ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A011502

A RANDOMIZED PHASE III DOUBLE BLINDED PLACEBO CONTROLLED TRIAL OF ASPIRIN AS ADJUVANT THERAPY FOR HER2 NEGATIVE BREAST CANCER: THE ABC TRIAL

Investigational agents: Aspirin and Placebo for Aspirin
Supplied by: Bayer; Distributed by: McKesson

ClinicalTrials.gov Identifier: NCT02927249

Stand-alone Companion Study: Alliance A211601

Participating NCTN Groups:
Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/SWOG; CCTG/Canadian Cancer Trials Group

Study Resources:

Expedited Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System

[redacted]

Protocol Contacts:

A011502 Nursing Contact

[redacted]

Pharmacy Contact

[redacted]

Alliance Biorepository at Washington University (WUSTL)

[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Washington University (WUSTL)

CONTACT INFORMATION

For regulatory requirements	For patient enrollments:	For data submission
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted]). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password.		
Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as instructed on the form.		
For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e. unrelated to patient eligibility, clinical treatment, or data submission Contact the CTSU Help Desk by phone or e-mail: [redacted]		

A RANDOMIZED PHASE III DOUBLE BLINDED PLACEBO CONTROLLED TRIAL OF ASPIRIN AS ADJUVANT THERAPY FOR HER2 NEGATIVE BREAST CANCER: THE ABC TRIAL

Eligibility Criteria (see Section 3.0)

Histologic documentation of women or men with HER2 negative breast carcinoma (See Section 3.2.1).

If ER and PR negative, tumor must be node positive or >2 cm and node negative. Patients must be registered within 18 months of diagnosis. pN1mic is eligible.

If ER and/or PR positive, tumor must be node positive and within 10 years of diagnosis. pN1mic is eligible. (See Section 3.2.2.)

Prior adjuvant treatment with chemotherapy and/or endocrine therapy, as determined by the treating physician, is allowed (see Section 3.2.3).

Prior regular NSAID/aspirin use (defined as ≥ 5 days per week) at any dose (including baby aspirin) allowed if stopped for at least 30 days prior to study entry and throughout study period (see Section 3.2.4).

If ER and/or PR positive, tumor must be node positive and within 10 years of diagnosis. pN1mic is eligible.

Patients must be ≥ 18 and < 70 years of age.

ECOG performance status 0-2.

Patients with a prior history of gastric/duodenal ulcers documented on endoscopy can be enrolled (see Section 3.2.7).

No history of GI bleeding (see Section 3.2.8).

No history of prior stroke (hemorrhagic or ischemic).

No concurrent anticoagulation with warfarin, heparin/heparin analogues, clopidogrel, direct thrombin inhibitors or direct Factor Xa inhibitors.

No history of atrial fibrillation or myocardial infarction.

No history of grade 4 hypertension (see 3.2.12).

No chronic (duration >30 days) daily use of oral steroids. Inhaled or topical steroids are allowed.

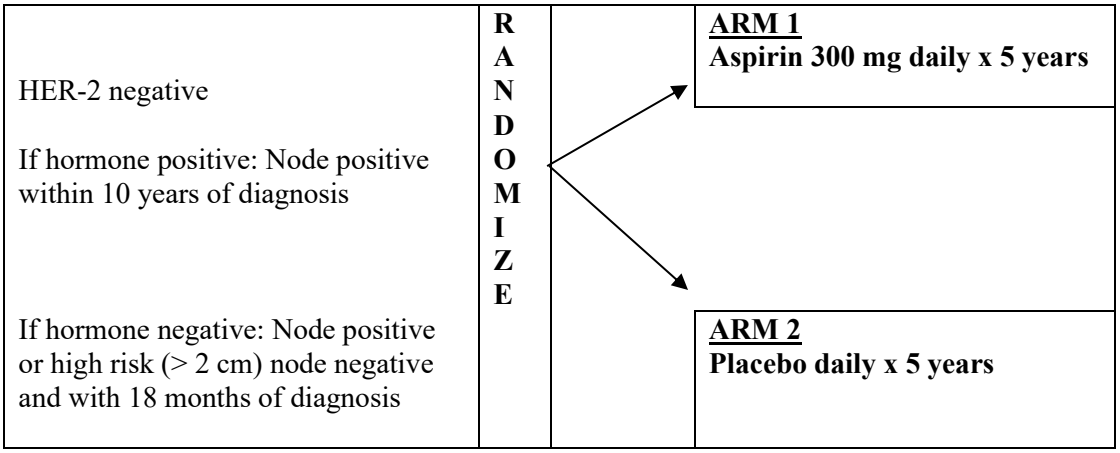
No known allergy to aspirin.

No prior invasive malignancy of any type within the past 5 years (see Section 3.2.15).

Concurrent enrollment on a non-chemotherapy treatment trial will be allowed, as long as that trial allows concurrent daily aspirin use.

No history of metastatic breast cancer

Schema



Stratification Factors
Hormone Receptor status**
1) Positive (either ER or PgR positive or unknown)
2) Negative (both ER and PgR negative)
Body Mass Index
1) Less than 30 kg/m^2
2) Greater than or equal to 30 kg/m^2
Breast Cancer Stage*
1) Stage I/II
2) Stage III
Time Since Diagnosis
1) ≤ 18 months
2) > 18 months

* Sites can use AJCC 7 or AJCC 8 because the anatomical staging remains unchanged between the versions.
** For patients who either have hormone receptor negative breast cancer or who are ER+ and completed hormone therapy within 6 months prior to registration to A011502, please consider enrolling to the companion study, A211601. See Section 4.3.

Patients who complete five years of study treatment will be followed annually until 10 years from registration. Patients who stop treatment before 5 years, will have a follow-up visit 6 months after end of protocol treatment and then annually until 10 years from registration.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Table of Contents

1.0 BACKGROUND

1.1 Rationale for Selected Approach and Trial Design

Multiple lines of evidence including preclinical and epidemiologic studies and clinical trial data present a compelling case for the potential of aspirin as adjuvant therapy. However, in order to become part of routine clinical care, a randomized placebo-controlled trial is crucial to definitively evaluate the risks and benefits for breast cancer survivors.

Selection of the aspirin dose was chosen to balance optimal therapeutic dose with potential toxicity. In the observational Nurses' Health Study (NHS) there was reduced breast cancer mortality among those who consumed aspirin as infrequently as 2-5 times per week, but there was a significant linear trend ($p<0.001$) indicating greater survival benefit with daily use. Although NHS did not assess dose, 35% took aspirin for heart disease prevention (likely 81 mg daily) whereas others took it for muscle or joint pain, headache, backache, menstrual cramps, or other reasons (likely 325 mg) [1]. One large meta-analysis and one large pooled analysis looking at cancer mortality among randomized trials of aspirin for cardiovascular and other diseases have been published. In the pooled data, subjects allocated to aspirin had a reduced risk of cancer with distant metastasis, mainly due to a reduced risk of metastatic adenocarcinoma (RR=0.52, 95% CI=0.35-0.75). Total survival and cancer survival rates were higher among those randomized to aspirin whether it was low-dose (<300mg) or high dose (>300mg) [2]. A meta-analyses of 11 studies also observed a significant reduction in cancer mortality with aspirin (RR 0.77 (95% CI 0.63-0.94). Of these studies, approximately 75% of subjects took 75-100 mg daily and 25% took > 200 mg daily [3]. However, most studies showing efficacy of aspirin in prevention of colorectal cancer prevention studies utilized 325 mg daily or higher. A pooled analysis of aspirin chemoprevention trials for colorectal adenoma found no difference between higher (300+ mg daily) versus lower (≤160 mg daily) in terms of overall reduction of adenoma, but higher dose aspirin appeared to reduce risk of advanced adenomas, more than lower dose aspirin [4]. A randomized, placebo-controlled trial among 861 hereditary colorectal cancer carriers found a decreased risk of cancer incidence with aspirin 600 mg daily compared to placebo (IRR 0.56 (95% CI 0.32-0.99) after accounting for multiple primary tumors in some individuals) [5]. In contrast, a previous study of lower dose aspirin in the primary prevention setting (the Women's Health Study) found no association with breast cancer incidence among 39,876 women aged 45 or older randomized to placebo or aspirin 100 mg every other day [6]. Therefore, although some data support the possible benefit of low dose aspirin (≤ 100 mg daily), other studies suggest a higher dose may be necessary with no clear consensus.

The primary effect of low dose aspirin (≤ 100 mg) is anti-platelet and anti-thrombotic. However, the higher dose of ≥ 300 mg daily is required to affect inflammatory pathways. In addition, several other possible mechanisms including inhibition of mTOR, PI3K, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) would also most likely need higher doses. Given the resources devoted to this study, the best scientific strategy would be to begin at the higher dose which would cover multiple possible mechanisms of actions with allowances for toxicity rather than including only the 81 mg dose and risk missing an effect. Unlike cardiovascular disease, the optimal dose for cancer prevention is unknown. If the current study utilized low dose aspirin and did not find an effect at the end of the study period, the scientific question would still remain as to whether higher dose (≥300 mg daily) would be effective. However, if the higher dose were ineffective in terms of cancer recurrence, this would be considered the definitive study.

A three arm study of placebo versus low dose (≤ 100 mg) versus higher dose (≥ 300 mg) with sufficient power for a primary endpoint of recurrence would necessitate a sample size of at least

4500 subjects which would add considerably to the cost and duration of the study. Thus, this trial is a two arm study of higher dose aspirin (≥ 300 mg) versus placebo.

Although this protocol was originally conceived using a starting dose of 325 mg daily with dose reductions to 81 mg, which are the commercially available doses in the United States, the protocol has been revised to a starting dose of 300 mg daily with per protocol dose reductions to 100 mg daily, which are the commercially available aspirin doses in Europe and other countries outside of the United States. This change is due to price and supply issues. The global/European division of Bayer was able to supply aspirin and placebo at a much less expensive price and faster timeline than the US division. For the published meta-analyses, pooled analyses, and USPTF evidence reviews for cardiovascular disease and cancer, all "low-dose" (≤ 100 gm daily) studies were pooled together and studies using 300 or 325 mg daily were pooled together, because effects were considered equivalent. Furthermore, although multiple pharmacodynamics/pharmacokinetic studies have been done comparing 81/100 to 300/325 demonstrating differences in activity, no published studies have evaluated differences between 81 versus 100 or 300 versus 325, since these were not considered biologically significant dose differences. Therefore, from the scientific standpoint, the change from 325 to 300 mg will not impact the chances of finding an effect or the risk/benefit ratio. Finally, the 300/100 mg doses align with the doses in the UK Add-Aspirin study, which will facilitate future pooling of the analyses.

1.2 Relevance for a Randomized Trial

Aspirin strongly merits a randomized trial, based on compelling in-vitro, in-vivo, and epidemiologic evidence of its potential to prevent recurrence and death among breast cancer survivors. Observational studies report up to 50% reduction in the risk of breast cancer recurrence and death with regular aspirin use. Before these findings could be considered standard of care, the benefits of aspirin need to be confirmed in a randomized controlled trial.

If proven effective, adding aspirin following the completion of adjuvant chemotherapy and/or concurrently with hormonal therapy would improve survival. It is also possible that aspirin may be associated with higher compliance than hormonal therapy, which can be poorly tolerated. For example, about 50% of American women with hormone-positive tumors do not finish the recommended 5 years of hormonal therapy, sometimes due to side effects such as joint pains or menopausal symptoms and sometimes because of cost. Outside the US, aspirin's low cost ($6 per year) would make it a major aid in developing nations unable to access expensive therapies.

All pertinent data (include phase 1-3 trial results, and any pilot or confidential data from companies that justify the use of the control and experimental arms).

1.3 Epidemiological Data: Prospective Observational Studies

1.3.1 Aspirin and breast cancer survival

The 2010 results from Nurses' Health Study (NHS), a prospective observational study, sparked tremendous interest in the potential for aspirin to improve breast cancer survival. Among 4,164 female registered nurses diagnosed with Stages I, II, or III breast cancer between 1976 and 2002, aspirin use after diagnosis was associated with a decreased risk of breast cancer death. The adjusted relative risks (RR) of death (95% confidence interval (CI)) for 1, 2-5, and 6-7 days of aspirin use per week compared to no use were 1.07 (0.70-1.63), 0.29 (0.16-0.52), and 0.36 (0.24-0.54), respectively (p for trend <0.0001). The association for dichotomous aspirin use (yes/no) was a nearly 50% decrease in breast cancer death, RR (95%CI) = 0.51(0.41-0.65). This association did not differ appreciably by stage, menopausal status, body mass index (BMI), and estrogen receptor status. Results were similar for distant recurrence [1].

Besides NHS, multiple other observational studies reported similar benefits for aspirin and/or NSAID's and breast cancer survival. Prior to 2010, two prospective studies evaluated NSAID use and breast cancer survival. Blair et al reported a reduced risk of breast cancer death (RR, 95% CI = 0.53, 0.30-0.93) for aspirin use after diagnosis among 591 postmenopausal women with breast cancer in the prospective Iowa Women's Health Study. In that study, aspirin and non-aspirin NSAID use was combined, but use of aspirin only (43%) was much more common than use of non-aspirin NSAIDs only (10%) or use of both (27%) [7]. Among 2,292 women with early stage breast cancer in a breast cancer survivor cohort, current regular use of ibuprofen (RR 0.56 [95% CI 0.32-0.98]), but not aspirin (RR 1.09 [95% CI 0.74-1.61]), was associated with a reduced risk of recurrence [8].

After our NHS study, three additional prospective observational studies of aspirin and breast cancer survival have been published. Among 1,024 breast cancer cases from a population-based case-control study followed for an average of 7 years, Li et al reported a non-statistically significant reduced risk of breast cancer death (RR=0.82, 95% CI, 0.54-1.24) and total mortality (RR=0.89, 95% CI, 0.53-1.52) among those using aspirin [9]. A Scottish registry study of 4,627 women with breast cancer found that post diagnosis aspirin use (75 mg dose) was associated with a lower risk of breast cancer mortality (RR, 95% CI = 0.42, 0.31-0.55) and all-cause mortality (0.53, 0.45-0.63), after adjustment for age, stage, treatment and pre-diagnosis aspirin use [10]. Finally, a nested case-control study of 27,426 women with breast cancer in the Swedish registry system was null for aspirin use assessed in most time periods, but reported a lower risk of death from breast cancer only when assessed within 6 months of death or the end of follow-up (RR, 95% CI=0.69, 0.56-0.86), which may reflect discontinuation of aspirin during terminal illness or confounding by indication. Aspirin use in this study was exclusively low-dose (75 or 160 mg) [11]. With the exception of the Swedish and Scottish registry data, detailed data on dose and duration were not available for the other studies, which may explain some of the differing results.

Because non-aspirin NSAID use has also been hypothesized to improve breast cancer survival, the question arises whether protective associations seen with aspirin use may be attributable to concomitant NSAID use. The epidemiologic studies varied as to how non-aspirin NSAID use was handled in the analyses, but most combined women who used ASA alone with those who used ASA and NSAIDs as ASA users and therefore the unique role of NSAIDs could not be determined. However, among the epidemiologic studies that showed a benefit of aspirin use and breast cancer mortality, a report by Blair et al from the Iowa Women's Health Study was the only study that clearly separated ASA from NSAID users. Among those taking only aspirin, the HR (95% CI) for breast cancer death was 0.53(0.30-0.93). Among those taking only non-aspirin NSAIDs, the HR was 0.67(0.28-1.57). Among those taking both ASA and NSAID, the HR was 0.82(0.46-1.48) [7]. In addition, the pooled data from the aspirin randomized controlled trials (RCT's) for cardiovascular disease (see Section 1.4.1) did not include non-aspirin NSAID use in their analyses. Most of the RCT's discouraged off protocol aspirin and NSAID use, so non-aspirin NSAID use is unlikely to have been a major confounder in the aspirin RCT's showing a benefit of aspirin.

In sum, the majority of prospective epidemiologic studies demonstrated an association between regular aspirin/NSAID use and improved breast cancer survival.

1.3.2 Aspirin/NSAIDs and breast cancer incidence

Results of individual studies regarding aspirin/NSAIDs and breast cancer incidence were mixed and not as strong as the breast cancer survival data. However, meta-analyses of NSAID or aspirin use have generally found a 9-30% reduced risk of breast cancer incidence

[12-15]. It is likely that aspirin more strongly affects breast cancer metastasis than cancer initiation, so would be more effective as an adjuvant therapy, rather than for primary prevention.

1.4 Clinical Trials in Cardiovascular Disease, Gastrointestinal Cancer, and Breast Cancer

1.4.1 Clinical trials: Randomized trials in cardiovascular diseases

In addition to the observational studies on aspirin and breast cancer survival, randomized trial data from cardiovascular disease have also demonstrated an effect of aspirin on cancer recurrence. Rothwell et al pooled data from 5 large randomized trials from the United Kingdom (UK) of aspirin to prevent vascular disease. The purpose of the pooled analysis was to examine the effect of aspirin on cancer metastases presenting during or after the trials' follow-up. In the pooled data, subjects allocated to aspirin had a reduced risk of cancer with distant metastasis, mainly due to a reduced risk of metastatic adenocarcinoma (RR=0.52, 95% CI=0.35-0.75). In addition, patients with adenocarcinoma who did not have metastasis at initial diagnosis and who remained on aspirin up to or after diagnosis had a markedly reduced risk of metastasis during follow-up (RR=0.31, 95% CI=0.28-0.72). Examination of case-fatality by individual cancers was hampered by small numbers, but there was a suggestion of reduced case-fatality for breast cancer (RR=0.16, 95% CI=0.02-1.19) [2]. Further corroboration was provided by a meta-analysis comparing data from observational studies to that from the UK randomized trials. The risk of breast cancer with distant metastases pooled from observational studies, (RR=0.58, 95% CI=0.20-1.71) was similar to that found in randomized trials, although due to small numbers it did not reach statistical significance [16]. These randomized data strongly implicate a role for breast cancer in preventing metastases, but need to be confirmed in a breast cancer clinical trial. The pooled data from the aspirin RCT's for cardiovascular disease did not include non-aspirin NSAID use in their analyses. Most of the RCT's discouraged off protocol aspirin and NSAID use and as described below in Section 1.7, off study use was in the range of 10-15%, so non-aspirin NSAID use is unlikely to have been a major confounder in the aspirin RCT's showing a benefit of aspirin.

1.4.2 Randomized controlled trials of aspirin for gastrointestinal cancer treatment

The largest amount of randomized cancer trial data pertains to patients with or at risk for colorectal cancer. The key studies are summarized below, since they provide insight on potential mechanism, dose selection, and toxicity in the setting of cancer prevention. For purposes of space and clinical relevance, studies on COX2 inhibitors and colorectal cancer will not be reviewed.

1.4.2.1 Primary polyp prevention

Four randomized trials including 2967 subjects evaluating aspirin for prevention of colorectal adenoma were combined in a meta-analysis [4]. All four studies included an arm with 300+ mg aspirin daily and two of the four studies also included a third arm (either 81 or 160 mg aspirin daily). There was a decreased risk of any adenoma with any dose of aspirin (RR 0.83 (95% CI 0.72-0.96)) compared to placebo which translated to an absolute risk reduction of 6.7%. There was no difference between higher (300+ mg daily) versus lower (≤160 mg daily) in terms of overall reduction of adenoma, but higher dose aspirin appeared to reduce risk of advanced adenomas, more than lower dose aspirin, arguing for the higher dose for the cancer prevention setting.

1.4.2.2 Primary chemoprevention for colorectal cancer

Although several randomized trials have evaluated aspirin for prevention of polyps, only one study published to date has colorectal cancer incidence as the primary endpoint. The Colorectal Adenoma/carcinoma Prevention Program (CAPP trial) randomized 861 carriers of Lynch syndrome to either aspirin 600 mg daily or placebo. At mean follow-up of 55.7 months and after accounting for multiple primary events in some subjects, there was a decreased incidence of colorectal cancer in the aspirin (IRR 0.56 (95% CI 0-.32-0.99). The effects were stronger for subjects who completed at least 2 years of treatment (IRR 0.37 [95% CI 0.18-0.78]) [5].

1.4.2.3 Adjuvant treatment for colorectal cancer

An early underpowered study of only 66 subjects with colorectal cancer showed an improvement in overall survival for subjects randomized to aspirin 600 mg twice per day compared to placebo, but the difference was not statistically significant (HR 0.65 (95% CI 0.02-18.06) [17]. Currently, the ASCOLT trial (Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers - NCT00565708) is a randomized phase III trial began enrolling subjects in 2009 with either Duke's C or high-risk Duke's B with random assignment to 200 mg aspirin daily or placebo and continues to accrue. Primary endpoint is disease free survival with accrual goal of 1200.

1.4.2.4 Adjuvant treatment for gastro-esophageal cancer

1716 Chinese patients who had undergone resection of either squamous cell carcinoma of the esophagus of adenocarcinoma of the cardia were randomly assigned to aspirin or placebo. Five year overall survival was improved for those taken aspirin (51.2%) compared to those on placebo (41%) (p=0.04 for the difference) [18].

As summarized, the colorectal cancers studies that demonstrated a benefit generally evaluated doses of 300 mg+ daily, arguing for utilizing this dose in the cancer setting.

1.5 Randomized Controlled Trials for Breast Cancer Treatment

In contrast to colorectal cancer, there are no randomized trials of aspirin for breast cancer treatment.

1.6 Compliance and Adherence to Aspirin in Prior RCT's

1.6.1 Compliance

Fortunately, there have been many large randomized controlled trials (RCT's) of aspirin in the cardiovascular and gastrointestinal fields with robust data on adherence and study design. Regarding compliance, we have excellent estimates based upon prior aspirin RCT's, such as the Women's Health Study (WHS), a randomized trial of 10 years of 100 mg aspirin QOD vs placebo for primary prevention of chronic disease among 39,876 healthy women aged 45 or older. Average compliance (defined as taking > 2/3 of study medication) was 76.1% overall at 5 years and over the 10 year study was high and similar for both arms: 73.7% (placebo) vs 72.5% (ASA) [19]. Similar to WHS, regular monitoring will be done by telephone to monitor adherence and off study use of aspirin/NSAIDs. However, the WHS was for primary prevention and among breast cancer survivors, adherence should be even higher. A more comparable study may be a meta-analysis of 4 aspirin trials (n= 1121 subjects) to prevent colorectal adenomas among high-risk subjects which showed even higher rates of adherence – 81% (placebo) vs 84% on aspirin (mean trial durations 3-4 years) [4]. Therefore, we anticipate that adherence should be similar among breast cancer survivors and across placebo and aspirin arms.

1.7 Non-Protocol Use of Aspirin/NSAIDs from RCT's

We also have robust estimates for cross-in/cross-out (e.g. off study use of aspirin/NSAIDs) from prior studies. In WHS, non-trial use of aspirin of >4 days per month at 5 years was 11.6% and averaged across the 10 year trial was similar in both groups – 13.0% (placebo) vs 12.7% (aspirin) [19]. In the Colon Polyp Prevention trial, off study use of aspirin/NSAIDs of > 4 days per month was 3.8% during the 1st year and 9.3% at study end (roughly 3-4 years) across both study arms [20]. In the Japanese Primary Prevention Project (n=14,464), an open label randomized trial of 100 mg aspirin daily vs no aspirin, off protocol use of any aspirin or antiplatelet agent was similar in both arms at 5 years (10.5% on aspirin and 10.4% on placebo) [21]. As can be seen from these other aspirin RCT's across a range of settings and study populations, all had cross-in/cross-out rates in the 10-15% range so we assume similar estimates among breast cancer survivors. None of these studies provided data on whether subjects who crossed-in/out differed from those who did not. Therefore, we acknowledge that there will be some cross-in/cross-out, but this should be low and more importantly, non-differential across aspirin and placebo arms. We have adopted the design of the other studies and will monitor non-trial aspirin/NSAID use and encourage subjects to use acetaminophen for symptoms if needed. For our proposal, compliance and cross-in/cross-out rates will be monitored every 6 months and will be submitted to the Data Safety and Monitoring Board for review. Similar to the other published aspirin RCT's and adjuvant hormonal therapies, we did not include stopping rules based upon non-compliance or cross-in/cross-out. However, we will monitor this closely and will reconsider if compliance is poor or cross-in/cross-out is unexpectedly high. Finally, it should be noted that all of the large aspirin RCT's allowed prior regular aspirin/NSAID users to enroll as long as they stopped use prior to study entry.

2.0 OBJECTIVES

2.1 Primary Objective

To compare the effect of aspirin (300 mg daily) versus placebo upon invasive disease free survival (iDFS) in early stage HER2 negative breast cancer patients.

2.2 Secondary Objectives

2.2.1 To compare the effect of aspirin versus placebo in early stage HER2 negative breast cancer patients upon:

a) Distant disease-free survival
b) Overall survival
c) Cardiovascular disease (see Section11.3)

2.2.2 To compare the toxicity of aspirin versus placebo in early stage HER2 negative breast cancer patients.

2.2.3 To assess adherence to aspirin and placebo among early stage HER2 negative breast cancer patients.

2.2.4 To bank tumor and germline deoxyribonucleic acid (DNA), plasma and urine collected at baseline and sequential plasma and urine collected 2 years later for future measurement of inflammatory markers.

2.2.5 To determine if there are subgroups of participants characterized by lifestyle factors associates with greater inflammation for whom there is greater benefit of aspirin versus placebo upon iDFS.

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.

- Psychiatric illness which would prevent the patient from giving informed consent.
- Patients who cannot swallow oral formulations of the agents.
- For women of reproductive potential, a member of the study team should discuss with them the potential risks of taking the study treatment during pregnancy in order to help them determine whether or not they would like to use an appropriate method of birth control, which are described in the model consent form.

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 1week later would be considered Day 7.

___ **3.2.1** Histologic documentation of women or men with HER2 negative **breast carcinoma and free of recurrence.** If neoadjuvant therapy was received, either initial clinical stage (determined by physical and or radiologic examination) or post-operative pathologic stage can be used for eligibility purposes, with the higher stage determining eligibility. Histologic documentation of node positivity is required for ER/PR positive tumors.

Bilateral or synchronous breast cancers are allowed, as long as both cancers are HER2 negative and at least one of the cancers meets eligibility.

___ **3.2.2** If ER and PR negative, tumor must be node positive or >2 cm and node negative. Patients must be registered within 18 months of diagnosis. pN1mic is eligible.

If ER and/or PR positive, tumor must be node positive and within 10 years of diagnosis. pN1mic is eligible.

___ **3.2.3** Prior adjuvant treatment with chemotherapy and/or endocrine therapy, as determined by the treating physician, is allowed. The last dose of chemotherapy or radiation therapy must be at least 30 days prior to study registration. Concurrent hormonal therapy is allowed.

___ **3.2.4** Regular NSAID/aspirin use at any dose (including baby aspirin) (defined as ≥ 5 days per week) is allowed if aspirin and/or NSAIDs are stopped for 30 days prior to study

entry and throughout the study period. Participants will be encouraged to use acetaminophen for minor pain and fever.

___ **3.2.5** Age ≥ 18 and < 70 years of age.

___ **3.2.6** ECOG performance status 0-2.

___ **3.2.7** Patients with a prior history of gastric/duodenal ulcers documented on endoscopy can be enrolled as long as the ulcers did not cause bleeding requiring a blood transfusion/major intervention.

For patients who are Helicobacter pylori positive, a course of Helicobacter pylori eradication treatment must have been completed.

___ **3.2.8** No history of GI bleeding requiring a blood transfusion, endoscopic or operative intervention.

___ **3.2.9** No history of any prior stroke (hemorrhagic or ischemic).

___ **3.2.10** No concurrent anticoagulation with warfarin, heparin/heparin analogues, clopidogrel, direct thrombin inhibitors, or direct factor XA inhibitors.

___ **3.2.11** No history of atrial fibrillation or myocardial infarction.

___ **3.2.12** No history of grade 4 hypertension, defined as hypertension resulting in life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive **crisis**).

___ **3.2.13** No chronic (duration >30 days) daily use of oral steroids. Inhaled or topical steroids are allowed.

___ **3.2.14** No known allergy to aspirin.

___ **3.2.15** No prior invasive malignancy of any type within the past 5 years except for current diagnosis of breast cancer, and any prior diagnosis of basal or squamous cell carcinoma of the skin.

Prior history of in situ carcinoma is allowed.

Patients with a prior history of any type of breast cancer greater than 5 years from study screening may participate in this study.

___ **3.2.16** Concurrent enrollment on a non-chemotherapy treatment trial will be allowed, as long as that trial allows concurrent daily aspirin use.

___ **3.2.17** No history of metastatic breast cancer.

4.0 PATIENT REGISTRATION/RANDOMIZATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted]In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted]

4.2 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website [redacted]) using your CTEP-IAM username and password;
- Click on Protocols in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select Alliance, and protocol number A011502.
- Click on Documents, select Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

4.2.3 Checking Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration Requirements

- **Informed consent:** The patient must be aware of the neoplastic nature of their disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Patient completed booklets:** Patient Life Style Measures of Inflammation booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A011502 CTSU site) and submitting the form via the Regulatory Submission Portal on the CTSU website (the portal is located under the Regulatory tab). Samples of the booklets are found in Appendix I, which are to be used for reference and IRB submission only. They are not to be used for patient completion.
- **The Alliance Prevention Committee study, A211601:** "Evaluation of mammographic breast density effect of aspirin: A companion study to Alliance study A011502," is a separate stand-alone companion protocol available to all institutions participating in Alliance A011502. All eligible patients enrolling to this study should be approached and invited to participate in Alliance A211601. Registration to A211601 may take place after a patient has been randomized to A011502.

4.4 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

4.5 Stratification Factors and Treatment Assignments

Patients will be stratified by Hormone Receptor (HR) status, enrollment time, stage (Stage I/II vs Stage III), and body mass index as below:

Hormone Receptor Status and enrollment time:

1) Positive (either ER or PgR positive or unknown) and $\leq$ 18 month since diagnosis

2) Positive (either ER or PgR positive or unknown) and > 18 months since diagnosis

3) Negative (both ER and PgR negative)

Breast Cancer Stage

1) Stage I/II

2) Stage III

NOTE: Sites can use AJCC 7 or AJCC 8 because the anatomical staging remains unchanged between the versions.

Body Mass Index

1) Less than 30 kg/ m^2

2) Greater than or equal to 30 kg/m^2

5.0 STUDY CALENDAR

The Pre-study testing interval is a guideline only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed ≤ 28 DAYS before registration: History and physical.

	Prior to Registration/ Randomization	Every 6 months from start of study treatment +/- 28 days*	At End of protocol Treatment	Post treatment follow-up
Tests & Observations				
History and Progress Notes	X	X	X (4)	X
Physical Examination	X	X	X (4)	X
Weight, BMI	X(1)	X (1)		
PS	X	X	X	
Height	X			
Pulse, Blood Pressure	X	X		
Adverse Event Assessment	X	X	X	
Patient Medication Diary		X (2)		
Evaluation of Disease Recurrence or new invasive disease		X (3)	X (4)	X (4)
For patients who agree to participate				
Lifestyle Measures of Inflammation assessments and Registration Fatigue and Uniscale Assessment	*See Section 6.2*			
Tissue, Blood and Urine samples for Future use	*See Section 6.3.* (5)			

*The first 6-month visit should be timed from the start of treatment. Subsequent visits should be timed based on the date of the previous visit.

1. BMI to be calculated at baseline and at 24 months.
2. The Patient Medication Log must begin the day the patient starts taking the study medication and must be completed per protocol and returned to the treating institution at each 6 month visit (see Section 7.0).
3. Patients should be evaluated for disease recurrence every 6 months while receiving study treatment according to Section 11.1.
4. Patients who complete five years of study treatment will be followed annually (+/- 28 days) until 10 years from registration. Patients who stop treatment before 5 years without an invasive disease event will have a follow-up visit 6 months (+/- 28 days) after end of protocol treatment and then followed annually (+/- 28 days) until 10 years from registration. Patients who stop treatment before 5 years due to an invasive disease event may receive treatment at physician discretion and will be followed annually (+/- 28 days) until 10 years from registration. All patients will be followed for all invasive disease events (locoregional and distant recurrence and new primaries in breast and non-breast sites) and survival for a maximum of 10 years from registration.
5. Sample should be drawn after consent, prior to the start of treatment.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login [redacted] using their CTEP-IAM username and password and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at [redacted] or by contacting the CTSU Help Desk at [redacted]

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

Patient completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see). Samples of questionnaire booklets are available in Appendix I for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff in person and site staff will enter patient into Rave.

6.1.1 Supporting documentation

This study requires supporting documentation for:

1) Eligibility, which includes the pathology report (including node positivity or tumor size >2.0 cm and node negative) with histologic documentation of pathologic staging, date of diagnosis and ER, PR, HER2 status (see Section 3.2.1).
2) Disease recurrence.
3) New invasive primary.

These pathology reports and any additional supporting documentation must be uploaded into RAVE at the time of Registration/Randomization and at the time of diagnosis of disease recurrence or new primary.

6.1.2 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

6.2 Lifestyle Measures of Inflammation

Measures	**Baseline (After agreement to participate, prior to drug start date)**	**At the end of 24 months of study treatment [1]**
Modified Parffenbarger Questionnaire	**X**	**X**
Sleep Quality Index (PSQI)	**X**	**X**
Center for Epidemiologic Studies-Depression Scale (CES-D)	**X**	**X**
Perceived Stress Scale (PSS)	**X**	**X**
Brief Pain Index	**X**	**X**

1. Patients who discontinue study treatment before 24 months will be asked to complete the measure at the concurrent 24-month study visit.

6.3 Specimen Collection and Submission

All participating institutions must ask patients for their consent to participate in the collection of specimens planned for A011502 future analysis, although patient participation is optional. For patients who consent to A011502 biospecimen banking (consent question #1) tissue, blood, and urine will be collected at the following time points for these studies. Sites are required to provide their own materials for biospecimen collection (blood vacutainer tubes and urine specimen containers) and shipping (IATA-compatible biospecimen shipping boxes with cold packs, where necessary.

	After consent signed, prior to treatment start	At the end of 24 Months of study treatment [1]	Storage/ Shipping conditions	Submit to:
Tissue				
1 Paraffin block from resection for patients undergoing upfront surgery * **OR** **1 Paraffin block for patients with residual disease after neoadjuvant chemotherapy*** **OR** **1 Paraffin block from initial diagnostic biopsy for patients who under-went neoadjuvant chemotherapy with complete or near complete pathologic response***	X		Ambient/ship overnight	WUSTL
Blood				
Whole blood				
EDTA tube Whole blood*	One 10 mL K2 or K3 EDTA lavender top anticoagulant vacutainer tube	One 10 mL K2 or K3 EDTA lavender top anticoagulant vacutainer tube	Cool pack/ship over night	WUSTL

*** See Sections 6.3.4 and 6.3.5** [1] Patients who discontinue study treatment will be asked to provide the whole blood and spot urine samples at the concurrent 24-month visit.

Urine				
Spot Urine			Cool pack/ship over night	
Spot Urine*	Two 15 ml falcon tubes with10ml of urine per tube	Two 15 ml falcon tubes with10ml of urine per tube		WUSTL

6.3.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All blood and urine specimens must be labeled with the protocol number (A011502), Alliance patient number, patient's initials, date and type of specimen collected (e.g., urine, whole blood).

Any surgical pathology tumor block or unstained slides submitted MUST be accompanied by a corresponding de-identified surgical pathology report labeled with the protocol number (A011502) and Alliance patient number.

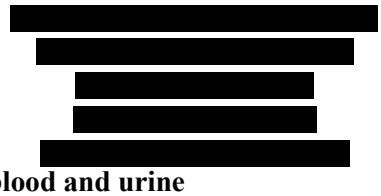
A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Ship specimens on Monday through Thursday only. Shipping by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays.

All specimens should be sent to the following address:

Alliance Biorepository at Washington University



6.3.2 Collection of tissue, blood and urine

For patients who consent to participate in the optional specimen collection and banking, tumor blocks will be banked for future analyses and potential correlative studies.

6.3.3 Collection of paraffin blocks

Paraffin blocks of primary tissue obtained from archival tumor specimens should be sent to the Alliance Biorepository at Washington University (WUSTL) within 30 days of patient registration/randomization.

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block. If, due to institutional policy, a block cannot be sent, three unstained slides, cut at 4-6 micron in thickness and mounted on charged glass slides will be requested. Slides should be labeled as follows: Each slide must be labeled with the specimen surgical pathology number and block number either via your institutions standard method for labeling clinical slides or using a permanent marker. Please DO NOT use sticky labels. The labeling of study number, patient ID, patient Initials, sample type, and collection time is no longer required on slides.

The goal of the Alliance Biorepository at Washington University is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. For this reason, it is preferred that the Alliance Biorepository at Washington University bank the block until the study investigator requests thin sections. Please contact the Alliance Biorepository at Washington University if additional assurances with your hospital pathology department are required.

Be certain to include a de-identified surgical pathology report, which includes the surgical pathology case number and tissue block identifier that matches the submitted block or labeled slides.

For patients who are simultaneously enrolled to another Alliance trial (e.g. A011401) at the same time as this study, and there is insufficient tissue available to be submitted separately for both studies, please prioritize the tissue for the current A011502 study and ship the tissue to the Alliance Biorepository at Washington University in St. Louis. Please select "not collected" in BioMS for the other trial to which the patient may be enrolled (e.g. A011401) for tissue submission, select "other" as the reason for not collecting the specimen, and note in the comments area that tissue has been submitted to for A011502 study, along with the A011502 participant ID.

For any questions regarding tissue submission for patients enrolled on any Alliance studies, please contact Melissa McKenna email: mlmckenna@wustl.edu. Phone: [redacted]

6.3.4 Blood sample submission

Collect 10 mL of venous blood in one K2 or K3 EDTA lavender top anticoagulant vacutainer tube. The tubes should be inverted approximately 8-10 times to mix the EDTA. Refrigerate sample until shipping. The sample should be placed in a biohazard bag and shipped according to IATA guidelines the same day as the blood is drawn on a cold pack by overnight courier service to the Alliance Biorepository at Washington University. Blood samples will be processed into plasma and buffy coat for long term storage by the Alliance Biorepository at Washington University (WUSTL).

6.3.5 Urine sample submission

Spot urine collection should follow institutional standard procedures. For each collection, 20 mls of urine should be transferred into two 15 ml falcon tubes (10 ml per tube) or any equivalent collection container, and be shipped overnight with a cold pack to the Alliance Biorepository at Washington University. Ensure that the collection containers are sealed, fluid-tight, and that lids will not become insecure during transit.

Urine samples will be stored as 2 ml aliquots in LN2 vapor until retrieved for correlative science assays.

Label blood and urine samples with the following identification:

- 1) Specimen procurement date and time
- 2) Alliance patient number
- 3) Alliance study number (A011502)
- 4) Specimen type: Whole blood; spot urine.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 28 days of registration/randomization. This is a double blinded, placebo controlled trial. Patients will be randomized with equal probability to receive treatment with aspirin or placebo.

7.1 Study Treatment

Agent	Dose	Route	Day
Aspirin/Placebo	One 300 mg tablet	Oral	Daily x 5 years

After registration, blinded, patient-specific supplies of aspirin/placebo are to be ordered by the site by completing the drug order form (see Section 10.0).

Patients should be given a six-month supply of study drug in order to correspond with study visit schedule in Section 5.0.

7.2 Adherence

Since patients will take oral medications at home without direct supervision, we will monitor drug compliance until the discontinuation of aspirin/placebo using A011502 Study Medication Logs (Appendix II). At study entry the patient will receive the Medication Log and be instructed on how to take the medication and how to use the Log. The patient will bring the Log to each visit where it will be reviewed with a member of the study team. The patient will then be given a new Log to record study medication until the next visit. If a patient cites reasons other than drug side effects for not taking the required medication, the reasons for missed doses will be reviewed and the importance of taking all doses on schedule will be reinforced. The study team member will document the patient-reported dosage in the patient's medical record and determine if the patient was compliant for that study period and document compliance on the appropriate study forms. Compliance is defined as patient self-report of taking 80% of study tablets.

Non-protocol use of aspirin and NSAIDs will also be monitored every 6 months along with study drug compliance.

7.3 Disease Recurrence and New Invasive Disease

Upon disease recurrence or new invasive second primary, except for basal or squamous cell carcinoma of the skin, protocol treatment will be discontinued and treatment will then be at the discretion of the treating physician.

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 **Patients should receive full supportive care** while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose must be recorded in the medical records.

8.1.2 **Antiemetics** may be used at the discretion of the attending physician. Analgesics and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose must be recorded in the medical records.

8.1.3 **Proton pump inhibitors (PPIs) may be used at the discretion of the treating study physician.**

*For patients who require a PPI, US sites only may order the PPI through the Alliance while funding is available. Instructions for ordering the PPI are located on the A011502 study pages on the Alliance and CTSU websites.

8.1.4 **Non-protocol use of aspirin and/or NSAIDs is discouraged. However, non-protocol use of these medications will not result in removal from study, but must be noted on**

the appropriate study form. Instead, use of acetaminophen for treatment of aches, pains, and fevers is encouraged.

8.1.5 Concomitant endocrine therapy

Patients with hormone receptor (ER and/or PR) positive disease should receive a minimum of 5 years of standard endocrine therapy (experimental agents/regimens are not permitted). Endocrine therapy should begin following completion of neoadjuvant chemotherapy and surgery, either before, during or after radiation therapy at discretion of oncologist. Selection of the agents is at the treating physician's discretion.

8.1.6 Study drug should be held while on lovenox or other daily anticoagulation medications.

8.1.7 Co-enrollment in other clinical trials

Patients are able to co-enroll on these studies only if they have completed radiation, chemotherapy or surgery and meet all other A011502 eligibility criteria. For the studies listed below, you do not need to ask for a separate confirmation from the A011502 Study Chair. However, for those studies that are NOT listed, please contact the study Protocol Coordinator at the email or phone number listed on the cover page of this protocol.

Trials for which co-enrollment is allowed:

Trials involving everolimus, palbociclib, PARP inhibitors, such as:

AFT-05 PALLAS: PALbociclib CoLlaborative Adjuvant Study: A Randomized Phase III Trial of Palbociclib With Standard Adjuvant Endocrine Therapy Versus Standard Adjuvant Endocrine Therapy Alone for Hormone Receptor Positive (HR+) / Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Early Breast Cancer (PALLAS).

Alliance A011401: Randomized Phase III Trial of Evaluating the Role of Weight Loss in Adjuvant Treatment of Overweight and Obese Women with Early Breast Cancer.

SWOG S1207: Phase III Randomized, Placebo-Controlled Clinical Trial Evaluating the Use of Adjuvant Endocrine Therapy +/- One Year of Everolimus in Patients with High-Risk, Hormone Receptor-Positive and HER2/Neu Negative Breast Cancer. e^3 Breast Cancer Study-Evaluating Everolimus with Endocrine Therapy.

Trials for which co-enrollment is allowed after completion of radiation and chemotherapy:

Per Section 3.2.3, all adjuvant treatment with chemotherapy and/or radiation must be completed at least 30 days prior to registration. A patient may enroll on A011502 after they have completed radiation therapy and/or chemotherapy on the following trials provided that they meet all other eligibility criteria.

Surgery trials:

ALLIANCE A011202: A Randomized Phase III Trial Comparing Axillary Lymph Node Dissection to Axillary Radiation in Breast Cancer Patients (cT1-3 N1) Who Have Positive Sentinel Lymph Node Disease After Neoadjuvant Chemotherapy.

Radiation trials:

NRG B51: A Randomized Phase III Clinical Trial Evaluating Post-Mastectomy Chest wall and Regional Nodal XRT and Post-Lumpectomy Regional Nodal XRT in Patients with Positive Axillary Nodes Before Neoadjuvant Chemotherapy Who Convert to Pathologically Negative Axillary Nodes After Neoadjuvant Chemotherapy.

Chemotherapy Trials:

ECOG EA1131: A Randomized Phase III Post-Operative Trial of Platinum Based Chemotherapy vs. Observation in Patients with Residual Triple-Negative Basal-Like Breast Cancer Following Neoadjuvant Chemotherapy after the completion of carboplatin or capecitabine.

NRG BR-003: A Randomized Phase III Trial of Adjuvant Therapy Comparing Doxorubicin Plus Cyclophosphamide Followed by Weekly Paclitaxel with or Without Carboplatin for Node-Positive or High-Risk Node-Negative Triple-Negative Invasive Breast Cancer

8.2 Dose Modifications

8.2.1 Dose Levels

Dose Level	Drug Name	Dose
0*	Aspirin	300 mg
-1	Aspirin	100 mg

*Dose level 0 refers to the starting dose.

If dose reduction below level -1 is required, permanently discontinue protocol therapy.

8.2.2 Hematologic Adverse Events

8.2.2.1 Grade 1 bleeding

For grade 1 bleeding, one level dose reduction will be allowed at physician discretion.

8.2.2.2 Grade 2 bleeding

For grade 2 bleeding, one level dose reduction will be required.

For recurrent Grade 2 bleeding after dose reduction, discontinue protocol therapy.

8.2.2.3 Grade 3 and 4 gastrointestinal bleeding or active gastrointestinal ulceration

Grade 3and 4 GI bleeding will require that the patient be permanently removed from protocol treatment.

8.2.2.4 Other grade 1 and 2 non-bleeding related gastrointestinal toxicity

A proton pump inhibitor will be prescribed for the patient at the discretion of the treating physician. Alternatively, at the discretion of the treating physician, one level dose reduction may be performed.

8.2.3 Cardiovascular toxicities and thrombotic events

8.2.3.1 For grade 3 or 4 cardiac ischemia/infarction or thrombosis: Permanently discontinue protocol therapy.

8.2.3.2 For grade 1 toxicity, no change in study drug dosage is required.

For grade 2 toxicity, reduce to dose level -1, at physician discretion. If dose is reduced, patients should continue at this dose for the duration of study treatment.

8.2.4 Intracranial hemorrhage: Permanently discontinue protocol therapy for any grade intracranial bleeding.

8.2.5 Macular Degeneration: Permanently discontinue protocol therapy for any grade macular degeneration considered related to aspirin/placebo.

8.2.6 Tinnitus or hearing loss: Permanently discontinue protocol therapy for any grade considered related to aspirin/placebo.

8.2.7 Dermatologic toxicities: Permanently discontinue protocol therapy for Stevens-Johnson syndrome or toxic epidermal necrolysis.

8.2.8 Other non-hematologic toxicities attributed to aspirin/placebo

For other grade 3 or 4 non-hematologic toxicities considered related to aspirin/placebo, interrupt aspirin/placebo, for a maximum of 28 days until toxicity improves to ≤ grade 2, then resume aspirin/placebo, with one dose reduction.

For recurrence of the same grade 3 or 4 non-hematologic toxicity considered related to aspirin/placebo, or if toxicity does not improve after 28 days, permanently discontinue aspirin/placebo.

For persistent grade 2 non-hematologic toxicity considered related to aspirin/placebo that the patient finds unacceptable, interrupt aspirin/placebo for a maximum of 28 days until toxicity improves to ≤ grade 1, then resume aspirin/placebo at the previous dose.

For recurrence of unacceptable grade 2 non-hematologic toxicity considered related to aspirin/placebo, or if grade 2 toxicity does not improve after 28 days, permanently discontinue aspirin/placebo.

8.2.9 Holding study drug for surgical procedures

Since aspirin can be associated with an increased risk of post-operative bleeding, some surgical procedures require stopping aspirin before and after a procedure. If the treating physician or surgeon determines that aspirin would be held for a procedure, then the study drug should be held for the same period of time. The total period that the study drug can be held for surgical procedures should not exceed 28 consecutive days.

8.3 Unblinding Procedures

Unblinding can be done only in cases of an emergency where knowledge of the treatment arm affects immediate medical management. Most medical emergencies and events attributed to study therapy can be adequately managed without knowledge of the treatment arm.

Follow the directions below for emergency unblinding procedures. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy, but will continue to be followed per Section 12.2.

Emergency Unblinding Procedures:

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling [redacted]

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., "A011502")
- Alliance patient ID number (e.g., "999999")
- Patient initials (e.g., "L,FM")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation.

After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer to the section on AE reporting procedures. NCI Guidelines: Adverse Event Reporting Requirements for further details.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Events: Solicited form is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

•

• CTCAE v 4.03 Term	• CTCAE v4.0 Organ Class (SOC)
• Gastrointestinal bleeding	• Gastrointestinal disorders
• Intracranial hemorrhage	• Nervous system disorders
• Epistaxis	• Respiratory, thoracic and mediastinal disorders
• Hematuria	• Renal and urinary disorders
• Dyspepsia	• Gastrointestinal disorders
• Gastritis	• Gastrointestinal disorders
• Bruising	• Injury, poisoning and procedural complications

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

***Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting beginning April 1, 2018. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site [redacted]All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>• Grade 1 Timeframes</th><th>• Grade 2 Timeframes</th><th>• Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

NOTE: Deaths clearly due to progressive disease should be reported via CTEP AERS

- Expedited AE reporting timelines defined:
  - ➢ "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - ➢ "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

  CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy

  Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms as outlined in the protocol.
- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.
- All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid

tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

- Treatment expected adverse events include those listed in Section 10.0 and in the package insert.
- When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at [redacted] The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

  In CTCAE v5.0, pregnancy loss is defined as "Death in utero," and any pregnancy loss should be reported expeditiously as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

  A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

10.0 DRUG INFORMATION

10.1 Aspirin or Aspirin-Matched Placebo

Aspirin/Placebo is IND exempt as used in this trial. This exemption has been determined by attestation that neither the investigator nor sponsor intends to seek a new indication for use or to support any other significant change in the labeling or product advertising for aspirin. This investigation will use an approved route of administration and dosage of aspirin and has no factors that increase the risk of the product. This investigation will be in compliance with 21CFR parts 56, 50, and 312.7 and neither the investigator nor the sponsor will promote or represent that aspirin is safe or effective for the context that is under investigation in this study. This investigation will not commercially distribute or test market the study agent, and will not unnecessarily prolong an investigation.

Procurement

Aspirin/placebo is an investigation agent supplied by Bayer and distributed by McKesson. Use the order form that is provided on the A011502 study page of the Alliance and CTSU web sites to order Aspirin/placebo. McKesson will ship a maximum of 2-year supply per shipment per patient to the site.

At the end of the trial, any expired or remaining supplies of study drug should be destroyed according to institutional procedure.

Formulation

Aspirin/placebo is supplied as matching tablets in 300 mg and 100 mg strength in 200 count bottles. Please see drug order form for further details regarding supply.

Aspirin 300mg tablets contain: 300mg acetylsalicylic acid, 30 mg powdered cellulose, 30mg maize starch, with coating of methacrylic acid-ethylacrylate copolymer, polysorbate 80, sodium laurilsulfate, talc, and triethyl citrate. Appearance is round coated white tablet 10mm in diameter and 407mg in weight.

Placebo 300mg tablets contain: 36mg calcium hydrogen phosphate dihydrate, 72mg microcrystalline cellulose, 15mg anhydrous citric acid, 198mg lactose monohydrate, 1mg magnesium stearate, 36mg maize starch, and 2mg colloidal anhydrous silica, with coating of methacrylic acid-ethylacrylate copolymer, talc, and triethyl citrate. Appearance is round coated white tablet 10mm in diameter and 407mg in weight.

Aspirin 100mg tablets contain: 100mg acetylsalicylic acid, 10 mg powdered cellulose, 10mg maize starch, with coating of methacrylic acid-ethylacrylate copolymer, polysorbate 80, sodium laurilsulfate, talc, and triethyl citrate. Appearance is round coated white tablet 7mm in diameter and 137mg in weight.

Placebo 100mg tablets contain: 12mg calcium hydrogen phosphate dihydrate, 24mg microcrystalline cellulose, 5mg anhydrous citric acid, 66mg lactose monohydrate, 0.4mg magnesium stearate, 12mg maize starch, and 0.67mg colloidal anhydrous silica, with coating of methacrylic acid-ethylacrylate copolymer, talc, and triethyl citrate. Appearance is round coated white tablet 7mm in diameter and 137mg in weight.

Storage and Stability

Store aspirin and placebo at room temperature 20° to 25°C (68° to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).”

Administration

Aspirin should be administered with food or full glass of water to minimize GI distress. Do not crush enteric coated tablets.

Reconciliation

Utilize the NCI oral DARF for documentation. Forms should be study specific and patient specific due to the double blind nature of the trial.

Drug Interactions

Aspirin is a minor substrate of CYP2C9. Inhibitors and inducers of CYP2C9 may alter aspirin exposure. Aspirin has the potential to have the following drug interactions:

Angiotensin converting enzyme (ACE) inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by concomitant administration of aspirin.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to indirect effects on the renin-angiotensin conversion pathway.

Anticoagulant/Antiplatelet therapy: Patients on concomitant anticoagulant and antiplatelet therapies are at increased risk of bleeding with concomitant aspirin due to competition at the renal tubule for secretion.

Anticonvulsants: Salicylates can displace protein-bound phenytoin and valproic acid, leading to decreases in phenytoin and valproic acid concentrations.

Beta blockers: The hypotensive effects of beta blockers may be diminished with concomitant aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt/fluid retention.

Diuretics: Diuretic effectiveness may be diminished with concurrent aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renally impaired.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Concomitant administration of NSAIDs and aspirin may lead to increased bleeding or decreased renal function. Avoid concurrent use.

Oral Hypoglycemics: Moderate aspirin doses may increase the effectiveness of oral hypoglycemic agents causing hypoglycemia.

Uricosuric Agents: (Probenecid and Sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

Pharmacokinetics

Absorption: Immediate, rapid and completely absorbed from gastrointestinal tract.

Distribution: Widely distributed to all tissues and fluids in the body including the central nervous system (CNS) and breast milk and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart and lungs. The protein binding of salicylate is concentration-dependent, i.e. non-linear.

Metabolism: Hydrolyzed to salicylate (active by esterases in GI mucosa, red blood cells, synovial fluid and blood; metabolism of salicylate occurs primarily by hepatic conjugation; metabolic pathways are saturable.

Excretion: Urine (75% as salicyluric acid, 10% as salicylic acid).

T1/2: Parent drug 15 to 20 minutes; Salicylates 3 hours.

Adverse Events

Cardiovascular: Cardiac arrhythmia, edema, hypotension, tachycardia.

Central Nervous System: Agitation, cerebral edema, coma, confusion, dizziness, fatigue, headache, hyperthermia, insomnia, lethargy, nervousness, Reye's syndrome.

Dermatologic: Skin rash, urticarial.

Endocrine & Metabolic: Acidosis, dehydration, hyperglycemia, hyperkalemia, hypernatremia (buffered forms), hypoglycemia (children).

Gastrointestinal: Gastrointestinal ulcer, duodenal ulcer, dyspepsia, epigastric distress, gastritis, gastrointestinal erosion, heartburn, nausea, stomach pain, vomiting.

Genitourinary: Postpartum hemorrhage, prolonged gestation, prolonged labor, proteinuria, stillborn infant.

Hematologic & Oncologic: Anemia, blood coagulation disorder, disseminated intravascular coagulation, hemolytic anemia, hemorrhage, iron deficiency anemia, prolonged prothrombin time, thrombocytopenia.

Hypersensitivity: Anaphylaxis, angioedema.

Neuromuscular & Skeletal: Acetabular bone destruction, rhabdomyolysis, weakness.

Otic: Hearing loss, tinnitus.

Renal: Increased blood urea nitrogen, increased serum creatinine, interstitial nephritis, renal failure (including cases caused by rhabdomyolysis), renal insufficiency, renal papillary necrosis

Respiratory: Asthma, bronchospasm, dyspnea, hyperventiliation, laryngeal edema, noncardiogenic pulmonary edema, respiratory alkalosis, tachypnea.

Miscellaneous: Low birth weight.

Postmarketing and/or case reports (Limited to important or life-threatening): Anorectal stenosis (suppository), atrial fibrillation (toxicity), cardiac conduction disturbance (toxicity), cerebral infarction (ischemic), cholestatic jaundice, colitis, colonic ulceration, coronary artery vasospasm, delirium, esophageal obstruction, esophagitis (with esophageal ulcer), macular degeneration (age-related), periorbital edema, rhinosinusitis.

- Nursing Guidelines
- 1. Patients may experience GI upset and or reflux. Treat symptomatically and monitor for effectiveness.
- 2. Aspirin can cause GI bleeding. Instruct patients to report any black tarry stools and/or hematemesis to the study team immediately.
- 3. Patients may experience increased bruising and/or bleeding. Instruct patients to report this to the study team.
- 4. Patients should be instructed not to take NSAID's in conjunction with aspirin. Concomitant use can lead to increased risk of bleeding and/or renal dysfunction.

10.2 Shipment of Study Drug Supply Directly to the Study Participant

Sites may ship a study participant's drug supply directly to the participant's place of residence if a site so chooses. The costs associated with the shipping of the participant's drug supply to their place of residence are the sole responsibility of the site. The Alliance will not reimburse a site for this cost.

McKesson will ship a maximum of 2-year supply per shipment per patient. Sites may distribute all or a portion of this supply to the participant. If a site were to elect to ship directly to the participant's place of residence, the Alliance recommends shipping the first of 6 months' supply. Subsequent 6 month supplies can be distributed directly to the participant during "scheduled "patient visits (see Study Calendar, Section 5.0).

Participants should be informed about storage requirements per protocol, Section 10.2, namely:

"Store Aspirin/Placebo at 15° to 30°C (59°to 86°F) in a dry place and keep the container tightly closed."

11.0 MEASUREMENT OF EFFECT

11.1 Evaluation of Breast Cancer Outcomes

Disease will be monitored according to ASCO guidelines [22]. The diagnosis of a first breast cancer recurrence or second primary can be made only when both the clinical and laboratory findings confirm the presence of disease. Suspicious findings do not constitute criteria for breast cancer recurrence. PET scans may be performed at the discretion of the investigator. However PET scans, in the absence of objective findings on CT, MRI, or other imaging studies do not meet the criteria of an acceptable method of determining breast cancer recurrence for this study. Any recurrence of malignant disease should be proven by biopsy whenever possible. Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the treating physician.

For all confirmed breast cancer recurrence or second primary cancers, the time to event will be based on the earliest date of diagnostic evidence. Initial diagnosis of the event should not be a first occurrence of symptoms, but must be based on a clinical assessment with objective findings, whether by physical exam or radiological determination that is subsequently confirmed (if applicable) as defined below.

11.1.1 Invasive ipsilateral breast cancer recurrence

Defined as evidence of invasive cancer in the ipsilateral breast or chest wall. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast or chest wall must have a biopsy of the suspicious lesion to confirm the diagnosis.

11.1.2 Invasive local/regional recurrence

Defined as the development of invasive tumor in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular, and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla. This can be confirmed with positive cytology or histologic biopsy.

11.1.3 Distant recurrence

Defined as evidence of invasive tumor in any areas of the body, with the exception of those defined as local or regional recurrence above.

11.1.4 Invasive contralateral breast cancer

Defined as evidence of invasive breast cancer in the contralateral breast or chest wall. This must be confirmed histologically.

11.1.5 Second primary invasive cancer (non-breast)

Defined as evidence of any non-breast second primary invasive cancer, excluding squamous or basal cell carcinoma of the skin and in situ carcinomas of any site. This must be confirmed histologically whenever possible.

11.2 Definitions of Analysis Variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

11.3 Evaluation of Cardiovascular Outcomes

11.3.1. Myocardial infarction

Both non-fatal and fatal myocardial infarctions are to be reported. Standard CTCAE adverse event definitions will be used.

11.3.2. Cerebrovascular event

Both fatal and non-fatal cerebrovascular events are to be reported. The definition of a cerebrovascular event will be based upon radiographic evidence of an ischemic or hemorrhagic stroke.

11.2.3 Need for cardiovascular procedures

All cardiovascular procedures including coronary artery bypass surgery, coronary stent placement, and/ angioplasty of coronary vessels are to be reported.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 Protocol treatment is for 5 years or until the first occurrence of invasive disease, as follows: Distant recurrence, locoregional recurrence, ipsilateral or contralateral breast cancer, second primary (non-breast) invasive cancer, or death from any

cause. Treatment after any of these events is at the discretion of the treating physician. (See Section 7.0 Treatment Plan).

12.1.2 Early discontinuation of study agent

If protocol treatment is discontinued early for reasons other than patient death or the invasive disease events listed above, such as, adverse events from A011502 protocol therapy, physician discretion, patient withdrawal, early unblinding or extraordinary medical circumstances, continue to follow the patient according to Section 12.2.

12.2 Patient Follow-up

Follow all patients enrolled on this study regardless of eligibility status, including those who do not receive any protocol therapy, or switch to non-protocol therapy, for a maximum of 10 years.

- Patients who complete five years of study treatment without a disease event will be followed annually for 10 years from registration for invasive disease events (locoregional and distant recurrence and new primaries in breast and non-breast sites) and survival.
- Patients who stop treatment before five years without a disease event will have a follow-up visit 6 months after end of protocol treatment, and then will be followed annually for 10 years from registration for invasive disease events (locoregional and distant recurrence and new primaries in breast and non-breast sites) and survival.
- Patients who stop treatment before five years due to a disease event will be followed annually for 10 years from registration for invasive disease events (locoregional and distant recurrence and new primaries in breast and non-breast sites) and survival.

Reports of all invasive disease events, i.e., first and subsequent, and survival are to be submitted yearly for the 10-year follow-up period.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a randomized double-blind placebo-controlled phase III trial of aspirin (300 mg daily) in non-metastatic HER2 negative breast cancer patients. Patients will be randomized 1:1 within stratum defined by: Hormone Receptor status (HR positive vs HR negative), body mass index (<30 vs ≥ 30 kg/m^2) and anatomic stage (Stage I/II vs III).

The primary objective of this trial is to compare the effect of aspirin versus placebo upon invasive disease free survival (iDFS).

13.2 Sample Size, Accrual Time and Study Duration

A stratified log-rank test will be used for the primary comparison of iDFS, with an overall one-sided Type I error of 0.025. Five year iDFS on placebo is assumed to be 77% based on results from the control arm of E5103. This study randomized 4994 patients to doxorubicin, cyclophosphamide, and paclitaxel plus or minus bevacizumab, and the patient population was similar to current eligibility criteria. An improvement in 5year iDFS to 82.2% would be considered clinically meaningful (HR = 0.75) and consistent with published data. Final analysis will occur at 381 IDFS events, in order to have 80% power to detect the target improvement.

A total sample size of 2936 patients will be enrolled in order to reach 381 iDFS events for final analysis. This assumes an accrual duration of 30 months including a 6 month ramp-up period to a maximum of 108 patients per month, and a constant hazard of loss-to-follow-up rate of 5% at 48 months in each arm.

An additional follow-up of 24 months is anticipated to reach final analysis, for a total study duration of 54 months from activation.

Because accrual was slower than anticipated, the eligibility criteria have been expanded although the sample size and overall analytic plan remain unchanged. Originally, subjects must have histologically confirmed invasive breast cancer and register within 12 months of initial diagnosis. The eligibility criteria have been extended to within 18 months of initial diagnosis for hormone receptor negative patients (HR-), and patients with hormone-receptor positive disease (HR+) would be eligible to participate within 10 years from initial diagnosis if there is no evidence of local/regional recurrence or metastatic disease. With the proposed change in study population, the primary objective will remain to compare the invasive disease free survival (iDFS) of patients randomized to receive aspirin (300 mg daily) versus placebo, and is defined as the interval from the defined as time from randomization to the first occurrence of any one of the following events for invasive disease: Distant recurrence, locoregional recurrence, ipsilateral or contralateral breast cancer, second primary (non-breast) invasive cancer or death from any cause as per section 13.3, and the primary analysis will be performed in an intention-to-treat manner, in which all patients including those who do not begin protocol therapy will be analyzed according to their assigned arm (13.3.3). The target effect-size will remain a 25% improvement in outcomes with the intervention (HR = 0.75), and under the assumption the risk of recurrence in HR+ disease is approximately constant even up to 20 years out from diagnosis (66), the number of IDFS events for final analysis would be reached under comparable timelines with the target sample size of 2936 patients. With the modification, the HR status stratification factor has been modified to be HR-positive patients that are less than or greater than 18 months out from initial diagnosis, and HR-negative patients, and a secondary analysis will be done to compare the efficacy in the subgroup of patients within 18 months of diagnosis, and explore outcomes and relationship to treatment in patients more than 18 months out from initial diagnosis with disease-free interval included as a covariate in multivariate regression models.

13.3 Primary Endpoint Analysis

Endpoints for efficacy use only invasive disease. Patients who withdraw consent for clinical or survival follow-up or lost patients will be censored at the date of withdrawal/loss according to disease and survival status known at that time.

13.3.1 Primary endpoint

The primary endpoint of this trial is invasive disease-free survival (iDFS), defined as time from randomization to the first occurrence of any one of the following events for invasive disease: Distant recurrence, locoregional recurrence, ipsilateral or contralateral breast cancer, second primary (non-breast) invasive cancer or death from any cause. Censoring will occur on the date the patient was last known to be alive and free from all invasive breast cancer and second invasive primaries.

13.3.2 Secondary Endpoint

Secondary endpoints for disease outcome include overall survival (OS) and distant disease free survival (DDFS). OS is defined as the time from randomization to death from any cause; surviving patients will be censored at the date last known to be alive. DDFS is defined as the time from randomization to the first occurrence of any one of the following events for invasive disease: Distant recurrence, second primary (non-breast) invasive cancer or death from any cause; censoring will occur at the date the patient was last known to be alive and free from distant invasive breast cancer and second invasive primaries.

Additional secondary endpoints include development of cardiovascular disease (including cerebrovascular events, myocardial infarction, or coronary artery disease requiring stent placement, angioplasty, or bypass surgery).

13.3.3 Analysis plans for primary and secondary endpoints

The primary analyses of iDFS will be performed in an intention-to-treat manner, in which all patients including those who do not begin protocol therapy will be analyzed according to their assigned arm. The primary determination of efficacy will be a time-to-event analysis using the Kaplan-Meier method for estimation, and the stratified log-rank test of iDFS to compare the aspirin arm versus the placebo arm (with stratum defined by hormone receptor status, BMI and stage), using the nominal alpha defined by the group sequential design, as given in Section 13.4.2. A secondary analysis to estimate efficacy will use a multivariate Cox proportional hazard model to evaluate differences between arms after adjusting for stratification factors and the additional covariates of known importance to breast cancer including age, tumor size, and number of involved nodes. Identical models will be used to evaluate differences between arms in DDFS and OS.

Planned subgroup analyses will evaluate the hazard ratio of aspirin to placebo in subgroups defined by the study stratifiers of hormone-receptor status and enrollment time (HR positive and enrolled $\leq$ 18 months from time from diagnosis vs HR positive and enrolled > 18 months from diagnosis vs HR negative) and body-mass index (less than 30 kg/m^2 vs at least 30 kg/m2). In addition to the WHO thresholds for underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (BMI $\geq$30kg/m^2), we will explore a linear association in the multivariate Cox model, based on the findings of Ligibel et al. that the prognostic relationship to disease-free survival with adjuvant chemotherapy was linear across the entire range of BMI observed at baseline. Further, an exploratory analysis will evaluate whether baseline factors are predictive of difference in clinical benefit of aspirin over placebo using multiplicative interactions in the Cox model. All tests of secondary objectives will use a two-sided Type I alpha of 0.05, and point estimates will be reported with 95% confidence intervals taken from Cox models.

Analyses of toxicity will be conducted on patients who receive at least one dose of aspirin or placebo. Toxicity will be reported by type and maximum grade using CTCAE v4.03 and contrasts of aspirin to placebo will use Fisher exact tests.

All study monitoring, data management and statistical analysis will be performed under the Alliance Statistics and Data Center.

13.4 Study Monitoring and Interim Analysis

13.4.1 Study monitoring

Interim monitoring will be conducted by the Alliance Data and Safety Monitoring Board (DSMB) and will be scheduled to coincide with the semi-annual calendar of the board's meetings. Under standard monitoring procedures, the DSMB will consider evidence regarding safety (adverse events, adherence) and the feasibility of completing the trial (accrual rate).

Adherence will be reported to the DSMB using descriptive statistics to summarize by arm compliance to study treatment and non-protocol use of aspirin and NSAIDs. For compliance, the proportion that completed 80% of the total number of study tablets over the past period (6 months) and a 95% confidence interval will be reported for the number of patients on treatment at each study visit. P-values from a two-sided Fisher exact test will

be provided to the DSMB to help with interpretation of the data, but they are not considered as formal hypothesis tests and will not trigger any decision rule on study status.

In addition, formal interim analyses are to be conducted to consider early stopping for futility. These interim analyses are timed to be occur after 50% of the total number of iDFS events are observed in order to sensitive to the known heterogeneity of recurrence rates over time for the two subpopulations of triple negative versus HmR-positive breast cancer, in which the former disease tends to recur earlier than the latter disease. Therefore, there will be no early stopping for superiority of aspirin over placebo in order to be able to fully address the question of treatment effect by breast cancer subtype.

13.4.2 Interim analysis for primary endpoint (IDFS)

Early stopping for futility is defined under a one-sided hypothesis of clinical benefit of aspirin and will be conducted using standard group sequential designs for phase III studies of time-to-event outcomes. Specifically, the Z-statistics from stratified log-rank tests will be calculated at each interim analysis. Futility boundaries will be defined using a Hang, Shih and DeCani Gamma beta-spending function (parameter = -5) whereby the futility boundary at the first interim analysis is close to observing no treatment effect with aspirin (HR = 1) [23]. Interim monitoring for futility will begin at the first DSMB meeting to occur when 50% of expected events are observed and continue to coincide with the semi-annual calendar of the board.

In addition to the boundary and observed Z-statistics, the DSMB will be provided Kaplan-Meier product limit estimators to the survival functions for each arm, and the corresponding hazard ratio (corr. HR) and 95% CIs from a stratified Cox proportional hazard model for iDFS.

The following table provides boundaries under the assumed rates of accrual and target hazard rates of iDFS that results three interim analyses for futility starting at exactly 50% information.

	First Interim	**Second Interim**	**Third Interim**	**Final Analysis**
iDFS Events:N (%)	**191 (50%)**	**247 (65%)**	**305 (80%)**	**381 (100%)**
Months from activation	34	40	46	54
Futility Bound critical Z (corr. HR)	-0.192 (1.03)	0.385 (0.96)	0.988 (0.89)	-
Superiority Bound: critical Z (corr.HR)	-	-		1.96 (0.82)
Nominal Alpha (Superiority)	-	-		0.025
Accumulated Alpha	-	-		0.025
Accumulated Beta	0.015	0.033	0.071	0.194

13.5 Statistical Section for Lifestyle Measures of Inflammation

Studies to evaluate epidemiologic measures of lifestyle that are potential pro-inflammatory states and modifying factors will be performed after the primary analysis to compare iDFS in patients randomized to receive aspirin versus placebo is completed. Studies to evaluate inflammatory markers from banked tumor and germline DNA, plasma and urine will be performed retrospectively once the primary analysis is completed and laboratory assays have been identified. The following statistical methods will be used in the analysis plans for secondary objectives relating to lifestyle measures and inflammatory markers derived from banked specimens.

Descriptive statistics (mean, standard deviation, median, interquartile range and range) will be used to summarize all quantitative measures obtained at baseline and at 2 years. Absolute change from baseline to the 2 year assessment will be summarized accordingly for patient reported instruments. For inflammatory markers, difference scores will be summarized and evaluated using either absolute or fold-change depending on background information for each assay output.

The following thresholds will be used to summarize lifestyle measures at baseline and at 2 years, and to define patient subgroups for evaluating differential treatment effects: Body mass index (BMI) categories will be defined according to the World Health Organization as underweight (<18.5 kg/m^2) or normal weight (18.5-24.9 kg/m^2) versus overweight (25-29.9 kg/m^2) or obese (BMI $\geq$30kg/m^2). The anticipated prevalence of overweight (30%) and obese (36.5%) patients are taken from Centers for Disease Control and Prevention report for US Women age 20 years or older [24]. Physical activity categories by a modified Paffenbarger questionnaire will be defined as sedentary (< 3 METs, 32% prevalence) versus CDC recommended (3-8.9 METs, 29% prevalence) or active ($\geq$ 9 METs, 39% prevalence) [25]. Sleep will be assessed with the Pittsburgh Sleep Quality Index (PSQI) with scores ranging from 0 to 21 and poor quality sleep defined as great than 5 [26]. The mean PSQI was 5.5 and 6.7 in cohorts of middle age white and black women, respectively [27]. A median PSQI of 9 was reported in early stage breast cancer patients with aromatase inhibitor induced musculoskeletal symptoms [28]. Depression will be assessed by the Center for Epidemiologic Studies-Depression scale-Revised (CESD-R) with scores ranging from 0 to 6 and possible depression defined as $\geq$16 [29, 30]. Median CESD-R as 10.5 in early stage breast cancer patients with aromatase inhibitor induced musculoskeletal symptoms [28].The Perceived Stress Scale (PSS) will be assessed using the 10 item scale (PSS-10) with scores less than 16 defining "normal" for breast cancer patients [31] with a prevalence of 61% in early stage breast cancer patients 12 months after initiation of chemotherapy [32]. Secondary and exploratory analysis will evaluate the lifestyle measures listed above as continuous factors and will evaluate individual items from the Brief Pain Inventory (BPI) dichotomized at $\geq$4 on the 0-10 Likert scales [33] Pain had a reported prevalence of 21% in early stage breast cancer patients taking aromatase inhibitors [34].

The hypothesis is that subgroups of participants, defined by lifestyle factors that are potential pro-inflammatory states, would receive greater treatment benefit from aspirin. The potential for any baseline state to modify the effect of treatment upon iDFS and OS will be evaluated using multivariate Cox proportional hazards models that include study stratification factors main effects and pairwise interaction between each dichotomous baseline factor and treatment arm. Simultaneous testing of the lifestyle factors will be performed, using a single likelihood ratio test (LRT) of a "full" model with all terms versus a "reduced" model with only main effects for treatment assignment, study stratification factors, and lifestyle factors. The LRT for the multivariable Cox regression model will use an alpha = 0.05. If the "full" model is found to be superior under the LRT, a stepwise backward-selection process will be used to identify the set of individual factors with the strongest interaction with treatment assignment, using a nominal

$p < 0.05$ for inclusion in the final model. The following table proves the effect sizes there will be 80% power to detect using the method of [35] for a marginal bivariable test with time-to-event data. Effect sizes are calculated for varying prevalences of pro-inflammatory states, assuming a quantitative interaction and final analysis occurs when 381 IDFS events (216 events in the placebo arm and 165 events in the aspirin arm).

Prevalence	Ratio of HRs
50%	0.56
40%	0.55
30%	0.53
20%	0.48

Association of measures of inflammatory states, factors or markers at 2-years with clinical outcome will be explored using landmark analyses of IDFS and OS in the subset of patients that are evaluable and event-free. All adjusted HRs and ratios of HRs from the final multivariable models will be reported with 95% confidence intervals. Hypothesis tests of inflammatory markers from banked biospecimen will be exploratory and hypothesis-generating using a nominal two-sided alpha = 0.05 for each analyte, and estimates of the false discovery rate (FDR) for multiple inflammatory markers that are potentially correlated will be obtained using the resampling-based Yekutieli-Benjamini method [36].

The pairwise correlations of baseline immune markers, states and factors, and changes from baseline, will be estimated within and across treatment arms using Spearman coefficients with empirical 95% confidence intervals drawn from the BCA bootstrap method. Unsupervised learning methods (e.g. agglomerative hierarchical clustering with Spearman correlation as the measure of distance) will be used to look for patterns of correlation among any multi-analyte markers of inflammation.

13.6 CDUS Reporting

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site [redacted]

13.7 Inclusion of Women and Minorities

Participating institutions will not exclude potential subjects from participating in this study solely on the basis of ethnic origin, gender or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire breast cancer population treated by participating institutions. The following enrollment is estimated from previous clinical trials conducted by this Group in a similar patient population.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	20	0	5	0	25
Asian	50	0	11	0	61
Native Hawaiian or Other Pacific Islander	10	0	5	0	15
Black or African American	285	5	49	1	340
White	2240	26	201	3	2470
More Than One Race	15	0	10	0	25
Total	2620	31	281	4	2936

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 COMPANION STUDY

14.1 Life Style Measures of Inflammation

The patient questionnaires for this study are only being made available in English. Study participants who do not speak, read or write English should not complete the questionnaires. Ad hoc translation of patient-completed measures is not permitted.

14.1.1 Background

There are several possible mechanisms for aspirin decreasing the risk of cancer recurrence with inflammation being one of them. We hypothesize that the effect of aspirin may be strongest in those participants who have lifestyle factors associated with inflammation. The lifestyle factors we have chosen to assess are body mass index, physical activity, sleep quality, depression, perceived stress, and pain for the reasons detailed below.

Many obese individuals develop a chronic low-grade inflammatory state that can possibly be assessed histologically and biochemically. Their enlarged adipocytes show higher expression of pro-inflammatory proteins such as TNFα, IL-6 and to recruit macrophages, all of which correlate with insulin resistance [37, 38] Simpson and Brown recently reviewed the role of inflammation and aromatase in obesity-related breast cancer [39]. The adipocytes in the breasts of obese women have been shown sometimes to be surrounded by macrophages forming crown-like structures and to have correlated increased aromatase activity as a consequence of increased generation of pro-inflammatory mediators [39-41]. Mouse models have shown that obesity increases tumor associated macrophage infiltration [42]. Physical activity of course ameliorates obesity and is of itself associated with lower markers of inflammation [43].

Stress-related changes in the hypothalamic-pituitary-adrenal (HPA) and the sympathetic nervous system (SNS) have been associated with low-grade inflammation by increasing systemic C-reactive protein (CRP) and IL-6 levels. Neuroendocrine stress pathways lead to increased secretion of epinephrine and norepinephrine has been shown to suppress cellular immunity, particularly NK cells. These stress pathways promote angiogenesis via proangiogenic cytokines VEGF and IL-6, and facilitate migration and invasion of tumor cells by inducing production of matrix metalloprotienases (MMP).

One interesting consideration is that these relationships could be bidirectional; an increased tumor inflammatory response could lead to increased subjective experience of depression and stress [38]. Chronic pain and depression frequently co-occur, and are thought to be linked by inflammation as the common mediator [44]. Sleep disturbances are common in those with chronic pain and in those with depression; experimental studies in healthy humans have shown that both prolonged and moderate sleep loss increase mediators of inflammation [45].

The available literature shows that these common factors among cancer patients are involved with inflammation in complex interactive ways. Measures of body mass index, physical activity, perceived stress, depression, pain, and sleep quality will be captured as part of the data collection at the same time as the blood collection which is baseline and 2 years.

14.1.2 Objective

To collect measures of lifestyle that are potential pro-inflammatory states and potential modifying factors, such as obesity, physical activity, stress, depression, pain and sleep loss. Our goal is to determine if there are subgroups of participants characterized by lifestyle factors associated with greater inflammation for whom aspirin may provide greater benefit.

14.1.3 Methods

Lifestyle measures of inflammation

14.1.3.1 Body mass index assessment

Body mass index will routinely measured at the time of routine clinical visits.

14.1.3.2 Recreational physical activity assessment

Recreational physical activity will be assessed using a modified Paffenbarger questionnaire that was originally developed for the Nurses' Health Study. Participants are asked to indicate the average time per week over the last year spent in a list of specific activities, selected to represent the most important contributors to total activity. Detailed validation study of the physical activity questionnaire has been conducted against both 1-week activity recalls and 7-day activity diaries. For total physical activity (in MET-hrs per week) the correlation for the overall sample with the recalls was 0.79 and with the records diaries was 0.62. Validity has also been documented by comparisons with activity diaries and resting pulse [46]. Finally, physical activity as measured by this questionnaire has shown important associations with multiple disease endpoints, including breast cancer survival, cardiovascular disease, and diabetes.

14.1.3.3 Sleep assessment

Sleep will be assessed with the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-administered 19-item questionnaire used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction during the last month. Scoring is based on a 0 to 3 scale, where a score of 3 reflects the negative extreme on the Likert Scale. A global score of five or greater indicates a "poor" sleeper [26].

14.1.3.4 Depression assessment

Depression will be assessed by the Center for Epidemiologic Studies-Depression scale revised (CESD-R). The CESD-R is a self-administered 20-item questionnaire to assess depressive symptoms over the past week that has been tested in healthy subjects, as well as patients with a history of breast cancer. A score of 16 or greater indicates depression within the preceding week [29, 30].

14.1.3.5 Perceived stress assessment

The Perceived Stress Scale (PSS) is a widely used scale to measure self-perception of stress. Designed for use in community samples, the questions are general and applicable to multiple populations. Fourteen, 10, and 4-item versions of the scale have been validated. It better predicts psychological symptoms, physical symptoms, and healthcare utilization than life-event scales [47]. We propose using the 10 item PSS (PSS-10) as normative values have been determined from large 2006 and 2009 probability samples of the U.S. Scores range from 0 (least perceived stress) to 40 (most perceived stress) with a mean of 16 for women [31].

14.1.3.6 Brief Pain Inventory

The Brief Pain Inventory is a widely used validated scale to measure pain over the last week. It has been used in many cancer clinical trials. To avoid participant burden, we have chosen two questions which are recommended by the Brief Pain Inventory

scoring manual and consensus guidelines as the ones that have been used most widely in clinical trials and best capture the pain experience [33, 48].

15.0 BIOSPECIMEN COLLECTION

15.1. Rationale

Although we do not currently have funding to perform biomarker analyses but we do have funding for the collection and processing of specimens, so we have decided to pursue a pragmatic approach of collecting biospecimens now, which will be at two time points: baseline prior to starting the intervention and after two years on study. Two years was chosen as the second collection time since that would present a uniform time for all subjects and would be within the time frame of the Department of Defense funding. Tumor blocks will also be collected at baseline. The plan for testing the banked samples will include a specific background, methods, and statistical section and will be submitted to NCI to be reviewed and approved according to NCTN procedures before any testing is done. As detailed in section 6, all biospecimens will be stored at the Alliance Biorepository at Washington University of St. Louis.

15.2. Biomarker selection

There are a large number of potential inflammatory markers that could be considered for correlative studies. Some of these are best measured in plasma, whereas others are best measured in a spot urine. Rather than committing to specific assays which may become outdated, we will submit a proposal at the time of analysis that would utilize assays that represent the state of the science and best reflect the best knowledge mechanistic pathways at that time.

Although there is large body of preclinical, epidemiologic, and pooled trial analysis data suggesting a possible role for aspirin as adjuvant therapy for cancer, the exact mechanisms are unknown and may vary by tumor site. Possible mechanisms include, but are not limited to: antiplatelet effect (platelet activation can lead to release of vascular endothelial growth factor (VEGF) , epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), cytokines such as interleukin-1β (IL-1 β) and IL-8, or proteases such as matrix metalloproteinase-2 (MMP2) and MMP9, which could promote angiogenesis, tumor growth, and metastases [49-51] and platelets may protect against immune mediated clearance by natural killer cells [52] and inhibition of the COX (COX expression has been associated with invasiveness and aggressiveness of breast tumors [53-55] and HER2 overexpression [55-57] and COX-2 inhibitors can enhance TNF-induced apoptosis [58], PIK3CA (aspirin use was associated with survival only in PIK3CA mutated colon cancer, not wildtype [59, 60], mTOR [61], NF kappa B [62] pathways. Urine specimens are also important since some measures of the prostaglandin pathway [63] and oxidative stress [64] are currently best measured in urine and proven stable over time [65]. These would not be an excessive burden on participants since it is a spot urine that could be done at the clinic visit. It should be noted that both of the large scale aspirin randomized trials (Add-Aspirin in the UK and ASCOLT for colorectal cancer in Asia) are also collecting urine samples. Given the varied possibilities for mechanistic/correlative studies, with some assays best done in tumor, some in plasma, some in DNA/RNA, and some in urine, all of these specimens will be collected.

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APPENDIX I LIFESTYLES MEASURES OF INFLAMMATION
Modified Paffenbarger Physical Activity Questionnaire

During the past year, what was your average time per week spent at each of the following recreational activities?

Walking or hiking outdoor (include walking to work): *(check one)*

☐ Zero	☐ 5-19 minutes	☐ One hour	☐ 2-3 hours	☐ 7-10 hours
☐ 1-4 minutes	☐ 20-59 minutes	☐ 1-1 ½ hours	☐ 4-6 hours	☐ 11+ hours

Jogging (slower than 10 minutes/mile): *(check one)*

☐ Zero	☐ 5-19 minutes	☐ One hour	☐ 2-3 hours	☐ 7-10 hours
☐ 1-4 minutes	☐ 20-59 minutes	☐ 1-1 ½ hours	☐ 4-6 hours	☐ 11+ hours

Running (10 minutes/mile or faster): *(check one)*

☐ Zero	☐ 5-19 minutes	☐ One hour	☐ 2-3 hours	☐ 7-10 hours
☐ 1-4 minutes	☐ 20-59 minutes	☐ 1-1 ½ hours	☐ 4-6 hours	☐ 11+ hours

Bicycling (include stationary machine): *(check one)*

☐ Zero	☐ 5-19 minutes	☐ One hour	☐ 2-3 hours	☐ 7-10 hours
☐ 1-4 minutes	☐ 20-59 minutes	☐ 1-1 ½ hours	☐ 4-6 hours	☐ 11+ hours

Calisthenics/aerobics/aerobic dance/rowing machine: *(check one)*

☐ Zero	☐ 5-19 minutes	☐ One hour	☐ 2-3 hours	☐ 7-10 hours
☐ 1-4 minutes	☐ 20-59 minutes	☐ 1-1 ½ hours	☐ 4-6 hours	☐ 11+ hours

Tennis, squash, or racquetball: *(check one)*

☐ Zero	☐ 5-19 minutes	☐ One hour	☐ 2-3 hours	☐ 7-10 hours
☐ 1-4 minutes	☐ 20-59 minutes	☐ 1-1 ½ hours	☐ 4-6 hours	☐ 11+ hours

Lap swimming: *(check one)*

☐ Zero	☐ 5-19 minutes	☐ One hour	☐ 2-3 hours	☐ 7-10 hours
☐ 1-4 minutes	☐ 20-59 minutes	☐ 1-1 ½ hours	☐ 4-6 hours	☐ 11+ hours

Other aerobic recreation (e.g. lawn mowing): *(check one)*

☐ Zero	☐ 5-19 minutes	☐ One hour	☐ 2-3 hours	☐ 7-10 hours
☐ 1-4 minutes	☐ 20-59 minutes	☐ 1-1 ½ hours	☐ 4-6 hours	☐ 11+ hours

On average, how many hours per week do you spend:

Standing or walking around at work: *(check one)*

☐ Zero	☐ 2-5 hours	☐ 11-20 hours	☐ 41-60 hours	☐ Over 90 hours
☐ 1 hour	☐ 6-10 hours	☐ 21-40 hours	☐ 61-90 hours	

Standing or walking around at home: *(check one)*

☐ Zero	☐ 2-5 hours	☐ 11-20 hours	☐ 41-60 hours	☐ Over 90 hours
☐ 1 hour	☐ 6-10 hours	☐ 21-40 hours	☐ 61-90 hours	

Sitting at work or while driving: *(check one)*

☐ Zero	☐ 2-5 hours	☐ 11-20 hours	☐ 41-60 hours	☐ Over 90 hours
☐ 1 hour	☐ 6-10 hours	☐ 21-40 hours	☐ 61-90 hours	

Sitting at home: *(check one)*

☐ Zero	☐ 2-5 hours	☐ 11-20 hours	☐ 41-60 hours	☐ Over 90 hours
☐ 1 hour	☐ 6-10 hours	☐ 21-40 hours	☐ 61-90 hours	

What is your usual walking pace outdoors? *(check one)*

- ☐ Easy, casual (less than 2 mph)
- ☐ Normal, average (2-2.9 mph)
- ☐ Brisk pace (3-3.9 mph)
- ☐ Very brisk/striding (4 mph or faster)
- ☐ Unable to walk

How many flights of stairs (not individual steps) do you climb daily? *(check one)*

- ☐ 2 flights or less
- ☐ 3-4
- ☐ 5-9
- ☐ 10-14
- ☐ 15 or more flights

Pittsburgh Sleep Quality Index

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time do you usually go to bed? **Usual Bed Time**_____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep at night? **Number of Minutes**_____

3. During the past month, what time have you usually gotten up in the morning? **Usual Getting Up Time**_____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.) **Hours of Sleep Per Night**_____

INSTRUCTIONS: for each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you:

	Not during the past month	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
(a) Cannot get to sleep within 30 minutes				
(b) Wake up in the middle of the night or early morning				
(c) have to get up to use the bathroom				
(d) Cannot breathe comfortably				
(e) Cough or snore loudly				
(f) Feel too cold				
(g) Feel too hot				
(h) Had bad dreams				
(i) Have pain				
(j) Other reason(s), please describe:				
How often during the past month have you had trouble sleeping because of this?				

6. During the past month, how would you rate your quality of sleep overall?

Very good Fairly good Fairly bad Very bad

7. During the past month, how often have you taken medicine (prescribed or over the counter) to help you sleep?

Not during the past month

Less than once a week

Once or twice a week

Three of more times a week

8. During the past month how often have you had trouble staying awake while driving, eating meals or engaging in social activities?

Not during the past month

Less than once a week
Once or twice a week
Three of more times a week

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all
Only a very slight problem
Somewhat of a problem
A very big problem

Center for Epidemiological Studies - Depression Scale Revised (CESD-R)

During the past week, how often have you felt this way?

	Last Week				
Below is a list of the way you might have felt or behaved. Please check the boxes to tell me how often you have felt in the past week or so.	**Not at all or Less than 1 day**	**1-2 days**	**3-4 days**	**5-7 days**	**Nearly every day for 2 week**
My appetite was poor.	0	1	2	3	4
I could not shake off the blues.					
I had trouble keeping my mind on what I was doing.					
I felt depressed.					
My sleep was restless.					
I felt sad.					
I could not get going.					
Nothing made me happy.					
I felt liked a bad person.					
I lost interest in my usual activities.					
I slept much more than usual.					
I felt like I was moving too slowly.					
I felt fidgety.					
I wished I were dead.					
I wanted to hurt myself.					
I was tired all the time.					
I did not like myself.					
I lost a lot of weight without trying to.					
I had a lot of trouble getting to sleep.					
I could not focus on the important things.					

Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts during <u>the last month</u>. In each case, please indicate with a check how often you felt or thought a certain way.

1. In the last month, how often have you been upset because of something that happened unexpectedly?		
___0=never	___1=almost never ___3=fairly often	___2=sometimes ___4=very often
2. In the last month, how often have you felt that you were unable to control the important things in your life?		
___0=never	___1=almost never ___3=fairly often	___2=sometimes ___4=very often
3. In the last month, how often have you felt nervous and "stressed"?		
___0=never	___1=almost never ___3=fairly often	___2=sometimes ___4=very often
4. In the last month, how often have you felt confident about your ability to handle your personal problems?		
___0=never	___1=almost never ___3=fairly often	___2=sometimes ___4=very often
5. In the last month, how often have you felt that things were going your way?		
___0=never	___1=almost never ___3=fairly often	___2=sometimes ___4=very often
6. In the last month, how often have you found that you could not cope with all the things that you had to do?		
___0=never	___1=almost never ___3=fairly often	___2=sometimes ___4=very often
7. In the last month, how often have you been able to control irritations in your life?		
___0=never	___1=almost never ___3=fairly often	___2=sometimes ___4=very often
8. In the last month, how often have you felt that you were on top of things?		
___0=never	___1=almost never ___3=fairly often	___2=sometimes ___4=very often
9. In the last month, how often have you been angered because of things that were outside of your control?		
___0=never	___1=almost never ___3=fairly often	___2=sometimes ___4=very often
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?		
___0=never	___1=almost never ___3=fairly often	___2=sometimes ___4=very often

BRIEF PAIN INVENTORY

Please rate your pain by circling the one number that best describes your pain at its worst in the last week.

(No pain) 0 1 2 3 4 5 6 7 8 9 10 (Pain as bad as you can imagine)

Please rate your pain by circling the one number that best describes your pain on the average.

(No pain) 0 1 2 3 4 5 6 7 8 9 10 (Pain as bad as you can imagine)

Registration Fatigue/Uniscale Assessments

These questions have been incorporated into the Baseline Lifestyles Measures of Inflammation booklet. This paper copy of the questions is for IRB purposes only.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX II A011502 STUDY MEDICATION LOG

Aspirin/Placebo Medication Log

Number of tablets Given:_____ Tablets Bottle(s) returned: Circle Yes or No
Total Daily Dose:_____ Number of tablets returned:_____

(*To be completed by a member of the study team)*

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

SPECIAL INSTRUCTIONS

1. Study tablets should be taken with food or a full glass of water.
2. Do not crush tablets.

Study Month #_____

DAY	Medication	DATE	TIME		Number of 300 mg or 100 mg tablets taken	Comments
Example	*Aspirin/placebo*	*07/01/2016*	*9:00*	*AM/PM*	*1 /300 mg*	
1	Aspirin/placebo			*AM/PM*	/	
2	Aspirin/placebo			*AM/PM*	/	
3	Aspirin/placebo			*AM/PM*	/	
4	Aspirin/placebo			*AM/PM*	/	
5	Aspirin/placebo			*AM/PM*	/	
6	Aspirin/placebo			*AM/PM*	/	
7	Aspirin/placebo			*AM/PM*	/	
8	Aspirin/placebo			*AM/PM*	/	
9	Aspirin/placebo			*AM/PM/*	/	
10	Aspirin/placebo			*AM/PM*	/	
11	Aspirin/placebo			*AM/PM*	/	
12	Aspirin/placebo			*AM/PM*	/	
13	Aspirin/placebo			*AM/PM*	/	
14	Aspirin/placebo			*AM/PM*	/	
15	Aspirin/placebo			*AM/PM*	/	
16	Aspirin/placebo			*AM/PM*	/	
17	Aspirin/placebo			*AM/PM*	/	
18	Aspirin/placebo			*AM/PM*	/	
19	Aspirin/placebo			*AM/PM*	/	
20	Aspirin/placebo			*AM/PM*	/	
21	Aspirin/placebo			*AM/PM*	/	
22	Aspirin/placebo			*AM/PM*	/	
23	Aspirin/placebo			*AM/PM*	/	
24	Aspirin/placebo			*AM/PM*	/	
25	Aspirin/placebo			*AM/PM*	/	
26	Aspirin/placebo			*AM/PM*	/	
27	Aspirin/placebo			*AM/PM*	/	
28	Aspirin/placebo			*AM/PM*	/	
29	Aspirin/placebo			*AM/PM*	/	
30	Aspirin/placebo			*AM/PM*	/	
31	Aspirin/placebo			*AM/PM*	/	

Patient initials: _____Date:_____

Comments:_____

Patient Alliance Study ID Number_____