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Randomized phase III trial on NIraparib-TSR-042 (dostarlimab) vs physician's choice CHEmotherapy in recurrent, ovarian, fallopian tube or primary peritoneal cancer patients not candidate for platinum retreatment: NItCHE trial (MITO 33)

Sponsor:	Fondazione Policlinico Universitario A. Gemelli IRCCS on behald of MITO Group
Principal Investigator:	Domenica Lorusso
Sponsor Protocol Number:	MITO 33
Study Drug Name:	Niraparib and Dostarlimab (TSR-042)
Clinical Phase:	III
Number of Subjects:	427
IND Number:	
EudraCT Number:	2020-000146-33
Date of Original Protocol:	06/04/2020
Date of Current Protocol:	07/09/2020
Version:	1.1

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (ICH – GCP E6 (R2)), with the Declaration of Helsinki, and with other applicable regulatory requirements including but not limited to Institutional Review Board/Ethics Committee (IRB/EC) approval.

Confidentiality Statement

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SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: Randomized phase III trial on NIraparib-TSR-042 (dostarlimab) vs physician's choice CHEmotherapy in recurrent, ovarian, fallopian tube or primary peritoneal cancer patients not candidate for platinum retreatment: NItCHE trial (MITO33)

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

_____ _____

Domenica Lorusso **Date**
MD
MITO Group

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INVESTIGATOR SIGNATURE PAGE

Declaration of the Investigator

Title: Randomized phase III trial on NIraparib-TSR-042 (dostarlimab) vs physician's choice CHEemotherapy in recurrent, ovarian, fallopian tube or primary peritoneal cancer patients not candidate for platinum retreatment: NItCHE trial (MITO 33)

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP E6 (R2)), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Investigator

_____ _____

Domenica Lorusso **Date**
MD
Fondazione Policlinico Universitario Agostino Gemelli IRCCS

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LIST OF ABBREVIATIONS AND DEFINITIONS

Table 1 List of Abbreviations

Abbreviation	Definition
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse even of special interest
AML	acute myeloid leukemia
AUC	area under the curve
BER	base excision repair
BRCA	breast cancer gene
CBC	complete blood count
CL	oral clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DDR	DNA damage repair
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
FE	food effect
gBRCA	germline breast cancer gene
GCSF	Granulocyte-colony stimulating factor
GBM	glioblastoma multiforme
hCG	human chorionic gonadotropin
HR	homologous recombination
HRD	homologous recombination deficiency
irAEIs	immune-related adverse events of interest
IUD	intrauterine device
LLN	Lower limit of normal
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NHEJ	non-homologous end joining
PARP	poly(ADP-ribose) polymerase
PFS	progression-free survival
P-gp	P-glycoprotein

Musacchio L, *et al. Int J Gynecol Cancer* 2021; 31:1369–1373. doi: 10.1136/ijgc-2021-002593

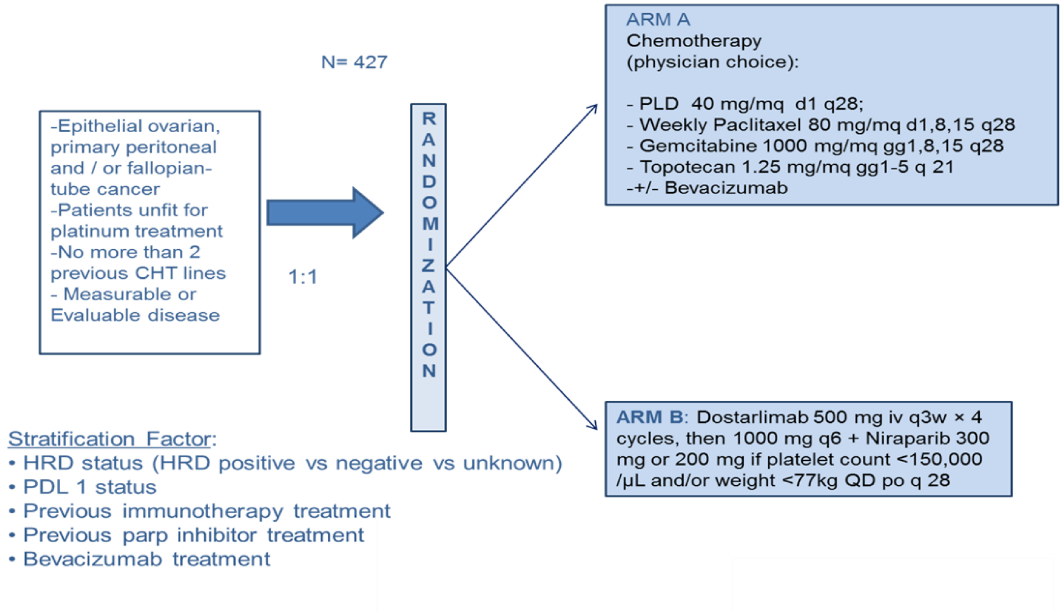
Abbreviation	Definition
PK	pharmacokinetics
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	patient reported outcomes
PS	performance status
QD	once a day
QTc	corrected QT interval
SAE	serious adverse event
TEAS	treatment-emergent adverse events
ULN	upper limit of normal

Musacchio L, *et al. Int J Gynecol Cancer* 2021; 31:1369–1373. doi: 10.1136/ijgc-2021-002593

1 INTRODUCTION

1.1 Study Design

This is a randomized phase 3 trial evaluating niraparib plus dostarlimab vs chemotherapy at physician's choice in the treatment of recurrent ovarian, fallopian tube or primary peritoneal cancer patients for which platinum is not an option



1.2 Primary Objective and Endpoint

Objective:

- To assess overall survival (OS)

Endpoint :

- Overall Survival (OS), defined as the days randomization and the date of death by any cause

Hypothesis:

The combination of niraparib-dostarlimab is expected to increase overall survival with respect to chemotherapy alone

1.3 Secondary Objective(s) & Endopoint (s)

Objectives:

- To assess progression free survival (PFS)
- To assess the time to first subsequent therapy (TFST)
- To assess the response rate (ORR)
- To assess the safety and tolerability of patients receiving chemotherapy or dostarlimab plus niraparib
- To assess patient-reported outcome (PRO) of patients receiving chemotherapy vs the combination of dostarlimab and niraparib using EORTC QLQC30, EORTCOV28, EQ-5DL

Endpoints:

- Progression free survival (PFS) defined as the time from the date of randomization to the earlier date of assessment of progression or death by any cause in the absence of progression. Progression will be assessed by RECIST v.1.1 criteria by the investigator. In a conservative approach the clinical condition deterioration which does not allow for radiologic evaluation will be considered as progression of disease;
- Time to first subsequent therapy (TFST) defined as the time interval from the date of randomization to earliest date of fist subsequent therapy or death;

- Response rate (ORR) defined as the percentage of patients with CR or PR, as assessed by RECIST v.1.1 criteria evaluated by the investigator;

- Adverse events (AEs) will be evaluated according to CTCAE vers 5.0. Safety endpoints include also the incidence of treatment-emergent AEs (TEAEs), clinically relevant changes in clinical laboratory parameters (hematology, chemistry) and ECG parameters;

- Patient reported outcomes will be measured by EORTC QLQC30, EORTCOV28, EQ-5DL. Responders are defined as improvement of >10 points on the PRO scales

Hypothesis:

- The combination of niraparib-dostarlimab is expected to increase PFS with respect to chemotherapy
- The combination of niraparib-dostarlimab is expected to increase TFST with respect to chemotherapy
- The combination of niraparib-dostarlimab is expected to produce an RR of equal or higher value with respect to chemotherapy
- The combination of niraparib-dostarlimab is expected to have an acceptable toxicity profile
- The combination of niraparib-dostarlimab is not expected to worsen patients quality of life with respect to chemotherapy alone

1.4 Exploratory Objective

Objective:

- To investigate the relationship between PD-L1 expression and efficacy of dostarlimab/niraparib treatment utilizing newly obtained or archival FFPE tumor tissue.
- To investigate the relationship between Combined Positive Score (CPS: Number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) relative to the

total number of viable tumor cells, multiplied by 100) and efficacy of dostarlimab/niraparib treatment utilizing newly obtained or archival FFPE tumor tissue.

- To investigate the efficacy of dostarlimab/niraparib treatment according to the previous use of parp and/or immunotherapy

- To investigate the relationship between lymphoid or myeloid-derived suppression cells (MDSC) or T-regulatory cells (T-regs) and response to dostarlimab/niraparib treatment using archival FFPE tumor tissue and blood sampling
- To assess the association between anti-tumor activity and genetic alterations (HRD and BRCA among others) that may indicate a specific genotype reflective of greater dependency on PD-1/PD-L1 checkpoint function or PARP inhibition.

2 BACKGROUND AND SIGNIFICANCE

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.[1] 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.[2,3] 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.[2,3]

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 (g*BRCA*mut) 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.[1] Non-*BRCA* deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors.[4] The rationale for anticancer activity in a subset of non-g*BRCA*mut tumors is that they share distinctive DNA repair defects with g*BRCA*mut carriers, a phenomenon broadly described as “BRCAness.”[5] 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.[6] 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.[7] 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*.[1,5,8]

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 g*BRCA*mut and without g*BRCA*mut; however, activity is more robust in patients with the germline mutation.[1,4,9-15] 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 Immune Surveillance and PD-1 Inhibitors

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[16] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and prognosis in various malignancies.[17-29] In particular, the presence of cluster of differentiation (CD)8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells seem to correlate with improved prognosis and long-term survival in many solid tumors.[25,30-36] The programmed death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control.[37] 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 (CTLA-4), 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[38] and in complex with its ligands were the first to be resolved,[39,40] 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.[41] 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 SHP-1 and SHP-2 to the ITSM within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T cell signaling cascade.[42] The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4.[43] 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.[44] Expression has also been shown during thymic development on CD4-/CD8- (double-negative) T cells,[45] as well as subsets of macrophages[46] and dendritic cells.[47] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types.[48] 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.[48] 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,[49,50] which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors.[51] As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer.[52]

2.3 Background of Niraparib

Niraparib is a potent, orally active PARP1 and PARP2 inhibitor being developed as a treatment for patients with tumors that harbor defects in the homologous recombination DNA repair pathway or that are driven by PARP-mediated transcription factors.

2.3.1 Nonclinical Experience

Nonclinical data on niraparib are discussed in detail in the niraparib Investigator's Brochure (IB). Briefly, in nonclinical models, niraparib has been observed to inhibit normal DNA repair mechanisms and induce synthetic lethality when administered to cells with homologous recombination defects. In a *BRCA1*-mutant xenograft study, niraparib dosed orally caused tumor regression, which was mirrored by a >90% reduction in tumor weight compared with control. In a *BRCA2*-mutant xenograft study, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib displayed strong antitumor activity in in vivo studies with *BRCA1*-mutant breast cancer (MDA-MB-436), *BRCA2*-mutant pancreatic cancer (CAPAN-1), and with patient-derived Ewing sarcoma mice models. Utilizing patient-derived ovarian

and breast cancer xenograft models, niraparib demonstrated response in both *BRCAmut* and *BRCA* wild-type tumors.

2.3.2 Clinical Experience

Niraparib clinical data are discussed in detail in the niraparib IB. In the Phase 1 clinical program, niraparib, as a monotherapy or in combination with chemotherapy, has been administered to 144 patients.

Phase 1 Study of Niraparib Monotherapy in Advanced Solid Tumors

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

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

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

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

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

Demographic and baseline characteristics were well balanced. Table 1 below shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (ie, g*BRCA*mut cohort, HRDpos cohort, and overall non-g*BRCA*mut cohort). In addition, median PFS in patients with HRDneg tumors was 6.9 months (95% confidence interval [CI]: 5.6, 9.6) in the niraparib arm, versus 3.8 months (95% CI: 3.7, 5.6) in the placebo arm, with a HR of 0.58 (95% CI: 0.361, 0.922) (p = 0.0226).

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

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

Source: PR-30-5011-C (NOVA main) CSR

Abbreviation: CI = confidence interval; CSR = clinical study report; gBRCAmut = germline BRCA mutation; HR = hazard ratio; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; NE = not evaluated; PFS = progression-free survival.

[a] PFS is defined as the time in months from the date of randomization to progression or death.

[b] Based on stratified log-rank test using randomization stratification factors.

[c] Based on the stratified Cox proportional hazards model using randomization stratification factors.

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

All 367 patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). The high

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

The most commonly observed nonhematologic TEAEs (all grades) observed in niraparib-treated compared with placebo-treated patients were nausea (74% vs. 35%), fatigue (46% vs. 32%), constipation (40% vs. 20%), and vomiting (34% vs. 16%). The majority of the nonhematological TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (all grades) of niraparib were anemia (49%), thrombocytopenia (46%), decreased platelet count (20%), and neutropenia (18%). Although Grade 3 or 4 hematologic laboratory AEs were common at the initiation of study treatment, no severe clinical sequelae were observed, and relatively few patients discontinued study treatment due to these AEs. Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these AEs beyond Cycle 3, indicating the overall effectiveness of the approach to dose modification. These TEAEs can be monitored routinely using standard assessments of hematological laboratory parameters, as is routine for patients with ovarian cancer receiving anticancer therapies. In the NOVA study, niraparib dose adjustment tended to occur early with most patients reaching their individual adjusted dose level at the end of Month 3 (ie, Cycle 3) of treatment.

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

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

Baseline Platelet Count and Weight as Predictors of Thrombocytopenia.

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

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

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

2.4 Background for Dostarlimab

Dostarlimab is an IgG4 humanized monoclonal antibody that binds with high affinity to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2. This antibody was generated based on a proprietary platform that utilizes affinity maturation to select highly-specific antibodies with desired functional characteristics. The functional

antagonist activity of dostarlimab was confirmed in a mixed lymphocyte reaction assay, demonstrating enhanced interleukin-2 (IL-2) production upon addition of dostarlimab. Furthermore, dostarlimab has an acceptable safety profile based on toxicology studies in cynomolgus monkeys. Additional information on the nonclinical and clinical experience with dostarlimab can be found in the dostarlimab IB.

2.4.1 Nonclinical Experience

Dostarlimab binds with high affinity to human and cynomolgus monkey PD-1. Dostarlimab blocks binding of soluble ligands to human PD-1 expressed on the surface of Chinese hamster ovary cells, with a 50% maximum inhibitory concentration (IC_{50}) of approximately 1 nM. Dostarlimab enhances T cell activation, as measured by the production of IL-2 from activated CD4+ T cells, with a 50% maximum effective concentration (EC_{50}) of approximately 1 nM. Full PD-1 receptor occupancy achieved by dostarlimab in human and cynomolgus monkey T cells from peripheral blood mononuclear cells was determined to occur at concentrations of approximately 1 µg/mL.

Linear pharmacokinetic (PK) was observed for dostarlimab over the dose range tested of 10 to 100 mg/kg. Sex had no effect on exposure. The volume of distribution at steady state was low and suggested minimal tissue penetration, which is commonly observed for therapeutic monoclonal antibodies. Weekly administration resulted in approximately 2- to 3-fold increase in dostarlimabexposure.

Administration of dostarlimab by a weekly IV dose (5 total doses) to cynomolgus monkeys at doses of 0, 10, 30, or 100 mg/kg was well tolerated and did not result in any TEAEs on clinical signs, body weight, food consumption, ECG, ophthalmology, safety pharmacology parameters, clinical pathology, gross pathology, organ weight, or histopathology. The no-observed-adverse-effects level was ≥100 mg/kg in this study.

2.4.2 Clinical Experience

Dostarlimab has been evaluated in one Phase 1 study to date. Study 4010-01-001 is an ongoing first-in-human Phase 1 study of dostarlimab to evaluate the safety and tolerability, PK, pharmacodynamics, and clinical activity of dostarlimab in patients with advanced solid tumors. The study is being conducted in 2 parts:

- Part 1 (dose escalation) of the study used a modified 3 + 3 design to evaluate 3 ascending weight-based doses of dostarlimab as follows: 1, 3, and 10 mg/kg administered every 2 weeks (Q2W) via IV infusion.
- Part 2 of the study is being conducted in 2 subparts (Part 2A and Part 2B) to explore the safety and clinical activity of dostarlimab administered as a fixed dose (ie, not weight based).
  - In Part 2A, following the completion of Part 1, the safety and tolerability of dostarlimab were evaluated at fixed doses of 500 mg every 3 weeks

(Q3W) and 1,000 mg every 6 weeks (Q6W) using a modified 6 + 6 design with up to 24 patients (6 patients/cohort).

- In Part 2B, the clinical activity, tolerability, and safety of dostarlimab at the RP2D will be evaluated in patients with specific tumor types. Up to 5 tumor types may be investigated in 6 expansion cohorts with approximately 65 patients enrolled in each cohort.

  As of 21 January 2019, a total of 627 patients have received at least 1 dose of dostarlimab. There were 18 on-study deaths and 52 study drug discontinuations due to AEs.

  Of the 335 subjects treated with dostarlimab monotherapy in Study 4010-01-001, 93.7% reported at least 1 TEAE, with events of fatigue, nausea, and diarrhoea being the most frequently reported. Study drug related TEAEs of Grade ≥3 were reported in 36 subjects (10.7%). SAEs occurred in 106 subjects (31.6%); in 21 of these subjects, these SAEs were considered study drug-related. Of the 292 subjects treated with dostarlimab in combination with other therapeutic agents, 94.5% reported at least 1 TEAE, with events of fatigue, nausea, and dyspnoea being the most frequently reported. SAEs occurred in 108 subjects (37.0%), and for 20 of 108 subjects, the SAEs were related to the study drug.

  As of 30 November 2018, 32 of 34 patients treated with dostarlimab monotherapy in Part 1 and Part 2A of Study 4010-01-001 had at least 1 post-baseline tumor assessment. Two patients achieved a partial response, and 7 patients achieved stable disease. One patient in Part 1 was still on study drug.

  Given this encouraging clinical activity in heavily pretreated patients with diverse tumor types, and the manageable safety profile of dostarlimab, the benefit-risk profile for use of dostarlimab for treatment of patients with advanced cancers appears positive. Clinical activity of dostarlimab monotherapy in specific tumor types is being further investigated in Part 2B of Study 4010-01-001. Clinical activity of dostarlimab in combination with other therapies in specific tumor types is being further investigated.

2.5 Dostarlimab and Niraparib Combination Treatment

2.5.1 Nonclinical Experience

The efficacy and tolerability of niraparib in combination with anti-PD-1 therapy was evaluated in several nonclinical models. The combination was well tolerated in all of these studies. The combination was first tested in a homologous recombination-deficient ovarian cancer mouse model derived from *BRCA* null genetic background,[61] as PARP inhibition was previously shown to increase immune cell infiltration in *BRCA*-deficient models.[62] In a study of a ovarian carcinoma mouse model,[63] niraparib

(50 mg/kg orally [PO] QD) and dostarlimab (5 mg/kg intraperitoneally [IP] twice weekly [BIW]) were administered to mice either alone or in combination for 16 days. The combination was tolerated with no treatment-related death. Almost all the tumors achieved complete regression upon treatment with niraparib, dostarlimab, and the combination. Complete regression was first observed on treatment Day 16 in 2 of 6, 1 of 6, and 4 of 6 mice from the niraparib, dostarlimab, and combination groups, respectively. These results suggest that the therapeutic approach of combining niraparib with dostarlimabmay provide additional benefit for patients with homologous recombination-deficient tumors.

Niraparib and anti-PD-1 combination treatment has also been evaluated in several syngeneic models representing breast cancer 1 and breast cancer 2 (*BRCA1/2*) wild-type tumors, one of which was the breast cancer mouse model LPA1-T22. In study of a syngeneic transplant breast cancer model, niraparib (50 mg/kg PO QD) and anti-PD-1 antibody (10 mg/kg IV BIW) were administered to mice either alone or in combination for 15 days. While these tumors were moderately responsive to niraparib or anti-PD-1 antibody alone, with average tumor growth inhibition of approximately 50% for niraparib and 30% for PD-1 antibody, synergistic anti-tumor activity with near-complete tumor growth inhibition (>95%) was achieved with the combination.[64] In a similar study using the lung squamous syngeneic model KLN205, stronger tumor growth inhibition was observed for the combination (52.3%) than for niraparib alone (36.7%) or anti-PD-1 alone (30.5%).[65] Together, these data support the therapeutic approach of combining niraparib with anti PD-1 agent in either *BRCA1/2* mutant or wild-type tumors.

2.5.2 Clinical experience

A phase Ib dose-finding study of niraparib and dostarlimab in patients with advanced or metastatic cancer was conducted. Dostarlimab was administered at the standard dose of 500 mg q 3 weeks for the first 4 cycles and 1000 mg q 6 weeks thereafter. Niraparib was administered at the dose of 200 (level dose 1) and 300 mg (level dose 2) QD every 3 weeks. Twenty-three patients were enrolled (16 at the dose level 1 and 7 at the dose level 2) and 2 DLTs were identified in the second dose level; the authors concluded that the niraparib dose for the phase 2 study (RP2D) was 200 mg QD continuously. (see Table 7 of Investigator Brochure for further details).

Among studies that investigate the utility of a combination of immune checkpoint blockade with PARP inhibitors, a TOPACIO trial and MEDIOLA study were recently presented at the European Society of Gynaecological ncology (ESGO) congress 2018.

The phase I/II TOPACIO trial (NCT02657889) administers escalating doses of niraparib with pembrolizumab in a heavily pretreated platinum-resistant, or secondarily platinum-refractory cohort. In the entire population, the estimated ORR and disease control rate were 25% and 68%, respectively. Among enrolled patients,

77% were BRCA wild type, and 52% HR deficiency negative; even in these two subgroups, the ORR were 24% and 27%, respectively[66].

The phase I/II basket MEDIOLA trial (NCT02734004), evaluated the combination of olaparib and durvalumab in selected advanced solid cancers.

In the phase II study among 32 patients with germline BRCA1/2 mutant platinum-sensitive ovarian cancer, disease control rate at 12 weeks and ORR were 81% and 63%, respectively. Within the 22 patients underwent one to two prior chemotherapies, the ORR was even more enhanced (68%). The most common reported adverse events of grade III or more were anaemia (12%) and increased lipase (9%), along with any-grade hypothyroidism (15%) and rash (12%)[67].

A phase III trial evaluating the combination of dostarlimab and niraparib as maintenance treatment is currently ongoing: FIRST trial (NCT03602859) was designed to assess platinum and dostarlimab, followed by niraparib and dostarlimab maintenance therapy, vs. standard platinum-based treatment followed by maintenance niraparib or placebo, as first-line treatment of advanced ovarian cancer.

Sigle agent Niraparib is dosed according to body weight and platelet basal count after the publication on retrospective Radar analysis of Nova trial[68] and prospective validation of the individualized dose regimen in Prima trial[69]

All the ongoing studies, designated to assess the combination of niraparib and dostarlimab maintenance therapy, allow niraparib administration at 300 mg dose regimen:

The OPAL trial is a phase II, open labelled, multi arm trial evaluating, in cohort A, Niraparib 300 mg or 200 mg PO QD according to body weight and basal platelets count, plus dostarlimab 500 mg/day IV Q3W followed by 1000 mg/day IV Q6W, plus bevacizumab 15 mg/kg IV in Cycles 1 Q3W

The MOONSTONE trial is a phase II, open labbeled, single arm trial evaluating Niraparib 300 mg or 200 mg PO QD according to body weight and basal platelets count , plus dostarlimab 500 mg/day IV Q3W followed by 1000 mg/day IV Q6W. In terms of toxicity, available data from MOONSTONE trial show that about 77% of treated patients reported at least 1 TEAE, and 53% of patients experienced an event that was Grade 3 or higher in severity. In patients treated with the combination of niraparib plus dostarlimab, the most frequently reported TEAEs (≥20% of patients) were nausea (41%), vomiting (29%), and fatigue (24%).
Two patients (12%) discontinued due to a TEAE (events of aspartate aminotransferase increased and failure to thrive).
A case of serious alanine aminotransferase increased in 1 patient was the only serious TEAE to be considered drug-related by the investigator. At the time of the cutoff date, there have been no serious TEAEs leading to death in patients with ovarian cancer treated with niraparib plus dostarlimab.

The FIRST trial is a double-blind, randomized trial evaluating niraparib and dostarlimab maintenance therapy at the dose regimen of Niraparib: 300 mg or 200mg

PO QD according to body weight and basal platelets count and Dostarlimab: 500 mg IV on Day 1 every 21 days followed by 1,000 m.

See Table 6 of Niraparib Investigator Brochure for further details on studies of niraparib in combination with pembrolizumab, dostarlimab in patients with advanced cancer.

In the ovarian cancer pooled safety population, over 99% of patients reported at least 1 TEAE for each treatment combination, with the exception of patients in the niraparib plus dostarlimab group (77%). Across treatment combinations, 53% to 90% of patients experienced an event that was Grade 3 or higher in severity. TEAEs leading to treatment discontinuation occurred in 12% to 29% of patients. No TEAEs leading to death were reported in combination therapy studies for the ovarian cancer Pooled Safety Population (See Table 16 of Niraparib Investigator Brochure for a summary of the safety profile by combination treatment).

2.6 Rationale for Current Study

Ovarian cancer is the second most frequent gynecologic neoplasia, after cervical cancer,but it is the first in order of mortality. [70] The main reasons for this high mortality rate are the lack of early symptoms accompanying the first diagnosis of disease, meaning that most patients present in an advanced stage, and the limited results obtained from treatments. In fact chemotherapy, although induces high objective response rates even in patients with an advanced stage, does not guarantee satisfactory results in terms of long-term control of the disease, since the vast majority of patients will experience progression of the disease after a variable time interval.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [71-75].

In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved

prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated Tcells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD -L1 and/or PD L2) [76-77]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma. [78] This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Dostarlimab is an immunoglobulin G4-kappa humanized monoclonal antibody that binds with high affinity to and has antagonist activity against PD-1 with an acceptable safety profile in animal toxicology studies. Dostarlimabis predicted to provide clinical benefit in patients across a range of tumor types, similar to that observed with the approved anti–PD-1 antibodies nivolumab and pembrolizumab. A phase I-IIA was conducted on 34 patients with advanced solid tumors with dostarlimab at different doses and schedules.Most common (>10%) adverse events were fatigue (35%), nausea (15%) and artralgia, decreased appetite and pruritis (12%) and dehydration. Signals of activity were reported in a patient with ovarian cancer who achieved a long lasting (26 weeks) partial response**.** The recommended phase 2 dose was estabilished at 500 mg q 21 days for the first 4 cycles and 1000 mg q 42 days thereafter [79].

Niraparib ia an orally available And selective poly (ADP-ribose) polymerase (Parp)1-2 inhibitor approved for maintenance treatment in patients with recurrent, platinum responsive ovarian, fallo pian tube and peritoneale cancer. It has been reported that Parp inhibitors may enhance the immune response in tumors treated with anti PD-1 therapy via generation of cytosolic DNA that activates T cell through the stimulation of interferon gene (STING) pathway, rendering tumors immunologically “hot” with an increase in infiltrating lymphocytes. When evaluate in preclinical models niraparib and anti-PDL 1 combination was well-tolerated and demonstrated a benefit both in BRCA-proficient and BRCA-deficient tumor models and in a BRCA1-null ovarian cancer syngeneic model, the combination enhanced the anti tumor activity and increate the durability of responses. [80] The Topacio trial was a dose-finding combination study of niraparib and Pembrolizumab in recurrent platinum resistant ovarian cancer and triple negative breast cancer. Forteen patients were enrolled (9 ovarian cancer and 5 breast cancer patients).Five ovarian cancer patients reported partial responses, 3 of them were BRCA wild type. No new safety signals were reported and the recommended phase 2 dose was oral Niparaob 200 mg once dayly and pembrolizumab 200 mg flat dose q 21. [81]

In this trial we expected to evaluate the efficacy of dostarlimab-niraparib in patients not suitable for platinum retreatment, regardless BRCA status.

This is a randomized phase 3 trial evaluating niraparib plus dostarlimab vs chemotherapy at physician’s choice in the treatment of recurrent ovarian, fallopian tube or primary peritoneal cancer patients for which platinum treatment is not an option.

Rationale for Study Population

Patients not candidate for platinum retreatment are those that do not respond to platinum chemotherapy (platinum refractory), those presenting relapsed disease within 6 months after the end of the last platinum treatment (platinum resistant) and those presenting contraindications to further platinum therapy for residual toxicity

(neurotoxicity for instance) or previous allergic reactions: all these patients need further chemotherapy with platinum non-cross resistant drugs.

Among drugs available for patients not candidate for platinum retreatment, topotecan, gemcitabine, weekly paclitaxel and pegylated liposomal doxorubicin are usually given as single agents, since the superiority of any combination chemotherapy has not been proven in resistant patients. According to published data, however, the response rate with these two drugs is poor (10-15%) and the time to progression short (4 months). Thus, new strategies are urgently needed and novel systemic acting compounds need to be identified and tested in prospective clinical trials.

2.7 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Given the low (<10%) response rate following the treatment with platinum non-cross resistant drugs (gemcitabine, weekly paclitaxel and pegylated liposomal doxorubicin) in platinum resistant patients, new treatment modalities and paradigms are needed to significantly improve the prognosis.

The aim of this trial is to improve survival, progression free survivale and disease contro rate of platinum-resistant ovarian cancer patients by combining PARPi therapy with the PD-1 inhibitor Dostarlimab.

(PARP) inhibitors are the first clinically approved drugs designed to exploit synthetic lethality. They have led to a major change in the treatment of advanced ovarian cancer, and altered the natural history of a disease with extreme genetic complexity and defective DNA repair via homologous recombination (HR) pathway.

Immunotherapy is emerging as a potential strategy to enhance traditional ovarian cancer treatments.

It seems that PARP inhibitor and biologic agent combinations appear well tolerated and clinically effective in both BRCA-mutated and wild-type cancers. They target differing aberrant and exploitable pathways in ovarian cancer, and may induce greater DNA damage and HR deficiency. The input of immunotherapy in ovarian cancer is based on the observation that immunosuppressive microenvironments can affect tumour growth, metastasis, and even treatment resistance.

Several studies has been investigating the utility of a combination of immune checkpoint blockade with PARP inhibitors. Preliminary data suggest the treatment efficacy also in populations not typically responsive to single agent PARP inhibitors. In terms of safety concerns, preliminary data revealed adverse events compatible with those of single-agent strategies. The most common reported toxicities of grade 3 or more included anaemia (17%), fatigue (6%), thrombocytopenia (3%), increased lipase (9%), along with any-grade hypothyroidism (15%) and rash (12%).

In conclusion, they shown reasonable tolerability of the combination, with no significant overlapping toxicities, accompanied by early evidence of efficacy.

Rationale for Objectives

2.8 Primary Objective and Endpoint

Objective:

- To assess overall survival (OS) defined as measured from the date of randomization to the date of death by any cause

Endpoint:

- Overall Survival (OS), defined as the days randomization and the date of death by any cause

Hypothesis:

The combination of niraparib-dostarlimab is expected to increase overall survival with respect to chemotherapy alone

2.9 Secondary Objective(s), Endpoint(s)& Hypothesis(es)

Objectives:

- To assess progression free survival (PFS) defined as the time from the date of randomization to the earlier date of assessment of progression or death by any cause in the absence of progression. Progression will be assessed by RECIST v.1.1 criteria by the investigator. In a conservative approach the clinical condition deterioration which does not allow for radiologic evaluation will be considered as progression of disease.
- To assess the time to first subsequent therapy (TFST) defined as the time interval from the date of randomization to earliest date of fist subsequent therapy or death
- To assess the response rate (ORR) defined as the percentage of patients with CR or PR, as assessed by RECIST v.1.1 criteria evaluated by the investigator.
- To assess the safety and tolerability of patients receiving chemotherapy or dostarlimab plus niraparib evaluated according to CTCAE vers 5.0. Safety

endpoints include also the incidence of treatment-emergent AEs (TEAEs), clinically relevant changes in clinical laboratory parameters (hematology, chemistry) and ECG parameters.

- To assess patient-reported outcome (PRO) of patients receiving chemotherapy vs the combination of dostarlimab and niraparib using EORTC QLQC30, EORTCOV28, EQ-5DL

Endpoints:

- Progression free survival (PFS) defined as the time from the date of randomization to the earlier date of assessment of progression or death by any cause in the absence of progression. Progression will be assessed by RECIST v.1.1 criteria by the investigator. In a conservative approach the clinical condition deterioration which does not allow for radiologic evaluation will be considered as progression of disease;

- Time to first subsequent therapy (TFST) defined as the time interval from the date of randomization to earliest date of fist subsequent therapy or death;

- Response rate (ORR) defined as the percentage of patients with CR or PR, as assessed by RECIST v.1.1 criteria evaluated by the investigator;

- Adverse events (AEs) will be evaluated according to CTCAE vers 5.0. Safety endpoints include also the incidence of treatment-emergent AEs (TEAEs), clinically relevant changes in clinical laboratory parameters (hematology, chemistry) and ECG parameters;

- Patient reported outcomes will be measured by EORTC QLQC30, EORTCOV28, EQ-5DL. Responders are defined as improvement of >10 points on the PRO scales

Hypothesis:

- The combination of niraparib-dostarlimab is expected to increase PFS with respect to chemotherapy

- The combination of niraparib-dostarlimab is expected to increase TFST with respect to chemotherapy

- The combination of niraparib-dostarlimab is expected to produce an RR of equal or higher value with respect to chemotherapy

- The combination of niraparib-dostarlimab is expected to have an acceptable toxicity profile
- The combination of niraparib-dostarlimab is not expected to worsen patients quality of life with respect to chemotherapy alone

2.10 Exploratory Objective

Objective:

- To investigate the relationship between PD-L1 expression and efficacy of dostarlimab/niraparib treatment utilizing newly obtained or archival FFPE tumor tissue.
- To investigate the relationship between Combined Positive Score (CPS: Number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) relative to the total number of viable tumor cells, multiplied by 100) and efficacy of dostarlimab/niraparib treatment utilizing newly obtained or archival FFPE tumor tissue.
- To investigate the efficacy of dostarlimab/niraparib treatment according to the previous use of parp and/or immunotherapy
- To investigate the relationship between lymphoid or myeloid-derived suppression cells (MDSC) or T-regulatory cells (T-regs) and response to dostarlimab/niraparib treatment using archival FFPE tumor tissue and blood sampling
- To assess the association between anti-tumor activity and genetic alterations (HRD and BRCA among others) that may indicate a specific genotype reflective of greater dependency on PD-1/PD-L1 checkpoint function or PARP inhibition.

Rationale for Measures

According to the 5th Ovarian Cancer Conseensus Conference which took place in Tokio in 2015, when median life expectation is less than or equal to 12 months in recurrent ovarian cancer patients, overall survival (OS) should be the preferred primary end-point in a randomized trials. Since we expected that most part of enrolled patients will have a median life expectation less that 12 months, OS seems the most reasonable primary end-point.

Secondary end point are those usually evaluated in interventional clinical trial such as progression free survival (PFS), response rate (RR), safety registered both with

Common Toxicity Criteria for Adverse Events (CTCAEs) given the great amount of inconsintencies among reported toxicities when evaluated by the clinicians or the patients, and quality of life with patients reported outcome (PRO) measurements. Moreover exploratory end points aiming at evaluating eventual relationship between PD-1/PDL-1 expression, tumor infiltrating lymphocytes and HRD and experimental treatment efficacy will be considered

3 PARTICIPANT SELECTION

3.1 Inclusion Criteria

a. Participant must have recurrent ovarian, Fallopian tube or primary peritoneal cancer not candidate for platinum retreatment; and in particular
   - platinum resistant patients (platinum-free interval 1-6 months from last dose of platinum)
   - patients for which platinum is contraindicated because of previous allergic reactions or residual toxicity (i.e nephrotoxicity or neurotoxicity)
   - patients not able(in physician's opinion) to receive further platinum or not willing (in patients' opinion) to receive further platinum

b. Participant must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1

c. Participants must have measurable disease or evaluable based on RECIST 1.1 (patients with only CA 125 increase without evidence of disease are not included).

d. Participant must be ≥ 18 years of age

e. Participant must have adequate organ function, defined as follows:
   - Absolute neutrophil count ≥ 1,500/μL
   - Platelets ≥ 100,000/μL
   - Hemoglobin ≥ 9 g/dL
   - Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 60mL/min using the Cockcroft-Gault equation
   - Total bilirubin ≤ 1.5 x ULN (≤2.0 in patients with known Gilberts syndrome) OR direct bilirubin ≤ 1 x ULN
   - Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN
   - International normalized ratio (INR) or prothrombin time (PT) ≤1.5× 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) ≤1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

f. Participant receiving corticosteroids may continue as long as their dose is stable for least 4 weeks prior to initiating protocol therapy.

g. Participant must agree to not donate blood during the study or for 90 days after the last dose of study treatment.

h. Participants must agree to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1.*

Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen.

i. Female participant has a negative urine or serum pregnancy test within 7 days prior to taking study treatment if of childbearing potential and agrees to abstain from activities that could result in pregnancy 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):

- ≥45 years of age and has not had menses for >1 year
- Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
- Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. See Section 4.4 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

j. Participant must agree to not breastfeed during the study or for 180 days after the last dose of study treatment.

k. Participant must be able to understand the study procedures and agree to participate in the study by providing written informed consent

3.2 Exclusion Criteria

a. Participant must not be simultaneously enrolled in any interventional clinical trial

b. Participants have received >2 previous CHT lines (previous treatment with parp inhibitors and/or anti check point inhibitors is allowed providing that at least 6 months from last treatment are intercurred)

c. Participant must not have had major surgery ≤ 3 weeks prior to initiating protocol therapy and participant must have recovered from any surgical effects.

d. Participant must not have received investigational therapy ≤ 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is shorter, prior initiating protocol therapy.

e. Participant has had radiation therapy encompassing >20% of the bone marrow within 2 weeks; or any radiation therapy within 1 week prior to Day 1 of protocol therapy.

f. Participant must not have a known hypersensitivity to niraparib and dostarlimab components or excipients.

g. Participant must not have received a transfusion (platelets or red blood cells) ≤ 4 weeks prior to initiating protocol therapy.

h. Participant must not have received colony-stimulating factors (eg, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) within 4 weeks prior initiating protocol therapy.

i. 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.

j. Participant must not have any known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)

k. Participant must not have a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent

l. Participant must not have had diagnosis, detection, or treatment of another type of cancer ≤ 3 years prior to initiating protocol therapy (except basal or squamous cell carcinoma of the skin and cervical cancer that has been definitively treated)

m. Participant must not have known, symptomatic brain or leptomeningeal metastases

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

o. Participant has a diagnosis of immunodeficiency or has received systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to initiating protocol therapy.

p. Participant has a known history of human immunodeficiency virus (type 1 or 2 antibodies).

q. Participant has known active hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (e.g., hepatitis C virus [HCV] ribonucleic acid [qualitative] is detected).

r. Participant has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg,

thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

s. Participant must not have a history of interstitial lung disease.

t. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

4 TREATMENT PLAN

4.1 Method of Treatment Assignment

This is a randomized phase III trial comparing physician's choice chemotherapy vs niraparib plus dostarlimab in recurrent ovarian, fallopian tube or primary peritoneale cancer not candidate for futher platinum based chemotherapy.

The patients must have received no more than 2 previous chemotherapy lines .

A web randomization list will be created via electronic Case Report Form (CRF). Stratification factors will include HRD status, previous treatment with parp and anti PD-1/PDL-1 inhibitors, Bevacizumab treatment and PDL1 expression.

HRD status will be evaluated with Foundation One test and tumor PD-L1 expression will be evaluated on archival pre-therapy lesion at Fondazione Policlinico Universitario A. Gemelli of Rome (the coordinating center).

Blood samples and tissue block will be sent to the coordinator center for translational analysis.

Clinic visits will occur in each cycle. Safety will be evaluated at each cycle by CTCAE vers 5.0 criteria. Response Evaluation Criteria in Solid Tumors (RECIST) will be used for tumor assessment via a computed tomography (CT) or magnetic resonance imaging (MRI) scan of abdomen/pelvis and clinically indicated areas, which is required at the end of every 12 weeks with a window of ± 7 days from date of visit until progression. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or lost to follow-up, scans should continue at the specified intervals. If a patient discontinues treatment for clinical progression and does not meet the criteria specified in the protocol, scans and CA-125 testing should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment. Quality of Life assessments are required at: Baseline, every 3 chemotherapy cycles and at the end of study (either at progression or after the last cycle of chemotherapy if patient refusing to continue treatment). Quality of life will be evaluated by EORTC QLQC30, EORTCOV28, EQ-5DL.

4.2 Treatment Regimen

ARM A

Chemotherapy at physician's choice between

Pegylated Liposomal Doxorubicin 40 mg/mq iv q 28

Weekly Paclitaxel 80 mg/mq d 1,8,15 q 28

Gemcitabine 1000 mg/mq d 1,8,15 q 28

Topotecan 1.25 mg/mq day 1-5 q 21

+/- Bevacizumab at defined scehedule

ARM B
Dostarlimab 500 mg q 3W for the fist 4 cycles, 1000 mg q 6W thereafter + Niraparib 300 mg or 200 mg if platelet count <150,000 /µL and/or body weight <77kg QD po q 28

Patients will continue to receive niraparib until disease progression (determined using RECIST v.1.1 criteria and clinical criteria), unacceptable toxicity, death, withdrawal of consent, or lost to follow-up, whichever comes first. Patients will continue to receive dostarlimab for a maximum of 2 years, or until disease progression (determined using RECIST v1.1 criteria and clinical criteria), unacceptable toxicity, death, withdrawal of consent, lost to follow-up, whichever may come first. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient.

4.2.1 Niraparib Administration

Niraparib will be administered as a flat-fixed, continuous daily dose 300 mg QD or Niraparib or 200 mg if platelet count <150,000 /µL and/or body weight <77kg QD po.

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.

4.2.2 Dostarlimab 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, followed by 1,000 mg on Day 1 of every 42-day cycle (i.e., Q6W) thereafter until the patient discontinues study treatment for a maximum of 2 years.

4.2.3 Other Agent Administration

Pegylated Liposomal Doxorurbicin will be administered at the dose of 40 mg/mq iv every 4 weeks in 1 hour. Weekly Paclitaxel will be administered at the dose of 80 mg/mq d 1,8,15 every 4 weeks in 1 hour. Gemcitabine will be administered at the dose od 1000 mg/mq d 1,8,15 every 4 weeks in 30 minutes. Topotecan will be administered at the dose of 1.25 mg/mq days 1-5 every 3 weeks in 30 minutes.

4.3 Prohibited Therapies

The following medications are prohibited while receiving protocol therapy:

- Systemic anticancer or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than niraparib and/or dostarlimab
- Radiation therapy encompassing >20% of the bone marrow is prohibited within 2 weeks prior to Day 1 and during study treatment. Note: Palliative radiation therapy to a small field >1 week prior to Day 1 of study treatment may be allowed.
- 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.
- Even though inhibition of CYP3A4 in the liver is not expected, the potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Therefore, caution is recommended when niraparib is combined with active substances the metabolism of which is CYP3A4-dependent and, notably, those having a narrow therapeutic range (eg, ciclosporin, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine).
- In vitro, niraparib weakly induces CYP1A2 at high concentrations and the clinical relevance of this effect could not be completely ruled out. The primary circulating metabolite of Niraparib is not a CYP1A2 inducer. Therefore, caution is recommended when niraparib is combined with active substances the metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (eg, clozapine, theophylline, and ropinirole)Niraparib is not an inhibitor of BSEP (bile salt export pump). In vitro, niraparib inhibits P-gp very weakly and BCRP (breast cancer resistance protein); with an IC50 = 161 µM and 5.8 µM, respectively. Therefore, a clinically meaningful interaction related to an inhibition of these

efflux transporters, although unlikely, cannot be excluded. Caution is then recommended when niraparib is combined with substrates of BCRP (eg, irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate)

- Niraparib is an inhibitor of MATE1 and -2 with IC50 of 0.18 μM and ≤ 0.14 μM, respectively. Increased plasma concentrations of co-administered medicinal products that are substrates of these transporters (eg, metformin) cannot be excluded. Inhibition of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)
- In vitro, niraparib weakly inhibits the organic cation transporter 1 (OCT1) with an IC50 = 34.4 μM. Caution is recommended when niraparib is combined with active substances that undergo an uptake transport by OCT1 such as metformin

- Systemic glucocorticoids for any purpose other than to manage symptoms of suspected irAEIs. (Note: Use of inhaled steroids, local injection of steroids, topical steroids, and steroid eye drops are allowed). If medically deemed necessary (e.g., acute asthma or chronic obstructive pulmonary disease exacerbation), Investigators are allowed to use their judgment to treat patients with systemic steroids. In such cases, systemic steroids should be stopped at least 24 hours prior to the next dose of dostarlimab.
- Live vaccines within 14 days prior to the first dose of study treatment. Seasonal flu vaccines that do not contain live viruses are allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, bacille Calmette-Guerin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.
- Prophylactic cytokines (ie, granulocyte colony-stimulating factor [GCSF]) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current American Society of Clinical Oncology (ASCO) guidelines.[80]

4.4 Birth Control

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):

methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

1) combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
   - oral
   - intravaginal
   - transdermal
2) progestogen-only hormonal contraception associated with inhibition of ovulation:
   - oral
   - injectable
   - implantable
3) intrauterine device (IUD)
   - intrauterine hormone-releasing system (IUS)
4) bilateral tubal occlusion
5) vasectomised partner
6) sexual abstinence.

4.5 Breast Feeding

Participants must not breast-feed while receiving protocol therapy and for 180 days following the last dose of protocol therapy

4.6 Blood Donation

Participants must not donate blood during the study or for 90 days after the last dose of protocol therapy.

4.7 Dose Escalation

No dose escalation is planned.

4.8 Treatment Discontinuation

Participants may continue dostarlimab for a maximum of 2 years and/or niraparib until one of the following criteria applies:

- Disease progression
- Serious or life-threatening adverse event (DLTs at first cycle)
- Severe noncompliance with protocol as judged by the Investigator and/or Sponsor
- Participant decision to withdraw
- Participant becomes pregnant
- Participant is diagnosed with MDS or AML (as confirmed by a hematologist)
- Participant is diagnosed with PRES (as confirmed by magnetic resonance of brain)
- Investigator, Sponsor, and/or GSK becomes aware of conditions or events that suggest a possible risk or hazard to participants if the clinical study continues

4.9 Duration of Follow Up

Participants will be followed for 5 years after removal from protocol therapy or until death, whichever occurs first.

4.10 Discontinuation from Study

Participants who discontinue from treatment will continue to be followed for overall survival until one of the following criteria apply:

- Withdrawal of consent
- Loss to follow-up
- Death from any cause
- Termination of the study

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

4.11 Participant Replacement Criteria

All randomized patients who have received at least one chemotherapy cycle will be included in the intention to treat analysis. All patients receiving at least 1 dose of study treatment will be evaluated for safety. In case of patients refusal of treatment soon after randomization or in case of impossibility to receive at least 1 chemotherapy cycle for any reasons, patients will be replaced (a maximum 10% replacement has been scheduled)

4.12 Dose Modifications

4.12.1 Niraparib

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

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

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

The dose interruption and modification criteria for niraparib for hematologic parameters will be based on blood counts and are outlined in Table 8. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period the patient must permanently discontinue treatment with niraparib.

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

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

Table 4: Niraparib Dose Modifications for Nonhematologic Adverse Reactions

Abnormality	**Intervention**
Non-hematologic CTCAE ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. Resume niraparib at a reduced dose.
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue niraparib.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Table 5: 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/μL	First occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at same or reduced dose per Table 3. If platelet count is < 75,000/μL, resume niraparib at a reduced dose per table 3.
	Second occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at a reduced dose per Table 3. Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone maximum dose reductions per Table 3.
Neutrophil count < 1,000/μL	Withhold niraparib for a maximum of 28 days and monitor blood counts until neutrophil counts return to ≥1,500/μL. Resume niraparib at a reduced dose per Table 3. Discontinue niraparib if neutrophil level has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone maximum dose reductions per Table 3.
Hemoglobin ≤ 8 g/dL	Withhold niraparib for a maximum of 28 days and monitor blood counts until hemoglobin returns to ≥9 g/dL. Resume niraparib at a reduced dose per Table 3. Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone maximum dose reductions per Table 3.
Hematologic adverse reaction requiring transfusion	For patients with platelet count ≤10,000/μL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Resume niraparib at a reduced dose per table 3.
Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.

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

In the case of thrombocytopenia, following the first occurrence, resumption of therapy may occur at the same dose or 1 dose level lower when the hematologic toxicity has resolved. Subsequent occurrences should trigger dose reduction upon resumption of

therapy. If the platelet count has not reverted within 28 days of interruption to ≥100,000/μL, then study treatment should be discontinued.

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.

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

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.

4.13 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 ≤1; dostarlimab will be permanently discontinued for any drug-related Grade 4 AE. Dostarlimab must be permanently discontinued for certain irAEIs as described in Table 6.

The specific immune-related AEs typically observed with anti-PD-1 antibodies will be managed according to the guidelines summarized below.[79]

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 7 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 6, dostarlimab should be withheld until the patient is clinically and metabolically stable and AEs have resolved to Grade ≤1. If systemic steroids are used as a part of irAEI management, the total dose of daily steroids should be equal to or less than 10mg prednisone at the time of resuming dostarlimab.

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

Table 6: 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 ≤ 5 × ULN or total bilirubin > 1.5 and ≤ 3 × ULN)	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4 (AST or ALT > 5 × ULN or total bilirubin > 3 × ULN)	Permanently discontinue (see exception below).[a]
T1DM or hyperglycemia	3 or 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)	Restart dosing in appropriately managed, clinically and metabolically stable patients, insulin replacement therapy is required.
Immune-related encephalitis	Any grade	Permanently discontinue.
Hypophysitis	2 to 4	For Grade 2 to 3 AEs, hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 to 1. For recurrence or worsening of Grade ≥2 hypophysitis after corticosteroid taper has been completed and patient is on adequate hormone replacement therapy, permanently discontinue. For Grade 4 AEs, permanently discontinue.
Hyperthyroidism	3	Restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.
Infusion-related reaction	2[b]	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4	Permanently discontinue.
Pneumonitis	2	Restart dosing when toxicity resolves to Grade 0 to 1. If Grade 2 recurs, permanently discontinue.
	3 or 4	Permanently discontinue.

Toxicity	Withhold Treatment for AE Grade	Restarting Treatment/Discontinuation
Rash	3	Restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.
Renal failure or nephritis	2	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4	Permanently discontinue.
Recurrence of AEs after resolution to Grade ≤1	3 or 4	Permanently discontinue.

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

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

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

4.13.1 Rescue Medications and Supportive Care Guidelines

During treatment with dostarlimab, patients should receive appropriate supportive care measures for AEs as deemed necessary by the treating Investigator, including but not limited to the items outlined below. Prophylactic cytokines (eg, GCSF) should be administered according to current ASCO guidelines.[80] 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.

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

Table 8:Dostarlimab Infusion Reaction Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, or IV fluids); prophylactic medications indicated for ≤24 h	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/h to 50 mL/h). Otherwise, dosing will be withheld until symptoms resolve, and the patient should be pre-medicated for the next scheduled dose. Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.	Patient may be pre-medicated 1.5 h (±30 min) prior to infusion of dostarlimab with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) • Acetaminophen 500 to 1000 mg PO (or equivalent dose of antipyretic)

CTCAE Grade	**Treatment**	**Premedication at Subsequent Dosing**
Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further study treatment administration.**	No subsequent dosing.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = oral.

Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of study treatment administration.

5 PHARMACEUTICAL INFORMATION

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

5.1 Niraparib

5.1.1 Identity

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) -1 and -2 inhibitor. Niraparib is also known as ZEJULA.

5.1.2 Potential Risks of Niraparib

The following adverse reactions (all CTCAE grades) have been reported in ≥20% of patients who received niraparib: anemia, thrombocytopenia, nausea, constipation, vomiting, fatigue, platelet count decreased, decreased appetite, headache, and insomnia. The median exposure to niraparib in these patients was 250 days.

The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 367 patients receiving niraparib: neutropenia, palpitations, asthenia, neutrophil count decreased, dizziness, dysgeusia, dyspnea, cough and hypertension. The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients receiving niraparib: tachycardia, dry mouth, mucosal inflammation, white blood cell count decreased, aspartate aminotransferase increased, alanine aminotransferase increased and photosensitivity reaction.

Special Warnings and Special Precautions for Use

- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) have been reported in niraparib-treated patients.
  If MDS and/or AML are confirmed while on treatment with niraparib, then niraparib should be permanently discontinued and the patient should be treated appropriately.

- 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.

, 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

- There have been rare reports 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. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with definitive discontinuation of niraparib and MRI radiological monitoring of the syndrome. The safety of reinitiating niraparib therapy in patients previously experiencing PRES is not known.

5.1.3 Packaging, Labeling and Storage

Niraparib is supplied by GSK in high-density polyethylene (HDPE) bottles with child-resistant plastic closures. 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.

5.1.4 Drug Accountability and Dispensing

The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Investigator Agreement or their qualified designees. The investigator, sub-investigators, or qualified designees also agree that the study drug(s) will be dispensed only to study subjects who have provided written informed consent and have met all entry criteria and in accordance with the instructions provided in the Storage and Handling Guidelines.

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.

Accountability will be recorded on source documents and on accountability records provided by the Sponsor. Additional instructions will be given during Site Inititation Visit.The pharmacist will dispense study treatment for each participant according to the protocol and storage and handling manual, if applicable.

5.1.5 Disposal and Destruction

Niraparib should be destroyed at the investigational site if permitted by local regulations.

5.2 Dostarlimab

5.2.1 Identity

Dostarlimab is an IgG4 antibody and will be supplied as a solution in vials containing 500 mg (50 mg/ml).

5.2.2 Potential Risks of dostarlimab

There is the potential for human anti-drug reactions to dostarlimab or hypersensitivity reactions. If these effects occur, whether acute or delayed, they may vary in severity from mild rash to severe anaphylaxis, and they may be life threatening. Reactions following IV infusion or subcutaneous injections of approved humanized monoclonal antibodies have been reported but are generally mild, typically occur during or within 24 hours after IV infusion and may include changes in heart rate and blood pressure, pyrexia, and arthralgia. A delayed reaction can occur 24 hours to 2 weeks after IV infusion and may resemble serum sickness. Injection site reactions may include redness, itching, swelling, or pain at the injection site. Patients should be monitored for such effects and emergency treatment must be available for promptly treating patients with immune reactions during infusions. As dostarlimab only has limited human experience, the investigator should be alert for other AEs, including idiosyncratic reactions. Refer to the current labels for pembrolizumab and nivolumab for additional information on potential class effects of mAb anti- PD-1 inhibitors.

5.2.3 Packaging, Labeling and Storage

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

5.2.4 Drug accountability and Dispensing

The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Investigator Agreement or their qualified designees. The

investigator, sub-investigators, or qualified designees also agree that the study drug(s) will be dispensed only to study subjects who have provided written informed consent and have met all entry criteria and in accordance with the instructions provided in the Storage and Handling Guidelines.

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.

All dispensing and accountability records should be stored in accordance to the institution regulations. The pharmacist will dispense study treatment for each participant according to the protocol and storage and handling manual, if applicable

5.2.5 Disposal and Destruction

Dostarlimab should be destroyed at the investigational site if permitted by local regulations.

5.3 Other Agent

Chemotherapy drugs (at physician's choice between weekly paclitaxel, gemcitabine, pegylated liposomal doxorubicin and topotecan plus or minus bevacizumab ad scheduled dose) represent standard of care in the treatment of recurrent ovarian cancer. The drugs will be provided by National Health System and packaged, labeled and stored according to local hospital giudelines. The management of drug toxicity will be performed according to published guidelines for chemotherapy toxicity management and local attitudes.

5.3.1 Dispensing

The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Investigator Agreement or their qualified designees. The investigator, sub-investigators, or qualified designees also agree that the study drug(s) will be dispensed only to study subjects who have provided written informed consent and have met all entry criteria and in accordance with the instructions provided in the storage and handling manual.

5.3.2 Disposal and Destruction

All the drugs (standard and experimental) will be destroyed at centres according to local practice. The Investigator or designee is responsible for maintaining accurate dispensing records of the study drug throughout the clinical study. The drug accountability log includes information including the enrollment number, amount dispensed, and amount 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 will be available for Sponsor review. The study monitor will assume the responsibility to reconcile the drug accountability log. The pharmacist will dispense study drug for each patient according to the protocol and pharmacy manual, if applicable.

6 CORRELATIVE STUDIES

Tumor tissue for biomarker analysis, from formalin fixed paraffin embedded tumor tissue sample or newly obtained formalin fixed biopsy of a tumor lesion, must be provided in the form of a tissue block.
An archival tumor tissue or a fresh biopsy will be taken at baseline, before any treatment initiation. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen.
If possible, a new fresh biopsy will be performed at the time of progression.

Blood sampling will be performed prior to initiation of treatment on Day 1, every three cycles in the treatment phase and at progression.

Tumor biopsies and blood sampling will be evaluated to investigate the relationship between PD-L1 expression and CPS score and response to dostarlimab, to identify biomarkers important for predicting responsiveness or resistance to dostarlimab therapy, to assess the association between anti-tumor activity and genetic alterations (HRD and BRCA among others) that may indicate a specific genotype reflective of greater dependency on PD-1/PD-L1 checkpoint function or PARP inhibition.

The samples will be collected and analysed at the coordinating center, Fondazione Policlinico Universitario A. Gemelli of Rome.

Assays will include, but are not limited to:

- Peripheral and intratumoral and possibly peritumoral evaluation of Treg and MDSC
- Circulating PD-L1 level
- Cytokine profiles through the evaluation of two panels including pro- and anti-inflammatory cytokines such as CD3, CD4, CD8 (immunoscore), PD1, PDL1, OX40-OX40L, FOXP3, ICOS, CTL-4, FOXP3, CD 95 and CD95-L

Table X-1 Summary of Research Tissue and Blood Specimen Collection

Research Sampling	Time point	Contents
Blood	Cycle 1 Day 1 Pre-Dose (within 30 min of dose)	1- 5mL EDTA Purple Top
	Cycle 4 Day 1 and cycle 7 day 1 Pre-Dose (within 30 min of dose)	1- 5mL EDTA Purple Top
	At progression	1- 5mL EDTA Purple Top

Fresh Tissue	When feasible a newly obtained core or excisional biopsy of a tumor lesion will be performed. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen. An optional new biopsy will be performed at the time of disease progression.	Paraffin embedded tumor block
Archival Tissue	At baseline before any treatment initiation	Paraffin embedded tumor block

7 SCHEDULE OF ASSESSMENTS

7.1 Screening

At Screening, the following procedures/tests will be performed:

- Informed Consent
- ECOG Performance Status
- Physical Exam
- Medical History and Concomitant Medications
- Vital Signs: systolic and diastolic blood pressures, weight and temperature
- Height
- Pregnancy testing within 7 days prior to initiating protocol therapy (if patients without hysterectomy and/or annessiectomy)
- CBC
- Comprehensive metabolic panel
- Coagulation
- CA125
- HBC/HCV testing
- Thyroid Panel: TSH, T3 or FT3, and FT4
- Urinalysis
- ECG
- CT scan or MRI (within 28 days from day 1 cycle 1)
- LVEF by Echocardiogram or MUGA scan, to be repeated if clinically indicated
- Bone scan should be obtained only if bone metastasis are suspected
- CT scan or MRI of the brain should be obtained only if neurological symptoms are present
- New obtained tumor biopsy or, if unavailable, paraffin embedded block of the primary tumor.

7.2 Day 1 Tretament Cycle

On Day 1(+/- 3 days) , the following procedures/tests will be performed:

- Vital signs: systolic and diastolic blood pressures, weight, and temperature
- CBC (to be repeated at cycle 1 if screening exams are not within 7 days prior to initiating protocol therapy)
- Comprehensive biochemistry panel (to be repeated at cycle 1 if screening exams are not within 7 days prior to initiating protocol therapy)
- Thyroid Panel: TSH, T3 or FT3, and FT4 (to be repeated at cycle 1 if screening exams are not within 7 days prior to initiating protocol therapy). Done on Cycle 2/Day 1 and every 6 weeks thereafter through the remainder of the study (can be done up to 7 days prior to dostarlimab administration) and at End of Treatment Visit.

- CA125
- Urinalysis (to be repeated at cycle 1 if screening exams are not within 7 days prior to initiating protocol therapy)
- Adverse event monitoring
- Blood samples for genetic and immunologic analysis (day 1 of cycle 1 and then every 3 cycles)
- Quality of life evaluation with EORTC QLQC30, EORTCOV28, EQ-5DL

  On Days 8 (+/-2 days) and 15(+/-2 days) CBCs, creatinine, ALT and AST will be performed.

7.3 Every 12 weeks (+/- 7 days)

The following procedures/tests will be performed:

- Quality of life evaluation with EORTC QLQC30, EORTCOV28, EQ-5DL.
- CT scan or MRI for tumor response evaluation (CT or MRI of the brain should be obtained if neurological symptoms are present and a MRI of the brain should be obtained in case of sign and symptoms of PRES)
- Blood samples for genomic and immunologic evaluation

7.4 End of Treatment

- Adverse event monitoring
- Quality of life evaluation with EORTC QLQC30, EORTCOV28, EQ-5DL.
- CT scan or MRI for tumor response evaluation
- CBC
- Comprehensive metabolic panel
- Coagulation
- CA125
- Thyroid panel: TSH, FT3 and FT4
- Blood samples for genomic and immunologic evaluation
- A new biopsy will be obtained, if feasible, at progression (optional)

7.5 Safety Follow-up

Follow-up visit should occur at least 30 days from the last administered dose of protocol therapy.

- Vital signs: systolic and diastolic blood pressures, weight, and temperature
- CBC
- Comprehensive metabolic panel
- Urine pregnancy test for females of childbearing potential
- Coagulation
- CA125

- Thyroid Panel: TSH, T3 or FT3, and FT4
- Urinalysis
- Physical Exam
- Adverse event monitoring
- Assess for MDS/AML

7.6 Long Term Follow-up

- Survival assessment
- Follow-up for MDS/AML

7.7 Unscheduled Assessments

- SAE monitoring

  If at any time after the study is completed, an Investigator becomes aware of an SAE that is considered related to the investigational product, the Investigator should report the SAE to the Sponsor Institution and GSK within 24 hours of becoming aware of the SAE

- Clinical Laboratory Assessments

  If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC also will be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume

  For any suspected MDS/AML case reported while a participant is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. Testing completed as part of standard of care is sufficient. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization criteria) and other sample testing reports related to MDS/AML. The site must keep a copy of the report with the participant's study file

8 STUDY CALENDAR

Screening assessments are to be conducted within 28 days prior to initiating protocol therapy unless otherwise specified. Screening assessments occurring within 1 week prior to initiating study treatment do not need to be repeated on Cycle 1 Day 1 unless otherwise specified.

Screening laboratory assessments must be done within 8 days prior to initiating protocol therapy. For women of childbearing potential, as defined in the eligibility criteria, a pregnancy test must be completed within 7 days prior to initiating protocol therapy. If a urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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

Study Procedures	**Screening**	**Cycle 1 (± 3 days)**				**Cycle 2 (± 3 days)**				**Cycle 3+ (± 3 days)**				**EOT**	**Safety Follow-Up**	**Long Term Follow-Up**
		D1	**D8**	**D15**	**D21**	**D1**	**D8**	**D15**	**D21**	**D1**	**D8**	**D15**	**D21**		**At least 30 days from last dose**	**Every 6 months for 2 years and annually thereafter until 5 years**
Written informed consent	X															
Inclusion/Exclusion Criteria	X															
Height	X															
Vital Signs[a]	X	X				X				X					X	
ECOG Performance Status	X															
Medical History[b]	X															
Concurrent Medications	X	X				X				X				X		
Physical Exam	X					X				X					X	
Adverse Event Monitoring	X	X	X	X	X	X				X				X	X	
ECG	X	if clinically indicated														
LVEF by echocardiogram or MUGA	X	only for PLD treatment or if chemotherapy is given in combination with Bevacizumab) to be repeated if clinically indicated														
Assess for MDS/AML		X				X				X				X	X	X
Pregnancy Testing[c]	X									X					X	
CBC[d]	X	X	X	X		X	X	X		X	X	X		X	X	
Comprehensive Metabolic Panel[e]	X	X	X	X		X	X	X		X	X	X		X	X	
CA125	X	X				X				X				X	X	
Coagulation	X	X[h]				X[h]				X[h]				X		
HBV/HCV test[i]	X															
Thyroid panel[j]	X					X				X				X	X	
Urinalysis	X[e]	X				X				X				X	X	

Study Procedures	**Screening**	**Cycle 1 (± 3 days)**				**Cycle 2 (± 3 days)**				**Cycle 3+ (± 3 days)**				**EOT**	**Safety Follow-Up**	**Long Term Follow-Up**
		D1	**D8**	**D15**	**D21**	**D1**	**D8**	**D15**	**D21**	**D1**	**D8**	**D15**	**D21**		**At least 30 days from last dose**	**Every 6 months for 2 years and annually thereafter until 5 years**
Blood samples for genomic and immunologic analysis		X (+/- 7 days								X				X		
Tumor byopsy[k]	x													X		
Bone marrow aspirate and biopsy[g]		X														
Survival assessment[f]																X
Tumor Assessment[l]	x									X				X		
Quality of life evaluation	x	X[l]								X				X		

Niraparib: Niraparib 200 or 300 mg, according to body weight and platelets count,QD q 3W
Dostarlimab: 500 mg q 3W for the fist 4 cycles, 1000 mg q 6W thereafter
Other Agent: chemotherapy (at physician's choice) at standard dose

a. Vital signs to include: systolic and diastolic blood pressures while the patient is in a seated position, weight, and temperature
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 ≤ 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 at every cycle on day 1, 8,15 (+/- 3 days). CBC must be repeated on day 1 Cylce 1 if screening exam are not within 7 days prior initiating protocol therapy.
e. Comprehensive metabolic panel to include: glycemia, serum creatinine, total bilirubin, aspartate aminotransferase and alanine aminotransferase, electrolytes, alkaline phosphatase, CPK, amilase, lipase. It should be collected at every cycle on day 1+/- 3 days and must be repeated on day 1 Cylce 1 if screening exam are not within 7 days prior initiating protocol therapy.
f. Overall survival to be followed for 5 years following the last dose of protocol therapy.
g. 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.

h. To be conducted per standard of care for participants on anticoagulant therapy
i. Only when medically indicated based on history and physical examination.
j. Thyroid panel to include TSH, T3 or FT3, and FT4. It must not be repeated on day 1 Cylce 1 if screening exam are within 7 days prior initiating protocol therapy Done on Cycle 2/Day 1and every 6 weeks thereafter through the remainder of the study (can be done up to 7 days prior to dostarlimabadministration), at End of Treatment Visit and when clinically indicated.
k. New obtained tumor biopsy or, if unavailable, paraffin embedded block of the primary tumor. A new biopsy will be performed at progression (optional)
l. Every 12 weeks (+/- 7 days). (CT or MRI of the brain should be obtained if neurological symptoms are present and a MRI of the brain should be obtained in case of sign and symptoms of PRES)

9 ADVERSE EVENT REPORTING

9.1 Definition of Adverse Events

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

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring 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.

9.2 Serious Adverse Events (SAEs)

Any untoward medical occurrence that, at any dose;

- Results in death;
- Is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization* or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event**

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

**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.

9.3 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
- Embyro-fetal toxicity

AESIs should be reported on SAE Report Forms whether serious or not, within 24 hours of awareness, as follows:

Investigator Reponsibility:

- MDS and AML along with other secondary cancers should be reported to the Sponsor Institution upon awareness for any patient who has received any study medication (regardless of the drug and of the timeframe since the last dose).
- Pneumonitis should be reported to the Sponsor Institution through 90 days after the last dose of study drug.
- Embryo-fetal toxicity should be reported as outlined in the Pregnancy reporting section.

Sponsor Responsibility:

- MDS and AML along with other secondary cancers should be reported by the Sponsor Institution to GSK upon awareness for any patient who has received niraparib (regardless of the timeframe since the last dose).
- Pneumonitis should be reported by the Sponsor Institution to GSK through 90 days after the last dose of niraparib.
- Embryo-fetal toxicity should be reported as outlined in the Pregnancy reporting section.

SAE report form will be notified by the Sponsor to GSK within 1 business day from receipt

9.4 Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure

- **Abuse:** is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.
- **Misuse:** medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Medication error:** is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** is a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. If an overdose with a GSK product, the Sponsor Institution and GSK should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose, should be reported.
- **Accidental /Occupational exposure:** is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure associated to the use of Niraparib or Dostarlimab must be reported on a Special Situations Report Form to the Sponsor Institution within 3 business days of awareness regardless of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an AE, an SAE Report Form must also be submitted to the Sponsor Institution within 24 hours of awareness.

The Sponsor Institution will forward the Special Situations Report Form to GSK within 2 business days and possible SAE form within 1 business day of awareness.

9.5 Assessment of Adverse Events

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

9.5.1 Severity Assessment

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

Please note that there is a distinction between **serious** and **severe** AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 9.2. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

9.5.2 Relationship to Study Drug

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

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

9.5.3 Assessment of Expectedness

If an event is judged to be as at least possibly related, the evaluation of expectedness should be made by the Sponsor based on knowledge of the reaction and the relevant product information documented in the SmPC and Investigator's Brochure of the study drugs.

9.6 Collection and Recording of Adverse Events

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

drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

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

All SAEs will be collected from the Inform Consent Form signing date, and must be throughout the study and for at least 30days after the last dose of protocol therapy.

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

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

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

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented in CRF 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.

9.7 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.

9.8 Reporting to the Sponsor Institution

All SAEs and AESIs must be reported to the Sponsor Institution within 24 hours of becoming aware of the initial SAE/AESI or any follow-up information regarding the SAE/AESI using the SAE reporting information below. SAEs/AESIs must be reported after study completion, if the SAE/AESI is assessed as study-drug related.

The SAE form must be completed as thoroughly as possible with all available details of the event, signed by the Investigator. If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

The SAE report must provide an assessment of causality to any study drug at the time of the initial report, to the Sponsor Pharmacovigilance, to the following address:

GB Pharma Services & Consulting

Email: **studysafety@gbpharmaservices.it**

Or at:

Fax No : +39 (0)382 302619 or +39 (0)382 1864425

9.9 Reporting to GSK

The Sponsor Institution must report all SAEs and all follow up information to GSK on an SAE Report Form within 1 business day of becoming aware of the initial event or follow-up information.

The PI 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 AESI Reporting Information
oax37649@gsk.com Fax Number: +44 (0)20 87547822

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.

9.10 Quarterly AE/SAE Reporting to GSK

On a quarterly basis the Sponsor Institution will provide GSK with a line listing of all adverse events (serious and non-serious) received during a defined quarter. The line listing will include a subject ID, the AE term, onset date, outcome, causality assessment, severity, and study drug dosing information.

9.11 Pregnancy

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

Each pregnancy must be reported by Investigators 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 within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

The Pregancy report form must be sent within 24 hours of awareness, to the Sponsor

Pharmacovigilance, to the following address:

GB Pharma Services & Consulting

Email: **studysafety@gbpharmaservices.it**

Or at:

Fax No : +39 (0)382 302619 or +39 (0)382 1864425

The Sponsor Institution will then forward all pregnancies formsassociated with GSK product including follow up outcomes and possible related SAE to GSK within 1 business day of awareness.

9.12 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), while the Sponsor will submit it to GSK per the governing institutional requirements and in compliance with local laws and guidelines.

9.13 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 TSO.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.

10 DATA REPORTING

10.1 Data submission

An electronic data capture system will be created to ensure quality assurance and facilitate data capture during clinical trials. The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes.

The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the Institutional Review Board (IRB) to have direct access to all documents pertaining to the study.

10.2 Data and Safety Monitoring

All aspects of the study will be carefully monitored with respect to Good Clinical Practices (ICH – GCP E6 (R2)) and standard operating procedures (SOPs) for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator or designee

This study will be conducted in accordance with ICH GCP E6 (R2) and the Declaration of Helsinki (Version 2013). The clinical study will also be carried out in keeping with national and local regulatory requirement(s). Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients with appropriate instructions.

All unused study materials will be returned to the Sponsor after the clinical phase of the study has been completed.

An IDMC will be established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participating patients in the study. The composition of the IDMC will consist of 3 independent individuals, including 1 biostatistician and 2 physicians. The IDMC is tasked with making a recommendation to the Sponsor based on their review to continue or stop the trial based on their assessment of efficacy and safety information.

11 STATISTICAL METHODS

11.1 Study Design and Endpoints

This is a randomized phase 3 trial evaluating niraparib plus dostarlimab vs chemotherapy at physician's choice in the treatment of recurrent ovarian, fallopian tube or primary peritoneal cancer patients for which platinum treatment is not an option.

The intent-to-treat (ITT) population will be defined as all patients randomized into the main study who have received at least one cycle of treatment. The ITT population is the primary analysis population for the efficacy analysis. For this analysis, patients will be analyzed as randomized.

Efficacy will also be analyzed using a per-protocol (PP) population. The PP population will consist of all patients randomized in the main study who do not have protocol deviations that may significantly impact the interpretation of efficacy results. Patients will be analyzed according to the treatment they actually receive.

The safety population includes all patients who received at least 1 dose of study medication. The safety population will be the primary analysis population for the safety analyses. Patients will be analyzed as treated.

Sample size, Accrual Rate and Study Duration

This is a randomized phase 3 trial. Median OS in the standard arm is about 13 months. An increase in OS in the experimental arm with an HR of 0.7 is expected (power 80%, alfa 0.05).

A total sample size of 427 patients will be required (194 patients per arm plus 10% drop out) with a total number of 247 events. With an extimated accrual rate of 14 patient/month, the total duration of the trial will be approximately 4 years.

The sample will be described in its clinical and demographic features using descriptive statistics techniques. Quantitative variables will be described using the following measures: minimum, maximum, range, mean and standard deviation. Qualitative variables will be summarized with absolute and percentage frequency tables. Normality of continuous variables will be checked using Kolmogorov-Smirnov test.

The primary objective will be achieved assessing Survival function with the Kaplan-Meier method. The Mantel-Cox log-rank test was used to compare different survival functions according to clinical and therapeutic factors.

Progression Free Survival (PFS) will be investigated as a survival function following the same model used for primary objective. The response rate (RECIST 1.1 Criteria) will be described applying descriptive statistics techniques, particularly absolute and percentage frequencies. Safety and tolerability will be assessed describing the type and frequencies of adverse events. Comparisons between the two groups will be performed with a $\chi 2$ test.

Statistical descriptive analysis will be performed on the EORTC QLQC30, EORTCOV28, EQ-5DL results.

Stratification Factors

Stratification factors are:

HRD status (HRD positive vs HRD negative or unknown)
PDL-1 status
Previous treatment with Parp Inhibitors (yes vs not)
Previous treatment with Immunotherapy (yes vs not)
Bevacizumab treatment (yes or not)

Early Activity Analysis

An early activity analysis will be performed after the first 83 patients being enrolled in the experimental arm. If at least 28 of them will be progression free at 12 weeks the hypothesis that probability of activity (P) is ≤ 0.25 will be rejected with a a target error rate of 0.05. If the number of patients progression free at 12 weeks will be ≤ 27 the hypothesis that P ≥ 0.4 will be rejected with a target error =0.1. (calculated with PASS v11)

Analysis of Primary Endpoints

The primary OS analysis will be performed using a stratified log-rank test on ITT population. The stratified Cox proportional hazards models will be used to estimate the treatment HR and its 95% CI. All analyses will include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using Kaplan-Meier methods. Two-sided 95 % confidence intervals will be provided where appropriate. Descriptive statistics will be used to summarize demographics and baseline characteristics.

Analysis of Secondary Endpoints

PFS will be analyzed using a stratified log-rank test. The stratified Cox proportional hazards models will be used to estimate the treatment HR and its 95% CI. In addition, Kaplan-Meier methodology will be used to descriptively summarize the data. Response rate wil be calculated summarizing complete and partial responses in each treatment arm.

The EORTC C30, OV28 and EQ-5DL will be used in this study. Changes from baseline in overall score, sub-scores, and individual items will be analyzed descriptively by treatment group. A repeated measures model adjusting for covariates and subject evaluating change in symptoms and QoL will be conducted. Time to symptom worsening will be analyzed using time-to-event methodology.

11.2 Safety Analyses

Adverse event terms will be coded using the current version of the Medical Dictionary and will be summarized for all treated participants. Incidence of AEs occurring during the study will be summarized by system organ class and preferred term. Adverse events will also be summarized by causality and grade. Serious adverse events will be listed separately. Descriptive summary statistics will be used to summarize changes over time in laboratory values, vital signs, physical examination findings, and ECG assessments for all treated participants. Laboratory parameter changes will be described using shift tables, relative to CTCAE.

12 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

12.1 Good Clinical Practice

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (Version 2013). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

12.2 Informed Consent

Before each patient is enrolled in the clinical study, written informed consent (ICF) will be obtained from the patient according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study treatment in such a manner that the patient is aware of the potential risks, inconveniences, or AEs that may occur. The patient should be informed that he/she is free to withdraw from the study at any time. The patient will receive all information that is required by regulatory authorities and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB/IEC-approved ICF prior to the start of the study.

The ICF must be signed and dated; 1 copy will be given to the patient and the Investigator will retain 1 copy as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/IEC, and signed by all patients subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

12.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the responsible IRB/IEC/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

12.4 Investigator Responsibilities

The Sponsor or its designee will conduct a study initiation visit to verify the qualifications of the Investigator, inspect the facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE reporting, and concomitant medication reporting, raw data collection forms, etc) designed to record all observations and other pertinent data for each patient receiving study treatment. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's Medical Monitor may review safety information as it becomes available throughout the study.

The Principal Investigator is responsible that the protocol is followed as it is, according to Good Clinical Practice.

12.5 Subject Confidentiality and Data Protection

All clinical study findings and documents will be regarded as confidential. The personal data will be processed according to the European General Personal Data Protection Code Regulation 679/2016.

Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality.

The Investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements.

The anonymity of participating patients must be maintained. Patients will be specified on study documents by their enrollment number or birth date, not by name. Documents that identify the patient (eg, the signed informed consent document) must be maintained in confidence by the Investigator.

12.6 Data Quality Assurance

The Sponsor or its designee will conduct a study initiation visit to verify the qualifications of the Investigator, inspect the facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant.

Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to Good Clinical Practices (ICH – GCP E6 (R2)) and standard operating procedures (SOPs) for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator or designee.

12.7 Access to Source Documents

An electronic data capture system to manage data collection will be utilized during this trial. The electronic data capture system is a software tool designed to ensure quality assurance and facilitate data capture during clinical trials. The system is fully Code of Federal Regulations (CFR) 21 part 11 compliant.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE reporting, and concomitant medication reporting, raw data collection forms, etc) designed to record all observations and other pertinent data for each patient receiving study treatment.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the Institutional Review Board (IRB) to have direct access to all documents pertaining to the study.

12.8 Study Monitoring

Monitoring and auditing procedures approved by the Sponsor will be followed, in order to comply with ICH – GCP E6 (R2) guidelines. On-site checking of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and by communications (letter, telephone, and fax).

All unused study materials will be returned to the Sponsor after the clinical phase of the study has been completed.

12.9 Audits and Inspections

Responsible IRB/IEC/Competent Authorities and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

12.10 Archival

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations. According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

12.11 Publications

Information regarding publication of study results is contained in the Steering Committee Charter.

13 REFERENCES

1. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med.* 2009;361(2):123-134.
2. De Lorenzo SB, Patel AG, Hurley RM, Kaufmann SH. The Elephant and the Blind Men: Making Sense of PARP Inhibitors in Homologous Recombination Deficient Tumor Cells. *Front Oncol.* 2013;3:228.
3. Jones P, Wilcoxen K, Rowley M, Toniatti C. Niraparib: A Poly(ADP-ribose) Polymerase (PARP) Inhibitor for the Treatment of Tumors with Defective Homologous Recombination. *J Med Chem.* 2015;58(8):3302-3314.
4. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol.* 2011;12(9):852-861.
5. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. *Nat Rev Cancer.* 2004;4(10):814-819.
6. Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011;474(7353):609-615.
7. Timms KM, Abkevich V, Hughes E, et al. Association of BRCA1/2 defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. *Breast Cancer Res.* 2014;16(6):475.
8. Turner NC, Ashworth A. Biomarkers of PARP inhibitor sensitivity. *Breast Cancer Res Treat.* 2011;127(1):283-286.
9. Kummar S, Ji J, Morgan R, et al. A Phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *Clin Cancer Res.* 2012;18(6):1726-1734.
10. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med.* 2012;366(15):1382-1392.
11. Sandhu SK, Schelman WR, Wilding G, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a Phase 1 dose-escalation trial. *Lancet Oncol.* 2013;14(9):882-892.
12. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet.* 2010;376(9737):235-244.
13. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med.* 2016;375(22):2154-2164.
14. Pujade-Lauraine E, Ledermann JA, Penson RT, et al. Treatment with olaparib monotherapy in the maintenance setting significantly improves progression-free survival in patients with platinum-sensitive relapsed ovarian cancer: Results from the phase III SOLO2 study. 48th Annual Meeting for the Society of Gynecologic Onocolgy. March 12-15, 2017. National Harbor, Maryland. Abstract# LBA-2.

15. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med.* 2017.
16. Disis ML. Immune regulation of cancer. *J Clin Oncol.* 2010;28(29):4531-4538.
17. Mei Z, Liu Y, Liu C, et al. Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis. *Br J Cancer.* 2014;110(6):1595-1605.
18. Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruneri G. Harmonization of the evaluation of tumor infiltrating lymphocytes (TILs) in breast cancer: recommendations by an international TILs-working group 2014. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2014;Sep 11.
19. Schatton T, Scolyer RA, Thompson JF, Mihm MC, Jr. Tumor-infiltrating lymphocytes and their significance in melanoma prognosis. *Methods Mol Biol.* 2014;1102:287-324.
20. Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. *Br J Cancer.* 2011;105(1):93-103.
21. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science (New York, NY).* 2011;331(6024):1565-1570.
22. Bremnes RM, Al-Shibli K, Donnem T, et al. The role of tumor-infiltrating immune cells and chronic inflammation at the tumor site on cancer development, progression, and prognosis: emphasis on non-small cell lung cancer. *J Thorac Oncol.* 2011;6(4):824-833.
23. Talmadge JE. Immune cell infiltration of primary and metastatic lesions: mechanisms and clinical impact. *Seminars in cancer biology.* 2011;21(2):131-138.
24. Shirabe K, Motomura T, Muto J, et al. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: pathology and clinical management. *International journal of clinical oncology.* 2010;15(6):552-558.
25. Nosho K, Baba Y, Tanaka N, et al. Tumour-infiltrating T-cell subsets, molecular changes in colorectal cancer, and prognosis: cohort study and literature review. *J Pathol.* 2010;222(4):350-366.
26. Bellati F, Visconti V, Napoletano C, et al. Immunology of gynecologic neoplasms: analysis of the prognostic significance of the immune status. *Curr Cancer Drug Targets.* 2009;9(4):541-565.
27. Oble DA, Loewe R, Yu P, Mihm MC, Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human melanoma. *Cancer Immun.* 2009;9:3.
28. Uppaluri R, Dunn GP, Lewis JS, Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in head and neck cancers. *Cancer Immun.* 2008;8:16.
29. Dunn GP, Dunn IF, Curry WT. Focus on TILs: Prognostic significance of tumor infiltrating lymphocytes in human glioma. *Cancer Immun.* 2007;7:12.

30. Chang WJ, Du Y, Zhao X, Ma LY, Cao GW. Inflammation-related factors predicting prognosis of gastric cancer. *World J Gastroenterol.* 2014;20(16):4586-4596.
31. Preston CC, Maurer MJ, Oberg AL, et al. The ratios of CD8+ T cells to CD4+CD25+ FOXP3+ and FOXP3- T cells correlate with poor clinical outcome in human serous ovarian cancer. *PLoS One.* 2013;8(11):e80063.
32. Yoon HH, Orrock JM, Foster NR, Sargent DJ, Smyrk TC, Sinicrope FA. Prognostic impact of FoxP3+ regulatory T cells in relation to CD8+ T lymphocyte density in human colon carcinomas. *PLoS One.* 2012;7(8):e42274.
33. Kim ST, Jeong H, Woo OH, et al. Tumor-infiltrating lymphocytes, tumor characteristics, and recurrence in patients with early breast cancer. *American journal of clinical oncology.* 2013;36(3):224-231.
34. Mathai AM, Kapadia MJ, Alexander J, Kernochan LE, Swanson PE, Yeh MM. Role of Foxp3-positive tumor-infiltrating lymphocytes in the histologic features and clinical outcomes of hepatocellular carcinoma. *Am J Surg Pathol.* 2012;36(7):980-986.
35. Liu F, Lang R, Zhao J, et al. CD8(+) cytotoxic T cell and FOXP3(+) regulatory T cell infiltration in relation to breast cancer survival and molecular subtypes. *Breast Cancer Res Treat.* 2011;130(2):645-655.
36. Kirk R. Risk factors. CD8+:FOXP3+ cell ratio is a novel survival marker for colorectal cancer. *Nat Rev Clin Oncol.* 2010;7(6):299.
37. Pedoeem A, Azoulay-Alfaguter I, Strazza M, Silverman GJ, Mor A. Programmed death-1 pathway in cancer and autoimmunity. *Clin Immunol.* 2014;153(1):145-152.
38. Zhang X, Schwartz JC, Guo X, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity.* 2004;20(3):337-347.
39. Lazar-Molnar E, Yan Q, Cao E, Ramagopal U, Nathenson SG, Almo SC. Crystal structure of the complex between programmed death-1 (PD-1) and its ligand PD-L2. *Proc Natl Acad Sci U S A.* 2008;105(30):10483-10488.
40. Lin DY, Tanaka Y, Iwasaki M, et al. The PD-1/PD-L1 complex resembles the antigen-binding Fv domains of antibodies and T cell receptors. *Proc Natl Acad Sci U S A.* 2008;105(8):3011-3016.
41. Cheng X, Veverka V, Radhakrishnan A, et al. Structure and interactions of the human programmed cell death 1 receptor. *J Biol Chem.* 2013;288(17):11771-11785.
42. Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett.* 2004;574(1-3):37-41.
43. Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. *Clin Cancer Res.* 2013;19(19):5300-5309.
44. Yao S, Chen L. PD-1 as an immune modulatory receptor. *Cancer Journal.* 2014;20(4):26.
45. Nishimura H, Agata Y, Kawasaki A, et al. Developmentally regulated expression of the PD-1 protein on the surface of double-negative (CD4−CD8−) thymocytes. *Int Immunol.* 1996;8(5):773-780.

46. Huang X, Venet F, Wang YL, et al. PD-1 expression by macrophages plays a pathologic role in altering microbial clearance and the innate inflammatory response to sepsis. *Proc Natl Acad Sci U S A.* 2009;106(15):6303-6308.
47. Pena-Cruz V, McDonough SM, Diaz-Griffero F, Crum CP, Carrasco RD, Freeman GJ. PD-1 on immature and PD-1 ligands on migratory human Langerhans cells regulate antigen-presenting cell activity. *J Invest Dermatol.* 2010;130(9):2222-2230.
48. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol.* 2008;26:677-704.
49. Guan J, Lim KS, Mekhail T, Chang CC. Programmed death ligand-1 (PD-L1) expression in the programmed death receptor-1 (PD-1)/PD-L1 blockade: a key player against various cancers. *Arch Pathol Lab Med.* 2017;141(6):851-861.
50. Taube JM, Anders RA, Young GD, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med.* 2012;4(127):127ra137.
51. Sanmamed MF, Chen L. Inducible expression of B7-H1 (PD-L1) and its selective role in tumor site immune modulation. *Cancer J.* 2014;20(4):256-261.
52. Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. *Curr Opin Immunol.* 2012;24(2):207-212.
53. Brabec V, Kasparkova J. Modifications of DNA by platinum complexes. Relation to resistance of tumors to platinum antitumor drugs. *Drug Resist Updat.* 2005;8(3):131-146.
54. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol.* 1989;7(11):1748-1756.
55. Mekhail TM, Markman M. Paclitaxel in cancer therapy. *Expert Opin Pharmacother.* 2002;3(6):755-766.
56. Moore KN, Herzog TJ, Lewin S, et al. A comparison of cisplatin/paclitaxel and carboplatin/paclitaxel in stage IVB, recurrent or persistent cervical cancer. *Gynecol Oncol.* 2007;105(2):299-303.
57. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med.* 2002;346(2):92-98.
58. Dizon DS. Treatment options for advanced endometrial carcinoma. *Gynecol Oncol.* 2010;117(2):373-381.
59. Molin Y, Fayette J. Current chemotherapies for recurrent/metastatic head and neck cancer. *Anticancer Drugs.* 2011;22(7):621-625.
60. Data on file.
61. Xing D, Orsulic S. A mouse model for the molecular characterization of BRCA1-associated ovarian carcinoma. *Cancer Res.* 2006;66(18):8949-8953.
62. Huang J, Wang L, Cong Z, et al. The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a BRCA1(-/-) murine model of ovarian cancer. *Biochem Biophys Res Commun.* 2015;463(4):551-556.

63. Meade M. *Efficacy evaluation of niraparib and TSR-042 alone and in combination against subcutaneous BRKras-luc murine ovarian carcinoma in female FVB mice.* Molecular Imaging;2016. TESA-201605b (MI2688).
64. Mills G. *Efficacy of niraparib as a single agent and in combination with PD-1 antibody in LPA1-T22 tumor model.* TESARO, Inc.;2017.
65. *Efficacy and PD study in KLN205 subcutaneous lung squamous cell cancer model.* Pharmaron;2016. PH-ON-TSB-KLN205-09032015.
66. Panagiotis A. Konstantinopoulos et al. Single-Arm Phases 1 and 2 Trial of Niraparib in Combination With Pembrolizumab in Patients With Recurrent Platinum-Resistant Ovarian Carcinoma. JAMA Oncol. 2019, 13;5(8):1141-9.
67. Susan M. Domchek et al. Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. Lancet Oncol. 2020, 21(9):1155-1164.
68. Mirza MR et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016, 1;375(22):2154-2164.
69. Gonzàlez-Martin A. et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019, 19;381(25):2391-2402.
70. Jemal A et al. Cancer statistics, 2009. CA Cancer J Clin 2009, 59:225–249.
71 Dudley ME, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.
72. Hunder NN, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.
73. Ölcher M, et al. Foxp3+ cell infiltration and granzyme B+/Foxp3+ cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59:909-19.
74. Okazaki T, et al. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. PNAS 2001;98(24):13866-71.
75. Greenwald RJ, et al. The B7 family revisted. Annu Rev Immunol 2005;23:515-48.
76. Study of Pembrolizumab (MK-3475) in Participants With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or Non-small Cell Lung Carcinoma (P07990/MK-3475-001/KEYNOTE-001) (NCT01295827)
77. Ribas A, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015 Jun 23. pii: S1470-2045(15)00083-2.
78. Robert C, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 ;372(26):2521-32.
79. Sachdev J, Patnaik A, Waipa J, et al. Safety, Pharmacodynamic and pharmacokinetic profile of TSR 042, an anti PD-1 monoclonal antibody in patients with advanced solid tumors. ESMO 2017 Abst 1185p
80. Konstantinoupulos P, Sachdev j, Schaswartzberg L. et al. Dose finding combination stad or Niraparib and Pembrolizumab In triple negative breast cancer and recurrent, platinum resistant ovarian cancer. ESMO 2017 Abstract 1443pd

81. Wang S, Xihao J, Sun K, et al. Preclinical evaluation of Niraparib in combination with PD-1/PD-L1 in mouse derived syncenic transplant model. AACR 2017 abst B16

82. Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents. *Cancer Cell.* 2015;28(6):690-714.
83. Hato SV, Khong A, de Vries IJ, Lesterhuis WJ. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. *Clin Cancer Res.* 2014;20(11):2831-2837.
84. Senovilla L, Vitale I, Martins I, et al. An immunosurveillance mechanism controls cancer cell ploidy. *Science (New York, NY).* 2012;337(6102):1678-1684.
85. Sevko A, Michels T, Vrohlings M, et al. Antitumor effect of paclitaxel is mediated by inhibition of myeloid-derived suppressor cells and chronic inflammation in the spontaneous melanoma model. *J Immunol.* 2013;190(5):2464-2471.
86. Liechtenstein T, Perez-Janices N, Gato M, et al. A highly efficient tumor-infiltrating MDSC differentiation system for discovery of anti-neoplastic targets, which circumvents the need for tumor establishment in mice. *Oncotarget.* 2014;5(17):7843-7857.
87. Pfannenstiel LW, Lam SS, Emens LA, Jaffee EM, Armstrong TD. Paclitaxel enhances early dendritic cell maturation and function through TLR4 signaling in mice. *Cell Immunol.* 2010;263(1):79-87.
88. Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol.* 2016;34(25):2969-2979.
89. Gadgeel S, Stevenson J, Langer C, et al. Pembrolizumab (pembro) plus chemotherapy as front-line therapy for advanced NSCLC: KEYNOTE-021 cohorts A-C. J Clin Oncol 34, 2016 (suppl; abstr 9016). .
90. Friedlander M, Meniawy T, Markman B, et al. A phase 1b study of the anti-PD-1 monoclonal antibody BGB-A317 (A317) in combination with the PARP inhibitor BGB-290 (290) in advanced solid tumors. J Clin Oncol 35, 2017 (suppl; abstr 3013).
91. Costa R, Carneiro BA, Agulnik M, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. *Oncotarget.* 2017;8(5):8910-8920.
92. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol.* 2006;24(19):3187-3205.
93. D'Addio F, Riella LV, Mfarrej BG, et al. The link between the PDL1 costimulatory pathway and Th17 in fetomaternal tolerance. *J Immunol.* 2011;187(9):4530-4541.
94. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.

95. Nishino M, Tirumani SH, Ramaiya NH, Hodi FS. Cancer immunotherapy and immune-related response assessment: The role of radiologists in the new arena of cancer treatment. *Eur J Radiol.* 2015;84(7):1259-1268.
96. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood.* 2009;114(5):937-951.
97. Clopper C, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika.* 1934;26(4):404-413.
98. U.S. Department of Health and Human Services. Food and Drug Administration Guidance for Industry. Drug Interaction Studies – Study Design, Data Analysis Implications for Dosing and Labeling Recommendations. February 2012.
99. Paclitaxel Injection, USP United States Prescribing Information. WG Critical Care, LLC. 2013.
100. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American journal of clinical oncology.* 1982;5(6):649-655.

APPENDIX 1 – PERFORMANCE STATUS

ECOG PS	KARNOFSKY PS
0—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—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare 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 personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.
**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960:11:7-33.

Available at: http://ecog-acrin.org/resources/ecog-performance-status

APPENDIX 2 – RESPONSE CRITERIA

Response will be assessed by RECIST v.1.1 criteria using investigator's review.

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