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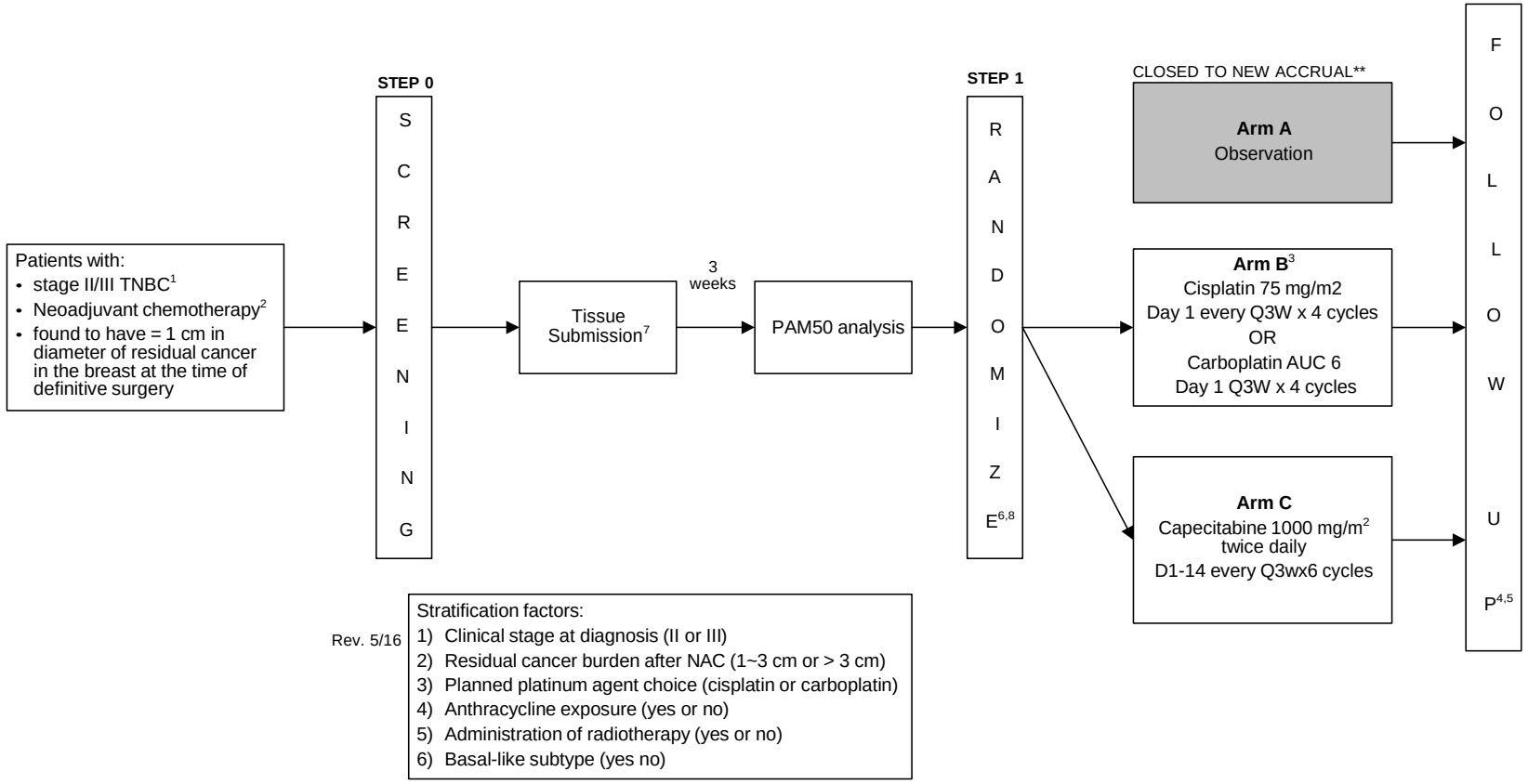
Schema



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Accrual = 750
1 cycle = 3 weeks

Rev. 6/16 1. TNBC: ER/PR less than 10% positive staining with weak intensity score, or less than 1% positive staining with weak or intermediate intensity score; HER2 negative per ASCO guidelines.

Rev. 6/16 2. Taxane ± anthracycline based; platinum agents or capecitabine not allowed.

3. Choice of platinum agent will be per treating physician discretion.

4. Primary Endpoint: IDFS in patients with basal-like TNBC.

5. Secondary Endpoints: IDFS in patient with non basal-like TNBC, OS and RFS.

6. Patients must have completed adjuvant radiotherapy (if applicable) prior to randomization.

Rev. 6/16 7. Tumor tissue from the residual disease on the definitive surgical specimen must be submitted within 21 weeks post surgery for PAM50 analysis for stratification as outlined in Section 10.2. Patients cannot be randomized to treatment until confirmation of PAM50 analysis from the Molecular Diagnostics Laboratory performing the assessments.

8. Females of child-bearing potential must have a blood test or urine study within 2 weeks prior to treatment initiation to rule out pregnancy.

**Arm A closed to new accrual in Addendum #3. New patients are randomized to Arm B or C

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

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

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

Rev. 6/16 **NOTE:** This study involves screening and randomization. Tumor tissue specimen must be submitted for PAM50 analysis for stratification.

Rev. 6/16 3.1 Eligibility Criteria for Screening and Molecular Profiling (STEP 0)

_____ 3.1.1 Age ≥ 18 years.

_____ 3.1.2 ECOG Performance Status 0 or 1 within 2 weeks prior to screening.

_____ 3.1.3 Female and male patients must have histologically confirmed triple negative (ER-/PR-/HER2-) invasive breast cancer, clinical stage II-III at diagnosis (AJCC 7th edition) based on initial evaluation by clinical examination and/or breast imaging.

Rev. 2/16 3.1.3.1 ER- and PR- should meet one of the following criteria:

____ ≤ 10% cells stain positive, with weak intensity score (Allred score ≤ 3)

____ ≤ 1% cells stain positive, with weak or intermediate intensity score (Allred score ≤ 3)

3.1.3.2 HER2 negative (not eligible for anti-HER2 therapy) will be defined as:

____ IHC 0, 1+ without ISH HER2/neu chromosome 17 ratio OR

____ IHC 2+ and ISH HER2/neu chromosome 17 ratio non-amplified with ratio less than 2.0 and if reported average HER2 copy number < 6 signals/cells OR

____ ISH HER2/neu chromosome 17 ratio non-amplified with ratio less than 2.0 and if reported average HER2 copy number < 6 signals/cells without IHC)

NOTE: Patients that originally present with synchronous bilateral tumors are eligible provided both tumors are TNBC, and at least one of them fulfills the remainder eligibility criteria of the protocol.

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_____ 3.1.4 Patients must have completed neoadjuvant taxane +/- anthracycline. Patients must NOT have received cisplatin or carboplatin or capecitabine as part of their neoadjuvant therapy regimen.

NOTE: Patients who received preoperative therapy as part of a clinical trial may enroll.

_____ 3.1.5 Must have completed definitive resection of primary tumor.

3.1.5.1 Negative margins for both invasive and ductal carcinoma in situ (DCIS) are desirable, however patients with positive margins may enroll if the treatment team believes no further surgery is possible and patient has received radiotherapy. Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible.

3.1.5.2 Either mastectomy or breast conserving surgery (including lumpectomy or partial mastectomy) is acceptable.

3.1.5.3 Sentinel node biopsy post neoadjuvant chemotherapy (i.e. at the time of definitive surgery) is allowed. Axillary dissection is encouraged in patients with lymph node involvement, but is not mandatory.

_____ 3.1.6 Post neoadjuvant chemotherapy, patients must be found to have residual invasive cancer in the breast at the time of definitive surgery. Residual cancer is defined as a contiguous focus of residual invasive cancer, in the breast, measuring ≥ 1 cm in diameter, and with more than minimal cellularity, as per local pathologist determination.

NOTE: The presence of ductal carcinoma in situ (DCIS) without invasion does not qualify as residual invasive disease in the breast.

_____ 3.1.7 Post-mastectomy radiotherapy is required for all patients with the following:

____Primary tumor ≥ 5 cm (prior to neoadjuvant chemotherapy [clinically] or at the time of definitive surgery) or involvement of 4 or more lymph nodes at the time of definitive surgery.

____For patients with primary tumors < 5 cm or with < 4 involved lymph nodes prior to neoadjuvant chemotherapy and at the time of definitive surgery, provision of post-mastectomy radiotherapy is at the discretion of the treating physician.

NOTE: Radiation of regional nodal basins is at the discretion of the treating radiation oncologist. Patients enrolled in clinical trials addressing local therapy after neoadjuvant chemotherapy are allowed to enroll.

Rev. 6/16 _____ 3.1.8 Breast radiotherapy (whole breast or partial) is required for patients who underwent breast-conserving therapy, including lumpectomy or partial mastectomy.

_____ 3.1.9 Adequate bone marrow and organ function based on the following tests. Laboratory values must be obtained within 8 weeks prior to screening for protocol therapy.

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3.1.9.1 Hemoglobin (Hgb) > 9.0 g/dL

Hgb: _____ Date of Test: _____

3.1.9.2 Platelets > 100,000 cells/mm^3

Platelets: _____ Date of Test: _____

3.1.9.3 Absolute neutrophil count (ANC) > 1500 cells/mm^3

ANC: _____ Date of Test: _____

3.1.9.4 Calculated creatinine clearance of > 50 mL/min using the Cockcroft-Gault formula:

Males: $\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$

Females: Estimated creatinine clearance for females × 0.85

Creatinine Clearance: _____Date of Test: _____

3.1.9.5 Bilirubin ≤ 1.5 x ULN upper limit of normal (except in patients with documented Gilbert's disease, who must have a total bilirubin ≤ 3.0 mg/dL)

Bilirubin: _____ Date of Test: _____

3.1.9.6 Aspartate aminotransferase (AST, SGOT) ≤ 2.5 × ULN

AST: _____ Date of Test: _____

3.1.9.7 Alanine aminotransferase (ALT, SGPT) ≤ 2.5 × ULN

ALT: _____ Date of Test: _____

_____ 3.1.10 No stage IV (metastatic) disease, however no specific staging studies are required in the absence of symptoms or physical exam findings that would suggest distant disease.

_____ 3.1.11 No clinically significant infections as judged by the treating investigator.

_____ 3.1.12 Patients with active ≥ CTCAE v.4 grade 2 neuropathy are ineligible.

Rev. 6/16 _____3.1.13 Adjuvant chemotherapy after surgery other than that specified in this protocol is not allowed. LHRH agonists and adjuvant bisphosphonate or denosumab use is allowed.

Rev. 6/16 _____ 3.1.14 Patients must have archived formalin-fixed paraffin-embedded (FFPE) tumor tissue specimen from the residual disease on the definitive surgical specimen available for PAM50 analysis for stratification.

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3.1.14.1 Tumor tissue specimen from the definitive surgery has been collected and is ready to ship to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) within 21 weeks post-surgery as indicated in Section 10.2.1.

The Molecular Diagnostics Laboratory (MDL) at MD Anderson Cancer Center will perform the PAM50 analysis and notify the ECOG-ACRIN Operations Office within three (3) weeks of receipt of the tumor tissue specimen via secure electronic messaging to the ECOG-ACRIN database.

NOTE: Every effort should be made to submit the tumor tissue specimen to the ECOG-ACRIN CBPF immediately.

Date of surgery: _____

Date tumor tissue sent to ECOG-ACRIN CBPF: _____

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3.2 Eligibility Criteria for Randomization (Step 1):

Screened patients will remain on the study and be randomized if they meet the above and following criteria. For patients randomized to the chemotherapy arms, Cycle 1/ Day 1 (platinum based or capecitabine) must start within 1 week (5 working days) following randomization.

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_____ 3.2.1 Must have PAM50 analysis by digital mRNA quantitation on the formalin-fixed paraffin-embedded tumor tissue specimen (FFPE) of the residual disease in the breast or axilla resected at the time of definitive surgery completed.

Date notified of eligibility per central PAM50 analysis:

_____ 3.2.2 ECOG Performance Status 0 or 1 within 2 weeks prior to randomization.

_____ 3.2.3 Patients must have completed adjuvant radiotherapy ≥ 2 weeks prior to randomization for protocol therapy, if applicable.

_____ 3.2.4 Patients must have completed treatment with any investigational agent ≥ 30 days prior to randomization for protocol therapy, if applicable.

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_____ 3.2.5 Patients must be randomized within 24 weeks from surgery

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_____ 3.2.6 Women must not be pregnant or breast-feeding due to risk of teratogenicity/ toxicity with capecitabine or platinum based therapy. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.

3.2.6.1 A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

3.2.6.2 Date of pregnancy blood test or urine study: _____

_____ 3.2.7 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study.

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_____ 3.2.8 Adequate bone marrow and organ function based on the following tests. Laboratory values must be obtained within 2 weeks prior to randomization.

3.2.8.1 Hemoglobin (Hgb) > 9.0 g/dL

Hgb: _____ Date of Test: _____

3.2.8.2 Platelets > 100,000 cells/mm^3

Platelets: _____ Date of Test: _____

3.2.8.3 Absolute neutrophil count (ANC) > 1500 cells/mm^3

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3.2.8.4 INR ≤ 2 for subjects not on anticoagulants; INR ≤ 3 for subjects on warfarin

3.2.8.5 Calculated creatinine clearance of > 50 mL/min using the Cockcroft-Gault formula:

Males: $\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$

Females: Estimated creatinine clearance for females × 0.85

Creatinine Clearance: _____Date of Test: _____

3.2.8.6 Bilirubin ≤ 1.5 x ULN (except in patients with documented Gilbert's disease, who must have a total bilirubin ≤ 3.0 mg/dL)

Bilirubin: _____ Date of Test: _____

3.2.8.7 Aspartate aminotransferase (AST, SGOT) ≤ 2.5 × ULN

AST: _____ Date of Test: _____

3.2.8.8 Alanine aminotransferase (ALT, SGPT) ≤ 2.5 × ULN

ALT: _____ Date of Test: _____