MD Anderson IND Sponsor Cover Sheet

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Protocol Title	Altering Adjuvant Therapy based on Pathologic Response to Neoadjuvant Dabrafenib and Trametinib (ALTER-PATH NeoDT)
Protocol Version	01
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1.0 BACKGROUND & RATIONALE

1.1 BACKGROUND

Clinical Stage III Melanoma

Clinical stage III melanoma is defined as patients with clinically detected, palpable (macroscopic) lymph nodes with or without in-transit or satellite metastases and no evidence of distant metastases. This group of patients is staged as at least Stage IIB/IIIC (by AJCC version 7) or IIIB/IIIC/IIID (by AJCC version 8) and has heterogeneous outcomes when viewed as a whole with 5-year survival varying from 32-83%[1].

In a recent analysis of 144 clinical Stage III melanoma patients with a BRAF mutation identified at MD Anderson, average time to disease relapse was less than 2 year, highlighting the high-risk nature of this disease stage (MD Anderson internal data). Traditionally, this group of patients have high-risk disease even with upfront surgery and newly available adjuvant therapy options including high dose ipilimumab[2], nivolumab[3], dabrafenib and trametinib[4] and pembrolizumab[5].

Neoadjuvant Therapy

Neoadjuvant (preoperative) therapy has a long history of use in a variety of solid tumors including breast cancer[6-7], rectal cancer[8], gastric cancer[9], esophageal cancer[10] and bladder cancer[11]. The use of neoadjuvant therapy in melanoma was previously limited in use due to limited number of drugs producing benefit and the most commonly used regimen was a multi-drug combination approach known as biochemotherapy. Although this regimen yielded response rates of approximately 40%, patients experienced extensive toxicity and required inpatient administration of this regimen[12-13]. However, as multiple new targeted and immunotherapy options have been FDA approved in melanoma since 2011 that have improved the survival of metastatic patients[14-16], there is great interest in using these agents in earlier stage disease patients.

Neoadjuvant therapy offers a number of potential advantages for patient care. Successful neoadjuvant therapy that results in tumor shrinkage can potentially render surgery less morbid[17-18]. Earlier administration of systemic therapy can potentially more expeditiously destroy micrometastses which may have the opportunity to grow during the relatively immunosuppressed period after surgery and subsequent recovery[19]. Response to neoadjuvant therapy can be helpful in determining patient prognosis as complete lack of viable tumor in the resected specimen (pathologic complete response or pCR) has been correlated with improved patient outcomes[7-11]. Additionally, neoadjuvant trials offer the opportunity for biomarker discovery as longitudinal blood and tumor samples can be obtained to facilitate study of mechanisms of treatment response or resistance[20]. Neoadjuvant therapy can be a robust platform for drug development and has been utilized as an avenue for new drug registration[21].

Prior to 2014, neoadjuvant therapy in melanoma traditionally had been limited to a multidrug regimen called biochemotherapy. This 5-drug regimen consisted of infusional therapy requiring inpatient hospital stays and was associated with significant hematologic toxicity, cardiac and pulmonary toxicities. This regimen did produce 22% partial response by imaging and pathologic complete response rates of approximately 26%[12]. Due to the toxicity and need for inpatient admission, this regimen was not widely used across the melanoma community.

Another neoadjuvant trial utilized ipilimumab 10mg/kg which was given intravenously every 3 weeks for 2 doses prior to surgery. In this trial, there were no pathologic complete responses and only a small number of patients achieving a minor pathologic response[22]. This regimen was thus not widely utilized in the neoadjuvant setting.

1.2 Modern Neoadjuvant Trials

Dabrafenib plus trametinib

There are two mature studies evaluating the combination of dabrafenib (150 mg twice daily) and trametinib (2 mg daily) in the neoadjuvant setting.

In the Combi-Neo trial (MD Anderson Protocol 2014-0409; NCT02231775), patients with stage IIIB/C (AJCC 7th edition) or oligometastatic stage IV *BRAF*-mutant melanoma were randomized to either surgery followed by standard of care adjuvant therapy (which could be observation alone, high dose interferon, pegylated IFN-α2b, high-dose ipilimumab, or biochemotherapy) or neoadjuvant combination dabrafenib and trametinib (8 weeks) followed by 44 weeks postoperatively. Interim analysis of the initial 21 patients enrolled demonstrated that neoadjuvant dabrafenib and trametinib was associated with a high imaging response rate (77%) and pCR rate of 58%. At a median follow-up of 18.6 months, neoadjuvant targeted therapy was associated with significantly better RFS than patients randomized to surgery followed by possible postoperative adjuvant therapy (HR 60.2, 95% CI 6.7-7965, $p<0.0001$).
There was also improved distant metastasis-free survival (HR 0.024, $p=0.001$) and trend towards improved overall survival (HR 0.28, [=0.22) for the neoadjuvant dabrafenib and trametinib treated patients. Of note, pCR patients had a trend towards improved relapse free survival and overall survival compared to the upfront surgery patients and did have statistically significant improvement in distant metastasis-free survival over non-pCR patients; indicating that pathologic responses can influence patient survival outcomes[23].

This regimen also showed a manageable safety profile for dabrafenib and trametinib, similar to that observed in patients with metastatic melanoma, with pyrexia and chills as the most commonly reported adverse events (AEs), none of which interfered with the ability to carry out planned surgery. There were no progression events during the neoadjuvant treatment and all patients were able to proceed to surgical intervention[23].

Due to the clear superiority in achieving the primary objective of improved progression free survival in the neoadjuvant dabrafenib and trametinib treated patients, the MD Anderson Data Safety Monitoring Board closed the randomized trial at only a quarter of the planned accrual[23]. Thus, our group re-designed the trial as a single-arm study of neoadjuvant dabrafenib and trametinib. This redesigned trial is now powered to determine patient survival outcomes based on the pathologic response at the time of surgery.

As of September 2019, a total of 37 patients have been treated with neoadjuvant, dabrafenib and trametinib on this protocol at MD Anderson with an overall pCR rate of 40%in the 32 patients who have gone to surgery. As additional patients have been treated, we have been able to ascertain trends in survival and recurrence. Specifically, in the patients who did not achieve a pCR, we have noted 11% of patients have experienced locoregional recurrence and 43% have developed CNS disease. In the patients who did achieve a pCR, locoregional relapse rate was 23% and CNS metastasis development was 8%. These data indicate clearly divergent outcomes in patients depending on pathologic response and demonstrate the need to improve outcomes in those not achieving a pCR (unpublished data). 17.6 months, 38% of patients developed distant extracranial relapse, 38% had loco-regional relapse and 23% intra-cranial relapse, including 35% of pCR patients[24].

Both of these studies demonstrate that neoadjuvant, dabrafenib and trametinib can achieve high rates of pCR and that pCR patients tend to have superior clinical outcomes compared to the non pCR patients. However, relapses, with tendency for CNS-specific relapse in the non pCR cohort of patients is a concerning finding.

Neoadjuvant immune checkpoint inhibitors

Pembrolizumab
NCT02434354 enrolled patients with clinical stage III or resectable stage IV melanoma. Patients received one dose of neoadjuvant pembrolizumab 3 weeks prior to surgery followed by a year of adjuvant pembrolizumab. Interestingly, 8/27 treated patients had pCR or near pCR (<10% viable tumor) at time of surgery. Neoadjuvant pembrolizumab was well tolerated with no major AEs prohibiting on- time surgical procedure. All patients with pCR or near pCR remain free of disease with median follow up time of 25 months; again, highlighting the prognostic importance of pCR[25].

Ipilimumab plus nivolumab
NCT02519322 is a phase 2 trial conducted at MD Anderson Cancer Center in which patients with clinically detected but resectable stage III and oligometastatic stage IV melanoma are randomized to receive either nivolumab alone (3 mg/kg every 2 weeks for up to 4 doses, Arm A) or in combination with ipilimumab (nivolumab 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks for up to 3 doses,

Arm B) prior to surgery. Adjuvant nivolumab (3 mg/kg every 2 months) will be administered postoperatively to patients on both arms for 6 months. In this single-institution trial run at MD Anderson Cancer Center, planned accrual was 40 patients, however this trial was closed after 23 patients were enrolled (12 patients to Arm A, 11 to Arm B) due to concerns about poor efficacy in Arm A and toxicity in Arm B. Neoadjuvant nivolumab (Arm A) was associated with pCR in 25% of patients and 25% radiographic response rate. However, 17% of patients receiving neoadjuvant nivolumab therapy were unable to proceed to surgery due to disease progression and development of distant metastases during neoadjuvant treatment. All patients who received neoadjuvant ipilimumab plus nivolumab (Arm B) underwent surgery, with 45% pCR and 73% radiographic response rate. However, patients who received neoadjuvant ipilimumab plus nivolumab also experienced significantly higher numbers of grade 3 treatment-related AEs (73% in Arm B versus 8% in Arm A), which at times led to surgical delays due to the need for high dose steroids to mitigate immune mediated toxicities[26].

The OpACIN trial randomized 20 patients with resectable, clinical nodal disease to adjuvant or neoadjuvant ipilimumab 3 mg/kg and nivolumab 1 mg/kg either as 4 doses given postoperatively or split as 2 doses given preoperatively and 2 doses postoperatively. Although most patients (18 of 20) were unable to complete all 4 planned doses due to grade 3 or 4 toxicities, neoadjuvant therapy produced 3 pCR and 3 near pCR of the 10 treated patients. Patients with pCR or near pCR had not developed any disease relapse with a median follow up of 25.6 months. In total, 4 patients in the adjuvant arm relapsed while 2 patients in the neoadjuvant arm relapsed with median 32 month follow up[27].

The OpACIN-Neo study (NCT02977052) is an open-label, three-arm phase II trial in which 86 stage III melanoma patients were randomized 1:1:1 to receive either: (Arm A) 2 courses of ipilimumab 3 mg/kg + nivolumab 1 mg/kg every 3 weeks; n=30; (Arm B) 2 courses of ipilimumab 1 mg/kg + nivolumab 3 mg/kg every 3 weeks, n=30; or (Arm C) 2 courses of ipilimumab 3 mg/kg, directly followed by 2 courses of nivolumab 3 mg/kg every 2 weeks, n=26, with the second dose of ipilimumab and the first dose of nivolumab given on the same day to keep the overall duration of therapy the same as the other two arms. Patients in all three treatment arms then undergo surgery at 6 weeks.

In Arm A, 47% of patients had pCR and 23% had near pCR and this cohort experienced 40% grade 3-4 immune mediated toxicities. In Arm B, 57% of patients had a pCR, 7% near pCR and 20% experienced grade 3-4 toxicities. In Arm C, 23% of patients had pCR, 23% had near pCR and grade 3-4 toxicity rate was 50%. Thus, the authors concluded that the combination therapy groups were most effective in producing pCR/near pCR but that toxicity was less in the group using ipilimumab 1mg/kg with nivolumab 3mg/kg[28].

Neoadjuvant checkpoint inhibitor therapy in combination with other therapies

There are also ongoing phase I and II studies to investigate combining immune checkpoint blockade with targeted therapies for patients with BRAF mutated melanoma.

The NeoTrio trial (NCT02858921) is a phase II study of patients with *BRAF* mutant resectable stage IIIB, IIIC and IV melanoma who are randomized to receive either dabrafenib plus trametinib for 2 weeks followed by pembrolizumab for 50 weeks (Arm A), concurrent dabrafenib plus trametinib and pembrolizumab for 52 weeks (Arm B), or pembrolizumab monotherapy for 52 weeks (Arm C). Of the 52 weeks of systemic therapy in each arm, 12 weeks are administered in the neoadjuvant setting and the remaining 40 weeks of therapy are administered in the adjuvant setting. The primary outcome is pathological response rate after 12 weeks of treatment, assessed at the time of surgery. Secondary outcomes include objective response rate by RECIST criteria, RFS, OS, and safety[29].

The NeoACTIVATE trial (NCT03554083) is enrolling BRAF mutated patients with vemurafenib (BRAF inhibitor), cobimetinib (MEK inhibitor) with atezolizumab (anti PD-L1 antibody) with clinical stage III melanoma. Neoadjuvant therapy is being administered for three months prior to surgery and an adjuvant phase with triplet therapy is also offered. The primary objective is pCR rate[29].

1.3 RATIONALE

Clinical Stage III melanoma patients with BRAF mutations represent a high-risk patient population with need for improved clinical outcomes from standard of care upfront surgery and adjuvant therapy. We have previously demonstrated that neoadjuvant dabrafenib and trametinib is safe, leads to pathologic complete response and improves EFS over standard of care surgery and adjuvant therapy[23] in MD Anderson protocol 2014-0409. At the time this protocol was starting enrollment, neoadjuvant therapy in melanoma was in its infancy and thus we proactively had engaged the melanoma research community to develop the International Neoadjuvant Melanoma Consortium which has worked to provide a frame- work for best practices for neoadjuvant trial design, patient enrolment, responses assessment and translational research. As part of these efforts, our group has been instrumental in defining the pathologic features of response to neoadjuvant therapy and have defined pCR as the absence of any residual invasive malignant cells on hematoxylin and eosin evaluation of the resected melanoma specimen. Near pCR is defined as less than 10% viable tumor. pPR is defined as less than 50% viable tumor cells or more than 50% fibrosis on pathological evaluation. pNR is defined as no viable tumor[31].

With additional patients enrolled and with the benefit of additional follow up time on protocol 2014- 0409, we have appreciated a trend towards development of CNS metastases in treated patients, specifically in patients not achieving a pCR to neoadjuvant therapy. Of 15 patients who have not achieved a pCR to neoadjuvant

dabrafenib/trametinib, 8 (53%) have experienced disease recurrence in the brain predominantly (unpublished data). Relapses have been seen shortly after completing the year duration of treatment (3 patients) or even while on dabrafenib/trametinib in the adjuvant setting (5 patients). Conversely, of those who have achieved a pCR, only 1/12 (8%) patients has relapsed with CNS disease. These data suggest that the patients who do not achieve a pCR are at high risk for recurrence and are in need of alternative adjuvant treatment options[23].

We have previously demonstrated that patients who do not achieve a pCR tend to have a more exhausted T cell phenotype in their baseline, on-treatment and surgical samples, characterized by higher amounts of PD-1 +, TIM-3+, LAG-3+ T cells compared to those who achieve a pCR[23]. We therefore hypothesize that addition of PD-1 blockade on the backbone of dabrafenib and trametinib in the adjuvant setting for patient who do not achieve a pCR will improve RFS outcomes compared to historical controls. There have been a number of prior trials utilizing BRAF/MEK inhibition with anti PD-1/PD-L1 in melanoma (NCT02910700, NCT02130466, NCT02027961) including the COMBI-I study which utilized dabrafenib, trametinib and spartalizumab in metastatic melanoma patients with BRAF V600 mutations. This study demonstrated the safety and efficacy of this approach (see section 3.2.1 for further details)[30] and thus we believe these agents will be appropriate for use in the adjuvant setting for the non pCR patients.

2.0 OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To determine the 12-month relapse free survival (RFS) rate in stage IIIB/C/D melanoma patients who, after 8 weeks of neoadjuvant dabrafenib and trametinib, do not achieve a pCR and receive adjuvant dabrafenib, trametinib and spartalizumab

2.2 SECONDARY OBJECTIVES

- To evaluate the safety of neoadjuvant dabrafenib and trametinib and adjuvant dabrafenib, trametinib and spartalizumab
- To determine the 12-month relapse free survival (RFS) rate in stage IIIB/C/D
- Melanoma patients who, after 8 weeks of neoadjuvant dabrafenib and trametinib, achieve a pCR and receive adjuvant dabrafenib and trametinib.
- To assess the recurrence patterns, distant metastasis-free survival (DMFS), and overall survival (OS) in all patients treated on protocol.

2.3 EXPLORATORY OBJECTIVES

- To assess immunological and molecular features of treatment response and resistance
- To assess circulating markers and correlate them with treatment response and relapse andtoxicity
- To assess the impact of neoadjuvant therapy on surgical resectablity

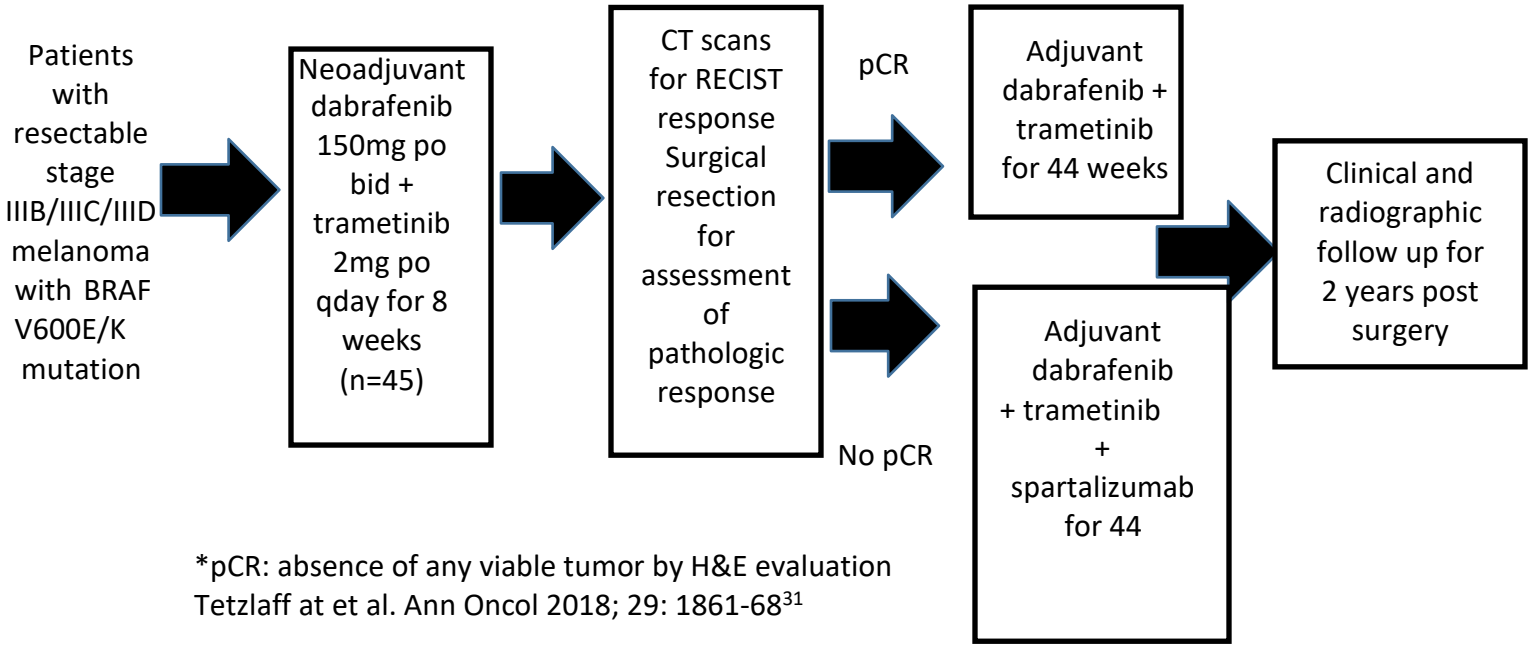
3.0 STUDY DESIGN

This is an open-label single arm Phase II study that aims to examine the strategy of altering adjuvant therapy depending on pathologic response to neoadjuvant dabrafenib and trametinib therapy. Clinical stage III B/C/D BRAF V600E/K mutation with resectable disease will be enrolled. Patients will undergo 8 weeks of neoadjuvant dabrafenib and trametinib, followed by restaging scans and then definitive surgery if disease remains resectable. Surgical pathology will be analyzed for pathologic complete response (pCR), which is defined as absence of any residual tumor by H&E assessment.
Near pCR will be defined as less than 10% viable melanoma in the surgical specimen. Pathologic partial response (pPR) is defined as less than 50% viable tumor in the surgical specimen. No pathologic response (pNR) is defined as ≥50% viable tumor in the surgical specimen[31].

Patients who achieve a pCR will continue with adjuvant dabrafenib and trametinib for an additional 44 weeks in order to complete a total 1 year of therapy. Patients who do not achieve a pCR after 8 weeks of neoadjuvant dabrafenib and trametinib will receive dabrafenib, trametinib and spartalizumab in the adjuvant setting for a total of 44 weeks. Patients with no resectable disease after neoadjuvant therapy will be removed from the study and replaced.

Longitudinal blood and tumor will be collected in accordance with the study schedule.

Figure 1: Study Overview



*pCR: absence of any viable tumor by H&E evaluation
Tetzlaff at et al. Ann Oncol 2018; 29: 1861-68[31]

3.1 Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

- Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form
- Patients must have histologically or cytologically confirmed clinically detected, node involved Stage IIIB/C/D melanoma by AJCC version 8[1] and surgically resectable disease. The definition of resectability can be determined by the patient's surgical oncologist and verified via discussion at Multidisciplinary Tumor Conference attended by melanoma medical and surgical oncology staff. Resectable tumors are defined as having no significant vascular, neural or bony involvement that would preclude complete resection or necessitate the use of adjuvant radiation. Only cases where a complete surgical resection with tumor-free margins can safely be achieved are defined as resectable.
- BRAF mutation-positive melanoma (V600E or V600K) based on report from a CLIA certified laboratory.
- Patients must have measurable disease, defined by RECIST 1.1[32]
- Patients who have been previously treated in the adjuvant setting with ipilimumab or interferon alpha or investigational vaccines for melanoma will be eligible for treatment after a 28 day wash-out period
- Patients who have previously received anti PD-1 in the adjuvant setting will be allowed if it has been six months or longer since previous drug exposure
- Age >=18 years
- ECOG performance status 0-1 (See Appendix A)
- Women of childbearing potential, defined as all women physiologically capable of becoming pregnant will be required to use highly effective methods of contraception during dosing and for 150-days after stopping treatment with spartalizumab. Highly effective contraception methods include:

- Highly effective contraception methods include:

a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

c. Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject

d. Placement of a non-hormonal intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.

Notes:

- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository) are not considered highly effective methods of contraception.
- Hormonal-based methods (e.g., oral contraceptives) are not considered as highly effective methods of contraception due to potential drug-drug interactions with dabrafenib.

- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

- Sexually active males must use a condom during intercourse while on treatment and for 150 days after stopping treatment with spartalizumab and should not father a child in this period. A condom is required to be used by vasectomized men as well during intercourse in order to prevent delivery of the drug via semen
- Organ function as defined below in Table 1:

Table 1: Organ function criteria

Hematological	
Absolute neutrophil count (ANC)	*≥1500/µL*
Platelets	*≥100 000/µL*
Hemoglobin	*≥9.0 g/dL or ≥5.6 mmol/L*[a]
Renal	
Creatinine OR Measured or calculated [b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	*≤1.5 × ULN OR* *≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN*
Hepatic	
Total bilirubin	*≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN*
AST (SGOT) and ALT (SGPT)	*≤2.5 × ULN*
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	*≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants*

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase);
AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase);
GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

3.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

- Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy, or biologic therapy) or investigational anti-cancer drug within 28 days
- Evidence of metastatic melanoma or patients with only in-transit metastases without involved nodes
- Prior BRAF or MEK inhibitor use
- Prior anti PD-1 or anti PD-L1 inhibitor use in last 6 months
- Prior malignancy active within the previous 2 years except for patient's prior diagnosis of melanoma and locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast with local control measures (surgery, radiation).
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only 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.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Any positive test result for hepatitis B or C and HIV virus indicating acute or chronic infection
- Known history of testing positive for human immunodeficiency virus or known acquired immunodeficiency syndrome
- History of severe hypersensitivity reaction to any monoclonal antibody
- History of Central serous retinopathy (CSR) or retinal vein occlusion (RVO), or predisposing factors to RVO or CSR (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes).
  Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of drugs. QTc interval ≥ 480 msec (≥ 500 msec for subjects with Bundle Branch Block) Uncontrolled arrhythmias
  Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system
  - Pregnant or lactating female
  - Unwillingness or inability to follow the procedures required in the protocol
  - Uncontrolled diabetes, hypertension or other medical conditions that may interfere with assessment of toxicity

Subjects with known glucose 6 phosphate dehydrogenase (G6PD) deficiency

3.3 TRIAL TREATMENT – Study Drugs and Administration Details

Table 2a: Neoadjuvant Treatment

Study Drug	Dose
Dabrafenib	150mg by mouth twice daily
Trametinib	2mg by mouth daily

Table 2b: Adjuvant Treatment of pCR patients

Study Drug	Dose
Dabrafenib	150mg by mouth twice daily
Trametinib	2mg by mouth daily

Table 2c: Adjuvant Treatment of non pCR Patients

Study Drug	Dose
Dabrafenib	150mg by mouth twice daily
Trametinib	2mg by mouth daily
Spartalizumab	400mg IV every 28 days

Table 3: Trial Treatments and Description

Table 3a: Neoadjuvant Treatment

Product	Dose	Dose Frequency	Route of Administration	Appearance	Storage Conditions (per label)
Dabrafenib	*150 mg*	*BID*	*By mouth*	*Capsules for oral use*	*Refer to study*
					treatment label
Trametinib	*2mg*	*Daily*	*By mouth*	*Tablets for oral use*	*Refer to Associated IB*

Table 3b: Adjuvant Treatment of pCR patients

Product	Dose	Dose Frequency	Route of Administration	Appearance	Storage Conditions (per label)
Dabrafenib	*150 mg*	*BID*	*By mouth*	*Capsules for oral use*	*Refer to Associated IB*
Trametinib	*2mg*	*Daily*	*By mouth*	*Tablets for oral use*	*Refer to Associated IB*

Table 3c: Adjuvant Treatment of non pCR Patients

Product	Dose	Dose Frequency	Route of Administration	Appearance	Storage Conditions (per label)
Dabrafenib	*150 mg*	*BID*	*By mouth*	*Capsules for oral use*	*Refer to Associated IB*

Trametinib	*2mg*	*Daily*	*By mouth*	*Tablets for oral use*	*Refer to Associated IB*
Spartalizumab	*400mg*	*Every 28 days*	*Intravenous*	*Liquid in vial for infusion*	*Refer to Associated IB*

3.3.1 Dose Selection Rationale

The dose of dabrafenib is 150mg BID which is the FDA approved dose for patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.
The dose of trametinib is 2mg daily, which is the FDA, approved dose for patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.
The dose of spartalizumab is 400mg every 28 days, administered as an intravenous infusion. In study [CPDR001X2101],PDR001 single-agent was administered as an intravenous infusion over 30 minutes at doses ranging from 1 to 10 mg/kg on an every 2 weeks (Q2W) schedule or at 3 and 5 mg/kg every 4 weeks (Q4W) schedules. Approximately dose proportional increase in exposure (C1D1 AUC0- 336) was observed with doses from 1 to 10 mg/kg and no DLTs were observed.
Accumulation of approximately 2.1-3.4-fold was observed with Q2W dosing and 1.6-2.2-fold with Q4W dosing. Population PK analysis indicated that the changes in exposure due to patient weight differences are minimal across the anticipated weight range of 30 to 150 kg for the patient population. Therefore, a flat dosing scheme was selected. Based on the safety profile observed in study [CPDR001X2101] and the expected Ctrough values, 400 mg Q4W is expected to be a safe and efficacious dose. For further details on spartalizumab, please see the investigator's brochure.

Prior Experience with Investigational Agents

The COMBI-I study is a multicenter trial exploring the safety and efficacy of dabrafenib, trametinib and spartalizumab in patients with BRAF V600 mutated unresectable or metastatic melanoma. In Part 1 of the trial (safety run-in cohort), standard dosing of dabrafenib (150mg orally twice daily), trametinib (2mg daily) and spartalizumab (400mg IV every 4 weeks) was utilized. A total of 9 patients were enrolled and there was no excessive toxicity seen and this dosing was utilized in Part 2 which was designed to be a biomarker exploration cohort. An additional 27 patients were treated on Part 2 for a total of 36 evaluable patients for safety and efficacy. At the time of data analysis, the median follow up time was 19.9 months (16.5-25.1 months range) and treatment was ongoing for 13 patients. All patients had some form of adverse event, with 78% having experienced a grade 3 toxicity. The most common grade 3 toxicities were pyrexia (17%) and pruritus (11%). Grade 3 laboratory evaluations were noted including elevated creatinine phosphokinase (8%), amylase (8%) and gamma-glutamyltransferase (8%) levels, in keeping with prior studies. All patients required dose adjustment/interruption to mitigate toxicities and 17% of patients had toxicities leading to cessation of the triplet therapy. In terms of efficacy, the overall response rate was 78% with 42% achieving confirmed complete response, which included 20% with elevated LDH at baseline and 40% with stage IV M1c disease. The median PFS was 23.7 months, including 10.7 months for higher risk patients with elevated LDH values at time of enrollment. The median duration of response was 20.7 months with 29% of responders experiencing subsequent progression. The median overall survival was not reached in this cohort. Part 3 of this trial which is a global, placebo-controlled randomized trial of dabrafenib, trametinib and placebo vs. dabrafenib, trametinib and spartalizumab is currently in enrollment[30].

3.3.2 Dose Modification

Dose Modification of Dabrafenib and Trametinib and Spartalizumab for General Toxicities Related to Study Drug(s)

In the event of a clinically significant grade 3 or 4 hematologic or non-hematologic AE, treatment may be withheld and supportive therapy administered as clinically indicated. If the toxicity or event resolves to baseline or Grade 1 in less than or equal to 21 days of stopping therapy, treatment may be restarted. Dose reduction should be considered as clinically indicated at the discretion of the treating oncologist. Any dose adjustment or interruption will be recorded.

If the toxicity does not resolve to at least Grade 1 in less than or equal to 21 days, withdrawal from the trial is recommended. However, if the investigator agrees that further treatment will benefit the subject, treatment can continue with a reduction of one or both study drugs.

Suggested dose reduction of each drug is as follows in Table 4. These dose reductions of dabrafenib and trametinib do not need to be made concurrently and will be up to the discretion of the treating investigator.

Table 4 Dose Levels

Drug	Starting Dose	Dose level -1	Dose level -2	Dose level -3
Dabrafenib	150mg BID	100mg BID	75mg BID	50mg BID
Trametinib	2mg daily	1.5mg daily	1.0 mg daily	----------
Spartalizumab	400mg IV every 28 days	----------	----------	----------

If treatment related toxicities occur that are specific to combination treatment of dabrafenib and trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exceptions shown below:

Exception where dose modification is necessary for **only dabrafenib**:

- Uveitis

Exception where dose modifications are necessary for **only trametinib**:

- Retinal vein occlusions (RVO) and retinal pigment epithelial detachment (RPED)
- Left ventricular ejection fraction (LVEF) reduction

If a subject's dose of dabrafenib and trametinib has been reduced per the dose modification instructions, re-escalation of the subject's dose is recommended provided the following criteria are met:

- a period of 4 weeks of treatment has passed since restarting dosing at the lower dose level and there is no recurrence of the AE
- the subject is deriving clinical benefit

General dose modification guidelines are provided in Table 5

Table 5 Dose Modification Guidelines – General

CTCAE Grade	Action and Dose Modification
Grade 1 or Grade 2 (tolerable)	Continue study treatments at same dose level (no dose modification)
Grade 2 (Intolerable)	
1st or 2nd occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 then restart at same dose level
3rd or occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 then restart at next lower dose level
4th or greater occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 then restart at two dose levels lower than the starting dose or discontinue treatments per investigator discretion
Grade 3	
1st occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 or baseline then restart at next lower dose level
2nd occurrence	Interrupt study treatments until toxicity resolves to ≤ grade 1 or baseline then restart at two dose levels lower than the starting dose
3rd occurrence	Discontinue treatments.
Grade 4	
1st occurrence	Discontinue treatments

For dabrafenib and/or trametinib related adverse events: if following an interruption of dabrafenib and trametinib, an AE doesn't recover to ≤ Grade 1 or baseline within 4 weeks, dabrafenib and trametinib must be discontinued.
No dose reductions are allowed for spartalizumab. Dose interruption for spartalizumab includes delaying or withholding the treatment for any reason as well as an interruption of treatment during an infusion. All dose interruptions and the reason for the dose interruption must be recorded. Dose interruption for spartalizumab includes delaying or withholding the treatment for any reason as well as an interruption of treatment during an infusion. Subjects with adverse events suspected to be related to spartalizumab including those of potential immune-mediated etiology (irAE) must be permanently discontinued from spartalizumab if (1) the AE doesn't recover to ≤ Grade 1 or baseline within 12 weeks and/or (2) the dose of steroids (for the management of irAE) remains > 10 mg/day prednisone or equivalent for >12 weeks. The 12 week timeframe will begin from the time the irAE reaches a grade that leads to spartalizumab interruption.

3.3.3 Dose Modification Guidelines – Adverse Events of Special Interest

Pyrexia

Mandatory dose modification and recommended clinical management for pyrexia syndrome suspected to be related to dabrafenib and/or trametinib treatment

Episodes of pyrexia syndrome have been observed in subjects receiving dabrafenib monotherapy or in combination with trametinib. The pyrexia syndrome is defined as treatment-related fever (≥ 38°C) or chills/rigors/night sweats or flu-like symptoms. In a minority of cases the pyrexia was accompanied by symptoms such as severe rigors/chills, dehydration, hypotension, dizziness or weakness and required hospitalization. The incidence and severity of pyrexia syndrome are increased when dabrafenib is used in combination with trametinib compared to dabrafenib monotherapy.

Dabrafenib and trametinib must be interrupted promptly at the very first symptom of pyrexia or its associated prodrome (chills or rigors or night sweats or flu-like symptoms) and should be restarted upon improvement of symptoms at the same dose if symptom free at least 24 hours.

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take non-steroidal anti-pyretics as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. In subjects experiencing pyrexia associated with rigors, severe chills, dehydration or hypotension, serum creatinine and other evidence of renal function should be monitored carefully during and following severe events of pyrexia.

Pyrexia accompanied by hypotension, dehydration requiring intravenous fluids, renal insufficiency and/or severe rigors, (dehydration requiring intravenous fluids, documented infectious cause should be reported as a SAE.

Guidelines for dose modification and management for pyrexia syndrome considered to be related to dabrafenib are provided in Table 6.

Table 6: Pyrexia Management Guidelines

Pyrexia		
Occurrence	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
1st occurrence and subsequent occurences [c]	• Educate patient about pyrexia syndrome and to immediately interrupt dabrafenib and trametinib at the very first symptom of pyrexia or its associated prodrome (chills or rigors or night sweats or flu-like symptoms). • Clinical evaluation for infection and hypersensitivity [a] • Laboratory work-up [a]	• Dabrafenib and trametinib must be interrupted promptly at the very first symptom of pyrexia or its associated prodrome (chills, rigors, night sweats or flu-like symptoms) and should be restarted upon improvement of symptoms at the same dose if symptom free at least 24 hours. • If pyrexia cannot be managed with interruption, dose reduction per

Pyrexia	
Occurrence	**Recommended adverse event management guidelines**
	• Administer anti-pyretic treatment with non-steroidal anti-inflamatory drugs (NSAID) and/or paracetamol [b] • Recommend oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated. • Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia. • Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.

[a] For subjects experiencing pyrexia, a clinical evaluation and laboratory work-up is mandatory for each event; thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), liver-function tests, blood culture, and urine culture.

[b] Anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended. Anti-pyretic treatment may include acetaminophen, ibuprofen, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment is recommended to be discontinued after three days in the absence of pyrexia.

3.3.4 Visual changes

Episodes of visual changes have been observed in subjects receiving trametinib. The causal relationship between a change in vision and the study treatment should be carefully explored and an ophthalmologist should be consulted. Special attention should be given to retinal (e.g., CSR) or retinal vein abnormalities (e.g., RVO).

TABLE 7 MANAGEMENT AND DOSE MODIFICATION GUIDELINES FOR VISUAL CHANGES

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1	• Consult ophthalmologist within 7 days of onset • Exclude CSR or RVO • Consult retinal specialist if available in case of CSR or RVO • Continue follow up examination(s) (by retinal specialist if available) for CSR and RVO	• Continue trametinib at the same dose level until ophthalmologic examination can be conducted[b] • If ophthalmologic examination cannot be performed within 7 days of onset, interrupt trametinib until CSR and RVO can be excluded and symptoms resolve • If CSR and RVO excluded restart trametinib at same dose level • CSR: Interrupt trametinib until symptoms resolve and exam (by retinal specialist if available) shows resolution; **report as SAE** • If CSR resolves restart with trametinib reduced by one dose level • RVO: **Permanently discontinue trametinib and report as SAE**
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Exclude CSR and RVO • Consult retinal specialist if available in case of RVO or CSR for follow-up exam • Continue follow up examination(s) (by retinal specialist if available) for CSR and RVO	• Interrupt trametinib until signs and symptoms have resolved to baseline • If CSR and RVO excluded and symptoms resolved to baseline restart trametinib reduced by one dose level • CSR: Interrupt trametinib until symptoms resolve and exam (by retinal specialist if available) shows resolution; **report as SAE** • If CSR resolves restart trametinib **reduced by one dose level** RVO: **Permanently discontinue study treatments and report as SAE**

Grade 4	• Consult ophthalmologist immediately • Exclude CSR and RVO • Continue follow up examination(s) (by retinal specialist if available) for CSR and RVO	• **Permanently discontinue trametinib** • **If CSR or RVO then report as SAE**

Abbreviations: CSR = central serous retinopathy; CTCAE = Common Terminology Criteria for Adverse Events; RVO = retinal vein occlusion; SAE = serious adverse event

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification

a. Refers to CTCAE Version 5.0 'Eye disorders – Other, specify
b. If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

3.3.5 Cardiovascular Toxicity

Cardiovascular adverse events have been seen in subjects receiving trametinib and dabrafenib, either as monotherapy or in combination. Dose modification of either agent may be required for decreased LVEF, hypertension or QTc prolongation.

3.3.6 Decreased Left Ventricular Ejection Fraction (LVEF)

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and with trametinib in combination with dabrafenib.
Therefore, a baseline echocardiogram will be performed to assess for adequate LVEF function. Repeat echocardiograms will be performed every 3 months during the duration of dabrafenib and trametinib therapy or at any point if patients develop heart failure symptoms. Management will be per the guidelines in Table 8.

TABLE 8 DOSE MODIFICATION GUIDELINES AND STOPPING CRITERIA FOR LVEF DECREASE

Clinic	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Symptomatic[a]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	• **Permanently discontinue trametinib.** • **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution
	Grade 4: resting LVEF <20%	

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; LLN = lower limit of normal; LVEF

= left ventricular ejection fraction;

a. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms ofpulmonary congestion and edema.

3.3.7 Hypertension

Any level of hypertension should be actively managed. Trametinib does not need to be interrupted while mild hypertension is brought under control; however, treatment interruption and dose-reduction are recommended for more severe or symptomatic hypertension (e.g. persistent systolic blood pressure (SBP) ≥160 mmHg or diastolic blood pressure (DBP) ≥100 mmHg despite antihypertensive treatment).

3.3.8 QTc Prolongation

Guidelines for dose modification and stopping criteria due to QTc-prolongation are provided in Table 9 below:

TABLE 9 WITHHOLDING AND STOPPING CRITERIA FOR QTC-PROLONGATION

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec	• Interrupt all study treatments until QTcB prolongation resolves to grade 1 or baseline • Recommend Testing serum potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level • If event recurs, permanently discontinue study treatments

Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula [a]: Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator agrees.

3.3.9 CUTANEOUS SQUAMOUS CELL CARCINOMA (CUSCC) AND KERATOACANTHOMA (KA)

Both cuSCC and KA have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib [GlaxoSmithKline Document Number

2011N126811_00, GlaxoSmithKline Document Number 2012N136095_00, and GlaxoSmithKline Document Number HM2009/00151/02]. These should be surgically removed according to institutional practices. Dose modification or interruption of study treatment is not required for cuSCC or KA, however they should be reported as an SAE (refer to Section 7.7).

3.4 MONITORING, INTERRUPTION, AND STOPPING CRITERIA FOR HEPATOBILIARY EVENTS

These liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology in alignment with the FDA Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009, www.fda.gov).

Liver chemistry stopping criteria 1-5 are defined as follows:

ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN (>35% direct bilirubin) (or ALT ≥ 3 x ULN and INR>1.5, if INR measured)

NOTE: If serum bilirubin fractionation is not immediately available and if ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN, subject should be discontinued from study treatments. Serum bilirubin fractionation should be performed if testing is available.

ALT ≥ 8 x ULN;ALT ≥ 5 x ULN but < 8 x ULN persists for ≥ 2 weeks; ALT ≥ 3 x ULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

3.5 Adverse events of special interest (AESI)

Adverse events of special interest include AEs of a potential irAE that are associated with spartalizumab treatment. An irAE may be experienced by subjects treated with spartalizumab due to its mechanism of action and predicted based on the reported experience with other immunotherapies that have a similar mechanism of action. Investigators must be vigilant and carefully identify AEs that may be suggestive of potential irAEs as their appearance may be sub- clinical and early diagnosis is critical for its adequate management and resolution.

An irAE is typically low grade and self-limited, often occurring after multiple doses, and most frequently involving the GI tract (diarrhea/colitis), skin (rashes), liver (hepatitis), lung (pneumonitis), kidneys (nephritis) and endocrine systems (a variety of endocrinopathies) and rarely CNS (encephalitis). Serological, immunological and histological assessments should be performed as deemed appropriate by the investigator, to verify the potential immune-related nature of the AE, and exclude a neoplastic, infectious or metabolic origin of the AE.

Severe grade or persistent lower grade irAEs typically require interrupting or permanently discontinuing treatment and administration of systemic steroids or other non-corticosteroid immunosuppressive medication when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants.

In some cases, it may be unclear to determine if an adverse event is immune related or not, thus the following dose reduction guidelines should be followed.

The following sections address the specific instructions for mandatory dose modifications and recommended management for AEs considered suspected to be related to study treatment. For subjects who do not tolerate the protocol-specified dosing schedule, dose interruptions or modifications are mandated in order to allow subjects to continue study treatment.

3.6 THERAPY ADMINISTRATION

3.6.1 Dabrafenib and trametinib administration

- Dabrafenib and trametinib will be provided by the Supporting Company, Novartis free of charge and will be disposed of per Institutional Guidelines
- Dabrafenib and trametinib should be taken as follows:
  Dabrafenib will be administered orally twice daily (BID) for Days 1-28 of a 28-day cycle.
- Trametinib will be administered orally once daily (QD) for Days 1-28 of a 28-day cycle.
- Subjects should be instructed to take the dabrafenib and trametinib concurrently in the morning, at approximately the same time every day. The second (evening) dose of dabrafenib (150 mg) should be administered approximately 12 (± 4) hours apart from the first dose (morning) of dabrafenib.
- Subjects should be instructed to swallow whole capsules of dabrafenib and not chew or open them.
- If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and wait for the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted
- If a subject misses a dose, he/she should be instructed not to double the next regularly scheduled dose. However, subject may take the missed dose immediately if the next scheduled dose is at least 6 hours later for dabrafenib and 12 hours later for trametinib. Subject may then take the next dose at the scheduled time.
- Subjects must avoid consumption of grapefruit, grapefruit hybrids, pomelos, star-fruit, Seville oranges or products containing the juice

of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications.

- Orange juice is allowed.
- No herbal or dietary supplements are permitted.
- Multivitamins are permitted.

3.6.2 Spartalizumab administration in adjuvant setting for non pCR patients

Spartalizumab (100mg liquid in vial for infusion solution) will be administered as a flat dose of 400mg intravenously over at least 30 minutes every 28 days in the adjuvant setting along with dabrafenib and trametinib in patients who have not achieved a pCR. Infusion can be up to 2 hours if clinically indicated. Subjects should not receive pre-medication to prevent infusion reaction before the first infusion of study treatment. If a subject experiences an infusion reaction, he/she may receive pre- medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the investigator. Spartalizumab will be provided by Novartis free of charge and will be disposed of per Institutional Guidelines.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a subject experiences a Grade 3 anaphylactic/anaphylactoid reaction, the subject will be discontinued from the study.

3.7 MANAGEMENT OF IRAES

Management of spartalizumab induced immune mediated adverse events should be as per the guidance documents in Appendix B.

If a patient does experience an irAE and prednisone is administered, reduce prednisone dose by 2.5 to 10.0 mg decrements every 3–7 days until physiologic dose (5 to 7.5 mg of prednisone per day) is reached. Consider to complete tapering over a period of at least 4 weeks. Slower tapering of corticosteroids therapy may be recommended if the adverse event is not showing improvement.

Once corticosteroid tapering is achieved at a level of 10 mg of prednisone/day (or equivalent) spartalizumab can berestarted.

3.8 CONCOMITANT AND EXCLUDED THERAPIES

The following medications or non-drug therapies are prohibited while on treatment in this study:

- Other anti-cancer therapies

3.8.1 Other investigational drugs

The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of study treatment. Any concomitant medication(s), including dietary supplements, taken during the study will be recorded. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. ConMeds will be recorded in both EMR and CRF.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

3.8.2 Prohibited Concomitant Medications

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of infusion reaction, irAEs, and for prophylaxis against imaging contrast dye allergy or replacement-dose steroids in the setting of adrenal insufficiency (providing this is <10 mg/day prednisone or equivalent), or transient exacerbations of other underlying diseases such as COPD requiring treatment for ≤ 3 weeks. If systemic corticosteroids are required for the control of infusion reactions, pyrexia or irAEs, it must be tapered and be at non-immunosuppressive doses (< 10 mg/day of prednisone or equivalent) before the next administration of study treatment.

If the dose of prednisone or equivalent cannot be reduced to less than 10 mg/day before the administration of next dose of study treatment then spartalizumab must be discontinued.

The use of live vaccines is not allowed through the whole duration of the study. Inactivated vaccines are allowed.

Dabrafenib induces CYP3A4- and CYP2C9- mediated metabolism and may induce other enzymes including CYP2B6, CYP2C8, CYP2C19 and UDP glucuronosyltransferases (UGT). Dabrafenib may also induce transporters (e.g., P-glycoprotein (P-gp)). Co-administration of dabrafenib and medicinal products which are affected by the induction of CYP3A4 or CYP2C9 such as hormonal contraceptives, warfarin or dexamethasone may result in decreased concentrations and loss of efficacy. If co- administration of these medications is necessary, monitor subjects for loss of efficacy or consider substitutions of these medicinal products. Use caution if co-administration of CYP2C or CYP3A4 substrates with narrow therapeutic index is required. Refer to the dabrafenib label for further information.

Based on *in vitro* and *in vivo* data, trametinib is unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes or transporters.

4.0 STUDY ASSESSMENTS

4.1 CRITICAL BASELINE ASSESSMENTS

Baseline (Screening) assessments obtained will include:

- Documentation of relevant medical history Complete physical examination, including weight and single height measurement
- Review of concomitant medications and documentation baseline toxicity information
- Verification of BRAF mutation at V600 position by a CLIA certified assay. Presence of BRAF by IHC is acceptable to begin screening evaluations.
- Documentation of surgical resectability from multi-disciplinary tumor conference
- Vital signs: blood pressure, temperature, respiratory rate, pulse rate
- Eastern Cooperative Oncology Group (ECOG) performance status
- Clinical laboratory tests: hematology, thyroid (TSH and fT4) and clinical chemistry
- Coagulation Panel (PT/PTT)
- Serum or urine beta-human chorionic gonadotropin (β-HCG) pregnancy test for female subjects of childbearing potential only
- 12-lead electrocardiogram (ECG)
- 2D complete echocardiogram for assessment of ejection fraction
- Ophthalmic exam by ophthalmologist to include indirect fundoscopic examination, visual acuity, visual field examination, tonometry, and direct fundoscopy, with special attention to retinal abnormalities that are predisposing factors for RVO or CSR
- Brain magnetic resonance imaging (MRI) with contrast or a computed tomography (CT) scan (with/without contrast) if MRI is contraindicated
- CT of the chest, abdomen and pelvis with contrast or PET/CT, imaging of body site of interest (neck, extremity) if indicated
- Research blood collection
- Research microbiome collection
- Research tumor biopsy

4.2 BASELINE CONFIRMATION OF BRAF MUTATION-POSITIVE MELANOMA

Patients may be enrolled and started on study if they have local molecular testing that is positive for BRAF mutation in the V600 position by a CLIA certified assay. Only patients with V600E or V600K mutations are eligible for enrollment. Presence of BRAF by IHC is acceptable to begin screening evaluations.

4.3 SCHEDULE OF ASSESSMENTS

Table 10 Time and Event Table—Neoadjuvant Phase

	Screening[J]	Cycle 1	Cycle 1	Cycle 2	Cycle 2
		Day 1	Day 15[K]	Day 1[K]	Day 28[K]
Informed consent	X				
Demographics	X				
Medical history	X				
Concurrent medications	X	X	X	X	X
AEs[a]	X	X	X	X	X
PE/Vitals/ECOG	X	X	X	X	X
Pregnancy test[b]	X				
CBC with diff[c]	X	X	X	X	X
Serum chemistry	X	X	X	X	X
Thyroid TSH, fT4	X				X
Coagulation	X				X
Echocardiogram	X				
12-lead EKG	X		X		X
Ophthalmic exam	X				
Research Tissue[d]	X				X (surgery)
Research Blood[e]	X		X	X	X

Research microbiome Collection[f]	X				X
Disease Assessment[g]	X				X
Surgical resection[h]					X
Dabrafenib and trametinib[i]		Continuous Daily Dosing			

a. Systolic and diastolic blood pressure, pulse rate, temperature, including weight and single height measurement.
b. Serum or urine β-hCG - For women of childbearing potential only within 7 days of start of study drugs.
c. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, AST, ALT, sodium
d. Mandatory biopsy at baseline and collection of residual tumor at surgery.
e. 50ml of blood will be obtained at each time point for correlative correlates
f. OMNIgene gut kits, or equivalent, will be provided for stool collection at screening and Cycle 2
g. PET/CT or CT of the chest, abdomen, pelvis (neck if clinically indicated) and brain MRI (or CT of the head with contrast if MRI is contraindicated).
h. Surgical resection of residual tumor if restaging scans show disease stability or response. If disease progression is confirmed, surgery may still occur if disease is still deemed resectable
i. Dabrafenib and trametinib will be held starting the day prior to planned surgical intervention.
j. Screening is defined as within 35 days prior to treatment initiation.
k. +/- 7 days

Table 11 Adjuvant Time and Event Table for Pathologic Complete Responders (dabrafenib and trametinib only)

	Post-operative	Week 12[i]	Week 16[i]	Week 20[i]	Week 24[i]	Week 28[i]	Week 32[i]	Week 36[i]	Week 40[i]	Week 44[i]	Week 48[i]	Week 52[i]	EOT[j]
Concurrent medications	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
PE/Vitals/ECOG[a]		X	X	X	X	X	X	X	X	X	X	X	X
CBC with diff		X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[b]		X	X	X	X	X	X	X	X	X	X	X	X
TSH, fT4				X			X			X			
Echocardiogram[c]		X			X			X			X		
12-lead EKG		X			X			X			X		X
Research Biopsy[d]			If evidence of disease recurrence or metastasis										

Research Blood[e]		X			X			X			X		X
Research microbi ome collectio n[f]		X						X					X
Disease Assessment[g]				X			X			X			X
Dabrafenib and trametinib dosing	X	Continuous Daily Dosing											

a. Includes systolic and diastolic blood pressure, pulse rate, temperature and weight.
b. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, AST, ALT, sodium.
c. Repeat echocardiogram will be performed at month 3 and 6 and at the discretion of the investigator if there are symptoms concerning for heart failure.
d. Should a biopsy be performed as part of standard practice, this study may request up to 4 additional cores for correlative studies.
e. 50ml of blood will be obtained at each time point for correlative correlates.
f. Micobiome will be collected at week 12, 36 and at recurrence. OMNIgene kits, or equivalent, will be provided
g. PET/CT or CT of the chest, abdomen, pelvis (neck if clinically indicated) and brain MRI (or CT of the head with contrast if MRI is contraindicated).
h. Dabrafenib and trametinib combination therapy will resume approximately two days after the patients is able to resume normal oral intake and ideally should be within 2 weeks of date of surgery. This visit could be a telephone assessment by research nurse
i. These time points are +/- 7 days.
j. End of treatment is defined as completion of 44 weeks of adjuvant dabrafenib/trametinib, experiencing SAE or intolerable

AE mandating discontinuation of treatment or the development of progressive disease.

Table 12 Adjuvant Time and Event Table for Pathologic Non-Responders (spartalizumab, dabrafenib and trametinib)

	Post Operative[h]	Week 12[i]	Week 16[i]	Week 20[i]	Week 24[i]	Week 28[i]	Week 32[i]	Week 36[i]	Week 40[i]	Week 44[i]	Week 48[i]	Week 52[i]	EOT[j]
Concurrent medications	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
PE/Vitals/ECOG[a]		X	X	X	X	X	X	X	X	X	X	X	X
CBC with diff		X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[b]		X	X	X	X	X	X	X	X	X	X	X	X
TSH, fT4				X			X			X			
Echocardiogram c		X			X			X			X		
12-lead EKG		X			X			X			X		X
Research Biopsy[d]			If evidence of disease recurrence or metastasis										
Research Blood[e]		X			X			X			X		X
Research microbiome collection[f]		X						X					X

Disease Assessment[g]				X			X			X			X
Spartalizumab		X	X	X	X	X	X	X	X	X	X		
Dabrafenib and trametinib dosing	X	Continuous Daily Dosing											

a. Includes systolic and diastolic blood pressure, pulse rate, temperature and weight.
b. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, AST, ALT, sodium.
c. Repeat echocardiogram will be performed at month 3 and 6 and at the discretion of the investigator if there are symptoms concerning for heart failure.
d. Should a biopsy be performed as part of standard practice, this study may request up to 4 additional cores for correlative studies.
e. 50ml of blood will be obtained at each time point for correlative correlates.
f. Micobiome will be collected at week 12, 36 and at recurrence. OMNIgene kits, or equivalent, will be provided
g. PET/CT or CT of the chest, abdomen, pelvis (neck if clinically indicated) and brain MRI (or CT of the head with contrast if MRI is contraindicated).
h. Dabrafenib and trametinib combination therapy will resume approximately two days after the patients is able to resume normal oral intake and ideally should be within 2 weeks of date of surgery. This visit could be a telephone assessment by research nurse
i. These time points are +/- 7 days.
j. End of treatment is defined as completion of 44 weeks of adjuvant dabrafenib/trametinib, experiencing SAE or intolerable AE mandating discontinuation of treatment or the development of progressive disease

4.4 SAFETY EVALUATIONS

4.4.1 Physical exams/ECOG/Vital Signs

A complete physical examination will be performed by a qualified physician or a midlevel provider (physician's assistant, nurse practitioner). Documentation of Eastern Cooperative Oncology Group status is required.

Baseline skin exam must be performed. Skin photography of new skin lesions or lesions that change during therapy recommended at each reassessment while the subject is on therapy.

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, and temperature. On days where vital signs are measured multiple times, temperature does not need to be repeated.

The performance status assessment is based on the ECOG scale:

0 Fully active, able to carry on all pre-disease performance without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work or office work).

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. 4– Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

4.4.2 ECG

12-lead ECG will be obtained as indicated in the Times and Events Tables in Section 7.2. Each 12-lead ECG will be performed after the subject has rested at least five minutes in a semi- recumbent or supine position.

$$\text{QTc (Bazett)} = \frac{\text{QT}}{\sqrt{\text{RR}}}$$

Those QTc values greater than 480msec as calculated by the machine must be confirmed manually using Bazett's formula given below:

If there are any clinically significant abnormalities including but not limited to a QTcB > 500msec, confirm with two additional ECGs taken at least 5 minutes apart.

4.4.3 Echocardiogram

An echocardiogram will be performed to assess cardiac ejection fraction and cardiac valve abnormalities as indicated in the Times and Events Tables in Section 7.2.
Echocardiography should include an evaluation for left ventricular ejection fraction and both right- and left sided valvular lesions. For each subject, the same procedure should be performed at the screening and as clinically warranted during the course of the study.

4.4.4 Ophthalmic

Patients will have a standard ophthalmic exam performed by an ophthalmologist at screening. The exam will include indirect fundoscopic examination, visual acuity, visual field examination, tonometry, and direct fundoscopy, with special attention to retinal abnormalities that are predisposing factors for RVO or CSR.

4.5 LABORATORY ASSESSMENTS

Hematology, clinical chemistry, and additional parameters to be tested are listed below:

Hematology

Platelet Count	RBC Indices:	Automated WBC Differential:
WBC Count (absolute)	MCV	Neutrophils
Hemoglobin		Lymphocytes
Hematocrit		Monocytes
		Eosinophils
		Basophils

Clinical Chemistry

BUN	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Total protein
Glucose	Total CO_2	Lactate dehydrogenase (LDH)	Albumin
Sodium	Calcium	Alkaline phosphatase	Phosphorus
Magnesium	TSH	Free T4	

4.6 BIOMARKER COLLECTIONS AND ANALYSES

Biospecimen Collection
For blood and tissue correlative studies, specimens will be collected as part of the protocol study assessments and stored for later analysis. Missed tissue or blood collections, will not be classed as a deviation. Below are proposed analysis for tissue and blood as availability and quality of each permits. The priority of analysis will be determined by investigators.
In the neoadjuvant setting, patients will have mandatory baseline biopsy as well as research collection of part of the surgical sample. On the occasion where available tissue or blood is limited and we did not receive enough for analysis or where the tissue or blood collection was missed, specimens collected from MD Anderson patients at the same time points as part of protocol 2012- 0846 and/or LAB00-063 may be requested for use as long as the patient has a valid informed consent. Available paraffin embedded tumor tissue from prior biopsies or excisions may also be collected as pre-treatment comparator samples, so long as the patient provides consent for use in this study.

Tissue will be collected as per the Institute guidelines and standard operating procedures. All samples will be processed, labeled, and stored in accordance with NCI best practices for biospecimens. General details regarding tissue procurement are indicated below:
Tumor Tissue: Each set of core biopsies or surgical specimen may be divided in up to 4 portions and processed as below for later analysis:

(1) FFPE for histology and IHC (25% of the specimen, or 1 core biopsy)
(2) Snap frozen tumor in a cryovial (75% of the specimen or 3 core biopsies)
Blood processing and storage for circulating correlative analysis:
Two 10 ml tubes of blood will be collected for PBMC isolation and cryopreserved, for subsequent evaluation. Plasma will be collected and stored at -80°C. One 10ml serum will be collected and stored at -80°C. Two 10ml tubes of blood will be collected for cfDNA and genomic DNA, for analysis of circulating tumor markers and genomic analysis.

Stool samples for microbiome analysis: OMNIgene Gut Kits, or equivalent, will be provided for stool sampling for microbiome analysis. The kits come with full instructions on use (Appendix C).

4.7 BIOMARKER ANALYSES

Tumor samples may be assessed for expression of immune or melanoma related genes, RNAs, and/or proteins to identify molecular or immune features of response and resistance. Methodologies may include, tissue availability permitting, single stain

immunohistochemistry (IHC) or multiplex IHC, DNA profiling (WES or targeted panel, TCR sequencing), expression profiling (RNAseq or panel-based such as Nanostring).
Analyses on blood may include flow cytometry, ctDNA, CTC, proteomics, cytokine, and exosomal studies. Additional immune and molecular analyses may be conducted per the discretion of the study team.
In addition to immune studies, we may assess circulating tumor cells (CTC) and circulating free DNA (cfDNA) in these patients during the course of therapy. Our hypothesis is that the levels of CTC and cfDNA will correlate with disease burden, and will decrease during therapy and will rise at time of relapse. We will use a microfluidics system to isolate and enrich CTC from peripheral blood at baseline, at week 3 on neoadjuvant therapy, at Week 8 (surgery), and at Weeks 12, 24 and 36 post surgery). Blood will also be drawn at relapse (when applicable) and these assays will be performed. We will use cfDNA plasma to perform ddPCR to determine CNV for two mutations (V600K and V600E).
There is a growing appreciation of the influence of host factors on treatment to therapy in patients with cancer, such as microbiome. Microbiome samples collected from these patients will provide insight into this patient population, previously unstudied. Analyses of the gut microbiome samples may include 16s or metagenome sequencing.

4.8 IMAGING ASSESSMENTS

Disease assessment will include imaging (computed tomography, magnetic resonance imaging) and physical examination (as indicated for palpable/superficial lesions). At screening, an MRI or CT of the head is required. At minimum, CT of the chest, abdomen and pelvis are required but additional imaging of affected areas (neck or extremities) may be required for documentation of target lesions.

Disease assessment will be completed within 35 days prior to the first dose of study drug, then as indicated in the Time and Events Tables Section 4.3. It is not necessary to repeat radiologic assessments at the final study visit if the subject was withdrawn due to disease progression. More frequent disease assessments may be performed at the discretion of the investigator. To ensure comparability between baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

Disease response will be recorded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to RECIST 1.1 criteria [31].

4.9 PATHOLOGIC ASSESSMENTS

All patients will be evaluated after 8 weeks of induction dabrafenib and trametinib therapy immediately prior to the planned surgical resection. All patients who experience a PR or SD will be eligible for surgical resection. Those patients who develop PD will be allowed to continue on to surgery as long as disease is still deemed resectable. Patients who initially had lymph node involvement but appear to have achieved a CR on imaging after the 8 week induction period will proceed on to completion lymph node dissection.
Tumor specimens of patients undergoing treatment will undergo evaluation for pathologic complete response (pCR) and pathologic partial response (pPR). pCR is defined as the absence of any residual invasive malignant cells on hematoxylin and eosin evaluation of the resected melanoma specimen. Near pCR is defined as less than 10% viable tumor. pPR is defined as less than 50% viable tumor cells or more than 50% fibrosis on pathological evaluation. pNR is defined as no viable tumor[31].
After surgery, pathology will be reviewed by pathology collaborators and formal reporting on tumor viability, fibrosis and necrosis will be reported. This report should be issued within 2 weeks of surgery date to allow for assignment of adjuvant therapy.

4.9.1 Surgical Ease Surveys

Assessment of surgical ease or difficulty after neoadjuvant therapy administration is not currently well understood. In order to obtain data on this important subject, we will be asking collaborating surgical oncologists to complete surveys on the subjective difficulty or ease of surgery compared to comparable surgery in patients who have not undergone neoadjuvant therapy. Surveys will be administered at time of patient trial enrollment, within 1 week of surgical resection and approximately 30 days after surgery is complete. These time-points are selected with the hope of obtaining initial thoughts on surgical difficulty and how this is altered by the neoadjuvant treatment. The 30-day post-operative survey is to capture complications, if any. Sample surveys are located in Appendix D. The surveys will be performed for the purpose of determining if neoadjuvant treatment influences the outcomes of surgery. Data will be recorded utilizing the Prometheus database.

5.0 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the first protocol intervention, even if the event is not considered to be related to study treatment. Medical conditions/diseases present before starting study therapy are only considered adverse events if they worsen after starting study treatment. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The investigator (or physician designee) isnresponsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

Recommended Adverse Event Recording Guidelines

Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

The Adverse Event Recording period will be from the first protocol intervention to 150 days after the last dose of study drug.

5.1 DEFINITION OF AN AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the

condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/serious adverse event [SAE]).

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

5.2 ADVERSE EVENT GRADING

Grading of AE's will be per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v.5.0).

The following categories and definitions of causal relationship to study medication as determined by a physician should be used for adverse events:

- Definitive: There is a reasonable causal relationship between the study medication product and the AE. The event responds to withdrawal of study medication (re-challenge), and recurs with re-challenge when clinically feasible.
- Probable: There is a reasonable causal relationship between the study medication and the AE. The event responds to re-challenge. Re-challenge is not required.
- Possible: There is reasonable causal relationship between the study medication and the AE. Re-challenge information is lacking or unclear.
- Unlikely: There is a temporal relationship to study medication administration, but

  there is not a reasonable causal relationship between the study medication and the AE.
- Unrelated: There is not a temporal relationship to study medication administration (too early, or late, or study medication not taken), or there is a

reasonable causal relationship between non-study medication, concurrent disease, or circumstance and the AE.

- The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

5.3 SERIOUS ADVERSE EVENT REPORTING (SAE)

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

SAE REPORTING

The principal investigator has the obligation to report all serious adverse events to the FDA (if applicable), IRB, and Novartis Patient Safety Department ***(For patients taking Novartis drugs)***.

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form), if applicable.

- To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 1 5 0 days after the patient has stopped study treatment or until the start of a new anti-neoplastic

medication if sooner than 150 days must be reported to Novartis within 24 hours of learning of its occurrence. If a subject starts a post-treatment antineoplastic therapy, then only adverse events suspected to be related to study treatment should be collected out to 150 days after discontinuation of PDR001. Reporting to Novartis should also occur within 30 days after the last dose of dabrafenib or 120 days after the last dose of trametinib, if the subject continued the combination partner more than 150 days after the last dose of PDR001). Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form along with the Novartis provided cover sheet to the Novartis Patient Safety department by email (**clinicalsafetyop.phuseh@novartis.com) **within 24 hours.**

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the reporting period described above period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Follow-up information is submitted in the same way as the original SAE Report. Each re- occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Patient Safety department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

PREGNANCIES

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its

occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be reported by the investigator to the Novartis Patient Safety department by email (clinicalsafetyop.phuseh@novartis.com).). Pregnancy follow-up should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices".

Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office. -
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 150 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 150 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

6.0 DATA MANAGEMENT

For the purposes of this study at data will be captured in a secure, password protected, encrypted and security compliant database (eg, CORe, Prometheus, MelCore). All patients will be registered in CORe before any study specific tests are performed. A brief explanation for required but missing data should be recorded as a comment. The investigator is required to retain, in a confidential manner, the data pertinent to the study for the duration of the study or the maximum period required by applicable regulations and guidelines or institutional procedures. If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (e.g., another investigator or IRB). Documentation of such transfer must be provided to the sponsor.

CORe, Prometheus, and Melcore are databases internally accessible to MD Anderson. Patient registration from all participating sites will be made through the CORe database. The Prometheus database will be used for clinical data capture on research participants, data entry on internal (MDACC) research patients will be performed by the MDACC's Department of Melanoma.

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner in the electronic case report forms (eCRFs) in the Prometheus database. All source documents will be available for inspection by the FDA and the MDACC IRB.

6.1 RECORDS RETENTION

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

The investigator must retain investigational product disposition records, source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g. medical records) for two years. The records must be available for review in conjunction with assessment of the facility, supporting systems, and relevant staff.

7.0 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Overview

This will be a Phase II, open-label study of dabrafenib in patients with clinical Stage III melanoma who harbor a BRAF V600E or V600K mutation. In patients who achieve a pCR at the time of surgery, they will continue on dabrafenib and trametinib in the adjuvant setting. For those patients who do not achieve a pCR at the time of surgery, they will be treated with dabrafenib, trametinib and spartalizumab in the adjuvant setting.

The primary objective is to independently determine the 12-month relapse-free survival (RFS) rate in stage IIIB/C/D melanoma patients who, after 8 weeks of neoadjuvant dabrafenib and trametinib, do not achieve a pCR and receive adjuvant dabrafenib, trametinib and spartalizumab.

Secondary objectives include assessing safety in both the neoadjuvant and adjuvant settings. Recurrence patterns, including assessment of distant metastasis-free survival and overall survival separately by pathologic response status will also be addressed. The 12 month RFS of patients who achieve a pCR after receiving neoadjuvant and adjuvant treatment with dabrafenib and trametinib will also be assessed.

Exploratory objectives include assessing immune and molecular features of response and resistance, assessing the association between circulating blood markers and treatment response and relapse, and assessing surgical resectability.

A total of 45 patients will be initially treated with dabrafenib and trametinib for 8 weeks. Patients will be assessed for pCR as defined above based on the results of their surgical pathology. Patients who achieve a pCR will continue with the dabrafenib and trametinib combination for an additional 44 weeks. Patients who do not achieve a pCR will have spartalizumab added to dabrafenib and trametinib for an additional 44 weeks.

Sample Size and Power

A sample size argument will be based upon patients who do not have a pCR. We expect approximately 60% of enrolled patients to not achieve a pCR after 8 weeks on the dabrafenib/trametinib combination. Historically, these patients experience a 12-month relapse-free survival (RFS) rate of 50%, and we hope to increase this to 75%. Under the assumptions of 2 years for patient accrual and an additional 2 years of follow-up after accrual ends, exponentially- distributed RFS times, and a two-sided exponential maximum-likelihood test with a 5% Type 1 error rate (alpha), a total of 24 non-pCR patients will provide 80% power to detect a minimum increase in RFS at 1 year to 75%. If 60% of patients do not have a pCR, we would need to enroll a total of 40 patients to have a total of 24 non-pCR patients, but to account for a potentially higher pCR rate and patient dropout, we will accrue a total of 45 patients.

Statistical Analyses

For the primary objective, separately by group (patients who do/do not achieve a pCR at 8 weeks), the 12-month RFS rate will be estimated with a 95% confidence interval by using the Kaplan-Meier method. RFS is defined from time of surgery to any recurrence event (local or distant disease development or death due to melanoma. In addition, in patients who do not achieve a pCR, the 12-month RFS rate will be compared with the historical rate of 50% by using a two-sided exponential MLE test. Cox proportional hazards regression models will be fit to assess the association between various clinical, demographic, and disease covariates and RFS separately by pathologic response group.

For safety, the rate of grade 3+ adverse events will be tabulated and presented by group. For overall survival (OS) and distant metastasis-free survival (DMFS), 12-month rates will be reported with 95% confidence intervals, and Cox regression models will be used to assess the association between similar covariates as above and both OS and DMFS separately by group. OS is defined as time from treatment initiation to death. DMFS is defined as time from treatment initiation to development of documented distant metastatic disease outside the loco-regional site of the primary tumor or lymph node metastasis.

For the exploratory objectives, immunological and molecular features will be assessed quantitatively at baseline and at surgical resection. Kruskal-Wallis tests will be used to compare these parameters at each time point between responders (pCR) and non-responders (no pCR). Changes in each parameter from baseline to surgery will also be compared between responders and non-responders. Circulating tumor markers will be assessed at baseline and several on-study time points. Markers and changes in markers over time will be compared between responders and non-responders by using Kruskal-Wallis tests. In addition, generalized linear mixed models may be used to model these markers over time.

Finally, to assess the impact of neoadjuvant therapy on surgical resectability, a survey will be provided to surgeons regarding the difficulty of surgery (Appendix D). These data will be subjective and will be summarized graphically as numbers permit.

The Investigator is responsible for completing an efficacy/safety summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. Please submit efficacy and toxicity summary for the first 5 patients after 8 weeks of treatment and every 5 patients thereafter. Copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

8.0 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

The investigator (i.e., the study site principal investigator) will obtain, from the MD Anderson Cancer Center Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment, if applicable.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the MD Anderson Cancer Center IRB of the deviation.

The MD Anderson Cancer Center IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice.

9.0 COMPLIANCE WITH TRIAL REGISTRATION AND RESULTS POSTING REQUIREMENTS

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.0 ETHICAL CONSIDERATIONS

The clinical study will be conducted in accordance with the current IRB- approved

clinical protocol; ICH Guidelines on Guidelines on Good Clinical Practice; and relevant policies, requirements, and regulations of the University of Texas MD Anderson Cancer Center IRB, and applicable federal agencies.

11.0 INFORMED CONSENT

The investigator (i.e., the study site principal investigator) will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator, or a sub-investigator(s) designated by the MD Anderson IND Office, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The investigator or sub-investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

12.0 STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

The investigator and the head of the medical institution (where applicable) agrees to allow the IND Office monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

- Monitoring visits will be conducted in a manner to ensure that the:
- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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APPENDICES

Appendix A: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix B: Management of Spartalizumab-Induced Immune Mediated AEs

Recommended clinical management for suspected immune-related diarrhea/colitis

Diarrhea/colitis (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 1 (Increase of < 4 stools per day over baseline) mild increase in ostomy output compared to baseline. Grade 2 (Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL) and/or abdominal pain/ mucus or blood in stool.	• Diet & Hydration • Loperamide: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/d. Continue until free of diarrhea for 12h • Diarrhea > 24h: loperamide 2 mg every two hours; maximum 16 mg/d. Consider adding oral antibiotics. • Diarrhea > 48h: loperamide 2 mg every two hours; maximum 16 mg/d. Consider other second-line therapies for diarrhea (e.g. (octreotide, oral diphenoxylate) and oral antibiotics • If grade 2 and no improvement in 5 days: consider oral steroids • If grade 2 diarrhea persists > 1 week consider gastroenterologist consultation and endoscopy to evaluate for colitis • If grade 2 persists for 5 days and worsening of symptoms or diffuse ulcerations and bleeding seen on endoscopy, initiat steroids (0.5 - 1 mg/kg/d of prednisone or equivalent) and continue until symptoms improve to grade 1. • If no improvement occurs, manage as per grade 3. Steroids should be tapered slowly • Sigmoidoscopy and biopsy can be considered and may assist in determining the duration of steroid taper based on the evidence of macroscopic and microscopic inflammation.
Grade 3 diarrhea: Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL; Grade 3 colitis: Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	• Clinical evaluation and hospitalization indicated; rule out bowel perforation and intravenous hydration. • Consider consultation with gastroenterologist and biopsy with endoscopy. • In addition to symptomatic treatment (diet, hydration, loperamide, antibiotics if indicated); initiate immediate treatment with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) is recommended. • When symptoms improve to ≤ grade 1, taper steroids slowly (see Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding. • If no improvement in 2-3 d: consider initiating infliximab 5 mg/kg and continue steroids. Note: infliximab is contraindicated in patients with sepsis or a perforation. Upon symptomatic relief initiate a prolonged steroid taper over 6 to 8 weeks. • If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg/d followed by a more prolonged taper and administer infliximab. • If symptoms persist despite the above treatment a surgical consult should be obtained.

Grade 4: Life-threatening consequences; urgent intervention indicated	Same as grade 3

Recommended clinical management for suspected immune-related liver laboratory alterations

Abnormal liver tests (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 2: AST or ALT > 3 × ULN to ≤ 5.0x ULN; or if baseline abnormal >3.0 – 5.0 x baseline or bilirubin > 1.5 × ULN to ≤ 3 × ULN ; or if baseline abnormal >1.5 – 3.0 x baseline (if patient meets criteria for Hy's law refer to	• Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values • Rule-out alternative causes (e.g. concomitant medications, infection, disease progression) • Consider prednisone (0.5-1 mg/kg/d) if liver tests worsen and/or significant symptoms
Grade 3 or 4: AST or ALT > 5.0 × ULN; or if baseline abnormal >5.0 x baseline. bilirubin > 3.0 × ULN; or if baseline abnormal >3.0 x baseline.	• Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values. • Consider viral serology (i.e. hepatitis A/B/C, CMV, and rule out other potential cause of liver injury such as concomitant medications or alcohol), consultation with hepatologist and liver biopsy to establish etiology of hepatic injury • If after 2-3 days new liver assessment shows worsening of laboratory test consider to initiate treatment with steroids prednisone 1-2 mg/kg/day or i.v. equivalents. • Add prophylactic antibiotics for opportunistic infections as appropriate • When symptoms/liver tests improve to grade ≤ 1, taper steroids over at least 4 weeks. • If serum transaminase levels or bilirubin do not decrease 48-72 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given as per institutional guidelines. • Infliximab is not recommended due to its potential for hepatotoxicity

Recommended clinical management for suspected immune-related rash and other skin events

Rash and other skin Events (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 1: rash covering < 10% Body Surface Area (BSA)	• Initiate prophylactic and symptomatic treatment measures. • Consider use of topical corticosteroids or urea containing creams in combination with oral antipruritics or moderate strength topical steroid (hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) • Reassess after 2 weeks.

Rash and other skin Events (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 2: 10-30% of BSA	• If tolerable, treat as per grade 1; • If intolerable, initiate systemic steroids (e.g. oral prednisolone 0.5- 1 mg/kg/d) and consider dose interruption until tolerable or recovery to grade ≤ 1 or baseline • If symptoms persist or recur consider skin biopsy**.**
Grade 3: More than 30% of BSA	• Obtain a skin biopsy and dermatology consult. • Initiate systemic steroids with 1mg/kg/d of prednisone or equivalent.
Grade 4: Life-threatening	Same as grade 3; additional measures as per local institutional guidelines
Other skin events	
Stevens-Johnson syndrome, toxic epidermal necrolysis	• Hospitalization and urgent dermatology consultation • Institute supportive care immediately as per institutional guidelines

Recommended clinical management for suspected immune-related nephritis

Nephritis (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 1: Creatinine > ULN to ≤ 1.5 × ULN); or if baseline abnormal >1 – 1.5 x baseline	• Monitor creatinine weekly • If creatinine return to baseline resume routine creatinine monitoring per protocol • Promote hydration and cessation of nephrotoxic drugs
Grade 2: Creatinine > 1.5 to ≤ 3 × ULN; or if baseline abnormal >1.5 – 3.0 x baseline	• Monitor creatinine every 2 to 3 days • Initiate 0.5 to 1 mg/kg/d prednisone or equivalents • If worsening or no improvement: 1 to 2 mg/kg/day prednisone or equivalents • Promote hydration and cessation of nephrotoxic drugs • Consult with specialist and consider renal biopsy

Grade 3: Creatinine >3.0 to ≤ 6.0 × ULN; or if baseline abnormal >3.0 – 6.0 x baseline	• Monitor creatinine every 1 to 2 days • Start 1 to 2 mg/kg/day prednisone or equivalents • Consult with nephrologist and consider renal biopsy
Grade 4: Creatinine > 6.0 × ULN	• Monitor creatinine daily • Initiate steroids with 1 to 2 mg/kg/d prednisone or equivalent • Consult with nephrologist and consider renal biopsy

Recommended clinical management for suspected immune-related pneumonitis

Pneumonitis (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• High-resolution CT with lung windows recommended, with serial imaging to monitor for resolution or progression. Repeat at least every 3 weeks • Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse oximetry recommended

Pneumonitis (NCI-CTCAE v5)	
Grade	**Recommended management**
	• Consultation of pulmonologist recommended
Grade 2: Symptomatic-medical intervention indicated; limits instrumental ADLs	• Perform high-resolution CT with lung windows • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Pulmonary function tests - if normal at baseline, repeat every 8 weeks • Bronchoscopy with biopsy and/or BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/d prednisone or equivalent as clinically indicated).
Grade 3: Severe symptoms; limits self-care ADLs; oxygen indicated Grade 4: Life- threatening respiratory compromise; urgent intervention required	• Hospitalization and pulmonary and infectious disease consultation • Methylprednisolone (1-2 mg/kg/d or equivalent) until symptoms improve to Grade ≤1, then slow taper over ≥4-6 weeks • If no improvement within 48 hours, consider infliximab and/or other immune-suppressive therapy, or i.v. Ig as per local guidelines • Empiric antibiotics

Recommended clinical managementfor suspected immune-related endocrinopathies

Endocrine events (NCI-CTCAE v5)	
Grade	**Recommended management**

Asymptomatic, intervention not indicated (e.g. hyperthyroidism or hypothyroidism)	• If TSH < 0.5 × LLN, or TSH > 2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated • Consider endocrinologist consult • If hypophysitis is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis) • Repeat labs in 1 to 3 weeks/MRI in 1 month if laboratory abnormalities persist but normal lab/pituitary scan
Symptomatic endocrinopathy (e.g., hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)	• Endocrinology consultation • Rule out infection/sepsis and other alternative causes with appropriate cultures and imaging • Evaluate hormone levels (e.g. ACTH, cortisol, FSH/LH, TSH, free T4, testosterone/estrogen), metabolic panel (e.g. Na, K, CO2, glucose), and imaging (e.g. brain MRI) as clinically indicated • Initiate hormone replacement therapy as appropriate • Consider steroids (methylprednisolone 1 to 2 mg/kg/d or equivalent) in case of sever hypophysitis or thyrotoxicosis • Replacement of appropriate hormones may be required as the steroid dose is tapered • Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis • Consider a beta-blocker in case of severe hyper-thyroidism.

Endocrine events (NCI-CTCAE v5)	
Grade	**Recommended management**
	• Consider hospitalization (e.g. in case of severe adrenal insufficiency/crisis), fluid replacement, and other supportive measures as clinically be initiate
Autoimmune diabetes (Grade 3 or symptomatic hyperglycemia)	• Initiate anti-glycemic therapy (i.e. insulin) as medically indicated and monitor glucose levels regularly until metabolic control is achieved • Evaluate for ketoacidosis as medically indicated • Consultation with endocrinologist • Consider hospitalization (e.g. in case of ketoacidosis)
Autoimmune diabetes (Grade 4 hyperglycemia or life-threatening complications)	Same as grade 3

Recommended clinical management for suspected infusion reaction or cytokine release syndrome

Infusion reaction (NCI-CTCAE v5)	
Grade	**Recommended management**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. • Consider slowing infusion rate until recovery of symptoms • May continue spartalizumab

Grade 2
Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs
	• Stop infusion
	• Additional medical therapy as per local institutional guidelines that may include:
	  • i.v. fluids
	  • Antihistamines
	  • NSAIDS
	  • Acetaminophen
	  • Narcotics
	  • Oxygen and corticosteroids as indicated
	• Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.
	• If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be re-premedicated for the next scheduled dose.
	• Patient may be premedicated 1.5h (± 30 minutes) prior to infusion with diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine) and acetaminophen 500-1000 mg p.o. (or equivalent dose of analgesic).
	• Consider permanent discontinuation of study treatment in case of recurring infusion reaction despite premedication and prolonged infusion

Grade 3:	• Stop infusion
Infusion reaction (NCI-CTCAE v5)	
Grade	**Recommended management**

Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
Grade 4:
Life-threatening; pressor or ventilatory support indicated
	• Additional medical therapy as per local institutional guidelines that may include:
	  • i.v. fluids
	  • Antihistamines
	  • NSAIDS
	  • Acetaminophen
	  • Narcotics
	  • Oxygen
	  • Corticosteroids
	  • Epinephrine
	• Close monitoring of vital signs, pulse oximetry and ECG as medically indicated until the subject is deemed medically stable.
	• Hospitalization as indicated

Recommended clinical management guidelines for suspected other potential immune-related events

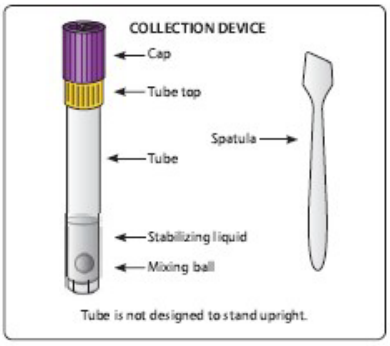
Other (i.e. Autoimmune neuropathy, Demyelinating polyneuropathy, Guillain Barre, Myasthenia Gravis-like syndrome, non-infectious myocarditis, pericarditis, pancreatitis, encephalitis, and Grade 3 Fatigue with rapid onset in absence of disease progression) (NCI-CTCAE v5)	
Grade	**Recommended management**
Mild (Grade 1)	Provide symptomatic treatment
Moderate (Grade 2)	• Consider treatment interruption until recovery to ≤ grade 1 or baseline. • Ensure adequate evaluation to confirm etiology or exclude other causes • Provide symptomatic treatment • Systemic corticosteroids may be indicated • Consider biopsy for confirmation of diagnosis • A specialist should be consulted
Severe (Grade 3)	• Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d and other therapies as appropriate • Monitor closely and consult with a specialist
Grade 4	• Hospitalization and consult with specialist • Initiate systemic corticosteroids (prednisone a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate
Encephalitis (any grade) or aseptic meningitis	• Rule out infectious or other causes of moderate to severe neurologic deterioration, and consult with specialist. • If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/d prednisone equivalents.
Guillain-Barre Severe peripheral or autonomic neuropathy, or transverse myelitis	• Hospitalization and consult with specialist

Myasthenia gravis	• Consult with specialist • Consider pyridostigmine and systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d; other therapies as appropriate (e.g. IVIG) • Hospitalization in case of severe cases
Other (i.e. Autoimmune neuropathy, Demyelinating polyneuropathy, Guillain Barre, Myasthenia Gravis-like syndrome, non-infectious myocarditis, pericarditis, pancreatitis, encephalitis, and Grade 3 Fatigue with rapid onset in absence of disease progression) (NCI-CTCAE v5)	
Grade	**Recommended management**
Myocarditis (any grade) or cardiac event grade ≥ 3	Urgent cardiology consult is essential to initiate high dose systemic corticosteroids (prednisone or equivalent). Hospitalization as indicated
Pancreatitis Amylase/lipase elevation	• Evaluate for pancreatitis (clinical assessment, abdominal imaging and/or magnetic resonance cholangiopancreatography as appropriate) • Treatment may be continued in case of asymptomatic, isolated enzyme elevations without evidence for pancreatitis • Initiate steroids in case of ≥ grade 2 acute pancreatitis
Autoimmune hemolytic anemia, hemolytic uremic syndrome, or acquired hemophilia grade ≥3	• Consult with specialist • Consider systemic corticosteroids and other therapies as appropriate (e.g. transfusion) per local institutional guidelines

Appendix C

OMNIgene·GUT

For microbiome



Summary and explanation of the kit:

OMNIgene·GUT provides the materials and instructions for collecting and stabilizing microbial DNA from a fecal sample.

Warnings and precautions:

- FOR EXTERNAL USE ONLY.
- Do NOT remove the yellow tube top from the tube.
- Do NOT spill the stabilizing liquid in the tube.
- Wash with water if liquid comes in contact with eyes or skin. Do NOT ingest.
- If collecting a liquid fecal sample, see separately provided user instructions.
- Small items may pose a choking hazard.

Storage: 15°C to 25°C

Ship in accordance to applicable regulations covering transport of biological specimens.
See MSDS at www.dnagenotek.com

Label legend:

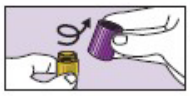
	Collect sample by (Use by)
REF	Catalog number
	Manufacturer
15°C 25°C	Storage instructions
	Caution, consult instructions for use
LOT	Lot number

USER INSTRUCTIONS

Read all instructions prior to collection

Procedure:

1 **IMPORTANT PREPARATIONS:**
- Empty your bladder before beginning the collection.
- Collect fecal sample free of urine or toilet water.
- Toilet paper or tissues may be required.



2 While holding the yellow tube top, unscrew ONLY the purple cap from the kit and set aside for later use.

IMPORTANT:
Do NOT remove the yellow tube top.
Do NOT spill the stabilizing liquid in the tube.

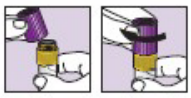
3 Use the spatula to collect a small amount of fecal sample.

4 Transfer the fecal sample into the yellow tube top. Repeat until the sample fills the yellow tube top.

IMPORTANT: Do NOT push sample into the tube.

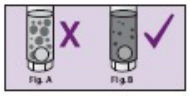
5 Scrape horizontally across the tube top to level the sample and remove any excess.

Wipe exterior of tube and top with toilet paper or tissue as needed.



6 Pick up the purple cap with the solid end facing down and screw onto the yellow tube top until tightly closed.

7 Shake the sealed tube as hard and fast as possible in a back and forth motion for a minimum of 30 seconds.



8 The fecal sample will be mixed with the stabilizing liquid in the tube; not all particles will dissolve.

IMPORTANT: Continue shaking if **large** particles remain as shown in Figure A.

9 Place spatula in original packaging or wrap in toilet paper and discard in garbage.

IMPORTANT: Send the sample for processing following the delivery instructions supplied separately by the kit provider.

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Appendix D: Neoadjuvant Therapy Surgical Resectability, Ease and Complications Questionnaire

Questionnaire 1 (Baseline/at time of trial enrollment)

- Surgeon name
- Patient idenitification
- Date of questionnaire
- Which lymph node basin(s) is involved? (can be more than one)
    - Femoral/Inguinal
    - Iliac/obturator
    - Axilla
    - Cervical
        - Level 1
        - Level 2
        - Level 3
        - Level 4
        - Level 5
    - Popliteal
    - Epitrochlear
    - Other, specify
- Number of involved lymph nodes?
- Largest dimension of largest lymph node?
- Suspected fixation or narrow margin to adjacent anatomic structure? (can be more than one)
    - Skin
    - Muscle/fascia
    - Artery
    - Vein
    - Nerve
- On a scale of 1-10 (1 = most easy, 10 = most difficult) how difficult do you anticipate the surgery will be if done now?
- Any remarks?
-

Questionnaire 2 (To be completed at pre-op visit after completion of neoadjuvant therapy)

- Surgeon name
- Patient identificaiton
- Date of questionnaire
- Which lymph node basin(s) is involved? (can be more than one)
    - Femoral/Inguinal

    - Iliac/obturator
    - Axilla
    - Cervical
        - Level 1
        - Level 2
        - Level 3
        - Level 4
        - Level 5
    - Popliteal
    - Epitrochlear
    - Other, specify
- Number of involved lymph nodes?
- Largest dimension of largest lymph node?
- Suspected fixation or narrow margin to adjacent anatomic structure? (can be more than one)
    - Skin
    - Muscle/fascia
    - Artery
    - Vein
    - Nerve
- On a scale of 1-10 (1 = most easy, 10 = most difficult) how difficult do you anticipate the surgery will be if done now?
- Do you think the resection is easier or more difficult compared to baseline?
    - No
    - Yes, specify
- Any remarks?

Questionnaire 3 (≤ 30 Days of surgery)

- Surgeon name
- Patient identification
- Date of questionnaire
- Date of surgery
- Which basin(s) did you resect? (can be more than 1)
    - Femoral/Inguinal
    - Iliac/obturator
    - Axilla
    - Cervical
        - Level 1
        - Level 2
        - Level 3
        - Level 4
        - Level 5

    - Popliteal
    - Epitrochlear
    - Other, specify
- Date of drain removal
- Did the patient have any complications ≤ 30 days postoperatively?
    - No
    - Yes, seroma/lymphocele
        - Please enter Clavien-Dindo Grade ……
    - Yes, surgical site infection
        - Please enter Clavien-Dindo Grade ……
- Was the patient re-operated?
    - No
    - Yes
- Was the patient re-admitted?
    - No
    - Yes
- Did the patient undergo any other interventions?
    - Drain replacement
    - Seroma/lymphocele aspiration
    - Oral or IV antibiotics
    - Opening of wound
    - Other, specify
- Any other complications (i.e. pneumonia, urinary tract infection, thrombosis, etc.)?
    - No
    - Yes, specify
        - Please enter Clavien-Dindo Grade ……
- Any remarks?

APPENDIX A. Classification of Surgical Complications

Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	intervention not under general anesthesia
Grade III-b:	intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
Grade IV-a:	single organ dysfunction (including dialysis)
Grade IV-b:	multi organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-.com/SLA/A3), the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit
www.surgicalcomplication.info

Clavien et al. Ann Surg 2009