Phase 1B Study of buparlisib with Bortezomib in Defined Genetic Subgroups of Patients with Relapsed or Refractory Multiple Myeloma

Chief Investigator: Professor Kwee Yong **Sponsor:** University of Birmingham

Trial Design

This is a prospective, open label, phase 1 dose-finding, multicentre clinical trial to determine the maximum tolerated dose (MTD) of buparlisib in combination with bortezomib using an escalating 3+3 design. Once the MTD has been determined, an additional 30 patients will be recruited to a dose expansion phase.

Objectives

The aim of this feasibility study is to confirm MTD of buparlisib in combination with bortezomib. The dose expansion phase will allow the safety of this novel combination in patients with relapsed/refractory multiple myeloma to be evaluated.

Trial Duration

Patients will be recruited over a five year period from selected Leukaemia and Lymphoma Research (LLR) Trials Acceleration Programme (TAP) Centres. Patients will be treated for eight cycles unless their disease progresses. Patients will be followed up at least 2 years post registration for survival.

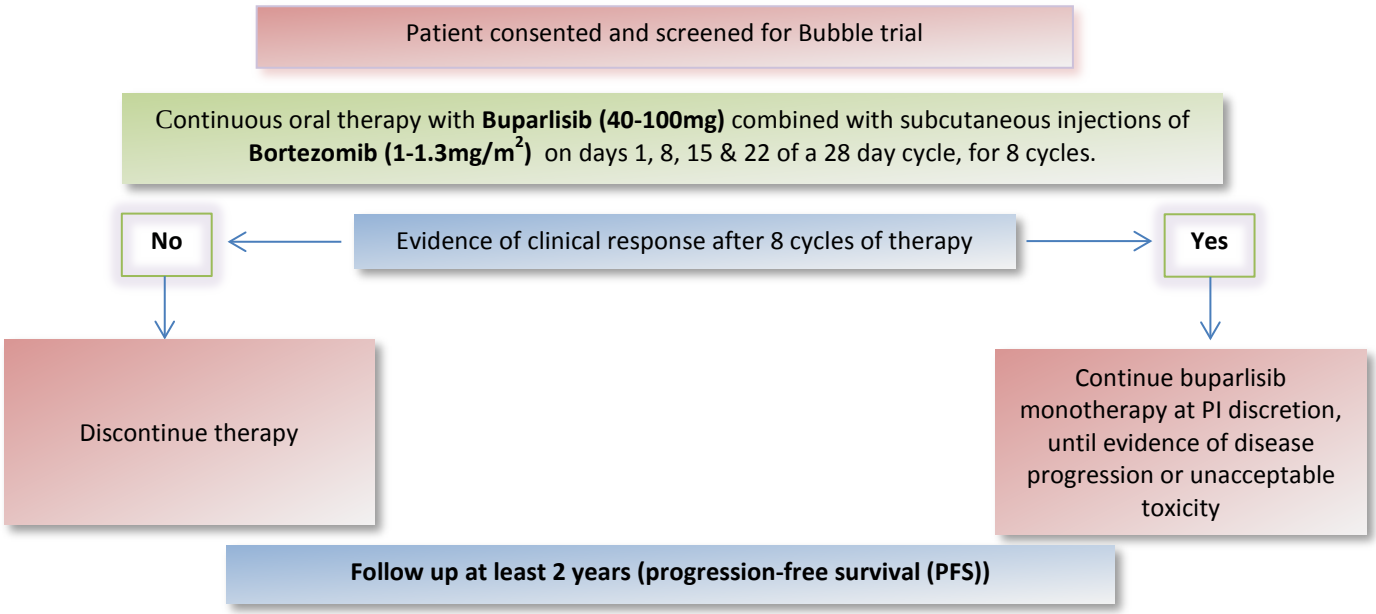
Primary Outcome Measures

- Incidence rate of dose limiting toxicities (DLT) (dose escalation phase)
- 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

Secondary Outcome Measures

- 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)
- 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)
- Overall response rate, duration of response and progression free survival of patients in defined sub-group treated with BKM-Bz (Dose expansion phase)

Trial Treatment



Key Inclusion Criteria

- Male or female aged ≥18 years of age
- ECOG performance status ≤2
- 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].
- Measurable disease as defined by one or more of the following criteria (assessed within 28 days prior to registration):
  - O serum paraprotein ≥ 5 g/L (for IgA patients whose disease can only be reliably measured by serum quantitative immunoglobulin (IgA): ≥ 7.5 g/L)
  - O Urine Bence Jones Protein: ≥ 200 mg/24 h
  - O Serum light chain assay: Involved free light chain (FLC) level ≥ 100 mg/L, provided serum FLC ratio is abnormal
- Life expectancy of at least 3 months
- Patient has adequate bone marrow and organ function defined by laboratory values in the protocol relating to Neutrophils, haemoglobin, Platelets, INR, Magnesium, Potassium, Calcium, Phosphorous, ALT, AST, bilirubin, serum creatinine, fasting plasma glucose and HbA1c

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

Key Exclusion Criteria

- Impaired cardiac function or clinically significant diseases, as defined in the protocol.
- Acute or chronic liver or renal disease
- Poorly controlled diabetes
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BKM
- Immunocompromised patients, including known seropositivity for HIV, current or chronic hepatitis B and/or hepatitis C infection.
- 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
- Concomitant or/ and previous therapy/drugs that precludes enrolment:
  - Prior treatment with PI3K or Akt inhibitors
  - Patient is concurrently using other approved or investigational antineoplastic agent
  - Received anti-myeloma therapy within 28 days of starting treatment
  - Drugs known to be moderate and strong inhibitors or inducers of isoenzyme CYP3A4
  - Increasing or chronic treatment (> 5 days) with corticosteroids or another immunosuppressive agent
  - Drugs with a known risk to induce Torsades de Pointes
  - Must have discontinued strong inducers for at least one week
  - Warfarin or other coumarin derived anti-coagulant
- Patient has a concurrent malignancy or malignancy within 3 years of study enrolment
- Patient has a score of ≥12 on the PHQ-9 questionnaire, or a GAD-7 mood scale score ≥15.
- 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)
- Participation in a prior investigational study within 30 days prior to enrolment or within 5-half- lives of the investigational product, whichever is longer
- Patient has a medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation
- CTCAE Grade ≥3 anxiety
- Pregnant or lactating women

Contact Details

Bubble Trial, Cancer Research UK Clinical Trials Unit,
University of Birmingham, Edgbaston, Birmingham, B15 2TT

Tel: 0121 415 9176 **Fax:** 0121 414 6061 **Email:** Bubble@trials.bham.ac.uk