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Standard Versus Modified Ipilimumab, in Combination With Nivolumab, in Advanced Renal Cell Carcinoma: A Randomized Phase II Trial (PRISM)

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DOI https://doi.org/10.1200/JCO.23.00236

ABSTRACT

PURPOSE Ipilimumab (IPI), in combination with nivolumab (NIVO), is an approved frontline treatment option for patients with intermediate- or poor-risk advanced renal cell carcinoma (aRCC). We conducted a randomized phase II trial to evaluate whether administering IPI once every 12 weeks (modified), instead of once every 3 weeks (standard), in combination with NIVO, is associated with a favorable toxicity profile.

METHODS Treatment-naïve patients with clear-cell aRCC were randomly assigned 2:1 to receive four doses of modified or standard IPI, 1 mg/kg, in combination with NIVO (3 mg/kg). The primary end point was the proportion of patients with a grade 3-5 treatment-related adverse event (trAE) among those who received at least one dose of therapy. The key secondary end point was 12-month progression-free survival (PFS) in the modified arm compared with historical sunitinib control. The study was not designed to formally compare arms for efficacy.

RESULTS Between March 2018 and January 2020, 192 patients (69.8% intermediate/poor-risk) were randomly assigned and received at least one dose of study drug. The incidence of grade 3-5 trAEs was significantly lower among participants receiving modified versus standard IPI (32.8% *v* 53.1%; odds ratio, 0.43 [90% CI, 0.25 to 0.72]; $P = .0075$). The 12-month PFS (90% CI) using modified IPI was 46.1% (38.6 to 53.2). At a median follow-up of 21 months, the overall response rate was 45.3% versus 35.9% and the median PFS was 10.8 months versus 9.8 months in the modified and standard IPI groups, respectively.

CONCLUSION Rates of grade 3-5 trAEs were significantly lower in patients receiving modified versus standard IPI. Although 12-month PFS did not meet the prespecified efficacy threshold compared with historical control, informal comparison of treatment groups did not suggest any reduction in efficacy with the modified schedule.

ACCOMPANYING CONTENT

Data Supplement

Protocol

Accepted September 9, 2023

Published November 6, 2023

J Clin Oncol 42:312-323

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INTRODUCTION

Ipilimumab (IPI) and nivolumab (NIVO), checkpoint inhibitors targeting cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and PD-1, respectively, are approved in combination as a frontline treatment option for patients with intermediate- or poor-risk advanced renal cell carcinoma (aRCC), as defined by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria.[1] The superiority of the combination over the previous standard of care, the VEGFR-targeted tyrosine kinase inhibitor, sunitinib, was established in the randomized phase III CheckMate 214 study.[2,3] IPI was administered at 1 mg/kg (IPI1) and NIVO was administered at 3 mg/kg (NIVO3), once every 3 weeks for four doses, followed by single-agent NIVO.

Dose and scheduling of IPI appear to correlate with treatment safety and tolerability. In the phase I CheckMate 016 study in aRCC, higher rates of toxicity were observed with IPI3+NIVO1 versus IPI1+NIVO3, given once every 3 weeks, on which basis the IPI1+NIVO3 regimen was taken forwards.[4] More formal comparison of these dosing regimens was undertaken in patients with metastatic melanoma, in the phase IIIb/IV CheckMate 511 study. IPI1+NIVO3, once every 3

CONTEXT

Key Objective

This randomized phase II trial was designed to investigate whether, in patients with advanced renal cell carcinoma, modified scheduling of ipilimumab (IPI), in combination with nivolumab, is associated with a favorable toxicity profile in comparison with standard dosing once every 3 weeks.

Knowledge Generated

Giving IPI every 12 weeks for four doses led to a significant reduction in the rate of grade 3-5 treatment-related adverse events. Rates of treatment discontinuation were also in favor of the modified schedule. Although not designed to formally compare arms for efficacy, no clear differences in response rate, progression-free survival, or overall survival were observed.

Relevance *(M.A. Carducci)*

Extended-interval dosing strategies for anti-cytotoxic T-lymphocyte associated protein 4 therapies have the potential to improve patient-reported outcomes by providing flexibility and convenience, while spacing out infusion time. This study suggests these longer dosing strategies can remain efficacious while reducing toxicity experienced by patients with renal cell cancer, much like other studies in lung cancer and melanoma.*

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

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weeks, was again associated with a significantly lower rate of grade 3-5 trAEs compared to IPI3+NIVO1, with similar survival rates at three years.[5]

Increased interval dosing of IPI has been explored in other settings, suggesting improved tolerability compared with dosing once every 3 weeks. The CheckMate 012 multiarm phase Ib study in patients with non–small-cell lung cancer (NSCLC) included cohorts receiving IPI once every 6 weeks and once every 12 weeks, in combination with NIVO.[6] Rates of treatment discontinuation because of trAEs were low (13% and 11%), with encouraging activity, leading to subsequent adoption of the once every 6 weeks regimen. Recently, the KEYNOTE-029 study in patients with metastatic melanoma has explored an alternative IPI dose and schedule in combination with pembrolizumab (anti–PD-1).[7] Standard-dose pembrolizumab (200mg, once every 3 weeks), plus 50 mg IPI every 6 weeks, was associated with a grade 3-5 trAE rate of 24%, with antitumor activity above the prespecified threshold of interest.

The PRISM trial was designed to formally establish whether scheduling of IPI once every 12 weeks, in combination with NIVO, was associated with an improved safety profile in comparison with conventional IPI dosing once every 3 weeks in the setting of aRCC. The comparative frequency of adverse events in the two arms was the primary end point.

METHODS

Patients

Adult patients (18 years and older) with untreated, locally advanced, or metastatic clear-cell renal cell carcinoma (RCC), measurable disease as per RECIST version 1.1, and a Karnofsky performance status score of ≥70 and who were belonging to any IMDC risk group were recruited from participating UK sites. IMDC favorable-risk patients were included as the study commenced before the results of CheckMate 214 were available. All patients provided written informed consent. Ethical approval was obtained from the Leeds East Research Ethics Committee (17/YH/0187). Further details of the trial Protocol (online only) were reported previously, including the full list of patient eligibility criteria.[8]

Study Design and Treatment

PRISM was a multicenter, phase II, parallel-group, randomized controlled trial. The primary end point of the trial was the proportion of participants experiencing a Common Terminology Criteria for Adverse Events (CTCAE; version 5.0) grade 3-5 adverse reaction within the first 12 months of trial treatment. The key secondary end point of the trial was an external comparison against historical progression-free survival (PFS) data associated with sunitinib, included to provide supportive evidence of efficacy.[9] Formal comparison with historical data was planned to occur only if the internal comparison of the primary end point achieved statistical significance. The efficacy statistics of the study was designed before the results of Checkmate 214, which is why benchmarking with sunitinib was used.

Participants were registered prospectively and underwent trial-specific assessments of eligibility.[8] Eligible participants were individually randomly assigned on a 2:1 basis to receive either modified scheduling or standard scheduling of treatment, respectively. Random assignment was performed

centrally by an automated 24-hour system provided by the Leeds Clinical Trials Research Unit (CTRU) using a minimization algorithm incorporating a random element. Minimization factors were the IMDC risk group (favorable/intermediate/poor risk), disease status (metastatic/locally advanced), and nephrectomy status (nephrectomy/no nephrectomy). Treatment allocation was not blinded to participants, medical staff, or trial staff.

Treatment schedules were altered once during the trial after the approval of NIVO dosing once every 4 weeks. Following this amendment, participants randomized to the modified schedule received four doses of combination 3 mg/kg NIVO plus 1 mg/kg IPI once every 12 weeks, with 240 mg maintenance NIVO once every 2 weeks between the first and second combination doses, and 480 mg maintenance NIVO once every 4 weeks between all other combination doses. Single-agent NIVO (480 mg, once every 4 weeks) continued after all combination doses had been administered until disease progression, unacceptable toxicity, or participant choice.

Participants randomized to the standard schedule received four doses of combination 3 mg/kg NIVO plus 1 mg/kg IPI once every 3 weeks, with 480 mg single-agent NIVO once every 4 weeks continuing thereafter, until disease progression, unacceptable toxicity, or participant choice. The Data Supplement (online only) shows all treatment schedules used in the trial for both treatment groups. In alignment with the CheckMate 214 study, only those participants completing their IPI induction phase were permitted to progress to single-agent NIVO maintenance. Participants were permitted to continue treatment beyond first progression on the basis of investigator-assessed clinical benefit, study drug tolerance, and stable performance status.

Trial Outcomes

The primary end point was the proportion of participants experiencing a CTCAE (version 5.0) grade 3-5 adverse reaction within the first 12 months of trial treatment. The key secondary outcome was PFS with the modified schedule, where PFS was calculated from random assignment to first documented evidence of disease progression or death, whichever occurred first. Secondary end points included safety and tolerability (assessed by serious adverse events and treatment compliance), overall response rate (ORR), duration of response, overall survival (OS), and response rate post–first progression.

Health-related quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ)-C30, Comprehensive Cancer Network Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19), and EuroQol 5-dimension (EQ-5D-5L) instruments. Given the exploratory nature of the analysis, missing QoL data were not imputed, unless an approach for handling missing data was specified in the appropriate scoring manual. All disease response assessments were graded locally according to RECIST version 1.1 on the basis of computed tomography scans once every 12 weeks. Extended follow-up data were collected 12 months after the final analysis for PFS and OS outcomes. This was performed after the primary analysis to explore the longer-term outcomes for the key groups.

Statistical Analysis

One hundred eighty-nine participants were required to formally assess both the safety and efficacy aspects of the primary objective in a hierarchical testing framework. Specifically, 178 participants would provide an 80% power to detect a clinically relevant reduction in CTCAE grade 3-5 toxicity rate from 40% to 22% with the modified schedule (equivalent to an odds ratio [OR], 0.42) using a two-sided 10% significance level and allowing for 5% attrition. Should the toxicity rate in the control arm be between 30% and 50%, the study would provide 80% power to detect ORs in the range of 0.38 to 0.45; these reductions are deemed clinically relevant. One hundred twenty participants were required in the modified schedule arm to target a minimum clinically relevant hazard ratio of 0.73 compared with historical sunitinib data, corresponding to 50.9% alive and progression-free at 12 months, giving 80% power at the one-sided 5% significance level. Given the 2:1 allocation ratio in favor of the modified schedule, this corresponds to a target sample size of 189 participants allowing for 5% attrition. No formal interim analysis was planned.

Analysis of trial end points was performed using SAS 9.4[10] by statisticians at Leeds CTRU, and a statistical analysis plan was written before any analyses were undertaken. Analysis was conducted using modified intention-to-treat (mITT) principles for the primary end point and all efficacy end points, meaning that participants were analyzed according to randomized allocation and were included in the analysis, provided that they had received at least one dose of trial treatment. Secondary safety analyses were conducted using the safety population, whereby participants were analyzed according to the treatment they received. Analysis of the safety (primary end point) and efficacy (key secondary end point) components of the primary objective was hierarchical to preserve the power of the trial.

For the primary end point, treatment groups were formally compared by fitting a logistic regression model adjusting for minimization factors. Adjusted ORs, alongside corresponding 90% CIs and *P* values, are presented. The results for the key secondary end point are based on the lower limit of the one-sided 95% CI for the proportion of patients alive and progression-free at 12 months postrandomization in the modified schedule arm. No formal comparison of PFS was performed between the modified and standard schedule arms; however, PFS has been summarized

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descriptively for treatment groups, alongside exploratory post hoc hazard ratios, and for IMDC intermediate-/poor-risk subgroups.

Other end points are summarized using appropriate descriptive statistics, alongside appropriate two-sided CIs.

RESULTS

The trial opened to recruitment on March 16, 2018, and completed recruitment on January 15, 2020, randomly assigning 195 participants from 15 sites. Of those, 192 participants formed the mITT population, with 128 in the modified schedule arm and 64 in the standard schedule arm. Three participants did not receive any trial treatment and were excluded. Participant flow is shown in the CONSORT diagram (Fig 1).

Baseline characteristics for the mITT population were well balanced between treatment groups (Table 1). The majority (133 of 192 [69.3%]) of participants had IMDC intermediate- or poor-risk disease.

Primary Analysis

Overall, 76 of 192 (39.6%) participants experienced a CTCAE grade 3-5 adverse reaction within the first 12 months of trial treatment, with 42 of 128 (32.8%) in the modified schedule and 34 of 64 (53.1%) in the standard schedule. In particular, lower rates of colitis (3.9% *v* 6.3%), arthralgia (1.6% *v* 7.8%), serum lipase increase (1.6% *v* 9.4%), and hypophysitis (0.8% *v* 3.1%) were observed among patients receiving modified scheduling compared with standard scheduling (Fig 2). The logistic regression model showed a statistically significant estimated OR of 0.43 (90% CI, 0.25 to 0.72; $P = .0075$) in favor of modified scheduling, after adjusting for minimization factors. The Data Supplement (Table S1) contains adjusted ORs and 90% CIs from the fitted model.

Safety, Toxicity, and Tolerability

Rates of treatment discontinuation because of treatment-related toxicity were lower among participants receiving modified scheduling (29 of 128 participants [22.7%]) compared with standard scheduling (25 of 64 participants [39.1%]; unadjusted risk difference: −16.4% [95% CI, −30.4 to −2.4]). The median (IQR) duration of treatment was 209 (105, 406) days and 84 (35, 314) days in the modified and standard schedule arms, respectively. The median (range) number of IPI doses received was 3 (1-4, modified) and 4 (1-4, standard).

Overall, 1,158 trAEs, 87 serious adverse reactions (SARs), and six suspected unexpected serious adverse reactions (SUSARs) were reported in the trial: 756 trAEs, 45 SARs, and

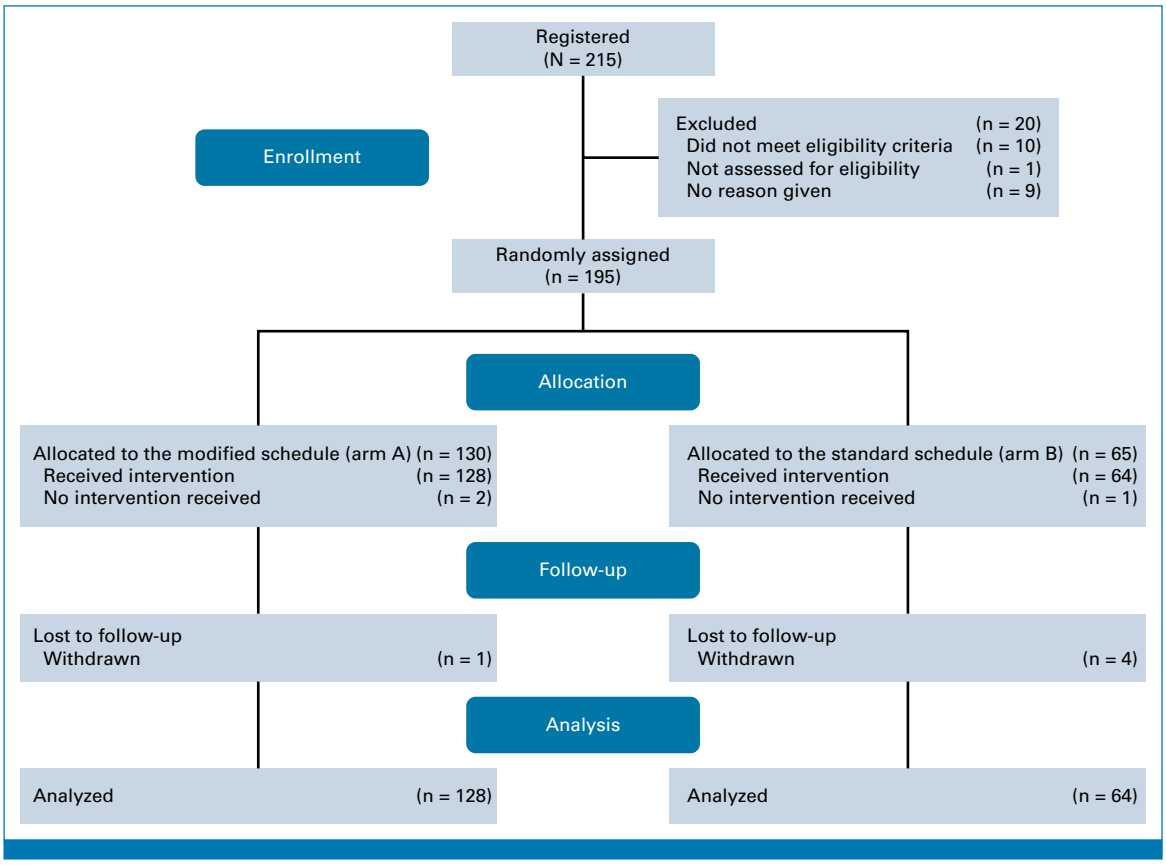

FIG 1. CONSORT flow diagram.

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TABLE 1. Baseline Patient Characteristics

Characteristic	Modified Schedule (arm A) (n = 128)	Standard Schedule (arm B) (n = 64)	Total (N = 192)
Age, years, median (range)	61 (39-81)	65 (28-81)	62 (28-81)
Sex, No. (%)			
Male	101 (78.9)	48 (75.0)	149 (77.6)
Female	27 (21.1)	16 (25.0)	43 (22.4)
IMDC prognostic group, No. (%)			
Favorable	38 (29.7)	21 (32.8)	59 (30.7)
Intermediate	67 (52.3)	32 (50.0)	99 (51.6)
Poor	23 (18.0)	11 (17.2)	34 (17.7)
Tumor PD-L1 expression, No./evaluable (%)			
<1%	52/92 (56.5)	27/43 (62.8)	79/135 (58.5)
≥1%	40/92 (43.5)	16/43 (37.2)	56/135 (41.5)
Previous nephrectomy, No. (%)	81 (63.3)	42 (65.6)	123 (64.1)
Disease type, No. (%)			
Metastatic	124 (96.9)	63 (98.4)	187 (97.4)
Locally advanced	4 (3.1)	1 (1.6)	5 (2.6)
Most common sites of metastasis, No. (%)			
Lung	89 (69.5)	51 (79.7)	140 (72.9)
Lymph node	39 (30.5)	21 (32.8)	60 (31.3)
Bone	23 (18.0)	12 (18.8)	35 (18.2)
Liver	18 (14.1)	8 (12.5)	26 (13.5)

Abbreviation: IMDC, International metastatic renal cell carcinoma database consortium.

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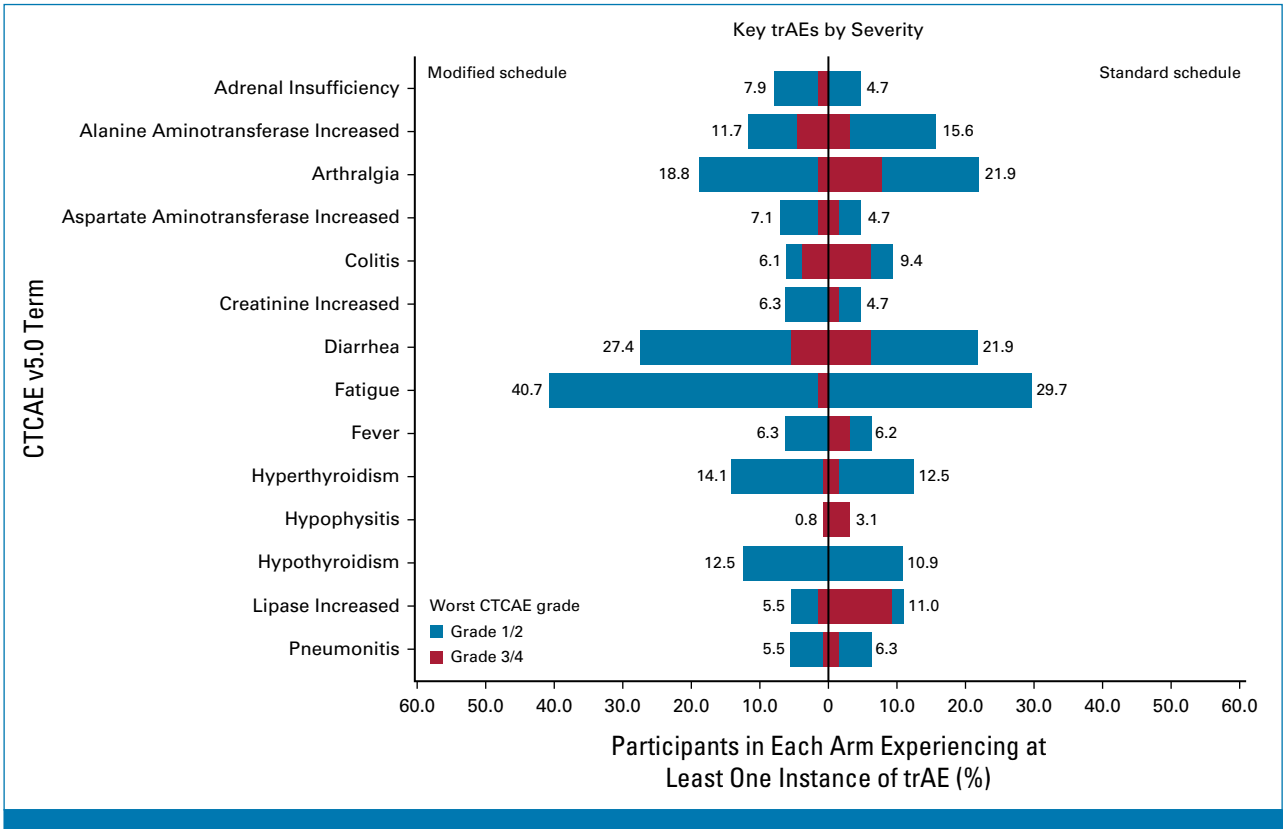

FIG 2. Key trAEs by severity. CTCAE, Common Terminology Criteria for Adverse Events; trAE, treatment-related adverse event.

four SUSARs in the modified schedule and 402 trAEs, 42 SARs, and two SUSARs in the standard schedule. Key clinical trAEs, by trial arm and CTCAE definition, are presented in Figure 2 alongside the maximum observed CTCAE grade. A plot including all trAEs that occurred in more than 2.5% of patients is presented in the Data Supplement (Fig S1).

Similar numbers and duration of treatment delays were observed between schedules. The number of participants experiencing at least one treatment delay or interruption was 88 of 128 (68.8%) and 37 of 64 (57.8%) for the modified and standard schedule, respectively. The mean (standard deviation [SD]) number of delays per participant was 1.5 (1.66) in the modified schedule arm and 1.4 (1.92) in the standard schedule arm.

Forty-seven deaths were observed among participants randomly assigned to the trial. The primary cause of death was most often related to RCC (modified schedule: 23 of 32 deaths [71.9%], standard schedule: 12 of 15 deaths [80%]). One treatment-related death because of immune-related hepatitis was reported in the modified schedule arm. All remaining deaths were attributed to other causes, including three that involved COVID-19.

Key Secondary Analysis

The median follow-up time at the time of final analysis for PFS was 21 months (95% CI, 17 to 22) using the modified schedule and 22 months (95% CI, 15 to 25) using the standard schedule. Kaplan-Meier curves summarizing PFS by arm are presented in Figure 3A. At 12 months post-randomization, the PFS estimate for the modified schedule was 46.1% (90% CI, 38.6 to 53.2). Therefore, formal comparison of the lower limit of the CI narrowly failed to exclude the historical control rate of 39.7% observed with sunitinib.[9]

The standard schedule PFS at 12 months postrandomization was 44.8% (32.1 to 56.7) and appears to be similar to the modified schedule PFS although it is important to recognize that the trial was not powered to detect a difference between arms. Exploratory analysis showed a post hoc unadjusted hazard ratio of 0.95 (95% CI, 0.67 to 1.36). Furthermore, PFS remained similar between arms with extended follow-up of participants, conducted 1 year after the trial follow-up period ended; median follow-up and Kaplan-Meier curves of the extended PFS data are presented in the Data Supplement (Fig S2). PFS by IMDC risk group and PD-L1 expression status (where available) is also available in the Data Supplement (Figs S3 and S4).

ORR and Duration of Response

The proportion of participants achieving a complete or partial response was 45.3% (95% CI, 36.5 to 54.4) with modified scheduling and 35.9% (95% CI, 24.3 to 48.9) with standard scheduling (Table 2). Median duration of response data is also presented in Table 2.

Overall Survival

The median follow-up time for OS was 32 months (95% CI, 31 to 34) using the modified schedule and 31 months (95% CI, 28 to 37) using the standard schedule. Kaplan-Meier curves summarizing OS by arm are presented in Figure 3B. The postrandomization OS estimate at 12 months was 88.3% (95% CI, 81.3 to 92.8) using modified scheduling and 84.1% (95% CI, 72.5 to 91.1) using standard scheduling. At 24 months, the OS estimate was 71.3% using modified scheduling and 73.7% using standard scheduling. Median OS was not reached (NR) in either arm. The trial was not designed to compare the two regimens directly. Exploratory analysis showed a post hoc unadjusted hazard ratio of 0.93 (95% CI, 0.56 to 1.54).

IMDC Intermediate- and Poor-Risk Patients

Exploratory Kaplan-Meier curves summarizing PFS and OS for participants with IMDC intermediate- or poor-risk disease by treatment arm are presented in Figure 4A and Figure 4B, respectively. The median PFS was 10.5 months and 8.6 months with modified and standard scheduling, respectively. The 12-month PFS estimates (95% CI) were 43.3% (32.7 to 53.3) in the modified arm and 46.1% (30.7 to 60.1) in the standard arm. The median OS was 38.5 (95% CI, 27.1 to NR) months in the modified arm and NR in the standard arm. The 24-month OS rates were 65.2% and 66.7% in the modified and standard arms, respectively. Among patients with IMDC intermediate- or poor-risk disease, the ORR was 46.7% (95% CI, 36.1 to 57.5) in the modified arm and 40.9% (95% CI, 26.3 to 56.8) in the standard arm (Table 2).

Quality of Life

Baseline scores were available for 115 of 128 (89.8%) modified schedule participants and 55 of 64 (85.9%) standard schedule participants. Scores were collected through week 61 although, beyond week 25, only a small number ($n \leq 21$) of standard schedule patients completed questionnaires.

QoL, as measured by QLQ-C30 global health status, FKSI-19 total score, and the EQ-5D-5L visual analog scale, did not meaningfully change from baseline at any time point in either arm (Figs 5A-5C). Considering the FKSI GP5 global item "bothered by side effects of treatment," mean scores were in favor of the modified schedule during the initial 12 weeks of treatment and subsequently in favor of the standard schedule beyond this time point. However, the 95% CI of mean scores was overlapping throughout (Data Supplement, Fig S5). Means (SDs) and corresponding 95% CIs by questionnaire subscales, time point, and arm are available in the Data Supplement (Figs S5 and S6).

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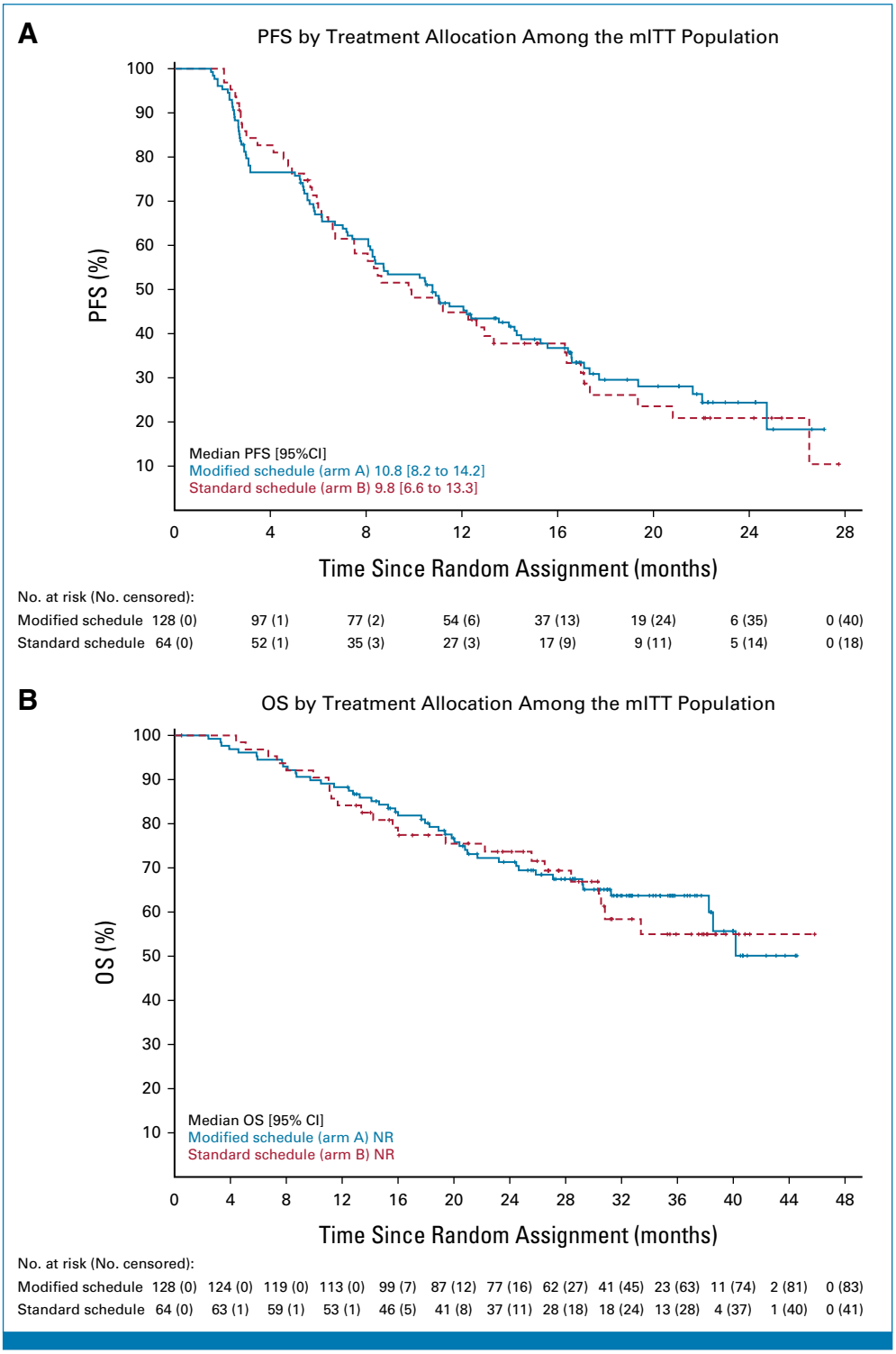

FIG 3. (A) PFS and (B) OS by treatment allocation among the mITT population. mITT, modified intention-to-treat; NR, not reached; OS, overall survival; PFS, progression-free survival.

DISCUSSION

The results of the PRISM study demonstrate that tolerability of IPI + NIVO in the frontline treatment of patients with aRCC can be improved by delivering IPI once every 12 weeks instead of once every 3 weeks. Health-related QoL was generally well maintained using either schedule. Although not designed to formally compare treatment arms for efficacy, no clear differences in ORR, PFS, and OS were observed at a minimum follow-up of 2 years.

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TABLE 2. Secondary Outcome Measures

Outcome	mITT Population		IMDC Intermediate/Poor Risk	
	Modified IPI (n = 128)	Standard IPI (n = 64)	Modified IPI (n = 90)	Standard IPI (n = 44)
ORR, % (95% CI)[a]	45.3 (36.7 to 53.9)	35.9 (24.2 to 47.7)	46.7 (36.1 to 57.5)	40.9 (26.3 to 56.8)
Best overall response, No. (%)				
Complete response	8 (6.3)	1 (1.6)	6 (6.7)	1 (2.3)
Partial response	50 (39.1)	22 (34.4)	36 (40.0)	17 (38.6)
Stable disease	40 (31.3)	26 (40.6)	23 (25.6)	17 (38.6)
Progressive disease	29 (22.7)	15 (23.4)	24 (26.7)	9 (20.5)
Missing	1 (0.8)	0 (0.0)	1 (1.1)	0 (0.0)
Duration of response, months, median (95% CI)	16.5 (13.1 to NR)	16.7 (12.6 to NR)		
Treatment tolerability,[b] %	68.8	57.8		
Unadjusted risk difference % (95% CI)	10.9 (−3.6 to 25.5)			
Treatment-related discontinuation, %	22.7	39.1		
Unadjusted risk difference % (95% CI)	−16.4 (−30.4 to −2.4)			
Treatment-related discontinuation before completing four IPI doses, %	20.3	31.3		
Participants receiving trial treatment postprogression	27	6		
Response rate after first progression,[c] % (95% CI)[a]	3.7 (0.09 to 19.0)	16.7 (0.42 to 64.1)		

Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IPI, ipilimumab; mITT, modified intention-to-treat; NR, not reached; ORR, overall response rate.

[a]Response was assessed according to RECIST, version 1.1.

[b]Defined as the proportion of participants experiencing at least one treatment delay/interruption.

[c]Response rate post-first progression is calculated as the percentage of responses observed amongst participants who continued receiving trial treatment post first-progression.

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Just over half of patients (53.1%) receiving standard scheduling in PRISM experienced a grade 3-5 trAE, which is consistent with the rate (47%) reported in CheckMate 214.[3] Rates of treatment discontinuation because of trAE associated with standard IPI were, however, higher in PRISM (39.1%) than in CheckMate 214, which, at 23%, is more akin to that observed with the modified PRISM schedule. The reasons for this difference are uncertain. It is possible, given the now more well-established potential for ongoing benefits beyond treatment discontinuation,[11] that a lower threshold to stop treatment was used by PRISM investigators.

Focusing on adverse events rather than efficacy as the primary end point is unusual, but not unprecedented in advanced renal cancer.[12] The purpose of PRISM was to establish if there were clear differences in tolerability by altering the drug schedule. If this was the case, and there were also promising efficacy signals, larger randomized phase III trials could be considered. We did not consider large noninferiority trials were justified without preliminary data.

The activity of standard IPI + NIVO in PRISM was broadly in line with previous data.[3] A higher proportion of patients had favorable-risk disease (31%) and a lower proportion had previous nephrectomy (63%) in PRISM compared with CheckMate 214 (23% and 82%, respectively), but, otherwise, study populations were similar. The median PFS of 9.8 months among the mITT PRISM population receiving standard IPI sits within the 95% CI (12.4 months [9.8 to 16.5]) of the CheckMate 214 intention-to-treat (ITT) population.[3] Among intermediate-/poor-risk patients, the corresponding figures were 8.6 months versus 11.6 months (95% CI, 8.4 to 15.5). The ORRs of 35.9% and 40.9% in this study are comparable with the 39% and 42% ORRs reported in CheckMate 214, when considering ITT and intermediate-/poor-risk patients, respectively.

The opportunity to optimize the dose and schedule of drugs, including immune checkpoint inhibitors, in cancer care to reduce cost, widen access, and improve safety is increasingly being recognized,[13] as exemplified by initiatives such as the US Food and Drug Administration's Project Optimus. This randomized phase II trial serves as an exemplar of such efforts. It does, however, have limitations. The decision to include favorable-risk patients reflects the design of the study before the results of the CheckMate 214 trial, which also included favorable-risk patients, were available. This is also reflected in the choice of single-agent sunitinib to benchmark the activity of the modified IPI schedule. The study did not meet the prespecified efficacy threshold (12-month PFS rate) using the modified schedule on the basis of this comparison. However, when considering both the mITT and the intermediate-/poor-risk subgroup of

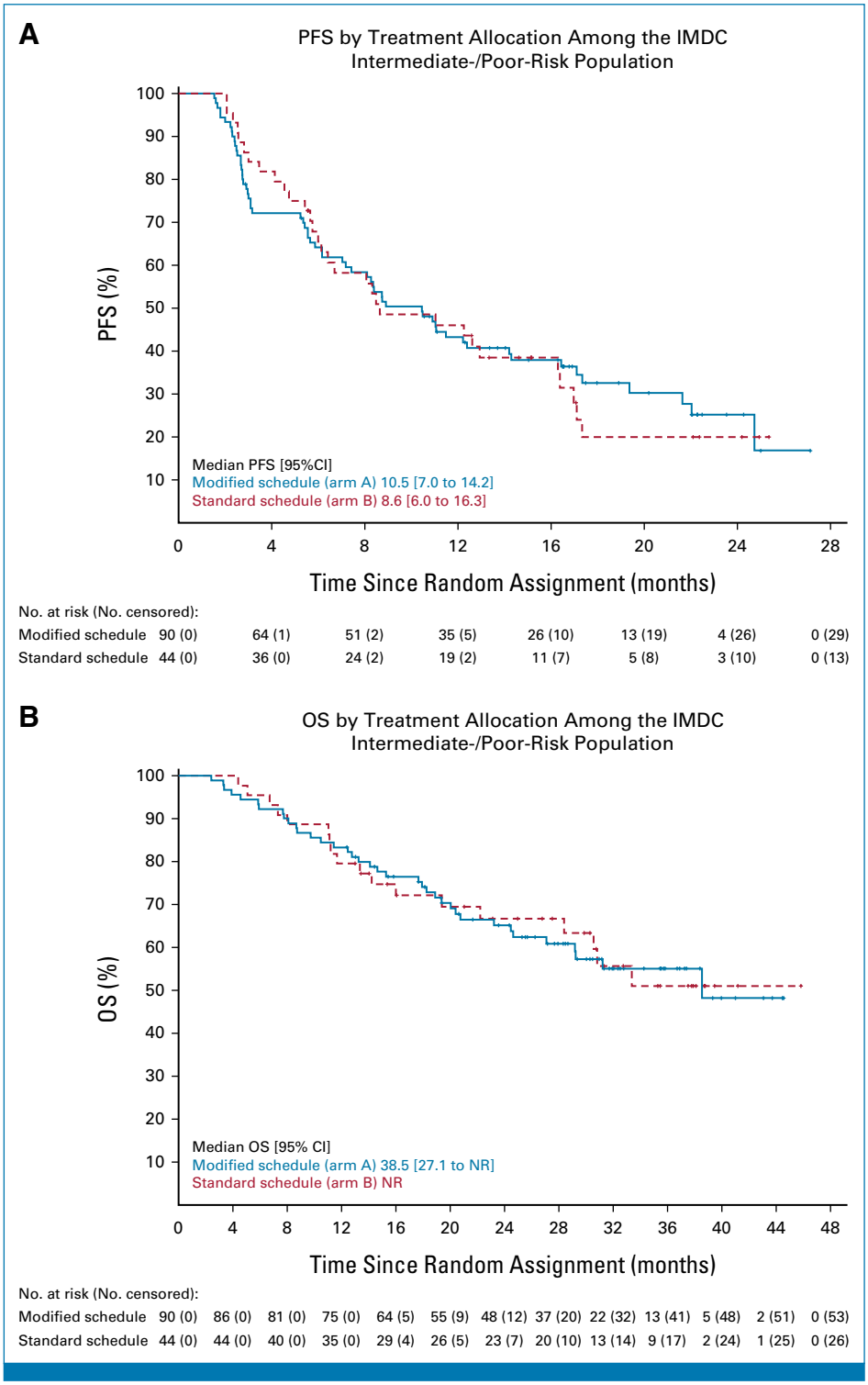

FIG 4. (A) PFS and (B) OS by treatment allocation among the IMDC intermediate-/poor-risk population. IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NR, not reached; OS, overall survival; PFS, progression-free survival.

participants, efficacy data by median PFS, 12-month PFS, and ORR were comparable between PRISM arms and were in line with the data from CheckMate 214. OS rates also remained similar between treatment arms although, with a median follow-up of 32 months, no definite conclusions regarding the impact on longer-term survival can be drawn. The fact that PRISM was not powered to compare treatment arms for efficacy represents a further limitation of our study.

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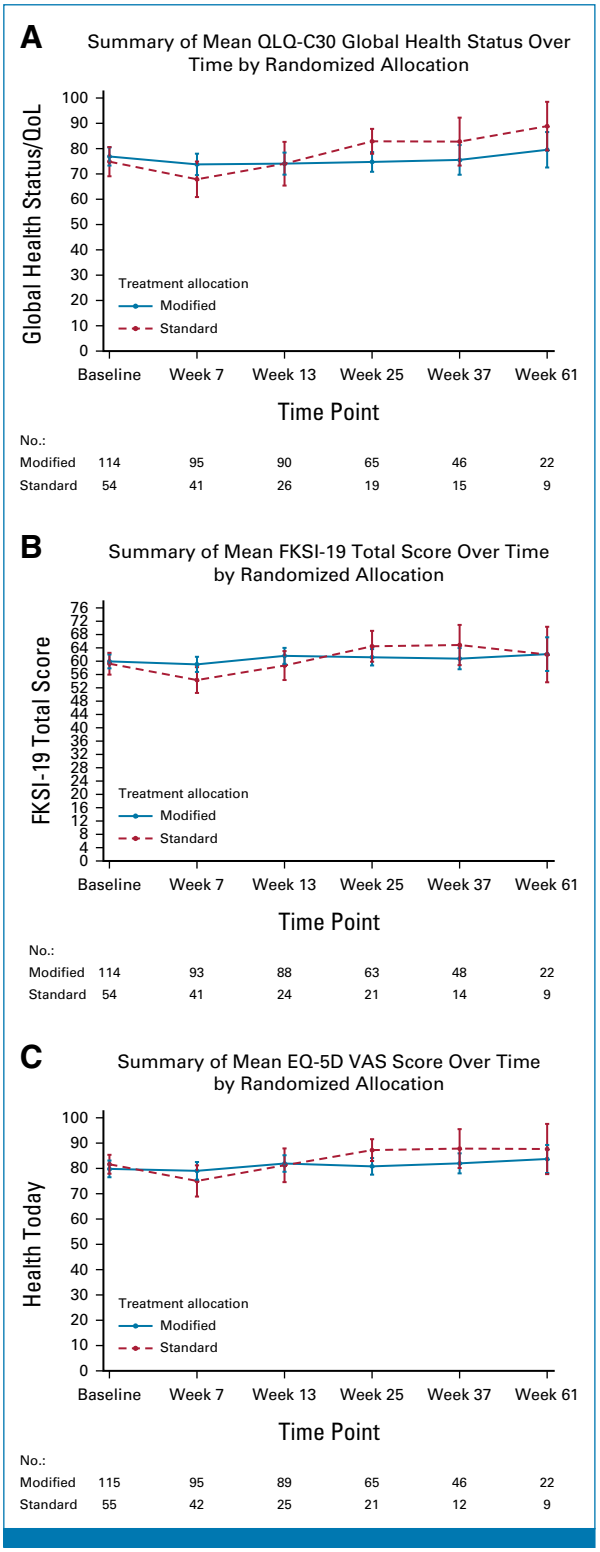

FIG 5. Summaries of mean (A) QLQ-C30 global health status, (B) FKSI-19 total score, and (C) EQ-5D VAS over time, by randomized allocation. EQ-5D, EuroQol 5-dimension; FKSI, Functional assessment of cancer-therapy Kidney Symptom Index; QLQ-C30, Quality of Life Questionnaire-C30; QoL, quality of life; VAS, visual analogue scale.

Large noninferiority trials would be needed to formally address this, which do not appear justified on the basis of our results, in the opinion of the authors.

It is concerning that patient-reported outcome data in PRISM did not track the trAE data. The reasons for this are unclear. The relationship between adverse events and QoL has been explored previously in aRCC, with inconsistent results.[12] Modification to the patient-reported outcome questions to better reflect immune-related toxicity has been suggested.[14]

Despite the introduction of IPI more than a decade ago, the mechanisms by which the CTLA-4 blockade induces both antitumor responses and trAE remain poorly defined. Intriguingly, however, preclinical studies suggest that CTLA-4–targeting agents that favor regulatory T-cell depletion within the tumor microenvironment, while avoiding peripheral T-cell activation, may be associated with a favorable toxicity profile, potentially paving the way for a new generation of safer and more efficacious anti–CTLA-4 antibodies.[15-17]

In conclusion, the results of the PRISM trial establish the superior safety of IPI dosing once every 12 weeks compared with once every 3 weeks, in combination with NIVO, in patients with aRCC. Although a formal internal efficacy comparison was not possible, no meaningful differences between treatment arms were observed on the basis of informal comparisons. Our data are consistent with studies in melanoma and NSCLC, suggesting that low dose and/or increased interval dosing of IPI, in combination with anti–PD-1 blockade, can remain efficacious while reducing toxicity experienced by patients.

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PRIOR PRESENTATION

Presented in part at the European Society for Medical Oncology 2021 Congress, Paris, France, September 16-21, 2021.

SUPPORT

Supported by Bristol Myers Squibb (Princeton, NJ) and by Yorkshire Cancer Research (YCR) through the YCR Center for Early Phase Clinical Trials.

CLINICAL TRIAL INFORMATION

ISRCTN95351638

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.23.00236.

DATA SHARING STATEMENT

Data supporting this work are available on reasonable request. All requests will be reviewed by relevant stakeholders, based on the principles of a controlled access approach. Requests to access data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance.

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ACKNOWLEDGMENT

We thank all the patients and clinical study teams who participated in the PRISM trial. We are grateful to the University of Leeds, United Kingdom, for sponsoring the trial and the University of Leeds CTRU for running the study. We thank Geraldine Murden, Hannah Buckley, and Heather Poad at the Leeds CTRU. We are grateful for the support and advice given by the Trial Steering Group (Professor Sarah Danson, Dr Natalie Charnley, Dr Kristian Brock) and the Data Management and Ethics Committee (Dr Hilary Glen, Professor Paul Lorigan and Mr Jamie Stobo). The authors would also like to thank Yorkshire Cancer Research and Bristol Myers Squibb who supported and funded the study.

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Standard Versus Modified Ipilimumab, in Combination with Nivolumab, in Advanced Renal Cell Carcinoma: A Randomized Phase II Trial (PRISM)

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No other potential conflicts of interest were reported.

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