BO25126, A Randomized Multicenter, Double-Blind, Placebo-Controlled Comparison of Chemotherapy Plus Trastuzumab Plus Placebo Versus Chemotherapy Plus Trastuzumab Plus Pertuzumab as Adjuvant Therapy in Patients with Operable HER2-Positive Primary Breast Cancer (APHINITY)

Fast Facts

Provided Drug: Pertuzumab/Placebo
CTCAE version 4.0

Inclusion Criteria
Patients must meet ALL of the following criteria in order to be eligible for this study:

1. Age ≥ 18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (see Appendix 3).
3. Non-metastatic operable primary invasive carcinoma of the breast that is:
   a) Histologically confirmed;
   b) Adequately excised:
      - Patients must have undergone either a total mastectomy or breast conserving surgery.
      - For patients who undergo conservative surgery, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible without additional resection.
      - For patients who undergo mastectomy, margins must be free of gross residual tumor. Patients with microscopic positive margins are eligible (see radiation therapy requirements).
   c) pTNM staging:
      Pathological classification of regional lymph nodes: micrometastases (tumor deposits > 0.2 mm) are considered pN1, but isolated tumor cells (ITC) are considered pN0.
      - For patients with node-positive disease (pN ≥ 1), any tumor size except T0
      - Node-negative patients are NOT allowable under Protocol Amendment B. Below applies to Protocol A ONLY:
         o For patients with node-negative disease (pN0) (Protocol A ONLY)
            o Tumor size must be > 1.0 cm OR
            o For tumor size between > 0.5 cm and ≤ 1.0 cm, at least one of the following features must be present: histologic/nuclear grade 3 OR negative for ER and PgR OR age < 35 years.
            o Enrollment of patients with node negative tumors ≤ 1.0 cm will be limited to < 10% of the total number of randomized patients.
      - For multifocal (the presence of two or more tumor foci within a single quadrant of the breast) or multicentric disease (the presence of two or more tumor foci within different quadrants of the same breast), the size of the largest invasive tumor is to be used to determine T stage.
      - Patients with synchronous bilateral invasive disease are eligible so long as both lesions are HER2 positive.
4. Known hormone receptor status (ER and PgR)
5. The interval between definitive surgery for breast cancer and randomization no more than 8 weeks (56 days) All procedures, including randomization, must occur during this period. The first cycle of chemotherapy must be administered within 7 days of randomization or on Day 56, whichever occurs first.
6. Baseline LVEF ≥ 55% measured by ECHO (preferred) or MUGA scan.
7. HER2-positive breast cancer confirmed by a central laboratory and defined as:
   - IHC 3+ in > 10% immunoreactive cells OR c-erbB2 gene amplification by in situ hybridization [ISH] (ratio of c-erbB2 gene signals to centromere 17 signals ≥ 2).
   - Availability of formalin-fixed paraffin-embedded (FFPE) tissue block with at least 5 mm invasive tumor and, wherever possible, a minor component of non-neoplastic breast tissue for central confirmation of HER2 eligibility, hormone receptor status and biomarker evaluation is mandatory (a minimum of 4 and up to 7 x 1mm cores will be taken for translational research (TR) and the block returned to site).
8. Completion of all necessary baseline laboratory and radiologic investigations prior to randomization.
9. Women of childbearing potential and male participants with partners of childbearing potential must agree to use a “highly-effective”, non-hormonal form of contraception or two “effective” forms of non-hormonal contraception by the patient and/or partner. Contraception must continue for the duration of study treatment and for at least 7 months after the last dose of study treatment.
10. Signed informed consent.

**Exclusion Criteria**
Patients meeting any ONE of the following criteria are not eligible for this study:
1. History of any prior (ipsi- and/or contralateral) invasive breast carcinoma.
2. History of non-breast malignancies within the 5 years prior to study entry*, except for the following: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinomas of the skin (*malignancies occurring more than 5 years prior to study entry are permitted if curatively treated with surgery alone).
3. Any "clinical" T4 tumor as defined by TNM, including inflammatory breast cancer.
4. Any node-negative tumor.
5. Any previous systemic chemotherapy (eg, neo-adjuvant or adjuvant) for cancer OR radiation therapy for cancer.
   - Patient with a past history of DCIS and/or LCIS are not allowed to enter the study if they have received any form of systemic therapy for its treatment; OR radiation therapy to the ipsilateral breast where invasive cancer subsequently develops.
   - Patients who had their DCIS/LCIS treated with surgery only are allowed to enter the study.
   - High risk patients who have received chemoprevention drugs in the past are not allowed to enter the study.
6. Prior use of anti-HER2 therapy (eg, lapatinib, neratinib or other tyrosine kinase inhibitors [TKIs]) for any reason or other prior biologic or immunotherapy for cancer.
7. Concurrent anti-cancer treatment in another investigational trial, including hormone therapy bisphosphonate therapy and immunotherapy.
8. Serious cardiac illness or medical conditions including but not confined to:
• History of documented heart failure or systolic dysfunction (LVEF < 50%),
• High-risk uncontrolled arrhythmias ie, atrial tachycardia with a heart rate ≥ 100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block),
• Angina pectoris requiring anti-anginal medication,
• Clinically significant valvular heart disease,
• Evidence of transmural infarction on electrocardiogram (ECG),
• Poorly controlled hypertension (eg, systolic > 180 mm Hg or diastolic > 100 mm Hg).

9. Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness (e.g., infections or poorly controlled diabetes).

10. Any of the following abnormal laboratory tests immediately prior to randomization:
• Serum total bilirubin > 1.5x upper limit of normal (ULN); in cases of known Gilberts syndrome a total bilirubin of 2x ULN is permitted,
• Alanine amino transferase (ALAT) and/or aspartate amino transferase (ASAT) >1.25x ULN,
• Alkaline phosphatase (ALP) > 2.5x ULN,
• Serum creatinine > 1.5x ULN,
• Total white blood cell count (WBC) < 2,500 / mm3(<2.5 x 10⁹/L),
• ANC < 1,500 / mm3 (< 1.5 x 10⁹/L),
• Platelets < 100,000 / mm3 (< 100 x 10⁹/L).

11. Pregnant or lactating women or women of childbearing potential without a negative pregnancy test (serum), within 7 days prior to randomization, irrespective of the method of contraception used.

12. Women of childbearing potential or less than one year after menopause (unless surgically sterile) who are unable or unwilling to use the contraceptive measures required by this protocol during and 7 months after the last dose of study medication (see Section 7.2.4).

13. Sensitivity to any of the study medications or any of the ingredients or excipients of these medications, including sensitivity to benzyl alcohol.

Pre-Study Parameters
1. HER2 determination by central review
2. H&P including height, weight, blood pressure, pulse, temperature and performance status
3. CBC and differential
4. CMP including LDH and direct bilirubin
5. Pregnancy test
6. Mammogram or breast MRI, CXR,
7. Bone scan and liver imaging if indicated
8. ECG and LVEF (ECHO preferred)
9. Concomitant meds
10. AE assessment
11. Quality of Life assessments
12. Mandatory tumor tissue and blood samples for biomarker studies
13. Optional blood samples for PGx analysis
ANTHRACYCLINE BASED CHEMOTHERAPY

Arm 1

- 3-4 cycles of anthracycline-containing chemotherapy
- 3-4 cycles of taxane-containing chemotherapy

- Trastuzumab 6mg/kg 3-weekly
- Pertuzumab 420mg IV 3-weekly

Arm 2

- 3-4 cycles, 3-4 cycles

- Trastuzumab 6mg/kg 3-weekly
- Placebo IV 3-weekly

Radiotherapy and/or endocrine therapy may be started after the end of adjuvant chemotherapy and in accordance with the protocol recommendations.

KEY

- 3-4 cycles of anthracycline-containing chemotherapy
- 3-4 cycles of taxane-containing chemotherapy
- Trastuzumab
- Placebo
- Pertuzumab

* Trastuzumab must be given at a 6mg/kg loading dose at the first trastuzumab cycle
** Pertuzumab must be given at a 420mg loading dose at the first pertuzumab cycle

NON-ANTHRACYCLINE BASED CHEMOTHERAPY

Arm 1

- 6 cycles

- Trastuzumab 6mg/kg IV 3-weekly
- Pertuzumab 420mg IV 3-weekly

Arm 2

- 6 cycles

- Trastuzumab 6mg/kg IV 3-weekly
- Placebo IV 3-weekly

Radiotherapy and/or endocrine therapy may be started after the end of adjuvant chemotherapy and in accordance with the protocol recommendations.

KEY

- 6 cycles of docetaxel + carboplatin (TC)
- Trastuzumab
- Placebo
- Pertuzumab

* Trastuzumab must be given at a 6mg/kg loading dose at the first trastuzumab cycle
** Pertuzumab must be given at a 420mg loading dose at the first pertuzumab cycle

Key personnel, patients, study management teams and sponsor will be blinded as to treatment assignment.