

CTSU NCIC MA.32 - A Phase III Randomized Trial of Metformin Versus Placebo on Recurrence and Survival in Early Stage Breast Cancer

Fast Facts

Metformin/placebo provided CTCAE v 4; AJCC v 7; RECIST n/a

The study population will consist of subjects with invasive breast cancer who, within the previous 12 months, have received the first histologic diagnosis of invasive breast carcinoma and have undergone definitive surgical treatment for invasive breast cancer. Subjects may have received, at the discretion of their treating physician, standard adjuvant loco-regional radiation, adjuvant endocrine treatment, trastuzumab or other biologics or bisphosphonates prior to or during study treatment. Chemotherapy (adjuvant or neoadjuvant), if given, must be completed at least 4 weeks prior to randomization.

Eligibility Criteria

1. Subjects must have histologically confirmed invasive breast cancer and be enrolled in the trial within 12 months after the first histologic diagnosis of invasive breast cancer. A core biopsy interpreted as invasive cancer meets this criterion; otherwise, the date of first histologic diagnosis will be the date of first surgical procedure that identifies invasive cancer (biopsy, lumpectomy or mastectomy). TNM Stage (AJCC Version7) must be one of the combinations presented in Section 5.1.4. Neoadjuvant subjects should have no evidence of clinical T4 disease prior to chemotherapy and surgery. Please refer to 5.1.4 for eligible cTNM classifications. 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.
2. 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 tumour cells only: pN0 (i+)
 - c)* clinically node negative, T1-2 tumours with sentinel lymph node biopsy positive in < 2 lymph nodes without extra-capsular extension or matted nodes and undergoing breast conserving surgery and whole breast irradiation (* excludes subjects treated with neo-adjuvant systemic therapy)
3. Definitive surgery and/or chemotherapy have been completed at least 4 weeks prior to randomization. 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.
4. Adjuvant subjects with the following pT pN combinations are eligible:
 - pT1c, pN0 *AND* at least one of the following tumor characteristics: histologic grade 3, lymphovascular invasion, negative estrogen and progesterone receptors, HER2 positive, Oncotype Dx recurrence score ≥ 25 (or if Oncotype Dx recurrence score is not available, Ki67 > 14%)

OR

 - Subjects with pT2-3, pN0

OR

 - Subjects with pT1-3, pN1-3

The eligibility of neo-adjuvant subjects is assessed on the basis of cTNM. The same eligible TNM combinations apply.
5. Estrogen and progesterone receptor status must be known. (*Receptor positive by immunohistochemistry: ERICA or PgRICA versus both receptors negative. It is recommended that ER and PgR assays be considered positive if there are at least 1% positive tumour nuclei in the sample on testing in the presence of expected reactivity of internal [normal epithelial elements] and external control.*)
6. HER2 status must be known. (*Positive = 3+ over-expression by IHC in > 30% of invasive tumor cells **OR** HER2 gene amplification by FISH/CISH > 6 HER2 gene copies per nucleus **OR** FISH/CISH ratio: HER2 gene copies to chromosome 17 signals of ≥ 2.2 . All other results will be considered negative.*)
7. Patients must have had a bilateral mammogram within 12 months prior to randomization, 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 and no mammogram within 12 months prior to randomization must, instead, have a physical examination of the chest wall to ensure there is no residual or recurrent disease at the time of randomization. The date of this examination is used in place of the mammogram date on the eligibility checklist.)

8. 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 randomization.
 - a. Chest X-Ray (or Chest CT) is mandatory
 - b. Bone scans (with x-rays of abnormalities) are required if alkaline phosphatase is elevated or if there are symptoms of metastatic disease
 - c. Abdominal imaging is required only if liver function tests (AST, ALT, Alkaline Phosphatase) are abnormal or if there are symptoms of metastatic disease
9. Hematology investigations (WBC, Granulocytes, Platelets, Hemoglobin) have been completed within 28 days prior to randomization and results are available.
10. Biochemistry investigations have been completed within 28 days prior to randomization and values are within the parameters required by the protocol:
 - a. AST < 1.8 X ULN
 - b. ALT < 1.8 X ULN
 - c. Alkaline Phosphatase < 2 X ULN
 - d. Serum Creatinine < 115 µmol/L (1.3mg/dL)
 - e. Serum Bilirubin < institution ULN (*except for subjects with Gilbert's Disease who are eligible despite elevated serum bilirubin level*)
11. ECOG Performance Status of 0, 1 or 2
12. Age ≥ 18 and < 75 and life expectancy of at least 5 years (18 years of age was used as a cut-off due to the lack of data indicating that breast cancer is a health issue in the < 18 years age group and metformin safety in pediatric patients has not been confirmed. Age > 80 carries increased risk of lactic acidosis and study intervention is for 5 years). Subjects must be accessible for treatment and follow-up. Investigators must assure themselves the subjects randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.
13. In accordance with NCIC CTG policy, protocol treatment is to begin within 10 working days of patient randomization.
14. Subject consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements. It will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the NCIC CTG Study Coordinator that such clearance has been obtained, before the trial can commence in that center. Because of differing requirements, a standard consent form for this trial will not be provided but a sample form is given in Appendix XII. A copy of the initial full board REB approval approved consent form must be sent to the central office. The patient must sign the consent form prior to randomization or registration. Please note that the consent form for this study must contain a statement which gives permission for the NCIC CTC and monitoring agencies to review patient records (see Section 16 for further details).

For the first 888 eligible English or French-speaking subjects only:

15. Subject is able (i.e. sufficiently fluent) and willing to complete the Quality of Life (EORTC QLQ C-30 and Trial Specific Checklist) in English or French. The baseline assessment must already have been completed at the time of enrolment. Inability (illiteracy in English or French, loss of sight or other equivalent reason) to complete questionnaires will not make the patient ineligible for the study; however, ability but unwillingness to complete the questionnaires will make the patient ineligible. (Once the target number of 888 subjects is achieved, this criterion will no longer need to be fulfilled.) [See Appendix VI].
16. English-speaking subjects who have completed the Quality of Life Questionnaire who are able (i.e. sufficiently fluent) and willing to complete Nurses' Health Study 11 Physical Activity Questionnaire and Block Alive Screener in English. The baseline assessment must already have been completed at the time of enrolment. Inability (illiteracy in English, loss of sight or other equivalent reason) to complete questionnaires will not make the patient ineligible for the study; however, ability but unwillingness to complete the questionnaires will make the patient ineligible. (This component of the study will close at the same time as the Quality Of Life sub-study.) [See Appendix VII].

Ineligibility Criteria

1. Subjects with a history of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumors curatively treated with no evidence of disease for ≥5 years.
2. Subjects with locally recurrent or metastatic breast carcinoma. (Subjects with prior invasive breast cancer at any time are not eligible).
3. Subjects whose axillary node status is unknown.
4. Known diabetes (type 1 or 2) or baseline fasting glucose > 7.0 mmol/L (126 mg/dL). (Sampled and assayed according to local institution's procedures.)
5. Known hypersensitivity or intolerance to metformin.

6. Any condition associated with increased risk of metformin-associated lactic acidosis (e.g. congestive heart failure defined as New York Heart Association [NYAA] Class III or IV functional status [see Appendix IX] history of acidosis of any type; habitual intake of 3 or more alcoholic beverages per day).
7. Currently taking metformin, sulfonylureas, thiazolidenediones or insulin for any reason.
8. Current or planned pregnancy or lactation in women of child-bearing potential (confirmed by negative pregnancy test within 7 days of randomization). Men should not father a child. (An effective method of birth control should be used while on study treatment which could include IUD, condoms or other barrier methods of birth control because the safety of metformin in pregnancy or in male fertility has not been established).
9. Concurrent or planned participation in randomized trials of weight loss or exercise interventions or trials targeting insulin, ICF-1 or their receptors, or involving P13K inhibitors (at the time of randomization)*.
* These interventions would interfere with the primary endpoint. (Also, in general, double randomizations in breast cancer trials for MA.32 patients are permitted only if the patient meets all the eligibility criteria for MA.32 and the sponsor of the previous trial has no objection to the patient also being enrolled in MA.32).

Pre-Study Parameters

1. History and physical including height, weight, performance status, blood pressure, date of LMP, menopausal status, waist and hip circumference, BMI, smoking history and alcohol intake, list on concomitant medications, AE evaluation
2. Lab including CBC with differential, CMP including **fasting glucose**, insulin, serum Vitamin B12, pregnancy test for women of child-bearing potential
3. Bilateral mammogram within 12 months of randomization.

Radiology – The following must be assessed between the date of first histologic diagnosis and the date of randomization.

1. Chest X-ray or chest CT (mandatory)
2. Bone scan (with x-rays of abnormal areas) if alkaline phosphatase is elevated or if there are symptoms of metastatic disease
3. Abdominal imaging if ALT, AST or Alkaline Phosphatase is elevated or if there are symptoms of metastatic disease

Treatment

See section 8 of protocol for complete treatment plan.

This is a blinded study.

Metformin/placebo provided.

	Medication	Dose	Route/Frequency	Duration
Arm 1	Metformin	850 mg	PO BID	5 years
Arm 2	Placebo	One caplet	PO BID	5 years