

FAST FACTS

ACCRU RU011201I A Randomized Phase III Trial of Eribulin Compared to Standard Weekly Paclitaxel as First- or Second-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

Commercial Agents: Paclitaxel

Drug Company Supplied: Eribulin mesylate (IND held by Eisai Inc.)

PATIENT ELIGIBILITY

See Study Schema on last page

Inclusion Criteria

1. Age ≥ 18 years.
2. Histologic confirmation of invasive adenocarcinoma originating in the breast.
3. Stage IV disease or Stage IIIC disease (using the 7th edition AJCC criteria) not amenable to local therapy.
4. Clinical or radiographic evidence of disease progression.
5. Documentation of HER2 negative breast cancer at the time of protocol registration. [**Note:** HER2 negativity is defined as 0 or 1+ by immunohistochemistry OR nonamplified or equivocal by FISH. Status may be defined on the basis of historic results on the breast primary or a metastatic site, whichever is most recent. Repeat biopsies are not required for participation in this protocol.]
6. Known hormone receptor status at the time of protocol registration. [**Note:** ER and/or PgR status are considered positive with a cut-off of $\geq 1\%$ invasive tumor cells. Status may be defined on the basis of historic results on the breast primary or a metastatic site, whichever is most recent. Repeat biopsies are not required for participation in this protocol.]
7. Prior systemic therapy as per the following criteria:
 - a. Patients must demonstrate resolution of all toxicities related to prior chemotherapy, endocrine therapy, or biologic therapy to grade ≤ 1 , including peripheral neuropathy, with the exception of alopecia (any grade permissible).
 - b. No more than one prior chemotherapy regimen for advanced or metastatic breast cancer is allowed. Prior chemotherapy for metastatic disease must have been completed ≥ 14 days prior to randomization.
 - Any single agent therapy, and any combination of cytotoxic, endocrine, biological targeted agents, and/or humanized antibodies, scheduled to be administered as a preplanned treatment, given concomitantly, sequentially or both, is considered one regimen.
 - Planned neoadjuvant chemotherapy and postoperative adjuvant chemotherapy is considered one regimen.
 - If the dosing of one or more of the chemotherapy components of a regimen must be reduced for toxicity, the modified version of the original regimen is not considered a new regimen.
 - If one or more of the chemotherapy components of a regimen must be omitted for toxicity, the modified version of the original regimen is not considered a new regimen.
 - If one of the chemotherapy components of a regimen must be replaced with another similar drug of the same therapeutic class, the modified version of the original regimen is not considered a new regimen. However, if a new component, dissimilar to any of the original components, is added to the regimen, the modified version is considered a new regimen.
 - If chemotherapy is interrupted for surgery or radiotherapy and then continues with an unchanged schedule and components, treatment is considered as one regimen despite the interruption.
 - c. Prior treatment may include a taxane as per the following criteria:
 - Prior Taxane (including paclitaxel) in the adjuvant or neoadjuvant setting is allowed, provided that the interval between the completion of (neo)adjuvant therapy and disease recurrence is >12 months.
 - Prior taxane in the metastatic setting is allowed, provided that the agent administered in the metastatic setting was not standard paclitaxel.
 - d. Any number of prior endocrine therapies is allowed and must be discontinued prior to randomization.
 - e. Any number of biologic therapies (*e.g.*, bevacizumab) or immunotherapies is allowed in the absence of co-administered chemotherapy and must have been completed ≥ 28 days prior to randomization.
 - f. Prior treatment with an investigational agent is allowed but must have been completed ≥ 28 days prior to randomization with resolution of all treatment-related toxicities to grade ≤ 1 .

9. Prior local therapy as per the following criteria:
 - a. Minor surgical procedures must be completed ≥ 7 days prior to randomization with documentation of adequate recovery from associated complications to grade ≤ 1 . These include (but are not limited to) laparoscopy, thoracoscopy, bronchoscopy, mediastinoscopy, endoscopic ultrasonography, skin biopsy, percutaneous needle biopsy, and routine dental procedures. As a precautionary measure, it is recommended, but not strictly required, that placement of a central venous access device, thoracentesis, or paracentesis be done 7 days before the initiation of protocol directed chemotherapy with documentation of adequate recovery from associated complication to grade ≤ 1 .
 - b. Major surgical procedures and open biopsies must be completed ≥ 28 days prior to randomization with documentation of adequate recovery from associated complications to grade ≤ 1 .
 - c. Prior radiotherapy must be completed ≥ 14 days prior to randomization with documentation of adequate recovery from associated toxicities to grade ≤ 1 .
10. Concurrent supportive therapy as per the following criteria:
 - a. Treatment with bisphosphonates or denosumab is allowed and recommended per the standard of care.
 - b. Therapeutic anticoagulation is allowed for patients on a stable dose of warfarin or low molecular weight heparin.
11. Radiographically measurable or non-measurable disease as per RECIST guidelines (version 1.1, see Section 11.0):
 - a. Measurable disease is defined as at least one lesion that can be accurately measured with the longest diameter as ≥ 1.0 cm by CT scan or ≥ 1.0 cm with calipers by clinical examination. The exceptions to these criteria are pathologic lymph nodes, which must be ≥ 1.5 cm in the short axis when assessed by CT scans with slice thickness ≤ 0.5 cm.
 - b. Non-measurable lesions include the following: small lesions (longest diameter < 1.0 cm for all lesions other than pathologic lymph nodes, which are ≥ 1.0 cm and < 1.5 cm in the short axis), bone metastases, pleural effusions, pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitis pulmonis, lymphangitis cutis, and abdominal masses not followed by CT or MRI.
12. ECOG performance status of 0, 1, or 2.
13. Life expectancy of > 12 weeks.
14. History of brain metastases as per the following criteria:
 - a. Patients with a history of resected brain metastases are eligible only if they are asymptomatic and have stable MRI scans for 3 consecutive months, including < 28 days of study registration.
 - b. Patients who receive stereotactic radiosurgery or whole brain radiation for brain metastases are eligible only if they are asymptomatic and have stable MRI scans for 3 consecutive months, including < 28 days of study registration.
15. Adequate organ function per blood work obtained ≤ 7 days prior to registration:
 - Absolute neutrophil count $\geq 1500/\mu\text{L}$.
 - Platelet count $\geq 100,000/\mu\text{L}$.
 - Hemoglobin ≥ 9 g/dL.
 - Total bilirubin ≤ 1.5 times the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia of Gilbert's syndrome.
 - SGOT (AST) and SGPT (ALT) $< 3x$ ULN except in the case of liver metastases, where $\leq 5x$ ULN is allowed.
 - Creatinine ≤ 2.0 mg/dL or creatinine clearance > 50 mL/min.
 - QTc interval ≤ 500 msec on the baseline electrocardiogram.
16. Negative pregnancy test done ≤ 72 hours prior to registration for women of childbearing potential only.

Note: All female subjects will be considered to be of child-bearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea, in the appropriate age group and without other known or suspected cause), or have been sterilized surgically (*i.e.*, bilateral tubal ligation ≥ 1 menstrual cycle prior to randomization, or have undergone a hysterectomy and/or bilateral oophorectomy).

All female subjects will be considered to be of child-bearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea, in the appropriate age group and without other known or suspected cause), or have been sterilized surgically (*i.e.*, bilateral tubal ligation ≥ 1 menstrual cycle prior to randomization, or have undergone a hysterectomy and/or bilateral oophorectomy). Female subjects of child-bearing potential must agree to use highly effective contraception during the study treatment and for 3 months after the final dose of study treatment. Female subjects exempt from this requirement are subjects who practice total abstinence. If currently abstinent, the subject must agree to use a double barrier method of contraception (*i.e.*, condom and occlusive cap [diaphragm or cervical/vault caps])

with spermicide or until they are established on highly effective contraception for at least one menstrual cycle if they become sexually active during the study treatment and for 3 months after the final dose of study treatment.

Highly effective contraception includes:

- Placement of intrauterine device or system
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault cap) with spermicide
- Vasectomized partner with confirmed azoospermia

Male subjects and their female partner who are of child-bearing potential (as defined above), and are not practicing total abstinence, must agree to use highly effective contraception during study treatment and for 3 months after the final dose of study treatment. If currently abstinent, the subject must agree to use a double barrier method of contraception if they become sexually active, or until they are established on highly effective contraception as described above.

17. Ability to complete questionnaire(s) independently or with assistance.
18. Willingness to provide blood and tissue samples for correlative research purposes (see Sections 6.1.2, 14.0, and 17.0). [Note: These tissue samples are from archived tissue, if available; new biopsies are not required.]
19. Ability to comprehend and respond to questions using a telephone keypad.

Exclusion criteria

1. Prior malignancy, other than carcinoma in situ of the cervix and non-melanoma skin cancers, unless the prior malignancy was diagnosed and definitively treated ≥ 5 years previously, there is no subsequent evidence of recurrence, and the patient is considered by a physician to be at $< 30\%$ risk of relapse.
2. Any of the following because this study involves an investigational agent whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown:
 - Pregnant women
 - Nursing women
 - Men or Women of childbearing potential who are unwilling to employ adequate contraception
3. Presence of a serious nonhealing wound, ulcer, or bone fracture.
4. History of CTCAE grade > 3 hypersensitivity to paclitaxel or Cremophor® EL.
5. Pre-existing peripheral neuropathy grade > 2 at registration.
6. Significant cardiovascular impairment (*e.g.*, New York Heart Association congestive heart failure of grade II or above, unstable angina, myocardial infarction within the past 6 months, or serious cardiac arrhythmia).
7. Subjects with known positive HIV status.
8. History of stroke or transient ischemic attack ≤ 6 months prior to registration.
9. History of uncontrolled seizures. [Note: Patients are eligible for the study if the seizures are well controlled with standard medications.]
10. Severe or uncontrolled intercurrent illness/infection.
11. Concurrent administration of any other investigational agent considered to have potential efficacy in the treatment of breast cancer.
12. Prior exposure to eribulin mesylate.

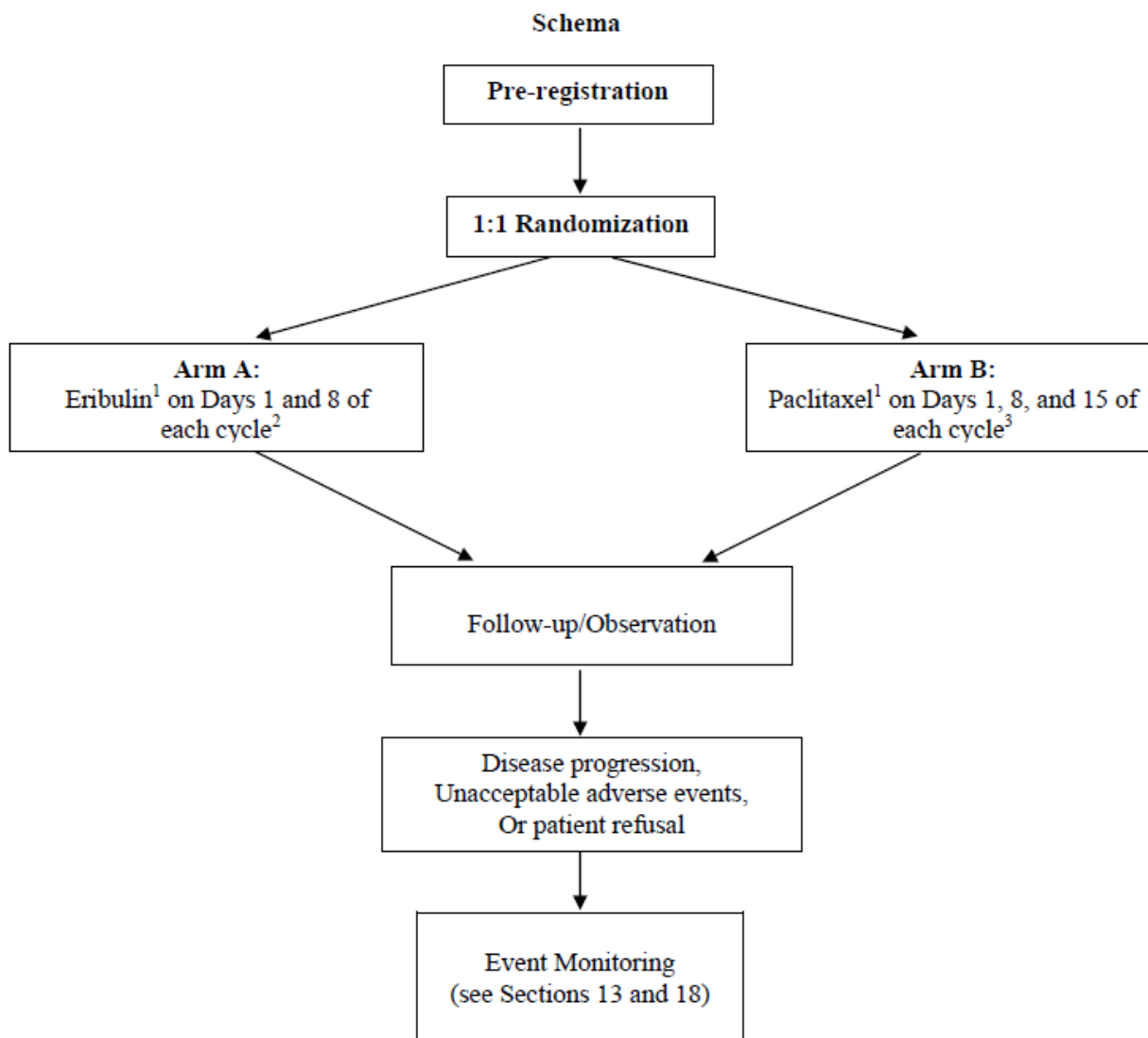
TREATMENT

Experimental: A

- Eribulin on Days 1 and 8 of each cycle (cycle length: 21 days)

Active Comparator: B

- Paclitaxel on Days 1, 8, and 15 of each cycle (cycle length: 28 days)



Treatment will continue until disease progression, unacceptable toxicity, or patient withdrawal.

PRE-STUDY PARAMETERS (refer to Table 4 for details)

- History, physical examination (including measurements of clinically evident disease), weight, height, BSA
- ECOG Performance Status (PS)
- Adverse event assessment
- Concomitant medications
- Pregnancy test (serum or urine β -HCG)
- CBC and CMP
- Contrast enhanced CT scans of chest/abdomen/pelvis (see Section 11.0)
- Bone scan
- Brain MRI with gadolinium
- Electrocardiogram
- Mandatory blood samples (see Section 14.0)
- Mandatory archived tissue sample (see Section 17.0)
- EORTC QLQ-CIPN20 (see Appendix IV)
- PRO-CTCAE (see Appendix V & VI)