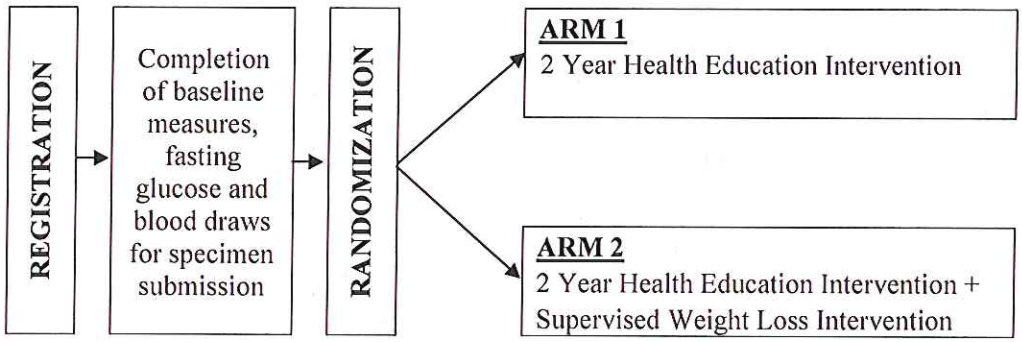
RANDOMIZED PHASE III TRIAL EVALUATING THE ROLE OF WEIGHT LOSS IN ADJUVANT TREATMENT OF OVERWEIGHT AND OBESE WOMEN WITH EARLY BREAST CANCER

Key Eligibility Criteria (see Section 3.0 for a full list of eligibility criteria):

- Histologic diagnosis of invasive breast cancer within the past 12 months
- Her-2 negative
- Eligible TNM stages include (see Section 3.2.1 for definitions):
  - ER and PR negative: T2-3N0 or T0-3N1-3
  - ER and/or PR positive: T0-3N1-3, or T3N0
- All adjuvant or neoadjuvant chemotherapy and surgery completed at least 21 days prior to registration
- Participants must be women
- Age ≥ 18 years
- ECOG Performance Status 0 or 1
- No comorbid conditions that would cause life expectancy of less than 4 years (see Section 3.2.7 for complete criteria)
- No diabetes mellitus currently being treated with insulin or sulfonylurea drugs
- BMI ≥27 kg/m2 at the time of study enrollment
- Self-reported ability to walk at least 2 blocks (at any pace)
- Able to read and comprehend English

Schema



Health Education Intervention (Arms 1 and 2):

All participants in both study arms will receive a 2-year health education intervention focused on breast cancer and general health topics. Patients will receive mailings of health education brochures, a health magazine subscription, and invitations to webinars and teleconferences that focus on breast cancer and other health topics.

Weight Loss Intervention (Arm 2 Only):

The standardized, 2-year, telephone-based weight loss intervention will include individual weight loss, caloric restriction and physical activity goals for each participant. It will be administered through semi-structured phone calls delivered by trained coaches at the BWEL Call Center located at Dana Farber Cancer Institute, and supplemented through print and on-line materials. The intervention will utilize a toolbox approach that will allow for tailoring for the individual participant.

Follow Up:

Patients are to be followed every 6 months for the first 3 years after study enrollment and then annually until 10 years from registration. The intervention will last 2 years or until disease recurrence/progression, new invasive primary cancer (other than BCC or SCC of skin that has been adequately treated) or patient withdrawal. **Please refer to the full protocol text for a complete description of the eligibility criteria and intervention plan.**

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Medical conditions such as uncontrolled infection (including HIV), or inflammatory bowel disease, which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

In addition:

- Women should not be known to be pregnant or nursing, and should not plan to become pregnant within two years from registration.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday four weeks later would be considered Day 28.

___ **3.2.1 Documentation of Disease:**

___ • Subjects must have histologically confirmed invasive breast cancer and registration must occur within 12 months after the first histologic diagnosis of invasive breast cancer.
  - A core biopsy interpreted as invasive cancer meets this criterion; if no core biopsy is performed, the date of first histologic diagnosis will be the date of first surgical procedure that identifies invasive cancer (biopsy, lumpectomy or mastectomy).
  - Neoadjuvant subjects should have no evidence of clinical T4 disease prior to chemotherapy and surgery. See eligible cTNM classifications below.
  - Bilateral breast carcinoma is allowed provided diagnoses are synchronous – that is, within 3 months of one another – and at least one of the two breast carcinomas meet the eligibility criteria and neither violates the eligibility criteria.

___ • Her-2 negative, defined as:
  - ISH ratio of < 2.0 (if performed)
  - IHC staining of 0-2+ (if performed)
  - Deemed to not be a candidate for Her-2 directed therapy.

- Eligible TNM Stages include:
  - **ER and PR** negative (defined as <1% staining for ER and PR by IHC):
    T2 or T3 N0, T0-3N1-3
  - **ER and/or PR** positive (defined as ≥ 1% staining for ER and/or PR on IHC):
    T0-3N1-3 or T3N0

    The eligibility of neo-adjuvant subjects is assessed on the basis of cTNM. The same eligible TNM combinations apply.
- No history of invasive breast cancer in 5 years prior to study registration other than the current diagnosis (prior DCIS at any time is acceptable).
- Patients must have had a bilateral mammogram within 12 months prior to registration, unless the initial surgery was a total mastectomy, in which case only a mammogram of the remaining breast is required. (Subjects with bilateral total mastectomies do not require imaging).
- Investigations, including chest X-ray or CT chest, bone scan (with radiographs of suspicious areas) and abdominal ultrasound or liver scan or CT abdomen have been performed between the first histologic diagnosis and the time of registration as detailed below.
  - Chest X-Ray, 2 view (or Chest CT, or PET/CT) is required only if clinically indicated or recommended by NCCN guidelines.
  - Bone scans (with x-rays of abnormal areas) are required only if clinically indicated or recommended by NCCN guidelines.
  - Abdominal imaging is required only if clinically indicated or recommended by NCCN guidelines.

3.2.2 Prior Treatment

- All adjuvant or neoadjuvant chemotherapy (at the discretion of the treating physician) and surgery completed at least 21 days prior to registration.

  Concomitant radiation, biologic therapy, hormonal therapy, and bisphosphonates are acceptable.
- Surgical margins must be clear of invasive carcinoma. If there is microscopic residual ductal in situ disease present at lumpectomy or total mastectomy margins, further excision is highly recommended. If further excision is not undertaken, the subject may still be entered on study, provided that in addition to breast or chest wall irradiation, a boost to the tumor bed is delivered. In situ lobular disease at the margin is acceptable.
- All subjects (both adjuvant and neo-adjuvant) must have sentinel lymph node biopsy and/or axillary lymph node dissection.

  Sentinel lymph node biopsy alone is allowed in the following instances:

  a) Sentinel lymph node biopsy is negative: pN0

  b) Sentinel lymph node biopsy is positive for isolated tumor cells only: pN0 (i+)

  c) Clinically node negative, T1-2 tumors with sentinel lymph node biopsy positive in < 2 lymph nodes without matted nodes and undergoing breast conserving surgery and tangential whole breast irradiation, or undergoing mastectomy and chest wall irradiation.

___ • All women who undergo breast conserving therapy must receive concomitant radiotherapy. Radiation after mastectomy is to be administered according to pre-specified institutional guidelines. Radiation can be administered either prior to or during protocol treatment.

___ • Patients with hormone receptor positive breast cancer as defined above must receive at least 5 years of adjuvant hormonal therapy in the form of tamoxifen or an aromatase inhibitor, alone or in combination with ovarian suppression. (NOTE: for patients with ER and PR staining in less than 5% of cells, hormonal therapy for at least 5 years is strongly recommended but not required). Hormonal therapy can be initiated prior to or during protocol therapy.

___ **3.2.3 Participants must be women.**

___ **3.2.4 Age ≥ 18 years**

___ **3.2.5 ECOG Performance Status 0 or 1.**

___ **3.2.7 Comorbid Conditions**

___ • No history of other malignancy within the past 4 years, except for malignancies with a >95% likelihood of cure (e.g. non-melanoma skin cancer, papillary thyroid cancer, in situ cervical cancer).

___ • No diabetes mellitus currently treated with insulin or sulfonylureas.

___ • No history of serious digestive and/or absorptive problems, including inflammatory bowel disease and chronic diarrhea that preclude adherence to the study diet.

___ • No history of severe cardiovascular, respiratory or musculoskeletal disease or joint problems that preclude moderate physical activity. Examples would include unstable angina, recent myocardial infarction, oxygen-dependent pulmonary disease, and osteoarthritis requiring imminent joint replacement. Moderate arthritis that does not preclude physical activity is not a reason for ineligibility.

___ • No prior bariatric surgery or planning to undergo this procedure within the next 2 years after study registration.

___ • No comorbid conditions that would cause life expectancy of less than 5 years.

___ • No history of psychiatric disorders that would preclude participation in the study intervention (e.g. untreated major depression or psychosis, substance abuse, severe personality disorder) or prevent the patient from giving informed consent.

___ **3.2.8 Other**

___ • BMI ≥27 kg/m^2 documented within 56 days prior to study registration.

___ • Self-reported ability to walk at least 2 blocks (at any pace).

___ • Not participating in another weight loss, physical activity or dietary intervention clinical trial. Co-enrollment in trials involving pharmacologic therapy is allowed. Participants in both arms are also allowed to pursue weight loss and physical activity programs on their own, as long as these programs are not provided as part of a clinical trial.

___ • Able to read and comprehend English.

Eligibility is restricted to individuals who can comprehend and read English given that participation in the study will require the ability to read lifestyle intervention materials and communicate with a coach through 42 phone calls over 2 years. Given the logistical and financial difficulties of supporting the intervention in multiple languages,

participation will be limited to individuals speaking English at this time. The study team plans to make the intervention available in additional languages sometime after study activation. This eligibility criterion will be modified with an amendment at that time.