ACCRU BBI608-336
A Phase III Randomized, Double-Blind, Placebo-Controlled Clinical Trial of BBI608 plus Weekly Paclitaxel vs. Placebo plus Weekly Paclitaxel in Adult Patients with Advanced, Previously Treated Gastric and Gastro-Esophageal Junction Adenocarcinoma

FAST FACTS

Commercial Agents: Paclitaxel
Drug Company Supplied: BBI608 and Placebo are supplied in matching capsules

PATIENT ELIGIBILITY

INCLUSION CRITERIA

1. Written, signed consent for trial participation must be obtained from the patient appropriately in accordance with applicable ICH guidelines and local and regulatory requirements prior to the performance of any study specific procedure.

2. Must have cytologically or histologically confirmed advanced gastric or GEJ adenocarcinoma that is metastatic or locally advanced and unresectable (with unresectability as defined by National Comprehensive Cancer Network Guidelines for Gastric Cancer [Version 2.2013] and Esophageal and Esophagogastric Junction Cancer [Version 2.2013]). GEJ cancers may include Siewert Class I, II, or III types [Siewert 1996]

3. Must have failed treatment with one regimen containing at least a platinum/fluoropyrimidine doublet for unresectable or metastatic disease. While not mandated, concomitant treatment with an anthracycline (epirubicin or doxorubicin) or anti-HER2 therapy (trastuzumab) in this setting is allowed. Patients who have progression of disease at any point during neoadjuvant or adjuvant treatment with a platinum/fluoropyrimidine doublet or < 6 months after the last dose of neoadjuvant or adjuvant treatment may be enrolled.

Treatment failure is defined as progression of disease (clinical or radiologic) during first line treatment for unresectable or metastatic disease or ≤ 6 months after last dose of first line treatment.

No additional prior lines of therapy in the metastatic setting will be allowed. A patient who has received neoadjuvant or adjuvant treatment, relapsed, and then received a platinum/fluoropyrimidine doublet as first-line treatment in the unresectable/metastatic setting would be allowed, however.

Patients who have received prior taxane therapy may be enrolled, so long as the taxane was administered in the adjuvant or neoadjuvant setting and progression occurred more than 6 months following completion of therapy. Patients who were intolerant to paclitaxel are not allowed, however.

4. Paclitaxel therapy is appropriate for the patient and is recommended by the Investigator.

5. Imaging investigations including CT/MRI of chest/abdomen/pelvis or other scans as necessary to document all sites of disease done within 21 days prior to randomization. Patients with either measurable disease OR non-measurable evaluable disease will be eligible.

6. Must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

7. Must be ≥ 18 years of age.

8. For male or female patient of child producing potential: Must agree to use contraception or take measures to avoid pregnancy during the study and for 6 months after the final dose of Paclitaxel or for 30 days for female patients and for 90 days for male patients, of the final BBI608/Placebo dose if Paclitaxel was not administered.

Adequate contraception is defined as follows:
• Complete abstinence: when this is in line with the preferred and usual lifestyle of the subject.
• Consistent and correct use of one of the following methods of birth control:
  a. male partner who is sterile prior to the female subjects entry into the study and is the sole sexual partner for that female subject; or
  b. implants of levonorgesterol; or
  c. injectable progestagen; or
  d. any intrauterine device (IUD) with a documented failure rate of less than 1% per year; or
  e. oral contraceptive pill (either combined or progesterone only); or
  f. two barrier methods, for example diaphragm with spermicide plus condom with spermicide to be used by the patient and the partner.

9. Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test within 5 days prior to randomization. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea > 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL). Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be of child bearing potential.

10. Must have alanine transaminase (ALT) ≤ 3 × institutional upper limit of normal (ULN) [≤ 5 ×ULN in presence of liver metastases] within 14 days prior to randomization.

11. Must have hemoglobin (Hgb) ≥ 9.0 g/dL within 14 days prior to randomization. Must not have required transfusion within 1 week of baseline Hgb assessment.

12. Must have total bilirubin ≤ 1.5 × institutional ULN [≤ 2.0 x ULN in presence of liver metastases] within 14 days prior to randomization.

13. Must have creatinine ≤ 1.5 × institutional ULN or Creatinine Clearance > 50 ml/min (as calculated by the Cockroft-Gault equation) within 14 days prior to randomization.

14. Must have absolute neutrophil count ≥ 1.5 x 10⁹/L within 14 days prior to randomization.

15. Must have platelet count ≥ 100 x 10⁹/L within 14 days prior to randomization. Must not have required transfusion within 1 week of baseline platelet assessment.

16. Other baseline laboratory evaluations, listed in Section 6.0, must be done within 14 days prior to randomization.

17. Patient must consent to provision of, and investigator(s) must confirm access to and agree to submit a representative formalin fixed paraffin block of tumor tissue in order that the specific correlative marker assays proscribed in Section 14.6 (Correlative Studies) of this protocol may be conducted. Submission of the tissue does not have to occur prior to randomization. Where local center regulations prohibit submission of blocks of tumor tissue, two 2 mm cores of tumor from the block and 10-30 unstained slides of whole sections of representative tumor tissue are preferred. Where it is not possible to obtain two 2 mm cores of tumor from the block, 10-30 unstained slides of representative tumor tissue are also acceptable. Where no previously resected or biopsied tumor tissue exists or is available, on the approval of the Sponsor/designated CRO, the patient may still be considered eligible for the study.

18. Patient must consent to provision of a sample of blood in order that the specific correlative marker assays proscribed in Section 14.6 (Correlative Studies) may be conducted.

19. Patients must be accessible for treatment and follow-up. Patients registered on this trial must receive protocol treatment and be followed at the participating center. This implies there must be reasonable geographical limits
placed on patients being considered for this trial. Investigators must ensure that the patients randomized on this trial will be available for complete documentation of the treatment, response assessment, adverse events, and follow-up.

20. Protocol treatment is to begin within 2 working days of patient randomization.

21. The patient is not receiving therapy in a concurrent clinical study and the patient agrees not to participate in other interventional clinical studies during their participation in this trial while on study treatment. Patients participating in surveys or observational studies are eligible to participate in this study.

EXCLUSION CRITERIA

1. Anti-cancer chemotherapy or biologic therapy if administered prior to the first planned dose of BBI608/placebo within period of time equivalent to the usual cycle length of the regimen. An exception is made for oral fluoropyrimidines (e.g. capecitabine, S-1), where a minimum of 10 days since last dose must be observed prior to the first planned dose of BBI608/placebo.

Radiotherapy, immunotherapy, or investigational agents within four weeks of first planned dose of BBI608/placebo, with the exception of a single dose of radiation up to 8 Gray (equal to 800 RAD) with palliative intent for pain control up to 14 days before randomization.

2. Prior taxane therapy in the neoadjuvant or adjuvant setting with progression occurring within 6 months of completion of taxane therapy; or any taxane therapy in the metastatic setting.

3. More than one prior chemotherapy regimen administered in the metastatic setting.

4. Major surgery within 4 weeks prior to randomization.

5. Any known symptomatic brain metastases requiring steroids. Patients with treated brain metastases must be stable for 4 weeks after completion of that treatment, with image documentation required. Patients must have no clinical symptoms from brain metastases and must be either off steroids or on a stable dose of steroids for at least 2 weeks prior to randomization. Patients with known leptomeningeal metastases are excluded, even if treated.

6. Women who are pregnant or breastfeeding.

7. Gastrointestinal disorder(s) which, in the opinion of the Qualified/Principal Investigator, would significantly impede the absorption of an oral agent (e.g. active Crohn’s disease, ulcerative colitis, and extensive gastric and small intestine resection).

8. Severe hepatic impairment as per the Paclitaxel Summary of Product Characteristics.

9. History of severe hypersensitivity to paclitaxel or to any of the excipients, including macrogolglycerol ricinoleate.

10. Unable or unwilling to swallow BBI608/placebo capsules daily.

11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure (≥ class II New York Heart Association NYHA), unstable angina pectoris (including angina symptoms at rest, new onset angina begun ≤ 3 months prior, or myocardial infarction ≤ 6 months prior), clinically significant cardiac arrhythmia requiring anti-arrhythmic therapy, clinically significant valvular or pericardial disease, severe uncontrolled arterial hypertension, significant pulmonary disease (shortness of breath at rest or mild exertion), uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements.

12. Peripheral neuropathy ≥ CTCAE Grade 2 at baseline
13. Patients with a history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix and in-situ cancer of the urinary bladder, or other solid tumors curatively treated with no evidence of disease for ≥ 3 years.


15. Any active disease condition which would render the protocol treatment dangerous or impair the ability of the patient to receive protocol therapy.

16. Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol.

PRE-TREATMENT EVALUATION (See Appendix I)

1. History and Physical Exam including:
   • Prior medical and therapeutic history
   • Vital signs, height, weight, ECOG performance status
   • Clinical tumor measurements
2. CBC, CMP, Phosphate, LDH, Magnesium
3. Urinalysis
4. ECG (12 lead)
5. CT/MRI scan of chest/abdomen/pelvis with tumor measurement and evaluation by RECIST 1.1 criteria 3 < 21 days
6. Correlative Studies
   • Submission of representative block of diagnostic tumor tissue
   • Blood sample collection
7. Serum or urine pregnancy test
   • Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)
8. Quality of Life • EORTC QLQ-C30

TREATMENT

Arm 1: Experimental: BBI608 plus Paclitaxel
   • BBI608 480 mg orally two times daily (960 mg total daily dose)
   • Paclitaxel 80 mg/m2 I.V. infusion on Days 1, 8, and 15 of every 4-week cycle

Arm 2: Placebo Comparator: Placebo plus Paclitaxel
   • Paclitaxel 80 mg/m2 I.V. infusion on Days 1, 8, and 15 of every 4-week cycle
   • Placebo orally two times daily