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TITLE: A Phase II Study of niraparib and dostarlimab with radiation in patients with metastatic pancreatic cancer

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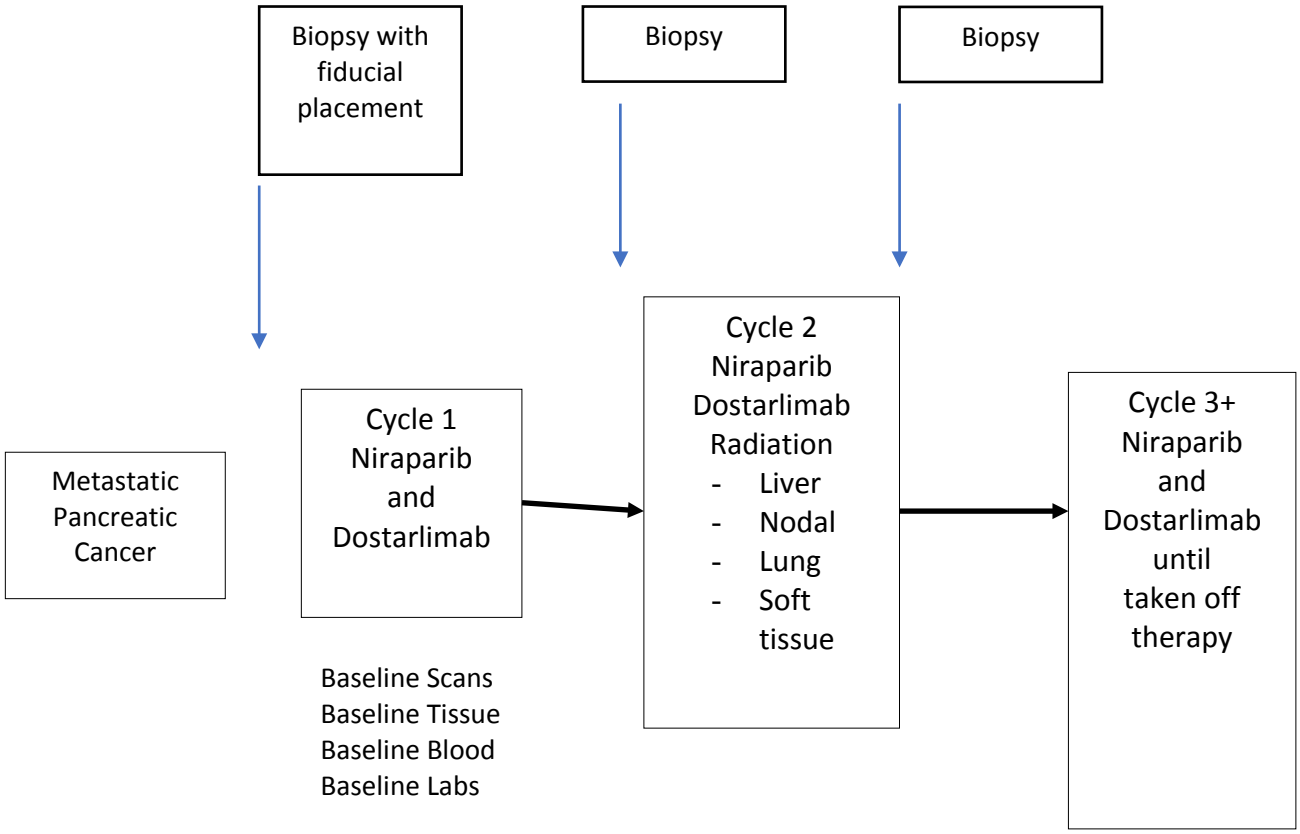
SCHEMA


Biopsy with fiducial placement
Biopsy
Biopsy
Metastatic Pancreatic Cancer
Cycle 1 Niraparib and Dostarlimab
Baseline Scans
Baseline Tissue
Baseline Blood
Baseline Labs
Cycle 2 Niraparib Dostarlimab Radiation
- Liver
- Nodal
- Lung
- Soft tissue
Cycle 3+ Niraparib and Dostarlimab until taken off therapy

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1. OBJECTIVES

1.1 Study Design

This two-stage single arm phase II trial will evaluate the efficacy of niraparib with dostarlimab and radiation therapy in patients with metastatic pancreatic cancer

1.2 Primary Objective

- To estimate the disease control rate of the combination of niraparib and dostarlimab with radiation in patients with metastatic pancreatic cancer by RECIST 1.1

1.3 Secondary Objectives

- To estimate the disease control rate of the combination of niraparib and dostarlimab with radiation in patients with metastatic pancreatic cancer by irRECIST
- To estimate progression-free survival in patients with metastatic pancreatic cancer treated with niraparib and dostarlimab with radiation
- To estimate overall survival in patients with metastatic pancreatic cancer treated with niraparib and dostarlimab with radiation
- To describe toxicity of niraparib and dostarlimab with radiation in patients with metastatic pancreatic cancer

1.4 Exploratory Objective

- To explore the potential synergistic effect of anti-PD1 and PARP inhibition with radiation using multiplexed immune IF and RNAseq, to assess the change in immune microenvironment between pre-treatment, post anti-PDI/PARP and post radiation biopsies
- To monitor response and define mechanisms of resistance to anti-PD1 and PARP inhibition with radiation using serial cfDNA analyses.
- Assess the relationship between MSI status and clinical outcomes.
- Assess patients' symptom burden and quality of life by combining objective endpoints with subjective patient reported outcomes.

2. BACKGROUND

2.1 Study Disease

Pancreatic cancer was the third leading cause of death from cancer in the United States in 2017 (Siegel 2017). The 5-year relative survival rate is a dismal 8% with most patients presenting with metastatic disease and treatment options limited to chemotherapy with median OS between 8.5-

11.1 months with one line of chemotherapy (Conroy 2011, Von Hoff 2013).

The homologous recombination repair (HRR) pathway is an important pathway in tumor biology allowing cancer cells a mechanism to resist damage by treatment modalities such a chemotherapy and radiotherapy. PARP enzymes are needed to repair DNA single strand breaks and inhibition of PARP enzymes leads to persistence of single strand breaks that will then become double stranded breaks, which are more problematic during DNA replication. During the process of repair, these breaks may be repaired by functioning HRR pathway proteins. Proteins such as BRCA1 and BRCA2 are required for repair of these double stranded DNA breaks through the HHR pathway (Curtin, 2012). Tumors with HR deficiency, such as those with mutant BRCA1 and BRCA2, have an impaired ability to repair themselves and are susceptible to PARP inhibition. PARP helps repair damaged DNA and blocking PARP may prevent cancer cells from repairing. Besides inducing cell-intrinsic apoptosis, recent studies have demonstrated that PARP inhibitors have immunoregulatory effects in the tumor microenvironment, which may enhance the sensitivity to immunotherapy (Huang, 2015). PARP inhibitors have been shown to have activity as monotherapy in tumors with existing DNA repair defects such as BRCA1 and BRCA2 and in combination therapy with chemotherapy, which induces DNA damage in ovarian cancer (Matulonis 2017, 2016). Ionizing radiation is also a known way to induce DNA breaks and there is ongoing work suggesting that PARP inhibitors may be used for radio sensitization.

Though the BRCA genes may be the most well-described genes involved with homologous repair, there are several other genes and their associated proteins such as ATM, CHK2, ATR, PALB and other Fanconi genes that are involved with DNA damage response and are mutated in many cancers and may expand the therapeutic potential for PARP inhibitors. A prospective characterization of pancreatic ductal adenocarcinoma (PDAC) patients found germline BRCA mutations in nearly 5% of patients; that is consistent with other data (Holter, 2015). In addition to germline mutations, there can be somatic mutations in the HRD pathway. A study by Waddell, et. al. identified germline and somatic mutations in eight other DNA-damage repair pathways in pancreatic cancer. They also demonstrated that patients with these mutations were more likely to have unstable patterns of genomic structural variation further suggesting expansion of the patient pool (Waddell, 2015). However, independent of HR defects, there is emerging clinical evidence that the combination of PARP inhibitors and anti-PD1 therapy may have activity in solid tumors with the ability to potentiate neoantigen production as one hypothesis. Inhibiting the DDR pathway in combination therapy is being explored in many solid tumors (Brown 2017). Given the immunomodulatory and radio-sensitizing effects of PARP inhibitors, we propose a combination of niraparib and dostarlimab with radiation. This may induce a synergistic anti-neoplastic effect, thus providing an opportunity for the expanded use of PARP inhibitors and immunothearpy in pancreatic cancers.

2.2 Niraparib

Niraparib is an orally available, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, with activity against PARP-1 and PARP-2 deoxyribonucleic acid (DNA)-repair polymerases (Jones 2015). Niraparib is being investigated for the treatment of ovarian, breast, and prostate tumors in patients with DNA-repair anomalies.

Phase 1 Study of Niraparib Monotherapy in Advanced Solid Tumors

Clinical activity data for niraparib administered as monotherapy in patients with ovarian cancer are available from 1 early-phase clinical study. In Parts A and B of the Phase 1 study PN001 (ClinicalTrials.gov identifiers: MK-4827-001 and 2008_501), 100 patients with advanced solid tumors who had received a median of 3 prior therapies were enrolled; 49 patients had ovarian cancer (13 platinum-sensitive, 35 platinum-resistant, and 1 platinum-refractory).[11] An additional 4 patients were enrolled in Part D of the study, which assessed pharmacokinetics only.[60]

The most common nonhematological TEAEs were nausea, fatigue, anorexia, constipation, vomiting, and insomnia. These TEAEs were mainly mild to moderate in severity, self-limiting, and manageable with standard treatments. Hematological toxicity appeared to be dose proportional and most frequently arose in the setting of cumulative doses. Anemia was reported in 48 (48%) of 100 patients and was Grade ≥3 in 10 (10%) of 100 patients. Thrombocytopenia was less common (35 [35%] of 100 patients) and was Grade ≥3 in 15 (15%) of 100 patients. Neutropenia was the least commonly reported (24 [24%] of 100 patients), and was Grade 3 in 4 (4%) of 100 patients at niraparib doses of 300 and 400 mg. In all cases, hematological TEAEs were uncomplicated and reversible. Twenty patients required dose reductions (usually by 1 dose level) for recurrent anemia or thrombocytopenia. Treatment was discontinued due to AEs in 7 patients, including the 4 patients who had DLTs during the first cycle and 3 patients who had Grade 3 vomiting, Grade 2 prolongation of QT interval, and Grade 3 prolongation of QT interval. No treatment-related deaths occurred.

Of the 49 patients, 22 had confirmed *BRCA1* or *BRCA2* mutation, of whom 20 were radiologically assessable. Eight (40%) of these 20 patients achieved a confirmed partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) and cancer antigen 125 (CA-125) Gynecologic Cancer Intergroup criteria at doses ranging from 80 to 400 mg per day. Median response duration was 387 days (range: 159 to 518 days). Three (33%) of 9 patients with platinum-resistant *BRCA*mut ovarian cancer had PR by RECIST and CA-125 criteria. In patients with platinum-sensitive disease, 5 (50%) of 10 patients (95% CI: 19 to 81) with BRCA1 or BRCA2 mutations had RECIST and CA-125 responses.

Phase 3 Study of Niraparib Monotherapy in Platinum-sensitive, Recurrent Ovarian Cancer

In the randomized, double-blind, Phase 3 NOVA trial (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer), a total of 553 patients were randomized at 107 centers worldwide. Patients were categorized according to the presence or absence of a g*BRCA*mut (g*BRCA* cohort and non-g*BRCA* cohort) within their tumors and the type of non-g*BRCA*mut and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily (QD). The primary end point was PFS. The study enrolled 203 patients in the g*BRCA*mut cohort and 350 patients in the non-g*BRCA*mut cohort. Among the 350 patients in the non-g*BRCA*mut cohort, 162 had tumors that were identified as homologous recombination deficiency positive (HRDpos), and 134 had tumors that were HRD negative (HRDneg). HRD status was not determined for 54 patients.

Demographic and baseline characteristics were well balanced. Table 1 below shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (ie, g*BRCA*mut cohort, HRDpos cohort, and overall non-g*BRCA*mut cohort). In addition, median PFS in patients with HRDneg tumors was 6.9 months (95% confidence interval [CI]: 5.6, 9.6) in the niraparib

arm, versus 3.8 months (95% CI: 3.7, 5.6) in the placebo arm, with a HR of 0.58 (95% CI: 0.361, 0.922) (p = 0.0226).

Table 1: Progression-Free Survival in Ovarian Cancer Patients in NOVA

	gBRCAmut Cohort		Non-gBRCAmut Cohort (Regardless of HRD Status)		HRDpos (Within non-gBRCAmut Cohort)	
	Niraparib (n = 138)	Placebo (n = 65)	Niraparib (n = 234)	Placebo (n = 116)	Niraparib (n = 106)	Placebo (n = 56)
Median PFS (95% CI)[(i)]	21.0 (12.9, NE)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value[(ii)]	< 0.0001		< 0.0001		< 0.0001	
HR (niraparib: placebo) (95% CI)[(iii)]	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	

Source: PR-30-5011-C (NOVA main) CSR
Abbreviation: CI = confidence interval; CSR = clinical study report; gBRCAmut = germline BRCA mutation; HR = hazard ratio; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; NE = not evaluated; PFS = progression-free survival.
[a] PFS is defined as the time in months from the date of randomization to progression or death.
[b] Based on stratified log-rank test using randomization stratification factors.
[c] Based on the stratified Cox proportional hazards model using randomization stratification factors.

The primary data to support the safety of treatment with niraparib are derived from the NOVA main study in which a total of 546 patients received study treatment.

All 367 patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). The high rate of TEAEs in the placebo group indicates the burden of prior chemotherapy and the patient's underlying ovarian cancer. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*mut and non-g*BRCA*mut cohorts. In the overall safety population, for the niraparib versus placebo treatment arms, the incidences of Grade 3 or 4 TEAEs (74% vs. 23%), serious adverse events (SAEs) (30% vs. 15%), TEAEs leading to treatment interruption (67% vs. 15%), TEAEs leading to dose reduction (69% vs. 5%), and TEAEs leading to treatment discontinuation (15% vs. 2%) were higher for niraparib than for placebo. There were no on-treatment deaths reported.

The most commonly observed nonhematologic TEAEs (all grades) observed in niraparib-treated compared with placebo-treated patients were nausea (74% vs. 35%), fatigue (46% vs. 32%), constipation (40% vs. 20%), and vomiting (34% vs. 16%). The majority of the nonhematological TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (all grades) of niraparib were anemia (49%), thrombocytopenia (46%), decreased platelet count (20%), and neutropenia (18%). Although Grade 3 or 4 hematologic laboratory AEs were common at the initiation of study treatment, no severe clinical sequelae were observed, and relatively few patients discontinued study treatment due to these AEs. Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these AEs beyond Cycle 3, indicating the overall effectiveness of the approach to dose modification. These

TEAEs can be monitored routinely using standard assessments of hematological laboratory parameters, as is routine for patients with ovarian cancer receiving anticancer therapies. In the NOVA study, niraparib dose adjustment tended to occur early with most patients reaching their individual adjusted dose level at the end of Month 3 (ie, Cycle 3) of treatment.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib. In the Phase 3 NOVA study, the incidence of MDS/AML in patients who received niraparib (5 of 367; 1.4%) was similar to its incidence in patients who received placebo (2 of 179; 1.1%). Guidance on monitoring patients for new AEs of MDS/AML and the follow-up of patients with suspected MDS/AML is provided.

Study PR-30-5011-C1 (NOVA corrected QT interval [QTc] substudy; n = 26) is an open-label evaluation of the effects of niraparib on QTc measurements in patients with histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. There were no reports of clinically significant abnormal electrocardiogram (ECG) changes, including QTc interval prolongation, attributed to niraparib. Administration of niraparib at the therapeutic dose did not prolong the QT interval. There was no correlation between the exposure level (i.e., plasma concentration) of niraparib and QTc changes (i.e., change in corrected QT interval calculated using Frederica's formula [ΔQTcF]).

Baseline Platelet Count and Weight as Predictors of Thrombocytopenia.

An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase I study, PN001. This analysis determined that baseline platelets had an impact on platelet nadir; lower baseline platelets (<180 10^9/L) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76%) or Grade ≥ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, Grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24%) compared to patients in the highest quartile (10%).

The potential relationship between body weight and TEAEs was further explored in an analysis to evaluate the correlation of grade 3 or 4 thrombocytopenia and baseline body weight. The lowest platelet count in the first 30 days was plotted versus baseline body weight to determine if low body weight identified a subgroup of patients with higher levels of thrombocytopenia during Cycle 1. In the first 30 days of treatment, a baseline body weight ≥77 kg is associated with a lower incidence of grade 3 or 4 thrombocytopenia (14%) relative to the group with body weight <58 kg (43%).

Finally, a classification tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing ≥Grade 3 thrombocytopenia within 30 days after the first dose of niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg **or** baseline platelet count <150,000 µL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of patients with a body weight >77 kg **and** a platelet count >150,000 µL. Further, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000 µL, and was only 206 mg for patients with body weight < 77 kg or platelet count <150,000 µL. Thus, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. These observations are to be confirmed in the present study with the inclusion of study treatment dosed at 200 mg (2 capsules of niraparib or placebo) in patients whose baseline weight is <77 kg or baseline platelet count is <150,000 µL.

2.3 Dostarlimab

Dostarlimab (TSR-042) is an IgG4-k humanized monoclonal antibody that binds with high affinity to PD-1 resulting in inhibition of binding to PD-L1 and PD-L2. This antibody was generated based on a proprietary platform that utilizes affinity maturation to select antibodies with desired functional characteristics. The functional antagonist activity of dostarlimab was confirmed in a mixed lymphocyte reaction (MLR) demonstrating enhanced interleukin-2 production upon addition of dostarlimab. Furthermore, dostarlimab has an acceptable safety profile based on toxicology studies in cynomolgus monkeys. Based on the dostarlimab preclinical data, dostarlimab is expected to result in similar clinical benefit in patients with a variety of tumors with results similar to antibodies of the same class (nivolumab and pembrolizumab) and thus dostarlimab is being evaluated clinically as an immunotherapy for advanced malignancies.

Clinical Experience

As of the clinical cutoff date of 21 January 2020 there were 4 ongoing Phase 1 studies, 3 ongoing Phase 2 studies, and 2 ongoing Phase 3 studies with dosarlimab. Study 4010-01-001 is a first-in-human study of dostarlimab to evaluate the safety and tolerability, PK, PDy, and clinical activity of dostarlimab in subjects with recurrent or advanced solid tumors. Dose escalation in Part 1 of the study continued to a maximally administered dose of 10 mg/kg Q2W and a MTD was not identified. No DLTs were observed in Part 1. Following completion of Part 1, Part 2A evaluated safety and tolerability of dostarlimab at 2 fixed dosing schedules of 500 mg Q3W and 1,000 mg Q6W. No DLTs were observed in Part 2A.

Dostarlimab Monotherapy

Study 4010-01-001 is an ongoing, first-in-human Phase 1 study of dostarlimab to evaluate the safety and tolerability, PK, pharmacodynamics (PDy), and clinical activity of dostarlimab in patients with recurrent or advanced solid tumors. A total of 21 subjects were dosed in the dose escalation phase of the study (Part 1). Dose escalation continued to a maximally administered dose of 10 mg/kg every 2 weeks (Q2W) and a maximum tolerated dose (MTD) was not

identified. No dose-limiting toxicities (DLTs) were observed. The PK of dostarlimab were dose-proportional across the dose range tested. Receptor occupancy was measured by direct binding of dostarlimab to PD-1 on T cells from subjects participating in Part 1 and by the dostarlimab-induced inhibition of interleukin-2 (IL-2) production after ex vivo stimulation of T cells from subjects participating in Part 1. Maximal receptor occupancy was achieved at all doses tested down to dostarlimab plasma concentrations as low as 2.435 µg/mL, and was maintained for approximately 29 days. The PK/PDy data was used to determine the flat dosing tested in Part 2A of the study. In this phase of the study, the safety and tolerability of dostarlimab was evaluated at 2 fixed dosing schedules: 500 mg every 3 weeks (Q3W) and 1,000 mg every 6 weeks (Q6W). No DLTs were observed in Part 2A. The recommended Phase 2 dose (RP2D) regimen was determined to be 500 mg Q3W for 4 cycles followed by 1,000 mg Q6W for all cycles thereafter, which is being evaluated in expansion cohorts for microsatellite instability-high (MSI-H) and microsatellite stable (MSS) endometrial cancer, non-small cell lung cancer (NSCLC), and non-endometrial MSI-H or polymerase ε-mutated cancer in Part 2B of study. The PK/PDy profile of subjects participating in Part 2B of the study was similar to that of subjects participating in Part 2A of the study.

Overall TEAEs in subjects who received dostarlimab monotherapy are summarized in Table 10. As of the data cutoff date, 527 subjects (98.5%) who were treated with dostarlimab monotherapy reported at least 1 TEAE. The overall incidence of subjects with study drug-related TEAEs was 67.5% (n=361). The majority of study drug-related TEAEs had a severity of Grade 1 or 2. Study drug-related TEAEs of ≥Grade ≥3 were reported in 70 subjects (13.1%). Serious TEAEs were reported in 205 subjects (38.3%), and 39 subjects (7.3%) had serious TEAEs assessed to be study drug-related (definitely related, related, or possibly related) by investigators. Forty-eight subjects (9.0%) discontinued study drug due to a TEAE. TEAEs leading to study drug discontinuation were assessed as study drug-related by the investigator for 25 subjects (4.7%). Sixteen subjects (3.0%) had a TEAEs leading to death; none were assessed as study drug-related by the investigator.

The most commonly reported TEAEs (>20%) with dostarlimab monotherapy were fatigue (25.6%), nausea (24.9%), anaemia (23.6%), and diarrhoea (21.5%). The majority of the ≥Grade 3 events occurred in 2% of subjects or less each, with the exception of anaemia (8.6%), dyspnoea (3.7%), abdominal pain (3.4%), fatigue (2.8%), hyponatraemia (2.8%), and pulmonary embolism (2.4%). The TEAEs occurring in at least 10% of subjects receiving dostarlimab monotherapy were generally considered not to be related to the study drug (ie, < 50% of TEAEs were related). Exceptions were the events of fatigue, pruritus, diarrhoea, fatigue, asthenia, and arthralgia: > 50% of these events were considered to be study drug-related.

As of July 2017, 32 of 34 subjects treated with dostarlimab monotherapy in Part 1 and Part 2A of Study 4010-01-001 had at least 1 post-baseline tumor assessment. Two subjects achieved a partial response: 1 subject with ovarian cancer who was treated with dostarlimab at 3 mg/kg followed by dostarlimab at 10 mg/kg and 1 subject with small cell lung cancer who was treated with dostarlimab at 10 mg/kg. Seven subjects achieved stable disease.

Dostarlimab Combination Therapies

Study 4020-01-001 is an open-label, first-in-human Phase 1 study of TSR-022, an anti-TIM3 antibody, that is being conducted in 2 parts in patients with advanced solid tumors. In Part 1C, dostarlimab is administered in combination with TSR-022 to establish the RP2D regimen for this study drug combination. In Part 2 of the study, the efficacy of TSR-022 ± dostarlimab is evaluated in patients with advanced solid tumors (expansion cohorts for melanoma, NSCLC, or colorectal cancer).
Study 3000-01-002 is an open-label, Phase 1b study of dostarlimab that is being conducted in 4 parts in patients with advanced or metastatic cancer. The study evaluates DLTs, safety, and tolerability of dostarlimab in combination with niraparib ± bevacizumab or carboplatin and paclitaxel ± bevacizumab. At the time of data cutoff, only Part A (dostarlimab in combination with niraparib) and Part B (dostarlimab in combination with carboplatin and paclitaxel) had subjects enrolled.
Study 4040-01-001 is an open-label, first-in-human Phase 1 study of TSR-033, an anti-LAG3 antibody, that is being conducted in 2 parts in patients with advanced solid tumors. In Part 1C, dostarlimab is administered in combination with TSR-033 to establish the RP2D regimen for this study drug combination. In Part 2 of the study, the efficacy of TSR-022 ± dostarlimab is evaluated in patients with advanced solid tumors (expansion cohorts for epithelial ovarian cancer, triple-negative breast cancer, and urothelial carcinoma). At the time of data cutoff, no subjects in this study had received dostarlimab.
A total of 51 subjects with heavily pretreated advanced solid tumors have been treated with dostarlimab in combination with other therapeutic agents: 28 subjects received dostarlimab in combination with TSR-022 in Study 4020-01-001, 9 subjects received dostarlimab in combination with niraparib in Part A of Study 3000-01-002, and 14 subjects received dostarlimab in combination with carboplatin and paclitaxel in Part B of Study 3000-01-002. The majority (80.4%) of subjects receiving dostarlimab combination therapy reported at least 1 TEAE, with events of fatigue and dyspnea being the most frequently reported. One DLT (Grade 3 aspartate aminotransferase increased) was reported in a subject in Part B of Study 3000-01-002.
Serious AEs occurred in 14 subjects, none of these events were considered study drug-related. One subject had at least 1 AE leading to study drug discontinuation (alanine aminotransferase increased and aspartate aminotransferase increased). Both events were considered study drug-related. No subject had an AE leading to death.

2.4 Radiation Therapy

2.4.1 Proton Beam Radiation Therapy

There have been unprecedented efforts in radiation oncology to develop and use sophisticated, conformal photon techniques in order to improve the outcome for cancer patients. The aim of these new techniques is to concentrate the radiation dose distribution more completely on the disease target, thereby sparing critical normal tissues and increasing the target dose. Toward this end, many advances have been made and examples of new developments include tomotherapy and intensity modulated photon therapy. At the same time, heavy, charged-particle programs, particularly those for proton therapy, have been developed. Proton therapy dose distributions are superior to those of photon therapy and this provides the potential to further improve clinical outcomes.

2.4.1.1 Characteristics of Proton Beams

The basis for the advantages of proton beams lies in the physical laws that determine the absorption of energy in tissues exposed to photon or proton beams. In a specific tissue, photons are absorbed exponentially whereas protons have a finite range dependent upon the initial proton energy. Therefore, the depth dose characteristics of the two beams are qualitatively different. Protons lose their energy in tissue mostly by coulombic interactions with electrons in the constituent atoms; however, a small fraction of energy is transferred through nuclear collisions. The energy loss per unit path length is relatively small and constant as the proton traverses the tissue until near the end of the proton range where the residual energy is lost over a short distance (approximately 0.7 cm in width at 80% of the maximum dose) and the proton comes to rest, resulting in a distinctive sharp rise in the tissue absorbed dose (energy absorbed per unit mass) - known as the Bragg peak. In physical terms, the magnitude of the transfer of energy to tissue per unit path length traversed by the protons is inversely proportional to the square of the proton velocity. The low dose region between the entrance and the Bragg peak is called the plateau of the dose distribution and the dose there is 30-40 percent of the maximum dose.
The Bragg peak is too narrow in extent to irradiate any but the smallest of targets, ablation of the pituitary gland for example. For the irradiation of larger targets/tumors the beam energy is modulated - several beams of closely spaced energies (ranges) are superimposed to create a region of uniform dose over the depth of the target. These extended regions of uniform dose are called "spread-out Bragg peaks" (SOBP).

In the usual clinical situation, more than one radiation beam is used in both x-ray and proton treatments. However, the advantage shown for protons using single beams is present for each and every beam used. Therefore, one cannot overcome the physical disadvantage of x-rays by the use of multiple beams or complex beam arrangements. In modern proton therapy facilities, which have isocentric gantries and sophisticated beam delivery and control systems, proton therapy capabilities are equivalent to those for state-of-the-art, conformal therapy using x- rays with respect to numbers of beams, beam directions and complex delivery techniques such as intensity modulation.

2.4.1.2 Intensity Modulated Radiation Therapy

Intensity-modulated x-ray therapy (IMXT) – the use of x-ray beams each of which is purposely made non-uniform over its cross-section – provides a new degree of freedom in treatment delivery and can lead to more conformal dose distributions. Protons, too, can be used in an intensity modulated mode (IMPT) similar to that for photons and, in an additional degree of freedom, are also made non-uniform in depth. The advantage that single beams of protons have over single beams of x-rays, which is maintained when multiple cross-firing beams of uniform intensity are employed, is similarly maintained when intensity modulation is employed.
In IMXT, the dose can be made to conform to the target volume while avoiding selected adjacent sensitive structures (although the dose uniformity within the target volume is strongly influenced by such selective avoidance and is often of undesirable magnitude). However, IMXT does not reduce the integrated dose delivered outside the target volume (as compared to standard conformal photon therapy); it only, in general, spreads that energy out over a larger volume. In our treatment planning intercomparisons (in nasopharynx, paranasal sinus, lung and Ewing's sarcoma) we have found that the integral dose for IMPT is a factor of two (on the average) less than for IMXT. Moreover, whatever improvement IMXT achieves over standard conformal x-

ray therapy, a comparable improvement is achieved when IMPT is compared to standard conformal proton therapy.

Pancreatic tumors have a number of normal structures in close proximity that have limited radiation tolerance including kidneys, liver, spinal cord, and stomach. The lack of exit dose from proton beam radiation can allow for reduced dose to these and other normal tissues.

2.4.2 Photon-based short course chemoradiation in pancreatic cancer

Dholakia and colleagues (2013) studied fractionated stereotactic body radiation therapy (SBRT) of 33 Gy photons in five fractions for locally advanced pancreatic cancer. They demonstrated local control of 83% at one year with minimal acute or late gastrointestinal toxicity and favorable survival compared to historical data.

2.5 Rationale

Niraparib is a potent inhibitor of PARP and given the immunomodulatory and radio-sensitizing effects of PARP inhibitors, we propose a combination of niraparib and dostarlimab with radiation. This may induce a synergistic anti-neoplastic effect, thus providing an opportunity for the expanded use of PARP inhibitors.

We hypothesize that with radiation, there will be efficacy of niraparib and dostarlimab in unselected metastatic pancreatic We plan to determine the safety and efficacy of niraparib and dostarlimab with XRT as well as correlative genomic and functional studies.

2.6 Correlative Studies Background

This study will incorporate correlative studies leveraging serial tumor biopsies and serial blood collection. We will explore the significance in DDR genes including, but not limited to BRCA1, BRCA2, PALB2, FANCD2, ATM, ATR, and CHEK2.

Centromeric and pericentromeric heterochromatin is comprised of large tandem arrays of repetitive elements called satellites, and these regions are known to be differentially methylated in a variety of malignancies (Jurka 2005). Analysis of all human satellites identified striking differential expression of certain satellite repeats in cancers (black) compared to normal tissues (white). The ALR, HSATII, and CATTCn satellites were found to be elevated in a wide variety of cancers including pancreatic, prostate, lung, ovarian, and renal cell carcinomas compared to normal tissues (Ting 2011). Out of these, HSATII was the most specific for cancer (Fig. 1, inset), and using RNA *in situ* hybridization (RNA-ISH) we confirmed high expression of this repeat across approximately 600 epithelial cancers including carcinomas of the pancreas, lung, prostate, breast, thyroid, and colon (Fig. 1). Interestingly, the expression of HSATII was found to be elevated in preneoplastic lesions indicating a potential importance in tumorigenesis. In addition, a growing amount of

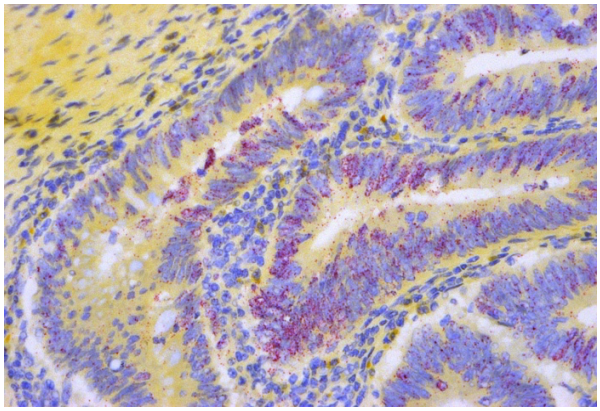

Fig. 1: HSATII RNA-ISH of human primary colon cancer, (Red dots = HSATII, Hematoxylin = blue nuclear counter stain). 200x magnification

literature indicates that these repeat RNAs are linked with DNA damage pathways and linked with the ATR (Flynn 2015) and BRCA (Zhu 2011) pathway. This would indicate that repeat RNAs may serve as a novel biomarker of DNA damage response and potentially a predictive biomarker of response to DNA damaging agents including niraparib and/or radiation.

More recently, we have discovered that satellite repeats behave similar to other endogenous retroviral elements as they are actively reverse transcribed in cancers (Bersani 2015) and they are enriched for specific CpG sequence motifs that are features usually associated with pathogen genomes (Greenbaum 2014, Greenbaum 2008, Greenbaum 2009). These features are capable of engaging pattern recognition receptors (PRRs) of the innate immune system and activating associated pathways. Many of the satellites (Fig. 2 red dots), were indeed divergent from other RNA species, but again the HSATII satellite had an exceptionally unique sequence content with highly anomalous CpG usage and low UpA compared to all other known non-coding RNAs in the human transcriptome (Fig. 2) (Tanne 2015). This anomalous CpG usage was similarly found in the mouse major satellite GSAT demonstrating common sequence motif usage between species despite having completely divergent sequences. Based on previous analyses in viruses, this CpG usage in satellite RNA was shown to initiate PRR signaling and trigger a robust innate immune response. Altogether, repeat RNAs can serve as novel biomarkers of DNA damage agents in the setting of immunotherapy.

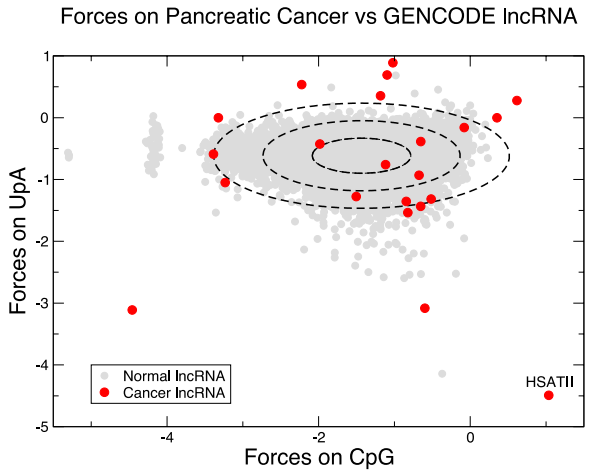

Fig. 2: Distribution of UpA and CpG bias in ncRNA taken from cancer (red) and GENCODE (gray). Each ellipse indicates one standard deviation from the mean value in GENCODE. HSATII has unusual CpG usage.

In addition to the tissue based analyses, this study will also incorporate blood based assessments of circulating tumor DNA (ctDNA) and peripheral blood T-cell Receptor (TCR) repertoire. These analyses will provide systemic measures of tumor and immune response that will complement the studies performed on tumor tissue. Furthermore, whole exome sequencing of baseline and progression ctDNA may help identify novel mechanisms of therapeutic resistance to dual checkpoint pathway blockade, which could provide critical guidance for the development of future therapeutic strategies.

2.7 Patient Reported Outcomes Background

Studying patients' symptom burden and QOL while they are participating in a clinical trial provides an opportunity to better understand their disease- and treatment-related outcomes. Patients' symptom burden and QOL are better indicators of their treatment tolerability than clinician-reported toxicity monitoring. Combining objective endpoints, such as response rate, with subjective patient-reported outcomes has become increasingly important in determining

efficacy, toxicity, and safety and for allowing comparisons across treatment arms (Edgerly). Additionally, evaluating patient-reported measures may help highlight patients' difficulties with treatment adherence by demonstrating additional side effects and toxicities of therapy (Berry). Increased attention to patients' symptom burden and QOL while they are participating in a clinical trial provides an opportunity to improve their quality of care (Oberguggenberger, Meyers). Thus, we aim to describe QOL, symptom burden and mood in this study population to help us better identify the side effects and challenges faced by patients with pancreatic cancer.

We will use the PRO-CTCAE and the Functional Assessment of Anorexia/ Cachexia (FAACT) to measure patient quality of life. The PRO-CTCAE is a patient-reported outcome measurement system developed to evaluate symptomatic toxicity in patients on cancer clinical trials. It was designed to be used as a companion to the Common Terminology Criteria for Adverse Events (CTCAE), the standard dictionary for adverse event reporting in cancer clinical trials.

The Functional Assessment of Anorexia/Cachexia Treatment (FAACT), part of the FACIT Measurement System, is composed of the FACT-G and the anorexia/cachexia subscale (A/CS). The FACIT Measurement System is a collection of QOL questionnaires targeted to the management of chronic illness. The FACT-G is a 27-item compilation of general questions divided into four primary QOL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. It is considered appropriate for use with patients with any form of cancer and has also been used and validated in other chronic illness condition.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

Participants must meet the following criteria on screening examination in order to be eligible to participate in this study:

3.1.1 Histologically or cytologically confirmed metastatic adenocarcinoma of pancreatic origin.

3.1.2 Age ≥ 18 years.

3.1.3 ECOG performance status ≤ 1.

3.1.4 Life expectancy of greater than 3 months.

3.1.5 Participants must have normal organ and marrow function as defined below:

– leukocytes	≥ 2,000/mcL
– absolute neutrophil count	≥ 1,500/mcL
– platelets	≥ 100,000/mcL
– hemoglobin	≥ 9 g/dL
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal(subjects with liver metastases can have an AST (SGOT) ≤ 5 x ULN

- creatinine ≤ 1.5 x ULN
  OR
- creatinine clearance* ≥ 60 mL/min (if using the Cockcroft-Gault formula)
- total bilirubin ≤ 1.5 x ULN (subjects with Gilbert Syndrome can have a total bilirubin < 3 x ULN)

*Creatinine clearance should be calculated per the following:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]} \times 1.23 \text{ (x 0.85 if female)}}{\text{Serum creatinine (micromol/L)}}$$

3.1.6 Women of childbearing potential (WoCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to initiating protocol therapy.

Nonchildbearing potential is defined as follows (by other than medical reasons):

- ≥45 years of age and has not had menses for >1 year
- Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
- Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. See Section 4.4 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.

3.1.7 Women of childbearing potential must agree to use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 6 months (30 days plus the time required for niraparib to undergo five half-lives/180 days) after the last dose of investigational drug.

3.1.8 Women must not be breastfeeding during the study or for 180 days after the last dose of investigational drug.

3.1.9 Men who are sexually active with WoCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving protocol therapy and who are sexually active with WoCBP will be instructed to adhere to contraception for a period of 6 months (180 days) after the last dose of investigational product.
(Women who are not of childbearing potential, i.e. are postmenopausal as defined in the eligibility criteria or surgically sterile, as well as azoospermic men do not require contraception.)

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

3.1.11 If applicable, stable dose of dexamethasone of 10mg or less for 4 weeks prior to initiation of investigational protocol therapy. Regimen must be completed >14 days prior to treatment start.

3.1.12 One previously unirradiated measurable lesion > 1 cm in size amenable to radiotherapy at a dose of 8 Gy x 3 and can meet dose constraints, and another unirradiated measurable lesion > 1 cm in size outside the radiation field that can be used as measurable disease.

3.1.13 Patients must have had at least one line of prior treatment. Any prior line of treatment is permitted, including adjuvant.

3.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded:

3.2.1 Systemic anticancer or biological therapy including prior chemotherapy, immunotherapy, targeted small molecule therapy within 14 days prior to investigational agent, or those who have not recovered (i.e., ≤ grade 1 or at baseline) from adverse events due to agents administered more than 2 weeks earlier. Participants with ≤ grade 2 neuropathy are an exception to these criteria and may qualify for the study. If the participant received major surgery, then they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.2.2 Received investigational therapy ≤ 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is shorter, prior initiating protocol therapy.

3.2.3 Major surgery ≤ 3 weeks prior to initiating protocol therapy and/or not recovered from any surgical effects.

3.2.4 Received radiation therapy encompassing >20% of the bone marrow within 2 weeks; or any radiation therapy within 1 week prior to day 1 of protocol therapy.

3.2.5 Received a transfusion (platelets or red blood cells) ≤ 4 weeks prior to initiating protocol therapy

3.2.6 Received colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) within 4 weeks prior to initiating protocol therapy.

3.2.7 Known history of Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment.

3.2.8 Known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

3.2.9 Active, known or suspected autoimmune disease that has required systemic treatment within the past 2 years other than vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

3.2.10 Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Participants are permitted to use topical, ocular, intraarticular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

3.2.11 Known history of active TB (Bacillus Tuberculosis). Testing is not required for eligibility purposes.

3.2.12 Known hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection. Testing is not required for eligibility purposes.

3.2.13 Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). These participants are at increased risk of lethal infections when treated with marrow suppressive therapy. Testing is not required for eligibility purposes.

3.2.14 Known ≥ Grade 3 immune-related AE with prior immunotherapy, with the exception of non-clinically significant lab abnormalities.

3.2.15 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, recent (within 90 days) myocardial infarction or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.16 Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.2.17 Known additional malignancy diagnosed, detected or treated ≤ 2 years prior to initiation of protocol therapy . Exceptions include basal cell carcinoma of the skin and squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

3.2.18 Known history of, or any evidence of active, non-infectious pneumonitis or interstitial lung disease. (Grade 1 asymptomatic pneumonitis is allowed if found during baseline CT scanning unless it is thought to be clinically relevant).

3.2.19 Active infection requiring systemic therapy

3.2.20 Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.2.21 Known hypersensitivity to niraparib and dostarlimab components or excipients.

3.2.22 History of severe hypersensitivity reaction to any monoclonal antibody

3.2.23 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Further imaging is not required for eligibility purposes.

3.3 Inclusion of Women and Minorities

We do not expect the inclusion and exclusion criteria to either over or under represent women, minorities, or underrepresented populations.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

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

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

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal

Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

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

5. TREATMENT PLAN

The intervention in this study is a combination of niraparib, dostarlimab, and radiation therapy.

This is a two-stage single-arm study. Participants will receive one cycle of niraparib + dostarlimab followed by a second cycle during which radiation therapy will also be given, followed by repeating cycles of niraparib/dostarlimab until the participant is taken off-therapy. There is no required order for dostarlimab, Niraparib or radiation therapy.

No investigational or commercial agents other than niraparib, dostarlimab and radiation therapy may be administered with the intent to treat the participant's malignancy.

5.1 Drug Therapy

5.1.1 Niraparib

Niraparib will be given orally (PO) at a dose of 200 mg daily. Dosing will commence on cycle 1 day 1 and will continue until the participant is taken off treatment (criteria in section 5.6, below).

Niraparib may be taken with or without food. Niraparib will be dispensed to participants at the start of each cycle. If niraparib is dose reduced, participant should continue to use current supply until their supply is exhausted. Missed or vomited doses should not be made up. If a participant misses a dose (greater than 12 hours from normal dosing time) of niraparib, they should skip that dose and take their next dose at its regularly scheduled time.

21 consecutive days is one treatment cycle for the first four cycles. Beginning with cycle 5, each cycle will last 42 days. Treatment will be administered on an outpatient basis, unless the participant is hospitalized.

The participant will be asked to maintain a medication diary of each dose of niraparib. The diary will be returned to the clinic staff at the end of each cycle or the beginning of the next cycle.

For safety monitoring, CBC should be drawn weekly during the first two cycles of Niraparib as indicated in Section 10, Study Calendar. Labs can be drawn at local hospitals if necessary. Blood pressure and heart rate monitoring will be required weekly for the first 2 months of therapy (until C3D15). After the first 2 months of therapy, blood pressure and heart rate monitoring must be checked monthly for the first year. For the weekly checks, monitoring at or near home is

acceptable.

5.1.2 Dostarlimab

Dostarlimab will be administered via a 30-minute IV infusion (with a -5 and +15-minute window permitted). Dosing will be 500mg every 3 weeks for the first 4 doses followed by 1000mg every 6 weeks for all subsequent cycles. Therefore, dosing is as follows:

- 500mg on C1D1
- 500 mg on C2D1
- 500 mg on C3D1
- 500 mg on C4D1
- 1000 mg on C5D1
- 1000 mg on C6D1
- Continuing with 1000 mg on the first day of each 42 day cycle until participant meets criteria in section 5.6, below.

The visit window for administration is +/- 7 days unless treatment is delayed for toxicity management. However, it is recommended that participants be kept on the original dosing scheduled based on C1D1 and maintain the dosing intervals as closely as possible to Q3W then Q6W.

In the case of an infusion-related reaction, please refer to section 6.2 Table 2, below, for treatment guidelines.

5.2 Radiation Therapy

Participants will receive 24 Gy given as 3 fractions of 8 Gy every other day or 2 days as needed. Treatment delays due to holidays will not constitute a protocol violation. Radiation will begin on Cycle 2 Day 1. It is not required radiation begin on a Monday.

5.2.1 Dose Specifications: 3D Conformal Radiotherapy (3DCRT), IMRT, Protons

Dose will be prescribed such that at least 80% of the PTV receives the prescription dose and will be scored as per protocol. The maximum allowable dose within the PTV is 120% of the prescribed dose. The minimum allowable dose within the PTV is >80% of the prescribed dose to a volume that is at least 0.1 cc. Safety should be prioritized, and underdosing at the periphery of the PTV is allowed to meet the dose constraints below.

Participants treated entirely via EBRT shall receive prescription doses to the PTV (with the above constraints). All attempts should be made to deliver the PTV dose with the above heterogeneity constraints with adherence to the critical structure parameters listed below.

See Section 5.2.5 below for specifics regarding when to implement a dose reduction. The final prescription dose will be reported specifically to the study coordinator and recorded on a patient-by-patient basis.

Dose constraints

Liver- V15< 700 cc
Brachial plexus- Dmax < 24 Gy
Trachea/Bronchus – Dose to 4cc < 14 Gy, Dmax < 24 Gy
Lung- V9<1500 cc, V11<1000cc
Trachea/Large bronchus- Max dose
Spinal cord- DMax < 18 Gy, Dose to 1.2 cc < 16 Gy
Mucosal surface (including esophagus, stomach, bowel) – Dmax < 15 G

5.2.2 Technical Factors

Photon RT will be delivered with megavoltage equipment at energies ≥6 MV, capable of daily image guidance; with multileaf collimator for intensity modulated radiation therapy is required. Inverse-planned IMRT, forward planned IMRT, VMAT, and 3D CRT are permitted.

Proton delivery system must deliver protons of sufficient energy to cover the target.

5.2.3 EBRT Localization, Simulation, and Immobilization

Simulation will be CT-based in all cases. The use of contrast at the time of simulation is recommended but not required. Participants will be positioned on a flat tabletop with a customized immobilization for stabilization and setup reproducibility. CT images should be acquired at a slice thickness of ≤3 mm. Target volumes and normal critical structures will be defined in the slices in which they are visualized. The 3DCRT cases must utilize “beam’s eye view” representations to define final beam aperture.

4Dimensional CT scan is required for liver and lung lesions.

5.2.4 Treatment Planning / Target Volumes

The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

The Gross Tumor Volume (GTV) is defined by the physician as all known disease as defined by the planning CT.

The Clinical Target Volume (CTV) is the GTV plus areas considered to contain microscopic disease, delineated by the treating physician. 0-10 mm expansion may be used at the discretion of the treating physician.

The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variability of treatment set up and internal organ motion. A range of 5-10 mm around the CTV is required to define each respective PTV. Superior and inferior margins (capping) should be 5-10 mm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the 5-10 mm margin in 3 dimensions.

The ICRU Reference Points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

Normal Critical Structures will be defined on the treatment planning CT scan and all structures will be contoured in their entirety as solid organs. See the ITC web site (**http://atc.wustl.edu**) to view examples of target and normal tissue contours.

The PTV forms the entire target as described. 3D conformal beams will be shaped to include the entire PTV and minimize dose to surrounding critical structures as described. Intensity modulated radiotherapy (IMRT) using inverse planning is permitted with constraints placed to adhere to critical structure dose limitations as defined above.

5.2.5 Critical Structures

Critical structure dose constraints shall remain consistent with Section 5.2.1, above. While every effort should be made to deliver prescription doses to the PTV as specified while adhering to these constraints, it is recognized that certain anatomical factors may prevent this.

For purposes of compliance, up to a 5% absolute increase in the volume of critical structure receiving greater than the specified dose will be considered “variation acceptable,” without a protocol deviation. Any increase in critical structure volume greater than 5% receiving more than the specified dose will be considered a “deviation unacceptable”. It is at this point that a reduction in coverage should be considered.

5.2.6 Treatment Verification

First day port films or portal images of each field along with orthogonal isocenter verification films (or images) must be obtained. If modifications are made in field shaping or design, a port film of each modified field along with orthogonal isocenter verification films (or images) is required on the first day’s treatment of that field. Thereafter, weekly verification films or images of orthogonal isocenter views (anterior to posterior and lateral projection) are required.

For IMRT**,** the intensity profiles of each beam must be independently verified and compared to the planned field intensity. Portal films are not required for IMRT, but orthogonal verification films are required, just as for 3DCRT. These images are to be archived by the institution for later review if requested by the study chair.

Daily on-line target localization (kV or MV imaging with fiducials, trans-abdominal ultrasound, or other) or off-line adaptive approaches to account for interfraction organ motion and setup variability are permitted on this study but not required. The use of image guidance or daily target localization including the specific type implemented must be documented by the treating physician and submitted to study headquarters.

Management of Radiation Dose to the Patient from Daily Localization
According to the literature, the estimates of patient dose per imaging study for various imaging systems vary considerably. The doses are in the range of 0.1 cGy BrainLab's ExacTrac planar kV-systems and can be considered negligible compared with doses from MV portal imaging and kV and MV CT. The doses from helical MV CT scans on a Tomotherapy unit are estimated to be in range from 1 to 3 cGy, similar to doses reported for kV cone beam CT on Elekta Synergy machine. The doses for MV cone beam CT vary from 1 cGy to 10 cGy depending on the field size. Thus, the doses for 3D imaging systems used one time each day are in the range of 0.1 to 10 cGy and can contribute from 0.06 to 6% to a daily dose of 1.8 Gy. As a technique of controlling participant dose, it is recommended that a QA procedure be established at each institution to verify the accuracy of the image registration software on a daily basis. This QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging to check that the registration software has functioned properly when a shift of participant position is carried out. Additionally, it is not recommended that an institution use a daily imaging technique that delivery greater than 3 cGy/dy to the patient. This limit dictates that repeat imaging on a particular day is held to a minimum when systems that deliver up to 3 cGy per study are used.

5.2.7 Quality Assurance

The institution will archive treatment prescription and verification images for later review by the study chair if requested. At least one port film or pretreatment alignment film per field along with the digital reconstructed radiographs (DRRs) from the treatment planning program or, alternatively, a simulation verification radiograph shall be acquired and kept for evaluation if requested except where geometrically impractical.

Cases which meet criteria as stated in Section 5.2.1 will be scored as per protocol. Cases which don't will be scored as violations. Note that any deviations from the treatment target volumes and normal tissue constraints are considered planning deviations only and are not protocol deviations or violations. Protocol treatment may proceed in these cases with the approval of the Overall PI.

Acceptable dose heterogeneity will be as follows: The maximum dose volume of the PTV must not be shared by a normal critical structure. (Section 5.2.4). The maximum point dose to normal critical structures outside the PTV including the unspecified tissue should not exceed the prescription dose. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

5.2.8 Dose Specifications / Technical Considerations: SBRT/Brachtherapy

SBRT considerations are the same as above.

5.2.9 Radiation Quality Assurance Reviews

The study co-chair will review dosimetry for all plans upon completion of study.

5.2.10 Monitoring Radiation Adverse Events

All participants will be seen during radiation therapy by a radiation oncologist or nursing staff. Any observations with respect to symptoms / side effects will be recorded. Clinical discretion may be used in managing radiotherapy-related side effects.

5.3 Pre-Treatment Evaluations

Following informed consent, all participants will undergo screening procedures within 28 days prior to registration to determine eligibility for study entry. Screening procedures include medical, surgical, cancer, and medication history; complete physical examination, including vital signs, height, and weight; Eastern Cooperative Oncology Group (ECOG) performance status; clinical laboratory assessments (complete blood count [CBC], serum chemistry, and urinalysis); and pregnancy test for women of childbearing potential. Labs completed on Cycle 1 Day 1 should re-meet eligibility prior to dosing.

Patients must have a baseline tumor assessment to determine extent of disease and confirm presence of measurable disease. Please refer to Section 10.0 for a complete list of baseline study requirements.

Initial tumor imaging at screening must be performed within 28 days prior to registration. Scans performed prior to the signing of the informed consent form as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to study registration.

Participants will undergo a biopsy at the time of fiducial placement if safely accessible by percutaneous approach.

Blood samples will be collected pre-dose for correlative analysis.

5.4 General Concomitant Medications

Any medication the participant takes during the study other than the study drugs, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the CRF.

Niraparib weakly induces cytochrome P450 (CYP)1A2 in vitro and is an insensitive substrate for P-glycoprotein (P-gp); therefore, investigators should be advised to use caution with drugs that are the sensitive substrates for CYP1A2 with a narrow therapeutic range, i.e. theophylline and tizanidine.

Patients are prohibited from receiving the following therapies during the treatment phase of this study:

- Systemic anticancer or biological therapy

- Immunotherapy or chemotherapy not specified in this protocol
- Investigational agents other than niraparib and dostarlimab
- Live vaccines within 30 days prior to the first dose of study drug and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacille
- Prophylactic cytokines (granulocyte colony-stimulating factor) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to ASCO guidelines.
- Systemic glucocorticoids for any purpose other than to manage symptoms of suspected immune-related adverse events. Note: use of inhaled steroids, local injection of steroids, and steroid eye drops are allowed. If medically deemed necessary (e.g. acute asthma or COPD 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.

5.5 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator, including but not limited to the items outlined below. Prophylactic cytokines (e.g. G-CSF) should be administered according to current ASCO guidelines after the first cycle.
Note: it may be necessary to perform additional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Supportive care should be provided at the discretion of the treating physician, but guidelines for treatment are as follows:

5.5.1 Pneumonitis:

- Treat with systemic corticosteroids, oral for Grade 2 (e.g., 0.5-1 mg/kg/day of prednisone or equivalent) and IV for Grade 3-4 (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 3-4.
- Consider prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

5.5.2 Diarrhea/Colitis

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 participants 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., 0.5-1.0 mg/kg/day of prednisone or equivalent). If symptoms persist or worsen with steroids, treat as Grade 3-4.

- For Grade 3 or 4 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. The patient may also be treated with Infliximab.
- Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.

5.5.3 Type 1 diabetes mellitus or ≥ Grade 3 hyperglycemia

For type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria, insulin replacement therapy is required.

5.5.4 Hypophysitis

- Treat with systemic corticosteroids, oral for Grade 2 (e.g., 0.5-1 mg/kg/day of prednisone or equivalent) and IV for Grade 3-4 (e.g., 1 to 2 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.

5.5.5 Hyperthyroidism or Hypothyroidism

Thyroid disorders have been reported with other PD-1 inhibitors occurring at any time during treatment. Monitor participants for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- Grade 2 HYPERthyroidism events
    - Consider non-selective beta-blockers (e.g., propranolol) as initial therapy.
- Grade 3-4 HYPERthyroidism
    - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids (e.g., 0.5-1 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.
- Grade 2-4 HYPOthyroidism
    - Thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

5.5.6 Hepatitis

- Treat with systemic corticosteroids, oral for Grade 2 (initial dose of 1- 2 mg/kg/day of prednisone or equivalent) and IV for Grade 3-4 (1-2 mg/kg/day of prednisone or equivalent)
- Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.

5.5.7 Renal Failure or Nephritis

- Treat with systemic corticosteroids, oral for Grade 2 (initial dose of 0.5-1 mg/kg/day of prednisone or equivalent) and IV for Grade 3-4 (1-2 mg/kg/day of prednisone or equivalent). Taper corticosteroids when symptoms improve to Grade 1 or less over no

less than 4 weeks.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Patients are permitted to stay on study beyond TIMC determined progression if they have not yet received radiation or their first set of protocol scans. Due to expected delayed treatment response prior to radiation, the decision to keep patients on trial past progression will be made by the treating physician. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (exceptions defined above)
- Intercurrent illness that prevents further administration of treatment including a diagnosis of MDS or AML
- Participant becomes pregnant
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Investigator, Sponsor, and/or GSK becomes aware of conditions or events that suggest a possible risk or hazard to participants if the clinical study continues
- Hospice: Patients who transition into hospice care will be taken off active follow-up and followed for survival data if possible, including date of death.

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

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

5.7 Duration of Follow Up

The first follow up visit or off treatment visit will be at least 30 days from the last dose of protocol therapy (+/- 7 days) or may coincide with the date of discontinuation of treatment (+/- 7 days) if the date of discontinuation is greater than 37 days after the last dose. Patients will either be seen in clinic or called every 12 weeks for the first two years of follow-up and then at least every 6 months for years 3-5.

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed to ensure resolution or stabilization of the adverse event.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study and followed for survival (if applicable) when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Termination of the study
- Hospice: Patients who transition into hospice care will be taken off active follow-up and followed for survival data if possible, including date of death.

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

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.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated below. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Radiation Dose Modifications

Radiation dose modifications and delays will be determined at the discretion of the treating physician.

6.2 Dostarlimab Dose Modifications

AEs (both non-serious and serious) associated with dostarlimab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment.

In general, dostarlimab must be withheld for drug-related Grade 3 toxicities, as well as for certain immune-related adverse events of interest (irAEIs), but may be resumed upon recovery to Grade ≤1; dostarlimab will be permanently discontinued for any drug-related Grade 4 AE. dostarlimab must be permanently discontinued for certain irAEIs as described in Table 2.

The specific immune-related AEs typically observed with anti-PD-1 antibodies will be managed according to the guidelines summarized below.

Immune-related Adverse Events of Interest and Guidelines for Management

Given the mechanism of action of dostarlimab, it is anticipated that activation of cellular immune system can be manifested as immune-related AEs. Based on available safety data from checkpoint inhibitors, treatment emergent adverse events (TEAEs) with the specific grades listed below were selected as immune-related adverse events of interest (irAEIs). The list of irAEIs may be updated upon emerging data.

Refer to Table 2 for details on the management of dostarlimab dose delays and discontinuation for specific irAEIs. Detailed guidance for the administration of rescue medications and supportive care are available below. For all irAEIs listed in Table 2, dostarlimab should be withheld until the patient is clinically and metabolically stable and AEs have resolved to Grade ≤1. If systemic steroids are used as a part of irAEI management, the total dose of daily steroids should be equal to or less than 10mg prednisone at the time of resuming dostarlimab.

All treatment delays (including any missed doses) and discontinuations, and the reason for delays or discontinuation of dostarlimab, should be documented.

Table 2: Guidelines for Treatment of Immune-related Adverse Events of Interest

Toxicity	**Withhold Treatment for AE Grade**	**Restarting Treatment/Discontinuation**
Uveitis	Symptomatic any grade	Restart when toxicity resolves to Grade 0. For any recurrent uveitis or uveitis resistant to topical steroids, permanently discontinue treatment.
Diarrhea/colitis	2 to 3	Restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.
AST, ALT, or increased bilirubin	2 (AST or ALT > 3 and ≤ 5 × ULN or total bilirubin > 1.5 and ≤ 3 × ULN)	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4 (AST or ALT > 5 × ULN or total bilirubin > 3 × ULN)	Permanently discontinue (see exception below)[a].
T1DM or hyperglycemia	3 or 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)	Restart dosing in appropriately managed, clinically and metabolically stable patients, insulin replacement therapy is required.
Immune-related encephalitis	Any grade	Permanently discontinue.

Toxicity	Withhold Treatment for AE Grade	Restarting Treatment/Discontinuation
Hypophysitis	2 to 4	For Grade 2 to 3 AEs, hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 to 1. For recurrence or worsening of Grade ≥2 hypophysitis after corticosteroid taper has been completed and patient is on adequate hormone replacement therapy, permanently discontinue. For Grade 4 AEs, permanently discontinue.
Adrenal Insufficiency	2 to 3	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 to 1. For recurrent or worsening ≥ 2 adrenal insufficiency while adequate hormonal replacement is continuing, permanently discontinue study drug.
	4	Permanently discontinue.
Hypo- and Hyperthyroidism	3	Hold until hormonal therapy results return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.
Infusion-related reaction	2[b]	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4	Permanently discontinue.
Pneumonitis	2	Restart dosing when toxicity resolves to Grade 0 to 1. If Grade 2 recurs, permanently discontinue.
	3 or 4	Permanently discontinue.
Rash	3	Restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.
Renal failure or nephritis	2	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4	Permanently discontinue.
Recurrence of AEs after resolution to Grade ≤1	3 or 4	Permanently discontinue.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; T1DM = type 1 diabetes mellitus; ULN = upper limit of normal.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week, then study treatment should be discontinued.

[b] Upon resolution within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 to 50 mL/h). Otherwise, study treatment will be withheld until symptoms resolve, and the patient should be pre-medicated for the next scheduled dose.

Rescue Medications and Supportive Care Guidelines

During treatment with dostarlimab, patients should receive appropriate supportive care measures for AEs as deemed necessary by the treating Investigator, including but not limited to the items outlined below. Prophylactic cytokines (eg, GCSF) should be administered according to current ASCO guidelines.

Note: It may be necessary to perform additional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the AE. Specific detailed management guidance from ASCO (2018), ESMO (2018) and NCCN (2019) for immune-mediated AE are provided in the weblink by Association of Community Cancer Centers. Investigators should follow these recommendations for management of the following events:

- Uveitis
- Pneumonitis
- Diarrhea/colitis
- Type I diabetes and grade 3 and 4 hyperglycemia
- Hypophysitis
- Adrenal insufficiency
- Hyperthyroidism and hypothyroidism
- Hepatitis
- Renal failure or nephritis

Management of Infusion-Related Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 3 shows treatment guidelines for patients who experience an infusion-related reaction associated with administration of dostarlimab.

Table 3: Dostarlimab Infusion Reaction Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, or IV fluids); prophylactic medications indicated for ≤24 h	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen	Patient may be pre-medicated 1.5 h (±30 min) prior to infusion of dostarlimab with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) • Acetaminophen 500 to 1000 mg PO (or

	• Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the 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/h to 50 mL/h). Otherwise, dosing will be withheld until symptoms resolve, and the patient should be pre-medicated for the next scheduled dose. Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.	equivalent dose of antipyretic)
Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**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 Investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further study treatment administration.**	No subsequent dosing.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = oral.
Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of study treatment administration.

6.3 Niraparib Dose Modifications

Dose interruption and/or modification of niraparib may be implemented due to nonhematologic or hematologic toxicities per the Investigator's judgement after Cycle 1.

Treatment must be interrupted for any nonhematologic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib (Table 3). If the nonhematologic toxicity is appropriately resolved to baseline or Grade ≤1 within 4 weeks (28 days) of the dose interruption period, the patient may restart treatment with niraparib but with a dose level reduction if prophylaxis is not considered feasible (see Table 5). If the event recurs at similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made according to Table 4.

If the toxicity requiring dose interruption has not resolved completely or to CTCAE Grade 1 during the maximum 4-week (28-day) dose interruption period, and/or the patient has already undergone a dose reduction to a minimum dose of 100 mg QD, the patient must permanently discontinue treatment with niraparib.

The dose interruption and modification criteria for niraparib for hematologic parameters will be based on blood counts and are outlined in Table 6. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period, the patient must permanently discontinue treatment with niraparib.

For major surgery while on study treatment, up to 4 weeks (28 days) of study treatment interruption is allowed. For patients whose initial dose is 3 capsules daily (300 mg/day), dose reductions to 2 capsules daily (200 mg/day) and subsequently to 1 capsule daily (100 mg/day) will be allowed. No further dose reduction will be allowed.

For patients whose initial dose is 2 capsules (200 mg/day), dose reduction to 1 capsule once daily (100 mg/day) will be allowed. No further dose reduction will be allowed.

Table 4: Recommended Dose Modifications for Adverse Reactions

Dose level	Initial Dose: 3 capsules per day	Initial Dose: 2 capsules per day
Starting dose	3 capsules once daily (300 mg/day)	2 capsules once daily (200 mg/day)
First dose reduction	2 capsules once daily (200 mg/day)	1 capsule once daily (100 mg/day)
Second dose reduction	1 capsule once daily (100 mg/day)	NA

Table 5: Niraparib Dose Modifications for Nonhematologic Adverse Reactions

Abnormality	Intervention
Non-hematologic CTCAE ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. Resume niraparib at a reduced dose.

Abnormality	Intervention
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue niraparib.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Hypertension: Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Pre-existing hypertension should be adequately controlled before starting niraparib treatment. Blood pressure and heart rate should be monitored at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with niraparib.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the niraparib dose, if necessary. In the clinical program, blood pressure measurements were obtained on Day 1 of each 28 day cycle while the patient remained on niraparib. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without niraparib dose adjustment. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Posterior Reversible Encephalopathy Syndrome (PRES): There have been rare reports (0.09% of clinical trial patients) of niraparib-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES). PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinstating niraparib therapy in patients previously experiencing PRES is not known.

Table 6: Niraparib Dose Modifications for Hematologic Toxicity

Laboratory Abnormality	Intervention
Monitor complete blood counts weekly for the first two cycles, then at the start of each following cycle for the next 11 months of treatment, and periodically after this time.	
Platelet count < 100,000/μL	First occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at same or reduced dose per Table 3. If platelet count is < 75,000/μL, resume niraparib at a reduced dose per Table 3.
	Second occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at a reduced dose per Table 3. Discontinue niraparib if the 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 < 1,000/μL	Withhold niraparib for a maximum of 28 days and monitor blood counts until neutrophil counts return to ≥1,500/μL. Resume niraparib at a reduced dose per Table3. 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 maximum dose reductions per Table 3.
Hemoglobin ≤ 8 g/dL	Withhold niraparib for a maximum of 28 days and monitor blood counts until hemoglobin returns to ≥9 g/dL. Resume niraparib at a reduced dose per Table 3. 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 maximum dose reductions per Table 3.
Hematologic adverse reaction requiring transfusion	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. Resume niraparib at a reduced dose per Table 3.
Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.

Abbreviation: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; QD = once daily.

Thrombocytopenia: In the case of thrombocytopenia, following the first occurrence, resumption of therapy may occur at the same dose or 1 dose level lower when the hematologic toxicity has

resolved. Subsequent occurrences should trigger dose reduction upon resumption of therapy. If the platelet count has not reverted within 28 days of interruption to ≥100,000/μL, then study treatment should be discontinued.

General Hematologic Toxicity: If dose interruption and/or modification is required at any point during study treatment because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until the AE resolves to the specified blood count levels. To ensure the safety of the new dose, weekly blood draws for CBC will be required for an additional 4 weeks after the AE has resolved, after which monitoring every 4 weeks may resume. CBC monitoring will continue every 4 weeks (ie, monthly) for the next 11 months of treatment, and periodically after this time.

Any patient requiring transfusion of platelets or red blood cells (≥1 unit) must undergo a dose reduction upon recovery if study treatment is resumed.

Myelodysplastic Syndromes (MDS) or Acute Myeloid Leukemia (AML): If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue study treatment.

7. EXPECTED TOXICITIES AND TOXICITY REPORTING

Participants will be monitored for adverse events and serious adverse events from the first dose of investigational agent through 30 days after the last dose of any study drug. All adverse events experienced by participants will be documented. Toxicities will be closely followed. Start and stop dates will be documented, as will changes in grade over time.

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 Events List for dostarlimab

Based on observed side effects from approved drugs of the same class/type (anti-PD-1 antibodies), the most common side effects of dostarlimab are (≥20%) are:

- Fatigue
- Anemia
- Nausea
- Decreased appetite
- Arthralgia
- Diarrhea
- Pruritus
- Vomiting
- Increase in the liver enzyme aspartate aminotransferase (AST)

- Asthenia
- Myalgia
- Rash
- Creatinine increase
- Hhypokalemia
- Hypothyroidism
- Muscular weakness

Side effects that were experienced by <1 include the following:

- Pneumonitis
- Autoimmune hemolytic anemia

Side effects that were experienced by patients taking anti-PD-1 antibodies:

- Inflammation of the skin
- Inflammation of the bowels/gut
- Inflammation of the lungs
- Inflammation of the liver
- Inflammation of the pituitary gland
- Too much/too little thyroid hormone
- Inflammation of the kidney
- Inflammation of the muscles
- Inflammation of the pancreas
- Inflammation of the brain

7.1.2 Adverse Event List for Niraparib

Side effects that were experienced by 10% or more of patients who took niraparib as a single drug therapy, include the following:

- Anemia
- Thrombocytopenia
- Neutropenia
- Constipation
- Nausea
- Vomiting
- Decreased appetite
- Headache
- Fatigue
- Abdominal pain
- Dyspepsia
- Cough
- Urinary tract infection
- Diarrhea
- Dyspnea

- Nasopharyngitis
- Insomnia
- Dysgeusia
- Palpitations
- Arthralgia
- Back pain
- Hypertension
- Leukopenia
- Dizziness
- Asthenia

Side effects that were experienced by 1% or more but fewer than 10% of patients who took niraparib as a single agent include the following:

- Neutropenic infection
- Photosensitivity
- Dysgeusia
- Conjunctivitis
- Hypokalemia
- Tachycardia
- Dry mouth
- Anxiety
- Nose bleeds
- Rash
- Muscle pain
- Mucositis/stomatitis
- Increases in liver enzyme
- Blood creatinine increase
- Weight loss
- Depression
- Bronchitis
- Peripheral edema

Serious side effects that resulted in the need for medical care:

- Decrease in platelets
- Decrease in red blood cells
- Decrease in neutrophil cells
- Hypertension
- Posterior Reversible Encephalopathy Syndrome (PRES)

Because niraparib is a PARP inhibitor, there is also a potential risk for developing acute myeloid leukemia and/or myelodysplastic syndrome (MDS).

7.1.3 Adverse Event List for Radiation Therapy

Likely (more than a 20% chance that this will happen)

- Abdominal Pain
- Nausea
- Vomiting
- Weight loss
- Fatigue
- Skin irritation and/or reddening
- Alopecia
- Increased risk of infection, including pneumonia
- Decreased blood counts, which may cause shortness of breath, dizziness, and fatigue
- Elevated liver function tests, which may cause fatigue and jaundice (yellowing of the skin and eyes)
- Low platelet count, which may cause an increase in chance of bleeding (nosebleeds, bruising, stroke, and/or digestive system bleeding), and patient may need a platelet transfusion

Occasional (Between a 3-20% chance that this will happen)

- Esophagitis
- Pneumonitis
- Liver damage
- Skin damage
- Slow wound healing

Rare but Serious (Less than a 3% chance that this will happen)

- Chest wall fracture
- GI bleed
- Bowel perforation
- Secondary cancer

7.2 Adverse Event Characteristics

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.

An AE may also be defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring any time after the first study treatment has been administered.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae

Adverse events that are listed above in section 7.1 are subject to expedited reporting only if the adverse event varies in nature, intensity, or frequency from the expected toxicity information that is provided.

Attribution of adverse events will be as follows:

- 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.

When reporting to GSK, attribution must be reported as either "related" or "not related'.

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

*Exception: Preplanned (at time of informed consent) hospitalization for elective procedures, for protocol compliance or social reasons, or for observation will not be considered criteria for an SAE. The reason for the planned hospitalization should be documented. Complications experienced during these hospitalizations must be reported as SAEs if hospitalization is prolonged due to AE, or if the complication meets other serious criteria).

An **Adverse Event of Special Interest** is defined as any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication to the Sponsor Institution and to GSK is required.

Adverse Events of Special Interest (AESI) for niraparib include the following [note: there are no AESI identified for dostarlimab]:

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

Report serious AESI on SAE Report Forms, as follows:

- MDS and AML along with other secondary cancers should be reported to the Sponsor Institution and to GSK upon awareness for any patient who has received niraparib (regardless of the timeframe since the last dose).

Assessment of Adverse Events

Each AE will be assessed by the investigator for severity and for a causal relationship with the study treatment as outlined below.

Severity Assessment

All AEs will be assessed by the Investigator for severity according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0: 27 November 2017; National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity grades 1 through 5 provide unique clinical descriptions of severity of each adverse event. The CTCAE v5.0 is available on the NCI/NIH website.

Please note that there is a distinction between **serious** and **severe** AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

7.3 Expedited Adverse Event Reporting

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

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

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	Gr. 2 & 3 AE Unexpected	Gr. 4 AE Expected	Gr. 4 AE Unexpected	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last					

intervention, the AE should be reported within 1 business day of learning of the event.

Relationship to Study Drug

The Investigator must provide a causality assessment regarding the relationship of the event with the study drug for all AEs. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- **Related:** A causal relationship between the medicinal product and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE, etc. Positive rechallenge/dechallenge is supportive.
- **Not Related**: A causal relationship between the medicinal product AE is not a reasonable possibility: there is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable

7.4 Collection and Recording of Adverse Events

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as, "How have you been feeling since your last study visit?" The Investigator will document the nature of AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All SAEs will be collected (within 24 hours of notification of the event) by the investigator to the sponsor from first day of study treatment, and must be throughout the study and for at least 30 days after the last dose of protocol therapy.

SAEs considered by the Investigator to be related to study medication will be reported regardless of the timeframe from last dose of protocol therapy.

All AEs will be documented for each patient from the signing of the ICF, and must be throughout the study and for at least 30 days after the last dose of protocol therapy.

Concomitant illnesses that existed before entry into the study are to be documented as medical history and will not be considered AEs unless the illness worsens after initiating protocol therapy.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented but not reported as an SAE. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.

7.5 Follow-Up of Adverse Events

All AEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

7.6 Reporting to GSK

SAEs (including by default serious AESI)

The Sponsor Institution must report all SAEs and all follow up information to GSK on a GSK-specific SAE Report Form or MedWatch form with accompanying coversheet or MedWatch form within 24 hours of becoming aware of the initial event or clinically significant follow-up information.

The Sponsor must provide a causality assessment and must sign and date all SAE Report Forms.

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).

Pregnancies

The Sponsor has the responsibility to monitor the outcome of all pregnancies reported during the Investigator Sponsored Trial.

The Sponsor must report all pregnancies associated with GSK product including follow up outcomes to GSK within 24 hours of awareness.

Each pregnancy must be reported on an Initial Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. Pregnancy is not an AE, and therefore does not need to be reported as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy on the Pregnancy Outcome Report Form. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form, reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor Institution and GSK within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Reporting Contact Information

GSK SAE and Pregnancy Reporting Information
Email: OAX37649@gsk.com Fax: +44(0) 208754 7822

Reporting Product Complaints for GSK Products

Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the Sponsor Institution or qualified designee to GSK QA (Email: tesaro.qa@gsk.com) within 1 working day of first becoming aware of the possible defect. The product and packaging components in question, if available, must be quarantined in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Per regulatory requirements, if an event is assessed by the Sponsor as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor to submit the SUSAR to Regulatory Authorities according to applicable regulations.

In addition, the SUSAR will be distributed to the Investigators/sites utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and GSK per the governing institutional requirements and in compliance with local laws and guidelines.

7.7 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI 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.

In addition, the SUSAR will be distributed to the Investigators/sites utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and GSK per the governing institutional requirements and in compliance with local laws and guidelines.

7.8 Reporting to Hospital Risk Management

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

7.9 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions to the Overall PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

8. PHARMACEUTICAL INFORMATION

8.1 Dostarlimab

8.1.1 Description

Dostarlimab is an IgG4 antibody.

8.1.2 Form

Dostarlimab will be supplied as a solution in vials containing 500 mg (50 mg/mL, respectively).

Dostarlimab drug product is a sterile solution, essentially free from visible particles, supplied as a single use vial for intravenous administration. The solution is clear and colorless. The drug product is formulated in 25 mM citrate, 100 mM arginine, 31 mM sodium chloride, 0.02% polysorbate 80, pH 6. The dostarlimab 500 mg has a protein concentration of 50 mg/ml with a deliverable volume of 10 mL.

8.1.3 Packaging, Labeling, and Storage

Dostarlimab for injection is supplied in vials containing 500 mg at a concentration of 50 mg/mL.

The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and non-patient-specific.

All study treatment supplies must be stored in accordance with the instructions and storage and handling guidelines. Until dispensed or administered to the patients, the study treatment will be stored in a securely locked area, accessible to authorized personnel only. Please see the Storage and Handeling Guidelines for further instructions on storing and hadeling Dostarlimab.

8.1.4 Availability

Dostarlimab is provided by GSK.
The medication provided for this study is to be used only as indicated in this protocol and only for the participants entered in this study.

Additional details can be found in the Storage and Handling Guidelines.

8.1.5 Preparation

Infusions must be prepared aseptically by the pharmacist or designee.

Dostarlimab must 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. Dostarlimab solution must not be added into airspace contained within the infusion bag. The final infusion bag/ syringe must not be shaken.

The maximum infusion volume is 250mL plus overfill.

8.1.6 Administration

The infusion should be administered using an intravenous infusion pump. dostarlimab should not be infused in the same intravenous 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 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.

8.1.7 Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study. Dostarlimab

Dispensation and accountability records will be maintained. The pharmacist will dispense study treatment for each patient according to the protocol.

8.1.8 Destruction and Return

Unused dostarlimab may be destroyed on site per standard procedure.

8.2 Niraparib

8.2.1 Description

Niraparib ([3S]-3-[4- phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP1 and PARP2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate.

8.2.2 Form

Niraparib will be supplied as 100mg capsules for oral administration.

8.2.3 Storage and Stability

Niraparib will be stored at room temperature; 15°C – 30°C. It should not be refrigerated or frozen. Until dispensed to the participants, Niraparib supplies must be stored in a securely locked area, accessible to authorized personnel only.

8.2.4 Administration

Participants will be instructed to take study drug at approximately the same time each day. Participants must swallow capsules whole; they should not be opened, crushed or chewed. Niraparib may be taken with or without food. Niraparib will be dispensed to participants at the start of each 21-day cycle for the first 4 cycles. Beginning at cycle 5, niraparib will be dispensed to participants on day 1 and day 22 of each 42-day cycle. Missed or vomited doses should not be made up.

8.2.5 Availability

Niraparib is provided by GSK.

The medication provided for this study is to be used only as indicated in this protocol and only for the participants entered in this study.

Additional details can be found in the Storage and Handling Guidelines.

8.2.6 Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study. Study drug accountability should be maintained by each site based on the capsules dispensed versus returned to the clinic at each visit and the number of days since the last visit.

8.2.7 Destruction and Return

The investigational site is responsible for destruction of study drug according to local regulations. Both the unused and expired study drug must be destroyed according to local regulations and procedures, and a copy of the destruction form must be filed in the study binder.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Serial blood = for cTDNA, CTC, flow cytometry, TCR repertoire, and ELISA
Tissue = DNA seq (Whole exome or genome), bulk and single-cell RNA seq, multiplex immunofluorescence, IHC, single cell RNA seq;TCR sequencing

9.1 Analysis for Repeat RNA Expression, DNA Damage Response, and Immune Infiltrates

We will analyze repeat RNA markers to predict response to DNA damaging agents and

activation of innate immune response. A total of 6 unstained slides of 5-micron thickness are requested for analysis. We have developed a RNA-ISH assay applicable to FFPE sectioned slides for repeat non-coding RNAs including HSATII. The assay has been automated but is not CLIA certified at this time. Given this early trial, we will assess this HSATII RNA-ISH and other repeats (TERRA, LINE1, HERVH) for exploratory biomarker development. In addition, we have found that these markers correlate to specific immune infiltrates. Notably, we have developed a combined RNA-ISH and immunohistochemistry, which has revealed a correlation of repeats with FOXP3 T-reg cell, CD163 macrophages, and CD8 T-cells.

As a complementary assay, we have developed computational pipelines to evaluate repeat RNAs using both standard Illumina RNA-seq as well as single molecule RNA-seq with the SeqLL platform. If available, we will perform RNA-seq on pretreatment and on treatment fresh frozen biopsies from patients on trial. RNA-seq will be done to quantify repeat RNAs, correlate to immune markers by RNA expression profiles, and correlate to DNA damage response genes.

Where available, we will additionally use 1-2 fresh cores for single-cell RNA-sequencing studies to further characterize immune cell subsets and cell states at high resolution. We have a well validated platform for performing single-cell transcriptomics. In brief, fresh biopsy cores will be immediately processed to create single cell suspensions for single cell RNAseq and TCR sequencing that will be performed by the Hacohen Lab at MGH and the Broad Institute . TCR sequencing will characterize the tumor infiltrating lymphocyte TCR repertoire over time. Single cell RNAseq will enable the study of gene programs at a single cell level. This will clarify the roles of various cell types within the tumor as well as the heterogeneity within those cell types.

In addition, participants will have the option to participate in DNA sequencing (targeted exome, whole exome, or whole genome) to assess effects of DNA damaging agents by quantifying total mutational burden, copy number variation, and chromosomal rearrangements. This optional testing will be done at the MGH Cancer Center or be evaluated by a third party (Foundation Medicine, Cambridge, MA).

In order to perform the RNA-ISH assay, we will obtain six (6) unstained formalin fixed paraffin embedded (FFPE) slides. These slides will be obtained prior to cycle 1, prior to cycle 2, and prior to cycle 3.

For both DNA and RNA sequencing we will request five (5) 50-mg fresh frozen tumor samples from biopsies done prior to cycles 1, 2, and 3. Total nucleic acids will be purified using the AllPrep DNA/RNA kit (Qiagen) or the total nucleic extraction kit (Ambion/Thermo Fisher). DNA will be subjected to targeted gene sequencing, whole exome, or whole genome sequencing using the Illumina next generation sequencing platform. RNA will be processed for RNA-seq with both Illumina Total RNA-seq protocol and SeqLL single molecule digital gene expression.

All slides for RNA-ISH and frozen tumor samples for RNA-seq will be sent to

Ting Laboratory
MGH Cancer Center

149 13th Street
CNY149 – 614
Charlestown MA 02129

9.2 Functional DNA Damage Response Biomarkers

Complementary to the studies described in Section 9.1, we will use any excess available tumor tissues for exploratory functional protein studies as described (Willers 2015). Using established protocols and depending on tissue availability we will generate organoid tumor cell lines and/or directly use fresh tumor tissue (volume equivalent of at least 1 core biopsy). Research specimens will be subjected to radiation, niraparib, or additional agents ex vivo and foci responses of proteins involved in the DNA damage response will be analyzed by immunofluorescence microscopy or immunohistochemistry. Additional molecular markers will be assessed as needed. The analysis is exploratory, seeking to correlate functional DNA damage response markers with tumor responses in individual patients. The studies will be mainly performed in the

Willers Laboratory
MGH Radiation Oncology CNY149-4406
149 13th Street
Charlestown, MA 02129

9.3 Blood-based Correlative Studies

Peripheral blood will be collected serially or by port draw throughout study treatment as specified in the studycalendar. 40mL of blood will be collected at each time point into two 10mL Streck cfDNA fixative tubes and two Becton Dickinson Mononuclear Cell Preparation Tubes, and tubes will be centrifuged to separate cell pellet from plasma, and each component will be aliquoted and frozen for subsequent analysis.

Blood samples in Streck cfDNA tubes can be shipped at room temperature (within 5 days of draw) to:
Corcoran Laboratory
Massachusetts General Hospital Cancer Center
149 13th St, Room 7330
Charlestown, MA 02129

Blood samples in BD Mononuclear Cell Preparation tubes will be sent on the day of draw to:
Ting Lab
Massachusetts General Hospital Cancer Center
Charlestown Navy Yard Building 124- 6-618B
13th Street Building 124
Charlestown, 02129

9.3.1 Serial monitoring of tumor burden and therapeutic resistance by circulating tumor DNA analysis

Cell free DNA will be isolated from serial plasma aliquots. PBMCs will be isolated and purified from the blood cell pellet and frozen separately for immune cell analyses. The T cell TCR locus

and gene expression profiles from these pellets will be characterized by RNA-seq to study T cell clonality and functionality over the course of therapy. For each patient one to two specific clonal mutations identified by exome sequencing of tumor tissue (above) will be used to track circulating tumor DNA (ctDNA) levels throughout treatment using custom mutation-specific droplet digital PCR probes as a personalized measure of tumor burden. This method will allow accurate monitoring of the response of overall tumor burden to treatment and can be correlated with radiologic endpoints, both as an additional measure of treatment response and as a potential method to discriminate between "pseudo-progression" and tumor progression. Cell free DNA isolated from baseline plasma and plasma obtained at progression will also be analyzed by whole exome sequencing using the Broad Institute blood biopsy platform to identify genetic changes that have emerged in tumor cells upon development of therapeutic resistance. Therapeutic resistance is often caused by molecular alterations affecting key target pathways, and these changes can frequently be detected in ctDNA upon progression. This will serve as an important discovery effort to identify potential mechanism of acquired resistance to therapy.

9.3.2 Assessment of T-cell Receptor (TCR) repertoire

Peripheral blood mononuclear cells (PBMCs) will be isolated from cell pellets from the serial peripheral blood draws. The TCR repertoire analysis will be performed using the Broad Institute sequencing platform. For each patient, the peripheral TCR repertoire will be tracked over the course of therapy and compared with the intratumoral TCR repertoire.

9.3.3 Potential Risks to Patients

These studies will involve peripheral blood draw only. Peripheral blood draws do involve a small risk of patient discomfort, bruising, or puncture site infection, but these risks are minimal. Furthermore, correlative blood draws will be performed at the same time as patients are havingroutine clinical blood laboratory assessments during study treatment, and thus will not involve any additional peripheral venipuncture.

9.4 Patient Reported Outcomes

The FAACT (Functional Assessment of Anorexia/ Cachexia Treatment) and a condensed version of the PRO-CTCAE will be used to assess patient reported outcomes at time of informed consent, after completion of each cycle, weekly during radiation therapy and when the patient comes off study.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 28 days prior to study registration unless otherwise specified. Scans and x-rays must be done ≤4 weeks prior to study registration. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Screening laboratory assessments must be done within 8 days prior to study registration. For women of childbearing potential, as defined in the eligibility criteria, a urine or serum HCG pregnancy test must be completed within 7 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.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Tests and Observations	Baseline	Day 1 Cycle 1 Niraparib/ dostarlimab	Day 1 Cycle 2 Niraparib /dostarlimab/ Radiation	Day 1 Cycles 3+ Niraparib /dostarlimab	First follow-up/off treatment visit (9)	Subsequent Follow-up (10)
Informed Consent	X					
Demographics and Medical History	X					
Physical Examination (1,2)	X	X	X	X	X	
Vital Signs and ECOG PS (2)	X	X	X	X	X	
Height, Weight (2, 3)	X	X	X	X		
ECHO or MUGA (15)	X					
Toxicity Assessment	X	X----------X				
Laboratory:						
CBC/platelets/diff (13)	X	X	X	X	X	
Serum chemistries (Na, K, BUN, Cr, Glucose, Calcium, Albumin, AST, ALT, Total bilirubin, Alk phos, CPK, lipase) (14)	X	X	X	X	X	
Creatinine clearance calculation (Cockroft Gault) (16)	X	X	X	X		
Thyroid panel (8)	X		X	X		
CA19-9 and CEA (4)	X		X	X	X	
Pregnancy test (5)	X	X	X	X		
Urinalysis	X	X	X	X	X	
Bone Marrow Aspirate and Biopsy (12)	X					
Research Blood for Correlative Studies (6)	X	X	X	X	X	
Tumor collection for Correlative Studies (11)	X	X		X		

Tests and Observations	Baseline	Day 1 Cycle 1 Niraparib/ dostarlimab	Day 1 Cycle 2 Niraparib /dostarlimab/ Radiation	Day 1 Cycles 3+ Niraparib /dostarlimab	First follow-up/off treatment visit (9)	Subsequent Follow-up (10)
Patient Reported Outcomes (NCI PRO-CTCAE and FAACT) (17)	X	X	X	X	X	
CT of Chest/ Abdomen/ Pelvis (or MRI)	X			X (7)	X	
Tumor Measurement	X			X (7)	X	
Concomitant Meds	X	X----------X				
Survival Status						X

1) Physical exam must include a general, basic neurologic assessment
2) Heart rate and blood pressure monitoring will be required weekly, in clinic if possible, for the first two months of or Niraparib/ Dostarlimab (until C3D15). After the first 2 months of therapy, blood pressure and heart rate monitoring must be checked monthly for the first year of treatment. For the weekly checks, monitoring at or near home is acceptable.
3) Height is only required at baseline.
4) Tumor markers will be drawn prior to or at the time of radiological evaluation with routine labs.
5) For women of child-bearing potential only (definition of non-childbearing potential in eligibility criteria). A serum or urine pregnancy test is required within 7 days of starting protocol therapy, every 9 weeks while on treatment, and at least 30 days after last dose of protocol therapy.
6) Correlative labs will be drawn at the following time points: Baseline, post-dose 1, pre-radiation, pre-cycle 3, and off-treatment.
7) Restaging scans (CT or MRI) are due after every two (42) day cycles (12 weeks) of Niraparib/ dostarlimab (pre-cycle 5, pre-cycle 7, pre-cycle 9, etc.) while on treatment.
8) Blood samples for the thyroid panel (i.e., TSH, T3 or FT3, FT4, or equivalent tests) are to be collected during screening, Cycle 2/Day 1, Cycle 4/Day 1, Cycle 5/Day 1, and the start of each cycle thereafter through the remainder of the study (blood samples can be collected up to 7 days prior to dostarlimab administration). TSH results do not need to be available prior to treatment.
9) The first follow up visit and/or off treatment visit will be at least 30 days from the last dose (+/- 7 days) or may coincide with the date of discontinuation of treatment (+/- 7 days) if the date of discontinuation is greater than 37 days after the last dose.
10) Patients will either be seen in clinic or called every 12 weeks for the first two years of follow-up and then at least every 6 months for years 3-5 and followed for survival status.
11) Tumor collection for correlative analysis will occur prior to cycle 1, prior to cycle 2, and prior to cycle 3 if safely accessible by percutaneous approach.
12) For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to GSK. A copy of the hematologist's report of aspirate/biopsy findings including a classification according to WHO criteria and other sample testing results related to MDS/AML will be provided to the PI and to GSK.
13) CBC to include absolute neutrophil count, platelets, and hemoglobin. CBC must be collected on Cycle 1 Day 1 and weekly during the first cycle. Labs completed on Cycle 1 Day 1 should re-meet eligibility prior to dosing. CBC should also be drawn weekly for the first two cycles of Niraparib/ Dostarlimab.

14) Treatment may be administered after review of hematology and chemistry laboratory values, while CPK result is pending if the patient is asymptomatic. It is preferred that CPK value be available prior to dosing, however dosing does not need to be delayed if CPK value is not available by time of dosing.
15) Clinically significant abnormalities on ECHO/MUGA will be determined by treating clinician. Patients with uncontrolled cardiovascular disease will be excluded per exclusion criteria.
16) Creatinine clearance calculation is not a parameter to receive treatment. Clinically significant abnormalities will be determined by treating clinician and managed per SOC.
17) Patient will be asked to complete Patient Reported Outcome Surveys at baseline, the end of each cycle, weekly during radiation and at the end of study.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 12 weeks while on treatment. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by BOTH the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer 2009) as well as the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) (Wolchok 2009) as administered by the Dana-Farber/ Harvard Cancer Center Tumor Imaging Metrics Core.

11.1.1 Response Review

Central review of baseline and restaging scans will be performed by the Dana-Farber Harvard Cancer Center Tumor Imaging Metrics Core.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0.

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

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

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

The primary endpoint is disease control defined as CR, PR or SD for at least 3 months based on RECIST 1.1 (section **11.1**). A 20% rate of disease control rate is specified under the alternative hypothesis as the minimum level of promising efficacy, while a 5% rate is specified as an upper bound under the null hypothesis of minimal or no activity. The null and alternative hypotheses reflect the virtually lack of therapeutic options for metastatic pancreatic cancer and the very poor prognosis overall.

13.1 Study Design

A two-stage design will be used to evaluate the efficacy of niraparib and dostarlimab combined with radiation. Initially, 15 patients will be enrolled during the first stage of accrual. If none of them were to achieve disease control, the protocol will be terminated with no further accrual. The probability of stopping early is 46% if the underlying rate of disease control were truly 5% in the patient population. If at least 1 of the first 15 patients were to achieve disease control, the protocol will proceed to enroll a total of 25 patients. Niraparib and dostarlimab combined with radiation will be considered to have promising activity in metastatic pancreatic cancer if at least 3 patients overall were to achieve disease control. The two-stage design provides 89% power to accept the treatment combination is associated with a 20% rate of disease control. On the other hand, the probability of a type 1 error is only 12% if the underlying rate of disease control were truly only 5%. The two-stage design is optimal as well as minimax based on the Simon criteria in meeting a target alpha level of 0.15.

13.2 Sample Size, Accrual Rate and Study Duration

The accrual duration is projected to be about 2 years to enroll a final total of 25 patients with metastatic pancreatic cancer. Each patient will be followed long-term up to 5 years for survival

according to the study calendar (section **10**).

13.3 Interim Monitoring Plan

The two-stage design (section **13.1**) implements an early stopping rule after the initial 15 patients have treated during the first stage and evaluated for disease response.

13.4 Analysis of Primary Endpoint

The disease control rate will be reported as a summary measure of disease response evaluated by RECIST 1.1 (section **11.1**) and estimated with the 95% confidence interval based on the exact binomial distribution.

13.5 Analysis of Secondary and Exploratory Endpoints

- The rate of disease control evaluated by irRECIST will be estimated with the 95% confidence interval based on the exact binomial distribution.
- Progression-free survival is defined as the duration from the first day of protocol treatment to the earlier date of disease progression or death due to any cause. PFS time will be censored at the date of last follow-up for surviving patients with disease control. The PFS rate will be estimated by the Kaplan-Meier method with 95% confidence intervals based on the complementary log-log transformation.
- Overall survival is defined as the duration from the first day of protocol treatment to the date of death due to any cause and will be censored at the date of last follow-up for patients still alive. The OS rate will be estimated by the Kaplan-Meier method with 95% confidence intervals based on the complementary log-log transformation.
- Toxicity associated with the combination of niraparib and dostarlimab with radiation will be summarized by category and grade.
- Serial tumor biopsies will be obtained at baseline in conjunction with fiducial placement, after cycle 1 of niraparib and dostarlimab and after cycle 2 following the addition of radiation. Tissue will be analyzed for repeat RNA expression and immune infiltrates (section **9.1**) by RNA-ISH and RNAseq assays. The immune markers will generally be analyzed at paired timepoints in order to isolate changes due to anti-PD1 and PARP inhibition alone and cooperative effects of combined inhibition and radiation. Standard parametric and non-parametric methods for analysis of paired data will be used, applying appropriate transformations as needed. As tumor biopsies may not be obtained on all patients and/or all timepoints, the marker analyses will be exploratory.
- Peripheral blood will be collected at the same timepoints as tumor biopsy as well as at off-treatment due to disease progression for serial analyses of ctDNA (**9.3.1**) and T-cell receptor (TCR) repertoire (**9.3.2**). ctDNA levels of one or two specific clonal mutations will be used as a personalized measure of overall tumor burden and correlated with radiologic endpoints. ctDNA at baseline and progression will be compared to identify genomic changes emerging at development of therapeutic resistance. Peripheral and intra-tumoral TCR repertoires will be compared within patients. ctDNA and TCR data will be analyzed primarily using graphical and descriptive methods to identify potential

trends and associations. Analyses will be exploratory and hypothesis-generating due to the optional assessments.

- The FAACT (Functional Assessment of Anorexia/ Cachexia Treatment) and a condensed version of the PRO-CTCAE will be used to assess patient reported outcomes at time of informed consent, after completion of each cycle, weekly during radiation therapy and when the patient comes off study. Analyses will be exploratory.

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All enrolled patients will be evaluable for toxicity starting from their first dose of protocol treatment.

13.6.2 Evaluation of the Primary Efficacy Endpoint

All eligible patients will be assessed for disease control and analyzed for efficacy, including those unevaluable according to RECIST 1.1 or irRECIST due to early discontinuation of protocol treatment for any reason or early death due to toxicity or disease.

14. 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.

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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 (*e.g.*, 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 NIRAPARIB DRUG DIARY

.1.1

Study Participant Self-Administration Drug Diary

DFCI Study Number: 19-538

Participant Name: _____

Your Doctor_____ Phone_____

Your Nurse_____ Phone_____

Dosing Instructions for Niraparib:

Your dose of Niraparib is _____ mg made up of _____ - _____ mg capsules.

- You should take your dose of niraparib once daily at approximately the same time.
- Please wash your hands after handling niraparib. If a caregiver is giving niraparib to you, they should wear disposable gloves. Extra care should be used if powder is observed to avoid contact with your skin or eyes. If contract does occur, flush eyes or skin with water.
- If you miss your dose of niraparib by less than 12 hours from your normal dosing time, the dose can be made up. If you missed your dose by more than 12 hours, wait until the next scheduled dosing time and take the next scheduled dose.
- If you vomit your dose of niraparib, do not re-dose. Resume dosing at your next scheduled dose.
- Capsules should be taken whole and not crushed, chewed, opened or dissolved in water.
- Niraparib can be taken with or without food and water.
- Store niraparib at room temperature (59°F-86°F (15°C-30°C)).
- Please bring this diary along with any empty or partially empty bottles to each study visit.

1.1.2

1.1.3 DOSING LOG: Cycle ____

Dosing Log Instructions

- Make sure to indicate the date, time, amount taken and any comments immediately following each dose.
- Bring your study drug containing all remaining medication, including empty bottles, to each visit.
- Once complete, provide this signed or initialed and dated dosing log to your study doctor or nurse.

Day	Date	Time of Dose	Number of Niraparib Capsules Taken	Comments *If dose was vomited, missed or skipped, indicate reason below.*
1		□am/□pm		
2		□am/□pm		
3		□am/□pm		
4		□am/□pm		
5		□am/□pm		
6		□am/□pm		
7		□am/□pm		
8		□am/□pm		
9		□am/□pm		
10		□am/□pm		
11		□am/□pm		
12		□am/□pm		
13		□am/□pm		
14		□am/□pm		
15		□am/□pm		
16		□am/□pm		
17		□am/□pm		
18		□am/□pm		
19		□am/□pm		
20		□am/□pm		
21		□am/□pm		

Participant Signature or Initials **Date**

APPENDIX C NCI PRO-CTCAE Survey

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 11 March 2020

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

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

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

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

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

5. In the last 7 days, did you have any HIVES (ITCHY RED BUMPS ON THE SKIN)?
○ Yes ○ No

6. In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe ○ Not applicable

7. In the last 7 days, did you have any UNUSUAL DARKENING OF THE SKIN?
○ Yes ○ No

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

English

Form created on 11 March 2020

Do you have any other symptoms that you wish to report?
○ Yes ○ No
Please list any other symptoms:
1. In the last 7 days, what was the SEVERITY of this symptom at its WORST?
○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

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

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

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

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