

AD \_\_\_\_\_

Award Number: DAMD17-00-1-0120

TITLE: UAB-Community Breast Cancer Network

PRINCIPAL INVESTIGATOR: Albert LoBuglio, M.D.

CONTRACTING ORGANIZATION: The University of Alabama at Birmingham  
Birmingham, AL 35294

REPORT DATE: July 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;  
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

20031204 047

# REPORT DOCUMENTATION PAGE

Form Approved  
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

<b>1. AGENCY USE ONLY (Leave blank)</b>		<b>2. REPORT DATE</b> July 2003	<b>3. REPORT TYPE AND DATES COVERED</b> Annual (15 Jun, 2002 -14 Jun, 2003)	
<b>4. TITLE AND SUBTITLE</b>  UAB-Community Breast Cancer Network			<b>5. FUNDING NUMBERS</b> DAMD17-00-1-0120	
<b>6. AUTHOR(S)</b>  Albert LoBuglio, M.D.				
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  The University of Alabama at Birmingham Birmingham, AL 35294  E-Mail: lobuglio@uab.edu			<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>  U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			<b>10. SPONSORING / MONITORING AGENCY REPORT NUMBER</b>	
<b>11. SUPPLEMENTARY NOTES</b>				
<b>12a. DISTRIBUTION / AVAILABILITY STATEMENT</b> Approved for Public Release; Distribution Unlimited				<b>12b. DISTRIBUTION CODE</b>
<b>13. ABSTRACT (Maximum 200 Words)</b>  The UAB Clinical Trial Network was aimed at forming a collaborative linkage between the UAB Comprehensive Cancer Center, community-based oncology practices and pharmaceutical sponsors, in order to provide access to high priority novel clinical trials to women with breast cancer within the community. Year 03 was dedicated to review of the Network activity by both the internal and external advisory board, which recommended modification of Network administrative and regulatory oversight activity. A thorough re-orientation and re-training of the research department at Georgia Cancer Specialists (GCS) was performed as part of a Corrective Action Plan following protocol adherence and compliance deficiencies noted during an FDA audit of a <u>non-Network protocol</u> . As a result, initiation of all new trials and patient accrual was voluntarily halted at GCS for 6 months, and then restarted in 2003 following successful passage of both an internal as well as external audit. Four Network breast cancer clinical trials active in Y02 completed accrual and have been closed. Total accrual from the Network sites was 49 for these trials. Following restart of patient accrual at GCS, two Network breast cancer trials were re-initiated and have accrued a total of 18 patients to date. Additional trials await initiation. Two clinical sites in Alabama have been added to our Network and activation of breast cancer trials at these sites is planned. We have received approval for a no-cost extension of funding into Year 04.				
<b>14. SUBJECT TERMS</b>  Translational breast cancer trials, Phase I/II breast cancer trials			<b>15. NUMBER OF PAGES</b> 19	
			<b>16. PRICE CODE</b>	
<b>17. SECURITY CLASSIFICATION OF REPORT</b> Unclassified	<b>18. SECURITY CLASSIFICATION OF THIS PAGE</b> Unclassified	<b>19. SECURITY CLASSIFICATION OF ABSTRACT</b> Unclassified	<b>20. LIMITATION OF ABSTRACT</b> Unlimited	

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)  
Prescribed by ANSI Std. Z39-18  
298-102

## Table of Contents

Cover .....	1
SF 298.....	2
Table of Contents .....	3
Introduction.....	4
Body.....	4-8
Key Research Accomplishments.....	4-8
Reportable Outcomes .....	9
Conclusions.....	9
References.....	9
Appendices.....	9

## **Introduction**

In 2000 we initiated a Clinical Trials Network linking the University of Alabama Comprehensive Cancer Center with community based oncology groups for the purpose of conducting high priority breast cancer clinical trials at the community level. The intent was to provide breast cancer patients in the community access to novel reagents, assist the community groups by providing efficient clinical trial management support, and in turn increasing accrual to Cancer Center supported clinical trials.

The Network currently consists of linkage to a 20-Clinic Hematology-Oncology Group Practice in metropolitan Atlanta (Georgia Cancer Specialists - GCS) and two recently initiated sites in Alabama (Birmingham Hematology-Oncology and Montgomery Cancer Center). Breast cancer clinical trials have been active to date only at the GCS site, with patient accrual at the new sites slated for 3<sup>rd</sup> quarter 2003.

A voluntary moratorium on new trial and new patient accrual was instituted at the GCS Network site from May 2002 till November 2002 in order to re-train and re-orient the research department staff following deficiencies in clinical trial conduct identified during an FDA audit of a non-Network clinical trial. Following a thorough Corrective Action Plan during this voluntary moratorium, GCS successfully passed both an internal and external QA/QC audit and accruals were re-initiated in November 2002.

Currently two breast cancer Network trials are active at the GCS site with a total accrual of 22 patients in the past 6 months. Additional initiations at the GCS and Alabama sites are planned.

A no-cost extension of the current funding has been approved to continue Network activity into 2004.

## **Body**

### **Key Research Accomplishments:**

#### **1. Task 16**

##### **Review and analysis of Y01-02 activity**

- The Internal Advisory Committee of the Cancer Center reviewed the accomplishment of the Network. An organizational restructuring was recommended to better improve communication and coordination of patient accrual at the Network site. The Network coordinator research nurse function was transferred to a research RN at the Network site.
- The Internal Advisory Committee also reviewed the current accomplishment of the Network as well as the Corrective Action Plan instituted by GCS to ensure GCP and protocol compliance, and was satisfied with the efforts and diligence of the Network partners to correct past deficiencies and put into place quality assurance/quality control (QA/QC) measures to ensure compliance.

- The Network concept was also presented to the External Advisory Committee of the Cancer Center, which reviewed the findings and deficiencies identified by the FDA on a non-Network protocol as well as the oversight responsibility and burden assumed by UAB for compliance and study adherence by GCS research. The Advisory Committee was of the opinion that UAB Cancer Center's research program could potentially be held accountable for protocol violation and non-compliance on part of the Network site, especially if a UAB PI was overall responsible for patient accrual and oversight. The Advisory Committee provided recommendations regarding safeguarding the Cancer Center's research program from liability and FDA sanctions.
- A recommendation that the Network assume independent IRB through a central IRB and that a Network PI be identified to assume responsibility for patient management enrolled at the Network site was proposed.
- Based upon the recommendations of the Internal and External Advisory Committee, a restructuring of the regulatory and budgetary oversight of the Network sites was proposed in order to avoid spill-over of liability to the Cancer Center. Furthermore it was decided that all Network sites would have an onsite PI, who would oversee the trial and be responsible for study management and oversight.

**2. Task 17 – Month 30  
Completion of Trials Initiated in Year 02**

- Following delay of orderly activation of clinical trials at Network site in Year 01, one phase I, two phase II and three phase III trials were activate in year 02 with a total accrual of 49 patients.
- By month 30, one phase I (UAB 0009), two phase II (UAB 9912 and UAB 0152) and one phase III (UAB 0028) clinical trials had achieved their targeted patient accrual and were closed. The total accrual for each trial is provided below.
- The voluntary accrual moratorium imposed by GCS to accomplish their re-training and re-orientation program (following FDA audit of a non-Network trial) resulted in a significant impediment and halting of clinical trials for over 6 months (months 21 – 28) Upon restarting of patient accrual in November 2003 (month 29), two of the phase III trials still accruing patients were re-initiated and patient accrual was restarted. As a result of the events patient accrual has undergone a substantial decrement during year 03 and did not meet the projected goals of the original proposal.
- As part of the re-orientation, the entire research department including investigators, research RNs, data managers and support staff underwent IRB recertification via UAB as well as via the NCI sponsored on-line program

- The entire research department including investigators, research RNs, data managers and support staff also underwent recertification in clinical trial processes through a certified external agency

**3. Task 18 – Month 25–36**

**Initiation of phase I clinical trials**

- Given the complexity of phase I clinical trials using novel agents and frequent need for in-patient monitoring, and rigorous pharmacokinetic sampling, it has not been possible to accomplish the previously planned activation of phase I breast cancer protocols at the Network sites. Such trials are often carried out at NIH-funded General Clinical Research Centers and thus was not readily feasible in the community.
- Most of the breast cancer phase I trials at UAB have been multi-center trials with 3 patients per cohort (max. 6 at MTD). Given the complexity of coordinating accrual at multiple sites for a restricted number of patients per dose level, the Network sites have not generally been included in these trials. Single center phase I/II trials initiated at UAB would be ideally suited for the Network and are being planned.

**4. Task 19 – Month 30 36**

**Initiation of phase II clinical trials**

- A number of phase II clinical trials are to be initiated and implemented in the second quarter of 2003 and will thus be conducted during the no-cost extension period of this grant. The community has a vast population of women requiring adjunctive chemotherapy for breast cancer, yet no trial fitting this patient population is available outside the cooperative group setting. A study to evaluate dose dense chemotherapy in the adjuvant setting is being awaited for Network activation.
- The following new breast cancer clinical trials are projected to be activated at the Network site in year 04 during the no-cost extension of the current funding period.
  - Phase II trial of novel aromatase inhibitor in the treatment of hormone responsive first line Metastatic breast cancer
  - Phase II trial of a novel dual Her1/Her2 tyrosine-kinase inhibitor for the treatment of Her2 negative patients with Metastatic breast cancer following failure of more than one prior therapy
  - Proposed randomized phase II study comparing QOL with Cytosan / Doxil versus Cytosan / Adriamycin as adjuvant therapy in node negative high risk breast cancer
  - Proposed phase III trial of adjuvant dose dense chemotherapy for Her2 – women with node positive breast cancer

- Funding mechanism for Network trials
  - It is clear that the Network concept has been difficult to initiate, and following a period of orderly progress, suffered a setback due to deficiencies in compliance and protocol adherence (in a non-Network trial). The process has provided practical insights into the complexities in the conduct of clinical trials in the setting of a busy and productive community practice. The Network partners have responded very effectively to the need to improve, re-train and re-orient the research department and are committed to quality clinical research. Funding mechanisms through pharmaceutical sponsors as well as peer-reviewed mechanisms to build upon the current established reorganized clinical trials operation will be pursued during this no-cost funding period.

**UAB-Community Breast Cancer Clinical Trials Network**

<b>Active Protocol</b>	<b>Patient Accrual – Year 03</b>
<b>UAB 0047</b> – A Multicenter Phase III Randomized Trial Comparing Docetaxel in Combination with Doxorubicin and Cyclophosphamide (TAC) Versus Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC → T) as Adjuvant Treatment of Operable Breast Cancer HER2NEU Negative Patients with Positive Axillary Lymph Nodes (BCIRG 005)	14
<b>UAB 0106</b> – A Multicenter Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC→T) With Doxorubicin and Cyclophosphamide Followed by Docetaxel and Trastuzumab (AC→TH) and With Docetaxel, Platinum Salt and Trastuzumab (TCH) in the Adjuvant Treatment of	8

<b>Active Protocol</b>	<b>Patient Accrual – Year 03</b>
Node Positive and High Risk Node Negative Patients with Operable Breast Cancer Containing the Her2Neu Alteration (BCIRG 006)	

<b>Closed Protocols</b>	<b>Total Network Accrual</b>
<b>UAB 9912</b> – A Phase II Study Using SGN-15 (cBR96-Doxorubicin Immunoconjugate) in Combination with Taxotere for the Treatment of Metastatic or Recurrent Breast Carcinoma	17
<b>UAB 0009</b> – A Phase I Clinical and Pharmacokinetic Evaluation of Oral CI-1033 Given as a Single Dose Daily in Patients with Advanced Nonhematologic Malignancies	4
<b>UAB 0028</b> – A Multicenter, Open-Label, Phase III, Randomized, Active-Controlled Trial Evaluating the Efficacy, Safety, and Pharmacokinetics of rhuMAb VEGF (BEVACIZUMAB), in Combination with Capecitabine Chemotherapy, in Subjects with Previously Treated Metastatic Breast Cancer	12
<b>UAB 0152</b> – A Multicenter Phase 2 Study of CI-1040 in Patients with Advanced Non-Small Cell Lung Cancer, Breast Cancer, Colon Cancer, or Pancreatic Cancer	6

## Reportable Outcomes

- **Presentations at ASCO 2003**
  - Hart LL, Nabell L, Saleh M, Sundaram S, Mauer A, Marshall J, McCune D, Sandler AS, Sing AP, Siegall C: A phase II study of SGN-15 (cBR96-doxorubicin Immunoconjugate) combined with docetaxel for the treatment of metastatic breast carcinoma. *American Society of Clinical Oncology 38<sup>th</sup> Annual Meeting*, May 31-June 3, 2003
  - Saleh MN, Irwin D, Burton G, Hargis JB, Chitambar C, Jones CM, Shapiro CL, Holmlund JT, Dorr A: Phase 2 trial of ISIS 2503, an antisense inhibitor of h-ras, in combination with weekly paclitaxel in the treatment of patients with metastatic breast cancer. *American Society of Clinical Oncology 38<sup>th</sup> Annual Meeting*, May 31-June 3, 2003

## Conclusion

The UAB Clinical Trials Network was established as a unique setup for the conduct of early phase I/II and phase III trials using novel agents in the community setting. While the patient base to support such an endeavor exists and patients in the community are very willing to participate in clinical trials, the experience of the past year has provided a measure of realism and revealed some of the difficulties encountered in operating a clinical trials network between a highly academic Cancer Center and a busy community based oncology practice.

The experience has been very insightful and the lessons learned have prepared us to revisit the goals and expectation of such a network affiliation as well as the need for more “hand-holding” if such an enterprise is to succeed and high quality cutting edge clinical research is to be conducted in the community setting.

While the goals and objectives proposed are achievable it is fair to say that the “return of investment” in terms of patient accrual and quality protocol compliance and adherence to GCP dictates that a slower start up pace and gradual incremental achievement should be aimed for.

## References

N/A

## Appendices

### Attachment 1:

**Georgia Cancer Specialists – Final Progress Report Submitted to the FDA, November 27, 2002**

**Attachment 2:  
Abstracts presented at ASCO 2003**

## Georgia Cancer Specialists Final Progress Report November 27, 2002

Area for Improvement	Corrective Action	Timeline/Documentation	Status	Compliance Measure
<p>Protocol-specific education and compliance</p>	<ul style="list-style-type: none"> <li>• Each protocol will be assigned a <i>Lead Coordinator</i> to become the protocol expert. He/she will be the go-to person for issues relating to this trial. They will also be responsible for communications with the sponsor and sharing information with the department.</li> <li>• The five protocols with the highest accrual/accrual potential will be reviewed by all staff.</li> <li>• The results of the FDA audit will be reviewed by all research staff.</li> <li>• All research staff to be inserviced on new protocols</li> <li>• Prior to re-starting accrual staff will undergo abbreviated re-orientation</li> </ul>	<ul style="list-style-type: none"> <li>• Lead CRC assigned for each protocol</li> <li>• Protocol-specific re-orientation and training occurred as follows:                             <ol style="list-style-type: none"> <li>1. BCIRG 005: 5/15/02</li> <li>2. BCIRG 006: 5/15 02</li> <li>3. ISIS 2503CS10: 5/29/02</li> <li>4. Pfizer CI 1040: 5/8/02</li> <li>5. Pfizer CI 1033: 5/8/02</li> </ol> </li> <li>• FDA Form 483 from audit of Genentech AV2107G reviewed, corrective Action Plan outlined and implementation timeline discussed. Follow-up compliance audits discussed and approved.</li> <li>• Following new protocols were initiated                             <ol style="list-style-type: none"> <li>1. Genta GL303 for CLL</li> <li>2. Genta GN304 for NSCLC</li> <li>3. Genta GL212 for Mantle Cell Lymphoma</li> </ol> </li> </ul>	<p>Complete</p>	<p>Quarterly Process Audit (Process Audit SOP states that the Regulatory Department will be responsible for audit)</p>
<p>Organizational structure (PI oversight)</p>	<ul style="list-style-type: none"> <li>• Patient Oriented Clinical Research is accorded divisional status within GCS with direct reporting to the Executive Management. Dr. Saleh is the Medical Director and sits on the board as an ex-officio member. This provides Dr. Saleh the ability to initiate new policies and procedures with the authority of the board.</li> </ul>	<ul style="list-style-type: none"> <li>• New organizational structure approved by the board 5/02</li> <li>• Research Nurse Manager position filled 8/26/02.</li> </ul>	<p>Complete</p>	<p>N/A</p>

Attachment 1

Area for Improvement	Corrective Action	Timeline/Documentation	Status	Compliance Measure
Communication	<p>The Director of Research Operations (James Gilmore, PharmD), the Research Nurse Manager (Mary Jane Waddell, RN, BSN), the CRCs, Data Managers, and pharmacy and regulatory personnel all report to Dr. Saleh.</p> <ul style="list-style-type: none"> <li>All research staff, PI, site sub-PIs, and representatives from the Clinical Operations Division of GCS attend weekly meetings where all patients on trial are discussed. Amendments, audit reports, compliance issues, corrective actions, and new policies and procedures are reviewed during this meeting. This meeting provides PI oversight of the research program.</li> <li>Meeting minutes are kept, Action Items with due dates are communicated and reviewed at each subsequent meeting to ensure compliance.</li> <li>The Director of Research Operations also attends monthly Clinical Operations Committee, Business Operations Committee, and EVP Committee meetings representing the Research Department.</li> <li>Research Nurse Manager attends monthly system-wide Nurse Manager Meeting representing the Research Department</li> </ul>	<ul style="list-style-type: none"> <li>Weekly Research Departmental meetings every Wednesday began 4/02. Meeting minutes are typed and kept on an exchange server accessible by all research staff.</li> <li>In addition to our general weekly meeting, each clinic has a clinic-specific meeting run by the site sub-PI. These meetings include clinic staff and provides a forum to disseminate information and resolve any clinic-specific issues. Minutes for these meetings are also kept and available on the exchanger server.</li> <li>Outcome of sponsor monitoring visits are discussed. Ongoing protocol and GCS education occurs at this meeting, and corrective action regarding deficiencies and deviations are implemented. This is formulated in response to sponsor's monitoring report</li> </ul>	Complete	Quarterly Process Audit
Protocol initiation attendance	<ul style="list-style-type: none"> <li>Per GCS Study Initiation SOP attendance at all protocol initiations will be mandatory for all research staff, PI and site sub-PIs</li> <li>Each protocol has a lead clinical research coordinator identified as the study resource.</li> </ul>	<ul style="list-style-type: none"> <li>Study Initiation SOP</li> <li>Since June 2002, 3 new trials have been initiated in compliance with our SOP. A lead CRC has been identified for each new protocol and a follow-up inservice with research staff has been conducted.</li> </ul>	Complete	Quarterly Process Audit
Patient eligibility confirmation and	<ul style="list-style-type: none"> <li>PI or site sub-PI and CRC must review all source documentation related to eligibility</li> </ul>	<ul style="list-style-type: none"> <li>Screening Visit SOP</li> <li>Policy has been implemented and is being closely</li> </ul>	Complete	Monthly Internal Audit

Attachment 1

Area for Improvement	Corrective Action	Timeline/Documentation	Status	Compliance Measure
documentation	<p>and sign eligibility checklist prior to patient enrollment. This documentation, including documentation of sponsor-granted exceptions, must be on hand prior to enrollment.</p> <ul style="list-style-type: none"> <li>All patients evaluated for protocol will undergo a "protocol specific clinic visit" by PI or sub-PI as formal component of eligibility screening to insure eligibility compliance</li> </ul>	monitored.		Quarterly Process Audit
Patient Enrollment and Consent process	<ul style="list-style-type: none"> <li>The PI (or site sub PI) will evaluate all new protocol patients prior to enrollment and at each of the study-specified visits.</li> <li>Patient consent will be obtained by the PI or site-sub PI in the presence of the research coordinator prior to enrollment onto study. This will be documented in both MD and CRC note</li> <li>All source documents necessary to document eligibility have to be on hand in order for the patient to be registered / enrolled and the eligibility check list has to be signed by PI or site sub PI and research coordinator</li> </ul>	<ul style="list-style-type: none"> <li>Informed Consent and Screening Visit Policy and Procedure</li> </ul>	Complete	Monthly Internal Audit Quarterly Process Audit
Radiographic Measurements	<ul style="list-style-type: none"> <li>All radiographic measurements will comply with protocol specifications. Central radiology review with Decatur Health Imaging.</li> <li>Each narrated radiology report will be accompanied by documentation of the bi-dimensional measurements of the identified index lesions and comparison to baseline. If this requirement is not met, the PI will assume responsibility for radiologic review</li> </ul>	<ul style="list-style-type: none"> <li>Meeting with DHI on 6/11/02. Compliance with SOP is being monitored on an ongoing basis and has led to substantial improvement with occasional requirement for re-reads.</li> </ul>	Complete	Monthly Internal Audit

Attachment 1

Area for Improvement	Corrective Action	Timeline/Documentation	Status	Compliance Measure
<p>Source Documentation</p>	<p>and reporting.</p> <ul style="list-style-type: none"> <li>All protocol required clinic visit notes will be dictated as STAT Research Note or electronically entered by investigator within 24 hours of patient visit, transcribed within 24-48 hours and physically signed and dated by the PI or site-sub PI.</li> <li>All nursing pre-treatment assessments will be performed by research coordinators. These notes will be dated and signed to denote authorship.</li> <li>Documentation of chemotherapy and/or study drug administration and related events will be performed by the respective clinic nurse with date and signature to denote authorship.</li> <li>The entire documentation of each patient encounter during study specific visits will be reviewed by the research coordinator to ensure compliance with source documentation requirements.</li> <li>If correction or changes to a patient note is required, a new Addendum Note must be initiated and signed off separately. No changes are to be made to the original note.</li> <li>Implementation of a new Research Source Documentation Form to be used for all research patients. This form will follow the patients through each stop during their treatment visits capturing all relevant information (AEs, labs, dose modifications, etc.) on one form. This will enhance protocol compliance and provide one uniform source document for each patient</li> </ul>	<ul style="list-style-type: none"> <li>Source Documentation Policy and Procedure</li> <li>Research Source Document Form Policy and Procedure</li> </ul>	<p>Complete</p>	<p>Monthly Internal Audit</p>

Attachment 1

Area for Improvement	Corrective Action	Timeline/Documentation	Status	Compliance Measure
Adverse Event Reporting	<p>visit.</p> <ul style="list-style-type: none"> <li>All Adverse Events are documented in the chart per GCP, GCS SOP, and protocol guidelines.</li> <li>All Serious Adverse Events are communicated to sponsor and respective IRB within 24 hours of knowledge of event. Formal report will follow with appropriate required documentation.</li> </ul>	<ul style="list-style-type: none"> <li>Adverse Event and Serious Adverse Event Reporting Policy and Procedure.</li> </ul>	Complete	<p>Monthly Internal Audit</p> <p>Quarterly Process Audit</p>
Drug accountability	<ul style="list-style-type: none"> <li>All research patient drug orders are pre-printed prior to each scheduled patient encounter to trigger a drug availability check and shipment of drug from central pharmacy to the on-site pharmacy tech.</li> <li>On the day of treatment, the patient is assessed by the research coordinator. If the patient is eligible to receive drug, the drug order is signed and dated by PI or sub-PI and CRC providing the appropriate study drug dosage per protocol (taking into consideration any protocol mandated dose modification).</li> <li>No drug is prepared by research pharmacy without signed drug order.</li> <li>The pharmacy technician will verify and document on the Research Source Documentation Form that appropriate sign-off for drug administration and dosage is in place before releasing study drug for administration.</li> </ul>	<ul style="list-style-type: none"> <li>Research Drug Accountability and Dispensing Policy and Procedure</li> <li>Day of Treatment Verification of Standard Chemotherapy Orders Policy and Procedure</li> </ul>	Complete	<p>Monthly Internal Audit</p> <p>Quarterly Process Audit</p>
External audit (Sponsor monitoring visits)	<ul style="list-style-type: none"> <li>To ensure protocol compliance and quality control, independent monitors from the pharmaceutical sponsors perform routine audits.</li> </ul>	<ul style="list-style-type: none"> <li>Monitoring Visits Policy and Procedure</li> <li>Monitoring Follow-up Letter Responses Policy and Procedure</li> </ul>	Complete	Quarterly Process Audit

Attachment 1

Area for Improvement	Corrective Action	Timeline/Documentation	Status	Compliance Measure
	<ul style="list-style-type: none"> <li>The PI, Research Nurse Manager, and the Research Data Outcomes Supervisor meet with the monitor for an exit interview following each visit.</li> <li>If the audit reveals areas of deficiency, the PI will respond to the audit report in writing with an outline of the corrective action. The IRB is copied on monitoring letters and GCS's response.</li> <li>Outcome of all monitoring visits is presented to research staff at weekly meetings for input and system-wide corrective action (if applicable)</li> </ul>			
Internal audit	<ul style="list-style-type: none"> <li>To ensure on-going protocol compliance and adherence to GCS Policies and Procedures, internal audits using a standard audit tool will be conducted by CRCs on a routine basis and findings reported at the weekly research meeting.</li> </ul>	<ul style="list-style-type: none"> <li>Internal Audit Policy and Procedure</li> </ul>	Complete	N/A
Process audit	<ul style="list-style-type: none"> <li>To ensure ongoing compliance with GCS SOPs, IRB reporting, monitor letter response, drug accountability, correct version of IC, meeting regularity and minutes taken, and initiation visit attendance, a quarterly audit of processes outlined in GCS SOPs will be conducted.</li> </ul>	<ul style="list-style-type: none"> <li>Process Audit Policy and Procedure</li> </ul>	Complete	N/A
GCS-UAB Network Audit	<ul style="list-style-type: none"> <li>To ensure on-going protocol compliance and adherence to GCP an independent auditor from UAB will routinely audit a representative sample of our study patient charts. A formal audit report with recommendation is provided to the PI for response.</li> </ul>	<ul style="list-style-type: none"> <li>Audit occurred during the week of July 22, 2002. Audit documented compliance with newly introduced corrective action plan. PI provided formal response to audit review.</li> </ul>	Complete	N/A

Attachment 1

Area for Improvement	Corrective Action	Timeline/Documentation	Status	Compliance Measure
Independent Audit	<ul style="list-style-type: none"> <li>To ensure compliance with GCP, GCS SOP and protocol, an independent consultant was contracted to review a representative sample of patients from each of our research clinics.</li> <li>These findings formed an objective basis for the determination of readiness of our research clinics to return to patient accrual.</li> </ul>	<p>Documentation</p> <ul style="list-style-type: none"> <li>Charts audited 8/6 - 8/20/2002. In follow up to the successful audit, we have instituted a graduated restart of our research program, with two research sites activated sequentially. Therefore, we have restarted patient accrual at our Northside research site as of Sept. 15, 2002 and re-activated 6 protocols with IRB approval. In October, our Stemmer research site underwent an audit and restarted based on a successful report. This site followed the same re-start plan as our Northside research site.</li> </ul>	Complete	N/A
Investigator and Staff Education	<ul style="list-style-type: none"> <li>Basic clinical research and GCP training identified as a need for the staff.</li> <li>Investigator training regarding human subject protection was identified as a need for the physicians and staff.</li> <li>Annual research staff education retreat</li> <li>Orientation of new research staff</li> </ul>	<ul style="list-style-type: none"> <li>Research training session titled "CRC Level I Training Workshop" was held on 6/5/02. The workshop was conducted by Jane Green, President of the Walter B. Morley Research Foundation. 20 staff members attended</li> <li>IRB Training session titled "Human Subjects Protections Training" held on 7/29/02. The course is CME approved and was taught by Shelia Moore, Director of the UAB IRB. The ½ day session was attended by 12 physicians and 22 staff members.</li> <li>GCS physicians interested in becoming investigators must have either attended the training session on 7/29/02 or complete an approved on-line course. To date, four additional investigators have completed the online certification.</li> <li>Only those physicians who have received appropriate certification will be listed on the 1572 and permitted to participate in clinical research.</li> <li>Research Staff Orientation SOP</li> </ul>	Complete	N/A

## Attachment 2

A phase II study of SGN-15 (cBR96-doxorubicin immunoconjugate) combined with docetaxel for the treatment of metastatic breast carcinoma

Year: 2003

Category: Antibodies

Abstract No: 696

Author(s): L. L. Hart, L. Nabell, M. Saleh, S. Sundaram, A. Mauer, J. Marshall, D. McCune, A. S. Sandler, A. P. Sing, C. Siegall; Florida Cancer Specialists, Fort Myers, FL; University of Alabama, Birmingham; Georgia Cancer Specialists, Atlanta; Sharp HealthCare, San Diego; University of Chicago, Chicago; Lombardi Cancer Center, Washington D.C.; Madigan Army Medical Center, Tacoma; Seattle Genetics, Inc., Bothell

Abstract: Prognosis of patients (pts) with metastatic breast carcinoma (BC) is poor with limited treatment options available. Consequently, there is a continued effort to develop new agents to improve the disease-free survival for these patients. SGN-15 is an antibody-drug conjugate (cBR96-Doxorubicin Immunoconjugate) that delivers doxorubicin to tumor tissues expressing the Lewis-y ( $Le^y$ ) antigen. Preclinical studies demonstrated significant enhancement of antitumor activity of SGN-15 when combined with a taxane agent. A phase II multicenter, open label study was conducted to evaluate the safety and efficacy of the combination of SGN-15 and docetaxel in the setting of metastatic BC. Patients received SGN-15 ( $175 \text{ mg/m}^2$ ) and docetaxel ( $30 \text{ mg/m}^2$ ) for 6 weekly infusions followed by a 2-week rest period (8-week course). Patients were evaluated for response after each treatment course and could receive a maximum of 6 courses. Eligibility criteria included documented metastatic BC,  $Le^y$  antigen expression, no more than two prior therapies for metastatic disease, and a life expectancy greater than 3 months. Twenty-seven of 30 pts were evaluable for response

(received at least one full course). Patient characteristics of evaluable pts: median age: 54 years old (range: 35-78), gender: 26 female and 1 male, and liver metastases: 10 pts. Five (1 PR, 4 MR) pts had an objective response by WHO criteria. One of these pts had a 70% reduction in metastatic liver lesions after the first course of therapy. Nine pts achieved SD after their first course of therapy. Toxicity associated with the SGN-15/docetaxel regimen was readily managed with conventional anti-emetic/diarrheal therapies. The majority of the Grade 3 toxicities were GI-related and self-limiting. Conclusion: The combination of SGN-15 and docetaxel is well tolerated with objective responses observed in the metastatic BC setting.

## Attachment 2

Phase 2 trial of ISIS 2503, an antisense inhibitor of h-ras, in combination with weekly paclitaxel in the treatment of patients with metastatic breast cancer.

Year: 2003

Category: Gene Therapy/Antisense Strategies

Abstract No: 829

Author(s): M. N. Saleh, D. Irwin, G. Burton, J. B. Hargis, C. Chitambar, C. M. Jones, C. L. Shapiro, J. T. Holmlund, F. A. Dorr; Georgia Cancer Specialists, Marietta, GA; Alta Bates Comprehensive Cancer Center, Berkeley, CA; Louisiana State University Health Sciences Center, Shreveport, LA; Kentuckiana Cancer Institute PLLC, Louisville, KY; Medical College of Wisconsin, Milwaukee, WI; C. Michael Jones, MD, PC, Germantown, TN; Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; Isis Pharmaceuticals, Inc., Carlsbad, CA

Abstract: ISIS 2503 is a 20-base antisense drug that specifically inhibits expression of H-ras mRNA and protein. In the MMTV-H-ras transgenic mouse model, ISIS 2503 demonstrated more than additive antitumor activity in combination with paclitaxel (Petit et al, Proc AACR 40:20, 1999, #136). We conducted a phase II trial of weekly paclitaxel, 80 mg/m<sup>2</sup>, in combination with ISIS 2503 at the recommended Phase 2 single-agent dose (6 mg/kg/day by 14-day continuous IV infusion repeated every 21 days). Eligibility: measurable metastatic breast cancer, no prior chemotherapy for metastatic disease. Prior adjuvant therapy was permitted, including prior taxanes if tumor progression was more than 6 months later. Treatment was continued for 12 weeks, and could continue until disease progression if toxicity was acceptable. Inpatient dose escalation of ISIS 2503 to 10 mg/kg/day, was permitted if toxicity permitted. Patients were assessed for response at 6-week intervals. Twenty-five female patients have been enrolled; PS 0/1/2, 11/12/1 (1 NA). Number of metastatic sites: 1 (12 pts), 2 (10 pts), 3(1 pt), (2 NA). Three patients had received adjuvant paclitaxel. Unaudited data show 123, 21-day treatment cycles administered (median 4, range 1-14). Six patients remain on treatment as of 12/12/02. Treatment has been well tolerated with no patient discontinuing treatment because of toxicity. Final dosing and treatment data are being collected. To date, response data are available for 17 patients: 8 PR (47%) and 4 SD (24%). This combination appears to have promising activity. Further data will be presented at the meeting.

Associated Presentation(s):

1. Phase 2 trial of ISIS 2503, an antisense inhibitor of h-ras, in combination with weekly paclitaxel in the treatment of patients with metastatic breast cancer.

Presenter: Mansoor Saleh (MD) Year: 2003

Session: Developmental Therapeutics - Molecular (Scientific Program)