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STUDY TITLE: Phase II Trial of Nivolumab in Combination with Talazoparib in Patients with Unresectable or Metastatic Melanoma and Mutations in *BRCA* or *BRCA*-ness

PRINCIPAL INVESTIGATOR: Dr. James Isaacs, MD
Department of Hematology and Oncology
Cleveland Clinic Taussig Cancer Institute
9500 Euclid Avenue, [redacted]
Cleveland, OH 44195
Ph: [redacted]

Email: [redacted]

CO-INVESTIGATORS: Lucy Boyce Kennedy, MD
Cleveland Clinic Taussig Cancer Institute
Ph: [redacted]
Email: [redacted]

STATISTICIAN: [redacted]

STUDY COORDINATOR: [redacted]

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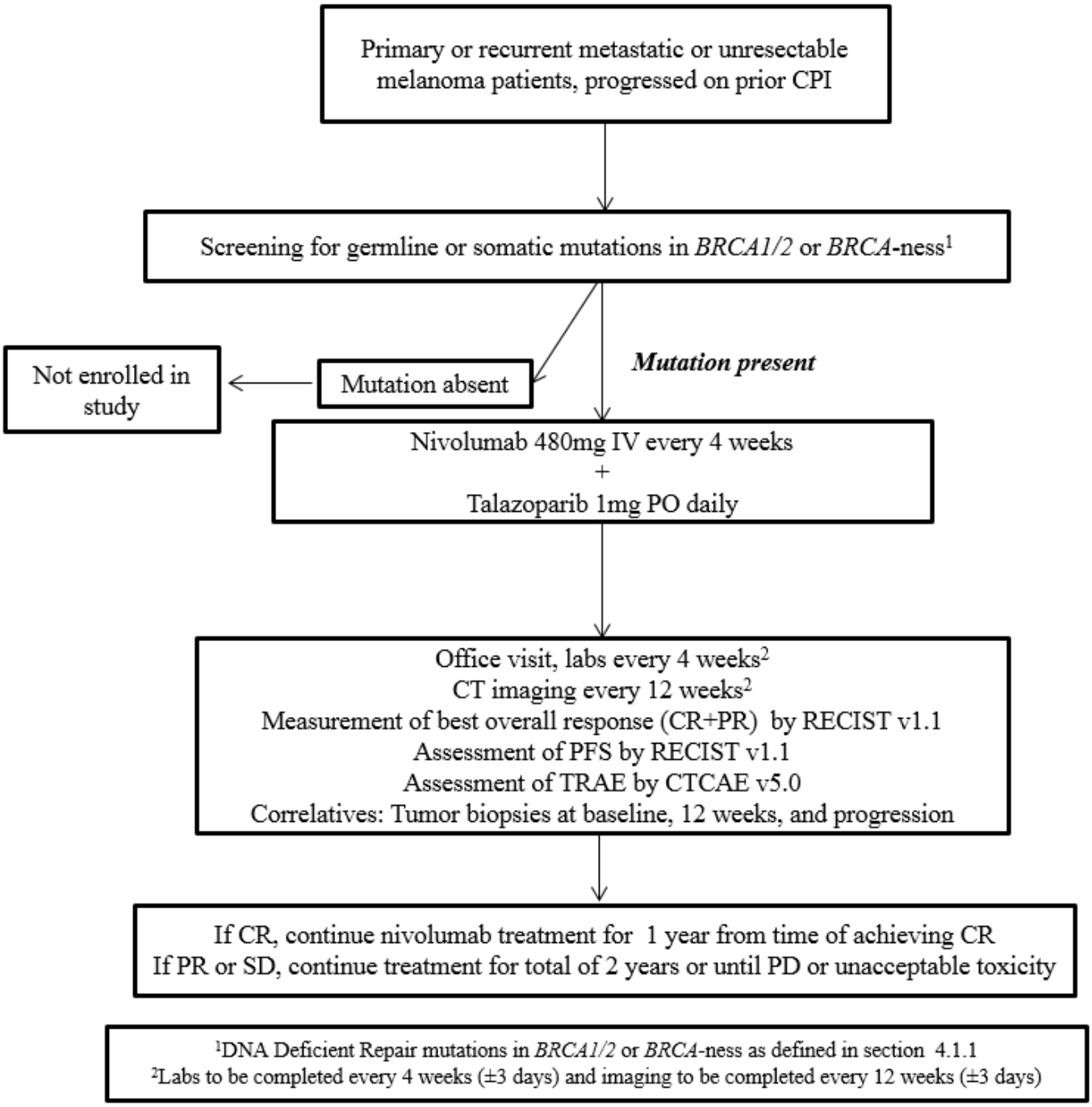
SUMMARY OF CHANGES

Protocol Date	Section	Change
11/4/2019	10.1.3	Updated number of vials to be sent to Dr. Diaz's lab from one to three
	14.0	Changed futility monitoring plan to a safety monitoring plan
1/17/2020	2.2	Added OS as a secondary objective
	2.3	Added ctDNA and CNV correlatives
	3.1	Removed mini-dose escalation phase
	3.1	Updated list of mutations/deletions for inclusion
	4.2.12	Allowed Pg-p inhibitor with modified Tala dosing
	10.1.3	Clarified collection of correlatives
	16.8	Added Personal/Family history Form
5/31/2020	6.4	Removed immunosuppressive agents (expect to treat adverse related events)
	4.2.2	Add for melanoma
12/3/2021	4.1.1	Add genomic marker of genomic loss of heterozygosity (gLOH) to the inclusion criteria
05/09/2023	Cover page, 8.4.1. Footer throughout.	Personnel changes including the PI transition from Dr. Funchain to Dr. Isaacs. Protocol version number and date changed in footer throughout.

STUDY SCHEMA



PROTOCOL SUMMARY

Protocol Number/Title	Phase II Trial of Nivolumab in Combination with Talazoparib in Patients with Unresectable or Metastatic Melanoma with Mutations in *BRCA* or *BRCA*-ness
Study Phase	II
Brief Background/Rationale	Current treatment for unresectable or metastatic melanoma includes monotherapy with nivolumab, with an objective response rate (ORR) of about 40% in the first line setting and about 15% in the refractory setting. Newer targeted therapies in melanoma are needed, especially once patients progress on standard therapies. "BRCA-ness" has not specifically been studied in melanoma; however, our own data from the only familial melanoma registry in the United States suggests a substantial presence of germline and somatic mutations in this patient population. In the first 130 melanoma patients accrued to our Gross Family Melanoma Registry at the Cleveland Clinic, 19% (25) had a germline pathogenic/likely pathogenic mutation, of which 52% (13) were in genes associated with BRCA1/2 and "BRCA-ness." This represents a significant proportion of patients with metastatic melanoma that could benefit from PARP inhibitor (PARPi) therapy. These findings are confirmed in The Cancer Genome Atlas (TCGA). Out of 470 skin cutaneous melanoma patients that have germline sequencing data available, 52 (11%) have pathogenic/likely pathogenic germline mutations, and 25 patients (5.3%) have mutations in "BRCA-ness" genes. Somatic mutations involving "BRCA-ness" are equally common in TCGA, 16% (n = 72) possess actionable/likely actionable mutations. Additionally, some data indicate that BRCA-ness genes may not be required for PARPi efficacy if a tumor is sensitive to immunotherapy. A recent study suggests that in addition to synthetic lethality, PARPi trap the PARP1/2 enzyme at sites of damaged DNA, and thus prevent DNA repair, replication, and transcription. In vitro studies have demonstrated that the PARPi, talazoparib, has more potent PARP trapping than other PARPi in clinical development (4-5). Additionally, PARPi-mediated DNA damage by talazoparib has been shown to increase the immunogenicity of tumor cells by promoting T cell and natural killer cell infiltration, and increasing tumor expression of PD-L1 in

	vitro and in vivo. Therefore, the use of talazoparib in combination with the immune checkpoint inhibitor (CPI), nivolumab, may have a synergistic immunotherapeutic and antitumor effect without requiring genes conferring "BRCAness." Biomarker selection strongly influences the efficacy of PARP inhibition. Mateo et al. looked at treatment with the PARPi olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC). This study showed that treatment with olaparib in patients with mCRPC who had germline defects in DNA repair genes led to a high response rate. Conversely, within the mCRPC cohort without a "BRCA-ness" marker, only a single responder was observed. Eligible alterations were in *BRCA1/2, ATM, PALB2, CHEK2, FANCA, HDAC2, RAD51, MLH3, ERCC3, MRE11*, and *NBN*. We propose that PARP inhibition with talazoparib will have synergistic antitumor activity in combination with nivolumab in unresectable and metastatic melanoma patients with DNA-repair defects, who have progressed on prior CPI therapy, and improve the ORR from 10% to 30% with limited toxicity.
Primary Objective	Determine the clinical efficacy of nivolumab plus talazoparib in patients who have progressed on prior CPI, unresectable or metastatic melanoma with *BRCA1/2* or other DNA damage repair mutations (defined as *BRCA*-ness), as measured by objective response rate (ORR).
Secondary Objectives	• Determine progression free survival (PFS) in unresectable or metastatic melanoma patients treated with nivolumab plus talazoparib. • Determine overall survival (OS). • Evaluate treatment-related adverse events in patients treated with nivolumab plus talazoparib.To assess the anti-tumor activity of nivolumab in combination with talazoparib in unresectable or metastatic melanoma patients with *BRCA1/2* or other DNA damage repair mutations (defined as *BRCA*-ness), as measured by immune-related objective response rate (irORR) every 12 weeks for a period of approximately 12 months.

	• Determine immune-related progression free survival (irPFS) in unresectable or metastatic melanoma patients treated with nivolumab plus talazoparib.
Correlative Objective(s)	• Measure adaptive and innate cellular immunofiltration into tumor (by tumor biopsies) and peripheral circulating T cells (by PBMCs) at baseline (pre-treatment), after treatment initiation (at about 12 weeks), and at time of progression, and to correlate activity with response to treatment. • Assess total somatic tumor mutation burden by sequencing at baseline (pre-treatment), after therapy at 12 weeks, and at time of progression to evaluate DNA landscape and its effect on sensitivity of combination nivolumab and talazoparib therapy. • Assess patient reported outcomes for adverse events while on combination therapy at baseline and before each cycle (about every 4 weeks) of nivolumab. • Assess ctDNA, CNV at baseline, at C2D1 and C3D1 and at time of progression.
Sample Size	37 patients
Disease sites/Conditions	Metastatic or unresectable melanoma
Interventions	Nivolumab 480mg intravenously every 4 weeks (28 days) + Talazoparib 1mg orally daily

ABBREVIATIONS

CCCC	Case Comprehensive Cancer Center
CRF	Case Report Form
DCRU	Dahm's Clinical Research Unit
DSTC	Data Safety and Toxicity Committee
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee
SOC	Standard of Care
CCF	Cleveland Clinic Foundation
UH	University Hospitals

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1.0 Introduction

1.1 Background of Melanoma and standard therapies

Cutaneous malignant melanoma is the most aggressive form of skin cancer, accounting for the large majority of skin cancer-related deaths. Incidence rates continue to increase for melanoma, it is the fifth most common cancer in men and women, with current estimate of 96,000 new diagnoses and 9,000 deaths annually in the United States.[1] Although early stage patients can be treated successfully with surgical resection in the majority, many will develop metastatic disease. Overall five year survival for all stages of melanoma is about 92%; however five year overall survival for metastatic melanoma is 23%.[1]

Prior to the advent of immunotherapy in 2011, median overall survival for metastatic melanoma was 6-8 months, with five year OS less than 10% with the use of dacarbazine or temozolomide chemotherapy.[2] Recently, treatment options for patients with advanced melanoma have expanded greatly with the United States (US) Food and Drug Administration (FDA) approval in 2011-2013 of the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody, ipilimumab, and the highly selective inhibitors of BRAFV600E, vemurafenib and dabrafenib. In addition, the MEK inhibitor, trametinib, also received FDA approval in 2013 for the treatment of patients with BRAFV600E mutant melanoma. Combination BRAF/MEK inhibitor therapy received FDA approval in 2014 based on a randomized Phase II study in which the combination showed superior efficacy relative to dabrafenib alone.

Current treatment of metastatic melanoma includes combined administration of anti-CTLA-4 immunotherapy with ipilimumab plus anti-programmed cell death receptor 1 (PD-1) immunotherapy with nivolumab or monotherapy with nivolumab.[3–7] In a phase 3 study by Larkin et al. (CheckMate 067), 945 previously untreated unresectable or metastatic melanoma patients were randomized 1:1:1 to receive nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone. The median progression-free survival was 14 months in the nivolumab plus ipilimumab group and in the nivolumab group, however higher adverse events of grade 3 or 4 toxicity were observed in the combination group (55.0%) compared to nivolumab monotherapy (14.3%).[3] The objective response rate (ORR) was 43.7% (95% CI, 38.1-49.3) in the nivolumab group, and 57.6% (95% CI, 52.0-63.2) in the combination group. In December 2014, the FDA approved nivolumab as a single agent for treatment in unresectable or metastatic melanoma. In Checkmate 066, advanced BRAF wild-type melanoma patients were randomized to receive nivolumab or dacarbazine as first line therapy. The objective response rate was 40% in the nivolumab group and 14% in the dacarbazine group.[8]

Once patients progress on prior anti-PD-1 therapy, limited treatment options are available. This refractory population includes patients who possess a targetable BRAF mutation and have already received combined BRAF/MEK inhibitor therapy and those who have received prior anti-PD-1 therapy, in whom response rates to salvage anti-PD-1 therapy or combination CTLA4/PD-1 inhibition are low. A recent retrospective study presented at

ASCO 2019 (n = 200) demonstrated that treatment after anti-PD-1 monotherapy with combination ipilimumab and nivolumab (n = 77) had an ORR of about 19%, single agent ipilimumab (n = 47) 4.2%, and re-challenge with BRAF/MEK inhibitor in the BRAF mutant subpopulation (n = 18) 22%.[9] Grade 3-4 toxicity or toxicity requiring treatment discontinuation was observed in 34% of patients in the combination ipilimumab/nivolumab arm. This finding is consistent with a prior study where patients treated with ipilimumab/nivolumab (n = 37) after failure with anti-PD-1 therapy had an ORR of 21% and 16% in patients treated with single agent ipilimumab (n=47).[10] Additionally, another retrospective study (n=398) presented at ASCO 2019 demonstrated that once patients progress on prior anti-PD-1 therapy, retreatment with anti-PD-1 achieved modest responses. Of 34 patients who received a second course of anti-PD-1 therapy, only five (14.7%) had an objective response; specifically, two (5.9%) achieved a CR and three (8.8%) had tumor shrinkage.[11] Ongoing trials in refractory metastatic melanoma aim to reach better salvage efficacy in ORR than with single agent anti-PD-1 therapy or combination CTLA4/PD-1 inhibition.

1.2 Nivolumab

Nivolumab is a humanized monoclonal IgG4 antibody that targets the PD-1 protein. This monoclonal antibody was evaluated in a phase I/II study in 296 patients with a variety of heavily pretreated malignancies, including 107 patients with melanoma.[12] Updated efficacy data with an additional one year follow up for the melanoma cohort showed that the overall ORR was 31% for the entire melanoma patient cohort and an additional 7% of patients had stable disease.[13] No clear-cut dose response relation was observed, although a dose of 3mg/kg had the highest response rate (41%). Median duration of response was 24 months.

Grade 3 or 4 treatment related adverse events (AE) were observed in 32 of 296 patients (14%) enrolled in the study.[12] A variety of autoimmune side effects were observed, including pneumonitis, vitiligo, hepatitis, hypophysitis, thyroiditis, and colitis.

Several phase 3 trials have been conducted to evaluate the efficacy and safety of nivolumab in unresectable or advanced melanoma. An international phase 3 randomized controlled trial by Weber et al. evaluated nivolumab as second-line or later-line therapy. Specifically, if patients had progressed after ipilimumab, (and if indicated) BRAF inhibitor therapy, they were randomly assigned to intravenous nivolumab 3mg/kg every 2 weeks or investigator choice chemotherapy (ICC) with decarbazine or paclitaxel combined with carboplatin. From December 2012-January 2014, 272 patients were randomized to nivolumab and 133 to chemotherapy. ORR of first 120 patient on nivolumab was 32% versus 10% in chemotherapy group. Grade 3-4 AEs related to nivolumab was observed in 12 (5%) of patients, which included increased lipase, transamintis, anemia, and fatigue.[4] Updates to this study showed longer median duration of response for nivolumab versus ICC (32 months vs. 13 months), and confirmed overall response rate of nivolumab (27% versus 10% in ICC).[14] Preliminary results of this study led to FDA approval of nivolumab in refractory melanoma on December 22, 2014.

A second phase 3 study by Robert et al. (CheckMate 066) randomly assigned 418 previously untreated patients with metastatic melanoma without a BRAF mutation to receive nivolumab 3mg/kg every two weeks and dacarbazine-matched placebo every three weeks or dacarbazine and placebo from January 2013 to February 2014. At one year, overall rate of survival was 73% in nivolumab group versus 42% in dacarbazine group. Median PFS was 5 months in nivolumab group versus 2.2 months in dacarbazine group. ORR was 40% versus 14%, respectively.[15] Three-year follow up of this study showed median OS of 37.5 months in nivolumab group and 11.2 months in dacarbazine group; three-year overall survival rates were 51.2% and 21.6% respectively. Treatment related grade 3/4 AEs were reported in 15.0% (31 of 206) of nivolumab treated patients, leading to 5% (10 of 206) discontinuing therapy. These included pruritis, diarrhea, and rash. Any grade AEs included vitiligo, erythema, hypothyroidism and infusion-related reaction.[16] This study led to FDA approval of nivolumab in treatment-naïve BRAF V600E wild-type unresectable or metastatic melanoma on November 23, 2015.

1.3 Talazoparib

Poly ADP ribose polymerase-1 (PARP1) is a protein responsible for repairing single-strand breaks in DNA. Mutations in BRCA1 and BRCA2 cause errors in DNA repair. Talazoparib is a potent, orally bioavailable, small molecule PARP inhibitor in development for the treatment of a variety of human cancers. Drugs that inhibit PARP1 cause multiple double strand breaks (DSBs) to form in tumors with BRCA1 and BRCA2 mutations that cannot be repaired, leading to cell death, a cytotoxic effect referred to as synthetic lethality. Studies have demonstrated clinical benefit with PARP inhibitors in treatment of germline *BRCA1/2*-mutant breast, ovarian, and prostate cancers. A more recent study suggests that PARP inhibitors trap the PARP1 and PARP2 enzyme at sites of damaged DNA, and thus prevent DNA repair, replication, and transcription.[17]

In vitro studies have demonstrated that the PARP inhibitor, talazoparib, has more potent PARP trapping than other PARP inhibitors in clinical development.[18,19] Additionally, PARP inhibitor-mediated DNA damage has been shown to increase the immunogenicity of tumor cells, as evidenced by talazoparib promoting T cell and natural killer cell infiltration in a murine model of ovarian cancer.[20] Talazoparib has also been shown to increase tumor expression of programmed death-ligand 1 (PD-L1) *in vitro* and *in vivo*.[21] Therefore, the use of talazoparib in combination with the immune checkpoint inhibitor, nivolumab, may have a synergistic immunotherapeutic and antitumor effect.

Talazoparib has been studied in Phase I and II (ABRAZO) trials in solid tumors, and in a Phase III (EMBRACA) study in locally advanced or metastatic breast cancer with germline *BRCA* mutations. In the Phase I trial, the most common adverse events related to talazoparib were anemia, thrombocytopenia, and mild-to-moderate fatigue.[22] Overall, talazoparib was tolerated well in the EMBRACA trial. Of 287 patients in the talazoparib arm, grade 3 or 4 hematologic adverse events, primarily anemia, occurred in 55% of the patients. Nonhematologic adverse events like diarrhea and nausea, occurred in 32% of patients; however, the majority of nonhematologic adverse events in the talazoparib group were grade 1 in severity. Patients treated with talazoparib (1 mg QD) had significantly

longer median progression-free survival than those receiving physician's choice of chemotherapy (8.6 vs. 5.6 months, respectively; 95% CI: 0.41–0.71; HR: 0.54; $p<0.0001$).[23] Patients who received talazoparib had significant overall improvements in patient-reported global health status/quality of life scores and a significantly greater delay in time to clinical deterioration.[24] Based on this study, talazoparib was approved for use by the US Food and Drug Administration for the treatment of adults with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in 2018.

1.3.1 Talazoparib Clinical Experience

Talazoparib is a potent, orally bioavailable, small molecule PARP inhibitor in development for the treatment of a variety of human cancers.

As of 30 November 2016, approximately 439 patients have received talazoparib in company-sponsored studies in hematologic malignancies and solid tumors. Studies in solid tumors include a Phase 1 study (PRP-001[22]) in advanced or recurrent solid tumors, a Phase 1 study in advanced malignancies (PRP-002), a Phase 2 study (673-201[25]) in locally advanced and/or metastatic breast cancer patients with a germline BRCA defect, a Phase 3 study (673-301[23]) in locally advanced or metastatic breast cancer with a germline BRCA defect, a Phase 1 hepatic impairment study (MDV3800-02), a Phase 1 absorption, distribution, metabolism and excretion (ADME) study (MDV3800-03[26]), and a Phase 1 study on cardiac repolarization (MDV3800-14[27]).

As of 30 November 2016, aggregate safety data from 3 company-sponsored clinical studies evaluating talazoparib monotherapy at the proposed dose of 1 mg QD in patients with advanced malignancies (Phase 1 studies PRP-001 and MDV3800-14 and Phase 2 study 673-201; 164 patients total) provide the basis for the most common treatment emergent adverse events (TEAEs). The most common TEAEs associated with talazoparib (>20%) occurring in patients who received 1 mg QD talazoparib were anemia (42.1%), fatigue (36.6%), nausea (29.3%), thrombocytopenia (25.6%), neutropenia (20.7%), and alopecia (20.1%). The most common Grade 3 or higher drug-related TEAEs occurring in ≥5% of patients were anemia (28.0%), thrombocytopenia (16.5%), and neutropenia (12.2%).

Serious AEs (SAEs) occurred in 52 of 164 patients (31.7%) who received 1 mg QD talazoparib. SAEs occurring in ≥2% of patients were pleural effusion (4.3%), anemia and dyspnea (3.7% each), and neoplasm progression and thrombocytopenia (2.4% each). Fourteen patients had SAEs considered related to talazoparib, which included anemia (3.0%); thrombocytopenia (2.4%); platelet count decreased (1.2%); and increased transaminases, neutropenic sepsis, and vomiting (0.6% each).

A total of 12 of 164 patients (18.8%) who received 1 mg QD talazoparib had a TEAE that led to death (6 associated with the underlying malignancy including 1 also associated with bronchopneumonia; 2 dyspnea; and 1 each disease progression, lung infection, hypoxia, and respiratory failure). Of these events, none were assessed as related to talazoparib.

Among the 164 patients who received 1 mg QD talazoparib, 19.5% had a TEAE that led to dose reduction and 57.3% had a TEAE that led to dose interruption. The most common TEAEs that led to dose reduction or interruption were associated with myelosuppression. Five of 164 patients (3.0%) treated with talazoparib at a dose of 1 mg QD permanently discontinued talazoparib due to a TEAE. The TEAEs that led to study drug discontinuation were anemia, increased ALT, increased AST, metastatic breast cancer, and dyspnea.

1.3.2 Clinical Efficacy of Talazoparib in Patients with Advanced Solid Tumors

A total of 110 patients with advanced tumors with DNA repair pathway abnormalities, particularly those associated with BRCA and phosphatase tensin homolog (PTEN) dysfunction, were enrolled in the Phase 1 study PRP-001, which was completed in March 2015.[22] The maximum tolerated dose (MTD) of talazoparib was defined as 1 mg QD and it was used in the expansion phase of the study in patients with breast, ovarian/primary peritoneal, and pancreatic cancer with deleterious germline mutations; small cell lung cancer (SCLC); and Ewing sarcoma. As of 13 February 2015, the proportion of patients with breast, ovarian/primary peritoneal, and pancreatic cancers with BRCA mutations who were treated with talazoparib at 1 mg QD and had objective responses according to RECIST v1.1 was 50% (7 of 14; 95% CI: 23.0, 77.0), 41.7% (5 of 12; 95% CI: 15.2, 72.3), and 20.0% (2 of 10), respectively. Cancer patients harboring BRCA mutations who are resistant to platinum-based chemotherapy display decreased sensitivity to PARP inhibitors.[28]

1.3.3 Clinical Efficacy of Talazoparib in Patients with Germline BRCA Mutations and Locally Advanced and/or Metastatic Breast Cancer

The ongoing Phase 2, open-label, 2-stage, 2-cohort study, 673-201, is evaluating talazoparib in patients with locally advanced or metastatic breast cancer with deleterious germline BRCA mutations. Enrolled patients included those who were platinum-sensitive (Cohort 1) and patients who received at least 3 prior chemotherapy regimens and no prior platinum therapy (Cohort 2). As of 1 September 2016, the data cut-off for the primary analysis, 83 patients with locally advanced or metastatic breast cancer with deleterious germline BRCA mutations were tumor evaluable (48 patients in Cohort 1; 35 patients in Cohort 2), and 9 patients were continuing on treatment. Efficacy analyses were conducted by independent central radiology assessment. The ORR was 20.8% (95% CI: 10.47, 34.99) in Cohort 1, 37.1% (95% CI: 21.47, 55.08) in Cohort 2 and 27.7% (95% CI: 18.45, 38.62) overall. This response rate, which included 2 CRs and 8 PRs in Cohort 1 and 13 PRs in Cohort 2, is considered clinically meaningful as these populations have a poor prognosis.[25]

The landmark EMBRACA phase 3, randomized, open-label trial for patients with advanced breast cancer and a germline BRCA1/2 mutation (n = 431) compared patients treated with single agent talazoparib (1mg daily) or standard single-agent chemotherapy of physician's choice. 287 were assigned to receive talazoparib. Median PFS was significant longer in the talazoparib group than in the standard-therapy group (8.6 months vs 5.6 months; HR 0.54; 95% CI 0.41-0271 $p<0.001$). The ORR was higher in the talazoparib group than in the standard-therapy group (62.6% vs. 27.7%; OR 5; 95% CI 2.9-8.8; $p<0.001$).

Additionally, patient-reported outcomes favored talazoparib; significant overall improvements and significant delays in the time to clinically meaningful deterioration were observed. Grade 3-4 hematologic events (anemia) occurred in 55% of patients who received talazoparib and 38% of patients who received standard therapy. Nonhematologic adverse events like diarrhea and nausea, occurred in 32% of patients; however, the majority of nonhematologic adverse events in the talazoparib group were grade 1 in severity.[23,24]

1.3.4 Pharmacokinetics of Talazoparib in Humans

PK analysis for talazoparib was conducted based on 6207 PK observations of 490 patients with advanced cancer from 4 clinical trials, Studies PRP-001, PRP-002, 673-201, and 673-301. The PK of talazoparib as a single agent was evaluated in 142 adult patients with cancer, including 109 patients with solid tumors (Study PRP-001) and 33 with hematologic malignancies (Study PRP-002). Doses of 0.025 mg to 2 mg were administered orally as a single dose or as QD doses. This dose range bracketed the 1 mg QD dose used in ongoing safety and efficacy studies, and provided a framework for assessing dose linearity. As the PK of talazoparib was similar in patients with solid tumors and hematologic malignancies, and no differences were apparent between males and females, the results are summarized collectively.

Oral absorption of talazoparib was rapid and independent of dose after administration of single or QD doses. Peak talazoparib concentrations were generally reached approximately 1 to 8 hours post-dose. Exposure increased approximately dose-proportionally with increasing doses. At 1 mg/day, the mean t1/2 was approximately 2 days; the mean apparent volume of distribution (V/F) was 415 L, indicating extensive extravascular distribution.

Steady state was reached in approximately 2 to 3 weeks with daily administration. Apparent oral clearance (CL/F) of talazoparib appeared to be dose linear, with a mean CL/F across doses of approximately 5 L/h. Renal excretion was a major elimination pathway for unchanged parent talazoparib. Following oral administration, 44% to 90.6% of the dose was recovered in urine as unchanged parent drug over 24 hours at steady state for doses up to 1 mg QD. Mean renal clearance ranged from 1.38 L/h to 4.96 L/h independent of dose, suggesting linear urinary elimination kinetics.

Following repeated administration at 1 mg QD, talazoparib accumulated approximately 2.4-fold relative to a single dose. At steady state, the mean maximum plasma concentration (Cmax) was 21.0 ng/mL (55 nM), the mean plasma trough concentration (Ctrough) was 3.72 ng/mL (9.87 nM), and the mean area under the plasma concentration-time curve (AUC) was 202 ng*h/mL (532 nM*h). The Ctrough of talazoparib at steady state at 1 mg QD is above the Ctrough values at the efficacious dose of 0.33 mg/kg daily used in some of the xenograft models (1.3 nM).

PK data from a food-effect study showed that food had no effect on the extent of absorption of talazoparib (AUC) but decreased the rate of absorption (Cmax was 46% lower and time to Cmax [Tmax] was 2.63 hours later); however, this reduction in the rate of absorption following a single dose is not clinically relevant because talazoparib accumulates 2.4-fold

at steady state after 1 mg QD dosing. Furthermore, AUC or Ctrough is thought to drive efficacy, not Cmax; therefore, talazoparib can be taken with or without food. Talazoparib is being administered without regard to food in ongoing safety and efficacy studies.

A preliminary population PK analysis used data from patients in Studies PRP-001 and PRP-002 to assess the effects of renal function on the PK of talazoparib. The talazoparib CL/F in patients with mild renal impairment (creatinine clearance [CLCR] 60-89 mL/min) was similar compared with patients with normal renal function (CLCR ≥90 mL/min). In patients with moderate renal impairment (CLCR 30-59 mL/min), the talazoparib CL/F was decreased by 44% from normal, resulting in higher talazoparib exposure.

The effect of renal impairment on talazoparib PK is also being investigated in the ongoing study MDV3800-01.

The effect of hepatic impairment on talazoparib PK is being investigated in the ongoing MDV3800-02 study.

The potential for talazoparib to affect the PK of other drugs was assessed through in vitro experiments and is described in the talazoparib IB.[29] For additional information on pharmacokinetics, metabolism, drug-drug interactions, safety, efficacy and any additional information on talazoparib, please refer to the investigator brochure.

1.3.5 Clinical Experience in Patients with mCRPC Treated with PARP Inhibitors as a Single Agent or in Combination with Immunotherapy

The PARP inhibitor olaparib given as single agent was evaluated in a Phase 2 study in 50 patients with previously treated mCRPC.[30] Of the 50 patients, all patients had received prior treatment with docetaxel, 49 (98%) had received abiraterone or enzalutamide, and 29 (58%) had received cabazitaxel. Of the 49 patients evaluable for response (defined either as an objective response according to RECIST v1.1, or as a reduction of at least 50% in the prostate-specific antigen (PSA) level or a confirmed reduction in the circulating tumor-cell count from 5 or more cells per 7.5 mL of blood to less than 5 cells per 7.5 mL), 16 patients achieved a response (33%; 95% CI: 20.0, 48.0). Homozygous deletions, deleterious mutations, or both were identified in DNA-repair genes in 16 patients (33%) and 14 of these patients (88%) achieved a response.

The combination of olaparib with durvalumab was evaluated in a Phase 1/2 study in 17 patients with mCRPC with and without somatic or germline DDR mutations. Overall, median radiographic progression-free survival (rPFS) for all patients was 16.1 months (95% CI: 4.5-16.1 months) with a 12-month rPFS of 51.5% (95% CI: 25.7-72.3%). Activity was seen in patients with alterations in DDR genes with median rPFS of 16.1 months (95% CI: 7.8-18.1 months). 53% (n = 9) had a radiographic and/or PSA response (defined as ≥50% decline in PSA). Patients with fewer peripheral myeloid-derived suppressor cells and with alterations in DDR genes were more likely to respond. The 12-month PFS probability was 83% (95% CI: 27.3-94.5%) in patients with mutations, compared to 36.4% (95% CI: 11.2-62.7%) for those without mutations ($p = 0.031$). Most

common treatment-related grade 3 or 4 adverse events were anemia (24%), lymphopenia (12%), infection (12%), and nausea (12%). Four patients had immune-related adverse events (irAEs) of any grade, including two with acute onset hearing loss, one with optic neuritis, and one patient with synovitis. All were treated with high-dose steroids and symptoms improved to near complete resolution with exception of one patient with hearing loss, who required use of a hearing aid.[31]

Veliparib given as a single agent was investigated in a Phase 1 dose-finding study in patients with advanced solid tumors; overall, 98 patients were enrolled, of whom 78 had disease with a germline BRCA defect.[32] Three patients with BRCA2 germline mutated mCRPC were enrolled at the recommended Phase 2 dose (RP2D) and were evaluable for response. In these patients, the ORR was 2/3 (66%) and all patients had a PSA reduction >50% with respect to baseline.

A Phase 1 study evaluated niraparib given as a single agent in 100 patients with advanced solid tumors.[33] A total of 23 mCRPC patients were enrolled and 21 of these received niraparib at 290 mg QD or 300 mg QD. No mCRPC patient achieved an objective response but 9 patients had SD with a median duration of 254 days (range: 124–375 days) and 1 patient had a >50% decrease in the concentration of PSA and had remained on study for 306 days.

RP2D for talazoparib in combination with avelumab is currently being studied in Phase 1b/2 trial NCT03330405 in patients with advanced or metastatic solid tumors. DLT rate of avelumab in combination with talazoparib is also being studied in this clinical trial.

Additionally, combination niraparib (200mg daily) and pembrolizumab (200mg IV every 21 days) was recently studied in a phase 2 trial of 55 patients with advanced or metastatic TNBC, and showed reasonable efficacy with a tolerable safety profile. This study found an ORR of 21% and DCR of 49% with a tolerable safety profile. Most common treatment-related adverse events of grade 3 or higher were anemia, thrombocytopenia, and fatigue; two patients experienced grade 3 immune-related adverse events.[34]

1.4 Rationale

Limited studies are available to understand the role of PARP inhibitors in treatment of melanoma. Czyz et al. conducted *in vitro* studies looking at the effect of the PARP inhibitor olaparib in eight DSB repair genes expressed in melanoma that were identified in The Cancer Genome Atlas (TCGA) database. Specifically, in melanoma cells displaying down regulation of the DSB repair gene LIG4, PARP inhibition alone and in combination with dacarbazine caused accumulation of toxic DSBs and apoptosis, suggesting that the phenomenon of synthetic lethality could be applied in melanoma.[35] Furthermore, this study showed that olaparib was selectively toxic to DSB repair deficient human melanoma

xenografts, which was further enhanced in the presence of dacarbazine. This suggests that melanomas could be sensitive to PARP inhibitor-mediated synthetic lethality due to their putative deficiencies in DNA repair pathways. Further elaborating on this concept, in the B16F10 murine syngeneic melanoma model, the PARP inhibitor (ABT-888), now known as veliparib, strongly potentiated temozolomide (TMZ) with significant antitumor efficacy in a dose-proportional manner, but did not show single agent activity.[36,37] Preclinical studies with PARP inhibitor therapy in DSB repair deficient melanoma tumors suggest a synthetic lethality and a synergistic effect.

In vitro studies have demonstrated that the PARP inhibitor, talazoparib, has more potent PARP trapping than other PARP inhibitors in clinical development.[18,19] Additionally, PARP inhibitor-mediated DNA damage has been shown to increase the immunogenicity of tumor cells, as evidenced by talazoparib promoting T cell and natural killer cell infiltration in a murine model of ovarian cancer.[20] Talazoparib has also been shown to increase tumor expression of programmed death-ligand 1 (PD-L1) *in vitro* and *in vivo*.[21] Furthermore, olaparib has been shown to increase cytotoxic T cell infiltration by augmenting STING (stimulator of interferon genes) intracellular pathway, an innate immune response activated by cytosolic DNA (perhaps a consequence of DNA damage by olaparib) that can lead to enhanced interferon (IFN) production and further T cell recruitment and activation.[38] Therefore, the use of talazoparib in combination with the immune checkpoint inhibitor, nivolumab, may have a synergistic immunotherapeutic and antitumor effect.

Middleton et al. conducted a Phase II randomized, controlled, double-blinded clinical trial evaluating veliparib with TMZ in patients with metastatic melanoma. Patients (n = 346) were randomized to veliparib 20mg with TMZ, veliparib 40mg with TMZ, or placebo with TMZ.[39] Median PFS was 3.7 [95% CI, 3.0-3.5], 3.6 [95% CI, 1.9-4.1], and 2 [95% CI, 1.9-3.7] months in the 20 mg, 40mg, and placebo arms, respectively. The ORR was 10.3%, 8.7%, and 7.0%. Although not statistically significant, the PFS was almost doubled in the combination arms compared to the placebo arm, supporting that PARP inhibition promotes synthetic lethality and potentiates TMZ activity in melanoma. PFS was better in patients receiving veliparib with low ERCC1 expression (5.6 vs. 1.9), wildtype BRAF V600 status (2.4 vs. 1.8), and positive p16 status (3.8 vs. 1.8) when compared to placebo.[39] ERCC1 is part of the nucleotide excision repair pathway. Low ERCC1 expression coupled with PARP inhibition may hinder DNA repair following TMZ exposure, leading to lethal DSBs during replication. These data suggest that biomarker selection may influence the efficacy of PARP inhibition when combined with TMZ.

Biomarker selection strongly influences the efficacy of PARP inhibition. A study by Mateo et al. looked at treatment with the PARP inhibitor olaparib in patients with metastatic castration-resistant prostate cancer with DNA-repair defects.[30] Of 49 patients, 16 had a response to olaparib (33%; 95% CI, 20-48). In these 16 patients, next-generation sequencing identified homozygous deletions, deleterious mutations, or both in DNA-repair genes, which included *BRCA1/2, ATM*, Fanconi anemia genes, and *CHEK2*. The hazard ratio for radiologic progression in the biomarker-positive group as compared with the biomarker-negative group was 0.24 (95% CI, 0.11-0.50). This study showed that treatment

with the PARP inhibitor olaparib in patients with metastatic prostate cancer who had germline defects in DNA-repair genes led to a high response rate.[30] Eligible alterations were in *BRCA1/2, ATM, PALB2, CHEK2, FANCA, HDAC2, RAD51, MLH3, ERCC3, MRE11*, and *NBN*. Many of these, specifically *BRCA1/2, ATM, ATR, PALB2, CHEK1/2, RAD51, FANCA*, and *HDAC* have been reported to have a synthetic lethal interaction with PARP inhibition, and have been termed "*BRCA*-ness."[17,40,41]

"*BRCA*-ness" has not specifically been studied in melanoma; however our imputations from TCGA data and our own data from a local familial melanoma registry suggest a substantial presence of germline and somatic mutations in this patient population. Huang et al. identified pathogenic germline mutations in all cancers using The Cancer Genome Atlas. Out of 470 skin cutaneous melanoma patients that have germline sequencing data available, 52 (11%) have pathogenic/likely pathogenic germline mutations, and 25 patients (5.3%) have mutations in *BRCA1/2* or "*BRCA*-ness."[42] Looking at somatic mutations involving *BRCA1/2* or "*BRCA*-ness" genes in melanoma in TCGA, 16% (n = 72) possess actionable/likely actionable mutations when variants of undetermined significance (VUS) are excluded. If VUS are included, 58% (n = 255) of patients possess likely actionable mutations.[43,44] Up to 63% of melanoma patients possess germline and/or somatic mutations in DSB repair genes that could be targeted with PARP inhibitor therapy. In the first 130 melanoma patients accrued to our Gross Family Melanoma Registry at the Cleveland Clinic, 19% (25) had a germline pathogenic/likely pathogenic mutation, of which 52% (13) were in genes associated with *BRCA1/2* and "*BRCA*-ness."[45] This represents a significant proportion of patients with metastatic melanoma that could benefit from PARP inhibitor therapy.

We propose that PARP inhibition with talazoparib at a dose of 1mg orally daily will have synergistic antitumor activity in combination with nivolumab 480mg intravenously every 4 weeks in unresectable and metastatic melanoma patients with DNA-repair defects in BRCA1/2 or BRCA-ness that have progressed on prior CPI therapy and improve the objective response rate from about 10% to 30% with limited toxicity.

1.5 Background and rationale of correlative studies

This study intends to characterize the activity of nivolumab in combination with talazoparib, with the aim of increasing the clinical benefit seen historically with single agent nivolumab. A key mechanistic hypothesis underpinning the combination is that increased DNA damage and cell death mediated by talazoparib will lead to enhanced immune priming and tumor immunogenicity, enabling a more effective anti-tumor immune response to be promoted by nivolumab. Given this hypothesis, one subgroup of patients likely to benefit from the combination will be those whose tumors are most sensitive to talazoparib-mediated cell death and DNA damage. Several biomarkers have the potential to identify patients with such increased sensitivity to talazoparib, one of these will be employed in the context of this study, the presence of pathogenic or likely pathogenic

germline or somatic defects in a panel of DDR genes.[46] A correlative study will include that prior to study enrollment, we will obtain tumor-biopsy samples from all patients to conduct biomarker studies from both germline and somatic DNA, including sequencing to identify genomic aberrations and tumor mutational burden (TMB) associated with sensitivity to PARP inhibition in this disease.

Complementing the DDR biomarkers described above, a number of assessments will be undertaken as correlatives to understand the immune context of patient tumors, which may also be a contributing factor in response to the combination of talazoparib and nivolumab. These include assessment of immune cell types in the tumor using immunohistochemistry, assessment of infiltrating immune cell number and phenotype by immunohistochemistry or flow cytometry, relative expression of genes representative of immune activation versus suppression by gene expression profiling, and assessment of mutational or neoantigen load within tumors.

To enable the above mentioned biomarker assessments, the collection of pre-treatment tumor specimens, including a tumor tissue sample from a biopsy performed during, or within 1 year of, the screening period. See section 4.0 for further clarification on pre-treatment tumor specimen.

Given the limited ability to assess tumor tissue-based biomarkers longitudinally, biomarkers will also be measured in peripheral blood at time points pre-treatment, post-treatment and at progression. The primary aim of these measurements is to identify mechanistic biomarkers for the combination of nivolumab and talazoparib. Such biomarkers may have value in predicting response to treatment.

In the event that clinical benefit is not observed or is transient, assessment of reasons for lack of benefit may help guide patient selection for future development of the combination. For these reasons, tumor biopsies performed at the End-of-Treatment (EOT) visit or in the event of permanent treatment discontinuation due to disease progression, are requested from patients, unless clinically contraindicated. If the Sponsor considers sufficient data have been obtained to confirm possible causes for lack of clinical benefit, collection of tumor tissue from EOT tumor biopsies may be discontinued.

1.5.1 Banked Biospecimen Collection Rationale

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS also can be used in research on melanoma. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited by local regulations or ethics committee (EC) decision.

2.0 Objectives

2.1 Primary Objective

The primary objective is to determine the clinical efficacy of nivolumab plus talazoparib in patients with unresectable or metastatic melanoma with *BRCA1/2* or other DNA damage repair mutations (defined as *BRCA*-ness), as measured by objective response rate (ORR) every 12 weeks for a period of approximately 12 months.

2.2 Secondary Objectives

- Determine progression free survival (PFS) in unresectable or metastatic melanoma patients treated with nivolumab plus talazoparib.

- Determine overall survival (OS) in unresectable or metastatic melanoma patients treated with nivolumab plus talazoparib.

- Evaluate treatment-related adverse events in patients treated with nivolumab plus talazoparib.

- To assess the anti-tumor activity of nivolumab in combination with talazoparib in unresectable or metastatic melanoma patients with *BRCA1/2* or other DNA damage repair mutations (defined as *BRCA*-ness), as measured by immune-related objective response rate (irORR) every 12 weeks for a period of approximately 12 months.

- Determine immune-related progression free survival (irPFS) in unresectable or metastatic melanoma patients treated with nivolumab plus talazoparib.

2.3 Correlative Objectives

- Measure adaptive and innate cellular immunofiltration into tumor (by tumor biopsies) and peripheral circulating T cells (by PBMCs) at baseline (pre-treatment), after treatment initiation (at about 12 weeks), and at time of progression, and to correlate activity with response to treatment.

- Assess total somatic tumor mutation burden by sequencing at baseline (pre-treatment), after therapy at 12 weeks, and at time of progression to evaluate DNA landscape and its effect on sensitivity of combination nivolumab and talazoparib therapy.

- Assess patient reported outcomes for adverse events while on combination therapy at baseline and before each cycle (about every 4 weeks) of nivolumab.

2.4 Endpoints

2.5 Primary Endpoint

Best overall response, defined as complete response (CR) and partial response (PR) by RECIST 1.1 recorded from the start of the treatment until disease progression or recurrence.

2.6 Secondary Endpoints

- PFS, defined as the time from the first dose of study treatment to the date of disease progression by RECIST 1.1 or death due to any cause, whichever occurs first.

- OS, defined as the time from the first dose of study treatment to the date of death.

- Number of participants with treatment-related adverse events, as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

- Immune-related overall response (irOR), defined as immune-related complete response (irCR) and immune-related partial response (irPR) by irRECIST (See Appendix 16.2) recorded from the start of the treatment until disease progression.

- irPFS, defined as the time from the first dose of study treatment to the date of disease progression by irRECIST or death due to any cause, whichever occurs first.

2.7 Correlative Endpoints

- Assess anti-tumor response by measure of immune-infiltration, including, but not limited to, expression of CD8, CD4, Treg (FOXP3), NK cells (CD56) into tumors, by flow cytometry and immunohistochemistry on tumor biopsies and peripheral blood mononuclear cells (PBMCs) at baseline, 12 weeks, and at progression.

- Assess longitudinal genomic evolution by sequencing and gene expression analysis at baseline, 12 weeks, and at progression to evaluate DNA landscape and its correlation to response.

- Assess patient reported outcomes for adverse events, as measured by PRO-CTCAE while on combination therapy at baseline and before each cycle (every 4 weeks) of nivolumab for a period of 12 months.

3.0 Study Design

3.1 Study Design and Schema

A phase II, single arm, multi-institutional, open label trial in a sample size of 37 primary or recurrent, unresectable or metastatic melanoma patients progressed on prior checkpoint inhibitor therapy with germline or somatic mutations in *BRCA1/2* or *BRCA*-ness. Prior to study enrollment, patients will initially be screened for germline or somatic mutations in one of the following genes: *ARID1A, ARID1B, ARID2, ATM, ATR, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CDK4, CDK12, CHEK1, CHEK2, DSS1, EMSY, ERCC3, FANCA, FANCD2, HDAC2, IDH1, LIG4, LIG3, MDC1, MLH1, MLH3, MRE11, NBN, PALB2, PRKDC, RAD50, RAD51, RAD54, XRCC6. Genomic markers of homologous*

repair deficiency such as gLOH are also permitted as inclusion criteria; other markers of HRD may be included as determined by review by the medical monitor. Prior to study enrollment, we will obtain tumor-biopsy samples to conduct biomarker studies from both germline and somatic DNA, including targeted panel and transcriptome sequencing to identify genomic aberrations associated with sensitivity to PARP inhibition in this disease. Patients with identified mutations listed above, will then be enrolled in the study. Patients will be treated simultaneously with standard of care therapy, nivolumab 480mg intravenously every 4 weeks plus investigational agent, talazoparib 1mg orally once daily. Beginning with Cycle 1 Day 1, all patients enrolled will simultaneously begin treatment with talazoparib 1mg daily, unless otherwise specified, and nivolumab 480mg every 4 weeks.

Patients will be assessed every 4 weeks and lab work will be obtained at that time. CT imaging scans will be obtained every 12 weeks to assess treatment response. If a patient achieves a CR, treatment with nivolumab will be continued for a total of one year from time of CR and talazoparib will be continued. In patients with partial response (PR) or stable disease (SD), treatment with both agents will be continued until the time of disease progression or adverse events.

3.2 Number of Subjects

Approximately 37 analyzable subjects will be enrolled in this trial. For sample size calculation please see Section 14.

3.3 Replacement of Subjects

Patients who receive at least one dose of treatment with nivolumab and talazoparib will contribute to the efficacy analysis. Any subject who receives at least one cycle or dose of treatment on this protocol is evaluable for toxicity. With 10% of patients potentially not evaluable due to drop out or loss to follow up, 37 patients would need to be enrolled for a total of 33 analyzable. Patients who are not evaluable are defined as patients who are consented and enrolled in the study, but have physically moved away that it would be too burdensome to follow up with institution, those who are lost to follow up defined as individuals who enroll but do not receive treatment, imaging, and are not present at scheduled office visits.

4.0 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

___ 4.1.1 Subjects must have a germline or somatic DNA damage repair mutation or deletion including any one of the following: *ARID1A, ARID1B, ARID2, ATM, ATR, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CDK4, CDK12, CHEK1, CHEK2, DSS1, EMSY, ERCC3, FANCA, FANCD2, HDAC2, IDH1, LIG3, LIG4, MDC1, MLH1, MLH3, MRE11, NBN, PALB2, PRKDC, RAD50, RAD51, RAD54, XRCC6, or gLOH*. The result may have been obtained from one of the following test providers: Myriad Genetics, Invitae, Ambry, Quest, Color Genomics, IMPACT, Foundation Medicine (tissue or ctDNA based), Tempus, Caris, Guardant, or another CLIA approved tissue and/or serum based next generation sequencing-based assay.

___ 4.1.2 Subjects must have histologically or cytologically confirmed diagnosis of primary or recurrent metastatic melanoma including cutaneous, mucosal, or uveal melanoma.

___ 4.1.3 Subjects must have received prior checkpoint inhibitor therapy (defined as anti-CTLA4 or anti-PD-1 or combination anti-CTLA4/anti-PD-1), either for metastatic or unresectable disease or adjuvant therapy.

___ 4.1.4 Age at the time of enrollment should be greater than 18 years. Because no dosing or adverse event data are currently available on the use of nivolumab in combination with talazoparib in subjects ≤18 years of age, children are excluded from this study.

___ 4.1.5 ECOG Performance status ≤ 2.

___ 4.1.6 Subjects must have normal organ and marrow function as defined below:

- Hemoglobin ≥ 9.0 g/dl
- Absolute neutrophil count ≥ 1,500/mcL
- Platelet count ≥ 90,000/mcL
- Bilirubin ≤ 1.5 x ULN (except in subjects with Gilbert Syndrome, who can have a total bilirubin < 3.0mg/dL)
- AST (SGOT) ≤ 3.0 X upper limit of normal
- ALT (SGPT) ≤ 3.0 X upper limit of normal
- Serum Creatinine Clearance ≥ 30mL/minute. See section 7.1 for talazoparib dose adjustment for renal impairment.
  CrCl< 30mL/minute has not been studied in talazoparib.

___ 4.1.7 Measurable disease as defined by RECIST 1.1 criteria

___ 4.1.8 During screening, while taking study drug, and until 5 months after taking the final dose of study drug, women of childbearing potential (WOCBP) must practice one of the following methods of birth control:

- Use double-barrier contraception method defined as male use of a condom and female use of a barrier method (e.g., contraceptive

sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]).

- Use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months before the first study drug administration.
- Use of an intrauterine device.
- Have a male partner who has had a vasectomy (at least 6 months prior to study enrollment).
- Or must abstain from sexual intercourse completely.

___ 4.1.9 During screening, while taking study drug, and until 7 months after taking the final dose of study drug, men who are sexually active with WOCBP must practice one of the following methods of birth control:

- Have had a vasectomy (at least 6 months prior to study enrollment).
- Use double-barrier contraception method defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]).
- Partner use of an intrauterine device.
- Partner use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months before the first study drug administration.
- Or must abstain from sexual intercourse completely

___ 4.1.10 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

___ 4.1.11 Ability to swallow pills.

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment.

___ 4.2.1 Prior treatment with a PARP inhibitor.

___ 4.2.2 Prior anti-cancer therapy for melanoma less than 14 days prior to first dose of study drug.

___ 4.2.3 Known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery

prior to study enrollment, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable.

___ 4.2.4 Subjects with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, poorly controlled congestive heart failure, unstable angina pectoris or psychiatric illness/social situations that would limit compliance with study requirements.

___ 4.2.5 Known HIV or AIDS-related illness

HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with talazoparib. In addition, these subjects are at increased risk of lethal infections when treated with marrow suppressive therapy. Appropriate studies will be undertaken in subjects receiving combination antiretroviral therapy when indicated.

___ 4.2.6 Prior organ transplantation including allogeneic stem-cell transplantation.

___ 4.2.7 Poorly controlled or uncontrolled autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition or prior therapy requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Patients with endocrinopathies controlled on replacement drugs are eligible.

___ 4.2.8 Major surgery within 4 weeks prior to study enrollment.

___ 4.2.9 Current use of corticosteroids at the time of study enrollment, EXCEPT for the following:

a. Intranasal, inhaled, topical steroids, eye drops or local steroid injection (eg, intra-articular injection)

b. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent

c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

___ 4.2.10 Diagnosis of Myelodysplastic Syndrome (MDS)

___ 4.2.11 Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or detectable HCV RNA if anti-HCV antibody screening test positive).

___ 4.2.12 Current or anticipated use of a P-glycoprotein (P-gp) inducer (avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort), or inhibitor of breast cancer resistance protein (BCRP) (curcumin, cyclosporine, elacridar [GF120918], and eltrombopag). P-glycoprotein (P-gp) inhibitor (amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir,

itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valspodar, and verapamil) are allowed, but require a dose modification of talazoparib, see section 7.1.1,

___ 4.2.13 Inability to swallow capsules or known intolerance to talazoparib or its excipients.

___ 4.2.14 Pregnant women are excluded from this study because animal studies have demonstrated that nivolumab and talazoparib may cause fetal harm when administered to pregnant women. Breastfeeding women are excluded from this study because nivolumab and talazoparib may be excreted in human breastmilk and the potential for serious adverse reactions in nursing infants.

___ 4.2.15 Persisting toxicity related to prior therapy > Grade 1.

4.3 Inclusion of Women and Minorities

Men, women and members of all races and ethnic groups are eligible for this trial.

5.0 Registration

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Cleveland Clinic Lead Study Coordinator and will be provided a study number by contacting the study coordinator listed on the cover page.

6.0 Treatment Plan

6.1 Treatment Regimen Overview

Treatment will be administered on an outpatient basis.
Patients found to have a mutation in *BRCA1/2* or *BRCA*-ness who have enrolled in the trial, will begin treatment with both talazoparib 1mg orally daily on Cycle 1 Day 1 and nivolumab 480mg intravenously every 4 weeks and continue without interruption, unless necessitated by an adverse event.

Patients will have labs, survey, and an office visit every 4 weeks, prior to administration of nivolumab. Patients will have imaging scans completed every 3 months.

If a CR is achieved, treatment duration for nivolumab and talazoparib will be continued until one year from CR. For PR or SD, patients will continue talazoparib 1mg daily and nivolumab 480mg every 4 weeks until disease progression, unacceptable toxicity, or for 24 months of therapy.

Appropriate dose modification for talazoparib is described in Section 7.0 and 7.1 for renal impairment. No dose modification is permitted for nivolumab. Dose delays are permitted for talazoparib and nivolumab to manage toxicity.

Reported adverse events and potential risks of talazoparib and nivolumab are described in Section 8.0.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

6.1.1 Talazoparib Administration

Subjects will take Talazoparib 1mg orally on Days 1-28 of each (28 day) cycle unless otherwise specified..
Patients should self-administer talazoparib orally QD, with or without food. The capsules should be swallowed whole with a glass of water without chewing, dissolving, or opening them prior to swallowing.

Patients should be instructed to take talazoparib at approximately the same time each day and to not take more than the prescribed dose at any time.

If a patient misses a day of treatment or vomits any time after taking a dose, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed.

Patients should complete the Dosing Diary after taking each dose. If the patient misses a day of treatment or takes a dose different than was prescribed, the reason for the missed dose or different dose must be recorded in the Dosing Diary. The Dosing Diary should be returned to the site at every cycle.

6.1.2 Nivolumab Administration

Subjects will receive Nivolumab 480mg on Day 1 of each (28 day) cycle. Nivolumab will be administered IV over 30 (+/- 5) minutes.

6.4 General Concomitant Medications and Supportive Care Guidelines

The following medications are prohibited during the study:

- Prednisone greater than 10 mg (except when used in the management of adverse events)
- Any concurrent antineoplastic therapy for melanoma (ie, chemotherapy, extensive radiation therapy, or standard or investigational agents for treatment of melanoma).
- P-gp inducers or BCRP inhibitors (Appendix 5; Section 16.5)

Because there is a potential for interaction of nivolumab and talazoparib with other concomitantly administered drugs through the cytochrome P450 system, P-gp or BCRP inhibitors, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes, P-gp or BCRP inhibitors. Please refer to Appendix 5; Section 16.5 for a complete list.

Palliative (limited-field) radiation therapy is permitted, if all of the following criteria are met:

- The lesion being considered for palliative radiation is not a target lesion.

Subjects should receive full supportive care, including transfusions of blood and blood products, cytokines, antibiotics, antiemetics, etc. when appropriate.

6.5 Criteria for Removal from Study

Patients will be treated per protocol until:

• Disease progression,

- Immune-related RECIST v1.1 will be used to guide treatment; if imaging shows progressive disease, patients can continue study treatment at the investigator's discretion until confirmatory assessment by imaging ≥ 4 weeks later.

• Intercurrent illness that prevents further administration of treatment,

• The investigator considers the cessation of treatment, for safety reasons, to be in the best interest of the subject.

• Unacceptable adverse event(s) (Defined as unacceptable treatment related toxicity, NCI CTCAE version 5.0 Grade 3 or 4 that fails to recover to < Grade 3 within 4 weeks),

• Subject decision to withdraw from treatment (partial consent) or from the study (full consent),

• Lost to follow-up

• Pregnancy during the course of the study for a child-bearing participant,

• Death, or

• Sponsor reserves the right to temporarily suspend or prematurely discontinue this study. The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

6.5.1 Withdrawal of Consent

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product (in which case the withdrawal of consent form is not applicable) or also from study procedures and/or posttreatment study follow-up (in which case a withdrawal of consent form should be provided and signed). In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

6.5.2 Lost to Follow-up

If a patient does not return for a scheduled visit, every effort should be made to contact the patient and report their ongoing status. The Investigator should inquire about the reason for withdrawal, request that the patient return all unused talazoparib, request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the Investigator should be reported and documented in the patient's medical records.

6.6 Duration of Follow Up

Subjects will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

7.0 Dose Delays/Dose Modifications

Following dosing interruption due to toxicity at any time in the study, the talazoparib dose may need to be reduced, based on the worst toxicity reported, when treatment is resumed.

Dose reduction should be made in accordance with the guidance provided in Section 7.2.

Dose reduction of talazoparib by 1 dose level at a time will be allowed depending on the type and severity of toxicity encountered. Doses less than 0.5 mg are not permitted. Patients unable to tolerate 0.5 mg QD, will be permanently discontinued from talazoparib, but may continue on single agent nivolumab. Dose reductions of nivolumab are not permitted, however dose delays are permitted. Available dose levels for dose reductions for talazoparib are listed in Table 1.

Table 4. Dose Levels for Dose Reductions of Talazoparib

Dose Level	Talazoparib Dose (Oral)
D0	1 mg QD
D-1	0.75 mg QD
D-2	0.5 mg QD [a]

[a] Talazoparib dose de-escalation below 0.5 mg QD is not allowed.
D = dose; QD = once daily

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intra-patient dose re-escalation is not allowed.

7.1 Dose Modification for Talazoparib for Patients with Renal Impairment

For patients with moderate renal impairment, defined as CLcr 30-59 mL/min, the recommended dose of Talazoparib is 0.75 mg once daily. Please see Section 1.3.4 for more information. Also described in prescriber information/package insert.

7.1.1 Dose Modification for Talazoparib for use with p-glycoprotein inhibitors

If patients must be co-administered a p-gp inhibitor (amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valspodar, and verapamil), the talazoparib dose should be reduced to 0.75mg daily.

7.2 Study Treatment Modifications for Nivolumab and Talazoparib Drug-Related Toxicity (excluding immune-related adverse events)

Recommended nivolumab and talazoparib treatment modifications in case of investigational product (talazoparib) related toxicity is shown in Table 2. The specific guidelines are applicable in cases which can be attributed to one of the therapies. The instructions should be followed in the column regarding the therapy that toxicity is attributed to. In cases where an AE is possibly related to both drugs, the guidelines in both columns for both drugs should be followed. Patients who stop nivolumab or talazoparib for unacceptable toxicity may continue treatment with the drug that is not considered to be responsible for the toxicity observed.

Table 2 Treatment Modifications for Nivolumab and Talazoparib Drug-Related Toxicity (excluding immune-related adverse events)

Toxicity	Talazoparib	Nivolumab
Hematologic Toxicities		
Grade 1 and Grade 2	-No requirement for dose interruption or dose reduction.	-Continue as per schedule.
Anemia Grade ≥ 3 (hemoglobin < 8g/dL)	-Hold talazoparib and monitor weekly until resolve to baseline. -Talazoparib may be reduced by 1 dose level per section 7.0. -Permanently discontinue if persists for >4 weeks without recovery to baseline. Refer to hematologist for evaluation including assessment of possible MDS/AML.	-Hold nivolumab. -Re-initiate nivolumab once toxicity Grade ≤ 1 or baseline. -Permanently discontinue nivolumab if toxicity does not resolve to Grade ≤ 1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on nivolumab only)
Neutropenia Grade ≥ 3 (ANC<1000/µL)	-Hold talazoparib and monitor weekly until ANC ≥1500/µL. -Resume talazoparib based on the following recovery times: • ≤1 week: No change. • >1 week: Talazoparib may be reduced by 1 dose level, per Section 7.0. -Permanently discontinue talazoparib if persists for >4 weeks without recovery to ANC ≥1500/µL. Refer to hematologist for evaluation including assessment of possible MDS/AML.	-Hold nivolumab. -Re-initiate nivolumab once toxicity Grade ≤ 1 or baseline. -Permanently discontinue nivolumab if toxicity does not resolve to Grade ≤ 1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on nivolumab only)
Thrombocytopenia Grade ≥ 3 (platelets <50,000/µL)	-Hold talazoparib and monitor weekly until platelets ≥75,000/µL.	-Hold nivolumab.

	-Resume talazoparib based on the following recovery times: • ≤1 week: No change. • >1 week: Talazoparib may be reduced by 1 dose level, per Section 7.0. -Permanently discontinue talazoparib if persists for >4 weeks without recovery to platelets ≥75,000/μL. Refer to hematologist for evaluation including assessment of possible MDS/AML	-Re-initiate nivolumab once toxicity Grade ≤ 1 or baseline. -Permanently discontinue nivolumab if toxicity does not resolve to Grade ≤ 1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on nivolumab only)
Non-hematologic Toxicities		
Grade 1 and Grade 2	-No requirement for dose interruption or dose reduction.	-Continue as per schedule.
Grade 3	-Hold talazoparib. Resume talazoparib reduced by 1 dose level if toxicity resolves to Grade ≤1 or baseline within 4 weeks. -**Exceptions are:** Nausea, vomiting, or diarrhea lasting ≤72 hours; fatigue lasting <5 days; hypertension controlled with medical therapy; increase in indirect bilirubin indicative of Gilbert's syndrome; serum lipase or amylase lasting ≤7 consecutive days without	-Hold nivolumab. -Resume once toxicity is Grade ≤1 or baseline. -Permanently discontinue if toxicities does not resolve to grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. -**Exceptions are:** Laboratory values that do not have any clinical correlate. -For suspected immune-related toxicities follow guidance in Section 7.4.

	clinical signs or symptoms of pancreatitis; endocrinopathies controlled with hormonal therapy; laboratory values that do not have any clinical correlate. -If the same Grade 3 toxicity recurs, reduce by 1 dose level. -Permanently discontinue if toxicity does not improve to Grade ≤1 or baseline within 4 weeks. **-Exceptions are:** Laboratory values that do not have any clinical correlate. -Permanently discontinue if Grade 3 liver test abnormality. -Re-challenge may be considered once toxicity is Grade ≤1 or baseline, if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is identified. -For suspected immune-related toxicities due to nivolumab that require nivolumab delay or discontinuation, talazoparib should also be placed on hold until toxicity is Grade ≤1 or baseline.	
Grade 4	-Permanently discontinue talazoparib **-Exceptions are:** Laboratory values that do not have any clinical correlate. .	-Permanently discontinue nivolumb. **-Exceptions are:** Laboratory values that do not have any clinical correlate. -For suspected immune-related toxicities follow guidance in Section 7.4.

Abbreviations: AML = Acute Myeloid Leukemia; ANC=Absolute Neutrophil Count; MDS=Myelodysplastic Syndrome.

7.3 Management of Nivolumab Related Infusion Reaction

For management of nivolumab related infusion reaction, follow Institutional guidelines.

In the absence of any such guidelines, or per provider discretion, apply the following:

For Grade 1 symptoms: (Mild reaction; itching, rash, hives, fever, rigors): Stop the infusion, notify provider and study nurse. Initiate normal saline infusion at 500ml/hr, titrate up to maintain systolic BP >100. Administer diphenhydramine 50mg IV. Remain at bedside and monitor subject until recovery from symptoms.

The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction such as SOB, chest tightness, back pain, which requires therapy or infusion interruption but responds promptly to symptomatic treatment): Follow above for Grade 1 and add oxygen at 2L via nasal cannula and titrate to keep O2 saturation > 92%, and give hydrocortisone 100mg IVP once; remain at bedside and monitor subject until resolution of symptoms. If symptoms progress, do not re-dose medications already given, move on to treatment for severe / Grade 3 reactions. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate.

Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, anaphylaxis, bronchospasm, stridor, wheezing, respiratory distress, angioedema, systolic BP < 80mm Hg, or LOC. Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion] recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated): Immediately discontinue infusion of nivolumab. Follow guidelines for Grades 1 and 2 and add the following: Activate emergency response team as appropriate. Administer

medications from Grade 1 and 2 reaction guidelines if not yet given and add Epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution.

Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued.

In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

7.4 Immune-Related Adverse Events Toxicity Management

For patients receiving nivolumab, any AE suspected to be immune-related (irAE) should be managed according to the guidance for management of irAEs per ASCO guidelines.[47]

Treatment of irAEs is mainly dependent on severity (NCI CTCAE v5.0 grade), management summarized per ASCO guidelines below:

- Grade 1: continue nivolumab with close monitoring.
- For grade 2 toxicities, hold nivolumab. Consider resuming when symptoms and/or laboratory values revert to grade 1 or less. Corticosteroids (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent) may be administered.
- Grades 1 to 2 (persistent): manage similar to Grades 3 to 4 AE.
- Grades 3 to 4: treat with high dose corticosteroids; if suspected to be related to nivolumab, talazoparib should be withhold until toxicity resolves to Grade ≤1 or baseline.
- For Grade ≥3 immune-related toxicities suspected to be related to nivolumab, talazoparib should be withheld until toxicity resolves to Grade ≤1 or baseline. Nivolumab should be held for grade 3 toxicities and high-dose corticosteroids (prednisone 1 to 2mg/kg/day or methylprednisolone IV 1 to 2mg/kg/day). Corticosteroids should be tapered over the course of at least 4-6 weeks. If symptoms do not improve with 48-72 hours of high-dose corticosteroid, infliximab may be offered for some toxicities.
- Grade 4 toxicities warrant permanent discontinuation of nivolumab, with the exception of endocrinopathies that have been controlled by hormone replacement.

Table 3. **Treatment Modification for irAEs Associated with Nivolumab**

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2 - 3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue.	Permanently discontinue.
Pneumonitis	2	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue.	Permanently discontinue.
AST, ALT, or increased bilirubin	2	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue.	Permanently discontinue.
Type 1 diabetes mellitus (if new onset) or hyperglycemia	T1DM or 3-4	Hold nivolumab for new onset T1DM or Grade3-4 hyperglycemia associated with evidence of beta cell failure.	Resume nivolumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with nivolumab can be continued while endocrine replacement therapy is instituted.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or

			inability to reduce corticosteroid to10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue.	Permanently discontinue.
Hypothyroidism		Therapy with nivolumab can be continued while thyroid replacement therapy is instituted.	Therapy with nivolumab can be continued while thyroid replacement therapy is instituted.
Renal failure or nephritis	2	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue.	Permanently discontinue.
Myocarditis	1-2	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue.	Permanently discontinue.
All other immune-related AEs[1]	3 or severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue.	Permanently discontinue.

Abbreviations: AE = Adverse Event; T1DM = Type 1 diabetes mellitus

[1]Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at provider discretion. Permanently discontinue study drug for persistent

Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

8.0 Adverse Events and Potential Risks

8.1 Talazoparib

A comprehensive list of all reported adverse events and any potential risks for talazoparib seen alone or in combination with nivolumab is detailed in Section 7.2. The recommended treatment and clinical management for the commonly occurring events is outlined in Section 7.2.

8.2 Definitions

8.2.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

8.2.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR

- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

For the purpose of this study the following events would not be considered adverse events and would not be recorded in the database:

- Abnormal laboratory findings considered associated to the original disease

8.2.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the investigational agent- (this must be assigned**

by an investigator, sub-investigator, or treating physician)

- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version **5.0** will be utilized for AE reporting.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.3 SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.4 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur on or after Cycle 1 Day 1 through 30 days after the final dose of study drug. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization. Planned surgeries or in-patient procedures are not considered SAEs.

8.4.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of

discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
    - Send all SAE medwatch forms to the Dr. James Isaacs(isaacsj3@ccf.org) and to cancersaeinbox@ccf.org. Please cc the lead study coordinator within 24 hours of discovery/notification of the event.
- The Lead Site Principal Investigator will review the SAE and report the event to the FDA, Pfizer, and IRB as applicable.
    - External sites are responsible for reporting SAEs to their local IRB per their local policies
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

Pfizer, Inc. Reporting Requirements:

- AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.5 SAEs and OnCore

- All SAEs will be entered into Overture™ and OnCore. A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into OnCore.

8.6 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.7 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.2.

9.1 Investigational Agent

9.1.1 Name of Agent _____Talazoparib_____

Other Names: _____Talzenna_____

Talazoparib will be provided by Pfizer. Talazoparib will be supplied as 0.25mg and 1mg capsules.
Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient.

Talazoparib should be stored at 15°C–30°C; 59°F–86°F) or per approved local label. All excursions should be brought to the Sponsor-Investigator's and Pfizer's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Pfizer.

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub investigator(s). During the study, Talazoparib will be administered orally as 1mg every 24 hours. Patients should be instructed to take their Talazoparib at about the same time each day with or without food. The capsules should be swallowed whole and must not be opened or dissolved. The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes during the study should be recorded.

If the patient forgets to take his/her dose, the dose is not made up, but is instructed to resume subsequent doses the next day as prescribed.

Drug Accountability:
The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Drug Destruction:
At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

9.2 Commercial Agent

9.2.1 Name of Agent _____Nivolumab_____

Other Names: _____Opdivo_____

Nivolumab will be obtained from commercial sources. Nivolumab will be supplied as a clear to opalescent, colorless to pale-yellow solution in a vial.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient.
To prepare the infusion, withdraw the required volume of nivolumab and transfer into an intravenous container. Dilute nivolumab with either 0.9% sodium chloride injection, USP or 5% dextrose injection, USP to prepare an infusion with a final concentration ranging from 1mg/mL to 10mg/mL. The total volume of infusion must not exceed 160 mL. For adult and pediatric patients with body weights less than 40 kg, the total volume of infusion must not exceed 4mL/kg of body weight. Mix diluted solution by gentle inversion. Do not shake. Discard partially used vials or empty vials of nivolumab. After preparation, store 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-46°F) for no more than 24 hours from the time of infusion preparation. Do not freeze.

All excursions should be brought to the Sponsor-Investigator's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by BMS.

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub investigator(s). During the study, nivolumab will be administered intravenously as 480mg every 4 weeks (28 days). Administer the infusion over 30 (+/- 5 minutes) minutes through an IV line containing a sterile, no-pyrogenic, low protein binding, in-line filter (pore size of 0.2-1.2 micrometers). Do not coadminister other drugs through the same IV line. Flush the IV line at the end of infusion. All dosages prescribed and dispensed to the patient and all dose changes during the study should be recorded.

Nivolumab is considered standard of care therapy. Financial responsibility for nivolumab should be that of insurance company. If insurance company is not responsible, then the cost of this agent will be the subject's responsibility.

10.0 CORRELATIVE STUDIES

10.1 Anti-Tumor Response by TILs and PD-L1 Expression

Assess anti-tumor response by measure of immune-infiltration of cells to include, but not limited to, CD8, CD4, Treg (FOXP3), NK cells (CD56), MDSCs into tumors, and PD-L1 expression on tumor by multiplex immunofluorescence, flow cytometry and immunohistochemistry on tumor biopsies and serum samples at baseline, 12 weeks, and at progression. As additional clinical and medical knowledge is learned from this study, additional analysis may be performed on prior collected blood and tissue specimens.

10.1.1 Background

Immunotherapy such as nivolumab functions to modulate the immune microenvironment. CD8+, CD4+ T cells, regulatory T cells (Tregs), Natural Killer cells (NK), among others are important contributors both to the function of and resistance to targeted therapy and immunotherapy.[48] The tumor microenvironment as well as the peripheral blood are dynamic and subject to change based on changes in tumor burden and therapy. There is need for prospective data demonstrating correlations between changes in peripheral blood and changes in the tumor microenvironment. The goal of this study is to evaluate the hypothesis that changes in the type and behavior of immunomodulatory cells in the peripheral blood will reflect tumor burden and that such changes will impact tumor burden and response while on therapy with nivolumab and talazoparib. Additionally, this study will further investigate the preclinical findings that PARP inhibitor-mediated DNA damage has been shown to increase the immunogenicity of tumor cells by promoting T cell and NK cell infiltration.[21]

10.1.2 Rationale for Analysis

Identifying an immunomodulatory effect by analyzing tumor infiltrating lymphocytes circulating immune cells will help identify patients that would respond better to combination therapy and decrease tumor burden. Please see section 14 for analysis plan.

10.1.3 Collection of Specimens

Tumor biopsies (fresh frozen preferred; however, FFPE acceptable if fresh frozen not available) and peripheral blood samples (peripheral blood mononuclear cells (PBMC)) will be collected prior to treatment (at time of enrollment, or archival FFPE tumor tissue), at 12 weeks (+/- 1 week) at time of imaging, and at time of progression will be collected. See Section 11.0. Blood samples at each time point will be drawn into two 8 ml heparinized (green top) tubes and two 4.5 mL Na Citrate tubes. PBMCs will be isolated by Ficoll separation method. For fresh frozen tumor biopsies, submission of 3-4 grams of tissue (equivalent of 2 to 3 passes of tissue, or 3-4 core biopsies) is preferred. For FFPE tissue, submission of 12-15 slides of 10µm thickness preferred; however, if unable to obtain, 12 slides of 10µm thickness or what is able to be obtained is sufficient.

10.1.4 Handling of Specimens

De-identify the specimen using a code specific for this trial and transport the specimen to [redacted] lab at the Cleveland Clinic.

Cleveland Clinic Lerner Research Institute
Tissue Processing and Immune Monitoring Lab
Attn: [redacted]
2111 E. 96th Street, [redacted]
Cleveland, OH 44106
Telephone: [redacted]
E-mail: [redacted]

10.1.5 Analytical Laboratory

The specimens will be analyzed in the laboratory of Dr. Marcela Diaz-Montero at the Cleveland Clinic of Case Comprehensive Cancer Center. Dr. Marcela-Diaz will provide overall guidance on experimental design and interpretation of results. Personnel in her laboratory will perform all staining, cytometry and analysis. Plasma and serum will also be frozen and stored for future analyses. Address is listed in 10.1.4.

10.1.6 Methods

Flow cytometry, TCR repertoire, and single cell sequencing.

10.2 Analysis of Longitudinal Genomic Evolution

Assess longitudinal genomic evolution by sequencing at baseline, at 12 weeks, and at progression to evaluate DNA landscape and its correlation to response. As additional clinical and medical knowledge is learned from this study, additional analysis may be performed on previously collected blood and tissue specimens.

10.2.1 Background

This study intends to characterize the activity of nivolumab in combination with talazoparib, with the aim of increasing the clinical benefit seen historically with single agent nivolumab. A key mechanistic hypothesis underpinning the combination is that increased DNA damage and cell death mediated by talazoparib will lead to enhanced immune priming and tumor immunogenicity, enabling a more effective anti-tumor immune response to be promoted by nivolumab. Given this hypothesis, one subgroup of patients likely to benefit from the combination will be those whose tumors are most sensitive to talazoparib-mediated cell death and DNA damage. Several biomarkers have the potential to identify patients with such increased sensitivity to talazoparib, one of these will be employed in the context of this study, the presence of pathogenic or likely pathogenic germline or somatic defects in a panel of DDR genes.[46] Whole exome sequencing of tumor tissue prior to initiation of treatment, after treatment, and at progression will identify mutational load while on therapy. The combination of talazoparib and nivolumab will increase DSBs and therefore increase levels of fragmented DNA both in the tumor and PBMCs, likely results in changes in mutational burden. This was shown in prior in vitro and in vivo studies.[49] If patients who respond to combination therapy are shown to have a higher tumor mutational burden, this would confirm mechanistic action of this combination and could generate hypothesis to further explore this combination in studies without mutations in *BRCA1/2* or *BRCA*-ness and more cancer patients could potentially derive benefit from this combination therapy.

10.2.2 Rationale for Analysis

Discussed in Section 10.2.1 and Section 14.

10.2.3 Collection of Specimens

See Section 10.1.3.

10.2.4 Handling of Specimens

All specimens are to be shipped to the lab of Dr. Marcela-Diaz.

10.2.5 Analytical Laboratory
Specimens will be analyzed in the lab of Dr. Marcela-Diaz.

10.2.6 Methods
DNA and RNA sequencing by NGS.

10.3. Assessment of Patient Reported Outcomes for Adverse Events
Assess patient reported outcomes for adverse events, as measured by PRO-CTCAE while on combination therapy at baseline and before each cycle (every 4 weeks) of nivolumab for a period of 12 months.

10.3.1 Background

Immunotherapy has transformed treatment for melanoma. A better understanding of toxicities, long-term effects of immunotherapy, and effect on patient's quality of life is needed, especially when introducing a second anti-cancer agent to immunotherapy. Patient-reported outcomes (PRO's) can help show clinical benefit in reducing disease related symptoms, provide more accurate estimates of toxicity, help model treatment costs and improve symptom management. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in clinical trials. PRO-CTCAE can be used and reported in conjunction with the CTCAE reports gathered by clinicians. It provides additional information that is complementary to existing safety and tolerability assessments reported by clinicians using the CTCAE.

10.3.2 Rationale for Analysis
Discussed in Section 14.

10.3.3 Collection of PRO-CTCAEs
Surveys will be administered to patients beginning prior to treatment (baseline), and every 12 weeks (at time of imaging and office visit) after treatment initiation.

10.3.4 Handling of PRO-CTCAEs
Surveys will be de-identified and sent electronically by secure email or postal mail to the study coordinator at the lead institution (address listed on first page of document) every three months until the end of the trial. During the trial, the study coordinator at each institution will be responsible for maintaining the PRO-CTCAE surveys.

10.3.5 Analytical Laboratory
N/A.

10.3.6 Methods
Utilize PRO-CTCAE form designed by NCI. The National Cancer Institute's PRO-CTCAE measurement system was developed as a companion to the Common Terminology Criteria for Adverse Events (CTCAE). It is not intended to be used as a stand-alone patient-reported

outcome. The current standard for grading and reporting all AEs in cancer clinical trials, including symptomatic AEs, is clinician grading using the CTCAE. The PRO-CTCAE measurement system includes an item library of 124 discrete items representing 78 symptomatic toxicities drawn from the CTCAE. As such, it provides a systematic yet flexible approach to capture symptomatic adverse events in trials of new cancer therapies.

Custom PRO-CTCAE form is in Appendix 16.7.

10.4 Additional correlative analysis, including, but not limited to, analysis of STING pathway on prior collected tissue and blood specimens to evaluate effects on immunogenicity of combination therapy; circulating tumor DNA (ctDNA) measurements, and copy number variation to evaluate their association with response to treatment.

10.4.1 Collection of Specimens

Blood will be collected in four 10mL Streck tubes for cell free DNA analysis at each of the following time points: before treatment initiation, at Cycle 2 Day 1 of nivolumab, at Cycle 3 Day 1, and at progression.

10.4.2 Handling of Specimens

All specimens are to be shipped to the lab of Dr. Marcela-Diaz.

10.4.3 Analytical Laboratory

Specimens will be analyzed in the lab of Dr. Marcela-Diaz.

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

Serum Chemistry:
Calcium, Chloride, Potassium, Sodium, Bicarbonate, Aspartate aminotransaminase, Alanine aminotransaminase, Alkaline Phosphatase, Total Bilirubin, Lactate dehydrogenase, Creatinine, Blood urea nitrogen (BUN), Glucose, Albumin, Total protein, creatine kinase

*Note for serum chemistries: Tests for AST, ALT, ALP and total bilirubin must be conducted concurrently and assessed concurrently.

Hematology: White blood cell (WBC) count with differential, Red blood cell count, Hematocrit, Hemoglobin, Platelet count, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin concentration (MCHC)

Coagulation factors: Prothrombin time, activated partial thromboplastin time, international normalized ratio (INR)

Urinalysis: Color, Appearance, Specific Gravity, pH, Protein, Glucose, Ketones, Blood, Bilirubin. Microscopy including WBC/High power field (HPF), RBC/HPF if clinically indicated

11.1.1 Screening Evaluation

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. Patients will have somatic or germline testing done and known mutational status prior to enrollment in this study. All screening evaluations, which include procedures listed below, must be completed within 4 weeks (28 days) prior to administration of protocol therapy unless otherwise noted

Pretreatment (or screening) Visit

The following procedures and assessments will be completed during pretreatment visit:

- Review of medical history, including cancer history and any prior testing regarding cancer-related genes.
- Review of all of the medications taken for the past month.
- Discuss contraception (birth control).
- Record height and weight.
- Physical examination by provider.
- Record blood pressure, heart rate and body temperature.
- Assess performance status.
- Have blood drawn for following:
    - To assess kidneys, liver, coagulation, bone marrow and thyroid function
    - To test for HBV, HCV
    - To be used for correlatives
    - CK
- Urinalysis
- βHCG – for WOCBP only
- Imaging (CT scan, PET scan, MRI) of all tumors present. Scans must be done ≤4 weeks (28 days) prior to administration of protocol therapy.
- A tumor biopsy is needed by the time of starting this study to determine if the patient has a mutation in *BRCA*/*BRCA*ness. Biopsy and germline sequencing does not have to be completed within the 28 day screening period.
- Tumor biopsy for correlative samples is optional. If patient has an archival biopsy prior to starting this study, this biopsy can be used for the screening correlative sample.

11.1.2 Treatment Period

The treatment period is a total of 24 months (26 cycles) maximum for each patient. If a patient achieves a CR, the patient will continue treatment for 12 months from the date of a confirmed CR (unless the 26 cycles comes first). Patients with stable disease or partial response, will continue on therapy for the full duration of the 24 months.

Study Treatment (Cycle 1 Day 1)

On the day study treatment is started, the following will be done:

- Discuss any cancer-related symptoms (such as fatigue, shortness of breath, pain, etc.) that patient has been experiencing for the 2 weeks prior to this day.
- Discuss contraception
- Record weight.
- Complete a survey reporting any cancer-related symptoms (PRO-CTCAE)
- Physical examination by provider
- Record blood pressure, heart rate and your temperature.
- Assess performance status
- Have blood drawn for chemistry, CBC, LDH, CK, PT/PTT
- The research center staff will give one bottle of talazoparib that contains enough capsules for at least 1 cycle of treatment.
- Administer nivolumab intravenously at a standard dose of 480 mg over 30 (± 5) minutes.
- Assess adverse events.

These same steps will occur every cycle (every 4 weeks). Patient will need to be seen on Day 1 (±3 day) of each cycle. Nivolumab will be administered every 4 weeks (28±3 days).

At All Day 1 Visits:

- Return the Dosing (Pill) Diary and any leftover talazoparib capsules in the bottle to the research center.
- Discuss contraception (birth control) that is being used.
- Record weight.
- Complete a survey reporting any side effects of the treatment drugs (PRO-CTCAE)
- Interval history, vitals, and physical examination by provider.
- Assess performance status.
- Have blood drawn for chemistry, CBC, LDH, CK
- Assess adverse events.

At Cycle 3 Day 1 (±3 days)

Procedures and lab tests listed above in: "At All Day 1 Visits." Additional procedures will include:

- Have blood drawn for correlatives
- Imaging (CT scan or PET scan, MRI if needed) of all body sites of tumor(s). This will be performed every 3 months (or about every 3 cycles) until progression.
- Optional tumor biopsy for correlatives (to assess TILs and TMB)
- Assess adverse events.

End of Treatment Visit

End of Treatment visit should occur within one week of the last treatment dose. Adverse events will be assessed.

- Return the Dosing (Pill) Diary and any leftover talazoparib capsules in their bottle to the research center.

- Assess adverse events.
- Discuss contraception being used.
- Record weight.
- Complete a survey reporting any side effects of the treatment drugs (PRO-CTCAE)
- Physical examination by provider.
- Record blood pressure, heart rate and body temperature.
- Assess performance status.
- Have blood drawn for chemistry, CBC, LDH, CK
- Imaging (CT scan or PET scan, MRI if needed) of all of your tumors may need to be performed, depending on the date of last scans.
- If patient progressed, will have a serum sample collected an optional tumor biopsy for correlative analysis

Discontinuation
If a patient progresses while on active treatment, the patient will come off treatment per physician discretion. Once off active treatment, the patient will come in for the 30 (± 7) day follow up/Off Study visit for safety evaluation per follow-up visit guidelines below. The patient will then be considered off study. Correlative samples should be collected for patients who progress while on treatment or during follow-up.

If a patient ends treatment due to unacceptable toxicities per physician discretion, the patient will continued to be followed per the follow up guidelines below until the start of new anti-cancer therapy at which point the patient will be considered off study.

Follow-Up Visits
The first follow up visit will occur at 30 (± 7) days after last dose of study treatment. The remaining follow up visits will occur every 90 (± 7) days post last dose of study treatment for a total of 24 months in follow up. Patients that progress during the follow up phase will no longer be followed for the study.

The following assessments will be completed:
- Interval history, vitals including weight, and physical examination by provider.
- Assess performance status.
- Have blood drawn for chemistry, CBC, LDH, CK, and correlatives (if necessary).
- Imaging (CT scan or PET scan, MRI if needed) of all body sites of tumor(s).
- Complete a survey reporting any side effects of the treatment drugs (PRO-CTCAE)
- Assess adverse events.

11.2 Calendar
Treatment cycles are 28 days long. Screening studies are to be conducted within 28 days prior to administration of protocol therapy.

A visit window of ±3 days is allowed for all labs and scans.

A visit window of ±3 days is allowed for treatment.
A visit window of ±7 days is allowed for 3 month follow-up visits

	Pre-treatment[1]	Cycle 1 Day 1 (± 3 days)	Cycle 2 Day 1 (± 3 days)	Cycle 3 + Ongoing Cycles Day 1 (± 3 days)	End of treatment/ Disease Progression [2]	30 Day Follow-up (± 7 days)[3]	Long-term Follow-Up (± 7 days)[4]
REQUIRED ASSESSMENTS							
Informed Consent	X						
History & Physical Exam	X	X	X	X	X	X	X
Vital signs[5]	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Concomitant Med Assessment	X	X	X	X	X		
PHC/FHC Assessment	X						
Discuss Contraception	X	X	X	X	X		
ECOG PS	X	X	X	X	X	X	X
Baseline Symptoms	X						
Adverse Event Assessment		X	X	X	X	X	X
Somatic/Germline Mutation Testing for *BRCA/BRCA-ness*[6]	X						
Pill Diary		X	X	X	X		
CBC with differential	X	X	X	X	X	X	X
PT/PTT	X						
Chemistry (See Section 11.0)	X	X	X	X	X	X	X
LDH	X	X	X	X	X	X	X
CK	X	X	X	X	X	X	X
TSH, free T3, free T4	X						
HBV and HCV tests[7]	X						
Serum HCG[8]	X						
Urinalysis	X						
DISEASE ASSESSMENT							
Tumor Measurements	X	Tumor measurements are repeated every 12 weeks (± 3 days). Documentation must be provided for subject removed from study for progressive disease.					X
Radiologic Evaluations	X	Radiologic measurements should be performed every 12 weeks (± 3 days).					X
TREATMENT							
Nivolumab		X	X	X			
Talazoparib dispensing		X	X	X			
CORRELATIVE STUDIES[9]							
PBMC Sample for TILs	X			X[9]	X		
Tumor Specimen for TILs/PDL1[10]	X			X[9]	X		
Tumor Specimen for sequencing[10]	X			X[9]	X		
PBMC Sample for sequencing	X			X[9]	X		
Blood sample for ctDNA, CNV	X		X	X[9]	X		

PRO-CTCAE		X	X	X	X	X	X

1. Pretreatment visit procedures must be completed within 28 days of Cycle 1 Day 1 visit unless specifically stated otherwise
2. Should occur within 7 days of discontinuation of study drug.
3. Should occur within 30 (±7) days of last dose of drug.
4. Patients will continue to be followed for 2 years after the last dose of treatment or until progression or until new anti-cancer treatment is initiated. Visits will be every 90 (±7) days from the date of last dose of study drug.
5. Vital signs to include temperature, pulse, respiratory rate, and blood pressure
6. Somatic/Germline Mutation Testing for *BRCA/BRCA*-ness does not need to be completed in 28-day pre-treatment window, as long as it is completed before study enrollment.
7. Includes HBV surface antigen and anti-HCV antibody test. If anti-HCV is positive, HCV RNA test must be performed
8. Only needed for patients who are WOCBP
9. Correlative Studies are only needed at screening, C3D1 (±3 days) and at progression, if that occurs (not needed at EOT unless patient has evidence of PD). With exception of correlative studies for ctDNA and CNV, which are also needed at C2D1 in addition to above time points.
10. Tumor specimens are optional.

12.0 MEASUREMENT OF EFFECT

Patients must have measurable disease at screening and will be evaluated for response on the basis of RECIST criteria version 1.1 (Appendix 1; Section 16.1) and immune-related RECIST criteria (Appendix 2; Section 16.2). Tumor measurements using physical examination, spiral CT scan, PET/CT and/or MRI or other appropriate techniques deemed suitable by the investigator will be performed at screening within 28 days of patient registration and repeated per study calendar (Section 11). Scans can be done more frequently per MD discretion; these scans will be submitted on an unscheduled disease assessment CRF.

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The Overture and OnCore™ Databases will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. Overture and OnCore™ are Clinical Trials Management Systems housed on secure servers maintained at Case Western Reserve University. Access to data through Overture and OnCore™ is restricted by user accounts and assigned roles. Once logged into the Overture or OnCore™ system with a user ID and password, Overture and OnCore™ define roles for each user which limits access to appropriate data. User

information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu.

Overture and OnCore™ are designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the Overture database. A calendar of events and required forms are available in Overture and OnCore™.

13.2 **Regulatory Considerations**

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP),

guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

In this phase II, single arm, multi-institutional, open label trial in primary or recurrent, unresectable or metastatic melanoma patients who progressed on prior checkpoint inhibitor therapy with germline or somatic mutations in *BRCA1/2* or *BRCA*-ness, we hypothesize that combination therapy with talazoparib and nivolumab will improve the objective response rate from 10% to 30% with limited toxicity. The primary objective is to estimate the clinical efficacy of nivolumab plus talazoparib in patients with unresectable or metastatic melanoma with *BRCA1/2* or other DNA damage repair mutations (defined as *BRCA*-ness), as measured by objective response rate (ORR) every 12 weeks for a period of approximately 12 months. This will be assessed by best overall response (CR+PR) by RECIST v1.1. Secondary objectives and their endpoints include PFS defined as time from first dose of treatment until disease progression, as assessed by RECIST v1.1, treatment related adverse events as assessed by CTCAE v5.0, anti-tumor activity as measured by irOR as assessed by irRECIST, and irPFS as assessed by irRECIST.

The historical ORR for anti-PD-1 re-challenge after progression is about 5%-10%. ORR for re-challenge with combination anti-PD-1/anti-CTLA4 inhibition after progression is about 15%-20%. The ORR for single agent PARP inhibitors in ovarian and breast cancer patients that harbor a mutation in BRCA is at least 50%; about 72% and 62% (SOLO3 and EMBRACA trials, respectively).

Sample Size Justification

To test this hypothesis with 90% power and a 2-sided binomial test with alpha of 0.10, 33 patients will need to be treated to achieve an improvement in ORR from 10% to 30%. With 10% of patients potentially not evaluable, 37 patients would need to be enrolled for a total of 33 patients that are analyzable. Patients who are not evaluable are defined as patients who are consented and enrolled in the study, but who physically move away that it would be too burdensome to follow up with institution, those who are lost to follow up defined as individuals who enroll but do not receive treatment, imaging, and are not present at scheduled office visits.

Bayesian Monitoring Rule for Safety

We will use the method of Thall *et al* to monitor toxicity in this study.[50] Unacceptable toxicity observed at the time the 11th patient has received three cycles of therapy is defined for this protocol as CTCAE Grade 3-4 non-hematological toxicities, excluding fatigue and endocrinopathies, which fail to resolve to Grade 1 despite appropriate supportive care. A point mass of 0.65 was used as target toxicity rate. Beta (0.65, 0.35) was used as non-informative prior distributions for toxicity rate. Total accrual will be 33 patients. Patients will be monitored in cohorts of 11, starting from the 11th patients. The trial will stop early if an excessive toxicity rate is observed. Formally, stop the trial early if Pr(Toxicity rate > 65%|data) > 0.9, i.e. we will stop the trial early if the posterior probability of toxicity rate being higher than 65% given data is higher than 0.9. Table 1

and 2 summarize the stopping boundaries for toxicity and operating characteristics based on the stopping rules.

Table 1. Summary of early stopping boundaries in cohorts of 11 for toxicity. E.g. If 9 or more patients experienced toxicity out of the first 11 patients, the trial will stop early; similarly, if 17 or more out of the first 22 patients experienced toxicity, the trial will stop early for safety.		
Stop Early if #Toxicities Observed ≥	9	17
Total #Patients Treated	11	22

Table 2. Summary of operating characteristics based on 10,000 simulations using stopping boundaries in table 1. For example, if the true toxicity rate is 0.65, the probability of early stopping is 0.26; if the true toxicity rate is 0.8, the probability of early stopping is 0.79.

Scenario	True Toxicity Rate	Pr(Early Stopping)	Average #Pts Treated	Average #Toxicity Observed
1	0.50	0.04	32.2	16.1
2	0.65	0.26	27.9	18.1
3	0.80	0.79	17.5	14.0

Interim Analysis

No planned interim analysis will be performed due to expected accrual rate for this study.

Analysis Plan

All baseline patient demographics and clinical characteristics will be summarized by mean/standard deviations and count/frequency for continuous and categorical variables respectively. All analyses will be completed as intent to treat.

Patients who receive at least one dose of treatment with nivolumab and talazoparib will contribute to the efficacy analysis. Any subject who receives at least one dose of treatment on this protocol is evaluable for toxicity. Proportion of patients with overall response will be estimated with corresponding 95% confidence interval. PFS and irPFS curves will be based on the Kaplan-Meier method. Overall response by irRECIST will be estimated as a proportion with corresponding 95% confidence interval.

All subjects will be included in the safety analysis, with toxicities graded according to NCI CTCAE v5.0. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawals and incidence of serious adverse events. Listing of adverse events by patients will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal.

Correlative Studies and Analysis Plan

Correlative studies include, but are not limited to: assessing anti-tumor response by measure of immune-infiltration of CD8, CD4, Treg (FOXP3), NK cells (CD56) into

tumors by flow cytometry, and PD-L1 expression on tumor by immunohistochemistry performed on tumor biopsies at baseline, 12 weeks, and at progression; and assessing total somatic mutation burden by sequencing at baseline, 12 weeks, and at progression to evaluate DNA landscape and its correlation to response. These studies will be performed on all patients enrolled in the study, unless deemed not evaluable. Parametric assumptions will be assessed using Shapiro-Wilk statistics and qqplots and non-parametric alternatives will be considered when necessary. Tumor infiltrating lymphocytes (CD8, CD4, Treg, NK cells), total mutational burden, and PD-L1 expression will be assessed using a mixed model approach, adjusting for repeated measurements over time and response (yes/no). If there are differences by time, pairwise contrasts will be utilized to assess for specific differences at various time points, adjusting for multiple comparisons using the Tukey method.

The final correlative objective of patient reported adverse events (PRO-CTCAE) will be summarized as percentages and frequencies, as described above in analysis plan.

Although exploratory, for 33 evaluable patients, we will be able to detect moderate effect sizes of 0.44 for all correlative outcomes listed above, with 90% power and two-sided level of significance of 0.10.

Accrual

About 225 primary or recurrent metastatic or unresectable melanoma patients are seen annually at seven institutions in the Regional Melanoma Translational Research Consortium (RMTRC), which include: Cleveland Clinic, University Hospitals, MetroHealth, University of Pittsburgh Medical Center, Roswell Park, Penn State, and Ohio State University. About 50 patients per year would meet eligibility criteria. Of these, about half are expected to enroll. The estimate annual accrual rate is 25 patients per year. At this rate, the accrual goal of 37 patients is anticipated to be completed within two years.

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16.0 APPENDIX
16.1 RECIST 1.1 Criteria

The determination of antitumor efficacy during this study will be based on objective tumor assessments made according to the RECIST system of unidimensional evaluation. Adapted from E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.[51]

Measurability of Tumor Lesions
At baseline, individual tumor lesions will be categorized by the investigator as either measurable or non-measurable by the RECIST criteria as described below.

Measurable:

Tumor lesion: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm);

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

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

Non-Measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 mm to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

NOTE: If measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be

selected on the basis of their size (lesion with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter for all target lesions will be calculated and recorded as the baseline sum longest diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment. All measurements should be performed using a caliper or ruler and should be recorded in metric notation in centimeters.
All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent."

Techniques for Assessing Measurable Disease
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical (physical) examination when both methods have been used to assess the antitumor effect of a treatment.

Definitions of Tumor Response

Target Lesions

Complete response (CR) is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial response (PR) is defined as a ≥30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions.

Progressive disease (PD) is defined as a ≥20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum of the longest dimensions recorded since the treatment started, or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest dimensions since the treatment started.

Non-Target Lesions

Complete response (CR) is defined as the disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD is defined as a persistence of ≥1 non-target lesions.

Progressive disease (PD) is defined as unequivocal progression of existing non-target lesions, or the appearance of ≥1 new lesion.

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

Confirmation of Tumor Response
To be assigned a status of PR or CR, changes in tumor measurements in patients with responding tumors must be confirmed by repeat studies that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

Determination of Tumor Response by the RECIST Criteria
When both target and non-target lesions are present, individual assessments will be recorded separately. Determination of tumor response at each assessment is summarized in the following table.

Response Evaluation Criteria in Solid Tumors

Target Lesions[1]	Non-Target Lesions[2]	New Lesions[3]	Tumor Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any response	Yes or No	PD
Any response	PD	Yes or No	PD
Any response	Any response	Yes	PD

[1] Measurable lesions only.
[2] May include measurable lesions not followed as target lesions or non-measurable lesions.
[3] Measurable or non-measurable lesions.

Determination of Best Overall Response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after start of the treatment at a minimum interval of 6 weeks.

16.2 Immune-related Response Criteria Derived From RECIST v1.1 (irRECIST)

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics.

This is particularly true for immunotherapeutic agents such as anti-CTLA4 and anti-PD-1\anti PD-L1 antibodies which exert the anti-tumor activity by augmenting activation and proliferation of T-cells, thus leading to tumor infiltration by T-cells and tumor regression rather than direct cytotoxic effects.[52,53] Clinical observations of patients with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) and World Health Organization (WHO) criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria.[54,55]

Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of patients who have an OS similar to those who have experienced CR or PR but were flagged as PD by WHO criteria.[54,55]

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST v1.1 (irRECIST).[56]

For irRECIST, with the exception of a complete response assessment, only target and new measurable lesions are taken into account.

In contrast to RECIST v1.1, the irRECIST:

- Requires confirmation of both progression and response by imaging at least 4 weeks from the date first documented, and

- Does not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the study.

irRECIST responses are defined as follows:

- **Overall immune-related complete response (irCR):** Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.

- **Overall immune-related partial response (irPR):** Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.

- **Overall immune-related stable disease (irSD):** Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions does not meet criteria for irCR or irPR (compared to baseline), or immune-related progressive disease (irPD, compared to nadir).

- **Overall immune-related progressive disease (irPD):** Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions increases ≥20% (compared to nadir), confirmed by a repeat, consecutive observation at least 4 weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (i.e., added to the target lesion measurements). A lymph node has to be ≥15 mm in short axis to be a measurable new lesion and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements.

New non-measurable lesions: Do not define progression but preclude irCR.

Overall responses derived from changes in target, non-target, and new lesions are outlined in the following table.

Overall Response Derived from Changes in Target, Non-target and New Lesions

Measurable disease	Non-measurable disease		
Target and New Measurable Lesions (Tumor Burden)[a]	**Non-Target Lesions**	**New, non-measurable Lesions**	**Overall response using irRECIST[b]**
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥30%	Absent/stable	Any	irPR
Decrease ≥30%	Unequivocal progression	Any	irPR
Decrease <30% and increase <20%	Absent/stable	Any	irSD
Decrease <30% and increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

[a] Decreases assessed relative to baseline
[b] Response (irCR and irPR) and progression (irPD) must be confirmed by a second, consecutive assessment at least 4 weeks apart.

16.3 Performance Status

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Full active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% if waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead

16.4 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (version 5.0, dated November 27, 2017) has been placed in the Study Reference Binder for this protocol. Alternatively, the NCI CTCAE may be reviewed online at the following NCI website:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

16.5 P-glycoprotein (PGP) INHIBITORS AND INDUCERS

P-gp Inhibitors:

- Carvedilol, cladribine, clarithromyacin, cobicistat, darunavir, dronedarone, erythromycin, amiodarone, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valspodar, and verapamil

P-gp Inducers:

- avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort

Inhibitor of breast cancer resistance protein (BCRP) (curcumin, cyclosporine, elacridar [GF120918], and eltrombopag

Notes:
Grapefruit, grapefruit juice and other foods that are known to inhibit P-gp activity should be avoided during treatment.
P-gp inhibitors require dose reduction of talazoparib to 0.75mg (see section 7.1.1).
P-gp inducers (including St. John's Wort also known as hypericum perforatum) are prohibited during treatment with talazoparib.

16.6 Pill Diary

SUBJECT PILL DIARY

Subject Name _____Protocol #_____Subject Study ID _____
Cycle #: _____ Month #: _____

INSTRUCTIONS FOR THE SUBJECT:

1. You will take 1 tablet of 1mg *Talazoparib* capsule(s) each day. ***Take the tablets with or without food, as you wish.***
2. Record the date, the number of tablets you took, and what time you took them.
3. If you have any comments please record them in the "Comments" column below.
4. Please bring your pill bottle and this form to your physician when you come for your next appointment.
5. Please sign your name at the bottom of the diary.

Date	Day	# of _____ mg *Talazoparib* capsule(s) and time taken	Comments
	1		
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	11		
	12		
	13		
	14		
	15		
	16		
	17		
	18		
	19		
	20		
	21		
	22		
	23		
	24		
	25		
	26		
	27		
	28		**Add/remove days as needed**

Subject's Signature: _____ Date: _____

16.7 PRO-CTCAE

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 1 August 2019

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

1.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, did you have any VOICE CHANGES?	
	○ Yes	○ No

3.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

5.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

6.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 1 August 2019

7.	In the last 7 days, how OFTEN did you have HEARTBURN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

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

9.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

10.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

11.	In the last 7 days, how OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, how much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 1 August 2019

12.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

13.	In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

14.	In the last 7 days, how OFTEN did you have ARM OR LEG SWELLING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ARM OR LEG SWELLING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

15.	In the last 7 days, how OFTEN did you feel a POUNDING OR RACING HEARTBEAT (PALPITATIONS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your POUNDING OR RACING HEARTBEAT (PALPITATIONS)? at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

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

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

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

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

20.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

21.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

22.	In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

23.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

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24.	In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

25.	In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

26.	In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

27.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

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28.	In the last 7 days, did you BRUISE EASILY (BLACK AND BLUE MARKS)?	
	○ Yes	○ No

29.	In the last 7 days, how OFTEN did you have NOSEBLEEDS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NOSEBLEEDS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

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

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16.8 Family/Personal History Questionnaire Form
***To be collected by research nurse at pre-treatment visit**

1. Do you have a **personal history** of another type of cancer, besides melanoma?

   Yes/no

2. If yes: How many?
3. If yes: What type(s) of cancer? Can choose one or multiple cancers from list

   below:

   a. Breast
   b. Ovarian
   c. Brain
   d. Colorectal
   e. Kidney
   f. Pancreas
   g. Prostate
   h. Uterine
   i. Other GU
   j. Other GI
   k. Other (field to write it other cancer)

4. If yes: What was/is the date of diagnosis for each cancer?
5. Do you have a **family history** of cancer? (Cancer in your parents, siblings,

   children, aunts/uncles, nephews/nieces, grandparents or grandchildren) Yes/no

6. If yes:

   a. Cancer in mother? Yes/no

      i. If yes: drop down type of cancer (able to select multiple)

b. Cancer in father? Yes/no
    i. If yes: drop down type of cancer (able to select multiple)
c. Do the same as above (separate drop down for each type of family member) for cancer in siblings, children
d. Do the same as above, also add drop down for maternal/paternal: grandmother, grandfather, aunts, uncles, nephews, nieces, other relative (specify).