**DF/HCC Protocol #:** 19-031

**TITLE: 'ADVANCE' (A Pilot Trial) ADjuVANt Chemotherapy in the Elderly: Developing and Evaluating Lower-Toxicity Chemotherapy Options for Older Patients with Breast Cancer**

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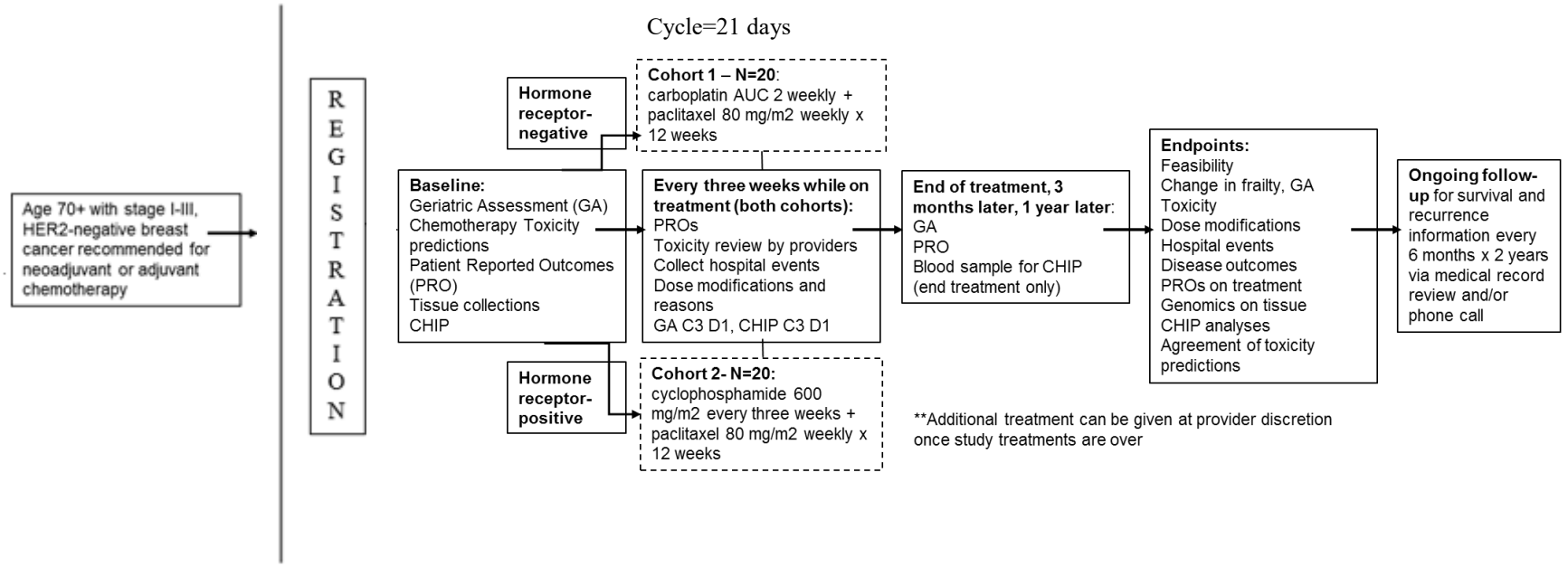
**Other Agent(s):** carboplatin, paclitaxel, cyclophosphamide (all commercial supply)

**Study Exempt from IND Requirements per 21 CFR 312.2(b).**

**Protocol Type / Version # / Version Date:** Original / Version 2 / March 20, 2019

## SCHEMA




N= 40

Additional abbreviations: CHIP= clonal hematopoiesis of indeterminate potential (CHIP)

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# 1. OBJECTIVES

## 1.1 Study Design

In this pilot study, we will evaluate the feasibility of two chemotherapy options, namely (1) carboplatin-paclitaxel and (2) cyclophosphamide-paclitaxel, for patients age ≥70 with breast cancer who are recommended by their providers to receive either neoadjuvant *or* adjuvant chemotherapy in the setting of triple negative and hormone receptor-positive disease, respectively. Forty total patients from DF/HCC and external sites will participate in this pilot. We will include a rich set of secondary outcomes and correlative studies, including toxicity assessment, patient experience, genomic profiling of tumors, and shorter-term breast cancer outcomes, among other exploratory endpoints. We will also examine the agreement of toxicity prediction by physician assessment, existing chemotherapy prediction models, and actual toxicity experienced. This trial will provide preliminary feasibility information in anticipation of a larger dedicated trial for older patients with breast cancer, a subgroup of patients in *urgent* need of prospective evidence to guide their care. This protocol is funded by an Alliance Cancer Control Program Pilot Award.

## 1.2 Primary Objectives

Primary Objective: Examine feasibility for each cohort, with feasibility defined as ≥80% of patients receiving ≥80% of intended therapy (including up to 2 dose changes for toxicity allowed).[1,2] In other words, participants in each cohort should receive ≥10 weeks of scheduled therapy that includes up to two dose reductions and/or treatment delays (i.e. up to 2 holds/reductions in total over at least 10 weeks of therapy, including one dose change for one agent or two dose changes/delays for one agent).

## 1.3 Secondary Objectives

Secondary Objectives (all exploratory):

- Examine changes in geriatric assessment/functional status over time for each cohort separately
- Describe the toxicities experienced by patients for each cohort using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (once every three weeks for 4 cycles)
- Examine patient-reported outcomes using the NCI PRO-CTCAE system's symptom reporting system at each treatment visit (once every three weeks for 4 cycles)
- Examine agreement between patient reported and provider reported CTCAEs
- Explore the differences in toxicities, severity of toxicities, and overall tolerance of each regimen
- Describe any dose modifications, treatment omissions, hospitalizations, emergency room evaluations, and early treatment cessation (and the reasons for these events) while on study treatment in each cohort
- Explore tumor genomics and tumor microenvironment on archived tissue samples obtained at baseline from surgery (adjuvant patients on each cohort)

- Examine tumor genomics and tumor microenvironment on paired archived biopsy and surgical samples from those having pre-operative therapy (neoadjuvant patients on each cohort)
- Compare the toxicity predictions based on provider assessment at baseline, a toxicity prediction model at start of therapy[3] and how these predictions correlate with actual grade 3 and higher toxicities experienced
- Examine blood for clonal hematopoiesis of indeterminate potential (CHIP) and associations of CHIP results with survival outcomes, breast cancer outcomes, and toxicity events, particularly hematologic toxicity events
- Examine invasive disease free survival, pathological response rates (for those receiving chemotherapy in the pre-operative setting), overall survival, cause of death when available, breast cancer-specific survival, sites of recurrence using medical record information or phone contact with patients, their proxies, or their treatment team with regard to recurrence)
- Explore toxicity at one year after completion of therapy on study (and collect all other treatments patients received for their cancers)
- Examine whether providers found the summary information provided from the baseline and end of treatment Geriatric Assessment helpful

## 2. BACKGROUND

### 2.1 Study Disease(s) and Additional Background

Older Women with Breast Cancer
The U.S. incidence of breast cancer among older women is expected to rise by 50% in the coming decades.[4] Although older patients with breast cancer often have favorable tumor subtypes[5] and present with early stages of disease[6,7] with significant competing causes of death,[8-10] breast cancer-specific outcomes for older patients are often worse than those seen in younger women.[7,8,11-13] Further, compared with younger patients, improvements in breast cancer survival over time have occurred at a slower rate for women aged ≥75.[13] In a recent study using Surveillance, Epidemiology, and End Results (SEER) registry data during 2000-2012, we observed worse breast cancer-specific deaths for every stage and breast cancer subtype for older patients, including those with both hormone receptor-positive and triple negative disease.[14] The reasons for worse outcomes in older patients are multifactorial and potentially related to under-treatment,[15-20] treatment-related toxicity, poor adherence to hormonal therapy,[21,22] and variable disease biology and genomics, although data on the genomic and biologic features in older women are sparse.[11,12,23] However, the available data demonstrating under-treatment, poor adherence to hormonal therapy, and frequent receipt of non-guideline therapy for older women suggest that suboptimal adjuvant treatment largely contributes to poor outcomes in women.

Potential Indications for Chemotherapy in the Older Patient
Although the vast majority of breast cancers in those aged ≥70 are hormone receptor-positive, approximately 10% are triple negative,[5] representing a substantial minority of cases (≅7,000 annually).[14] Older patients with all breast cancer subtypes are more likely to receive non-standard adjuvant care,[15,18] and although this may be appropriate in some cases where hormonal therapy is sufficient or toxicity or comorbidity concerns with chemotherapy are paramount, older

patients are significantly under-treated. Further, in the setting of triple negative disease in particular, older patients do not have an 'easy' therapeutic option such as hormonal therapy, and often don't receive systemic therapy, likely leading to worse outcomes. Development of a therapeutic regimen that is tolerable and efficacious for a subgroup of patients who may benefit from chemotherapy could have a substantial impact on disease outcomes. On CALGB 49907,[24] patients aged ≥65 with breast cancer were randomized to standard chemotherapy with AC or CMF vs. capecitabine in attempts to develop a lower toxicity adjuvant treatment option for patients. Over 600 patients enrolled to this study, exhibiting the national support and feasibility of conducting chemotherapy-based dedicated trials for older patients with breast cancer.

In this pilot study, we will administer neoadjuvant or adjuvant weekly chemotherapy in two simultaneously-enrolled cohorts of 20 patients each for patients age ≥70 years. In cohort 1, we will administer weekly carboplatin-paclitaxel for 12 weeks to those with triple negative (TN) breast cancer, a regimen we have modified from other neo/adjuvant breast cancer studies, including CALGB 40603. In cohort 2, we will administer every-three-week cyclophosphamide with weekly paclitaxel for 12 weeks to those with hormone receptor-positive disease, a regimen adapted from traditional docetaxel-cyclophosphamide (TC),[25] with the use of weekly paclitaxel (in place of every three weekly docetaxel) in our study to minimize toxicity.[26] In both cohorts, we will avoid anthracyclines, agents which are known to be associated with higher risk for cardiotoxicity and myelodysplasia/leukemia in older patients.[27-29]

Lack of Prospective Data for Older Patients with Breast Cancer
Accrual of older patients to cancer clinical trials remains challenging. Although older patients have been shown to enroll on research protocols as frequently as younger patients if a clinical trial is offered,[30] multiple barriers to accrual have been identified, including comorbidity, physician/patient preferences, concerns about losing continuity with primary oncologists, distance and time considerations, and age itself.[30-42] Thus far, specific efforts to improve enrollment of under-represented sub-groups to clinical trials have included educational initiatives,[43] enhanced consenting,[44-47] policy recommendations,[48-50] and a limited number of trials dedicated to older patients.[24,51,52] Despite these efforts and the fact that the majority of cancers occur in older adults, the accrual of older U.S. patients across cancer types has remained stagnant: approximately 25% of all trial participants for National Cancer Institute trials during 2000-2011 were age ≥65 years, and 10% were age ≥75.[49,53] Further, in a recent analysis of breast cancer-specific Alliance clinical trials,[54] we observed that the proportion of older breast cancer enrollees did not meaningfully improve during 1985-2012. Our pilot study directly addresses accrual issues for older patients by dedicating this pilot study to this patient subgroup, with an anticipated, larger dedicated adjuvant trial for older patients to follow in the future.

## 2.2 Other Agent(s)

In this pilot, pragmatic study, we will be using all commercially available chemotherapy agents commonly-used in the neo/adjuvant breast cancer setting. All agents will be administered per routine care and billed to commercial insurance. In cohort 1 (triple negative), we will administer carboplatin and paclitaxel. In cohort 2 (hormone receptor positive, HER2-negative), we will administer cyclophosphamide and paclitaxel.

Carboplatin and paclitaxel in triple negative (TN) disease:
In breast cancer, neo/adjuvant carboplatin and paclitaxel have been examined in clinical trials primarily when combined with other agents, such as anthracycline-based on alkylating-based therapies such as the case in GeparSixto trial,[55] CALGB 40603[56] and the GEICAM.2006-003 study.[57] There are also some data in the metastatic breast cancer setting with this combination, demonstrating activity and tolerability.[58] Further, multiple studies have evaluated this regimen in older adults with lung cancer with established dosing for this combination,[59-61] though neo/adjuvant chemotherapy protocols with carboplatin-paclitaxel alone in breast cancer have not been evaluated rigorously. In one study which included 120 patients with locally advanced breast cancer of any subtype, where patients were assigned to receive paclitaxel or nab-paclitaxel with carboplatin (with trastuzumab when HER2+), 80% of tumors had some degree of response. There are no details provided for the age of study participants beyond reporting a cut-off of +/- 45 years of age, but the grade 3 and higher toxicity rate was relatively low, with neutropenia as the main grade 3-4 toxicity for those receiving paclitaxel-carboplatin.[62] One additional relevant study[63] examined the use of neoadjuvant carboplatin and docetaxel in those with TN disease, demonstrating pathological complete response rates comparable to those reported for patients receiving carboplatin in addition to anthracycline-taxane-based regimens. However, the median age was 51 years on this trial and 28% of patients experienced a grade 3 or 4 toxicity, limiting its use in an older group of patients and further suggested that an alternative schedule may be appealing for this patient subset. Although no study has directly compared the efficacy and toxicity of q3 week vs. weekly carboplatin or paclitaxel specifically, once per week dosing is a well-established method of administration and is felt to likely cause less hematologic toxicities with more 'titratable' dosing. This regimen is very appealing for administration in the older patient with TN disease and is often used instead of q3 week therapy to mitigate toxicity, though it has not been studied for this subgroup specifically.

Cyclophosphamide and paclitaxel ('modified TC')
The adjuvant 'TC' regimen with docetaxel as the taxane is a well-established adjuvant regimen[25] in breast cancer and is used often by U.S. oncologists and in older patients.[64] In addition, a relatively large neoadjuvant study administered docetaxel and carboplatin to patients with triple negative disease, showing high pathological CR and near-pathological CR rates but with 28% of patients experiencing a grade 3-4 toxicity event.[63] The taxane-carboplatin is appealing, though there is consensus in the oncology community that paclitaxel is likely better tolerated than docetaxel, making it a more appealing treatment to pair with cyclophosphamide, particularly in the older patient. Although neo/adjuvant evaluations of our 'modified TC' have not been conducted, paclitaxel and cyclophosphamide are a part of the standard recommended chemotherapy backbone of AC-T and have been evaluated as sequential therapy in CALGB 9741 with well-established tolerability and efficacy.[65] Further, our modified TC regimen has been evaluated in the metastatic setting and was found to be efficacious and tolerable, with a planned regimen of weekly paclitaxel 80 mg/m2 and cyclophosphamide 600 mg/m2 every three weeks x 4 cycles for a total of 12 weeks in our study.[66] Other small studies have also examined alternative taxane-cyclophosphamide regimens demonstrating tolerability and preliminary efficacy, primarily in the metastatic setting.[67-70] This regimen is appealing and is planned for patients on this cohort with hormone receptor-positive, HER2-negative cancers.

## 2.3 Rationale and Significance

This study directly addresses gaps in knowledge and will obtain pilot, prospective data on the utility and feasibility of two potential treatment options for older patients who are expected to significantly benefit from adjuvant chemotherapy. This trial is pragmatic in design and will model standard care practices with administration of commercially-available regimens without mandated dose adjustments or dose holds (leaving management up to the treating provider). This study will provide crucial preliminary data to support the design of a larger study, facilitating the design of prospective clinical trials in populations at higher risk for poor outcomes and under-representation in essentially all clinical trials to date. There is significant momentum on a national level to increase clinical trial participation for older adults with cancer, with recent symposia, policy statements, and working groups on this topic conducted by the FDA, NIH/NCI, and ASCO. The New York Times even wrote a piece about this issue on April 13, 2018, entitled, "The Clinical Trial is Open. The Elderly Need Not Apply."[71] This pilot is in line with a national agenda to increase the evidence base for this group of patients and will set up the study team to develop a timely and relevant, larger scale clinical trial.

## 2.4 Correlative Studies Background

### 2.4.1 Geriatric Assessment (GA)

In recent years, a greater emphasis has been put on functional age rather than chronological age given the vast heterogeneity of medical comorbidity and functional status for any given age. The geriatric assessment was designed with this in mind and identifies older adults who have diminished life expectancy and/or are at risk for hospitalization and functional decline. [72,73] Data have also shown the value of a geriatric assessment in weighing risks and benefits for cancer treatment in older patients, [74-76] although a traditional assessment is time consuming and might be challenging to incorporate broadly. To overcome this, a brief assessment was designed by Dr. Hurria and colleagues which included validated and reliable measures which are primarily self-administered and require minimal resources and time by providers.[77] This assessment was tested for feasibility, and in the 93 patients enrolled on a CALGB trial, the median time to complete the geriatric assessment tool was 22 minutes and 87% of patients completed their portion without assistance. Patients were generally satisfied with questionnaire length and reported no difficult questions. All providers completed their portion of the assessment as well. This assessment is now incorporated more widely across protocols in older patients with cancer and will be administered to participants longitudinally while on study (see time points in Study Calendar).

Information gathered from the GA has been shown to help predict toxicity in patients receiving chemotherapy[3] and offers valuable information on physical function, nutrition, comorbidity, social support, mood, etc. Obtaining this information over time will provide reach information about the impact chemotherapy has on each patient.

See Table 1 below and Appendix A for patient component, Appendix B for healthcare professional component. In a short provider survey (emailed to the treating provider after a summary of the GA is provided (Appendix L) from the baseline and end of treatment GAs), we will ask providers whether they found this information useful (Appendix M)

| Table 1. Components of Geriatric Assessment | |
|---|---|
| **Domain assessed** | **Tests to be administered (Appendices A and B)** |
| **Functional status** | • OARS MFAQ (IADL) [78,79]<br>• MOS Physical Functioning [80]<br>• Karnofsky Performance Status Rated Healthcare Professional [81]*<br>• Karnofsky Performance Status Rated by Patient [82]<br>• Timed "Up and Go" [83]*<br>• Number of falls in last 6 months |
| **Comorbidity** | OARS Physical Health Section |
| **Medication Review** | Patient reports number and names of medications, herbs, or vitamins |
| **Cognition** | Blessed Orientation-Memory-Concentration Test* |
| **Psychological Status** | Mental Health Inventory (MHI)-17 |
| **Nutritional Status** | • % Unintentional Weight Loss in last 6 months<br>• Body Mass Index |
| **Social Functioning and Social Support** | • MOS Social Activity Limitation Scale<br>• MOS Social Support Survey Subscale |
| Abbreviations: OARS, Older American Resources and Services; MFAQ, Multidimensional Functional Assessment Questionnaire; IADL, Instrumental Activities of Daily Living ; MOS, Medical Outcomes Study; *Items completed by the healthcare professional- see Appendix B (Karnofsky performance status, Timed Up and Go, and Blessed Orientation-Memory-Concentration test). | |

### 2.4.2 Chemotherapy Toxicity Prediction and Agreement with Observed Toxicity

Dr. Hurria and colleagues have developed a model that predicts for development of grade 3 and higher toxicity for patients with cancer receiving chemotherapy. This toxicity model is being validated in a breast cancer-specific cohort currently as well. In this study, we will complete a chemotherapy toxicity prediction assessment in each patient at baseline, using clinical, demographic, and GA variables from the above-mentioned questionnaires (age, cancer type, standard chemotherapy dose information, hemoglobin, Creatinine clearance, hearing, number of falls in the last 6 months, ability to take medications without assistance, limitations in walking 1 block, and social activity.)[3]

We will also ask treating providers at baseline to estimate the likelihood of a grade 3 or higher toxicity event (hematologic and non-hematologic toxicity by provider estimate) as best they can in one question in addition to the patient's European Cooperative Oncology Group (ECOG) Performance Status (Appendix C).

At the end of the 12 weeks of chemotherapy, we will then examine the agreement between the actual toxicity that occurred (using both provider and patient-reported outcome assessments) with what was predicted by the toxicity model and provider estimate. We will also examine toxicity at 3 months and 12 months after treatment completion.

### 2.4.3 Patient-reported Outcomes (PRO-CTCAE)- Appendix D

There are no published data on the specific toxicities of the treatment combinations to be used in this study in an elderly population, and certainly none that incorporate patient-reported outcomes. PROs are an important part of new drug evaluation, and may play a role in regulatory approval of novel agents in oncology.[84] They have also been shown to improve survival when collected in a standardized way.[85] PROs can be the consequences of disease and/or its treatment

as reported by the patient. PROs are evaluated through the use of questionnaires developed to assess topics a patient can report about his or her own health and are often completed electronically. This includes symptoms, physical functioning, and mental health.

The current standard mechanism for reporting toxicities in cancer research is clinician-only reporting using items from the National Cancer Institute (NCI) CTCAEs. In multiple studies, PRO measures have improved the predictive accuracy of clinician CTCAE reporting. In a prospective study including lung cancer patients PRO measurements of toxicities better reflected patients' underlying state and functional status than clinician's evaluation [86]. Although PROs have been well validated [86-88], these examinations have not specifically evaluated for feasibility and accuracy in an older patient group.

We will focus our PRO questions (Appendix D) on the toxicities felt to be most commonly experiences by patients receiving the agents to be administered in our trial. Patients will be asked to complete the paper-based survey at baseline, on Day 1 of each treatment cycle, at the end of therapy, and 3 months and 12 months after therapy completion. We are using the PRO-CTCAE items developed by the NCI (https://healthcaredelivery.cancer.gov/pro-ctcae/) in order to allow patients to self-report the above symptomatic adverse events. These are available in many languages and the appropriate language can be used as necessary for each patient. The primary purpose of the inclusion of PRO-CTCAE is to further evaluate toxicities and the agreement with toxicities collected using clinician-reported CTCAEs in clinic.

### 2.4.4 Tissue and Blood Collections for Genomics and CHIP

Tumor Genomics:
We have little information on the variability in biology and genomics of cancers in older women, let alone within specific subtypes of breast cancer. Archived formalin-fixed paraffin-embedded (FFPE) tissue samples from each participant's biopsy and/or surgery will also be requested and banked for genomic studies as well as the tumor microenvironment studies noted below. We will perform comprehensive genomic analyses on DNA and RNA obtained from these baseline tumor and blood samples to define the molecular features associated with cure and recurrence. For tumor samples, this will include whole exome sequencing (WES) and transcriptome analysis (RNA-seq). For baseline blood samples, this will include ultra low pass WES, targeted sequencing, and/or WES.[89]

Tumor Microenvironment:
Prior pre-clinical work led by Dr. McAllister's lab demonstrated that the immune microenvironment of breast cancer is different between young and old individuals and accounts for differences in disease progression in an age-dependent manner.[90] Hematopoietic and immune systems undergo profound changes that lead to diminished immune function with age. These changes make elderly individuals more susceptible to infections, autoimmune disorders and a greater incidence of cancer. In particular, skewing of hematopoiesis toward myeloid lineages over lymphoid lineages, increased central and effector memory T-cells over naïve T-cells, and reduced TCR and BCR repertoires leading to diminished immune responsiveness are commonly observed in aging individuals. In general, young breast cancer patients have a worse prognosis compared to older individuals; however, older patients suffer co-morbidities with

treatment, resulting in poor outcome. Analysis of tumor tissue from young and elderly patients revealed that the tumors from young women are genetically distinct from those of older women. Dr. McAllister's pre-clinical modeling replicated these findings and we attributed much of the difference to infiltration of hematopoietic and immune cells into the tumor tissue.[90] Unpublished additional pre-clinical studies from Dr. McAllister's lab have taught us that responses to therapy, particularly immunotherapy, are different between young and old mice, in large part due to the physiological effects of aging on the tumor immune microenvironment. Understanding the underlying biology and physiology of age-dependent effects on breast cancer is critical. Our proposed studies could guide appropriate treatment of older individuals and pave the way toward age-stratified therapies that improve survival for both young and older patients.

Tumor Microenvironment will be explored in both archived (formalin-fixed paraffin-embedded, FFPE) samples for all patients and fresh frozen samples for those who consent to tissue collections at the time of their surgery (for Dana-Farber patients only who have surgery at Brigham and Women's and Brigham and Women's Faulkner).

- FFPE analyses: (Requisition in Appendix F)
  We will characterize the immune microenvironment in tumor tissue in older breast cancer patients by immunohistochemistry and RNA sequencing. We will perform CycIF imaging technology, which utilizes multiplexing to visualize up to 60 proteins in an individual tissue section. The technique will allow us to perform the intended characterization without requiring numerous tumor sections. We will quantify numbers of cell types of interest using CellProfiler image analysis tools, and score the localization of each immune component within the tumor tissue. We will be blinded to the patient age during analysis and the tissues will be analyzed by at least 2 investigators.

  We will perform RNAseq on tissues of suitable quality in order to assess gene expression signatures with particular emphasis on immune-related pathways, including but not limited to innate and adaptive immunity, interferon signaling, inflammation, tumor proliferation, and antigen processing and presentation machinery.

- Fresh Tissue analyses (Requisition in Appendix H):
  In those with fresh tissue collected who have surgery at Brigham and Women's or Brigham and Women's Faulkner, we will perform flow cytometry on fresh tissue (can be frozen at time of biopsy/surgery) using our complete immune cell panels to extensively characterize the immune cellular microenvironment. Fresh tissue samples will also be prepared for generation of cell lines and/or patient-derived xenografts in immunocompromised mice whenever possible.

- Clonal hematopoiesis of indeterminate potential (CHIP) (Requisition in Appendix I):
  Prior work led by Dr. Ebert's lab[91-93] at DFCI has described the phenomenon and clinical importance of clonal hematopoiesis. In their initial studies, somatic mutations in the peripheral blood of otherwise healthy individual were identified using a targeted next generation sequencing platform. As expected, the presence of these clonal hematopoietic mutations, termed CHIP, was associated with an increased risk of developing hematologic malignancy. Surprisingly, CHIP was also associated with an increased risk of ischemic

cardiac events and overall mortality, a finding that was subsequently confirmed in a mouse model and likely the result of aberrant inflammation mediated by the mutant hematopoietic cells. In large population studies, the best-defined risk factors for developing CHIP are aging, exposure to cytotoxic chemotherapy, and exposure to radiation. To date, well-defined, prospectively studied cohorts of older patients with serial evaluations over time have not been performed. Using serially collected blood samples, we will assess for CHIP in women on this study and determine if CHIP is correlated with breast cancer outcomes, overall survival, response to therapy, and toxicity with therapy, with a focus on hematologic toxicities. This work will be done in close collaboration with Dr. Ebert's lab, under the direction of Drs. Christopher Gibson and Peter Miller.

All samples will be sent directly at room temperature to the The Pasquarello Tissue bank at Dana-Farber. We will bank the following in anticipation of these analyses 1) whole blood cell pellet (for DNA), 2) plasma and 3) viable mononuclear cells. This can all be done from 10-20ml EDTA whole blood (2 purple top tubes). This is considered routine processing for the tissue bank. Processing and banking of peripheral blood samples will include a separation phase with isolation and freezing of peripheral blood mononuclear cells (PBMCs). We will prepare pooled, barcoded libraries from genomic DNA isolated from banked PBMC, perform liquid phase capture using probes designed against all known genes mutated in clonal hematopoiesis, and perform deep sequencing on the Illumina platform. We will utilize the sequencing data processing pipeline developed by the Sequencing Platform at the Broad Institute. This platform analyzes reads and qualities produced by the Illumina software for each sample and produces, at the end of the pipeline, a single BAM file representing the sample. Somatic single-nucleotide variations are detected using MuTect. We evaluate the fraction of all bases suitable for mutation calling whereby a base is defined as covered if at least 30 reads overlap the base. Passing single nucleotide variants found within coding areas of the genome are annotated for the chromosomal location, the type of the variant, the codon change and the change in the protein sequence. Insertions and deletions in coding areas (both frameshift and in-frame) are detected by using the algorithm Indelocator.

## 3. PARTICIPANT SELECTION

### 3.1 Eligibility Criteria

3.1.1 Participants must have histologically or cytologically confirmed breast cancer that is human epidermal growth factor receptor 2 negative (HER2-negative) per the most recent 2018 ASCO CAP guidelines[94]

3.1.2 Estrogen Receptor and Progesterone immunohistochemistry (IHC) status must be known; any status is eligible, but this will define in which cohort a patient will enroll:

Additional eligibility for cohort 1: Triple negative disease- defined as IHC staining of <10% for ER and PR per local pathology review

Additional eligibility for cohort 2: Hormone receptor-positive disease defined as IHC for ER or PR >/= 10% per local pathology review

3.1.3 Men and women are eligible

3.1.4 Age 70 and older at the time of protocol registration

3.1.5 Non-metastatic, invasive breast cancer (scans are not required to document non-metastatic disease- any staging work-up is up to the treating provider's discretion)

3.1.6 Recommended to have either neoadjuvant chemotherapy or adjuvant chemotherapy per their treating provider.

3.1.7 Any surgery, nodal assessment, radiation, hormonal therapy is left up to the treating provider but should not occur concurrently with study therapy. If any additional chemotherapy is planned by a treating provider, this must occur AFTER all study-related chemotherapy is completed.

3.1.8 Any patient receiving pre-operative hormonal therapy and who is then recommended for adjuvant chemotherapy is eligible, though hormonal therapy should be held during study treatment administration

3.1.9 All study-related chemotherapy must be given prior to surgery if neoadjuvant therapy is planned or adjuvantly if postoperative chemotherapy is planned. For example, giving 6 doses pre-operatively and 6 doses postoperatively is not allowed on study.

3.1.10 There are no restrictions on life expectancy, ECOG Performance Status, or baseline blood values or organ function; Appropriateness of chemotherapy treatment is left up to the treating provider but providers should be ok with the full starting doses of each agent.

3.1.11 Participants must be willing to fill out surveys over time or designate a proxy to answer on their behalf.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.1.13 Patients who do not speak or read English are eligible as long as adequate interpreter services are available or the surveys are available in the preferred language (i.e. PRO surveys are available in many languages)

## 3.2 Exclusion Criteria

3.2.1 Participants who have already received chemotherapy for the current cancer. Prior diagnoses of breast cancers are allowed, provided that the treating provider feels that the current cancer represents a new primary breast cancer and *not* recurrent disease.

3.2.2 Participants who are receiving any other investigational or anti-cancer agents. Any additional radiation, hormonal therapy or chemotherapy planned should be administered once the study treatments have completed.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cyclophosphamide, carboplatin, and paclitaxel.

3.2.4 Prior chemotherapy receipt is allowed in the setting of treatment of other/prior cancers, but no prior carboplatin (cohort 1), cyclophosphamide (cohort 2), or paclitaxel (both cohorts) receipt in the last 2 years is allowed (given toxicity and possible efficacy concerns)

### 3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial and is encouraged. We wish to be as inclusive as possible in enrollment.

## 4. REGISTRATION PROCEDURES

### 4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

### 4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

### 4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the coordinating center through the Project Manager. The required forms can be found in Section 4.4

Following registration, participants should begin protocol therapy within 7 days. Issues that would cause treatment delays should be discussed with the Overall PI. If the subject does not

receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

### 4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and faxed to 617-632-5152 or e-mailed to ctopm@dfci.harvard.edu to the project manager:

- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist
- Consent Process Documentation
- Baseline exam note including medical/surgical history
- Pathology report (diagnosis and receptor status)

To complete the registration process, the project manager will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (DF/HCC Policy: REGIST-101) and register the participant on the protocol. The project manager will fax or e-mail the participant study number and confirmation of registration to the participating site

**NOTE: Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Standard Time Monday through Friday.** If a same-day registration is required, it should be discussed in advanced with the DF/HCC Project Manager.

## 5. TREATMENT PLAN

### 5.1 Treatment Regimen

Each cycle will consist of 3 weeks of treatment, with a total of 4 cycles of planned treatment. Treatment will be administered intravenously on an outpatient basis per institutional guidelines, without planned breaks, unless this is of clinical need. Agents may be administered within +/- 3 days of their expected date. A skipped dose for a planned vacation or non-medical reason will not count against feasibility (see endpoint definitions for further detail).

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are left to the treating provider and are not mandated. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Cohort 1: Triple negative disease
**As above, patients will be considered triple negative if their local IHC assays show estrogen receptor-negative AND progesterone receptor-negative status (defined as <10% by local review for the purposes of this study).**

Treatment, either in the neoadjuvant/adjuvant setting will include 12 weeks of commercially supplied, standard dose, weekly carboplatin (AUC 2) and paclitaxel 80 mg/m$^2$ administered

consecutively per institutional guidelines.

| Table 2: Regimen Description- COHORT 1- TRIPLE NEGATIVE DISEASE | | | | | | |
|---|---|---|---|---|---|---|
| **Agent** | **Premedications; Precautions** | **Hydration** | **Dose** | **Infusion** | **Schedule** | **Cycle length** |
| **PACLITAXEL*** | Per institutional guidelines<br><br>*Recommendations in Section 5.3.1* | Per institutional guidelines<br><br>*None recommended* | 80 mg/mg$^2$ | Per institutional guidelines<br><br>*Recommend 60 mins* | Days 1, 8, 15 | 21 days (3 weeks) |
| **CARBOPLATIN*** | Per institutional guidelines<br><br>*Recommendations in Section 5.3.2* | Per institutional guidelines<br><br>*Recommendations in Section 5.3.2* | AUC 2 | Per institutional guidelines<br><br>*Recommend 30-60 mins* | Days 1, 8, 15 | |
| *Standard institutional hypersensitivity medications should be used to treat hypersensitivity reactions but are not required as pre-medications | | | | | | |

Cohort 2: Hormone receptor-positive disease

**As above, patients will be considered hormone receptor-positive if their local IHC assays show positive estrogen receptor OR progesterone receptor status (defined as >/=10% by local review for the purposes of this study).**

Treatment, either in the neoadjuvant/adjuvant setting will include 12 weeks of commercially supplied, standard dose, weekly paclitaxel 80 mg/m$^2$ plus standard dose cyclophosphamide 600 mg/m$^2$ every three weeks.

| Table 3: Regimen Description- COHORT 2- HORMONE RECEPTOR-POSITIVE DISEASE | | | | | | |
|---|---|---|---|---|---|---|
| **Agent** | **Premedications; Precautions** | **Hydrations** | **Dose** | **Infusion** | **Schedule** | **Cycle Length** |
| **CYCLOPHOSPHAMIDE** | Per institutional guidelines<br><br>*Recommendations in Section 5.3.3* | Per institutional guidelines<br><br>*Recommendations in Section 5.3.3* | 600 mg/m$^2$ | Per institutional guidelines<br><br>*Recommend 60 mins* | Day 1 | 21 days (3 weeks) |
| **PACLITAXEL*** | Per institutional guidelines<br><br>*Recommendations in Section 5.3.1* | Per institutional guidelines<br><br>*None recommended* | 80 mg/mg$^2$ | Per institutional guidelines<br><br>*Recommend 60 mins* | Days 1, 8, 15 | |
| *Standard institutional hypersensitivity medications should be used to treat hypersensitivity reactions but are not required as pre-medications | | | | | | |

## 5.2 Pre-Treatment Criteria

### 5.2.1 Cycle 1, Day 1 and Subsequent Cycles

For cohorts 1 and 2
There are no mandated laboratory requirements for treatment, institutional guidelines should be followed. The following is suggested for general criteria at baseline and at each weekly treatment but this is up to the discretion of the provider/institutional preferences:

- Absolute neutrophil count (ANC) >1000/mcL
- Platelets >100,000/mcL
- Total bilirubin <1.3 mg/dL
- Creatinine 1.6 mg/dl or creatinine clearance >/= 50 cc/minute

Over the course of treatment, providers should consider dose reductions or treatment holds for the offending agent in the setting of any grade 3 or higher toxicity (other than alopecia) or a clinically significant grade 1-2 toxicity. Providers may proceed with treatment as they feel appropriate (for example, if treatment is administered despite platelets of 80,000/mcL, this will not be a protocol violation, but we will capture as a toxicity event and any dose modification will be captured too).

Providers may skip or omit treatments as they feel is clinically indicated and if treatment doses wish to be made up, treatments can continue for longer than 12 weeks but should not exceed 12 actual treatment days for each agent (i.e. if carboplatin and paclitaxel are both held during week 4, treatments may continue through week 13 if desired by the treating provider. As another example, if only one agent is held one week and the other agent is given, the provider can provide an additional week of the omitted treatment if desired). At any point in a time, if an agent is held for than three consecutive weeks, providers may consider not returning to that agent but there is no mandated treatment cessation; this is left to the treating provider.

## 5.3 Agent Administration

### 5.3.1 Paclitaxel Administration

Paclitaxel will be administered as an IV infusion per institutional guidelines at a dose of 80mg/m2 weekly x 12 weeks (4 cycles). Dosing calculation guidelines will follow institutional policies. Hydration is per institutional policies. The recommended infusion time is approximately 60 minutes. For Cohort 1, paclitaxel should be administered prior to carboplatin.

*Hypersensitivity reactions prophylaxis:* It is recommended that all patients be pre-medicated prior to paclitaxel administration to prevent severe hypersensitivity reactions. Such premedication may consist of 12 mg (orally) dexamethasone administered approximately 30 to 60 minutes before paclitaxel, 25 mg (IV) diphenhydramine (or its equivalent) administered 30 to 60 minutes prior to paclitaxel, and 20 mg famotidine (IV) or equivalent H2 blocker administered 30 to 60 minutes before paclitaxel. If different institutional guidelines exist for administration or premedication for weekly paclitaxel, then the investigator should use their standard practice.

*Growth factor support:* Use of growth factors is left to the treating physicians' discretion. Use of growth factor with filgastrim (neupogen) is allowed but not mandated, but treatment with pegfilgastrim (neulasta) is not recommended given the weekly schedule of the chemotherapy to be administered.

5.3.2 Carboplatin Administration

The dose of carboplatin in this study is AUC of 2 mg/mL*min administered by IV infusion per institutional standard practice (recommended infusion time of approximately 30 to 60 minutes). Hydration is per institutional guidelines (recommend 500 mg/hour, continuous IV, over 2 hours for a total of 1 liter). Observation period after carboplatin administration will follow institutional guidelines.

Dose will be based on the Calvert formula:

$$\text{Carboplatin dose (mg)} = \text{AUC} \times (\text{GFR} + 25) \text{ where GFR is glomerular filtration rate}$$

$$\text{Maximum carboplatin dose (mg)} = \text{target AUC (mg/mL} \bullet \text{min)} \times (150 \text{ mL/min})$$

GFR is estimated using the Cockcroft–Gault formula for creatinine clearance:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

The total dose of carboplatin for each patient will be per institutional guidelines.

Carboplatin should be administered after paclitaxel.

Carboplatin as well as premedication is to be administered and stored in accordance with local prescribing information and local institutional guidelines. For further details, see the carboplatin Package Insert or Summary of Product Characteristics.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin

*Growth factor support:* Use of growth factors is left to the treating physicians' discretion. Use of growth factor with filgastrim (neupogen) is allowed but not mandated, but treatment with pegfilgastrim (neulasta) is not recommended given weekly nature of the chemotherapy to be administered.

### 5.3.3 Cyclophosphamide

The dose of cyclophosphamide in this study is 600 mg/m$^2$ administered by IV infusion per institutional standard practice (recommended infusion time of approximately 60 minutes). Dosing calculation guidelines will similarly follow institutional policies.

Pre-medications and hydration are per institutional guidelines.

The observation period after administration will follow institutional guidelines. Patients receiving paclitaxel should receive cyclophosphamide first, followed by paclitaxel.

## 5.4 General Concomitant Medication and Supportive Care Guidelines

See dosing table above and Section 5.3 for suggestions on pre-medications. All pre-medications should be given per institutional guidelines. It is recommended that anti-emetics be considered for both cohorts for a few days after each treatment is given.

## 5.5 Criteria for Taking a Participant Off Protocol Therapy

Participants will be planned for 12 weekly doses of therapy in either cohort. If a dose is missed and there is a desire to make it up, treatment administration may occur over longer than 12 weeks and is left up to the treating provider. However, the duration of therapy will depend on individual response to treatment, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for 4 cycles or until one of the following criteria applies:

- Completion of protocol-defined therapy
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

### 5.6 Duration of Follow Up

Participants will be followed for up to two years after study treatment completes or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

### 5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Completion of protocol-defined follow-up
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

As above in Section 5.2.1, dose delays and modifications will be made per provider discretion and are not mandated. We will collect reasons for treatment holds, omissions, delays, and dose modifications at the start of each cycle will also collect the descriptions and grading scales for toxicities using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website. We will collect all grade 2 and higher toxicities.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

### 7.1 Adverse Event List(s) for Commercial Agent(s)

Refer to the FDA approved package insert for detailed information each agent.

### 7.1.1 Expected Adverse Events for Paclitaxel:

*Myelosuppresion*
Myelosuppression occurs in the majority of patients (neutropenia, leukopenia, thrombocytopenia, and anemia). Myelosuppression is dose related, schedule related, and infusion-rate dependent and, in general, rapidly reversible upon discontinuation.

*Anaphylactic-Like Reactions*
Hypersensitivity is thought to be caused by the Cremophor vehicle. Minor symptoms include hypotension, flushing, chest pain, abdominal or extremity pain, skin reactions, pruritus, dyspnea, and tachycardia. More severe reactions include hypotension requiring treatment, dyspnea with bronchospasm, generalized urticaria, and angioedema. The majority (53%) of the reported reactions occurred within 2-3 minutes of initiation of treatment and 78% occurred within the first 10 minutes. Reactions usually occurred with the first and second doses.

*Cardiovascular toxicity*
Atrial arrhythmia (sinus bradycardia [usually transient and asymptomatic], sinus tachycardia, and premature beats); significant events include syncope, hypotension, other rhythm abnormalities (including ventricular tachycardia, bigeminy, and complete heart block requiring pacemaker placement), and myocardial infarction. Hypertension (possibly related to concomitant medication – Dexamethasone) may also occur.

*Neurotoxicity*
Sensory (taste changes); peripheral neuropathy; arthralgia and myalgia (dose-related, more common when colony-stimulating factors are also administered); seizures; mood alterations; neuroencephalopathy; hepatic encephalopathy; motor neuropathy; and autonomic neuropathy (paralytic ileus and symptomatic hypotension).

*Dermatologic toxicity*
Alopecia (universal, complete and often sudden, between days 14- 21); injection site reactions (erythema, induration, tenderness, skin discoloration); infiltration (phlebitis, cellulitis, ulceration, and necrosis, rare); radiation recall; and rash.

*Gastrointestinal toxicity*
Nausea, vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis (neutropenic enterocolitis), ischemic colitis, and pancreatitis.
Hepatic: Increased AST, ALT, bilirubin, alkaline phosphatase; hepatic failure, and hepatic necrosis.

*Other:* Fatigue, headache, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities (sensation of flashing lights, blurred vision).

### 7.1.2 Expected Adverse Events for Carboplatin

*Hematologic Toxicity*
Bone marrow suppression is the dose-limiting toxicity of carboplatin, including thrombocytopenia, neutropenia and anemia. Fever has also been reported in patients with neutropenia. Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leukopenia and thrombocytopenia. The incidence of anemia increases with increasing exposure to carboplatin.

*Gastrointestinal Toxicity*
Carboplatin, as a single agent or in combination, is significantly less emetogenic than cisplatin; however, patients previously treated with emetogenic agents, appear to be more prone to vomiting. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Other gastrointestinal effects observed frequently were constipation and diarrhea.

*Neurologic Toxicity*
Peripheral neuropathies have been observed in patients receiving carboplatin, with mild paresthesias occurring most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk for peripheral neuropathies. Although the overall incidence of peripheral neurologic side effects induced by carboplatin is low, prolonged treatment, particularly in cisplatin pretreated patients, may result in cumulative neurotoxicity.

*Nephrotoxicity*
Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid hydration and/or forced diuresis. Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving carboplatin, and it appears to be the most useful test for correlating drug clearance and bone marrow suppression. Patients with a baseline value of 60 mL/min or more are more likely to experience a reduction below this value during carboplatin therapy.

*Hepatic Toxicity*
Abnormal liver function tests, including transaminitis, have generally been mild and reversible, although the role of metastatic tumor in the liver may complicate the assessment in many patients.

*Electrolyte Changes*
The following serum electrolytes have been found to be abnormally decreased with treatment with carboplatin: sodium, potassium, calcium and magnesium. Electrolyte supplementation is not routinely administered concomitantly with carboplatin, and these electrolyte abnormalities are rarely associated with symptoms.

*Allergic Reactions*
Hypersensitivity has been reported with carboplatin. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, ie, rash,

urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

*Injection Site Reactions*
Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance. Necrosis associated with extravasation has also been reported. For complete details on adverse reactions please see the carboplatin package insert.

7.1.3 Expected Adverse Events for Cyclophosphamide

*Myelosuppression*
Primarily leucopenia, but also thrombocytopenia.

*Gastrointestinal*
Nausea and vomiting (cyclophosphamide is considered moderately to highly emetogenic; onset of symptoms is somewhat delayed at 6-10 hours after administration).

*Genitourinary*
Sterile hemorrhagic cystitis (related to the accumulation of the acrolein metabolite in the bladder; minimize with hydration).

## 7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

## 7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.3.2 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3 For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any unexpected grade 4 toxicities and any grade 5 (death) regardless of study phase or attribution.

7.3.4 DF/HCC Expedited Reporting Guidelines

Given the well-known safety profile of these agents, in the context of this protocol, only grade 4 (unexpected) and 5 adverse events will be reported to the DFCI IRB.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.3.5 Protocol-Specific Adverse Event Reporting Exclusions

## 7.4 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

## 7.5 Routine Adverse Event Reporting

Grade 2 and above adverse events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, etc.) must also be reported in routine study data submissions.**

# 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

## 8.1 COMMERCIAL AGENTS TO BE ADMINISTERED

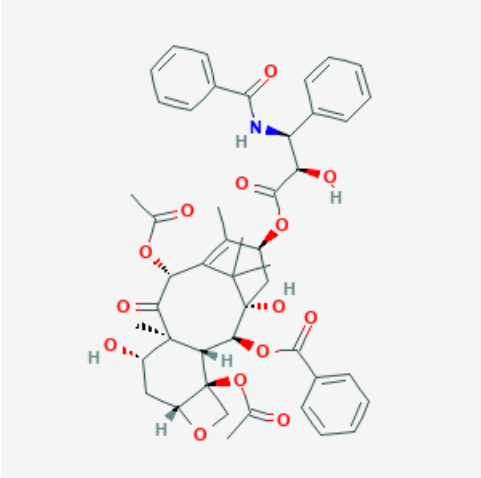
### 8.1.1 Paclitaxel

#### 8.1.1.1 Description

Other Names
Taxol (NSC 125973)

Classification
Antimicrotubule agent.

Paclitaxel promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions. The chemical structure is provided here:



#### 8.1.1.2 Form

For this protocol, 80 mg/m2 of paclitaxel will be administered by IV infusion as an approximately 1- hour infusion weekly for 12 weeks.

#### 8.1.1.3 Route of Administration

Administration of paclitaxel should follow institutional guidelines, and may slightly deviate from the suggested administration guidelines in the remainder of this paragraph to accommodate different institutional practice. Paclitaxel is administered as an IV infusion over approximately 60 minutes.

#### 8.1.1.3 Storage and Stability

Store vials in original cartons and packaging between 20 and 25 degrees C (68 and 77 degrees F). Protect from light. Refrigeration or freezing will not harm the product. If a precipitate forms upon refrigeration, the precipitate will redissolve upon reaching room temperature. Discard the

vial if cloudiness or precipitate remains. Prepared infusion solution is stable at ambient temperature (approximately 25 degrees C) and lighting conditions for up to 27 hours.

#### 8.1.1.4 **Compatibility**

Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Ketoconazole may inhibit paclitaxel metabolism, based on *in vitro* data. Prescription of concomitant drugs should address the Launch Lexi-Interact™ Drug Interactions Program.

#### 8.1.1.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

#### 8.1.1.6 **Availability**

Paclitaxel is commercially available agent. Each institutional pharmacy should assure availability for the study.

#### 8.1.1.7 **Preparation**

Preparation of paclitaxel should follow each institutional guideline, and may slightly deviate from the suggested preparations guidelines in the remainder of this paragraph to accommodate different institutional guidelines. Paclitaxel may be diluated in 0.9% sodium chloride injection, USP or 5% dextrose injection, USP. Paclitaxel must be prepared in glass, plypropylene or plyolefin containers and non-PVC containing (nitroglycerin) infusion sets. In-line filtration with a 0.22 micron filter is required.

#### 8.1.1.8 **Ordering**

As paclitaxel is commercially available, each study site is responsible for prescribing and ordering study drugs for study participants enrolled at their site. Study drugs will the billed to patients as standard of care.

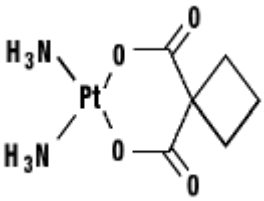
#### 8.1.1.9 **Destruction**

Unused and used supplies of paclitaxel should be destroyed according to institutional guidelines

### 8.1.2 **Carboplatin**

Carboplatin, like cisplatin, produces predominantly intrastrand and interstrand DNA crosslinks. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

Carboplatin is a platinum coordination compound. The chemical name for carboplatin is platinum, diammine[1,1-cyclobutanedicarboxylato(2-)- *O*,*O*′]-, (*SP*-4-2), and carboplatin has the following structural formula:




Carboplatin is a crystalline powder with the molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

#### 8.1.2.1 **Form**

Carboplatin will be obtained commercially and is available as a sterile, pyrogen-free, 10 mg/mL aqueous solution in 5-mL, 15-mL, 45-mL, and 60-mL vials. Carboplatin may be diluted in 0.9% sodium chloride injection, USP or 5% dextrose injection, USP. Needles or IV administration sets containing aluminum parts that may come in contact with carboplatin should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency. Carboplatin as well as premedication is to be administered and stored in accordance with local prescribing information and local institutional guidelines.

#### 8.1.2.2 **Storage and Stability**

Carboplatin is a premixed aqueous solution of 10 mg/mL that can be further diluted to concentrations as low as 0.5 mg/mL with 5% dextrose in water (D5W) or 0.9% sodium chloride injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin aqueous solutions be discarded 8 hours after dilution.

Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F); excursions permitted from 15°-30°C (59°-86°F). Vials should be protected from light. Carboplatin multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation.

#### 8.1.2.3 **Compatibility**

Carboplatin can be further diluted with 5% dextrose in water or 0.9% sodium chloride injection, USP.

#### 8.1.2.4 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

#### 8.1.2.5 **Availability**

Carboplatin is commercially available.

#### 8.1.2.6 **Preparation**

Carboplatin should be prepared according to institutional guidelines.

#### 8.1.2.7 **Administration**

For complete details on drug preparation, administration, storage conditions, clinical pharmacology, pharmacokinetics, known precautions, warnings and adverse reactions please see the carboplatin package insert.

#### 8.1.2.8 **Ordering**

Carboplatin is commercially available. Check with the site Director of Pharmacy and/or the site research pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered before the protocol is activated.
For complete details on drug preparation, administration, storage conditions, clinical pharmacology, pharmacokinetics, known precautions, warnings and adverse reactions please see the carboplatin package insert.

#### 8.1.2.9 **Accountability**

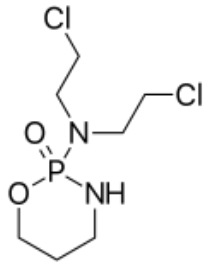
The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

#### 8.1.2.10 **Destruction and Return**

At the end of the study, unused supplies of should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

### 8.1.3 **Cyclophosphamide**

Cyclophosphamide is an alkylating agent of the nitrogen mustard type. An activated form of cyclophosphamide alkylates, or binds, to DNA. Its cytotoxic effect is mainly due to cross-linking of strands of DNA and RNA, and to inhibition of protein synthesis. The chemical structure is the following:




8.1.3.1 **Form**

Cyclophosphamide is commercially available as powder for reconstitution in 500mg, 1g and 2g vials. Please refer to the package insert for complete product information. Reconstitute 500mg, 1g and 2g vials with 25, 50, or 100ml of sterile water for injection for a final concentration of 20mg/ml. Vigorous shaking and/or gentle warming may be necessary. Preparation of cyclophosphamide is per institutional standards.

8.1.3.2 **Storage**

Store intact vials of cyclophosphamide of powder at room temperature (15-30°C). Reconstituted solutions are stable for 24 hours at room temperature or for 6 days in the refrigerator (2-8°C). Store vials in original cartons and packaging between 20 and 25 degrees C (68 and 77 degrees F). Protect from light. Refrigeration or freezing will not harm the product. If a precipitate forms upon refrigeration, the precipitate will redissolve upon reaching room temperature. Discard the vial if cloudiness or precipitate remains. Prepared infusion solution is stable at ambient temperature (approximately 25 degrees C) and lighting conditions for up to 27 hours. Solutions further diluted for infusion in 0.9% NaCl or D5W are stable for 24 hours at room temperature and 6 days (36 hours for D5W) under refrigeration.

8.1.3.3 **Compatibility**

Cyclophosphamide can be further diluted with 5% dextrose in water or 0.9% sodium chloride injection, USP.

8.1.3.4 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.3.5 **Availability**

Cyclophosphamide is commercially available.

8.1.3.6 **Preparation**

Cyclophosphamide should be prepared according to institutional guidelines.

#### 8.1.3.7 **Administration**

For complete details on drug preparation, administration, storage conditions, clinical pharmacology, pharmacokinetics, known precautions, warnings and adverse reactions please see the cyclophosphamide package insert.

#### 8.1.3.8 **Ordering**

Cyclophosphamide is commercially available. Check with the site Director of Pharmacy and/or the site research pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered before the protocol is activated. For complete details on drug preparation, administration, storage conditions, clinical pharmacology, pharmacokinetics, known precautions, warnings and adverse reactions please see
the carboplatin package insert.

#### 8.1.3.9 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

#### 8.1.3.10 **Destruction and Return**

At the end of the study, unused supplies of should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

## 9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

### 9.1 Laboratory Correlative Studies

#### 9.1.1 **Blood Collection for CHIP analyses**

Two purple top EDTA tubes will be collected from all patients on both cohorts at the below timepoints:

- Baseline
- Week 6 of treatment
- Week 12 or at treatment completion.

##### 9.1.1.1 Handling and Shipping

These samples will not require processing but should be shipped ambient to Dana-Farber Cancer Institute at the below address, per Appendix I instructions.

Dana-Farber Cancer Institute
Pasquarello Tissue Bank- CMCF, J614-J616
1 Jimmy Fund Way
Boston, MA 02115

9.1.1.2 Sites Performing Correlatives
DFCI

9.1.2 **Tissue Collection Studies:**

Archived formalin-fixed paraffin-embedded (FFPE) tissue samples from each participant's biopsy and/or surgery (likely surgery due to the amount of tissue requested) will also be requested and banked for genomic studies as well as the tumor microenvironment studies as noted below.

A letter in Appendix G may accompany tissue requests and summarizes the tissue needs for this study. All tissue requests for archived samples should be made within 30 days of a patient's surgery so that if insufficient tissue is present at biopsy, we have allowed time for surgeries to occur and to obtain more tissue.

All samples from biopsies and/or surgeries will be sent to DFCI study staff and divided into 2 samples for (1) genomic testing and for (2) tumor microenvironment testing. Samples should be divided in ½ whenever possible, with 10+ slides for each study component. If there is scant tissue to allow for both analyses, study staff should request additional tissue whenever possible (using surgical tissue, biopsy tissue, or both) in attempt to complete both studies. If additional tissue is not available, study staff should consult with Dr. Freedman, the Principal Investigator, on what the priority and plan should be for tissue provision.

If a tumor block is provided, the DFCI study team will have the tissue sectioned into the number of slides described below by the BWH Standardized Histopathology Lab (SHL). Blocks will then be returned to pathology departments and/or originating centers.

For DFCI only: if patients are enrolled on both ADVANCE and 'Elevate' protocols, only ONE collection has to be done for both studies for genomics/microenvironment.

9.1.2.1 **Tissue Genomics**

The following specimens are required for gene profiling (can be sent from archived tissue from biopsy or surgery):

- 1 paraffin block (or 10-15 unstained, uncharged slides)

If there is insufficient tumor sample, submit 2 cores of invasive tissue using a 1.2 mm diameter coring tool or a paraffin blck.

Label the block and slide with the DFCI Participant ID, site MRN, subject initials, site of

collection, date of collection, and protocol number.

These samples will be combined with those on the Elevate trial (DFCI protocol 18-634) for a larger-scale analysis. *For DFCI-treated patients on both protocols, tumor genomics and microenvironment studies do NOT need to be repeated or sent twice. This is not relevant for other ADVANCE sites as they will not have 'Elevate' open.*

Any unused specimens may be stored for future use at DFCI. Confirmation of request of block or slides should be provided within 30 days of a patient's surgery; however failure to request within this timeframe will not be considered a protocol violation.

Handling and Shipping: See Appendix E for Specimen Requisition form and full instructions for shipping to DFCI.

Sites Performing Correlatives:
Broad Institute

#### 9.1.2.2 **Tissue Microenvironment**

The following archived and fresh tissue will be collected. See Appendices F and H for detailed information. All analyses will be conducted by Drs. McAllister and Goreczny.

- Paraffin block containing tumor tissue
  **OR**
- At least ten 5 micron sections on charged, unstained slides
- If possible and sufficient tissue, please send ten additional 5-7micron sections on regular non-coated slides (total of 20 slides)

In those with fresh tissue collected and who have surgery at Brigham and Women's or Faulkner Hospital (≈10-12 patients), we will perform flow cytometry on fresh tissue (can be frozen at time of biopsy/surgery) using our complete immune cell panels to extensively characterize the immune cellular microenvironment. Fresh tissue samples will also be prepared for generation of cell lines and/or patient-derived xenografts in immunocompromised mice.

These samples will be combined with those on the Elevate trial (DFCI protocol 18-634) for a larger-scale analysis. *For DFCI-treated patients on both protocols, tumor genomics and microenvironment studies do NOT need to be repeated or sent twice. This is not relevant for other ADVANCE sites as they will not have 'Elevate' open.*

Handling and Shipping: See Appendix F and H for Specimen Requisition form and full instructions for shipping to DFCI.

Sites Performing Correlatives:
Harvard Institutes of Medicine

## 9.2 Survey Studies

Table 5: Summary of Surveys/Assessments

| Questionnaire/Survey | Baseline | Day 1 of each cycle[2] | C3D1 | End of Chemotherapy | 3 months post treatment | 12 months post treatment |
|---|---|---|---|---|---|---|
| Geriatric Assessment (GA) (patient and Healthcare provider) – See section 9.2.1 | X[1, 3] | | X | X | X | X |
| Provider Baseline Survey – See section 9.2.2 | X | | | | | |
| Patient Reported Outcomes (PRO-CTCAE) – See section 9.2.4 | X | X | | X | X | X |
| Provider Survey on GA Utility See section 9.2.3 | X [4] | | | X [4] | | |

[1] Geriatric assessment may be done cycle 1 day 1 (C1D1) if not done at baseline
[2] Except C1D1 unless baseline assessment not done previously
[3] The Demographic survey is only required at baseline as part of the patient GA
[4] Should be completed one week after GA summary provided

The following surveys and assessments will be completed on study and can be found in Appendices A-D and L.

- Geriatric Assessment (Patient and Provider)-
- Provider Baseline Survey
- Patient-Reported Outcomes (PRO-CTCAE)
- Provider Survey on GA Utility

Table 5 summarizes the schedule for these surveys. In general, surveys organized by timepoint are below:

- Baseline (all surveys)
- D1 of each cycle (PRO-CTCAE only)
- C3D1 (GA only)
- End of chemotherapy (Geriatric Assessment, PRO-CTCAE, Provider Survey on GA Utility)
- 3 Months Post Treatment (Geriatric Assessment and PRO-CTCAE)
- 12 Months Post Treatment (Geriatric Assessment and PRO-CTCAE)

Information pertaining to each type of survey/assessment is outlined below and detailed in Section 2.4.

### 9.2.1 Geriatric Assessment

The Geriatric Assessment (GA) is to be conducted in-clinic at baseline (if this time point is missed, baseline assessment can also be done on C1D1), Cycle 3 Day 1, at the end of chemotherapy, 3 months post-treatment and 12 months post-treatment. This will include both patient and healthcare professional assessments at each time point (Appendix A and B). The

Demographics Section (Section 1) of the patient assessment only needs to be completed at baseline.

*If patients are also enrolled on Elevate (DFCI patients only), the GA at baseline or any overlapping time points does not need to be repeated and should be done **once**.*

Table 1 in Section 2.4.1 outlines the components of the Geriatric Assessments.

### 9.2.2 Provider Baseline Survey on toxicity prediction

The Provider Survey is conducted only at baseline. In the three-question survey, treating providers are asked the likelihood of a grade 3 or higher toxicity event (hematologic and non-hematologic toxicity by provider estimate) as well as the patient's European Cooperative Oncology Group (ECOG) Performance Status (Appendix C). This can be conducted by email or paper.

### 9.2.3 Provider Survey on GA Utility

A summary report of a patient's Geriatric Assessment from baseline and end of treatment (Appendix L) should be sent to the provider by email within one week of patient's completion of they survey (i.e. one summary report is generated at baseline and a separate summary report is generated at end of therapy).

Within one week of the summary report, a survey (Appendix M) will then be sent by email to the receiving provider to ask three questions about the utility of having this information and how it might affect that patient's care.

*If a patient is also enrolled on Elevate (DFCI patients only), the baseline GA summary and provider survey should occur on whichever protocol was initiated first. However, the end of treatment GA summary and survey should still occur on ADVANCE.*

### 9.2.4 Patient Reported Outcomes (PRO-CTCAE)

The direct link to the specific PROs (approximately 40 brief questions on symptoms experienced in the last 7 days) to be used for this study is below and is available in many languages (English, traditional Chinese, Czech, Danish, Dutch, French, French Canadian, German, Greek, Hungarian, Italian, Japanese, Korean, Polish, Russian, Spanish).

Appendix D has screen shots of the survey in English but all surveys in all available languages can be printed directly from the NCI website survey link below. It is preferred to print the survey from the link in Appendix D to increase the font size and readability. We will also offer an email link for this survey which is established with assistance from our DFCI Survey and Data Management Core. Once on the survey link, you can click on the language of interest to get the survey for printing. Toxicity will be examined with PROs at baseline, on day 1 of each cycle, treatment completion, and 3 months and 12 months after treatment completion

PRO-CTCAE questionnaire:
https://healthcaredelivery.cancer.gov/proctcae/build.php?r=H76krM4DOAi

## 10. STUDY CALENDAR

Treatments along with their coinciding study assessments should be administered within ± 3 days of the protocol-specified date whenever possible, unless otherwise noted in the Calendar or unless a treatment hold is occurring for clinical reasons. Patient and provider surveys (i.e. GA, PRO-CTCAE, etc) may be administered within +/- 7 days of the protocol-specified date, unless otherwise noted in the Calendar or unless a treatment hold is occurring for clinical reasons. If a treatment is skipped for toxicity or other reason, please perform the assessment as soon as treatment is resumed. If one agent is held but the other is given, study assessments can occur as outlined below. There are no mandated imaging studies for pre-treatment staging, post-operative staging, or follow-up care. All care should be done per usual standard care.

## Table 6: Study Calendar

| Tests and Procedures | Baseline (or C1D1) | Weekly x 12 doses | D1 of each cycle (every 21 days) | Cycle 3 Day 1 | End of chemotherapy | Surgery (preoperative therapy patients only) | 3 months post-treatment (+/- 1 month) | 12 months post treatment (+/- 2 months) | Up to 2 yrs after therapy completion |
|---|---|---|---|---|---|---|---|---|---|
| **Clinical Assessments [b]** | | | | | | | | | |
| Clinical labs for treatment [a] | | X | | | | | | | |
| Toxicity assessment with provider | | | X | | | | | X | |
| Medical record review for AEs, hospitalizations, disease outcomes, survival | X | | X | | | | X | X | X (~ every 6 months) |
| **Patient Surveys and Provider Surveys/Assessments [b]** | | | | | | | | | |
| Demographics survey [c] | X | | | | | | | | |
| Geriatric Assessment (GA)—patient & provider [c, d] | X | | | X | X | | X | X | |
| Frailty [e] | X | | | | X | | | X | |
| Provider Baseline Survey [f] | X | | | | | | | | |
| NCI's PRO-CTCAE [95] | X | | X | | X | | X | X | |
| Provider GA summary provided | X [h] | | | | | | | | |
| Provider Survey on GA Utility (See Section 9.2.3) | X [h] | | | | X [h] | | | | |
| **Tissue and Blood Sample Collections [b]** | | | | | | | | | |
| Archived tissue sample (See Section 9.1.2) | X | | | | | | | | |
| Fresh tissue sample (See Section 9.1.2) | | | | | | X | | | |
| Blood sample for CHIP (See Section 9.1) | X [i] | | | X | X | | | | |
| **End of Study Patient Engagement** | | | | | | | | | |
| Certificate of appreciation (Appendix K) | | | | | | | | X | |
| Letter for patients [g] | | | | | | | | | X |

a. There are no mandated laboratory requirements for treatment; per institutional guidelines. See Section 5.2.1
b. All assessments should happen +/- 3 days of protocol specified time point (unless otherwise noted in the calendar, i.e post-treatment visits); patient/provider surveys may be completed +/- 7 days of protocol specified time point (unless otherwise noted in the calendar, i.e post-treatment visits).
c. This is a part of the Geriatric Assessment (GA) but only done at baseline. See Appendix A for all patient sections of the GA. For DFCI patients enrolled on Elevate (18-634), the GA at baseline or at any overlapping time points does not need to be repeated and should be done **once**.

d. See Appendix B for healthcare professional sections of the GA. Sections include: Karnofsky PS, Timed "Up and Go", Blessed-Orientation-Memory-Concentration (BOMC) test. This is for all patients, but for DFCI patients only, if patients are also enrolled to the Elevate study (18-634), the GA at baseline or at any overlapping time points does not need to be repeated and should be done **once**.
e. Additional surveys are not required as this is calculated using the GA responses from patients. This is for all patients, but for DFCI patients on Elevate (18-634), the baseline assessment does not need to be repeated if already calculated on 18-634. Calculated by study team using the below index[96,97]:
Guerard, E. J., et al. (2017). "Frailty Index Developed From a Cancer-Specific Geriatric Assessment and the Association With Mortality Among Older Adults With Cancer." J Natl Compr Canc Netw 15(7): 894-902.
f. Can be done on paper or email at baseline; see Appendix C for the three-question survey (includes toxicity estimation and ECOG PS).
g. IRB approved end of study letter will be sent to patients whenever results are presented or published. Patients may be off study at this time, but will have consented to an optional study of receiving trial results.
h. In order for provider to complete the Provider Survey on GA Utility, the GA summary report should be sent to provider within one week of patient completing each GA. See Appendix L and M. If DFCI patients are also enrolled on Elevate (18-634), this survey only has to be done once and not repeated for this study if already done as a part of Elevate.
i. If a DFCI patient is also on Elevate (18-634), CHIP does not need to be repeated if a baseline test was already collected, but all other time points should be collected.

# 11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

## 11.1 Data Reporting

### 11.1.1 Method

We will use the Inform database to capture information from medical record reviews and tissue/blood sample results. Data elements to be included in the centralized study data repository will include baseline demographics, comorbidity, date of diagnosis, and disease characteristics. All survey data will be specifically entered and maintained securely on the CATI DATSTAT survey tool (password protected) that was created for this study by the DFCI Data and Survey Management core. Patients will have the option to do the surveys through an email link, on paper, or by phone. When patients complete the survey through the link, the data will go directly into the CATI collection tool. For patients doing the survey on paper (or by phone if a patient was missed in clinic), the research coordinator will submit the data from the survey into the CATI. Longitudinal data will include up-to-date treatment information, survey data for each time point, and recurrence and survival data. We will also log all sample collections from tissue and blood sources, as well as results from any relevant testing done. These databases will be available online to study staff, but only with a secure, password-protected login system

This study will be run from Dana-Farber Cancer Institute. Study staff will computerize the data from the patient questionnaires. In addition, study staff will computerize medical information on each of the study participants into the centralized, secure database. For patients invited into the study but who choose not to participate, there will be no retention of patient identifiers. Study staff will record the age, race, date of surgery, and treating institution of all patients who decline participation to allow for demographic comparison of participants and nonparticipants.

Data will be collected, coded, and managed by study staff only. Data and software will be backed up on a nightly basis as per our institutional norm.

## 11.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of

intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

### 11.3 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix J.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

### 11.4 Collaborative Research and Future Use of Data and Biospecimens

Tissue, blood, bodily fluids, and other materials derived from these will be collected in this study to analyze genes, DNA, RNA, proteins and cells for the study's correlative endpoints and potential future research, utilizing new types of biomarker testing as it becomes available.

These samples and any data generated as a part of these clinical trials may be used for future research studies and may be provided to collaborating investigators both within and outside of the DF/HCC for either correlative endpoints or secondary use. Samples and data may be shared with outside non-profit academic investigators, as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate. When samples or data are sent to collaborators and when any research is performed on them, all information will be identified with a code, and will not contain any PHI, such as name, birthday, or MRNs.

In order to allow the greatest amount of research to be performed on the specimens and information generated as a part of this trial, researchers in this study may share results of genetic sequencing with other scientists. De-identified specimen or genetic data may be placed into one of more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). The results from the correlative research on this study will be shared with these public databases. Through such databases, researchers from around the world will have access to de-identified samples or data for future research. More detailed information, beyond the public database, may only be accessed by scientists at other research centers who have received special permission to review de-identified data.

## 12. STUDY TIMELINES

We aim to enroll 40 patients across all participating sites over approximately 12 months.

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Study Design/Endpoints

This is a feasibility study, aimed to examine our ability to administer neo/adjuvant chemotherapy

to older patients with breast cancer using two distinct regimens for triple negative and hormone receptor-positive, HER2-negative disease without excessive toxicity. Given the small sample size of this trial, this study is not powered on disease outcomes or laboratory assessments, but we will collect and descriptively analyze many study elements, some of which will be combined with other studies of older patients with breast cancer as described below.

Any patient who receives one dose of chemotherapy on study will be included in analyses. Any patient who screens or registers but never starts therapy will be replaced so that a total of 40 evaluable patients will be included. If patients who are approached decline enrollment, we will capture the reasons for declining.

## 13.2 Primary Endpoint

Primary Endpoint: Feasibility for each cohort, with feasibility defined as ≥80% of patients receiving ≥80% of intended therapy with up to 2 dose changes for toxicity.[1,2] Participants in each cohort should receive ≥10 weeks of scheduled therapy including up to two dose reductions and/or treatment delays (i.e. up to 2 holds/reductions in total, including one dose change for one agent or two dose changes/delays for one agent).

## 13.3 Secondary Endpoints

Given small sample sizes, these outcomes will be descriptive and exploratory but will provide preliminary information to inform further study.

1. Changes in GA over time.
   We will examine various elements of the GA including functional status, social support, number of falls and nutritional status over time for patients on each chemotherapy cohort and at the 3-month follow-up visit. The trajectory of recovery will also be explored for patients who report decline in one of the domains. We will also use specific elements of the GA to predict for and examine associations with toxicity and outcomes. We will also ascertain how much providers felt the information from the GA was useful and if they liked the way the information was presented.

2. Toxicity.
   We will describe the toxicities experienced by patients for each cohort at each cycle using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (once every three weeks for 4 cycles) and will examine hematologic and non-hematologic toxicities by grade and type and offending agent. We will focus on grade 2 or higher events that are possibly, probably, or definitely related to treatment. We will also examine toxicity at 3 months after treatment and at 12 months after treatment completes to assess for persisting symptoms or resolution of symptoms.

3. NCI PRO-CTCAE.
   We will describe the PROs reported by patients for each cohort using our NCI PRO-CTCAE surveys done at the start of each chemotherapy cycle, end of treatment, 3 months after treatment ends, and at one year after treatment ends. We will also examine

correlations between Provide-reported CTCAE in #2 with patient-reported events.

4. Consequences of toxicity or disease events.
   We will describe any dose modifications, treatment omissions, hospitalizations, emergency room evaluations, and early treatment cessation (and the reasons for these events) while on study treatment and in follow-up for each cohort. We will compare toxicity events in an exploratory fashion for the cohorts and by patient variables and demographics.

5. Tumor immune microenvironment.
   We will explore tumor genomics and tumor microenvironment on archived tissue samples obtained at baseline from surgery (adjuvant patients on each cohort). We will also explore tumor microenvironment on paired archived biopsy and surgical samples from those having pre-operative therapy, where fresh tissue will also be available (neoadjuvant patients on each cohort). We will describe the findings with regard to mutations found, mutational burden, differences in mutation profiles by disease subtype, and will have the ability to combine these data with those on protocol 18-634, the 'Elevate' trial, which is a longitudinal cohort of older patients where similar sample collections and analyses are planned.

6. Toxicity predictions.
   We will describe the toxicities predicted and the severity of toxicities predicted by provider estimates at baseline (Appendix C). We will also calculate the toxicity risk prediction using Dr. Hurria's prediction model at start of therapy[3] and how these predictions correlate with one another and actual grade 3 and higher toxicities experienced using correlation coefficients.

7. CHIP analyses.
   We will examine blood for clonal hematopoiesis of indeterminate potential (CHIP) and associations of CHIP results with survival outcomes, breast cancer outcomes, and toxicity events, particularly hematologic toxicity events that occur while on chemotherapy.

8. Invasive disease-free survival – this will be defined as the as occurrence of any of the following over the initial 2-year and potential 5-year period[98] for all patients on study:

   - Ipsilateral invasive breast cancer recurrence
   - Regional invasive breast cancer recurrence
   - Distant recurrence
   - Death attributable to any cause
   - Contralateral invasive breast cancer
   - Second non-breast invasive cancer

9. Local recurrences- this will be defined as the number of in-breast recurrences, chest wall recurrences after mastectomy, and axillary recurrences over the initial 2-year and 5-year period for all patients on study:

10. Distant recurrences- This will be defined as the number of recurrences occurring with or without localized recurrence that have occurred distant to the breast, namely metastatic disease.

11. Overall survival – This is defined as the time from registration to death due to any cause or censored at date last known alive. We will also examine breast cancer-specific survival and cause of death for all 40 patients.

12. Progression-Free survival (PFS): This is defined as the time form registration to the earliest of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

13. Tumor genomics: We will describe the mutations seen on archived tumors and mutational load. This will be combined with tumor samples from protocol 18-634, The 'Elevate' trial which is an observational cohort for non-metastatic breast cancer patients who are 70 and older.

## 13.4 Sample Size, Accrual Rate and Study Duration

With an accrual goal of 40 patients, we anticipate that 5-15 patients at each site will enroll over the course of 6-9 months, with approximately 4-6 patients per month across all centers. Any patient who receives one dose of chemotherapy on study will be included in analyses. Any patient who screens or registers but never starts therapy will be replaced so that a total of 40 evaluable patients will be included. If patients who are approached decline enrollment, we will capture the reasons for decline. The active part of the study will end at the three-month time point for follow-up, but we will follow patients using medical records for up to 2 years after their study treatment completes.

| **Accrual Targets** | | | | | | |
|---|---|---|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | | | | |
| | **Females** | | **Males** | | **Total** | |
| Hispanic or Latino | 5 | + | 0 | = | 5 | |
| Not Hispanic or Latino | 33-34 | + | 1-2 | = | 35 | |
| **Ethnic Category: Total of all subjects** | 38-39 (A1) | + | 1-2 (B1) | = | 40 (C1) | |
| **Racial Category** | | | | | | |
| American Indian or Alaskan Native | 1 | + | 0 | = | 1 | |
| Asian | 5 | + | 0 | = | 5 | |
| Black or African American | 5 | + | 0 | = | 5 | |
| Native Hawaiian or other Pacific Islander | 2 | + | 0 | = | 2 | |
| White | 25-26 | + | 1-2 | = | 27 | |
| **Racial Category: Total of all subjects** | 38-39 (A2) | + | 1-2 (B2) | = | 40 (C2) | |
| | (A1 = A2) | | (B1 = B2) | | (C1 = C2) | |

### 13.5 Analysis of Primary Endpoints

Primary analysis population includes any patient who receives treatment. Feasibility will be achieved if upper bound of two-sided 90% confidence interval using the exact binomial methods covers 80% response rate, which is consistent with observing 29 patients among the 40 patients we enroll.

### 13.6 Analysis of Secondary Endpoints

All analyses of exploratory endpoints in this study are exploratory in nature. For baseline continuous endpoint data, descriptive statistics, including mean, standard deviation, minimum and maximum values, will be provided for each cohort. For categorical data, the number and percentage of patients in each category will be provided by cohort. For survival endpoints, the distributions of PFS and OS in each cohort will be estimated using Kaplan-Meier methods with 90% confidence bands.

### 13.7 Interim Monitoring Plan

Because this study is a pilot study of 20 patients in each cohort alone using relatively standard therapy for breast cancer, there is no interim plan for monitoring of cessation of study accrual.

## 14. PUBLICATION PLAN

The results will be presented and released to patients in a IRB-approved letter as soon as they have been analyzed, within 24 months of reaching the end of the study. We will first examine the primary endpoint of feasibility and will then perform additional secondary analyses as outlined which may be reported separately or in the future. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

## 15. REFERENCES

1. Laurent M, Paillaud E, Tournigand C, et al. Assessment of solid cancer treatment feasibility in older patients: a prospective cohort study. Oncologist 2014;19:275-82.
2. Sud S, Lai P, Zhang T, Clemons M, Wheatley-Price P. Chemotherapy in the oldest old: The feasibility of delivering cytotoxic therapy to patients 80 years old and older. J Geriatr Oncol 2015;6:395-400.
3. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29:3457-65.
4. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758-65.
5. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106.
6. American Cancer Society. Breast Cancer Facts and Figures 2015-2016. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-046381.pdf
7. Schonberg MA, Marcantonio ER, Li D, Silliman RA, Ngo L, McCarthy EP. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. J Clin Oncol 2010;28:2038-45.
8. Schonberg MA, Marcantonio ER, Ngo L, Li D, Silliman RA, McCarthy EP. Causes of death and relative survival of older women after a breast cancer diagnosis. J Clin Oncol 2011;29:1570-7.
9. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med 1994;120:104-10.
10. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. Jama 2001;285:885-92.
11. Chen HL, Zhou MQ, Tian W, Meng KX, He HF. Effect of Age on Breast Cancer Patient Prognoses: A Population-Based Study Using the SEER 18 Database. PLoS One 2016;11:e0165409.
12. Partridge AH, Hughes ME, Warner ET, et al. Subtype-Dependent Relationship Between Young Age at Diagnosis and Breast Cancer Survival. J Clin Oncol 2016;34:3308-14.
13. Smith BD, Jiang J, McLaughlin SS, et al. Improvement in breast cancer outcomes over time: are older women missing out? J Clin Oncol 2011;29:4647-53.
14. Freedman RA, Keating NL, Lin NU, et al. Breast cancer-specific survival by age: Worse outcomes for the oldest patients. Cancer 2018;124:2184-91.
15. Griggs JJ, Culakova E, Sorbero ME, et al. Social and racial differences in selection of breast cancer adjuvant chemotherapy regimens. J Clin Oncol 2007;25:2522-7.
16. Freedman RA, Hughes ME, Ottesen RA, et al. Use of adjuvant trastuzumab in women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer by race/ethnicity and education within the National Comprehensive Cancer Network. Cancer 2013;119:839-46.
17. Freedman RA, He Y, Winer EP, Keating NL. Trends in racial and age disparities in definitive local therapy of early-stage breast cancer. J Clin Oncol 2009;27:713-9.
18. Freedman RA, Vaz-Luis I, Barry WT, et al. Patterns of chemotherapy, toxicity, and

short-term outcomes for older women receiving adjuvant trastuzumab-based therapy. Breast Cancer Res Treat 2014;145:491-501.
19. Vaz-Luis I, Keating NL, Lin NU, Lii H, Winer EP, Freedman RA. Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. J Clin Oncol 2014;32:927-34.
20. Vaz-Luis I, Lin NU, Keating NL, et al. Treatment of early-stage human epidermal growth factor 2-positive cancers among medicare enrollees: age and race strongly associated with non-use of trastuzumab. Breast Cancer Res Treat 2016;159:151-62.
21. Biggers A, Shi Y, J. C, et al. Medicare D Subsidies and Racial Disparities in Persistence and Adherence With Hormonal Therapy. J Clin Oncol 2016;Published online before print on October 24, 2016.
22. Farias AJ, Du XL. Association Between Out-Of-Pocket Costs, Race/Ethnicity, and Adjuvant Endocrine Therapy Adherence Among Medicare Patients With Breast Cancer. J Clin Oncol 2017;35:86-95.
23. Shak S, Petkov VI, Miller DP, et al. Breast Cancer Specific Survival in 38,568 Patients with Node Negative Hormone Receptor Positive Invasive Breast Cancer and Oncotype DX Recurrence Score Results in the SEER Database. Presented at the San Antonio Breast Cancer Research Symposium 2015.
24. Muss HB, Berry DA, Cirrincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med 2009;360:2055-65.
25. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. J Clin Oncol 2009;27:1177-83.
26. Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005;23:5542-51.
27. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Coll Cardiol 2012;60:2504-12.
28. Wolff AC, Blackford AL, Visvanathan K, et al. Risk of marrow neoplasms after adjuvant breast cancer therapy: the national comprehensive cancer network experience. J Clin Oncol 2015;33:340-8.
29. Freedman RA, Seisler DK, Foster JC, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome among older women receiving anthracycline-based adjuvant chemotherapy for breast cancer on Modern Cooperative Group Trials (Alliance A151511). Breast Cancer Res Treat 2017;161:363-73.
30. Kemeny MM, Peterson BL, Kornblith AB, et al. Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol 2003;21:2268-75.
31. Kornblith AB, Kemeny M, Peterson BL, et al. Survey of oncologists' perceptions of barriers to accrual of older patients with breast carcinoma to clinical trials. Cancer 2002;95:989-96.
32. Javid SH, Unger JM, Gralow JR, et al. A prospective analysis of the influence of older age on physician and patient decision-making when considering enrollment in breast cancer clinical trials (SWOG S0316). Oncologist 2012;17:1180-90.
33. Lara PN, Jr., Higdon R, Lim N, et al. Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrollment. J Clin Oncol 2001;19:1728-33.

34. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21:1383-9.
35. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061-7.
36. Simon MS, Du W, Flaherty L, et al. Factors associated with breast cancer clinical trials participation and enrollment at a large academic medical center. J Clin Oncol 2004;22:2046-52.
37. Gross CP, Filardo G, Mayne ST, Krumholz HM. The impact of socioeconomic status and race on trial participation for older women with breast cancer. Cancer 2005;103:483-91.
38. Unger JM, Hershman DL, Albain KS, et al. Patient income level and cancer clinical trial participation. J Clin Oncol 2013;31:536-42.
39. Basche M, Baron AE, Eckhardt SG, et al. Barriers to enrollment of elderly adults in early-phase cancer clinical trials. Journal of oncology practice / American Society of Clinical Oncology 2008;4:162-8.
40. Kimmick G. Clinical trial accrual in older cancer patients: The most important steps are the first ones. J Geriatr Oncol 2016;7:158-61.
41. Ayodele O, Akhtar M, Konenko A, et al. Comparing attitudes of younger and older patients towards cancer clinical trials. J Geriatr Oncol 2016;7:162-8.
42. Avis NE, Smith KW, Link CL, Hortobagyi GN, Rivera E. Factors associated with participation in breast cancer treatment clinical trials. J Clin Oncol 2006;24:1860-7.
43. Kimmick GG, Peterson BL, Kornblith AB, et al. Improving accrual of older persons to cancer treatment trials: a randomized trial comparing an educational intervention with standard information: CALGB 360001. J Clin Oncol 2005;23:2201-7.
44. Coyne CA, Xu R, Raich P, et al. Randomized, controlled trial of an easy-to-read informed consent statement for clinical trial participation: a study of the Eastern Cooperative Oncology Group. J Clin Oncol 2003;21:836-42.
45. Treweek S, Lockhart P, Pitkethly M, et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. BMJ Open 2013;3.
46. Treweek S, Pitkethly M, Cook J, et al. Strategies to improve recruitment to randomised controlled trials. Cochrane Database Syst Rev 2010:MR000013.
47. Hack TF, Whelan T, Olivotto IA, et al. Standardized audiotape versus recorded consultation to enhance informed consent to a clinical trial in breast oncology. Psychooncology 2007;16:371-6.
48. Hurria A, Cohen HJ, Extermann M. Geriatric Oncology Research in the Cooperative Groups: A Report of a SIOG Special Meeting. J Geriatr Oncol 2010;1:40-4.
49. Hurria A, Dale W, Mooney M, et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J Clin Oncol 2014;32:2587-94.
50. Hurria A, Levit LA, Dale W, et al. Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement. J Clin Oncol 2015;33:3826-33.
51. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013;31:2382-7.
52. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med

2004;351:971-7.
53. Mohile S, Hurria A, Dale W. Introduction to U13 supplement. J Geriatr Oncol 2016;7:223-4.
54. Freedman RA, Foster JC, Seisler DK, et al. Accrual of Older Patients With Breast Cancer to Alliance Systemic Therapy Trials Over Time: Protocol A151527. J Clin Oncol 2017;35:421-31.
55. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014;15:747-56.
56. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 2015;33:13-21.
57. Alba E, Chacon JI, Lluch A, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study. Breast Cancer Res Treat 2012;136:487-93.
58. Vernieri C, Milano M, Mennitto A, et al. Antitumor activity and safety profile of weekly carboplatin plus paclitaxel in metastatic breast cancer: a ten-year, monocentric, retrospective study. Breast Cancer Res Treat 2017;165:365-73.
59. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378:1079-88.
60. Socinski MA, Okamoto I, Hon JK, et al. Safety and efficacy analysis by histology of weekly nab-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer. Ann Oncol 2013;24:2390-6.
61. Maemondo M, Inoue A, Sugawara S, et al. Randomized phase II trial comparing carboplatin plus weekly paclitaxel and docetaxel alone in elderly patients with advanced non-small cell lung cancer: north japan lung cancer group trial 0801. Oncologist 2014;19:352-3.
62. Huang L, Chen S, Yao L, Liu G, Wu J, Shao Z. Phase II trial of weekly nab-paclitaxel and carboplatin treatment with or without trastuzumab as nonanthracycline neoadjuvant chemotherapy for locally advanced breast cancer. Int J Nanomedicine 2015;10:1969-75.
63. Sharma P, Lopez-Tarruella S, Garcia-Saenz JA, et al. Efficacy of Neoadjuvant Carboplatin plus Docetaxel in Triple-Negative Breast Cancer: Combined Analysis of Two Cohorts. Clin Cancer Res 2017;23:649-57.
64. Barcenas CH, Niu J, Zhang N, et al. Risk of hospitalization according to chemotherapy regimen in early-stage breast cancer. J Clin Oncol 2014;32:2010-7.
65. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-9.
66. Masuda N, Nakayama T, Yamamura J, et al. Phase I study of combination therapy with weekly paclitaxel and cyclophosphamide for advanced or recurrent breast cancer. Cancer Chemother Pharmacol 2010;66:89-94.
67. Kutomi G, Ohmura T, Satomi F, et al. A phase I study of combination therapy with nanoparticle albumin-bound paclitaxel and cyclophosphamide in patients with metastatic or

recurrent breast cancer. International journal of clinical oncology / Japan Society of Clinical Oncology 2015;20:474-9.
68. Sessa C, Pagani O, Martinelli G, et al. Dose-finding study of paclitaxel and cyclophosphamide in women with advanced breast cancer. Semin Oncol 1997;24:S17-52-S17-57.
69. Pagani O, Sessa C, Martinelli G, et al. Dose-finding study of paclitaxel and cyclophosphamide in advanced breast cancer. Ann Oncol 1997;8:655-61.
70. Cyclophosphamide and Paclitaxel With or Without Trastuzumab in Stage I-II Breast Cancer Who Have Undergone Surgery. https://clinicaltrials.gov/ct2/show/results/NCT01106898?sect=X70156&view=results#outcome1-NCT01106898.
71. https://www.nytimes.com/2018/04/13/health/elderly-clinical-trials.html Accessed May 29, 2018.
72. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007;25:1824-31.
73. Extermann M, Aapro M, Bernabei R, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005;55:241-52.
74. Freyer G, Geay JF, Touzet S, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. Ann Oncol 2005;16:1795-800.
75. Maione P, Perrone F, Gallo C, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 2005;23:6865-72.
76. Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer 2009;115:4547-53.
77. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. J Clin Oncol 2011;29:1290-6.
78. Fillenbaum GG, Smyer MA. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. Journal of gerontology 1981;36:428-34.
79. Fillenbaum GG. Screening the elderly. A brief instrumental activities of daily living measure. Journal of the American Geriatrics Society 1985;33:698-706.
80. Stewart AL W, J.E. Jr. Measuring functioning and well-being: The Medical Outcomes Study approach. Durham, NC: Duke University Press; 1992.
81. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 1980;45:2220-4.
82. Loprinzi CL, Laurie JA, Wieand HS, et al. Prospective evaluation of prognostic variables from patient-completed questionnaires. North Central Cancer Treatment Group. J Clin Oncol 1994;12:601-7.
83. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39:142-8.
84. Rock EP, Kennedy DL, Furness MH, Pierce WF, Pazdur R, Burke LB. Patient-reported outcomes supporting anticancer product approvals. J Clin Oncol 2007;25:5094-9.
85. Basch E, Deal AM, Dueck AC, et al. Overall Survival Results of a Trial Assessing

Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA 2017;318:197-8.
86. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. Journal of the National Cancer Institute 2009;101:1624-32.
87. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol 2004;22:3485-90.
88. Petersen MA, Larsen H, Pedersen L, Sonne N, Groenvold M. Assessing health-related quality of life in palliative care: comparing patient and physician assessments. Eur J Cancer 2006;42:1159-66.
89. Adalsteinsson V, Ha G, Freeman S, et al. Scalable whole-exome sequencing of cell-free DNA reveals high concordance with metastatic tumors. Nature communications 2017; in press.
90. Marsh T, Wong I, Sceneay J, et al. Hematopoietic Age at Onset of Triple-Negative Breast Cancer Dictates Disease Aggressiveness and Progression. Cancer Res 2016;76:2932-43.
91. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. N Engl J Med 2017;377:111-21.
92. Gibson CJ, Lindsley RC, Tchekmedyian V, et al. Clonal Hematopoiesis Associated With Adverse Outcomes After Autologous Stem-Cell Transplantation for Lymphoma. J Clin Oncol 2017;35:1598-605.
93. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood 2015;126:9-16.
94. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018;36:2105-22.
95. National Cancer Institute: Division of Cancer Control and Population Sciences. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). https://healthcaredelivery.cancer.gov/pro-ctcae/. Accessed May 25, 2018.
96. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci 2007;62:722-7.
97. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet 2018;391:1775-82.
98. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol 2007;25:2127-32.

**APPENDIX A GERIATRIC ASSESSMENT – PATIENT QUESTIONNAIRE**

*Note: demographics in section I only need to be asked at baseline. Other components should be asked each time the GA is administered.*

Responsible person name (Nurse,or CRA) _____

Date assessment was completed_____

Person completing the assessment (patient, other. If other, please explain relationship to patient)

_____

## I. DEMOGRAPHICS

We would like to know a bit more details about you so we know about the characteristics of people participating in the Elevate study. You may skip any questions you prefer not to answer but we assure you this is for demographics only and your answers will be kept completely confidential.

1. What is the highest grade you finished in school? *(Mark one with an X.)*
   - ☐ Less than 9 years of school
   - ☐ Some high school (9-11 years)
   - ☐ High school graduate, or GED
   - ☐ Some college or technical school
   - ☐ College degree graduate
   - ☐ Graduate degree
   - ☐ Post graduate education, but no higher degree
   - ☐ I prefer not to answer

2. What is your marital status? *(Mark one with an X.)*
   - ☐ Married
   - ☐ Domestic partnership
   - ☐ Widowed
   - ☐ Divorced
   - ☐ Separated
   - ☐ Never married
   - ☐ I prefer not to answer

*3.* With whom do you live? *(Mark all that apply with an X.)*
   - ☐ Spouse / partner
   - ☐ Parents/ parents-in-law
   - ☐ Girlfriend / boyfriend
   - ☐ Live alone
   - ☐ Children aged 18 years or younger
   - ☐ Children over aged 18 years
   - ☐ Other relative, specify: _____
   - ☐ Others, specify: _____

4. What is your current employment status? *(Mark one with an X.)*
   - ☐ Employed 32 hours per week or more
   - ☐ Employed less than 32 hours per week
   - ☐ Retired
   - ☐ Unemployed
   - ☐ Homemaker
   - ☐ Disabled
   - ☐ On medical leave
   - ☐ Student full-time
   - ☐ Other, specify: _____

5. What is your current annual household income?
   - ☐ Less than $20,000
   - ☐ $20-40,000
   - ☐ $40,001-$60,000
   - ☐ $60,001-$80,000
   - ☐ $80,001-$100,000
   - ☐ More than $100,000
   - ☐ I prefer not to answer

6. In what country were you born?
   - ☐ US
   - ☐ Other _____

7. Is English your first language?
   - ☐ Yes
   - ☐ No → 7A. If no, what is your first language? _____

8. Do you consider yourself to be Hispanic or Latina? Hispanic, Spanish, or Latina is a person of Mexican, Puerto Rican, Cuban, South or Central American, or other Spanish culture of origin, regardless of race.
   - ☐ Yes, Hispanic or Latina
   - ☐ No, not Hispanic or Latina

9. Which of the following would you use to describe yourself? *Check all that apply.*
   - ☐ Native Hawaiian or other Pacific Islander
   - ☐ American Indian or Alaska Native
   - ☐ Asian
   - ☐ Black or African American
   - ☐ White
   - ☐ Other (write in) _____

10. Which one of the following best describes the location of where you live?

☐ Urban (you live in a city)
☐ Suburban (you live in a suburb of a city, within 30 miles of a city)
☐ Rural (you live outside the city, in the countryside, over 30 miles from a city)
☐ Other (please describe) _____

**APPENDIX A, continued**
**GERIATRIC ASSESSMENT – PATIENT QUESTIONNAIRE**
**(Note: provider component is in appendix B)**

Responsible person name (Nurse,or CRA)_____

Date assessment was completed_____

Person completing the assessment (patient, other. If other, please explain relationship to patient)

_____

☐ **Mark box with an "X", if form was not completed at specified timepoint and specify reason:**

*(Mark one with an X):* ☐ Patient refused ☐ Patient withdrew consent ☐ Not done
☐ Other, specify: _____

**A. DAILY ACTIVITIES***

**PATIENT INSTRUCTIONS:** Indicate your response by marking an X in one box per question.

**1.** Can you use the telephone?
☐ without help, including looking up and dialing
☐ with some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the phone number or dialing)
☐ completely unable to use the telephone

**2.** Can you get to places out of walking distance?
☐ without help (can travel alone on buses, taxis, or drive your own car)
☐ with some help (need someone to help you or go with you when traveling); or
☐ unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance

**3.** Can you go shopping for groceries or clothes (assuming you have transportation)?
☐ without help (taking care of all shopping needs yourself, assuming you have transportation)
☐ with some help (need someone to go with you on all shopping trips)
☐ completely unable to do any shopping

**4.** Can you prepare your own meals?
☐ without help (plan and cook full meals yourself)
☐ with some help (can prepare some things but unable to cook full meals yourself)
☐ completely unable to prepare any meals

**5.** Can you do your housework?
☐ without help (can clean floors, etc.)
☐ with some help (can do light housework but need help with heavy work)
☐ completely unable to do any housework

**6.** Can you take your own medicines?
- ☐ without help (in the right doses at the right time)
- ☐ with some help (able to take medicine if someone prepares it for you and/or reminds you to take it)
- ☐ completely unable to take your medicines

**7.** Can you handle your own money?
- ☐ without help (write checks, pay bills, etc.)
- ☐ with some help (manage day-to-day buying but need help with managing your checkbook and paying your bills)
- ☐ completely unable to handle money

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

## B. PHYSICAL ACTIVITIES*

**1.** The following items are activities you might do during a typical day. How much does your health limit you in these activities? **(*Mark an X in the box on each line that best reflects your situation.*)**

| Activities | Limited a lot | Limited a little | Not limited at all |
|---|---|---|---|
| **A.** Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports | ☐1 | ☐2 | ☐3 |
| **B.** Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | ☐1 | ☐2 | ☐3 |
| **C.** Lifting or carrying groceries | ☐1 | ☐2 | ☐3 |
| **D.** Climbing several flights of stairs | ☐1 | ☐2 | ☐3 |
| **E.** Climbing one flight of stairs | ☐1 | ☐2 | ☐3 |
| **F.** Bending, kneeling, or stooping | ☐1 | ☐2 | ☐3 |
| **G.** Walking more than a mile | ☐1 | ☐2 | ☐3 |
| **H.** Walking several blocks | ☐1 | ☐2 | ☐3 |
| **I.** Walking one block | ☐1 | ☐2 | ☐3 |
| **J.** Bathing or dressing yourself | ☐1 | ☐2 | ☐3 |

* MOS, Physical Functioning Scale – Stewart, A.L. and Ware, J.E., 1992

## C. CURRENT HEALTH RATING

Which one of the following phrases best describes you at this time? *(Mark one with an X.)*

1. Would you say your general health is?
   - ☐ Excellent
   - ☐ Very good
   - ☐ Good
   - ☐ Fair
   - ☐ Poor

2. Which one of the following phrases best describes you at this time? *Please choose only one.*
   - ☐ Normal, no complaints, no symptoms of disease
   - ☐ Able to carry on normal activity, minor symptoms of disease
   - ☐ Normal activity with effort, some symptoms of disease
   - ☐ Care for self, unable to carry on normal activity or do active work
   - ☐ Require occasional assistance but able to care for most of personal needs
   - ☐ Require considerable assistance for personal care
   - ☐ Disabled, require special care and assistance
   - ☐ Severely disabled, require continuous nursing care

3. Besides breast cancer, have you been told by a doctor or health care professional that you had another type of cancer (other than non-melanoma skin cancers)?
   - ☐ No
   - ☐ Yes

4. Have you been told by a doctor or health professional that you have diabetes, including borderline diabetes or pre-diabetes?
   - ☐ No
   - ☐ Yes → How much does diabetes interfere with your activities?
     - ☐ Not at all
     - ☐ A little
     - ☐ A great deal

5. Do you need help from other people with household chores or to go shopping?
   - ☐ No
   - ☐ Yes

6. By yourself without help, how difficult is it for you to walk a quarter of a mile (about 3 city blocks)?
   - ☐ Not at all
   - ☐ A little difficult
   - ☐ Very difficult
   - ☐ I can only do it with a cane or walker

7. Which best describes your cigarette use?
   - ☐ Never smoked
   - ☐ Smoked less than 100 cigarettes in your life
   - ☐ Current smoker

8. In the past 12 months, how many times did you stay in the hospital overnight?
   - ☐ None - I did not stay in the hospital overnight
   - ☐ Once
   - ☐ Two times or more

---

**D. FALLS**

9. How many times have you fallen in the last 6 months? _____

---

**E. YOUR FEELINGS***

10. Do you often feel sad or depressed?
    - ☐ No
    - ☐ Yes

11. On average, how would you describe your level of anxiety? Please circle the number (0-10) that best reflects your feelings **during the past week, including today**.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No anxiety | | | | | | | | | | Anxiety as bad as it can be |

* Mahoney et al., 1994; LASA – Locke et al., 2007

**F. YOUR HEALTH***

Do you have any of the following illnesses at the present time, and if so, how much does it interfere with your activities: **Not at All, A Little, or A Great Deal?**

12. Other cancers or leukemia
    - ☐ No
    - ☐ Yes → How much does it interfere with your activities?
      - ☐ Not at all
      - ☐ A little
      - ☐ A great deal

13. Arthritis or rheumatism

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

14. Glaucoma

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

15. Emphysema or chronic bronchitis

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

16. High blood pressure

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

17. Heart trouble

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

18. Circulation trouble in arms or legs

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

19. Stomach or intestinal disorders

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

20. Osteoporosis

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

21. Liver Disease

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

22. Stroke

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

23. Depression

☐ No
☐ Yes →

How much does it interfere with your activities?
☐ Not at all
☐ A little
☐ A great deal

24. How is your eyesight (with glasses or contacts)?
    - ☐ Excellent
    - ☐ Good
    - ☐ Fair
    - ☐ Poor
    - ☐ Totally blind

25. How is your hearing (with a hearing aid, if needed)?
    - ☐ Excellent
    - ☐ Good
    - ☐ Fair
    - ☐ Poor
    - ☐ Totally deaf

26. Do you have any other physical problems or illnesses (other than listed in questions 12-25) at the present time that seriously affect your health?
    - ☐ No
    - ☐ Yes, specify: _____

    → How much does this interfere with your activities?
    - ☐ Not at all
    - ☐ Somewhat
    - ☐ A great deal

27. Have you lost weight without trying over the last 6 months?
    - ☐ No
    - ☐ Yes →

    How much have you lost?
    _____ pounds

28. What is your weight now? _____ pounds

29. What was your weight 6 months ago? _____ pounds

30. How many medications (either prescribed or over-the-counter), herbs, or vitamins do you currently take? _____ number of medications

31. Please list all prescribed or over-the-counter medicines, herbs, or vitamins you are currently taking (doses not necessary).

| | |
|---|---|
| 1. | |
| 2. | |
| 3. | |
| 4. | |
| 5. | |
| 6. | |
| 7. | |
| 8. | |
| 9. | |
| 10. | |
| 11. | |
| 12. | |

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

## G. HEALTH QUESTIONNAIRE*

**INSTRUCTIONS:**

32. Please tell us how you have been feeling within the past month. Please mark an "X" in the box on each line that best reflects your situation.

| **How much of the time during the past month:** | **All of the Time** | **Most of the Time** | **A Good Bit of the Time** | **Some of the Time** | **A Little of the Time** | **None of the Time** |
|---|---|---|---|---|---|---|
| a. Has your daily life been full of things that were interesting to you? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. Did you feel depressed? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. Have you felt loved and wanted? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. Have you been a very nervous person? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. Have you been in firm control of your behavior, thoughts, emotions, feelings? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| f. Have you felt tense or high-strung? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| g. Have you felt calm and peaceful? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| h. Have you felt emotionally stable? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| i. Have you felt downhearted and blue? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| j. Have you felt restless, fidgety, or impatient? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| k. Have you been moody, or brooded about things? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| l. Have you felt cheerful, light-hearted? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| m. Have you been in low or very low spirits? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| n. Were you a happy person? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| o. Did you feel you had nothing to look forward to? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| p. Have you felt so down in the dumps that nothing could cheer you up? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| q. Have you been anxious or worried? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

* MHI-17 – Stewart, A.L. and Ware, J.E., 1992

## H. SOCIAL ACTIVITIES*

1. During the past 4 weeks, how much time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? *(Mark one with an X.)*

   ☐ 1 All of the time
   ☐ 2 Most of the time
   ☐ 3 Some of the time
   ☐ 4 A little of the time
   ☐ 5 None of the time

2. Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition? *(Mark one with an X.)*

   ☐ 1 Much less socially active than before
   ☐ 2 Somewhat less socially active than before
   ☐ 3 About as socially active as before
   ☐ 4 Somewhat more socially active as before
   ☐ 5 Much more socially active than before

3. Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems? *(Mark one with an X.)*

   ☐ 1 Much more limited than others
   ☐ 2 Somewhat more limited than others
   ☐ 3 About the same as others
   ☐ 4 Somewhat less limited than others
   ☐ 5 Much less limited than others

* MOS, Social Activities – Stewart, A.L. and Ware, J.E., 1992

## I. SOCIAL SUPPORT*

**INSTRUCTIONS:** People sometimes look to others for companionship, assistance or other types of support. How often is each of the following kind of support available to you if you need it? (*Mark an X in the box on each line that best reflects your situation.*)

| | **None of the Time** | **A Little of the Time** | **Some of the Time** | **Most of the Time** | **All of the Time** |
|---|---|---|---|---|---|
| 1. Someone to help you if you were confined to bed. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. Someone you can count on to listen to you when you need to talk. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. Someone to give you good advice about a crisis. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. Someone to take you to the doctor if you needed it. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. Someone to give you information to help you understand a situation. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. Someone to confide in or talk to about yourself or your problem. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. Someone to prepare your meals if you were unable to do it yourself. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. Someone whose advice you really want. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. Someone to help you with daily chores if you were sick. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. Someone to share your most private worries and fears with. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. Someone to turn to for suggestions about how to deal with a personal problem. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. Someone who understands your problems. | ☐ | ☐ | ☐ | ☐ | ☐ |

* MOS Social Support Survey – Sherbourne, C.D. and Stewart, A.L., 1991

## J. SPIRITUALITY/RELIGION*

**Directions:** Please answer the following questions about your religious beliefs and/or involvement. (Please mark an "X" in the box on each line that best reflects your situation.)

1. How often do you attend church or other religious meetings? *(Mark one with an X.)*
   - ☐ 1 More than once/wk
   - ☐ 2 Once a week
   - ☐ 3 A few times a month
   - ☐ 4 A few times a year
   - ☐ 5 Once a year or less
   - ☐ 6 Never

2. How often do you spend time in private religious activities, such as prayer, meditation or Bible study? *(Mark one with an X.)*
   - ☐ 1 More than once a day
   - ☐ 2 Daily
   - ☐ 3 Two or more times/week
   - ☐ 4 Once a week
   - ☐ 5 A few times a month
   - ☐ 6 Rarely or never

*The following section contains 3 statements about religious belief or experience. Please mark the extent to which each statement is true or not true for you.*

3. In my life, I experience the presence of the Divine (i.e., God). *(Mark one with an X.)*
   - ☐ 1 Definitely true of me
   - ☐ 2 Tends to be true
   - ☐ 3 Unsure
   - ☐ 4 Tends *not* to be true
   - ☐ 5 Definitely *not* true

4. My religious beliefs are what really lie behind my whole approach to life. *(Mark one with an X.)*
   - ☐ 1 Definitely true of me
   - ☐ 2 Tends to be true
   - ☐ 3 Unsure
   - ☐ 4 Tends *not* to be true
   - ☐ 5 Definitely *not* true

5. I tried hard to carry my religion over into all other dealings in my life. *(Mark one with an X.)*
   - ☐ 1 Definitely true of me
   - ☐ 2 Tends to be true
   - ☐ 3 Unsure
   - ☐ 4 Tends *not* to be true
   - ☐ 5 Definitely *not* true

* DUREL: Duke University Religion Index – Koenig et al., 1997

## APPENDIX A: QUESTIONS CONCERNING THE BASELINE QUESTIONNAIRE

*Note: Questions concerning the baseline questionnaire only need to be asked at baseline.*

Responsible person name (Nurse,or CRA) _____

Date assessment was completed_____

Person completing the assessment (patient, other. If other, please explain relationship to patient)

_____

Thank you so much for completing the baseline ADVANCE survey! We now want to ask a few questions about how the survey went for you."

1. Were any of the questions difficult to understand?
   ☐ No
   ☐ Yes

   If Yes, which questions were they?

   | |
   |---|
   | |

2. Was the time it took to answer all the questions too long, just right or too short?
   ☐ Too short → How long would you have liked the questionnaire to be? ☐☐ minutes
   ☐ Just right
   ☐ Too long → How long would you have liked the questionnaire to be? ☐☐ minutes

   Which items would you remove?

   | |
   |---|
   | |

3. Did you find any of the questions upsetting?
   ☐ No
   ☐ Yes

   If Yes, which questions were they?

   | |
   |---|
   | |

   Could you tell us why they were upsetting?

   | |
   |---|
   | |

4. Do you think the questionnaire left out any questions that were important to ask?

   | |
   |---|
   | |

**THAT IS ALL THE QUESTIONS WE HAVE. THANK YOU.**

## APPENDIX B GERIATRIC ASSESSMENT FOR THE HEALTH CARE PROFESSIONAL

**I. This form completed by:** ***(Mark all that apply with an X.)***

☐ Physician ☐ Nurse ☐ CRA

Assessment Period (as applicable to this study)

☐ Baseline ☐Cycle 3 Day 1 ☐ End of Treatment ☐3 Months Post-tx ☐12 Months Post-Tx

**Mark box with an "X", if form was not completed at specified timepoint and specify reason:** *(Mark one with an X.)*

☐ Patient refused ☐ Patient withdrew consent ☐ Not done

☐ Other, specify _____

(For assessment date, record approximate date form was to be completed.)

**II. FUNCTIONAL STATUS**

A. KPS (Healthcare professional rated*)

Please rate your assessment of patient's Karnofsky Performance Status as of date this form is completed. *(Scale is listed below.)* ☐☐☐ %

| % | CRITERIA |
|---|---|
| **100** | Normal: no complaints; no evidence of disease |
| **90** | Able to carry on normal activity; only minor signs or symptoms of disease |
| **80** | Normal activity with effort; some signs or symptoms of disease |
| **70** | Cares for self, but unable to carry on normal activity or do active work |
| **60** | Requires occasional assistance, but is able to care for most personal needs |
| **50** | Requires considerable assistance and frequent medical care |
| **40** | Disabled; requires special care and assistance |
| **30** | Severely disabled; hospitalization is indicated although death not imminent |
| **20** | Very sick; hospitalization necessary; active supportive treatment necessary |
| **10** | Moribund; fatal processes progressing rapidly |
| **0** | Dead |

* Physician KPS – Karnofsky, D.A., et al., 1948

B. Timed "Up and Go"*

**INSTRUCTIONS:** The timed "Up and Go" measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm [approximately 1.5 ft]), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/her regular footwear and uses their customary walking aid (none, cane, walker, etc.) No physical assistance is given. The subject starts with his back against the chair, his arm resting on the chair's arm, and his walking aid in hand. He is instructed that on the word "go", he is to get up and walk at a comfortable and safe pace to a line on the floor 3 meters (approximately 10 feet) away, turn, and return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stop-watch can be used to time the performance.

Time to perform "Up and Go" ☐☐.☐ seconds

* Timed "Up and Go" – Podsiadlo, D. and Richardson, S., 1991

---

**III. COGNITION** ***This section is only completed Pretreatment and at the end of treatment***

| **ORIENTATION-MEMORY-CONCENTRATION TEST**** | | | |
|---|---|---|---|
| | **Patient's Response** | **Maximum errors** | **Final Score Weight score** |
| 1. What year is it now? [without looking at a calendar] | ☐☐☐☐ | 1 | ☐☐ x 4 = ☐☐ |
| **2.** What month is it now? [without looking at a calendar] | ☐☐ | 1 | ☐☐ x 3 = ☐☐ |
| **Memory Phrase:** Repeat this phrase after me: 'John Brown, 42 Market Street, Chicago' | | | |
| **3.** About what time is it? [ within 1 hour – without looking at your watch] | ☐☐:☐☐ | 1 | ☐☐ x 3 = ☐☐ |
| **4.** Count backwards 20 to 1. | | 2 | ☐☐ x 2 = ☐☐ |
| **5.** Say the months in reverse order. | | 2 | ☐☐ x 2 = ☐☐ |
| **6.** Repeat the Memory Phrase. | | 5 | ☐☐ x 2 = ☐☐ |
| | | | **TOTAL SCORE:** ☐☐ |

**Scoring**: For items 1 to 3, the response is either correct (score 0) or incorrect (score 1). For items 4 to 6, add one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all scores in "Final Score" column. Data from participants found to have gross cognitive impairment as determined by the Orientation-Memory-Concentration Score ≥11 will be excluded from the analysis. Maximum score = 28.

** OMC – Katzman, R., et al., 1983

## IV. SCORING

Did the patient score ≥11 on the Orientation-Memory-Concentration Test?

☐ No
☐ Yes (**If yes, notify the patient's treating physician.)**

## V. NUTRITION

What is the patient's height? (*from patient's chart*) ☐☐☐ cm

What is the patient's current weight? (*from patient's chart*) ☐☐☐ kg

What was the patient's weight approximately 6 months ago? *(from patient's chart or patients self-report)* ☐☐☐ kg

**APPENDIX C PROVIDER SURVEY AT BASELINE**
(Can be done on paper or email)

1. What is your best estimate of this patients ECOG PS status? See table below for reference if needed: _____

| Grade | ECOG |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| 5 | Dead |

2. As best as you can estimate, what do you think the likelihood is for this patient to develop a grade 3 or higher (severe of life threatening) toxicity event during their chemotherapy course?

   - ☐ Less than or equal to 10%
   - ☐ 10-20%
   - ☐ 21-40%
   - ☐ 41-60%
   - ☐ >60%
   - ☐ I am not sure, can't answer

3. As best as you can estimate, if a grade 3 or higher (severe or life threatening) toxicity event occurs, which do you think is/are most likely to occur in this patient? Please select up to three.

   - ☐ Neutropenia
   - ☐ Anemia
   - ☐ Thrombocytopenia
   - ☐ Liver dysfunction
   - ☐ Nausea or vomiting
   - ☐ Diarrhea
   - ☐ Fatigue
   - ☐ Pain or arthralgia
   - ☐ Poor appetite or weight loss
   - ☐ Mucositis
   - ☐ Neuropathy
   - ☐ Rashes
   - ☐ Infection
   - ☐ Pulmonary symptoms such as cough, shortness of breath
   - ☐ Other _____

## APPENDIX D PATIENT REPORTED OUTCOMES

The direct link to the specific PROs (approximately 40 brief questions on symptoms experienced in the last 7 days) to be used for this study is below and is available in many languages (English, traditional Chinese, Czech, Danish, Dutch, French, French Canadian, German, Greek, Hungarian, Italian, Japanese, Korean, Polish, Russian, Spanish). Appendix D has screen shots of the survey in English but all surveys in all available languages can be printed directly from the NCI website survey link here. Once on the survey link, you can click on the language of interest to get survey for printing. Patients will also be sent an email link for the survey in case they prefer to fill it out this way.

https://healthcaredelivery.cancer.gov/pro-ctcae/build.php?r=H76krM4DOAi

# NCI PRO-CTCAE™ ITEMS

**Item Library Version 1.0**
**English**
**Form created on 11 September 2018**

**As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...**

| | | | | | |
|---|---|---|---|---|---|
| 1. | In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 2. | In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 3. | In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 4. | In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 5. | In the last 7 days, how OFTEN did you have NAUSEA? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 6. | In the last 7 days, how OFTEN did you have VOMITING? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your VOMITING at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 7. | In the last 7 days, how OFTEN did you have HEARTBURN? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | |
|---|---|---|
| 8. | In the last 7 days, did you have any INCREASED PASSING OF GAS (FLATULENCE)? | |
| | ○ Yes | ○ No |

| | | | | | |
|---|---|---|---|---|---|
| 9. | In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 10. | In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 11. | In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |

| | | | | | |
|---|---|---|---|---|---|
| 12. | In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 13. | In the last 7 days, what was the SEVERITY of your COUGH at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 14. | In the last 7 days, how OFTEN did you have ARM OR LEG SWELLING? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your ARM OR LEG SWELLING at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 15. | In the last 7 days, how OFTEN did you feel a POUNDING OR RACING HEARTBEAT (PALPITATIONS)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your POUNDING OR RACING HEARTBEAT (PALPITATIONS)? at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | |
|---|---|---|
| 16. | In the last 7 days, did you have any RASH? | |
| | ○ Yes | ○ No |

| | | | | | |
|---|---|---|---|---|---|
| 17. | In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 18. | In the last 7 days, did you have any HAIR LOSS? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | |
|---|---|---|
| 19. | In the last 7 days, did you LOSE ANY FINGERNAILS OR TOENAILS? | |
| | ○ Yes | ○ No |

| | | |
|---|---|---|
| 20. | In the last 7 days, did you have any RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS? | |
| | ○ Yes | ○ No |

| | | |
|---|---|---|
| 21. | In the last 7 days, did you have any CHANGE IN THE COLOR OF YOUR FINGERNAILS OR TOENAILS? | |
| | ○ Yes | ○ No |

| | | | | | |
|---|---|---|---|---|---|
| 22. | In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 23. | In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 24. | In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 25. | In the last 7 days, what was the SEVERITY of RINGING IN YOUR EARS at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 26. | In the last 7 days, what was the SEVERITY of your PROBLEMS WITH CONCENTRATION at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did PROBLEMS WITH CONCENTRATION INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 27. | In the last 7 days, what was the SEVERITY of your PROBLEMS WITH MEMORY at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did PROBLEMS WITH MEMORY INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 28. | In the last 7 days, how OFTEN did you have PAIN? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your PAIN at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 29. | In the last 7 days, how OFTEN did you have a HEADACHE? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 30. | In the last 7 days, how OFTEN did you have ACHING MUSCLES? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 31. | In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 32. | In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 33. | In the last 7 days, how OFTEN did you feel ANXIETY? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 34. | In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 35. | In the last 7 days, were there times when you had to URINATE FREQUENTLY? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, how much did FREQUENT URINATION INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 36. | In the last 7 days, how OFTEN did you have LOSS OF CONTROL OF URINE (LEAKAGE)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, how much did LOSS OF CONTROL OF URINE (LEAKAGE) INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 37. | In the last 7 days, what was the SEVERITY of your DECREASED SEXUAL INTEREST at its WORST? | | | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe | ○ Not sexually active | ○ Prefer not to answer |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 38. | In the last 7 days, what was the SEVERITY of your PAIN DURING VAGINAL SEX at its WORST? | | | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe | ○ Not sexually active | ○ Prefer not to answer |

| | | |
|---|---|---|
| 39. | In the last 7 days, did you BRUISE EASILY (BLACK AND BLUE MARKS)? | |
| | ○ Yes | ○ No |

| | | | | | |
|---|---|---|---|---|---|
| 40. | In the last 7 days, how OFTEN did you have UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTTIME (NOT RELATED TO HOT FLASHES/FLUSHES)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTTIME (NOT RELATED TO HOT FLASHES/FLUSHES) at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| Do you have any other symptoms that you wish to report? | |
|---|---|
| ○ Yes | ○ No |

Please list any other symptoms:

| | | | | | |
|---|---|---|---|---|---|
| 1. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 2. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 3. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 4. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 5. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

## APPENDIX E TUMOR TISSUE REQUISITION FOR GENOMIC STUDIES ON ARCHIVED SAMPLES

### TUMOR TISSUE REQUISITION FOR GENOMIC STUDIES

Complete this form and include with the tumor tissue specimen shipment. Label ALL materials with participant initials, DFCI participant study ID, and the date the specimen was obtained. **Include a pathology report** with any archival tissue specimens being submitted.

Ship specimen(s) to: Dana-Farber Cancer Institute, Attn: ADVANCE STUDY TEAM, 450 Brookline Ave Dana 157, Boston, MA 02215. Email the DFCI Clinical Research Coordinator when sample is shipped.

**Specimen Information**

| Protocol: ADVANCE – DF/HCC 19-031 | | |
|---|---|---|
| Participant Initials (FML): _____ | DFCI Participant Study ID Number: _____ | Date specimen(s) shipped: _____ |
| Site: ☐ Right breast ☐ Left breast ☐ Lymph Node | Pathology reports included ☐ | |

| **Specimen Type** *(indicate inclusion in shipment by checking box)* | **Pathology Number(s) or Serial Coding** | **Quantity submitted** | **Date specimen obtained** |
|---|---|---|---|
| | | | |
| ☐ 10-15 slides, uncharged and unstained | | | |
| ☐ 1 paraffin block | | | |
| **If insufficient tumor sample from surgery** | | | |
| ☐ 2 core invasive tissue using a 1.2 mm diameter coring tool | | | |

**Responsible contact: _____**

**Shipment Tracking #:_____**
**Email: _____**
**Phone number: _____**

**Site: _____**

## APPENDIX F SPECIMEN REQUISTION FORM FOR TISSUE SPECIMENS **(ARCHIVED SPECIMENS ONLY FOR TISSUE MICROENVIRONMENT- PLEASE SEE SEPARATE REQUISTION FOR GENOMICS)**

**ALL FIELDS MUST BE LEGIBLY COMPLETED IN PEN**

**Case ID** _____

**Study Number**_____

**Hospital/Institution Name**_____

**Collection Date**_____

**Biopsy/Surgical site (circle all that apply):**

Breast Lymph Node

**Tissue Derived from (circle all that apply):**

Biopsy Surgery

**Tissue Accession Number(s):** _____

**Shipment Contains (enter number next to item on all that apply):**

FFPE Block(s): _____ 5um USS: _____ 5-7um USS: _____

**Protocol Name/Number: ADVANCE – DF/HCC 19-031**

**Shipment and tracking number** _____

**SPECIMEN COLLECTION:**

- Please send the following:
  - Paraffin block containing tumor tissue OR
  - At least ten 5 micron sections on charged, unstained slides
  - If possible and sufficient tissue, please send ten additional 5-7micron sections on regular non-coated slides (total of 20 slides)
  - Pathology report, if not already provided with other samples

**STORAGE AND TRANSPORT:**

Please send the archival samples ambient to the address below, with an email notification to Haley Gagnon (DFCI CRC) at haleyc_gagnon@dfci.harvard.edu.

Dana-Farber Cancer Institute
ATTN: ADVANCE STUDY TEAM
450 Brookline Ave, DA157
Boston, MA 02215

The DFCI study team will then deliver samples to Dr. McAllister's lab at 750 Harvard Institutes of Medicine, 77 Avenue Louis Pasteur, Boston, MA 02215

## APPENDIX G TISSUE REQUISTION LETTER FOR PATHOLOGY DEPTS.

Dear Pathologist,

The patient detailed below is enrolled in research protocol #19-031, The 'ADVANCE' study, led by Dana-Farber Cancer Institute. This study is funded by Susan G. Komen and will examine treatment receipt, barriers, and experiences for older patients with breast cancer and will explore tissue genomics and tumor microenvironment for this understudied group of patients.

As part of this study, we are requesting tissue from previously collected breast samples. In total, **please send the following from this patient's previously collected breast biopsy specimen and/or surgical specimen, containing tumor.**

- **10 (5-micron thick) sections on unstained, uncharged slides for genomics and**
- **10 (5-micron thick) sections on unstained, charged slides for tissue microenvironment studies**

**In addition, if there is sufficient tissue, please also send:**

- **10 (5-7 micron thick) sections on regular non-coated slides**

**(A total of 20-30 slides)**

**OR**

- **One rich tumor block** (and we will cut slides at our pathology facility)

If this amount of tissue is not available, we would appreciate if you could send us any number of slides that can be afforded. Please include a pathology report with the sample.

The tissue can be mailed to us at the below address. Please feel free to contact the project's Clinical Research Coordinator or the study PI, Rachel Freedman (rafreedman@partners.org) with any questions. We are so appreciative of your time and effort and your important contribution to this study. The patient's information is below:

The tissue can be mailed to me us at:
Dana-Farber Cancer Institute
Attn: ADVANCE STUDY TEAM
450 Brookline Avenue, DA157
Boston, MA 02215

Any blocks and/or unused slides will be returned in a timely fashion. Please feel free to contact us at tthe email or phone above with any questions.

The patient's information is below:

**Name:**
**DOB:**
**Procedure:** **Procedure Date:**
**Accession Number:**

Thank you!

## APPENDIX H SPECIMEN REQUISTION FORM FOR TISSUE SPECIMENS

### **(FROZEN BREAST SURGICAL SPECIMENS ONLY FOR DFCI PATIENTS HAVING SURGERY BWH or BWH at FAULKNER ONLY)**

**Protocol Number: ADVANCE – DF/HCC 19-031**

| Patient ID | Date collected | Tissue specimen |
|---|---|---|
| | | |

Date of Shipment: _____

Site Name: _____

Site Contact Name: _____

Site Contact Phone Number: (_____)_____

Site Contact E-Mail: _____

Comments:_____

__

SAMPLE COLLECTION **AT BWH or Faulkner Hospital (MONDAY-FRIDAY)**:

1. Surgical specimens Farber should be immediately placed in a conical tube containing 45mLs of RPMI media and kept on wet ice (Do not freeze).
2. Please contact Dr. Gregory Goreczny (814-758- 2904;ggoreczny@bwh.harvard.edu) and/or Dr. Sandra McAllister (617-223-1297; smcallister1@bwh.harvard.edu) in advance of the procedure to notify them of an upcoming surgery. A member of the study team will arrange to come to BWH or BWH @ Faulkner to pick up specimens from pathology. If tissue is not available prior 5pm, tissue should not be collected. Tissue will ultimately be delivered to and stored at the following address:

Dr. Sandra McAllister
750 Harvard Institutes of Medicine
77 Avenue Louis Pasteur
Boston, MA 02215
Phone: 617-525-4929

## APPENDIX I CHIP SAMPLES (BLOOD) REQUISITION FORM

**Protocol number: ADVANCE- DFCI 19-031**
**Case Number / Participant Study ID:**_____
**Hospital/Institution Name**_____
**Collection Date**_____**Collection Time** _____**(**both required**)**
**Time Point collected (circle one):**
**Baseline** **C3 Day 1** **end of treatment**

_____, M.D.
**FIRST AND LAST NAME of Submitting Physician**

_____
**First and Last Name of Person Shipping the tube**

**ALL FIELDS MUST BE LEGIBLY COMPLETED IN PEN (No pencil)**

**Submitted for:**
☐ **CHIP processing and banking**

SAMPLE COLLECTION: **Two 10cc EDTA tubes** **as per protocol**

SAMPLE STORAGE AND TRANSPORT:
1. The blood sample can be transported and stored at room temperature (6-37 ºC) until processing. Do NOT refrigerate or freeze the sample.
2. Samples must be processed **within 3 days of collection**, but best results are obtained if the sample is processed as soon as possible.
3. Do not submit clotted samples.
4. Ship within **at ambient temperature** priority overnight, M-Thursday. Do not collect on Friday, unless same day delivery.

TUBE PRECAUTIONS:
- DO NOT FREEZE OR REFRIGERATE TUBES.
- Do not use tubes after expiration date.
- Fill the tube completely; overfilling or under filling of tubes will result in an incorrect blood-to-additive ratio and may lead to incorrect analytic results

Samples should be hand delivered or shipped by same day courier or overnight parcel directly to:

**Dana-Farber Cancer Institute**
**Smith Receiving**
**ATTN: Doreen Hearsey, Pasquarello Tissue Bank- CMCF, J614-J616**
**1 Jimmy Fund Way**
**Boston, MA 02115**
**Lab # 617-632-3087**
**FAX 617-394-261**
**E-mail**: DFCIPasquarelloLab@DFCI.harvard.edu
https://pasquarello-tissue-bank.dana-farber.org/

Email notification should be sent to DFCIPasquarelloLab@DFCI.harvard.edu and xx@partners.org to alert DFCI staff of the expected shipment. In this email, please include tracking #, protocol #, and sample information in the email.

## APPENDIX J DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA AND SAFETY MONITORING PLAN

***DFCI IRB Protocol #: 19-031***

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# 1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

## 1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

## 1.2 Multi-Center Data and Safety Monitoring Plan Definitions

**DF/HCC Multi-Center Protocol**: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

**Lead Institution:** One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (Food and Drug Administration (FDA), etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

**DF/HCC Sponsor:** The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA ). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

**Participating Institution:** An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

**Coordinating Center:** The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

**DF/HCC Office of Data Quality (ODQ):** A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

**DF/HCC Research Informatics Office (RIO):** A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

## 2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

### 2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Rachel Freedman, MD, MPH will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials), as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.

- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

## 2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting pPolicy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

## 2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.

- Submit protocol and/or amendments to their local IRB of record.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

## 3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

### 3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

### 3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

## 3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

## 3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

## 3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

## 3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

### 3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

## 3.7 DF/HCC Multi-Center Protocol Registration Policy

### 3.7.1 Participant Registration and Randomization

Please refer to Protocol Section 4.3 and 4.4 for participant registration information. Treatment cannot begin until site has received confirmation that participant has been registered with DF/HCC CTMS.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

## 3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

## 3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to the IRB according to their institutional policies and procedures.

## 3.10 Data Management

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study. A CATI DATSTAT survey tool will be used to collect survey data on this study.

Please see Section 11.1 for Data Reporting Requirements.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

# 4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.

Participating Institutions should order their own agent regardless of the supplier.

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

## 5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

### 5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Additionally, a plan will be formulated to provide regular and ongoing communication to Participating Institutions about study related information which will include participation in regular Lead Institution initiated teleconferences. Teleconferences will occur every 2 weeks to one month and will continue regularly until completion of accrual. Upon completion of accrual, teleconferences may occur monthly until all patients complete protocol therapy. Upon completion of protocol therapy, teleconferences may occur every 3 months until study completion. Additional communication may be distributed via "Newsletter" or email as deemed appropriate by DF/HCC Sponsor.

**On-Site Monitoring:** On-site monitoring will occur on an as-needed basis. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the visit. In addition, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the Participating Site. On-site monitoring visits can be substituted with remote (virtual) monitoring visits at the discretion of the Principal Investigator.

**Remote Monitoring:** Remote monitoring will be performed on an as-needed basis by the Clinical Trial Monitor. Sites will be asked to provide source documentation via fax, email, or mail as specified by the Clinical Trial Monitor for virtual monitoring.

### 5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

### 5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

## 6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Policies, and the Code of Federal Regulations (CFR).

### 6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

### 6.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

### 6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the

DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

## 6.4 Participating Institution Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

**APPENDIX K CERTIFICATE OF COMPLETION**

# Certificate Of Participation

**RECIPIENT NAME**
is thanked for their phenomenal participation on the ADVANCE trial! Thank you so much!

Presented By: _____

On This Day: _____

## APPENDIX L– GERIATRIC ASSESSMENT SUMMARY FOR PROVIDERS

*This is an example template of the email that should be sent to the provider within one week of patient completion of GA survey. This can be done through RedCap, email, or in person with providers.*

Dear Provider,

As you know, your patient, _____, is enrolled on the ADVANCE study. At baseline in all patients, we perform a geriatric assessment which asks patients about functional status, comorbidity, medications, psychological status, and social support/functioning. In addition, our team performed a brief memory test and a timed 'up and go test' and performance status for objective testing of functional status.

Here is a summary of the results for your patient, excluding medication use, since we assume you have assessed this as part of your evaluation in clinic. You may use this information as you see appropriate. We will contact you over email for a very short survey about whether you found these results useful.

Time point: (choose one) BASELINE END OF TREATMENT

| Geriatric Assessment Results | |
|---|---|
| **Domain assessed** | |
| **Functional status** | Karnofsky Performance Status = xx<br>Timed "Up and Go" = xx seconds to stand up, walk 10 feet, and return to a chair<br>Challenges with IADLs reported =<br>Number of falls reported in the last 6 months = xx |
| **Comorbidity** | Comorbidities reported by patient: |
| **Cognition** | Blessed Orientation-Memory-Concentration Test score = xx (deficits were the following: xxx) |
| **Psychological Status** | Report of anxiety or depression |
| **Nutritional Status** | Significant weight loss in the last 6 months = yes/no |
| **Social Functioning and Social Support** | Limitations reported in social support and functioning = |
| | |

Let us know if you have any questions. Thank you for your support of this study!

Sincerely,

_____on behalf of the ADVANCE study

## APPENDIX M PROVIDER SURVEY ON GA UTILITY

*This can be done through RedCap, email, or in person with providers.*

Approximately one week ago, you received a summary of results from the baseline Geriatric Assessment your patient, _____,completed on the ADVANCE study. We would like to ask you 4 brief questions about whether this information was helpful to you. Please answer as honestly as possible. Your answers will be kept completely confidential.

1. Did you review the results of the Geriatric Assessment when they were provided to you?
   - ☐ Yes
   - ☐ No
   - ☐ Not sure

   1A. If yes, did you find the layout and way the information was provided easy to read?
   - ☐ Yes
   - ☐ No
   - ☐ Suggestions? _____

2. Did you find the information provided helpful in caring for this patient?
   - ☐ Yes
   - ☐ No
   - ☐ Not sure

3. Did the information result in any changes in your management or referrals you would not have otherwise made, even if something minor?
   - ☐ Yes → please answer 3A below
   - ☐ No
   - ☐ Not sure

   3A. If yes, can you tell what it was? _____

Thank you so much for participating and for your support of the ADVANCE study!

Rachel Freedman, MD, MPH
Study PI