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PRINCIPAL INVESTIGATOR: Adam Brufsky, MD, PhD

CONTRACTING ORGANIZATION: University of Pittsburgh,  
Pittsburgh, PA 15260

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b>  The University of Pittsburgh Cancer Institute, the Magee-Women's Hospital, the Hematology-Oncology Associates of the UPCI (HOA), the Pittsburgh Clinical Research Network, Inc. (PCRN), the Magee Womancare Breast Cancer Volunteer Program, and the Pittsburgh Branch of the National Association for the Advancement of Colored People (NAACP) are collaborating to form the Pittsburgh Breast Cancer Consortium (PBCC). The focus of this partnership is the rapid clinical development of new agents for the treatment of metastatic breast cancer (MBC). The PBCC will conduct innovative phase I and phase II clinical trials testing new approaches in the treatment of MBC. Accrual to these trials will derive from a consortium of Pittsburgh regional, community based oncology practices of the HOA in collaboration with the Magee-Women's Hospital/University of Pittsburgh Cancer Institute Comprehensive Breast Cancer Center (CBCC). The specific aims of this proposal are (1) to develop a breast cancer clinical trials infrastructure to allow the rapid phase I and phase II development of novel agents for the treatment of breast cancer with a strong emphasis on community-based practice involvement; and (2) to evaluate multiple agents, as well as combinations of agents, using this infrastructure.					
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Final report: Pittsburgh Breast Cancer Consortium:

Principal Investigator: Adam Brufsky, MD, PhD Introduction:

The University of Pittsburgh Cancer Institute, the Magee-Women's Hospital, the Hematology-Oncology Associates of the UPCI (HOA), the Pittsburgh Clinical Research Network, Inc. (PCRN), the Magee Womancare Breast Cancer Volunteer Program, and the Pittsburgh Branch of the National Association for the Advancement of Colored People (NAACP) are collaborating to form the Pittsburgh Breast Cancer Consortium (PBCC). The focus of this partnership is the rapid clinical development of new agents for the treatment of metastatic breast cancer (MBC). The PBCC will conduct innovative phase I and phase II clinical trials testing new approaches in the treatment of MBC. Accrual to these trials will derive from a consortium of Pittsburgh regional, community based oncology practices of the HOA in collaboration with the Magee-Women's Hospital/University of Pittsburgh Cancer Institute Comprehensive Breast Cancer Center (CBCC). The Consortium will be centered at the University of Pittsburgh Cancer Institute (UPCI), an NCI-designated Comprehensive Cancer Center. The UPCI, which has an outstanding clinical trials support infrastructure, will provide the template for development of central data management, coordination oversight, trials auditing, biostatistical support, pharmacokinetic analysis, and interaction with industrial partners. The PBCC will establish the mechanisms for the conduct of new studies, with a strong emphasis on community-based practice involvement. In addition, the PBCC will be overseen and advised by a central governing board for the Consortium, meeting monthly, composed of representatives of the UPCI, the HOA, the PCRN, the volunteer group, and the NAACP.

The specific aims of this proposal are (1) to develop a breast cancer clinical trials infrastructure to allow the rapid phase I and phase II development of novel agents for the treatment of breast cancer with a strong emphasis on community-based practice involvement; and (2) to evaluate multiple agents, as well as combinations of agents, using this infrastructure.

In this final report, we will detail how our objectives were met. The workstatement will be used as a template. To briefly summarize, we built the infrastructure of the PBCC and conducted clinical trials of novel agents and combinations of agents. As noted in the original proposal, priorities of industrial sponsors change, as do the availability of agents. While we did not conducted all of the proposed clinical trials, other trials were conducted in the PBCC.

Body:

Statement of Work:

Task 1: Develop the PBCC Infrastructure (Months 1-12)

- Recruit and train nurse-coordinators. This was done. Our governing committee decided that the best method of increasing community nurse coordinator support of PBCC clinical trials would be to buy time from existing community coordinators. The PBCC paid for three full time coordinators at the central site at Magee-Women's Hospital as well a 2/9 FTE of each of nine community coordinators. Each of the coordinators accrued 9-12 patients per year onto PBCC clinical trials.
- Recruit and train data managers. This has been done. There are currently two data managers supported by the PBCC worked at Magee-Women's Hospital.
- Educate community oncologists about the PBCC. Dr. Brufsky met quarterly with small groups (6-10) community oncologists to discuss PBCC trials and accrual goals. Physicians participating in the PBCC are received wall plaques announcing their participation.

Initiate PBCC governing board and set schedule of meetings. Our governing board met bimonthly.

- Initiate protocol processing through the PCRN and IRB. This has been done. Two trials from the Lilly Corporation have been initiated through PCRN (now renamed CRS) solely, and at least fifteen trials for MBC were been initiated in total.
- Test existing UPCI-Based Intranet and PCRN protocol Web server and develop PBCC Web site. The protocols were transferred to a novel clinical trials management application (CTMA) and were available across our network.

Task 2: Evaluation of Novel Compounds for the Treatment of Metastatic Breast Cancer (MBC) in the PBCC (Months 1-36) (As noted above, certain protocols were not initiated and were replaced during the first 18 months of this award)

- Phase I trial of 17-AAG (anti-HSP 90). This trial was completed, and results were presented at ASCO 2003. A manuscript was published (Ramanathan RK, Trump DL, Eiseman JL, Belani CP, Agarwala SA, Zuhoswki EG, Lan J, Potter DM, Ivy SP, **Brufsky A**, Wong M, Tutchko S, Egorin MJ. Phase I Pharmacokinetic-Pharmacodynamic Study of 17-(Allylamino)-17- Demethoxygeldanamycin (17AAG, NSC 330507), A Novel Inhibitor of Heat Shock Protein 90, in Patients With Refractory Advanced Cancers. Clin Cancer Res 2005; 11(9): 3385-91).

- Phase II trial of L-778.123 (farnesyltransferase inhibitor) in MBC. This trial was completed.

This work was never published, although the trial was completed as the compound did not show activity in MBC.

- Phase II trial of oral dexamethasone and calcitriol in MBC. Due to the departure of Dr. Trump from the UPCI, this trial was not performed.
- Phase II trial of MUC-1 peptide vaccination in women with MBC. This trial was not performed, due to difficulties in obtaining adequate titers of antibodies in the vaccinated women.
- Phase II trial of trastuzumab and tamoxifen in tamoxifen-resistant MBC. This trial was not performed due to lack of support from the sponsor.

Other trials performed by the PBCC:

Phase II trial of Carboplatin/Taxotere/Herceptin in MBC (Aventis). This trial was added to the PBCC in October 2000, and accrual thereafter was also rapid. This trial was completed in September 2002, and was presented at ASCO 2003. This data served as the basis for a large adjuvant trial of TCH (BCIRG 006) in early stage Her2 positive breast cancer, which became the standard of care for this entity.

A phase II. Multicenter. Randomized. Open-Label. Dose Comparison Study of Recombinant Human Chorionic Gonadotropin for Third Line Treatment of Metastatic Breast Cancer in Postmenopausal Women (Ares-Serono). We accrued 12 patients in the PBCC (12% of total) in this Multicenter trial. The trial is complete, and there was no activity of this compound. The data were not published by the company.

Phase II trial of Gemcitabine/Herceptin in MBC (Lilly). This multicenter trial was brought to the PBCC by the PCRN in March 2002. This trial is continuing, with the PBCC responsible for 18 of the 42 accruals nationally. This study was presented at ASCO ( Brufsky A, Orlando M, Fox K, Jame A, Katherine T, Franco S, Vincent H, Terry E, LaTrice H, Steven S, Allen M. *Phase II study of gemcitabine (Gem) and trastuzumab (T) combination therapy in patients (pts) with HER2-overexpressing metastatic breast cancer (MBC). First stage results. Br Ca Treat Res 2004 19:3047a.*)

Phase II Trial of Randomized Trial of Gemcitabine Plus Docetaxel vs. Docetaxel Plus Capecitabine in Metastatic Breast Cancer in 1<sup>st</sup> and 2<sup>nd</sup> Line Patients. This multicenter trial was also brought to the PBCC by the PCRN in March 2002. This trial is continuing, with the PBCC responsible for 13 of the 151 accruals nationally. This study resulted in a publication: (Seidman AD, **Brufsky A**, Ansari RH, Hart LL, Stein RS, Schwartzberg LS, Stewart JF, Russell CA, Chen SC, Fein LE, De La Cruz Vargas JA, Kim SB, Cavalheiro J, Zhao L, Gill JF, Obasagu Ck, Orlando M, Tai DF. Phase III trial of gemcitabine plus docetaxel versus capecitabine plus docetaxel with planned crossover to the alternate single agent in metastatic breast cancer. Ann Oncol 2011; 22(5): 1094-1101.)

A Phase II Clinical Trial of BMS-247550 (<NSC 710428), an Epothilone B Analog, in Patients with Breast Cancer (NCI). The PBCC initiated this trial in May

2003. This trial continues, with the PBCC accruing 8 of the 45 patients nationally. This study resulted in a publication: (Low JA, Wedam SB, Lee J, Berman A, **Brufsky A**, Yang X, Poruchynsky M, Steinberg S, Fojo T, Swain SM. A Phase II Clinical Trial of Ixabepilone (BMS-247550), an epothilone B analog, in metastatic and locally advanced breast cancer. J Clin Oncol 2005; 23(12): 2726-34.)

A Phase I Trial Evaluating the Safety of Intramuscular Injection of HER-2 Protein Autovac in Patients with Breast Cancer (Pharmexa). This trial was initiated in June 2003. The PBCC accrued 5 of the planned 11 patients. This trial is now complete, and results were presented at the European Breast Cancer Conference in Copenhagen in February 2004. The study was not published by the sponsor.

Phase I Dose-Escalation Study of Thrice Weekly Recombinant Human Interleukin-2 in Combination with Trastuzumab in Subjects with Her2/neu Positive Metastatic Breast Cancer (Chiron). This trial opened in January 2003. The PBCC accrued 4 of the 14 patients enrolled nationally. This trial was published (Mani A, Roda J, Young D, Caligiuri MA, Fleming GF, Kaufman P, **Brufsky A**, Ottman S, Carson WE 3<sup>rd</sup>, Shapiro CL. A phase II trial of trastuzumab in combination with low-dose interleukin-2 (IL-2) in patients (PTS) with metastatic breast cancer (MBC) who have previously failed trastuzumab. Breast Cancer Res Treat. 2009; 117(1):83-9.)

#### Task 3: Dissemination of Research Results (Months 18-36)

- Presentation of PBCC infrastructure results to USAMRMC-BCRP Symposium (Month 24).  
Dr. Brufsky will attend the DOD meeting in September 2004 and present results.
- Preparation and publication of results from clinical studies from months 1-24 <Months 24-36). This was performed as noted above.
- Visits to the PBCC for industry representatives, faculty, and community physicians (Months 18-36). This was also completed. Dr. Brufsky presented results of the PBCC infrastructure to the Pennsylvania Breast Cancer Coalition Annual Meeting in Harrisburg, PA on October 8, 2003. In addition, Dr. Brufsky gave a presentation to the Pittsburgh community on the PBCC in Greensburg, PA on October 23, 2003.

#### Key Research Accomplishments

- Recruited and trained 3 nurse coordinators and 2 data managers
- Assembled PBCC governing board
- Developed PBCC Web site

- Completed or assisted in completion of six phase I and phase II clinical trials in refractory, metastatic breast cancer with substantial community involvement and accrual

### **Reportable Outcomes**

Ramanathan RK, Trump DL, Eiseman JL, Belani CP, Agarwala SA, Zuhoswki EG, Lan J, Potter DM, Ivy SP, **Brufsky A**, Wong M, Tutchko S, Egorin MJ. Phase I Pharmacokinetic-Pharmacodynamic Study of 17-(Allylamino)-17-Demethoxygeldanamycin (17AAG, NSC 330507), A Novel Inhibitor of Heat Shock Protein 90, in Patients With Refractory Advanced Cancers. *Clin Cancer Res* 2005; 11(9): 3385-91.

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### **Conclusions:**

The PBCC has had a very successful several years in the rapid accrual to multiple phase I and phase II trials for refractory, metastatic breast cancer and provides an excellent example of a successful community-academic partnership.