ISRCTN38949950 https://doi.org/10.1186/ISRCTN38949950

MAdCaP: MDM2 inhibition and Abiraterone in Carcinoma of the Prostate

Submission date 07/10/2013	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 07/11/2013	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 20/05/2022	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-idasanutlin-with-abiraterone-or-enzalutamide-for-men-with-prostate-cancer-who-havent-had

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
2013-002014-13

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Sponsor reference number: GN12ON129

Study information

Scientific Title
A phase I/randomised phase II trial of abiraterone acetate with or without RO5503781 in patients with metastatic castration resistant prostate cancer (mCRCP) who have not previously received docetaxel

Acronym
MAdCaP

Study objectives
To establish if the addition of RO5503781 to abiraterone improves radiological progression-free survival (PFS) in patients with mCRPC.

Ethics approval required
Old ethics approval format

Ethics approval(s)
West of Scotland Research Ethics Service, 10/03/2014, REC ref: 14/WS/0001

Study design
Open-label dose escalation study followed by a randomised placebo-controlled double blind multi-centre phase II study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Prostate cancer

Interventions
Phase I
After a single dose pharmacokinetic (PK) study on day 7 of cycle 1 patients will commence combination treatment on day 1 of cycle 1 and will continue on treatment until confirmed disease progression, intolerable toxicity or withdrawal. Prednisolone will continue until the final dose of abiraterone. Prednisolone may be continued or tapered off and stopped after this, off study, at the investigators discretion.

Phase II
Patients will be randomized in a 1:1 ratio to either the control arm (Arm A) or experimental arm (Arm B). The study will be double-blinded.
Control Arm A:
1. Abiraterone (1000mg PO daily, days 1 - 28)
2. Prednisolone (5mg PO twice daily, days 1- 28)
3. Placebo (PO twice daily, days 1 5).
A cycle length is 28 days.

Upon confirmed radiological progression, patients will be permitted to continue abiraterone and add in open label RO5503781 (days 1 5) until further progression (defined by PSA).

Experimental Arm B:
1. Abiraterone (1000mg PO daily, days 1 - 28)
2. Prednisolone (5mg PO twice daily, days 1- 28)
3. RO5503781 (PO twice daily, days 1 5).
A cycle length is 28 days.

Patients will commence treatment on day 1 and will continue on treatment until confirmed disease progression, intolerable toxicity or withdrawal. Prednisolone will continue until the final dose of abiraterone. Prednisolone may be continued or tapered off and stopped after this, off study, at the investigator's discretion.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Abiraterone acetate, RO5503781

Primary outcome measure
Radiological progression free survival [as per Prostate Cancer Working Group (2) (PCWG2)] Patients will have CT and bone scans at baseline then every 8 weeks for the first 24 weeks, thereafter every 12 weeks until progression is confirmed. Progression-free survival will be measured from the date of randomisation to the date of progression or date of death (any cause) for those who do not progress.

Secondary outcome measures
1. Prostate-specific antigen (PSA) response rate will be the proportion of patients achieving >50% drop in PSA for greater than 4 weeks. Patients will have PSA measured every 4 weeks.
2. Radiological response rate will be as per RECIST 1.1 for those patients with measurable disease at baseline.
3. For patients crossing over from placebo, PSA response rate will be the proportion of patients achieving >50% reduction in PSA from the point of cross over for > 4weeks
4. Biochemical and radiological PFS will be defined as the time from randomisation until the either PSA progression or radiological progression, (both as defined in PCWG2) or death (any cause) for patients who do not progress.
5. Pharmacokinetics (PK) of RO5503781 with and without abiraterone (phase I only)
6. Pharmacokinetics of abiraterone with and without RO5503781 (phase I only)
7. Pharmacokinetics of abiraterone in combination with RO5503781
Pharmacokinetics samples will be taken in the dose escalation phase of the study to explore the PK of both drugs alone and in combination.

Overall study start date
28/02/2014

Completion date
28/02/2020

Eligibility

Key inclusion criteria
1. Histologically proven adenocarcinoma of the prostate with documented metastases (where the metastatic lesions are confined to 1 or 2 lesions on a bone scan. These must be confirmed by a second modality (e.g. CT, MRI or biopsy).
2. Availability of archival tumour samples. Where patients are willing to undergo a biopsy as part of the study, these specimens may be used as an alternative where no archival specimen is available.
3. Proven disease progression since last change in therapy defined by at least one of the following:
3.1. Prostate-specific antigen (PSA) progression. This must be based on a series of at least three successively increasing readings each taken at least 7 days apart. The 3rd reading must be >= 2ng /ml. In the event where an intermediate reading is lower than a previous reading, then the patient will still be eligible (i.e. the three readings do not need to be consecutive). The first of the three readings must have been obtained after commencing the previous systemic therapy, or, in the case of androgen receptor antagonists, after discontinuing.
3.2. Radiographic progression since commencing last systemic anti-cancer therapy as defined by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 (Eisenhauer et al. 2009 Eur J Cancer. 4 5:2 2 8) for non-bone disease or the appearance of two or more new lesions on a bone scan.
4. Castrate levels of serum testosterone (<1.7nmol/l)
5. On-going castration therapy

6. Male aged 18 or over
7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) = 0 or 1
8. Haemoglobin (Hb)>= 10g/dL; platelets >= 150 x 109/L; neutrophils >=1.5 x109/L
9. Bilirubin < 1.5 x ULN; alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) < 2.5 x ULN
10. Serum potassium ≥ LLN; Alb ≥ 30 g/L
11. Serum creatinine < 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min
12. Able to swallow study drugs
13. Life expectancy of more than 3 months
14. Provision of written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Male

Target number of participants
132 in total (phase I: 3 -18 and phase II: 114)

Key exclusion criteria
1. Prior cytotoxic chemotherapy for castration resistant prostate cancer (patients may have received previous or ongoing bisphosphonates, eg. zoledronate, or denosumab)
2. Prior ketoconazole, abiraterone, MDV3100 (enzalutamide), TAK-700 (orteronel) or other novel anti-hormonal therapies
3. Uncontrolled hypertension (BP≥ 160 / 95 mmHg)
4. Significant heart disease as evident by myocardial infarction (MI) or arterial thrombotic events in past 6 months, severe unstable angina, or New York Heart Association class (NYHA) III or IV heart failure or class II to IV heart failure or cardic ejection fraction measurement of <50%.
5. Other anticancer therapy [apart from Luteinizing-hormone-releasing hormone (LHRH) agonist / antagonist] within 4 weeks (6 weeks for bicalutamide). This includes radiotherapy and therapeutic radionucleotides. Where patients are receiving bisphosphonates or denosumab they must have been on a stable dose for at least 6 weeks prior to starting study drug.
6. The requirement for strong opiates to control cancer related pain in the two weeks before study entry (codeine and tramadol are permitted)
7. Patient with a partner of child-bearing potential who is not using a highly effective method of contraception, who is unwilling to use condoms during the study and for 30 days after the last dose of study drug
8. Patients with known coagulopathy, platelet disorder or history of non-drug induced thrombocytopenia
9. Patients receiving oral or parenteral anti-coagulants/anti-platelet agents (chronic daily treatment with aspirin with doses >325 mg po daily, clopidogrel, low molecular weight heparin, or dagibatran, etc.) prior to the start of study therapy are excluded. Patients may receive anticoagulant flushes for maintenance of indwelling catheters.
10. Patients with known bone marrow disorders which may interfere with bone marrow recovery

(due to tumor involvement, fibrosis) (e.g. Concomitant myelodysplastic syndrome)
11. Patients who refuse blood products

Date of first enrolment
28/02/2014

Date of final enrolment
03/07/2017

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
Beatson West of Scotland Cancer Centre
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Sponsor information

Organisation
NHS Greater Glasgow and Clyde (UK)

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Sponsor type
Hospital/treatment centre

Website

http://www.nhsggc.org.uk/r&d

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Industry

Funder Name
Roche (UK)

Alternative Name(s)
F. Hoffmann-La Roche Ltd, F. Hoffmann-La Roche & Co, F. Hoffmann-La Roche AG, Roche Holding AG, Roche Holding Ltd, Roche Holding, Roche Holding A.G., Roche Holding, Limited, F. Hoffmann-La Roche & Co.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Funder Name
Cancer Research UK (CTAAC) (UK); CRUK Grant award No: A15846

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		25/12/2020	20/05/2022	No	No
HRA research summary			28/06/2023	No	No