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14. ABSTRACT A total of two hundred eight (208) specimens have been submitted to Precision for this study. One hundred twenty-two (122) subjects have been enrolled in this study to date. Out of those patients, thirty-five (35) were discontinued. Thirty-two (32) subjects were discontinued for not having a chemoresponse assay result, two (2) subjects were discontinued for being lost to follow-up, and one (1) subject was discontinued for an adverse experience on her SOC chemotherapy. Five (5) subjects are considered to be pre-enrolled at the time of this report. There are no safety issues (anticipated or unanticipated) to report for a study-related procedure. A total of twenty-nine (29) principal investigators have now been approved by the DoD to participate in this study. Since beginning the study, two (2) of these sites have been closed. Precision is currently working with eleven (11) US Oncology research sites and 16 Precision-managed sites. An additional one (1) site is in the start-up stage. Precision held its second investigator meeting in conjunction with the ASBS Conference in Washington DC on April 30, 2011. Subject screening and monitoring activities are ongoing. Strategies for increasing enrollment have been implemented and new sites are currently being identified to replace the sites that have been closed.					
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Introduction

The objective of this study is to develop a biomarker to predict pathological complete response in women treated with neoadjuvant chemotherapy for breast cancer. Such a biomarker would assist physicians in selecting the most effective chemotherapy for the individual patient. The anticipated biomarker will take into account clinical factors (such as tumor stage, tumor size, and age), phenotypic characteristics of the tumor (determined by pathological immunohistochemistry and *ex vivo* chemoresponse assay), and genotypic characteristics of the tumor and patient (determined by genomic profiling via gene expression analysis of tumor RNA). It is expected that collective consideration of all of these factors will be more predictive of patient response to therapy than any of them alone.

Approximately 224 evaluable subjects will be recruited from approximately 20 – 30 US sites. Women with measurable operable invasive breast cancer diagnosed by core needle biopsy will be eligible for this study. Additional tumor specimens will be obtained prior to the start of chemotherapy via core needle biopsies to be used for the *ex vivo* chemoresponse assay and tumor genomic analysis (gene expression), respectively.

All subjects will receive neoadjuvant chemotherapy with one of two standard of care regimens that must consist of the following agents: doxorubicin (A), cyclophosphamide (C), and a taxane (T) such as docetaxel, paclitaxel, or Abraxane (nanoparticle albumin-bound paclitaxel [nab-paclitaxel]); or, docetaxel (T) and cyclophosphamide (C). These must be administered per NCCN guidelines by the treating physician.

Upon completion of chemotherapy treatment, women will undergo lumpectomy, modified radical mastectomy or other surgical procedure determined appropriate by the investigator and at that time will be evaluated for pathological response. At the time of lumpectomy, modified radical mastectomy, or other surgical procedure, additional tumor excess may be sent to Precision Therapeutics, Inc. (Precision) for exploratory analysis if there is no pathologic complete response (pCR), if there are sufficient tumor cells to send, and if the subject agrees to have her excess tumor cells sent to Precision for this purpose.

During the subject's course of participation on the study, the treating physician will remain blinded to the results of the chemoresponse assay and genomic analysis. If it is determined there is no pCR at the time of lumpectomy, modified radical mastectomy or other surgical procedure, or if the subject's condition deteriorates while on chemotherapy and she needs to stop treatment, upon request, Precision will make available a subsequent report to the physician containing additional information about chemotherapy drugs other than ACT that may benefit future treatment decisions for the patient.

Overall Progress

A total of two hundred eight (208) specimens have been submitted to Precision for this study. One hundred twenty-two (122) subjects have been enrolled in this study to date. Out of those patients, thirty-five (35) were discontinued. Thirty-two (32) subjects were discontinued for not having a chemoresponse assay result, two (2) subjects were discontinued for being lost to follow-up, and one (1) subject was discontinued for an adverse experience on her SOC chemotherapy. Five (5) subjects are considered to be pre-enrolled at the time of this report. There are no safety issues (anticipated or unanticipated) to report for a study-related procedure.

A total of twenty-nine (29) principal investigators have now been approved by the DoD to participate in this study. Since beginning the study, two (2) of these sites have been closed. Precision is currently working with eleven (11) US Oncology research sites and 16 Precision-managed sites. An additional one (1) site is in the study start-up stage.

The following investigators have been closed due to inactivity and staffing issues respectively: Dr. Chevinsky and Dr. Mackey.

Precision held its second investigator meeting in conjunction with the ASBS Conference in Washington DC on April 30, 2011.

Detailed progress made between the period of June 11, 2010 – November 1, 2011

I. Work with a total of 29 investigators remains ongoing and is detailed in the table below (*sites highlighted in grey are closed*). 10 investigators for US Oncology fall under a general Study Investigator (SI), Dr. Michael Danso, for a total of 11 sites.

Participating Sites	Status Update
Richard Fine, MD Advanced Breast Care 790 Church Street, Suite 410 Marietta, GA 30060	• Approved for enrollment by the DoD • Actively screening subjects
Judy Tjoe, MD Aurora Health Care Inc. 8000 Montana Milwaukee, WI 53219	• Approved for enrollment by the DoD • Actively screening subjects
Susan Boolbol, MD Beth Israel Hospital 10 Union Square East, Suite 4E New York, NY 10003	• Approved for enrollment by the DoD • Actively screening subjects
Beth DuPree, MD Bott Cancer Center at the Holy Redeemer Hospital 1648 Huntingdon Pike Meadowbrook, PA 19046	• Regulatory paperwork has been received • Contract negotiation pending • IRB approval received
Mark Gittleman, MD Breast Care Specialists, PC 250 Cetronia Road, Suite 302 Allentown, PA 18104	• Approved for enrollment by the DoD • Actively screening subjects

Michael Berry, MD Breast Clinic of Memphis 1385 West Brierbrook Road Germantown, TN 38138	• Approved for enrollment by the DoD • Actively screening subjects
Theodore Potruch, MD BreastCare 2020 Goldring Ave., Suite 206 Las Vegas, NV 89106	• Approved for enrollment by DoD • Actively enrolling and screening subjects
John West, MD BreastLink 230 South Main Street, Suite 100 Orange, CA 92868	• Approved for enrollment by the DoD • Actively screening subjects
Peter Beitsch, MD Cancer Solutions 7777 Forest Lane, Suite C-760 Dallas, TX 75320	• Approved for enrollment by the DoD • Actively enrolling and screening subjects
Walton Taylor, MD Leading Edge Research, P.A. 9229 LBJ Freeway Dallas, TX 75243	• Approved for enrollment by the DoD • Actively enrolling and screening subjects

Aaron Chevinsky, MD Morristown Memorial Hospital (aka AtlanticHealth) 95 Madison Avenue, Ste 304c Morristown, NJ 07960	• Closed on September 16, 2011 due to inactivity and non-responsiveness.
Pat Whitworth, MD Nashville Breast Center, P.C. 300 20th Avenue North, Suite 401 Nashville, TN 37203	• Approved for enrollment by the DoD • Actively screening subjects
James Mackey, MD and Robin Skrine, MD Southlake Oncology 1545 E. Southlake Boulevard, Suite 280 Southlake, TX 76092	• Closed on September 14, 2011 due to staffing and logistical issues.
Laura Lawson, MD St. Thomas Research Institute 4230 Harding Road Nashville, TN 37205	• Approved for enrollment by the DoD • Actively screening subjects
Adam Brufsky, MD University of Pittsburgh Medical Center / University of Pittsburgh Cancer Institute / Magee Women's Hospital of UPMC 300 Halket Street Pittsburgh, PA 15213-3180	• Approved for enrollment by the DoD • Actively screening subjects
William Dooley, MD University of Oklahoma Health Sciences Center 1000 Stanton L. Young Blvd., LIB 121 Oklahoma City, OK 73117	• Approved for enrollment by the DoD • Actively screening subjects
Agustin Garcia, MD University of Southern California / Norris Comprehensive Cancer Center 1441 Eastlake Avenue Los Angeles, CA 90033	• Approved for enrollment by the DoD • Actively screening subjects
Michael Danso, MD US Oncology Network Virginia Oncology Associates 5900 Lake Wright Dr Norfolk, VA 23502	• Total number of US Oncology sites is 11 • Approved for enrollment by the DoD • Actively screening subjects
Ekaterini Tsiapali, MD Women and Infants Hospital of RI 101 Dudley Street Providence, RI 02905	• Approved for enrollment by the DoD • Actively screening subjects

II. To date, two (2) Investigator Meetings have been held in conjunction with the American Society of Breast Surgeons (ASBS). The meeting that occurred at the 2011 ASBS conference on April 30th included a small group of Investigators and research personnel. The progress of the study was reviewed, with specific emphasis on: Q1 2011 achievements, top enrolling sites and the activation of US Oncology.

One challenge that the study currently faces is a very high screen fail rate. The reasons for screen failures were discussed as well as approaches that the sites can take to help reduce these occurrences.

Problem Areas

I. Regulatory Requirements and Timeline for Site Approvals to Enroll

As this is the first federally funded award received by Precision Therapeutics, there has been a learning curve within our Clinical Trials Department regarding the regulatory requirements, specifically OHRP FWA coverage, of these projects. Throughout the past several years DOD site approvals have taken as long as six (6) months to be issued as the sites have applied for FWA numbers or gathered remaining information for the review process.

With our most recent site submissions to the DOD we feel that our Clinical Trials team has now developed a strong understanding of these requirements as well as having fostered a productive relationship with the human protection officer responsible for these reviews. We feel that future submissions will lack errors previously identified which should greatly reduce the time to open sites for enrollment.

II. Drug Shortages

It has recently come to our attention that physicians are experiencing a nationwide shortage in supply of one of our standard of care drugs of interest for this patient population: adriamycin. It is not yet known what the impact of this shortage will have on eligibility of patients, how long it will last or what alternatives are available. Currently we are aware of two (2) patients that were unable to participate on the study due to the unavailability of adriamycin. In order to best support our physicians, we plan to educate the sites on programs that may be available to obtain this vital therapy.

III. Meeting enrollment benchmarks for active sites. Precision continues to work with sites to help meet the monthly accrual targets. Precision has closed one inactive, non-responsive site so that another may be opened in its place to enroll patients.

Work to be Performed in Next Quarter

I. Paperwork for Dr. DuPree will be obtained and submitted to the DoD for final review and approval.

II. At least five (5) new sites will be identified that may be able to open quickly on the study and contribute to enrollment.

III. We will continue to schedule Site Initiation Visits (SIVs) to train sites on both the protocol requirements and the use of OpenClinica's EDC system, and conduct Interim Monitoring Visits (IMVs) to monitor the data on subjects enrolled in the study.

IV. We will continue to work with OpenClinica to test and approve necessary changes to the database to reflect the most current version of the protocol and case report forms.

V. We will continue to monitor the obstacles or issues of the study, assess tissue collection procedures and viability of tissue from study sites, and make strides in accruing eligible subjects in this study.

Key Research Accomplishments

Not applicable

Reportable Outcomes

Not applicable

Conclusion

Not applicable

References

Not applicable

Supporting Data

Not applicable

ATTACHMENT 1

Anticipated Accrual from Q2 2011 through Q4 2012

Quarter	Patients Enrolled	Total
Q2 2011	70	70
Q3 2011	24	94
Q4 2011	21	115
Q1 2012	34	149
Q2 2012	30	179
Q3 2012	28	207
Q4 2012	19	226