysis. The majority of patients were male (82%; n = 68), had ECOG performance status of 0-1 (99%; n = 82), and had International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor-risk disease[9] (67%; n = 56; Table 1). With regard to histology, 96% (n = 80) were clear cell, 8% (n = 7) had sarcomatoid differentiation, and 15% (n = 12) had rhabdoid differentiation. Forty-two patients (51%) were treatment naïve.

Arm Allocation

Of the 83 patients who initiated treatment, 69 underwent arm allocation. Fourteen patients did not undergo arm allocation because of PD (n = 7) or toxicity (n = 7; Fig 1; Appendix Table A2, online only). Of the patients who discontinued treatment because of toxicity, the median treatment-free interval was 5.2 months (range, 1.2-20.4 months). Twelve patients were assigned to arm A (10 PR, one unconfirmed PR, and one SD) and 57 patients were assigned to arm B (28 SD, 29 PD). At the time of analysis, three patients in arm A had discontinued the study (two because of toxicity, one because of PD), and 54 patients in arm B had discontinued the study (11 because of toxicity, 37 because of PD, five for other reasons; one death was unrelated to study treatment).

Treatment Exposure

The median number of nivolumab induction cycles received was 4 (range, 1-8): median number in arm A patients was 4 (range, 2-8), median number in arm B patients was 4 (range, 2-6), and median number in patients who withdrew from study before arm allocation was 2 (range, 1-6). Of the 57 patients in arm B, 50 received two doses of ipilimumab, six received one dose, and one received no ipilimumab. The median duration of treatment for arm B patients was 3.7 months (range, 1-24 months).

Outcomes of Induction Nivolumab

The objective response rate (ORR) including PR and unconfirmed PR within 6 months of nivolumab induction was 14% (n = 12; 90% CI, 9% to 22%; Fig 2; Appendix Table A3, online only). The ORR was 17% (n = 7) in treatment-naïve patients and 12% (n = 5) in previously treated patients. Response rates were similar in patients with IMDC favorable (15%; n = 4) and intermediate/poor-risk disease (14%; n = 8).

Outcomes of Arm A Patients

Arm A continued enrollment after the futility assessment, given seven of the first nine patients did not have PD after the first imaging assessment. Of the 12 patients allocated to arm A, five (42%; 90% CI, 18% to 68%) remained off nivolumab at 1 year post-treatment discontinuation (Fig 3; Appendix Table A4, online only). Four patients restarted nivolumab within 6 months after treatment discontinuation (three because of PD; one was still in PR). Three patients who have not reached the 1-year mark are still in active follow-up.

Outcomes of Arm B Patients

Of the 57 patients allocated to arm B, two patients (4%) converted to a confirmed PR (90% CI, 1% to 11%), both of whom were previously treated, did not have sarcomatoid/rhabdoid differentiation, and had PD as best response to nivolumab induction (Table 2). Duration of response was 9.2 and 10.9 months, and both patients ultimately discontinued treatment because of PD. Rates of SD and PD as best response were 46% (n = 26) and 40% (n = 23), respectively. The median duration of disease control (maintenance of a PR or SD; n = 28) from arm B start was 10.4 months (95% CI, 5.5 to 13.0 months), and median PFS from arm B start was 4.7 months (n = 45 events/57 patients; 95% CI, 2.7 to 8.3 months; Fig 4A).

TABLE 1. Baseline Patient and Disease Characteristics

Characteristic	Treatment Naïve (n = 42)	Previously Treated (n = 41)	Total (n = 83)
Median age at study entry, years (range)	60 (33-7)	63 (50-75)	61 (33-79)
Sex			
Female	3 (7.1)	12 (29.3)	15 (18.1)
Male	39 (92.9)	29 (70.7)	68 (81.9)
Race			
White	38 (90.5)	37 (90.2)	75 (90.4)
Other	4 (9.5)	4 (9.8)	8 (9.6)
Histology			
Clear cell	41 (97.6)	39 (95.1)	80 (96.4)
Other[a]	1 (2.4)	2 (4.9)	3 (3.6)
Sarcomatoid differentiation			
No	36 (85.7)	40 (97.6)	76 (91.6)
Yes	6 (14.3)	1 (2.4)	7 (8.4)
Rhabdoid differentiation			
No	34 (81)	37 (90.2)	71 (85.5)
Yes	8 (19)	4 (9.8)	12 (14.5)
M stage at original diagnosis			
M0	11 (26.2)	10 (24.4)	21 (25.3)
M1	14 (33.3)	6 (14.6)	20 (24.1)
MX	17 (40.4)	25 (61)	42 (50.6)
ECOG performance status			
0	31 (73.8)	24 (58.5)	55 (66.3)
1	10 (23.8)	17 (41.5)	27 (32.5)
2	1 (2.4)	0 (0)	1 (1.2)
IMDC risk group			
Favorable	13 (31)	14 (34.1)	27 (32.5)
Intermediate	22 (52.4)	23 (56.1)	45 (54.2)
Poor	7 (16.7)	4 (9.8)	11 (13.3)
Prior nephrectomy			
No	7 (16.7)	4 (9.8)	11 (13.3)
Yes	35 (83.3)	37 (90.2)	72 (86.7)
Lines of prior therapy			
0	42 (100)	0 (0)	42 (50.6)
1	0 (0)	31 (75.6)	31 (37.3)
2	0 (0)	8 (19.5)	8 (9.6)
≥ 3	0 (0)	2 (4.9)	2 (2.4)

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.
[a]One collecting duct and two papillary RCC.

Overall Survival

The median follow-up for overall survival was 19.5 months (range, 2.5-28.1 months). Overall, 19 deaths were observed (arm A [n = 1], arm B [n = 12], and patients who withdrew from the study before arm allocation [n = 6]; Fig 4B). The median overall survival has not been reached. The 18-month overall survival was 79% (95% CI, 67% to 87%).

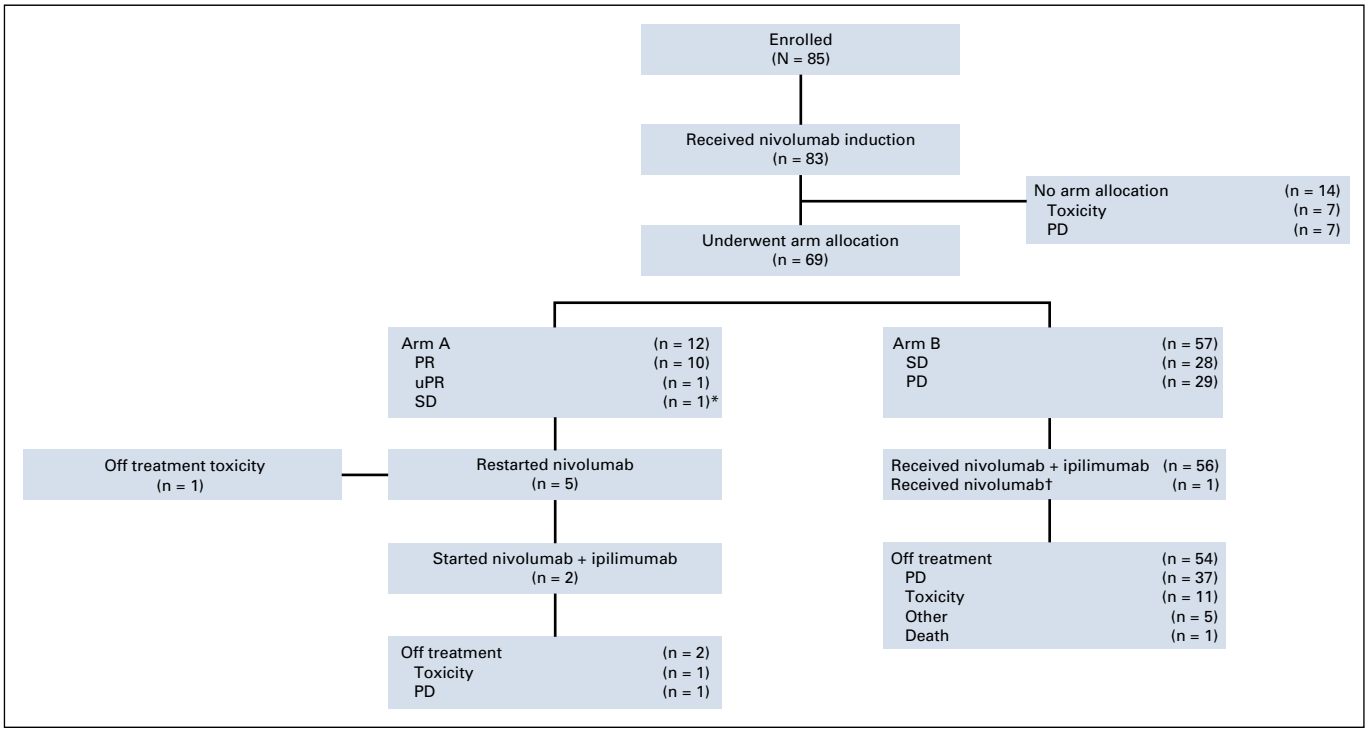

FIG 1. Consort diagram. (*) The non–partial response (PR) patients allocated to arm A represent protocol violations. (†) Received nivolumab alone given infusion reaction to nivolumab, which precluded receipt of ipilimumab. PD, progressive disease; uPR, unconfirmed partial response; SD, stable disease.

Adverse Events

During nivolumab induction, any grade and grade 3-4 TRAEs occurred in 80% (n = 66) and 7% (n = 6) of patients, respectively. Seven patients (8%) required prednisone ≥ 40 mg or the equivalent; seven patients (8%) discontinued treatment because of toxicity, and 12 patients (14%) had a dose delay because of toxicity (Appendix Table A5, online only). In arm B, any grade and grade 3-4

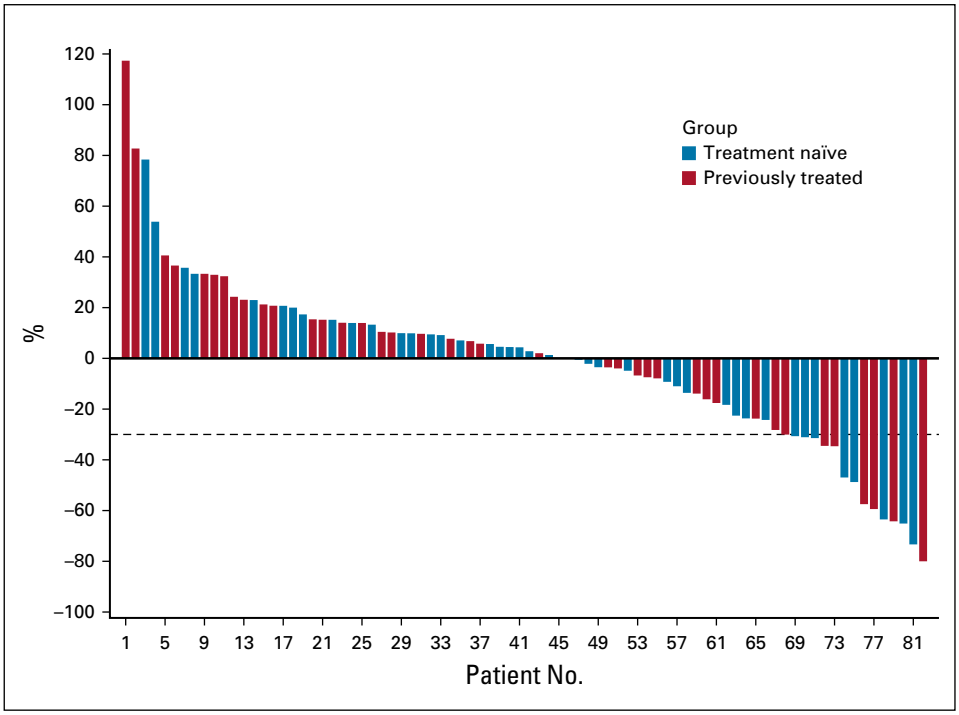

FIG 2. Waterfall plot of maximum percent decline in target lesion during induction nivolumab. Blue, treatment naïve. Red, previously treated.

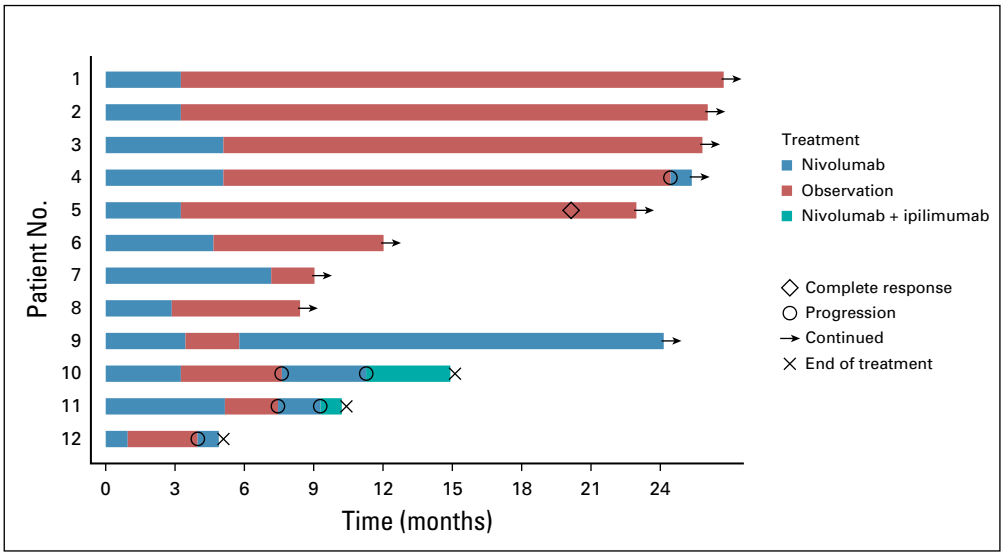

FIG 3. Swimmer plot of arm A treatment and outcomes. Patient 4 had stable disease with nivolumab induction, and patient 12 had an unconfirmed partial response to nivolumab induction.

TRAEs occurred post-ipilimumab initiation in 81% (n = 46) and 25% (n = 14) of patients, respectively. Ten patients (18%) required prednisone ≥ 40 mg or the equivalent, 11 patients (19%) discontinued treatment of toxicity, and 18 patients (32%) had a dose delay because of toxicity (Appendix Table A6, online only). There were no treatment-related deaths.

DISCUSSION

In our multicenter, phase II adaptive trial, we addressed several clinically relevant questions for the management of advanced RCC. We investigated the efficacy of nivolumab followed by the addition of two doses of ipilimumab in patients without a PR or CR within 2-6 months of nivolumab. Given the lack of CRs (0%) and low PR/CR conversion rate (4%), our data do not support a strategy of nivolumab followed by two cycles of ipilimumab in nivolumab nonresponders. Furthermore, we investigated nivolumab discontinuation in patients with a confirmed PR/CR within 6 months of nivolumab initiation. Although a subset of patients treated with nivolumab maintained durable responses off treatment at 1 year (42%), the number of patients evaluated for nivolumab discontinuation was too small to assess the value of this approach in nivolumab responders.

Our study used a novel adaptive design to investigate therapy de-escalation strategies in advanced RCC. We did not generate sufficient evidence to overturn the approach of combination nivolumab plus ipilimumab as opposed to sequential immune checkpoint blockade. Furthermore, 17% of patients were not allocated to a treatment arm, affecting the sample size in each treatment arm and further illustrating the limitations of sequential treatment strategies. Although formal comparisons with the phase III CheckMate-214 study cannot be performed given differing patient populations and study design, we demonstrated numerically inferior CR and ORR with our adaptive strategy. Immune checkpoint inhibitors have called for revised clinical endpoints to assess treatment efficacy. Although overall survival remains a gold standard endpoint, depth, durability of response, and treatment-free survival have become important endpoints to consider when selecting therapy options for patients. PD-1 and CTLA-4 inhibition have complementary effects on T-cell activation and prevention of T-cell exhaustion.[10] Preclinical models have demonstrated that combined PD-1 and CTLA-4 blockade is

TABLE 2. Arm B Treatment Response

Response	Treatment Naïve (n = 25)	Previously Treated (n = 32)	Total (n = 57)
CR	0 (0)	0 (0)	0 (0)
PR	0 (0)	2 (6)	2 (4)
SD	14 (56)	12 (38)	26 (46)
PD	8 (32)	15 (47)	23 (40)
Unevaluable	3 (12)	3 (9)	6 (11)

NOTE. Data are No. (%).

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

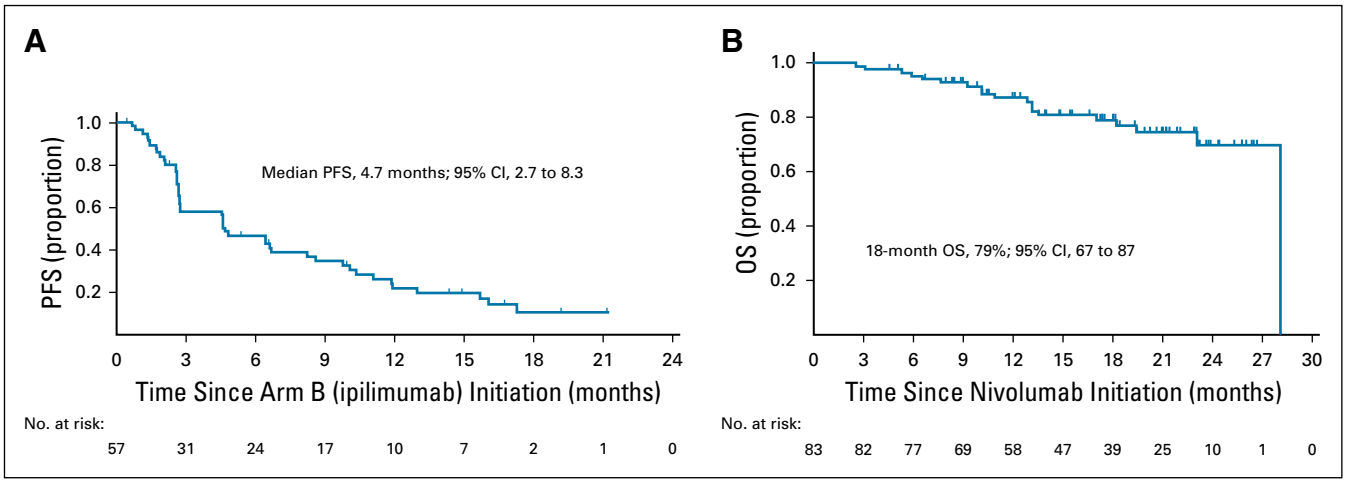

FIG 4. Kaplan-Meier estimate of (A) progression-free survival (PFS) from ipilimumab initiation for arm B patients and (B) overall survival (OS) for the total patient population.

superior to either strategy alone.[11,12] Studies of RCC evaluating combined upfront versus sequential PD-1 and CTLA-4 blockade are limited. Our study fills an unmet need in the field investigating sequential CTLA-4 blockade in patients not responding to nivolumab.

The role of nivolumab monotherapy in treatment-naïve patients with advanced RCC has yet to be defined. In patients with clear-cell RCC having received one to two prior VEGF targeted therapies, the ORR to nivolumab is 25%, and median time to response was 3.5 months (range, 1.4-24.8 months).[1] The KEYNOTE-427 study, which evaluated pembrolizumab in treatment-naïve clear-cell RCC, demonstrated response rates of 36.4% with median time to response of 2.8 months (range, 2.5-12.9 months).[13] In our study, in which approximately 50% of patients were treatment naïve, we demonstrated a 6-month response rate to nivolumab of 14%. Our study likely underestimates the response to nivolumab monotherapy given that (1) we mandated arm allocation by 6 months of initiation of nivolumab and thus only captured early responders, and (2) a subset of patients discontinued treatment because of toxicity during induction nivolumab, and we did not follow their response after study discontinuation (n = 7).

It is informative to place our study results in the context of two additional adaptive studies investigating nivolumab monotherapy followed by the addition of ipilimumab. The TITAN RCC trial was a phase II adaptive study in patients with treatment-naïve or previously treated advanced RCC (N = 207).[14] This study demonstrated a response to induction nivolumab of 28.7% (n = 31/108) for treatment-naïve patients and 18.2% (n = 18/99) for previously treated patients. Overall, the TITAN RCC study (ClinicalTrials.gov identifier: NCT02917772) demonstrated a low CR rate (2.9%), and the PR/CR conversion rate was approximately 10%. The HCRN-GU-260 study also investigated the role of nivolumab plus ipilimumab in patients without a response to nivolumab monotherapy.[15] The response to induction nivolumab (within 48 weeks) was 31.7% (n = 39/123). The overall CR rate was low (5.7% for monotherapy and 0% for salvage therapy), and the PR conversion rate was 13.3%. Furthermore, because of the study design, less than 50% of SD/PD patients were eligible for salvage therapy. Collectively, these data, combined with the results of our study, demonstrate that salvage ipilimumab results in low CR and PR/CR conversion rates. The value of the addition of ipilimumab to nivolumab in treatment-naïve patients will be answered in the phase III CA209-8Y8 study (ClinicalTrials.gov identifier: NCT03873402). Although it is difficult to place the utility of this study in the context of expanding immunotherapy combinations for patients with advanced RCC, this study was mandated by the European Medicines Agency to identify the contribution ipilimumab to frontline nivolumab.

A novel aspect of our study design was to investigate the effect of treatment discontinuation in nivolumab responders. We demonstrated that a subset of patients (42%) maintained durable responses beyond 1 year after nivolumab discontinuation, exceeding the prespecified metric of success for this arm. Longer follow-up is necessary because three patients who remain off treatment have not reached the 1-year assessment timepoint, and they were conservatively included as nonresponders. Although the low number of patients allocated to arm A (n = 12) preclude definitive conclusions about this approach, the data warrant additional investigation, and a randomized discontinuation trial may be merited to formally evaluate this strategy. In the absence of a predictive biomarker to identify patients most likely to benefit from treatment discontinuation and the low number of patients allocated to this, we would not recommend early (4- to 6-month) therapy discontinuation in the absence of toxicity or progression.

With regard to toxicity, rates of grade 3-4 TRAEs and treatment discontinuation for toxicity in our study were within the rates observed with nivolumab from CheckMate-025[1] and nivolumab and ipilimumab from CheckMate-214.[2] We observed more TRAEs than observed with single-agent nivolumab but fewer than those observed with nivolumab combined with four doses of ipilimumab.

Although this study was a prospective, multicenter adaptive trial, there are several limitations. At the time our study was designed, data in melanoma demonstrated that approximately 40% of patients treated with ipilimumab were not able to receive all four intended doses.[16] Additionally, CheckMate-016 investigating differing dosing regimens of nivolumab and ipilimumab in RCC demonstrated differences in toxicity between regimens.[17] For this reason, the study only tested the addition of two doses of ipilimumab. The study included a heterogeneous patient population including both treatment-naïve and previously treated patients and patients with nonclear-cell RCC. The study had a small sample size with a limited number of patients allocated to arm A, precluding definitive conclusions about therapy discontinuation. Although the study protocol mandated confirmation of responses, response assessments were investigator assessed. Finally, baseline tissue biomarkers of response, including PD-L1 status and CD8+ T-cell infiltration, are currently underway to better define responding patients.

In summary, our novel, multicenter, phase II trial addressed important clinically relevant questions in the field regarding optimizing the use of immune checkpoint blockade in patients with advanced RCC. Using a response-adaptive design, we investigated the sequential addition of two doses of ipilimumab to nivolumab nonresponders and discontinuation of nivolumab in responding patients. Our data highlight that nivolumab followed by response-based addition of two cycles of ipilimumab results in a lack of CRs and a low PR/CR conversion rate. Additionally, early nivolumab discontinuation in the absence of toxicity resulted in durable responses in a subset of patients. Based on these findings, we cannot recommend a response-based adaptive strategy for nivolumab and ipilimumab, and recommend upfront dual checkpoint blockade in patients eligible to receive this treatment. We are currently investigating novel biomarkers of response and resistance to therapy to better optimize treatment strategies for patients.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.02295

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APPENDIX

Study Design

Response was investigator assessed by RECIST version 1.1. In patients who experienced a response, subsequent imaging assessments were used for response confirmation, which was mandated by the study protocol. Confirmation of progressive disease was required unless deemed clinically detrimental by the investigator. Baseline measurements to assess response were reset at the initiation of ipilimumab for arm B. After treatment discontinuation, an optional tumor biopsy was performed. Toxicity was assessed by Common Terminology Criteria for Adverse Events version 4.0.

Hypothesis Selection

The null and alternative hypothesis rates were selected based on historical data at the time the trial was launched. In patients with renal cell carcinoma who were previously treated, the published response rates to nivolumab monotherapy range from 25% to approximately 29% (McDermott D, et al: J Clin Oncol Jun 20;33(18):2013-20., 2015; Motzer R, et al: N Engl J Med Nov 5;373(19):1803-13., 2015). Given that our study included both treatment-naïve and previously treated patients, we assumed 29% (23 of 80) of patients would have a confirmed partial response or complete response transitioning to arm A, the remaining 57 patients with progressive disease or confirmed stable disease transitioning to arm B. The overall enrollment was 83, accounting for 4% early dropout during the induction phase.

For arm A, there were no prior data for this novel treatment approach. The study design was to distinguish a true durable partial response/complete response rate of 35% from 10%, which was considered clinically meaningful from investigators' perspectives. For arm B, a small phase I (CheckMate 016) reported an objective response rate of 45% in patients treated with different dosing regimens of nivolumab and ipilimumab. Because our study included patients who did not respond to initial nivolumab and patients received salvage therapy with two doses of ipilimumab, a partial response/complete response rate of 20% would be considered promising in this population.

Futility Monitoring

To ensure that discontinuation of nivolumab was not detrimental for patients with initial confirmed partial response/complete response, a futility assessment was planned after nine of 23 arm A patients (39%) had undergone at least one imaging assessment since discontinuing nivolumab. Because we targeted the 1-year remission rate of at least 35% in arm A, an early progressive disease rate of 60% or higher at first scan post-treatment discontinuation would indicate the failure of this treatment approach. Therefore, if we observed five or more of the first nine patients experiencing progressive disease, enrollment of arm A would be suspended. If the true early progressive disease rate is 60% or higher, the probability of observing five or more patients with progressive disease out of nine patients is at least 73% (early stopping probability).

Arm B used a Simon's two-stage design. If one or fewer partial responses/complete responses are observed in the first 20 patients, arm B will be suspended. If two or more partial responses/complete responses are observed, an additional 37 patients will be enrolled for a total of 57 evaluable patients. The regimen will be declared worthy of additional study if six or more partial responses/complete responses are observed. These decision rules result in a 73% probability of stopping early (at the end of the first stage) if the regimen is inactive. The design yields a 92% probability (statistical power) of declaring the regimen active given a true partial response/complete response rate of 20% or 5% probability of declaring the regimen active given a true partial response/complete response rate of 5% or less.

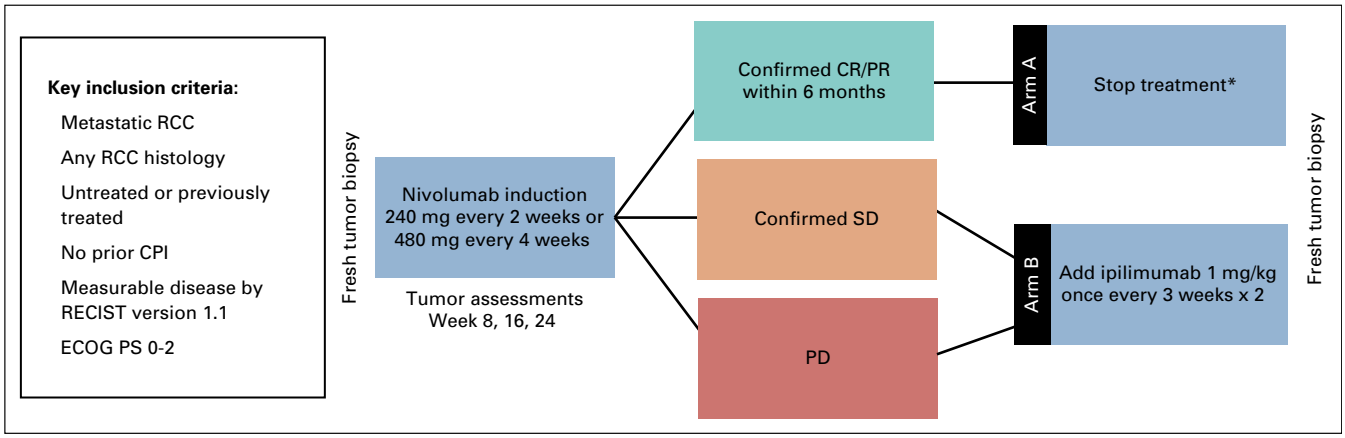

FIG A1. OMNIVORE study schema. (*) If a patient developed progressive disease (PD) after treatment discontinuation, nivolumab was reinitiated; if PD persisted or recurred, ipilimumab 1 mg/kg once every 2 weeks × 2 was added. Futility assessment was performed after the first nine patients enrolled. CPI, checkpoint inhibitor; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response; SD, stable disease; RCC, renal cell carcinoma.

TABLE A1. Efficacy Endpoint and Definition

Endpoint	Definition
Nivolumab induction (all patients)	
Objective response rate	No. and proportion of patients with confirmed CR or PR within 6 months of nivolumab monotherapy
Overall survival	Time since initiation of nivolumab monotherapy until death as a result of any cause or censored at date last known alive
Arm A	
Durable response rate at 1 year off nivolumab	No. and proportion with durable CR or PR at 1 year after nivolumab cessation in all patients assigned to arm A
Treatment-free interval	Time since last dose of nivolumab (before cessation) until reinitiation of nivolumab for disease progression or censored at date of last known treatment free for those who are alive and have not resumed treatment
Arm B	
Objective response rate	No. and proportion of patients in arm B who converted to CR or PR after ipilimumab was added
Duration of disease control	Start of arm B treatment until disease progression (by RECIST version 1.1 or clinical progression) in patients who had CR, PR, or SD in arm B, or censored at date of last disease evaluation for those who had not progressed
Progression-free survival	Time since the start of arm B treatment until progression (by RECIST version 1.1 or clinical PD) or death from any cause or censored at date of last disease evaluation for those who are alive and have not experienced disease progression

Abbreviations: CR, complete response; PD, partial disease; PR, partial response; SD, stable disease.

TABLE A2. Disposition of Patients Discontinuing the Study During Induction Nivolumab Because of Toxicity (n = 7)

Patient ID	At Time of Study Discontinuation: No. of Nivolumab Cycles Completed	At Time of Study Discontinuation: Percent Target Lesion Change	At Time of Study Discontinuation: Overall Response	Treatment-Free Interval (months)[a]	Next-Line Treatment	Overall Survival (months)[b]
1	4	5.3	PD[c]	20.4	Axitinib	26.5
2	1	−11.0	SD	1.8	Nivolumab	19.4
3	6	−14.2	SD	1.2	Nivolumab	10.2
4	4	5.6	SD	5.5	Pazopanib	12.5
5	6	−1.2	SD	8.5	Not started	14.8
6	1	−2.2	SD	5.2	Cabozantinib + investigational agent	13.5
7	2	−30.7	uPR	3.0	Cabozantinib	8.9

Abbreviations: ID, identification; PD, progressive disease; SD, stable disease; uPR, unconfirmed partial response.
[a]Time since last nivolumab injection to start of next-line therapy or last follow-up.
[b]From nivolumab initiation to death or last follow-up.
[c]Nontarget lesion progression.

TABLE A3. Summary of Objective Response to Nivolumab Induction According to Prior Treatment Status and IMDC Risk Group

	PR		uPR		SD		PD	
Treatment Status	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Prior treatment								
Treatment naïve (n = 42)	5	12	2	5	25	60	10	24
Previously treated (n = 41)	5	12	—	—	12	29	24	59
IMDC risk group								
Favorable (n = 27)	3	11	1	4	14	52	9	33
Intermediate (n = 45)	6	13	1	2	18	40	20	44
Poor (n = 11)	1	9	—	—	5	45	5	45
Total (n = 83)	10	12	2	2	37	45	34	41

Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PD, progressive disease; PR, partial response; SD, stable disease; uPR, unconfirmed partial response.

TABLE A4. Baseline Characteristics and Treatment Response Parameters for Patients Allocated to Arm A (n = 12)

	Baseline Characteristics				Nivolumab Induction	Arm A (observation)		Arm A2 (nivolumab)		Arm A3 (nivolumab + ipilimumab)		Off Treatment		
Patient ID	IMDC	Sarcomatoid	Rhabdoid	Lines of Prior Treatment	Response	Months Off Nivolumab	Response at Last Follow-Up	Total Cycle	Response	Total Cycle	Response	Off	Reason	Death
1	Intm	Yes	No	0	PR	23.5	PR							0
2	Intm	No	No	1	PR	22.8	PR							0
3	Fav	No	No	0	PR	20.7	PR							0
4	Intm	Yes	Yes	0	SD[a]	19.4	PD	1	NA					0
5	Intm	No	No	0	PR	19.7	CR							0
6	Fav	No	No	1	PR	7.4	PR							0
7	Fav	No	No	1	PR	1.9	NA							0
8	Poor	No	Yes	0	PR	5.6	PR							0
9	Intm	No	No	2	PR	2.3	PR	20	PR[a]					0
10	Intm	No	Yes	0	PR	4.4	PD	4	PD	4	SD	Off A3	Toxicity	0
11	Intm	No	Yes	1	PR	2.3	PD	2	PD	1	PD	Off A3	PD/ toxicity	1
12	Fav	No	No	0	uPR[a]	3.0	PD	1	—			Off A2	Toxicity	0

Abbreviations: CR, complete response; fav, favorable; ID, identification; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; intm, intermediate; NA, not available; PR, partial response; SD, stable disease; uPR, unconfirmed partial response.

[a]These events were designated as protocol violations. Two patients were allocated to arm A without having documentation of a confirmed PR. Additionally, one patient who was still in a response off treatment with nivolumab was resumed on nivolumab by the treating investigator.

TABLE A5. Maximum Grade by Toxicity Type for Treatment-Related Toxicities From Nivolumab Induction (n = 83)

	Toxicity Grade					
Toxicity Type	**1**	**2**	**3**	**4**	**Total**	**Percent**
Total No. of events	113	40	12	2	167	
Fatigue	21	5			26	31
Rash	14	3			17	20
Pruritus	8	3			11	13
ALT increased	7	1			8	10
Diarrhea	5	3			8	10
Nausea	7				7	8
AST increased	2	4			6	7
Arthralgia	2	3			5	6
Arthritis	4				4	5
Cough	2	1			3	4
Creatinine increased	2		1		3	4
Dry mouth	3				3	4
Dyspnea	1	2			3	4
Hypothyroidism	1	2			3	4
Pneumonitis		3			3	4
Blood bilirubin increased	1		1		2	2
Generalized muscle weakness	1		1		2	2
Headache	2				2	2
Hyperglycemia			1	1	2	2
Hyperkalemia			2		2	2
Hyperthyroidism	2				2	2

NOTE. Data are No. unless otherwise indicated.

TABLE A6. Maximum Grade by Toxicity Type for Treatment-Related Toxicities From Arm B (n = 57)

	Toxicity Grade					
Toxicity Type	**1**	**2**	**3**	**4**	**Total**	**Percent**
Total Events	77	37	20	3	137	
Rash	8	4			12	21
Arthralgia	7	3	1		11	19
Pruritus	7	2			9	16
Fatigue	4	4			8	14
AST increased	4	1	1		6	11
Nausea	3	3			6	11
ALT	3	1	1		5	9
Diarrhea	3	1	1		5	9
Headache	4				4	7
Hyperglycemia			2	2	4	7
Hypothyroidism	1	3			4	7
Myalgia	2	2			4	7
Colitis		1	2		3	5
Dyspnea		2	1		3	5
Hyperthyroidism	3				3	5
Hyponatremia	1		1	1	3	5
Pain	3				3	5
Vomiting	2	1			3	5
Adrenal insufficiency			2		2	4
Back pain	1	1			2	4
Cough	2				2	4
Hypophysitis		1	1		2	4
Mucositis oral	1	1			2	4
Pneumonitis		1	1		2	4
Weight loss	2				2	4

NOTE. Data are No. unless otherwise indicated.