ISRCTN04813360 https://doi.org/10.1186/ISRCTN04813360

A CR-UK phase I study of BKM120 in patients with non-small cell lung cancer (NSCLC) receiving thoracic radiotherapy

Submission date
25/01/2013

Recruitment status
No longer recruiting

Registration date
29/01/2013

Overall study status
Completed

Last Edited
24/06/2019

Condition category
Cancer

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

Plain English summary of protocol
http://www.cancerresearchuk.org/cancer-help/trials/a-study-looking-adding-biological-therapy-to-radiotherapy-non-small-cell-lung-cancer-bkm120

Contact information

Type(s)
Scientific

Contact name
Ms Stasya Ng

Contact details
Old Road Campus
Roosevelt Drive
Headington
Oxford
United Kingdom
OX3 7DQ
-
octo-BKM120@oncology.ox.ac.uk

Additional identifiers

ClinicalTrials.gov (NCT)
NCT02128724

Clinical Trials Information System (CTIS)
2012-003762-40

Protocol serial number
13615

Study information

Scientific Title
A CR-UK phase I dose escalation study of BKM120 in patients with non-small cell lung cancer (NSCLC) receiving thoracic radiotherapy

Acronym
BKM120

Study objectives
This study will be a single-centre, open-label, 3+3 cohort, dose escalation phase I study of the use of BKM120 in combination with thoracic radiotherapy. Patients with incurable NSCLC requiring palliative thoracic radiotherapy will be eligible for entry.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee South Central - Oxford B, 07/01/2013, ref: 12/SC/0674

Primary study design
Interventional

Study design
Non-randomised open-label 3+3 cohort dose-escalation phase I study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: National Cancer Research Network; Subtopic: Lung Cancer; Disease: Lung (non-small cell)

Interventions
BKM120 Cohort 1, 50 mg OD (days 1-14). 20 Gy in 5 fractions (days 8-14)
BKM120 Cohort 2, 80 mg OD (days 1-14). 20 Gy in 5 fractions (days 8-14)
BKM120 Cohort 3, 100 mg OD (days 1-14). 20 Gy in 5 fractions (days 8-14)
BKM120 Cohort 4, At maximum tolerated dose (MTD) (days 1 to 28). 20 Gy in 5 fractions (days 22 - 28)

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
BKM120

Primary outcome(s)
The safety, dose-limiting toxicity (DLT) and MTD of BKM120 with radiotherapy

Key secondary outcome(s)
Current secondary outcome measures as of 19/07/2016:
1. To evaluate Akt phosphorylation as a predictive marker of response to BKM120; Timepoint(s): Determine phosphorylation status of Akt in peripheral blood mononuclear cells (PBMC) at baseline, during BKM120 treatment and following BKM120 + RT treatment
2. To investigate potential biomarkers that correlate with response to BKM120; Timepoint(s): Measure tumour pAkt and Phosphatase and tensin homolog (PTEN) levels and then identify mutation status of RAS, PI3K and EGFR by PCR
3. To investigate whether BKM120 alters tumour hypoxia and perfusion; Timepoint(s): Changes in 18F-Misonidazole uptake as detected by PET-CT scans. Changes in blood flow as detected by perfusion CT

Previous secondary outcome measures:
1. To evaluate Akt phosphorylation as a predictive marker of response to BKM120; Timepoint(s): Determine phosphorylation status of Akt in peripheral blood mononuclear cells (PBMC) at baseline, during BKM120 treatment and following BKM120 + RT treatment
2. To investigate potential biomarkers that correlate with response to BKM120; Timepoint(s): Measure tumour pAkt and Phosphatase and tensin homolog (PTEN) levels and then identify mutation status of RAS, PI3K and EGFR by PCR
3. To investigate whether BKM120 alters tumour hypoxia and perfusion; Timepoint(s): Changes in 18F-Misonidazole uptake as detected by PET-CT scans

Completion date
17/10/2017

Eligibility

Key inclusion criteria
Current inclusion criteria as of 02/03/2017:
1. Evidence of histologically confirmed NSCLC of any stage
2. Thoracic lesion requiring palliative radiotherapy and which has been identified on a scan within eight weeks of starting the trial
3. Male or female, age >= 18 years at the day of consenting to the study
4. Life expectancy of at least 16 weeks
5. Eastern Cooperative Oncology Group (ECOG) performance score of 0-2
6. Patient is able to swallow and retain oral medication
7. The patient is willing to provide written informed consent and is likely to comply with the protocol for the duration of the study, and scheduled follow-up visits and examinations
8. Haematological and biochemical indices within the ranges shown below:
8.1. Haemoglobin (Hb) >= 9.0 g/dL
8.2. Absolute neutrophil count >= 1.5 x 109/L
8.3. Platelet count >=100 x 109/L
8.4. International Normalised Ratio (INR) <= 1.5
8.5. Potassium, calcium and Magnesium Within normal range
8.6. Alanine aminotranferease (ALT) and aspartate aminotransferase (AST) not above normal range or< =3.0 times ULN if liver metastases are present
8.7. Total serum bilirubin not above normal range, or <=1.5 times ULN if liver metastases are

present or total bilirubin <=3.0 times ULN if the chief investigator is satisfied that the patient has well documented Gilbert's disease and absence of other contributing disease process at the time of diagnosis
8.8. Creatinine <= 1.5 x ULN
8.9. Fasting plasma glucose (FPG) <= 120mg/dL [6.7 mmol/L]

Previous inclusion criteria from 19/07/2016 to 02/03/2017:
1. Evidence of histologically confirmed NSCLC of any stage
2. Thoracic lesion requiring palliative radiotherapy and which has been identified on a scan within eight weeks of starting the trial
3. Male or female, age >= 18 years at the day of consenting to the study
4. Life expectancy of at least 16 weeks
5. Eastern Cooperative Oncology Group (ECOG) performance score of 0-1
6. Patient is able to swallow and retain oral medication
7. The patient is willing to provide written informed consent and is likely to comply with the protocol for the duration of the study, and scheduled follow-up visits and examinations
8. Haematological and biochemical indices within the ranges shown below:
8.1. Haemoglobin (Hb) >= 9.0 g/dL
8.2. Absolute neutrophil count >= 1.5 x 109/L
8.3. Platelet count >=100 x 109/L
8.4. International Normalised Ratio (INR) <= 1.5
8.5. Potassium, calcium and Magnesium Within normal range
8.6. Alanine aminotranferease (ALT) and aspartate aminotransferase (AST) not above normal range or< =3.0 times ULN if liver metastases are present
8.7. Total serum bilirubin not above normal range, or <=1.5 times ULN if liver metastases are present or total bilirubin <=3.0 times ULN if the chief investigator is satisfied that the patient has well documented Gilbert's disease and absence of other contributing disease process at the time of diagnosis
8.8. Creatinine <= 1.5 x ULN
8.9. Fasting plasma glucose (FPG) <= 120mg/dL [6.7 mmol/L]

Original inclusion criteria:
1. Evidence of histologically confirmed NSCLC of any stage
2. Thoracic lesion requiring palliative radiotherapy and which has been identified on a scan within eight weeks of starting the trial
3. Male or female, age >= 18 years at the day of consenting to the study
4. Life expectancy of at least 16 weeks
5. Eastern Cooperative Oncology Group (ECOG) performance score of 0-1
6. Patient is able to swallow and retain oral medication
7. The patient is willing to provide written informed consent and is likely to comply with the protocol for the duration of the study, and scheduled follow-up visits and examinations
8. Haematological and biochemical indices within the ranges shown below:
8.1. Haemoglobin (Hb) >= 9.0 g/dL
8.2. Absolute neutrophil count >= 1.5 x 109/L
8.3. Platelet count >=100 x 109/L
8.4. International Normalised Ratio (INR) <= 1.5
8.5. Potassium, calcium and Magnesium Within normal range
8.6. Alanine aminotranferease (ALT) and aspartate aminotransferase (AST) within normal range or< =3.0 times ULN if liver metastases are present
8.7. Total serum bilirubin within normal range, or <=1.5 times ULN if liver metastases are present or total bilirubin <=3.0 times ULN if the chief investigator is satisfied that the patient has well documented Gilberts disease and absence of other contributing disease process at the time of

diagnosis
8.8. Creatinine <= 1.5 x ULN
8.9. Fasting plasma glucose (FPG) <= 120mg/dL [6.7 mmol/L]

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
21

Key exclusion criteria
1. Previous chemotherapy or biological therapy within four weeks of starting study treatment
2. Treatment with any other investigational agent, or participation in another interventional clinical trial within 28 days prior to enrolment
3. Patient has not recovered to grade 1 or better (except alopecia) from related side effects of any prior antineoplastic therapy
4. Treatment at the start of study treatment with any drugs known to be moderate or strong inhibitors or inducers of isoenzyme CYP3A4, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug.
5. Presence of active uncontrolled or symptomatic CNS metastases. Patients with asymptomatic CNS metastases may participate in this trial. Any prior local treatment for CNS metastases must have been completed treatment >= 28 days prior to enrolment in the trial (including surgery and radiotherapy).
6. Patient has poorly controlled diabetes mellitus (HbA1c > 8 %)
7. Previous exposure to PI3K, mTOR, or AKT inhibitor
8. Patient has a known hypersensitivity to any of the excipients of BKM120
9. Previous thoracic radiotherapy treatment
10. Any previous extra-thoracic radiotherapy within 28 days prior to enrolment
11. Medically documented history of or active major depressive episode, bipolar disorder, obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or risk of doing harm to others
12 .Patient meets the cut-off score of >= 12 in the PHQ9 or a cut-off of >= 15 in the GAD7 mood scale, respectively, or selects a positive response of '1, 2, or 3' to question number 9 regarding potential for suicidal thoughts ideation in the PHQ9 (independent of the total score of the PHQ9)
13. Patient has >=CTCAE grade 3 anxiety
14. Other psychological, social or medical condition, physical examination finding or a laboratory abnormality that the
Investigator considers would make the patient a poor trial candidate or could interfere with

protocol compliance or the interpretation of trial results.
15 .Patient has a concurrent malignancy or has had any malignancy (other than NSCLC) in the last 3 years prior to start of study treatment (with the exception of adequately treated basal or squamous cell carcinoma or cervical carcinoma in situ)
16. Patient has had major surgery within 14 days of starting the study drug.
17. Patient has any other concurrent severe, and/or uncontrolled medical condition that would, in the investigator's judgement contraindicate patient participation in the clinical study (e.g. chronic pancreatitis, chronic active hepatitis).
18. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BKM120.
19. Patients who are known to be serologically positive for Hep B, Hep C or HIV.
20. Patient has active cardiac disease including any of the following:
20.1. LVEF < 50% as determined by MUGA scan or ECHO
20.2. QTc > 480 msec on screening ECG (using the QTcF formula)
20.3. Patient is taking a medication that has a known risk of causing QT interval prolongation or inducing Torsades de Pointes, and the treatment cannot be discontinued or switched to an alternative medication.
20.4. Angina pectoris that requires the use of antianginal medication
20.5. Ventricular arrhythmias except for benign premature ventricular contractions
20.6. Any other cardiac arrhythmia not controlled with medication
20.7. Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication
20.8. Conduction abnormality requiring a pacemaker
20.9. Valvular disease with documented compromise in cardiac function
20.10. Symptomatic pericarditis
20.11. History of myocardial infarction within 6 months of entering the trial
20.12. History of congestive heart failure(New York Heart Association functional classification III-IV)
20.13. Documented cardiomyopathy
21. Pregnant or breastfeeding women, or women of childbearing potential unless effective methods of contraception are used. Women of childbearing potential must use highly effective methods of contraception. Oral contraception, injected or implanted hormonal methods are not allowed as BKM120 potentially decreases the effectiveness of hormonal contraceptives. Acceptable methods of contraception are either:
21.1. True abstinence
21.2. Surgical sterilization
21.3. Male partner sterilization
Or use of a combination of any two of the following (a+b):
a) Placement of an IUD or IUS
b) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidalfoam/gel/film/cream/vaginal suppository . Female patients must use acceptable methods of contraception must continue to use contraception for at least 4 weeks after completing BKM120. Male patients (and their female partners) will need to continue to use use contraception for at least 16 weeks after completing BKM120. Women of childbearing potential must have a negative serum pregnancy test <= 72 hours prior to initiating treatment

Date of first enrolment
31/03/2013

Date of final enrolment
31/08/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Churchill Hospital
Oxford
United Kingdom
OX3 7LE

Sponsor information

Organisation
University of Oxford (UK)

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK (UK)

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

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Oxford Cancer Imaging Centre (UK)

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Sarah Pearson (octo-enquiries@oncology.ox.ac.uk).
Type of data: PET imaging data
When the data will become available and for how long: Currently available, no specific limit on duration at present.
By what access criteria will be shared: Internal/external researchers will have to complete a data sharing form (available on request) specifying amongst other details the motivation of their request, background, rationale, details of funding and approvals and also agree to specific conditions of data sharing. There is no specific restriction on the types of analyses at present and upon approval data will be transferred using a secure method.
Consent: Consent not specifically obtained but the data is completely anonymised including scan dates. This is in compliance with the MRC's Good Practice Principles for Sharing Individual Participant Data From Publicly Funded Clinical Trials V1.0 4.2.2.
Ethical/legal restrictions: The researchers would expect the research to be ethically approved where required and for legal compliance as appropriate.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2019	19/06/2019	Yes	No
Basic results		18/10/2018	18/10/2018	No	No
HRA research summary			28/06/2023	No	No