CONQUER CANCER FOUNDATION
of the American Society of Clinical Oncology

The Campaign to Conquer Cancer

November 17, 2015

Hayley Dinerman
Executive Director
Triple Negative Breast Cancer Foundation
PO Box 204
Norwood, NJ 07648-0204

Dear Ms. Dinerman,

Earlier this year, CCF launched The Campaign to Conquer Cancer, an initiative that is inspiring doctors, survivors, researchers and our incredible supporters to come together to take down cancer. We are making progress toward achieving this goal every day and we are so appreciative that the Triple Negative Breast Cancer Foundation has joined us in this effort through its support of our Grants and Awards program.

Your generous gift has helped make possible the work of Dr. Karen Cadoo, a 2014 Conquer Cancer Foundation of ASCO Young Investigator Award recipient. I am very pleased to share with you Dr. Cadoo's final research update, which can be found on the following pages. We remain incredibly grateful for the opportunity you have provided Dr. Cadoo, whose potential to change the lives of those affected by cancer has grown exponentially thanks to your support.

Should you have any questions about Dr. Cadoo's work, please do not hesitate to reach out to Susan Sandler, our Associate Director of Foundation Giving. Susan may be reached by email at Susan.Sandler@Conquer.org or by phone at 571-483-1436.

Together with the support of the Triple Negative Breast Cancer Foundation and the work of Dr. Karen Cadoo, we will take down cancer.

Sincerely,

Nancy R. Daly, MS, MPH
Executive Director and
Chief Philanthropic Officer

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conquercancerfoundation.org
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Recipient: Karen Cadoo, MBBS (MBBCh or MBChB)
Grant: 2014 Conquer Cancer Foundation of ASCO Young Investigator Award
Institution: Memorial Sloan Kettering Cancer Center
Project Title: Targeting Heat shock protein 90 (HSP90) in the management of advanced human epidermal growth factor receptor-2 positive (HER2+) and triple negative breast cancers.
Grant Term: October 01, 2014 – September 30, 2015

Lay Summary:
This project is looking to find better treatment for advanced HER2 positive and triple negative breast cancers. Heat shock protein 90 (HSP90) is found in both normal and cancer cells but is more active in cancer cells. HSP90 sends messages which are important to the cancer cells. Blocking these messages with an HSP90 inhibitor drug can help to kill the cancer cells. We want to test an HSP90 inhibitor with chemotherapy for patients who have triple negative breast cancer and the combination with anti-HER2 therapy for patients who have HER2 positive breast cancer. Based on previous work we believe that these will be good treatments.

We are excited about this trial and we are working on an earlier step which has told us the correct dose of the HSP90 inhibitor when it is given with chemotherapy. We also saw that the treatment was safe and most people felt well with it. Encouragingly, half the patients who had the treatment benefitted. We are encouraged the progress we have made so far however we have expanded the earlier part of the trial so we have not yet got to the part outlined in this project. We remain committed and we will move to the next part and completion of the project as soon as possible.

Given our enthusiasm for this type of therapy we are also working with another company to develop a different HSP90 inhibitor. There is also excellent laboratory and early trial information which shows that the drug works in triple negative breast cancer. Again, we think it will work better when given with chemotherapy, which makes the cancer more vulnerable to HSP90 inhibitor. We have completed a protocol to look at this HSP90 inhibitor with chemotherapy for patients with triple negative breast cancer and we are also working to get this trial open.

At the same time we are collecting tumor tissue from patients with breast cancers at the time of their surgery. This allows us to look at changes in HSP90 in the tumor tissue with HSP90 inhibitor therapy. This helps us to understand why some tumors respond well to treatment but others do not. It also will help us understand whether tumors that do not respond well to chemotherapy are better treated with the addition of this targeted agent. We hope that this will guide our work in developing better treatments for triple negative breast cancer.

I am also working on a project looking at the possibility for a blood sample to function as a “liquid biopsy” in breast cancer. We are looking at the amount of a specific type of DNA in blood samples from patients with all types of metastatic breast cancer, including patients

with triple negative breast cancer. We are excited because we have shown that the amount of this DNA can predict how much disease a patient has, whether they are benefiting from their treatment and how well they do. We think this early data is very promising and we hope that in the future this simple blood test will allow us to better understand how aggressive a patients metastatic breast cancer is, how fast it will grow, what treatment it will respond to, and when a when a treatment change is needed.

We are excited about this body of work and we continue to strive to make things better for patients with breast cancer. I am grateful to the Conquer Cancer Foundations Young Investigator Award and the Triple Negative Breast Cancer Foundation for the support that has made my participation in these projects feasible.

Scientific Summary:
The primary aim of this project is to assess the combination of HSP90 inhibition with chemotherapy for patients with triple negative and human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer (MBC). While there have been remarkable advances in therapy for patients with HER2+ MBC, unfortunately not all patients respond to these therapies and for the majority of those who do benefit this benefit is transient and subsequent disease progression is almost inevitable. In the setting of triple negative breast cancer (TNBC) there are still no approved targeted agents, cytotoxic therapy remains the only available standard of care and management of this disease remains challenging. This significant unmet need urgently warrants new and more effective therapies. Given the excellent preclinical and clinical data, we are excited about the potential of HSP90 inhibition to enhance the effect of chemotherapy in these disease subtypes and we are committed to the development of this class of drugs. We acknowledge the challenges of earlier generation of HSP90 inhibitors, whereby toxicity limited dosing, likely limiting their potential for effect. We are enthusiastic however about the later generation inhibitors which are more potent and associated with a more favorable toxicity profile, facilitating optimal dose delivery. This project plans to assess the combination of HSP90 inhibition with paclitaxel in TNBC and the combination with trastuzumab in HER2+ MBC. We plan pre and post therapy biopsies to assess target inhibition and identify potential biomarkers response and resistance. This data will be crucial for the future development of this therapeutic approach - if we can appropriate identify in advance tumors which will respond we can ensure that only patients who are likely to benefit will receive this therapy.

We remain excited about this project and the potential for benefit from this approach in these challenging therapeutic settings. We continue to work on our phase I study of ganetespib with paclitaxel and HER2 targeting agents in HER2+ MBC. This study is providing important safety and feasibility data to facilitate our phase2 study. We have defined the recommended phase two dose of ganetespib in combination with paclitaxel and trastuzumab as 150mg/m2. This combination was safe and well tolerated, with no grade 3/4 adverse events related to ganetespib and the most common reported adverse events are diarrhea, fatigue, anemia and rash. Promising in a heavily pretreated group of patients with HER2+ MBC (median 3 prior lines of therapy in the metastatic setting including pertuzumab and T-DM1 in the majority of patients), we have shown a clinical

benefit rate (complete response+ partial response+stable disease >24 weeks) of 50%. We will present this data at San Antonio Breast Cancer Symposium in Dec 2015.

Due to an unforeseen need to expand the phase I study, to enroll additional patients to assess this strategy in combination with pertuzumab, there has been a delay in moving forward with our phase 2 trial, we anticipate completion of this expanded portion by the end of this calendar year. In addition we were working in collaboration with New York University Cancer Institute (NYU). However due to a change in personnel whereby Dr. Komal Jahveri, one of my co-mentors on this project, has relocated to Memorial Sloan Kettering Cancer Center (MSKCC), the study has been closed at NYU and the IND (investigational new drug) application has been transferred to MSKCC. The phase two study will now be run as a single site study at MSKCC.

We are excited about the progress we have made and remain committed (as does our Sponsor) to this research and we will move to the phase two portion and completion of the project as soon as it is feasible. Given our enthusiasm for HSP90 inhibition and the huge unmet need in TNBC we have also engaged in a partnership with another company to develop their HSP90 inhibitor, PUH71, with taxane chemotherapy patients with triple negative MBC. There is also excellent laboratory data demonstrating effect of their drug in this combination. PUH71 is in the early phase of development, a dose finding phase I study was led by Dr. John Gerecitano with my mentor, Dr. Shanu Modi and was reported at the A.S.C.O. Annual Meeting 2015. This demonstrated the drug was well tolerated and clinical benefit was demonstrated in a number of diseases including breast cancer. Specifically a patient with TNBC who had received 4 prior lines of therapy, achieved disease shrinkage with 300mg/m2 single agent PUH71 which has been defined as the maximum tolerated dose. Very excitingly, PUH71 can be labeled with 124I without altering its biochemical properties which paves the way for 124I-PUH71 PET imaging providing a potential surrogate marker of intratumoral pharmacokinetics. We believe the greatest potential for HSP90 inhibition comes in combination with chemotherapy which provides stress to the tumor environment with greater dependence on HSP90 chaperoning and we are enthusiastic about the potential for this drug in combination with chemotherapy. We have therefore completed a protocol to explore the potential of PUH71 with paclitaxel in a phase I study for patients with TNBC, the next step is to work toward study opening.

In parallel with these efforts we have been working to better understand the mechanisms of response and resistance to HSP90 inhibitors in human breast cancers ex-vivo. We hope that this data will help guide us in the ongoing development of these agents in breast cancer. We are exploring the effects of HSP90 inhibitors on the growth, viability and induction of apoptosis in different types of breast cancer ex vivo. Our hypothesis, based on the results in cultured cancer cell lines is that increased expression of HSP90 and pAKT within the tumor are associated with response to HSP90 inhibition. In addition we propose that there will be a corresponding decline in HSP90 client proteins in tumors that are responding, e.g. HER2 and Bcl-xl. Although analysis of existing breast cancer cell lines has furthered our understanding of the disease and been hypothesis generating, we believe that the behavior or cancer cells in 2-D culture differs significantly from those propagated in murine models. Specifically, the ability of cancers to grow and metastasize in mice is greater if they have been maintained in mice rather than in 2-D culture. We are

specifically generating models of the molecular subtypes of breast cancer (luminal A, luminal B, HER2 enriched, basal like (triple negative usually) breast cancer) to better understand the natural history of disease and potential for drug response in each subtype. In addition we are exploring if circulating exosomes and cell free DNA in peripheral blood can correlate with histological, biochemical and pharmacological features in breast cancer tumor cells. We are correlating these features with response to HSP90 inhibition and exploring if this can be demonstrated via peripheral blood sample.

In addition, I am also working on a separate project assessing the role of circulating cell free DNA to function as a "liquid biopsy" in breast cancer. We are assessing the quantity of circulating cell free DNA in blood samples from patients with all subtypes of metastatic breast cancer, including patients with TNBC. We have demonstrated (paper in progress) that the quantity of cell free DNA is prognostic, reflects disease burden and correlates with response to current treatment in metastatic TNBC. This is an exciting development in the arena in of circulating DNA and TNBC – to date a number of investigators have focused on the tracking of tumor specific alterations in plasma samples from patients with breast cancer and previous work in TNBC, using that approach of following a tumor specific mutation, failed to demonstrate a correlation between the circulating tumor DNA and progression free and overall survival. Therefore we are particularly encouraged by our findings which have demonstrated correlation between the total quantity of circulating DNA and patient outcomes.
We hope that in the future this simple blood test will allow us to better understand how aggressive a patients metastatic breast cancer is, how fast it will grow, what treatment it will respond to and when a when a treatment change is needed.

We are excited about this body of work and we continue to strive to make things better for all patients with breast cancer. I am grateful to the Conquer Cancer Foundations Young Investigator Award and the Triple Negative Breast Cancer Foundation for the salary support that has made my participation in
these projects feasible.

Publications:

Title: Advances in molecular and clinical subtyping of breast cancer and their implications for therapy.
Year: 2013
Type: Review Article
Status: Published
URL: http://www.ncbi.nlm.nih.gov/pubmed/24012401
Description: This article reviews the intrinsic classification system and the clinically defined subtypes of breast cancer. We review the molecular drivers of each subtype and discuss implications for prognosis, clinical management, and future directions.

Title: Management of unusual histological types of breast cancer.
Year: 2012
Type: Review Article

Status: Published
URL: http://www.ncbi.nlm.nih.gov/pubmed/22826373
Description: This review addresses breast cancers of unusual histological subtype with an approximate incidence =1%. Each tumor subtype described represents a small but real cohort of patients with breast cancer and the available literature is amalagamated in this review.

Title: Palbociclib: an evidence-based review of its potential in the treatment of breast cancer.
Year: 2014
Type: Review Article
Status: Published
URL: http://www.ncbi.nlm.nih.gov/pubmed/25177151
The cell-cycle regulatory process is critical in oncogenesis and therapeutic resistance.
Description: Palbociclib is a potent inhibitor of CDK4 and -6, we describe the preclinical and clinical data relating to the activity of palbociclib in breast cancer and the plans for the future development of this agent.

Title: Biological subtypes of breast cancer: current concepts and implications for recurrence patterns
Year: 2013
Type: Review Article
Status: Published
Description: We discuss the three broad phenotypes of breast cancer used in clinical practice; ER/PR+, HER2+ and triple negative breast cancer (characterized by lack of expression of ER/PR/HER2) and the influence of these subtypes on the potential for breast cancer recurrence and patterns of disease spread.

Career Progress:
Since my YIA application I have been promoted to Assistant Attending in Medical Oncology at Memorial Sloan Kettering Cancer Center, treating women with breast and gynecologic cancers.

San Antonio Breast Cancer Symposium 2014 poster presentation:

A phase I clinical trial of ganetespib (heat shock protein 90 inhibitor) in combination with paclitaxel and trastuzumab in human epidermal growth factor receptor-2 positive (HER2+) metastatic breast cancer

Authors: Jhaveri K, **Cadoo K**, Chandarlapaty S, Teplinsky E, Speyer J, D' Andrea G, Patil S, Haque S, Friedman K, Heese S, Neville D, Esteva F, Hudis C, Modi S

The European Cancer Congress 2015 poster presentation:

Re-treating with carboplatin and paclitaxel as first line therapy for recurrent endometrial cancer in patients who have previously received this regimen in the adjuvant setting

K. Cadoo, D. Halpenny, M. Phillips, C. Aghajanian

San Antonio Breast Cancer Symposium 2015 accepted for poster presentations:

a. Phase 2 study of dose-dense doxorubicin and cyclophosphamide followed by eribulin mesylate with or without prophylactic growth factor for adjuvant treatment of early-stage breast cancer

Karen Cadoo, MD; Peter A. Kaufman, MD; Clifford Hudis, MD; Cassandra Chang, BS; Erhan Berrak, MD; James Song, PhD; Andrew D. Seidman, MD; Tiffany A. Traina, MD

b. A Phase I trial of Ganetespib (Heat shock protein 90 inhibitor) in combination with Paclitaxel and Trastuzumab in Patients with Human Epidermal Growth Factor Receptor-2 positive (HER2+) Metastatic Breast Cancer (MBC)

Komal Jhaveri, Eleonora Teplinsky, Sarat Chandarlapaty, David Solit, **Karen Cadoo**, James Speyer, Gabriella D'Andrea, Sylvia Adams, Sujata Patil, Sofia Haque, Kent Friedman, Deirdre Neville, Francisco Esteva, Clifford Hudis, Shanu Modi

Video Abstract: Palbociclib: an evidence-based review of its potential in the treatment of breast Cancer: https://www.dovepress.com/palbociclib-an-evidence-based-review-of-its-potential-in-thetreatment-peer-reviewed-article-BCTT