



A phase II study of niraparib with dostarlimab therapy as neoadjuvant treatment for patients with *BRCA*-mutated breast cancer

TBCRC #: TBCRC-056

DF/HCC Protocol #: 20-371

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Supporters: Johns Hopkins University on behalf of the Translational Breast Cancer Research Consortium (TBCRC); GSK

Agents: Niraparib, Dostarlimab; supplied by GSK

IND #: 150729

IND Sponsor: Erica Mayer, MD, MPH

Protocol Type / Version # / Version Date: Sponsor Amendment 7/ Version 6/ August 29, 2024.



SCHEMA

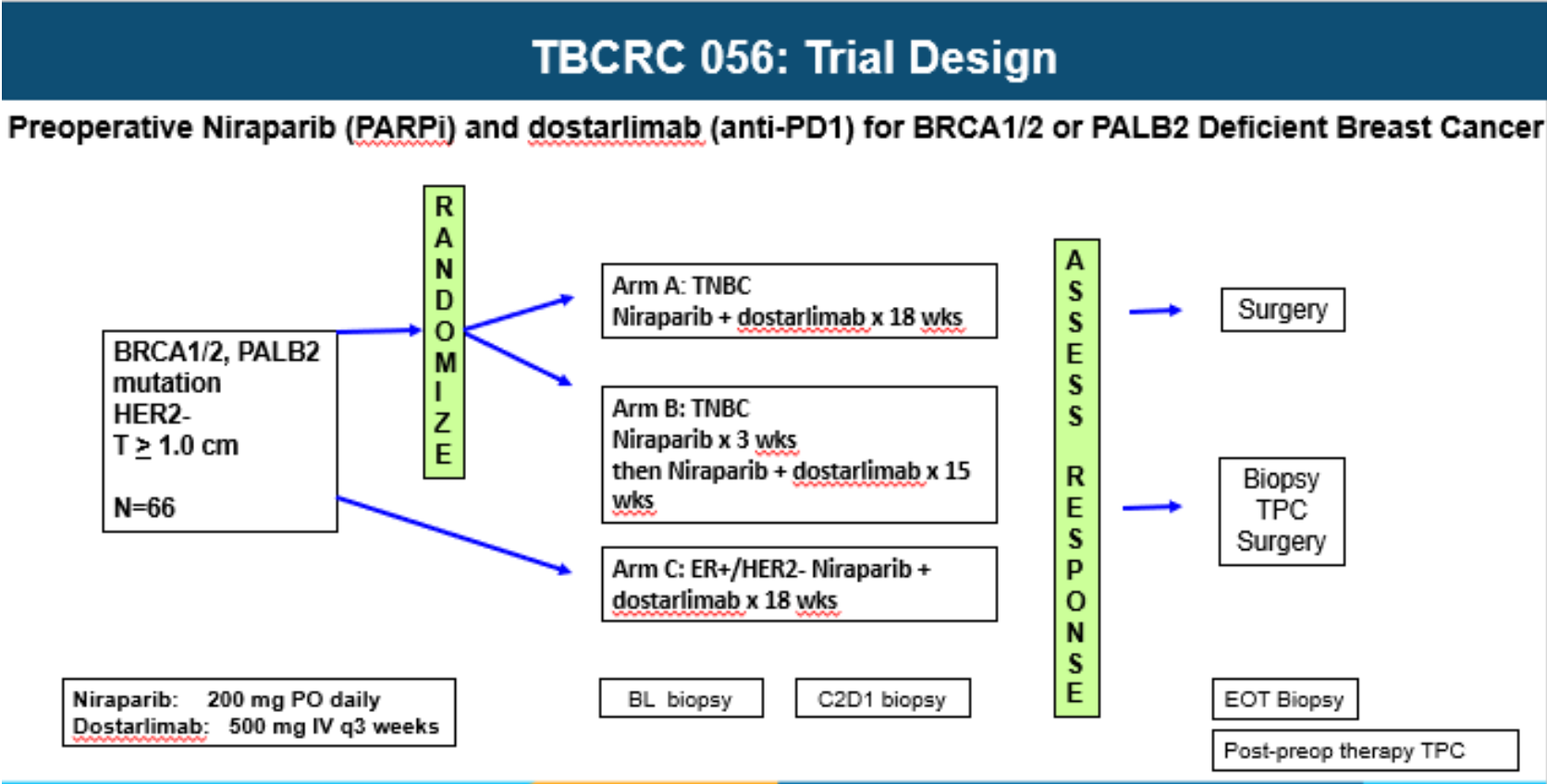


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1. OBJECTIVES

1.1 Study Design

This is an open-label, randomized phase II study examining niraparib with the PD1-antibody dostarlimab in the neoadjuvant treatment of *BRCA*-mutated or PALB2-mutated breast cancer. Participants will be randomized 1:1 to receive either treatment with the combination (**Arm A**), or a 3-week lead-in of niraparib monotherapy followed by treatment with the combination (**Arm B**). In addition, an exploratory cohort of estrogen receptor (ER) positive HER2-negative participants will be enrolled to **Arm C**. A total of 66 participants will be accrued, 23 evaluable participants to Arm A, 23 evaluable participants to Arm B, and 19 participants to Arm C. Participants will be treated for a total of 18 weeks. At the completion of 18 weeks, participants will either undergo surgery, or crossover to receive pre-operative chemotherapy depending on clinical response, as judged by the treating provider.

1.2 Primary Objectives

- To evaluate the pathologic complete response (pCR) rate of preoperative combined niraparib and PD-1 blockade in patients with early stage TNBC with *BRCA*-mutations or PALB2-mutations.
- To assess the change in tumor-infiltrating lymphocytes (TILs) pre- and post-treatment with niraparib alone and with preoperative combined niraparib and PD-1 blockade in patients with early stage *BRCA*-mutated or PALB2-mutated TNBC (via multiplex immunofluorescence).

1.3 Secondary Objectives

- To explore the pCR rate and changes in TILs (via multiplex immunofluorescence) in participants with ER-positive HER2-negative *BRCA*-mutated or PALB2-mutated breast cancer.
- To explore the rate of RCB 0/1 response with preoperative combined niraparib and PD-1 blockade in patients with early stage TNBC and ER-positive HER2-negative breast cancer with *BRCA*-mutations or PALB2-mutations.

1.4 Correlative Objectives

- To assess changes in immune checkpoint protein expression after niraparib alone and after combined niraparib and PD-1 blockade (via multiplex immunofluorescence).
- To assess activation of the STING pathway after niraparib alone and after combined niraparib and PD-1 blockade (via immunohistochemistry).
- To assess changes in expression of kynurenine and indoleamine 2,3 dioxygenase (IDO) post-niraparib and post-combined niraparib and PD-1 blockade (via mass spectrometry).
- To assess changes in mutational load and neoantigen expression post-niraparib alone and post-combined niraparib and immune checkpoint blockade (via whole-exome sequencing).
- To assess changes in immune signatures post-niraparib alone and post-combined niraparib and PD-1 blockade (via RNA-sequencing).
- To assess changes in blood-based biomarkers post-niraparib alone and post-combined niraparib and PD-1 blockade.

2. BACKGROUND

2.1 Study Disease and Rationale

Triple-negative breast cancer (TNBC) is defined by the absence of expression of estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), and progesterone receptor (PR). TNBC accounts for approximately 15-20% of all breast cancer subtypes, and are usually characterized by high histologic grade, earlier age of diagnosis, and increased likelihood to develop local-regional and distant metastases^{1,2}.

BRCA1 and *BRCA2* germline mutation carriers are at a significantly increased risk for the development of breast cancer, with lifetime risk estimates placed as high as 87%³. A TNBC phenotype is present in more than half of breast cancers diagnosed in women with *BRCA1* mutations, and approximately 20% of women with *BRCA2* mutations^{2,3}. These malignancies can be characterized by deficiencies in the homologous recombination (HR) pathway, making them potentially susceptible to inhibition with poly (ADP-ribose) polymerase (PARP) inhibitors⁴⁻⁶. Multiple mechanisms exist for the synthetic lethality of HR deficiency and PARP inhibition, including (1) the requirement for HR after PARP inhibitor-mediated inhibition of base excision repair; (2) the requirement for HR to bypass PARP inhibitor-induced trapped PARP-DNA complexes; and (3) the requirement for the PARP-pol θ complex to function in alternative end-joining in HR-deficient cells⁷.

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2.2 Niraparib

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2.3 Dostarlimab

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Dostarlimab Monotherapy

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2.4 Correlative Studies Background

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[REDACTED] mononuclear cells will be collected from all participants.
Blood based biomarkers will include:



3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study.

- 3.1.1 Participants must have histologically or cytologically confirmed invasive breast cancer Stage I to III with primary tumor size at least 1.0 cm defined by physical exam or imaging (whichever is larger). In the case of a multifocal, multicentric, or bilateral disease, the largest lesion must be ≥ 1.0 cm and designated as the “index” lesion for tumor evaluations. Patients with inflammatory breast carcinoma are not eligible.
- 3.1.2 Participants must have documentation of ER and PR testing by IHC according to local institutional guidelines in a CLIA-approved setting. Central confirmation of ER/PR status is not required. All tumors must be HER2 negative.
 - **Arms A and B:** Target lesion must be ER and PR negative ($<10\%$ staining) by local review.
 - **Arm C:** Target lesion must be ER and/or PR positive ($\geq 10\%$ staining) by local review.
- 3.1.3 Participants must have documented HER2-negative invasive tumor according to local institutional guidelines in a CLIA-approved setting. Central confirmation of HER2 status is not required. HER2 negative is defined as:
 - 0 or 1+ by IHC, OR
 - Lack of gene amplification with HER2/CEP17 ratio < 2 by ISH, OR
 - Copy number < 6 by ISH

- 3.1.4 Participants must have documented germline mutation in BRCA1, BRCA2, or PALB2 that is deleterious or suspected to be deleterious (known or predicted to be detrimental/lead to loss of function). Mutation must be identified through a CLIA-approved laboratory. *Final determination of eligibility for any discordant results in pathogenicity will be made by the sponsor-investigator. A formal eligibility exception will not be required in these cases as long as approval by overall study PI is granted and documented.*
- 3.1.5 Participants with multifocal, multicentric or bilateral disease are eligible if at least one lesion meets criteria for the study. In this circumstance, the investigator must determine which will represent the target lesion to be assessed for response. This should remain consistent throughout the study. The target lesion should be selected on the basis of its size (lesion with the longest diameter) and suitability for accurate repetitive measurements.
- 3.1.6 Participants with an eligible target lesion, and another small HER2+ tumor (for example, < 6 mm), may be eligible for enrollment following discussion and agreement with the overall principal investigator. *A formal eligibility exception will not be required in these cases as long as approval by the sponsor-investigator is granted and documented.*
- 3.1.7 Female or male ≥ 18 years of age
- 3.1.8 Breast imaging should include imaging of the ipsilateral axilla. For subjects with a clinically positive axilla by physical examination or imaging, axillary tissue acquisition is required. For patients with a clinically negative axilla by examination and imaging, tissue acquisition is not required. For equivocal imaging findings, tissue acquisition (a needle aspiration, core biopsy) is required. SLN biopsy before neoadjuvant therapy is not allowed.
- 3.1.9 ECOG performance status of 0 or 1
- 3.1.10 Adequate organ and bone marrow function as defined below:
- Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$
 - Platelet count $\geq 100,000/\text{mm}^3$
 - Hemoglobin ≥ 9 g/dl
 - Total serum bilirubin $\leq 1.5 \times$ institutional upper limit of normal (ULN), (≤ 2.0 in patients with documented Gilbert's Syndrome)
 - AST (SGOT) and ALT (SGPT) $\leq 2.5 \times$ institutional ULN
 - Serum or plasma creatinine $\leq 1.5 \times$ institutional ULN, OR calculated creatinine clearance > 50 mL/min using the Cockcroft-Gault equation
 - International normalized ratio (INR) OR prothrombin time (PT) $\leq 1.5 \times$ ULN. Participants who are receiving anticoagulant therapy are eligible as long as PT or partial thromboplastin (PTT) is within therapeutic range of intended use of

anticoagulants. Activated partial thromboplastin time (aPTT) must be $\leq 1.5 \times$ ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

- 3.1.11 Premenopausal women must have a negative urine or serum pregnancy test within 14 days of treatment start. Women are considered non-childbearing (by other than medical reasons) if they:
- are ≥ 45 years of age and without menses for >1 year
 - have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy with a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
 - are post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation otherwise the patient must be willing to use an adequate barrier method throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. See Section 5.8.1 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
- 3.1.12 Male and female participants of childbearing potential must agree to adhere to adequate contraception as defined in the protocol for the duration of study participation and for 180 days after the last dose of study treatment.
- 3.1.13 Female participants must agree to not breastfeed during the study or for 180 days after the last dose of study treatment.
- 3.1.14 Participants must agree to not donate blood during the study or for 90 days after the last dose of study treatment.
- 3.1.15 Ability to understand and willingness to sign an informed consent document.
- 3.1.16 Ability to swallow and retain oral medication.
- 3.1.17 Patients undergoing breast conserving therapy (i.e., lumpectomy) should not have any contraindications to radiation therapy.
- 3.1.18 Participants must be willing to undergo the mandatory research biopsy at baseline and after 3 weeks on study treatment. Participants who undergo an attempted research biopsy procedure for the purpose of this protocol and in whom inadequate tissue is obtained are not required to undergo a repeat biopsy in order to continue on the protocol.

3.2 Exclusion Criteria

- 3.2.1 Stage IV breast cancer.
- 3.2.2 Concurrent therapy with any other investigational product
- 3.2.3 Prior treatment for the current breast cancer, including prior chemotherapy, immune therapy, hormonal therapy, radiation, or investigational therapy for this diagnosis.
- 3.2.4 Excisional biopsy of the primary tumor and/or excision of axillary lymph nodes, including sentinel lymph node biopsy (SLNB), prior to study treatment.
- 3.2.5 Participants with a history of malignancy are ineligible except in the following circumstances:
 - Individuals with a history of invasive breast cancer are not eligible unless they have been disease-free for a minimum of three years.
 - Individuals with a malignancy history other than invasive breast cancer are eligible if they have no active malignancy and are deemed by the investigator to be at low risk for recurrence of that malignancy.
 - Individuals with the following cancer history are eligible: adequately treated non-melanoma skin cancers, curatively treated *in situ* cancer of the cervix, ductal carcinoma *in situ* (DCIS) of the breast, stage 1 grade 1 endometrial carcinoma.
 - Other exceptions may exist following agreement with the sponsor-investigator
- 3.2.6 Patients with a diagnosis of immunodeficiency, or currently receiving systemic steroid therapy or any other form of immunosuppressive within 7 days prior to the first dose of study treatment. Use of local corticosteroid injections (e.g. intra-articular injections), inhaled, intranasal, ophthalmic, and topical corticosteroids, and subjects requiring corticosteroid pre-medication for hypersensitivity reactions (e.g. CT scan pre-medication) are allowed.
- 3.2.7 Patients with autoimmune disease that has required systemic treatment within the past 2 years (i.e. with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- 3.2.8 Patients with a history of interstitial lung disease or pneumonitis.
- 3.2.9 Patients who have received a live vaccine within 2 weeks prior to the start of study treatment.
- 3.2.10 Patients who have undergone any major surgery within 3 weeks prior to study entry: patients must have recovered to baseline from any effects of any major surgery.

- 3.2.11 Patients with concurrent HIV infection are eligible provided they meet the following criteria:
- CD4+ T-cell (CD4+) counts ≥ 350 cells/uL
 - No history of AIDS-defining opportunistic infection within 12 months prior to enrollment
 - Any medication used in an ART regimen must have no known interaction with the study agents
- 3.2.12 Patients with active or chronic Hepatitis B or C are eligible provided they meet the liver function laboratory criteria described in 3.1.10 and cannot be on any medication with a known interaction with the study agents
- 3.2.13 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.14 History of allergic reactions attributed to compounds of similar chemical or biologic composition to niraparib, dostarlimab, or their excipients.
- 3.2.15 Transfusion (platelets or red blood cells) ≤ 4 weeks prior to initiating protocol therapy.
- 3.2.16 Known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

3.3 Inclusion of Women and Minorities

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in the clinical trial outlined. Every effort will be made to include patients from minority populations.

4. REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

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

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

The eligibility checklist(s) and all pages of the consent form(s) will be emailed to the Office of Data Quality (ODQ) at qact@partners.org. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

An email confirmation of the registration and/or randomization will be sent to the study coordinator(s) from the registering site, treating investigator and registering person immediately following the registration and/or randomization.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the sponsor investigator.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Dana-Farber Cancer Institute by the Project Manager. To verify slot availability, participating sites may email or call the Project Manager. The required forms in section 4.4 should be emailed to the Project Manager.

Following registration, participants should begin protocol therapy within 7 business days. Issues that would cause treatment delays should be discussed with the sponsor-investigator.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should

- Completed and signed DF/HCC Eligibility Checklist
- Signed participant consent form
- HIPAA authorization form
- Required laboratory test results including: Hematology (CBC with differential), serum chemistries (creatinine and/or creatinine clearance, bilirubin, ALT, and AST), thyroid function tests and pregnancy test (if applicable)
- Baseline imaging reports with tumor measurements (MRI/Mammogram/Ultrasound)
- Pathology report confirming diagnosis and ER/PR/HER2 status
- Genetic testing results
- Clinic visit note with medical history, physical exam, vital signs and ECOG

To complete the registration process, the Project Manager will

- follow the DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol
- Email the study team at the participating site with the participant study number, treatment

assignment and to confirm registration

NOTE: Participants **MUST** be registered prior to the start of protocol treatment. Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Project Manager.

5. TREATMENT PLAN

5.1 Pre-Treatment Criteria

5.1.1 Cycle 1, Day 1

Patients who completed screening assessments > 5 days prior to cycle 1 day 1 should have cycle 1 day 1 laboratory values that re-meet eligibility criteria. If screening assessments were completed ≤ 5 days prior to cycle 1 day 1, laboratory tests do not need to be repeated on cycle 1 day 1 and the screening laboratory values can be used as the cycle 1 day 1 value.

5.1.2 Subsequent Treatment Visits

With every treatment visit, vital signs, physical examination and laboratory tests will be performed. Pre-treatment criteria will include:

- Absolute neutrophil count $\geq 1,000/\text{mcL}$
- Platelets $\geq 100,000/\text{mcL}$
- Total bilirubin, $\leq 1.5\times$ institutional ULN. (≤ 2.0 in patients with known Gilberts syndrome)
- AST(SGOT) / ALT (SGPT) $\leq 3.0 \times$ institutional ULN if baseline was normal OR $\leq 1.5-3.0 \times$ baseline if baseline was abnormal
- Serum or plasma creatinine $\leq 1.5 \times$ institutional ULN, or calculated creatinine clearance $> 50 \text{ cc/min}$ using the Cockcroft-Gault equation

Management guidelines for specific toxicities associated with study treatment are located in Section 6.

5.2 Clinical Tumor Evaluation and Breast Imaging

All patients are required to have breast imaging (for example, ultrasound (US) or MRI) for accurate tumor measurements prior to registration and prior to surgery, within 4 weeks of completion of protocol therapy to evaluate response. MRI is recommended, although other imaging modalities (mammogram, ultrasound) are permitted if practical or financial considerations preclude MRI, as long as the target lesion can be adequately measured. This same imaging modality must be used at screening, if disease progression is suspected, and prior to surgery to assess tumor response.

Prior to neoadjuvant therapy, for subjects with a clinically positive axilla by physical examination or clearly positive by imaging, axillary tissue acquisition is required. For patients with a clinically negative axilla by examination and imaging, tissue sampling is

not required. For equivocal imaging findings, tissue acquisition (a needle aspiration, core biopsy) is required. SLN biopsy before neoadjuvant therapy is not allowed.

It is recommended that subjects with clinical Stage III disease have staging studies, for example CT scans of chest, abdomen and pelvis or PET CT, performed during screening to rule out metastatic disease.

In addition to at screening and prior to treatment on Day 1, clinical evaluation of the breast and axilla by physical exam will occur at cycles 2-6 to evaluate tumor growth. In participants who are clinically suspicious for disease progression, it is a strongly recommended that imaging be performed to confirm prior to removal from protocol therapy. The same imaging modality used at baseline should be used. If imaging confirms disease progression, protocol therapy should be discontinued, and the participant should receive a standard neoadjuvant chemotherapy regimen. These patients will remain on study in follow-up.

5.3 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in **Section 7**. Appropriate dose modifications are described in **Section 6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.3.1 Niraparib

Participants will take niraparib by mouth once daily and keep record in a diary (refer to Appendix D). Niraparib can be taken with or without food. Doses of niraparib should be taken approximately 24 hours apart with a $\pm$ 12 hour dosing window. Doses that would be outside of this time range should be considered missed and should not be taken. Vomited doses should not be retaken. Niraparib capsules should be swallowed whole and should not be chewed, opened, or dissolved. On days where both niraparib and dostarlimab will both be administered, order of administration does not matter (participants may take niraparib before or after the dostarlimab infusion is completed).

5.3.2 Dostarlimab

The dostarlimab infusion should be administered using an intravenous (IV) infusion pump. Dostarlimab should not be infused in the same IV line with other products. A 0.2 or 0.22 micron, low-protein binding, in-line filter should be used during administration of dostarlimab. Dostarlimab will be administered using a planned 30-minute IV infusion (with a -5 minute and +15 minute window permitted). Authorized medical personnel will be responsible for the administration of medication throughout the study. Placement of an indwelling intravenous catheter for administration of infusions will be at the discretion of the treating investigator.

The infusion line should be primed with D5W or G5W or the infusion solution of dostarlimab. The line should be primed via gravity to minimize air bubbles within the infusion line.

At the end of the infusion, a D5W or G5W infusion bag should be hung to flush the line. The volume of D5W or G5W flushed through the line should be (at minimum) consistent with the volume of drug that is held with the line. This will ensure that the entire dose has been infused. The flush should be administered using the same final rate. Do not increase the infusion rate while flushing the line.

5.3.3 Arm A: Combination Treatment Arm

Participants randomized to receive combination treatment with niraparib and dostarlimab will receive niraparib at a dose of 200 mg by mouth once daily and dostarlimab at 500 mg IV once every 3 weeks beginning on cycle 1 day 1. Participants will be treated for a total of 18 weeks or 6 cycles, and participants will receive a total of six dostarlimab infusions.

ARM A COMBINATION TREATMENT REGIMEN DESCRIPTION					
AGENT	PRECAUTIONS / PREMEDICATIONS	DOSE	ROUTE	SCHEDULE	TOTAL TREATMENT DURATION
Niraparib	None	200 mg	Oral	Daily beginning with cycle 1 day 1	18 weeks
Dostarlimab	None	500 mg	IV	Once every 3 weeks beginning with cycle 1 day 1, infusions administered on: 1. Cycle 1 Day 1 2. Cycle 2 Day 1 3. Cycle 3 Day 1 4. Cycle 4 Day 1 5. Cycle 5 Day 1 6. Cycle 6 Day 1	

5.3.4 Arm B: Niraparib Monotherapy Arm

Participants randomized to receive niraparib monotherapy will receive three weeks of niraparib alone at a dose of 200 mg by mouth once daily. Dostarlimab will be added at a dose of 500 mg IV once every 3 weeks beginning on day 22 (week 4 day 1). Administration of niraparib will continue at 200 mg once daily by mouth and dostarlimab will continue at 500 mg IV once every 3 weeks. Participants will be treated for a total of 18 weeks, and participants will receive a total of five dostarlimab infusions.

ARM B NIRAPARIB MONOTHERAPY FOLLOWED BY COMBINATION TREATMENT REGIMEN DESCRIPTION					
AGENT	PRECAUTIONS / PREMEDICATIONS	DOSE	ROUTE	SCHEDULE	TOTAL TREATMENT DURATION
Niraparib	None	200 mg	Oral	Daily beginning with cycle 1 day 1	18 weeks
Dostarlimab	None	500 mg	IV	Once every 3 weeks beginning with cycle 2 day 1, infusions administered on: 1. Cycle 2 Day 1 2. Cycle 3 Day 1 3. Cycle 4 Day 1 4. Cycle 5 Day 1 5. Cycle 6 Day 1	15 weeks

5.3.5 Arm C: ER+ Breast Cancer

Participants with hormone-receptor positive disease will be enrolled to Arm C and will receive niraparib at a dose of 200 mg once daily by mouth and dostarlimab at 500 mg IV once every 3 weeks beginning on cycle 1 day 1. Participants will be treated for a total of 18 weeks, and participants will receive a total of six dostarlimab infusions. Concurrent endocrine therapy is not allowed in this arm.

ARM C TREATMENT REGIMEN DESCRIPTION					
AGENT	PRECAUTIONS / PREMEDICATIONS	DOSE	ROUTE	SCHEDULE	TOTAL TREATMENT DURATION
Niraparib	None	200 mg	Oral	Daily beginning with cycle 1 day 1	18 weeks
Dostarlimab	None	500 mg	IV	Once every 3 weeks beginning with cycle 1 day 1, infusions administered on: 1. Cycle 1 Day 1 2. Cycle 2 Day 1 3. Cycle 3 Day 1 4. Cycle 4 Day 1 5. Cycle 5 Day 1 6. Cycle 6 Day 1	

5.4 Definitive Breast Surgery

Based on response, participants will either undergo definitive surgery after completion of protocol therapy or receive additional anti-cancer treatment at the treating investigator's discretion prior to definitive surgery. Participants who require additional neoadjuvant treatment will remain on study, and data on the type of post-protocol crossover treatment and response to therapy at definitive surgery will be collected. Tissue collection in the form of tumor biopsy is required prior to initiation of crossover therapy.

Participants undergoing definitive breast surgery without additional neoadjuvant treatment should have the surgery at least 2 weeks but no more than 6 weeks after the last dose of protocol therapy.

Ipsilateral axillary node evaluation is required at the time of surgery. Type of axillary evaluation is at the discretion of the treating surgeon. If contralateral mastectomy is performed concurrently, the pathology report from the contralateral breast must also be submitted for review.

At time of definitive breast surgery, tissue will be collected under the supervision of a surgical pathologist for all participants and will be submitted to Dana-Farber Cancer Institute.

See **Section 9** and the Lab Manual for additional guidance on surgical specimen collection.

5.5 At-Home Blood Pressure Monitoring

Blood pressure monitors will be provided by each site at study start, per institutional policy. For the first two months of treatment on study, the study participant will self-administer weekly at-home monitoring of heart rate and blood pressure. The participant will complete a diary (refer to Appendix E) to return at next cycle initiation. A clinical member of the study team at the investigative site is responsible for documenting in the research chart or medical record any abnormal findings.

5.6 Additional Safety Monitoring

A safety event of interest is defined as an adverse event or abnormal laboratory value assessed as suspected to be trial treatment related (possible, probable or definite) and unrelated to disease or disease progression that occurs while receiving any protocol therapy. Toxicities and lab values will be categorized and graded according to CTCAEv5.0. See section 14.3 for the supplemental safety monitoring plan for all patients receiving treatment in the study.

1. Any grade ≥ 3 non-hematologic, non-hepatic adverse event with the following exceptions:
 - Grade 3 nausea that resolves in ≤ 3 days,
 - Grade 3 fatigue that resolves to $\leq$ grade 2 in ≤ 5 days,
 - Grade 3 fever ($>40^{\circ}\text{C}$ for ≤ 24 hrs),
 - Grade 3/4 lab values that are not considered clinically significant,
 - Grade 3 rash that resolves to $\leq$ grade 2 in ≤ 7 days with therapy equivalent to prednisolone 10 mg/day or less,
 - Grade 3 arthralgia that can be managed with supportive care that resolves to $\leq$ grade 2 within 7 days,
 - Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine replacement without systemic steroids (not including replacement steroids for adrenal insufficiency).
2. Grade ≥ 4 neutropenia ($\text{ANC} < 500\text{uL}$) lasting > 7 days.
3. Grade ≥ 3 febrile neutropenia.
4. Grade ≥ 4 anemia.
5. Grade ≥ 4 thrombocytopenia or grade 3 with clinically significant bleeding.

6. Grade ≥ 3 or more elevation of serum hepatic transaminase (ALT or AST) lasting > 7 days.
7. Grade ≥ 3 elevation in AST or ALT AND total bilirubin $> 2 \times$ ULN
8. Grade ≥ 3 pneumonitis.

5.7 General Concomitant Medication and Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator, including but not limited to anti-emetics, antidiarrheals, systemic corticosteroids to address suspected immune related adverse events, and blood product transfusion.

5.8 Prohibited Medications or Therapies

- No investigational or commercial agents or therapies other than dostarlimab and niraparib may be administered with the intent to treat the participant's malignancy.
- Concurrent endocrine therapy is not allowed for participants randomized to Arm C
- Live vaccines are prohibited within 14 days prior to the first dose of study treatment and for the duration of the study treatment period. Seasonal flu vaccines that do not contain live viruses are permitted
- Prophylactic cytokines (i.e., granulocyte colony-stimulating factor [GCSF]) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current American Society of Clinical Oncology (ASCO) guidelines
- Systemic glucocorticoids for any purpose other than to manage symptoms of suspected irAEs. (Note: Use of inhaled steroids, local injection of steroids, topical steroids, and steroid eye drops are allowed). If medically deemed necessary (e.g., acute asthma or chronic obstructive pulmonary disease exacerbation), Investigators are allowed to use their judgment to treat patients with systemic steroids. In such cases, systemic steroids should be stopped at least 24 hours prior to the next dose of dostarlimab.

Management guidelines for specific toxicities associated with study treatment are located in **Section 6**.

5.8.1 Acceptable Methods of Contraception

Participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation beginning with time of consent, during the study treatment and for 180 days after last dose of study treatment(s)

The following methods are acceptable:

- Non-hormonal (copper) intrauterine device
- Bilateral tubal occlusion/ligation
- Vasectomized partner
- Sexual abstinence, if the preferred and usual lifestyle of the subject
- Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of spermicide or another contraceptive method to result in

a failure rate of < 1%

5.9 Criteria for Taking a Participant Off Treatment

Protocol therapy will continue for 18 weeks or until one of the below listed criteria applies.

It is strongly recommended that suspicion of disease progression by clinical exam, determined by the treating investigator, be confirmed with imaging. The imaging modality should be the same as baseline. These participants with confirmed disease progression should be removed from protocol therapy and receive a standard pre-operative chemotherapy regimen. These participants will remain on study in follow up.

Participants will be considered off-treatment when one of the following criteria applies:

- Completion of 18 weeks of protocol therapy
- Disease Progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), per protocol
- Patient Compliance. Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Withdrawal of Consent. Participant decides to withdraw from the protocol therapy
- Physician Discretion. General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator, including participant pregnancy or new diagnosis of MDS or AML

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

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with [REGIST-OP-1](#).

In the event of unusual or life-threatening complications, treating investigators must immediately notify the sponsor-investigator.

5.10 Duration of Follow Up

Participants will be followed for up to five years following the completion of protocol treatment, with time measured from the date of surgery, including those who change to an alternative crossover neoadjuvant therapy in the case of significant residual disease after completion of neoadjuvant protocol therapy. For patients who change to an alternative crossover neoadjuvant therapy, data on the type of post-protocol therapy and response to therapy at definitive surgery will be collected. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

All participants will be followed annually for 5 years or until closure of the study (whichever is sooner), for occurrence of MDS or AML, disease recurrence, information on post-protocol therapy, and survival status. This follow-up may occur via in-person visit, phone call, or chart review.

5.11 Criteria for Taking a Participant Off- Study

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

- Completion of 5 years of Follow Up
- Lost to follow-up
- Withdrawal of consent
- Death
- Termination of the study by the study sponsor

For participants who are thought to be lost to follow-up, at least 3 documented attempts, including 1 via certified mail, should be made to contact the participant before the participant is deemed lost to follow-up.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Delays

Study agents may be held for a maximum of 4 weeks to allow for recovery from toxicity considered at least possibly related to the study regimen.

Study agents may be held independently of each other if attribution of the toxicity is known as judged by the treating investigator. For example, a participant may receive their niraparib dose while dostarlimab is being held or vice versa. In the event that toxicity attribution is unknown, uncertain, or both study agents contribute to the toxicity in the opinion of the treating investigator, both study agents must be held.

Reasonable effort should be made to administer the total number of dostarlimab infusions (Arms A and C: 6 infusions, Arm B: 5 infusions). In the event of a dose delay on day 1 of a week that results in dostarlimab being held, the counting of days will also be delayed, so that the day the participant resumes dosing with dostarlimab will be considered the first day of the week.

Subsequent assessments and evaluations will be delayed accordingly to account for the delayed dosing of dostarlimab.

In the event dosing of niraparib is held, the counting of week days and assessment schedule will continue without interruption. For example, a participant who does not receive their week 6 day 10 – week 6 day 12 doses due to toxicity will restart dosing on week 6 day 13 and proceed with their next scheduled visit as previously planned (week 7 day 1). Interim visits may be conducted as clinically necessary to manage toxicity; however, the assessment and evaluation schedule will not be delayed.

6.2 Dose Modifications

The dose of niraparib may be reduced in accordance with the table below. If the reduced dose of 100 mg daily is not tolerable, no further dose reduction is allowed and niraparib should be discontinued. Once a participant's dose of niraparib has been reduced, it may not be re-escalated.

TABLE 5: NIRAPARIB DOSE LEVELS	
DOSE LEVEL	NIRAPARIB DOSE
0	200 mg daily
-1	100 mg daily
Further dose reduction	Discontinue Niraparib

Dose reductions of dostarlimab will not be permitted. Participants who are unable to tolerate dostarlimab at the assigned dose should discontinue dostarlimab and remain on niraparib.

6.3 Toxicity Management Guidelines

Management of toxicities considered at least possibly related to the study regimen are detailed in the tables below.

Any hematologic toxicity is assumed related to niraparib, as dostarlimab has no known serious hematologic toxicity. Table 6 describes niraparib management in the setting of hematologic toxicity. If niraparib is held for hematologic toxicity, dosing with dostarlimab may continue per study schedule.

TABLE 1: NIRAPARIB TOXICITY MANAGEMENT^{A,B,C,D}		
EVENT TERM	CTCAE GRADE OR SEVERITY	NIRAPARIB MANAGEMENT
Platelet Count Decreased	Grade 1: Platelet Count 75,000 – 99,999/ μ L	1st Occurrence: Hold until platelet count is $\geq$ 100,000 with weekly blood counts for CBC monitored until recovery and for an additional 4 weeks. Resume at the same dose or with one dose level reduction of niraparib based on clinical judgment. 2nd Occurrence: Hold until platelet count is $\geq$ 100,000 with weekly blood counts for CBC monitored until recovery and for an additional 4 weeks.

		If recovered within 28 days, resume with one dose level reduction of niraparib. Discontinue niraparib if platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Platelet Count Decreased	≥ Grade 2: Platelet Count < 75,000/μL	Hold until platelet count is ≥ 100,000 with weekly blood counts for CBC monitored until recovery and for an additional 4 weeks. Resume with one dose level reduction of niraparib. For patients with platelet count ≤ 10,000/μL, platelet transfusion should be considered. If there are other risk factors such as co administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Discontinue niraparib if platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil Count Decreased	≥ Grade 3	Interrupt dosing until neutrophil counts are ≥ 1500/μL with weekly blood counts for CBC monitored until recovery and for an additional 4 weeks. Niraparib may then be resumed at a reduced dose. Discontinue niraparib if neutrophil level has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Anemia	≥ Grade 3	Interrupt dosing until hemoglobin is ≥ 9 g/dL with weekly blood counts for CBC monitored until recovery and for an additional 4 weeks. Niraparib may then be resumed at a reduced dose. Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Other Non-Hematologic Toxicities Not Otherwise Specified	≥ Grade 3	For clinically significant toxicity, hold until resolution to ≤ Grade 1 or baseline. Upon recovery, if toxicity is attributed at least in part to niraparib (or attribution is unknown or uncertain), niraparib should be reduced by one dose level. Exceptions include: • Asymptomatic laboratory abnormalities that resolve to ≤ Grade 1 or baseline within 48 hours of repletion. • Grade 3 nausea, vomiting, diarrhea, or constipation that was not optimally managed and that resolves to ≤ Grade 1 or baseline within 48 hours of appropriate medical management. In the case of the above exceptions, hold dosing until resolution of the toxicity to ≤ Grade 1 or baseline. Niraparib may be resumed at the same dose level or at a reduced dose level as judged by the treating investigator. Laboratory repletion may occur on the same day as treatment.
A. Patients must be referred to a hematologist for further evaluation and to rule out a diagnosis of MDS/AML if any of the following criteria are met: ○ Transfusion is required on more than 1 occasion ○ The treatment-related hematologic toxicities have not recovered to CTCAE ≤ Grade 1 or baseline within 4 weeks If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must be permanently discontinued from study treatment. B. Any patient requiring transfusion of platelets or red blood cells, or hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if study treatment is resumed. C. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient, or as considered clinically appropriate by the treating investigator. D. Patients must be referred to a specialist to rule out a diagnosis of PRES (Posterior reversible encephalopathy syndrome) If a diagnosis of PRES is confirmed, the patient must be permanently discontinued from study treatment.		

TABLE 2: DOSTARLIMAB TOXICITY MANAGEMENT		
EVENT TERM	CTCAE GRADE OR SEVERITY	DOSTARLIMAB MANAGEMENT
Pneumonitis	Grade 2	1st Occurrence: Hold until toxicity resolves to $\leq$ Grade 1. Initiate systemic corticosteroid therapy as clinically indicated. 2nd Occurrence: Permanently discontinue dostarlimab.
Pneumonitis	$\geq$ Grade 3	Permanently discontinue dostarlimab. Consultation with a specialist with experience in management of immune-mediated pneumonitis is strongly suggested to assist with following treatment plan: ○ Treat with systemic corticosteroids, oral for Grade 2 (e.g., 0.5 to 1 mg/kg/day of prednisone or equivalent) and IV for Grade 3 or 4 (e.g., 1 to 2 mg/kg/day of prednisone or equivalent). ○ Administer additional anti-inflammatory measures, as needed. ○ Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks. ○ If Grade 2 and no improvement or worsening over 2 weeks, treat as Grade 3 or 4. ○ Consider prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration. ○ Permanently discontinue if no complete or partial resolution within 4 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 4 weeks of initiating steroids.
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN Or Total bilirubin increases to more than 1.5 and up to 3 times the ULN	Hold until resolution to $\leq$ Grade 1 or baseline. Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks. Permanently discontinue if no complete or partial resolution within 4 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 4 weeks of initiating steroids.
Hepatitis with no tumor involvement of the liver)	AST or ALT increases to more than 8 times the ULN Or Total bilirubin increases to more than 3 times the ULN	Consultation with a specialist with experience in management of immune-mediated hepatitis is strongly suggested. Permanently discontinue dostarlimab.
Hypophysitis	Grade 2 – 3	1st Occurrence: Initiate hormone replacement therapy. Hold until hormone levels return to adequate levels by laboratory values and restart dosing when toxicity resolves to $\leq$ Grade 1. 2nd Occurrence or Worsening: If recurrence or worsening occurs following completion of steroid taper while adequate hormone replacement therapy is continuing, permanently discontinue dostarlimab

Hypophysitis	Grade 4	Consultation with a specialist with experience in management of immune-mediated hypophysitis is strongly suggested. Permanently discontinue dostarlimab.
Adrenal Insufficiency	Grade 2 – 3	1st Occurrence Initiate hormone replacement therapy and hold until toxicity has resolved to $\leq$ Grade 1. 2nd Occurrence or Worsening: If recurrence or worsening occurs while adequate hormone replacement therapy is continuing, permanently discontinue dostarlimab.
Adrenal Insufficiency	Grade 4	Consultation with a specialist with experience in management of immune-mediated adrenal insufficiency is strongly suggested. Permanently discontinue dostarlimab.
Hypothyroidism	Grade 2-4	Hold until toxicity resolves to $\leq$ Grade 1.

TABLE 2: DOSTARLIMAB TOXICITY MANAGEMENT		
EVENT TERM	CTCAE GRADE OR SEVERITY	DOSTARLIMAB MANAGEMENT
		Thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care. For grade 3/4 toxicity, consultation with a specialist with experience in management of immune-mediated thyroid dysfunction is strongly suggested Permanently discontinue dostarlimab for grade 4 toxicity.
Hyperthyroidism	Grade 2	Hold until toxicity resolves to $\leq$ Grade 1. Consider non-selective beta-blockers (e.g., propranolol) as initial therapy.
Hyperthyroidism	Grade 3-4	Consultation with a specialist with experience in management of immune-mediated thyroid dysfunction is strongly suggested. Treat with an initial dose of IV corticosteroids followed by oral corticosteroids (e.g., 0.5 to 1 mg/kg/day of prednisone or equivalent). Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered Permanently discontinue if no complete or partial resolution within 4 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 4 weeks of initiating steroids. Grade 4 toxicity: permanently discontinue dostarlimab.
Hyperglycemia or Type 1 Diabetes (<i>associated with metabolic acidosis or ketonuria</i>)	$\geq$ Grade 3	Consultation with a specialist with experience in management of immune-mediated diabetes is strongly suggested. Initiate insulin therapy. Hold until participants become clinically and metabolically stable. Continue to monitor blood glucose levels and adjust insulin replacement therapy as clinically appropriate.
Immune-Mediated Nephritis and Renal Dysfunction	Grade 2-3	Hold until toxicity resolves to $\leq$ Grade 1. Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks. Permanently discontinue if no complete or partial resolution within 4 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 4 weeks of initiating steroids.
Immune-Mediated Nephritis and Renal Dysfunction	Grade 4	Consultation with a specialist with experience in management of immune-mediated renal dysfunction is strongly suggested. Permanently discontinue dostarlimab.

Immune-Mediated Colitis	Grade 2 – 3	Hold until toxicity resolves to $\leq$ Grade 1. Monitor carefully for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 diarrhea/colitis that persists >3 days, administer oral corticosteroids (e.g., 0.5 to 1.0 mg/kg/day of prednisone or equivalent). If symptoms persist or worsen with steroids, treat as Grade 3 or 4. For Grade 3 diarrhea/colitis that persists >3 days, treat with IV steroids (e.g., 1 to 2 mg/kg/day of prednisone or equivalent) followed by high-dose oral steroids. Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks. Permanently discontinue if no complete or partial resolution within 4 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 4 weeks of initiating steroids.
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TABLE 2: DOSTARLIMAB TOXICITY MANAGEMENT		
EVENT TERM	CTCAE GRADE OR SEVERITY	DOSTARLIMAB MANAGEMENT
Immune-Mediated Colitis	Grade 4	Consultation with a specialist with experience in management of immune-mediated colitis is strongly suggested. Permanently discontinue dostarlimab.
Immune-Mediated Myocarditis	≥ Grade 2	Permanently discontinue dostarlimab.
Immune-Mediated Rash	Grade 3	Hold until toxicity resolves to ≤ Grade 1. If confirmed SJS (Stevens-Johnson syndrome), TEN (toxic epidermal necrolysis), or DRESS (drug rash with eosinophilia and systemic symptoms) permanently discontinue dostarlimab.
Immune-Mediated Rash	Grade 4	Consultation with a specialist with experience in management of immune-mediated rash is strongly suggested. Permanently discontinue dostarlimab.
Immune-Mediated Encephalitis	Any	Consultation with a specialist with experience in management of immune-mediated encephalitis is strongly suggested. Permanently discontinue dostarlimab.
Neurological Toxicities	Grade 2	Hold until toxicity resolves to ≤ Grade 1. Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks. Permanently discontinue if no complete or partial resolution within 4 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 4 weeks of initiating steroids.
Neurological Toxicities	≥ Grade 3	Permanently discontinue dostarlimab.
Infusion-Related Reactions	Grade 1 – 2	Refer to Section 6.3.3.1/Table 8 for detailed infusion-related reaction management guidelines.
Infusion-Related Reactions	≥ Grade 3	Permanently discontinue protocol therapy. Refer to 6.3.3.1/Table 8 for detailed infusion-related reaction management guidelines.

Other Toxicities Not Otherwise Specified	Grade 3 - 4	First Occurrence: Hold until toxicity resolves to $\leq$ Grade 1. Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks. Permanently discontinue if no complete or partial resolution within 4 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 4 weeks of initiating steroids. Second Occurrence: permanently discontinue dostarlimab. Grade 4 toxicity: permanently discontinue dostarlimab.
Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient, or as considered clinically appropriate by the treating investigator.		

6.3.1.1 Dostarlimab Infusion-Related Reactions

Signs and symptoms usually develop during or shortly after dostarlimab infusion and generally resolve completely within 24 hours of completion of infusion. Please follow the instructions below for management guidelines.

TABLE 8: DOSTARLIMAB INFUSION-RELATED REACTION MANAGEMENT		
CTCAE GRADE	TREATMENT	PREMEDICATION AT SUBSEQUENT DOSING
1	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the treating investigator.	None

2	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the treating investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further dostarlimab treatment administration.	Patient may be premedicated 1.5 hour ($\pm$ 30 minutes) prior to infusion of dostarlimab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
≥ 3	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the treating investigator. Hospitalization may be indicated. Patient is permanently discontinued from further dostarlimab treatment administration.	No subsequent dosing

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Expected Toxicities

7.1.1 Adverse Event List for Niraparib

The following adverse reactions (all CTCAE grades) are considered expected for safety reporting purposes.

The following adverse have been reported in $\geq 20\%$ of patients who received niraparib: anemia, thrombocytopenia, nausea, constipation, vomiting, diarrhea, abdominal pain, fatigue, decreased appetite, headache, heartburn, and insomnia.

The following adverse reactions and laboratory abnormalities have been identified in ≥ 10 to $< 20\%$ of patients receiving niraparib: neutropenia, platelet count decreased, leukopenia, dizziness, dyspnea, cough, urinary tract infection, back pain, joint pain, palpitations, common cold symptoms, and hypertension.

The following adverse reactions and laboratory abnormalities have been identified in ≥ 1 to $< 10\%$: asthenia, depression, anxiety, epistaxis, muscle pain, peripheral edema, hypokalemia, dry mouth, rash, elevated liver enzymes, elevated creatinine levels, weight loss, bronchitis, conjunctivitis, dysgeusia, photosensitivity, allergic reaction, cognitive impairment, MDS/AML tachycardia, mucosal inflammation.

The following adverse reactions and laboratory abnormalities have been identified in $< 1\%$: new primary cancer, pneumonitis, embolic events, febrile neutropenia, neutropenic sepsis, hypertensive crisis, PRES, confusion, hallucination, and MDS/AML.

Additional information regarding adverse events can be found in the current version of the Investigator Brochure and/or US Package Insert.

7.1.2 Adverse Event List for Dostarlimab

The following adverse reactions (all CTCAE grades) are considered expected for safety reporting purposes.

The following adverse reactions (all CTCAE grades) have been reported in $\geq 10\%$ of patients received dostarlimab monotherapy: fatigue, nausea, anemia, diarrhea, vomiting, arthralgia, hypothyroidism, increase in the liver enzyme aspartate aminotransferase (AST), increase in the liver enzyme aspartate alanine transferase (ALT), fever, and immune-mediated skin reactions (rash, itching, blisters, peeling or redness of skin, skin sores).

The following adverse reactions and laboratory abnormalities have been identified in ≥ 1

to <10% of patients who received dostarlimab monotherapy, include the following: immune-mediated endocrinopathy (thyroid, pituitary, and adrenal glands), immune-mediated Pneumonitis (dyspnea, chest pain, and cough), chills, muscle pain, feeling weak, pancreatitis, colitis, and decreased appetite.

The following adverse reactions and laboratory abnormalities have been identified in <1% of patients who received dostarlimab monotherapy: autoimmune hemolytic anemia, thyroiditis, inflammation of pituitary gland, diabetic ketoacidosis, type 1 diabetes mellitus, uveitis, polymyalgia rheumatic, nephritis, myasthenia gravis, immune-mediated arthritis, encephalitis, myocarditis, hepatitis, gastritis, esophagitis, enteritis, vasculitis gastrointestinal, myositis, systemic inflammatory response syndrome, and infusion related reactions.

In addition, there are very rare but serious side effects seen when dostarlimab was given in combination with other medicines: Guillain-Barre syndrome and hemophagocytic lymphohistiocytosis.

Additional information regarding adverse events can be found in the current version of the Investigator Brochure and/or US Package Insert.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **For expedited reporting purposes only:**
 - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
 - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting)
- **Attribution of the AE:**
 - Definite – The AE *is clearly related* to the study treatment.
 - Probable – The AE *is likely related* to the study treatment.
 - Possible – The AE *may be related* to the study treatment.
 - Unlikely – The AE *is doubtfully related* to the study treatment.
 - Unrelated – The AE *is clearly NOT related* to the study treatment.
- **Expectedness:**
 - **Expected** adverse events are those adverse events that are listed or characterized in the current adverse event list, the Investigator Brochure or is included in the informed consent document as a potential risk.
 - **Unexpected** adverse events are those not listed in the current Investigator Brochure

(I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the I.B.

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Sponsor-Investigator.

Investigators **must** report to the Sponsor-Investigator any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 90 days (or as soon as the participant begins a new anti-cancer regimen) of the last dose of treatment.

For multi-institution studies where a DF/HCC investigator is serving as the Sponsor-Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC (listed in sections 7.3 and 7.4). The Sponsor-Investigator and Coordinating Center should be notified of SAEs within 1 working day of learning of the event.

7.3 DF/HCC Expedited Adverse Event Reporting

The following adverse events must be reported to the DFCI IRB according to the expedited reporting guidelines:

- All locally occurring Adverse Events that are *Serious*, *Unexpected*, and there is a *Reasonable Possibility* the Adverse Event is related to the study intervention should be reported to the IRB.

7.4 DF/HCC Expedited Reporting Procedures

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

- All life threatening and fatal Serious Adverse Events (grade 4 and 5) considered serious, unexpected, and related, must be submitted via a written adverse event report to OHRS **within 5 working days** from notification of the event.
- For all other Serious Adverse Events considered serious, unexpected, and related, a full written adverse event report must be submitted to OHRS **within 10 working days** from notification of the event.
- Any unrelated adverse event does not require reporting to OHRS except grade 5 events which must be reported at the time of continuing review.

7.5 External Site Expedited Reporting Guidelines

Other investigative sites will report SAEs to their respective IRB according to their local IRB's policies and procedures for reporting adverse events. A copy of the submitted institutional AE form will be forwarded to the Coordinating Center.

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

7.6 Expedited Reporting to GSK

The Sponsor Institution or delegate from reporting institution must report all SAEs, pregnancy in female participants and pregnancy in female partners of male study participants, and all followup information to GSK on the MedWatch 3500A form with an accompanying coversheet within 24 hours of becoming aware of the event. The report must include the name of the Sponsor-Investigator, and either the DFCI or TBCRC protocol number. A physician investigator from the reporting institution will review any reports prior to submission and provide causality assessment.

If supporting documentation is included in the submission to GSK (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), please redact any patient identifiers (including Medical Record number).

GSK SAE, Pregnancy, and AESI Reporting Information
OAX37649@gsk.com Fax Number: +44(0) 20 8754 7822

7.6.1 SAE Definition for Reporting to GSK

For the purposes of reporting to GSK, a serious *adverse event* is defined as any untoward medical occurrence from initial dose of study intervention through 90 days of last study intervention that:

- Results in death
- Is life-threatening
 - Note: This means that the patient is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
 - Any AE that prolongs hospitalization will be considered an SAE.
 - Exception: Preplanned hospitalization (e.g., for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, the reason for the planned hospitalization should be captured in medical history.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s)

Note: An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.6.2 GSK Adverse Events of Special Interest

Select non-serious AEs and SAEs are also known as Adverse Events of Special Interest.

Adverse Events of Special Interest (AESI) for niraparib are the following:

- Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)
- Secondary cancers (new malignancies [other than MDS or AML])
- Pneumonitis
- Embryo-fetal toxicity

AESIs should be collected from first dose of study intervention and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the Sponsor Institution and GSK throughout the duration of study participation including follow-up
- Pneumonitis should be reported to the Sponsor Institution and GSK through 90 days after the last dose of study drug (or until the start of alternate anti-cancer therapy, whichever occurs first).
- Embryo-fetal toxicity should be reported to the Sponsor Institution and GSK throughout the duration of study participation including follow-up.

7.7 Expedited Reporting to the Food and Drug Administration (FDA)

The principal investigator, as study sponsor, will be responsible for all communications with the FDA. The sponsor-investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.8 Expedited Reporting to Hospital Risk Management

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

7.9 Routine Adverse Event Reporting

All grade 2 or higher adverse events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. Abnormal laboratory values or diagnostic tests will not be reported on the case report forms unless they induce clinical signs or symptoms, require treatment or further diagnostic tests or result in a dose hold or modification. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

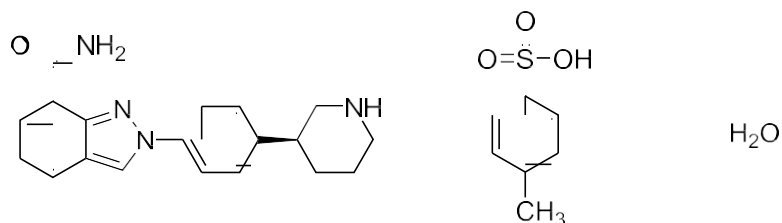
8. PHARMACEUTICAL INFORMATION

8.1 Niraparib (Zejula)

8.1.1 Description

Chemical Name: [3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]

Chemical Structure:



Molecular formula: C₂₆H₃₀N₄O₅S

Molecular Weight: 510.617 daltons

8.1.2 Form

Investigational niraparib drug product is formulated as a dry blend of niraparib tosylate monohydrate and lactose monohydrate lubricated with magnesium stearate. The active potency is 100 mg in size 0 hard gelatin capsules.

8.1.3 Storage and Stability

All investigational study drug supplies must be stored at room temperature (20°C-25°C), excursions are permitted between (15°C-30°C).

Investigational niraparib drug product is packaged in high-density polyethylene (HDPE) white bottles with a two-piece, pulp-backed, head-induction-foil inner seal, tamper evident cap. The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. Until dispensed to the patients, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

8.1.4 Handling

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

8.1.5 Availability

Niraparib will be supplied as an investigational agent by GSK.

8.1.6 Administration

Participants will take niraparib by mouth once daily. Niraparib can be taken with or without food. Doses of niraparib should be taken approximately 24 hours apart, there is a ± 12 hour dosing window. Doses that would be outside of this time range should be considered missed and should not be taken. Vomited doses should not be retaken. Niraparib capsules should be swallowed whole and should not be chewed, opened, or

dissolved. On days where both niraparib and dostarlimab will both be administered, order of administration does not matter (participants may take niraparib before or after the dostarlimab infusion is completed).

8.1.7 Ordering

Niraparib will be ordered through an electronic system from GSK by site pharmacy personnel.

8.1.8 Accountability

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

8.1.9 Destruction and Return

Expired or returned supplies of niraparib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. At the end of the study, unused supplies of niraparib should also be destroyed according to institutional policies and destruction will be documented in the Drug Accountability Record Form.

8.2 Dostarlimab

8.2.1 Description

Dostarlimab is a humanized mAb that binds to PD-1 and blocks the interaction between PD-1 and ligands PD-L1 and PD-L2. Dostarlimab is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian expression system.

Chemical Name: Anti-PD-1 mAb, IgG4

Structure: An anti-PD-1 IgG4 mAb derived from a stable CHO cell line. The protein consists of 2 heavy chains and 2 light chains with a single N-linked glycosylation on each heavy chain.

8.2.2 Form

The drug product is a sterile liquid formulation, essentially free from visible particles, supplied as single-use vials for IV administration. The drug product is formulated in citrate buffer (pH 6.0 ± 0.5). The vials are aseptically filled to allow for a delivered volume of 10.0 mL. The sterility of the product is ensured through aseptic processing and sterility testing.

TABLE 3: COMPOSITION OF DOSTARLIMAB DRUG PRODUCT	
COMPONENT/EXCIPIENT	CONCENTRATION
Dostarlimab	50 mg/mL
Citrate ¹	25 nM
Arginine	100 mM
Sodium Chloride	31 mM
Polysorbate 80	0.02% (w/v)
Abbreviation: w/v = weight per volume percent.	
^{1.} Consists of sodium citrate dihydrate and citric acid.	

8.2.3 Preparation

Dostarlimab may be prepared in an IV bag at a concentration of 2-20 mg/mL. Dostarlimab may be diluted in Dextrose 5% (D5W) or Glucose 5% (G5W) in Sterile Water for Infusion only. DO not use filter needles during the preparation of dostarlimab. DO not add the dostarlimab solution into airspace contained within the infusion bag or shake the final infusion bag. Please keep in mind the overfill volume of the pre-filled D5W or G5W infusion bags and allowed concentration in this preparation process.

1. Set all vials aside for approximately 30 minutes to allow them to reach room temperature.
2. Remove the equal dose volume of dostarlimab from a pre-filled D5W or G5W infusion bag.
3. To minimize the air-liquid interface, remove as much airspace as possible that is contained within the infusion bag prior to adding dostarlimab.
4. Visually inspect the vial(s) for particulate matter and discoloration. If upon immediate inspection foreign particles (e.g. opaque particles) are observed or if the solution is discolored do not use.
5. Slowly withdraw the required dose volume from the dostarlimab vial.
6. Inject the solution into the infusion bag. It is important to inject the dostarlimab solution directly into the D5W or G5W rather than into air space that may remain within the infusion bag. Avoid foaming within the infusion bag.
7. Gently invert or massage the infusion bag to mix the solution. Avoid shaking or excessive agitation.
8. Visually inspect for particulate matter and discoloration. If upon immediate inspection foreign particles (e.g. opaque particles) are observed or if the solution is discolored do not use.
9. Label the infusion bag per institutional standard practice.
10. Hand-carry the final infusion to the clinical staff avoiding any shaking or excessive agitation. Do not use a pneumatic tubing system to deliver this product to the end user.

8.2.4 Compatibility

No other medications or products should be administered via the same IV infusion line.

8.2.5 Storage and Stability

Dostarlimab for injection is supplied in vials containing 500 mg at a concentration of 50 mg/mL. Dostarlimab is aseptically filled into 8R Fiolax Type I borosilicate clear glass vials, stoppered with a chlorobutyl elastomer stopper laminated with fluoropolymer and sealed with an aluminum overseal with a flip-off cap.

Unused supplies of dostarlimab are to be stored under refrigerated conditions (or under refrigeration), 2°C-8°C. Dostarlimab vials are to remain in cartons intact until time of preparation.

Prepared dostarlimab in IV bags must be administered within 24 hours of dilution. The IV bag may be stored at 2°C-8°C for up to 24 hours and at room temperature for up to 6 hours. To decrease the risk of microbial contamination, limit the storage of the diluted drug product to 4 hours at room temperature once sterility is broken.

8.2.6 Handling

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

8.2.7 Availability

Dostarlimab is an investigational agent that will be supplied by GSK.

8.2.8 Administration

The infusion should be administered using an intravenous (IV) infusion pump. Dostarlimab should not be infused in the same IV line with other products. A 0.2 or 0.22 micron, low-protein binding, in-line filter should be used during administration of dostarlimab. Dostarlimab will be administered using a planned 30-minute IV infusion (with a -5 minute and +15 minute window permitted). Authorized medical personnel will be responsible for the administration of medication throughout the study. Placement of an indwelling intravenous catheter for administration of infusions will be at the discretion of the treating investigator. On days where both niraparib and dostarlimab will both be administered, order of administration does not matter (participants may take niraparib before or after the dostarlimab infusion is completed).

8.2.9 Ordering

Dostarlimab will be ordered through an electronic system from GSK by site pharmacy personnel.

8.2.10 Accountability

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

8.2.11 Destruction and Return

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

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Specimen Submission Requirements

The following specimens are to be submitted to the indicated lab. Instructions for collection, processing, labeling, and shipment are included within the Study Manual.

Specimen Type	Collection Time Point									Shipping Condition	Ship to
	Baseline Pre-Treatment	C2 D1	C3 D1	C4 D1	C5 D1	C6D 1	End of Treatment (pre-surgery)	Definitive Breast Surgery	Recurrence		
FFPE block with H&E slide ^a	X							X	X	Ambient temperature	BOC Translational Team
ctDNA (two 10 mL Streck tubes) ^b	X	X	X	X	X	X	X		X	Ambient temperature	DFCI (T-Hub)
PBMCs (two 10mL CPT tubes) ^c	X	X	X	X	X	X	X		X	Ambient Temperature	DFCI (T-Hub)
Germline DNA (one 10 mL purple top EDTA tube) ^d	X									Ambient temperature	DFCI (T-Hub)
Research Biopsy (Fresh and frozen)	X	X					X			Frozen in OCT & formalin	DFCI (T-Hub)

tumor tissue) ^e											
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- 20 unstained slides 4-5 microns thick representative of residual disease at time of surgery may be submitted in lieu of an FFPE block. A corresponding H&E slide must be submitted with slides or FFPE block. Baseline/Screening tissue should be from patient's definitive core biopsy.
- 2 Streck tubes will be collected for ctDNA PRIOR to dosing at Baseline, C2D1, C3D1, C4D1, C5D1, C6D1, and at time of treatment completion/ discontinuation, prior to surgery and at recurrence (if/when applicable).
- 2 CPTs collected PRIOR to dosing at Baseline, C2D1, C3D1, C4D1, C5D1, C6D1, and at time of treatment completion/ discontinuation, prior to surgery and at recurrence (if/when applicable).
- Sample for germline DNA should be collected at Cycle 1 Day 1. If missed, this sample can be drawn at any time during treatment
- Baseline and C2D1 biopsies are mandatory for all participants. C2D1 biopsies must occur PRIOR to dosing. The end of treatment biopsy is required in all participants who will receive additional pre-operative therapy prior to surgery. The biopsy should be performed prior to initiating the subsequent therapy

9.2 Research Tumor Biopsies

Tumor Biopsy will be performed at the following time-points:

- Mandatory Baseline (Pre-Treatment):** to be performed up to 2 weeks prior to starting treatment. Participants enrolled to Arm B must have the on-treatment biopsy prior to their first dose of dostarlimab.
- Mandatory Cycle 2/Week 4 Day 1:** to be performed on Cycle 2 Day 1. Every effort should be made to perform the biopsy on this day, though a $\pm$ 2-day window will be provided. This biopsy must occur PRIOR to the C2D1 dostarlimab infusion.
- At the completion of the protocol treatment period, participants who will receive additional neoadjuvant anti-cancer therapy prior to definitive surgery are **required** to undergo a post-treatment biopsy if clinically feasible. This biopsy may be obtained any time prior to the initiation of the additional therapy. Participants who will not go on to receive additional pre-operative therapy following the completion of the treatment period do not need to undergo a post-treatment biopsy.

Research breast core biopsies of the target lesion will be obtained from all participants. These research biopsies are mandatory. It is strongly recommended that core biopsies be image-guided. If a clip was not placed at the time of diagnostic biopsy, one should be placed at the time of the pre-treatment research biopsy.

Collection supplies for research biopsy samples will be in the research sample collection kit provided by Slope. Please see the Study Manual for detailed instructions for collection, processing, labeling and shipping of research biopsy samples.

9.3 Translational Research Blood Collection

9.3.1 ctDNA (Streck Tubes) Blood Collection

Blood will be collected for ctDNA analysis via 2 10 mL Streck tubes prior to dosing at Baseline, C2D1, C3D1, C4D1, C5D1, C6D1, and at time of treatment completion/ discontinuation.

The end of treatment sample must be collected prior to initiating any additional neoadjuvant therapy, in participants who require additional treatment prior to surgery,

Collection tubes for research blood samples will be in the research sample collection kit. Please see the Study Manual for detailed instructions for collection, processing, labeling and shipping of ctDNA samples.

9.3.2 Peripheral Blood Mononuclear cells (PBMCs) Blood Collection

Blood will be collected for PBMC analysis via 2 10 mL CPT tube prior to dosing at Baseline, C2D1, C3D1, C4D1, C5D1, C6D1, and at time of treatment completion/discontinuation.

The end of treatment sample must be collected prior to initiating any additional neoadjuvant therapy, in participants who require additional treatment prior to surgery,

Collection tubes for research blood samples will be in the research sample collection kit. Please see the Study Manual for detailed instructions for collection, processing, labeling and shipping of PBMC samples.

9.3.3 Germline DNA Blood Collection

One 10 mL Lavender top [EDTA] tube of whole blood will be collected at baseline for extraction of germline DNA. If it is missed, the sample may be drawn at any time during treatment.

Collection tubes for research blood samples will be in the research sample collection kit. Please see the Study Manual for detailed instructions for collection, processing, labeling and shipping of germline sample collection.

9.4 Surgical Specimen Sample Collection

Tumor tissue from definitive breast surgery will be submitted for all participants in the form a representative FFPE block of residual tumor. If a patient has a pCR, there will be no tumor tissue available, however pathology will still be reviewed at DFCI.

Slides and tissue block of the tumor excision should be sent to DFCI within 60 days of surgery.

Please see the Lab Manual for additional information on collection, labeling, and shipping of surgical specimens.

10. SPECIMEN BANKING

The sponsor-investigator and collaborators have approval by the TBCRC to use all research biospecimens collected during the conduct of this trial to address the research questions described in the protocol document. All future use of residual or repository specimens collected in this trial for purposes not prospectively defined will require review and approval by the TBCRC according to its established policies, whether the specimens are stored in a central site or at a local institution in a virtual repository.

Secondary use of biospecimens for new endpoints must be submitted to the TBCRC Central Office for possible review by the TBCRC Correlative Science Review Committee.

11. STUDY CALENDAR

All subjects must sign an informed consent document prior to initiation of any study related procedures. Screening laboratory evaluations may be done up to 28 days prior to the start of therapy.

For women of childbearing potential, as defined in the eligibility criteria, a pregnancy test must be completed within 14 days prior to initiating protocol therapy. If a urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Each cycle length is 3 weeks or 21 days long. There is a +/- 2-day window for study assessments, including research sample collection, and treatment administration.

Cycle/Day	Screening	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	End of Treatment ^L / Pre- Surgery	Surgery ^I	Post-Treatment Follow-up Visit ^K	5 years of Follow- Up	EDC Timepoints
Window	Within 28 days of starting therapy unless otherwise noted	+/- 2 Days	+/- 2 Days	+/- 2 Days	+/- 2 Days	+/- 2 Days	+/- 2 Days	Within 4 weeks of last therapy intervention	Completed within 6 weeks but no sooner than 2 weeks after the last dose of study medication	Within 6 weeks of definitive surgery or within 6 weeks from EOT	+/- 3 Months	
Physical exam/ clinical tumor assessment (with ECOG at baseline) ^A	X	X	X	X	X	X	X	X		X		Baseline, Cycles 1-6 Day 1, and EOT
Vital signs, weight, height ^B	X	X	X									Baseline
CBC w/diff ^C	X	X	X	X	X	X	X	X		X		Baseline, Cycles 1-6 Day 1, and EOT
Serum Chemistry ^D	X	X	X	X	X	X	X	X		X		Baseline, Cycles 1-6 Day 1, and EOT
Cortisol								X				
TSH, T3 or FT3, Free T4 ^E	X		X		X		X			X		Baseline, C2D1, C4D1, and C6D1
Coagulation (PT/PTT)	X							X				Baseline and EOT
Pregnancy Test ^F	X			X		X		X				Baseline, C3D1, C5D1, and EOT
Adverse Event Evaluation ^G	X	X	X	X	X	X	X	X		X	X ^J	Baseline, Cycles 1-6 Day 1, EOT, and Follow-up
Radiologic evaluation/Breast Imaging ^A	X							X				Baseline and Pre-surgery

Cycle/Day	Screening	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	End of Treatment ^{L/} Pre- Surgery	Surgery ^I	Post-Treatment Follow-up Visit ^K	5 years of Follow-Up	EDC Timepoints
Research blood collection (see section 9)		X	X	X	X	X	X	X			X	Baseline, C3D1, C5D1, and EOT
Research biopsy collection (see section 9) ^H	X		X					X ^H				
Research archival tissue	X								X		X	

- A. In participants who are clinically suspicious for disease progression, it is a strongly recommended that imaging be performed to confirm prior to removal from protocol therapy. The same imaging modality used at baseline should be used. If imaging confirms disease progression, protocol therapy should be discontinued, and the participant should receive a standard neoadjuvant chemotherapy regimen. These patients will remain on study in follow-up.
- B. Vital signs at screening to include heart rate, blood pressure, respiratory rate, height and weight. For the first two months of treatment, weekly in person or at-home blood pressure and heart rate will be monitored. See Section 5.5 for additional information.
- C. Labs should be obtained weekly for the first cycle (week 2 day 1 and week 3 day 1); local labs are permitted.
- D. Sodium, potassium, chloride, CO₂, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT], lactate dehydrogenase (LDH), direct bilirubin, calcium.
- E. Thyroid Function Tests are required at screening, cycle 2 day 1, and then q6 weeks.
- F. Female subjects of childbearing potential as defined in the eligibility criteria must have a serum or urine beta-hCG pregnancy test within ≤ 14 days prior to initiating protocol therapy, every 6 weeks, and within 6 weeks of last dose
- G. Adverse events will be collected until 90 days after last dose of study treatment. After completion of study treatment, AEs may be collected and assessed in person or via phone call.
- H. Every effort should be made to have the C2D1 (or week 4 day 1) biopsy occur on C2D1. C2D1 biopsy MUST occur prior to the C2D1 dostarlimab infusion. The end of treatment biopsy is required in all participants who will receive additional non-protocol anti-cancer therapy prior to surgery. The biopsy should be performed prior to initiating the subsequent therapy. See Section 9 and the study Lab Manual for additional information.
- I. Definitive surgery to be completed within 6 weeks but no sooner than 2 weeks after the last dose of study medication in participants who will not undergo additional neoadjuvant anti-cancer treatment.
- J. All participants will be followed annually for 5 years or until closure of the study (whichever is sooner), for occurrence of MDS or AML, disease recurrence, information on post-protocol therapy, and survival status. This follow-up may occur via in-person visit, phone call, or chart review. Blood and tissue collected in follow-up at time of recurrence, if applicable.
- K. Post-treatment follow-up visit to occur within 6 weeks of definitive surgery, including patients who had additional pre-operative anti-cancer treatment. In the event a patient does not undergo definitive surgery post-treatment follow-up visit to occur within 6 weeks from EOT.
- L. For patients needing additional neoadjuvant treatment, EOT is to occur within 4 weeks prior to initiating additional pre-op anti-cancer treatment

12. MEASUREMENT OF EFFECT

12.1 Target Lesions

A baseline imaging study of the breast is required; ultrasound, mammogram, or MRI may be pursued at the discretion of the treating investigator. The baseline imaging must be obtained within 28 days of beginning therapy. Imaging is also required at the completion of protocol therapy and should occur within 28 days of the last dose of protocol therapy and must occur prior to surgery. All efforts should be made to use the same imaging modality at baseline and after completion of protocol therapy.

In the event of multifocal or multicentric disease in the breast, the treating investigator must determine which will represent the target lesion. This should remain consistent throughout the study. The target lesion should be selected on the basis of its size (lesion with the longest diameter) and suitability for accurate repetitive measurements (either by imaging techniques or clinically).

12.2 Pathologic Response

The residual cancer burden (RCB) method as described by Symmans et al.¹⁶ will be used to assess response. RCB 0/I will be considered good response; RCB II/III will be considered poor response. RCB0 will be considered pCR. Pathologic complete response in the lymph nodes is defined as no detectable invasive tumor by H&E. All patients with significant residual disease who proceed to alternative therapy will be considered to belong to the poor response group.

RCB is determined from: bidimensional diameters of the primary tumor bed in the resection specimen (d1 and d2), the proportion of the containing metastatic carcinoma (LN), and the diameter of the largest metastasis in an axillary lymph node. Largest bidimensional measurements of the residual primary tumor bed are recorded from the macroscopic description in the pathology report and confirmed after review of corresponding slides. If multiple tumors are present, the dimensions of the largest are recorded. Bidimensional measurements of the primary tumor bed (millimeters) are combined as follows: The proportion of invasive carcinoma (finv) within the cross-sectional area of the primary tumor bed is estimated from the overall percent area of carcinoma (%CA) and then corrected for the component of *in situ* carcinoma (%CIS): $\text{finv} = (1 - (\% \text{CIS}/100)) \times (\% \text{CA}/100)$. The transformed terms are then scaled to match the 95th percentiles of their respective distributions, and added to define the RCB index¹⁶. RCB score can be calculated using the following tool:

<http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3>

13. DATA REPORTING / REGULATORY REQUIREMENTS

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

13.1 Data Reporting

13.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

13.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

13.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the sponsor-investigator, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13.3 Multicenter Guidelines

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the sponsor-investigator, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in **Appendix B**.

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

- Each participating institution will order the study agent(s) directly from GSK. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

13.4 Protocol Review and Amendments

Unless otherwise specified, each participating institution must obtain its own IRB approval. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The participating site IRB should approve the consent form and protocol within 90 days of receipt from the sponsor.

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to implementation.

The Protocol Chair (or his designee) is responsible for the coordination and development of all protocol amendments and will disseminate this information to the participating centers.

13.5 Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.6 Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

13.7 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, <http://www.clinicaltrials.gov>.

Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

13.8 Collaborative Research and Future Use of Data and Biospecimens

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

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

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

centers who have received special permission to review de-identified data.

13.9 Reporting to the NCI

As a provision of funding from the NCI under the Dana-Farber Cancer Institute Breast Cancer SPORE, the NCI will be notified should there be any temporary or permanent suspension of the trial. This notification will be inclusive of any actions taken by the FDA, institutional IRB, institutional PI, or commercial sponsor. Additionally, any major changes in the scope or aims of the study that would affect the objectives of the funding grant will be communicated to the NCI.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

This is an open label, randomized phase II study examining niraparib with the PD1-antibody dostarlimab in the neoadjuvant treatment of *BRCA*-mutated or *PALB2*-mutated breast cancer. Participants will be randomized 1:1 to receive either treatment with the combination (**Arm A**), or a 3-week lead-in of niraparib as monotherapy followed by treatment with the combination (**Arm B**). An additional small exploratory cohort of participants with ER-positive breast cancer will be enrolled to **Arm C**.

Descriptive statistics will be used to summarize the distribution of TILs observed at baseline and after 3 weeks of therapy (e.g. mean, standard deviation, median, and inter-quartile range) in cohorts of TNBC and ER+/HER2- BC. The number and proportion of participants achieving pCR among all participants who initiate protocol therapy will be summarized with a two-sided 90% exact confidence interval. Patients who do not undergo surgery are considered non-pCR.

The primary evaluation of change in TILs within each arm will be based on a Wilcoxon signed rank test (absolute difference) using a one-sided alpha = 0.05 for each arm. The ADAPT study from Liedke et al shows that in TNBC patients treated with neoadjuvant chemotherapy (NACT), the TIL measurements at baseline (N=323) and after 3 weeks of therapy (N=226) were 29.5% (standard deviation: 24.4%) and 38.4% (standard deviation: 27.9), respectively. In paired measurements, the mean change from baseline to 3 weeks was 31%. We propose that if the average increase in TILs is 30% after 3 weeks of the neoadjuvant therapy, then the therapy is considered effective in influencing TILs. With 20 evaluable paired specimens anticipated per arm, there will be 96% power to detect an increase in TILs of 30% under an assumption of an additive shift model with a Gaussian common density function, when the standard deviation is as high as 37.5. For the exploratory analysis in ER+/HER2- BC, variability in change in TILs is unknown, but with at least 14 evaluable pairs there will be 86.1% power to detect the same effectsize (0.8 standardized units) in change in TILs.

With a 12% assay failure rate for paired specimen anticipated, a total sample size of n = 46 TNBC patients will be targeted.

For TNBC patients (Arms A and B), a two-stage binomial exact test using a one-sided Type I error alpha of 0.05 will be used to evaluate the pCR rate in all participants who initiate protocol therapy. Patients who do not undergo surgery are considered non-pCR. The pCR rate for patients receiving

preoperative chemotherapy for TNBC based on prior studies ranges from 20- 40%, depending on the regimen (Tung et al JCO 2020, Mayer et al Ann Oncol 2020, Sikov et al JCO 2014). We therefore propose that if the proportion of participants experiencing pCR is less than 30% (null hypothesis) then the 18-weeks of neoadjuvant therapy is considered minimally effective. We will conduct an interim analysis for futility when approximately 50% of TNBC patients have been enrolled and 18 (39%) have completed surgery to allow for assessment of the pCR rate. If 4 or more patients have a pCR, we will continue to stage 2 of the study. There is a 50.1% probability of stopping the trial early if the pCR rate is 20% and a 16.5% probability of stopping the trial early if the pCR rate is 30%. With total targeted sample size of 46, if there are 20 or more complete responses ($\geq 43\%$), the regimen will be declared worthy of further study. In a previous study (Litton et al JCO 2019), six months of preoperative monotherapy with a PARP inhibitor in 14 patients with gBRCA-positive triple negative disease and pathologic response outcome data showed a 53% rate of pCR. Our study differs in that (1) we will be reducing the duration of PARP inhibitor therapy to 18 weeks but (2) the addition of the PD1-antibody. Hence, we set our target to be a pathologic complete response rate of 50% and if it is met, there is 84.9% power to reject the null hypothesis at the end of the study.

For ER+/HER2- BC patients, the analysis of pCR will be exploratory and estimation-only, and reported with a two-sided exact 90% confidence interval. The table below demonstrates the level of precision for n = 19 evaluable patients.

Table 4: Level of Precision for n = 19 Evaluable Patients					
Observed pCRs; n (%)	0	2 (11%)	4 (22%)	6 (33%)	8 (44%)
90% Conf. Int,	(0 – 15%)	(2% - 31%)	(8% - 44%)	(16% - 55%)	(24% – 66%)

Within each arm, the association between changes in TILs and pCR will be evaluated using a two-sample Wilcoxon rank sum test, and the log odds ratio for a fixed change in TILs will be estimated using a simple logistic regression model.

The rate of RCB 0/1 response with preoperative combined niraparib and PD-1 blockade in patients with early stage TNBC (Arm A and B) and ER-positive HER2-negative breast cancer (Arm C) with *BRCA*-mutations or *PALB2*-mutated will be estimated and the associated two-sided 90% exact confidence interval will be reported.

14.2 Sample Size and Study Duration

A total of 66 participants will be accrued, 23 evaluable participants to Arm A, 23 evaluable participants to Arm B, and 19 participants to Arm C. The total study enrollment period is estimated to be approximately 3years.

14.3 Safety

The maximum grade of each adverse event (AE) type will be summarized as frequency (and %) of patients experiencing the AE, tabulated according to body system and AE type, separately according to study arm. The summaries may be without regard to relation and in the subset considered as related to study treatment(s).

Supplemental Safety Monitoring

In addition to regular reporting of AEs to the DSMB, sequential boundaries will be used to monitor safety of patients receiving niraparib with the PD1-antibody dostarlimab in case of unexpectedly high AEs, providing guidance to pause enrollment for further safety review if excessive numbers of these AEs are observed. The safety-evaluable population will include all patients across the three arms, for whom AEs of at least the first cycle of protocol therapy have been recorded in the database or an SAE has been reported.

The criteria are defined such that the probability of pausing is 0.05 if the true rate of these AEs is 25%, and the probabilities of pausing are 0.18, 0.72 or 0.98 if the true rates are 30%, 40% or 50%.¹⁹ The table below gives the criteria for pausing enrollment in order to more fully evaluate safety.

Criteria for pausing enrollment because of AEs to more fully evaluate safety, for sample size up to 66 patients (pause if the number of toxicities is equal to or exceeds (i.e. $\geq$) the boundary).

N pts in safety-eval. population	4	5-6	7-9	10-11	12-14	15-16	17-19	20-22	23-25
Boundary	4	5	6	7	8	9	10	11	12
N pts in safety-eval. population	26-28	29-31	32-34	35-36	37-40	41-43	44-46	47-49	50-52
Boundary	13	14	15	16	17	18	19	20	21
N pts in safety-eval. population	53-55	56-58	59-61	62-66					
Boundary	22	23	24	25					

15. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

It is understood that any manuscript or releases resulting from the collaborative research must be approved by the Protocol Chair and will be circulated to applicable participating sites/investigators prior to submission for publication or presentation.

Additionally, any publication of study data and results must conform to the publications policy as stated in Translational Breast Cancer Research Consortium's (TBCRC) "Policies and Procedures".

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (<i>e.g.</i> , light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B MULTICENTER DATA AND SAFETY MONITORING PLAN

INTRODUCTION

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

1.1 Purpose

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

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

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

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

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

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

Coordinating Center: The entity (i.e., Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc.) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in

applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

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

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

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1 DF/HCC Sponsor

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

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

2.2 Coordinating Center

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

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

2.3 External Site

A External Sites is an institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC investigator. The External Sites acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Sites is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document.

The general responsibilities for each External Site may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their IRB of record. For studies under a single IRB, the Coordinating Center will facilitate any study-wide submissions.
- Maintain regulatory files as per ICH GCP and federal requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e., teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.

- Submit Serious Adverse Event (SAE) reports to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to the Sponsor, Coordinating Center, and IRB of record as applicable.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.
- Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

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

3.2 Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** External sites will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.
- **Revisions for life-threatening causes:** External Sites will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.
- **Protocol closures and temporary holds:** External Sites will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

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

External Sites must send their version of the informed consent document to the Coordinating Center for sponsor review and approval. If the HIPAA authorization is a separate document, please submit to the sponsor for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In these cases, the approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites must follow the DF/HCC requirement that only attending physicians obtain initial informed consent and any re-consent that requires a full revised consent form.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

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

3.5 IRB Re-Approval

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

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

3.6 Participant Confidentiality and Authorization Statement

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

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

the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

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

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

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

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

Please refer to Protocol Section 4 for participant registration information. Treatment cannot begin until site has received confirmation that participant has been registered with DF/HCC CTMS.

3.7.2 Initiation of Therapy

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

3.7.3 Eligibility Exceptions

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

3.8 DF/HCC Protocol Case Number

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

3.8.1 Protocol Deviations, Exceptions and Violations

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

3.8.2 Definitions

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

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

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

3.8.3 Reporting Procedures

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

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

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

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

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

3.9 Safety Assessments and Toxicity Monitoring

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

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

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

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol Section 7.3.

External sites must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the [DFCI IRB Adverse Event Reporting Policy](#).

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

3.9.2 Guidelines for Processing IND Safety Reports

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

3.10 Data Management

DF/HCC develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC RIO provides a web based training for all eCRF users.

3.10.1 Data Forms Review

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

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

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

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

4. REQUISITIONING INVESTIGATIONAL DRUG

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

External sites should order their own agent regardless of the supplier.

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

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

5. MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

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

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

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

On-Site Monitoring: On-site monitoring will occur on an as-needed basis. External Sites will be required to provide access to participants’ complete medical record and source documents for source

documentation verification during the visit. In addition, External Sites should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the External Site. On-site monitoring visits can be substituted with remote (virtual) monitoring visits at the discretion of the Principal Investigator.

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

5.2 Monitoring Reports

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

5.3 Accrual Monitoring

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

A minimum of 3 participants per site annually is recommended for Phase II trials. However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site/annually should be a minimum target for each site.

6. AUDITING: QUALITY ASSURANCE

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

6.1 DF/HCC Internal Audits

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

6.2 Audit Notifications

It is the External Site's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

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

6.4 External Site Performance

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

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.

APPENDIX C SAE COVERSHEET

URGENT	Central Safety Department Clinical SAE, Pregnancy & Incidents Coversheet (For Oncology ISS Use Only)													
⇄ Date GSK Staff or CRO received report: _____ ⇄ Study Type: Investigator-Sponsored Study To: Central Safety Case Management Group: Global CMG (UK) Email: OAX37649@gsk.com Fax: +44(0) 20 8754 7822 CC: external.research@gsk.com														
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%;">Date Sent: _____</td> <td style="width: 50%;"># of Pages Sent Including Coversheet: _____</td> </tr> <tr> <td>From: _____</td> <td>Investigator Telephone No. : _____</td> </tr> <tr> <td>Country: _____</td> <td>Investigator Fax No.: _____</td> </tr> <tr> <td>cc: _____</td> <td>cc Fax No.: _____</td> </tr> <tr> <td colspan="2">Country of Reporter, if different from above: _____</td> </tr> <tr> <td colspan="2">Follow up Contact Name and Email address: _____</td> </tr> </table>			Date Sent: _____	# of Pages Sent Including Coversheet: _____	From: _____	Investigator Telephone No. : _____	Country: _____	Investigator Fax No.: _____	cc: _____	cc Fax No.: _____	Country of Reporter, if different from above: _____		Follow up Contact Name and Email address: _____	
Date Sent: _____	# of Pages Sent Including Coversheet: _____													
From: _____	Investigator Telephone No. : _____													
Country: _____	Investigator Fax No.: _____													
cc: _____	cc Fax No.: _____													
Country of Reporter, if different from above: _____														
Follow up Contact Name and Email address: _____														
Report type: Initial ☐ Follow-up ☐ Protocol Name: (or Named Patient): _____ Subject No. : _____ Sponsor Investigator: _____														
Comments (e.g. missing fields etc.): _____ _____ _____														

APPENDIX D NIRAPARIB DRUG DIARY

STUDY PARTICIPANT SELF_ADMINISTERED DIARY: NIRAPARIB

PATIENT INSTRUCTIONS:

- Take your medications exactly as prescribed by your doctor. See the next page for specific dose for the medication that you are taking on this study.
- Keep Niraparib capsules in the bottle(s) provided and do not transfer them to any other container. Store at room temperature.
- Niraparib should be taken by mouth once per day at approximately the same time every day with a glass of water or other beverage.
- Niraparib can be taken with or without food
- Capsules must be swallowed whole. Do not chew, crush, dissolve or divide.
- If a dose is missed for any reason and it is less than 12 hours from usual time of dosing, then you may take that dose. If it is more than 12 hours after the dose time, the missed dose should be skipped and NOT taken. You should resume regular dosing at the next scheduled time. If you miss a dose, record “0” for Number Taken on the next page.
- **Missed, held or vomited doses will not be made up.**
- You may not receive live virus and/or bacterial vaccines while on study treatment
- Bring any unused study drug, all empty containers, and drug diary to next clinic visit.

FOR CLINIC USE ONLY:	
Provide one diary per cycle	
Complete patient identifiers and medical team contact information	
When patient returns pill bottles and diary, perform a pill count and record adherence information in the box to the right OR in the patient record.	
Date Dispensed:	Date Returned:
# capsules dispensed:	# capsules returned:
# capsules that should have been taken:	
Discrepancy Notes:	
Staff initials and date (after review of completed diary):	

STUDY PARTICIPANT SELF-ADMINISTERED DIARY: NIRAPARIB

Participant Name/Identifier: _____ Cycle #: _____
Your MD: _____ Phone: _____
Your RN: _____ Phone: _____

NIRAPARIB INSTRUCTIONS

How much: Your dose is: _____

When: Take each dose once per day at the same time each day.

Record the date, time, and number of tablets taken in the chart below after each dose every day.

Day	Date	Time (specify am/ pm)	Number of Capsules	Comments
<i>Example</i>	2/10/2020	8:15 am	2	
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				
Complete with the study staff when the diary is collected/returned:			Patient initials: _____	
			Date: _____	

APPENDIX E BLOOD PRESSURE AND HEART RATE DIARY

STUDY PARTICIPANT SELF-ADMINISTERED DIARY: HEART RATE AND BLOOD PRESSURE

Participant Name/Identifier: _____ Cycle #: _____
Your MD: _____ Phone: _____
Your RN: _____ Phone: _____

PATIENT INSTRUCTIONS:

1. When taking your blood pressure reading, sit with your back straight and supported, feet flat on the floor and your arm supported at heart level. Place the cuff on your arm directly above the bend of the elbow. Sit still for **five (5) minutes** before taking a measurement.
2. Your blood pressure readings have two numbers. The **first number** is the pressure in your blood vessels during a heartbeat (systolic), and the **second number** is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, normal blood pressure is 120/80).
3. Your heart rate is the number of times your heart is beating in a minute
4. Record the date, then record your blood pressure and heart rate using the provided blood pressure monitor once a week.
5. If your systolic pressure is **greater than 140** **OR** your diastolic blood pressure is **greater than 90**, or if you develop symptoms possibly related to high blood pressure (headache, visual disturbances, etc.) **please contact your clinical care team for instructions.**

Please bring this form to every clinic visit or appointment.

Week	Date	BP reading (systolic/diastolic)	Heart rate reading (beats per minute)	Comments
<i>example</i>	<i>1/1/2022</i>	<i>120 / 80</i>	<i>74</i>	
1		/		
2		/		
3		/		
Complete with the study staff when the diary is collected/returned:			Patient initials: _____ Date: _____	