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Phase I/Ib Study of Nivolumab and Veliparib in Patients with Advanced Solid Tumors and Lymphoma with and without Alterations in Selected DNA Repair Genes

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ALK	Anaplastic lymphoma kinase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BMS	Bristol-Myers Squibb
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CLIA	Certified Laboratory Improvement Amendments
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse Large B-cell Lymphoma
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
HR	Heart rate
irAE	Immune-related Adverse Event
irRECIST	Immune-related RECIST
IV (or iv)	Intravenously
LTF	Lost to Follow-up
MMR	Mismatch Repair
MSI-H	Microsatellite Instability High
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non Small-Cell Lung Cancer
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PARP	Poly (ADP-ribose) Polymerases
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed Death-1
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase

SJS	Stevens-Johnson Syndrome
SPGT	Serum Glutamic Pyruvic Transaminase
TEN	Toxic Epidermal Necrolysis
TIL	Tumor Infiltrating Lymphocyte
TMZ	Temozolomide
TNBC	Triple Negative Breast Cancer
WBC	White Blood Cells

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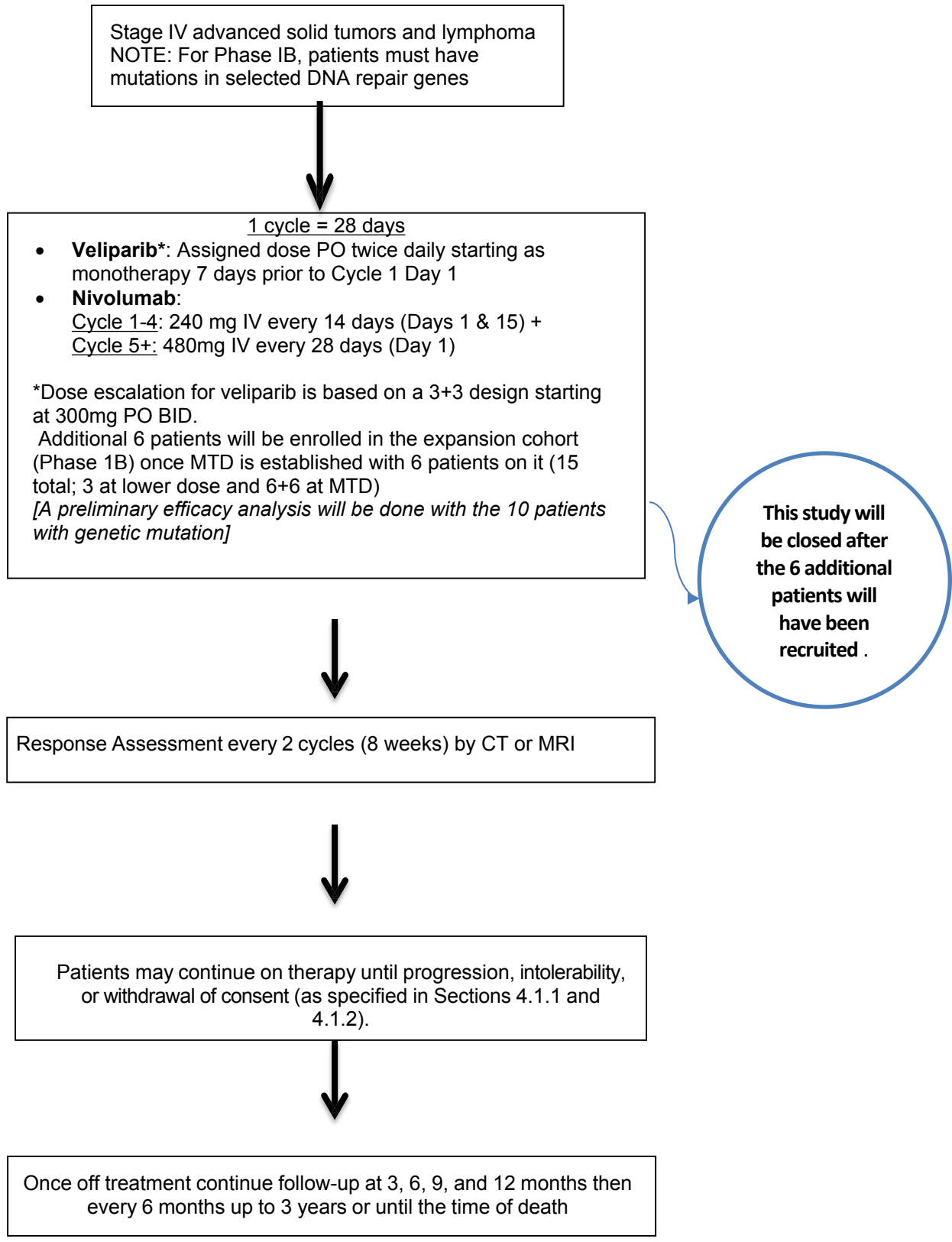
STUDY SCHEMA



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STUDY SUMMARY

Title	Phase I/IB study of nivolumab and veliparib in patients with advanced solid tumors and lymphoma with and without mutations in selected DNA repair genes
Version	3/3/2020 (Amendment 7)
Study Design	Phase I/IB
Study Center	Northwestern University

	Primary Objectives: A. To Identify the maximum tolerated dose (MTD) for combination treatment of nivolumab and veliparib in patients with advanced solid tumors and lymphoma with and without mutations in selected DNA repair genes. Secondary Objectives: A. To evaluate the toxicities and tolerability of nivolumab and veliparib in the study population. B. To evaluate the efficacy of veliparib and nivolumab measured by overall response rate (ORR), clinical benefit rate (CBR), and progression free survival (PFS) using RECIST v1.1, Lugano classification, and irRECIST. For the preliminary efficacy analysis, ORR will be computed at the first imaging (8 weeks). Preliminary efficacy will be evaluated by RECISTv 1.1. As exploratory analysis, irRECIST will be used to obtain preliminary efficacy as well. All ORR will use the first imaging time point whether RECIST or irRECIST. C. To evaluate Overall Survival (OS) at 3 years from the start of treatment. D. To evaluate the proportion of patients alive and progression free at 24 weeks in this population. Exploratory Objectives: A. Biomarker tests will be performed at baseline using fresh tissue (or archived if a fresh biopsy is not feasible), as well as from blood samples at Cycle 1 Day 1, Cycle 3 Day 1, and the End of Treatment visit.To evaluate if any of the following predict response to veliparib in combination with nivolumab: • Tissue PD-L1 protein expression • Immune cell infiltration markers B. To demonstrate the pharmacodynamic effects of veliparib and nivolumab on biomarkers including PD-L1, TILs, T cell subpopulations, and T cell receptor genotype.

Sample size	The initial study design was to accrue a total of up to 50 patients for 48 evaluable) to the study in two phases: dose escalation and dose expansion. The original design anticipated a total of 6-18 patients with advanced solid tumors or lymphoma in the dose escalation phase; 9 patients were enrolled, including 3 at lowest dose and 6 that were treated at the MTD of 400 mg BID. It is still planned for 6 patients with advanced solid tumors and lymphoma with mutations in selected DNA repair genes to be enrolled into the expansion cohort to receive the maximum tolerated dose of veliparib in combination with nivolumab. However, due to funding issues, the study will perform an early analysis of preliminary efficacy after the next 6 patients are enrolled in the expansion cohort, all with the genetic mutation. Of the 6 patients already at MTD, 4 have the genetic mutation. No responses were observed in any patient at MTD. Total number of patients at the end of adding 6 more patients with mutation will be 4+6=10. The study will be considered a "success" if the lower exact 90% confidence limit is > 10%, i.e. when 3 or more successes are observed. . According to the modified plan for the current trial, the study will be closed after the 6 additional patients will have been recruited."

Diagnosis & Key Eligibility Criteria	Key Inclusion Criteria: 1. Patients must have a histologically documented (either primary or metastatic site) diagnosis of metastatic or advanced solid cancer (stage IV or unresectable) or aggressive lymphoma. *NOTE: The following histologies will be excluded given known response to PD-1/PD-L1 inhibitor monotherapy; non-small cell lung cancer, squamous cell carcinoma of head and neck, melanoma, renal cell carcinoma, bladder cancer, Hodgkin's lymphoma, Merkel cell carcinoma, and MSI-H colorectal cancer.* 2. All patients must have received at least one line of systemic treatment. 3. Patients who progressed on single agent PD-1/PD-L1 inhibitors are allowed. 4. Patients must be ECOG performance status of 2 or less and have normal organ function. 5. For expansion cohort, patients should have alterations in selected DNA repair genes in their tumors, as listed in 3.1.6. *Please note: This eligibility criteria is also applicable for patients enrolled for the preliminary expansion cohort to conduct preliminary efficacy analysis*. Key Exclusion criteria: 1. Patients who have had chemotherapy or radiotherapy ≤ 14 days prior to entering the study are not eligible. 2. Patients may not have received systemic chemotherapy ≤ 28 days prior to registration. 3. Patients are not eligible who have had major surgery ≤ 14 days of registration. 4. Patients are not eligible who have received prior PARP inhibitors (including but not limited to veliparib, talazoparib, rucaparib, and olaparib). 5. Patients are not eligible who have received prior immunotherapy including interleukin-2 and immune checkpoint antagonists and/or agonists (including but not limited to PD-1, PD-L1, CD137, or OX40). *NOTE: Single agent anti-CTLA4 monoclonal antibody treatments are permitted. Cancer vaccine therapies are permitted.* 6. Patients are not eligible who have had a prior allogeneic stem cell transplant. NOTE: Autologous stem cell transplant is acceptable. Patients with autoimmune diseases are excluded.

Treatment Plan	Patients will be treated using a dose escalation plan based on a 3+3 design. The starting dosing for veliparib will be 300 mg PO twice daily, and treatment will begin as monotherapy during a 7-day induction period. Patients in Phase Ib will be treated at the MTD. Nivolumab combination therapy will begin Cycle 1 Day 1 as follows: Cycle 1-4: 240 mg IV every 14 days (Day 1 & 15) Cycle 5+: 480mg IV every 28 days (Day 1 of each cycle). Combination treatment will continue until disease progression unacceptable toxicity, or withdrawal of consent. This treatment plan is applicable for patients in both the dose escalation and dose expansion cohorts.
Statistical Methodology	The primary analysis will be based on toxicity and maximum tolerated dose. For all analyses, the intent-to-treat (ITT) population will be used to include all evaluable patients. Clinical benefit rate will be defined as stable disease (for ≥12 weeks) and complete or partial response by the Response Evaluation Criteria in Solid Tumors (RECIST). Lugano classification will be used for lymphomas. Maximum response prior to disease progression will be used. The overall response rate will be estimated by the proportion of overall response, and its 90% lower bound will be estimated using the exact binomial distribution. If this lower bound > 10% (ie. at least three responses are observed) the trial will be considered a success. Additionally**,** we will evaluate overall response rate, *separately* for patients with and for those without genetic mutation entertained in this study, Early analysis of preliminary efficacy will be based on the patients with genetic mutation (n=10). Response is defined as complete or partial response using RECIST guidelines in a similar manner. We will also perform similar analyses using Immune Related RECIST (irRECIST). Duration of response, defined as the duration from the first documentation of clinical benefit to the first documented progressive disease or death of any cause, whichever occurs first, will also be analyzed. For patients alive and progression-free at the time of data cut off, duration of response will be censored as of the last tumor assessment date. Duration of response will only be evaluated for the subgroup of patients with a clinical benefit using the Kaplan-Meier method.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Significant unmet need in treatment of advanced cancers:

Despite the success of molecularly targeted drugs against the activity of one or more proteins involved in tumorigenesis, these agents only benefit a small proportion of patients. Many tumors do not possess an actionable mutation and have limited therapeutic options for subsequent therapy. The advent of immune checkpoint inhibitors has expanded therapeutic options and produced durable responses among immunogenic tumors. However, response is only seen in a poorly defined subset of patients and many patients are refractory to such treatment or relapse after such therapy. We must investigate ways to increase the number of patients with different histologies that may benefit from immune checkpoint inhibition and extend duration of response through the use of novel combination therapy.

1.2 Synthetic lethality of PARP inhibitors:

Inhibitors of poly (ADP-ribose) polymerases (PARP) have demonstrated the biological concept of synthetic lethality.[1-3] Two genes are synthetically lethal if loss of either alone is viable whereas concurrent loss results in cell death.[4] It has been demonstrated that BRCA1 and BRCA2 dysfunction sensitized cells to PARP inhibition, resulting in genomic instability, cell cycle arrest, and apoptosis.[5] It is thought that PARP inhibitors utilize the homologous recombination [6] deficiency in BRCA-deficient cells to cause an increase in persistent single strand breaks (SSBs), resulting in collapsed replication forks and ultimately creating double strand breaks (DSB).[2,7] HR-deficient cells are unable to maintain the integrity of the genome and become nonviable. PARP inhibitors have now demonstrated efficacy for the treatment of ovarian cancer with BRCA mutations.[8,9] Identification of other mediators of cellular response to PARP inhibitors may reveal additional patient populations that could benefit from this therapeutic approach.

1.3 Tumors with BRCA-like gene defects as a distinct entity:

We have queried a publicly available database (COSMIC) to obtain the overall frequency of mutations of DNA repair genes. We demonstrated that DNA repair genes are mutated at the average frequency of 5% across various tumor types. As with *ALK* rearranged non-small cell lung cancer, these unique subgroup of patients make up a molecularly defined rare group of cancer. It is well known that germ-line mutations in DNA repair pathway genes have been associated with various hereditary cancer syndromes. BRCA 1/2 mutated hereditary breast and ovarian cancer syndrome is a prime example.

There are a number of solid tumors that harbor defects in homologous recombination repair outside of BRCA 1/2 that are referred to as “BRCA-like” tumors or possessing “BRCAness.”[10] Loss or disruption of proteins necessary for HR such as *RAD51, ATM, ATR, CHK1, CHK2, FANCD2*, and *FANCA* are observed in a variety of tumors. In muscle-invasive bladder cancer, patients with tumors with mutations in DNA repair genes such as *ATM, ERCC2, FANCD2, PALB2, BRCA1*, or *BRCA2* demonstrated better survival outcome after cystectomy compared to patients with tumors without mutations. In pancreatic cancer, genomic instability co-segregated with inactivation of DNA repair genes including *ATM, BRCA1, BRCA2* or *PALB2.* The individuals with defects in these DNA repair mechanisms demonstrated better treatment responses. These observations suggest that somatic mutations in HR DNA repair pathway genes may form a distinct entity across different histologies.

Recently it has been shown that BRCA1/2-mutated tumors were associated with significantly higher CD8+/CD4+ ratio of tumor infiltrating lymphocytes (TILs) and significantly higher peritumoral T cells. These findings support an additional mechanism for the improved survival of patients with BRCA1/2-mutated ovarian cancers in addition to increased sensitivity to platinum chemotherapy[11].

1.4 Rationale of PARP inhibitors in BRCA like tumors:

It is expected that tumors displaying inherent or acquired DNA repair defects would most likely respond to PARP inhibition[12]. Ongoing research suggests HR deficiency, rather than a specific mutation in the BRCA genes, may be the main driver of cytotoxicity of PARP inhibition.[13] The BRCA-like behavior has been described based on clinical and molecular features that parallel germline BRCA mutation-associated cancer characteristics. The major clinical BRCA-like behavior identified is susceptibility to platinum compounds and other DNA-damaging agents.[14,15]

Recent trial (ARIEL2) in ovarian cancer demonstrated that a use of PARP inhibitor (rucaparib) was associated with higher PFS rates among patients with BRCA mutations and BRCA-like wild-type ovarian cancer compared to biomarker-negative tumors. The median PFS for mutation carriers was not reached after 9.4 months, compared with 7.1 months for patients with BRCA-like tumors and 3.7 months for participants who were biomarker negative[16]. There are also ongoing efforts to develop a predictive genomic companion diagnostics of HR deficiency that can help determine potential patients who would benefit from PARP inhibitor treatment.

1.5 Overall somatic mutation burden of tumor and defects in DNA repair mechanisms:

Mutations in critical genes such as those involved in DNA repair will likely result in genomic instability and subsequent hypermutability. For example, it is well known that mismatch repair (MMR) deficient tumors have extremely high mutation rates. Similarly, in muscle-invasive bladder cancer, mutations in either of the DNA repair genes (ATM, ERCC2, FANCD2, PALB2, BRCA1, or BRCA2) were associated with higher somatic mutation burden as measured by non-synonymous single nucleotide variant (SNV) and higher T cell clonality as measured by lower T cell receptor (TCR) diversity index. This hypermutable state generated by defects in the DNA repair mechanism may be responsible for altering the tumor 'mutanome', resulting in the production of highly tumor-specific mutated 'neo-antigens', potentially increasing the efficacy of immunotherapies.[17] Tumor infiltrating lymphocytes (TILs) from adoptive cell transfer-treated melanoma patients were found to show specificity for mutated tumor proteins, and further screening to estimate their ability to bind T cell major histocompatibility complex positively correlated with tumor regression. In multiple tumor types, immunogenicity of mutated tumor neo-antigens correlated with patient survival and increased TILs. Patients with MMR deficient colorectal cancer as well as MMR deficient non-colorectal cancers treated with PD-1 inhibitors have demonstrated better response compared with patients MMR proficient tumors. Furthermore, in ovarian cancer and triple negative breast cancer (TNBC) where BRCA1 or 2 mutations are more prevalent than other subtypes, favorable responses to immune checkpoint inhibitors have also been reported.

1.6 Veliparib

1.6.1 Clinical development of Veliparib

Veliparib is a novel small molecule that is a potent inhibitor of PARP-1 and PARP-2 (Investigator's Brochure; edition 9 – 12 June 2015). PARPs are enzymes involved in DNA repair. In cells under oxidative stress, veliparib inhibits the PARP induced formation of poly-(ADP-ribose) (PAR). In cellular assays, veliparib increases sensitivity of tumor cells to DNA-damaging agents including platinum agents, irinotecan, cyclophosphamide, temozolomide (TMZ) and radiation. In preclinical tumor models, veliparib enhances the anti-tumor efficacy of DNA crosslinking agents (cisplatin, carboplatin), alkylating/methylating agents (TMZ, cyclophosphamide), topoisomerase inhibitors (irinotecan) and radiation. Veliparib has been shown to enhance the efficacy of carboplatin in several xenograft tumor models. In the BRCA1 deficient MX-1 model, veliparib administered at doses as low as 25 mg/kg/day significantly enhanced the efficacy

of carboplatin. (Investigator's Brochure; edition 9 – 12 June 2015)

Veliparib is being investigated in AbbVie-sponsored studies, in Investigator initiated
studies (IIS), and in CTEP-sponsored studies. In these studies, veliparib is administered as monotherapy, combined with a variety of chemotherapeutic agents, including alkylating agents, platinums, and topoisomerase inhibitors, and radiation or combined with radiation therapy across an array of tumor types, including melanoma, glioma, prostate, breast, and colon.

1.6.2 Clinical efficacy of Veliparib

Summary preliminary or final efficacy data from AbbVie sponsored studies have shown that veliparib has activity in combination with temozolomide (TMZ), radiotherapy and chemotherapy. A phase II study evaluating veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1or BRCA2 mutation showed a response rate of 26% (90% CI: 16%-38%, CR: 2, PR: 11); for platinum-resistant and platinum-sensitive patients the proportion responding was 20% and 35%, respectively.[9] Data from non-AbbVie sponsored studies show veliparib has activity as monotherapy for treatment of ovarian cancer[18] and activity in combination with carboplatin + paclitaxel for treatment of early breast cancer.[19] Veliparib is currently in Phase 2 and Phase 3 clinical development in combination with several DNA-damaging agents across a variety of cancer indications including a planned combination of Nivolumab in NSCLC.

1.6.3 Clinical safety of Veliparib

In the veliparib clinical development program, veliparib has been administered as monotherapy and as combination therapy to subjects with various solid tumors. Veliparib has been administered in doses up to 500 mg BID as monotherapy and up to 400 mg BID in combination with cytotoxic chemotherapies or radiation therapy. (Investigator's Brochure; edition 9 – 12 June 2015). The overall safety experience with veliparib, as monotherapy or in combination with other therapeutics, is based on experience in approximately 3700 subjects treated to date (of which approximately 250 patients treated with single agent veliparib). Some of the common side effects with veliparib monotherapy (≥10%) include constitutional symptoms such as fatigue, loss of appetite, dysguesia, feeling dizzy, sleep disturbance; Gastrointestinal side effects such as nausea, vomiting, diarrhea, constipation; hematological toxicity such as anemia, leucopenia and thrombocytopenia; increased liver enzymes and blood sugars. Less frequent (<10%), but potentially severe events included dehydration and seizures. Very rare side effects include secondary malignancy (<1%) and Myelodysplastic syndrome (<0.1%), however were not seen in veliparib monotherapy studies.

1.7 Nivolumab

1.7.1 Clinical development of Nivolumab

Nivolumab (BMS-936558, MDX-1106) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HunMab) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [cd279]) cell surface membrane receptor (Investigator Brochure version 2014). PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an “exhausted” phenotype. Nivolumab anti-tumor activity has been investigated in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC).

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment [21]. Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality. PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma, renal, esophageal, gastric, ovarian, pancreatic, lung, and other cancers (Investigator Brochure version 2014) [22-28].

Nivolumab has been evaluated as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapy (such as ipilimumab), anti-angiogenesis therapy, and targeted therapies in completed and ongoing BMS-sponsored clinical trials in NSCLC, melanoma, RCC, hepatocellular carcinoma (HCC), gastrointestinal (GI) malignancies including colorectal cancer with microsatellite instability (MSI), and triple-negative breast cancer (TNBC) with an expanding group of indications (Investigator Brochure version 2014). Nivolumab is currently FDA approved for the treatment of patients with: (i) unresectable or metastatic melanoma and disease progression after ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor; (ii) patients with metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy.

1.7.2 Clinical efficacy

Nivolumab has demonstrated clinical activity as monotherapy and as combination therapy with ipilimumab in several tumor types, including RCC, melanoma, NSCLC, and some lymphomas. The majority of responses was durable and exceeded 6 months (Investigator Brochure version 2014). Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. ORs were observed at all doses. Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Heavily pretreated patients with NSCLC treated with nivolumab (1, 3, or 10mg/kg) achieved median OS across all dose cohorts of 9.9 months with response rates of 17% and median duration of response 17 months [29]. In addition, responses were similar between both squamous and non-squamous carcinoma cohorts in this study. A subsequent phase 3 study compared nivolumab to docetaxel in second-line treatment setting of advanced squamous cell carcinoma among 272 patients. Nivolumab arm demonstrated superior median OS (9 vs 6 months), 1 year survival rate (42 vs 24%), response rates (20 vs 9%), and significantly lower rates of grade 3-4 treatment related adverse events (7 vs 55%) [30]. These results supported the FDA approval of nivolumab for second-line treatment of advanced squamous cell carcinoma following treatment with platinum-based chemotherapy.

Nivolumab has also clinically meaningful activity in RCC. A phase II study treated 168 patients with advanced clear cell RCC with progression after agents targeting VEGF pathway at three doses of nivolumab (0.3, 2 and 10mg/kg) [31].

Median overall survival was 18, 25, and 24 months for the three dose cohorts, respectively. Response rates were in average 20% with only 11% incidence of grade 3-4 treatment-related adverse events. In an advanced melanoma phase 1 study, nivolumab and ipilimumab were administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen) [20]. The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses 1 mg/kg nivolumab and 3 mg/kg ipilimumab, with tumor reduction of 80% or more (modified World Health Organization criteria). In the sequenced-regimen (33 patients), the objective response rate (ORR) was 20%. These results demonstrate significant clinical activity of nivolumab across multiple histologies with favorable toxicity profile.

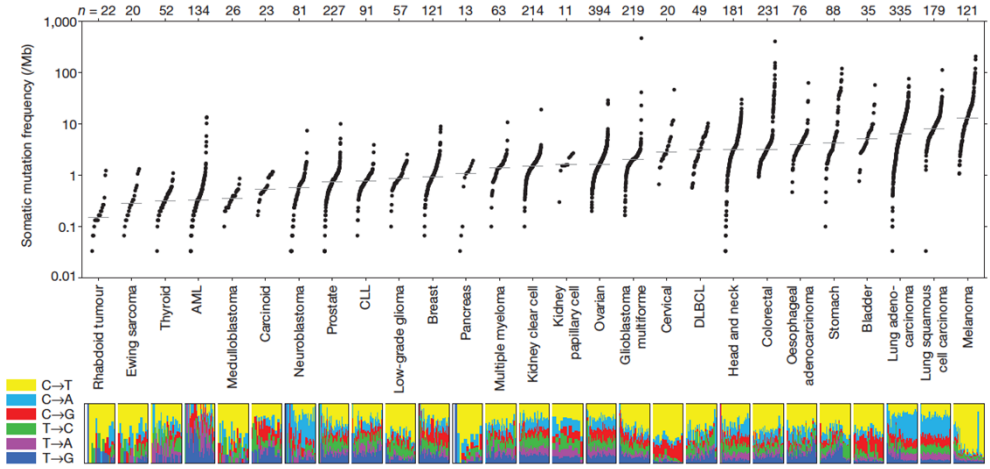
1.7.3 Clinical safety

The overall safety experience with nivolumab, as monotherapy or in combination with other therapeutics, is based on experience in approximately 4,000 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation adverse events (AEs), which may be numerically greater in subjects with NSCLC, because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab + ipilimumab in subjects with melanoma. Thus far, the combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases with a greater frequency [20].

1.8 Rationale for Nivolumab and Veliparib combination:

Previous studies have demonstrated that tumors with the highest genomic instability and somatic mutational burden, such as melanoma, non-small cell lung cancer, and bladder cancer have favorable responses with immune checkpoint inhibitor therapy (Figure 1). The widely acceptable hypothesis is that tumors with more mutations likely generate more neoepitopes, which can be recognized by tumor infiltrating T cells. Checkpoint blocking antibodies activate these T cells *in vivo* and induce anti-tumor immunity, thereby causing tumor responses.

Figure 1.
Somatic mutation frequency and various tumor types



Higher genomic instability may also predict response to PARP inhibitors. For instance, smokers with non-small cell lung cancer (NSCLC) that also had higher genomic mutational burden, showed better response to a PARP inhibitor compared with nonsmokers. Screening for defective DNA repair mechanisms may select patients with higher mutation burden who will likely respond to combination therapy.

In addition to utilizing the concept of synthetic lethality by utilizing PARP inhibition in tumors with defects in selected DNA repair mechanisms, we hope to increase the genomic instability and mutational epitopes produced in these tumors, making them more susceptible to the immune checkpoint inhibitor therapy. With the help of immunotherapy, durable responses likely difficult to achieve with targeted therapy with PARP inhibitors may be realized via functioning memory T cells targeting tumor mutanomes generated and activated by the immune checkpoint inhibitors.

Recently, it has been shown in a syngeneic murine model of BRCA-/- ovarian cancer that PARP inhibition (talazoparib) significantly increased the number of peritoneal CD8+ T cells and NK cells as well as their production of IFN-γ and TNF-α[32]. This implies that PARP inhibition induces not only cancer cell-intrinsic apoptosis but also cancer cell-extrinsic antitumor immune effects. This finding suggests possible synergistic effect of PARP inhibitor and immunotherapy in cancer.

Nivolumab is an immune checkpoint inhibitor to programmed cell death protein 1 (PD-1) that is FDA approved for the treatment of advanced melanoma and metastatic squamous cell carcinoma of the lung. Veliparib is a PARP inhibitor that has shown promising activity in the treatment of germline BRCA1/2 mutated ovarian tumors. Given the non-overlapping side effect profiles and different therapeutic targets of these agents, this combination of agents may improve efficacy without compromising toxicity. Compared to monotherapy with either of these agents, the combination approach may increase the ORR and survival outcome and possibly broaden number of tumor histologies and their subtypes that will respond to such treatment. Therefore, we propose a clinical trial with nivolumab and veliparib combination.

PARP inhibitor monotherapy or immune checkpoint inhibition may each result in clinical responses in a select group of tumors, especially tumors that are characterized by the presence of high mutational burden. Genomic instability due to mutations in DNA repair has been shown in both pre-clinical and clinical studies to predict response to PARP

inhibitors Immune checkpoint inhibitors yield impressive clinical responses in melanoma and non-small cell lung cancer, two cancers with very high mutational loads NSCLC that arise in smokers, the subset of lung tumors with the highest mutational load, are particularly susceptible to treatment with nivolumab or with veliparib . Smokers with NSCLC treated with nivolumab had a significantly higher response rate and improved survival outcomes relative to non-smokers . Similar data showing RR, PFS, and OS improvements in subjects who smoke were recently published for veliparib .

Advanced Solid Tumors and Lymphoma Harboring Alterations in Selected DNA Repair Genes are a rational target for treatment with PARP inhibition with checkpoint inhibitors, because approximately 5% are defective in the homologous recombination DNA repair pathway due to germline, somatic and epigenetic mutations in BRCA1 and BRCA2 and, to a lesser extent, from mutations in other homologous repair proteins . These indications therefore have an increased mutational load, suggesting a moderate amount of neoantigen derived from point mutations, which could be increased in the presence of PARP inhibition .

In pre-clinical studies, PARP inhibitors are associated with immunomodulation. PARP inhibitors promote local antigen release after tumor exposure to radiation or DNA-damaging agents, which may result in systemic antitumor response. . In a BRCA1-mutated ovarian cancer xenograft model, PARP inhibition increased the number of peritoneal CD8+ T cells and natural killer cells, and increased production of interferon γ and tumor necrosis factor α . Though data from pre-clinical cancer models treated with combination PARP inhibition and checkpoint inhibition are limited, veliparib does not antagonize α-PD-1 in a MC-38 syngeneic mouse model (AbbVie Investigator's Brochure, data on file).

Taken together, these data suggest that PARP inhibition with veliparib may be complementary to immune checkpoint modulation with nivolumab in yielding clinical benefit in patients with Advanced Solid Tumors and Lymphoma Harboring Alterations in Selected DNA Repair Genes

1.9 Rationale for the current study design

The study will be done in patients with advanced solid tumors or lymphoma with or without identified mutations in specified DNA repair genes involved in homologous recombination repair pathway (only the expansion cohort will require such mutations). Therefore, it will be a multi-histology basket trial with a molecularly driven expansion cohort. The effect of veliparib monotherapy has been shown in germline BRCA1/2 mutated ovarian cancer. Hence, this patient group will be excluded from the population. In addition to safety evaluation, this study is designed as a multi-histology navigation trial to explore the proof-of-principle in efficacy in this novel combination treatment in various cancer types that are refractory to standard of care treatment options.

The initial study design was to accrue a total of up to 50 patients (for 48 evaluable) to the study in two phases: dose escalation and dose expansion. The original design anticipated enrolling 6-18 patients with advanced solid tumors or lymphoma in the dose escalation phase, followed by 15-32 patients in a two-stage expansion phase. For the dose escalation, a standard 3+3 design was chosen to determine the MTD of the novel combination To date, 9 patients have been enrolled and the dose escalation phase is complete, including 6 patients that were treated at the MTD of 400 mg BID.

However, due to funding issues, the study will adopt a modified plan for the expansion cohort, and will perform an early analysis of preliminary efficacy after the next 6 patients are enrolled in the expansion cohort.

This **modified plan for expansion cohort**, will accrue 6 new patients with genetic

alteration for early preliminary efficacy assessment, which together with 4 previously treated patients with genetic mutation will provide total of 6+4=10 patients, with genetic mutation. ORR will be computed at the first imaging (8 weeks). Preliminary efficacy will be evaluated by RECISTv 1.1. As exploratory analysis, irRECIST will be used to obtain preliminary efficacy as well. All ORR will use the first imaging time point whether RECIST or irRECIST.

The study will be considered a success if the lower 90% exact confidence bound will be > 10% , i.e. if three or more successes out of n=10 are observed.

. According to the modified plan for the current trial, the study will be closed after the 6 additional patients will have been recruited.

This same treatment plan will be used for patients in both the dose escalation and dose expansion cohorts.

1.10 Rationale for Dosing

1.10.1 Nivolumab flat dose regimen

The safety and efficacy of 240 mg (monotherapy) Q2W flat dose of nivolumab has recently received IRB approval and is expected to be similar to the 3 mg/kg Q2W dosing regimen. Using the population PK (PPK) model, exposure of nivolumab at 240 mg flat doses is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight in nivolumab clinical trials. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat doses compared to 1mg/kg and 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

In addition, nivolumab 480 mg administered once every 4 weeks (Q4W) is currently under investigation. The less frequent dosing regimen is designed to afford more convenience to the target patient populations. The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) to provide an approximately equivalent dose of nivolumab 3 mg/kg Q2W. Exposures following nivolumab 480 mg Q4W regimen are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk. Hence, the flat doses of 240mg and 480mg nivolumab are under investigation.

1.10.2 Veliparib Dosing

A veliparib dose of 400mg po bid is the phase 2 recommended dose for veliparib monotherapy. A prior phase 1 study shows that it is safe to start at 300mg po bid in combination with nivolumab. Thus the dose escalation will begin at 300mg veliparib twice a day and escalate to a final dose level 2 of 400mg.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoint

To identify maximum tolerated dose (MTD) for the combination treatment of nivolumab and veliparib in patients with advanced refractory solid cancers and lymphoma.

2.2 Secondary Objectives & Endpoints

2.2.1 To evaluate the safety and tolerability of nivolumab and veliparib in patients with advanced refractory solid cancers and lymphoma with and without mutations in selected DNA repair genes.
The endpoint will be the number, frequency, and severity of adverse events (as defined by the NCI CTCAE v4.03).

2.2.2 To evaluate the efficacy of treatment with nivolumab and veliparib in this population by objective response rate (ORR, defined as partial response (PR) + complete response (CR)), clinical benefit rate (CBR, defined as stable disease (SD) for ≥12 weeks, PR, + CR), and Progression Free Survival (PFS, defined as the time from treatment initiation to documented disease progression) using RECIST criteria v1.1 or Lugano criteria.

For the preliminary efficacy analysis, ORR will be done at the first imaging (8 weeks). Preliminary efficacy will be evaluated by RECISTv 1.1. As exploratory analysis, irRECIST will be used to obtain preliminary efficacy as well. All ORR will use the first imaging time point whether RECIST or irRECIST.

2.2.3 To evaluate efficacy of treatment with nivolumab and veliparib in this population by ORR, CBR, and immune-related PFS (irPFS) using irRECIST criteria.

2.2.4 To evaluate Overall Survival (OS) in this population at 3 years from the start of treatment. OS is defined as the time from treatment initiation until death due to any cause.

2.2.5 To evaluate the proportion of patients alive and progression free at 24 weeks in this population.

2.3 Exploratory Objectives & Endpoints

The main goals of the objectives listed below are to identify predictive biomarkers beyond the genetic mutations by which treatment is assigned, and to identify resistance mechanisms to the nivolumab and veliparib combination using additional genetics and tumor immunology-based assessment platforms

Biomarker tests will be done at baseline using fresh tissue (or archived if a fresh biopsy is not feasible) , as well as from blood samples at Induction Day 1, Cycle 1 Day 1, Cycle 3 Day 1, and the End of Treatment visit.

2.3.1 To evaluate if any of the following predict response to veliparib in combination with nivolumab:

- Tissue PD-L1 protein expression
- Immune cell infiltration markers

2.3.2 To demonstrate the pharmacodynamic effects of veliparib and nivolumab on biomarkers including PD-L1, TILs, T cell subpopulations, and T cell receptor genotype.

2.3.3 To assess the dynamic change in both immune and genomic biomarkers in blood that may correlate with response to veliparib.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with advanced solid tumors and lymphoma with and without mutations in selected DNA repair genes, where the expansion cohort will be reserved for patients with DNA repair gene mutations as listed in 3.1.6. This will be a single-center trial conducted at Northwestern University.

The initial study design was to accrue a total of up to 50 patients for 48 evaluable) to the study in two phases: dose escalation and dose expansion. The original design anticipated a total of 6-18 patients with advanced solid tumors or lymphoma in the dose escalation phase; 9 patients were enrolled, including 3 at lowest dose and 6 that were treated at the MTD of 400 mg BID. It is still planned for 6 patients with advanced solid tumors and lymphoma with mutations in selected DNA repair genes to be enrolled into the expansion cohort to receive the maximum tolerated dose of veliparib in combination with nivolumab. However, due to funding issues, the study will perform an early analysis of preliminary efficacy after the next 6 patients are enrolled in the expansion cohort, all with the genetic mutation.. According to the modified plan for the current trial, the study will be closed after the 6 additional patients will have been recruited.

Approximately 5 potentially eligible patients will be seen per month, and it is anticipated that at least 2 per month will be accrued. Patients will be recruited by all participating investigators in respective clinics within the Northwestern University Cancer Center network. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Young Kwang Chae at (312) 926-4248.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have a histologically documented (either primary or metastatic site) diagnosis of advanced solid tumor cancer (stage IV or unresectable) or aggressive lymphoma (diffuse large B cell lymphoma, mantle cell lymphoma, T cell lymphoma, and NK cell lymphoma).
***NOTE**: The following histologies will be excluded given known response to PD-1/PD-L1 inhibitor monotherapy: non-small cell lung cancer, squamous cell carcinoma of head and neck, melanoma, renal cell carcinoma, bladder cancer, Hodgkin's lymphoma, Merkel cell carcinoma, and MSI-H colorectal cancer.*
***NOTE**: Patients with deleterious BRCA 1/2 mutated ovarian cancer will be excluded given its presumed efficacy with veliparib monotherapy.*

3.1.2 All patients must have received, and be relapsed/refractory to at least one line of systemic therapy.
***NOTE**: This does not include surgery or radiation alone. Patients may have received any number of systemic therapies*
***NOTE**: For patients with aggressive lymphoma, there should be no other standard therapies that would confer survival benefit.*

3.1.3 All patients with relapsed/refractory lymphoma must have received or be ineligible for autologous stem cell transplant or be ineligible for allogeneic stem cell transplant.
***NOTE**: Patients must not have had a prior allogeneic stem cell transplant.*

3.1.4 Patients must have measurable disease as per appropriate guidelines:

- Solid tumors: by RECIST v1.1
- Lymphoma: Patient has at least one measurable nodal lesion (≥2 cm) according to Lugano classification. If the patient has no measurable nodal lesions ≥2 cm in the long axis at screening, then the patient must have at least one measurable extra-nodal lesion.

3.1.5 Patients must have the ability to understand and the willingness to sign a written consent prior to registration in the study.

3.1.6 For expansion cohort patients, the profiling must reveal at least one mutation in the following selected DNA repair genes involved in cell cycle arrest signal transduction, BRCA1 pathway, Fanconi's proteins pathway, and RAD51 pathway: [*ATR, ATM, CHEK1, CHEK2, BRCA1, BRIP1, BAP1, BARD1, FANCD2, FANCE, FANCC, RAD50, FANCA, RAD51, BRCA2, PALB2, CDK12 (ENSG00000167258, also known as CRK7, CRKR, CRKRS), POLE, POLD1, BRAC2, PRKDC, ERCC2, POLQ, MRE11A, NBN (*MBS1*)*], or at least one gene amplification in *FANCD2, FANCE, FANCC, FANCA, C11orf30* (EMSY*)*.
Please note: This eligibility criteria is also applicable for patients enrolled for the preliminary expansion cohort to conduct preliminary efficacy analysis.

***NOTE**: Tissue or blood cell free DNA are allowed for genomic profiling of tumor. Profiling should have been performed at a CLIA certified lab ≤1 year prior to registration.*
***NOTE**: Patients in the dose escalation phase are not required to have such mutations. Although genomic profiling is not required for dose escalation patients, it is encouraged in these patients prior to or after study registration if feasible.*

3.1.7 Patients must be age ≥ 18 years; both male and females are eligible.

3.1.8 Patients must exhibit an ECOG performance status of ≤2.

3.1.9 Patients must have adequate organ and bone marrow function ≤ 14 days prior to registration, as defined below (Note: Blood transfusion or growth factors is not permitted within 14 days of registration):

absolute neutrophil count	≥ 1.5 x 10^9/L
hemoglobin	≥ 9 g/dL
platelets	≥ 100 x 10(9)/L
Total bilirubin	≤ 1.5 x ULN
Alanine amino transferase and aspartate aminotransferase	≤ 5 x ULN
Calculated creatinine clearance according to the Cockcroft and Gault equation	≥ 50 mL/min

3.1.10 Females of child-bearing potential (FOCBP) and men who are sexually active with FOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment and the designated post-treatment period (5 months for females and 7 months for males; see Appendix A for details on appropriate contraception methods)

***NOTE**: A FOCBP is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:*

- *Has not undergone a hysterectomy or bilateral oophorectomy*
- *Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)*

3.1.11 FOCBP must have a negative pregnancy test ≤7 days prior to registration.

3.1.12 Patients must be able to swallow oral medication.

3.2 **Exclusion Criteria**

3.2.1 Patients who have had radiotherapy ≤ 14 days prior to registration are not eligible.

3.2.2 Patients who have received systemic chemotherapy or investigational agents ≤ 28 days prior to registration are not eligible.

3.2.3 Patients are not eligible who have had major surgery ≤ 14 days prior to registration. Please contact PI and QAM for questions about specific surgical procedures.

3.2.4 Patients are not eligible who have received prior PARP inhibitors (including but not limited to veliparib, talazoparib, rucaparib, and olaparib).

3.2.5 Patients are not eligible who have received prior immunotherapy including interleukin-2 and immune checkpoint antagonists and/or agonists (including but not limited to PD-1, PD-L1, CD137, or OX40).
***NOTE**: Single agent anti-CTLA4 monoclonal antibody treatments are permitted. Cancer vaccine therapies are permitted.*

3.2.6 Patients with the following histologies are not eligible for either study cohort given known response to PD-1/PD-L1 inhibitor monotherapy:
Non-small cell lung cancer, squamous cell carcinoma of head and neck, melanoma, renal cell carcinoma, bladder cancer, Hodgkin's lymphoma, Merkel cell carcinoma, and MSI-H colorectal cancer

3.2.7 Patients with deleterious BRCA 1/2 mutated ovarian cancer are not eligible.

3.2.8 Patients are not eligible who have had a prior allogeneic stem cell transplant.
***NOTE**: Autologous stem cell transplant is acceptable*.

3.2.9 Patients who are taking any herbal (alternative) medicines are NOT eligible for participation. Patients must be off any such medications by the time of registration for ≥ 14 days.
***NOTE**: Vitamin supplements are acceptable.*

3.2.10 Patients requiring systemic treatment with corticosteroids (>10mg daily prednisone equivalents) or other immunosuppressive medications ≤14 days prior to first dose of study drug are not eligible.
NOTE: Inhaled and intranasal corticosteroids are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type

hypersensitivity reaction caused by a contact allergen) is permitted.

3.2.11 Patients who receive a live attenuated vaccine ≤28 days prior to registration are not eligible.

3.2.12 Patients must have no history of CNS metastasis at the screening assessment.
***NOTE**: Patients with stable brain mets which have been treated are eligible. Patients with suspected symptoms of CNS metastasis should undergo CNS imaging at the time of screening to rule out active metastasis.*

3.2.13 Patients who have had a prior severe infusion reaction to a monoclonal antibody are not eligible.

3.2.14 Patients are not eligible who have a history of or active autoimmune disease within the past 3 years with the following exceptions:
- Vitiligo or alopecia
- Hypothyroidism on stable doses of thyroid replacement therapy
- Psoriasis not requiring systemic therapy within the past 3 years

3.2.15 Patients with a history of primary immunodeficiency disease or tuberculosis are not eligible.

3.2.16 Patients who have an uncontrolled current illness including, but not limited to any of the following, are not eligible:
- Uncontrolled pulmonary, renal, or hepatic dysfunction
- Ongoing or active infection requiring systemic treatment including hepatitis B and hepatitis C
- Known active or chronic viral hepatitis or human immunodeficiency virus (HIV)
- Psychiatric illness/social situations that would limit compliance with study requirements
- Clinically significant gastrointestinal disease or digestive dysfunction compromising absorption of veliparib
- Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints

3.2.17 Female patients who are pregnant or nursing are not eligible.

3.2.18 Patients with a prior diagnosis of cancer must not have received treatment in the last 3 years prior to registration.
NOTE: treatments used as a recurrence prevent are eligible.

***NOTE**: Patients with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.*

3.2.19 Patients must not have a history of prior stroke, transient ischemic attack (TIA), pulmonary embolism, or untreated deep vein thrombosis.
***NOTE**: Patients may be eligible if they have received at least 3 months of anticoagulation for a deep vein thrombosis.*

4.0 TREATMENT PLAN

4.1 Overview

In Phase 1, patients will be treated with a dose escalation plan for veliparib based on a 3+3 study design. The initial patient cohort will be treated with veliparib 300 mg PO twice daily and nivolumab as follows (1 cycle = 28 days):

Cycle 1-4: 240 mg IV every 2 weeks and
Cycle 5+: 480mg IV every 4 weeks

See section 4.2 for treatment administration and dosing modifications based on the planned 3+3 study design. Total cycle length is 28 days (4 weeks). Combination treatment will continue until progression of disease or intolerability with scans occurring every 8 weeks (see section 4.7.1 for possible treatment beyond progression). Patients in the expansion cohort (Phase1B) will be treated with the MTD, that is now established. This same treatment plan will be used for patients in both the dose escalation and dose expansion cohorts.
Patients will undergo a fresh tissue biopsy prior to study enrollment, unless deemed to be clinically inappropriate per PI, to evaluate pharmacodynamic changes in immune-related biomarkers. Correlatives will be assessed as detailed in section 9.0.

[Please note: . According to the modified plan for the current trial, the study will be closed after the 6 additional patients in the expansion cohort will have been recruited.]

4.2 Treatment Administration

Table 4.1: Dosing of Nivolumab and Veliparib

Drug	Dose	Route	Schedule
Nivolumab (Opdivo)	**C1-4**: 240mg **C5+**: 480mg	IV	**Cycle 1-4**: every 14 days **Cycle 5+**: every 28 days until progression of disease, intolerable toxicity, or withdrawal of consent
Veliparib	Phase I: Starting dose 300mg (see 4.3 for escalation) Phase Ib: MTD	PO	Twice a day about 12 hours apart starting 7 days before C1D1 (Induction monotherapy) continuing until progression of disease, intolerable toxicity, or withdrawal of consent

4.2.1 Veliparib

Veliparib is administered orally twice a day starting on Day 1 of each cycle. Subjects will self-administer the morning and evening doses of veliparib approximately 12 hours apart in the same calendar day. Each dose of veliparib will be taken with a glass of water and consumed over as short a time as possible (i.e., not slower than 1 capsule every 2 minutes) with or without food. During veliparib treatment, standard antiemetic therapy may be administered as appropriate, including a combination of standard antiemetic's (i.e., 5-HT3 receptor antagonists, steroids, and prochlorperazine, and/or promethazine).

It is recommended that if a subject misses a scheduled dose of veliparib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose but should wait and take the next regularly scheduled dose.

If the subject vomits within 15 minutes of taking veliparib, another dose will be administered. The dose may only be repeated once. If more than 15 minutes has passed from the time of oral dosing then no additional doses will be taken.

Patients will maintain a drug diary for dosing compliance each cycle. Completed drug diaries will be returned at the beginning of each cycle along with any leftover veliparib tablets and drug bottles.

See section 4.3 for details on dose escalation during Phase I and section 4.4 for toxicity management

4.2.2. Nivolumab

During Cycle 1-4, nivolumab will be administered at a fixed dose of 240 mg intravenously over approximately 30 minutes (-5 / +15 minutes) every 2 weeks (Day 1 and 15 of each cycle). Starting with Cycle 5, nivolumab will be administered at 480mg IV over 30 minutes (-10 / +15 minutes) every 4 weeks (Day 1 of each cycle). There is no premedication required for infusion. Veliparib oral doses can be taken independently of the nivolumab administration schedule.

4.2.2.1 Treatment Monitoring

Subjects will be monitored before, during, and after the 30- or 60-minute infusion of nivolumab with vital signs as follows:

Table 4.2: Time Points for Vital Signs

Before Infusion	
Pre-dose	Vitals up to 30 minutes prior
During Infusion	
Every 15 minutes	Vitals ± 5 minutes
After infusion	
Immediately following	Vitals within 5 minutes after
30 minutes post	Vitals ± 5 minutes
60 minutes post (1st & 2nd doses)	Vitals ± 5 minutes
3 hour observation (1st dose only)	Observation only

In the event of a Grade ≤ 2 infusion-related reaction, the infusion rate of nivolumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In subjects experiencing Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (eg, diphenhydramine) may be administered at the discretion of the investigator. If the infusion-related reaction is severe or prolonged, methylprednisolone 125 mg (or the equivalent) should be administered as well. Investigators may administer steroids at their discretion as clinically indicated and per their institution's guidelines.

Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

4.3 Dose Escalation

Table 4.3: Dose levels based on 3 + 3 design for veliparib and nivolumab

Dose Level	Veliparib	Nivolumab

-1	200 mg PO twice daily	C1-4: 240 mg IV every 2 weeks C5+: 480mg IV every 4 weeks
1	300 mg PO twice daily	C1-4: 240 mg IV every 2 weeks C5+: 480mg IV every 4 weeks
2	400 mg PO twice daily	C1-4: 240 mg IV every 2 weeks C5+: 480mg IV every 4 weeks

The above dose escalation plan is based on a 3 + 3 design with the starting dose of veliparib as 300 mg PO twice daily and nivolumab as 240mg IV every 2 weeks. Each cycle will be 28 days (4 weeks) in length.

4.3.1 Definition of DLT (Dose limiting toxicity)

Toxicity will be assessed using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03 unless otherwise specified. A DLT is defined as an AE or abnormal laboratory value assessed as at least possibly related to the study medication, occurs ≤ 28 days following the first dose of veliparib and nivolumab and meets any of the criteria listed below. Whenever a patient experiences toxicity that fulfills the criteria for a DLT, treatment with the study drug combination will be interrupted until resolution to ≤ Grade 1 or baseline, and the toxicity will be followed up until resolution. All adverse events specified below will be DLT's except those that are clearly and incontrovertibly due to extraneous causes.

The following events will be considered DLT's:

1. Grade ≥ 3 non-hematologic toxicities that represent at least a 2-grade increase from baseline with the following exceptions:
    a. Nausea, vomiting, and diarrhea lasting ≤48 hours
    b. Electrolyte abnormalities resolving within ≤24 hours
    c. Hypersensitivity reactions
    d. Alopecia
2. Grade 4 thrombocytopenia (platelets < 25.0 x 10^9/L)
3. Grade 3 thrombocytopenia with bleeding (platelets <50.0 x 10^9/L)
4. Grade 4 neutropenia (ANC < 0.5 x 10^9/L)
5. Grade 3 febrile neutropenia with fever lasting for > 7 days
6. Grade 4 febrile neutropenia of any duration
7. Dosing delay due to toxicity for > 14 consecutive days from the date nivolumab or veliparib is due.

4.3.2 Dose Escalation 3+3 Rule

Table 4.4: Dose escalation plan based on 3 + 3 design for veliparib and nivolumab

Number of Subjects with DLT in the First Cycle	**Escalation Decision Rule**
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Add 3 more subjects at current dose level. • If < 2 of 6 subjects (or < 33% of subjects) experience DLT, dose escalation will proceed to the next dose level. • If ≥ 2 of total 6 subjects (or ≥ 33% of subjects) experience DLTs, then dose escalation will be stopped.*
≥ 2 out of 3 or 6	Dose escalation will be stopped.*

*For dose level 1, additional subjects will be enrolled at the previous lower dose level (-1) as needed to establish MTD with 6 patients.

*If dose escalation is stopped at dose level 2, dose level 1 will be established as the MTD if it enrolled 6 patients (<2 of 6 patients had DLT). If dose level 1 enrolled only 3 patients (0 of 3 had DLT's), 3 more patients will be added to dose level 1 to establish the MTD. From there, dose level -1 will be utilized in the case that ≥2 patients have DLT.

NOTE: Whichever dose level is declared the MTD must have 6 total patients treated at that level. For example, if 3 patients are treated at level 2 and 0 patients experience DLT, escalation would then proceed to level 3. However, if ≥ 2 patients at level 3 experience DLT, enrollment to level 2 would need to be re-opened to enroll an additional 3 patients at that level (with 0 or 1 DLT observed in 6 total patients) in order to declare level 2 the MTD.

4.3.3 Dose **expansion:**

The initial study design was to accrue a total of up to 50 patients (for 48 evaluable) to the study in two phases: dose escalation and dose expansion. The original design anticipated a total of 6-18 patients with advanced solid tumors or lymphoma in the dose escalation phase.9 patients were enrolled, including 6 that were treated at the MTD of 400 mg BID.

However, due to funding issues, the study will adopt a modified plan for the expansion cohort, and will perform an early analysis of preliminary efficacy after the next 6 patients are enrolled in the expansion cohort.

This **modified plan for expansion cohort**, will accrue 6 new patients with genetic alteration for early preliminary efficacy assessment, which together with 4 previously treated patients with genetic mutation will provide total of 6+4=10 patients, with genetic mutation. ORR will be computed at the first imaging (8 weeks). Preliminary efficacy will be evaluated by RECISTv 1.1. As exploratory analysis, irRECIST will be used to obtain preliminary efficacy as well. All ORR will use the first imaging time point whether RECIST or irRECIST.

Patients in this cohort will be treated at the MTD and the same treatment schedule will be followed as was done in the escalation phase**.**

The study will be considered a success if the lower 90% exact confidence bound will be > 10% , i.e. if three or more successes out of n=10 are observed.

According to the modified plan for the current trial, the study will be closed after the 6 additional patients will have been recruited.

4.4 Toxicity Management & Dose Delays/Modifications

Each patient will be assessed for the development of toxicity according to the timeframe referenced in Table 5. Toxicity will be assessed according to the NCI CTCAE V4.03.

Veliparib doses may be reduced or delayed up to 28 days according to Table 4.3 and the toxicity management guidelines in Table 4.5. Missed doses will be skipped with each cycle continuing as originally planned.

Nivolumab doses cannot be modified but can be delayed or discontinued according to Table 4.6. Missed doses will be skipped, resuming at the next scheduled treatment visit.

Since the mechanism of action of nivolumab leads to T-cell activation and proliferation, immune related adverse events (irAE) may be observed, and be similar to that of other PD-1/PD-L1 checkpoint inhibitors, and may include immune-mediated pneumonitis, enterocolitis, dermatitis, hepatitis, and endocrinopathies.

Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (i.e. infection or PD), an immune-mediated etiology should be considered for signs or symptoms of pneumonitis, enterocolitis, dermatitis, hepatitis, and endocrinopathy. In addition to the dose modifications shown in Tables 4.4 and 4.5, it is recommended that management of irAEs follow the guidelines outlined for other immune checkpoint inhibitors. These guidelines recommend the following:

- Subjects should be evaluated to identify any alternative etiology
- In the absence of clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related
- Topical or inhaled steroid therapy should be considered for low-grade events
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event
- More potent immunosuppressives (i.e. infliximab, mycophenolate mofetil, etc.) should be considered for events not responding to systemic steroids

If the investigator has any question in regards to an AE being an irAE, the investigator should immediately contact the principal investigator. Treatment modifications will not be required for AEs that are clearly not attributed to investigational drugs (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

Nausea and vomiting have been commonly observed in clinical trials with veliparib. Gastrointestinal toxicities, predominantly nausea and vomiting, were observed with veliparib as single-agent therapy and most frequently reported at higher doses (300 – 400 mg BID). Of the subjects treated with single agent veliparib at 300 – 400 mg BID dose levels, 15% required dose reduction, 5% delayed or interrupted dosing and 2% discontinued due to nausea. To optimize dose intensity and maintain subject quality of life, early initiation or prophylactic management with scheduled anti-emetic therapy (5HT-3 antagonists, metoclopramide, prochlorperazine) and/or lorazepam should be considered. In addition, it has also been observed that tolerance to these toxicities may develop over time. Management should include counseling regarding these toxicities and may include interruption of dosing, dose modification or veliparib discontinuation.

Treatment modifications may be required in the event of treatment-related toxicity. General guidelines regarding treatment modification are provided in Table 4.5 and 4.6. **Dose modifications should be implemented only if toxicities are attributed to respective drugs (nivolumab or veliparib). If there is uncertainty or overlapping toxicities, both drugs should be held and or dose modified according to the guidelines.**
All toxicities will be graded according to NCI CTCAE V4.03 (Appendix B).

Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Similarly if a male patient impregnates a female, the treating physician should be informed.

4.5 Dose Reductions

4.5.1 Veliparib

The following are guidelines for dose reductions, delays and discontinuation of veliparib monotherapy.

Subjects should have an ANC ≥ 1,500/mm^3 and a platelet count ≥ 100,000/mm^3 prior to each cycle.

For any subject who experiences Grade 3 or 4 toxicity despite optimal supportive care (with the exception of anemia, alopecia, and non-treatment related clinically insignificant laboratory abnormalities), and the toxicity is not attributable to underlying disease, the veliparib dose will be held until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 is present at the time of study entry. Interruptions of veliparib for events that are clearly not related to therapy (e.g., underlying cancer, planned surgical procedures, or acute viral illnesses), do not necessitate a dose reduction.

The dose of veliparib will be managed according to Table 4.5 below, and the dose levels in Table 4.3:

Table 4.5: Veliparib related toxicity management guidelines

Toxicity	Grade	Dose Adjustment and Management Recommendations
Hematologic Toxicities		
Anemia	1 ≥10.0 – LLN g/dL	No dose adjustment required.
	2 ≥8.0 – <10.0 g/dL	No dose adjustment required
	3 <8.0 g/dL	Dose interruption for up to 28 days until recovery to grade ≤ 2 Re-initiate veliparib at the same dose.
	4 Life threatening consequences; urgent intervention indicated	Discontinue veliparib.
Thrombocytopenia	1 ≥75 x 10^9/L	No dose adjustment required
	2 ≥50 x 10^9 /L – <75 x 10^9/L	Dose interruption for up to 28 days until recovery to ≤ 1. Re-initiate veliparib at the same dose level. If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤ 1 and reduce veliparib to the next lower dose level.
	3 ≥25 x 10^9 /L - <50 x 10^9/L	Dose interruption for up to 28 days until recovery to Grade ≤ 1. Re-initiate veliparib at the next lower dose level. If toxicity recurs at Grade 3: temporary dose interruption until recovery to Grade ≤ 1 and reduce veliparib to the next lower dose level.
	4 <25 x 10^9/L	Dose interruption for up to 28 days until recovery to grade ≤ 1. Re-initiate veliparib at the next lower dose level. If toxicity recurs at grade 4: discontinue veliparib.

Toxicity	Grade	Dose Adjustment and Management Recommendations
Absolute Neutrophil Count	1 ≥1.5 x 10^9/L	No dose adjustment required
	2 ≥1.0 - <1.5 x 10^9/L	No dose adjustment required
	3 ≥0.5 - <1.0 x 10^9/L	Dose interruption for up to 28 days until recovery to ≥1.0 x 10^9 /L. Re-initiate veliparib at the same dose level. If toxicity recurs at Grade 3: temporary dose interruption until recovery to > 1.0 x 10^9 /L and reduce veliparib to the next lower dose level.
	4 <0.5 x 10^9/L	Dose interruption for up to 28 days until recovery to ≥1.0 x 10^9 /L. Re-initiate veliparib at the same dose level. If toxicity recurs at Grade 4: temporary dose interruption until recovery to > 1.0 x 10^9 /L and reduce veliparib to the next lower dose level.
Lymphopenia	1 ≥800/mm^3	No dose adjustment required
	2 ≥500 - <800/mm^3	No dose adjustment required
	3 ≥200 - <500/mm^3	Dose interruption for up to 28 days until recovery to Grade ≤ 1. Re-initiate veliparib at the next lower dose level. If toxicity recurs at Grade 3: temporary dose interruption until recovery to Grade ≤ 1 and reduce veliparib to the next lower dose level.
	4 <200/mm^3	Dose interruption for up to 28 days until recovery to grade ≤ 1. Re-initiate veliparib at the next lower dose level. If toxicity recurs at grade 4: discontinue veliparib.
Non-Hematologic Toxicities		
Myelodysplastic syndrome/Acute Myeloid Leukemia		Discontinue veliparib
Pneumonitis		Discontinue veliparib
Embryro-Fetal Toxicity		If patient becomes pregnant, discuss with the patient the potential hazard to the fetus.
Nausea	5-HT3 antagonists (ondansetron, granisetron, palonosetron), dopamine antagonists (prochlorperazine, metoclopramide) and lorazepam were most frequently used to manage veliparib-associated nausea. Anti-emetics should be initially prescribed on a specified schedule (e.g., no PRN). Multiple concomitant anti-emetic medications may be needed in some cases for effective nausea management. Example regimens and combinations to consider include: ○ Ondansetron 4 or 8 mg BID ○ Lorazepam 0.5 mg Q8H ○ Ondansetron 8 MG Q8H; prochlorperazine 10 MG Q6H ○ Lorazepam 1 mg Q8H; prochlorperazine 10 mg Q6H; ondansetron 8 mg Q8H ○ Lorazepam 1 mg Q8H; ondansetron 8 mg Q8H; omeprazole 20 mg QD	

<table>
<tr><th>Toxicity</th><th colspan="2">Grade</th><th>Dose Adjustment and Management Recommendations</th></tr>
<tr><td></td><td colspan="3">In addition to the use of anti-emetic medications, investigators should rely on standard clinical practice and local/country guidelines for nausea management. Patients should be proactively counseled about adherence to the prescribed supportive care.

Dose Interruptions
Nausea related to veliparib can be managed with dose interruptions, if it is not responsive to anti-emetic therapy. Due to the half-life of veliparib of approximately 4 – 6 hours, symptom improvement/resolution typically occurs within 1 to 3 days of treatment interruption. If no improvement of symptoms is observed within this time frame, relationship of the event to veliparib should be re-evaluated.

Dose Reductions
Subjects experiencing nausea at the initial dose level that cannot be controlled with anti-emetics should be dose reduced. If the subject was receiving anti-emetics at the initial veliparib dose level, it is also recommended that the same anti-emetic regimen be continued at the reduced veliparib dose level until symptom resolution or significant improvement. Dose reductions to below 200 mg BID are not expected to be necessary.
If nausea does not improve sufficiently at the reduced dose, further dose reduction to the next lower dose level is recommended. Interruption of veliparib dosing may be attempted to determine if nausea is indeed related to veliparib.</td></tr>
<tr><td rowspan="5">All non-hematologic AE's attributable to veliparib in the combination treatment cycles</td><td>Grade</td><td colspan="2">Dose Adjustment and Management Recommendations</td></tr>
<tr><td>1</td><td colspan="2">No dose adjustment required. Initiate appropriate medical therapy and monitor.</td></tr>
<tr><td>2</td><td colspan="2">-Dose interruption for up to 28 days until recovery to ≤ Grade 1. Initiate appropriate medical therapy and monitor.
-Re-initiate veliparib at the same dose
-If the same toxicity recurs at Grade 2, interrupt until recovery to ≤ Grade 1. Re-inititate veliparib at the next lower dose level.</td></tr>
<tr><td>3</td><td colspan="2">-Dose interruption for up to 28 daysuntil recovery to ≤ Grade 1. Initiate appropriate medical therapy and monitor.
-Re-initiate veliparib at the same dose
-If the same toxicity recurs at Grade 2, interrupt until recovery to ≤ Grade 1. Re-inititate veliparib at the next lower dose level.
-If toxicity recurs at Grade 3, discontinue veliparib.</td></tr>
<tr><td>4</td><td colspan="2">Discontinue veliparib and treat with appropriate medical therapy</td></tr>
</table>

4.5.2 Nivolumab Toxicity Management

<table>
<tr><th colspan="3">Table 4.6: Nivolumab related toxicity management guidelines</th></tr>
<tr><th colspan="3">Immune-Mediated Reactions</th></tr>
<tr><th colspan="3">Immune-related Adverse Events (Overall Management)
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment- emergent toxicities graded per NCI CTCAE v4.03.</th></tr>
<tr><th>Grade</th><th>Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td>Grade 1</td><td>Continue dosing</td><td rowspan="2">It is recommended that management of irAEs follow the guidelines presented in this table and refer to the nivolumab investigator brochure
• Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.)</td></tr>
<tr><td>Grade 2</td><td>Hold study drug up to 28 days until resolution to ≤ Grade 1 or baseline
• If toxicity worsens</td></tr>
</table>

	then treat as Grade 3 or Grade 4 • If toxicity improves then treat at next scheduled treatment date	• In the absence of a clear alternative etiology, all events should be considered potentially immune related. • Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events • Systemic corticosteroids (e.g., prednisone or IV equivalent) should be considered for persistent low-grade or severe (Grade ≥3) events • If symptoms recur or worsen during corticosteroid tapering, increase the corticosteroid dose until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate • More potent immunosuppressives – TNF antagonist class (e.g., infliximab) or mycophenolate, etc.) should be considered for events not responding to systemic steroids after discussion with study physician • Discontinuation of study drug is not mandated for Grade3 / Grade4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.)
Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below	
Grade 4	Permanently discontinue study drug/study regimen	

Pneumonitis/ILD **See section 7.2.5 for a description of AESI's (Adverse Events of Special Interest). Such AESI's should be monitored carefully and discussed with the treating physician (PI or sub-I) to determine attribution.*		
Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		• Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below • Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
Grade 1	No dose hold required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies.	For Grade 1 (Radiographic Changes Only) • Monitor and closely follow up in 2-3 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work- up and then as clinically indicated • Consider pulmonary and infectious disease consult • Re-image at least every 3 weeks
Grade 2	Hold study drug up to 28 days until resolution to ≤ Grade 1 or baseline: • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves then treat at next scheduled treatment date	For Grade 2 (Mild to Moderate New Symptoms) • Monitor symptoms daily and consider hospitalization • Discuss with study physician and consider systemic steroids (e.g., prednisone 1- 2mg/kg/day or IV equivalent) • Reimaging as clinically indicated • If no improvement within 3-5 days, additional workup and treatment with IV methylprednisolone 1mg/kg/day should be considered • If no improvement within 3-5 days, further immunosuppressive therapy (e.g., infliximab) should be considered. • Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics • Consider pulmonary and infectious disease consult
Grade 3 or 4	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening • Discuss with study physician • pulmonary and infectious disease consult

		• Hospitalize the patient • Supportive Care (oxygen, etc.) • Initiate empiric IV corticosteroids (e.g., methylprednisolone or equivalent) at 1 to 2 mg/kg/day • If no improvement within 3-5 days, additional workup and treatment with additional immunosuppressive therapy (e.g., infliximab) should be considered • Once improving, gradually taper steroids over ≥6 weeks and consider prophylactic antibiotics
Diarrhea/ Enterocolitis		
Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		• Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits) • Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, etc.) • Steroids should be considered if an alternative etiology is not determined, even for low grade events, in order to prevent potential progression to higher grade event • Use analgesics carefully; they can mask symptoms of perforation and peritonitis
Grade 1	Continue dosing	• Close monitoring for worsening symptoms • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide
Grade 2	Hold study drug up to 28 days until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves then treat at next scheduled treatment date	• Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide • Rule out infectious etiologies prior to steroid initiation: ○ If event is persistent (> 3-5 days) or worsens, consider prednisone 0.5 to 1 mg/kg/day or IV equivalent ○ If not responsive within 3-5 days, consider IV corticosteroids (e.g., methylprednisolone IV or equivalent) at 0.5-1.0 mg/kg/day ○ If event is not responsive within 3-5 days or worsens, additional workup and treatment with IV methylprednisolone 1-2mg/kg/day should be considered • If no improvement within 3-5 days, further immunosuppressives (e.g., infliximab) should be considered • Consult study physician if no resolution to ≤ Grade 1 in 3-4 days • Once improving, gradually taper steroids over ≥4 weeks
Grade 3 or 4	Permanently discontinue study drug/study regimen	• Discuss with study physician • Monitor stool frequency and volume and maintain hydration • Urgent GI consult and imaging as appropriate • Initiate empiric IV corticosteroids (e.g., methylprednisolone IV or equivalent) at 1 to 2 mg/kg/day • If no improvement within 3-5 days, consider further immunosuppressives (e.g., infliximab). • Caution: Ensure GI consult to rule out bowel perforation and refer to label before using infliximab. Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics

Hepatitis (Elevated LFTs) **See section for 7.2.5 for a description of AESI's, defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN. Such AESI's should be monitored carefully and discussed with the treating physician (PI or sub-I) to determine attribution.*		
Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		• Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin • Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
Grade 1	Continue dosing. If it worsens, treat as Grade 2 event	• Continue LFT monitoring per protocol
Grade 2*	Hold Study drug up to 28 days until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If improves then treat at next scheduled treatment date	• Discuss with study physician if no resolution to ≤ Grade 1 in 1-2 days • Recheck LFT's in 1 to 2 days. If event is persistent (> 3-5 days) or worsens, consider prednisone 0.5 to 1 mg/kg/day or IV equivalent. • If no improvement within 3-5 days, consider additional workup and treatment with IV methylprednisolone 2-4mg/kg/day ○ If no improvement within 3-5 days after methylprednisolone, consider further immunosuppressives (e.g., mycophenolate mofetil) ○ Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
Grade 3 or higher	For elevations in transaminases ≥ 5 × ULN, or elevations in bilirubin ≥ 3 × ULN, permanently discontinue study drug/study regimen.	• Discuss with the study physician • Initiate empiric IV corticosteroids (e.g., methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day ○ If no improvement within 3-5 days, consider further immunosuppressive therapy (e.g., mycophenolate mofetil) ○ If still no further improvement within 3-5 days consider other immunosuppressive therapy per local guidelines • Hepatology consult, abdominal workup, and imaging as appropriate. • Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
Immune-Mediated Nephritis and Renal Dysfunction		
Any Grade		• Monitor and evaluate renal function tests (comprehensive chemistry panel) • Evaluate for alternative etiologies
Grade 1	Continue dosing.	• Continue comprehensive chemistry plan per protocol
Grade 2 or 3	Hold Study drug up to 28 days until resolution to ≤ Grade 1 or baseline If toxicity worsens then treat as Grade	• Discuss with the study physician • Consider empiric steroids at a dose of 0.5 to 1 mg/kg/day or IV equivalent. • Consider renal biopsy with nephrology consult

	3 or Grade 4 • If improves to baseline then treat at next scheduled treatment date	• Monitor creatinine every 2-3 days
Grade 4	Permanently discontinue study drug/study regimen	• Discuss with the study physician • Nephrology consult • Monitor creatinine daily • Administer corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) serum creatinine elevation and permanently discontinue. For severe (Grade 3) withhold and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue.
Rash (excluding Bullous skin formations)		
Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED**
Grade 1	Continue dosing.	Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug up to 28 days until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves then resume administration at next scheduled dose	• Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) • Consider moderate-strength topical steroid • If no improvement of rash/skin lesions occurs within 3-5 days or is worsening, discuss with study physician and consider systemic steroids prednisone 0.5 to 1 mg/kg/day or IV equivalent • Consider dermatology consult • Consider skin biopsy if persistent for >1-2 weeks or recurs
Grade 3**	Hold study drug up to 28 days until resolution to ≤ Grade 1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 28 days, then permanently discontinue Study drug	• Discuss with study physician • Consider hospitalization • Monitor extent of rash [Rule of Nines] • Consult dermatology • Consider skin biopsy (preferably more than o as clinically feasible. • Initiate empiric IV corticosteroids (e.g., methylprednisolone IV or equivalent) at 1 to 2 mg/kg/day • Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics ***If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN*
Grade 4**	Permanently discontinue	

	study drug/study regimen	*is diagnosed, permanently discontinue I-O therapy.*
Endocrinopathy (e.g. hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)		
Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		• Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. • Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) • Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. • If a subject experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
Grade 1	Continue dosing.	For Grade 1: (including those with asymptomatic TSH elevation) • Monitor patient with appropriate endocrine function tests • If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
Grade 2	Hold study drug up to 28 days until resolution to ≤ Grade 1 • If worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2: (including those with symptomatic endocrinopathy) • Discuss with study physician • Initiate hormone replacement as needed for management • Evaluate endocrine function, and as clinically indicated, consider pituitary scan • For subjects with abnormal endocrine work up, consider short-term, high-dose corticosteroids (e.g., methylprednisolone or IV equivalent) with relevant hormone replacement (e.g., levothyroxine, hydrocortisone, or sex hormones) • For subjects with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.
Grade 3	Hold study drug up to 28 days until endocrinopathy symptom(s) are controlled. Resume study drug/study regimen administration if controlled at the next scheduled dose.	• Discuss with study physician • Initiate empiric IV corticosteroids (e.g., methylprednisolone IV or equivalent) at 1 to 2 mg/kg/day • Administer hormone replacement therapy as necessary • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity • Consult endocrinologist • Once improving, gradually taper immunosuppressive steroids over ≥4 weeks
Grade 4	Permanently discontinue study drug/study regimen	
Immune mediated Neurotoxicity (except Myasthenia Gravis and Guillain-Barre)		
Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		• Subjects should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and

		medications, etc.) • Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness) • Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) • Symptomatic treatment with neurological consult as appropriate
Grade 1	Continue dosing	
Grade 2	• For acute motor neuropathies or neurotoxicity, hold study drug up to 28 days until resolution to ≤ Grade 1 • For sensory neuropathy/neuro pathic pain, consider holding study drug up to 28 days until resolution to ≤ Grade 1 or baseline. ○ If toxicity worsens then treat as Grade 3 or Grade 4 ○ If toxicity improves then treat at next scheduled treatment date	• Discuss with the study physician • Consider Neurology Consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) • Consider systemic steroids prednisone 1- 2mg/kg/day or IV equivalent at 0.5 to 1 mg/kg/day • If no improvement within 3-5 days, consider additional workup and treatment with additional immunosuppressive therapy (e.g. IVIgG)
Grade 3 or higher	Permanently discontinue study drug/study regimen	• Discuss with study physician • Consult Neurology Consult • Consider hospitalization • Consider empiric IV corticosteroids (e.g., methylprednisolone or IV equivalent) at 1 to 2 mg/kg/day • If no improvement within 3-5 days, consider additional workup and treatment with additional immunosuppressants (e.g. IVIgG) • Once stable, gradually taper steroids over ≥4 weeks
Immune- mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		
Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		• The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability

		• Subjects should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune- mediated peripheral neuromotor syndromes can be particularly challenging in subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. o Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult • Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation • Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapheresis (or IVIgG, as an alternative)
Grade 1	Continue dosing.	• Discuss with the study physician • Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above • Consider a neurology consult unless the symptoms are very minor and stable
Grade 2	Hold study drug up to 28 days until resolution to ≤ Grade 1 or baseline Permanently discontinue study drug if it does not resolve to ≤ Grade 1 within 28 days or if there are signs of respiratory insufficiency or autonomic instability	Grade 2 : Moderate • Discuss with the study physician • Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above • Obtain a Neurology Consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIgG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase [17] inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.

		• Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative).
Grade 3 or higher	Permanently discontinue study drug/study regimen.	For severe or life threatening (Grade 3 or 4) events: – Discuss with study physician – Recommend hospitalization – Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapharesis or IVIgG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase [17] inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative).
Infusion- related reactions		
Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		• Management per institutional standard at the discretion of investigator • Monitor subjects for signs and symptoms of infusion- related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event (up to 4 hours) Subsequent infusions may be	• Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator • Consider premedication per institutional standard prior to subsequent doses

	given at 50% of the initial infusion rate	
Grade 3 or 4	Permanently discontinue study drug/study regimen.	Manage severe infusion- related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)
Non- immune Mediated Reactions		
Grade	**Dose Modifications**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard.
1	No dose adjustment.	Treat accordingly as per institutional standard
2	Hold study drug up to 28 days until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug up to 28 days until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days AND resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration at next scheduled dose. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms	Treat accordingly as per institutional standard

	and as per Investigator's clinical judgment and in consultation with the sponsor)	

4.6 Concomitant Medications/Treatments

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), taken during the study will be recorded.

Investigators may prescribe concomitant medications or treatments (eg, acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in the bulleted list below. Patients may continue baseline medications that were initially deemed appropriate by the investigator at screening.

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study:

- Any investigational anticancer therapy (within 28 days prior to registration)
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy on non-target lesions only), immunotherapy, biologic or hormonal therapy for cancer treatment. (within 14 days prior to registration, 28 days for systemic chemotherapy)
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-alpha blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. Temporary courses of corticosteroids for treatment of underlying or concurrent illness or in the setting of palliative radiotherapy may be permitted upon discussion with the PI.
- Live attenuated vaccines during the study within 28 days prior to registration through 180 days after the last dose of both drugs
- Herbal and natural remedies (within 14 days prior to registration)

4.7 Duration of Therapy (for both dose- escalation and dose- expansion phase)

Patients may continue with treatment until any of the following occur:

- Disease progression, unless the patient meets criteria for continuing treatment beyond progression. See section 4.7.1 for details.
- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from either study treatment or the study as a whole
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures)

4.7.1 Continuation of Investigational Therapy after Progression

In the event of an initial assessment of PD (based on RECIST Version 1.1), a subject may continue to receive the assigned study treatment as long as none of the criteria listed below are met.

1. Confirmed PD: An initial assessment of PD by RECIST 1.1 or Lugano criteria will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later (see section 6.1.7 & Appendix C, respectively). If any subsequent tumor assessment shows progression per RECIST v1.1 or Lugano criteria in the overall tumor burden (the sum of diameters of target lesions and new lesions), when compared to the initial PD assessment (the sum of diameters of target lesions and new lesions), then PD is confirmed.
2. Meets any of the other investigational product discontinuation criteria (Section 4.6)
3. Clinical symptoms or signs indicating significant PD, for example the benefit-risk ratio of continuing therapy is no longer justified.
4. Decline in ECOG performance status.
5. Threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention, and continuation of study therapy would prevent institution of such intervention.

4.8 Duration of Follow Up (for both dose- escalation and dose- expansion phase)

After patients come off treatment they will be followed up at 3, 6, 9, 12 months and then every 6 months for 3 years (from the start of the treatment) for survival and progression of disease via either clinic visits or phone calls.

4.9 Removal of Subjects from Study Treatment and/or Study as a Whole (for both dose- escalation and dose- expansion phase)

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression
- Patient experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)

Patients who are permanently discontinued from receiving investigational product will be followed for disease progression and safety, including the collection of any protocol- specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or administered subsequent therapy. All subjects will be followed for survival and disease progression. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

4.10 Patient Replacement

If a patient is enrolled in the study but comes off study before cycle 1 day 1 of

treatment, the patient may be replaced.

5.0 STUDY PROCEDURES

Table 5: Study timeline

	Screening[a,b,c]	Induction (7 days)[c]	Cycle 1 (Cycle=28 days)			Cycle 2-4		Cycle 5 +	End of Treatment[o]	Follow Up[p]
		D1	D1	D8	D15	D1	D15	D1		
Study window				±1 day	±1 day	±3 days	±3 days	±3 days	±7 days	q3months
Informed Consent	X									
Medical History	X		X	X		X		X	X	
Physical Exam	X	X	X	X	X	X	X	X	X	
Vitals signs[d,l]	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X	X	X			X	X	X	
AE reporting[q]		X	X	X	X	X	X	X	X[q]	X[q]
Concomitant Medications		X	X	X	X	X	X			X
CMP[e]	X	X	X	X	X	X	X	X	X	
CBC with differential [f]	X	X	X	X	X	X	X	X	X	
Pregnancy test [g]	X[g]		X							
Thyroid function test[h]	X									
PT/INR	X[i]									
Imaging (CT or MRI)[j]	X					X[j]		X[j]	X	
Tumor biopsy[k]	X									
Mutation testing	X[r]									
Blood for Tumor Markers[l]		X	X			X[l]			X	
Nivolumab infusion[m]			X		X	X	X	X[m]		
Veliparib[n]		X	X			X		X		
Survival										X

a. Informed consent must be signed ≤ 30 days before registration. If signature is outside that window the patient must sign a new consent.
b. Pre-study H&P and all labs must be ≤ 14 days before registration. Tumor measurements and radiologic evaluations must be ≤28 days before registration.
c. The maximum time interval between registration and the first dose of study drug will be 14 days.
d. Vital signs include pulse and blood pressure.Weight will be recorded at baseline. Height will be recorded at baseline only.
e. Serum Chemistry will include calcium, chloride, magnesium, phosphorus, creatinine, sodium, potassium, blood urea nitrogen, bicarbonate, glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, and total protein.

f. CBC: Performed pre-dose at each treatment visit (Day 1 & 15 of Cycles 1-4, and Day 1 of Cycle 5+). For patients experiencing significant drop in WBCs or platelets felt related to treatment, CBCs should be obtained more frequently (weekly or more frequently) to assess timing for retreatment or need for transfusion support.

g. Serum or urine test only for women of childbearing potential; must be tested within 7 days prior to registration as well as C1D1 (within 24 hours prior to nivolumab treatment).

h. Thyroid function tests will include thyroid stimulating hormone (TSH) with reflexfree T4. This will be done at baseline then only as clinically indicated thereafter.

i. PT/INR is required at baseline (≤ 28 days prior to registration) for patients on anticoagulants.

j. Imaging (either CT scan or MRI and PET if applicable) will be performed at screening, ≤28 days prior to registration. The same modality used at baseline should be used throughout for imaging. CT imaging will include chest, abdomen, and pelvis. Neck will be included only if measurable lesions are present. Scans will then take place every 2 cycles (8 weeks) starting with Cycle 3 Day 1 (- 7 days). Tumor measurements will be performed using RECIST 1.1 or Lugano classification. Progressive Disease (PD) must be confirmed by repeat scan within 8 weeks.

k. Patients will undergo a fresh tissue biopsy prior to study enrollment, unless deemed to be clinically inappropriate per PI. If a fresh biopsy is not feasible, an archival tissue sample should be obtained (a cell block is preferred, however 15 unstained slides will suffice). Tissue should be obtained by any means possible, but patients will not be excluded from the study if tissue is not available. The samples will be obtained for correlative studies – see section 9.0 and separate lab manual for details.

l. Study labs will be collected for tumor markers pre-dose on Induction Day 1, C1D1, C3D1, and at the End of Treatment visit. See section 9.0 and separate lab manual for more details.

m. Nivolumab will be administered as follows:

   Cycles 1-4: given at a fixed dose of 240mg IV over 30 minutes (-5 / +15 minutes) every 2 weeks

   Starting with Cycle 5 Day 1: 480mg IV over 30 minutes (-10 / +15 minutes) every 4 weeks until disease progression, intolerability, or withdrawal of consent.

   Vital signs will be monitored prior to, throughout, and after the nivolumab infusion according to Table 4.2.

n. Veliparib will be taken orally at the assigned dose twice a day until disease progression, intolerability, or withdrawal of consent. It will be initiated as monotherapy during a 7-day induction period. Starting with Cycle 1 Day 1, veliparib will be given twice daily in combination with scheduled nivolumab infusions. Veliparib may be taken with or without food. Patients will be given a drug diary to maintain for compliance. Veliparib dosing may take place independently of nivolumab. On the day of a study visit, lab values should be checked against sections 4.4 and 4.5 for continued dosing.

o. The end of treatment visit should occur 30 days after the last dose of study treatment (± 7 days) or before starting another line of treatment, whichever comes first.

p. After patients come off treatment they will be followed up at 3, 6, 9, and 12 months and then every 6 months for 3 years for survival and progression of disease via either clinic visits or phone calls.

q. Adverse events will be followed from the time of consent until 30 days after treatment discontinuation (100 days for SAE's).

r. For patients in the expansion phase of the study, mutation testing is required within 1 year of registration (see 3.1.6 for details)

6.0 ENDPOINT ASSESSMENT

6.1 Solid tumors

6.1.1 Response will be evaluated using the modified Response Evaluation Criteria in Solid Tumors, based on RECIST v1.1.[35]

6.1.2 Clinical evaluation and tumor assessments will be performed as indicated in Table 6, based on physical examination and radiologic evaluation.

6.1.3 Any lesion that has been previously treated with radiotherapy should be considered as a non-target lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a target lesion.

6.1.4 Definitions for measurable and non-measurable lesions, and criteria for response, should be based on RECIST v1.1.

6.1.5 Measurable Disease

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

6.1.6 Non-measurable Disease

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

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

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

6.1.7 Response criteria

- **Complete Response (CR)** - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.
- **Partial Response (PR)** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Objective Response Rate** – the sum of complete responses and partial responses
- **Progressive Disease (PD)** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- **Stable Disease (SD)** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.2 Lymphoma

6.2.1 Response will be evaluated, using the Lugano classification for assessment of Lymphoma.[36] See Appendix C for specific response assessment criteria.

6.2.2 Clinical evaluation and tumor assessments will be performed periodically, as shown in Table 6, based on evaluation of spleen and liver, physical examination for superficial disease and B symptoms, radiologic evaluation, and appropriate laboratory studies.

6.2.3 A lesion is categorized based on the location as either a nodal lesion or an extranodal lesion if it is located in organs other than lymph nodes or nodal mass, but including spleen and liver.

6.2.4 All tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

- Measurable nodal and extranodal lesions:
  A lesion will be called measurable if it can be measured accurately in 2 perpendicular dimensions and:
  -For nodal lesion, if the long axis is >15 mm, regardless of the length of the short axis
  -For extranodal lesion, if the long and short axes are ≥10 mm.
  Patients should have at least one measurable nodal lesion greater than 20 mm in the long axis.
  In cases where the patient has no measurable nodal lesions greater than 20 mm in the long axis at screening, then the patient must have at least one measurable extranodal lesion.

6.2.5 Classification of lymph nodes

- Lymph nodes are classified according to their size and/or relationship to the disease:
  -A lymph node meeting the measurability requirement, but with long axis > 15 mm (e.g. short axis cannot be measured accurately) will constitute a non-measurable nodal lesion.
  -A lymph node not meeting the measurability criteria, but with a size of 11 mm to 15 mm in the long axis and >10 mm in the short axis will be checked for relationship to disease:
  -If it is thought to be disease related, it will constitute a non-measurable nodal lesion
  -If it is not thought to be disease related, it will constitute an abnormal lymph node, but not a lesion.
  All other lymph nodes will be considered normal and will not constitute nodal lesions.

6.2.6 Criteria for normalization of lesions

- The normalization of lesions is defined as follow:
  -A measurable nodal lesion must become ≤ 15 mm in long axis to be considered normalized.
  -A non-measurable nodal lesion must decrease to ≤10 mm in the short axis and be ≤ 15 mm in long axis to be considered normalized.
  -An extranodal lesion must disappear completely (assigned a size of 0 mm x 0 mm) to be considered normalized.

6.3 Immune-related RECIST (irRECIST)

6.3.1 In addition to above, tumor response for both solid tumors and lymphoma will be assessed by the irRECIST for investigational purposes, not assessment of primary objective.[37] In RECIST v1.1, the appearance of new lesions indicates PD. However, in irRECIST, new measurable lesions are incorporated in the tumor burden, which is used to determine irPD, immune-related partial response (irPR), and immune-related complete response (irCR). New nonmeasurable lesions preclude irCR. Under RECST v1.1, there is no confirmation for PD. Under irRECIST, responses and irPDs must be confirmed by consecutive scans at least 4 weeks apart, assuming no clinical deterioration. We will define immune-related clinical benefit rate as immune-related stable disease (irSD), irPR, or irCR.

Table 6: Immune-related Response Evaluation Criteria: Overall Response

Tumor Burden (Baseline and New)	Non-Target Lesions (Baseline and New)	Response
Disappearance of non-nodal lesions. All pathologic lymph nodes <10 mm (short axis)	Disappearance of non-nodal lesions. All pathologic lymph nodes < 10 mm (short axis)	irCR
≥30% decrease from baseline	Any	irPR
≥20% increase from nadir and at least 5 mm	Any	irPD
Neither sufficient decrease to qualify for PR, nor sufficient increase to qualify for PD	Any	irSD
Disappearance of all non-nodal lesions. All pathologic lymph nodes <10 mm	Any other than disappearance of all non-nodal lesions and reduction of pathologic lymph nodes <10 mm	irPR
Not all evaluated	Any	irNE

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irNE = immune-related not evaluable; irSD = immune-related stable disease;
-Tumor burden is the sum of single diameters (short axis for nodal lesions, longest diameter for other lesions) for the target lesions. In subsequent scans, the diameters of new measurable lesions are added to the tumor burden.
-Best overall response based on 2 consecutive measurements at least 4 weeks apart.

6.4 Primary Endpoint

The primary objective is to identify maximum tolerated dose (MTD) for the combination treatment of nivolumab and veliparib.
The MTD will be defined as the highest dose that causes dose-limiting toxicities (DLTs) in <2 of 6 patients and is determined for this study..

6.5 Secondary Endpoints

6.5.1 Secondary endpoints include the number, frequency, and severity of adverse events (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE version 4.03) will be recorded.

6.5.2 To evaluate the efficacy of treatment with nivolumab and veliparib in this population by objective response rate (ORR, defined as partial response (PR) + complete response (CR)), clinical benefit rate (CBR, defined as stable disease (SD) for ≥12 weeks, PR, + CR), and Progression Free Survival (PFS, defined as the time from treatment initiation to documented disease progression) using RECIST criteria v1.1 or the Lugano 2014 classification for assessment of Lymphoma[36].

For the preliminary efficacy analysis, ORR and other measures will be computed separately for patients with and those without genetic mutations, at the first imaging (8 weeks). Preliminary efficacy will be evaluated by RECISTv 1.1. As exploratory analysis, irRECIST will be used to obtain preliminary efficacy as well. All ORR will use the first imaging time point whether RECIST or irRECIST.

6.5.3 To evaluate efficacy of treatment with nivolumab and veliparib in this population by ORR, CBR, and immune-related PFS (irPFS) using irRECIST criteria.

6.5.4 To evaluate Overall Survival (OS) in this population at 3 years from the start of treatment. OS is defined as the time from treatment initiation until death due to any cause.

6.5.5 To evaluate the proportion of patients alive and progression free at 24 weeks in this population.

6.6 Exploratory Endpoints

6.6.1 Biomarkers predictive of response include assessment of tissue-based immunohistochemical expression of PD-L1; TILs; peripheral T cell subpopulations; changes in tissue and peripheral T cell receptor sequencing, HLA genotype, and immune-related candidate gene signatures at baseline.

6.6.2 To demonstrate the pharmacodynamic effects of veliparib and nivolumab on biomarkers including PD-L1, TILs, T cell subpopulations, and T cell receptor genotype.

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires high level monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner from the time of consent until 30 days after treatment discontinuation (100 days for SAE's) at scheduled times during a trial (see Section 5 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign

(including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 100 days after the last administration of study drug, must be reported upon discovery or occurrence.
An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event itself.
- **Is *life-threatening*.**
  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 *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- **Results in *persistent or significant disability or incapacity*.**
- **Is a *congenital anomaly/birth defect.***
- **Is an *important medical event*.**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a

serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Exceptions to AE and SAE definitions

Generally speaking, any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, as described above. Likewise, any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE. However, for the purposes of this study, neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as AEs or SAEs under the following circumstances:

- Hospitalization or prolonged hospitalization is for a diagnostic or elective surgical procedure for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization is required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization is required for study-directed therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the principal investigator.
- Hospitalization or prolonged hospitalization is due to social reasons (i.e. awaiting transport home).
- Pregnancy is not considered a serious adverse event, any patients who become pregnant during the study should discontinue the study immediately. Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within 30 days or five half-lives after the treatment period, whichever is longer.

7.2.5 Adverse Event of Special Interest (AESI)

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring. An AESI may be serious or non-serious. The close monitoring and discussion of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product. The following are considered to be AESI:

- **Hepatic Function Abnormality**
  Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

  If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE.

  If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the

AE/SAE. Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal". The investigator will review the data with the PI. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

- **Pneumonitis**
  Adverse events of pneumonitis are also of interest, as pneumonitis has been observed with anti-PD-1 and anti-PD-L1 mAbs. Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

7.2.6 Other events requiring immediate reporting

Overdose

An overdose is defined as a patient receiving a dose of investigational product in excess of dose detailed in this protocol.

Any overdose of a study patient with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event. If the overdose results in an AE, the AE must also be recorded on the AE eCRF. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE. The investigator will use clinical judgment to treat any overdose.

Pregnancy

Pregnancy in a female patient who has received investigational product is required to be reported within 24 hours of knowledge of the event.

Patients who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. The pregnancy will be followed for outcome of the mother and child (including any premature terminations).

7.2.8 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the appendices. Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study's phase and risk level, as outlined in the DSMP.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must

also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned Quality Assurance Monitor (QAM) within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University) and to participating sites whom have reporting responsibilities to Northwestern University. Participating sites should follow their local IRB guidelines for reporting to their local IRBs. .

- Any death of an NU subject that meets the NU IRB's reporting criteria will be promptly reported .
- Any death or unanticipated problem of a non-NU subject should be reported to the lead site promptly. Death and other unanticipated problems that meet NU IRB reporting criteria should be submitted to the NU IRB by the lead site per their posted timelines. .
- Information pertaining to an NU subject that fits into any of the categories listed on the Reportable New Information page will be reported to the NU IRB per their posted timelines.

7.3.3.3 Reporting to the FDA (completed by the NU QAM)

The NU QAM will handle all FDA reporting in accordance with the following:
The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-

threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.3.4 Reporting to BMS and Abbvie

SAE reports (including death by any cause), up to 100 days post study drug discontinuation, regardless of attribution will be reported within 24 hours to BMS Global Safety and Abbvie (using the NU CRO SAE Form and referencing the BMS and Abbvie study numbers, CA 209-783 and A15-831, respectively). The assigned study coordinator will facilitate all reporting to BMS Global Safety and Abbvie and email QA a copy of the report upon completion.

BMS Global Safety can be notified at:

Email Address: Worldwide.Safety@BMS.com
Facsimile Number: 609-818-3804

Abbvie can be notified at:

Email Address: PPDINDPharmacovigilance@abbvie.com

8.0 DRUG INFORMATION

8.1 Veliparib (generic name)

8.1.1 Other names

Chemical Name: 1H-Benzimidazole-7-carboxamide, 2-[(2R)- 2-methyl-2-pyrrolidinyl]-
Associated Name(s): 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimadazole-4-carboxamide,
ABT-888, A-861695.0

8.1.2 Classification - type of agent

Veliparib is a targeted PARP1 and PARP2 inhibitor

8.1.3 Mode of action

Veliparib is a poly (ADP-ribose) polymerase (PARP) inhibitor, an enzyme involved in DNA repair.

8.1.4 Storage and stability

Capsules should be stored in the original container at 15° to 25°C (59° to 77°F). All clinical supplies of the oral solution should be stored in the original container at 15° to 25°C (59° to 77°F) and protected from light. Extended release tablets should be stored in the original container at 15° to 25°C (59° to 77°F).

8.1.5 Protocol dose specifics

Dose escalation will start with veliparib 300 mg PO twice daily (level 1). The 3+3 design (per section 4.2) will be utilized to find the MTD. MTD dose will be used for the expansion cohort

8.1.6 Preparation

Immediate Release Capsule

Dosage Form: Immediate release capsules
Strength: 10, 20, 40, 50, and 100 mg
Components: Microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. May contain FD&C blue #1, FD&C yellow #6, or FD&C yellow #5

Oral Solution

Dosage Form: Oral solution
Strength: 5 and 10 mg/mL
Component: A-861695.0, water, citric acid, sodium citrate, xylitol, sodium benzoate

Extended Release Tablet

Dosage Form: Extended release tablets
Strength: 200 mg
Component: Hypromellose, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, iron oxide red, iron oxide black, may contain anhydrous citric acid and/or mannitol

8.1.7 Route of administration for this study

The capsules will be taken by mouth (PO).

8.1.8 Incompatibilities

Veliparib is not a potent inhibitor nor inducer of cytochrome P450s.

8.1.9 Availability & Supply

Investigational products will be supplied by AbbVie in containers with identical appearances in coded kits for each product respectively. Each investigational product kit has a unique number that is printed on all labels within the kit (i.e., the outer carton label and the label of each container within the carton). Each carton is labeled with the same unique sequence number range. Veliparib will be supplied in capsule form.

Veliparib will be provided to Northwestern University by AbbVie, Northwestern University will request veliparib submitted via email indicating the amount of bottles required to the contact below:.

Email: IISoncologysupport@abbvie.com

Please allow approximately 10 days for drug delivery.

8.1.10 Side effects

At present, there have been approximately 3700 patients exposed to veliparib (ABT-888). Of these, approximately 250 patients were exposed to veliparib as a single agent

In these studies, the most frequently reported adverse events (≥10%) of veliparib were:

- Feeling sick to your stomach (Nausea) (72.7%)
- Feeling tired (52.2%)
- Decreased red blood cells or hemoglobin (the part of blood that carries oxygen to your body) (41.4%)
- Vomiting (41.4%)
- Decreased white blood cells; decreased lymphocytes and decreased neutrophils (blood cells that help fight infections) (decreased white cells

29.7%, decreased lymphocytes 28.1% and neutrophil count decreased 20.9%)
- Decreased appetite (22.5%)
- Diarrhea (21.7%)
- Decreased platelets (blood cells which help clot blood and prevent bleeding) (21.3%)
- Constipation (18.5%)
- Stomach pain (15.7%)
- Headache (14.9%)
- Feeling dizzy (14.9%)
- Increases in liver enzymes (AST and Blood alkaline phosphatase increased), that can indicate liver injury or changes in liver function (12.9% and 9.6%)
- A change in the sense of taste (12.0%)
- Difficulty falling asleep and/or staying asleep (11.6%)
- Increased blood sugar (11.2%)

Less frequent (<10%), but potentially severe events include:
- Dehydration (5.6%)
- Seizures (1.2%)

Uncommon (<1%), but medically important event:
- Secondary malignancy*

Rare (<0.1%), but medically important event:
- Myelodysplastic syndrome (MDS)*

* These events were not seen in Veliparib Monotherapy studies. The percentage noted is from all subjects treated with Veliparib.

8.1.11 Nursing implications
Veliparib will be administered as an oral capsule. Subjects will self-administer the morning dose of veliparib and the evening doses of veliparib approximately 12 hours after the morning dose with or without food in the same calendar day. Veliparib dose should be followed by a glass of water (approx. 240 mL). It is recommended that if a subject misses a scheduled dose of veliparib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose but should wait for the next regularly scheduled dose.

8.1.12 Return and Retention of Study Drug
All unused investigational products will be returned to an AbbVie-authorized depot or disposed of upon authorization by AbbVie according to the investigational site policy.

8.2 Drug name: Nivolumab

8.2.1 Other names
ONO-4538, BMS-936558, or MDX1106, Opdivo

8.2.2 Classification - type of agent
Human IgG4 anti-PD-1 monoclonal antibody

8.2.3 Mode of action
Nivolumab receptor-blocking antibody which acts as an immunomodulator by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on

activated T cells.

8.2.4 Storage and stability

Nivolumab solution for infusion is a sterile, non-pyrogenic single-use, isotonic aqueous solution. Vials must be stored in a secure, limited-access location at 2 to 8 degrees C (36 to 46 degrees F) and protected from light, freezing, and shaking. The product is a clear to opalescent solution, which may contain proteinaceous and extraneous particulates. The product is intended for IV administration. The drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Opened or accessed vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered.

After preparation, store the Nivolumab infusion either:

- at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.
- Do not freeze.

8.2.5 Protocol dose specifics

A fixed dose of 240 mg IV every 2 weeks for 4 cycles; 480mg IV every 4 weeks thereafter

8.2.6 Preparation

- Nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.
- Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white amorphous particles.
- Mix by gently inverting several times. Do not shake.
- Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag.
- If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall.
- Do not enter into each vial more than once. Do not administer as an IV push or bolus injection.
- Nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL.

8.2.7 Route of administration for this study

Intravenous infusion. Do not administer as an IV push or bolus injection. Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter.

8.2.8 Incompatibilities

No incompatibilities between nivolumab injection and polyvinyl chloride (PVC), DEHP (di[2-ethylhexyl]phthalate), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed. Nivolumab should not be infused concomitantly in the same intravenous line with other medicinal products.

8.2.9 Availability & Supply

Nivolumab will be supplied by the study as 100 mg/Vial (10 mg/mL) clear to

opalescent, colorless to pale yellow liquid in 10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals. May contain particles.

A supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS. The first request may take place upon screening of the first patient. The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is imperative that only drug product designated for this protocol number be used for this study.

Drug re-supply request form should be submitted electronically 10 business days before the expected delivery date. Deliveries will be made Tuesday through Friday. When assessing need for resupply, keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific.

8.2.10 Side effects

Below are safety data from 268 subjects with unresectable or metastatic melanoma and 117 patients with metastatic squamous NSCLC who received nivolumab alone. Related side effects reported in subjects receiving nivolumab alone were:

Very Frequent – Expected to occur in more than 20% of people (more than 20 out of 100 people): Fatigue (50%), Dyspnea (38%), Musculoskeletal pain (36%), Rash (21%), Increased AST (28%), Increase alkaline phosphatase (22%), Hyponatremia (25-38%)

Frequent - Expected to occur in 10% to 20% of people (10 to 20 out of 100 people): Pruritus (19%), Cough (17%), URI (11%), Peripheral edema (10%), Increased ALT (16%), Hyperkalemia (15%)

Not Frequent – Expected to occur in less than 10% of people (less than 10 out of 100 people): ventricular arrhythmia, iridocyclitis, infusion-related reactions, increased amylase, increased lipase, dizziness, peripheral and sensory neuropathy, exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis

Deaths thought to be related to nivolumab when given alone were reported in approximately 0.5% of subjects treated (approximately 1 out 200 people).

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab Investigator Brochure and appendix D of this protocol.

8.2.11 Nursing implications

Each dose of investigational product should be administered using the following

guidelines:

1. Investigational product must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein or central line. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion-related reaction due to the administration of the solution at low temperatures.
2. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available. Investigational product must not be administered via IV push or bolus but as a slow IV infusion. The entire content of each IV bag will be infused using an infusion pump.
3. The infusion lines should be attached only at time of use. Lines used for infusion during dose administration will need to be equipped with 0.22- or 0.2-µm in-line filters.
4. The duration of the investigational product administration will be recorded.

Nivolumab will be administered as an IV infusion over approximately 30 minutes or 60 minutes (for 240mg or 480mg dosing, respectively). Vitals will be measured before, during, and after each infusion (see section 4.2 for details). When an IV bag is used for the infusion, the IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice).

8.2.12 Return and Retention of Study Drug

The clinical study team will be responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to and returned not used by the subjects and the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. A copy of the drug destruction certificate must be retained at the end of the study for submission to BMS.

Table 8 – Nivolumab Product Description:(Other names = MDX-1106, ONO-4538, anti-PD-1

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01)* for Injection	100 mg (10 mg/vial)	10mL vial	5 vials per carton / open label	Clear to opalescent, colorless to pale yellow liquid. May contain particles	**BMS-936558-01 Injection** must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing

8.3 Combination of Veliparib and Nivolumab

8.3.1 Side Effects when veliparib and nivolumab are given together

To our knowledge, no clinical trials combining veliparib and nivolumab have

been reported. A phase 1b, open label, dose escalation and expansion study to investigate the safety, pharmacokinetics and antitumor activity of another anti-PD-1 monoclonal antibody BGB-A317 in combination with the PARP Inhibitor BGB-290 in Subjects with advanced solid tumors is currently recruiting in Australia, with currently no other sites recruiting outside of Australia (ClinicalTrials.gov Identifier: NCT02660034). Possible side effects associated with the drug combination will hence be carefully monitored in the current study and information updated as more data becomes available.

9.0 CORRELATIVES/SPECIAL STUDIES

9.1 Sample Collection Guidelines

Tissue: A fresh tissue biopsy of the primary tumor or a metastatic site at baseline will be collected if appropriate. If a fresh tissue biopsy is not feasible, archival tissue should be collected (if available, cell block preferred or 15 unstained slides) by any means possible. Unavailability of tissue will not exclude patients. Fresh tissue biopsies will be performed using an image-guided core needle at the aforementioned time points according to institutional practice. Tumor samples will be stored and may be used for additional correlative studies at a later date such as, but not limited to, immunohistochemistry, tumor mutation analysis, and proteomic analysis.

Blood: Blood samples will be drawn pre-dose on Induction Day 1, C1D1, C3D1, and at the End of Treatment visit. See lab manual for further details and tube types.

9.2 Sample Processing, Storage, and Shipment

Refer to the lab manual for sample collection, processing, storage, and shipment information.

9.3 Assay Methodology

9.3.1 Biomarker Analysis (Tissue and Blood)

Formalin-fixed, paraffin-embedded tumor specimens will be stained with anti-PD-L1 monoclonal antibodies. PD-L1 will be scored as a percentage by two independent pathologists who are unaware of clinical data. PD-L1 staining as a predictive measure will be explored at various thresholds of positivity.

TILs (CD8+, CD4+, nuclear FOXP3+) will be quantified by immunohistochemistry and assessed on hematoxylin and eosin stained tumor sections. TIL subsets will be classified as intraepithelial (iTILs) or stromal (sTILs), where iTILs are defined as the percentage of lymphocytes in direct contact with tumor cells, and sTILs are defined as the percentage of lymphocytes relative to the tumor stroma. Scoring, as a continuous percentage, will be performed by two independent pathologists who are unaware of clinical data.

Population of CD4+, CD8+, and regulatory T cells (CD4+/CD25+) will be counted by cell sorting of PBMCs. Expression of CD4, CD8, and FOXP3 will be also examined in the tumor tissues to estimate relative ratio between T helper cells, killer T cells, and regulatory T cells.

Blood will be collected at C1D1, C3D1, and the End of Treatment visit for biomarker analysis.

9.3.2 Flow Cytometry (Blood)

Lymphocyte subsets (CD3, CD4, CD8, CD19, and CD56) will be analyzed at C1D1,

C3D1, and EOT according to absolute cell numbers per microliter of whole blood, percent representation among all lymphocytes, and coexpression of the activation markers CD25, HLA-DR, and CD45RO using automated flow cytometric techniques at the Zhang laboratory, at Northwestern University,
Address:
Bin Zhang's Laboratory
300 E. Superior St.
Tarry Building 4-726
Chicago, IL 60611
Ph: 312-503-2435
Email: Bin.Zhang@northwestern.edu

Please refer to laboratory manual for more details

9.3.3 Immune and Genomic Biomarkers

To assess the dynamic change in both immune and genomic biomarkers in blood that may correlate with response to veliparib. Blood will be collected prior to starting veliparib (Induction Day 1) and pre-dose on C1D1.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This will be a phase I/IB study of nivolumab and veliparib in patients with advanced solid tumors and lymphoma harboring mutations in selected DNA repair genes.

The **primary endpoint** is to evaluate the toxicities and tolerability of nivolumab and veliparib and to identify the maximum tolerated dose for combination treatment.

Secondary endpoints include ORR according to irRECIST, PFS at 24 weeks, time until death or disease progression, and to identify additional predictive biomarkers and resistance mechanisms to treatment using additional genetic and immunology-based assessment platforms. For the preliminary efficacy analysis, ORR will be computed at the first imaging (8 weeks). Preliminary efficacy will be evaluated by RECISTv 1.1. As exploratory analysis, irRECIST will be used to obtain preliminary efficacy as well. All ORR will use the first imaging time point whether RECIST or irRECIST.

Exploratory endpoints include biomarkers predictive of response include assessment of tissue-based immunohistochemical expression of PD-L1; TILs; peripheral T cell subpopulations; changes in tissue and peripheral T cell receptor sequencing, HLA genotype, and immune-related candidate gene signatures at baseline.

Pharmacodynamic biomarker assessment will include changes in tissue based immunohistochemical expression of PD-L1; TILs; peripheral T cell subpopulations, and T cell receptor genotype at baseline and after two months of treatment with veliparib and nivolumab.

10.2 Sample Size and Accrual

The initial study has recruited 3 patients at the lower dose and 6 at the MTD. Of these 6 at the MTD, 4 have genetic mutation of interest, and 2 do not. The study will, due to lack of funding and other reasons recruit 6 more patients with genetic mutation of interest. The response rate will be computed separately for 4+6 = 10 patients with genetic mutation.

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Dose Escalation Phase

The expected number of patients in the dose escalation phase will be in the range of 6 to

18 based on the 3+3 design.

Expansion Cohort
The initial study design was to accrue a total of up to 50 patients (for 48 evaluable) to the study in two phases: dose escalation and dose expansion. The original design anticipated a total of 6-18 patients with advanced solid tumors or lymphoma in the dose escalation phase; 9 patients were enrolled, including 6 that were treated at the MTD of 400 mg BID. Due to funding issues, the study will perform an early analysis of preliminary efficacy after the next 6 patients are enrolled in the expansion cohort.
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As stated above, in **the modified plan for expansion cohort**, will accrue 6 new patients with genetic alteration for early preliminary efficacy assessment, which together with 4 previously treated patients with genetic mutation will provide total of 6+4=10 patients, with genetic mutation. ORR will be computed at the first imaging (8 weeks). Preliminary efficacy will be evaluated by RECISTv 1.1. As exploratory analysis, irRECIST will be used to obtain preliminary efficacy as well. All ORR will use the first imaging time point whether RECIST or irRECIST.

The study will be considered a success if the lower 90% exact confidence bound will be > 10% , i.e. if three or more successes out of n=10 are observed.

I According to the modified plan for the current trial, the study will be closed after the 6 additional patients will have been recruited."

10.3 Data Analyses Plans

The primary analysis will be on the intent-to-treat (ITT) population, including all evaluable patients. Clinical benefit rate will be defined as stable disease (for ≥12 weeks), complete or partial response by both the Response Evaluation Criteria in Solid Tumors (RECIST) and irRECIST or Lugano Criteria 2014. Maximum response prior to disease progression will be used. The overall response rate will be estimated by the proportion of overall response, and its 80% confidence..

Additionally, we will evaluate overall response rate, defined as complete or partial response using RECIST or Lugano Criteria 2014 guidelines in a similar manner. We will also perform similar analyses using Immune Related RECIST (irRECIST). Duration of response, defined as the duration from the first documentation of clinical benefit to the first documented progressive disease or death of any cause, whichever occurs first, will also be analyzed. For patients alive and progression-free at the time of data cut off, duration of response will be censored as of the last tumor assessment date. Duration of response will only be evaluated for the subgroup of patients with a clinical benefit using the Kaplan-Meier method.

PFS is defined as the time from treatment initiation to documented disease progression. OS is defined as the time from the start of treatment until death due to any cause. For patients alive at the time of data cut-off, PFS and OS will be censored as of the last tumor assessment date or known to be alive, respectively. The PFS and OS will be estimated using the Kaplan-Meier method. The number, frequency, and severity of adverse events (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE version 4.03) will be recorded.

Baseline percent PDL1 expression, TILs (sTILs, iTILs, and their ratio), and changes in T

cell subpopulations will be used as a continuous variable to predict clinical benefit or overall response rates using appropriate statistical summaries. Cox proportional hazards regression will be used to compare how these biomarkers are associated with PFS and OS as well.

Changes in these biomarkers will also be analyzed to assess for pharmacodynamic effects of treatment. Continuous variables will be analyzed using either paired t-tests, signed rank tests or repeated measures analysis of variance.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by BMS and Abbvie. In the event that external participating sites are added, amendments will be distributed by the lead institution (Northwestern) to all external sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research Office at Northwestern University before enrollment to study. Please contact the assigned QAM or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep

original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

Training on eCRF completion will be provided at the time of site activation. Please refer to the eCRF demonstration videos on the CRO website for additional instructions on registering a patient.

The QAM will review the registration, register the patient, assign a subject identification number, and send a confirmation of registration to study personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document). Generally, all data are due within 10 days of each study visit.

11.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to NOTIS for additional information). The level of risk attributed to this study requires high level monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to NOTIS for additional data submission instructions.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:
- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Reportable New Information(RNI) if it:
- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).

- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Clinical Trial Audit Committee (CTAC), as outlined in the DSMP.

11.8 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, articles, data, text, diagrams, abstracts, posters, charts, slides, pictures, or clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. The assigned QAM will prepare a preliminary data summary (to be approved by the DMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigators wish to obtain DMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM including justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

NU shall provide BMS with a copy of each Publication at the earliest practicable time, but in any event not less than thirty (30) days prior to its submission to a journal, publisher or meeting or fifteen (15) days prior to any public disclosure of any manuscript or other public disclosure (e.g., presentations)..

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APPENDICES

APPENDIX A- CONTRACEPTION REQUIREMENTS

Investigators shall counsel FOCBP and male subjects who are sexually active with FOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise FOCBP and male subjects who are sexually active with FOCBP on the use of highly effective methods of contraception from the time of treatment initiation to 5 months (for FOCBP) or 7 months (for males with FOCBP partners) after the last dose of nivolumab. Highly effective methods of contraception have
a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION
a) Male condoms with spermicide
b) Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by FOCBP subject or male subject's FOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug.
c) Nonhormonal IUDs, such as ParaGard®
d) Tubal ligation
e) Vasectomy.
f) Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION
a) Diaphragm with spermicide
b) Cervical cap with spermicide
c) Vaginal sponge
d) Male Condom without spermicide*
e) Progestin only pills by FOCBP subject or male subject's FOCBP partner
f) Female Condom*
*A male and female condom must not be used together

APPENDIX B- COMMON TOXICITY CRITERIA FOR ADVERSE EVENTS

Toxicity will be graded according to the NCI's Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE version 4.0 can be accessed at the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX C – LUGANO 2014 RESPONSE CRITERIA

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to < 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

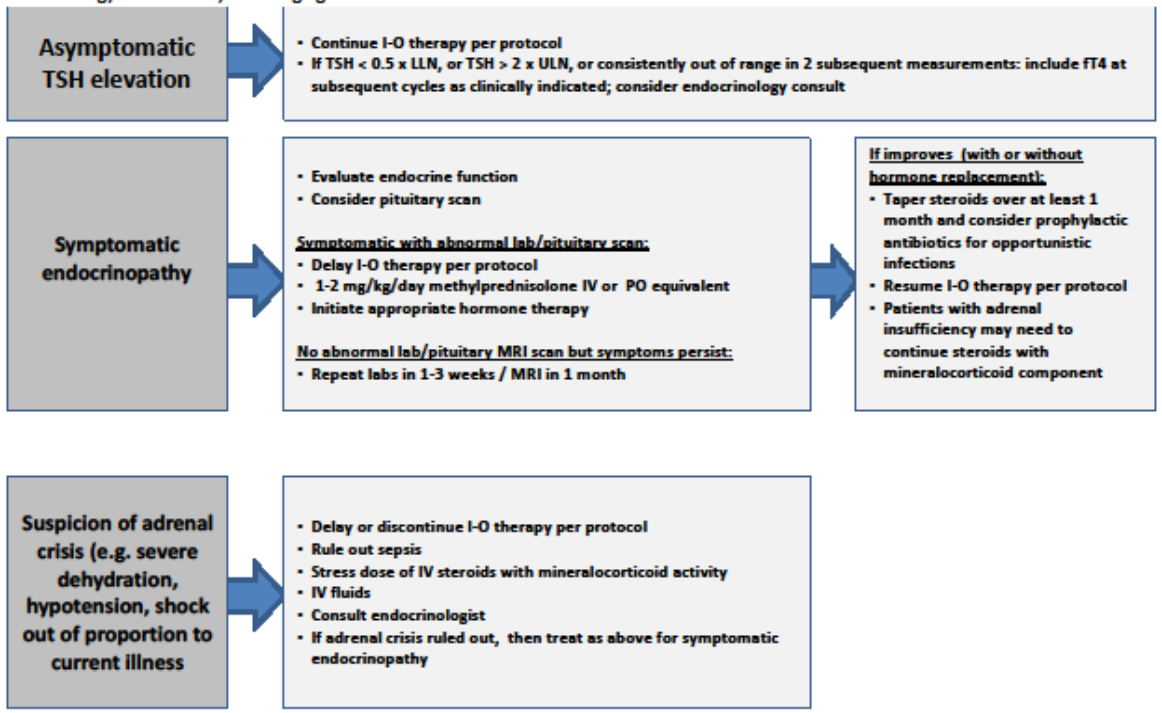
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions < 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node _ 1.5 cm in any axis A new extranodal site _ 1.0 cm in any axis; if _ 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to Lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

APPENDIX D – ADVERSE EVENT ALGORITHMS

Recommended management algorithms for suspected nivolumab related endocrinopathy, gastrointestinal toxicity, hepatotoxicity, neurologic toxicity, pulmonary toxicity, renal toxicity and skin toxicity.

Endocrinopathy Management Algorithm

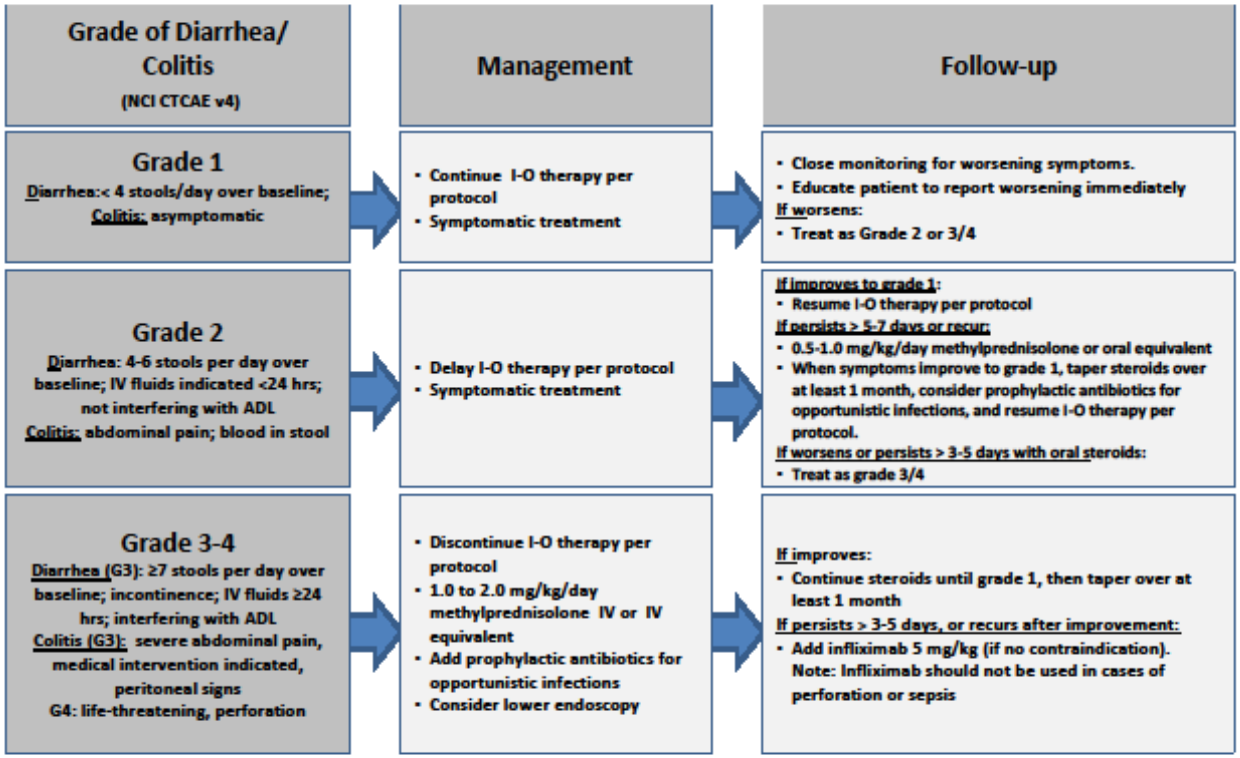
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

GI Adverse Event Management Algorithm

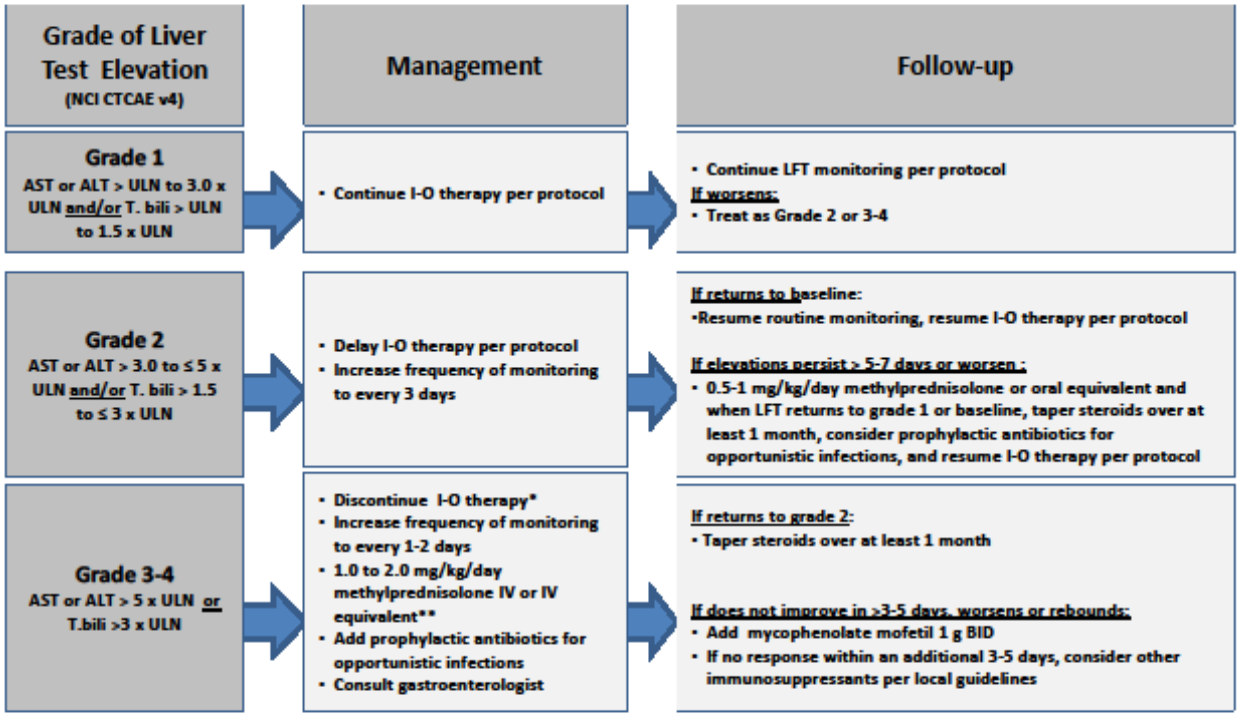
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



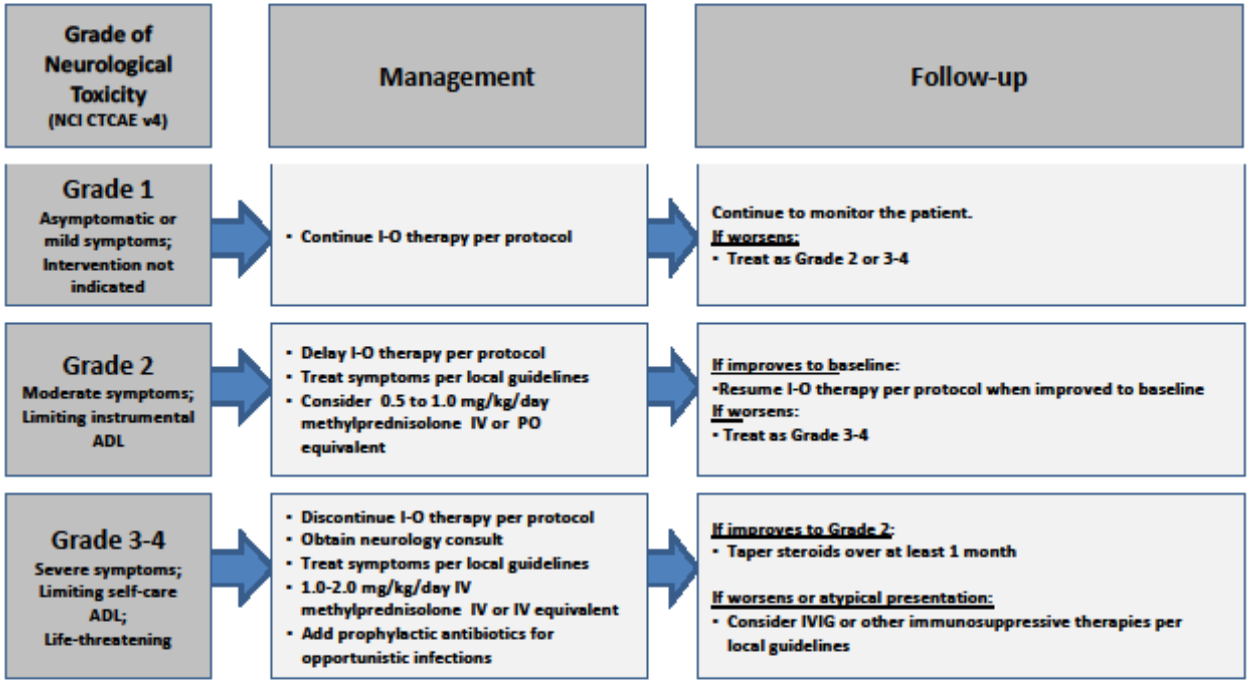
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

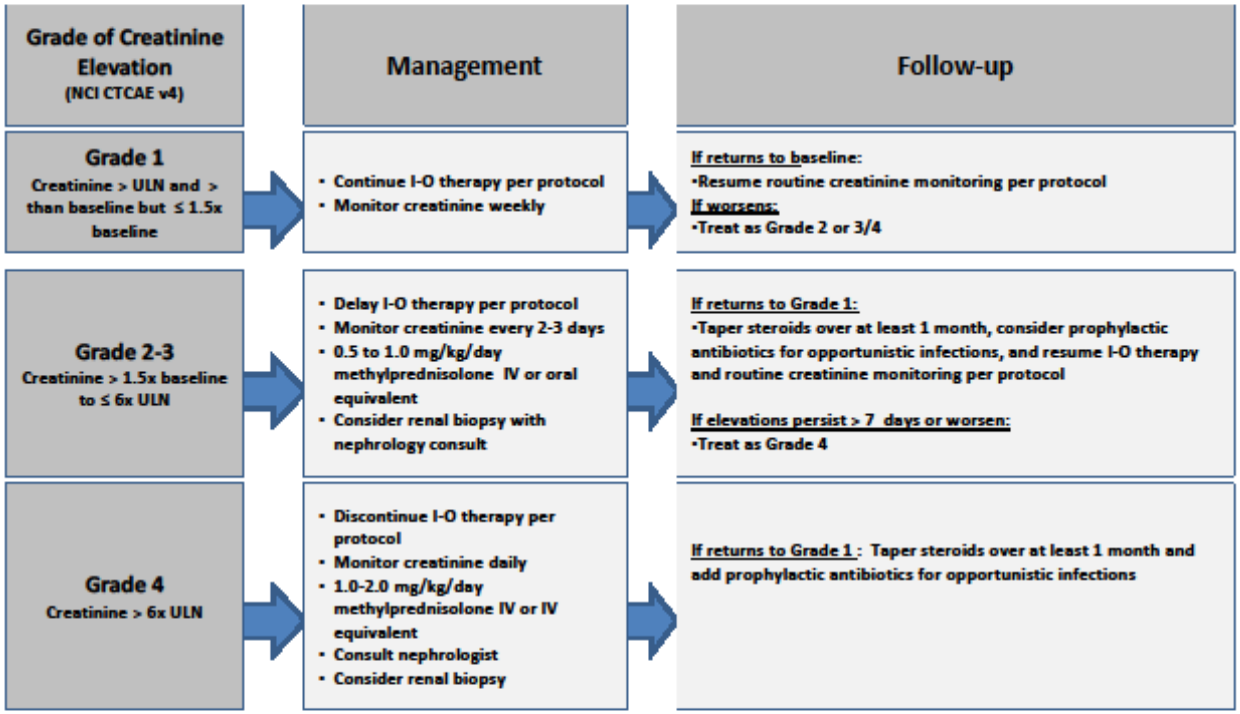
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks **If worsens:** • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days **If improves:** • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics **If not improving after 2 weeks or worsening:** • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	**If improves to baseline:** • Taper steroids over at least 6 weeks **If not improving after 48 hours or worsening:** • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

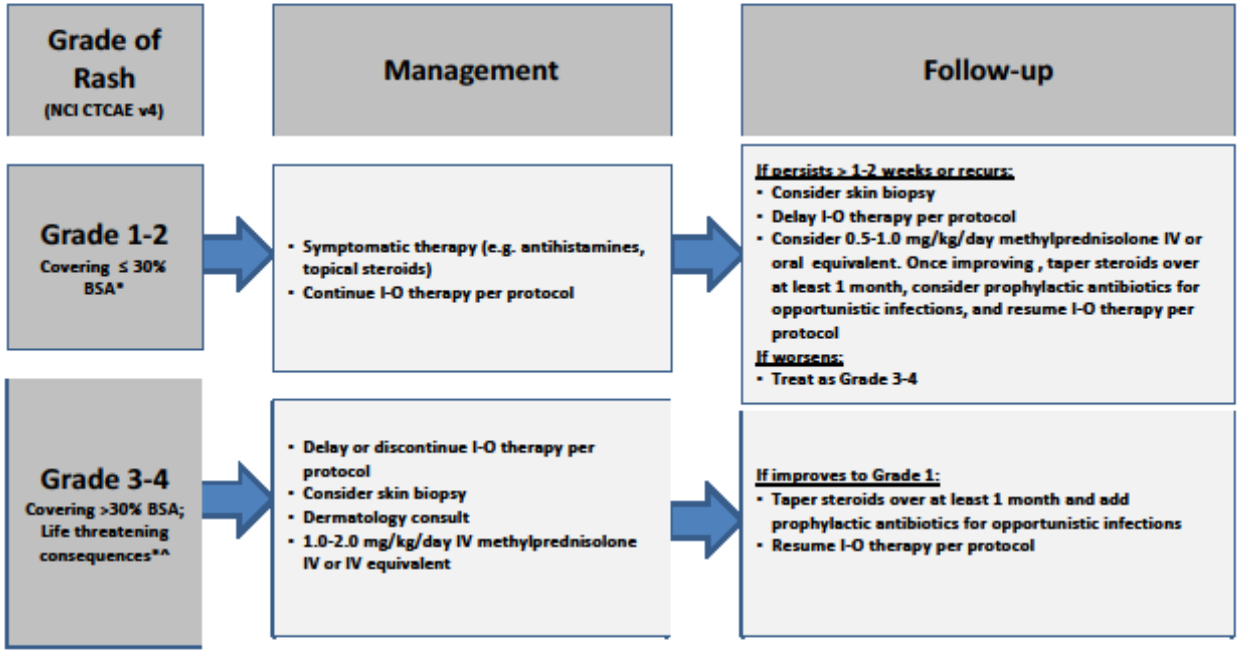
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-Otherapy.

APPENDIX E- PROTOCOL SUMMARY OF CHANGES

Amendment 1 (FDA Response) – December 20, 2016			
Section(s) Affected	***Prior version***	***Amendment 1***	***Rationale***
Cover Page	Listed IND Number as "TBD"	Includes IND Number: 133333	New information available
Study Summary (Objectives); 2.2.6 (Secondary Objectives & Endpoints); 6.5.6 (Secondary Endpoints)	Included the following secondary objective: "To evaluate ORR to nivolumab and veliparib in patients with prior exposure to single agent PD-1/PD-L1 inhibitors"	Removes secondary objective of ORR in patients with prior exposure to PD-1/PD-L1	To correct discrepancy; patients who have prior PD-1/PD-L1 exposure are excluded by 3.2.5
3.0 (Patient Eligibility)	15-30 patients would be accrued in the expansion cohort n/a	15-32 patients will be accrued to the expansion cohort. Adds: "Patients will be recruited by all participating investigators in respective clinics within the Northwestern University Cancer Center network."	To account for evaluable patients and add up to a total accrual of up to 50 patients Clarification at IRB request
3.1.1 (Inclusion Criteria); 3.2.7 (Exclusion Criteria)	n/a	Adds the following note / exclusion: "Patients with germline BRCA 1/2 mutated ovarian cancer will be excluded given its presumed efficacy with veliparib monotherapy."	Clarification requested by FDA to be consistent with language in section 1.9
3.1.2 (Inclusion Criteria)	n/a	Adds the following note: "For patients with aggressive lymphoma, there should be no other standard therapies that would confer survival benefit."	Clarification requested by FDA
4.0 (Treatment Plan)	Numbered tables 1-	Re-numbers tables 4.1-4.	Simplification for clarity
4.3.1 (Definition of DLT)	"The treating physician should provide attribution to study drugs for all AE's to the best of his or her ability, however the following events will still be classified as DLT's if attribution is not available."	Removes prior language and adds: "All adverse events specified below will be DLT's except those that are clearly and incontrovertibly due to extraneous causes."	Clarification requested by FDA. Investigator attribution is not appropriate for a new combination treatment including an unapproved therapy
4.3.1 (Definition of DLT)	Did not include hematologic toxicity as DLT	Adds the following hematologic DLTs: • Grade 4 thrombocytopenia (platelets < 25.0 x 10^9/L) • Grade 4 neutropenia (ANC < 0.5 x 10^9/L) • Grade 3 febrile neutropenia with fever lasting for > 7 days • Grade 4 febrile neutropenia of any duration	FDA request given the possible hematologic toxicities associated with veliparib.
	Lists the following DLT's:	Changes non-hematologic	Simplified based on

	• Grade 4 vomiting or diarrhea • Grade 3 nausea, vomiting, or diarrhea lasting for >72 hours • Other Grade ≥ 3 toxicities possibly related to either veliparib or nivolumab (Note: any alopecia and transient grade 3-4 laboratory abnormalities including asymptomatic LFTs/amylase/lipase that are not clinically significant will not be considered DLTs.	DLT criteria to read as follows: Grade ≥ 3 non-hematologic toxicities that represent at least a 2-grade increase from baseline and are possibly related to either veliparib or nivolumab with the following exceptions: a. Nausea and vomiting lasting ≤48 hours b. Electrolyte abnormalities resolving within ≤24 hours c. Hypersensitivity reactions d. Alopecia	language from another Phase I/II protocol using veliparib in combination therapy. FDA request to remove LFT's as exception and elaborate on "transient" lab abnormalities. New language is more concise and clear.
4.3.2 (Dose Escalation 3+3 Rule)	Allowed for up to 9 patients to be enrolled at dose level 1 to establish the MTD at dose level 1.	• Removes this language – only 6 patients may be treated to establish MTD, and there are no exceptions for dose level 1. • Exception to dose level 1 has been clarified – if dose escalation is stopped at dose level 1, patients may be enrolled at dose level -1 to establish MTD.	• FDA safety request that MTD is reached when 2 out of 6 patients experience a DLT. • Clarification. Was previously unclear when dose level -1 would be utilized.
4.4 (Toxicity Management & Dose Delays/Modifications)	Referred to the "Schedule of Events Table"	Changes to "Table 5"	Corrected for consistency
10.2 (Sample Size and Accrual)	Sample size referenced 30 total patients without differentiating between the overall sample size and that in the expansion cohort. Also referenced 30 patients "per histological cohort"	Adds separate headings for the dose escalation phase and the expansion cohort, and removes language referring to histological cohorts.	FDA request for clarification on non-coherent language. Clarifies that 30 total patients refers only to the expansion cohort, and that total accrual for the study will be up to 50. The histological cohorts were included by mistake and do not align with the study design.
Amendment 1 (FDA Response 2.0) – December 21, 2016			
Section(s) Affected	***Prior version***	***Amendment 1***	***Rationale***
4.3.1 (Definition of DLT)	Listed as DLT: "Grade ≥ 3 non-hematologic toxicities that represent at least a 2-grade increase from baseline and are possibly related to either veliparib or nivolumab with the	Removes phrase "and are possibly related to either veliparib or nivolumab"	FDA request to eliminate physician attribution in the case of DLT's for new combination treatment including an unapproved therapy

	following exceptions"		
4.3.1 (Definition of DLT)	n/a	Adds the following DLT: "Grade 3 thrombocytopenia with bleeding (platelets <50.0 x 10^9/L)"	FDA request given possible hematologic toxicities associated with veliparib
4.7.1 (Continuation of Investigational Therapy after Progression)	Patients were allowed to continue treatment beyond progression unless confirmed by a subsequent scan; however, there was a concession for patients to continue treatment if PD was confirmed but they were receiving clinical benefit.	Replaces language to mirror another ongoing immunotherapy trial and remove the concession for clinical benefit: "Confirmed PD: An initial assessment of PD by RECIST 1.1 or Lugano criteria will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later (see section 6.1.7 & Appendix C, respectively). If any subsequent tumor assessment shows progression per RECIST v1.1 or Lugano criteria in the overall tumor burden (the sum of diameters of target lesions and new lesions), when compared to the initial PD assessment (the sum of diameters of target lesions and new lesions), then PD is confirmed."	FDA request to align more closely with current immunotherapy trials.
5.0 (Study Procedures)	Superscript on scan procedures listed as "g"	Scan superscripts refer to footnote "h"	Correction of discrepancy.

Amendment 2 – April 27, 2017
Approved by Scientific Review Committee: May 2, 2017

Section(s) Affected	***Prior version***	***Amendment 2***	***Rationale***
Cover Page	Listed all faculty and staff from the Authorized Personnel List (APL)	Removes Ricardo Costa, Amanda Williams, Ellen Dammrich, Hannah Garrett, and Frank Giles from sub-investigator list	Administrative – it is no longer a requirement to list all people from APL on the cover page
Abbreviations	Abbreviation list was incomplete	Adds relevant abbreviations from the protocol	Administrative
Schema; Study Summary; 4.1 (Overview)	n/a	Re-formats treatment plan description for simplicity	Clarifications
Schema	n/a	Adds that response assessment will be by CT or MRI	Clarifications
Study Summary	Objectives had inconsistent description of study population	Includes full description of the study population in the primary objective, leaving the others vague	Clarifications to simplify
Study Summary; 2.3 (Exploratory Objectives and Endpoints); 6.6 (Exploratory	Correlative samples were to be sent for cfDNA analysis at Guardant laboratories	Removes objective and correlative sample collection for cfDNA	Removed due to logistical issues with Guardant

<table>
<tr><td>Endpoints); 9.3.2 (Flow Cytometry)</td><td></td><td></td><td></td></tr>
<tr><td>Study Summary</td><td>Patients in the expansion cohort must have alterations in selected DNA repair genes</td><td>Adds note to refer to 3.1.6, which lists specific examples of DNA repair genes</td><td>Clarification</td></tr>
<tr><td>Study Summary; 3.2 (Exclusion Criteria)</td><td>Patients cannot have chemotherapy or radiation within 14 days, but further down it states that patients cannot have systemic chemotherapy within 28 days</td><td>Reformats eligibility so that these two statements are next to each other</td><td>Clarification to avoid confusion of chemotherapy washout period</td></tr>
<tr><td>3.2.1, 3.2.3 (Exclusion Criteria)</td><td>Exclusionary statements were ambiguous:
“…≤ 14 days prior to entering the study”
“…≤ 14 days of registration”</td><td>Revises language to be more clear:
“…≤ 14 days prior to registration”</td><td>Revised for cohesiveness</td></tr>
<tr><td>3.2.10, 3.2.11 (Exclusion Criteria)</td><td>Corticosteroids and live attenuated vaccines were listed as exclusionary medications in section 4.6 but not listed in exclusion criteria</td><td>Adds corticosteroids and live attenuated vaccines to exclusion criteria</td><td>Revised for consistency</td></tr>
<tr><td>4.2 (Treatment Administration</td><td>n/a</td><td>Adds table to summarize dosing details and schedules of both study drugs; updates subsequent table numbers and references to be sequential</td><td>Added for clarity</td></tr>
<tr><td>4.2.1 (Veliparib)</td><td>n/a</td><td>Patients will maintain a drug diary and return drug bottles, extra drug, and diaries at each study visit</td><td>Added for clarity</td></tr>
<tr><td>4.2.2 (Nivolumab); 5.0 (Study Procedures)</td><td>Nivolumab infusion windows were as follows:
Over 30 mins (±5 mins)
Over 60 mins (±10 mins)</td><td>Updates nivolumab infusion windows:
Over 30 mins (-5 / +15 mins)
Over 60 mins (-10 / +15 mins)</td><td>Allows for flexibility of infusion duration without compromising safe administration</td></tr>
<tr><td>4.5.1 (Veliparib)</td><td>Dose delays and discontinuation were referenced for veliparib/placebo</td><td>Removes reference to placebo</td><td>Correction – there is no placebo in the study</td></tr>
<tr><td>4.5.2 (Nivolumab Toxicity Management)</td><td>Some toxicity recommendations were inconsistent with the I-O algorithms in Appendix G</td><td>Updates table 4.6 as follows:
<table><tr><th>Prior version</th><th>Changed to</th></tr><tr><td>“No dose modifications”</td><td>“Continue dosing”</td></tr><tr><td colspan="2">Reduced dosing recommendations for methylprednisolone dosing under G2 and G3 pneumonitis, G2 and G3 diarrhea</td></tr><tr><td colspan="2">Pneumonitis</td></tr><tr><td colspan="2">Refers to section 7.2.5 for management for AESI’s</td></tr><tr><td>G1: monitor for 2-4 days</td><td>Monitor for 2-3 days
Re-image</td></tr></table></td><td>To align with BMS-provided AE algorithms for immune-oncology products and correct discrepancies</td></tr>
</table>

		every 3 weeks G3: Taper over 4 weeks / Taper over 6 weeks *Hepatitis* Refers to section 7.2.5 for management of AESI's *Nephritis* Discontinue for G3 or G4 / Discontinue only for G4 G2 or 3 Adds: Consider renal biopsy; Monitor creatinine q2-3 days G4 Adds: Monitor creatinine daily	
4.6 (Concomitant Medications / Treatments)	Excluded medications did not have washout window listed	Adds washout periods to align with exclusion criteria and as clinically appropriate	Added for clarity
4.6 (Concomitant Medications / Treatments); 7.2.5 (Adverse Events of Special Interest)	Referred to Medical Monitor for discussion on corticosteroids	Replaces "Medical monitor" with "PI"	Since Northwestern is the sponsor, there is no medical monitor
5.0 (Study Procedures)	Listed "HPI"	Replaces "HPI" with "Medical History"	Medical history should include more than just "History of Present Illness"
	n/a	Adds specifications for vitals (pulse, blood pressure, weight, and height at screening, footnote d)	Clarification
	Thyroid function tests were to include free T3	Removes free T3 from thyroid testing	Not clinically necessary
	n/a	Adds "Mutation testing" as a screening requirement within 1 year for patients in the expansion cohort (footnote q)	To align with requirements of eligibility criteria
	n/a	Adds q3months to "Follow-up" column	Clarification
7.2.5 (Adverse Event of Special Interest (AESI))	The description of AESI's referenced rapid communication from the investigator to the sponsor.	Removes references to rapid reporting (within 24 hours) and the "sponsor" or "medical monitor". AESI's will just merit close monitoring and discussion with the PI.	There are no reporting requirements for such AESI's, but PI feels that they are worthy of close monitoring and further discussion.
8.1.9 (Availability & Supply)	Listed two individual emails for ordering veliparib: Bina.patel@abbvie.com Kathleen.ramsdell@abbvie.com	Removes individual emails and replaces with: IISoncologysupport@abbvie.com	Administrative. Updated information from Abbvie.
9.3.2 (Flow Cytometry)	Flow analysis was to be performed in Bin Zhang's laboratory	Flow analysis will be performed in Northwestern's Flow Core	Correction
10.3 (Data Analysis Plan)	Response will be evaluated by RECIST and irRECIST	Adds that response will be evaluated by Lugano Criteria	Clarification to include lymphoma

			patients
Amendment 3 – May 26, 2017 *Approved by Scientific Review Committee: June 7, 2017*			
Section(s) Affected	***Prior version***	***Amendment 3***	***Rationale***
5.0 (Study Procedures "m")	On the day of a study visit, veliparib should be taken in clinic after the blood draw.	Veliparib dosing may take place independently of nivolumab. On the day of a study visit, lab values should be checked against sections 4.4 and 4.5 for continued dosing.	Not necessary to delay dosing until after blood draw since there are no PK's. Patients should follow their normal schedule to avoid confusion and missed doses.
Amendment 4 – November 15, 2017 *Approved by Scientific Review Committee:*			
Section(s) Affected	***Prior version***	***Amendment 4***	***Rationale***
Cover Page	Included Benedito Carneiro and Cesar Santa-Maria as sub-investigators	Removes Benedito Carneiro and Cesar Santa-Maria as sub-investigators	Administrative; faculty members no longer work at Northwestern
Abbreviations	n/a	Adds SJS and TEN as abbreviations	To account for updates in nivolumab toxicity management and Appendix D
4.5.2 (Nivolumab Toxicity Management)	• Grade 3 or higher hepatitis: discontinue for elevations in transaminases **≥8x ULN** or bilirubin **≥5x ULN** • Grade 2 or 3 renal dysfunction: "Consider renal biopsy" • n/a	• Grade 3 or higher hepatitis: discontinue for elevations in transaminases **≥5x ULN** or bilirubin ≥**3x ULN** • Grade 2 or 3 renal dysfunction: "Consider renal biopsy **with nephrology consult**" • Grade 3 or 4 rash: Adds note to monitor for SJS and TEN and discontinue if confirmed	To align with AE algorithms in Appendix D
5.0 (Study Procedures)	n/a	• Adds PT/INR at baseline for patients on anticoagulants • Updates footnote lettering	Elevated INR may be considered a DLT. DSMC requested a baseline requirement to serve as a reference for possible DLT's.
8.2.4 (Storage and Stability); 8.2.6 (Preparation); 8.2.8 (Incompatibilities)	n/a	Replaces language with internal nivolumab template language (same content)	For consistency with other protocols involving nivolumab
8.2.9 (Availability & Supply)	Did not specify timing for drug re-supply requests	Replaces language with internal nivolumab template language. Drug re-supply should be submitted 10	Updated for accuracy per BMS

		business days before the delivery date	
8.2.12 (Return & Retention of Study Drug)	n/a	Updates table to reflect accurate packaging of nivolumab product	Clarification
Appendix A	n/a	Adds timeframe of contraception requirements for both females (5 months) and males (7 months) after the last dose of nivolumab	To align with BMS template and requirements
Appendix D	Contained outdated AE Management Algorithms. Specific outdated parameters include: Hepatic: • Discontinue for AST/ALT >5xULN **and/or** Tbili >3xULN Pulmonary (G3-4): • Includes example immunosuppression Renal (G2-3): • "Consider renal biopsy" Skin (G3-4): • n/a	Updates AE Management Algorithms to align with nivolumab IB v16. Specific changes to AE management include: Hepatic: • Discontinue for AST/ALT > 5xULN **or** Tbili > 3xULN Pulmonary (G3-4): • Removes examples of immunosuppression Renal (G2-3): • "Consider renal biopsy with nephrology consult" Skin (G3-4): Adds footnote: "If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy."	Updated per BMS for consistency with new nivolumab IB v16 and additional or clarified safety measures.

Amendment 5 – February 20th, 2019

Section(s) Affected	***Prior version***	***Amendment 5***	***Rationale***
Study summary Study schema Background section 1.9 , Section 3.0; Section 4.1(treatment overview) and Section 4.3.3 (Dose expansion) 4.7,4.8,4.9 and Statistics section 10.	Previous language stating the design and analysis plan of the dose escalation and dose expansion phases of this Phase 1/1B study. The initial study design was to accrue a total of up to 50 patients for 48 evaluable) to the study in two phases: dose escalation and dose expansion.	This language along with adequate details and calculations have been added for the new plan : According to this modified dose expansion plan, the study will perform an early analysis of preliminary efficacy after the 6 more patients are enrolled in the expansion cohort, all with the genetic mutation. Of the 6 patients already at MTD, 4 have the genetic mutation. Total number of patients at the end of adding 6 more patients with mutation will be 4+6=10. The patients will be treated at MTD and the same	***To facilitate future funding for a possible larger scale trial***

		treatment schedule will applicable for these patients as was used in the escalation phase. The study will be considered a "success" if the lower exact 90% confidence limit is > 10%, i.e. when 3 or more successes are observed. According to the modified plan for the current trial, the study will be closed after the 6 additional patients will have been recruited.	
Study summary Section 2 and Section 6 (Objectives and endpoints) and Section 10(statistics)	Previous list of objectives and endpoints	Added language to state that "For the preliminary efficacy analysis, ORR will be computed at the first imaging (8 weeks). Preliminary efficacy will be evaluated by RECISTv 1.1. As exploratory analysis, irRECIST will be used to obtain preliminary efficacy as well. All ORR will use the first imaging time point whether RECIST or irRECIST."	***To align with the preliminary efficacy analysis plan for the expansion cohort, as stated in the rest of the protocol***
Study summary and Section 3.1.6 (Inclusion criteria	Language stating that the patients in the expansion cohort should have alterations in selected DNA repair genes in their tumors.	Added a note to clarify that this criteria is also applicable for the patients enrolled in the preliminary efficacy portion of the expansion cohort. Added BRIP1 mutation in the eligible mutated gene list.	***For clarity*** ***Recent data supports the the fact that it is BRCA related gene***.

Section 3.1.10 Inclusion criteria	Details about use of contraception during and after study treatment	Added language stating that the post treatment period is 5 months for females and 7 months for males, for which they are required to agree to follow instructions for use of contraception.	***Based on information provided by BMS***
Throughout	Language indicating that MTD will be established in the future	Language updated to indicate that MTD has been established	***MTD has been established with 6 patients(4 with mutation and 2 without mutation)***
Section 4.5.2 Table 4.6 Nivolumab Toxicity management	Details about Nivolumab related toxicity management guidelines	Added language that in addition to the recommendation that management of irAEs follow the guidelines presented in the table , users should also refer to the Nivolumab IB	***As mandated by BMS***
Section 4.2.2 and Section 5 (footnote 'm') Nivolumab infusion	Language indicated that starting with Cycle 5, nivolumab will be administered at 480mg IV over 60 minutes (-10 / +15 minutes) every 4 weeks (Day 1 of each cycle)	The infusion time for nivolumab in this situation has been modified to 30mins (-10/+15 minutes)	***Based on Nivolumab IB, version 17***

Section 7.3.3.4 Reporting to BMS and Abbvie	Details about SAE reporting	Added language to state that SAEs will be reported up to 100days post study drug discontinuation	***For clarity and to be consistent with rest of the protocol***
Section 8.2.12 Return and retention of study drug Nivolumab	Details regarding return and retention of Nivolumab stating responsibilities of the site and Investigator	Added language to state that a copy of the drug destruction certificate must be retained at the end of the study for submission to BMS	***For clarity***
Section 11.8 Publication policy	Template language indicated that BMS may be included as an author in publications	Removed this language since the contract with BMS does not allow it.	***To align with BMS policy***
Amendment 6 – October 3rd , 2019			
Section(s) Affected	***Prior version***	***Amendment 6***	***Rationale***
Exclusion criteria 3.2.1	Patients who have had chemotherapy or radiotherapy ≤ 14 days prior to registration are not eligible. ***NOTE****: Patients may not have had systemic chemotherapy within 28 days.*	Exclusion criteria modified to state : "Patients who have had radiotherapy ≤ 14 days prior to registration are not eligible." The note has been removed.	***For clarity. Chemotherapy has been addressed in criteria 3.2.2***

Exclusion criteria 3.2.2	Patients are not eligible who have received systemic chemotherapy or investigational agents ≤ 28 days prior to registration	Criteria reworded to state: "Patients who have received systemic chemotherapy or investigational agents ≤ 28 days prior to registration are not eligible"	***For better presentation and clarity.***
Exclusion criteria 3.2.18	Patients with a prior diagnosis of cancer must not have received treatment in the last 3 years prior to registration.	Added a caveat to this criteria "NOTE: treatments used as a recurrence prevent are eligible.*"*	***For flexibility and clarity***
Section 5, footnote d	Vital signs included pulse, blood pressure and weight with height being recorded only at baseline.	Vital signs now include pulse and blood pressure only .Weight will now be recorded at baseline along with height.	***To minimize deviations and for ease in clinic.***
Section 5 footnote h	"Thyroid function tests will include thyroid stimulating hormone and free T4."	Footnote modified to state: "Thyroid function tests will include thyroid stimulating hormone (TSH) with reflex free T4."	***To facilitate only necessary procedures.***

Section 9.3.2 Flow cytometry	The samples were being delivered to the Flow Core at Northwestern University	The samples will now be delivered to Zhang laboratory, at Northwestern University. Address: Bin Zhang's Laboratory 300 E. Superior St. Tarry Building 4-726 Chicago, IL 60611 Ph: 312-503-2435 Email: Bin.Zhang@northwestern.edu	***Automated flow cytometric analysis will be done at the Zhang laboratory***
Amendment 7 dated 3.3.2020			
Section(s) Affected	***Prior version***	***Amendment 7***	***Rationale***
Title page	Sarika Jain, MD was listed as a Sub-Investigator	Removed Sarika Jain, MD	***Dr.Jain has left NU***
Section 7.3.3.2 Reporting to NU IRB	Previous template language	Replaced with current language that aligns with NU IRB policies.	***To align with current requirements and policies***