ISRCTN95351638 https://doi.org/10.1186/ISRCTN95351638

PRISM – A Phase II trial testing alternate schedules of combination Ipilimumab-Nivolumab therapy for patients with advanced and metastatic renal cell carcinoma

Submission date
04/12/2017

Recruitment status
No longer recruiting

Registration date
19/12/2017

Overall study status
Completed

Last Edited
19/01/2024

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Kidney cancer is the 13th most common cancer worldwide and the 7th most common cancer in Europe, with over 100,000 new cases diagnosed in Europe each year. Around 90% of these kidney cancers are renal cell carcinomas (RCC), and outcomes for patients with RCC vary widely. In recent years studies have demonstrated the potential of immunotherapy drugs in treating RCC, essentially harnessing the body's immune system to treat the cancer. One of these treatments is combination Nivolumab and Ipilimumab therapy which bind to two antibodies known as PD-1 and CTLA-4, but the combination of both drugs can cause significant treatment-related toxicities and side effects which can lead patients to discontinue treatment. This study aims to test two different methods of scheduling Nivolumab and Ipilimumab to try and reduce the number and severity of those side effects for patients, and thus allow more patients to continue treatment for longer.

Who can participate?
Adults aged 18 and older who have RCC.

What does the study involve?
Participants are allocated to one of two groups. Those in the first group receive a modified schedule of IV Ipilimumab combined with IV Nivolumab every 12 weeks (Weeks 1, 13, 25, 37) for a total of 4 doses. Participants will also receive nivolumab alone every 2 weeks in between the first and second doses of nivolumab plus ipilimumab and nivolumab alone every 4 weeks in between the second and third, and third and fourth doses of nivolumab plus ipilimumab. Participants will continue to receive nivolumab alone every 4 weeks following the 4 doses of combined treatment. Those in the second group receive the standard treatment schedule. Participants receive treatment in specialist hospital cancer units either fortnightly or every 4 weeks. Participants are followed up for safety for 100 days post last dose of trial drug or until death.
(updated 21/05/2019, previously: Participants are allocated to one of two groups. Those in the

first group receive a modified schedule of IV Ipilimumab combined with IV Nivolumab every 12 weeks (Weeks 1, 13, 25, 37) with fortnightly flat dose IV Nivolumab between combination doses. Those in the second group receive the standard treatment schedule. Participants receive treatment in specialist hospital cancer units either fortnightly or every 4 weeks. Participants are followed up for safety for 100 days post last dose of trial drug or until death.)

What are the possible benefits and risks of participating?
Whichever treatment schedule a patient receives they will still be receiving the combination treatment of Nivolumab and Ipilimumab. As with most cancer treatments there are unfortunately several adverse side effects associated with treatment for RCC, some of which may require additional treatments or medications to manage them. Some of the most common side effects of these treatments are: anaemia, gastrointestinal disorders like diarrhoea and vomiting, fatigue, dehydration, shortness of breath and dizziness, susceptibility to infections, muscle weakness, blurred vision, joint pain, and rashes, all of varying degrees of severity, but not every patient will experience all/many of these. All patients on the trial will be monitored by hospital staff and these side effects managed as best as possible.

Where is the study run from?
Clinical Trials Research Unit at the University of Leeds (UK) and takes place in 15 hospitals in the UK.

When is the study starting and how long is it expected to run for?
August 2016 to March 2022

Who is funding the study?
Bristol-Myers Squibb Pharmaceuticals Limited (UK)

Who is the main contact?
1. Ms Heather Poad
2. Mr Chris Linsley
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2017-001476-33

Protocol serial number
35020

Study information

Scientific Title
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

Acronym
PRISM

Study objectives
The overall aim of the study is to determine whether alternative scheduling of Ipilimumab (Q12W vs Q3W), when given in combination with Nivolumab, is associated with a favourable toxicity profile and sufficient activity to warrant further investigation, with additional evaluation of potential benefits in terms of discontinuation rates and quality of life (QoL), in patients with mRCC.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Yorkshire and the Humber – Leeds East Research Ethics Committee, 28/07/2017, ref: 17/YH/0187

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Renal Cancer

Interventions
Eligible participants are randomised 2:1 to one of two groups. Those in the first group receive a modified schedule of IV Ipilimumab combined with IV Nivolumab every 12 weeks (Weeks 1, 13, 25, 37) with fortnightly flat dose IV Nivolumab between combination doses. Those in the second group receive the standard treatment schedule of combination IV Ipilimumab and IV Nivolumab every 3 weeks for 4 doses (Weeks 1, 4, 7, 10). Patients will receive treatment in specialist hospital cancer units either fortnightly or every 4 weeks.

Upon receipt of four combination doses in either arm, flat dose IV Nivolumab is administered fortnightly until disease progression or treatment discontinuation (due to either treatment related toxicities or other reasons). The duration of the trial intervention is variable for individual participants and continues until disease progression, death or treatment discontinuation for any reason. The trial follows participants to disease progression or death (whichever occurs earlier), with safety follow-up continuing until 100 days post last dose of trial drug.

Intervention Type
Other

Phase
Phase II

Primary outcome(s)
The proportion of participants experiencing a grade 3/4 adverse reaction within initial 12 months of treatment as measured via adverse event (AE) reporting, where an AE has been clearly marked as an adverse reaction (AR) by the investigator. All grade 3/4 AEs judged by the investigator or sponsor as having a reasonable suspected causal relationship to nivolumab, ipilimumab or the combination of the two, will qualify as grade 3/4 ARs. AEs will be collected for all participants from the time of start of protocol treatment until 100 days post cessation of trial therapy and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events V4.03 (NCI-CTCAE), with those ARs occurring within the first 12 months of receiving the first dose of any trial drug contributing to this endpoint.

Key secondary outcome(s))
Key Secondary outcome measure:
Progression free survival as measured by time in days from randomisation until disease progression of death. Disease progression will be locally assessed by 12 weekly CT scans, with progression defined according to the RECIST v1.1 criteria; details of deaths occurring within the trial will be collected. The key secondary endpoint will be the proportion of patients alive and progression free at 12 months post randomisation.

Secondary outcome measures:
1. Safety and toxicity as reported based on the occurrence of ARs, serious adverse events (SAEs), serious adverse reactions (SARs) and SUSARs as graded by CTCAE v4.03 and as defined in section 15.1 of the trial protocol. AEs will be collected for all participants from the time of start of protocol treatment until 100 days post cessation of trial therapy with those AEs judged by the investigator or sponsor as having a reasonable suspected causal relationship to nivolumab, ipilimumab or the combination of the two, qualifying as ARs, SARs or SUSARs as appropriate.

Additionally, AEs that satisfy the seriousness criteria defined in section 15.1 of the protocol qualify as SAEs.
2. Treatment tolerability as measured by the proportion of participants experiencing a dose delay or interruption during treatment.
3. Discontinuation rates due to treatment related toxicity as measured by the proportion of participants whose treatment was discontinued specifically due to treatment-related toxicities at any point during the trial
4. Discontinuation rates due to 'other' reasons as measured by the proportion of participants whose treatment was discontinued for any reason other than treatment-related toxicities at any point during the trial
5. Overall response rate as measured by the proportion of participants who achieve either partial response or complete response (PR or CR) as their best response to treatment prior to first progression (both as defined under RECIST v1.1) assessed via 12-weekly CT scans
6. Duration of response as measured by the length of time in days between the first observation of at least PR in a participant until either disease progression or death
7. Response rate post-progression (for those receiving treatment beyond progression) as measured by the proportion of participants that were treated beyond progression who show a PR or CR best response compared to measurements of disease taken at the time of first RECIST-defined progression
8. Overall survival as measured by the length of time in days from the date of randomisation to the date of death from any cause for a participant. Participants who are still alive at the time of analysis will become censored at the date they were last known to be alive
9. Health related quality of life as measured by EQ-5D-5L, EORTC QLQ-C30, FACT FKSI-19 and study-specific symptoms questionnaires at Baseline, Week 7, Week 13, then every 12 weeks until disease progression or Week 60, whichever is earlier

Completion date
01/03/2022

Eligibility

Key inclusion criteria
1. Aged 18 years or over
2. Diagnosed with advanced (not amenable to curative surgery) or metastatic RCC
3. Histopathologically confirmed clear cell renal cell cancer (or with a component of clear cell)
4. Evidence of measurable disease as per RECIST v1.1 (ie, ≥1 malignant tumour mass that can be accurately measured in at least 1 dimension ≥ 20 mm with conventional computerized tomography scan or Magnetic Resonance Imaging [MRI], or ≥10 mm with spiral CT scan using a 5 mm or smaller contiguous reconstruction algorithm). Bone lesions, ascites, peritoneal carcinomatosis or miliary lesions, pleural or pericardial effusions, lymphangitis of the skin or lung, cystic lesions, or irradiated lesions are not considered measurable
5. Life expectancy of ≥ 6 months
6. Karnofsky Performance Status (KPS) of at least 70%
7. Required laboratory values within 14 days prior to registration:
7.1. WBC ≥ 2000/µL
7.2. Neutrophils ≥ 1500/µL
7.3. Platelets ≥ 100 x103/µL
7.4. Haemoglobin > 9.0 g/dL
7.5. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance (CrCl) ≥ 40 mL/min (Cockcroft and Gault or Wright formula may be used according to local practice)
7.6. AST and ALT ≤ 3 x ULN

7.7. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
8. Able to give written informed consent and willing to follow trial protocol
9. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug (See Appendix 2 for details).
10. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG)
11. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product.
12. Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
195

Key exclusion criteria
1. Breast feeding
2. Prior systemic therapy for RCC (previous participation in adjuvant studies allowed, providing the patient was on the observation/placebo arm – this may require unblinding of the patient)
3. Participants who have undergone any prior systemic anti-cancer treatment, including with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways (previous participation in adjuvant studies allowed, providing the patient was on the observation/placebo arm – this may require unblinding of the patient)
4. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
5. Participants who test positive for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection
6. Participants who test positive for human immunodeficiency virus (HIV) or have known acquired immunodeficiency syndrome (AIDS)
7. Untreated brain metastases. (Patients are not eligible if brain metastases treated only with whole brain radiotherapy. Patients are eligible if previous brain metastases treated with

complete surgical resection, Stereotactic Brain Radiation Therapy (SBRT), or gamma knife with no subsequent evidence of progression and asymptomatic. Patients are not eligible if brain metastases treated only with whole brain radiotherapy).
8. Active, known or suspected autoimmune disease. (Subjects are permitted to enrol if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger).
9. Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration. (Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease).
10. Uncontrolled adrenal insufficiency
11. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.
12. Palliative radiotherapy less than 14 days prior to first dose of study drug
13. Any history of hypersensitivity to any of the trial medications or excipients
14. Poorly controlled or serious medical or psychiatric illness that, in the Investigator's opinion, is likely to interfere with participation and/or compliance in this clinical trial

Date of first enrolment
31/01/2018

Date of final enrolment
31/03/2020

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
St James's Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
West Yorkshire
Leeds
United Kingdom
LS9 7TF

Study participating centre
Addenbrooke's Hospital
Cambridge University Hospitals NHS Trust
Hills Road
Cambridgeshire
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Bristol Haematology and Oncology Centre
University Hospitals Bristol NHS Trust
Horfield Road
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United Kingdom
BS2 8ED

Study participating centre
Mount Vernon Hospital
The Hillingdon Hospitals NHS Trust
Rickmansworth Road
Northwood
United Kingdom
HA6 2RN

Study participating centre
Royal Marsden Hospital
The Royal Marsden NHS Trust
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
Weston Park Hospital
Sheffield Teaching Hospitals NHS Trust
Whitham Road
Sheffield
United Kingdom
S10 2SJ

Study participating centre
Royal Free Hospital
Royal Free London NHS Trust
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
The Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
Castle Hill Hospital
Castle Road
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Study participating centre
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Wilmslow Road
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Western General Hospital
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Study participating centre
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United Kingdom
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Study participating centre
Royal Wolverhampton Hospitals NHS Trust
New Cross Hospital
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Study participating centre
Velindre Cancer Centre
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Cardiff
United Kingdom
CF14 2TL

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Industry

Funder Name
Bristol-Myers Squibb Pharmaceuticals Limited

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study is not expected to be made available.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/11/2023	18/01/2024	Yes	No
Results article		20/01/2024	19/01/2024	Yes	No
Protocol article	protocol	14/11/2019	18/11/2019	Yes	No
HRA research summary			28/06/2023	No	No