BKM120

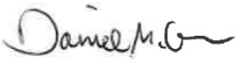
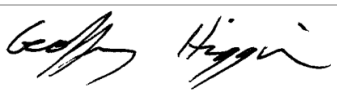
A CR-UK phase I study of BKM120 in patients with non-small cell lung cancer (NSCLC) receiving thoracic radiotherapy

Palliative thoracic radiotherapy plus BKM120

Statistical Analysis Plan

Version number 3.0, 18 Oct 2017

Based on Protocol version 7.0, 12 Jan 2017
Centre for Statistics in Medicine

	Name	Title/Role	Signature	Date
Author	Vicky Strauss	Senior Trial Statistician		18Oct2017
Reviewer	Seid Mohammed	Trial Statistician		18Oct2017
Reviewer	Daniel McGowan	Clinical Lecturer		26 Oct 2017
Reviewer	Stasya Ng	Trial Manager		26 Oct 2017
Approver	Geoffrey Higgins	Chief Investigator		20 Oct 2017

Sponsored by the University of Oxford
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1. INTRODUCTION

This document details the proposed presentation and analysis for the main paper(s) reporting results from the **phase I dose escalation study of the PI3K inhibitor BKM120, given concomitantly with palliative radiotherapy for the treatment of Non-Small Cell Lung Cancer (NSCLC).** The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

1.1 Key Personnel

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2. BACKGROUND INFORMATION

Lung cancer is the most common malignancy in industrialised countries. In 2008 approximately 41000 people in the UK were diagnosed with lung cancer, of which approximately 80% were due to non-small cell lung cancer (NSCLC). In the same year there were over 35000 deaths due to lung cancer, reflecting the poor prognosis associated with the disease. Radiotherapy (RT) plays an important role in the management of patients with NSCLC. Patients with non-metastatic disease may be treated with radical RT alone (Stage I-II), or with combination radical chemo-RT treatment (Stage III). Patients with metastatic disease (Stage IV) or with disease not amenable to radical RT treatment, often receive palliative thoracic RT in order to alleviate their symptoms.

The overall prognosis associated with NSCLC remains very poor despite improvements associated with combined modality treatment and with technical advances enabling the delivery of more accurate RT treatment.

Pre-clinical data suggests that BKM120 renders tumour cells more sensitive to ionising radiation and reduces tumour hypoxia and perfusion. All of these effects may enhance the efficacy of RT treatment.

This trial will therefore assess whether BKM120 can be safely combined with thoracic RT treatment and whether it alters the tumour microenvironment in a way that is likely to improve RT.

2.1 Objectives

2.1.1 Primary Objective

The primary aim in the dose escalation phase of the trial is to determine the safety, dose-limiting toxicity (DLT) and MTD of BKM120 when administered concomitantly with thoracic radiotherapy in patients with incurable NSCLC.

2.1.2 Secondary Objective

The secondary aim is to investigate whether BKM120 alters tumour hypoxia and perfusion.

2.1.3 Tertiary/Exploratory Objective

The tertiary aims are:

- To evaluate Akt phosphorylation as a predictive marker of response to BKM120
- To investigate potential biomarkers that correlate with response to BKM120

2.2 Study Design

This study is a single-centre, open-label, 3+3 design dose escalation phase studying the use of BKM120 in combination with thoracic RT. A dose expansion phase and a further cohort of patients, referred to as Cohort 4 are also incorporated. Patients with incurable NSCLC requiring palliative thoracic RT are eligible for entry (refer to Section 2.3 for full details of eligibility criteria).

The dose escalation phase of the study ended upon the declaration of the MTD of BKM120 in August 2015 (details will be reported in the statistical report). The study is currently recruiting to the expansion phase.

The trial will recruit 2-30 evaluable patients presenting with any stage of NSCLC, requiring palliative RT treatment.

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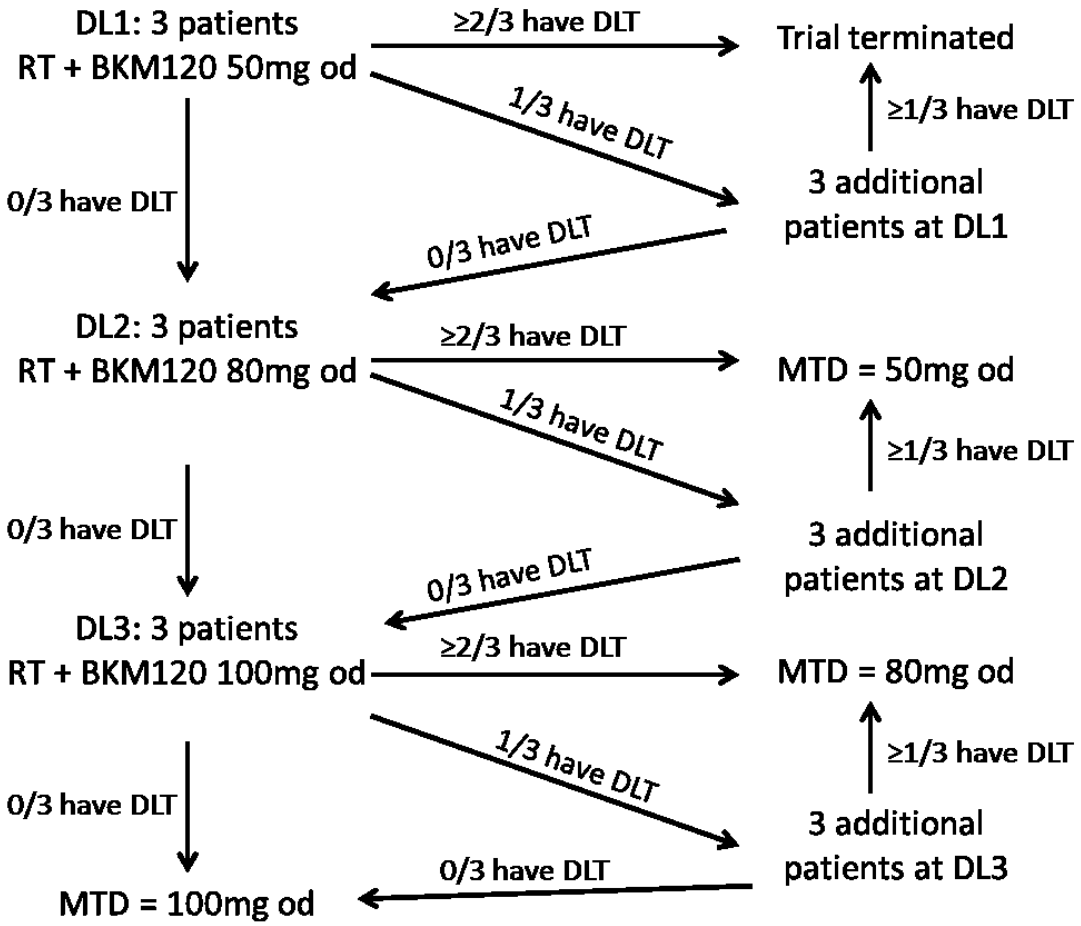
2.2.1 Dose Escalation Phase

The escalation phase consisted of three cohorts of patients, each treated at different dose levels of BKM120: the starting dose of 50mg, the escalated dose of 80mg and the highest dose level of 100mg. This phase of the study used a standard 3+3 dose escalation design to determine the MTD of BKM120, illustrated in Figure 1.

Figure 2.1: Dose escalation phase trial design of dose escalation



2.2.1.1 Dose Limiting Toxicity

The following was considered a DLT if it occurred at any point whilst the patient was on study and was based on clinical and laboratory toxicity assessments (NCI-CTCAE version 4.0):

1) Any ≥ grade 3 non-haematological toxicity (excluding nausea, vomiting or diarrhoea) that requires hospital admission or which does not resolve to ≤ grade 2 within 7 consecutive days of optimal treatment.
2) Any ≥ grade 3 nausea, vomiting or diarrhoea will be considered DLT only if any of them persist for >48 hours despite maximum supportive care.
3) ≥ Grade 3 pneumonitis
4) Any ≥ grade 4 haematological toxicity.
5) Mood deterioration from baseline DLT will be any grade ≥3 mood change if BL score of 2. DLT will be any grade ≥2 mood change if BL score of ≤ 1.

2.2.1.2 Evaluability

A patient was deemed evaluable for the dose escalation analysis if they completed their time on study or experienced a DLT beforehand.

2.2.1.3 Maximum Tolerated Doses

The MTD was defined as the highest dose of BKM120 in combination with radiotherapy at which no more than 1 of 6 evaluable patients or 0 of 3 evaluable patients experienced a DLT.

2.2.2 Dose Expansion Phase

Upon completion of the dose escalation phase, an expansion phase will consist of a further 6 evaluable patients, i.e. 6 patients with a pair of analysable scans for imaging parameter derivation (refer to the Imaging Analysis Plan V1.0 16Jun2016). The patients in the expansion phase are treated at the MTD level of BKM120 with palliative RT to investigate whether BKM120 alters tumour hypoxia and perfusion.

2.2.3 Cohort 4

As stated in the Protocol V7.0, this cohort will only be opened if there is no evidence of BKM120 induced changes in the tumour hypoxia and perfusion in cohorts 1-3 (including the expansion phase), i.e. if more than 50% of the patients treated with the MTD of BKM120 (n = 9 to 12) are defined as non-responders (refer to Section 2.8.2). A total of six patients will be entered into Cohort 4 to reinvestigate whether BKM120 alters tumour hypoxia and perfusion by increasing the intake of BKM120 at the MTD level, treated in combination of palliative RT.

As stated in the TMG Minutes 09Jun2017, the recruitment will be completed by 31Aug2017, regardless of whether there is a need to open cohort 4 or not.

An interim imaging data review was also taken place on 08Jun2017 by Dr Daniel McGowan to confirm there are more than 50% non-responders among 9 patients treated with the MTD of BKM120.

2.2.4 Duration of the Study

Date start of recruitment:	January 2013
Number recruited in the escalation phase:	11 patients
Number to be recruited for expansion cohort:	6 patients
Number to be included for Cohort 4 (if opened):	6 patients
Date of expected end of recruitment:	August 2017
Date of expected end of follow-up:	October 2017
Date of expected final analysis:	January 2018

2.2.5 Participating Centres of the Study

The study is conducted in a single centre (Oxford, UK).

2.3 Treatment Interventions

The Investigational Medicinal Product (IMP) in this trial is BKM120 (Buparlisib) in patients with NSCLC receiving thoracic RT. BKM120 has previously been used in a single-agent phase I study and is currently being used in clinical trials in combination with both chemotherapies (e.g. paclitaxel and carboplatin) and biological therapies (trastuzumab) but there are currently no trials combining BKM120 with RT treatment.

In the dose escalation phase, patients were assigned to the appropriate BKM120 dose level according to the 3+3 dose escalation design. BKM120 was not escalated above 100mg, as this dose has previously been established as the recommended phase two dose for future single agent studies. In the expansion phase, treatment will be as per the dose escalation phase, but with all patients treated at the MTD level of BKM120. Patients in Cohort 4 will have 3 weeks of BKM120 at the MTD level. Dosage details of BKM120 and RT are given in Table 2.1.

Table 2.1: Treatment doses planned per BKM120 dose cohort

Dose Level	RT	BKM120	BKM120 dose escalation plan
1	20Gy in 5 fractions (days 8 - 14)	50 mg od (days 1 to 14)	Three patients will be entered If 0/3 have DLT proceed to DL2 If 1/3 have DLT expand dose level to a total of 6 patients. If none of the additional 3 patients develop DLT, proceed to DL2. If any further patient(s) develop DLT (≥ 2/6) the MTD is exceeded and the trial will be terminated.
2	20Gy in 5 fractions (days 8 - 14)	80 mg od (days 1 to 14)	Three patients will be entered If 0/3 have DLT proceed to DL3. If 1/3 have DLT expand dose level to a total of 6 patients. If none of the additional 3 patients develop DLT, proceed to DL3. If any further patient(s) develop DLT (≥ 2/6) the MTD will be defined as 50mg od.
3	20Gy in 5 fractions (days 8 - 14)	100 mg od (days 1 to 14)	Three patients will be entered If 0/3 have DLT then the MTD is 100 mg od. If 1/3 have DLT expand dose level to a total of 6 patients. If none of the additional 3 patients develop DLT, the RPTD is 100 mg bd. If any further patient(s) develop DLT (≥ 2/6) the MTD will be defined as 80mg od.
Expanded cohort at MTD	20Gy in 5 fractions (days 8 - 14)	MTD dose (days 1 to 14)	Once the MTD has been reached a further 6 patients will be treated at the MTD of BKM120 with palliative RT.
4	20Gy in 5 fractions (days 22 – 28)	At MTD (days 1 to 28)	This cohort will only be used if there is no evidence of BKM120 induced changes in the tumour microenvironment on functional imaging in cohorts 1-3. A total of six patients will be entered into this cohort.

BKM120 is supplied as 10mg and 50mg hard gelatin capsules and administered on a continuous daily dosing from the morning of day 1, until the morning of the day of the final RT treatment.

All patients will receive palliative RT in 20Gy in 5 fractions in the last week of BKM120 treatment.

2.4 Eligibility

All patients will be screened for inclusion and exclusion criteria within 4 weeks prior to the first dose of BKM120. Written informed consent must be obtained before any study specific procedures are performed. The Investigator will determine patient eligibility based on the following criteria.

2.4.1 Inclusion Criteria

A patient is eligible for inclusion in this study if all of the following criteria apply:

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. 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:

Lab Test	Value required
Haemoglobin (Hb)	≥ 9.0 g/dL
Absolute neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥100 x 10^9/L
International Normalised Ratio (INR)	≤ 1.5
Potassium, calcium and Magnesium	Within normal range
ALT and AST	Not above normal range or ≤3.0 times ULN if liver metastases are present
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
Creatinine	≤ 1.5 x ULN
Fasting plasma glucose (FPG)	≤ 120mg/dL [6.7 mmol/L]

2.4.2 Exclusion Criteria

A patient is not eligible for the trial if any of the following criteria apply:

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 PHQ-9 or a cut-off of ≥ 15 in the GAD-7 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 PHQ-9 (independent of the total score of the PHQ-9)
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. Patients who are known to be serologically positive for Hepatitis B, Hepatitis C or HIV.
19. Patients who are known to be serologically positive for Hepatitis B, Hepatitis C or HIV.
20. Patient has active cardiac disease including any of the following:
    - Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - QTc > 480 msec on screening ECG (using the QTcF formula)
    - 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.
    - Angina pectoris that requires the use of anti-anginal medication
    - Ventricular arrhythmias except for benign premature ventricular contractions
    - Any other cardiac arrhythmia not controlled with medication
    - Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication
    - Conduction abnormality requiring a pacemaker
    - Valvular disease with documented compromise in cardiac function
    - Symptomatic pericarditis
    - History of myocardial infarction within 6 months of entering the trial
    - History of congestive heart failure(New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
21. Pregnant or breast-feeding women, or women of childbearing potential unless effective methods of contraception are used. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, 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:
    - True abstinence: When this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (eg calendar, ovulation, sympotothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception].
    - Surgical sterilization: Have had bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking BKM120. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female study patients, the vasectomised male partner should be the sole partner for that patient]
    - Or use of a combination of any two of the following (a+b):
        a) Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        b) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/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 contraception for at least 16 weeks after completing BKM120. Women of child-bearing potential must have a negative serum pregnancy test ≤ 72 hours prior to initiating treatment

2.5 Trial Closure

The end of the trial is defined as the last visit of the last patient enrolled in the trial i.e. approximately 6 weeks post completion of BKM120 plus radiotherapy. The sponsor and the Chief Investigator reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

2.6 Sample Size

Between 2 and 18 patients were to be recruited to the dose escalation phase. A 3+3 cohort design was used to establish the MTD of 50mg, 80mg and 100mg for BKM120 with palliative RT. In August 2015, the escalation phase closed recruitment with a total of 11 patients recruited. The expansion phase intends to recruit an additional 6 evaluable patients treated at the MTD of BKM120 with palliative RT.

Recruitment ended on 31Aug2017. A total of 10 patients have been recruited in the expansion phase. Among 10 recruited, 6 had evaluable FMIO-PET scans.

2.7 Randomisation

BKM120 is not a randomised study; no randomisation is performed.

2.8 Definition of Outcomes

2.8.1 Primary Outcome

The MTD of BKM120 was defined as the highest dose of BKM120 in combination with thoracic RT at which no more than 1 of 6 evaluable patients or 0 of 3 evaluable patients experienced a DLT. The definition of a DLT and evaluability can be found in Section 2.2.1.1 and Section 2.2.1.2, respectively.

The trial management group (TMG) declared the MTD in August 2015 (refer to the statistical report).

2.8.2 Secondary Outcomes

As stated in the Protocol V7.0,

Changes in ^{18}F-Misonidazole retention and in blood flow between pre and post BKM120 treatment are defined as response to BKM120 treatment based upon changes in tumour hypoxia and perfusion as detected by ^{18}F-Miso PET-CT scans and perfusion CT scans respectively. Each patient will be classified as a 'responder' or 'non-responder' on the basis or their pre- and post- BKM120 imaging. Those patients whose imaging demonstrates the presence of a physiological response on either perfusion CT and/or 18F-Misonidazole PET-CT will be classified as a 'responder' whilst those that do not show a response on either imaging modality will be classed as a 'non-responder'.

As stated in the IAP V1.0_01Jun2016,
Hypoxia will be measured using TBR_{mean} or TBR_{volume} (tumour-to-blood ratio) from each PET-CT scan.
From perfusion-CT, blood flow (BF), blood volume (BV) and mean transit time (MTT) will be derived.

In the file of secondary Analysis Template For IEPTOC V2.0_07Apr2016,

For each parameter, patients will be classified as 'responders' if their differences are ≥ 10% for at least one of the hypoxia parameters. The cut-off of 25% for perfusion will be used to define perfusion responders. Patients will be classified as 'responders' to Buparlisib if they are deemed as a responder to hypoxia or perfusion.

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2.9 Outcomes Assessment Schedule

2.9.1 Escalation and Expansion Phase

	Day-28 to day -2	Day -1	Day 1	Day 8	Day 14	Day 28	Day 56
Written Informed Consent Screening	X						
Written Informed Consent Main Study	X						
Demography	X						
Inclusion/exclusion criteria	X						
Relevant medical history/current medical conditions	X						
Diagnosis and extent of cancer	X						
Prior antineoplastic therapy	X						
^{18}F-Miso PET-CT and Perfusion CT scans		X		X			
Blood samples from ^{18}F-Miso PET-CT		X		X			
Vital signs		X		X	X	X	X
Height		X					
Weight		X		X	X	X	X
Physical examination		X		X	X	X	X
ECOG performance status	X	X		X	X	X	X
Patient self-rating mood scales for depression (PHQ-9) and anxiety (GAD-7)	X	X		X	X	X	X
ECG	X				X		X
Prior/concomitant medications	X			X	X	X	X
Adverse Events		X	X	X	X	X	X
Haematology	X			X	X	X	X
Clinical chemistry	X			X	X	X	X
Lipase	X				X		X
Fasting plasma glucose (FPG)	X			X	X	X	X
HbA_{1C}	X						
Liver Function Tests	X			X	X	X	X
Blood test for pAkt measurement	X			X	X	X	X
Coagulation (INR)	X			X	X	X	X
Urinalysis	X				X		X
Dispensing of BKM120		X					
BKM120[a]			Once daily				
Radiotherapy				20 Gy in 5 fractions			
Pregnancy test (if applicable)		X	If clinically indicated				

[a] BKM120 taken at 50mg, 80mg, 100mg (cohorts 1-3 of the escalation phase respectively) or MTD (expansion phase) once daily continuously on days 1-14

3. QUALITY CONTROL AND DATA VALIDATION

3.1 Data Cleaning

Day-to-day monitoring of data entered into the trial database is carried out by the Oncology Clinical Trials Office (OCTO) staff.

The trial statisticians, based in the Centre for Statistics in Medicine (CSM), will perform routine data cleaning to ensure the integrity of the data.

3.2 Data Derivation and Manipulation

Data derivation/manipulation will be checked to ensure validity of the derived data, where appropriate. Calculations performed by the computer can be checked by hand for the smallest of 5% or 20 observations within the dataset, where appropriate.

3.3 Validation of Results

It is not intended that the analyses will be repeated by a statistician independent of the trial.

4. DATA MONITORING COMMITTEE AND INTERIM ANALYSES

An Independent Early Phase Trial Oversight Committee (IEPTOC) will be in place to monitor the safety and progress of the trial. This committee meets approximately twice a year to monitor recruitment to the trial and protocol compliance as well as adverse events.

The primary research question of the dose escalation phase has been answered, with the MTD of BKM120 determined (refer to the statistical report). Formal interim analyses took place to decide and agree on whether or not to dose-escalate in the dose escalation phase of the trial.

There are no planned statistical interim analyses for this trial. Statistical interim analyses will only be performed if requested by IEPTOC.

However, imaging data will be monitored throughout the trial by the Trial Management Group (TMG) to ratify Dr Daniel McGowan's decision on the imaging evaluability.

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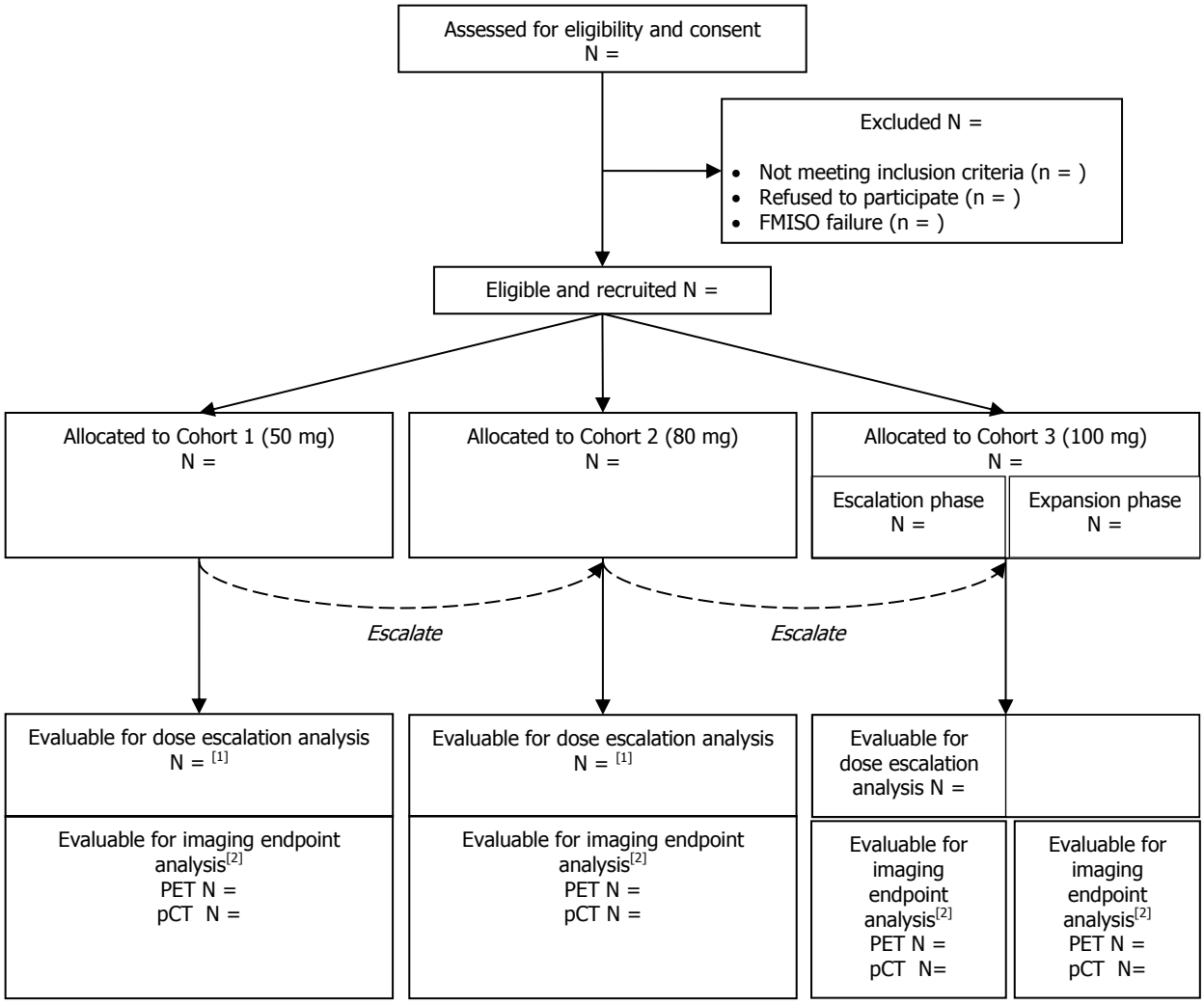
5. DESCRIPTIVE ANALYSES

5.1 Representativeness of Study Sample and Patient Throughput

Patient throughput for dose escalation phase will be illustrated using CONSORT flow diagram, as suggested in Figure 5.1.

Figure 5.1: CONSORT flow diagram



Additionally, reasons for non-participation will be reported.
Protocol deviations will be reported.

5.2 Baseline Comparability of Escalation and Expansion Phases

A table showing characteristics of dose escalation phase patients and dose expansion phase at baseline will be presented to show comparability of the groups. Numbers (with percentages) for binary and categorical variables and means (with standard deviations), or medians (with ranges) for continuous variables will be presented; there will be no tests of statistical significance nor confidence intervals for differences between groups on any baseline variable.

Characteristics to be described in tabular form include:

Table 5 Baseline characteristics

Characteristics	Dose escalation phase			Expansion cohort
	Cohort 1	Cohort 2	Cohort 3	
Demographic				
Age				
Gender				
Height				
Weight				
IMC				
Physical exam				
ECOG performance status				
Height				
Weight				
BMI				
SBP				
DBP				
Temperature				
Pulse rate				
Haematology				
Haemoglobin				
WBC				
Platelets				
Neutrophils				
Lymphocytes				
INR				
Biochemistry				
Sodium				
Potassium				
Calcium				
Magnesium				
Phosphate				
Urea				
Creatinine				
Albumin				
Bilirubin				
Alkaline phosphatase				
AST				
ALT				
LDH				

5.3 Comparison of Losses to Follow-up

5.3.1 Dose escalation phase

The numbers and pattern of losses to follow-up over the duration of the study will be reported for duration of BKM120 treatment (14 days) and for the duration of dose escalation decision (56 days) for each cohort and all cohorts together.

5.3.2 Expansion phase

The numbers and pattern of losses to follow-up over the duration of the study will be reported for duration of BKM120 treatment (14 days) and for the duration of the study evaluations (56 days) for all patients treated at the MTD of BKM120 with palliative RT.

5.4 Description of Available Data

The patterns of availability of toxicity, primary and secondary outcomes data, from baseline to end of follow-up, will be summarised for the each phase of the trial (escalation and expansion).

Evaluability of imaging data will be documented in the non-CRF imaging data. It has been decided to exclude patients with very small volume of baseline hypoxia as using the scan for the responder analysis would be inappropriate. No formal clarification of small volume is provided, but, potential excluded cases will be discussed with TMG.

As of TMG09Jun2017, it was decided to exclude BKC3114 because this patient had baseline hypoxia of 0.5ml in a 110ml tumour (BKM120_TMGMinutes_V1.0_09Jun2017).

The completeness of the data will be described but no missing data will be imputed.

5.5 Description of Compliance with Therapy

A summary of the treatment received in dose escalation phase 1 will be provided. This will include information in terms of treatment with BKM120 from day 1 to 14 and RT from day 8 to 14 and doses for all patients of each cohort.

A summary of the treatment received in expansion phase will be provided. This will include information in terms of treatment with BKM120 from day 1 to 14 and RT from day 8 to 14 and doses for all patients. Deviations from protocol including loss to follow-up, withdrawal by clinician and withdrawal of consent will be included.

5.6 Unblinding of Randomised Treatments

This is not a placebo controlled trial and therefore it is not blinded.

5.7 Reliability

Data validation checks for the analysis specified in this SAP will be performed as per OCTRU SOPs.
Reliability-Quality control plans are as documented in the IAP_V1.0_01Jun2016.

6. DEFINITION OF POPULATIONS FOR ANALYSIS

Dose escalation phase:
The primary dose escalation analysis will include all patients completing 14 days of BKM120 treatment and 56 days of evaluation or patients who withdraw early after experiencing DLT.

Dose escalation phase:
The primary safety and tolerability analysis will be based on all patients receiving a study dose level of 50mg, 80mg and 100mg BKM120.

Dose expansion phase:

The primary safety and tolerability post-treatment analysis will be based on all patients who receive at least one MTD dose of BKM120.

Secondary endpoints:
The secondary tumour hypoxia and perfusion analysis will include all patients who have data available from both scans (pre-BKM120 and post-BKM120).

7. ANALYSES TO ADDRESS PRIMARY AIMS

It is expected that STATA and R will be used for the analysis.

7.1 Statistical Methods Used for Analysis of Primary Outcomes

The primary dose escalation phase I analysis will be to find the MTD that is defined as the dose of BKM120 in combination with RT which no more than 1 of 6 patients or 0 of 3 patients experience a DLT. MTD analysis will be a frequency of patients with DLT according to dose escalation of BKM120 (50mg, 80mg, 100mg). DLT will be based on any observed toxicity attributed either to BKM120 or its interaction with RT, and MTD analysis will be a frequency of patients with DLT within study treatment:

1) Any ≥ grade 3 non-haematological toxicity (excluding nausea, vomiting or diarrhoea) that requires hospital admission or which does not resolve to ≤ grade 2 within 7 consecutive days of optimal treatment.
2) Any ≥ grade 3 nausea, vomiting or diarrhoea will be considered DLT only if any of them persist for >48 hours despite maximum supportive care.
3) ≥ Grade 3 pneumonitis
4) Any ≥ grade 4 haematological toxicity.
5) Mood deterioration from baseline DLT will be any grade ≥3 mood change if BL score of 2. DLT will be any grade ≥2 mood change if BL score of ≤ 1.

Note that mood alteration is a difference of at least one grade from baseline measurements on the mood questionnaires and this could also be judged on psychiatric interview.

The primary safety analysis will be a summarisation of descriptive statistics with patients grouped according to dose cohort. Toxicity grading using NCI CTCAE V4.03, physical examination, biochemistry and haematology data will be summarised across time.

7.2 Adjustment of P Values for Multiple Testing

No formal adjustment for multiple significance testing is intended.

7.3 Missing Data

No missing data will be imputed

7.4 Pre-specified Subgroup Analysis

No subgroup analysis is planned.

7.5 Treatment by Centre Interaction

This is a single centre trial. Consequently, no treatment by centre interaction analysis is planned.

7.6 Sensitivity Analysis

None specified.

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8. ANALYSIS TO ADDRESS SECONDARY AIMS

These investigate other aspects to determine the effect of BKM120 on secondary aims.

8.1 Evaluation/Definition of Secondary Outcomes (where applicable)

Secondary outcomes

- Changes in ^{18}F-Misonidazole uptake as detected by PET-CT scans.
- Changes in blood flow as detected by perfusion CT.

8.2 Statistical Methods Used for Analysis of Secondary Outcomes

For each of the parameters, mean (SD) and/or median (IQR) per cohort will be used to summarise the data, split by cohort (1,2,3+expansion). % change between parameters from each scan for each patient will also be presented in Table 8.1. Mean/median % change per cohort will be provided. Table 8.1 can also be repeated to report the results for TBR_{mean} (hypoxia) and BF, BV and MTT (perfusion) parameters.

Table 8.1: TBR_{volume} derived from PET-CT scans for hypoxia evaluation

Patient	TBR_{volume}		
	First Scan	Second Scan	% Change
1			
2			
…			
9			
Cohort-specific mean/median			

Patients will be defined as "responders" or non-responders as described in Section 2.8.2. Number of responders and non-responders per cohort will be reported.

Box-and-whisker plots will be used to display each of the parameters in the pre and post treatment and also Waterfall plots be used to show the percentage change in each of the parameters for each patient.

An appropriate statistical test (either paired t-test or Mann-Whitney U test) will be used to test the change of the pre and post scan results (if % change is zero or not) regardless of the dose they have received. But no formal statistical test will be used to test whether changes from the first to second scan are different between the three dose levels of Buparlisib because of the small sample size.

9. ANALYSIS OF EXPLORATORY AIMS

These investigate other aspects to determine the effect of BKM120 on exploratory aims.

9.1 Evaluation/Definition of Exploratory Outcomes (where applicable)

Exploratory outcomes

- To evaluate Akt phosphorylation as a predictive marker of response to BKM120
- To investigate potential biomarkers that correlate with response to BKM120

9.2 Statistical Methods Used for Analysis of Exploratory Outcomes

Details of this analysis will be defined in the statistical report if a statistical support is required. If the statistical support is not required, it would be defined in a separate lab report.

The proportion of cells staining with a pAKT antibody will be presented for patients classed as 'responders' and 'non-responders' using means (with standard deviations) and/or medians (with ranges) and will be compared using Mann-Whitney U test.

Number (with percentages) of patients with mutation status of potential biomarkers (eg p53, RAS, PI3K, EGFR) will be presented and compared between 'responders' and 'non-responders' using chi-square test or Fisher's Exact test (as appropriate).

9.3 Additional Exploratory Analysis Not Specified Prior to Receiving Data

Any analyses not specified in the analysis protocol will be exploratory in nature. The exploratory nature of the analysis and the indication for carrying out the analysis will be described in any publication or presentation.

10. SERIOUS ADVERSE EVENTS

The period for adverse event collection and recording will be from when the first patient has the first dose of BKM120 to the end follow-up of last recruited patient.

For each patient, adverse events will be collected from the time of their first dose of BKM120 to the end of follow-up.

Serious adverse events are defined as those that are fatal, life threatening, disabling or require in-patient hospitalisation or prolongation of hospitalisation, results in persistent or significant incapacity/disability, is a congenital anomaly or birth defect or is any other medically important event. For further details see Section 13 of the Protocol.

Serious adverse events for each cohort 1-3 will be summarized by descriptive statistics. An overall category for any serious adverse event will also be summarized as will the number of patients with at least one SAE. Results will be shown overall and separately for the dose escalation and expansion phase. The analysis will be conducted in evaluable patients (patients who have at least one study dose of BKM120) in each phase. A summary of adverse events will be made as part of the safety and tolerability primary aim (see section 7.1).

11. DOCUMENT HISTORY

Version No.	Version Date	Author	Significant changes from previous version together with reasons
1.0	19Oct2012	CC	First version based on Protocol version 0.12, 01Oct2012
2.0	13Nov2012	CC	Updated based on Protocol version 1.0, 07Nov2012. Minor changes including some grammatical corrections and improvements to the content
2.1	31Jul2015	PV	Updated based on Protocol version 5.0, 07Jul2014. Updates based on SBL comments from previous version. Changes on duration of study, consort diagrams, patients groups for analysis, sensitivity analysis and minor grammatical corrections. Added list of abbreviations/definitions
2.3	13Oct2017	VS	Updated based on protocol version 7.0, 12 Jan 2017.
2.4	16Oct2017	VS	Updated based on comments from SN and SM.
3.0	18Oct2017	VS	Updated based on comments from SN, SM and DM