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Phase II Study of Niraparib and TSR-042 in Patients with Germline or Somatic BRCA1/2 and PALB2-related Pancreatic Cancer

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Mayo Clinic Cancer Center

MC1841: Phase II Study of Niraparib and TSR-042 in Patients with Germline or Somatic *BRCA1/2* and *PALB2*-related Pancreatic Cancer

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FDA IND #:	141914

Trial Supported by:
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Drug Availability:

Supplied Investigational Agents: niraparib, TSR-042
Drug Company Supplied: niraparib, TSR-042 (GSK)

√Study contributor(s) not responsible for patient care

Document History	Effective Date
Amendment 1	29Dec2020
Activation	29Dec2020
Amendment 2	pending

Protocol Resources

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*No waivers of eligibility allowed

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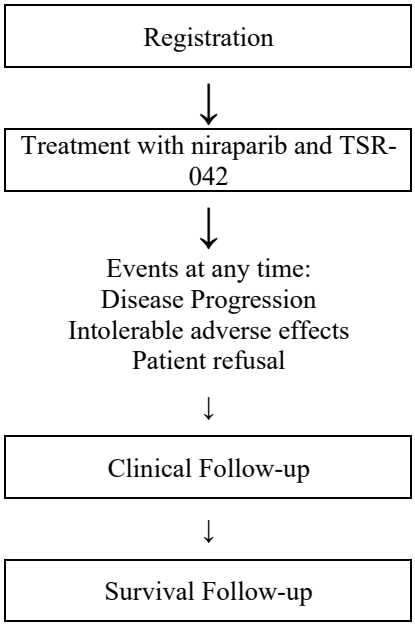
Schema



Cycle = 21 days

Treatment with niraparib and TSR-042 will continue until confirmed progressive disease according to iRECIST, clinical progression, intolerable adverse effects or patient/investigators decision, whichever is applicable.

Generic name: niraparib Brand name(s): ZEJULA® Availability: Investigational	Generic name: TSR-042, dostarlimab Brand name(s): N/A Availability: Investigational

1.0 Background

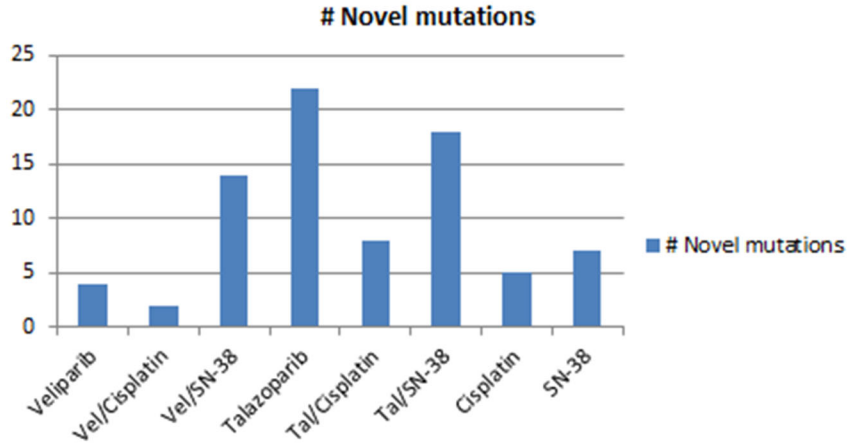
Pancreatic cancer is currently the 4th leading cause of cancer death in the US and will soon cause the death of more Americans than breast cancer. Therapies are very limited and largely ineffective. In our own data sequencing 3,000 patients with pancreatic cancer (accepted in JAMA), approximately 3% of pancreatic cancer patients harbor germline mutations in DNA repair genes such as *BRCA1/2 and PALB2*, and are therefore potential candidates for PARP-inhibitor therapy. In addition, somatic mutations in Homologous Recombination Repair (HRR) genes can confer sensitivity as well, and have been reported to double the number of patients potentially eligible for such therapy. Recently, Waddell et al defined 5 subtypes of pancreatic adenocarcinoma, with *BRCA*-like tumors, categorized as such by genomic instability, comprising 15-20% of pancreatic cancer, with the latter identified as a potential target for immunotherapy strategies. (1) In breast and ovarian BRCA-mutant tumors, neoantigen load alone did not correlate with T-cell infiltration, suggesting that other therapies to disrupt the tumor microenvironment may be necessary to induce an immune response. (2) The Keynote-162 study of niraparib and pembrolizumab has validated this approach, with early reports of impressive efficacy. Of the first 8 platinum-resistant ovarian cancer patients, 4 had confirmed responses, and 4 had stable disease. One triple negative breast cancer patient (of 5) had SD for 10 cycles. (3) Although unselected trials in pancreatic cancer with immunotherapy alone have yet to be successful, we hypothesize that induced genetic variation with PARP inhibition disrupting the tumor microenvironment and increasing neoepitope expression can sensitize tumors to immune checkpoint inhibition.

We are currently funded by a Project in our NCI Pancreas SPORE grant to more fully define genetic identification of this subset of patients and develop a therapeutic strategy. We have developed preliminary data (Figure 1) with RNAseq suggesting that potent PARP inhibition (in this case, talazoparib) is associated with gain of novel mutations in pancreas cell lines, even compared to cisplatin alone, or irinotecan alone. In addition, double-stranded break repair deficient tumors are associated with increased expression of genes involved in antitumor immunity, including CD8 positive T cell activators and regulatory molecules, in a similar pattern of that seen with MMR deficient tumors. (4)

We propose that a combination of PARP inhibition and anti-PD1 therapy has valuable therapeutic potential in this subset of pancreatic cancer. The strong activity seen in the dose escalation phase of Keynote 162 in refractory ovarian and TNBC cancer hold promise for pancreatic cancer as well, as long as properly selected patients are enrolled. No reports have been published for the combination of PARP inhibition and checkpoint blockade in pancreatic cancer to date. However, given the potential for neoepitope formation in patients with defective HRR deficiency upon exposure to PARP inhibition, we propose that there could be an additive or synergistic effect of the combination in HRR deficient pancreatic cancer. HRR deficient pancreatic cancer has largely been defined to date based on mutations in well-established genes such as *BRCA1/2* and PALB2. However, more DNA repair associated genes are becoming associated with risk for pancreatic cancer and may well impact tumor phenotype.

Therefore, we propose this single arm-cohort study. The goal would be to evaluate the combination of niraparib and TSR-042 in patients with germline or somatic mutations in *BRCA1/2 or PALB2*.

Fig. 1: Novel Mutations in CAPAN-1 Cells after exposure by RNAseq



Pre-clinical data:

There are in vitro studies to suggest that the immunotherapy in combination with PARP inhibition provides synergy.(Higuchi, Flies et al. 2015) In a syngeneic model of breast cancer, PARP inhibition was shown to increase PD-L1 expression (Figure 1 from Jiao et al). (Jiao, Xia et al. 2017) Additionally in the same set of experiments, to corroborate these findings of extent of PARP inhibition (through measurement of PARylation enzyme activity, which are inhibited by PARP inhibitors), showed an inverse correlation (Figure 2 – see below). This supports that high level of PARP activity suppresses PD-L1 expression or stated another way, PARP inhibition was led to increased PD-L1 expression in these tumors.(Jiao, Xia et al. 2017)

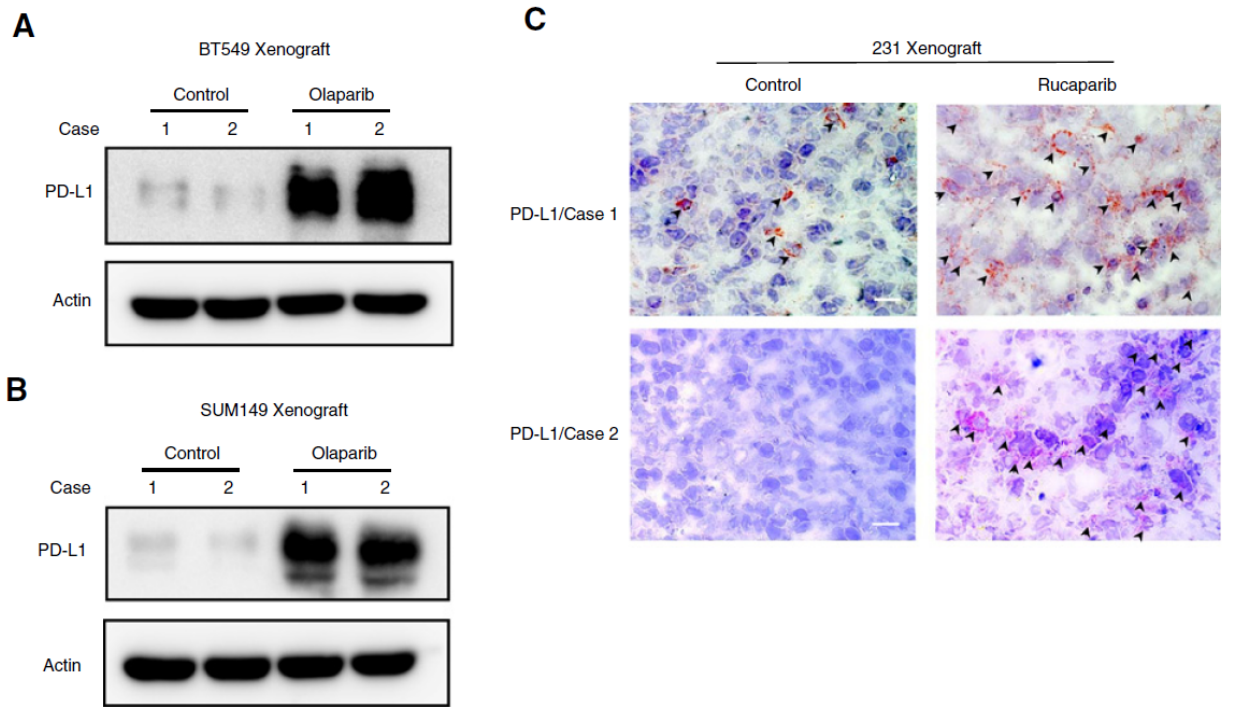
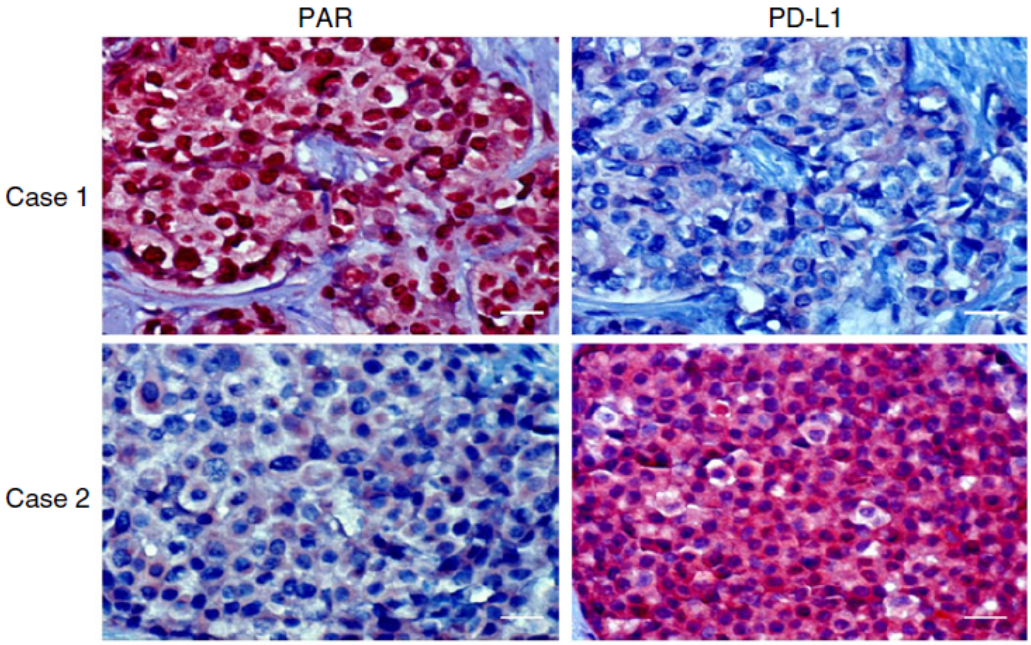


Figure 1: PARPi upregulates PD-L1 expression in xenograft tumors. A–C, BT549 (A), SUM149 (B), andMDA-MB-231 cells (C)were inoculated into the mammary fad pad of nude mice, and the mice with established tumors were treated with olaparib or rucaparib. Tumors were then isolated to evaluate PD-L1 expression by immunoblotting (A and B) or IHC staining (C). Black arrowheads, detected PD-L1 signals. Scale bar, 50 mm.

[From Open Access Article Jiao et al: (Jiao, Xia et al. 2017)]



		PAR			
		–/+	++/+++	Total	*P* value
PD-L1	–/+	15 (12.9%)	65 (56.0%)	80 (69.0%)	
	++/+++	14 (12.1%)	22 (19.0%)	36 (31.0%)	
	Total	29 (25.0%)	87 (75.0%)	116 (100.0%)	*P* = 0.02

Figure 2: Inverse correlation between PAR and PD-L1 in surgical specimens of breast cancer. Top, representative images of IHC staining of PAR and PD-L1 in human breast cancer tissues (n ¼ 116). Scale bar, 50 mm; bottom, correlation analysis between PAR and PD-L1 was analyzed using the Pearson c2 test (P ¼ 0.02). A P value of less than 0.05 was considered to be statistically significant.

[From Open Access Article Jiao et al: (Jiao, Xia et al. 2017)]

PARP inhibition combinatorial strategies:

PARP inhibitors are being explored in various clinical trials in combination with various other classes of drugs.(Drean, Lord et al. 2016) These include chemotherapies, targeted therapies, novel targeted therapies, as a radiation sensitizer, endocrine therapies and most recently several trials exploring the combination with immunotherapies.(Schaefer, James et al. 2011, Drean, Lord et al. 2016, Papa, Caruso et al. 2016) This as noted above has been of particular interest in patients with homologous-repair related breast and/or ovarian cancers as well as increased interest to study this

now in prostate and pancreas cancers.(Javle, Golan et al. 2016, Ang and Tan 2017, Golan and Javle 2017, Ramakrishnan Geethakumari, Schiewer et al. 2017, Turk and Wisinski 2018)

Furthermore, there is some data to support use of immunotherapy for BRCA-related tumors whereby immunotherapy alone could potentially be effective.(Matsuo, Spragg et al. 2018) The addition of PARP inhibition to further help augment responses in an aggressive disease like pancreas cancer would be of further value with rationale to supports its use as outlined. Figure 3 from a recent review summarizes some of the ways how some of the 'DNA-damaging' drugs including PARP inhibition can affect the immunogenicity of tumors.(Brown, Sundar et al. 2018)

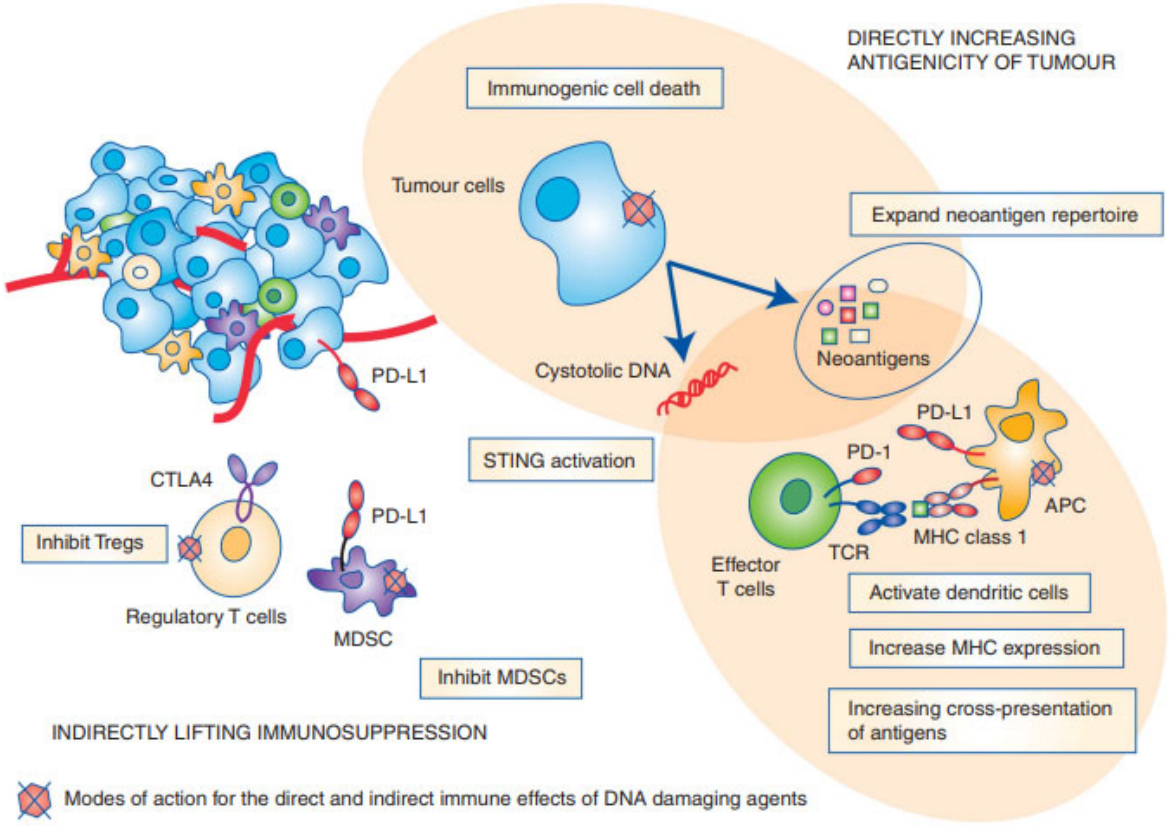


Figure 3: Mechanisms by which DNA damaging agents affect the immunogenicity of tumors From Open Access Article (Brown, Sundar et al. 2018)

Current PARP inhibitor and immunotherapy combination trials:

At present, there are several clinical trials trying to explore this combination in various tumor types where HR-deficiency plays a role. These include but are not limited to the following:

ICI	Tumour group	Target population	DDR agent	Phase	Arms	Planned n	Trial status	NCT	Citation/remarks
Durvalumab	Breast Gastric Ovarian SCLC	3rd line 2nd line Platinum sensitive 2nd line	Olaparib	1/2	Olaparib + Durvalumab	133	Recruiting	NCT02734004	
	NSCLC/ SCLC Breast Ovarian Colorectal Prostate	2nd or higher line TNBC, < 3 prior lines Platinum resistant 3rd line mCRPC	Olaparib	1/2	Durvalumab + Olaparib Durvalumab + Cediranib Durvalumab + Olaparib + Cediranib	338	Recruiting	NCT02484404	
	Ovary	gBRCA	Olaparib	1/2	Olaparib + Durvalumab + Tremelimumab	39	Not yet recruiting	NCT02953457	
	NSCLC HNSCC	Refractory	AZD6738	1	AZD6738 + Durvalumab	114	Recruiting	NCT02264678	Has other arms involving AZD 6738 with other agents
Tremelimumab	Ovarian	2nd line +	Olaparib	1/2	Tremelimumab + Olaparib	50	Recruiting	NCT02571725	gBRCA only
Pembrolizumab	Breast Ovarian	Up to 3 prior lines Up to 4 prior lines	Niraparib	1/2	niraparib + pembrolizumab	114	Recruiting	NCT02657889	TNBC only Platinum resistant/ refractory only
Nivolumab	NSCLC Adv solid tumours	1st line metastatic Refractory to std therapy	Carboplatin + paclitaxel or pemetrexed + Veliparib Veliparib	2 1	Veliparib + nivolumab + platinum doublet chemotherapy Veliparib + platinum doublet chemotherapy Veliparib + Nivolumab	184 50	Recruiting Not yet recruiting	NCT02944396 NCT03061188	NA
Atezolizumab	Breast	Any prior therapy allowed	Veliparib	2	Veliparib Atezolizumab veliparib + atezolizumab	90	Recruiting	NCT02849496	TNBC + gBRCA only
BGB-A317	Adv solid tumours	2nd line +	BGB-290	1	BGB-A317 + BGB-290	124	Recruiting	NCT02660034	

Abbreviations: DDR = DNA damage response; gBRCA = germline BRCA; HNSCC = head and neck squamous cell cancer; ICI = immune checkpoint inhibitor; mCRPC = metastatic castration-resistant prostate cancer; NA = not available; NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer; TNBC = triple-negative breast cancer.

From Open Access Article: (Brown, Sundar et al. 2018) Ongoing combination trials with DDR and immune checkpoint inhibitors (www.clinicaltrials.gov)

Resources available:

Mayo Clinic Cancer Center operates in 3 physical sites – Rochester, MN, Phoenix, AZ, and Jacksonville, Fl. We have pancreatic cancer expertise at all 3 sites, with annual unique pancreatic adenocarcinoma patients seen upwards of 700 patients. TEMPUS, FoundationOne, Carris or equivalent testing will be performed on patients as part of standard of care testing. We anticipate 5-8% of patients to be eligible for cohort based on our experience and published data on frequency of *BRCA1/2*, and *PALB2* mutations. Given genomic testing is now done as part of standard of care, we anticipate rapid accrual.

All 3 sites are fully capable of research blood draws and biopsies. Tissue will be managed in FFPE, which will not require special handling or shipping. Fresh samples would also be collected for xenograft and/or organoid development and potentially RNA-Seq. There is one Mayo Clinic IRB and Cancer Center approval process, and though all 3 sites contract independently, there is an internal requirement for budgets to align within a tight range of one another. We have recently hired a program coordinator for our pancreas cancer group to speed timelines for trial development.

Publication plan:
ASCO/ASCI GI, Journal of Clinical Oncology likely in 2019/20

2.0 Goals

2.1 Primary Goal

To determine antitumor activity as measured by disease control rate at 12 weeks (DCR12) as assessed using iRECIST in select homologous recombination repair (HRR) deficient pancreatic cancer patients with HRR deficiency (defined as mutations in *BRCA 1/ 2,* or *PALB2*)

2.2 Secondary Goals

2.21 To assess adverse events according to the current National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) and other safety parameters.

2.22 To assess the time to next treatment (TTNT), objective response rate (ORR), time to and duration of response and duration of confirmed stable disease according to iRECIST.

2.23 To assess progression-free survival.

2.24 To assess overall survival.

2.3 Correlative Research

2.31 To assess germline DNA and serum markers of immune response.

2.32 To determine changes in circulating tumor DNA (ctDNA) profile after therapy with a PARPi and a PD-1 inhibitor.

2.33 To study mechanisms of resistance in ctDNA profile after therapy with a PARPi and a PD-1 inhibitor.

2.34 To assess the tumor microenvironment for immune related changes (immune infiltration, PD-L1 and PD-1 expression, tumor-infiltrating lymphocytes [TIL]).

2.35 To assess genetic profile of the tumor pre- and post-treatment.

2.36 To determine changes in the cytokine profile pre- and post-treatment.

3.0 Registration Patient Eligibility

3.1 Registration - Inclusion Criteria

3.11 Presence of either a germline deleterious mutation or somatic deleterious mutation in any one of the genes in our proposed gene-panel as determined by any of the commercially available or institutional testing platforms.

Note: The somatic mutation could be either on a tissue-based test or the circulating tumor DNA (ctDNA)-based assay. The 6 genes that would determine eligibility would be: *BRCA1/2, PALB2, BARD1, RAD51c, RAD51d*.

3.12 Provide written informed consent

3.13 Age ≥ 18 years

3.14 Histological/cytological confirmation of diagnosis of metastatic pancreatic ductal adenocarcinoma

3.15 At least one but no more than two prior lines of systemic therapy for metastatic disease (maintenance therapy is not considered a line of treatment).

Note: Patients who have not had any prior chemotherapy can refuse chemotherapy and be considered eligible. This refusal and their reason for refusal would have to be documented.

3.16 Received a platinum agent as part of first or second line treatment (unless contraindicated).

3.17 ECOG performance status of 0 or 1

3.18 Adequate hematologic and end-organ function as evidenced by the following ≤14 days prior to registration:

a. Serum creatinine ≤1.5 x ULN or eGFR ≥60mL/min using the Cockroft-Gault Equation
b. Hemoglobin ≥9.0 g/dL
c. Absolute neutrophil count ≥1500/μL
d. Platelets ≥100x10^9/L
e. Total bilirubin ≤1.5 x ULN, (2.0 x ULN for subjects with Gilbert's disease)
f. Aspartate Transaminase (AST) and Alanine Transaminase (ALT) ≤2.5x ULN (for subjects with hepatic metastases ≤5 x ULN)
Note: One time repeat testing to meet eligibility is allowed. If more testing is required, discuss with PI.
g. 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

3.19a Evaluable or measurable disease per iRECIST (See Section 11.0).

3.19b Life expectancy of ≥3 months

3.19c Willingness to consent to translational studies

3.19d Willingness to undergo repeat biopsies of tumor lesions amenable to biopsy.

Note: While biopsies are mandatory, subjects are allowed to participate if no lesions are amenable to biopsy, or if biopsy is not possible due to safety.

3.19e Willingness to not donate blood during the study or for 90 days after the last dose of study treatment

3.19f Willingness to not breastfeed during the study or for 90 days after the last dose of study treatment

3.19g Negative pregnancy test done ≤7 days prior to registration, for persons of childbearing potential only.

3.2 Registration - Exclusion Criteria

3.21 Known hypersensitivity to any component of study treatments (either niraparib and/or TSR-042 or similar medications).

3.22 Prior treatment with the combination of PARP inhibition and immunotherapy (either CTLA-4 or anti-PD1/PD-L1 therapies). Prior treatment consisting of monotherapy with either PARP inhibitors and/or with immunotherapy are allowed. Treatment with PARPi or PD1 inhibitor as the most recent treatment prior to enrollment is not allowed.

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

3.24 Radiotherapy ≤ 2 weeks prior to first study treatment or radionuclide treatment ≤ 4 weeks of first study treatment.

3.25 Live attenuated vaccine administration within 30 days prior to registration and/or expected during study period.

3.26 Known brain metastases, uncontrolled seizure disorder, or active neurologic disease which in the opinion of the investigator would impede participation within the trial. Subjects with treated brain metastases are allowed to enroll.

3.27 Allogenic bone marrow transplantation or high-dose chemotherapy requiring hematopoietic stem cell rescue.

3.28 Received a transfusion (platelets or red blood cells) ≤ 4 weeks prior to registration.

NOTE: patients are also deemed ineligible if they have received a transfusion ≤ 4 weeks prior to first dose of niraparib.

3.29a Received colony-stimulating factors (eg, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) ≤ 4 weeks prior to registration.

NOTE: patients are also deemed ineligible if they have received colony-stimulating factors ≤ 4 weeks prior to first dose of niraparib.

3.29b 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.

3.29c Known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)

3.29d ≤ 4 weeks since receiving treatment with another investigational drug, or anti-cancer therapy, or within a time interval less than at least 5 half-lives of the investigational agent (whichever is shorter), or insufficient recovery (to the judgement of the investigator) from adverse events due to such a previously administered agent, except for alopecia prior to initiating protocol therapy. Bisphosphonate therapy and RANKL inhibitors are not considered anti-cancer therapy.

3.29e Inadequate recovery from toxicity and/or complications from previous interventions, including due to major surgery to the judgement of the investigator. Minor surgery allowed up to 3 weeks from registration.

3.29f Primary or secondary immunodeficiency, including immunosuppressive disease, and immunosuppressive doses of corticosteroids (e.g., prednisone > 20 mg per day during 2 weeks prior to first study treatment) or other immunosuppressive medications at dose levels that to the judgement of the investigator would preclude participation within the past 4 weeks prior to registration. Subjects with HIV who are stable on highly active antiretroviral therapy (HAART) will not be excluded.

3.29g 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).

3.29h Pregnant or lactating.

3.29i Clinically significant, active, bacterial infections that, to the judgement of the investigator makes it undesirable for the subject to participate in the study.

3.29j Persons of childbearing potential (POCBP) or those capable of causing pregnancy whose sexual partners are POCBP who are unwilling or unable to use an effective method of contraception for at least 1 month prior to study entry, for the duration of the study, and for at least 180 days after the last dose of study drug.

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 an adequate barrier method throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. Information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

3.29k History or active TB (Bacillus Tuberculosis) that in the investigator's opinion would preclude participation within the study.

3.29l Any gastro-intestinal conditions that to the judgement of the investigator would interfere with the absorption of niraparib.

3.29m Active, known or suspected unstable auto-immune disease, are excluded from this study. Exceptions to this criterion are all auto-immune disease that have remained stable within the past 3 months on corticosteroids (≤ prednisone 20 mg or equivalent) prior to first study treatment are allowed to enroll. Patients with autoimmune diseases that do not require active immunosuppression are also allowed to enroll.

Note: Paraneoplastic disease as a cause of auto-immune phenomenon will not be considered as auto-immune disease and are allowed to enroll.

3.29n Evidence of serious uncontrolled medical disorder, active infection or mental disorder that, to the judgement of the investigator, makes it undesirable for the subject to participate in the study or that would jeopardize compliance with the protocol. 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

3.29o Prior malignancy which required active systemic treatment within 2 years prior to first study treatment. Exceptions are: successfully treated squamous cell carcinoma of the skin, superficial bladder cancer, and in situ carcinoma of the cervix. Since patients with *BRCA* 1/2 or *PALB2* can have other tumors, as long as they have been definitively treated, it would not be considered an exclusion.

4.0 Test Schedule

4.1 Test schedule for niraparib and TSR-042 in Pancreatic Cancer

Tests and procedures	Screening[1]		Baseline[2]	Cycle 1		End of Each Cycle	Clinical Follow-up (30 days after EOT)
	≤30 days prior to Registration	≤14 days prior to Registration		Day 8	Day 15		
Window*	**-30 days**	**-14 days**		**±3 days**	**±3 days**	**±3 days**	**±5 days**
History, physical exam, PS[3]		X	X			X	X
Height		X					
MSI/MMR status[4]		X					
Adverse event assessment		X	X	X[5]	X[6]	X	X
Pregnancy test[7]		X	X			X	X
Hematology[8]		X	X[9]	X	X	X	X
Chemistry[10]		X	X[11]			X	X
Thyroid Panel		X				X[12]	X
Urinalysis		X	X			X	X
HBV/HCV test	X						
PT/PTT/INR		X				X[13]	

[1] One time retesting of single or multiple screening assessments is allowed per investigator's discretion in case patient does not meet specified inclusion and exclusion criteria.

[2] Patients are deemed ineligible if they have received a transfusion or colony-stimulating factors ≤ 4 weeks prior to first dose of niraparib. (refer to Sections 3.28 and 3.29a)

[3] Physical examination includes vital signs (temperature, blood pressure, pulse) and weight; and should be performed at screening and on the days treatment is being administered, prior to TSR-042 treatment. Blood pressure and heart rate monitoring will be required weekly for the first 2 months of therapy (until C3D15). After the first 2 months of therapy, blood pressure and heart rate monitoring only needs to be checked on D1 of each new cycle. For the weekly checks, monitoring at or near home is acceptable.

[4] Collect and record MSI/MMR status (if known)

[5] Cycle 1 Day 8 Adverse Event Assessments will be done clinically but they will not be captured in Rave until end of cycle for worst grade in the cycle.

[6] Cycle 1 Day 15 Adverse Event Assessments will be done clinically but they will not be captured in Rave until end of cycle for worst grade in the cycle.

[7] Persons of childbearing potential: a serum pregnancy test must be performed ≤7 days prior to registration followed by a confirmatory urine pregnancy test ≤7 days prior to study treatment start (if necessary). Pregnancy test will be performed before initiating protocol therapy, every 3 cycles (i.e. end of Cycles 3 and 6), and at Clinical Follow-Up visit.

[8] Hematology includes: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential and platelet count. Blood sampling for all safety laboratory tests should be performed at the end of the cycle, prior to the next treatment administration.
NOTE: hematology testing must be performed on Cycle 1 Day 1

[9] Labs do not need to be repeated if collected ≤ 7 days prior to start of Cycle 1.

[10] Chemistry includes: SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, creatinine, calcium, phosphate, glucose, sodium (Na), and potassium (K). Blood sampling for all safety laboratory tests should be performed at the end of the cycle, prior to the next treatment administration. Baseline labs do not need to be repeated if collected ≤ 7 days prior to Cycle 1 Day 1.

[11] Labs do not need to be repeated if collected ≤ 7 days prior to start of Cycle 1.

[12] Thyroid panel to include TSH, T3 or FT3, and FT4. Done at the end of Cycle 1 and every 6 weeks thereafter through the remainder of the study (can be done up to 7 days prior to TSR-042 administration) and at End of Treatment Visit.

[13] Testing required only when clinically indicated. Will require coagulation tests (PT/PTT/INR) prior to biopsies.

Tests and procedures	Screening[1]		Baseline[2]	Cycle 1		End of Each Cycle	Clinical Follow-up (30 days after EOT)
	≤30 days prior to Registration	≤14 days prior to Registration		Day 8	Day 15		
Window*	**-30 days**	**-14 days**		**±3 days**	**±3 days**	**±3 days**	**±5 days**
CA19-9		X				X	
Bone marrow aspirate and biopsy			X[14]				
Tumor measurement by CT, MRI, or Bone Scan[15]	X					X	
Patient Medication Diary						X	
Research Collections							
Research blood samples[R]			X		X	X[16]	
Research tissue samples[17, R]			X			X	

Cycle = 21 days; R = Research funded

4.2 Survival Follow-up

	Survival Follow-up				
	q. 3months until PD	At PD	After PD q. 6 months	Death	New Primary
Survival Follow-up	X	X	X	X	X

1. If a patient is still alive 5 years after registration, no further follow-up is required

[14] For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist. 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. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to GSK. Will only be collected once while on study. Upload this documentation into the Supporting Documents form within Rave.

[15] All lesions identified at screening should be followed using the same imaging procedure (i.e. either CT or MRI). A bone scan should only be done if clinically indicated and performed as needed if the patient develops symptoms or signs of bone disease. If bone metastases are present at screening, bone scans during treatment should be performed in addition to and at the same time as the CT/MRI-scans only to confirm complete response. Response should be assessed based on iRECIST criteria. Starting at screening and then at 6-week intervals while on study treatment and until immune confirmed objective progressive disease (iCPD) according to iRECIST (See Section 11.0).

[16] Research blood sample collected at end of Cycles 1, 2, 4, and (last day) End of Treatment (ie. progression) (See Section 14.1).

[17] Research tissue sample collection to be performed at baseline (after registration, prior to treatment), end of Cycle 4, and (last day) End of Treatment (ie. progression). The (last day) End of Treatment collection is optional. Only allowed to be omitted if there are no lesions amenable to biopsy or if biopsy is not possible due to patient safety. Will require coagulation tests (PT/PTT/INR) prior to biopsies.

5.0 Stratification Factors OR Grouping Factor:

Grouping factor: Platinum unexposed vs platinum exposed but not refractory vs platinum resistant.

6.0 Registration/Randomization Procedures

6.1 Registration /Registering a patient

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the Mayo Clinic Research Site Management Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (http://ccswww/training/index.html) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MC Research Site Management Office (507) 284-2753. If the patient was fully registered, the MC Research Site Management Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Verification of materials

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Site Management Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Site Management Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Site Management Office is no longer necessary.

6.4 Correlative Research Mandatory

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19b, 14.1 and 17.1*)*.

6.5 Banking

At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of pancreatic cancer at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.6 Treatment on protocol

Treatment on this protocol must commence at a Mayo Clinic Rochester/Arizona/Florida institution under the supervision of a medical oncologist.

6.7 Treatment start

Treatment cannot begin prior to registration and must begin ≤30 days after registration.

6.8 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.9a Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9b Study drug

Study drug is available on site.

6.9c Blood draw kits (Include if kits must be used for this study)

Blood draw kit is available on site (See Section 14.0).

6.9d Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. 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.

7.0 Protocol Treatment

7.1 Treatment Schedule

Use actual weight or estimated dry weight if fluid retention

- Quality Control and Definitions of Deviations will be done according to the guidelines in Appendix IV

7.11 Treatment medication table

Agent	Dose Level	Route	ReRx	Days*
niraparib	200 mg	Oral	Once daily	1-21
TSR-042	Cycles 1-4: 500 mg	IV	Q3W	1
	Cycles 5+: 1000 mg	IV	Q6W	1

***Each cycle is 21 days.**

7.12 TSR-042

TSR-042 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 other 21-day cycle (i.e., Q6W) thereafter until the patient discontinues study treatment.

7.13 Niraparib

Niraparib will be administered as a flat-fixed, continuous daily dose. 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.

7.14 Drug Release Instructions

When enrolling a patient to the study, the patient must be enrolled to the Tesaro platform (4G Prancer RTSM) to assign vial and bottle numbers for the study drugs. To do so, you must:

- Log into the platform at https://tesaro.4gclinical.com/login
- Enroll the patient in the platform
- Enter specific treatment dates for each cycle
- Obtain IV vial numbers and pill bottle numbers at each time point.
  NOTE: pharmacy is unable to dispense medications/treatment without the vial and bottle numbers entered in the pharmacy column before investigator sign and release

If you have any questions, please contact the Tesaro help desk:

- Phone: (855) 299-3496 or (781) 489-3200
- Submit a ticket on Tesaro web page via "4G Clinical Help Center"

7.2 Self-administration statement

Patients can be instructed in administration techniques and granted treatment independence with nursing staff approval.

7.3 Return to consenting institution

For this protocol, the patient must return to the consenting institution for evaluation at least every 21 days during treatment, 30 days after end of treatment (clinical follow-up), and every 3 months during survival follow-up (see Section 4.2).

7.4 Treatment by local medical doctor (LMD)

Treatment by a local medical doctor (LMD) is not allowed.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

⟶ ***ALERT:*** ***ADR reporting may be required for some adverse events (See Section 10.0)*** ⟵

8.1 Dose Levels (Based on Adverse Events in Tables 8.*2* and 8.3)

Dose Level	niraparib	TSR-042
1*	200 mg once daily (two 100 mg capsules)	500 mg q3w or 1000 mg q6w
-1	100 mg once daily (one 100 mg capsule)	500 mg q3w or 1000 mg q6w

*Dose level 1 refers to the starting dose.

NOTE: If either of drug A or drug B is discontinued, the patient can continue on the other drug, unless specified otherwise in the dose modification tables. If both are discontinued, the patient will go to survival follow-up (Section 4.2).

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 5.0* unless otherwise specified*** ← ←

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

8.2 Dose Modifications at the of new cycle of therapy (specific for TSR-042)

Day 1 of Subsequent Cycles

CTCAE System/ Organ/ Class	Adverse Event	Withhold Treatment for AE Grade	Restarting Treatment/Discontinuation
Endocrine disorders	Hypophysitis	2 to 4	For Grade 2 to 3 AEs, hold TSR-042 for a maximum of 6 weeks OR Hold TSR-042 until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when AE 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	Hold TSR-042 for a maximum of 6 weeks or until AE resolves to Grade 0 to 1
		4	Permanently discontinue
Gastrointestinal disorders	Diarrhea/colitis	2 to 3	Hold TSR-042 for a maximum of 6 weeks or until AE resolves to Grade 0 to 1
		4	Permanently discontinue
Infections and infestations	Encephalitis infection (immune-related)	Any grade	Permanently discontinue
Injury, poisoning and procedural complications	Infusion-related reaction	2[a]	Hold TSR-042 for a maximum of 6 weeks or until AE resolves to Grade 0 to 1
		3 or 4	Permanently discontinue
Investigations	Alanine aminotransferase (ALT) increased or Aspartate aminotransferase (AST) increased or Blood bilirubin increased	2 (AST or ALT >3 and ≤5 × ULN or total bilirubin >1.5 and ≤3 × ULN)	Hold TSR-042 for a maximum of 6 weeks or until AE resolves to Grade 0 to 1
		3 or 4 (AST or ALT >5 × ULN or total bilirubin >3 × ULN)	Permanently discontinue (see exception below)[b]

CTCAE System/ Organ/ Class	Adverse Event	Withhold Treatment for AE Grade	Restarting Treatment/Discontinuation
Metabolism and nutrition disorders	Glucose intolerance (T1DM) or Hyperglycemia	3 or 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)	Hold TSR-042 for a maximum of 6 weeks or until appropriately managed patients are clinically and metabolically stable per investigator's discretion. OR Hold TSR-042 until AE resolves to Grade 0 to 1.
Renal and urinary disorders	Acute kidney injury (Renal failure or nephritis)	2	Hold TSR-042 until AE resolves to Grade 0 to 1
		3 or 4	Permanently discontinue
Respiratory, thoracic and mediastinal disorders	Pneumonitis	2	Hold TSR-042 until toxicity resolves to Grade 0 to 1. If Grade 2 recurs, permanently discontinue
		3 or 4	Permanently discontinue
Skin and subcutaneous tissue disorders	Rash (acneiform or maculopapular)	3	Hold TSR-042until AE resolves to Grade 0 to 1
		4	Permanently discontinue
Any	Recurrence of AEs after resolution to Grade ≤1	3 or 4	Permanently discontinue

[a] 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, TSR-042 will be withheld until symptoms resolve, and the patient should be pre-medicated for the next scheduled dose.

[b] 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.

8.3 Dose Modifications Based on Interval Adverse Events (occurring within a cycle of treatment, specific for niraparib)

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
All	Non-laboratory CTCAE* ≥Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	niraparib	Hold niraparib for a maximum of 28 days or until resolution of adverse reaction Resume niraparib at a reduced dose per. Table 8.1
Blood and lymphatic system disorders	Anemia ≥Grade 2	niraparib	Hold niraparib for a maximum of 28 days and monitor blood counts weekly until hemoglobin returns to ≥9 g/dL Resume niraparib at a reduced dose per Table 8.1 Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily*
Investigations	Neutrophil count decreased <1,000/μL or Hemoglobin<8 g/dL	niraparib	Hold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/μL or hemogloblin ≥9 g/dL. Resume niraparib at a reduced dose per Table 8.1 Discontinue niraparib if neutrophil or hemoglobin levels have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.*

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Investigations	Platelet count decreased Grade 1 <100,000/μL)	niraparib	First occurrence: • Hold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL • Resume niraparib at same dose per Table 8.1 Second occurrence: • Hold 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 8.1 Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.*
Investigations	Platelet count decreased Grade 2 (<75,000/μL)	niraparib	First occurrence: • Hold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL • Resume niraparib at reduced dose per Table 8.1 Second occurrence: • Hold 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 1 • Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.*

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Investigations	Platelet count decreased (Grade 4) requiring transfusion	niraparib	For patients with platelet count ≤10,000/μL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Resume niraparib at a reduced dose.
Neoplasms	AML/DS	niraparib	Permanently discontinue niraparib.
Nervous System Disorders	Reversible posterior leukoencephalopathy syndrome / Posterior reversible encephalopathy syndrome (PRES)	niraparib	Treat symptoms, including control of hypertension. Permanently discontinue niraparib.
Vascular	Hypertension	niraparib	Manage with antihypertensive medicinal products. Resume niraparib at reduced dose per Table 8.1. For Grade 3 or higher: Hold niraparib until resolve to Grade 0. Resume niraparib at reduced dose per Table 8.1. Permanently discontinue niraparib in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

** Use the following to describe actions in the Action column:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle.

It is not recommend to reduce niraparib below 100 mg daily.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.21 Neutropenia

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

9.22 Anemia

Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.

9.23 Thrombocytopenia

Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.4 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Immunotherapy-related Adverse Events

Patients should be monitored for signs and symptoms of immunotherapy-related adverse events, which include but are not limited to the following:

- **Pneumonitis**
  - For Grade 2 events, treat with systemic corticosteroids (1mg/kg daily prednisone equivalent). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For Grade 3-4 events, immediately treat with intravenous steroids (1-2mg/kg prednisone equivalent). Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/colitis** Patients should be carefully monitored 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 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For Grade 2 diarrhea/colitis, administer oral corticosteroids (1mg/kg daily prednisone equivalent).
  - For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids (1-2mg/kg prednisone equivalent).
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 Diabetes Mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  For **T1DM** or **Grade 3-4** Hyperglycemia:
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**
  - For Grade 2 events, treat with corticosteroids (1mg/kg daily prednisone equivalent). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For Grade 3-4 events, treat with an initial dose of IV corticosteroids (1-2mg/kg prednisone equivalent) followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or hypothyroidism** Thyroid disorders can occur 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 events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid (1-2mg/kg prednisone equivalent) followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
    - For Grade 3-4 events, treat with intravenous corticosteroids (1-2mg/kg prednisone equivalent) for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal failure or nephritis**
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Rash**
  - Grade 2 - Treat symptomatically with topical steroid cream, as well as antihistamines (i.e., loratidine, diphenhydramine, etc.). For patients that do not respond, consider starting steroids at 0.5 mg/kg prednisone or equivalent.
  - Grade 3 - As above for Grade 2 and start steroids at 1 mg/kg prednisone or equivalent.
  - If any signs of Steven Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TENS), immediately hospitalize patient and treat with high dose IV steroids (1 gram methylprednisolone) and consult dermatology.

- **Management of Infusion Reactions:**
  - Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

- Table 9.51 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of TSR-042

9.51 Infusion reaction treatment guidelines

NCI 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 subject 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, IV fluids); prophylactic medications indicated for ≤24 hrs	**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 subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 adverse events despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be pre-medicated 1.5h (±30 minutes) prior to infusion of TSR-042 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine) Acetaminophen 1000 mg po (or equivalent dose of antipyretic)
Grades 3 or 4 Grade 3: Prolonged (i.e., 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting	Mayo Sites – attach to MCCC Electronic SAE Reporting Form Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu **Send to GSK**: OAX37649@gsk.com Fax Number: ***+44(0) 20 8754 7822***
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form AND attach MedWatch 3500A	Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu **Send to GSK**: OAX37649@gsk.com Fax Number: ***+44(0) 20 8754 7822***

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

a. Identify the grade and severity of the event using the CTCAE version 5.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are

mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.
- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

*Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported in an expedited manner[1]
Blood and lymphatic system disorders	Anemia	≤Grade 4
Endocrine disorders	Hypothyroidism	≤Grade 3
	Hyperthyroidism	≤Grade 3
	Hypophysitis	≤Grade 3
Gastrointestinal disorders	Diarrhea	≤Grade 3
Investigations	Alkaline phosphatase increased	≤Grade 3
	Aspartate aminotransferase increased	≤Grade 3
	Blood bilirubin in creased	≤Grade 3
	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood cell decreased	≤Grade 4
Respiratory, thoracic and mediastinal disorders	Pneumonitis	≤Grade 3
Skin and subcutaneous tissue disorders	Rash acneiform	≤Grade 4
	Rash maculo-papular	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol

- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:
- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives,

rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report Form for investigational agents or commercial/investigational agents on the same arm.

Submit MedWatch 3500A Form

Mayo Clinic Cancer Center (MCCC) Institutions:

Attach the MedWatch form to the electronic Mayo Clinic Cancer Center Safety Reporting Form, which will send a copy to the following email address: CANCERCROSAFETYIN@mayo.edu. This email will be managed by the SAE, IND and Safety Reporting Coordinators.

Forward a copy to GSK: OAX37649@gsk.com
Fax Number: ***+44(0) 20 8754 7822***10.43

Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report Form. The Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Disease progression"** under the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND will be reported per SAE timelines. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

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

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this Form.

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v5.0 **unless** alternate grading is indicated in the table below:

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Anemia	X	X
Endocrine disorders	Hypothyroidism	X	X
Gastrointestinal disorders	*Baseline number of stools*	X	
	Diarrhea		X
General disorders	Fatigue	X	X
	Fever	X	X
	Pain	X	X
Immune system disorders	Allergic reaction		X
Investigations	Alanine aminotransferase increased	X	X
	Aspartate aminotransferase increased	X	X
	Blood bilirubin increased	X	X
	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Metabolism and nutrition disorders	Hyperglycemia	X	X
Respiratory, thoracic and mediastinal disorders	Dyspnea	X	X
Skin and subcutaneous tissue disorders	Rash acneiform	X	X
	Rash maculopapular	X	X

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 GSK - Additional Event Reporting Instructions

10.81 Pregnancy Reporting

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

Each pregnancy must be reported on a Pregnancy Notification 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 Follow-Up Form. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Follow-Up 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 Follow-Up Form reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor Institution and GSK within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

10.82 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

- Embryo-fetal toxicity

AESIs should be reported on SAE Report Forms whether serious or not, as follows:

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

10.83 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 with a GSK product must be reported on a GSK SAE Report Form with associated coversheet to the Sponsor Institution and to GSK within 5 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 and to GSK within 24 hours of awareness.

10.84 Reporting to GSK

The Sponsor Institution must report all SAEs and all follow up information to GSK on a GSK SAE Report Form, accompanied by the GSK coversheet within 24 hours of becoming aware of the initial event or follow-up information.

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

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

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

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

10.85 Suspected Unexpected Serious Adverse Reactions (SUSARs)

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

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

10.86 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 GSKQA 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.

10.87 GSK Reporting Requirements for ALL Serious Adverse Events:

The following must be reported:

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 (defined as follows: --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)

11.0 Treatment Evaluation/Measurement of Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)[17] and iRECIST criteria[18] which is discussed further starting in Section 11.5 below. Since iRECIST still uses RECIST 1.1 principles, the RECIST 1.1 criteria is also in this section as well.

Changes in the largest diameter (unidimensional measurement) of the tumors and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 6 weeks.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

- A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.
- A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions:

- If there is a soft tissue component that has grown since completion of radiation.
- Bone metastases with a soft tissue component are considered measureable.

11.22 Non-Measurable Disease

- All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.
- Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
    - As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline and a positive FDG-PET at follow-up:
    - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
    - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
    - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance has been described in the protocol and supported by disease-specific medical literature for the indication

However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

11.33 Measurement at Follow-up Evaluation:

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

Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Treatment/Intervention Effect

11.41 Target Lesions & Target Lymph Nodes

- The protocol defined irradiated tumor will not be considered for response in the primary endpoint.
- The protocol defined irradiated tumor will be considered for secondary endpoint response.
- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as “Target Lesions”

and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in Section 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

- Note: If fewer than 5 (for phase III trials replace with "3") target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.431 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:
  - Disappearance of all target lesions.
  - Each target lymph node must have reduction in short axis to < 1.0 cm.
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.41).
- Progression (PD): At least one of the following must be true:
  - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  - At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  - See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.432 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:
  - Disappearance of all non-target lesions.
  - Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.
- Progression (PD): At least one of the following must be true:
  - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  - Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
  - See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.431

11.45 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.5 Immune-Related Response Assessment (iRECIST)

All study endpoints requiring measurement data will be assessed per RECIST criteria (defined above). Patients will not be required to end study participation at the first evidence of progression since Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size of malignant lesions, or undetectable lesions becoming detectable. For this reason, iRECIST[18] will be utilized in order to help to make the decision to remove a patient from the study after first evidence of progression. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression. Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix.

11.51 Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but not longer than 9 weeks after iUPD.

For patients that had an iUPD in the previous assessment, iCPD is confirmed in two ways:

1) Existing iUPD gets worse in any lesion type (target, non-target, or new lesions) which contributed to the current iUPD status (a patient can have more than one of the following sources of iUPD).

If iUPD was at least partially based on…	**Then iCPD is confirmed if…**
Target lesions	A cumulative increase (can occur over multiple assessments) of at least 5 mm in the absolute value of the sum from the first occurrence of the current iUPD
Non-target lesions	Any increase in the non-target lesion burden from the first occurrence of the current iUPD
New lesions	A cumulative increase (can occur over multiple assessments) of at least 5 mm in the absolute value of the sum of those considered to be target new lesions or any new lesions (from the first occurrence of the current iUPD)

2) RECIST 1.1 criteria are met in lesion types (target, non-target, or new lesions) which did not contribute to current iUPD status, including the appearance of new lesions.

If a patient meets either (or both) of these criteria, they are considered to have confirmed progression (iCPD). See Appendix III for examples of confirming progression.

11.52 New Lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria, and recorded as New Lesion-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of NLT should NOT be included in the sum of measures of original target lesions identified at baseline.

Progression is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 9 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR and increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of new lesions.

The following table summarizes how to use iRECIST in a number of different scenarios.

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: - further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: - previously identified T lesion iUPD SOM ≥5 mm and / or - NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: - previously identified T lesion iUPD ≥5 mm and / or - previously identified NT lesion iUPD (need not be unequivocal) and /or - size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on - increase in size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same.
** In any lesion category.
*** Previously identified in assessment immediately prior to this TP.

11.6 Definitions of Analysis Variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 Descriptive Factors

12.1 Prior treatment: 1 vs 2 vs 3+

12.2 Mismatch repair status: proficient vs deficient

12.3 Deleterious mutation: BRCA 1 vs BRCA 2 vs PALB2

12.4 Exposed to platinum treatment: yes vs no

12.5 Refractory to cancer treatment: yes vs no

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are iCR, iPR, or iSD will continue treatment per protocol.

13.2 Progressive disease (iCPD)

Patients who develop iCPD while receiving therapy will have an end of treatment visit, then a clinical follow-up visit then go to the survival follow-up phase.

13.3 Off protocol treatment

Patients who go off protocol treatment for reasons other than iPD will have an end of treatment visit, then a clinical follow-up visit 30 days post-treatment, then go to the survival follow-up phase per Section 4.0.

13.4 Duration of therapy for iCR

Patients who achieve a iCR will receive treatment until confirmed progressive disease according to iRECIST, clinical progression, intolerable adverse effects, or patient/investigators decision. They will have an end of treatment visit, then a clinical follow-up visit 30 days post-treatment, then go to survival follow-up.

13.5 Duration of therapy for iPR or iSD

Patients who are in iPR, iSD or iUPD will continue on treatment until confirmed progressive disease according to iRECIST, clinical progression, intolerable adverse effects, or patient/investigators decision. They will have an end of treatment visit, then a clinical follow-up visit 30 days post-treatment, then go to survival follow-up. Subsequent treatment is at the discretion of their attending physician.

13.6 Non-CNS iCPD

Patients who develop non-CNS iCPD at any time should have an end of treatment visit, then a clinical follow-up visit 30 days post-treatment, then go to the survival follow-up phase. These patients should be treated with alternative chemotherapy if their clinical status is good enough to allow further therapy.

13.7 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per Section 4.0 of the protocol.

- If the patient never received treatment, on-study material must be submitted. Survival Follow-up will be required per Section 4.0 of the protocol.

13.8 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per Section 4.0 of the protocol.

13.9 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Research (Section for more information)	Specimen Purpose (check all that apply)	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline	Cycle 1 Day 15	End of Cycle 1	End of Cycle 2	End of Cycle 4	EOT	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Circulating Tumor DNA	☒ Correlative ☐ Eligibility Confirmation ☐ Banking	Blood	Cell-Free DNA BCT Streck	10mL (3 tubes)	X	X	X	X	X	X	No	*Ambient Shipping*
Evaluation of Serum Cytokine Profile by ELISA	☒ Correlative ☐ Eligibility Confirmation ☐ Banking	Blood	Red Top Tube	10 mL (1 tube)	X	X	X	X	X	X	No	*Refrigerate Shipping*
Circulating biomarker work, including DNA and Proteomic based studies	☒ Correlative ☐ Eligibility Confirmation ☐ Banking	Blood	EDTA	10 mL (2 tube)	X	X	X	X	X	X	No	*Refrigerate Shipping*
RNA Extraction based studies	☐ Correlative ☐ Eligibility Confirmation ☒ Banking	Blood	PaxGene RNA	2.5 mL (1 tube)	O	O	O	O	O	O	No	*Ship Frozen (dry ice)*

X = Mandatory, O = Optional

14.2 Collection and Processing

14.21 Kits will be used for this study. Kits to be ordered through Biospecimens Collection and Processing (BAP) in Rochester. All specimens must be collected **Monday - Friday.**

14.22 Label specimen tube(s) with protocol number, patient study ID number, and time and date blood is drawn. Samples when processed at Mayo Biorepositories Florida will be labeled with RLIMS label containing subject ID, study name, specimen type and volume.

14.23 Collect and process all blood/blood products according to the instructions below. All samples will be shipped to MCR Rochester for processing and storage. Samples will be processed in Rochester as indicated below.

14.231 The cell free DNA Streck tube for circulating tumor DNA should be collected at room temperature. Centrifuge the Streck tube within 2 hours of collection at 1600g for 10 minutes at 10°C. Carefully pipette up to 5mL of plasma into a 15mL specimen tube. Centrifuge sample at 3,220g for 10 minutes at 10°C. Transfer the platelet poor plasma into (2) 5mL cryovials and freeze cryovials at -80°C and store.

14.232 The Red Top tube should be incubated at room temperature for 30 minutes to allow the clotting process to complete. Centrifuge the Red Top Tube at lab standards (2000g x 10min at 4°C). Carefully transfer serum into (4) 2mL cryovials and freeze cryovials at -80°C and store.

14.233 The 10mL EDTA tubes for circulating biomarker work is to be centrifuged at lab standards (2000g x 10min at 4°C). Carefully transfer the plasma into (4) 2mL cryovials per 10mL EDTA tube and the white blood cells (buffy coat layer) into (1) 2mL cryovial. Freeze all cryovials at -80°C and store.

14.234 The PAXgene RNA tube for RNA bases studies is to be accessioned into BAP and follow a step down freezing process based on manufacturer's recommendation (see Appendix IV).

14.3 Shipping and Handling

14.31 Kits will be used for this study.

14.311 Kits will be supplied by the Rochester Biospecimen Accessioning and Processing (BAP).

14.312 The kit contains collection supplies for specimens.

14.32 Shipping Specimens

Specimens must be shipped on the day they are collected.

Specimens will be shipped in a dual-temperature shipping container. Place the refrigerated EDTA and No Additive tubes with a properly prepared cold pack in one compartment. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen. Place the Streck tubes in the ambient compartment of the dual-temperature shipping container.

Ship the frozen PaxGene RNA tube with dry ice in the properly labeled frozen shipping container.

14.33 Handling Specimens

Verify that ALL sections of the BAP Requisition form and specimen collection labels are completed and filled in correctly. BAP will retain residual whole blood, plasma, white blood cells, DNA, and serum for future research studies according to patient consent information.

15.0 Drug Information

15.1 TSR-042 (dostarlimab)

15.11 Background

TSR-042 is a humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) isotype that binds with high affinity to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2. TSR-042 is produced by recombinant DNA technology in a mammalian expression system using a stable Chinse hamster ovary (CHO) cell line.

15.12 Formulation

TSR-042 50 mg/mL drug product is a single use sterile liquid formulation that can readily be diluted in an IV solution for intravenous administration. It is a pH 6.0 formulation containing 50 mg/ml TSR-042, 25 mM sodium citrate, 100 mM arginine, 31 mM sodium chloride, and 0.02% polysorbate 80. The deliverable volume in each vial is 10 mL.15.13

15.13 Preparation and storage

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

15.14 Administration

TSR-042 is administered as an intravenous infusion in accordance with the Storage and Handling Guidelines provided by GSK.

15.15 Pharmacokinetic information

Absorption: TSR-042 is administered IV, thus absorption is not applicable.
Distribution: The Vss of TSR-042 was determined in subjects participating in Part 1 of Study 4010-01-001 following a 30-minute IV infusion. The mean Vss was 74.2, 71.7, and 60.7 mL/kg following the administration of 1, 3, and 10 mg/kg, respectively. These results suggest a limited distribution outside the vascular space, which is consistent with the behavior of endogenous IgG.
Metabolism: TSR-042 is a therapeutic mAb IgG4, which is expected to be catabolized into small peptides, amino acids, and small carbohydrates by lysosome through fluid-phase or receptor-mediated endocytosis.
Elimination: The clearance of TSR-042 was determined in subjects participating in Part 1 of Study 4010-01-001 following single IV infusion. The mean clearances were 0.201, 0.117, and

0.152 mL/h/kg for the 1, 3, and 10 mg/kg dose groups, respectively. Body weight (range 45.6 to 145.6 kg) was not a significant covariant for TSR-042 clearance. The estimated terminal t½ was approximately 13 to 18 days.

15.16 **Potential Drug Interactions**

No drug-drug interaction studies have been conducted. Monoclonal antibodies such as TSR-042 are not substrates for cytochrome P450 or drug transporters, and are unlikely to be cytokine modulators. Additionally, pharmacokinetic drug-drug interactions of TSR-042 with small molecule drugs are not expected. There is no evidence of drug-drug interactions mediated by non-specific clearance of lysosome degradation for antibodies.

15.17 **Known potential adverse events**

Common potential adverse events (>10%):
Central nervous system: Fatigue
Dermatologic: Pruritus, rash, maculopapular rash
Endocrine & metabolic: immune-mediate endocrinopathy – especially thyroid, pituitary and adrenal
Gastrointestinal: Nausea, diarrhea, vomiting, decreased appetite
Hematologic: Anemia
Neuromuscular & skeletal: arthralgia

Less common potential adverse events, 1% - 10%:
Hepatic: increased AST, increased ALT
Respiratory: immune-mediated pneumonitis—dyspnea, chest pain, cough

Rare potential adverse events, <1%:
Gastrointestinal: immune-mediated colitis

15.18 **Drug procurement**

Investigational TSR-042 will be supplied free of charge by GSK.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.2 Niraparib (Zejula®, formerly MK-4827)

15.21 **Background**

Niraparib is an orally available, potent, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)1 and PARP2 inhibitor being developed as a monotherapy agent for tumors with defects in the homologous recombination (HR) DNA repair pathway and as a sensitizing agent in combination with cytotoxic agents and radiotherapy as well as in combination with immune-oncology biologics.

15.22 **Formulation**

Investigational Niraparib is available for clinical trials as 100 mg capsules filled with a dry blend of niraparib tosylate monohydrate, lactose monohydrate, and magnesium stearate in a hard gelatin capsule.

15.23 **Preparation and storage**

Niraparib 100 mg capsules are packaged in high density polyethylene (HDPE) bottles fitted with child-resistant plastic closures. Niraparib 100-mg capsules

have a proposed shelf-life of up to 36 months when stored in the intended container closure system and under the conditions specified in the Storage and Handling Guidelines.

15.24 **Administration**

Capsules should be administered once daily at approximately the same time each day.

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

If a patient vomits or misses (greater than 12 hours from normal dosing time) a dose of niraparib, an additional dose should not be taken. The next dose should be taken at the regularly scheduled time.

15.25 **Pharmacokinetic information**

Niraparib exhibits linear pharmacokinetics (PK), and exposure is dose proportional. Absorption and clearance are dose-independent (range: 30 to 400 mg).

Absorption: Following a single-dose administration of 300-mg niraparib under fasting conditions, niraparib was measurable in plasma within 30 minutes, and the mean Cmax for niraparib was reached in about 3 hours. Following multiple-oral doses of niraparib from 30 mg to 400 mg QD, accumulation of niraparib was approximately 2-fold.

The systemic exposures (Cmax and AUC) to niraparib increased in a dose-proportional manner when the dose of niraparib increased from 30 mg to 400 mg. The absolute bioavailability of niraparib is approximately 73%, indicating minimal first-pass effect.

Concomitant intake of a high-fat meal did not significantly affect the PK of niraparib after administration of 300 mg of niraparib.

Distribution: Niraparib was moderately bound to human plasma proteins (approximately 83.0%). The apparent Vd/F was 1220 L, indicating extensive tissue distribution of niraparib. In a population PK analysis, the Vd/F of niraparib was 1074 L in patients with cancer.

Metabolism: Niraparib is metabolized primarily by CEs to form a major inactive metabolite, M1. In a mass balance study, M1 and M10 (the subsequently formed M1 glucuronides) were the major circulating metabolites. The mean t½ of M1 was 88 hours. The exposure ratio of M1 to niraparib was approximately 1.3- to 2.2- fold in plasma.

Elimination: Following a single oral 300-mg dose of niraparib, the mean t½ of niraparib ranged from 48 to 51 hours (approximately 2 days). In a population PK analysis, the CL/F of niraparib was 16.2 L/h in patients with cancer. Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following administration of a single oral 300-mg dose of [14C]-niraparib, on average, 86.2% (range: 71% to 91%) of the dose was recovered in urine and feces over 21 days. Radioactive recovery in urine accounted for 47.5% (range: 33.4% to 60.2%) and in feces for 38.8% (range: 28.3% to 47.0%) of the dose. In pooled samples collected over 6 days, 40.0% of the dose was recovered in the urine primarily as metabolites, and 31.6% of the dose was recovered in the feces primarily as unchanged niraparib.

15.26 Potential Drug Interactions

No formal drug interaction studies have been performed with niraparib. Neither niraparib nor the major metabolite M1 is an inhibitor of any drug-metabolizing CYP enzymes. A clinically meaningful drug interaction via inhibition of CYPs is highly unlikely.

Niraparib weakly induces CYP1A2 in vitro; therefore, investigators should be advised to use caution with drugs that are sensitive substrates for CYP1A2 with a narrow therapeutic range, i.e., theophylline and tizanidine. M1 is not a CYP1A2 inducer.

15.27 Potential adverse events

Common potential adverse events (>10%):
Cardiac: Hypertension, palpitations
Central nervous system: Fatigue, headache, insomnia, dizziness
Gastrointestinal: Nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, dysgeusia
Genitourinary: Urinary Tract Infection
Hematologic: Anemia, neutropenia, thrombocytopenia
Neuromuscular & skeletal: back pain, arthralgia
Respiratory: Cough, Dyspnea, nasopharyngitis

Less common potential adverse events, 1% - 10%:
Cardiac: Tachycardia, peripheral edema,
Central nervous system: Depression, anxiety
Endocrine & metabolic: Hypokalemia, increased gamma-glutamyl transferase
Gastrointestinal: mucositis, stomatitis, dry mouth
General: decrease in weight
Hematologic: leukopenia,
Hepatic: increased AST, increased ALT
Ophthalmic: Conjunctivitis
Neuromuscular: myalgia,
Renal: Increased serum creatinine
Respiratory: epistaxis

Rare potential adverse events <1%:
Acute myelocytic leukemia, hypertensive crisis, myelodysplastic syndrome

15.28 Drug procurement

Investigational Niraparib will be supplied free of charge by GSK.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.29 Nursing Guidelines

15.291 QTc prolongation can be seen. Monitor patient's concomitant medications for potential overlap of other medications that prolong the QTc interval.

15.292 Fatigue was common. Instruct patient in energy conserving lifestyle.

15.293 Gastrointestinal side effects, included diarrhea, anorexia, and nausea. Instruct patients to report these side effects and treat symptomatically. Monitor for effectiveness of intervention.

15.294 Dyspnea and cough have been seen. In addition isolated cases of pneumonitis have been seen. Instruct patient to report any shortness of breath to the study team.

15.295 Pain including headache, back and extremity pain have been reported. Administer analgesics as needed and assess for their effectiveness.

15.296 Monitor CBC w/differential as anemia, thrombocytopenia, and neutropenia are common. Instruct patients to report any unusual bruising or bleeding and/or sign/symptoms of infection to the health care team.

15.297 Electrolyte abnormalities have been seen with agent. Monitor closely.

15.298 Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the niraparib dose, if necessary. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

15.299 Posterior revsersible encephalopathy syndrome (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. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib.

16.0 Statistical Considerations and Methodology

16.1 Primary Endpoint and Analysis:

This is a single arm Phase II study designed to determine as primary endpoint the disease control rate at 12 weeks (DCR12), using the standard iRECIST criteria of patients receiving the combination of niraparib and TSR-042. Because the study features a heterogeneous population featuring 3 different genetic/somatic mutations, there will be no interim analysis. The study will stay remain open, unless a higher than expected toxicity issue is identified.

DCR12 definition and determination:
For this protocol, the patients must undergo response scanning according to the iRECIST criteria. The DCR12 is defined as the percentage of patients who have either iCR, iPR or iSD at 12 weeks. Patients who have developed a iUPD at 6 weeks will only be considered to have achieved disease control at 12 weeks, if at 12 weeks there is no confirmation of disease progression (iCPD) and the patient regresses to either iCR, iPR or iSD. DCR will be analyzed descriptively as a point estimate with a 95% confidence interval.

The primary endpoint will assess the disease control rate at 12 weeks (DCR12), using the standard iRECIST criteria (see Section 11.0, where 11.5 specifically discusses iRECIST). All eligible patients who are registered and start treatment will be evaluable for the DCR12. A 1-stage design will be utilized (see below). This design has 80% power to detect an improvement in DCR12 from 25% to 50%, with a significance level of 0.10. See 1-stage design details below:

Final analysis: We will enroll 19 eligible patients total. As various different types of mutations are to be included, various response patterns are possible; therefore the result

(expressed as the DCR12) might indicate but will not definitively be able to conclude that the treatment is worthwhile. If at least 8 patients are a success for DCR12 in the first 19 eligible patients (41%), the treatment will be considered worthy of further investigation. Otherwise, depending upon per mutations results, the study might continue or the treatment is considered unworthwhile and can be permanently closed due to lack of efficacy.

16.2 Secondary Endpoints and Analysis:

The following endpoints will be assessed as well: objective response rate (ORR), duration of confirmed stable disease according to iRECIST, time to next treatment (TTNT), overall survival , time to and duration of confirmed response, progression-free survival, and adverse events.

Response rate: The confirmed response rate (by iRECIST) will be assessed. Any confirmed response that occurs during the first 8 cycles of treatment will count as a success (24 weeks). Per iRECIST, responses need to be confirmed (2 consecutive responses at least 4 weeks apart) to count as a response. We will also assess the duration of confirmed stable disease according to iRECIST. All eligible patients who are registered and start treatment will be evaluable for response.

Time to next treatment (TTNT): The TTNT is defined as the time from the end of study treatment to receiving the next treatment. TTNT will be estimated using the Kaplan-Meier method.

Overall Survival: Overall Survival (OS) is defined as the time from study entry to death from any cause. OS will be estimated using the Kaplan-Meier method.

Time to and Duration of Confirmed Response: The time to response and duration of confirmed responses will be assessed using the Kaplan-Meier method, where the time to response will be the time from registration to confirmed response and the duration of confirmed response will be defined as the time from the first documented date of confirmed response (CR or PR) to the date at which progression is first documented.

Progression-Free Survival: Progression-free survival (PFS) is defined as the time from study entry to the first of either disease progression or death from any cause, where disease progression will be determined based on iRECIST criteria. PFS will be estimated using the Kaplan-Meier method.

Adverse events: The maximum grade for each type of adverse event will be summarized using CTCAE version 5.0. The frequency and percentage of grade 3+ adverse events will be estimated. We'll also assess AEs at least possibly related to treatment as well.

16.3 Translational endpoints

The goals of the translational studies are to assess germline DNA and serum markers of immune response, to determine changes in circulating tumor DNA (ctDNA) profile after therapy with a PARPi and a PD-1 inhibitor, to study mechanisms of resistance in ctDNA profile after therapy with a PARPi and a PD-1 inhibitor, to assess the tumor microenvironment for immune related changes (immune infiltration, PD-L1 and PD-1 expression, tumor-infiltrating lymphocytes [TIL]), to assess genetic profile of the tumor pre- and post-treatment, and to determine changes in the cytokine profile pre- and post-treatment.

Due to the limited sample size, these analyses will be hypothesis generating and descriptive in nature. Descriptive statistics will be summarized and the blood and tissue marker data will be correlated with clinical endpoints (response, DCR12, duration of

response, OS, PFS, advere events, etc.). For time-to-event data, the Kaplan-Meier method will be used. For categorical data, we'll use the Fisher's exact test. For marker data used to predict binary outcomes (i.e. response vs. no response), we'll use Logistic regression models.

16.4 Total sample size and study duration

To account for possible drop-outs, cancellations, etc. we plan to accrue 20 total patients. We plan to accrue around 2 patients per month, so the study accrual phase should be around 10 months total. The final analysis can be done around 24 months after the study begins, which includes time for data entry, clean-up, and analysis.

16.5 Data & Safety Review

16.51 Reviews

The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rule: The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. Accrual may be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (ie, an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

- If 3 or more of the first 10 patients (or 30% or more of all patients after 10 are accrued) experience a Grade 4 AE. With exceptions: cytopenia, fatigue,
- If 2 or more experience a Grade 5 AE at any time.

After consideration by the study team (study chair, statistician, etc.), a decision will be made as to whether accrual can be resumed.

16.6 Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group.

16.61 Statistical analysis by subset

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.62 Regional population

The geographical region served by MCCC has a population which includes approximately 10% minorities. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	9	9	18
Ethnic Category: Total of all subjects*	**10**	**10**	**20**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	0	1	1
White	9	9	18
Racial Category: Total of all subjects	**10**	**10**	**20**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Research Study (Section for more information)	Specimen Purpose (check all that apply)	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Baseline	End of Cycle 4	End of Treatment (any reason)	Process at site? (Yes or No)	Temperature conditions for storage/ shipping	Sample Storage Location
Tumor Collection (For xenograft and/or organoid)	☒ Correlative ☐ Eligibility Confirmation ☐ Banking	Fresh Tissue Core (1 core each)	(1) 50mL Conical with MEM	X	X		Yes in Rochester MCA, MCF ship on ice	Wet Ice	Dr. Couch's Lab
Identification/ Characterization of Intratumoral Immune Cells and BRCAness by IHC and CyTOF	☒ Correlative ☐ Eligibility Confirmation ☐ Banking	Archive FFPE Tissue or Fresh Tissue Cores	FFPE blocks (preferred) or 7 unstained glass slides with 4 micron-thick sections		X	O	Yes	Ambient	Dr. Couch's Lab
Large Panel Sequencing with low pass genome for copy number, tumor mutation burden	☒ Correlative ☐ Eligibility Confirmation ☐ Banking	Archive FFPE Tissue or Fresh Tissue Cores	Ten (10) unstained glass slides with 5 micron thick sections & One (1) H&E stained Slides		X		Yes	Ambient	Dr. Couch's Lab
Tumor Collection for DNA and RNA future studies	☐ Correlative ☐ Eligibility Confirmation ☒ Banking	Fresh Tissue Cores (up to 2 cores)	(2) Snap Frozen Cores	O			Yes	Frozen / Liquid Nitrogen	MCR BAP
Tumor Collection for DNA and RNA future studies	☐ Correlative ☐ Eligibility Confirmation ☒ Banking	Fresh Tissue Cores (up to 2 cores)	(1) FFPE Block	O			Yes	Ambient	Dr. Couch's Lab
Tumor Collection for DNA and RNA future studies	☐ Correlative ☐ Eligibility Confirmation ☒ Banking	Fresh Tissue Core (1 core)	(1) RNA Later	O			Yes	Frozen / Dry Ice	MCR BAP

X = Mandatory, O = Optional

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

Along with original diagnostic slides, include pathology reporting form, surgical pathology report and operative report.

17.3 Correlative Tissue Collection

17.31 For Research Biopsy:

- Image guided biopsies are recommended where feasible.
- Frozen tissue will be handled and processed for specific processes through BAP.
- FFPE Core shall be created from fresh tissue biopsy procedures.
- Tissue Kits will not be provided for this protocol
- Ship frozen samples to MCR BAP for storage.
- Lab contact for fresh tissue samples (on ice):
  Dr. Fergus Couch
  Stabile Building, 2-43, 200 1st Street SW
  Rochester, MN 55905
  (contact is Anil Belur Nagaraj 507-284-7904 – pager)

17.32 Paraffin Embedded Tissue

Paraffin embedding procedure will follow standard practices. Tissue will be placed in formalin cassette, processed and embedded. Afterwards, tissue will be sectioned based on Table 17.1.

If samples will not be tested shortly after collection, they will be stored as FFPE Blocks at Dr. Couch's lab until sectioned for testing:
Dr. Fergus Couch
Stabile Building, 2-43, 200 1st Street SW
Rochester, MN 55905
(contact is Anil Belur Nagaraj 507-284-7904 – pager)

17.33 Frozen Tissue

BAP MCR will collect fresh tissue cores and store at -80°C for extraction of DNA and RNA. Any remaining tissue is to be stored in BAP MCR, until investigator requests for further studies.

Tissue must be snap frozen in liquid nitrogen and remain frozen at -80°C in storage.

17.34 Fresh Tissue for xenograft

For core biopsies from locally recurrent or metastatic biopsy prior to initiation of therapy, will be placed into a labeled specimen container of MEM with protocol number, study patient ID number, and date and time sample is obtained. Specimens are to be delivered to Dr. Fergus Couch's laboratory detailed below.

Dr. Couch's Laboratory
Stabile Building, 2-43, 200 1st st SW
Rochester, MN 55905
(contact is Anil Belur Nagaraj 507-284-7904 – pager)

17.4 Background and Methodology

17.41 For tissue biopsies before, during and post treatment, goal is to study changes in tumor microenvironment and mutational status post-exposure to PARP inhibition and immunotherapy. The biopsy samples will be biobanked for these analyses in the future. These would include assessment of PD-L1 expression and assessment of mutational status pre- and post-exposure to immunotherapy. PD-L1 expression and changes in microenvironment would be assessed by immunohistochemistry using standard approved antibodies.

17.42 For assessment of mutational status, comprehensive tumor based genetic testing will be performed to study changes in mutational load to exposure of PARP inhibition and immunotherapy over time.

17.43 If feasible, samples would also be collected for xenograft development for potential future studies looking into drug based studies and to study uptake of grafts from these patients.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

See Section 4.2.

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis, progression, and genetic sequencing prior to study entry as well as for evidence of response to study therapy and progression after study therapy. These documents should be submitted within 14 days of registration (for prior to study entry materials) or within 14 days after the visit at which response or progression is determined.

If a bone marrow aspirate collection is conducted (as indicated in the test schedule for subjects diagnosed with MDS/AML), the biopsy report will be required as supporting documentation.

18.6 Labeling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the Cancer Center Systems homepage.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded

- Research testing on blood and tissue specimens.
- Research biopsies at Baseline, Cycle 4 and optional EOT

19.3 Other budget concerns:

GSK will provide Mayo Clinic with niraparib and TSR-042 and funding to support the costs of running this study.

20.0 References

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14. Schaefer, N. G., E. James and R. L. Wahl (2011). "Poly(ADP-ribose) polymerase inhibitors combined with external beam and radioimmunotherapy to treat aggressive lymphoma." Nucl Med Commun 32(11): 1046-1051.
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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
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
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Patient Medication Diary

Name_____ **Study ID Number**_____

Please complete this diary on a daily basis. Write in the amount of the dose of niraparib that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

If you experience any health/medical complaints or take any medication other than niraparib, please record this information.

Week of:_____

Study Drug	***Day 1***	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***
Niraparib							

Week of:_____

Study Drug	***Day 8***	***Day 9***	***Day 10***	***Day 11***	***Day 12***	***Day 13***	***Day 14***
Niraparib							

Week of:_____

Study Drug	***Day 15***	***Day 16***	***Day 17***	***Day 18***	***Day 19***	***Day 20***	***Day 21***
Niraparib							

Patient signature: _____

Comments:

_____

_____

_____

Use a separate sheet of paper if more space is needed.

My next scheduled visit is: _____

If you have any questions, please call: _____

Study Coordinator Use Only

Number of pills returned _____ Number of vials returned: _____

Discrepancy Yes____/No____ Verified by _____ Date_____

Appendix III Examples of confirmed progression

The following examples show how a patient that is currently an iUPD can become an iCPD (confirmed progression). These examples all use target lesion growth as the source of the first progression (iUPD) and show how additional information in future assessments can lead to iCPD. The examples are not exhaustive, but are meant to be illustrative of how iCPD can occur. Similar examples can be created where non-target lesions and/or new lesions led to the initial iUPD.

1) iUPD due to target lesion growth from baseline followed by iCPD due to continued growth of target lesions (by at least 5 mm).

	Baseline	TP1	TP2
T lesions (sum)	100	125	132
NT lesions	Pres	No change	No change
New lesions		None	None
TP response (R)		PD	PD
TP response (iR)		iUPD	iCPD

2) iUPD due to target lesion growth from baseline followed by iCPD due to gradual continued growth (over 2 assessments) of target lesions (by at least 5 mm from time of first iUPD).

	Baseline	TP1	TP2	TP3
T lesions (sum)	100	125	128	132
NT lesions	Pres	No change	No change	No change
New lesions		None	None	None
TP response (R)		PD	PD	PD
TP response (iR)		iUPD	iUPD	iCPD

3) iUPD due to target lesion growth from baseline followed by iCPD due to new lesion appearing after start of iUPD. This iCPD is based on criteria #2 outlined in Section 11.5.1.

	Baseline	TP1	TP2
T lesions (sum)	100	125	125
NT lesions	Pres	No change	No change
New lesions		None	1 new lesion
TP response (R)		PD	PD
TP response (iR)		iUPD	iCPD

4) iUPD due to target lesion growth from baseline followed by iCPD due to additional target lesion growth as well as a new lesion.

	Baseline	TP1	TP2
T lesions (sum)	100	125	132
NT lesions	Pres	No change	No change
New lesions		None	1 new lesion
TP response (R)		PD	PD

Appendix IV PAXgene Manufacturer's Recommendations

Information below is from manufacturer's website: https://www.qiagen.com/us/resources/
Document: "PAXgene Blood RNA System Brochure"

An introduction to the **PAXgene** Blood RNA System (IVD)

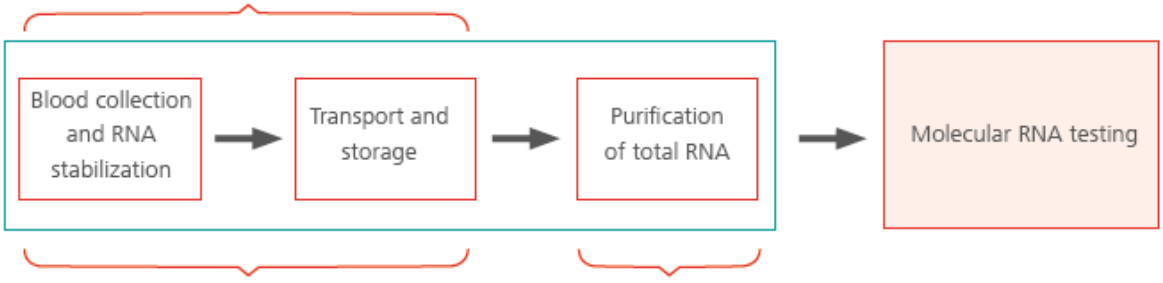
Key features and benefits of the PAXgene Blood RNA workflow
Detection and quantification of intracellular RNA transcripts.

Challenge
- RNA transcript levels change dramatically, often within minutes of blood collection, as a result of postphlebotomy gene induction, cell death or enzymatic RNA degradation. This can lead to artificial up or downregulation of gene expression levels that are not representative of the real RNA transcript profile in the body.
- Lack of standardized methods for RNA collection and purification from blood increases variability in RNA quality and yield.

Solution
- Stabilize intracellular RNA at the point of blood collection.
- Integrate and standardize the workflow from blood collection to pure RNA.

The PAXgene Blood RNA System is the first IVD-marketed* product for the collection, storage and transportation of whole blood with stabilization of intracellular RNA in a closed tube and subsequent isolation and purification of intracellular RNA for RT-PCR used in molecular diagnostic testing. Performance characteristics for the PAXgene Blood RNA System have only been established with FOS and IL1B gene transcripts. The user is responsible for establishing appropriate PAXgene Blood RNA System performance characteristics for other target transcripts.

PAXgene Blood RNA workflow

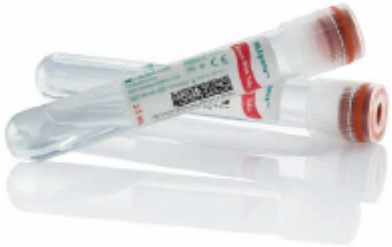


PAXgene Blood RNA Tube:
- A single tube for blood collection, RNA stabilization, specimen transport and storage
- Prefilled with RNA stabilization reagent to provide RNA stabilization
- Blood cell lysis in tube simplifies RNA purification
- Consistent blood draw volume and blood-to-additive ratio

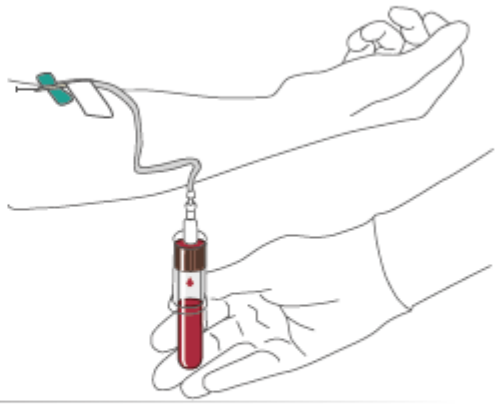
PAXgene Blood RNA Kit:
- Optimized for purification of cellular RNA from stabilized blood
- Generates quality RNA
- Efficient and easy-to-follow manual or automated protocols
- Multiple processing options available

* Only when the PAXgene Blood RNA Tube (762165) is used in combination with the PAXgene Blood RNA Kit (762164 or 762174).

The **PAXgene** Blood RNA Workflow



Collect blood according to instructions into a PAXgene Blood RNA Tube.

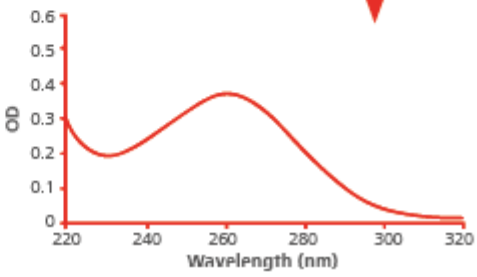


Transport and store the filled PAXgene Blood RNA Tube as described in the product circular. Incubate tubes for at least 2 hours at room temperature prior to processing.

Follow instructions in the kit handbook to pellet and wash nucleic acids and transfer as instructed for processing. Follow the manual or automated protocol of your chosen PAXgene RNA or miRNA purification kit to obtain quality RNA.

Complete purification with a final elution and heat denaturation of RNA.

The PAXgene Blood RNA System results in quality RNA ready to be used in downstream applications.



PAXgene Blood RNA and miRNA product selection guide (RUO, IVD)

Multiple processing options

Depending on your requirements, the PAXgene Blood RNA and miRNA Systems provide pure RNA and miRNA from both manual and automated protocols.

Analyte	Throughput	Protocol and instrument	Average time per run	Number of samples processed	Kit to use
RNA (>200 nt*)	Low	Manual	90 min for 12 samples	1–12	PAXgene Blood RNA Kit (IVD)
		Automated on QIAcube	151 min for 12 samples		
RNA/miRNA (all sizes, optimized for small RNA)	Medium	Automated on QIAsymphony	2.5 h for 24 samples	24–72	QIAsymphony PAXgene Blood RNA Kit (RUO)
RNA/miRNA (all sizes, optimized for small RNA)	Low	Manual	90 min for 12 samples	1–12	PAXgene Blood miRNA Kit (RUO)
		Automated on QIAcube	125 min for 12 samples		
RNA (>200 nt*)	High	Manual	3.5 h for 96 samples	96	PAXgene 96 Blood RNA Kit (RUO)

IVD = in vitro diagnostic; RUO = for Research Use Only, not for use in diagnostic procedures
* nt = nucleotides

See the PreAnalytiX website www.preanalytix.com or contact QIAGEN technical services or your local QIAGEN distributor to discuss how to process your PAXgene Blood RNA Tubes.

Ordering Information

IVD products	Contents	Cat. no.
PAXgene Blood RNA Tubes (100)	100 PAXgene Blood RNA Tubes	762165
PAXgene Blood RNA Kit (50)	50 PAXgene Spin Columns, 50 PAXgene Shredder Spin Columns, Processing Tubes, RNase-Free DNase I, RNase-Free Reagents and Buffers. To be used in conjunction with PAXgene Blood RNA Tubes.	762164 (North America) 762174* (Other countries)
RUO products		
QIAsymphony PAXgene Blood RNA Kit (96)†	For 96 preps: 2 Reagent Cartridges, Enzyme Racks, Accessories and RNase-Free Buffers. To be used in conjunction with PAXgene Blood RNA Tubes.	762535
PAXgene 96 Blood RNA Kit (4)†	4 PAXgene 96 RNA Plates, 4 PAXgene 96 Filter Plates, Buffers, Proteinase K, RNase-free DNase Sets, AirPore Tape Sheets and Collection Vessels. To be used in conjunction with PAXgene Blood RNA Tubes.	762331
PAXgene Blood miRNA Kit (50)†	For 50 RNA preps: PAXgene Spin Columns, PAXgene Shredder Spin Columns, Processing Tubes, Microcentrifuge Tubes, RNase-Free DNase, RNase-free Reagents and Buffers. To be used in conjunction with PAXgene Blood RNA Tubes.	763134
Accessories		
BD Vacutainer Push Button Blood Collection Set	21G ¾ inch (0.8 x 19 mm) needle, 12 inch (305 mm) tubing with luer adapter, 50/box, 200/case	367344
BD Vacutainer Safety-Lok Blood Collection Set	21 G, ¾ inch (8.8 x 19 mm) needle, 12 inch (305 mm) tubing with luer adapter, 50/box, 200/case	367286 (CE) 367281 (US)
BD Vacutainer One-Use Holder	Case only for 14 mm and 16 mm diameter, 2000/case	364815
BD Vacutainer Plus Serum Tubes	13 x 75 mm x 4.0 mL draw with red BD Hemogard closure and paper label, 100/box, 1000/case	368975 (CE) 367812 (US)

* Not available in all countries, please inquire.

† For Research Use Only. Not for use in diagnostic procedures.

For up-to-date licensing information and product-specific disclaimers, see the respective PreAnalytiX or QIAGEN kit handbook or user manual. PreAnalytiX and QIAGEN kit handbooks and user manuals are available at www.preanalytix.com and www.qiagen.com or can be requested from PreAnalytiX technical services.

Trademarks: PAXgene®, PreAnalytiX® (PreAnalytiX GmbH); QIAGEN®, QIAcube®, QIAsymphony® (QIAGEN Group); Agilent® (Agilent Technologies, Inc.).

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BLOOD · TISSUE · BONE MARROW
The better the source, the more to eXplore.

Appendix V Patient Blood Pressure and Heart Rate Monitoring Diary

Name _____ **Study ID Number** _____

Please complete this diary on the dates specified below. You will be asked to the record the requested information once a week for the first 2 months of therapy while on this study.

If you are in the clinic for any of the visits listed below for this study, please leave the space blank as the study staff will record your blood pressure and heart rate during your visit.

Cycle / Day	***Date (dd/mmm/yyyy)***	***Blood Pressure Systolic/Diastolic (top/bottom number)***	***Heart Rate (beats per minute)***
Cycle 1 Day 1			
Cycle 1 Day 8			
Cycle 1 Day 15			
Cycle 2 Day 1			
Cycle 2 Day 8			
Cycle 2 Day 15			
Cycle 3 Day 1			
Cycle 3 Day 8			
Cycle 3 Day 15			

Patient signature: _____

Comments:

_____

_____

_____

Use a separate sheet of paper if more space is needed.

My next scheduled visit is: _____

If you have any questions, please call: _____