
Article:
Vasudev, N.S. orcid.org/0000-0001-8470-7481, Ainsworth, G., Brown, S. et al. (24 more authors) (2023) Standard Versus Modified Ipilimumab, in Combination With Nivolumab, in Advanced Renal Cell Carcinoma: A Randomized Phase II Trial (PRISM). Journal of Clinical Oncology. ISSN 0732-183X

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

Standard versus modified ipilimumab, in combination with nivolumab, in advanced renal cell carcinoma: a randomized Phase II trial (PRISM)

Naveen S. Vasudev[1], Gemma Ainsworth[2], Sarah Brown[2], Lisa Pickering[3], Tom Waddell[4], Kate Fife[5], Richard Griffiths[6], Anand Sharma[7], Eszter Katona[2], Helen Howard[2], Galina Velikova[1], Anthony Maraveyas[8], Janet Brown[9], Carmel Pezaro[10], Mark Tuthill[11], Ekaterini Boleti[12], Amit Bahl[13], Bernadett Szabados[14], Rosamonde E. Banks[1], Joanne Brown[1], Balaji Venugopal[15], Poulam Patel[16], Ankit Jain[17], Stefan N. Symeonides[18], Paul Nathan[7], Fiona J. Collinson[2], Thomas Powles[14]

1. Leeds Institute of Medical Research at St James's, University of Leeds, St James's University Hospital, Leeds, UK
2. Clinical Trials Research Unit, University of Leeds, Leeds, UK
3. Royal Marsden Hospital, London, UK
4. Department of Medical Oncology, Christie Hospital, Manchester, UK
5. Addenbrooke's Hospital, Cambridge, UK
6. The Clatterbridge Cancer Centre, Liverpool, UK
7. Mount Vernon Cancer Centre, Middlesex, UK
8. Castle Hill Hospital, Hull, UK
9. Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK
10. Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
11. Department of Oncology, Oxford University Hospitals NHS Foundation Trust, UK
12. Royal Free London NHS Foundation Trust, London, UK
13. Bristol Haematology and Oncology Centre, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK
14. Barts Cancer Institute, Queen Mary University of London, London, UK
15. Institute of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK
16. Division of Cancer & Stem Cells, School of Medicine, University of Nottingham, Nottingham UK
17. The Royal Wolverhampton NHS Trust, Wolverhampton, UK
18. Edinburgh Cancer Centre, Western General Hospital, NHS Lothian, Edinburgh, UK

Corresponding author:
Dr Naveen Vasudev
University of Leeds & St James's University Hospital, Leeds, LS9 7TF, United Kingdom
Email: n.vasudev@leeds.ac.uk
Twitter: @nav_vasudev

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)

Running head
Standard vs. modified ipilimumab in aRCC

Acronym List

Abbreviation	Definition
aRCC	Advanced renal cell carcinoma
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
CTRU	Clinical Trials Research Unit
EORTC	European Organisation for Research and Treatment of Cancer
FDA	U.S. Food and Drug Administration
FKSI	Functional assessment of cancer-therapy Kidney Symptom Index
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IPI	Ipilimumab
mITT	Modified intention-to-treat
NIVO	Nivolumab
NR	Not reached
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
RECIST	Response Evaluation Criteria in Solid Tumours
SAR	Serious adverse reaction
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
TKI	Tyrosine kinase inhibitor
TrAE	Treatment-related adverse event
UK	United Kingdom
VEGFR	Vascular endothelial growth factor receptor

Abstract

PURPOSE: Ipilimumab, in combination with nivolumab, is an approved front-line 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 ipilimumab 12-weekly (modified), instead of 3-weekly (standard), in combination with nivolumab, is associated with a favorable toxicity profile.

PATIENTS AND METHODS: Treatment naïve patients with clear cell aRCC were randomized 2:1 to receive four doses of modified or standard ipilimumab, 1 mg/kg, in combination with nivolumab (3 mg/kg). The primary endpoint was the proportion of patients with a grade 3-5 treatment-related adverse event (trAE) amongst those who received at least one dose of therapy. The key secondary endpoint was 12-month progression-free survival (PFS) in the modified arm compared to 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 randomized and received at least one dose of study drug. The incidence of grade 3-5 trAE was significantly lower amongst participants receiving modified versus standard ipilimumab (32.8% v 53.1%; odds ratio 0.43 [90% confidence interval: 0.25, 0.72]; p-value=0.0075). 12-month PFS (90% CI) using modified ipilimumab was 46.1% (38.6, 53.2). At a median follow-up of 21 months, overall response rate was 45.3% versus 35.9% and median PFS was 10.8 months versus 9.8 months, in the modified and standard ipilimumab groups, respectively.

CONCLUSIONS: Rates of grade 3-5 trAE were significantly lower in patients receiving modified versus standard ipilimumab. Although 12-month PFS did not meet the pre-specified efficacy threshold compared to historical control, informal comparison of treatment groups did not suggest any reduction in efficacy with the modified schedule.

Context Summary

Key Objective

This randomized phase II trial was designed to investigate whether, in patients with advanced renal cell carcinoma (aRCC), modified scheduling of ipilimumab, in combination with nivolumab, is associated with a favourable toxicity profile in comparison to standard 3-weekly dosing

Knowledge Generated

Giving ipilimumab every 12 weeks for four doses led to a significant reduction in the rate of grade 3-5 treatment related adverse events (trAE). Rates of treatment discontinuation were also in favour of the modified schedule. Although not designed to formally compare arms for efficacy, no clear differences in response rate, PFS or OS were observed

Relevance

The role of ipilimumab in aRCC remains subject to debate and the optimal dose and schedule of this agent in this setting is undefined. Our results support the hypothesis that the timing of CTLA-4 therapy is not crucial to achieve efficacy and can lead to a reduction in trAE

Introduction

Ipilimumab (IPI) and nivolumab (NIVO), checkpoint inhibitors targeting CTLA-4 and PD-1 respectively, are approved in combination as a front-line 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 prior standard of care, the VEGFR-targeted tyrosine kinase inhibitor (TKI), sunitinib, was established in the randomized phase III CheckMate 214 study.[2,3] IPI was administered at 1 mg/kg (IPI1) and NIVO at 3 mg/kg (NIVO3), once every three 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, 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 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 to three-weekly dosing. The CheckMate 012 multi-arm phase Ib study in patients with non-small cell lung cancer (NSCLC) included cohorts receiving six-weekly and 12-weekly IPI, in combination with NIVO.[6] Rates of treatment discontinuation due to trAEs were low (13% and 11%), with encouraging activity, leading to subsequent adoption of the six-weekly regimen. Recently, the KEYNOTE-029 study in patients with metastatic melanoma

has explored alternative IPI dose and schedule in combination with pembrolizumab (anti-PD-1).[7] Standard dose pembrolizumab, plus 50 mg IPI every six weeks, was associated with a grade 3-5 trAE rate of 24%, with anti-tumor activity above the pre-specified threshold of interest.

The PRISM trial was designed to formally establish whether 12-weekly scheduling of IPI, in combination with NIVO, was associated with an improved safety profile in comparison to conventional three-weekly IPI dosing, in the setting of aRCC. The comparative frequency of adverse event in the two arms was the primary endpoint.

Methods

Patients

Adult patients (≥18 years) with untreated, locally advanced or metastatic clear-cell RCC, measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, Karnofsky performance-status score ≥70, and 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 only have been reported previously, including the full list of patient eligibility criteria.[8]

Study Design and Treatment

PRISM was a multi-centre, phase II, parallel-group, randomized controlled trial. The primary endpoint 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 endpoint 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 endpoint achieved statistical significance. The efficacy statistics of the study was designed prior to 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 randomized on a 2:1 basis to receive either modified scheduling or standard scheduling of treatment, respectively. Randomization was performed centrally by an automated 24-hour system provided by Leeds Clinical Trials Research Unit (CTRU), utilizing a minimization algorithm incorporating a random element. Minimization factors were 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 or trial staff.

Treatment schedules were altered once during the trial, following the approval of four-weekly NIVO dosing. Following this amendment, participants randomized to the modified schedule received four doses of combination 3 mg/kg NIVO plus 1 mg/kg IPI at 12-weekly intervals, with two-weekly 240 mg maintenance NIVO between the first and second combination doses, and four-weekly 480 mg maintenance NIVO between all other combination doses. Four-weekly 480 mg single-agent NIVO 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 at three-weekly intervals, with four-weekly 480 mg single-agent NIVO continuing thereafter, until disease progression, unacceptable toxicity, or participant choice. **Appendix 1** 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, based on investigator-assessed clinical benefit, study drug tolerance and stable performance status.

Trial outcomes

The primary endpoint 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 randomization to first documented evidence of disease progression or death, whichever occurred first. Secondary endpoints 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 was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 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 quality of life 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 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 based on 12-weekly computed

tomography scans. Extended follow-up data was 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

189 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 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. 120 participants were required in the modified schedule arm to target a minimum clinically relevant hazard ratio of 0.73 compared to 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 endpoints was performed in SAS 9.4[10] by statisticians at Leeds CTRU, and a statistical analysis plan written prior to any analyses being undertaken. Analysis was conducted using modified intention-to-treat (mITT) principles for the primary endpoint and all efficacy endpoints, meaning participants were analyzed according to randomized allocation, and were included in the analysis provided 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 endpoint) and efficacy (key secondary endpoint) components of the primary objective was hierarchical, to preserve the power of the trial.

For the primary endpoint, treatment groups were formally compared by fitting a logistic regression model adjusting for minimization factors. Adjusted ORs, alongside corresponding 90% confidence intervals (CIs) and p-values are presented. Results for the key secondary endpoint are based on the lower limit of the one-sided 95% CI for the proportion of patients alive and progression-free at 12 months post-randomization in the modified schedule arm. No formal comparison of PFS was performed between the modified and standard schedule arms, however PFS has been summarized descriptively for treatment groups, alongside exploratory post-hoc hazard ratios, and for IMDC intermediate/poor risk subgroups.

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

Results

The trial opened to recruitment on 16th March 2018 and completed recruitment on 15th January 2020, randomizing 195 participants from 15 sites. Of those, 192 participants formed the mITT population, 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 Consolidated Standards of Reporting Trials (CONSORT) diagram (**Error! Reference source not found.**).

Baseline characteristics for the mITT population were well balanced between treatment

groups (**Table 1**). The majority (133/192 (69.3%)) of participants had IMDC intermediate- or poor-risk disease.

Primary analysis

Overall, 76/192 (39.6%) of participants experienced a CTCAE grade 3-5 adverse reaction within the first 12-months of trial treatment, 42/128 (32.8%) with the modified schedule and 34/64 (53.1%) with 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 amongst patients receiving modified scheduling compared to standard scheduling (Error! Reference source not found.). The logistic regression model showed a statistically significant estimated OR of 0.43 (90% CI: 0.25, 0.72, p=0.0075) in favor of modified scheduling, after adjusting for minimization factors. **Supplementary table S1** contains adjusted ORs and 90% CIs from the fitted model.

Safety, toxicity, and tolerability

Rates of treatment discontinuation due to treatment-related toxicity were lower amongst participants receiving modified scheduling (29/128 participants (22.7%)), compared to standard scheduling (25/64 participants (39.1%)) (unadjusted risk difference: -16.4% (95% CI: -30.4%, -2.4%)). The median (interquartile-range) duration of treatment was 209 (105, 406) days and 84 (35, 314) days using the modified and standard schedule, respectively. The median (range) number of IPI doses received was 3 (1-4) (modified) and 4 (1-4) (standard).

Overall, 1158 trAEs, 87 serious adverse reactions (SARs) and six suspected unexpected serious adverse reactions (SUSARs) were reported in the trial; 756 trAEs, 45 SARs and 4 SUSARs with the modified schedule and 402 trAEs, 42 SARs and 2 SUSARs with the standard schedule. Key

clinical TrAEs, by trial arm and CTCAE definition, are presented in **Error! Reference source not found.** alongside the maximum observed CTCAE grade. A plot including all TrAEs that occurred in more than 2.5% of patients is presented in **Supplementary Figure 1**.

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) using the modified schedule and 1.4 (1.92) using the standard schedule.

Forty-seven deaths were observed amongst participants randomized to the trial. The primary cause of death was most often related to RCC (modified schedule: 23/32 deaths (71.9%), standard schedule: 12/15 deaths (80%)). One treatment-related death due to 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

Median follow-up time at the time of final analysis for PFS was 21 months (95% CI: 17, 22) using the modified schedule and 22 months (95% CI: 15, 25) using the standard schedule. Kaplan-Meier curves summarizing PFS by arm are presented in **Error! Reference source not found.A**. At 12-months post-randomization, the progression-free survival estimate for the modified schedule was 46.1% (90% CI: 38.6, 53.2). Therefore, formal comparison of the lower limit of the confidence interval narrowly failed to exclude the historical control rate of 39.7% observed with sunitinib.[9]

Standard schedule PFS at 12-months post-randomization was 44.8% (32.1%, 56.7%) and appears similar to the modified schedule, although it is important to recognize 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, 1.36). Furthermore, PFS remained similar between arms with extended follow-up of participants, conducted one year after the trial follow-up period ended; median follow-up and Kaplan-Meier curves of the extended PFS data are presented in **Supplementary Figure S2**. PFS by IMDC risk group and PD-L1 expression status (where available) is also available in **Supplementary Figures 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%, 54.4%) with modified scheduling, and 35.9% (95% CI: 24.3%, 48.9%) with standard scheduling (**Table 2**). Median duration of response data are also presented in **Table 2**.

Overall Survival

Median follow-up time for OS was 32 months (95% CI: 31, 34) using the modified schedule and 31 months (95% CI: 28, 37) using the standard schedule. Kaplan-Meier curves summarizing OS by arm are presented in Error! Reference source not found.**B.** The post-randomization OS estimate at 12 months using modified scheduling was 88.3% (95% CI: 81.3%, 92.8%) and 84.1% (95% CI: 72.5%, 91.1%) using standard scheduling. At 24 months, the OS estimate using modified scheduling was 71.3% and 73.7% using standard scheduling. Median OS was not reached 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, 1.54).

IMDC intermediate- and poor-risk patients

Exploratory Kaplan Meier curves summarizing PFS and OS in participants with IMDC intermediate- or poor-risk disease by treatment arm are presented in Error! Reference source not found.**A** and **4B,** respectively. Median PFS was 10.5 months and 8.6 months with modified and standard scheduling, respectively. Twelve-month PFS estimates (95% CI) were 43.3% (32.7%, 53.3%) in the modified arm and 46.1% (30.7% 60.1%) in the standard arm. Median OS was 38.5 (95% CI 27.1, not reached (NR)) months in the modified arm and not reached in the standard arm. 24-month OS rates were 65.2% and 66.7% in the modified and standard arms, respectively. Amongst patients with IMDC intermediate- or poor-risk disease, the ORR was 46.7% (95% CI: 36.1%, 57.5%) in the modified arm and 40.9% (95% CI: 26.3%, 56.8%) in the standard arm (**Table 2**).

QoL

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

Quality of life (QoL), as measured by QLQ-C30 global health status, FKSI-19 total score and the EQ5D-5L visual analogue scale, did not meaningfully change from baseline at any time point in either arm (Error! Reference source not found.**A-C**). 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 were overlapping throughout (**Supplementary figure S5**). Means (SDs) and corresponding 95% CIs by

questionnaire subscales, time-point, and arm are available in **Supplementary Figures S5-S6.**

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 12-weekly instead of three-weekly. 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 two years.

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 due to 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 on-going benefit beyond treatment discontinuation,[11] that a lower threshold to stop treatment was employed by PRISM investigators.

Focusing on adverse events rather than efficacy as the primary endpoint 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 was also promising efficacy signals, larger randomized phase III trials could be considered. We did not consider large non-inferiority trials were justified without preliminary data.

The activity of standard IPI+NIVO in PRISM was broadly in line with prior data.[3] A higher proportion of patients had favorable risk disease (31%) and a lower proportion had prior nephrectomy (63%) in PRISM compared to CheckMate 214 (23% and 82%, respectively), but, otherwise, study populations were similar. The median PFS of 9.8 months amongst the mITT PRISM population receiving standard IPI sits within the 95% CI (12.4 months [9.8-16.5]) of the CheckMate 214 ITT population.[3] Amongst intermediate/poor-risk patients, corresponding figures were 8.6 months vs 11.6 months [95% CI 8.4-15.5]). The ORRs of 35.9% and 40.9% in this study are comparable to 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 FDA'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 pre-specified efficacy threshold (12-month PFS rate) using the modified schedule based on this comparison. However, when considering both the mITT and intermediate/poor risk subgroup of participants, efficacy data by median PFS, 12-month PFS and ORR were comparable between PRISM arms and were in line with 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. Large non-inferiority trials would be needed to formally address this, which do not appear justified based on our results, in the opinion of the authors.

It is concerning that patients reported outcome data in PRISM did not track the irAE data. The reasons for this are unclear. The relationship between adverse events and quality of life 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 ipilimumab more than a decade ago, the mechanisms by which CTLA-4 blockade induces both anti-tumor responses and irAE remain poorly defined. Intriguingly, however, pre-clinical studies suggest that CTLA-4 targeting agents that favor regulatory T cell depletion within the tumor microenvironment, whilst 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 12-weekly compared to three-weekly IPI dosing, in combination with NIVO, in patients with aRCC. Whilst a formal internal efficacy comparison was not possible, no meaningful differences between treatment arms were observed based on 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 whilst reducing toxicity experienced by patients.

Figure Legends

Figure 1. CONSORT flow diagram

Figure 2. Key treatment-related adverse events by severity

Figure 3. (A) Progression-free survival and (B) Overall survival by treatment allocation amongst the mITT population

Figure 4. (A) Progression-free survival and (B) Overall survival by treatment allocation amongst the IMDC intermediate/poor risk population

Figure 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

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.

Funding statement
The PRISM study was funded by Bristol-Myers Squibb (Princeton, NJ), supported by Yorkshire Cancer Research (YCR) through the YCR Centre for Early Phase Clinical Trials.

Acknowledgements
We thank all the patients and clinical study teams who participated in the PRISM trial. We are grateful to the University of Leeds, UK 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.

Author contributions

Conception and design: Naveen Vasudev, Thomas Powles, Sarah Brown, Paul Nathan, Galina Velikova, Fiona Collinson
Provision of study material or patients: Naveen S. Vasudev, Lisa Pickering, Tom Waddell, Kate Fife, Richard Griffiths, Anand Sharma, Anthony Maraveyas, Janet Brown, Carmel Pezaro, Mark Tuthill, Ekaterini Boleti, Amit Bhal, Balaji Venugopal, Poulam Patel, Ankit Jain, Stefan Symeonides, Paul Nathan, Thomas Powles
Collection and assembly of data: Gemma Ainsworth, Sarah Brown, Eszter Katona, Helen Howard, Bernadett Szabados, Rosamonde Banks, Joanne Brown
Data analysis and interpretation: Naveen Vasudev, Gemma Ainsworth, Sarah Brown, Galina Velikova, Lisa Pickering, Tom Waddell, Kate Fife, Paul Nathan, Fiona Collinson, Thomas Powles
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

References

1. Heng DYC, Xie W, Regan MM, et al: Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 27:5794-5799, 2009
2. Motzer RJ, Escudier B, McDermott DF, et al: Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. J Immunother Cancer 8, 2020
3. Motzer RJ, Tannir NM, McDermott DF, et al: Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 378:1277-1290, 2018
4. Hammers HJ, Plimack ER, Infante JR, et al: Safety and Efficacy of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study. J Clin Oncol 35:3851-3858, 2017
5. Lebbé C, Meyer N, Mortier L, et al: Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial. J Clin Oncol 37:867-875, 2019
6. Hellmann MD, Rizvi NA, Goldman JW, et al: Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol 18:31-41, 2017
7. Long GV, Robert C, Butler MO, et al: Standard-Dose Pembrolizumab Plus Alternate-Dose Ipilimumab in Advanced Melanoma: KEYNOTE-029 Cohort 1C, a Phase 2 Randomized Study of Two Dosing Schedules. Clin Cancer Res 27:5280-5288, 2021
8. Buckley HL, Collinson FJ, Ainsworth G, et al: PRISM protocol: a randomised phase II trial of nivolumab in combination with alternatively scheduled ipilimumab in first-line treatment of patients with advanced or metastatic renal cell carcinoma. BMC Cancer 19:1102, 2019
9. Motzer RJ, Hutson TE, Cella D, et al: Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 369:722-31, 2013
10. SAS Institute Inc.: SAS® 9.4 Statements: Reference. Cary, NC: SAS Institute Inc. , 2013
11. Regan MM, Jegede OA, Mantia CM, et al: Treatment-free Survival after Immune Checkpoint Inhibitor Therapy versus Targeted Therapy for Advanced Renal Cell Carcinoma: 42-Month Results of the CheckMate 214 Trial. Clin Cancer Res 27:6687-6695, 2021
12. Escudier B, Porta C, Bono P, et al: Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. J Clin Oncol 32:1412-8, 2014
13. Hirsch I, Goldstein DA, Tannock IF, et al: Optimizing the dose and schedule of immune checkpoint inhibitors in cancer to allow global access. . Nat Med 28:2236-2237, 2022
14. Bergerot CD, Malhotra J, Bergerot P, et al: Patients' Perceptions Regarding the Relevance of Items Contained in the Functional Assessment of Cancer Therapy Kidney Symptom Index-19. Oncologist, 2023
15. Du X, Liu M, Su J, et al: Uncoupling therapeutic from immunotherapy-related adverse effects for safer and effective anti-CTLA-4 antibodies in CTLA4 humanized mice. Cell Res 28:433-447, 2018
16. Hong MMY, Maleki Vareki S: Addressing the Elephant in the Immunotherapy Room: Effector T-Cell Priming versus Depletion of Regulatory T-Cells by Anti-CTLA-4 Therapy. Cancers (Basel) 14, 2022
17. Gan X, Shan Q, Li H, et al: An anti-CTLA-4 heavy chain-only antibody with enhanced T(reg)

depletion shows excellent preclinical efficacy and safety profile. Proc Natl Acad Sci U S A 119:e2200879119, 2022

Tables

Table 1: Baseline patient characteristics

	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 – n (%)			
Male	101 (78.9)	48 (75.0)	149 (77.6)
Female	27 (21.1)	16 (25.0)	43 (22.4)
IMDC prognostic group – n (%)			
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 – n / evaluable (%)			
Less than 1%	52/92 (56.5)	27/43 (62.8)	79/135 (58.5)
Greater than or equal to 1%	40/92 (43.5)	16/43 (37.2)	56/135 (41.5)
Previous nephrectomy – n (%)	81 (63.3)	42 (65.6)	123 (64.1)
Disease type – n (%)			
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 – n (%)			
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)

PD-L1: programmed death ligand-1; *IMDC:* International metastatic renal cell carcinoma database consortium

Table 2: Secondary outcome measures

	mITT population		IMDC Intermediate/Poor risk	
	Modified IPI (n=128)	**Standard IPI (n=64)**	**Modified IPI (n=90)**	**Standard IPI (n=44)**
Overall Response Rate, % (95% CI)*	45.3 (36.7, 53.9)	35.9 (24.2, 47.7)	46.7 (36.1, 57.5)	40.9 (26.3, 56.8)
Best overall response, n (%)				
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)
Median duration of response, months (95% CI)	16.5 (13.1-NR)	16.7 (12.6-NR)		
Treatment tolerability^, %	68.8	57.8		
Unadjusted risk difference % (95% CI)	10.9 (-3.6, 25.5)			
Treatment-related discontinuation, %	22.7	39.1		
Unadjusted risk difference % (95% CI)	-16.4 (-30.4, -2.4)			
Treatment-related discontinuation prior to completing 4 IPI doses, %	20.3	31.3		
Participants receiving trial treatment post-progression	**Modified IPI (n=27)**	**Standard IPI (n=6)**		
Response rate post first-progression,** % (95% CI) *	3.7 (0.09, 19.0)	16.7 (0.42, 64.1)		

* Response was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1.

^ Defined as the proportion of participants experiencing at least one treatment delay/interruption

** Response rate post-first progression is calculated using the number of participants who continued receiving trial treatment post first-progression as the denominator.