

## SUMMARY OF PROTOCOL CHANGES

For Protocol Amendment 4 to: **5**

UCCC Protocol #: UCCI-HN-19-03

Protocol Date: 30 NOVEMBER 2021

#	Section	Change
V5	3.1 Eligibility Criteria	Updating inclusion criteria to include confirmation that patients have measurable disease per RECIST v1.1.
V5	3.1 Eligibility Criteria	Updated Eligibility Criteria 16 to note that women must have adequate contraception through 180 days post last dose of study drug treatment.
V5	Table 7 Niraparib Dose Modifications	Included language that for suspected MDS/AML or prolonged hematological toxicities.
V5	11 Study Calendar	Removed language that baseline evaluations must be completed within one week of starting trial therapy. This language was not removed from NCI template. Protocol already includes windows for required baseline evaluations.
V%	11 Study Calendar	Added CBC at Cycle 1 Day 22 based on updates to the IB

**UCCC Protocol #:** UCCI-HN-19-03

**ClinicalTrials.gov Identifier:** NCT04313504

**Title:** An Open-label, Phase II Study Evaluating the Efficacy of Niraparib and Dostarlimab (TSR-042) in Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma Patients.

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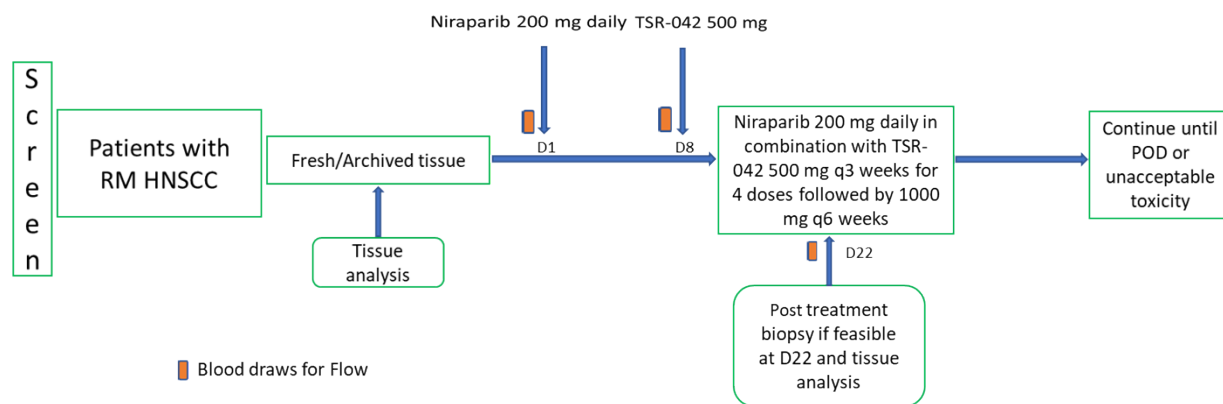
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## SCHEMA



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## 1. OBJECTIVES

### 1.1 Primary Objectives

- To determine the best overall response of the combination of dostarlimab and niraparib in patients with recurrent and/or metastatic HNSCC patients.

### 1.2 Secondary Objectives

- To determine treatment emergent adverse events, serious adverse events associated with dostarlimab in combination with niraparib in recurrent and/or metastatic HNSCC patients.
- To determine the progression free survival (PFS) and overall survival (OS) of the combination of dostarlimab and niraparib in patients with recurrent and/or metastatic HNSCC patients.

### 1.3 Exploratory Objectives

- Correlation of the activity of niraparib and dostarlimab with the molecular profile of the tumor (IHC and RNA analysis of pre and post-tumor samples) to associate gene expression signatures with clinical benefit from this drug combination.
- Evaluate for a mutational profile including mismatch repair (MMR) deficiency and homologous recombination DNA damage repair (HR-DDR) deficiencies and overall genomic alteration index (mutation burden index) that associates with clinical benefit from combination in recurrent and/or metastatic HNSCC patients.
- To determine immunogenicity, PD-L1 expression on tumor, PD1 expression on T cells, T cell functionality with niraparib and dostarlimab combination.

## 2. BACKGROUND

### 2.1 Recurrent and Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)

Head and neck squamous cell cancer (HNSCC) is the sixth most common cancer type worldwide and accounts for approximately 350,000 deaths per year.<sup>1,2</sup> Approximately 30 to 40% of patients with HNSCC present with stage I or II (early stage) disease. In general, these patients are treated with either primary surgery or definitive radiation therapy (RT).<sup>3</sup> However, patients who present with advanced stage disease (Stage III or IV) not only pose a treatment challenge but also have a higher risk of both local recurrence and distant metastasis. Combined modality approaches (surgery, RT, and/or chemotherapy) are generally required to optimize the chance for long-term disease control for patients with advanced stage disease. These combined modality approaches include primary surgery followed by postoperative RT or concurrent chemoradiotherapy (CRT), induction chemotherapy (addition of chemotherapy prior to surgery and/or RT), concurrent CRT without surgery, or sequential therapy (induction chemotherapy followed by concurrent CRT)

without surgery. Despite advances in the treatment of localized HNSCC, 15 to 50% of patients will develop recurrent disease,<sup>4</sup> which is further, complicated by lack of reliable salvage treatment options. Tissues of the head and neck such as skin, nerves, blood vessels, and spinal cord normally receive maximally tolerated radiation doses during the initial course of RT, therefore, re-irradiation exposes these tissues to excessive toxicity and complications. Subsequent surgery may not be possible due to previous surgeries and anatomical logistics. Therefore, upon relapse, palliative chemotherapy, using either single or multiple agents (often with Epidermal Growth Factor Receptor (EGFR) inhibitors like Cetuximab and Immunotherapies with pembrolizumab or Nivolumab), becomes the mainstay of management with lower response rates of 15-20%. Therefore, novel drug combinations with immunotherapy are needed to increase treatment efficacy in a safe manner. Fanconi Anemia (FA) and FA-related DNA repair pathways alterations have been associated with cumulative tumor mutational burden (TMB) due to genomic instability. DNA pathway repair mutations have been reported in 17% of sporadic HNSCC. ATM loss has been reported in 60% of human HNSCC biopsies and FA-related defects were reported in 15-21% of human HNSCC biopsies and cell lines. PARP inhibition (PARPi) has already demonstrated efficacy as a single agent in cancers which harbor a DNA repair defect, most notably, BRCA mutant breast and ovarian cancer and now being studied in HNSCC.

Despite the effectiveness of the two therapies, there appears to be little clinical data examining the response rates of adding PARP inhibitors to PD-1 inhibitors. Our trial represents one such effort, where we will be testing the combination of niraparib (PARP inhibitor) with the Programmed Death-1 (PD-1) inhibitor dostarlimab.

## **2.2 Pharmaceutical and Therapeutic Background**

### **2.2.1 Background of PARP and Homologous Recombination Deficiency**

Poly (ADP-ribose) polymerase (PARP)1 and PARP2 are zinc-finger deoxyribonucleic acid (DNA)-binding enzymes that play a crucial role in DNA repair.<sup>5</sup> Upon formation of DNA breaks, PARP binds at the end of broken DNA strands, a process that activates its enzymatic activity.

Activated PARP catalyzes the addition of long polymers of adenosine diphosphate (ADP)-ribose onto PARP and several other proteins associated with chromatin, including histones and various DNA repair proteins.<sup>6,7</sup> This results in chromatin relaxation, fast recruitment of DNA repair proteins, and efficient repair of DNA breaks. In this manner, PARP plays a key role in sensing DNA damage and converting it into intracellular signals that activate the base excision repair (BER) and single-strand break repair pathways. Normal cells repair up to 10,000 DNA defects daily, and single-strand breaks are the most common form of DNA damage. Cells that are unable to repair this burden of DNA damage, such as those with defects in the homologous recombination or BER pathways, are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. They enter the S phase (DNA replication) of the cell cycle with unrepaired single- and double-strand breaks. Pre-existing single-strand breaks are converted to double-strand breaks as the replication machinery passes. Accumulated double-strand breaks present during S phase are repaired by homologous recombination. Homologous recombination

is the preferred repair pathway because it is associated with a much lower error rate than other forms of repair. Cells that are unable to perform DNA repair via homologous recombination (e.g., due to inactivation of genes required for homologous recombination, such as breast cancer [*BRCA1*]- or breast cancer 2 [*BRCA2*]-mutated cells) are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. These cells accumulate stalled replication forks during S phase and are more likely to use the error-prone nonhomologous end joining (NHEJ) or alternative (alt)-NHEJ pathways to repair double-strand breaks in DNA. Accumulation of errors in DNA by NHEJ contributes to mutation burden that promotes the development of cancer. Over time, the buildup of excessive DNA errors in combination with the inability to complete S phase (because of stalled replication forks) contributes to cell death.<sup>6,7</sup>

Treatment with PARP inhibitors could represent a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline *BRCA* mutation (*gBRCAmut*) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on NHEJ, alt-NHEJ, and BER for maintenance of genomic integrity. PARP inhibitors block alt-NHEJ and BER, forcing tumors with *BRCA* deficiencies to use the error-prone NHEJ to fix double-strand breaks.<sup>5</sup> Non-*BRCA* deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors.<sup>8</sup> The rationale for anticancer activity in a subset of non-*gBRCAmut* tumors is that they share distinctive DNA repair defects with *gBRCAmut* carriers, a phenomenon broadly described as “BRCAness.”<sup>9</sup> DNA repair defects can be caused by germline or somatic alterations to the homologous recombination DNA repair pathway. In a recent analysis of approximately 500 high-grade serous ovarian adenocarcinoma tumors, approximately 50% contained homologous recombination defects.<sup>10</sup> A subset of these tumors had biologically plausible molecular alterations that may make them sensitive to PARP inhibition by niraparib. A similar analysis of triple-negative breast cancer indicates that 43% to 44% of these patients have tumors with homologous recombination defects.<sup>11</sup> Homologous recombination is a complex pathway, and several genes other than *BRCA1* and *BRCA2* are required either to sense or repair DNA double-strand breaks via the homologous recombination pathway. Therefore, PARP inhibitors are also selectively cytotoxic for cancer cells with deficiencies in DNA repair proteins other than *BRCA1* and *BRCA2*.<sup>5,9,12</sup>

Recent clinical studies have shown PARP inhibitors to be active in breast and ovarian cancer. Clinical anticancer activity with PARP inhibitors has been seen in both patients with *gBRCAmut* and without *gBRCAmut*; however, activity is more robust in patients with the germline mutation.<sup>5,8,13-19</sup> In summary, treatment with PARP1/2 inhibitors represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair. Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of the tumor cells than that of normal cells.

## 2.2.2 Immune Surveillance and PD-1 inhibitors

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.<sup>20</sup> Accumulating evidence shows a correlation

between tumor-infiltrating lymphocytes in cancer tissue and prognosis in various malignancies.<sup>21-33</sup> In particular, the presence of cluster of differentiation (CD)8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells correlate with improved prognosis and long-term survival in many solid tumors.<sup>29,34-40</sup> The programmed death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control.<sup>41</sup> The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed death-ligand 1 [PD-L1] and programmed -death ligand- 2 [PD-L2]). The structures of murine PD-1 alone<sup>42</sup> and in complex with its ligands were the first to be resolved,<sup>43,44</sup> and more recently the nuclear magnetic resonance-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported.<sup>45</sup> PD-1 and family members are Type I transmembrane glycoproteins containing an Ig variable type (V-type) domain responsible for ligand binding and a cytoplasmic tail, which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine based- switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP1 and SHP-2 to the ITSM within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3 $\zeta$ , PKC $\theta$ -, and ZAP70, which are involved in the CD3 T cell signaling cascade.<sup>46</sup> The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4.<sup>47</sup> PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, T regs, and natural killer cells.<sup>48</sup> Expression has also been shown during thymic development on CD4-/CD8- (double-negative) T cells,<sup>49</sup> as well as subsets of macrophages<sup>50</sup> and dendritic cells.<sup>51</sup> The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types.<sup>52</sup> PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is predominantly expressed on antigen presenting- cells found in lymphoid tissue or chronic inflammatory environments.<sup>52</sup> Both ligands are Type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor,<sup>53,54</sup> which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors.<sup>55</sup> As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer.<sup>56</sup>

### 2.2.3 Niraparib

Niraparib is an orally available, potent, and highly selective PARP1 and PARP2 inhibitor. Niraparib co-crystallizes with the human PARP1 catalytic domain and has been shown to inhibit PARP1 and PARP2 activity in vitro with a half-maximal inhibitory concentration (IC50) of 3.8 and 2.1 nM, respectively. In cultured cells, niraparib inhibited PARP-dependent PARylation

stimulated by DNA damage with an IC50 of 4 nM and a 90% inhibitory concentration (IC90) of 40 nM.

Niraparib demonstrated a 25- to 200-fold increased cytotoxicity against cancer cell lines that were engineered to be homologous recombination deficiency (HRD) via BRCA1 or BRCA2 silencing or that carried BRCA1 or BRCA2 mutations, as compared to control cell lines capable of homologous recombination. Treatment of xenograft-bearing mice with clinically relevant doses resulted in tumor regression in BRCA and ATM mutant tumor models. At the doses used in these studies, 90% PARP inhibition was observed in tumors for up to 24 hours after a single dose. Additionally, PARP inhibition in tumor tissue was greater and more durable than PARP inhibition in the corresponding PBMCs, where inhibition levels were  $\leq 50\%$  24 hours after dosing.

Niraparib has also been evaluated in more than 30 ovarian cancer (OC) patient-derived xenograft (PDX) and tumor cell line-derived xenograft models. Tumor regression has been observed in BRCA1 and BRCA2 mutant xenografts and in HRDpos wild-type BRCA (BRCAwt) models. Additionally, tumor growth inhibition (TGI) was observed in some models that were HRDneg as defined by the Myriad myChoice HRD test.

Niraparib is currently being developed as a therapy for tumors with defects in the homologous recombination DNA repair pathway including OC, triple-negative breast cancer (TNBC), non-small cell lung cancer, and prostate cancer either as a monotherapy or in combination with immunotherapy or androgen receptor-targeted therapies.

Niraparib as a single agent is currently or has been evaluated in phase I trials as well as in multiple combination studies (refer to Niraparib Investigator Brochure). As of the clinical cutoff date of 19 August 2018, a total of 1,379 patients have received at least 1 dose of niraparib in GSK/TESARO-sponsored studies and comprise. The highest dose studied in the Phase 1 trials was 400 mg QD, and the dose-limiting toxicity (DLT) at this dose was thrombocytopenia. The recommended Phase 2 dose for niraparib monotherapy was 300 mg QD, and this dose was subsequently approved in the United States (US) in March 2017 and in the European Union (EU)/European Economic Area (EEA) in November 2017 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response (CR) or partial response (PR) following platinum-based chemotherapy.

Safety of niraparib has been established using a Pooled Patient Population from 13 GSK/TESARO-sponsored studies and 1 MSD-sponsored study (PN001) of niraparib conducted prior to and following its approval. In the Pooled Safety Population, over 98% of niraparib-treated patients reported at least 1 Treatment Emergent Adverse Event (TEAE). Approximately 72% of patients experienced an event that was Grade 3 or higher in severity. TEAEs leading to treatment discontinuation occurred in approximately 18% of patients. TEAEs leading to death occurred in 29 of 1,379 (2.1%) patients. The most frequently reported TEAEs (events. TEAEs leading to death occurred eg, nausea, vomiting, and constipation), constitutional (eg, fatigue and decreased appetite), hematological (eg, anemia and thrombocytopenia), neurological (eg, headache), or psychiatric (eg, insomnia) in nature. The events were generally considered related to study drug but were mostly mild (Grade 1) to moderate (Grade 2) in severity. Grade 3 or

higher TEAEs consisted primarily of hematological events (eg, anemia [26%], thrombocytopenia [21%], and neutropenia [8.8%]) and investigations (eg, platelet count decreased and neutrophil count decreased), followed by gastrointestinal events (nausea [5.1%], vomiting [4.1%], and abdominal pain [3.7%]).

#### 2.2.4 Dostarlimab (TSR-042)

Dostarlimab is a humanized IgG4 mAb that binds with high affinity and specificity to PD-1, thereby inhibiting the binding of PD-1 to both PD-L1 and PD-L2. This antibody was generated using a proprietary platform that employs affinity maturation to select highly specific antibodies with desired functional characteristics. The functional antagonist activity of dostarlimab was confirmed in an MLR assay, demonstrating enhanced IL-2 production upon addition of dostarlimab. Furthermore, dostarlimab has an acceptable safety profile based on toxicology studies in monkeys and in other nonclinical experiments. Based on published clinical experience with antibodies of the same drug class and the nonclinical data for dostarlimab, the safety and activity profile of dostarlimab is in line with the expectations for this class of agent, supporting its clinical investigation in patients with cancer. Dostarlimab is currently being developed as a monotherapy for patients with recurrent or advanced solid tumors including endometrial cancer (MSS and MSI-H tumors), NSCLC, and non-endometrial MSI-H and polymerase  $\epsilon$ -mutated cancer. In addition, dostarlimab developed as a combination therapy with other therapeutic agents for patients with advanced solid tumors (including melanoma, NSCLC, and colorectal cancer) or advanced or metastatic cancer (including endothelial ovarian cancer, triple-negative breast cancer, and urothelial carcinoma).

In Part 1 (dose escalation) of Study 4010-01-001, 21 subjects were dosed with dostarlimab Q2W: 6 subjects at 1 mg/kg, 3 subjects at 3 mg/kg, and 12 subjects at 10 mg/kg. Data from 20 of these subjects have been used for PK parameter calculations. In Part 2A of Study 4010-01-001, 2 fixed dose regimens, 500 mg Q3W (n=6) and 1,000 mg Q6W (n=7), were evaluated for both safety and PK. Dostarlimab PK continues to be evaluated in Part 2B of Study 4010-01-001 through sparse sampling for all subjects upon administration of first, fourth, fifth, eighth, and twelfth doses at predose and 0.5 and 1.5 hours post dose. For the first 4 doses, subjects received dostarlimab at 500 mg with a 21-day cycle (Q3W). Starting at dose 5, subjects received dostarlimab at 1,000 mg with a 42-day cycle (Q6W). There was an approximately 2-fold dostarlimab accumulation after 4 doses of 500 mg Q3W. The dostarlimab concentrations at Cycle 5 and Cycle 8 are comparable, while the concentration was slightly increased at Cycle 12. Unless otherwise directed by a specific protocol, the recommended dose of dostarlimab as monotherapy is 500 mg every 3 weeks for 4 cycles followed by 1,000 mg every 6 weeks for all cycles thereafter.

As of 21 January 2019, 335 subjects with heavily pretreated advanced solid tumors have been treated with dostarlimab in Study 4010-01-001: 21 subjects in Part 1 and 314 subjects in Part 2A and 2B (refer to dostarlimab investigator brochure for more information). The majority of these subjects (93.7%) reported at least 1 TEAE, with events of fatigue, nausea, and diarrhea being the most frequently reported. Study drug-related TEAEs of Grade  $\geq 3$  were reported in 36 subjects (10.7%). The majority of these study drug-related events occurred in only 2 subjects each, with

the exception of fatigue (6 subjects), alanine aminotransferase increased (4 subjects), anemia (4 subjects), aspartate aminotransferase increased (3 subjects), and lipase increased (3 subjects). Serious adverse events (SAEs) occurred in 106 subjects (31.6%); in 21 of these subjects, these SAEs were considered study drug-related. Thirty-one subjects (9.3%) had an adverse event (AE) leading to study drug discontinuation. Of the 31 subjects, 17 subjects (5.1%) had an AE leading to study drug discontinuation that was considered study drug-related. Nine subjects (2.7 %) developed an AE not related to study drug that led to death. No study drug-related AE leading to death was reported.

### 2.3 Rationale for Combination of niraparib and dostarlimab

Fanconi Anemia (FA) and FA-related DNA repair pathways alterations have been associated with cumulative tumor mutational burden (TMB) due to genomic instability. DNA pathway repair mutations have been reported in 17% of sporadic HNSCC. PARP inhibition (PARPi) has already demonstrated efficacy as a single agent in cancers which harbor a DNA repair defect, most notably, BRCA mutant breast and ovarian cancer and now being studied in HNSCC. Despite the effectiveness of the PD-1 and PARP inhibition individually, little clinical data exists for the combination. In vitro, PARPi upregulates PD-L1 expression in breast cancer lines and animal models via inactivation of glycogen synthase kinase 3 (GSK3 $\beta$ ). Interestingly, blockade of PD-L1 re-sensitized PARPi treated cells to induce T-cell killing. Combination of PARPi and anti-PD-L1 therapy significantly increased therapeutic efficacy in vivo compared to single agent. Additionally, GSK3 is also a key upstream kinase that regulates PD-1 expression in CD8 T cells and inhibition of GSK3 blocks PD-1 expression resulting in increased function of CD8 cytotoxic T cells. Furthermore, PD-1 inhibition in the setting of high TMB, which may be caused or exacerbated by PARP inhibition, is associated with a better and longer duration of response. We hypothesize that PARP inhibition sensitizes tumors to immunotherapy drugs ultimately increasing response rates without overlapping toxicity. Therefore, in this study, we will be investigating the combination of dostarlimab, an immunoglobulin G4k humanized monoclonal antibody targeting PD-1, with niraparib.

The combination of niraparib and PD-1 inhibitors has been studied in other cancers. TOPACIO/KEYNOTE-162 is an open-label Phase 1/2 clinical study of niraparib in combination with pembrolizumab in patients with advanced or metastatic TNBC and in patients with recurrent OC <sup>57</sup>. Phase 1 of the study evaluated the DLTs of combination treatment with niraparib and pembrolizumab and established the recommended Phase 2 dose of 200 mg oral niraparib QD in combination with 200 mg IV pembrolizumab on Day 1 of each 21-day cycle. Phase 2 of the study evaluated the clinical activity of and duration of response to combination treatment with niraparib and pembrolizumab for patients with recurrent platinum-resistant OC. The overall response rate (ORR) for OC was 18% (90% CI, 11%-29%), with a disease control rate of 65% (90% CI, 54%-75%). The most common TRAEs (both phase 1 and 2) were fatigue (28 [53%]), nausea (22 [42%]), anemia (19 [36%]), and constipation (19 [36%]). The most common at least grade 3 were anemia (11 [21%]) and thrombocytopenia (5 [9%]). No treatment-related patient deaths or cases of myelodysplastic syndrome or acute myeloid leukemia occurred. Immune-related adverse effects occurred in 10 patients (19%) with grade 3 or greater in 3 patients (6%). No grade 4 immune-related adverse effects occurred.

JASPER is an open-label, multi-arm, Phase 2 study that is evaluating the safety and efficacy of niraparib administered alone and in combination with a PD-1 inhibitor (pembrolizumab or dostarlimab) in patients with non-small cell lung cancer (locally advanced and metastatic) whose tumors have high PD-L1 expression (NCT03308942). Combination therapy in this patient population was administered as 200 mg oral niraparib QD plus 200 mg IV pembrolizumab on Day 1 of each 21-day cycle in stage 1, and 200 mg oral niraparib QD plus dostarlimab 500 mg IV in cycles 1 to 4 and 1000 mg IV starting cycle 6 in stage 2. Safety and efficacy data are pending on this study.

The STAR study (NCT04068753) is a phase II study in recurrent or progressive cervical cancer investigating the combination of niraparib (200mg daily) and dostarlimab (500 mg IV, every three weeks for 4 cycles followed by 1000 mg every six weeks for up to two years). The primary objective is efficacy and response rate. This study is ongoing.

Based on the above combination studies and on average body WT of 75 kg, a fixed dose of 200 mg oral niraparib QD is included in the current study. Given that the combination treatment did not result in higher than expected AEs of each agent when used alone, the single agent recommended dose of dostarlimab 500 mg every 3 weeks for 4 cycles followed by 1,000 mg every 6 weeks for all cycles thereafter will be used on this study in combination with niraparib. Reviewing the above AEs, there is minimal expected overlap in treatment related toxicity of the two agents.

## 2.4 Correlative Studies Background

It is well known that human cancers exhibit genomic instabilities and an increased mutation rate that greatly increase their reliance on DDR pathways. When DDR is activated, PARP1 binds to single-strand and double-stranded breaks working to repair the defects.<sup>58</sup> As mentioned in the background, PARPi gained popularity in breast and ovarian cancers showing that PARPi selectively kills homologous repair (HR) deficient cancer cells. While the mechanism of action is up for debate, it is thought that PARPi cytotoxicity results from the accumulation of single-stranded breaks, leading to replication fork collapse and double stranded breaks.<sup>59</sup> In vitro, PARPi has been shown to have an effect on both HR-deficient and HR-proficient HNSCC cell lines. In HR-deficient cells, PARPi acts as radiosensitizer in both HPV positive and negative cells lines by disabling DNA replication fork elongation.<sup>59,60</sup> PARPi works as a radiosensitizer in HR-proficient cells in a similar manner, but as expected, much higher doses are needed to see an effect as compared to HR-deficient cells lines.<sup>61</sup>

As previously stated, BRCA1 and BRCA2 mutations are well recognized as molecular targets for PARPi in many cancers.<sup>62</sup> Although HR mutations rarely occur in HNSCC, as identified by only 6% of patients exhibiting BRCA1/2 mutations, alternative HR repair genes that are susceptible to PARPi have been identified in HNSCC.<sup>63</sup> Mutations in the Fanconi anemia (FA) pathway as well as mutations in ataxia telangiectasia (ATM) and PTEN have been linked to HR-deficient HNSCC.<sup>64-67</sup> Therefore, other markers outside of BRCA1 and BRCA2 are necessary to identify HR-deficiency.

As mentioned previously, via GSK3 inactivation, PARPi can elicit an anti-tumor immune

response through decreased PD-1 expression on CD8+ T-cells, thereby increasing the cytotoxic capabilities of T-cells.<sup>68</sup> Recent work from Ding *et al.* has shown PARPi can also elicit an anti-tumor immune response through stimulator of interferon genes (STING) signaling in Brac1-deficient ovarian tumors.<sup>69</sup> Upon PARPi, there is an increase in peripheral and intratumoral functionally active CD4+ and CD8+ T-cells. Mechanistically, this occurs via activation of the STING pathway in antigen presenting cells, specifically dendritic cells. The described immune responses were specific to HR-deficient ovarian cancer mouse models, not HR-proficient models. The immunomodulatory effects of PARPi in HNSCC are relatively unknown, especially in combination with PD-1 inhibition.

Therefore, in this study we will investigate: (1) Correlation of the activity of niraparib and dostarlimab with the molecular profile of the tumor (IHC and RNA analysis of pre and post-tumor samples) to associate gene expression signatures with clinical benefit from this drug combination with special attention to GSK3 and STING pathways. (2) Evaluate for mutations in DDR pathways as well as overall genomic alteration index (mutation burden index) that associates with clinical benefit from combination in recurrent and/or metastatic HNSCC patients. (3) Determine immunogenicity, PD1 expression on T cells, T cell functionality before and after niraparib and dostarlimab combination.

### **3. PATIENT SELECTION**

#### **3.1 Eligibility Criteria**

1. Patients must have histologically, or cytologically confirmed recurrent or metastatic non cutaneous HNSCC for which there are no surgical or radiation curative options.
2. Patients must have failed at least one line of prior therapy, including surgery, radiation therapy, chemotherapy and/or an anti-PD1/PDL1 inhibitor.
3. Patients must have evaluable/measurable disease, according to RECIST version 1.1, as assessed by the Investigator. Lesions in prior radiation field must have demonstrated progression on subsequent imaging in order to qualify.
4. Age  $\geq 18$  years at time of study entry
5. ECOG performance status  $\leq 2$  (Karnofsky  $\geq 60\%$ , see Appendix A).
6. Patients must have adequate organ and marrow function as defined below:
  - leukocytes  $\geq 3,000/\text{mcL}$
  - absolute neutrophil count  $\geq 1,500/\text{mcL}$
  - Hemoglobin  $\geq 9.0 \text{ g/dL}$
  - platelets  $\geq 100,000/\text{mcL}$
  - total bilirubin  $\leq 1.5 \times$  institutional upper limit of normal (ULN)
  - OR
  - direct bilirubin  $\leq 1 \times \text{ULN}$

- AST(SGOT)/ALT(SGPT)  $\leq 2.5 \times$  institutional ULN (5x ULN acceptable for those with known liver metastases)
  - Serum creatinine  $\leq 1.5 \times$  institutional ULN
    - OR
  - Calculated creatinine clearance  $\geq 50$  mL/min by the Cockcroft-Gault formula (see Appendix B).
  - International normalized ratio (INR) or prothrombin time (PT)  $\leq 1.5 \times$  ULN unless
  - patient is receiving anticoagulant therapy as long as PT or partial thromboplastin (PTT) is within therapeutic range of intended use of anticoagulants. Activated partial thromboplastin time (aPTT)  $\leq 1.5 \times$  ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulant
7. Patients must be able to swallow pills. Feeding tubes are allowable as long as patient can swallow pills.
  8. Archival tissue must be available or patient must be willing to provide fresh biopsy (core or excisional).
  9. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
  10. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
  11. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
  12. Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression for at least 4 weeks without need for corticosteroid are eligible.
  13. Patients with known untreated, asymptomatic brain metastases (i.e., no neurological symptoms, no requirement for corticosteroids, no or minimal surrounding edema, no lesion  $> 1.0$  cm and a maximum of 3 lesions) are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.
  14. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
  15. Participant must agree to not donate blood during the study or for 90 days after the last dose of study treatment.

16. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Female participant has a negative serum pregnancy test within 7 days prior to taking study treatment if of childbearing potential and agrees use an adequate method of contraception from screening through 180 days after the last dose of study treatment, or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):
  - $\geq 45$  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 an adequate barrier method throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. **See 6.8** 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.
17. Male participant agrees to use an adequate method of contraception (see **Section 6.8** for a list of acceptable birth control methods) starting with the first dose of study treatment through 3 months after the last dose of study treatment. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
18. Male participant agrees not donate sperm during niraparib therapy and for 3 months after receiving the last dose.
19. Participant must agree to not breastfeed during the study or for 30 days after the last dose of study treatment.
20. Participant receiving corticosteroids may continue as long as their dose is stable ( $\leq 10$ mg prednisone daily) for least 4 weeks prior to initiating protocol therapy.
21. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
22. Ability to understand and the willingness to sign a written informed consent document.

### **3.2 Exclusion Criteria**

1. Patients with nasopharyngeal and salivary gland tumors will be excluded.
2. Patients with a prior or concurrent malignancy that is symptomatic, progressing and/or

requires treatment, and whose natural history have the potential to interfere with the safety or efficacy assessment of the investigational regimen are not eligible for this trial.

3. Patients who have had chemotherapy or radiotherapy within 2 weeks prior to entering the study. *Palliative radiotherapy is allowable and does not require wash out.* Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
4. Patients who have not recovered from adverse events due to prior anti-cancer therapy (i.e., have residual toxicities > Grade 1) with the exception of alopecia. *Grade 2 neurotoxicity is allowable as long as clinically stable.*
5. Patients who are receiving any other investigational agents or simultaneously enrolled in any interventional trial.
6. Participant must not have had major surgery  $\leq$  3 weeks prior to initiating protocol therapy and participant must have recovered from any surgical effects.
7. Participant must not have received investigational therapy  $\leq$  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.
8. Participant must not have a history of interstitial lung disease, (non-infectious) pneumonitis that required steroids and has current pneumonitis.
9. Prior exposure to both immunotherapy drugs (PD-1, PDL-1, CTLA-4 inhibitors) and PARP inhibitors. Single exposure to either immunotherapy or PARP inhibitors is allowable.
10. Patient experienced  $\geq$  Grade 3 immune-related AE with prior immunotherapy, or recurrent immune-related AEs of any grade that required discontinuation of prior immunotherapy, with the exception of non-clinically significant lab abnormalities.
11. History of allergic reactions attributed to compounds of similar chemical or biologic composition to niraparib or dostarlimab.
12. Patients with uncontrolled intercurrent illness.
13. Patients with psychiatric illness/social situations that would limit compliance with study requirements.
14. Requirement of any use of steroids greater than the equivalent of 10mg prednisone daily is not allowed.
15. Patients with history of autoimmune diseases requiring immunosuppressive treatment in addition to or instead of steroids are excluded.

16. Participant must not have received a transfusion (platelets or red blood cells)  $\leq$  4 weeks prior to initiating protocol therapy.
17. Participant must not have received colony stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte macrophage colony stimulating factor, or recombinant erythropoietin) within 4 weeks prior initiating protocol therapy.
18. Participant has had any known Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted  $>$  4 weeks and was related to the most recent treatment.
19. Participant must not have any known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).
20. Pregnant women are excluded from this study because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with niraparib or dostarlimab, breastfeeding should be discontinued if the mother is treated with niraparib or dostarlimab.
21. Participant has received a live vaccine within 14 days of initiating protocol therapy. Examples of live vaccines include, but are not limited to, the following: intranasal influenza, measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

### **3.3 Inclusion of Women and Minorities**

Women and minorities will be included.

## **4. REGISTRATION PROCEDURES**

### **4.1 Patient Registration**

For all subjects at both the University of Cincinnati and any other participating sub-site(s), the University of Cincinnati PI, Dr. Wise-Draper, must confirm subject eligibility prior to registration.

To register a patient, the following documents should be completed by the both the UC and sub-site research teams and emailed to the coordinating center PI and UC study monitor:

- a. Signed patient consent form
- b. Source documents verifying every inclusion and exclusion criteria

Upon receipt, the UC PI (or delegated UC team member) will confirm subject eligibility. Once, confirmed, the UC research team or sub-site may then proceed to register the subject to enrolled status within the study EDC.

## **4.2 General Guidelines**

Following registration, patients should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator and study Monitor should be notified of cancellations as soon as possible.

## **5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES**

### **5.1 Biomarker Plan**

**Table 1: List of Biomarker Assays in Order of Priority**

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
1	Genomic Mutational Analysis, TMB analysis	Whole Exome Sequencing and Next Generation Sequencing	Integrated  Genomic analysis to determine rate of MMR deficiency and DDR defects	M	Baseline only	FFPE Slides	10 slides	Caris
1	Mismatch Repair	Immunohistochemistry	Integrated  IHC analysis to determine MMR defects	M	Baseline only	FFPE slides	10 slides (combined with #1)	Caris
2	RNA Expression Analysis	RNA Seq	Exploratory  for correlation of expression signatures before and after treatment	O	Baseline and Day 22	FFPE Slides and scroll	10 slides and 1 tissue scroll	Caris
3	Protein Expression Analysis	Immunohistochemistry	Exploratory  For correlation of immune, GSK3 and STING Pathway markers before and after treatment	O	Baseline and Day 22	FFPE Slides	10 slides	Wise-Draper/Translational Laboratory
4	Characterization of peripheral blood immune activation	Flow Cytometry	Exploratory  For Immune Cell Quantitation and Activation	O	Baseline, Day 8 and Day 22	PBMCs isolated from Whole Blood	4 EDTA tubes (40 mls) per time point	Wise-Draper/Translational Laboratory
5	Cytokine analysis	ELISA and/or Luminex	Exploratory  To detect cytokine expression	O	Baseline, Day 8 and Day 22	Plasma isolated from blood and serum from red-top serum tubes	5mL of plasma will be isolated from the whole blood collected for PBMC isolation. In addition, serum will be isolated from red-top tubes.	Wise-Draper/Translational Laboratory

6	Characterization of circulating tumor DNA	Digital PCR	Exploratory  To assess presence of known mutations as identified via Caris genomic mutational analysis	O	Baseline, Day 8, and Day 22	Plasma isolated from blood	5mL of plasma will be isolated from the whole blood collected for PBMC isolation	Yaping Liu Laboratory
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**Table 2. Specimen Collection Schedule**

Specimen Type	Baseline (Pre-treatment)	Day 8	Day 22
Tissue (30 FFPE slides and 1 scroll but block preferred to be sectioned as needed by Translational Laboratory)	X		
Fresh biopsy (18 gauge core or larger or excisional) and prepared as block			X
Blood (45mls in 4 10mL EDTA tubes and 1 5mL red-top serum tube)	X	X	X

## 5.2 Integrated Correlative Studies

Please consult the study lab manual for more details.

### Genomic Tissue Analysis

- Collection of Specimen(s): Tumor block (10 FFPE slides) will be collected at screening and day 22; Archival is acceptable for pre-treatment
- Handling of Specimens(s): Normal operating procedures
- Shipping of Specimen(s): Ship per standard operating procedures; Notify CTO Lab by email at ctolabuccc@ucmail.uc.edu, ***the day of shipping the sample***.
- Site Performing Correlative Study: University of Cincinnati, Wise-Draper/Translational Laboratory; CARIS
- MSI and TMB will be determined by NGS, MMR will be also be determined by IHC
- The following HR-DDR pathologic gene mutations will be evaluated by NGS: *ARID1A, ATM, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CHEK1/2, FANCA/C/D2/E/F/G/L, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, or WRN*
- Phenotypic Homologous Repair Deficiency (HRD) will also be assessed by comparing previously platinum sensitive (no relapse within 6 months) vs. platinum resistant patients and sensitivity to PARPi

### 5.3 Exploratory/Ancillary Correlative Studies

Please consult the study lab manual for more details.

#### RNA and Protein Expression Analysis

- Collection of Specimen(s): Tumor block (if block is unavailable, 20 FFPE slides may be permissible but need verification from PI) will be collected at screening and Day 22; Archival is acceptable for pre-treatment
- Handling of Specimens(s): Normal operating procedures
- Shipping of Specimen(s): Ship per standard operating procedures; Notify CTO Lab by email at [ctolabuccc@ucmail.uc.edu](mailto:ctolabuccc@ucmail.uc.edu), ***the day of shipping the sample***.
- Site Performing Correlative Study: University of Cincinnati, Wise-Draper/Translational Laboratory

#### Peripheral Blood Immune Phenotypes

- Collection of Specimen(s): 4 EDTA 10ml tubes will be collected at baseline (pre-treatment), Day 8, and Day 22
- Handling of Specimens(s): Do not shake or freeze tubes;
- Label each tube as follows:
  - Clinical trial study number (HN1903)
  - Subject's (ID) (site number, patient ID example: HN02-01)
  - Date the tube was drawn (example: 2/2/2018)
  - Time of blood draw (example: 15:00)
  - Study time-point (example: Day 1)
    - Isolation of PBMCs to be performed after delivery to laboratory on-site.

#### Shipping of Specimen(s):

- Isolated PBMCs will be stored in liquid nitrogen at site and batch shipped according to standard operating procedures.
- Place sample in absorbent pack and 95kPa biohazard specimen transport bag along with sample requisition form.
- Place biohazard specimen bag containing frozen PBMCs into a frozen shipping box and cover with approximately 3lbs of dry ice.
- Follow IATA shipping instructions and standards by properly labeling all shipping boxes to prevent delays.
- Attach provided FedEx Airbill to the shipping box.
- Ship per standard operating procedures; Notify CTO Lab by email at [ctolabuccc@ucmail.uc.edu](mailto:ctolabuccc@ucmail.uc.edu), ***the day of shipping the sample***.
- Samples to be shipped Monday-Thursday only via FedEx Priority Overnight.

Site(s) Performing Correlative Study: University of Cincinnati, Wise-Draper/Translational Laboratory and Ohio State University

#### Cytokine Levels

- Collection of Specimen(s): Plasma will be isolated from whole blood prior to isolation of PBMCs for phenotypic analysis. Additionally, one 5mL red-top serum tube will be

collected and serum will be isolated.. Tubes will be collected at baseline (pre-treatment), Day 8, and Day 22 as previously stated.

Handling of Specimens(s): Do not shake or freeze tubes;

- Label each tube as follows:
- Clinical trial study number (HN1903)
- Subject's (ID) (site number, patient ID example: HN02-01)
- Date the tube was drawn (example: 2/2/2018)
- Time of blood draw (example: 15:00)
- Study time-point (example: Day 1)
- Separation of plasma to be performed after delivery to laboratory below

Shipping of Specimen(s):

- Isolated plasma will be stored at site in a -80 degree freezer and batch shipped according to standard operating procedures.
- Place sample in absorbent pack and 95kPa biohazard specimen transport bag along with sample requisition form.
- Place biohazard specimen bag containing frozen PBMCs into a frozen shipping box and cover with approximately 3lbs of dry ice.
- Follow IATA shipping instructions and standards by properly labeling all shipping boxes to prevent delays.
- Attach provided FedEx Airbill to the shipping box

Ship per standard operating procedures; Notify CTO Lab by email at [ctolabuccc@ucmail.uc.edu](mailto:ctolabuccc@ucmail.uc.edu) **the day of shipping the sample.**

Site(s) Performing Correlative Study: University of Cincinnati, Wise-Draper/Translational Laboratory and Ohio State University

Characterization of circulating tumor DNA

- Collection of Specimen(s): Plasma will be isolated from whole blood prior to isolation of PBMCs for phenotypic analysis. No additional tubes will be collected outside of the 40mL of whole blood in 4 EDTA tubes. Tubes will be collected at baseline (pre-treatment), Day 8, and Day 22 as previously stated.

-

Handling of Specimens(s): Do not shake or freeze tubes;

- Label each tube as follows:
- Clinical trial study number (HN1903)
- Subject's (ID) (site number, patient ID example: HN02-01)
- Date the tube was drawn (example: 2/2/2018)
- Time of blood draw (example: 15:00)
- Study time-point (example: Day 1)
- Separation of plasma to be performed after delivery to laboratory below

Shipping of Specimen(s):

- Isolated plasma will be stored at site in a -80 degree freezer and batch shipped according

- to standard operating procedures.
- Place sample in absorbent pack and 95kPa biohazard specimen transport bag along with sample requisition form.
- Place biohazard specimen bag containing frozen PBMCs into a frozen shipping box and cover with approximately 3lbs of dry ice.
- Follow IATA shipping instructions and standards by properly labeling all shipping boxes to prevent delays.
- Attach provided FedEx Airbill to the shipping box

Ship per standard operating procedures; Notify CTO Lab by email at [ctolabuccc@ucmail.uc.edu](mailto:ctolabuccc@ucmail.uc.edu), **the day of shipping the sample.**

Site(s) Performing Correlative Study: Will be processed at University of Cincinnati, Wise-Draper/Translational Laboratory and Ohio State University and analyzed in Yaping Liu's Laboratory at Cincinnati Children's Hospital Medical Center.

## 6. TREATMENT PLAN

**The Trial Flow Chart - Section 11** summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

### 6.1 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history. Medical history should be graded per CTCAE v.5 to aid in assessment of potential grade changes with respect to adverse events.

### 6.2 Prior and Concomitant Medications Review

#### Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial (time of consent). Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

#### Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

### 6.3 Disease Details and Treatments

### 6.3.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

### 6.3.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

### 6.3.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

### 6.3.4 Assignment of Screening/Study Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to eligibility being confirmed. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. The University of Cincinnati will provide any sub-sites with instructions for the methods to be used in assigning screening information to potential subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit. The screening number will be their study number as well once they are allocated to treatment.

### 6.3.5 Trial Compliance

Interruptions from the protocol specified treatment plan for **greater than 4 weeks delay of niraparib or dostarlimab doses** will result in permanent discontinuation.

The total volume of dostarlimab infused will be compared to the total volume prepared to determine compliance with each dose of dostarlimab administered. Treatment with standard therapies will be prepared and administered as per the approved product label.

## 6.4 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in **Section 10**. Appropriate dose modifications are described in **Section 7**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

<b>Table 3. Regimen Description</b>				
<i>Agent</i>	<i>Premedications; Precautions</i>	<i>Dose</i>	<i>Route</i>	<i>Schedule</i>
Niraparib**	No premedications No steroids	200 mg	Oral	Daily
Dostarlimab	No premedications	500 mg for first 4 doses followed by 1000 mg every 6 weeks (42-day cycle)	IV over 30 min	Day 8 of Cycle 1 then Day 1 of subsequent cycles
** The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course at Day 1 of each cycle.				

#### 6.4.1 Niraparib

Patients will receive Niraparib starting on Day 1. Niraparib will be administered as continuous daily dose according to Table 3 above. Niraparib should be swallowed whole and not opened, crushed or chewed. Food does not significantly affect the absorption of niraparib; therefore, niraparib may be taken without regard to meals. Participants should take doses at approximately the same times each day. Bedtime administration may be a potential method for managing nausea. 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.

If niraparib is dose reduced, participants should be instructed to continue using their current supply at their new dose until their supply has been exhausted.

Participants must be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed and documented.

#### 6.4.2 TSR-042 Administration

TSR-042 will be administered via a 30-minute (-5-minute/+15-minute infusion window allowed) IV infusion on Day 8, then Day 1 of every 21-day cycle (i.e., Q3W) at 500 mg for the next 3 doses, followed by 1,000 mg on Day 1 of every 42-day cycle (i.e., Q6W) thereafter until the patient discontinues study treatment.

### 6.5 Clinical Procedures/Assessments

#### 6.5.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. Please refer to **section 10** for detailed information regarding the assessment and recording of AEs.

#### 6.5.2 Full Physical Exam

The investigator or qualified designee will perform a full physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Full physical exam requires assessment of major organ sites (Constitutional, Head and Neck, Cardiovascular, Pulmonary, Abdominal, Musculoskeletal, Lymph, Neurological, and Skin).

#### 6.5.3 Directed Physical Exam

Except for at screening, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

#### 6.5.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

Blood pressure and heart rate monitoring will be required weekly for the first 2 months of therapy. After the first 2 months of therapy, blood pressure and heart rate monitoring needs to be checked monthly for the first year and at scheduled clinic visits and as clinically indicated thereafter while the patient is taking niraparib. Subjects will not be provided with a BP/HR log. Subjects will self-monitor using their own personal devices or utilizing resources at local pharmacies or clinics.

#### 6.5.5 Eastern Cooperative oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (**see Appendix A**) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

#### 6.5.6 Tumor Imaging and Assessment of Disease

Pre-operative imaging will be performed at each institution and only site investigators (PI or Sub-PIs) may determine the assessment of disease recurrence.

### 6.5.7 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 4.

**Table 4. Laboratory Tests**

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum $\beta$ -human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	( $\beta$ -hCG) †
Platelet count	Alanine aminotransferase (ALT)	Protein	Total triiodothyronine (T3) (Reflex testing only)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free thyroxine (T4) (Reflex testing only)
Red Blood Cell Count		Microscopic exam ( <i>If abnormal</i> )	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	CO <sub>2</sub> or bicarbonate	Urine pregnancy test †	Prothrombin time PT/INR
Absolute Lymphocyte Count	Calcium		Partial Thromboplastin Time (PTT)
	Chloride		ACTH
	Glucose		Cortisol
	Phosphorus		
	Potassium		
	Sodium		
	Creatinine		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin ( <i>If total bilirubin is elevated above the upper limit of normal</i> )		
	Total protein		
	Blood Urea Nitrogen		
† Done on all women of child-bearing potential			

### 6.5.8 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal, should be followed in accordance with the safety requirements outlined in **Section 10**. Patients have the option of withdrawing from treatment only (therefore entering survival follow-up) or withdrawing from study. This should be documented clearly in the study EDC (REDCap) and within source documentation.

## 6.6 Visit Requirements

Visit requirements are outlined in **Section 11.0** - Trial Flow Chart.

### 6.6.1 Screening

Potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in eligibility requirements. Visit requirements are outlined in **Section 11.0** – Trial Flow Chart.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Laboratory tests and ECOG PS are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 7 days prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria and they have not yet started treatment; however, the cost of re-screening tests will not be covered by the study. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

### 6.6.2 Treatment Period

Visit requirements are outlined in **Section 11.0** – Trial Flow Chart.

### 6.6.3 On Treatment Imaging

Patients will undergo imaging (CT of affected target areas- ideally CT with contrast unless contraindication; MRI also acceptable) during screening phase and prior to C3D1 (-1 week) and then every 12 weeks beginning C6D1 (+/- 2 weeks) thereafter. If patient has a PR or CR, confirmation scans are required at 4 weeks after scan in which response was first observed.

The specific method of imaging to use (CT, CT with contrast, MRI) should remain consistent for the patient throughout the study, but may change per the subject's clinical needs. This determination for which imaging method to use will rely on the treating investigator's clinical discretion.

#### 6.6.4 Biopsy

A fresh biopsy must be obtained on day 22 +2weeks/- 1 week if clinically feasible. Biopsy should be at least 18 gauge core or excisional and sent to pathology for block preparation and shipped to the Wise-Draper/Translational laboratory (see Correlative section).

#### 6.6.5 End of Treatment Visit/30 Day Safety Follow-Up Visit

Refer to **Section 11.0** – Trial Flow Chart for specific visit requirements.

The mandatory Safety Follow-Up Visit should be conducted at least 30 days after the last dose of trial treatment but no later than 60 days after the last does of trial treatment. All AEs that occur prior to the 30 Day Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs and AEs that occur within 90 days after the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

If a patient will be initiating a new anti-cancer treatment after completion of study treatment but before 30 days post-study treatment have elapsed (or withdraws consent to all active treatment and follow-up activities such that the 30 day safety visit will not occur), then the events listed in the EOT (End of Treatment) visit should occur to ensure a safety assessment happens as soon as withdrawal to capture AEs before any new anti-cancer therapies start.

The 30 Day Safety Follow-up Visit and EOT visit can be the same day. For visits occurring close to the 30 day post treatment timeframe (e.g. Day 25 post treatment) the PI has discretion to consider such a visit to count for 30 day post-treatment safety follow-up.

#### 6.6.6 Survival Follow-up

Once a subject experiences confirmed progression or starts a new anti-cancer therapy, or withdraws consent to active treatment the subject moves into the survival follow-up phase and should be contacted by telephone or seen in clinic every 6 months (24 weeks +/- 2 weeks) for the first 2 years then annually (+/- 1 month) to assess for survival status until death, withdrawal of consent, or at the end of the study, whichever occurs first. Patients will be followed up to 5 years from the date of their last treatment.

### 6.7 General Concomitant Medication and Supportive Care Guidelines

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy
- Investigational agents other than niraparib and dostarlimab
- Radiation therapy is prohibited within 2 weeks prior to Day 1 and during study treatment. Note: Palliative radiation therapy to a small field may be allowed. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
- Any surgery that involves tumor lesions. Note: Administration of radiation therapy or surgery done that involves tumor lesions will be considered as disease progression at the time the procedure is performed.
- Niraparib weakly induces Cytochrome P450 (CYP)1A2 in vitro and is a relatively poor substrate for P-glycoprotein (P-gp); therefore, investigators are advised to use caution with the substrates for CYP1A2 with a narrow therapeutic range, i.e. theophylline and tizanidine.
- Live vaccines within **14** days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids should be avoided if possible. Steroids are allowed as short bursts of 5-7 days if required for clinical indication (i.e. COPD) or to modulate symptoms from an adverse event of suspected immunologic etiology. The chronic use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Prophylactic cytokines (ie, granulocyte colony-stimulating factor [G-CSF]) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current American Society of Clinical Oncology (ASCO) guidelines.

Subjects, who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management other than specified as allowed, should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

## **6.8 Contraception/Birth Control**

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

Male participants who are sexually active with partners of childbearing potential must agree to the use of a highly effective form of contraception throughout their participation beginning from the time of consent, during the study, and for 90 days after the last dose

of study treatment(s). Male participants must not donate sperm for 90 days after receiving the last dose of study treatments.

Highly effective forms of contraception are defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

## **6.9 Breast Feeding**

Participants must not breast-feed while receiving protocol therapy and for 30 days following the last dose of protocol therapy

## **6.10 Duration of Therapy**

In the absence of treatment delays due to adverse events(s), treatment may continue until disease progression, patient's decision to withdraw, intercurrent illness that prevents further administration of treatment, patient non-compliance, or termination of the study or the drug manufactured can no longer provide the study agent.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the study EDC (RedCAP) and within study source documentation.

## 6.11 Duration of Follow-Up

After removal from study active treatment, patients will be **followed for survival up to five years** or until death or becoming lost to follow-up, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event(s).

## 7. DOSING DELAYS/DOSE MODIFICATIONS

If an AE cannot be determined to be directly related to niraparib or dostarlimab (investigator feels it may be related to both agents), then individual guidelines for stopping, restarting or discontinuing should be followed for each drug below.

### 7.1 Niraparib

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 6). If the nonhematologic toxicity is appropriately resolved to baseline or Grade  $\leq 1$  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 6.

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. *However, dostarlimab may be continued if AE felt to be unrelated to dostarlimab.*

The dose interruption and modification criteria for niraparib for hematologic parameters will be based on blood counts and are outlined in Table 7. 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.

**Table 5: Recommended Dose Modifications for Adverse Reactions**

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

**Table 6: Niraparib Dose Modifications for Non-Hematologic Toxicity**

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

### 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 7: Niraparib Dose Modifications for Hematologic Toxicity**

Laboratory Abnormality	Intervention
Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time.	
Platelet count < 100,000/ $\mu$ L	<p><u>First occurrence:</u>            Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to <math>\geq 100,000/\mu</math>L.            Resume niraparib at same or reduced dose per Table 5.            If platelet count is &lt; 75,000/<math>\mu</math>L, resume niraparib at a reduced dose per table 5.</p> <p><u>Second occurrence:</u>            Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to <math>\geq 100,000/\mu</math>L.            Resume niraparib at a reduced dose per Table 5.            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 maximum dose reductions per Table 5.</p>
Neutrophil count < 1,000/ $\mu$ L	<p>Withhold niraparib for a maximum of 28 days and monitor blood counts until neutrophil counts return to <math>\geq 1,500/\mu</math>L.            Resume niraparib at a reduced dose per Table 5.            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 5.</p>
Hemoglobin $\leq 8$ g/dL	<p>Withhold niraparib for a maximum of 28 days and monitor blood counts until hemoglobin returns to <math>\geq 9</math> g/dL.            Resume niraparib at a reduced dose per Table 5.</p> <p>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 5.</p>
Hematologic adverse reaction requiring transfusion	<p>For patients with platelet count <math>\leq 10,000/\mu</math>L, 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.</p> <p>Resume niraparib at a reduced dose per table 5.</p>

Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.
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Abbreviation: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; QD = once daily.

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 resuming therapy. If the platelet count has not reverted within 28 days of interruption to  $\geq 100,000/\mu\text{L}$ , then study treatment (niraparib) should be discontinued.

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 (i.e., monthly) for the next 11 months of treatment, and periodically after this time. If patient is taken off treatment, CBC monitoring should occur weekly until Hg  $>9$ .

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

MDS and AML, including cases with fatal outcome, have been reported with the use of niraparib. In clinical trials, the duration of niraparib treatment in patients prior to developing MDS/AML varied from 1 month to  $>4$  years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received platinum-containing chemotherapy regimens and many had also received other DNA-damaging agents and radiotherapy. Some of the patients had a history of bone marrow suppression.

For suspected MDS/AML or prolonged hematological toxicities, the patient should be referred to a hematologist for further evaluation. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue study treatment.

For major surgery while on study treatment, up to 4 weeks (28 days) of study treatment interruption is allowed.

## 7.2 Dostarlimab

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  $\leq 1$ ; TSR-042 will be permanently discontinued for any drug-related Grade 4 AE. TSR042 must be permanently discontinued for certain irAEIs as described in Table 8. However, niraparib may continue if AE is felt to be unrelated to niraparib.

The specific immune-related AEs typically observed with anti-PD-1 antibodies will be managed according to the guidelines summarized below.<sup>70</sup>

### 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 8 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 8, dostarlimab should be withheld until the patient is clinically and metabolically stable and AEs have resolved to Grade  $\leq 1$ . 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, should be documented

**Table 8: Guidelines for Treatment of Immune-related Adverse Events of Interest**

Toxicity	Withhold Treatment for AE Grade	Restarting Treatment/Discontinuation
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 $\leq 5 \times$ ULN or total bilirubin $> 1.5$ and $\leq 3 \times$ ULN)	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4 (AST or ALT $> 5 \times$ ULN or total bilirubin $> 3 \times$ ULN)	Permanently discontinue (see exception below). <sup>a</sup>
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.

<b>Toxicity</b>	<b>Withhold Treatment for AE Grade</b>	<b>Restarting Treatment/Discontinuation</b>
Immune-related encephalitis	Any grade	Permanently discontinue.
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 $\geq 2$ hypophysitis after corticosteroid taper has been completed and patient is on adequate hormone replacement therapy, permanently discontinue. For Grade 4 AEs, permanently discontinue.
Hyperthyroidism	3	Restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.
Infusion-related reaction	2 <sup>b</sup>	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 $\leq 1$	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.

<sup>a</sup> For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by  $\geq 50\%$  relative to baseline and lasts for at least 1 week, then study treatment should be discontinued.

<sup>b</sup> 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.

### 7.2.1 Management of Drug Reactions

During treatment with TSR-042, 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.<sup>71</sup> Note: It may be necessary to perform additional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the AE. The following sections detail specific guidance by type of AE.

#### **Pneumonitis**

- Treat with systemic corticosteroids, oral for Grade 2 (e.g., 0.5 to 1 mg/kg/day of prednisone or equivalent) and IV for Grade 3 or 4 (e.g., 1 to 2 mg/kg/day of prednisone or equivalent).
- Administer additional anti-inflammatory measures, as needed.
- Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.
- If Grade 2 and no improvement or worsening over 2 weeks, treat as Grade 3 or 4.
- Consider prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

#### **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 patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- For Grade 2 diarrhea/colitis that persists  $>3$  days, administer oral corticosteroids (eg, 0.5 to 1.0 mg/kg/day of prednisone or equivalent). If symptoms persist or worsen with steroids, treat as Grade 3 or 4.
- For Grade 3 or 4 diarrhea/colitis that persists  $>3$  days, treat with IV steroids (eg, 1 to 2 mg/kg/day of prednisone or equivalent) followed by high-dose oral steroids.
- Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.

#### **Type 1 Diabetes Mellitus or Grade 3 or 4 Hyperglycemia**

For type 1 diabetes mellitus and for Grade 3 or 4 hyperglycemia associated with metabolic acidosis or ketonuria, insulin replacement therapy is required.

## **Hypophysitis**

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

## **Hyperthyroidism or Hypothyroidism**

Thyroid disorders have been reported with other PD-1 inhibitors occurring at any time during treatment. Monitor patients 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: Consider non-selective beta-blockers (eg, propranolol) as initial therapy.
- Grade 3 or 4 HYPERthyroidism: Treat with an initial dose of IV corticosteroids followed by oral corticosteroids (eg, 0.5 to 1 mg/kg/day of prednisone or equivalent). Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Grade 2 to 4 HYPOthyroidism: Thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

## **Hepatitis**

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

## **Renal Failure or Nephritis**

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

### 7.2.2 Dose Modifications for Dostarlimab

Dose reductions or dose escalations are not permitted.

### 7.2.3 Criteria to Resume Dostarlimab

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade  $\leq$ 1 or baseline value, or as above.

#### 7.2.4 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 9 shows treatment guidelines for patients who experience an infusion-related reaction associated with administration of dostarlimab.

**Table 9: Dostarlimab Infusion Reaction Treatment Guidelines**

<b>CTCAE Grade</b>	<b>Treatment</b>	<b>Premedication at Subsequent Dosing</b>
<b>Grade 1</b> 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.

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
<p><b>Grade 2</b></p> <p>Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, or IV fluids); prophylactic medications indicated for <math>\leq 24</math> h</p>	<p>Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to:</p> <ul style="list-style-type: none"> <li>- IV fluids</li> <li>- Antihistamines</li> <li>- NSAIDs</li> <li>- Acetaminophen</li> <li>- Narcotics</li> </ul> <p>Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.</p> <p>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.</p> <p>Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.</p>	<p>Patient may be pre-medicated 1.5 h (<math>\pm 30</math> min) prior to infusion of dostarlimab+ with:</p> <ul style="list-style-type: none"> <li>- Diphenhydramine 50 mg PO (or equivalent dose of antihistamine)</li> <li>- Acetaminophen 500 to 1000 mg PO (or equivalent dose of antipyretic)</li> </ul>

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
<p><b>Grade 3:</b> 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)</p> <p><b>Grade 4:</b> Life-threatening; pressor or ventilatory support indicated</p>	<p><b>Stop Infusion.</b> Additional appropriate medical therapy may include but is not limited to:</p> <ul style="list-style-type: none"> <li>- IV fluids</li> <li>- Antihistamines</li> <li>- NSAIDs</li> <li>- Acetaminophen</li> <li>- Narcotics</li> <li>- Oxygen</li> <li>- Pressors</li> <li>- Corticosteroids</li> <li>- Epinephrine</li> </ul> <p>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.</p> <p><b>Patient is permanently discontinued from further study treatment administration.</b></p>	<p>No subsequent dosing.</p>

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.

## 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in **Section 10.1**.

### 8.1 Investigational Agents

#### 8.1.1 Niraparib

##### Availability

Niraparib is an investigational agent supplied to investigators by GSK.

##### Agent Ordering and Agent Accountability

Niraparib 100-mg capsules are packaged in HDPE bottles fitted with child resistant plastic closures (CRC). The study treatment will be open-label and will not be participant-specific. Detailed information on the product can be found in the Niraparib Storage and Handling Guidelines. All study treatment supplies must be stored in accordance with the manufacturer's instructions and package labeling. Until dispensed to the participants, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

Niraparib shipments will be managed through IRT system, PRANCER. Sites will be responsible for enrolling subjects in PRANCER, and shipments will be sent based on number of patients in PRANCER. The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatment throughout the clinical study. The study treatment accountability log includes information including a patient identifier, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as 'returned' and kept separate from the products not yet dispensed. All dispensing and accountability records should be stored in accordance to institution regulations. The pharmacist will dispense study treatment for each participant according to the protocol and storage and handling manual, if applicable. Prior to dispensing, IMPs will be stored in a securely locked area, accessible to authorized study personnel only. If niraparib is dose reduced, participants should be instructed to continue using their current supply at their new dose until their supply has been exhausted. Participants must be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed and documented.

#### Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from GSK.

#### Investigator Brochure (IB) Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff. Refer to the current Niraparib IB for a complete summary for non-clinical and clinical information including safety, efficacy and pharmacokinetics.

### 8.1.2 Dostarlimab

#### Availability

Dostarlimab is an investigational agent supplied to investigators by GSK.

#### Agent Ordering and Agent Accountability

Dostarlimab is an IgG4 antibody and will be supplied as a solution in vials containing 500 mg (50 mg/ml). Expiration dates are printed on the product label. The product should be stored between 2°C and 8°C, and in accordance with the IB or protocol as provided by the Sponsor.

Dostarlimab shipments will be managed through IRT system, PRANCER. Sites will be responsible for enrolling subjects in PRANCER, and shipments will be sent based on number of patients in PRANCER. All dispensing and accountability records should be stored in accordance

to the institution regulations. The pharmacist will dispense study treatment for each participant

#### Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from GSK.

#### Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff. Refer to the current dostarlimab IB for a complete summary for non-clinical and clinical information including safety, efficacy and pharmacokinetics.

## **8.2 Other Investigational Agent(s) Information**

### **8.2.1 Niraparib:**

#### Product description:

The niraparib drug product is provided as 100-mg capsules filled with a dry blend of 159 mg niraparib tosylate monohydrate (equivalent to 100 mg free base), lactose monohydrate, and magnesium stearate in a hard gelatin capsule. Niraparib 100-mg capsules are packaged in high-density polyethylene (HDPE) bottles fitted with child-resistant plastic closures (CRC). All investigational medicinal products (IMPs) are labeled in accordance with Good Manufacturing Practices and the applicable national regulations.

Solution preparation (how the dose is to be prepared): N/A

#### Storage requirements:

All IMPs must be stored in accordance with directions provided in the IB. Prior to dispensing, IMP will be stored in a securely locked area, accessible to authorized study personnel only. Healthcare providers and patients should be aware that niraparib tablets or capsules may be coated with a dust of residual, hazardous drug that could be inhaled, absorbed through the skin, ingested, or spread to other locations. In order to ensure safe handling, the use of single gloves for administration of intact tablets or capsules is recommended. No other protective gown, respiratory protection, or eye/face protection is required. Full instructions are available in the Safe Handling and Disposal of Zejula® (niraparib) provided to all sites.

Stability: Niraparib 100-mg capsules have a proposed shelf-life of up to 36 months when stored in the intended container closure system and under the conditions specified in the Pharmacy Manual. Niraparib tablets should be stored in accordance with directions provided in the Pharmacy Manual and package labeling. Long-term stability studies of the tablet are ongoing in order to establish a recommended shelf-life and support ongoing clinical use.

#### Route of administration:

Oral. Food does not significantly affect the absorption of niraparib; therefore, niraparib may be taken without regard to meals.

If a patient vomits or misses a dose of niraparib, an additional dose should not be taken. The next dose should be taken at the regularly scheduled time.

## 8.2.2 Dostarlimab

### Product description:

Dostarlimab for injection is supplied in vials containing 500 mg at a concentration of 50 mg/mL with a delivery volume of 10.0 mL. This has the formulation of: dostarlimab, citrate, arginine, sodium chloride, and polysorbate 80. The drug product is a sterile liquid in citrate buffer (pH 6.0±0.5) supplied as single-use vials for IV administration. This product is aseptically processed; sterility is confirmed through sterility testing of the drug product.

### Solution preparation (how the dose is to be prepared):

There are 2 dostarlimab presentations, 20 mg/mL dostarlimab with a delivery volume of 8.0 mL and 50 mg/mL dostarlimab with a delivery volume of 10.0 mL. Both presentations are sterile liquids in citrate buffer (pH 6.0±0.5), supplied as single-use vials for IV administration.

### Storage requirements:

The product should be stored between 2°C and 8°C, and in accordance with the Pharmacy Manual or protocol as provided by the Sponsor.

Stability: N/A

### Route of administration:

Dostarlimab will be administered via a 30-minute (-5-minute/+15-minute infusion window allowed) IV infusion on Day 1 of every 21 day cycle (i.e., Q3W) at 500 mg for the first 4 doses (with first dose on Cycle 1 which is a 28 day cycle to be given on Day 8), followed by 1,000 mg on Day 1 of every 42 day cycle (i.e., Q6W) thereafter until the patient discontinues study treatment.

## 9. STATISTICAL CONSIDERATIONS

### 9.1 Study Design/Endpoints

#### Primary Endpoint:

1. Overall Response

Measured by assessing best overall response (Complete Response [CR] + Partial Response [PR] + Stable Disease [SD]) using RECIST 1.1 in subjects in recurrent and/or metastatic HNSCC patients receiving combination of niraparib and dostarlimab. Responses will be summarized as frequencies and percentages.

#### Secondary Endpoints:

1. Rate of all Adverse Events  
As determined by CTCAE v5.0 in subjects with recurrent and/or metastatic HNSCC receiving combination of niraparib and dostarlimab
2. Progression Free Survival (PFS): measured from the time of treatment allocation to

- the time of progression after initiation of protocol treatment or death from any cause.
3. Overall Survival (OS): defined as the time from treatment allocation to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Kaplan Meier methods will be used to estimate overall survival and progression free survival generating median survival estimates with 95% confidence intervals (95% CIs). Multivariable survival modeling (overall survival and progression free survival) will be performed using Cox proportional hazards models and to generate Hazard Ratios (HR) and 95% CIs, with adjustment for potential patient confounders such as age, sex, smoking status, etc. We will also use the log-rank test and Cox model to compare the PFS and OS between the trial data and historical data if patient level data available. An interim analysis will be done throughout study at the PI and statistician discretion.

#### Exploratory Endpoints:

The goal of this collateral study is to identify possible patterns in responders and non-responders. This will be done by (1) characterizing the type of tumor infiltrating lymphocytes (TILs) that are present at baseline, PDL1 expression on tumor and PD-1 expression on T cells pre and post-treatment (2) identify inflammatory gene expression signatures by RNA analysis (3) evaluate mutational profile and overall genomic alteration index (mutation burden index) to associate clinical benefit from the drug combination.

Scatter plots and histograms will be used to examine the Exploratory endpoints for the presence of unusual outliers, normality and potential non-linearity. Continuous endpoints will be log-transformed if not normally distributed. The endpoints using samples before and after treatment will be compared using paired T tests. When endpoints are compared between three or more groups, ANOVA model will be used. The ANOVA will be followed up with post-hoc pairwise comparisons. A chi-square test will be used to investigate the categorical exploratory endpoints. For IHC, the percentage of positive cells per area will be multiplied by the staining intensity for each tumor to determine quantitative expression pre- and post-treatment.

## **9.2 Sample Size/Accrual Rate/Statistical Analysis**

We plan to recruit a total of 23 patients with recurrent or metastatic HNSCC for our study. Previous studies have shown a best overall response of 50% using PD-L1 inhibitor in HNSCC. In our study, where we will be using a combination of 2 drugs (PD-1 inhibitor and Niraparib), our preliminary sample size calculations show that we will be able to detect a statistically significant difference between the overall response of 0.5 in the PD-L1 inhibitor group and the overall response of at least 0.75 in the combination group. The projected 95% confidence interval for the response rate with 23 patients is estimated to be between 57.3% and 92.7%. These calculations are done under the assumptions of the Simon's Two-Stage Minimax design and performed with 0.05 significance threshold and 80% detection power. During the first stage, 14 patients will be accrued. If 7 or fewer responses (including CR, PR and SD at first 8 week scan) are observed, the trial will be terminated at the first stage. If in the investigator opinion, a patient is deriving clinical benefit despite radiographic measured progressive disease (PD) within the first 8 weeks, a confirmatory scan at 4 weeks after initial scan may be performed to

determine response. If patient is still considered to have PD from baseline at confirmatory scan, they will be considered to a non-responder.

Additionally, studies have reported the rate of Grade 3-4 adverse events (AEs) as 11% for PD-L1 inhibitor and 37% for niraparib respectively. In our proposed study using the combination of PD-1 inhibitor and Niraparib, we expect the rate Grade 3 AEs of 50%. However, if during the first stage (first 14 patients), more than 60% of Grade 3 adverse events are recorded, a stopping rule will be employed and the study will be stopped for concerns of safety of the combination. If 8 or more responses (including CR, PR and SD) are observed and the study is not stopped due to concerns of safety of the combination, 9 additional patients will be accrued for a total of 23. We will also plan to do secondary analysis based on PD-L1 combined positive score (CPS) and p16/HPV status.

Once data are collected, descriptive statistics and frequency tables of the continuous and categorical outcomes will be created to summarize all patient characteristics. All AEs and response rates will be calculated and compared using Chi-square tests and Fisher's exact tests. All confidence intervals and p-values will be reported. A threshold of 0.05 will be used as a significance threshold. An interim analysis will be done throughout study at the PI and statistician discretion.

### PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	3	0	0	5
White	6	11	0	0	16
More Than One Race	1	1	0	0	2
Total	9	14	0	0	23

## 10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

### 10.1 Adverse events

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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 at any time after the time of randomization and/or treatment assignment, including baseline or washout periods, even if no 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.

The severity (grade) of an adverse event may be determined by a study coordinator using the CTCAE Version 5.

The causal relationship (attribution) to study drug or intervention is determined by a study physician and should be used to assess all adverse events (AE). Any attribution provided to GSK should only utilize related/not related. For all other study reporting the casual relationship must be one of the following:

1. Unrelated – The AE is clearly NOT related to the study drug or intervention
2. Unlikely – The AE is doubtfully related to the study drug or intervention
3. Possible – The AE may be related to the study drug or intervention
4. Probable – The AE is likely related to the study drug or intervention
5. Definite – The AE is clearly related to the study drug or intervention

The expectedness of the occurrence of an adverse event is determined by a study physician and should be used to help determine whether prompt reporting requirements to regulatory authorities (IRB, FDA etc...) are required.

1. Expected – An adverse event is expected if it is described as an anticipated risk in the Investigator Brochure (IB) and described within this protocol as a known adverse event.
2. Unexpected – If an adverse event is not described within the IB, or within this protocol or consent form as an expected risk to subjects then the AE will be considered to be unexpected.

### 10.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Fatality/Death
- Is Life Threatening
- Inpatient or Prolonged Hospitalization
- Persistent or Significant Disability or Incapacity
- Congenital abnormality or birth defects
- Is an important medical event. Medical and scientific judgment should be exercised in determining whether situations or events should be considered serious adverse events: an important medical event may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the study drug.

The following are NOT considered to be SAEs for the purposes of this protocol:

1. Elective surgery, planned prior to signing consent.
2. Admissions per protocol for planned medical/surgical procedures
3. Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)

### 10.3 Adverse Event of Special Interest (AESI)

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:

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

GSK requires only serious AESIs to be reported from Investigator-sponsored studies (ISS). Report serious AESI on the SAE Report Form, 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).
- Pneumonitis should be reported to the Sponsor Institution and to GSK through 90 days after the last dose of niraparib.

#### **10.4 Other safety considerations**

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

#### **10.5 Collection and Recording of Adverse Events and Serious 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, non-leading question such as, "How have you been feeling since your last study visit?" The Investigator or qualified designee 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 from the signing of the ICF, and must be collected throughout the study and for at least 90 days after the last dose of protocol therapy or until commencement of a new anti-cancer therapy or death whichever occurs first.

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 collected for each patient from the signing of the ICF, and must be collected throughout the study and for at least 90 days after the last dose of protocol therapy or until commencement of a new anti-cancer therapy or death whichever occurs first.

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.

#### **10.6 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.

Adverse events should be reported as SAEs if they become serious. Follow-up is also required AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

### 10.7 Reporting of Serious Adverse Events

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study should be reported on the GSK SAE Report Form within 24 hours of becoming aware of the initial SAE/AESI or any follow-up information regarding the SAE/AESI.

All SAEs that are attributable to study participation (definitely, probably, or possibly related), and which are unexpected must be promptly reported to the University of Cincinnati PI within 24 hours of occurrence, and to the FDA if needed and the IRB of record per IRB reporting requirements. A MedWatch Form 3500A must be completed **in addition to** the GSK SAE Report Form and Coversheet for all AEs that are serious, unexpected and probably or possibly related. The MedWatch Form 3500A can be accessed at: <https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting>

### 10.8 Reporting SAEs to GSK

The Sponsor Institution must report all SAEs and all follow up information to GSK on an SAE Report Form within 24 hours of becoming aware of the initial event or follow-up information. Provide this information using the GSK SAE reporting form and Coversheet.

The Sponsor Institution 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).

GSK SAE, Pregnancy, and Serious AESI Reporting Information	
Email: <a href="mailto:OAX37649@gsk.com">OAX37649@gsk.com</a>	
Fax: +44(0) 208754 7822	

On at least an annual basis, the Sponsor Institution will provide a copy of the safety reports submitted to applicable Regulatory Authorities or IECs. Annual reports should be provided to GSK within 3 business days of submission to the applicable regulatory body.

### 10.9 Comprehensive Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

### 10.10 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented in Redcap. Any pregnancy occurring in a patient or patient's partner from the time of consent to 180 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old.

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

The Sponsor Institution 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.

### 10.11 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Per regulatory requirements, if an event is assessed by the Sponsor Institution as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor Institution 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.

### 10.12 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be

reported via the routine reporting mechanisms outlined in **section 10.3**

### 10.13 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

### 10.14 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 within 1 working day of first becoming aware of the possible defect to GSK QA at [tesaro.qa@gsk.com](mailto:tesaro.qa@gsk.com). The product and packaging components in question, if available, must be stored 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.

## 11. STUDY CALENDAR

Scans and x-rays must be done  $\leq 4$  weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Study Procedures	Screening	Cycle 1 (4 week cycle)				Cycle 2-4 (3 week cycles)	Cycle 5+ (6 week cycles)	EOT <sup>o</sup>	Safety Follow-Up <sup>o</sup>	Long Term Follow-Up
	-28 days to D1	D1 <sup>p</sup>	D8 +/- 1 day	D15 +/- 1 day	D22 +/- 1 day	D1 +/- 3 days	D1 +/- 3 days		At least 30 days from last dose	Every 6 months for 2 years and annually thereafter
Written informed consent	X									
Inclusion/Exclusion Criteria <sup>l</sup>	X									
Niraparib daily <sup>m</sup>		X	X	X	X	X	X			
Dostarlimab q 3 weeks x 4 doses/cycles followed by q 6 weeks			X			X	X			
Height	X									
Vital Signs <sup>a</sup>	X	X	X	X	X	X	X		X	X
ECOG Performance Status	X	X				X	X	X	X	
Medical History <sup>b</sup>	X									
Concurrent Medications	X	X				X	X	X		
Physical Exam	X	X				X	X	X	X	
Adverse Event Monitoring <sup>s</sup>	X	X				X	X	X	X	
Assess for MDS/AML		X				X	X	X	X	X
Pregnancy Testing <sup>c</sup>	X					X	X		X	

Study Procedures	Screening	Cycle 1 (4 week cycle)				Cycle 2-4 (3 week cycles)	Cycle 5+ (6 week cycles)	EOT <sup>o</sup>	Safety Follow-Up <sup>o</sup>	Long Term Follow-Up
	-28 days to D1	D1 <sup>p</sup>	D8 +/- 1 day	D15 +/- 1 day	D22 +/- 1 day	D1 +/- 3 days	D1 +/- 3 days		At least 30 days from last dose	Every 6 months for 2 years and annually thereafter
CBC <sup>d</sup>	X	X	X	X	X	X <sup>d</sup>	X	X	X	
Comprehensive Metabolic Panel <sup>e</sup>	X	X				X	X	X	X	
Coagulation	X	X <sup>i</sup>							X	
HBV/HCV test <sup>j</sup>	X									
TSH <sup>k</sup>	X					X	X	X	X	
ACTH & Cortisol			X			X	X			
Urinalysis	X	X				X	X	X	X	
Correlative blood draw <sup>f</sup>		X	X		X					
Archival tissue collection <sup>r</sup>	X									
Correlative biopsy					X <sup>q</sup>					
Bone marrow aspirate and biopsy <sup>h</sup>		X								
Survival assessment <sup>g</sup>								X	X	X <sup>g</sup>
Tumor Assessment <sup>n</sup>	X					X	X			

Study Procedures					Cycle 2-4 (3 week cycles)	Cycle 5+ (6 week cycles)	EOT <sup>o</sup>	Safety Follow-Up <sup>o</sup>	Long Term Follow-Up
	Screening	Cycle 1 (4 week cycle)							
	-28 days to D1	D1 <sup>p</sup>	D8 +/- 1 day	D15 +/- 1 day	D22 +/- 1 day	D1 +/- 3 days	D1 +/- 3 days	At least 30 days from last dose	Every 6 months for 2 years and annually thereafter

**Niraparib:** Starting dose 200 mg PO daily

**Dostarlimab:** IV 500 mg every 3 weeks for first 4 doses (starting on day 8) followed by 1000 mg every 6 weeks (42-day cycle)

- a) Vital signs to include: systolic and diastolic blood pressures while the patient is in a seated position, weight, pulse and temperature. Blood pressure and heart rate monitoring will be required weekly for the first 2 months of therapy (until C3D15 for studies on a 21d cycle). After the first 2 months of therapy, blood pressure and heart rate monitoring needs to be checked monthly for the first year and at scheduled clinic visits and as clinically indicated thereafter while the patient is taking niraparib. For the weekly checks, monitoring at or near home is acceptable. Blood pressure should be adequately controlled with anti-hypertensives before starting therapy.
- b) Medical History should include all prior anticancer therapy
- c) Female subjects of childbearing potential as defined in the eligibility criteria must have a serum or urine beta-hCG pregnancy test within  $\leq 7$  days prior to initiating protocol therapy, every 3 cycles (i.e. C4D1, C7D1) and at Safety Follow-Up visit.
- d) CBC to include absolute neutrophil count, platelets, and hemoglobin. CBC must be collected on Cycle 2 Day 8 +/- 3 days.
- e) Comprehensive metabolic panel to include: serum creatinine, total bilirubin, aspartate aminotransferase and alanine aminotransferase.
- f) Correlative PD blood draws, 4 10 ml EDTA tubes for each time point and 1 5mL red top serum tube. The first correlative blood collection may be collected at any time after the subject is confirmed to be eligible but before the first dose of study drug. If this first blood collection is missed, then no additional correlative blood samples should be collected during the study.
- g) Overall survival to be followed for 5 years following the last dose of protocol therapy. Follow-up occurs every 6 months (every 24 weeks +/- 2 weeks) for the first 2 years then annually (+/- 1 month). See section 6.6.6 Survival Follow-up.
- h) 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.
- i) To be conducted per standard of care for participants on anticoagulant therapy
- j) Only when medically indicated based on history and physical examination.
- k) TSH will be collected at each time point. T3 or FT3 and FT4 will only be collected as reflex testing.
- l) After a subject is registered (eligibility criteria is confirmed to be met) they must start protocol treatment within 28 days
- m) Subjects will be provided with a medication diary. Study staff will perform drug accountability - patients should return bottles and diaries on Day 1 of each cycle so CRC can count and document accountability on an ongoing basis.
- n) Scans to be performed during screening phase and prior to C3D1 (-1 week) and then every 12 weeks beginning C6D1 (+/- 2 weeks) thereafter.
- o) End of Treatment should occur within 30 days of last dose of treatment or when patient is withdrawn from study (whichever occurs first.). 30 Day should occur at least 30 but not more than 60 days post-treatment. See section 6.6.5 EOT/30 Day Safety for more information and details on timing.
- p) Labs must be performed within 3 days of D1 and continue to meet eligibility criteria.
- q) Biopsy must be at least 18 gauge core or larger. Block to be prepared by pathology histology core and transferred to Wise-Draper/Translational Core. Biopsy can be obtained at D22 +2 weeks/- 1 week if clinically feasible.
- r) Archival tissue block preferred but 30 FFPE slides and scroll acceptable. If unable to obtain archival tissue, fresh biopsy must be obtained.
- s) SAE and AE collection begins at the time of consent. All AEs & SAEs must be collected through 90 days after the date of the last study treatment, or subject begins a new anti-cancer therapy, or expires whichever occurs first.

## 12. MEASUREMENT OF EFFECT

Although the clinical benefit of the combination of Niraparib and Dostarlimab has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 8 weeks. In addition to a baseline scan, confirmatory scans will also be obtained 4 weeks following initial documentation of an objective response.

## **12.1 Antitumor Effect – Solid Tumors**

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. 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 new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

### **12.1.1 Definitions**

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with Niraparib and Dostarlimab.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

### **12.1.2 Disease Parameters**

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm ( $\geq 2$  cm) by chest x-ray or as  $\geq 10$  mm ( $\geq 1$  cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the lesion has progressed after radiation treatment, then it may be considered evaluable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm ( $\geq 1.5$  cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter  $< 10$  mm [ $< 1$  cm] or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm [ $\geq 1$  to  $< 1.5$  cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### 12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and  $\geq 10$  mm ( $\geq 1$  cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

2. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
3. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
4. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy

in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

#### 12.1.4 Response Criteria

##### 12.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Note: Modified iRECIST is also being used in that given that immunotherapy is being administered in this protocol, patients may remain on study at first progression if investigator feels the patient is deriving clinical benefit. However, if in subsequent scans, the lesions continue to progress beyond previous scan, the patient will be considered to have progressive disease and should be taken off protocol. Any question should be discussed with the sponsor.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

##### 12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

**Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

**Progressive Disease (PD):** Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator). The same note about PD under target lesions also applies here.

#### 12.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Best Overall Response includes CR, PR and SD.

#### For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
<ul style="list-style-type: none"><li>• See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</li><li>** Only for non-randomized trials with response as primary endpoint.</li><li>*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</li></ul>				
<p><u>Note:</u> Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration.</i>” Every effort should be made to document the</p>				

objective progression even after discontinuation of treatment.

iRECIST Note: Given that immunotherapy is being given in this protocol, patients may remain on study at first progression if investigator feels the patient is deriving clinical benefit. However, if in subsequent scans, the lesions continue to progress beyond previous scan, the patient will be considered to have progressive disease and should be taken off protocol. Any question should be discussed with the sponsor.

#### For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
<ul style="list-style-type: none"> <li>• ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised</li> </ul>		

#### 12.1.5 Duration of Response

Duration of response: The duration of response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Duration of overall response/clinical benefit: The duration of overall response is measured similar to duration of stable disease. CR, PR and SD is included in overall response/clinical benefit in this protocol.

#### 12.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

#### 12.1.7 Overall Survival

OS is defined as the duration of time a patient is alive from start of treatment until time of

death.

### **13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS**

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

#### **13.1 Study Oversight**

This protocol is monitored at several levels, as described in this section. The UC Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events. The UC Principal Investigator has access to the data at all times through the study EDC, RedCAP.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via RedCAP and timely reporting of adverse events. This includes timely review of data collected on electronic CRFs submitted via RedCAP as well as review of any source documentation collected locally.

This study will also be reviewed in accordance with the enrolling institution's data safety monitoring plan.

#### **13.2 Data Reporting**

Data collection and storage at the University of Cincinnati will be managed by the University of Cincinnati Cancer Center, Clinical Trials Office (UCCC CTO). The UCCC CTO will maintain storage of all clinical data in accordance with federal guidelines and GCP. Data will be entered in a secure, password protected storage database, OnCore and/or RedCAP. All hardcopies of data will be securely maintained (in a locked room or cabinet) and will only be accessible to members of the study team or UCCC CTO personnel.

Study data collected at sub-sites should be stored securely per local policies, and be made accessible to UC as required.

- Data and Safety Monitoring

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.

Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients. Immediately after the study is approved and before the first patient is enrolled, investigators will meet, develop and finalize all measurements/variables for the study. Each patient, once enrolled, will be provided a unique ID for the study. Personal information, such as name, SSN, address, phone number and DOB, will be de-identified whenever possible from

study records. Confidentiality will be maintained during the phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations.

Exceptions may be made under circumstances where there are serious adverse events or when it is deemed appropriate for patient safety.

Study progress will be monitored regularly by the UCCC Data Safety Monitoring Board (DSMB). Membership consists of persons independent of, and without any conflicts of interest with, this trial. The DSMB includes experts in the fields of relevant clinical expertise (oncology) and biostatistics.

It is the responsibility of the UC Investigator to ensure that the DSMB is apprised of all new safety information relevant to the study. Study progress & safety information will be prepared by the DSMB Coordinator with input from the UC PI as to the current status of the trial. This compiled information presented to the DSMB will include: a narrative summary from the UC PI as to trial progress and identification of any trends of significance or explanation of any SAEs or other safety related events; the accrual rate with projected completion date for the accrual phase; exclusion rates and reasons; pretreatment characteristics of patients accrued when relevant; and, the frequency and severity of adverse events.

The DSMB will function in an advisory capacity and recommendations/requests from the DSMB will be reviewed by the UC investigator and promptly addressed.

The study data from participating sub-sites will be reviewed remotely via the study EDC RedCAP and in person by the Study Monitor as per the Clinical Monitoring Plan (Plan kept on file with UCCC CTO office).

#### **14. SMART IRB**

This study will utilize the Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform (SMART IRB) master IRB reliance agreement to establish reliance arrangements with research sub-sites. Launched in 2016, SMART IRB is currently funded by the NIH Clinical and Translational Science Awards (CTSA) Program, grant number UL1TR002541-01S1. The platform serves as a roadmap for institutions to implement The National Institutes of Health (NIH) Policy on the Use of a Single Institutional Review Board for Multisite Research.

The UC IRB will perform initial review and continuing oversight of the protocol and research sites in accordance with the human subjects protection requirements of its FWA, the FWAs of relying IRBs, the federal regulations, and ethical principles referenced therein.

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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 FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

(1) <u>Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey <i>et al.</i>, 2009).</u>		
Formulae:		
<b>Race and Sex</b>	<b>Serum Creatinine (SCr), <math>\mu\text{mol/L}</math> (mg/dL)</b>	<b>Equation</b>
<b>Black</b>	Female $\leq 62$ ( $\leq 0.7$ )	$\text{GFR} = 166 \times (\text{SCr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
	Female $> 62$ ( $> 0.7$ )	$\text{GFR} = 166 \times (\text{SCr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
	Male $\leq 80$ ( $\leq 0.9$ )	$\text{GFR} = 163 \times (\text{SCr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
	Male $> 80$ ( $> 0.9$ )	$\text{GFR} = 163 \times (\text{SCr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$
<b>White or other</b>	Female $\leq 62$ ( $\leq 0.7$ )	$\text{GFR} = 144 \times (\text{SCr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
	Female $> 62$ ( $> 0.7$ )	$\text{GFR} = 144 \times (\text{SCr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
	Male $\leq 80$ ( $\leq 0.9$ )	$\text{GFR} = 141 \times (\text{SCr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
	Male $> 80$ ( $> 0.9$ )	$\text{GFR} = 141 \times (\text{SCr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$
SCr in mg/dL; Output is in mL/min/1.73 m <sup>2</sup> and needs no further conversions.		
(2) <u>eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey <i>et al.</i>, 2006).</u>		
$175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if black)		
Output is in mL/min/1.73 m <sup>2</sup> and needs no further conversions.		
(3) <u>Estimated creatinine clearance (CLCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).</u>		
$\text{CLCr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \{ \times 0.85 \text{ for female patients} \}$		
Followed by conversion to a value normalized to 1.73 m <sup>2</sup> with the patient's body surface area (BSA).		

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