

BUBBLE: Buparlisib with bortezomib in relapsed or refractory multiple myeloma

Submission date 18/03/2015	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 09/04/2015	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 16/03/2023	Condition category Cancer	<input type="checkbox"/> Individual participant data

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

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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 = $1.5 \times 10^9/L$
 - 6.2. Haemoglobin = 90 g/L
 - 6.3. Platelets = $100 \times 10^9/L$
 - 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 III/IV), 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

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Study participating centre

University Hospital of Wales

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Study participating centre

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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
Plain English results			24/05/2022	No	Yes