Statement of Work

Title: Risks of Long-term Adverse Events in Breast Cancer Patients Treated with Adjuvant Chemotherapy

Background:
Breast cancer mortality rates have declined over the past 20 years and although much of the improvements in mortality have been attributed to early diagnosis and adjuvant treatment of early stage breast cancer, these treatment regimens are associated with substantial short-term toxicity and risk of long-term adverse effects, such as secondary malignancies, neuropathy, cognitive impairment, and cardiotoxicity. Until recently, women with breast cancer have received adjuvant chemotherapy based on clinical recurrence risk classification using qualitative tumor characteristics, such as size, type and grade, receptor status, and histology, although increasingly gene expression profiling is being used to direct adjuvant therapy choices. Nevertheless, many women will still receive adjuvant chemotherapy that will have only a modest effect on disease-free and overall survival. These patients may receive limited benefit from chemotherapy and an improved understanding of these long-term adverse risks of treatment could help to inform clinical decision-making about adjuvant chemotherapy (i.e., women with low risk of recurrence could avoid potential toxicity and morbidity of adjuvant chemotherapy). Even when use of chemotherapy is indicated, patients are seldom informed about the specific risks for long-term and late effects, which could potentially inform treatment decision-making. Yet, no systematic reviews or risk appraisal have addressed this question.

Long-term and late adverse effects (e.g., leukemia, congestive heart failure, neuropathy, cognitive dysfunction, infertility) of chemotherapy are widely acknowledged, but their risks are not explicitly considered in currently available risk prediction models. This limits the ability of clinicians and patients to weigh the potential harms versus benefits of adjuvant chemotherapy in treatment decision making. Randomized trials of adjuvant chemotherapy have predominantly focused on evaluating the reduction in cancer recurrence and on treatment-associated short-term adverse effects. Less attention has been given to long-term adverse effects of these cytotoxic drugs, which may have significant negative impacts on health and QOL for breast cancer survivors long after their treatment ends.

The aim of this statement of work (SOW) is to estimate the rates of long-term adverse effects of commonly used adjuvant chemotherapy regimens for breast cancer by conducting a systematic review of the literature and by analyzing data collected from a clinical trial of over 5,000 patients with node-positive breast cancer. This project is critical not only to define what we currently know about treatment harms, but perhaps more importantly, to identify gaps in existing knowledge that will guide future research. This project will help inform NCI in the planning and prioritizing future research initiatives developing patient-level risk prediction model to assist patients and clinicians in making informed decisions about the benefits and risks of adjuvant chemotherapy for early stage breast cancer.

Contractor Requirements:

The Contractor is to provide adequate equipment, supplies, facilities, and scientific materials necessary for carrying out the requirements of this SOW. The Contractor shall work on several key tasks, including but not limited to the following:

1. Evaluate the literature on long-term adverse events following treatment with adjuvant chemotherapy in breast cancer patients draft a manuscript reporting the findings. Specifically, information from published literature on chemotherapy agents commonly used in the U.S. for breast cancer adjuvant therapy (i.e., anthracyclines, cyclophosphamide, taxanes, and trastuzumab) and the risk of chemotherapy-related adverse events (i.e., cardiac toxicity, ovarian failure, secondary malignancies,

neurotoxicity, and cognitive dysfunction) will be systematically reviewed and described. The completed manuscript will be submitted to a peer-reviewed journal. (Task 1)

2. Conduct secondary analyses using data from the NSABP B-30 trial to estimate the frequency and impact of adverse events resulting from adjuvant chemotherapy and draft a manuscript reporting the findings. Data from the NSABP B-30 trial, which enrolled over 5,000 node-positive breast cancer patients who were randomized to three different treatment arms containing an anthracycline and a taxane, will be analyzed by the contractor and will supplement finding from the systematic review (task 2).

Government Responsibilities

The Contracting Officers Representative (COR) will review draft deliverables and provide the contractor with timely comments.

Reporting Requirements and Deliverables

The Contractor shall deliver the following items:

1. Final report in the form of a manuscript detailing the literature on long-term adverse events following treatment with adjuvant chemotherapy for breast cancer. Due date: March 1, 2015
2. Final report in the form of a manuscript describing the data from the NSABP B-30 trial. Due date: March 1, 2015

All deliverables should be submitted electronically and hard copies submitted upon request.

The writing of the manuscripts will be led by the contractor and will be co-authored by the NCI investigators. It will include all conventional subsections (i.e., Introduction/Background, Methods, Results, Discussion). Authorship credit for the manuscripts will be determined based on the degree of involvement in the development of the final manuscripts by the contractor and NCI investigators.

Payment

Two payments shall be made after the completion and acceptance by the Government of each deliverable and submission of an invoice.

Period of Performance:

Performance shall be from April 1, 2014 - March 31, 2015.

Inspection and Acceptance Criteria:

The Contractor's work products will be subject to the review and approval of the COR. Any deficiencies identified must be corrected prior to final approval. The COR will complete review of the work within 1 month. If no comments or request for revisions are provided to the contractor within 1 month, the deliverables will be considered acceptable.