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BUBBLE: Buparlisib with bortezomib in relapsed or refractory multiple myeloma

Submission date 18/03/2015	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 09/04/2015	**Overall study status** Completed	
Last Edited 16/03/2023	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-of-buparlisib-and-bortezomib-for-myeloma-bubble

Contact information

Type(s)
Public

Contact name
Ms Louise Hopkins

Contact details
Cancer Research UK Clinical Trials Unit, University of Birmingham
Centre for Clinical Haematology
Queen Elizabeth Hospital
Birmingham
United Kingdom
B15 2TH
+44 (0) 121 371 7861
Bubble@trials.bham.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2014-002477-10

Protocol serial number
18609

Study information

Scientific Title
Phase 1B Study of buparlisib with bortezomib in defined genetic subgroups of patients with relapsed or refractory multiple myeloma

Acronym
BUBBLE

Study objectives
To determine the maximum tolerated dose of buparlisib in combination with bortezomib. Once the MTD has been determined, an additional 30 patients will be recruited to a dose expansion phase. The expansion phase of the study is designed to estimate the overall response rate that may be achieved in a defined genetic subpopulation of patients by the addition of buparlisib to bortezomib.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London-Chelsea Research Ethics Committee , ref: 15/LO/0304

Study design
Non-randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Cancer; Subtopic: Haematological Oncology; Disease: Myeloma

Interventions
All patients will be registered to receive a combination of the bortezomib and buparlisib. Patients will be treated with daily buparlisib (orally) and bortezomib (sub-cutaneously) administered on days 1, 8, 15 and 22 of a 28 day cycle. Patients will receive up to 8 cycles of combined therapy.

Dose escalation phase
Patients will be allocated to one of four dose combination levels (Table 2) in a 3+3 trial design. The decision as to whether to escalate, expand or stop a cohort will depend on the number of dose-limiting-toxicities (DLTs) experienced.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)

1. Buparlisib 2. Bortezomib

Primary outcome(s)
1. Incidence rate of dose limiting toxicities (DLT) (dose escalation phase)
2. Safety: frequency, duration and severity of adverse events (AE's) and serious adverse events (SAE's) , as well as abnormalities in laboratory tests, ECG changes

Key secondary outcome(s))
1. Key: Safety
Frequency and length of treatment delays, dose reductions for each drug, dose intensities (% of protocol specified dose) of each drug, number of discontinuations for toxicity (dose expansion phase)
2. Exploratory: Biomarkers
Percentage of patients whose bone marrow tumour cells are successfully tested in each of the following assays: FISH for IgH translocations, IHC for cyclin D2, IHC for pAkt (dose expansion phase)
3. Exploratory: Efficacy
Overall response rate, duration of response and progression free survival of patients in defined sub-group treated with BKM-Bz (dose expansion phase)

Completion date
09/04/2021

Eligibility

Key inclusion criteria
1. Male or female aged at least 16 years of age
2. ECOG performance status ≤ 2
3. Confirmed diagnosis of relapsed/refractory MM according to International Myeloma Working Group (IMWG) guidelines (2003) with 1-4 prior lines of therapy (i.e., relapsed from plateau phase, or refractory to last therapy). [Note: Prior treatment with bortezomib is permitted, provided the patient achieved at least a partial remission (PR) and had not progressed within 6 months of the last dose of bortezomib].
4. Measurable disease as defined by one or more of the following criteria (assessed within 28 days prior to registration):
4.1. Serum paraprotein = 5 g/L (for IgA patients whose disease can only be reliably measured by serum quantitative immunoglobulin (IgA): = 7.5 g/L)
4.2. Urine Bence Jones Protein: = 200 mg/24 h
4.3. Serum light chain assay: Involved free light chain (FLC) level = 100 mg/L, provided serum FLC ratio is abnormal
5. Life expectancy of at least 3 months
6. Patient has adequate bone marrow and organ function as defined by the following laboratory values:
6.1. Neutrophils = 1.5 x 109/L
6.2. Haemoglobin = 90 g/L
6.3. Platelets = 100 x 109/L
6.4. International normalised ration (INR) = 1.5
6.5. Magnesium within normal limits of institution or correctable with supplements
6.6. Potassium and calcium (corrected for albumin) within normal limits of institution or correctable with supplements
6.7. Phosphorous = LLN or correctable with supplements

6.8. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) = 1.5 x ULN upper limit of normal range (or <3.0 x ULN if liver metastases are present)
6.9. Total serum bilirubin < ULN (or = 1.5 x ULN if liver metastases are present; or total bilirubin = 3.0 x ULN with direct bilirubin within normal range in patients with well documented Gilbert's Syndrome, which is defined as presence of several episodes of unconjugated hyperbilirubinemia with normal results from CBC count (including normal reticulocyte count and blood smear), normal liver function test results, and absence of other contributing disease processes at the time of diagnosis
6.10. Serum creatinine = 1.5 x ULN. If the serum creatinine is = 1.5 x ULN, then a 24-hour creatinine clearance must be conducted and the result must be = 50ml/minute
6.11. Fasting Plasma Glucose = 120 mg/dL or 6.7 mmol/L
6.12. HbA1c = 8%
7. Patient is able to swallow and retain oral medication
8. Patient has signed the Informed Consent (ICF) prior to any screening procedures being performed and is able to comply with protocol requirement

Expansion phase only: Patients whose bone marrow MM cells stain positive for cyclin D2 and/or phospho-Akt, and/or whose MM cells harbour the t(4;14) or t(14;16) translocations

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Impaired cardiac function or clinically significant diseases, including any one of the following:
1.1. Symptomatic congestive heart failure
1.2. History of documented congestive heart failure (New York Heart Association functional classification IIIIV), documented cardiomyopathy
1.3. Left Ventricular Ejection Fraction <50% as determined by ECHO
1.4. Acute myocardial infarction =6 months prior to starting study drug
1.5. Unstable angina pectoris
1.6. Serious uncontrolled cardiac arrhythmia
1.7. Symptomatic pericarditis
1.8. QTcF >480 msec on the screening ECG (using the QTcF formula)
1.9. Currently receiving treatment with medication that has a known risk to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug.
2. Other clinically significant heart disease
3. Acute or chronic liver disease
4. Acute or chronic renal disease
5. Poorly controlled diabetes mellitus
6. Impairment of GI function or GI disease that may significantly alter the absorption of BKM)
7. Known hypersensitivity to any of the excipients of buparlisib

8. History of photosensitivity reactions to other drugs
9. Patients with chronic pulmonary disease, including dyspnoea at rest from any cause, or with interstitial lung disease, are excluded from study entry
10. Immunocompromised patients, including known seropositivity for HIV, current or chronic hepatitis B and/or hepatitis C infection.[Note: testing is not mandatory to be eligible for the study. However, if subject is at risk for having undiagnosed HBV/HCV (due to history of injection drug use or due to geographic location, for example), testing at screening should be considered]
11. Patients who have other concurrent severe and/or uncontrolled medical conditions that would, in the investigator's judgment, contraindicate patient participation in the clinical study (eg. active or uncontrolled severe infection, chronic active hepatitis, immuno-compromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc.)
12. Concomitant or/ and previous therapy that precludes enrolment:
13. Prior treatment with PI3K or Akt inhibitors
14. Patient is concurrently using other approved or investigational antineoplastic agent
15. Received antimyeloma therapy within 28 days of starting treatment, except for dexamethasone, which must be stopped at least 48 hours prior to starting treatment (must have recovered to at least grade 1 or better (except alopecia) from related side effects of any prior antineoplastic therapy)
16. Patient who has received wide field radiotherapy = 4 weeks or limited field radiation for palliation = 2 weeks prior to starting study drug or who have not recovered to grade 1 or better from related side effects of such therapy (except alopecia)
17. Major surgery within 14 days prior to starting study drug or the patient has not recovered from major side effects of the surgery
18. Receiving any of the following drugs at the time of study registration:
18.1. Drugs known to be moderate and strong inhibitors or inducers of isoenzyme CYP3A4 including herbal medications
18.2. Currently receiving increasing or chronic treatment (> 5 days) with corticosteroids or another immunosuppressive agent, as chronic administration of corticosteroids (>5 days) can induce CYP3A4. The following uses of corticosteroids are permitted: single doses; e.g., with standard premedication for taxanes; topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular)
18.3. Receiving drugs with a known risk to induce Torsades de Pointes
18.4. the patient must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the treatment is initiated. Switching to a different medication prior to starting study treatment is allowed.
18.5. Warfarin or other coumarin derived anticoagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed
19. Patient has a concurrent malignancy or malignancy within 3 years of study enrolment
20. Patient has a score of =12 on the PHQ-9 questionnaire, or a GAD7 mood scale score =15.
21. Patient selects a response of "1, 2 or 3" to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation
(independent of the total score of the PHQ-9)
22. Patient has a medically documented history of or active major depressive episode
23. Participation in a prior investigational study within 30 days prior to enrolment or within 5-half-lives of the investigational product, whichever is longer
24. Patient has a history of non-compliance to medical regimen or inability to grant consent;
25. Pregnant or lactating women
26. Adults or reproductive potential not willing to practice effective contraception during the trial and for up to 8 weeks after IMP

Date of first enrolment

01/04/2016

Date of final enrolment
14/11/2017

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
University of Birmingham
Edgbaston
Birmingham
United Kingdom
B15 2TT

Study participating centre
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
University Hospital Southampton Foundation Trust
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Sponsor information

Organisation
University of Birmingham (UK)

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
Bloodwise

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from the Trial Management Group by contacting bubble@trials.bham.ac.uk who will consider requests for data sharing following the end of trial on 09-Apr-2021 or publication of trial results, whichever comes last.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			16/03/2023	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Plain English results			24/05/2022	No	Yes