Randomized Trial of Hypofractionated Whole Breast Irradiation Versus Conventionally Fractionated Whole Breast Irradiation for Ductal Carcinoma in Situ and Early Invasive Breast Cancer

1.0 Background

1.1 Background and epidemiology

Ductal carcinoma in situ (DCIS) is a premalignant disease of the breast that, if left untreated, carries a high propensity for transformation to invasive carcinoma. Approximately 68,000 women are diagnosed with ductal carcinoma in situ of the breast on a yearly basis in the United States.[1] Current treatment for localized DCIS consists of either breast conserving surgery (BCS) alone, BCS followed by whole breast irradiation (BCS+WBI) or mastectomy.[2] Approximately 70% of women with DCIS in the United States are treated with BCS. Of these, about half will be treated with radiation therapy following breast conserving surgery.

Invasive breast cancer is the most common cancer diagnosed in women in the United States, with approximately 182,000 cases per year, and is the second most common cause of cancer death, with approximately 40,000 deaths per year.1 More than 100,000 women per year in the United States are diagnosed with early invasive breast cancer, which herein is defined as pathologic stage T1-2 N0-1. Accepted local-regional treatments for early invasive breast cancer consist of breast conserving surgery followed by WBI or mastectomy (typically without post-mastectomy radiation). Approximately 66% of women with early invasive breast cancer choose breast conserving surgery, and up to 90% will subsequently receive WBI.[3,4]

1.2 Radiation therapy for DCIS and early invasive breast cancer

Four large, multi-center randomized clinical trials have demonstrated conclusively that BCS+WBI, as compared to BCS alone, lowers the subsequent risk of both invasive and in situ ipsilateral breast tumor recurrence (IBTR) for women with DCIS (Table 1).[58] Clinical trials and institutional series indicate that the risk of IBTR in patients with DCIS treated with BCS+WBI is approximately 1% per year.[5-9] To date, all of the randomized studies to investigate the role of radiotherapy in the treatment of DCIS have used a conventional fractionation scheme which consists of 2 Gy delivered on a daily basis, five days per week, for approximately five weeks. Although not used in the randomized trials, many centers also routinely employ a five to eight fraction boost to the tumor bed for patients with DCIS.[10]

For women with early invasive breast cancer, multiple randomized clinical trials and a large meta-analysis have demonstrated that BCS+WBI, as compared to BCS alone, lowers the relative risk of IBTR by approximately 60-70% and improves 15-year overall survival.[11] The vast majority of the literature comparing BCS+WBI to BCS in early invasive breast cancer also used daily fractions of 2 Gy or less to doses of approximately 45 – 50 Gy to the whole breast. A tumor bed boost of 10-16 Gy in 5 to 8 fractions is commonly utilized following CF-WBI based on 10-year results of a prospective randomized trial that included 5,318 patients and found that a tumor bed boost, when added to CF-WBI, significantly lowered the risk of IBTR.[10]

Based on the randomized clinical trials, fractionation schemes characterized by a daily dose of 2 Gy or less, referred to herein as conventionally fractionated whole breast irradiation (CF-WBI), have represented the historical standard of care for radiation therapy to the whole breast in the United States for DCIS and early invasive breast cancer.[12,13] Although CF-WBI has been demonstrated to be both safe and effective in the treatment of DCIS and early invasive breast cancer, it has certain shortcomings, principally the inconvenience to patients associated with receipt of daily treatment for up to seven weeks and the cost of treatment, both in terms of the actual health care expenditures and also costs to the patient and society due to time away from home and work.[14]

1.3 Hypofractionated whole breast irradiation (HF-WBI) for Early Invasive Breast Cancer

Growing evidence from four recently published randomized clinical trials (Canadian,[15-17] Royal Marsden Hospital/Gloucester Oncology Center (RMH/GOC),[18,19] and Standardization of Breast Radiotherapy (START) A and B,[20,21]) has demonstrated that hypofractionated whole breast irradiation (HF-WBI), in which the dose per fraction is increased while the total dose delivered to the breast is decreased, confers long-term toxicity, local control, and survival outcomes comparable to CF-WBI for early invasive breast cancer with up to 12 years median follow up (Table 2, Appendix D).[15,17-21] At present, substantial controversy exists among radiation oncologists in the United States regarding the extent to which HF-WBI should be incorporated into routine clinical practice. For example, the American Society for Radiation Oncology (ASTRO) has recently completed an evidence-based guideline on fractionation for whole breast irradiation and concluded that the available evidence has demonstrated that HF-WBI has been proven equivalent to CF-WBI for patients who meet the following criteria: 50 years of age or older, disease stage pT1-2 pN0, not treated with chemotherapy, and treated with a radiation dose homogeneity within ±7% in the central axis plane.[22] For patients not meeting these criteria, the authors of the ASTRO guideline refused to render a recommendation as to the appropriateness of HF-WBI due to substantial disagreements regarding interpretation of the published literature and wide variation in practice patterns among the authors. The ASTRO guideline specifically highlighted two areas of ongoing controversy regarding HF-WBI: 1) whether or not it is safe to add a tumor bed boost following HF-WBI, and 2) whether or not it is safe to use HF-WBI in patients receiving anthracycline- or taxane-based chemotherapy.[22] The limited amount of data pertaining to use of HF-WBI in patients receiving a tumor bed boost and/or chemotherapy is a major obstacle to its widespread adoption in the United States, as approximately 85% of American radiation oncologists routinely use a tumor bed boost in their practice[23] and chemotherapy is routinely used for patients with tumors greater than 1 cm or node-positive disease.[24]

With regard to a tumor bed boost, none of the patients in the Canadian randomized trial received a tumor bed boost.[17] Sixty-one percent of patients in the START A trial and 43% of those in the START B trial undergoing breast-conserving surgery received the optional tumor-bed boost of 10 Gy in 5 fractions.[20,21] Entry into the START trials was stratified by intention to give a tumor-bed boost, but the outcomes for whether a boost was actually used have not yet been reported.[20,21] The RMH/GOC trial included a substudy in which 723 patients were randomized to receive no boost or a boost of 14 Gy in 7 fractions to the tumor bed.[18,19] The rates of IBTR in relation to the use of a boost have not been reported. Patients allocated to receive a boost had a higher risk of breast induration and telangiectasia than those who received no boost, but there was no difference between these groups in breast appearance (assessed photographically by a blinded observer), proportion of fair or poor cosmetic results, or risks of breast shrinkage, breast distortion, breast edema, arm swelling, or shoulder stiffness. However, results were not further divided according to whether patients received HF-WBI or CF-WBI, so it is not possible to determine whether one regimen was preferable when a boost was used. Further, the risk of a fair or poor cosmetic outcome in this trial was high (58-74% at 10 years), raising concern that the overall treatment plan did not result in optimal cosmesis, irrespective of assigned dose and use of a boost. One randomized trial including 1,024 women with invasive breast cancer 3 cm or smaller and negative surgical margins treated with HF-WBI (50 Gy in 20 fractions of 2.5 Gy) compared a tumor-bed boost of 10 Gy in 4 fractions or no boost.[25] With a median follow-up duration of 3.3 years, receipt of a tumor-bed boost was associated with a lower risk of IBTR, a higher risk of telangiectasia, and no difference in patient-reported cosmetic outcome. However, the relatively short length of follow-up in this trial precluded firm conclusions as to the long-term toxicity profile of a tumor-bed boost in patients receiving HF-WBI. In addition, the effective biologic dose of the HF-WBI regimen used in this trial was higher than that of the HF-WBI arms of the Canadian and START trials.[15,16,21]

With regard to chemotherapy, anthracycline-containing and taxane-containing regimens were used in 25% and 1%, respectively, of patients in the START A trial and in 13% and 0.4%, respectively, of patients in the START B trial.[20,21] The fraction of patients receiving anthracyclines or taxanes in the Canadian and RMH/GOC trials was not reported, although it is likely that anthracyclines and taxanes were used very infrequently during the era in which those trials were conducted.[15,17-19]

Given the currently available data, the majority of experts comprising the ASTRO fractionation guideline task force reported that they routinely consider using HF-WBI in patients with early invasive breast cancer who have received chemotherapy or require a tumor bed boost, but a minority voiced concern that the currently published randomized data does not rule out an increased risk of normal tissue toxicity when HF-WBI is used sequentially with chemotherapy or a tumor bed boost. As a result, the ASTRO evidence-based guideline called for further investigation of HF-WBI for early invasive breast cancer in these two common clinical situations.

With regard to other clinical and pathologic selection criteria for use of HF-WBI, risk of IBTR after breast-conserving surgery followed by adjuvant WBI decreases as age increases, and is particularly high for younger women ages 40 and under.[26] The reasons for this discrepancy are not fully understood, but one possibility is that the sensitivity of breast cancer to radiation therapy may vary with age. Thus, it may be necessary to consider younger and older women as two distinct patient populations when evaluating the appropriateness of HF-WBI. Approximately 21% to 30% of patients enrolled in clinical trials comparing HF-WBI with CF-WBI were age 50 years or younger at diagnosis.[15-21] The effect of age on outcome has only been reported for the Canadian trial, which stratified entry by age (younger than 50 years versus 50 years or older).[15,17] A preplanned analysis found that HF-WBI was equivalent to CF-WBI in both groups.[15-17] However, the Canadian trial included only 305 women under 50, and no further division of results by age was performed within this group (e.g., age 40 years or younger versus age 41 to 49 years). Authors of the ASTRO whole breast fractionation guideline could not reach agreement on the appropriateness of HF-WBI for women under the age of 50 years; although the majority reported using HF-WBI for women under the age of 50 years, a minority felt that further data was needed.[22] Given this lingering uncertainty, for our trial we plan to exclude the youngest patients with the highest risk of recurrence (those under the age of 40 years) but include patients ages 40 years and older.

With regard to nodal status, radiation therapy to the supraclavicular fossa is generally indicated for patients with pathologic stage N2 or N3 breast cancer. Radiation therapy to the supraclavicular fossa is used on occasion for patients with N1 breast cancer who have additional risk factors for supraclavicular failure. To date, there is relatively little data regarding the safety of hypofractionated radiation to the supraclavicular fossa, and there is concern that such treatment could lead to a higher risk of late radiation-induced brachial plexopathy. However, for patients with N1 breast cancer for whom supraclavicular radiation is not planned, the ASTRO guideline indicates that “the majority of task force members thought that HF-WBI could be used”, although few patients with these characteristics were included in the randomized trials. Accordingly, we plan to study patients with N0 or N1 breast cancer who will be receiving whole breast radiation alone without addition of a third field to treat the supraclavicular lymph nodes.

1.4 <u>HF-WBI for DCIS</u>

None of the prospective randomized trials comparing CF-WBI to HF-WBI included women with DCIS.[15,17-21] To the best of our knowledge, only one phase II study has examined the efficacy and safety of HF-WBI in the treatment of DCIS.27 This study enrolled 59 patients who have been followed for a median of 3 years and no ipsilateral breast tumor recurrences were reported. A total of 91% of patients experienced good or excellent cosmetic outcome based on physician report, but patient reported cosmetic outcomes were not included in this study.

Theoretically, it is expected that the documented equivalence of HF-WBI to CF-WBI for invasive breast cancer should also extend to DCIS. Nevertheless, given the fact that patients with DCIS have been excluded from the randomized trials comparing CF-WBI to HF-WBI, many radiation oncologists continue to be reluctant to recommend HF-WBI for patients with DCIS and the ASTRO fractionation guideline concluded that “that data were insufficient to allow an evidence-based recommendation for or against HF-WBI for women with DCIS”.[22]

1.5 <u>Cosmetic outcome of WBI</u>

In studying the side effect profile of WBI, a key outcome is the cosmetic result of the treated breast, which reflects not only the goal of breast conserving therapy (preservation of the breast with acceptable cosmesis) but also the extent to which normal tissue is damaged by radiation therapy. To date, however, none of the randomized trials to compare HF-WBI to CF-WBI have used a validated instrument to assess patient-reported cosmetic outcome.[15,17-21] The Canadian trial assessed cosmetic outcome using photographic assessment evaluated by a trained research nurse who was not blinded to the randomization arm.[15,17] In contrast, the START A and B trials did incorporate patient-reported cosmetic outcomes, but rather than developing a validated instrument these trials simply asked patients about overall change in breast appearance using a four-point scale.[20,21] Another limitation of currently available randomized trials comparing HF-WBI to CF-WBI is that they were conducted in Canada and the United Kingdom, and it is not known whether cosmetic standards may differ between these countries and the United States.[28]

To our knowledge, the best instrument available to assess patient-reported cosmetic outcome following BCS+WBI is the Breast Cancer Treatment Outcomes Scale (BCTOS), which was derived from a series of 185 women treated with BCS+WBI for DCIS or early invasive breast cancer.[29] This questionnaire consists of 22 items from which internally consistent subscales regarding cosmetic outcome, functional status, and breast pain were developed (Appendix K). Each item is rated on a scale of 1 to 4, with 1 indicating no difference between the treated and untreated breast and area, 2 indicating slight difference between treated and untreated breast and area, 3 indicating moderate difference between treated and untreated breast and area, and 4 indicating large difference between treated and untreated breast and area. Each subscale is calculated by computing the arithmetic mean of the answers for each of the items relevant to the given subscale. Thus, the score for each subscale is a continuous variable ranging from 1 to 4. In the original publication, the mean BCTOS cosmetic score was 2.24 with a standard deviation of 0.77 and a range of 1 to 4. Currently the BCTOS is being used in the pivotal phase III intergroup trial comparing WBI to accelerated partial breast irradiation (NSABP B-39/RTOG 0413).

Physician-reported cosmetic outcomes have been historically reported as a single four-level variable in RTOG trials: excellent, good, fair, and poor.[30] This scoring system derives from a scoring system developed at Harvard and is widely used in current literature (Appendix G).[31]

1.6 Radiogenomic Predictors of Radiation Toxicity

In the past decade, interest has grown in identifying genomic polymorphisms that correlate with risk of radiation toxicity, under the premise that certain genetic polymorphisms correlate with an individual's baseline normal tissue radiosensitivity.[32-36] If such polymorphisms can be reliably identified and rigorously validated, their presence could be determined prospectively in patients, thereby impacting the decision to offer radiation therapy or selection of an appropriate radiation dose, allowing treatment to be tailored to an individual patient's genomic profile. To date, polymorphisms affecting DNA-repair pathways and the fibrotic response to tissue injury have been implicated as potentially associated with risk of radiation toxicity.[32-42] However, many of these studies investigated multiple polymorphisms with multiple putative outcomes, and thus risk of a false positive result was high due to the problem of multiple comparisons. Accordingly, confirmatory studies are essential to establish any one putative polymorphism as clinically relevant. One such polymorphism that has been identified in early studies is the C-509T variant allele in the transforming growth factor-beta (TGF-b) gene, with a study in 167 breast cancer patients reporting a statistically significant three-fold increased risk of radiation-induced fibrosis among patients who were heterozygous or homozygous for the variant allele, in comparison to wild type patients. This study used the Subjective, Objective, Medical Management, Analytic (SOMA) scale to assess late radiation-induced fibrosis.[43] Our collaborators in the Department of Epidemiology have already established their experience in measuring this allele and correlating its impact on risk of radiation pneumonitis in patients with lung cancer.[44]

1.7 Rationale for Study Design

Currently, both HF-WBI and CF-WBI are accepted treatment regimens used commonly in the community setting in North America and are endorsed by the ASTRO guideline on fractionation for whole breast irradiation. Nevertheless, there remains some uncertainty regarding whether there may be any clinically meaningful differences in these two standards of care, To gain further information regarding the safety and efficacy of HF-WBI in the treatment of DCIS and early invasive breast cancer, we plan to initiate a prospective randomized trial to compare HF-WBI to CF-WBI following conservative surgery for breast cancer. All patients will receive a

tumor bed boost with a final dose dependant on final margin status. We will stratify patients according to chemotherapy (yes/no), margin status (< 2 mm vs > 2 mm), breast size (D cup or higher versus C cup or lower), post-lumpectomy/pre-radiation physician-assessed cosmetic outcome, and treatment location (Houston area facilities vs. Banner MD Anderson vs MD Anderson Orlando). The primary objective of this study is to compare patient-reported cosmetic outcome at 3 years using the BCTOS for patients assigned to HF-WBI versus CF-WBI. Specifically, we will compare the 2 treatment arms with respect to the percent of women with adverse cosmetic scores at 3 years after completion of breast conserving surgery, as determined by the patient-reported BCTOS. A BCTOS cosmesis score of 2.5 or higher has been chosen a priori to indicate an adverse cosmetic outcome. Secondary aims will include comparing physicianassessed cosmetic outcome and risk of IBTR for patients treated with HF-WBI versus CF-WBI.

This study will address current concerns in the United States regarding adoption of HF-WBI by including a validated patientreported cosmesis scale as the primary outcome measure and by including patients treated with a tumor bed boost with or without chemotherapy. In addition, investigating this question in women with DCIS will provide important data on the efficacy of HF-WBI in this sizeable patient cohort who were excluded from randomized trials of HF-WBI.

If HF-WBI is shown to confer cosmetic and tumor control outcomes comparable to CF-WBI, such a finding could help to promote its adoption in the United States, leading to major public health benefits, as HF-WBI is both more convenient and less expensive than CF-WBI.[14] In addition, improvements in the convenience of radiation therapy for DCIS could potentially increase utilization of radiation therapy following BCS for DCIS which is currently only approximately 50%.[45] In contrast, if this study demonstrates unacceptable cosmetic outcomes of HF-WBI in this cohort in the United States, such a finding would provide important evidence to suggest that HF-WBI should be studied carefully and cautiously prior to widespread adoption of HF-WBI for both DCIS and invasive breast cancer in the United States.

Thus, a study to evaluate patient-reported cosmetic outcomes for patients in the United States treated with HF-WBI followed by a tumor bed boost as compared to CF-WBI followed by a tumor bed boost should provide a meaningful addition to the literature that will help to guide radiation oncologists in the United States as they consider adopting HF-WBI.

As a secondary aim, we will conduct an optional, translational study to determine whether the C-509T variant allele of TGF-b is associated with an increased risk of late radiation-induced fibrosis. This study will help to confirm or refute the putative association of this allele with radiation toxicity, thereby bringing this finding either closer to clinical application or providing evidence that it should not be further explored.

Table 1. Prospective Clinical Trials Comparing BCS versus BCS+WBI for DCIS

	EORTC 10853	NSABP B-17	SWE-DCIS	UKCCCR
Sample Size	1010	818	1067	1701
Median Follow-up	10.5 years	10.8 years	5.2 years	4.3 years
Dose	50 Gy/25 Fractions	50 Gy/25 Fractions	50 Gy/25 fractions, 48 Gy/20 fractions, or 54 Gy in split course	50 Gy/25 Fractions
Sample Characteristics & Exclusions	DCIS<5 cm. 100% with clear surgical margins. Excluded patients with evidence of invasive carcinoma or Paget's disease of nipple.	Pre- and post-menopausal. 100% with clear surgical margins. DCIS and LCIS eligible. Excluded patients with axillary disease and prior non-skin cancer.	90% with clear surgical margins. Excluded prior non-skin cancer, invasive carcinoma or intracystic carcinoma in situ, Paget's disease of nipple, ongoing pregnancy.	Tumors detected by screening. 100% with clear surgical margins. Excluded LCIS, atypical ductal hyperplasia without DCIS, unknown margin status, and Paget's disease of nipple.
Outcome	10-year invasive or non-invasive local recurrence	12-year invasive or non-invasive ipsilateral breast recurrence	5-year invasive or non-invasive ipsilateral breast recurrence	5-year invasive or non-invasive ipsilateral breast recurrence
BCS (% Recurrence)	26%	32%	22%	14%
BCS + RT (% Recurrence)	15%	16%	7%	6%
HR for Effect of RT	0.53 (0.40 to 0.70)	Not provided	0.33 (0.24 to 0.47)	0.45 (0.24 to 0.85) (invasive) 0.36 (0.19 to 0.66) (non-invasive)

Table 2. Oncologic Outcomes for Randomized Clinical Trials Comparing Hypofractionated Whole Breast Irradiation with Conventionally Fractionated Whole Breast Irradiation

Trial	**Median Follow up** (years)	**Timepoint for outcome reporting** (years)	**Arm**			**N**	**IBTR**		**Local-Regional Recurrence**		**Disease-Free Survival**		**Overall Survival**	
			Dose (Gy)	# Fr	# Days		%	P	%	P	%	P	%	P
Canada[15-17]	12	10	50	25	35	612	7.5	.	.	.	.	.	84.4	.
			42.5	16	22	622	7.4	<.001*	.	.	.	.	84.6	0.79
RMH/GOC[18,19]	9.7	10	50	25	35	470	12	†	.	.	.	.	.	.
			42.9	13	35	466	9.6	†	.	.	.	.	.	.
			39	13	35	474	15	†	.	.	.	.	.	.
START A[20]	5.1	5	50	25	35	749	3.2	.	3.6‡	.	86	.	89	.
			41.6	13	35	750	3.2	0.74	3.5‡	0.86§	88	0.33§	89	0.81§
			39	13	35	737	4.6	0.40	5.2‡	0.35§	85	0.33§	89	0.99§
START B[21]	6.0	5	50	25	35	1105	3.3	.	3.3‡	.	86	.	89	.
			40	15	21	1110	2.0	0.21	2.2‡	0.35	89	0.02	92	0.03

* The hypothesis that the 42.5 Gy arm is worse than the 50 Gy arm is rejected at P<.001.
† P-value for the comparison of the 42.9 Gy arm to the 39 Gy arm was significant at P=0.027. P-values were > 0.05 for the comparisons of the 42.9 Gy arm to the 50 Gy arm, and the 39 Gy arm to the 50 Gy arm.
‡ Only local or regional relapses inside the irradiated volume were included in this outcome.
§ P-values as compared with the control arm of 50 Gy in 25 fractions.

Abbreviations: Fr: fractions; IBTR (ipsilateral breast tumor recurrence); RMH/GOC: Royal Marsden Hospital/Gloucester Oncology Center; START: Standardization of Breast Radiotherapy.

2.0 Objectives

2.1 Primary

2.1.1 To compare patient-reported cosmetic outcome at 3 years using the BCTOS for patients assigned to HF-WBI versus CFWBI. Specifically, we will compare the 2 treatment arms with respect to the percent of women with adverse cosmetic scores at 3 years after completion of breast conserving surgery, as determined by the patient-reported BCTOS. A score of 2.5 or more indicates an adverse cosmetic outcome.

2.2 Secondary

2.2.1 To determine patient-reported cosmetic outcome using the BCTOS at 6 months, 1, 2, 4, and 5 years.

2.2.2 To determine physician-rated cosmetic outcome at 6 months, 1, 2, 3, 4, and 5 years using the Radiation Therapy and Oncology Group (RTOG) scale for physician assessment.30 Physician outcome will be determined using photographic assessment and scored by a panel of three attending physicians specializing in breast cancer who will be blinded to the patient randomization arm.

2.2.3 To determine the level of agreement between patient-rated cosmetic outcome and physician-rated cosmetic outcome at the various timepoints assessed.

2.2.4 To determine the 5-year and risk of pathologically-confirmed invasive and/or in situ ipsilateral breast tumor recurrence (IBTR) for patients with DCIS and early invasive breast cancer.

2.2.5 To determine patient-reported functional status and breast pain using the BCTOS at 6 months, 1, 2, 3, 4, and 5 years after treatment.

2.2.6 To determine maximal acute (within 6 weeks of treatment) and late (more than 6 weeks after treatment) skin and soft tissue toxicities using the NCI CTCAE v4.0 scale.

2.2.7 To determine the relationship between the volume of breast tissue receiving excessive dose (defined as greater than 105% of the prescription dose) and the risk of adverse cosmesis.

2.2.8 To determine the relationship between bra cup size and the risk of adverse cosmesis.

2.2.9 To determine whether there is a statistical interaction between breast volume and volume of tissue receiving greater than 105% of the prescription dose in predicting adverse cosmesis.

2.2.10 To determine in an exploratory analysis whether any other demographic, clinical, and pathologic factors correlate with risk of adverse cosmesis, quality of life, body image, image investment, and risk of IBTR.

2.2.11 To determine if the C-509T variant allele of TGF-b is associated with an increased risk of grade 2 or higher fibrosis (as determined by the SOMA scale) three years after completion of radiation.

2.2.12 To compare the cost of radiation for the two treatment arms.

2.2.13 To compare patient quality of life, body image, and appearance investment for the two treatment arms using the FACT-B, Appearance Schemas Inventory-Revised (ASI-R), and Body Image Scale, respectively.

2.2.14 To contribute additional blood samples to protocol LAB02-086 which is a case-control study investigating DNA repair phenotypes and genotypes in breast cancer.

2.2.15 To assess the psychometric profile of the FACT-B version 4 in collaboration with investigators from the Department of Medical Social Science, Northwestern University Feinberg School of Medicine.

2.2.16 To determine the influence of oncoplastic lumpectomy on the following outcomes:
physician and patient reported cosmetic outcomes, other patient reported health-realted quality of life outcomes, and photographic measurements of brease cosmetic outcome.

3.0 Patient Eligibility

3.1 <u>Conditions for patient eligibility</u>

3.1.1 Pathologically confirmed ductal carcinoma in situ of the breast or early invasive breast cancer defined as pathologic stage Tis, T1, or T2, N0, N1mic, or N1a (pathologic staging of the axilla is required for all patients with invasive disease but is not required for patients with DCIS only). (Upfront pathologic stage cannot be assigned to patients treated with neoadjuvant chemotherapy. For such patients, the criteria for pathologic stage shall be applied to the initial clinical stage).

3.1.2 Treatment with breast conserving surgery.

3.1.3 Final surgical margins must be negative, defined as no evidence for ductal carcinoma in situ or invasive breast cancer touching the inked surgical margin. If the invasive or in situ breast cancer approaches within less than 1 mm of the final surgical margin, then a re-excision is strongly encouraged. Lobular carcinoma in situ at the final surgical margin will be disregarded. **3.1.4** Age 40 years or older. This age cutoff is justified because breast cancers in women under the age of 40 are known to have a significantly higher risk of IBTR presumably due to underlying biologic differences.[10,22]

3.1.5 Female sex.

3.1.6 Attending radiation oncologist declares intention to treat the whole breast only and that a third radiation field to treat regional lymph nodes is not planned (radiation of the undissected level I/II axilla with high tangents is allowed).

3.1.7 If the patient has a history of a prior non-breast cancer, all treatment for this cancer must have been completed prior to study registration and the patient must have no evidence of disease for this prior non-breast cancer.

3.1.8 Patients must be enrolled on the trial within 12 weeks of the later of two dates: the final breast conserving surgical procedure or administration of the last cycle of cytotoxic chemotherapy.

3.2. <u>Conditions for patient ineligibility</u>

3.2.1 Pathologic or clinical evidence for a stage T3 or T4 breast cancer.

3.2.2 Pathologic evidence for involvement of 4 or more axillary lymph nodes, or imaging evidence of involvement of infraclavicular, supraclavicular, or internal mammary lymph nodes.

3.2.3 Clinical or pathologic evidence for distant metastases.

3.2.4 Any prior diagnosis of invasive or ductal carcinoma in situ breast cancer in either breast.

3.2.5 Current diagnosis of bilateral breast cancer.

3.2.6 History of therapeutic irradiation to the breast, lower neck, mediastinum or other area in which there could potentially be overlap with the affected breast.

3.2.7 Patients not fluent in English or Spanish. (The BCTOS will be available in these two languages)

3.2.8 Patient is pregnant.

4.0 Additional Pretreatment Information

4.1 The treating physician must document his/her intent to use whole breast irradiation without addition of a third field to treat regional lymph nodes (use of high tangent fields to treat the level I/II axilla is allowed; use of an electron field matched to the tangents fields to ensure adequate coverage of the in breast tumor bed is also allowed).

4.2 For patients with invasive cancer, the patient must have either completed chemotherapy, refused chemotherapy, or been evaluated by a medical oncologist who specified that chemotherapy was not recommended at this time.

5.0 Registration Procedure

5.1 Patients will be registered by the research nurse in the Breast Radiation Oncology Clinic at the University of Texas MD Anderson Cancer Center or by the staff within the Clinical Research Support Center for patients enrolled through the Regional Care Centers.

5.2 Authority will be delegated to an individual(s) at MD Anderson Orlando, MD Anderson Albuquerque, and Banner MD Anderson to register patients in CORe (or patients from these institutions may be registered in aCORe according to section 5.1 if requested by these institutions).

6.0 Radiation Therapy

6.1 <u>Treatment/Dose Specifications</u>

6.1.1 External beam radiation therapy will be used exclusively in this study. Brachytherapy is not allowed.

6.1.2 Radiation therapy must begin within 12 weeks of the later of these two dates: the date of final breast conserving surgery or the date of the last infusion of cytotoxic chemotherapy.

6.1.3 The prescription dose for patients assigned to the HF-WBI arm will be 42.56 Gy in 16 fractions delivered to the whole breast on consecutive treatment days. A treatment day is defined as a normal business day, typically Monday – Friday excluding institutional holidays. The prescription dose for the tumor bed boost for patients assigned to HF-WBI will be 10 Gy in 4 fractions delivered on consecutive treatment days for patients with negative margins ($\geq$ 2 mm from DCIS or invasive carcinoma and closest inked surgical margin) and 12.5 Gy in 5 fractions delivered on consecutive treatment days for patients with close surgical margins (< 2 mm from DCIS or invasive carcinoma and closest inked surgical margin). The boost will begin on the treatment day following completion of whole breast irradiation.

6.1.4 The prescription dose for patients assigned to the CF-WBI arm will be 50 Gy in 25 fractions delivered to the whole breast on consecutive treatment days. The prescription dose for the tumor bed boost for patients assigned to CF-WBI will be 10 Gy in 5 fractions delivered on consecutive treatment days for patients with negative margins ($\geq$ 2 mm from DCIS or invasive carcinoma and closest inked surgical margin) and 14 Gy in 7 fractions delivered on consecutive treatment days for patients with close surgical margins (< 2 mm from DCIS or invasive carcinoma and closest inked surgical margin). The boost will begin on the treatment day following completion of whole breast irradiation.

6.1.5 In the event of severe acute toxicity during the course of radiotherapy (as determined by the treating physician), whole breast irradiation may be placed on hold for up to 3 treatment days and be replaced with the tumor bed boost to allow acute toxicity to subside. In this case, whole breast irradiation must resume upon discontinuation of the boost, and the total doses contributed from whole breast irradiation and the tumor bed boost will remain as stipulated in section 6.1.3 for patients in the HF-WBI arm and section 6.1.4 for patients in the CF-WBI arm.

6.1.6 The prescription points for whole breast irradiation and the tumor bed boost will be selected at the discretion of the treating radiation oncologist to balance target coverage versus dose homogeneity.

6.1.7 Inhomogeneity corrections will be used in dose calculations.

6.2 <u>Technical Factors</u>

6.2.1 Radiation will be delivered using a linear accelerator with a nominal energy $\geq$ 6 MV.

6.2.2 Three-dimensional dose compensation will be used when needed to minimize dose inhomogeneity throughout the target volume using multileaf collimators and/or wedges.

6.2.3 Prone positioning may be utilized to improve normal tissue sparing when thought to be indicated by the treating radiation oncologist.

6.2.4 Respiratory gating with the deep inspiration breath hold technique may be utilized to minimize exposure of the heart to radiation when thought to be indicated by the treating radiation oncologist.

6.3 Localization, Simulation, and Immobilization

6.3.1 The tumor bed will be located on the basis of the treatment planning computed tomography scan supplemented by preoperative imaging data when available.

6.3.2 Patients will undergo computed tomography-based simulation with an axial slice thickness no greater than 5 mm.

6.3.3 Patients will be immobilized using a breast board and vacuum-lock bag or other institution-specific immobilization techniques in standard use at the discretion of their treating physician.

6.4 Treatment Planning/Target Volumes

6.4.1 Whole breast irradiation will be planned and delivered with traditional tangent fields, with the superior border set at approximately the inferior margin of the ipsilateral clavicular head, the medial border set at midline on the skin between the two breasts, the inferior border set 1-2 cm below in inframammary fold, and the lateral border set at approximately the mid-axillary line to ensure all palpable breast tissue is included within the fields. The posterior (deep) border of the medial and lateral tangent borders will be aligned to ensure that neither tangent field diverges into critical structures. A cardiac block may be utilized by the treating physician if it does not compromise coverage of the whole breast. Every effort should be made to minimize cardiac exposure.

6.4.2 Treatment of the level I/II axillary lymph nodes with high tangent fields is allowed. In such cases, the level I/II axillary lymph nodes should be contoured using the treatment planning CT images to assist with field delineation.

6.4.3 The clinical target volume will be defined as the seroma cavity and tumor bed clips (when present) as visualized on the treatment planning computed tomography scan. The clinical target volume will be trimmed such that it does not approach within 5 mm of the skin surface.

6.4.4 The tumor bed boost will be delivered with electrons or photons at the discretion of the treating radiation oncologist. The tumor bed boost will be delivered to the clinical target volume plus a radial margin of 1.5-2.0 cm at the discretion of the treating radiation oncologist. A second treatment planning computed tomography scan, with compression of the tumor bed or repositioning of the patient, may be obtained to assist in planning the tumor bed boost.

6.4.5 The treating physician should strive to minimize dose inhomogeneity within the breast. Any technique including the use of a wedge, three-dimensional dose compensation with a multi-left collimator, and/or intensity modulated radiation therapy is

permitted. In treating the whole breast, use of an electron field matched to the tangent fields is allowed if needed to ensure adequate coverage of the tumor bed in the whole breast.

6.5 Critical Structures

6.5.1 With respect to the lung, no more than 3 cm of lung shall be included in the tangent field as measured from the rib-lung interface to the deepest aspect of the tangent field.

6.5.2 The heart shall be excluded or the cardiac volume minimized from the tangent fields. This can be achieved through use of a cardiac block, deep inspiration breath hold, or other geometric means.

6.6 Compliance Criteria

6.6.1 Plans will be considered acceptable if they adhere to the field borders as described in 6.4.1 and the clinical target volume is completely encompassed within the geometric projection of the tangent fields.

6.6.2 The treating physician shall treat the patient with CF-WBI, regardless of randomization arm, if either of the following occur: (1) in the judgment of the treating physician, the heart cannot be excluded from the fields without compromising tumor coverage; or (2) > 1 cubic centimeter of breast tissue is expected to receive $\geq$ 108% of the prescription dose despite all efforts to optimize homogeneity.

6.6.3 A treatment break of up to 3 treatment days is acceptable. A break of 4 or more days will be considered a variation.

6.6.4 If the patient receives less than 95% of the intended whole breast radiation dose this will be considered a minor violation. If the patient receives less than 90% of the intended whole breast radiation dose this will be a major violation.

6.6.5 If, at the time of treatment planning, the treating physician feels that delivery of a tumor bed boost may be unsafe due to the clinical size of the seroma cavity, then the tumor bed boost may be omitted at the discretion of the treating radiation oncologist. This will be considered a variation, and patients not receiving a boost will be reported separately in outcomes analyses.

6.7 Radiation Therapy Quality Assurance Reviews

All cases will be presented for peer review in accordance with the policy of the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center or participating institution. To improve radiation therapy quality assurance processes, we will collaborate with the MD Anderson Cancer Center Radiation Oncology Medical Physicists to develop and evaluate new treatment planning techniques, first in a retrospective manner by utilizing “test” cases of participants who have already completed radiation therapy. Participants enrolled on this trial (2010-0559) may have their radiation treatment plans/ images or other study-related information collected under the 2010-0559 protocol such as toxicities, oncologic history, demographics, etc reviewed retrospectively under MD Anderson IRB- approved protocols RCR03-400 and/ or PA16-0379.

6.8 Radiation Adverse Events

Events that may occur include fatigue, skin erythema, dry or moist desquamation, hyperpigmentation, alopecia, tenderness, and swelling. Uncommon side effects include breast cellulitis or abscess and severe breast pain. In the long term, breast changes may occur including fibrosis, hyper- or hypo-pigmentation, telangiectasia, shrinkage/breast asymmetry, poor cosmesis, and edema. Uncommon side effects that may occur after completion of radiation include upper extremity lymphedema, rib fracture, pneumonitis, pulmonary fibrosis, pericarditis, ischemic heart disease, and heart failure.

6.9 Adverse Events and Serious Adverse Events Reporting Requirements

We will follow institutional guidelines at the University of Texas M. D. Anderson Cancer Center.

7.0 Drug Therapy

Not applicable to this study.

8.0 Surgery

All patients in this study will undergo breast conserving surgery, either with or without “oncoplastic” techniques including reduction mammoplasty. Placement of radio-opaque clips to define the extent of the lumpectomy cavity is encouraged but not required.

9.0 Other Therapy

9.1 Permitted Supportive Therapy

All supportive therapy indicated for optimal medical therapy during the course of radiation will be permitted for this study. Supportive therapy will be documented as concomitant medication. Supportive therapy may include, but is not limited to, the following:

- Radiodermatitis creams or ointments
- Topical steroids
- Oral antipruritics
- Oral analgesics to include non-narcotic and narcotic medications
- Antibiotic therapy as indicated for breast infection
- Nutritional supplementation

10.0 Tissue/Specimen Submission

10.1 Blood procurement. One-time 4-cc blood samples will be drawn into heparinized green-top tubes for each of the eligible subjects who grant consent. Blood drawn at the Main Campus may be hand delivered to Dr. Liao's laboratory. Blood drawn at regional care centers will be sent via courier to the Diagnostic Center at the Main Campus, where it will or picked up by a Radiation Oncology Research staff and delivered to Dr. Liao's lab. Preprinted labels with study identification numbers will be placed on each blood tube. A transmittal slip (multiple-copy form) will accompany each blood sample, and a copy will be retained in the Study Coordinator’s office. All samples will be logged in TissueStation as per institutional requirements. Blood drawn at participating institutions outside of the greater Houston area will be sent via overnight carrier to Tanisha Davis, RN Research Nurse, Division of Radiation Oncology, UT MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1210 Houston, TX 77030, Phone: 713-563-8698 (Office).

10.2 The genotype of the C-509T, G915C, and T869C alleles of the TGF-b gene will be determined by Dr. Liao's laboratory using polymerase chain reaction restriction fragment length polymorphism assessment according to their previously published methods.[44]

10.3 The Molecular Diagnostic Laboratory (MDL) at MD Anderson will use the collected DNA samples to develop and optimize a new assay for the detection of the C－509T (rs1800469) variant allele of TGFB1 (GenBank NC_000019.10). Up to 120 DNA samples will be required for evaluate performance characteristics determined by the MDL at MD Anderson Cancer Center. As this test will be used for clinical purposes, the MDL is certified under the Clinical Laboratory Improvement Act (CLIA) of 1988 to perform high complexity clinical laboratory testing.

To accomplish this, a real-time polymerase chain reaction assay will be applied to DNA samples to genotype rrs1800469 (dbSNP) of the TGFB1 gene using the QuantStudio 7 Flex Fast Sequence Detection System (PE Applied Biosystems). M13-tagged primers will be designed to confirm ASO-PCR findings using traditional Sanger sequencing. Concordance between the two methods, reproducibility, and limit of detection will be tested and established.

11.0 Patient Assessments

11.1 Study Parameters:

See Appendix C.

11.2 Evaluation During Study:

11.2.1 Patients will undergo weekly evaluations during radiation therapy, history and physical exam approximately 6 months (+/2 months) after completing radiation therapy, and yearly (+/-3 months) history and physical exam for the 5 years following radiation therapy. Patients may be followed more frequently at the discretion of the treating radiation oncologist. After completing five years of follow up, patients will be off study and may be discharged to either the Institution’s Cancer Survivors Clinic or to their primary medical doctor.

11.2.2 The schedule for surveillance mammography is as follows: at the six month follow up visit, at the one year follow up visit, and yearly thereafter while on study. However, the routine standard of care for mammographic follow up in the community in which the patient is treated is also acceptable. The routine standard of care in the community is typically mammographic follow up approximately once per year. Skin thickness on post-treatment mammograms may also be measured as a surrogate for skin toxicity from radiation.

11.2.3 Abnormal findings on mammography or clinical exam will be further investigated with additional imaging modalities such as ultrasound. Findings that remain suspicious after additional imaging should be biopsied to determine the presence or absence of ipsilateral breast tumor recurrence.

11.3 **Patient-Rated Evaluations**

11.3.1 The Breast Cancer Treatment Outcomes Scale will be used to score cosmetic outcome from 1 to 4, with a score of 2.5 or higher indicating adverse cosmetic outcome (Appendix K).

11.3.2 The Breast Cancer Treatment Outcomes Scale will also be used to assess the domains of functional status and breast pain on a scale of 1 to 4, with a score of 2.5 or higher indicating adverse outcome (Appendix K).

11.3.3 The FACT-B is a validated instrument used to assess quality of life for women with breast cancer and will be used to assess general quality of life and will be scored according to standard guidelines that accompany the instrument.

11.3.4 The Body Image Scale (BIS) is a validated instrument that will be used to assess body image and will be scored according to standard guidelines for this instrument. This is not required for Spanish-only speakers because the questionnaire is only available in English.

11.3.5 The Appearance Schemas Inventory-Revised (ASI-R) is a validated instrument to assess appearance investment and will be scored according to standard guidelines for this instrument. This is not required for Spanish-only speakers because the questionnaire is only available in English.

11.3.6 The BCTOS, FACT-B, BIS, and ASI-R will be administered within 14 days prior to start of radiation treatment and at the following timepoints measured from the date of completion of radiation therapy: 6 months (+/- 2 months), 1, 2, 3, 4, and 5 years (+/- 3 months annually). These questionnaires may be mailed to non-returning patients by regular mail (with provision of a selfaddressed stamped envelope for return mail) or encrypted email. Patients may also be contacted by telephone. If the patient loses a breast during the follow up interval, the BCTOS will no longer be required.

11.3.7 Patients will be given the opportunity to watch an informational video about the protocol.

11.4 **Physician-Rated Evaluations**:

11.4.1 Baseline physician-rated cosmesis will be scored by the treating radiation oncologist within 14 days prior to start of radiation treatment using RTOG criteria. Patients will be stratified for randomization according to whether their treating physician rates their cosmetic outcome as excellent or good versus fair or poor (Appendix G). For documentation, photographs will be taken prior to radiation therapy as well. Photographs will be framed to include the low neck down to the upper abdomen and will be taken with arms at the side and patients will be asked to remove all jewelry prior to photography. Five views will be obtained: right lateral, right anterior oblique, anteroposterior, left anterior oblique, and left lateral. When possible, photographs will be obtained in the Department of Plastic Surgery three-dimensional photography suite, thereby enabling quantitation of breast size and position. All photographic data will be stored the Radiation Oncology Access to Data Systems (ROADS) (https://roads.mdanderson.org) database for this study. Access to the photos will be limited only to those study personnel with a need to view photos and will be logged using ROADs. Photographs may also be stored on a password-protected institutional drive with access limited only to those study personnel with a need to view and upload photographs. Photographs obtained in the three-dimensional photography suite will be de-identified through removing the patient's head and, afterwards, such de-identified photographs may be securely transferred to the University of Texas at Austin where one of the study collaborators (Dr. Mia Markey) is located and/or to the University of Houston where another study collaborator (Dr. Fatima Merchant) is located. Dr. Markey's lab and/or Dr. Merchant's lab will be able to use sophisticated image processing algorithms to quantitate metrics related to breast size and position. This data will be stored in a secured database system supported by UT Austin Information Technology Services or the University of Houston Information Technology Services. Research personnel at UT Austin and University of Houston will undergo training on research with human participants and on the university's information technology security policies. All data sent to UT-Austin and University of Houston will be deidentified and coded by patient registration number only.

11.4.2 For follow up evaluations, photographs as described above will be obtained at 6 months (+/- 2 months), 1, 2, 3, 4, and 5 years (+/- 3 months annually) from the date of completion of radiation therapy. A group of at least three attending physicians with expertise in breast cancer (physician specialty may include radiation oncology, surgical oncology, or plastic surgery), blinded to the randomization arm, will score the photographs using RTOG criteria and will attempt to reach consensus for each patient and timepoint. In the absence of consensus, scores from each physician will be averaged. A mean physician-reported cosmetic score higher than 2.5 will be considered excellent/good cosmesis and a score less than or equal to 2.5 will be considered fair/poor cosmesis. Patients not returning for a protocol-specific follow-up visit may have their photographs taken by their local physician or by a family member and sent to Dr. Smith. Patients will be encouraged to return to their treating radiation oncologist for the 3-year follow-up visit as the primary objective is cosmesis at 3 years post treatment. If the patient loses the treated breast during the follow up interval, photographs will no longer be required. Selected, representative baseline and follow up photographs without identifying features (i.e. without tatooes or other identifying markings) may be included as representative images in the decision aid developed under protocol 2016-0878.

11.4.3 For completion of the Follow-Up Form (Appendix O), for patients not returning to their treating physician for a protocolspecific follow-up visit, the local physician may be requested to complete this form and return to research staff in a provided selfaddressed stamped return envelope.

11.5 **Treatment planning parameters**

11.5.1 The volume of breast tissue receiving excessive dose > 105% of the prescription dose will be determined using treatment planning software.

11.5.2 Breast volume will be determined using the total volume of irradiated tissue receiving at least 90% of the prescription dose.

11.5.3 The maximal point dose within the breast will also be recorded.

11.5.4 The volume of the clinical target volume in cubic centimeters will be recorded.

11.5.5 The separation at the central axis will be recorded.

11.6 <u>Summary of all study forms and data collected</u>

11.6.1 Acute Toxicity Form (Appendix H)

Purpose – This form captures information regarding physician-reported toxicities that occur during radiation therapy treatment. The form should be filled out and signed weekly by the treating physician at the time of the weekly treatment visit. Toxicities are graded by number using the NCI CTCAE v4.0 scale as per the protocol. This form should also be used to document any toxicities that are documented during unscheduled follow up visits that occur within six weeks of completing radiation therapy. Any adverse events noted must also be reported to the IRB and Protocol Principal Investigator in accordance with Section 5.0 herein. *This form is not for IRB submission, but for recording the toxicities in the research database.*
Timeline for completion – Filled out and signed by an attending physician at the time of each weekly treatment visit. The protocol does not require the patient to be evaluated by a physician within six (6) weeks of completing radiation. However, if such an encounter takes place, and the patient is experiencing any toxicity with a grade higher than documented at the last treatment visit, this form should be filled out and signed by the attending physician.

11.6.2 FACT-B v.4 (Appendix I)

Purpose – Documents health-related quality of life for breast cancer patients. This form is available in both English and Spanish and patients should be allowed to use the language that they prefer.
Timeline for completion – Completed at time of registration and during each scheduled follow up visit (at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years after the end of radiation treatment).

11.6.3 Body Image Scale (BIS) (Appendix I)

Purpose – This form captures information regarding patient-reported body image. This form is only available in English. Patients fluent only in Spanish are not required to fill it out.
Timeline for completion – Completed at time of registration and during each scheduled follow up visit (at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years after the end of radiation treatment).

11.6.4 Appearance Schemas Inventory-Revised (ASI-R) (Appendix I)

Purpose – This form captures information regarding patient-reported image investment. This form is only available in English. Patients fluent only in Spanish are not required to fill it out.

Timeline for completion – Completed at time of registration and during each scheduled follow up visit (at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years after the end of radiation treatment).

11.6.5 Dosimetry Form (Appendix J)

Purpose – This form captures technical details regarding the radiation therapy plan. It should be filled out by a dosimetrist. Any questions can be referred directly to the study PI (bsmith3@mdanderson.org, 713-404-4182 pager, 713-563-2380 office).
Timeline for completion – Filled out by a certified medical dosimetrist within four weeks of completing radiation.

11.6.6 Breast Cancer Treatment Outcomes Scale (BCTOS) (Appendix K and L)

Purpose – Documents patient-reported cosmetic outcome, breast pain, and functional status by comparing the affected breast and area to the unaffected breast and area. This form is available in both English and Spanish and patients should be allowed to use the language that they prefer.
Timeline for completion – Completed at time of registration and during each scheduled follow up visit (at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years after the end of radiation treatment).

11.6.7 Baseline Data Collection Form (Appendix N)

Purpose – Outlines protocol-specific baseline characteristics and includes the following:

- Participant Demographics (Name, medical record number, age, race, origin).
- Baseline health characteristics (menopausal status, height, weight).
- Tumor characteristics (stage, size, histology, ER/PR/Her2-neu status)
- Treatment characteristics (date of surgery, receipt and type of chemotherapy)

Timeline for completion – At time of registration.

11.6.8 Follow Up Form (Appendix O)

Purpose – Records the following information to report any patient encounter that occurs more than six (6) weeks after completing radiation:

- Treatment with endocrine therapy
- Any recurrences
- Any surgical procedures on the treated or untreated breast
- Toxicity data

Timeline for completion – Filled out and signed by the attending physician at each scheduled follow up visit (at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years after the end of radiation treatment). This form should also be filled out and signed by the attending physician to document any unscheduled follow up visit that occurs more than 6 (six) weeks after completion of radiation therapy.

11.6.9 Off Study Form (Appendix P)

Purpose -The Off Study Form is submitted if the participant removes herself from the protocol prior to the five-year follow up visit or if the patient expires.
Timeline for completion – Completed at the time of notification that the patient has removed herself from the protocol or at the time of notification of patient death.

11.6.10 Randomization Form (Appendix Q)

Purpose – documents stratification factors:

- Bra cup size
- Chemotherapy
- Margin status
- Baseline cosmesis

Timeline for completion – At time of registration.

11.6.11 Treatment Summary (Appendix R)

Purpose – Records the following information related to the time the participant receives protocol treatment:

- Treatment start and end dates
- Total dose and number of fractions

·This form will only be filled out by the participating institutions MD Anderson Orlando and Banner MD Anderson. The data will be imported directly from Mosaiq into ROADs for other sites.

Timeline for completion – This note will be dictated into Clinic Station for all patients treated at MD Anderson Main Campus or Regional Care Centers within 30 days of completion of radiation therapy. There is no requirement for a copy of the Clinic Station Treatment Summary to be kept in the study file for patients treated at MD Anderson Orlando or the Main Campus, as salient information from the treatment summary will be important into the trial database directly from the Mosaiq radiation oncology treatment record. For patients treated at MD Anderson Orlando, a hard copy of the Treatment Summary will be submitted.

11.6.12 Breast Photographs

Purpose -To create a photographic record of the appearance of the patient's breasts:

·Includes five pictures (right lateral, right anterior oblique, anteroposterior, left anterior oblique, and left lateral). Pictures shall be taken as per instructions in section 11.4 of the protocol.

Timeline for completion – Completed at time of registration and during each scheduled follow up visit (at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years after the end of radiation treatment).

11.7 All data will be collected at The University of Texas MD Anderson Cancer Center and will be stored on HIPPAAcompliant institutional computer systems. The Radiation Oncology Access to Data Systems (ROADS) (https://roads.mdanderson.org) will be used to track all data. Forms may be filled out directly into the ROADS database for this trial, thereby obviating the need for paper forms.

If a patient chooses to no longer follow-up with Radiation Oncology or Surgical Oncology but does not withdraw consent, we will continue to follow their chart for recurrence information.

11.8 It is expected that approximately 10 patients per year will be enrolled at MD Anderson Orlando and 10 patients per year at Banner MD Anderson. These institutions will be expected to comply with the Data and Quality Monitoring Plan as outlined in Appendix S.

It is permissable for each center to accrue more or less patients that the expected accrual, provided that the total number of randomized and treated patients accrued to the protocol does not exceed 288.

12.0 Data Collection

All data will be collected at The University of Texas M. D. Anderson Cancer Center and will be stored on HIPPAA-compliant institutional computer systems.

13.0 Statistical Considerations

13.1 **<u>Primary Endpoint:</u>** The primary endpoint for this study is the patient-reported cosmesis score on the BCTOS at 3 years after completing radiation therapy. Cosmesis scores range from 1 to 4, and scores of 2.5 or more indicate adverse cosmetic outcomes. Our objective is to show that the proportion of patients treated with HF-WBI with adverse cosmetic outcomes is not more than 10% greater than the proportion of patients treated with CF-WBI with adverse cosmetic outcomes.

A cutoff point of 2.5 was chosen in defining adverse cosmetic outcome for several reasons. First, if a patient scores 2.5 or higher, this means that, on average, they feel that their treated breast is at least moderately different from the untreated breast (ie they rated more domains as moderate or higher change rather than mild or less change). In the opinion of the clinical investigators on this trial, a patientreported moderate difference between the treated and untreated breast is clinically relevant. Second, in the initial study using the Breast Cancer Treatment Outcomes Scale (BCTOS), the mean BCTOS cosmetic score was 2.23 with a standard deviation of 0.77. The BCTOS cosmetic score stratified at a cutoff of 2.5 was not reported. However, given the mean and standard deviation, we estimate that in the initial study of the BCTOS the percent of women with a cosmetic score of 2.5 or higher was approximately 35-40%. Our study's power calculation is based on the assumption that the adverse cosmetic score will be 35% in the HF-WBI arm and 40% in the CF-WBI arm. Accordingly, we believe that the cutoff we selected for defining adverse cosmesis will yield a risk of adverse cosmesis that is in concert with the assumptions built into our power calculation.

As reported in the START A and START B trials,[20,21] we expect the proportion of patients treated with CF-WBI experiencing an adverse cosmetic outcome at 3 years to be about 40%. For the current study, if we assume an alpha/beta ratio of 3.4 Gy for late normal tissue toxicity,[22] the equivalent doses in 2 Gy per fraction to the tumor bed in the HF-WBI arm are 58.7 Gy for patients with widely negative margins and 61.4 Gy for patients with close margins, slightly less than the tumor bed doses of 60 Gy and 64 Gy, respectively, that will be used in the CF-WBI. Accordingly, we make the *a priori* assumption that the risk of adverse cosmetic outcome will be slightly lower in the HF-WBI arm than in the CF-WBI arm.

Patients with early breast cancer are generally highly compliant with follow up care. For example, in the four main randomized trials comparing HF-WBI to CF-WBI (cited in the protocol), the number of patients lost to follow up ranged from 0% - 1.3%. We will analyze sociodemographic correlates of trial participation status and outcomes, including patient sociodemographic characteristics as well as geographic (neighborhood) characteristics. In addition, local failures requiring a mastectomy are rare in this population, typically less than 3% at 3 years. As a result, we do not anticipate patient drop out being a major concern. Nevertheless, as a conservative measure we plan to conduct a sensitivity analysis in which patients who do drop out prior to 3 years will be considered to have an adverse cosmetic outcome.

13.2 **Sample Size:** If we assume that 35% of patients treated with HF-WBI will have adverse cosmetic scores and 40% of patients treated with CF-WBI will have adverse cosmetic scores, a sample size of 274 patients (137 randomized to each treatment arm) will yield 90% power with a 1-sided significance level of 0.10 for testing the following hypothesis:

$$H_0\text{: } P_{HF\text{-}WBI} - P_{CF\text{-}WBI} \geq 0.10$$

$$H_1\text{: } P_{HF\text{-}WBI} - P_{CF\text{-}WBI} < 0.10$$

where PHF-WBI is the proportion of patients treated with HF-WBI who have adverse cosmetic outcomes at 3 years and PCFWBI is the proportion of patients treated with CF-WBI who have adverse cosmetic outcomes at 3 years. We also expect a loss rate of 5% due to death, loss to follow up, or local recurrence requiring mastectomy which will prevent assessment of cosmetic outcome, Accounting for this, our study will require a sample size of 288 patients (144 on each arm).

13.3 **Randomization:** Patients will be randomized to HF-WBI or CF-WBI using CORe. Randomization will be stratified by the post-lumpectomy/pre-radiation physician-reported cosmetic score (excellent/good versus fair/poor), bra cup size (D or higher versus C or lower), receipt of chemotherapy (yes/no), margin status (< 2 mm vs $\geq$ 2 mm), and treatment location (Houston area facilities vs Banner MD Anderson vs MD Anderson Orlando).

13.4 **Interim Analysis:** The accrual rate is expected to be 100 patients per year, and the primary outcome is measured at 3 years. Therefore, it is impractical to conduct an interim analysis of non-inferiority or futility.

13.5 **Primary Analysis**

13.5.1 We will use descriptive statistics to summarize the demographic and clinical characteristics of the patients by treatment arm.

13.5.2 We will use a chi-square test, stratified by randomization strata with a 1-sided significance level of 0.10 to test the hypothesis stated above. We will also estimate the proportion of patients in each treatment group with an adverse cosmetic outcome at 3 years with a 95% confidence interval.

13.6 **Secondary Analyses**

13.6.1 For each treatment arm we will tabulate the scores on the BCTOS at 6 months, 1, 2, 3, 4, and 5 years. Adverse cosmetic outcome will be defined as scores of 2.5 or more. We will use McNemar's test to assess changes in cosmetic outcome from 2 to 5 years and from 5 to 10 years within each treatment arm. We will use a chi-square test stratified by randomization strata to compare scores on the BCTOS for the two treatment arms at 2, 3, and 5 years.

13.6.2 For each treatment arm, we will tabulate the physician-rated cosmetic outcome using the Radiation Therapy and Oncology Group (RTOG) scale for physician assessment at 6 months, 1, 2, 3, 4, and 5 years. We will dichotomize the outcomes as excellent/good and fair/poor, and we will use McNemar's test to assess changes in cosmetic outcome from 2 to 5 years within each treatment arm. We will use a chi-square test stratified by randomization strata to compare scores for the two treatment arms at 6 months, 1, 2, 3, 4, and 5 years.

13.6.3 We will estimate with 95% confidence intervals the concordance between the BCTOS and the RTOG scale for physician assessment for classifying adverse cosmetic outcome at 6 months, 1, 2, 3, 4, and 5 years.

13.6.4 We will use the product-limit method of Kaplan and Meier to estimate with 95% confidence intervals the 5-year and 10year probability of pathologically confirmed invasive and/or in situ ipsilateral breast tumor recurrence (IBTR) stratified by treatment arm and tumor type (DCIS or early invasive breast cancer). Patients will be censored at the time of death or distant recurrence.

13.6.5 For each treatment arm we will tabulate the patient-reported functional status and breast pain as measured by the BCTOS at 6 months, 1, 2, 3, 4, and 5 years. Scores of 2.5 or more will indicate adverse outcomes, and we will estimate with 95% confidence intervals the proportions of patients in each treatment arm with adverse outcomes at each assessment time.

13.6.7 For each treatment arm we will tabulate the maximal acute (within 6 weeks of completing treatment) and late (more than 6 weeks) skin and soft tissue toxicities using the NCI CTCAE v4.0 scale. In accordance with prior studies, we will also report the outcomes of fibrosis and telangiectasia using the SOMA scale.[43]

13.6.8 We will use logistic regression methods to model the logit of the probability of patient reported adverse cosmetic outcome at each assessment time and the volume of breast tissue receiving >105% of the prescription dose as a function of treatment arm, breast size, and other demographic and clinical factors.

13.6.9 The one-sided Fisher's exact test will be used to test the association between the presence of at least one copy of the C509T variant allele and risk of grade 2 or higher fibrosis at three years as reported using the SOMA scale. This strategy will yield 83% power to detect a 15% absolute difference in risk of grade 2 or higher fibrosis at a significance level of 0.05 assuming that 150 patients participate in this component of the study, the baseline risk of fibrosis in the wild type group is 5%, and the frequency of the variant allele in the population is 0.33. For hypothesis generation, we will use the two-sided Fisher's exact test to test the association between the C-509T, G915C and T869C variant alleles in TGF-b and early and late radiation-related toxicities captured using the CTCAE v4.0 and the risks of fibrosis and telangiectasia captured using the SOMA scale.

13.6.10 The cost of radiation for the two treatment arms will be compared using the Wilcoxon 2-sample test.

13.6.11 Data collected from the FACT-B, BIS, and ASI-R will be used to conduct exploratory analyses to identify putative cutpoints for these measures that could potentially discriminate between the two treatment arms. In addition, we will use longitudinal data analysis methods to describe how patient's scores for these measures may change over time and if treatment arm impacts this change.

13.6.12 DNA repair phenotypes and genotypes and their associations with baseline clinical-pathologic covariates will be assessed in accordance with the statistical methods outlined in protocol LAB02-086.

13.6.13 Skin thickness on available post-treatment mammograms will be compared between the two treatment arms using the Wilcoxon two-sample test.

13.6.14 To study the psychometric properties of the FACT-B v.4, we will provide a de-identified dataset to investigators at the Department of Medical Social Science, Northwestern University Feinberg School of Medicine. This dataset will include the following data collected at baseline: sociodemographic and clinicopathologic covariates, physician-reported cosmetic outcome, and item-level patient responses to the FACT-B v.4, Breast Cancer Treatment Outcomes Scale, Appearance Schemas Inventory-Revised, and Body Image Scale. The dataset will include the following data collected at
6 and 12 months: physician-reported cosmetic outcome and item-level patient responses to the FACT-B v.4, Breast Cancer Treatment Outcomes Scale, Appearance Schemas Inventory-Revised, and Body Image Scale. Patient identifiers will be removed from the provided dataset, and randomization arm will not be provided. A flag variable will be created for each patient-reported outcome instrument to indicate whether the instrument was filled out using a paper form or an iPad. Internal consistency reliability will be estimated for each multi-item subscale with Cronbach's coefficient alpha. Cronbach's coefficient alpha is a measure of how closely correlated a set of items are with each other. A Cronbach's coefficient alpha of 0.70 or greater is generally considered acceptable for group comparisons. Several types of validity will be evaluated, including (1) construct-related: convergent and divergent validity, known-groups validity, (2) criterionrelated: associations with criterion measures (valid measures of the same concept), (3) responsiveness: sensitivity to change, and (4) comparison of alternative methods of administration (paper vs. iPad). Standard statistical tests for continuous and categorical data will be performed, e.g., t-tests, analysis of variance, chi-squared tests, correlation coefficients. Effect sizes will be estimated to evaluate minimally important differences.

13.7 Toxicity Monitoring

Within each treatment arm we will monitor the rate of CTCAE v4.0 grade 3 or higher acute radiation-induced dermatitis developed within 6 weeks of completion of radiation therapy. If we have reason to believe that the rate of acute dermatitis is more than 20% in either treatment arm we will stop the trial.

We will employ the following monitoring rule as a guide in assessing whether we are observing excess CTCAE v4.0 grade 3 or higher acute dermatitis. This rule is based on the method proposed by Thall et al.[46] We assume a beta(0.4, 1.6) prior distribution for the rate of CTCAE grade 3 or higher acute dermatitis. T his distribution has a mean of 20% and a standard deviation of 23%.

We will stop the trial if the Pr(CTCAE grade 3 or higher acute dermatitis > 20% | data) > 0.90 on either treatment arm. That is, if there is more than a 90% chance that the CTCAE grade 3 or higher acute dermatitis rate is more than 20% on either treatment arm we will stop the trial. We will monitor patients in cohorts of size 20 within each treatment arm. This monitoring rule gives us the following stopping boundaries.

Stop the trial if, within either treatment arm, the

[# patients with CTCAE grade 3+ acute dermatitis / # of patients evaluated] $\geq$ 7/20, 12/40, 17/60, 22/80.

The operating characteristics of this monitoring rule are summarized in the following table. From this table we see that if the rate of CTCAE v4.0 grade 3 or higher acute dermatitis within 6 weeks of radiation therapy is 30% we have an 81.3% probability of stopping the study early, with a median sample size of 40 patients on each treatment arm. Also, if the rate of CTCAE grade 3 or higher acute dermatitis within 6 weeks of radiation therapy is 15% we have only a 3.2% chance of stopping the study early. P_{25}, P_{50}, and P_{75} are the first quartile, median, and third quartile of the sample size for each treatment arm.

Operating Characteristics of Toxicity Monitoring Rule				
Rate of CTCAE Grade 3+ Moist Desquamation within 6 weeks of Radiation Therapy	Probability of Stopping Early	Sample Size		
		P_{25}	P_{50}	P_{75}
0.05	< 0.001	100	100	100
0.10	0.003	100	100	100
0.15	0.032	100	100	100
0.20	0.173	100	100	100
0.25	0.491	40	100	100
0.30	0.813	20	40	80
0.35	0.962	20	20	40
0.40	0.996	20	20	40

14.0 References

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