BerGenBio AS

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Eligibility Criteria

Protocol Title: A Phase I multicenter open-label study of BGB324 as a single agent and in combination with cytarabine in patients with acute myeloid leukemia or high/intermediate (int-2) risk myelodysplastic syndrome which overexpresses axl

Protocol Number: BGBC003

Version and Date: 1.1 26 June 2014

9.1 Inclusion Criteria

1. Provision of signed written informed consent
2. Histological or cytological confirmation of one of the following:
   a) AML which is sensitive to BGB324 *ex vivo* as defined by an IC_{50} of $\leq$2.5 μM
   b) Part A: High risk group MDS, according to IPSS Risk Stratification, expressing Axl by FCM
   c) Part B: High/intermediate (int-2) risk group MDS, according to IPSS Risk Stratification, expressing Axl by FCM
3. Patients with AML:
   a) Relapsed or refractory disease (Part A)
   b) Newly diagnosed who are unsuitable for intensive chemotherapy (Part B)
4. European Cooperative Oncology Group (ECOG) performance status 0, 1 or 2 [Appendix 1]
5. Male or female, age 18 years or older
6. Female patients of childbearing potential must have a negative serum pregnancy test within 3 days prior to taking their first dose of BGB324. Male patients and female patients of reproductive potential must agree to practice highly effective methods of contraception (such as hormonal implants, combined oral contraceptives, injectable contraceptives, intrauterine device with hormone spirals, total sexual abstinence, vasectomy) throughout the study and for $\geq$3 months after the last dose of BGB324. Female patients are considered NOT of childbearing potential if they have a history of surgical sterility or evidence of post-menopausal status defined as any of the following:
   a) Natural menopause with last menses >1 year ago
   b) Radiation induced oophorectomy with last menses >1 year ago
   c) Chemotherapy induced menopause with last menses >1 year ago

9.2 Exclusion Criteria

1. Pregnant or lactating
2. Abnormal left ventricular ejection fraction on echocardiography (less than the lower limit of normal for a patient of that age at the treating institution)
3. History of an ischaemic cardiac event including myocardial infarction within 3 months of study entry
4. Congestive cardiac failure of > Grade 2 severity according to the NYHA [Appendix 2] as defined as symptomatic at less than ordinary levels of activity
5. Unstable cardiac disease including unstable angina or hypertension as defined by the need for change in medication within the last three months

6. History or presence of bradycardia (less than or equal to 60 BPM) or history of symptomatic bradycardia, left bundle branch block, cardiac pacemaker or significant atrial tachyarrythmias
7. Current treatment with any agent that may prolong QT interval and may cause Torsade de Points [Appendix 3] which cannot be discontinued at least two weeks prior to treatment
8. Known family or personal history of long QTc syndrome or ventricular arrhythmias including ventricular bigeminy
9. Previous history of drug-induced QTc prolongation
10. Screening 12-lead ECG with a measurable QTc interval according to Fridericias correction > 450 ms
11. Abnormal serum potassium, calcium or magnesium levels according to the local laboratory
12. Ongoing infection requiring systemic treatment
13. Inadequate liver function as demonstrated by serum bilirubin ≥1.5 times the upper limits of normal range (ULN) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times the ULN (or ≥5 times the ULN in the presence of liver involvement by leukemia)
14. Inability to tolerate oral medication
15. Existing gastrointestinal disease affecting drug absorption such as celiac disease or Crohns disease
16. Previous bowel resection
17. Evidence of ongoing gastrointestinal graft versus host disease
18. Haematopoetic stem cell transplantation within 6 months
19. Impaired renal function as demonstrated by creatinine ≥1.5 times the ULN or creatinine clearance of ≤50 mL/min determined by Cockcroft-Gault formula
20. Radiotherapy or chemotherapy within the 14 days prior to the first dose of BGB324 being administered (other than hydroxyurea)
21. Receiving an investigational anti-cancer treatment concurrently or within 14 days or five half-lives of either the parent drug or any active metabolite prior to the start of BGB324
22. Unresolved CTCAE Grade 2 or greater toxicity (other than stable toxicity) from previous anti-cancer therapy excluding alopecia
23. Any evidence of severe or uncontrolled systemic conditions (e.g., severe hepatic impairment) or current unstable or uncompensated respiratory or cardiac conditions which makes it undesirable for the patient to participate in the study or which could jeopardize compliance with the protocol
24. Active, uncontrolled central nervous system (CNS) disease including CNS leukemia
25. Active infection with human immunodeficiency virus (HIV), hepatitis B or C viruses – screening for viral infections is **not** required for entry to this study
26. Major surgery within 28 days prior to the start of BGB324 – excluding skin biopsies and procedures for insertion of central venous access devices
27. Known hypersensitivity to cytarabine (Ara-C) or its excipients