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TITLE: Randomized Trial of Aspirin as Adjuvant Therapy for Node-Positive Breast Cancer

PRINCIPAL INVESTIGATOR: Michelle Holmes

CONTRACTING ORGANIZATION: Brigham and Women's Hospital, Boston, MA

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6. AUTHOR(S)

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

In the United States, more than 3 million women are living after a breast cancer diagnosis. There is great need for additional breast cancer adjuvant treatments that are low-cost and low toxicity. These would not only save thousands of lives, but offer improved quality of life for those who do not tolerate current treatments, and treatment options to women in developing countries who currently get none.

We will enroll 2936 women with HER2 negative non-metastatic breast cancer with a 1:1 randomization to aspirin 300 mg daily versus placebo. Primary endpoint is invasive disease-free survival (including local and distant). Secondary endpoints include recurrence-free interval (local and distant), overall survival, cardiovascular disease, toxicity, and adherence. We will exclude those at high risk of bleeding complications with aspirin (>age 70, history of prior stroke, significant gastrointestinal bleeding, anticoagulation) or those with indications for taking aspirin (history of myocardial infarction or atrial fibrillation) Breast cancer advocates will be involved in the creation of all recruitment letters, consent forms, and information sheets. We would conduct the trial in a multi-center collaboration of the Brigham and Women's Hospital, Dana Farber Harvard Cancer Institute, and the Alliance for Clinical Trials in Oncology. The research infrastructure, long-standing leadership roles in clinical trials, and ability to rapidly accrue subjects make the assembled research team ideal to lead a US trial within the proposed time frame.

15. SUBJECT TERMS

Breast cancer, adjuvant treatment, aspirin, randomized controlled trial

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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TABLE OF CONTENTS

1. INTRODUCTION:

There is great need for additional breast cancer adjuvant treatments that are low-cost and low toxicity. We believe aspirin holds great promise, and propose a randomized controlled trial to test that promise. There is compelling epidemiologic, in-vitro, and in-vivo, evidence of aspirin's potential. We will enroll 2936 women with HER2 negative non-metastatic breast cancer with a 1:1 randomization to aspirin 300 mg daily versus placebo. Primary endpoint is invasive disease-free survival (including local and distant). Secondary endpoints include recurrence-free interval (local and distant), overall survival, cardiovascular disease, toxicity, and adherence. We hypothesize that breast cancer survivors randomized to aspirin will have fewer recurrences and longer recurrence-free survival than those on placebo.

2. KEYWORDS:

Breast cancer, adjuvant treatment, aspirin, randomized controlled trial

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The goals and milestones listed below pertain to months 49-60 in the approved SOW:

Specific Aims 1 & 2: ClinIcal Trial

- Screen subjects and consent eligible subjects to study (months 6-30) – Began December 2016 and completed, December 2020
- Assign participants to one of two randomized groups study (months 6-30) – Began December 2016 and completed, December 2020
- Distribute study medication for the first 6 months study (months 6-30) – Began December 2016 and completed, December 2020
- Review accrual statistics to ensure that accrual goals will be met (every 6 months) – This is actually done every month. Began December 2016 and occurred on weekly basis
- Assess participants every 6 months while on study (months 12-30) – Began December 2016, ongoing
- Assess for toxicity and adverse events (ongoing) – Began December 2016, ongoing
- Assess for need for dose reduction (ongoing) – Began December 2016, ongoing
- Assess for need for proton pump inhibitor (ongoing) – Began December 2016, ongoing
- Assess compliance with study drug (months 12-60) Began December 2016, ongoing
- Coordinate with sites and data for data collection (months 6-60) – Began December 2016, ongoing
- Data cleaning (months 54-55) – Began December 2020, ongoing

- Perform data analysis (months 55-58) – Began April 2021
- Present data at Alliance and national oncology meetings (months 59-60)
- *Milestone achieved: Meet accrual goal for subjects (month 30)* -Prior to the COVID19 pandemic, the accrual goal of 100 subjects had been met. As expected, accrual significantly declined in April and May 2020, but increased after that, and the total accrual goal was achieved and exceeded in December 2020. – see Section 5: Changes, Problems
- *Milestone Achieved: Report findings from characteristics of baseline population (month 30-32))* - This was not achieved due to delay in subject accrual. Data analyses began April 2021. see Section 5: Changes, Problems
- *Milestone Achieved*: *Report findings from Study (month 60)* This was not achieved due to delay in subject accrual – see Section 5: Changes, Problems.

Specific Aim 3: Creation of biospecimen and epidemiologic biobank

- Collection of tumor specimens at baseline (months 6-30) – Began December 2016, ongoing
- Collection of blood and urine specimens at baseline (months 6-30) – Began December 2016, ongoing
- Storage and cataloguing of specimens (months 6-60) – Began December 2016, ongoing
- Collection of covariate data on sleep, stress, BMI, etc. (months 6-60) – Began December 2016, ongoing
- *Milestone Achieved: Complete biospecimen collection and creation of a biospecimen respository (month 60).* This is ongoing and not completed due to delay in subject accrual.
- *Milestone Achieved: Submit research grants on correlative works using biospecimens and epidemiologic data (months 50-60)* A sub-study evaluating changes in mammographic density among triple negative breast cancer patients enrolled on the aspirin stud was activated through the Alliance and is accruing subjects. The funding for the sub-study is through the National Cancer Institute

What was accomplished under these goals?

Referring to the SOW:

Specific Aims 1 & 2: Clinical Trial

- We began enrollment on Dec. 8, 2016. This included screening, randomization, distribution of study medication, collection of biospecimens, collection of epidemiologic data, collection of information on toxicity and adverse events, need for dose reduction, and need for proton pump inhibitor. The Alliance Data Safety and Monitoring Board last

met on May 14, 2021 and did not find any issues regarding adverse events or efficacy. Specifically, there were no grade 3 or 4 adverse events attributed to study drug. No interventions were recommended.

- As of December 25, 2020, 3,021 subjects have been registered and randomized on the aspirin study. Accrual goal of 2,936 has been met. The study closed to accrual on December 4, 2020. Subjects already in the pipeline when accrual closed caused the slight increase of subjects enrolled over the accrual goal.

Specific Aim 3: Biorepository

- As of September 25, 2021, 74% have submitted biospecimens (blood and/or tumor) and 92% have submitted a lifestyle questionnaire
- A sub-study evaluating changes in mammographic density among triple negative breast cancer patients enrolled on the aspirin stud was activated through the Alliance and is accruing subjects. The funding for the sub-study is through the National Cancer Institute

Additional Achievements, not in the SOW

- The first External Advisory Board meeting was held 11/21/16 . A trials in progress poster was presented at the semi-annual Alliance for Clinical Trials Oncology meeting in May 2017 at the annual American Society for Clinical Oncology meeting in June 2017. Our Patient Advocates publicized the study at the National Advocate Leadership Summit for the National Breast Cancer Coalition in May 2017.
- The second External Advisory Board meeting was held on 11/13/17. During the meeting we discussed slow accrual. The advice was given to liberalize the inclusion criteria (please see Section 5 Problems and Changes to document what was suggested). A trials in progress poster was presented at the semi-annual Alliance for Clinical Trials Oncology meeting in November 2017 and May 2018 and at the annual American Society of Clinical Oncology meeting in June 2018. The advocates publicized the work at the San Antonio Breast Symposium in December 2017.
- December 2018 Patient Advocate Maggie Carvan publicized the trial at the San Antonio Breast Cancer Conference. The External Advisory Board met on December 10, 2018 and members were updated on study progress and protocol amendments. A trials in progress poster was presented at the annual American Society of Clinical Oncology meeting in June 2019
- The External Advisory Board met on February 3, 2020. A trials in progress poster was presented at the annual American Society of Clinical Oncology meeting in June 2020.

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?
Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

The statistical power is driven by the number of cancer events as well as total enrollment. More time will be needed to await occurrence of cancer events, so a second one year no cost extension was requested and approved. Please see Section 5: Problems and Changes for these details.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

After initial accrual delays which were mitigated by a change in inclusion criteria, we encountered further accrual delays due to the COVID-19 pandemic. However, we did reach and exceed our total accrual by December 2020.

As mentioned before, the statistical power to find an effect is driven by the number of cancer events as well as total enrollment. More time will be needed to await occurrence of cancer events, so a second one year no cost extension was requested and approved.

Median follow up time is currently 18.5 months. In one additional year of follow up, it is estimated we would have 84 more events in our study population. One additional year of follow would also allow us to achieve the 30 months of follow up that we had estimated in our original application that we would need. Therefore, this additional one year NCE would now provide us with the amount of follow up time we had estimated would be needed in our original application.

Changes that had a significant impact on expenditures

A major cost of the trial is the $1400 per patient enrollment fee paid to the Alliance. As accrual was behind, these expenditures took longer than expected. As we have now reached total accrual, we are catching up with patient enrollment and expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/ or select agents

Significant changes in use or care of human subjects

None in the past year.

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

Nothing to report

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers, and presentations.

Chen WY, Winer EP, Ballman KV, Partridge AH, Carey LA, Openshaw TH, Visvanathan K, Symington B, Matyka C, Carvan M, Holmes MD. ABC trial (AO11502) A randomized phase III double blinded placebo controlled trial of aspirin as adjuvant therapy for breast cancer. 2020 Annual meeting of the American Society for Clinical Oncology.

Website(s) or other Internet site(s)

Nothing to report

- **Technologies or techniques**
  Nothing to report

- **Inventions, patent applications, and/or licenses**

  Nothing to report

- **Other Products**

  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Project Role: Nearest person-month worked: Contribution to project:	Michelle Holmes Principal Investigator No change Dr. Holmes has worked on protocol revisions & recruitment materials, and has interacted closely with Drs. Winer and Chen, the Patient Advocates, and the subcontractors to coordinate all aspects of the collaborative team to assure that all aspects of the trial are carried out in a timely and financially responsible manner, and to assure the highest standards of patient safety and scientific rigor.
Name: Project Role: Nearest person-month worked: Contribution to project:	Anna Weiss Alliance Principle Investigator (U. of Chicago) No change Dr Weiss has given input to protocol revisions, as well as coordinated Alliance staff during the enrollment process
Name: Project Role: Nearest person-month worked: Contribution to project:	Laura Hoffman Alliance Senior Protocol Coordinator (U. of Chicago) No change Ms. Hoffman has helped, submit documents to the Alliance and NCI for approval, and coordinated multiple conference calls to assure input from all key personnel. Ms. Silva took over the role in July 2018.
Name: Project Role: Nearest person-month worked: Contribution to project:	Sumithra J. Mandrekar Alliance Principal Investigator (Mayo Clinic) No change Dr. Mandrekar has provided input on statistical sections of the protocol, and supervised Ms. Poley
Name: Project Role: Nearest person-month worked: Contribution to project:	Karla Ballman Alliance Masters Statistician (Mayo Clinic) No change Ms Ballman has provided input on data collection, and created the data collections system using a Medidata Rave build
Name: Project Role:	Kristina Laumann Alliance Data Manager (Mayo Clinic)

Nearest person-month worked: Contribution to project:	No change Ms. Laumann helped create the data collections system using a Medidata RAVE build
Name: Project Role: Nearest person-month worked: Contribution to project:	Kristen Perkins Alliance Data Manager (Mayo Clinic) No change Ms. Perkins helped create the data collections system using a Medidata RAVE build and create the CRF's.
Name: Project Role: Nearest person-month worked: Contribution to project:	Mark Watson Principle Investigator, Biorepository (Washington Univ.) No change Dr. Watson provided details for the biospecimen repository collection for the protocol and he provided input into the protocol design

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Bayer Pharma AG, Mullerstr 178, 13353 Berlin, Germany is supplying both aspirin and placebo for this trial at no cost to the trial. We have executed a contract with them to do so on May 13, 2016.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: