MSK Protocol Cover Sheet

A Phase I Study of Rucaparib Administered Concurrently with Postoperative Radiotherapy in Patients with Triple Negative Breast Cancer with an Incomplete Pathologic Response Following Neoadjuvant Chemotherapy

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

The primary objective of the study is to determine the maximum tolerated dose (MTD) of rucaparib in combination with breast and nodal radiotherapy (RT) in women with triple negative breast cancer (TNBC) with residual disease following neoadjuvant chemotherapy or high grade hormone receptor (HR) positive disease with high volume residual following neoadjuvant chemotherapy. Secondary objectives are to describe the toxicities and disease outcomes and to identify biomarkers of locoregional relapse following rucaparib plus RT.

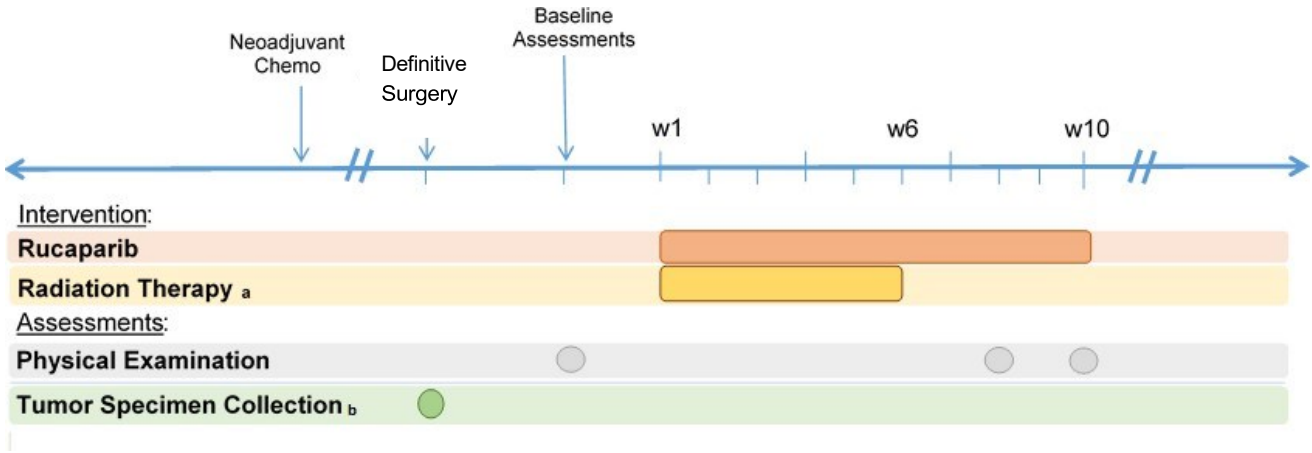
This is an amended protocol in which we add additional negative dose escalation levels to allow probing of the MTD into lower doses of rucaparib. In the original design, we had one -1 dose level, but we have exceeded the observed DLT for the TITE-CRM threshold at this level (see Biostatistics, section 14). We now add 3 additional de-escalation (-2, -3, and -4 dose levels). It is not surprising that even low dose levels of a PARP inhibitor may have radiosensitizing effects; for this reason we add 3 additional de-escalations.

Eligibility criteria include stage I-III TNBC patients with residual invasive disease following neoadjuvant chemotherapy (NAC), as well as high grade HR positive disease with high volume residual (4 or more positive axillary nodes, or 5 cm or more of residual breast disease) after NAC. Tumor tissue will be collected at the time of surgery, if available, precluding the need for an extraneous biopsy.

Treatment will consist of rucaparib at one dose level (200 mg QD, 300 mg QD, 200 mg BID, 300 mg BID, 400 mg BID, 500 mg BID, 600 mg BID) throughout a 6-week course of RT and then 4 weeks of maintenance rucaparib, at the same dose level, following RT. RT dose will consist of 50 Gy in 2 Gy/fraction to the breast or post-mastectomy chest wall, with or without nodes plus a 10 Gy boost to the lumpectomy cavity or (optionally) to the mastectomy scar (total dose 60 Gy). Patients will be followed for evaluation of toxicity with weekly assessments during the 10-week study period. For post-mastectomy patients not treated with a boost (ie only 5 weeks of radiation), rucaparib will be continued for 4 weeks post-RT for a total of 9 weeks. Patient-reported outcomes will be assessed and subject drug diaries will be maintained. Patients will then be followed every 3-6 months for two years, as per standard follow-up care.

The trial will be monitored using a TITE-CRM (TIme-To-Event Continual Reassessment Modulation) design[1]. The target rate for dose-limiting toxicity (DLT) is 30%. DLT will be defined as toxicities probably or definitely related to the study drug observed during the study period. A detailed definition of dose-limiting toxicity (DLT) for this trial is defined in Section 9.5.

The target accrual is 30 patients, to be accrued within 2 years.



a. Radiation dose is 50 Gy/25 fractions to the whole breast or chest wall +/- regional nodes plus a 10 Gy/5 fractions boost to the lumpectomy cavity. Mastectomy patients may also receive scar boosts; rucaparib will continue for 4 weeks post-RT (total of 9-10 weeks depending on whether a boost is used).
b. Tumor tissue will will be procured from the lumpectomy or mastectomy specimens, as well as from the baseline diagnostic cores, if available.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

- The primary objective is to determine the maximum tolerated dose of rucaparib that can be administered concurrently with standard doses of radiotherapy to the breast/chest wall +/- regional nodes.

- Secondary objectives are:

    - To describe the nature of toxicity that develops when rucaparib is administered concurrently with RT.
    - To assess locoregional relapse and distant relapse.
    - To evaluate biomarkers (HRD status) correlated with locoregional relapse following rucaparib administered concurrently with RT.
    - To evaluate the presence of tumor infiltrating lymphocytes (TILs) and correlate this with locoregional relapse. .
    - To assess patient reported satisfaction and quality of life with treatment using the Breast Cancer Treatment Outcomes Scale (BCTOS)
    - To determine the rate of poor cosmetic outcomes from both provider and patient perspectives up to 2 years after rucaparib + RT using the RTOG (Radiation Therapy Oncology Group) cosmesis scale[2] and digital images.

3.0 BACKGROUND AND RATIONALE

Triple negative breast cancer (TNBC), defined as estrogen receptor and progesterone receptor levels <1% and HER2-negative (0-1 + by immunohistochemistry or HER2/CEP17 ratio <2 or HER2 signals/cell <4 by in-situ hybridization constitutes 10-15% of breast cancers, but is disproportionately associated with rapid growth, early locoregional recurrence and metastasis and unfavorable prognosis compared to other subtypes of breast cancer[3]. TNBCs are characterized by a genomic profile that is similar to BRCA1-mutation carriers, indicative of defects in the BRCA pathway[4]. Although rarely mutated in sporadic breast cancer, BRCA1 expression has been reported to be reduced in a small number of sporadic tumors, particularly in TNBC[5-7]. BRCA1 and BRCA2 are only two of many proteins involved in executing homologous recombination repair (HRR)[8]. A subset of sporadic breast cancers may also have defects in HRR, in the absence of mutations in either BRCA1 or BRCA2[9,10]. The frequency of BRCA1-BRCA2-RAD51 pathway defects in breast cancer has been quantified in 60 invasive breast cancer patients using an HRR assay developed at Memorial Sloan-Kettering Cancer Center. The incidence of HRR deficiency was the highest among TNBC patients (48%), compared to other subtypes (29% in HER2+, 21% in ER+)[11].

3.1 Rationale of Rucaparib plus Radiation Therapy

PARP is an enzyme involved in repair of endogenous or RT-induced single strand breaks (SSB). Inhibition of that pathway by a PARP inhibitor results in the accumulation of large amounts of SSBs, which can be converted to DSBs. In HRR-proficient cells, these DSBs are repaired by homology-directed repair. In HRR-deficient cells, however, such as cells with loss of BRCA1, BRCA2 or other proteins involved in the complex BRCA1-BRCA2 pathway, the repair machinery of the cell can be overwhelmed, leading to error-prone repair by alternative mechanisms. Inhibition of homologous recombination or PARPs may be well tolerated in isolation, but combined inactivation of these distinct DNA-repair pathways can result in cell death through synthetic lethality. In addition to its role in DNA repair, PARP has been shown to play a role in mitosis, where its inhibition has been proposed to lead to chromosome segregation errors, aneuploidy and in some cases, mitotic cell death[12-14]. Although chemotherapy and RT are common treatments for TNBC, there are no effective biomarkers that can reliably predict the sensitivity of these tumors to these treatments. By assaying the function of the HRR pathway using a combination of genomic and functional metrics, we aim to increase the accuracy of identifying TNBC patients who would maximally benefit from DNA repair-based therapies.

Given their mechanism of action, there is considerable interest in the potential of PARP inhibitors as radiation-sensitizing agents. In preclinical models, BRCA1 and BRCA2-deficient cells have been shown to be sensitive to PARP inhibitors. However, clinical studies utilizing PARP inhibitors in unselected sporadic TNBC have failed to show benefit of PARP inhibitors in improving progression-free survival [15]. There is scant data on locoregional outcomes following PARP inhibitor and RT.

Recently, a Phase I trial of veliparib and post-mastectomy RT in breast cancer patients with locally recurrent or inflammatory breast cancer reported dose-limiting toxicities in 4/30 patients[16]. Four dose levels of veliparib were tested (50 to 200 mg BID) with concurrent RT to the chest wall and nodes (50 Gy). Severe acute toxicity did not exceed 30%, even at the highest tested dose of veliparib (200 mg BID). Using these findings, the planning of a phase II trial testing the efficacy of veliparib and RT in breast cancer patients is currently in development. These findings underscore the importance of additional studies assessing the safety of PARP inhibitors with RT.

In a recently published series of 233 women with clinical Stage II-III breast cancer who underwent neoadjuvant chemotherapy (NAC), mastectomy and post-mastectomy RT at MSKCC, the rate of pathologic complete response (pCR) in TNBC patients was only 23%[17]. Failure to achieve pCR resulted in a higher 5-year locoregional recurrence rate compared to patients with HER2+ and hormone receptor-positive breast cancer (26% vs. 7% and 4%, $p<0.001$). Moreover, others have demonstrated the residual disease after neoadjuvant chemotherapy in TNBC is associated with significantly worse progression-free and overall survival[18]. The single notable effort to escalate therapy in these patients was recently reported by Masuda et al[19] in the *New England Journal of Medicine*. In this phase III randomized trial, patients with incomplete responses after neoadjuvant chemotherapy were randomized to consolidation capecitabine vs null. Overall survival was longer in the capecitabine group. Although the trial was for all comers, the greatest improvement was seen in TNBC cases (OS 79 vs 70% at 5 years). Taken together, these results demonstrate the need for additional treatment intensification in TNBC patients with residual disease after neoadjuvant chemotherapy. Recently, the Keynote-522 has altered the landscape of early TNBC, and is a seminal trial that randomized 1174 women receiving NAC for early TNBC to either chemotherapy alone or with pembrolizumab 200 mg/m2 every 3 weeks (2:1) (Schmid NEJM). Among the first 602 patients randomized, the pathological complete response rate (primary endpoint) was higher in the pembro arm (64.8%) compared to placebo (51.2%). The co-primary endpoint of event-free survival was also better with pembro, 91.3% vs 85.3%. These effects appeared to independent of PDL-1 status.

3.2 Study Disease: TNBC Residual Invasive Disease after NAC and BCS

TNBC patients who achieve less than a pCR to NAC are an ideal target population for combination treatments of PARP inhibitor and RT because: 1) effective locoregional therapies in such patients are lacking 2) RT is routinely indicated in such patients for enhancement of local disease control 3) the prevalence of HRR deficiencies in TNBC is high.

Rucaparib (CO-338) is a small molecule inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) being developed for cancers associated with homologous recombination deficiency (HRD). Rucaparib has been shown to potently inhibit PARP-1, PARP-2, and PARP-3 and has demonstrated activity in a background of breast cancer gene 1 and 2 (*BRCA1* and *BRCA2*) mutations in both clinical and nonclinical studies.

Rucaparib doses have been based upon review of the existing trials with rucaparib and the recommended starting dose for continuously administered oral monotherapy (600 mg BID). Timing of rucaparib administration in relation to radiotherapy has been based upon review of clinical studies evaluating orally-administered rucaparib. These studies showed rapid absorption of rucaparib, with peak plasma levels generally occurring within 1.5 to 6 hours postdosing.

The combination of RT with rucaparib may result in additive adverse events. This trial therefore aims to characterize the safety and tolerability of the combination of RT and rucaparib. Additionally, DNA repair-based correlates, such as HRR deficiencies, that we will study in this trial will yield invaluable insight into the rational construction of future studies of combination therapies with rucaparib. The

Breast Cancer Treatment and Outcomes Scale (BCTOS) is a validated instrument that will be used to assess patient reported outcomes (PRO) after treatment. The instrument was developed specifically for assessing PROs after lumpectomy and whole breast RT, and is divided into 3 subscales for cosmetic status, functional status, and pain [20], Appendix B.

We are well-poised at MSKCC to conduct the proposed trial, given the large volume of women with TNBC treated annually with NAC, our experience in conducting clinical trials that integrate DNA repair-based assays and the unique resource of the MSKCC Powell lab, which has developed analytically-validated techniques to prospectively assess treatment response to PARP inhibition and RT.

In addition to TNBC, we also consider patients with hormone-receptor (HR+) positive breast cancer with high volume residual after NAC to be candidates for local-regional escalated therapy. In the Cortazar meta-analysis, HR+/Her2- patients with grade 3 disease were more likely to achieve pathCR compared to grade 1 / 2 , but non-responding grade 3 patients did demonstrably worse in terms of event-free survival[21]. A similar was finding was noted in a retrospective from MDACC examining patients treated with NAC, wherein high grade disase was an independent predictor of LRR[22]. Thus we propose including women with HR+/Her2- breast cancer with grade 3 disease and either 1) ypT3 or higher disease in the breast (>5 cm of residual disease) or 2) ypN2a or higher disease in the nodes, as candidates for escalated LRR treatment with concurrent PARPi.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-arm Phase I study conducted to determine the maximum tolerated dose of rucaparib administered concurrently with radiotherapy to the breast/chest wall +/- regional nodes in triple negative breast cancer patients with incomplete pathologic response following NAC.

The trial will be monitored using TITE-CRM as described in Section 14.0, and the dose level escalated or de-escalated accordingly. Subjects will receive rucaparib at their assigned dose level, beginning with Dose Level 0. Two patients will be enrolled to Dose Level 0, and DLTS will be assessed before starting the TITE-CRM dose escalation algorithm. Throughout the trial, at least 2 patients must be observed for their entire acute toxicity period (70 days) before any dose escalation is allowed.

Dose Escalation Schedule	
Dose Level	Dose of Rucaparib administered concurrently with radiation therapy to the breast / chest wall +/- regional nodes
Dose Level -4	200 mg QD
Dose Level -3	300 mg QD

Dose Level -2	200 mg BID
Dose Level -1	300 mg BID
Dose Level 0	400 mg BID
Dose Level 1	500 mg BID
Dose Level 2	600 mg BID

4.2 Intervention

Treatment will consist of rucaparib at one dose level (200 mg QD, 300 mg QD, 200 mg BID, 300 mg BID, 400 mg BID, 500 mg BID or 600 mg BID) concurrently with a 6-week course of radiotherapy and 4 additional weeks of maintenance rucaparib at the same dose level.

Radiotherapy will consist of 50 Gy in 2 Gy per fraction to the breast or chest wall with or without regional nodes plus a 10 Gy boost to the lumpectomy cavity, to a total dose of 60 Gy. A 10 Gy boost to the post-mastectomy scar is allowed at the discretion of the treating physician.

Weekly assessments for DLTs will be performed throughout RT, and every other week during the maintenance rucaparib period.

4.3 Correlatives

In an effort to identify the homologous recombination deficient (HRD) phenotype as a biomarker that can predict the sensitivity of TNBC tumors to study treatment, patients will undergo tumor specimen collection from their original diagnostic core biopsies as well as specimens from their post-neoadjuvant definitive surgery specimens if they are available. We will also evaluate presence of TILs in the pre-chemotherapy core specimens as biomarkers for local-regional and distant relapse.

Correlatives are further detailed in Section 10.0.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Rucaparib camsylate (formerly known as PF-01367338 and AG-014447) is an oral formulation with a molecular weight of 555.67 Daltons. Rucaparib tablets for oral administration will be supplied by Clovis. Please refer to the Investigator Brochure.

Drug Name:	Rucaparib
INN:	Rucaparib

Formulation:	Tablet; film coated 200 mg – blue, round, embossed with C2 250 mg – white, diamond, embossed with C25 300 mg – yellow, oval, embossed with C3
How Supplied:	200, 250mg and/or 300 mg strength (based on free base) in high-density polyethylene bottles or equivalent with child-resistant caps. Patients may receive 1 or more strengths.
Storage Conditions:	Store at room temperature, with no special storage conditions.

Study drug containers containing rucaparib tablets will be labeled according to national regulations for investigational products.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Female, ≥ 18 years of age.
2. Non-metastatic, histologically or cytologically-confirmed TNBC (defined as ER <1%, PR <1%, her-2-neu 0-1+ by IHC or FISH-negative or as per MD discretion), with evidence of residual disease in the breast or lymph nodes after neoadjuvant chemotherapy, at the time of definitive surgical treatment.
3. Non-metastatic, histologically or cytologically-confirmed hormone-receptor positive, Her2/neu negative breast cancer (defined as ER >1% or PR >1% AND Her-2/neu 0-1+ by IHC or FISH-negative, or as per MD discretion), with evidence of residual grade 3 invasive breast cancer AND either 1) >5 cm of residual disease in the breast OR 2) ≥ 4 axillary LNs in the axilla after neoadjuvant chemotherapy, at the time of definitive surgical treatment.
4. Definitive surgical treatment with breast-conserving surgery or mastectomy and axillary lymph node evaluation.
5. At least 6-month life expectancy, ECOG Performance status < 2.
6. Willingness to discontinue any cytotoxic chemotherapeutic agents and biologic therapy at least 2 weeks prior to the start of RT.

7. Adequate organ function (assessed within 30 days prior to initiation of protocol treatment, unless otherwise indicated) as follows:

Hematology	
Absolute Neutrophil Count (ANC)	≥1500/mm^3
Platelet Count	≥100,000/mm^3
Hemoglobin	≥9.0 g/dL (after transfusion if required)
Renal Function	
Creatinine	Serum ≤ 1.5 mg/dL or Creatinine Clearance ≥ 45 mL/min[a]
Hepatic Function	
Bilirubin	≤ 1.5 mg/dL[b]
Aspartate Aminotransferase (AST)	≤ 2.5 x ULN
Alanine Aminotransferase (ALT)	≤ 2.5 x ULN

ULN = upper normal limit of institution's normal range

a. *If calculated creatinine clearance is < 45mL/min, a 24-hour urine collection for creatinine clearance may be performed*
b. *Subjects with documented Gilbert's disease may have bilirubin up to 2.5 mg/dL*

8. Negative serum pregnancy test within 14 days prior to study treatment if a woman has child-bearing potential. Subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
9. Ability to swallow and retain oral medications.
10. Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.
11. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the duration of study participation. Should a woman become pregnant while participating on study, she should inform the treating physician immediately.

6.2 Subject Exclusion Criteria

1. Gross residual tumor on imaging, or positive margins after breast conserving surgery that are un-excised, as radiation dose in the study will be limited to 60 Gy.
2. Complete pathologic response to NAC.
3. Receipt of PARP inhibitor prior to RT.
4. Pregnant or expecting to conceive within the projected duration of the trial, starting with screening visit through 180 days after the last dose of trial treatment.
5. Prior history of radiation therapy to the ipsilateral breast and/or regional nodes is not allowed (prior RT to other sites is permitted).
6. Patients with breast augmentation implants are excluded.
7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to rucaparib.
8. Concomitant anti-neoplastic treatment is not allowed during protocol treatment and should be completed at least 2 weeks prior to commencement of protocol treatment, with resolution of associated acute toxicities. Bisphosphonates are permitted without restriction even during protocol treatment. Maintenance pembrolizumab is permitted during the protocol treatment.
9. Significant comorbidity: Patients with clinically significant and uncontrolled major disease or disorder that could exacerbate potential toxicities, confound safety assessments, require excluded therapy for management, or limit study compliance.
10. Ongoing therapy with other investigational agents. Patients may not be receiving any other investigational agents.
11. Unresolved toxicity from other agents. Patients with unresolved CTCAE v4.03 Grade 3 or greater toxicity from prior administration of another investigational drug and/or anti-cancer treatment are not eligible.

7.0 RECRUITMENT PLAN

This study will be available to all patients seen at Memorial Sloan Kettering Cancer Center and multicenter sites, who meet the eligibility criteria outlined in Section 6.0.

MSK is a large referral center for breat cancer in general and TNBC in particular. The Department of Radiation Oncology treats 900 new breast cancer patients across the network with post-lumpectomy or post-mastectomy RT. Estimating approximately 20% of these are TNBC patients, and approximately 70% of these received neoadjuvant chemotherapy. The pathCR rates are approximately 20%. Based on these assumptions, we should have approximately 100 eligible patients annually. Assuming a 15% participation rate, we should be able to complete the study in 2 years. Dr. Atif J Khan will facilitate accrual across Radiation Oncology. The investigators take due

notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. The registration procedure will be conducted as described in Section 15.0. Patients will not receive payment for their participation on this study.

8.0 PRETREATMENT EVALUATION

All baseline/screening procedures will take place after completion of surgery and within 30 days prior to initiation of protocol therapy, unless otherwise indicated.

- Signed informed consent
- Pathologic confirmation of TNBC or eligible hormone-receptor positive breast cancer
- History and physical examination including height, weight, vital signs (temperature, pulse rate, respiratory rate, blood pressure, pulse oximetry), performance status (ECOG), adverse event monitoring and review of medications
- 12-lead electrocardiogram (EKG)
- Serum pregnancy test for all women of childbearing potential
- CBC with differential and platelet count
- Complete metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, bilirubin, alkaline phosphatase, AST, ALT, corrected calcium, magnesium)
- Patient outcomes questionnaire (BCTOS), if applicable
- Patient and Physician Cosmesis evaluations
- Digital Breast Images
- If germline BRCA status is not known at the time of study registration, patients will be referred to their respective Genetics department for evaluation of germline BRCA status and other genes, at the discretion of the treating physician and consulting geneticists.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Rucaparib Administration

Rucaparib will be administered concurrently with radiotherapy, commencing on the evening following the first radiation treatment, and then twice daily throughout the standardized 6-week course of radiation treatment to the breast with or without regional nodes. Subjects will receive rucaparib at their assigned dose level, beginning with dose level 0. Subjects will be instructed to take rucaparib as morning and evening doses, separated by approximately 12 hours, at the same time each day (BID dosing). Rucaparib treatment will be continued throughout the course of RT, including weekends or holidays when radiation fractions may not be administered. Rucaparib administration will continue for four weeks after the final fraction of RT.

Treatment will be administered on an outpatient basis. Subjects will receive sufficient quantities of capsules of rucaparib for administration every 2 weeks over the study duration. Subjects will be provided self-administration instructions and subject drug diaries to record the date and time study drug was taken. Subjects will be instructed to store study drug according to the label, subjects should return all study drug bottles and their drug diaries at their study visits.

Daily oral rucaparib should be taken with a glass of water, with or without a meal. Tablets should be swallowed whole without crushing or chewing. In case of vomiting after a dose of rucaparib, the dose should not be re-administered. If a patient misses a dose and less than 4 hours have passed since the scheduled dose time, the dose should be immediately taken. If more than 4 hours have passed since the scheduled time, the subject should not take the missed dose and wait to take the next scheduled dose.

9.2 Radiation Treatment

RT will be performed using external beam ionizing radiation in accordance with standard practice. The dose of radiation will be a standard regimen/fractionation used after neoadjuvant chemotherapy and breast conserving surgery/mastectomy: 50 Gy, delivered in twenty-five 2 Gy fractions over 5 weeks. In lumpectomy patients, a 10 Gy boost, delivered in five 2 Gy fractions over one week to the lumpectomy cavity is mandatory. In mastectomy patients, a 10 Gy boost delivered in five 2 Gy fractions over one week to the mastectomy scar is optional. The total prescribed dose will be 60 Gy in thirty 2 Gy fraction sizes for lumpectomy patients, and 50-60 Gy for mastectomy patients

. Conformance with dose parameters and constraints as specified in RTOG1304/NSABP-B51 is strongly suggested but not required.

The study can be found at: https://www.ctsu.org/Master/SimplePage.aspx?ascx=ProtocolsReport

RT will be administered using megavoltage linear accelerators once daily, 5 days per week (excluding weeks that include holidays, where the number of treatment days will be at the treating physician's discretion).

Details on radiation treatment, including the radiation consultation note, treatment plan, and treatment summary will be collected.

9.3 Research Biopsy

Tumor tissue will be collected from the diagnostic and the lumpectomy specimens, if available, precluding the need for an extraneous biopsy. Tissue analyses are detailed in Section 10.0.

9.4 Subsequent Therapies

Initiation of systemic therapy after completion of protocol treatment is at the discretion of the treating investigator, but should be delayed until no earlier than 30 days following completion to allow for assessment of acute toxicity and to allow full recovery for the sequelae of study treatment, unless such a delay would be harmful to the subject. Specifically, treatment with adjuvant capecitabine and/or pembrolizumab is allowed at the discretion of the treating physicians. Adjuvant endocrine therapy is allowed at the discretion of the treating physician and can be started before, during, or after protocol therapy.

Additional surgery is also at the discretion of the treating investigator but is not recommended for 30 days following the last RT session to allow evaluation of DLT and resolution of acute toxicity during that period. However, if delaying a surgical procedure would be harmful to the subject, surgery is allowed at the discretion of the treating investigator.

9.5 Definition of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) will be defined as toxicities probably or definitely related to the study drug observed during the 70 days that include 6 weeks of radiotherapy and 4 weeks of maintenance rucaparib therapy, as follows:

- Confluent moist desquamation, defined as the presence of a single, contiguous region of moist desquamation that exceeds 25 cm^2 in area
- Absolute Neutrophil Count <1,000/mm^3, with or without fever
- Platelet count <50,000/mm^3
- Hemoglobin <8.0 g/dl
- Any ≥ Grade 3 non-hematologic toxicity by the NCI CTCAE version 4.03, not including Grade 3 ALT/AST elevation provided bilirubin and alkaline phosphatase meet criteria in Section 11.2
- Any toxicity requiring a RT dose delay exceeding 5 business days

Toxicities meeting this definition and occurring during the observation period of 10 weeks (70 days) will influence the dose level assignment of the TITE-CRM algorithm if these toxicities are deemed probably or likely related to study therapy.

Sites should contact the coordinating center as soon as possible (within one business day) when a DLT occurs or seems imminent. Sites should call Dr. Atif J Khan, and send an email to Dr. Atif J Khan and study coordinator.

9.6 Concomitant Treatment and Supportive Care Guidelines

Prior and subsequent systemic therapy is allowed, with a 2-week washout required for all anti-cancer agents, including cytotoxic chemotherapeutic agents, immunotherapy, biologic therapy, and targeted therapies. There are no limitations on the type or number of prior regimens. Bisphosphonates are permitted without restriction even during protocol treatment.

No surgery is to be performed while the patient is receiving protocol therapy. At least three weeks must elapse since completion of surgery before initiation of protocol therapy.

Any medication or vaccine including over-the-counter and prescription medicines, vitamins, and herbal supplements that the subject is receiving at screening up to the week 10 visit should be recorded in source documents and case report forms. Administration dates (start and end dates), dose, and frequency will be recorded. Any change in concomitant therapy during the study period will be recorded.

Subjects should receive the best supportive care and treatment during the study as appropriate, including transfusion of blood and blood products, oxygen therapy, nutritional support, intravenous fluids, and treatment with appropriate medications (antibiotics, antiemetics, antidiarrheals, and analgesics, etc.).

Questions regarding prior or concomitant therapy should be directed to the Principal Investigators.

9.6.1 Hematopoietic Growth Factors and Blood Products

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines.

https://one.mskcc.org/sites/pub/pharmacy/guidelines/IVMedGuide/IVMedGuidelines.pdf

Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

9.6.2 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on results of in vitro CYP interaction studies, caution should be used for concomitant medications with narrow therapeutic windows that are substrates of CYP2C19, CYP2C9, and/or CYP3A. Selection of an alternative concomitant medication is recommended.

Table 4A. Examples of CYP Substrates with Narrow Therapeutic Range

CYP Enzyme	Substrates with Narrow Therapeutic Range [a]
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

The table is based on US Department of Health and Human Services, Food and Drug Administration, CDER. Draft Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. February 2012; Available from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf.

a. CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

9.6.3 Anticoagulants

Caution should be exercised in patients receiving rucaparib and concomitant warfarin (Coumadin) as rucaparib showed a mixed inhibition of CYP2C9 in vitro. If appropriate, low molecular weight heparin should be considered as an alternative treatment. Patients taking warfarin should have international normalized ratio (INR) monitored regularly per standard clinical practice.

9.6.4 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions.

In vitro data showed that rucaparib is an inhibitor of P-gp and thus patients taking digoxin, a P-gp substrate, should have their digoxin levels monitored regularly via standard clinical practice. Caution should also be exercised for concomitant use of certain statin drugs (e.g., rosuvastatin and fluvastatin) due to potential increase in exposure from inhibition of BCRP and CYP2C9.

9.7 Study Duration

Treatment is expected to continue for a total of ten weeks (70 days), as described, unless delayed by adverse events, or discontinued due to meeting criteria described in Section 13.1

Following the ten week course of study treatment, follow up visits will continue every 3-6 months for two years, or as per standard follow-up care. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

9.8 Study Assessment Visit Windows

A window of ±5 days will pertain to visits to allow flexibility for patient scheduling (±15 days for follow-ups beyond week 10).

10.0 EVALUATION DURING TREATMENT/INTERVENTION

The below time and events table reflects 6-week course of rucaparib and RT, including boost. Note that participants receiving a 6-week course of rucaparib and RT will continue rucaparib maintenance therapy at the same dose level for 4 weeks after RT completion.

Table 10A.

	Pre-Study (within 30 days of starting treatment)	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Follow up[b]**
Rucaparib[a]		X	X	X	X	X	X	X	X	X	X	
Radiation therapy		X	X	X	X	X	X					
Informed Consent	X											
Demographics	X											
Medical History	X											
Concomitant medications	X	X		X			X		X		X	
Physical Exam[b]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X	X	X		X		X	X
Vital signs[c]	X	X		X			X		X		X	X
Height	X											
Weight	X											

ECOG Performance Status	X											
CBC with differential and platelets	X	X		X			X		X		X	
Metabolic panel[d]	X	X		X			X		X		X	
12-lead ECG	X											
Pregnancy test[e]	X	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]
Tumor specimen procurement[f,g]	X											
Patient Outcomes Questionnaire - BCTOS[h,i]	X											X
Patient Cosmesis evaluation (RTOG)[h,i]	X											X
Physician Cosmesis evaluation (RTOG)[h,i]	X											X
Digital breast images[j]	X											X
Drug diary		X	X	X	X	X	X	X	X	X	X	

a. Rucaparib will be administered concurrently with RT, commencing with fraction #1 and daily throughout RT
b. Patients will be seen by either their medical or radiation oncologist with only one toxicity assessment per visit. Follow up every 6 months for 2 years. Follow-up windows will be +/- 15 days.
c. Vital signs include: temperature, pulse rate, respiratory rate, blood pressure, pulse oximetry.
d. Metabolic panel containing: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, bilirubin, alkaline phosphatase, AST, ALT, corrected calcium, magnesium.
e. Pregnancy test to occur within 14 days prior to study treatment
f. Tumor specimen taken at time of definitive surgery if available
g. Blood draw for germline DNA for control whole exome sequencing.
h. BCTOS and cosmesis evaluations at baseline and at year 1 and 2.
i. BCTOS and cosmesis evaluations only for breast-conservation patients and mastectomy patients with reconstructions.
j. Digital photographs at baseline and at year 2.

k. It is strongly encouraged that women of childbearing potential undergo monthly serum pregnancy testing while you are taking study drug and for 6 months afterward. These tests can be completed at a local location and the patient should share these results with MSK.

Table 10B

Evaluation	Definition
Medical History	Medical history will be obtained and documented. It will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator.
Concomitant Medications	Medications will be recorded, if any, taken by the subject during the trial. Concomitant medication and supportive care guidelines are detailed in Section 4.3. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 6.0.
Physical Exam	A complete physical exam will be performed during the screening period and documented. Clinically significant abnormal findings should be recorded as medical history.
Vital signs	Vital signs (temperature, blood pressure, respiration rate, and pulse oximetry) assessed at screening, wk 1, wk 3, wk 6, wk 8 and wk 10, as specified in Table 10A.
Laboratory Assessments	For documentation of any hematologic abnormalities meeting CTCAE v 4.03 adverse event criteria, CBC with differential and platelets and a complrehensive metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, bilirubin, alkaline phosphatase, AST, ALT, corrected calcium, magnesium) will be drawn at baseline, week 1, week 3, week 6, week 8, and week 10.
Adverse Event Monitoring	All adverse events will be assessed and documented at study visits described, regardless of whether the event is a dose limiting toxicity. Events will be graded according to CTCAE 4.03 and entered into the study database.
Tumor Specimen	Formalin-fixed paraffin embedded specimens from the diagnostic cores and the lumpectomy specimen will be collected if available.
Drug Diary	Patients will be given a drug diary to record compliance with administration of study drug rucaparib. Patients will be educated on use of the patient diary prior to receiving study drug. Drug diaries will be reviewed for completion at patient visits.

Follow-up Visits	Subjects who discontinue trial treatment will move into the follow-up phase and should be assessed every 6 months for 2 years by a medical oncologist or radiation oncologist,
Patient Reported Outcomes and Cosmesis	Patients will report patient satisfaction using the Breast Cancer Treatment Outcome Scale (BCTOS) (Appendix B). This self-report instrument has been used in a number of studies for this purpose and has both reliability and validity[20] Patients will first complete this after informed consent, and then at multiple intervening assessment points up to 2-years of follow-up (see study calendar, Table 10A). At the same time points, patients will also score cosmesis using the RTOG 4-point scale with supplemental questions (Appendix C). The RTOG cosmetic evaluation will also be completed by the radiation oncologist after consent and prior to treatment. This will be done using the RTOG scale with supplemental questions, using criteria established in previous RTOG trials (Appendix D).
Digital Images	Digital images of patients' breasts will be taken after consent and prior to initiation of treatment, as well as at 2 years (see Study Calendar, Table 10A). The images will be taken using the cameras available in radiation oncology simulation rooms. The initial images can be ideally be taken at the time of simulation. The images will be uploaded in the patients radiation oncology EMR, which is a secure, password protected EMR and where the patients routine set-up pictures are stored. Two pictures will be taken at each time point, taking care to exclude the patient's face. The first image will be of the breast to be treated and at a 45 degree oblique angle with arms elevated overhead. The second image should be at a straight angle and frontal view of both breasts taken in either a standing or seated position with the patient's hands on her hips, taking care to exclude her face. These pictures will be taken at baseline (prior to any treatment), and at to 2 years.

BCTOS (Appendix B):

The Breast Cancer Treatment Outcome Scale (BCTOS) is a 22-item measure of perceived aesthetic (e.g., breast shape) and functional status (e.g., pain, mobility) after breast

conserving surgical treatment and radiotherapy (BCT)[17]. This self-report instrument has demonstrably high reliability and validity, and is commonly used in this setting, allowing for cross comparison between trials of BCT. These endpoints will be assessed at baseline prior to start of RT, and at year 1 and 2. This tool includes items that focus specifically on radiotherapy-relevant symptoms (e.g., reports of skin problems, tenderness in the breast, hardness in the breast due to enhanced fibrosis, and pain).
Patients are asked to rate the items with respect to the magnitude of differences between the treated and untreated breast areas on a 4-point scale (1 = None, 2 = Slight, 3 = Moderate, 4 = Large). The BCTOS is scored to form three subscales: functional status (7 items), cosmetic status (8 items), and breast specific pain (3 items). The remaining 4 items (i.e., arm heaviness, fit of sleeve, arm swelling, and breast swelling) are not scored, but are included in the instrument as exploratory items because of their potential clinical importance. Each subscale is scored by calculating the mean of the item responses and ranges from 1 to 4. In the initial BCTOS validation, internal consistency reliability was 0.91 for functional status, 0.89 for cosmetic status, and 0.81 for breast specific pain

RTOG cosmesis scales:

The RTOG has developed patient (Appendix C) and physician (Appendix D) reported cosmesis assessment tools. These tools are notable for their simplicity, and although their validity has not been published by RTOG, they have been used in two recently completed but not reported seminal trials of breast RT- RTOG 0413/NSABP B39 and RTOG 1005[1]. The control arms from these data sets will serve as important controls for us to compare to, hence we will use them.

Digital photographs assessment:

The EORTC Breast Cosmetic Rating system is a digital photographic method that has been utilized in prior radiation studies and shown to be reliable and valid in detecting effects of radiation morbidity[21,22]. This method compares the radiated breast with the contralateral untreated side and qualitatively evaluates: breast size, breast shape, position of the nipple, shape of the areola, appearance of the surgical scar, skin pigmentation changes, and a global cosmetic score based on all of the factors. Each parameter is scored independently; the global score is scored qualitiatively to account for the other factors. Characteristics are graded on a four-point scale: 0, excellent or no difference; 1, good or small difference; 2, fair or moderate difference; and 3, poor or large difference. One non-treating physician and one nurse will score each set independently. Discrepancies will be resolved by consensus.

10.1 Tumor Specimen Collection Guidelines

MSK is equipped with the necessary laboratory infrastructure (i.e. the Powell Lab) to conduct the exploratory studies. Patients will be consented for research retrieval, if available, of their initial diagnostic core biopsy specimens and their lumpectomy/mastectomy specimens. This consent should preferably happen in parallel to this study and on protocol 12-245. Patients not consenting to 12-245 can participate in the correlatives research of this study through an optional consent clause in the informed consent. Specimens will be collected and transported to the Integrated Genomics Operations core at MSKCC. The specimens will be evaluated by H&E for adequacy and to plan for microdissection if it is needed. The core, led by Agnes Viale, is experienced in handling FFPE material and extracting DNA and RNA from

such specimens. However, the results of our assays (determining HR-proficient vs HR-deficient) are not necessary for patients to receive the study treatment and will only be shared with the study statistician and primary investigator. Patients who are unable to obtain a definitive HRR status will not be excluded from analysis of the primary endpoint of the study, but may not be counted towards the secondary and exploratory objectives of the study.

For patients not consenting to 12-245, but opting into this study's specimen collection will have a baseline blood draw for germline exome sequencing as part of the pair with tumor exome sequencing.

10.1.2 Tumor Specimen Evaluation

MSKCC Homologous Recombination Repair (HRR) Assay

At MSKCC we have been very interested in measuring the proficiency of homologous repair in cancer cells as a correlate of subsequent treatment sensitivity. Although this current study is clearly a phase I study to understand the tolerability of rucaparib, we will collect correlative data with the intention of establishing the feasibility of our research methods and identifying testable hypotheses for larger subsequent patient cohorts. One of our primary research hypotheses, which we are evaluating across multiple studies, is that pre-existing homologous recombination deficiency (HRD) predict for better clinical outcomes (local control, disease-free survival), while HR proficiency results in treatment resistance. We have recently described our methods for evaluating HR patency in paraffin-embedded archived patient specimens as an alternate to our earlier assay based on the quantification of RAD51 foci in cancer cells subjected to ex-vivo ionizing radiation. In our original assay [23], we used fresh tumor specimens from which a single cell suspension was created, half of which was irradiated, and the other half mock-treated. Cell nuclei were then analyzed for the formation of γH2AX, BRCA1, and RAD51 in both irradiated and un-irradiated cells using confocal microscopy. In our alternate method, we have shown that exome sequencing to evaluate the status of a panel of candidate HR genes as well as evaluation for previously described structural signatures associated with HRD [(large-scale state transitions (LST), telomeric regions with allelic imbalance (ntAI), large segments with loss-of-heterozygosity (LOH)], can accurately predict for HRD [24]. In particular bi-allelic inactivation in one or more HR DNA repair genes was found to be significantly associated with functional HRD and with higher LST scores. Our treatment cohort will be unique in that we will have access to 1) original pre-treatment diagnostic cores 2) post-chemotherapy residual disease cores 3) germline DNA.

Formalin-fixed, paraffin-embedded (FFPE) core needle specimens will be retrieved and transported to the MSKCC Integrated Genomics Operations (IGO) core (Agnes Viale, Core Facility Head). Using standard molecular biology techniques, DNA will be extracted using the DNeasy kit (Quiagen, Valencia, CA) to isolate genomic DNA and whole exome sequencing will be performed. This will allow us to look at LST (large-scale state

transitions), ntAI, LOH as well as our previously defined list of 95 HR effectors or regulators. To assign tumors to the HR proficient vs deficient categories, we will begin by screening for high LST scores. Patients with high LST scores will then be evaluated for bi-allelic inactivation in one or more HR related genes. Patients with evidence of both suggestive structural alterations AND bi-allelic loss in a candidate HR gene on their diagnostic core specimens will be scored as HRD. All other patients will be scored as HR proficient. We will also perform sequencing on the post-therapy residual, and stratify patients by receipt of platinum agents. We will compare the mentioned parameters of HRD in pre and post-therapy specimens. Our provisional hypothesis is that our cohort of non-responders will be enriched for HR proficiency compared to unselected TNBC tumors or HR+ tumors.

Immune Correlates

A large body of research using experimental animal models indicates that the immune system controls the development of cancer through immune surveillance mechanisms[25]. Histologic analyses of solid malignancies reveal that they are infiltrated by various cells of the innate and adaptive immune system[26]. Therapeutic modulation of the immune system for clinical benefit in cancer patients has been demonstrated by numerous modalities, including antibody blockade of inhibitory molecules, adoptive T cell transfer, and autologous cell-based vaccines [27-29]. A recent large-scale meta-analysis of the correlation of tumor infiltrating T cells with survival clearly establishes that a relative high density of TH1 and cytotoxic memory T cells correlated with a favorable prognosis in the majority of cancers [30].

Tumor infiltrating lymphocytes (TILs) may be a useful histological predictor of benefit from chemotherapy in breast cancer patients, although it has not been established whether or not response to chemotherapy would be specific to a class of chemotherapy. Specific to breast cancer, the evaluation of TILs has been shown in the GeparSixto (GBG 66) trial to be relevant for response to chemotherapy in triple negative and Her2-positive early breast cancers[31,32]. In this analysis, a lymphocyte predominant pattern of infiltrate was predictive of a complete pathologic response to neoadjuvant chemotherapy. Similarly, the association of TILs and response to trastuzumab and chemotherapy (epirubicin/cyclophosphamide with docetaxel +/- capecitabine) was evaluated in 156 HER2+ patients from the neoadjuvant GeparQuattro trial [33]. TILs were associated with higher responses to the trastuzumab and chemotherapy combination, and tumor-mediated immunosuppression was evident in the lymphocytic infiltrate, with PD-1 and IDO1 significantly predictive of trastuzumab benefit.

The prognostic value of TILs has also been validated in a combined analysis of two Phase III randomized adjuvant breast cancer clinical trials[32,34-37]. In these studies, the percentage of intratumoral and stromal lymphocytes in pre-treatment tumor biopsies was found to be an independent predictor of pCR in both the training and validation cohorts. Higher TIL pathologic scores were associated with a better prognosis: for every 10% increment in stromal TIL, a 14% reduction of risk for recurrence or death was observed (p=0.02), and for every 10% increment in intratumoral TIL, a 28% risk reduction was seen (p=0.06). Multivariate analysis confirmed stromal TIL to be an independent prognostic marker of disease-free survival.

Collectively, these data suggest that the natural course of breast cancer as well as the response to therapy is linked to the degree by which the tumor is recognized by the immune system. Response to radiotherapy may be also be predicted by the level of TIL, however data supporting this in breast cancer is scant. In squamous cell carcinoma of the head and neck as well as rectal cancer however, TILs can predict response to combination chemoradiotherapy[38,39]. The induction of an immune response by radiotherapy may also have important consequences. Several studies have shown the various mechanisms by which RT stimulates the immune system. One effect of localized tumor irradiation is the exposure of a large amount of tumor antigens in the form of necrotic and apoptotic tumor cells[40]. The contexts in which these antigens are presented to the immune system are also impacted by tumor irradiation. Tumor radiotherapy leads to an inflammatory tumor microenvironment by inducing the expression of several proinflammatory cytokines[41]. In addition, upregulation of major histocompatibility molecules and costimulatory molecules can potentiate effector cytolytic T cell responses[42].

The pretreatment core specimens from this study will allow for the comprehensive assessment of TILs which will be correlated to response. Participants in this study are by definition incomplete responders to cytotoxic chemotherapy, and we would anticpate proportionally lower TILs compared to unselected or responding patients. Data from patients on our other trials or projects will serve as controls and will allow us to compare TIL profiles. We will perform RNA sequencing of these specimens for the TIL expression signature as another assessment of pre-existing TILs. This will provide important insight into the role of the tumor immunity in the response to chemoradiotherapy. In addition the assessment of homologous recombination can also factor into the endogenous response of the immune system to the tumor as well as response to therapy. The effect of homologous recombination on tumor immunity is not well characterized, however the induction of microsatellite instability as a pathway of carcinogenesis has clearly been linked to tumor immune response[43]. Tumor cells with deficient DNA mismatch repair develop microsatellite instability and the resulting tumors are densely infiltrated by TILs[44]. It is suggested that mismatch repair deficiency leads to numerous insertion/deletions that ultimately translate to the generation of tumor-specific neopeptides that can then be recognized by the immune system[45]. Radiation administered to a tumor with an underlying homologous recombination defect may lead to significant “epitope spreading” resulting in the induction of an immune response against newly recognized tumor associated antigens. This study will begin to address the immune consequences of tumor genomic instability. There is currently no accepted methodology for quantitatively scoring TILs in core biopsies before neoadjuvant chemotherapy. We will arbitrarily define tumors with stromal TILs greater than 20% as being positive for TILs.

Cell-free DNACollection for circulating tumor DNA

For patients consenting to 12-245, we will collect ctDNA at 3 time points: baseline (within 30 days of starting treatment), week 3 of RT+rucaparib, and then at week 10. ctDNA has been shown to correlate with treatment response in several tumor types including in breast cancer46.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Toxicities of Study Intervention

Toxicities of Radiation Therapy

Anticipated toxicities include radiation skin reaction, as well as possible radiation pneumonitis or pericarditis (which may also occur in the absence of a radiosensitizing agent when breast/chest wall and nodal radiotherapy is administered). Treating investigators should manage any toxicities that develop using standard medications, such as topical agents for skin reaction and steroids for pneumonitis.

Toxicities of Rucaparib

Rucaparib is an FDA-approved agent for treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. It is investigational for use in TNBC and HR+ breast cancer. A comprehensive list of toxicities may be found in the investigator's brochure. Principal side effects of rucaparib are listed in Table 11A.

Table 11A Principal side effects of Rucaparib

Central Nervous System	Fatigue, dizziness
GI	Nausea, decreased appetite, diarrhea, vomiting, elevated ALT/AST, dyspepsia, elevated blood cholesterol
Heme	Anemia, febrile neutropenia; decreased WBC, , neutropenia; thrombocytopenia elevated creatinine
Miscellaneous	Fever, lymphopenia

11.2 Dose Modifications

Radiation therapy may be withheld due to acute toxicity at the discretion of the treating investigator without being considered a dose-limiting toxicity if the treatment break is no greater than 5 days. All radiation treatment breaks should be recorded, including details regarding duration of break and reason.

Rucaparib dose will not be modified on this study. Treatment with rucaparib should be held if any of the following are observed:

Table 11B

Toxicity	Rucaparib Treatment Action	Timing for Restarting Rucaparib Treatment

Confluent moist desquamation (single, contiguous region of moist desquamation that exceeds 25cm2 in area)	Record DLT	Discontinue rucaparib
Any toxicity requiring a radiotherapy dose delay exceeding 5 business days	Record DLT	Discontinue rucaparib
Grade 3 or 4 hematologic toxicity Includes defined DLTs: Absolute Neutrophil count <1,000/mm3 (with or without fever) Platelet count <50,000/mm3 Hemoglobin <8.0 g/dl	Record DLT	Discontinue rucaparib
Grade 3 or 4 non-hematologic toxicity Except for: • alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines • Grade 3 ALT/AST elevation (see below)	Record DLT	Discontinue rucaparib
Grade 4 ALT/AST elevations	Hold rucaparib	Restart treatment when values have returned to ≤ Grade 2. Monitor liver function tests weekly for 3 weeks after reintroduction of rucaparib. Any toxicity requiring a radiotherapy dose delay exceeding 5 business days should be recorded as a DLT and rucaparib discontinued.

Grade 3 ALT/AST elevations	Continuation of rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided: • bilirubin is < ULN • alkaline phosphatase is < 3x ULN and • there are no other signs of liver dysfunction	Monitor liver function tests weekly until resolution to ≤ Grade 2. If patient has Grade 3 ALT/AST and continues on rucaparib, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before rucaparib can be resumed at current dose.
Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.	Hold rucaparib upon investigator discretion	Restart drug, per investigator discretion, at assigned study dose level (no dose reduction). Note: any toxicity requiring a radiotherapy dose delay exceeding 5 business days should be recorded as a DLT and rucaparib discontinued. Drug holds exceeding 5 business days will be reviewed by the PI and discussed by the study team and the treating physicians If the patient restarts Rucaparib after a break, missed doses will not be made up. The patient will take Rucaparib until the conclusion of the initially scheduled 10 weeks.

11.3 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be elicited by asking the patient a non-leading question (eg, “Have you experienced any new or changed symptoms since we last asked/since your last visit?”). The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE). Symptoms reported spontaneously by the patient during the physical examination would also qualify

as an AE (and hence documented on the AE CRF, not on the physical examination CRF, which is reserved for physical signs or findings).

Refer to **Section 17.2** for details and reporting requirements on Adverse Events, Serious Adverse Events, Events of Special Interest.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary endpoint of the study is defining the MTD of rucaparib in combination with RT to the breast/chest wall with or without regional nodes.

The trial will be monitored using TITE-CRM, which is described in Section 14.0.

Sample Size

The study will enroll 30 patients who are able to complete the acute observation period without a dose-limiting event, or who experience a DLT for the estimation of the dose-toxicity function. We expect to accrue about 4 patients about every two months, therefore completing accrual in approximately 1-2 years.

Cohort Size

Subjects will be recruited as available and allocated to treatment according to the estimated toxicity rates. No formal cohort size is required; however, at least 2 patients must be observed for their entire acute toxicity period (70 days) before dose escalation is allowed. This rule will be followed throughout the trial.

Endpoint Definition

Locoregional relapse is defined as a recurrence of disease in the breast, chest wall, axilla, supraclavicular or internal mammary areas. Distant relapse is defined as a recurrence of breast cancer in any part of the body outside of the locoregional sites described above (ie bone, liver, brain).

Evaluability

Any subject receiving at least one dose of rucaparib and at least one fraction of RT will be considered evaluable for toxicity. Subjects who do not initiate treatment with either rucaparib or RT will be replaced and will not influence the TITE-CRM dose assignment algorithm. Any subject who discontinues trial therapy after receiving at least one dose of rucaparib and one radiotherapy fraction, but prior to completing the entire course of study treatment for reasons not due to toxicity, will also be replaced. These subjects will not count toward the sample size goal of 30 subjects; however, partial information from discontinuing subjects up until the date of discontinuation will be used by the TITE-CRM algorithm when making dose level assignments. Thus, these subjects' information will NOT be used following the date of discontinuation for future dose assignments. At the trial's conclusion, posterior estimates for the probability of toxicity at each dose level will be

made using only the 30 subjects with complete data (i.e. subjects that complete the acute observation period without a dose-limiting event, or those that experience a DLT).

13.0 CRITERIA FOR REMOVAL FROM STUDY

Participants will be removed from study when any of the criteria listed in Section 13.1 applies. All reasons for discontinuation of therapy should be documented clearly in the medical record. The patient should be followed-up per protocol.

13.1 Discontinuation of Treatment

Reason for discontinuation from study will be documented in the Case Report Form, and may include:

- Non-compliance with the study protocol, including not attending the majority of scheduled visits
- Unacceptable major toxicity
- Intercurrent illness or condition that would in the judgment of the treating investigator, significantly affect assessment of clinical status or require discontinuation of study treatment
- Subject's request
- Study closure

13.2 Study Withdrawal

Reasons for withdrawal from study include:

- Subject withdrawal of consent
- Subject lost to follow up
- Study termination

14.0 BIOSTATISTICS

The primary endpoint of the study is defining the MTD of rucaparib in combination with RT to the breast/chest wall with or without regional nodes.

The trial will be monitored using TITE-CRM. Assuming a model for the time to occurrence of toxic response as a function of dose, the method allows information from all enrolled patients to be used when allocating a new patient to a dose level. Subjects can be continuously recruited throughout the trial, as long as patients are treated at a dose consistent with the current safety profile.

The definition of dose-limiting toxicity (DLT) for this trial is defined in Section 9.5 above.

The acute observation period for toxicity is defined as 10 weeks, which includes the 6-week rucaparib and radiotherapy treatment course and a 4-week post RT rucaparib maintenance period.

The target rate for dose-limiting toxicity is 30%. This level was selected upon rates of toxicity observed in a recent phase I study of veliparib + chest wall RT in breast cancer patients [14]. The target rate will define the maximum tolerated dose (MTD) of rucaparib given concurrently with radiotherapy for residual invasive disease after neoadjuvant chemotherapy.

The expected rates of acute toxicity have been estimated based upon previous treatment experience with radiotherapy for these indications, and clinically acceptable maximal levels of toxicity. These rates will be re-estimated throughout the conduct of this trial as treatment experience is accrued.

Dose allocation

Phase I dose levels corresponding to expected toxicity rates are presented in the following table. Rucaparib will be escalated in this protocol as shown below, concurrently with a standard radiotherapy treatment plan, delivered in 2 Gy fractions, 5 days a week, over 5-6 weeks, delivered to the breast or chest wall with or without regional nodal basins. Intrasubject escalation of the rucaparib dose is NOT allowed.

Regimen level	Expected probability of toxicity
-1 (300 mg BID)	10%
0 (400 mg BID)	17%
1 (500 mg BID)	24%
2 (600 mg BID)	30%

Doses will be allocated to patients according to the TITE-CRM criterion, as summarized here. Start of the CRM algorithm is dose level 0.

As of 8/7/2019, we have accrued 7 out of 30 patients to this trial. Two patients were accrued to dose level 0 (400 mg BID) and 5 to dose level -1 (300 mg BID). Based on the data, dose level -1 has been found to exceed our targeted 30% DLT rate. We have therefore added three additional lower dose levels, one at 200 mg BID (dose level -2), another at at 300 mg QD (dose level -3) and a third at 200 mg QD (dose level -4). The revised dose allocation table and revised expected probability of toxicity is provided in the table below. The expected probability of toxicity takes into account accrued data up to 8/7/2019. All the patients will be is determined by the TITE-CRM based on all patient toxicities.

Regimen level	Expected probability of toxicity
-4 (200 mg QD)	20%
-3 (300 mg QD)	30%

-2 (200 mg BID)	40%
-1 (300 mg BID)	50%
0 (400 mg BID)	62%
1 (500 mg BID)	70%
2 (600 mg BID)	76%

- When a patient presents for enrollment on this trial, the probability of toxicity will be estimated for each dose level, based upon the initial expectations of toxicity and the incidence of toxicity in patients already treated, weighted by the amount of time those patients have been followed during the acute observation period. The level that has estimated toxicity closest to the target rate subject to conditions below, will be selected.
- In the extremely rare event a patient is removed from study prior to completing the acute observation period, for reasons unrelated to toxicity, the patient will be considered not to have experienced a DLT event. The patient will contribute her weighted follow-up experience to the estimate of the probability of toxicity up until the date of discontinuation. Her information will not be used following the date of discontinuation.
- The dose level cannot be escalated until at least two patients have been observed for the entire acute toxicity period (70 days). This rule will be followed throughout the trial.
- Dose escalation is restricted to one level between adjacent patients.
- There is no restriction on the number of levels that the dose may be reduced between patients.
- A maximum of 4 patients per calendar month can be enrolled.
- Patients 1 and 2 will be assigned to dose level 0.
- For patients 3 to 15, the dose level estimated to have probability of DLT closest to but not exceeding the target rate, 30%, by more than 5% (i.e. 35% predicted probability) will be assigned to the newly enrolled patients.
- For patients 16 to 30, the dose level with probability of DLT closest to, but not exceeding the target rate, 30%, will be assigned the newly enrolled patient.

  Under this allocation schema, the dose level of rucaparib will increase until toxicity is observed, and then will tend to vary around the level producing the target rate of toxicity. In order to allocate treatments, the protocol statistician must be notified promptly of all dose-limiting toxicities.

  The TITE-CRM algorithm selects the MTD as the dose level yielding a toxicity rate closest to the target toxicity level from either above or below. In our last two rules above, we will override the TITE-CRM algorithm so that dose assignments will be made closest to the target toxicity level, not exceeding it by 5% for the first 15 patients and not exceeding it for patients 16 to 30. This is a conservative approach. Thus, the true conduct of the trial will have lower

expected toxicity rates than indicated in the operating characteristics shown below. Allowing 5% above the target toxicity for the first 15 patients is still more conservative than the TITE-CRM without the override rules we have written in. The rule is different for the first 15 patients to allow for a slightly faster dose escalation.

Regimen level	Rucaparib dose	Prior estimates	Scenario 1	Scenario 2	Scenario 3	Scenario 4
-1	300 mg BID	10%	10%	10%	17%	24%
0	400 mg BID	20%	17%	17%	24%	30%
1	500 mg BID	30%	24%	30%	30%	40%
2	600 mg BID	40%	30%	40%	40%	50%

Operating Characteristics

As listed in table 1 below, we will examine 6 dose levels and it is our prior expectations that dose level 2 is the MTD. Our initial estimates of DLT probabilities are: 0.10, 0.20, 0.30, and 0.40 for doses -1-2, respectively. The operating characteristics of this trial design were evaluated using repeated simulations of possible trial conditions, both near to and far from expectation for toxicity. Four trial scenarios are presented in the table below. First, the true probability of toxicity at each dose level is as expected. Second and third, the true probability of toxicity at each dose level is mildly higher than expected. Fourth, the true probability of toxicity at each dose level is moderately higher than expected. The dose level at our target toxicity is in gray. The trial begins at dose level 0.

Table 1: Hypothetical Scenarios

Through 1000 simulated trials with the above parameters, we expect the method to behave in the following way, assuming the 4 hypothetical scenarios described in the table above.

All simulations were sun and summarized using the R package *dfcrm*. It is assumed that patients will be accrued according to a Poisson arrival process, at a rate of 4 per every 70 days.

Table 2: Percent of simulated trials that selected each dose under each scenario

Dose levels	-1	0	1	2
Scenario 1	.4%	9.7%	26.5%	63.4%
Scenario 2	1.0%	20.5%	49.4%	29.1%
Scenario 3	7.7%	26.8%	40.7%	24.8%
Scenario 4	30.2%	43.2%	22.7%	3.9%

Table 3: Expected number of patients treated at each dose under each scenario

Dose levels	-1	0	1	2
Scenario 1	1.576	4.645	7.546	16.233
Scenario 2	2.342	6.932	10.053	10.673
Scenario 3	4.428	7.972	8.502	9.098
Scenario 4	9.239	9.586	6.787	4.388

Table 4: Average toxicities across trials at each dose

Dose levels	-1	0	1	2
Scenario 1	.139	.768	1.715	4.753
Scenario 2	.224	1.154	2.975	4.203
Scenario 3	.716	1.861	2.486	3.587
Scenario 4	2.136	2.866	2.683	2.190

Based on the above scenarios, the trial is estimated to take a median of 19-20 months to complete.

Amended Operating Characteristics

Due to the observed data, we have amended the trial to include three cohorts, -2, -3 and -4. The scenarios and simulations have now been adjusted as follows: (note tables are numbered Table 1a, Table 2a, Table3a, and Table 4a, where 'a' refers to amended scenarios and simulations. As of 8/7/2019, 7 patients are on trial. A total of 23 out of 30 patients remain to be accrued.

Table 1a: Hypothetical Scenarios

	Dose	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
-4	200 mg QD	1	1	1	10	20	30
-3	300 mg QD	4	5	5	20	30	40
-2	200 mg BID	6	10	10	30	40	45
-1	300 mg BID	12	20	20	40	45	50
0	400 mg BID	16	25	30	50	50	55
1	500 mg BID	20	30	40	60	55	60

2	600 mg BID	30	45	50	70	60	65

Through 1000 simulated trials with the above parameters, we expect the method to behave in the following way, assuming the 6 hypothetical scenarios described in Table 1a above:

Table 2a: Rate a dose is selected under each scenario

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
-4	0	0	0	0.025	0.22	0.556
-3	0	0	0.002	0.236	0.429	0.275
-2	0.007	0.017	0.033	0.419	0.226	0.113
-1	0.028	0.173	0.235	0.258	0.09	0.037
0	0.136	0.298	0.442	0.058	0.023	0.016
1	0.296	0.36	0.253	0.003	0.011	0.002
2	0.533	0.152	0.035	0.001	0.001	0.001

Table 3a: Expected number of patients treated at each dose under each scenario

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
-4	0.212	0.319	0.369	2.504	6.248	10.166
-3	0.341	0.611	0.774	4.733	5.934	4.642
-2	2.909	3.725	3.992	7.626	5.67	4.643
-1	2.932	4.737	5.475	4.89	2.966	2.085
0	3.681	5.103	6.345	2.231	1.317	0.876
1	4.957	4.912	4.085	0.778	0.587	0.418
2	7.968	3.593	1.96	0.238	0.278	0.17

Table 4a: Average number of toxicities across trials at each dose

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
-4	0.003	0.006	0.003	0.248	1.211	10.166

-3	0.014	0.024	0.045	0.906	1.706	4.642
-2	0.17	0.31	0.39	2.214	2.243	4.643
-1	0.356	0.909	1.027	1.873	1.351	2.085
0	0.547	1.232	1.852	1.121	0.668	0.876
1	0.961	1.417	1.644	0.475	0.316	0.418
2	2.262	1.561	0.967	0.162	0.166	0.17

Safety Analysis

Safety evaluations will be based on the incidence, intensity, and type of adverse events, and clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Safety variables will be tabulated and presented for all patients in the study. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

All adverse events occurring on study will be listed in by-patient data listings. Treatment emergent events will be tabulated, where treatment emergent is defined as any adverse event that occurs after administration of the first dose of study drug and through the End of Study visit or up through 30 days after the last dose of study drug or radiotherapy, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered drug-related by the investigator. Events that are considered related to treatment (possible, probably, or definitely drug-related) will also be tabulated. Deaths, serious adverse events and events resulting in study discontinuation will be tabulated.

Change from baseline in clinical laboratory parameters will be summarized across time on study, and the frequency of clinically significant abnormal laboratory values will be tabulated. Similarly, changes in vital sign parameters will be summarized over time, and any abnormal values will be tabulated.

Details on the TITE-CRM

Under the CRM paradigm, the relationship between dose and toxicity is summarized by a single-parameter (α) logistic model that represents the assumed relationship prior to the collection of any patient data. Information about the relationship between dose and toxicity can be summarized using the distribution of the parameter, updated according to the current data. For instance, we can estimate the probability of toxicity at assigned doses and the subsequent target dose as a function of α based on the current data. The toxicity results will be summarized as follows.

The distribution of α updated according to the current data and the corresponding dose-toxicity model will be calculated. Predictive intervals concerning the toxicity parameter will be provided using this updated distribution of α.

The posterior distribution of toxicity, which display the probability a future patient will experience toxicity at a given dose based on the current data, will be calculated for each tested level. The dose level of rucaparib that produces the target rate of toxicity will be determined from this.

The proportion of subjects encountering toxicity at each dose level will be reported.

Analysis of Secondary Endpoints

Toxicity profiles will be tabulated and summarized. Locoregional relapse and distant relapse will be estimated using Kaplan-Meier methods.

Correlations between locoregional and distant relapse with HRD status (deficient vs proficient) and stromal TILs (present vs absent) will be evaluated using Kaplan-Meier estimates and a log-rank test. Patient satisfication, quality of life, and cosmetic outcomes will be summarized descriptively and graphically. Note, for the cosmesis outcome based on the RTOG scale as provided in the appendix, excellent and good cosmesis will be grouped together, and fair and poor will be grouped together. The rate of fair/poor cosmesis will be calculated and described. All statistical analyses of secondary endpoints are considered to be exploratory in nature as the sample size is expected to be small in this phase I study. Analyses will be done over all 30 patients accrued to the study and by dose cohort.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to completea protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming that the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

There is no randomization in this study.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator(CRC) from the Department of Radiation Oncology (Breast Service) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Clinical Research Database–CRDB). Source documentation will be available to support the computerized patient record.

The data that will be used to assign the next dose level will come from Medidata and CRDB via queries. The queries will normally be run by the CRC; however other members of the research team can be given access to run this particular query. The results of this query will be emailed to the PI and the statistician. The PI must then check the query results to determine if all toxicity data are correct and up-to-date. If the data are correct, the PI will acknowledge this by replying as such to this email. The statistician will use this data and run the TITE-CRM algorithm using scripts created in R to assign the next dose assignment. The statistician will send an email to the PI and CRC providing the MRN, name of the newly registered patient, and dose assignment. Once this is approved and signed by the PI, the CRC will register the patient and dose into CTMS.. If any data are incomplete or incorrect, the PI will inform the CRC. The CRC will correct the data and indicate to the PI when this is done. The process defined above will then run again and the PI will be notified to indicate correctness of the data, the statistician will run the R scripts, and the PI will be asked to approve the dose assignment.

16.1 Quality Assurance

Regular registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits may be conducted by the study team, at a minimum of once per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials”, which can be found at http://cancertrials.nci.nih.gov/researchers/dsm/index.html.

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data Safety and Monitoring Plans can be found on the MSK Intranet

at:
https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance(e.g., protocol monitoring,compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees : *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Memorial Sloan-Kettering Cancer Center has filed forms HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races will be accepted into the protocol. The proposed study population is as described in section 7.0.

Exclusion of Lactating or Pregnant Women: Children have been excluded from this study. Triple negative breast cancer is an adult cancer. Thus, the relevance of this drug to the pediatric population has not been established. Lactating and pregnant women are also excluded because of potential anti-proliferative effects of chemotherapy that may be harmful to the developing fetus or nursing infant.

Benefits: Taking part in this study may or may not make your health better. We do know that the information from this study will help doctors learn more about rucaparib in combination with radiation therapy as a treatment for cancer. This information could help future cancer patients. You may receive information from physical examinations, laboratory tests, or other testing that is done in this study but these tests may not have any impact on your health.

Costs: The patient will be responsible for the costs of standard medical care, including EKG, scans, drug administration fees and all hospitalizations, even for complications of treatment. Rucaparib will be supplied to patients by Clovis at no cost. Patients will not be responsible

for the costs of blood procurement obtained for research purposes, the digital images, and the questionnaires.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: Patients may be eligible for other investigational studies, or choose standard of care options.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors) may review patients' records and pathology slides, as required.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

Adverse events of special interest (AESI):

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESIs), as these events have been observed in patients exposed to cytotoxic chemotherapy (eg, platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib. Patients in rucaparib clinical studies diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, as well as a deleterious BRCA mutation. Based on these confounding factors, there is insufficient scientif ic evidence to conclude that MDS and AML are causally related to rucaparib. Clovis has added these potential risks to all Informed Consent Forms (ICFs) / Patient Information Sheets (PISs). AESI's (both serious and non-serious) will be reported to Clovis within 24 hours of awareness and will continue to be reported to Clovis under SAE reporting requirements.

Adverse events (AEs) of pneumonitis have been reported with PARP inhibitor treatment, including in clinical studies evaluating rucaparib. To date, 10 serious clinical study cases and 7 non-serious clinica l study cases of pneumonitis have been reported; overall, cases were reported in approximately 0.6% patients. In clinical studies evaluating rucaparib as monotherapy, cases of pneumonitis were reported in approximately 0.1% patients. Currently, however, there is a lack of understanding of a mechanist ic

link between pneumonitis and PARP inhibitor treatment. Cases of pneumonitis lack a consistent clinical pattern, and are often confounded with risk factors, such as cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy. To achieve a better understanding of whether there is a relationship between pneumonitis and rucaparib treatment, Clovis has designated pneumonitis as an AESI to gather information on all reported cases. Reportable conditions that fall under this AESI include: pneumonitis, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia.

AESIs will be reported using AE and SAE reporting as described above. More information on AESIs for rucaparib is provided in the rucaparib IB.

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to Good Clinical Practice and protocol guidelines.

A note will be placed in the participant's medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

18.1 Future Unspecified Use of Biospecimens

The informed consent form will inform patients of the purpose of banking samples for future use, their rights in relation to it, and the safeguards in place to protect the confidentiality of their health information.

In the course of the research, a research finding may be obtained that, in the opinion of the MSK PI, may be critical to the preventive care of the participant or their family. When this occurs, the MSK PI will communicate that finding to the MSK IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant.

In the event that the GAP determines that the finding should be discussed with the participant, results will be returned to the Site Principal Investigator via the study team. If the participant has consented to be re-contacted, site policies on returning these research findings to the patient should be followed.

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20.0 APPENDICES

Appendix A: Subject Drug Diary for BID dosing

Appendix B: Questionnaire: Breast Cancer Treatment Outcome Scale (BCTOS)

Appendix C: RTOG Cosmesis Assessment – Patient

Appendix D: RTOG Cosmesis Assessment – Physician

Appendix E: Subject Drug diary for QD Dosing