TITLE: A Multi-Center Phase I/II Open Label Study to Evaluate Safety and Efficacy in Participants with Metastatic BRAF-mutant Melanoma Treated with Encorafenib with and without Binimetinib in Combination with Nivolumab and Low-dose Ipilimumab. (QUAD 01: Quadruple Therapy in Melanoma)

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DOCUMENT HISTORY

Document	Date of Issue		Summary of Change
Original Protocol	Date		Not Applicable
Amended Protocol	4/12/21	Amended inclusion and exclusion criteria on pages 4, 5, 27, and 33	Allow for up to 6 weeks of previous targeted therapy
Amended Protocol	9/1/21	Expanded Table 5 to clarify assessment and visits	Clarified provider visits and nursing visits through week 14
Amended Protocol	10/17/21	Amended inclusion and exclusion criteria on pages 4, 5, 27, and 33	Allow for up to 1 cycle of previous immunotherapy
Amended Protocol	03/18/2022	Amended exclusion criteria page 33	Clarification to thromboembolic event

Amendment 1

Expanded inclusion criteria to allow up to 6 weeks of targeted therapy prior to enrollment on trial.

Rationale:

High risk patients with elevated LDH, liver metastases, and brain metastases were presenting to accrual sites after having received targeted therapy prior to enrollment. This expanded inclusion criteria was adopted to expedite trial accrual.

Major Changes:

- Expanded inclusion criteria throughout protocol.

Amendment 2

Expanded Table 5 to clarify assessments through week 10. After week 14, follow up visits will be monthly with CBC, CMP, and TSH laboratory assessments and physical exam prior to nivolumab 480mg flat dose, and imaging every 12 weeks while on treatment per protocol.

Rationale:

Clarify treatment and monitoring.

Major Changes:

- Expanded Table 5 to expand schedule through week 10.

Amendment 3

Expanded inclusion criteria to allow up to one cycle of immunotherapy prior to enrollment on trial.

Rationale:

After meeting with Principal Investigators at participating sites to discuss enrollment, decision was made to allow one cycle of immunotherapy prior to enrollment based on data from SECOMBIT and DREAM-Seq trials which have established sequential therapy with upfront immunotherapy as a standard of care. While dual checkpoint inhibition with CTLA4 and PD1 is the most likely combination, we will also allow single agent immunotherapy as well. This will allow patients who were started on checkpoint inhibition in the community to participate and increase accrual.

Major Changes:

- Expanded inclusion criteria throughout protocol.

Amendment 4

Changes to exclusion criteria to allow patients with history of thromboembolic events that are on stable dosing of anti-coagulants per investigator discretion.

Rationale:

The PI in conjunction with the treating investigators has identified that protocol exclusion criteria #12 is at odds with a common presentation of relevant patients for this protocol and is potentially adverse to the best treatment of such patients. The treatment population for the protocol are those with high-risk and/or large tumor burden, where concurrent venous thromboembolism is a common occurrence.

Major changes:

- Updates to exclusion criteria

SYNOPSIS

Clinical Protocol HCC 20-190

Protocol Title:

A Multi-Center Phase I/II Open Label Study to Evaluate Safety and Efficacy in Participants with Metastatic *BRAF*-mutant Melanoma Treated with Encorafenib with and without Binimetinib in Combination with Nivolumab and Low-dose Ipilimumab. (QUAD 01: Quadruple Therapy in Melanoma).

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Encorafenib 450 mg orally (PO) daily (QD) plus binimetinib 45 mg PO twice daily (BID) together with nivolumab administered intravenously (IV) at 3mg/kg and ipilimumab administered IV at 1 mg/kg every 3 weeks for 4 doses, followed by nivolumab administered IV at 480mg every 4 weeks until progression or discontinuation due to toxicity.

Concurrently, a triple therapy arm will be explored with encorafenib 300 mg PO QD together with ipilimumab administered IV at 1mg/kg and nivolumab 3mg/kg IV every 3 weeks for 4 doses, followed by nivolumab administered at 480mg every 4 weeks until progression or discontinuation due to toxicity.

Tolerability of the two arms will be compared, and a recommended phase II regimen (RP2R) will be determined.

After determination of treatment regimen, expansion cohorts will further explore the preliminary efficacy and further describe the toxicity profile of the triplet or quadruplet regimen in high-risk cohorts including symptomatic brain metastases or liver metastases with elevated lactate dehydrogenase (LDH) or bulky systemic disease burden.

Study Phase: 1/2

Research Hypothesis: Treatment with encorafenib + nivolumab + ipilimumab (triple therapy) and/or treatment with encorafenib + binimetinib + nivolumab + ipilimumab (quadruple therapy) will demonstrate adequate safety and tolerability in unresectable or metastatic *BRAF*-mutant melanoma high-risk patients.

Objectives

Primary Objective

- To nominate a recommended phase II regimen (RP2R) of triple or quadruple therapy with encorafenib (+/- binimetinib) + nivolumab and + ipilimumab in *BRAF*-mutated, metastatic melanoma.

Secondary Objectives

- To estimate the RECIST response rate of triple or quadruple therapy in high-risk populations of *BRAF*-mutated, metastatic melanoma.
- To estimate the CNS clinical benefit rate (CBR, defined as complete response [CR] + partial response [PR] + stable disease [SD] > 6 months) per RANO-MB criteria of triple or quadruple therapy in *BRAF*-mutated, metastatic melanoma to the CNS
- To describe the toxicity, using Criteria for Adverse Events version 5 (CTCAEv5), of triple or quadruple therapy in *BRAF*-mutated, metastatic melanoma
- To summarize the progression-free survival of triple or quadruple therapy in high-risk populations of *BRAF*-mutated, metastatic melanoma

Exploratory Objective

- To evaluate the association between treatment response and baseline tumor mutational burden, changes in the tumor microenvironment (interferon [*IFN*]-associated gene expression), T cell clonality, and other biospecimens before and after therapy.
- To evaluate the overall survival (OS) of triple or quadruple therapy in high-risk population of *BRAF*-mutated, metastatic melanoma

Study Design

This is an open label, multi-site, phase 1/2 study of encorafenib +/- binimetinib + nivolumab + ipilimumab for the treatment of patients with unresectable or metastatic *BRAF*-mutated melanoma in high risk cohorts.

Study participants will consist of metastatic melanoma patients harboring $BRAF^{V600E/K}$ mutation without previous frontline therapy or recently started treatment with up to 6 weeks of targeted therapy, or one cycle of immunotherapy (or > 6 months from adjuvant therapy). Toxicity from prior treatment must have resolved to ≤ Grade 1 and not included previous Grade 3–4 immune-related adverse events (irAEs) that required treatment discontinuation or previous Grade 2 immune-related uveitis or pneumonitis.

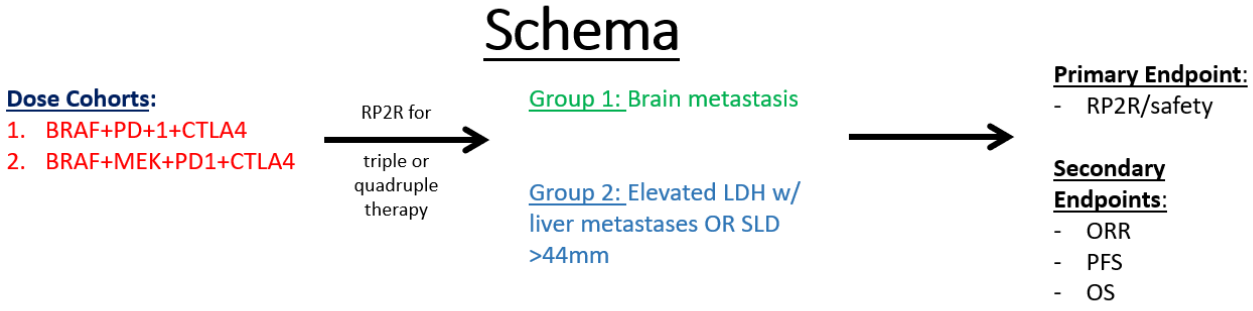
Phase I, Cohort 1: Twelve patients will be treated with 300mg encorafenib and 3mg/kg nivolumab and 1 mg/kg ipilimumab. The dose limiting toxicity (DLT) for cohort 1 will be evaluated between weeks 1-6.

Phase I, Cohort 2: Upfront quadruple therapy with 450mg encorafenib, 45mg binimetinib, 3mg/kg nivolumab and 1mg/kg ipilimumab will be investigated with 12 participants. DLT window for phase I, cohort 2 will be evaluated at weeks 1–6.

Upon establishment of RP2R schedule, only participants with advanced melanoma who are treatment naïve in metastatic setting or have had up to 6 weeks of targeted therapy, or one cycle of immunotherapy, or who have progressed on adjuvant therapy for more than 6 months following completion of adjuvant therapy (either BRAF-MEK or PD1 Ab) will be eligible for participation in high risk disease cohort expansion (Groups 1 or 2).

Phase II will employ the RP2R schedule from Phase I and investigate the early efficacy in participants with high risk features who are less likely to derive benefit from standard treatment approaches and who may benefit from quadruple therapy despite the potential for increased toxicity. These will include: Group 1) symptomatic brain metastases [up to 30 patients] and Group 2) Elevated LDH >1x upper limit of normal (ULN) with: a) liver metastases OR b) bulky visceral disease (sum of longest diameter (SLD) > 44mm) [combined with Group 1 up to 60 total patients].

Following initiation of triple or quadruple therapy, participants will be followed for safety and response. Safety assessments will be a high priority with on-going Bayesian toxicity monitoring and efficacy assessments every 12 weeks. Based on prior targeted, immune, and triplet therapy studies, we anticipate up to 30–50% DLT and will consider temporary suspension of trial enrollment with a DLT > 75% as determined by CTCAEv5. Treatment efficacy will be documented using RECIST 1.1 and RANO-BM criteria, recorded every 4-12 weeks, and immune-RECIST (iRECIST) and immune-RANO (iRANO) criteria.



Study Population

Phase I RP2R finding

Key Inclusion Criteria:

- Patients with histologically confirmed metastatic or unresectable *BRAF*$^{V600E/K}$ mutant melanoma
- Patients must be greater than 6 months from adjuvant therapy (if any given) and/or have recently started treatment with up to 6 weeks of targeted therapy, or one cycle of immunotherapy
- Patients must meet criteria for inclusion into either Phase II expansion cohorts listed below – Brain Metastases or Elevated LDH/Bulky Visceral Disease

Key Exclusion Criteria:

- Uveal melanoma

- Participants with a non-melanoma related 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.
- History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); history of retinal degenerative disease.

Phase II: High-risk Expansion Groups

Group 1: Brain Metastases

Key Inclusion Criteria:

- Metastatic melanoma involving the brain but excluding leptomeningeal disease
- Treatment with stereotactic radiosurgery must have occurred ≥14 days prior to start of study treatment. If prior radiosurgery was pursued, then at least one evaluable lesion must not have been irradiated. Prior whole-brain radiation is not allowed.
- Symptomatic brain parenchymal metastases not requiring urgent radiation are permitted as well as patients on a stable dose of corticosteroids equivalent to 4 mg dexamethasone daily for the preceding 10 days prior to first dose.
- Eligible patients with prior local therapy to all brain lesions must have demonstrated progression of pre-existing target lesions per RANO-BM criteria.

Group 2: Elevated LDH with Liver Metastases OR Bulky Visceral Disease

Key Inclusion Criteria:

- LDH >1x ULN
- Total body SLD > 44mm (including but not limited to liver metastases) or metastatic melanoma involving the liver
- **Study Drug:**

Study Drugs for QUAD 01	
Medication	**Potency**
Nivolumab	10 mg/mL
Ipilimumab	5 mg/mL
Encorafenib	75 mg capsule
Binimetinib	15 mg tablet

Study Assessments

The primary safety endpoint will be assessed using the CTCAEv5 criteria at 6 weeks with continuous Bayesian toxicity monitoring in phase II.

Statistical Considerations: Rates of DLTs and objective responses will be estimated with one sided confidence intervals

Sample Size: Phase I, two cohorts of 12 patients, 24 in total.

Phase 2 at RP2R selected from Phase I, two cohorts with up to 30 patients in cohort 1, remainder in cohort 2 for a total of 60.

Endpoints: Rate of DLT attributable to the therapeutic agents; objective response rate

Analyses

- For both the phase I and phase II cohorts, once the phases have completed accrual, inference for safety will be based on one sided confidence intervals. DLT rates will be calculated with one sided upper 90% confidence intervals. If the upper bound is lower than 75% the investigator may declare the regimen to be safe for further evaluation.
- If 4 or fewer DLTs are observed among 12 patients the upper bound of an exact 90% confidence interval will be less than 60%
- Provision is made for early stopping in the phase II cohorts by invoking a Bayesian continuous monitoring plan. Beginning with the 5th patient DLTs will be compiled for calculating the posterior probability of excess toxicity. Thereafter if an unexpected excess toxicity rate is observed the trial will be suspended pending UPMC Hillman DMSC vs. other review.
- The following table provides a decision table for trial suspension.

Number of Evaluable Patients (Inclusive)	Suspend if there are This many DLTs	Number of Evaluable Patients (Inclusive)	Suspend if there are This many DLTs
0-4	-----	17	14
5	5	18-19	15
6-7	6	20	16
8	7	21	17
9	8	22-23	18
10-11	9	24	19
12	10	25	20
13	11	26-27	21
14-15	12	28	22
16	13	29	23

- In the phase II cohort, the estimated objective response and clinical benefit rates will be estimated with an 80% one sided lower confidence interval.

Operating characteristics of possible decision rules in phase II

If a 30-patient phase II cohort is completed the following decisions are possible:

If 23 or more DLTs are observed among 30 patients the combination can be considered as too toxic and a DLT rate ≥ 75% cannot be ruled out

Objective response criteria will be summarized with response rates and calculated intervals of progression free survival.

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1. INTRODUCTION AND STUDY RATIONALE

This is a phase I open label study of encorafenib +/- binimetinib + nivolumab + ipilimumab in participants with unresectable or metastatic *BRAF*$^{V600E/K}$ -mutant melanoma. Once a recommended phase II regimen (RP2R) is determined, expansion into known high risk patient groups: 1) symptomatic brain metastases and 2) elevated liver enzymes with hepatic metastases will be investigated for safety and efficacy.

Both targeted therapy (BRAF + MEK inhibitors) and immunotherapy (anti-PD-1 + anti-CTLA-4) are approved in the US and EU for metastatic or unresectable *BRAF*$^{V600E/K}$ mutant melanoma. Targeted therapy has an initial response rate of 75%, however the median PFS is only 11–14 months [1–4]. Single agent immunotherapy with anti-PD-1 has a lower initial response rate of 30–40%, however the addition of anti-CTLA-4 (ipilimumab) can increase that to 60% [5]. Relative to targeted therapy, immunotherapy has greater potential to induce long- lasting remissions in a subset of patients [1,6].

Early phase trials have combined targeted therapy with anti-PD-1 which report increased PFS compared to targeted or immunotherapy alone [4,5,7], and the phase III IMspire 150 trial of targeted + anti-PD-1 (two targeted + one immunotherapy "triple") therapy vs. targeted therapy alone recently met its primary endpoint of increased PFS [8]. Results of the proposed study combining targeted (encorafenib +/- binimetinib) and (two) immunotherapies (nivolumab + ipilimumab) [*triple or quadruple therapy] will detail the safety and efficacy of this novel treatment for high risk patients who historically have not responded to doublet or triplet therapy.

*Triple therapy in this protocol will be with two immunotherapy agents, whereas IMspire150 triple therapy contained two targeted agents.

1.1 Study Rationale

1.1.1 Disease Background

Cutaneous melanoma is the fifth leading cause of cancer in the United States with 96,480 estimated new cases in 2019 leading to 7,230 deaths [9]. The majority of melanomas have mutations in the mitogen-activated kinase (MAPK) pathway, important for cell signaling, growth, and survival [10]. The most common mutation in the MAPK pathway is through constitutive activation of the BRAF kinase via mutation, which occurs in 40-60% of cases. More than 97% of BRAF mutations occur at codon 600 [11]. The most common mutation (~90%) results in a substitution of valine for glutamic acid at position 600 (V600E) [12], while the V600K mutation represents ~8% [11]. BRAF mutant melanoma is clinically more aggressive than BRAF wild type, and is more frequent in younger patients and/or in anatomical regions without chronic sun damage [13].

Up to one-third of patients already have multifocal and rapidly progressing disease when metastatic melanoma is first detected [14]. These high-risk patients commonly have brain and visceral organ involvement, and are known to have poorer responses to either targeted or immunotherapy [15–17] (see Section 1.1.3).

1.1.2 Treatment of Metastatic BRAF-mutant Melanoma

In 2010, treatment options for metastatic melanoma were systemic chemotherapy with dacarbazine or high dose interleukin 2 (IL-2), neither of which significantly impacted OS and few survived > 1 year [18,19]. Immunotherapy with checkpoint inhibitors targeting cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and programmed cell-death protein 1 (PD-1), and later targeted therapies against BRAF and MEK kinases have been approved, improving OS and leading to durable remissions in a subset of patients.

1.1.2.1 Immunotherapy

Ipilimumab

The inhibitory CTLA-4 receptor is expressed on T cells and regulates the amplitude of T cell activation in early stages [20]. In 2011, ipilimumab, an anti-CTLA-4 antibody was approved as the first drug to demonstrate a survival benefit in melanoma. The pivotal phase III study of ipilimumab showed an OS benefit in previously treated metastatic melanoma vs. an investigational peptide vaccine gp100 [21]. In a second phase III trial of treatment naïve patients, ipilimumab + dacarbazine had improved OS compared to dacarbazine alone [22]. Importantly, extended follow up showed that ipilimumab resulted in long-term survival in approximately 20% of patients [23].

Nivolumab

Programmed death receptor 1 (PD-1) is another inhibitory immune checkpoint receptor expressed on the surface of T cells. Its primary ligand, programmed death ligand 1 (PD-L1), can be expressed in the tumor microenvironment on tumor cells and tumor-infiltrating macrophages. Programmed death ligand 2 (PD-L2) is preferentially expressed by antigen presenting cells [20]. Nivolumab is a monoclonal antibody that blocks the interaction between PD-1 and PD-L1/PD-L2. CheckMate 037 was a phase III trial of nivolumab in ipilimumab-refractory patients that demonstrated improved ORR and PFS vs. chemotherapy [1]. CheckMate 066 was a phase III study in previously untreated, BRAF V600-non mutated melanoma that demonstrated improved ORR and PFS vs. dacarbazine [3].

Combination ipilimumab and nivolumab

CheckMate 067 evaluated nivolumab plus ipilimumab in previously untreated stage III/IV melanoma against either nivolumab or ipilimumab alone. Both the combination therapy and nivolumab monotherapy were more efficacious than ipilimumab monotherapy in primary endpoints of ORR, PFS, and OS [6,24–26]. Importantly, long term follow up and subgroup analysis suggests that nivolumab plus ipilimumab may confer improved OS vs. nivolumab monotherapy in patients with PD-L1 expression < 1%, with a HR of 0.68 [27]. Overall, the addition of immunotherapy with PD-1 and CTLA-4 inhibition has increased metastatic melanoma 5-year OS to > 50% [28].

Grade 3/4 adverse events (AEs) in CheckMate 067 occurred in 59% of combined therapy patients. The most common Grade 3 event in the combination therapy arm was diarrhea

(9%), the most common Grade 4 event was increased lipase (5%). Treatment related AEs of any Grade that led to discontinuation of treatment were reported in 40% of patients in the combination group, including Grade 3/4 events that led to discontinuation (30%). Colitis was the most common cause for discontinuation (10%). Grade 3 increased AST and ALT occurred in 18 and 25% of the combination therapy group.

1.1.2.2 Targeted Therapy

Encorafenib

Encorafenib is a second generation, potent and selective ATP-competitive inhibitor of BRAFV600-mutant kinase. The most significant difference between encorafenib and other second generation BRAF inhibitors is its increased dissociation half-life of 30 hours, compared to dabrafenib (2 h) and vemurafenib (0.5 h) [29]. This leads to a decreased off-rate, leading to decreased AEs and prolonged inhibition of target [30,31]. Encorafenib also has higher potency with a half-maximal inhibitory concentration (IC_{50}) of 40 nmol/L, compared to the higher IC_{50}s of dabrafenib (<100 nmol/L) and vemurafenib (<1 µmol/L) [32]. Encorafenib 450 mg orally QD together with binimetinib 45 mg orally BID have been approved by the US FDA and in the EU for the treatment of unresectable or metastatic melanoma with a BRAFV600E or V600K mutation as detected by an FDA-approved test. Encorafenib is known to induce CYP3A4. Therefore, hormonal birth control agents are permissible only when combined with other highly effective means of contraception.

Binimetinib

Binimetinib is a selective allosteric, ATP-uncompetitive inhibitor of MEK1 and 2 that has a shorter half-life than other MEK1/2 inhibitors, which may provide more rapid resolution of toxicity upon dose interruption [33]. MEK inhibitors were developed contemporaneously with BRAF inhibitors, and fortuitously found to block a common mechanism of resistance to BRAF-inhibitor monotherapy [27,34]. Binimetinib 45 mg orally BID in combination with encorafenib 450 mg orally QD has been approved by the US FDA and in the EU for the treatment of unresectable or metastatic melanoma with a BRAFV600E or V600K mutation as detected by an FDA-approved test.

Encorafenib and binimetinib combination

The COLUMBUS trial is a randomized Phase 3 trial evaluating the efficacy and safety of the combination of encorafenib and binimetinib compared to vemurafenib and encorafenib monotherapy in patients with locally advanced, unresectable or metastatic melanoma with BRAFV600 mutation. COLUMBUS demonstrated improved tolerability in the encorafenib 450 mg QD + binimetinib 45 mg BID (COMBO450) arm compared with single-agent encorafenib 300 mg QD [33,35]. This is consistent with previous literature that suggests the combination of a MEK inhibitor and a BRAF inhibitor results in improved tolerability compared with either agent alone [3,36–38]. The updated PFS for the COMBO450 arm was 14.9 months, with all subgroups favoring COMBO450 arm [17].

A total of 68% of patients experienced Grade 3/4 AEs in the COMBO450 arm, with similar rates in other arms. These AEs led to discontinuation of treatment in 16% of patients, and dose reduction/interruption in 55%. Among patients receiving encorafenib and binimetinib combination therapy in the COLUMBUS study, the most common adverse reactions (≥ 20%, all grades) were fatigue (43%), nausea (41%), diarrhea (36%), vomiting (30%), abdominal pain (28%), arthralgia (26%), myopathy (23%), hyperkeratosis (23%), rash (22%), headache (22%), constipation (22%), visual impairment (20%), and serous retinopathy (20%). Most of these toxicities were generally reversible and manageable by supportive medical care, dose modifications or discontinuation. Other clinically important adverse reactions occurring in < 10% of patients were facial paresis, pancreatitis, panniculitis, drug hypersensitivity and colitis. The most common laboratory abnormalities (≥ 2%, Grade 3 or 4) were increased GGT (11%), increased ALT (6%), increased creatine phosphokinase (5%), increased fasting glucose (5%), increased creatinine (4%), anemia (4%), hyponatremia (4%), increased AST (3%), neutropenia (3%) and lymphopenia (2%).

1.1.2.3 Combination Targeted and Immunotherapy

The combination of the BRAF inhibitor vemurafenib with the CTLA-4 checkpoint-blocking antibody ipilimumab resulted in hepatic dose-limiting toxicity (DLT), leading to discontinuation of the development of this combination [39]. However, this was before addition of MEK inhibitors to BRAF inhibitors was shown to decrease toxicity through mitigating paradoxical MAPK activation [40].

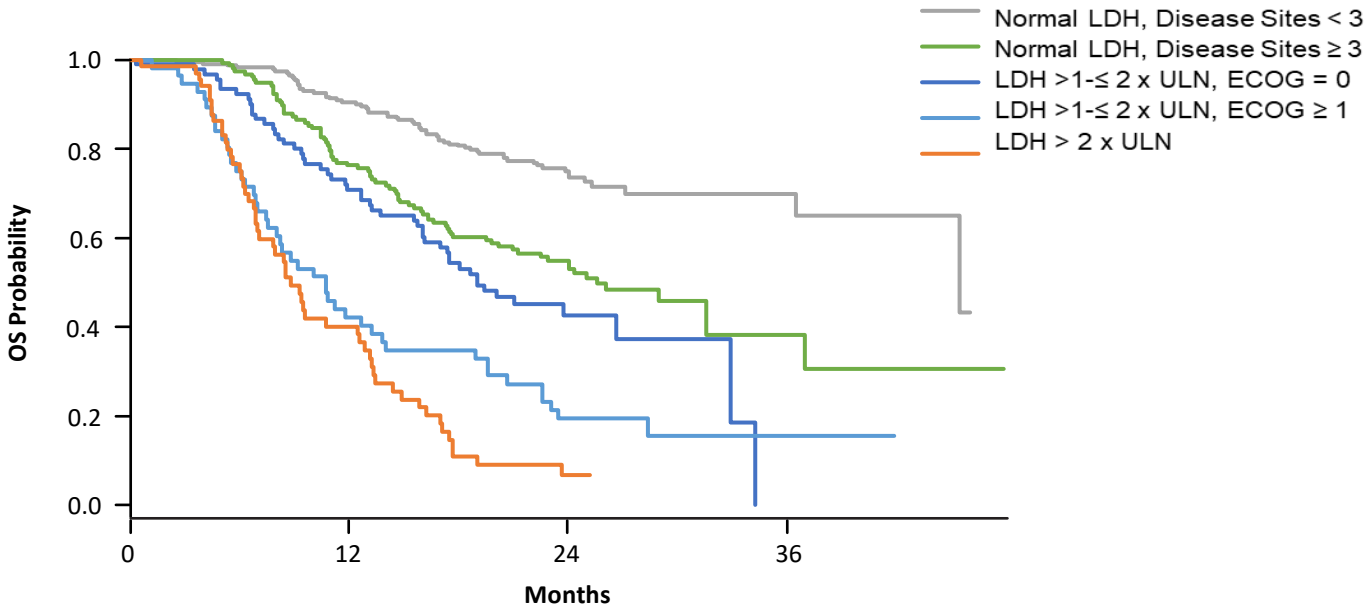
Trials are ongoing to compare sequencing of targeted therapy vs. immunotherapy (such as EA6134 and SECOMBIT) with retrospective studies postulating predictive markers such as severity of disease and specific BRAF mutations to suggest preferred sequential therapy [14,41]. However, it is well documented across oncology that some patients progress rapidly in the 1st line setting making 2nd line therapy unavailable or ineffective.

Animal model studies suggest that BRAF and MEK inhibition can increase T cell infiltration of tumors and upregulate markers of immune activation including IFNγ and MHC[42], with serial biopsies from patients on treatment describing similar findings. These observations have led to on-going registration intent clinical trials with triple therapy (BRAF + MEK inhibition + anti-PD-1). These studies appear potentially promising with triple therapy being described as tolerable with encouraging ORR of 67%–85% [5,43,44], and the AACR 2020 plenary session of the TRILOGY Phase III data which showed that the primary endpoint of PFS has been met [45]. This has led to FDA approval for this triplet regimen. In contrast however the COMBI-I trial of dabrafenib, trametinib and spartalizumab did not meet the primary endpoint. Triple therapy therefore is a standard of care option for metastatic/unresectable BRAF mutant melanoma, however the exact role of the therapy remains unclear and there are still high-risk patient groups that do not respond well to BRAF-MEK-PD1/L1 triple therapy.

1.1.3 High-risk Patient Groups have Unmet Need

Patients with brain/liver/bone metastases and high LDH have worse outcomes on BRAF + MEK inhibition [46] as well as checkpoint immunotherapy [18]. A retrospective analysis of 617 patients across three trials treated with dabrafenib and trametinib (targeted therapy) details the disparity in outcomes between patients with poor prognostic factors. Shown below graphically is the difference in OS in patients with elevated LDH or multiple disease sites. LDH 2x the upper limit of normal (ULN) had a one year overall survival of 40%, compared to over 90% 1 year survival for normal LDH levels [36]. These clinically high-risk patients would benefit the most from an escalation in therapy where the increased risk of toxicity would be offset by improved survival.

OS by LDH, Number of Disease Sites, and ECOG[a]



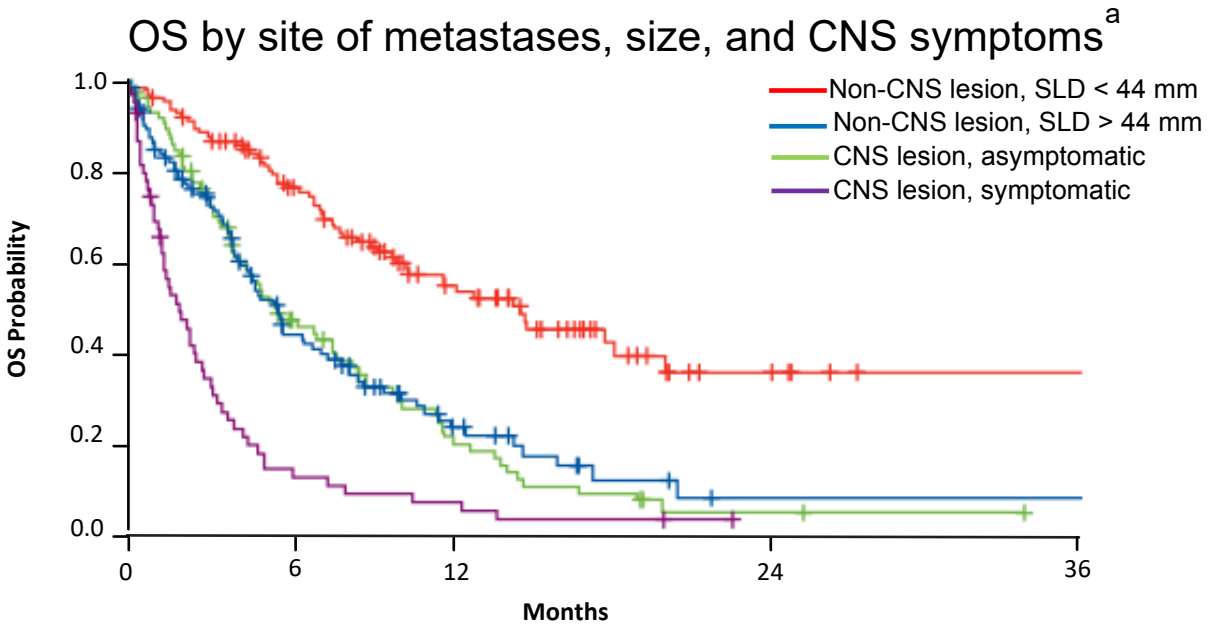
a:Factors Identified by Regression Tree Analysis, Long et al 2015

Multiple studies suggest that within these populations specifically, CTLA-4 blockade may have the most potent ability to generate long term clinical benefit. On a molecular level we observe from COMBI-I that triplet therapy appears to disproportionately benefit patients with tumors demonstrating high tumor mutational burden (TMB) and an active immune tumor microenvironment as measured by an IFNγ linked gene expression profile (GEP), i.e. TMB/GEP^{hi}, and does not seem to particularly improve the response rate or PFS of patients with TMB/GEP^{low} tumors relative to historical controls [47].

1.1.3.1 Brain Metastases

Melanoma is third leading cause of cranial metastases after lung and breast cancer [9]. More than 20% of patients with metastatic melanoma have brain metastases at diagnosis [48,49], and 75% will develop brain metastases [50]. Similar to patients with elevated LDH discussed above, patients with brain metastases have much worse outcomes compared

to non-CNS metastases groups. OS with brain metastases after starting dabrafenib and trametinib is a median of 5.8 months if asymptomatic, if symptomatic median survival is only 2.0 months after progression on dabrafenib and trametinib [36].



a:Factors Identified by Regression Tree Analysis, Long *et al* 2015.
Central Nervous System (CNS), Sum of longest diameter (SLD)

Conventional therapy for metastatic melanoma with brain metastases historically consisted of whole brain radiation therapy (WBRT) for multiple metastases and stereotactic radiosurgery for limited numbers of metastases [51]. Prognosis for brain metastases remains poor, with an expected OS of only four months [52–54]. Recent investigations suggest little or no benefit for WBRT and that systemic therapy likely improves outcomes over radiation in general [55,56]. Targeted and immunotherapy trials for brain metastases have had some improvements in OS summarized below, however there remain high risk groups with symptomatic disease that have been excluded from most trials due to their poor outcomes.

In the phase 2 BREAK-MB trial, BRAF monotherapy (dabrafenib) exhibited clinical activity in BRAF V600E mutant melanoma with brain metastases. The overall intracranial response rate was 39% (n = 139) and had a manageable safety profile [36].

COMBI-MB is a phase 2 BRAF + MEK inhibitor (dabrafenib + trametinib) trial evaluating BRAFV600-mutant melanoma brain metastases 0.5–4.0 cm, excluding leptomeningeal disease [57]. Previous treatment with immunotherapy is allowed and current corticosteroid use is permitted however no anti-epileptic treatment is permitted, excluding symptomatic

patients except in exploratory cohorts. The primary endpoint of intracranial response was met, with 58% of patients achieving response by investigator review. In exploratory cohorts, 59% of symptomatic patients (n = 17) had an intracranial response. Most intracranial and extracranial responses were seen by week 4 in primary endpoint cohorts and by weeks 4–8 in exploratory cohorts. The most common AEs of COMBI-MB were included pyrexia (n = 34/125, 54%), headache (n = 46/125, 37%), asthenia (n = 40/125, 32%), diarrhea (n = 40/125, 32%), nausea (n = 40/125, 32%), and chills (n = 37/125, 30%). Dose interruptions and reductions due to AEs were necessary in 62 (50%) and 28 (22%) of 125 patients, respectively. Discontinuations due to AEs occurred in 12 (10%) of 125 patients, mostly due to ejection fraction decreased (n = 4/125, 3%) and pyrexia (n = 3/125, 2%).

A retrospective, multicenter case series analysis of BRAF-mutant patients harboring metastatic brain metastases treated with encorafenib and binimetinib was recently published [58]. The intracranial objective response rate was 33%, with an intracranial benefit rate (CBR: proportion of patients with complete response + partial response + stable disease) of 63% with a median duration of response of 22 weeks. Forty-six percent of patients (11/24) received steroids during treatment, and median time to intracranial response was 6 weeks. This was in a population heavily pre-treated (median of 2.5 prior lines of therapy) and 88% (21/24) had previous BRAF + MEK inhibitor therapy. Median LDH was 190 U/L, and intracranial objective response rate was similar between LDH > 250 at baseline vs. LDH < 250 baseline, 29% and 35% respectively. AEs were Grade 1 and 2 in severity, except for one Grade 3 myalgia. The most common AEs were fatigue (17%) and myalgia (13%). Two patients experienced retinal detachment. One patient had intra-retinal fluid after one dose of encorafenib + binimetinib that resolved after holding binimetinib and patient resumed binimetinib 11 days later. A total of 4 patients (17%) dose-reduced one or both agents during study due to myalgia, neuropathy, or nausea/vomiting/fatigue. Of the four patients, two continued treatment, one discontinued due to progression, and another discontinued due to neuropathy.

CheckMate 204 is a Phase II trial for melanoma patients with > 1 measurable, non-irradiated melanoma brain metastases (MBM) 0.5–3.0cm. Asymptomatic patients not on steroids or anti-epileptics are treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg, then nivolumab maintenance. The intracranial clinical benefit rate (CBR; proportion of patients with complete response + partial response + stable disease) is 29% (n = 101), with 26% partial response and 4% stable disease [59]. Toxicity was similar to nivolumab + ipilimumab in non-brain metastatic patients. An amendment added an exploratory cohort of symptomatic patients on steroids (n = 20). For symptomatic patients (n = 18) the intracranial overall response rate was 16.7% and CBR was only 22% [60].

Anti-PD1 Brain Collaboration (ABC) was a phase II trial for melanoma patients with active brain metastases, including patients that had previously received targeted therapy with BRAF and MEK inhibitors. When patients with asymptomatic untreated brain metastases received combined ipilimumab and nivolumab as their first therapy, 56% (15/27) achieved

an intracranial response and 19% (5/27) achieved a CR [37]. No new or unexpected toxicities were associated with drug therapy in this study.

1.1.3.2 Elevated Liver Enzymes and Bulky Disease

A meta-analysis of 617 BRAF mutant melanoma patients randomly assigned to dabrafenib + trametinib in BRF11320, COMBI-d, and COMBI-v was subjected to regression tree analysis to identify prognostic factors for response to therapy [36]. Four prognostic groups of baseline factors were identified to predict progression free survival: normal LDH with less than 3 sites of metastases, normal LDH with more than 3 sites of metastases, LDH up to 2x upper limit of normal (ULN), and LDH > 2x ULN. Normal LDH with less than 3 sites of metastases had the longest 1-year PFS and (68%) and OS (90%) (n = 237). Overall response was seen in 65% (60/93) with LDH concentration of one to two times ULN and ECOG of 0; 48% (27/56) with LDH concentration of one to two times ULN and ECOG of 1; and 50% (35/70) with LDH concentration at least two times the ULN.

A retrospective recursive portioning analysis modeled associations between pre-specified covariates and survival outcomes from BRIM-2, BRIM-3, BRIM-7, and co-BRIM studies in which patients were treated with dacarbazine, vemurafenib, or cobimetinib + vemurafenib [46]. PFS and OS were longest in patients with LDH < 2x ULN and sum of longest diameters of target lesions (SLDs) < 44 mm. In the most favorable subgroup (normal LDH and SLD < 44 mm), 3-year OS rates were 53.3% in the cobimetinib + vemurafenib cohort. Among patients with gene expression data, recursive partitioning analysis identified an immune activated gene expression profile (GEP) as significant prognostic factor for PFS in those with normal LDH.

1.1.4 Quadruple Therapy

A phase I study of low dose ipilimumab in combination with pembrolizumab after progression on anti-PD-1 shows that low-dose ipilimumab is well tolerated and potentially efficacious as 2nd line therapy [61]. Of 22 patients enrolled, 17 were evaluable, with a disease control rate (DCR; complete response + partial response + stable disease) of 76%. PFS at 6 months was 75%, and 14% (3/22 patients) having Grade 3/4 AEs (hyperglycemia, acute kidney injury, diarrhea, acneiform rash). Interestingly, out of 11 response-evaluable patients with staining available, DCR was 100% in PD-L1 positive (n = 3) and 88% in PD-L1 negative (n = 8) tumors. The phase II continuation of this study had 67/70 accrued patients available for analysis of treatment response, with median length of treatment on prior PD1 Ab of 4.8 months. There were 4 CR, 17 PR, and 16 SD for a RR of 31 % (21/67) in evaluable patients, and 30% (21/70) in all enrolled patients. Median PFS was 4.7 months with 21% (15/70) of patients experiencing > Grade 3–4 drug-related AEs, the most common being diarrhea and rash. PD-L1 status did not correlate with RR[62].

These results marry well with frontline data of the same combination generated in the KEYNOTE–029 study (Long 2017). KEYNOTE-029 was a phase 1 study of 4 cycles of low-dose ipilimumab + pembrolizumab followed by pembrolizumab maintenance. PFS at one year was 69%, with OS of 89%. Grade 3/4 AEs occurred in 45% (n = 69) patients, and discontinuation of pembrolizumab and ipilimumab occurred in 14% (n = 22).

The use of low dose ipilimumab plus anti-PD-1 combination is generally well tolerated and only somewhat more toxic than PD1 alone. Observing that the increased toxicity from BRAF + MEK + PD1 triplet therapy appears to be disproportionately related to targeted therapy and not irAEs, low dose ipilimumab with anti-PD1 may disproportionately benefit patient populations that still have high need and would justify increased risk of toxicity. Particularly high risk patients include GEP/TMB^{low} [47], symptomatic brain metastases [59] and elevated LDH or liver metastases [15,46].

Therefore, triplet and quadruplet therapy of BRAF+/-MEK+PD1+CTLA4 inhibition will be explored in this phase 1/2 study. Phase I will explore the safety and tolerability of triplet therapy with BRAF+PD1+CTLA4 inhibition while simultaneously evaluating quadruplet therapy of BRAF+MEK+PD1+CTLA4. It will then expand into safety/preliminary efficacy cohorts: 1) Symptomatic brain metastases (inverse of CHECKMATE 204) [59], 2) Liver metastases with elevated LDH OR sum of target lesion distance (SLD) >44mm [36,46].

1.2 Research Hypothesis

Treatment with encorafenib +/- binimetinib combined with both nivolumab and ipilimumab will demonstrate adequate safety and tolerability, as well as a favorable benefit/risk profile, to support further clinical testing.

1.3 Objectives

Primary Objective

- To nominate a recommended phase II regimen (RP2R) of triple or quadruple therapy with encorafenib +/- binimetinib + nivolumab + ipilimumab in *BRAF* mutated, metastatic melanoma.

Secondary Objectives

- To estimate the RECIST response rate of triple or quadruple therapy in high risk populations of *BRAF* mutated, metastatic melanoma.
- To estimate the CNS clinical benefit rate (CBR, defined as complete response [CR] + partial response [PR] + stable disease [SD] >6 months) per RANO-MB criteria of triple or quadruple therapy in BRAF mutated, metastatic melanoma to the CNS
- To describe the toxicity of triple or quadruple therapy in *BRAF* mutated, metastatic melanoma using the Criteria for Adverse Events version 5 (CTCAEv5)
- To summarize the progression-free survival of triple or quadruple therapy in high risk populations of *BRAF* mutated, metastatic melanoma

Exploratory Objectives

2. To evaluate treatment response as correlated with baseline tumor mutational burden, changes in the tumor microenvironment (IFN associated gene expression), T cell clonality, and other biospecimens before and after triple or quadruple therapy.
- To evaluate the overall survival (OS) of triple or quadruple therapy in high-risk population of *BRAF*-mutated, metastatic melanoma

1.4 Product Development Background

1.4.1 Pharmacology

Nivolumab

Nivolumab is a fully human, IgG4 (kappa) isotype monoclonal antibody that binds to PD-1 with nanomolar affinity (dissociation constant [Kd], 3.06 nM) and a high degree of specificity. Nivolumab blocks binding of PD-1 to its ligands PD-L1 and PD-L2. Nonclinical in vitro testing of nivolumab demonstrated that binding to PD-1 results in enhanced T-cell proliferation and release of IFNγ *in vitro* in MLR and cytomegalovirus assays. Additional details are provided in the current version of the nivolumab IB.

Ipilimumab

Ipilimumab is a fully human IgG1 (kappa) monoclonal antibody that has specificity and a high affinity for human CTLA-4. The calculated dissociation constant value from an average of several studies was 5.25 nM. Binding of ipilimumab to purified, recombinant human CTLA-4 antigen was also demonstrated by enzyme-linked immunosorbent assay with half-maximal binding at 15ng/mL, whereas saturation was observed at approximately 0.1 µg/mL. No cross-reactivity was observed against human CD28. Ipilimumab completely blocked binding of B7.1 and B7.2 to human CTLA-4 at concentrations higher than 6 and 1 µg/mL, respectively. Additional details are provided in the current version of the ipilimumab IB.

Encorafenib

Encorafenib is a selective, ATP-competitive BRAF inhibitor for BRAFV600-mutated cells. The most significant difference between encorafenib and other second generation BRAF inhibitors is its increased dissociation half-life of 30 h, compared to dabrafenib (2 h) and vemurafenib (0.5 h) [29]. This leads to a decreased off-rate, leading to decreased AEs and prolonged inhibition of target [30,31]. Encorafenib also has higher potency with half-maximal inhibitory concentration (IC_{50}) of 40 nmol/L, compared to the higher IC_{50}s of dabrafenib (< 100 nmol/L) and vemurafenib (< 1 µmol/L) [32].

Binimetinib

Binimetinib is a potent, adenosine triphosphate-uncompetitive, highly selective allosteric inhibitor of MEK1/2 [63]. Binimetinib has nanomolar activity against MEK enzyme (half-maximal inhibitory concentration, 12 nM) and inhibits ERK phosphorylation in human cell lines. Binimetinib potently inhibits the proliferation of a subset of cells in human cancer cell lines and is particularly active in cells harboring activating mutations in the *BRAF*, *NRAS*, and *KRAS* genes.

1.4.1.1 Pharmacokinetics

Nivolumab

The safety and efficacy of the 480 mg Q4W flat dosage of nivolumab are similar to those of the approved nivolumab 240 mg flat dose or 3 mg/kg Q2W dosage. The nivolumab dosage of 480 mg Q4W was based on clinical data and modeling and simulation approaches using population pharmacokinetic (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) has been used (BMS Protocol CA017003). Nivolumab clearance and volume of distribution were found to increase as the bodyweight increases, but less than proportionally with increasing weight, indicating that milligram per kilogram dosing represents an over-adjustment for the effect of body weight on nivolumab PK. Using the PPK model, the overall distributions of nivolumab average steady-state exposures are comparable after treatment with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W, although the flat dose regimen of 480 mg Q4W is predicted to result in approximately 40% higher steady-state peak concentration (Cmaxss) and approximately 20% lower steady-state trough concentrations compared to the reference regimen of 3 mg/kg Q2W (BMS Protocol CA017003). Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Although nivolumab Cmaxss is predicted to be higher following 480 mg Q4W, these exposures are predicted to be lower than or within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program and are not considered to put participants at increased risk. The exposures predicted following administration of nivolumab 480 mg Q4W are on the flat part of the exposure-response curves for previously investigated tumors (melanoma and NSCLC) and are not predicted to affect efficacy.

Regarding PK, nivolumab dosing at 480 mg Q4W is expected to result in similar time average steady state concentrations (Cavgss) as nivolumab 3 mg/kg Q2W. In addition, nivolumab exposures following 480 mg are predicted to be below those observed at doses up to 10 mg/kg Q2W (used in the phase 1 nivolumab clinical program) that have been shown to be safe and well tolerated [64].

Ipilimumab

Ipilimumab has a terminal half-life of approximately 15.4 days. The expected in vivo degradation of monoclonal antibodies into small peptides and amino acids occurs via biochemical pathways that are independent of cytochrome P450 enzymes. The population pharmacokinetics (PPK) of ipilimumab was studied with 785 participants and demonstrated that PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time invariant. Upon repeated dosing of ipilimumab, administered every three weeks, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab clearance of 16.8 mL/h from the PPK analysis is consistent with that determined by PK analysis. The terminal half-life (T-HALF) and Vss of ipilimumab calculated from the model were 15.4 days, and 7.47 L, which are consistent with that determined by non-compartmental analysis (NCA). Volume of central (Vc) and peripheral compartment were found to be 4.35 L and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and subsequently into extracellular fluid space. Clearance of ipilimumab and Vc were found to increase with an increase in body weight. Nevertheless, there was no significant increase in exposure with increase in body weight when dosed on a mg/kg basis, supporting dosing of ipilimumab based on a weight normalized regimen. Additional details are provided in the ipilimumab Investigator Brochure (IB).

Encorafenib

Encorafenib is administered orally with 85% bioavailability, reaching maximum post-dose concentration in 2 h with a 6-h half-life. Food intake delays absorption of the medication but does not alter overall absorption. It is metabolized by cytochrome 450 enzymes (CYP3A4, CYP2C19, and CYP2D6) and 20 unique metabolites have been identified, which are excreted equally in urine and feces. Furthermore, 2% and 5% of the absorbed medication is excreted unchanged in urine and feces, respectively [29].

Binimetinib

Binimetinib is a potent, selective, non-ATP-competitive allosteric inhibitor of MEK1 and 2. It is taken orally with rapid absorption; median time of maximal absorption is 1.48 hours [29]. A low-fat meal increases maximum plasma concentration (Cmax) by an average of 29%, whereas a high-fat meal decreases Cmax by an average of 17%, both compared to the fasting state. Both low- and high-fat food intake increased time to maximal absorption, however, did not affect the amount of binimetinib absorbed. Binimetinib is metabolized by several primary and secondary biotransformations; cytochrome 450 enzymes (CYP1A2 and CYP2C19) account for 17.8% of clearance via N-demethylation, whereas direct glucuronidation accounts for approximately 62.2% of

clearance (Sun 2018). In addition, 62.3% of binimetinib is excreted in the feces, 31.4% in urine, and 6.5% is excreted unchanged in urine.

1.4.2 Clinical Experience

Nivolumab + Ipilimumab

The combination of nivolumab and ipilimumab was first evaluated in a phase I trial of metastatic/unresectable cutaneous melanoma (CA209-004) [26]. Long term follow up from all cohorts (n = 94) shows a 3 year OS rate of 63% and the median OS has not yet been reached [65]. This includes cohort 8, nivolumab 1 mg/kg and ipilimumab 3 mg/kg, the dosage selected for the following Phase II and III trials (CheckMate 069 and 067) [2,23,66]. Long term OS rates have been consistent across nivolumab and ipilimumab trials, with the 2 year OS rate in CheckMate 069 of 64% similar to the 3 year OS rate in CheckMate 067 (58%) and the 3 year OS rate in CA209-004 (63%) [65].

In both CheckMate 067 and 069, nivolumab was administered at 1 mg/kg and ipilimumab at 3 mg/kg (NIVO1 + IPI3), once every 3 weeks for four doses, followed by nivolumab monotherapy at 3 mg/kg once every 2 weeks. In CheckMate 067, treatment related Grade 3 and 4 AEs were reported in 55% of patients who received combination therapy, which led to discontinuation of treatment in 29% in the first 9 months [23].

Phase IIIb/IV CheckMate 511 study was conducted to determine whether nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (NIVO3 + IPI1) decreases AEs in patients with metastatic melanoma. Incidence of treatment-related Grade 3 to 5 AEs was significantly lower in patients treated with NIVO3 + IPI1 (61 [33.9%] of 180 patients; 95% CI, 27.0% to 41.3%) compared with the NIVO1 + IPI3 group (86 [48.3%] of 178 patients; 95% CI, 40.8% to 55.9%; P = .006) [67]. Rates of treatment-related AEs were lower in patients treated with NIVO3 + IPI1; however, the overall lower incidence of treatment-related Grade 3 and 4 AEs in NIVO3 + IPI1 group compared with the NIVO1 + IPI3 group was a result of lower rates of hepatic (7.2% v 16.3%), GI (6.1% v 10.7%), and endocrine (2.8% v 7.3%) AEs. ORR and PFS were similar between groups, including across LDH levels, BRAF mutation status, and PD-L1 status, although the authors caution that the study was not powered to detect these differences. Importantly, duration of therapy was longer for NIVO3+IPI1 treatment than for NIVO1+IPI3 and is borne out with the higher rate of discontinuation as a result of treatment-related AEs in the NIVO1+IIPI3 group.

2. ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the participants of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to participants. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to participants and any updates. The investigator or BMS should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. In situations where consent cannot be given to participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the participants, prior to the beginning of the study, and after any revisions are completed for new information.

5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participants' signed ICF and, in the US, the participants' signed HIPAA Authorization. The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Participants unable to give their written consent (eg, stroke or participants with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator. The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

3. INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open label, multi-site, phase 1/2 study of encorafenib +/- binimetinib + nivolumab + ipilimumab for the treatment of participants with unresectable or metastatic BRAF-mutated melanoma in high risk cohorts.

Study participants will consist of metastatic melanoma patients harboring BRAFV600E/K mutation without previous frontline therapy or recently started treatment with up to 6 weeks of targeted therapy, or one cycle of immunotherapy (or >6 months from adjuvant therapy). Toxicity from prior treatment must have resolved to ≤ Grade 1 and not included previous Grade 3–4 irAEs that required treatment discontinuous or previous Grade 2 immune-related uveitis or pneumonitis.

Phase I, Cohort 1: Twelve patients will be treated with triple therapy: 300 mg encorafenib and 3mg/kg nivolumab and 1 mg/kg ipilimumab. Dose-limiting toxicity (DLT) for Cohort 1 will be evaluated at week 6.

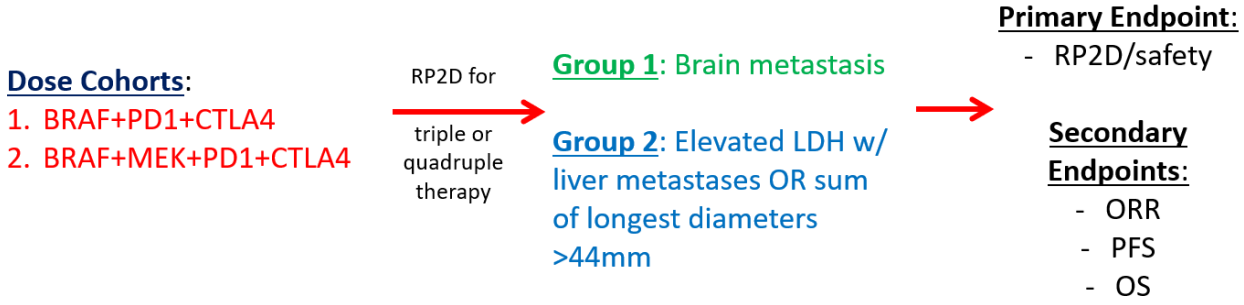
Phase I, Cohort 2: Upfront quadruple therapy (450mg encorafenib, 45mg binimetinib, 3mg/kg nivolumab, and 1mg/kg ipilimumab) will be investigated with twelve patients. DLT for Phase I, Cohort 2 will be evaluated at week 6.

Prior studies with triplet therapies combining anti PD-1/PD-L1, BRAF, and MEK inhibition have shown Grade 3–4 AEs occurring from 58%–73% [5,43,44,68]. These initial cohorts were small and did not use the newer, more potent and specific BRAF/MEK inhibitor pair encorafenib/binimetinib. We are allowing an initial DLT rate up to 75% in a continuous Bayesian monitoring protocol (See Statistics Section 8). We anticipate most of the toxicities to be additive and not synergistic and based on earlier recognition and treatment of immunotherapy AEs (see Appendix 6) and very specific AEs from encorafenib and binimetinib (see Appendix 2 and 3), we anticipate being able to create a safe RP2R dosing schedule.

Upon establishment of RP2R schedule, only participants with advanced melanoma who are either treatment naïve in the metastatic setting, have recently started treatment with targeted therapy within the past 6 weeks, or one cycle of immunotherapy, or who have progressed on adjuvant therapy more than 6 months following completion of adjuvant therapy (either BRAF-MEK or PD1 Ab) will be eligible for participation in high risk disease cohort expansion (Groups 1 or 2, see Schema below).

Phase II will take the RP2R schedule from Phase I and apply it to patients who may derive the most benefit from triple or quadruple therapy: Group 1) symptomatic brain metastases [up to 30 patients] and Group 2) LDH > 1x ULN with liver metastases OR bulky visceral disease (sum of longest diameter (SLD) > 44 mm) [up to 60 patients when combined with Group1].

Schema



Enrolled participants will be evaluated for safety and efficacy throughout the study and during follow up at the time points indicated on the time and events schedules presented in Tables 5.2.1 – 5.2.3. Response to treatment will be assessed in the intracranial (Group 1) and extracranial compartments (Group 2) and will be evaluated by serial radiographic assessment every 12 weeks until documented progression, withdrawal of consent, or the end of the study.

Follow-up Phase for each enrolled subject begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy). Participants will be followed for efficacy and OS. Treatment decisions will be based on local imaging evaluations using RANO-BM for intracranial lesions and RECIST 1.1 for extracranial lesions [69,70].

Additional imaging may be performed for patient care at the discretion of the investigator. All efficacy objectives will be based on Investigator assessment at the study site.

Safety will be evaluated for all treated participants using the NCI CTCAE version 5.0. Safety assessments will be based on medical review of AE reports, vital sign measurement results, physical examinations, and clinical laboratory tests.

3.1.1 Screening Phase

3. Screening begins by establishing the subject's initial eligibility and signing of the ICF.
4. The first 24 patients will be enrolled in the Phase I Cohort 1 (triple therapy with encorafenib, nivolumab, and ipilimumab) or Phase I Cohort 2 (upfront quadruple therapy of encorafenib, binimetinib, ipilimumab, and nivolumab)
5. After RP2R is determined, Phase II patients will be enrolled preferentially into Group 1 (brain metastases) if possible; otherwise if they meet criteria will be enrolled into Group 2 (liver metastases with bulky disease and/or elevated LDH), total enrollment goal is 60 between the two groups.

3.2 Post Study Access to Drug

At the end of the study, BMS will not continue to provide BMS supplied study drug to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate care to treat the condition under study. Participants who continue to respond at the end of on study treatment may be prescribed study medication through commercial supply.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent
    a. Participants must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
    b. Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.
2. Age ≥18 years
3. Histologically confirmed diagnosis of unresectable or metastatic melanoma
4. Presence of BRAFV600E/K mutation in tumor tissue as determined in a CLIA certified laboratory
5. Patients are required to submit archival biopsy material, if available, and submit research blood samples prior to first dose. Ten patients in each Phase I cohort will undergo fresh biopsy. These will be the first 10 unless medical or societal factors (e.g. COVID19) limit the pursuit of research biopsies.
6. Patients must be greater than 6 months from completion of adjuvant therapy (if any given) and/or treatment naïve in the metastatic setting or have recently started targeted therapy within the last 6 weeks, or one cycle of immunotherapy.
7. Prior radiotherapy must have been completed at least 2 weeks prior to study drug administration.
8. An ECOG Performance Status of 0 or 1. If enrolling in Group 1 of Phase II, can have Performance Status from 0-2.
9. Measurable disease by CT or MRI per RANO-BM (brain metastases) OR RECIST v1.1 criteria
10. Must have high risk features described as described in Phase II expansion cohort – EITHER brain metastases as described in Phase II Group 1 OR Elevated LDH/Bulky Visceral Disease as described in Phase II Group 2.

11. Adequate bone marrow, organ function, and laboratory parameters:
    a. ANC > 1.5 x 10^9 /L;
    b. Hemoglobin > 8 g/dL with or without transfusions;
    c. Platelet > 100 x 10^9 /L;
    d. Serum creatinine ≤ 1.5 × ULN, OR calculated creatinine clearance > 50 mL/min by Cockcroft-Gault formula, OR estimated glomerular filtration rate > 50 mL/min/1.73 m
12. Patient IS permitted to be on corticosteroids if related to disease burden and MAY have symptomatic brain lesions as long as radiation or surgical intervention is not deemed to be urgently necessary.
    a. Symptomatic intracranial metastases may be on steroids at a total daily dose of no higher than 4 mg of dexamethasone or equivalent that is stable or tapering for 10 days prior to first treatment,
    b. have no immediate need for SRT or surgery (within 3 week prior to first treatment),
    c. have a performance status of 0–2 and
    d. have had no experience of seizure within 10 days prior to first treatment.
13. Female patients of childbearing potential must have a negative serum β-HCG test result during screening prior to first dose
14. Females of childbearing potential must agree to protocol-approved methods of contraception, and to not donate Ova from Screening until 30 days of last dose of study drug.
15. Male patients must use contraception that is highly effective or acceptable, and not donate sperm from Screening until 90 days after the last dose of study drug.
16. The patient is deemed by the Investigator to have the initiative and means to comply with scheduled visits, treatment plan and study procedures.

3.3.2 Exclusion Criteria

1. Known hypersensitivity or contraindication to any component of study treatment or their excipients.
2. Previous Grade 3-4 AEs, or discontinuation of PD-1 or CTLA-4 inhibitor therapy, or BRAF/MEK inhibitor therapy
3. Inability to swallow and retain study treatment

4. Impairment of gastrointestinal function or disease which may significantly alter the absorption of study treatment (e.g., active ulcerative disease; uncontrolled nausea, vomiting or diarrhea; malabsorption syndrome; small bowel resection).
5. Participants with a non-melanoma related 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.
6. Participants with active, known or suspected autoimmune disease including those who have required systemic anti-rheumatic therapies in the preceding 2 years. Participants 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.
7. Impaired cardiovascular function or clinically significant cardiovascular disease including, but not limited to, the following:
    a. History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting) < 6 months prior to Screening
    b. Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2)
    c. A known LVEF < 50% as determined by MUGA or ECHO
    d. Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite current therapy
    e. History or presence of clinically significant cardiac arrhythmias (including resting bradycardia, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia)
    f. Baseline QTcF interval ≥ 480 ms.
8. Second malignancy that requires active treatment or would interfere with treatment efficacy evaluation. Participants with a second malignancy treated with curative intent are eligible.
9. On-going or use of systemic antibiotics during the preceding 2 weeks prior to enrollment
10. Known acute or chronic infection with hepatitis B or hepatitis C virus. Participants treated with curative anti-viral therapy are eligible.

11. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) even if fully immunocompetent on ART—due to the unknown effects of HIV on the immune response to combined nivolumab plus ipilimumab or the unique toxicity spectrum of these drugs in patients with HIV.
12. Clinically unstable thromboembolic event despite anti-coagulation. Patients on stable dosing of anti-coagulants per investigator discretion are eligible.
13. Use of herbal supplements, medications or foods that are moderate or strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 ≤ 1 week prior to the start of study treatment (Section 4.5.1).
14. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); history of retinal degenerative disease.

3.3.3 Phase II Group 1 Specific Criteria

1. For Phase II Group 1 (Brain Metastases): Patients may have an ECOG status of 0–2 and IS permitted to be on corticosteroids if related to disease burden and MAY have symptomatic brain lesions as long as radiation or surgical intervention is not deemed to be urgently necessary.
    a. Symptomatic intracranial metastases may be on steroids at a total daily dose of no higher than 4 mg of dexamethasone or equivalent that is stable or tapering for 10 days prior to first treatment,
    b. have no immediate need for SRT or surgery (within 3 week prior to first treatment),
    c. have had no experience of seizure within 10 days prior to first treatment.

3.3.4 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40

mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 weeks minimum for transdermal products
- 8 weeks minimum for oral products. Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as permitted in brain metastasis cohort).
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of melanoma with the exception of targeted therapy initiated within the last 6 weeks, or one cycle of immunotherapy).

3.4.2 Other Restrictions and Precautions

Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

3.5 Discontinuation of Participants from Treatment with Study Drugs

Participants MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation (see Section 4.3.5)

All participants who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5 - Study Assessment and Procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Follow Up

Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 Study Assessments and Procedures until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Participants should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-up

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant as noted above. Lost to follow-up is defined by the inability to reach the participant after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death. If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4. STUDY DRUG

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are nivolumab and ipilimumab. See Table 4-1.

Table 4.1: Study Drugs for QUAD-01

Product Description/Class and Dosage Form	**Potency**	**IP/Non-IMP**	**Blinded or Open Label**	**Packaging/Appearance**	**Storage Conditions (per Label)**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP	Open-Label	Clear to opalescent colorless to pale yellow liquid. May contain particles.	2 to 8°C. Protect from light, freezing and shaking.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open-Label	Clear, colorless to pale yellow liquid. May contain particles.	2 to 8°C. Protect from light and freezing.
Encorafenib	50 or 75 mg	Non-IMP	Open-Label		
Binimetinib	45mg	Non-IMP	Open-Label		

4.2 Non-Investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products. In this protocol encorafenib and binimetinib are non-investigational products.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

Please refer to the current version of the encorafenib, binimetinib, nivolumab and ipilimumab IBs and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information.

Nivolumab

Nivolumab vials must be stored at a temperature of 2° C to 8° C and should be protected from light, freezing, and shaking. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab IB section for “Recommended Storage and Use Conditions” and/or pharmacy reference sheets. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab is to be administered as an IV infusion per institution SOC using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery, but the total drug concentration of the solution

cannot be below 0.35 mg/mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Ipilimumab

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-(2-ethylhexyl)phthalate) or glass containers and is stable for 24 h at 2 ºC–8ºC or room temperature/room light (RT/RL). For ipilimumab storage instructions, refer to ipilimumab IB and/or pharmacy reference sheets. Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

Ipilimumab is to be administered as an IV infusion per institution SOC, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

Encorafenib

Encorafenib 450 (quadruple) or 300 (triple) mg will be administered PO QD continuously. Patients should take encorafenib daily in the morning at approximately the same time every day.

Binimetinib

Binimetinib 45 mg will be administered PO BID continuously. Patients will be instructed to take binimetinib 12 ± 2 h apart in the morning and in the evening at approximately the same times every day.

Encorafenib and binimetinib should be taken together, if applicable, and without regard to food. Patients will be instructed to swallow the capsules/tablets whole with a large glass of water and not to chew or crush them.

4.4 Method of Assigning Subject Identification

QUAD-01 study is an open-label study. Patients must not start protocol treatment prior to registration in the Clinical Trials Management Application (CTMA). Participants can be enrolled after eligibility criteria are met. Registration will require the following information: 1) protocol name and number, 2) date treatment begins, 3) subject name, 4) date of birth, 5) primary study physician, 6) confirmation of eligibility, 7) and verification that the informed consent was signed.

4.5 Selection and Timing of Dose for Each Subject

Dosing and schedules for QUAD-01 are outlined in Table 4.5A and 4.5B. The investigational products nivolumab at 3mg/kg and ipilimumab at 1mg/kg will be given every 3 weeks for the first 4 treatments, then switched to single agent nivolumab at 480mg flat dose for up to one year. Encorafenib with or without binimetinib will be dosed as shown in Table 4.5A.

Table 4.5A: Dosing Schedule for Phase I

	Day 1 Week 1	**Day 1 Week 2**	**Day 1 Week 3**	**Day 1 Week 4**	**Day 1 Week 5**	**Day 1 Week 6**	**Day 1 Week 7**
Cohort 1: Triple therapy (encorafenib + nivolumab + ipilimumab)	300 mg encorafenib PO daily	300 mg encorafenib PO daily	300 mg encorafenib PO daily	300 mg encorafenib PO daily	300 mg encorafenib PO daily	300 mg encorafenib PO daily	300 mg encorafenib PO daily
	3mg/kg Nivolumab			3mg/kg Nivolumab			3mg/kg Nivolumab
	1mg/kg Ipilimumab			1 mg/kg Ipilimumab			1 mg/kg Ipilimumab
Cohort 2: Quadruple therapy (encorafenib + binimetinib + nivolumab + ipilimumab)	450 mg encorafenib PO daily	450 mg encorafenib PO daily	450 mg encorafenib PO daily	450 mg encorafenib PO daily	450 mg encorafenib PO daily	450 mg encorafenib PO daily	450 mg encorafenib PO daily
	45 mg binimetinib PO BID	45 mg binimetinib PO BID	45 mg binimetinib PO BID	45 mg binimetinib PO BID	45 mg binimetinib PO BID	45 mg binimetinib PO BID	45 mg binimetinib PO BID
	3mg/kg Nivolumab			3mg/kg Nivolumab			3mg/kg Nivolumab
	1mg/kg Ipilimumab			1 mg/kg Ipilimumab			1 mg/kg Ipilimumab

*Investigational products nivolumab and ipilimumab will be administered every 3 weeks for the first four doses, then single agent nivolumab will be administered every 4 weeks at flat dose of 480mg for up to one year.

Table 4.5B: Dosing Schedule for Phase II

	Day 1 Week -2	**Day 1 Week -1**	**Day 1 Week 1**	**Day 1 Week 2**	**Day 1 Week 3**	**Day 1 Week 4**	**Day 1 Week 5**
Group 1: Brain metastases	RP2R	RP2R	RP2R	RP2R	RP2R	RP2R	RP2R
Group 2: Elevated LDH OR Bulky Visceral Disease SLD > 44 mm	RP2R	RP2R	RP2R	RP2R	RP2R	RP2R	RP2R

4.6 Concomitant Therapy

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines and/or herbal supplements) must be recorded in the eCRF and medical records. Details regarding all prior anticancer treatment will also be recorded in the eCRF and medical records.

Any medication received within 28 days before the first dose of study treatment and within 30 days after the last dose of study treatment, or until the patient begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF and medical records. Any addition, deletion or change in the dose of these medications will also be recorded. Details of prior antineoplastic treatments including number of prior metastatic regimens will also be recorded.

Unless specifically prohibited, concomitant medications may be administered at the Investigator's discretion to manage the patient's medical condition and to conform to standard practice during the Treatment Period.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

a. Reason for use.
b. Dates of administration including start and end dates.
c. Dosage information (using generic drug names when possible), including dose and frequency.

Immunotherapy
Nivolumab and Ipilimumab are monoclonal antibodies that are cleared by catabolic processes and do not have drug-drug interaction guidelines.

Targeted therapy
Encorafenib

Encorafenib is a reversible inhibitor of CYP2B6, CYP2C9, CYP3A4 and UGT1A1. It is also a time-dependent inhibitor of CYP3A4 and induced CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2B6, CYP2C9, CYP3A4 and UGT1A1 or those substrates that have a narrow therapeutic index.

There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least 1 form of non-hormonal contraception is required for females of childbearing potential during participation in this study. Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib.

Encorafenib has been identified as being metabolized by CYP3A4 and to a lesser extent by CYP2C19 in vitro. Concomitant use of moderate CYP3A4 inhibitors should be avoided. If use of a moderate CYP3A4 inhibitor is unavoidable, short-term use (≤ 30 days) following discussion with the Sponsor may be permitted with an accompanying dose reduction to one-half of the encorafenib dose prior to use of the moderate CYP3A4 inhibitor. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the encorafenib dose that was taken prior to initiating the CYP3A4 inhibitor.

Investigators should use caution when administering encorafenib with concomitant medications with a known, conditional or possible risk to prolong the QT interval and/or induce torsade de pointes. Patients receiving such medications must be carefully monitored for potentiating of toxicity due to any individual concomitant medication and may require dose titration of the concomitant medication.

Binimetinib

In vitro, binimetinib has been identified to be primarily metabolized by glucuronidation. Strong inducers of UGT1A1 should be taken with caution when co-administered with binimetinib.

For tabulated CYP substrates, inhibitors and inducers to be used with caution or avoided, please consult the FDA website: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

4.7 DLT

DLT-evaluable participants will be defined as participants who in the DLT evaluation period received ≥66% of encorafenib and/or binimetinib doses and at least one dose each of nivolumab and ipilimumab.

For Cohort 1, encorafenib and nivolumab and ipilimumab will be administered on day 1 week 1. The DLT evaluation period will extend from day 1 of week 1 to the end of week 6 and captured in the medical records.

For Cohort 2, encorafenib, binimetinib, nivolumab and ipilimumab will be administered on day 1 week 1. The DLT evaluation period will extend from day 1 week 1 to the end of week 6 and captured in the medical records.

DLT Definition: A DLT is defined as any AE or laboratory abnormality that is not explained by underlying disease, disease progression, intercurrent illness, or concomitant therapies that either meets the criteria described below or results in the inability to tolerate at least 66% of the planned dose of encorafenib +/- binimetinib and at least one dose each of nivolumab and ipilimumab during Cycle 1. CTCAEv5 will be used for grading.

Dose delay criteria apply for all drug-related AEs (regardless of whether or not the event is attributed to nivolumab, ipilimumab, encorafenib, or binimetinib. If investigator can

attribute AE to either targeted or immunotherapy, may hold one and continue the other, otherwise delaying all study drugs is appropriate.

Specific DLT Criteria
Hematologic

- Grade 4 anemia
- Grade 4 neutropenia (for > 7 consecutive days) or Grade 4 febrile neutropenia
- Grade 4 thrombocytopenia (of any duration).
- Grade 3 thrombocytopenia with clinically significant bleeding regardless of duration or requirement of platelet transfusion

Pancreas

- Symptomatic serum amylase or lipase elevation, medical intervention required (pancreatitis Grade 3 or higher)

Gastrointestinal disorders

- Nausea and vomiting ≥ Grade 3 for > 3 days despite optimal anti-emetic therapy
- ≥ Grade 3 diarrhea for > 5 days despite optimal antidiarrheal treatment (which could include steroids).

Hepatobiliary

- Total bilirubin Grade ≥ 4
- For participants with normal baseline AST and ALT values
    - AST or ALT >8x ULN
- For participants with normal baseline AST and ALT and normal baseline bilirubin value:
    - AST or ALT > 3.0 × ULN combined with total bilirubin > 2.0 × ULN without evidence of cholestasis
- For participants with abnormal baseline AST or ALT or abnormal baseline bilirubin value:
    - [AST or ALT > 2 × baseline AND > 3.0 × ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 × baseline AND > 2.0 × ULN] without evidence of cholestasis

Hypertension

- ≥ Grade 3 hypertension related to the study medication if it persists > 7 days despite optimal anti-hypertensive treatment

- Grade 4 hypertension of any duration

Cardiac

- ≥ Grade 3 cardiac event that is symptomatic or requires medical intervention

Pneumonitis

- Grade 2 pneumonitis if it persists > 7 days despite treatment with corticosteroids
- ≥ Grade 3 pneumonitis of any duration

Immune-related Toxicities (except pneumonitis)

- Grade 3 immune-related toxicities that persist > 14 days with same severity despite treatment with corticosteroids.
- Grade 4 immune related toxicities of any duration ≥ Grade 3 infusion related reaction

Eye disorders – Retinal

- Retinopathy or retinal detachment Grade ≥ 3, confirmed by ophthalmic examination
- Retinal vascular disorder including RVO, confirmed by ophthalmic examination

Eye disorders – Visual disturbances without ocular (retinal) changes

- Blurred vision, flashing lights, floaters: Grade ≥ 3

Eye disorders – Other (specify)

- Grade ≥ 3 for > 21 consecutive days
- Grade 4 confirmed by ophthalmic examination

Other hematologic and nonhematologic toxicities

- Any other Grade ≥ 3 AE except: a. Lymphocyte count decreased (lymphopenia) Grade ≥ 3 unless clinically significant

Renal dysfunction

- Calculated GFR decrease of 50% from baseline
- Proteinuria 24-h urine protein > 2 g/24 h

Events which will NOT be considered DLT for the purposes of this protocol:

- Clinically insignificant laboratory values ≤ Grade 2. For laboratory values ≥ Grade 3, the maximum allowable time limit for correction of electrolyte abnormalities to ≤ Grade 1 is 72 h.
- Cutaneous squamous cell carcinoma (CuSCC), basal cell carcinoma, and new primary melanoma which are manageable with surgical excision alone

4.8 Management Guidelines for Immunotherapy (I-O) Agents

I-O agents are associated with irAEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered I-O agents in this protocol.

Early recognition and management of irAEs may mitigate severe toxicity. Management algorithms have been developed from extensive experience with nivolumab and ipilimumab to assist investigators in assessing and managing the following groups of irAEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological

The clinical nature of AEs noted with encorafenib and binimetinib will determine the role of the above algorithms for use in toxicities related to its use in this study. The algorithms recommended for utilization in this protocol are included in Appendix 2.

Table 4.2 Reference Adverse Events (AEs) and toxicity Management Guidelines

ADVERSE EVENTS	NIVOLUMAB	IPILIMUMAB	ENCORAFENIB	BINIMETINIB
DIARRHEA/COLITIS	X	X	X	X
ABNORMAL LIVER ENZYME TEST	X	X	X	X
SKIN RASH	X	X	X	X
SERIOUS SKIN REACTION	X	X	X	X
NEPHRITIS	X	X	X	X
PNEUMONITIS	X	X		
ENDOCRINE EVENTS	X	X	X	X
HAND FOOT SKIN REACTION	X	X	X	X
NEUTROPENIA AND THROMBOCYTOPENIA	X	X	X	X
ABNORMAL LABORATORY RELATED AES	X	X	X	X
ASYMPTOMATIC AMYLASE/LIPASE ELEVATION	X	X	X	X
INFUSION REACTION AND CYTOKINE RELEASE SYNDROME	X			
LVEF			X	X
HYPERTENSION			X	X
NEW MALIGNANCIES			X	X
PYREXIA			X	X
VISUAL CHANGES			X	X
HYPERGLYCEMIA			X	X
HEMORRHAGE			X	X
THROMBOTIC EVENTS				X

*X indicates study treatment that may need to be modified

4.9 Management Guidelines for Targeted Therapy

See Appendix 2 and 3.

4.10 Guidelines for Permanent Discontinuation

• Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

• Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:

− Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

− Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation

− Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

♦ Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

• Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:

− AST or ALT > 8 x ULN

− Total bilirubin > 5 x ULN

− Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

• Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:

− Grade 4 neutropenia ≤ 7 days

− Grade 4 lymphopenia or leukopenia

− Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The Study PI should be consulted for Grade 4 amylase or lipase abnormalities.

− Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

• Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:

− Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the Study PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

− Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Study PI. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the Study PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

• Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing.

Note: If a subject experiences a severe AE during induction treatment (ie, the combination of nivolumab and ipilimumab) that requires discontinuation from further treatment with the combination, continuing treatment with nivolumab monotherapy may be considered contingent on discussion with and approval by the Study PI.

Exceptions to Permanent Discontinuation of study drug dosing under the following situations:

• Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.

• Participants with the following conditions where in the investigator’s opinion continuing study drug administration is justified:

− Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy.

4.11 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported

within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 5.0) guidelines.
Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:
For Grade 1 symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30minutes before additional nivolumab administrations.

For Grade 2 symptoms: (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for <24 hours):
Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further BMS-936558 will be administered at that visit.

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly f or IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

5. STUDY DESIGN

5.1 Overall Design

Table 5.2.1 details assessments for Phase 1 Cohort 1, and Table 5.2.2 for Phase 1 Cohort 2. Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol.

- For the first 6 weeks, all assessments have a ± 3 day window unless otherwise indicated.
- After the first 6 weeks, all assessments have a ± 7 day window, unless otherwise indicated. Additional assessment may be performed as clinically indicated.

If study drug is being held due to toxicity, then the scheduled visits and assessments should still be performed per protocol (except dose administration), unless otherwise specified.

Table 5.2.2: Phase I Cohort 1															
Trial Period:	**Screen Phase**	**Treatment**										**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	**Screen**	**D1 W1**	**D1 W2**	**D1 W3**	**D1 W4**	**D1 W5**	**D1 W6**	**D1 W7**	**D1 W8**	**D1 W9**		**D1W 14 (+)**	**Discon**	**Safety Follow-up**	**Follow Up Visits**
Scheduling Window (Days):	28 days	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	100 days post discon	Every 12 weeks post discon
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior and Concomitant Medication Review	X	X			X			X			X	X			
Trial Treatment Administration[a]		X			X			X			X	X			
Review Adverse Events	X	X			X			X			X	X			
Nursing Call Check-Up			X	X		X	X		X	X		X			
Physical Examination	X	X			X			X			X	X	X	X	X
Vital Signs	X	X			X			X			X	X	X	X	X
ECOG Performance Status	X	X			X			X			X	X	X	X	X
Pregnancy Test	X														
EKG	X														
CBC with Differential	X	X	X	X	X			X			X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X	X	X			X			X	X	X	X	X
HCV, HIV, HepB	X														
TSH (T3, FT4 if TSH abnormal)	X	X	X	X	X			X			X	X	X	X	X
Research blood collection[b]	X				X								X		
Archival tumor collection	X														
Fresh tumor biopsy[c]	X				X[c]										
Imaging[d]	X														

a. Encorafenib and binimetinib are given continuously. Nivolumab and ipilimumab are given for four doses every 3 weeks then nivolumab is given monthly for up to one year.

b. Blood will be drawn at baseline, week 4, week 12 (or with first restaging imaging) and at progression/end of treatment

c. Ten patients in each Phase Ib cohort will undergo fresh biopsy prior to treatment and between the 1st and 2nd doses of ipilimumab (between weeks 4-7). These will be the first 10 unless medical or societal factors (e.g. COVID19) limit the pursuit of research biopsies.

d. During treatment: Every 12 weeks (± 7 days). End of Treatment (EOT): if a scan was not conducted within 30 days prior to end of study treatment. Efficacy follow-up: Every 12 weeks starting from the last assessment until documented disease progression per RECIST 1.1 (unless meeting criteria for treatment beyond progression), withdrawal of consent, lost to follow-up, or death irrespective of start of new anti-neoplastic therapy.

e. Table 5.2.2: Phase I Cohort 2

Trial Period:	**Screen Phase**	**Treatment**											**End of Treatment**	**Post-Treatment**	
Treatment Cycle/Title:	**Screen**	**D1 W1**	**D1 W2**	**D1 W3**	**D1 W4**	**D1 W5**	**D1 W6**	**D1 W7**	**D1 W8**	**D1 W9**	**D1W 10**	**D1W 14 (+)**	**Discon**	**Safety Follow-up**	**Follow Up Visits**
Scheduling Window (Days):	28 days	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	100 days post discon	Every 12 weeks post discon
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior and Concomitant Medication Review	X	X			X			X			X	X			
Trial Treatment Administration[a]		X			X			X			X	X			
Review Adverse Events	X	X			X			X			X	X			
Nursing Call Check-Up			X	X		X	X		X	X		X			
Physical Examination	X	X			X			X			X	X	X	X	X
Vital Signs	X	X			X			X			X	X	X	X	X
ECOG Performance Status	X	X			X			X			X	X	X	X	X
Pregnancy Test	X														
EKG	X														
CBC with Differential	X	X	X	X	X			X			X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X	X	X			X			X	X	X	X	X
HCV, HIV, HepB	X														
TSH (T3, FT4 if TSH abnormal)	X	X	X	X	X			X			X	X	X	X	X
Research blood collection[b]	X				X								X		
Archival tumor collection	X														
Fresh tumor biopsy[c]	X				X[c]										
Imaging[d]	X														

a. Encorafenib and binimetinib are given continuously. Nivolumab and ipilimumab are given for four doses every 3 weeks then nivolumab is given monthly for up to one year.

b. Blood will be drawn at baseline, week 4, week 12 (or with first restaging imaging) and at progression/end of treatment

c. Ten patients in each Phase Ib cohort will undergo fresh biopsy prior to treatment and between the 1st and 2nd doses of ipilimumab (between weeks 4-7). These will be the first 10 unless medical or societal factors (e.g. COVID19) limit the pursuit of research biopsies.

d. During treatment: Every 12 weeks (± 7 days). End of Treatment (EOT): if a scan was not conducted within 30 days prior to end of study treatment. Efficacy follow-up: Every 12 weeks starting from the last assessment until documented disease progression per RECIST 1.1 (unless meeting criteria for treatment beyond progression), withdrawal of consent, lost to follow-up, or death irrespective of start of new anti-neoplastic therapy.

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments during the Screening or Lead-in period will not be permitted (this does not include parameters that require a confirmatory result) unless there was a technical error in performance of the lab test and the first result is invalid.

Any new result will override the previous result (*ie*, the most current result prior to dosing) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.2 Safety Assessments

5.2.1 Medical History, Physical Exam, Physical Measurements

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be performed within 28 days prior to first dose.

Baseline local laboratory assessments should be done within 14 day prior to first dose and are to include: CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, Hep B/C (HBV sAG, HCV antibody, or HCV RNA).

While on-study and during follow-up, local laboratory assessments are to be conducted as specified below.

Participants will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. Once participants reach the survival follow-up, either in-person visits or documented telephone calls/email correspondence to assess the subject's status are acceptable.

AEs and laboratory values will be graded according to the NCI-CTCAE version 5.0. Oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be assessed at each on-study visit prior to dosing. The start and stop time of the study therapy infusions should be documented.

Physical examinations are to be performed as specified in Section 5.1 and as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious AE page.

On treatment local laboratory assessments are to be completed within 72 hours prior to dosing.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up

phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

If a subject shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

5.2.2 Vital Signs

Vital signs consist of blood pressure, heart rate, respiratory rate, pulse oximetry and temperature measurements. Vital signs will be obtained as outlined above.

5.2.3 Imaging Assessment for Study

CT and MRI scans (section 5.4) will be assessed locally per the modified RECIST 1.1 criteria and RANO BM criteria [69,70]. Up to 5 extracranial and 5 intracranial lesions will be followed for efficacy per the criteria. Please refer to Appendix 1 and 5 for guidelines regarding images, target lesion selection and response criteria.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

Clinically significant radiologic findings or changes from baseline scans will be coded as AEs or serious AEs according to the criteria described in Section6.

5.2.4 ECOG Status

ECOG performance status will be evaluated at the screening evaluation and at each visit as outlined.

5.2.5 AE Monitoring

AEs will be evaluated according to the NCI CTCAE Version 5.0 on a continuous basis starting from when the subject takes the first dose of study administration, up to and including Follow-Up and End of Treatment visits (at minimum, for 100 days following last dose of study drug). Serious AEs (SAEs) must be collected from the time period following p first dose of study drug to and including follow-up (refer to section 5.4).

5.2.6 Laboratory Test Assessments

Results of all safety laboratory collections must be obtained and reviewed in advance of study drug dosing, as applicable. Amylase and lipase should be collected with the chemistry collection, but these lab results do not require review prior to dosing.

Serum Chemistry includes comprehensive metabolic panel (albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, glucose, potassium, sodium, total bilirubin and protein, alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase) with magnesium, phosphorous, amylase, lipase, lactate dehydrogenase. A free-T4 and free-T3 will be performed reflexively for out of range TSH values. A CBC with differential is to be obtained. The CBC with differential includes hemoglobin, hematocrit, white blood cells, platelets (direct platelet count), erythrocyte sedimentation rate, WBC differential enumeration of total and percentage of neutrophils, lymphocytes, eosinophils, basophils and monocytes.

5.3 Efficacy Assessments

Assessment of extracranial disease (by CT scan or other approved modalities) and intracranial disease (by MRI scan) will be performed per the schedule above and using criteria in Appendix 5. Investigators may obtain more frequent follow-up MRI scans as medically indicated. Baseline assessments should be performed within 28 days prior to first dose of study drug utilizing CT or MRI for systemic lesions and within 28 days for brain lesions (MRI only). In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, pelvis, brain, and all known sites of disease and should use the same imaging method as was used at baseline. Participants will be evaluated for tumor response beginning at 12 weeks (± 7 days) and every 12 weeks (± 7 days) thereafter, until disease progression is documented, or treatment is discontinued (whichever occurs later).

For extracranial disease assessment, contrast-enhanced computed tomography (CT) scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen and pelvis and other areas of disease are to be performed for tumor assessments as above. Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRI's should be acquired with slice thickness of <5 mm with no gap (contiguous). Use of CT component of a PET/CT scanner: Combined modality scanning such as with FDGPET/CT is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a FDGPET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MRI scans: Bi-dimensional and three-dimensional contrast enhanced MRI of the brain will be acquired. Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points. Cases of suspected radiologic disease progression will be confirmed by an MRI performed at least 4 weeks after the initial radiological assessment of progression.

5.3.1 Confirmation of scans

Verification of Response: Confirmation of intracranial response will be confirmed by an MRI performed at least 4 weeks after the initial radiological assessment per investigator discretion or SOC. If repeat scans confirm overall response (OR), then response should be declared using the date of the initial scan. If repeat scans do not confirm OR, then the subject is considered not to have had an OR.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal and will be confirmed by a CT or MRI performed at least 4 weeks after the initial radiological assessment of progression per investigator discretion or SOC. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease.

5.3.2 Algorithms for Response Assessment

5.3.2.1 Safety

The primary endpoint of the study is safety and tolerability of triple or quadruple therapy and will be assessed in Phase I.

5.3.2.2 Secondary Endpoints – Efficacy

Secondary efficacy endpoints of the study include PFS and ORR in all randomized participants.

5.4 Biomarker Assessments

A variety of factors that could potentially predict clinical response to triplet or quadruple therapy will be investigated in peripheral blood and in tumor specimens. Data from these investigations will be evaluated for associations with response, survival (OS, PFS) and/or safety (AE) data. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with melanoma or immunotherapy treatment. Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate Lab Manual.

Biomarkers

Biomarker measures of baseline and on-treatment peripheral blood, serum, and tumor samples will be used to identify pharmacodynamic markers of treatment. Additional biomarkers related to mechanism of action and markers associated with clinical response to encorafenib +/- binimetinib + nivolumab + low dose ipilimumab will be explored.

A detailed description of each biomarker sample analysis and assessment is described below and a schedule of biomarker sample collections is provided in the table. Further details of blood and tissue collection and processing will be provided in the Lab Manual.

Peripheral blood and tumor tissue will be collected prior to therapy and at selected time points on treatment. If a biopsy or surgical resection is performed at the on treatment or at the time of recurrence or suspected recurrence, tumor sample should also be submitted for analysis. If biomarker samples are drawn but study treatment(s) is not administered, samples will be retained. Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of specimens will be provided in a separate Lab Manual at the time of study initiation.

Study Day of Sample Collection*	Serum[a]	Whole Blood[a]	Tumor Biopsy[a,b]	Plasma ctDNA[a]
Screening	X	X	X	X
Prior to dose at week 4	X	X		X
Between week 4-7			X	
At 12 week restaging	X	X		X
At progression	X	X		X

* Protocol specified windows apply to biomarker assessments
[a] Instructions for the collection and processing of all samples will be provided in the laboratory manual.
[b] Fresh tumor biopsy will only be collected in Phase I

Biomarker Measures

Immunomodulatory properties of encorafenib with and without binimetinib in combination with nivolumab and ipilimumab will be investigated in peripheral blood and tumor samples as detailed below.

Peripheral Blood Studies Peripheral blood samples will be taken prior to initiation of study therapy and on designated time points post-treatment. Above samples will be analyzed for the following measures:

Peripheral Blood Soluble Factors (Serum and Plasma) Baseline and post-treatment modulation of serum levels of chemokines, cytokines and other immune mediators will be assessed by techniques that may include, but are not limited to ELISA, LC-MS.

Immunophenotyping Peripheral blood samples will be taken prior to initiation of study therapy and at designated time points on-treatment. These whole blood or PBMC samples may be used for characterization of the immune cell subsets in the peripheral blood. Analyses may include, but not necessarily be limited to, the proportion of T, B, and NK cells; monocytes and MDSCs as well as their function status measured by Ki67.

Peripheral Blood Genomic and Gene Expression Profiling Peripheral biomarker measures: PBMCs, plasma, serum, or RNA/DNA derived from whole blood may be used for future exploratory analyses such as, but not limited to assessment of gene expression,

tumor mutational burden (TMB), to assess biomarkers of immune cell populations associated with tumor type or therapy.

T Cell Receptor sequencing DNA-derived from whole blood or PBMCs may be used for the assessment of T cell receptor repertoire by genomic sequencing technologies.

Tumor Biopsies and Tumor-Based Biomarker Measures Mandatory tumor biopsy specimens will be obtained at baseline and on-treatment to characterize immune cell populations and expression of selected tumor markers. Study participants should have tumor lesions large enough to undergo repeated biopsies (pre- and on-treatment), excisional or at least obtainment of 4 core biopsy specimens. Pathologic confirmation is strongly encouraged at the time of tumor biopsy to confirm adequate tissue collection and biopsy quality. Participants who undergo biopsy or excision for clinical indications should have any tumor that remains preserved for biomarker analysis. Detailed information for the collection and processing of all samples will be provided in the Lab Manual.

In addition to fresh tumor biopsy, participants are required to submit an archival formalin-fixed paraffin-embedded (FFPE) specimen, if collected prior to the enrollment, if available. The archival tumor tissue sample will be used to compare the expression of putative biomarkers to expression in the fresh tumor biopsy.

The pharmacodynamic effects of encorafenib with and without binimetinib in combination with nivolumab and ipilimumab on intratumoral immune response in biopsy samples will be assessed by gene expression analysis or single cell analysis and calculated as fold change (or percent changes) compared to baseline.

Characterization of tumor microenvironment cell population and immune infiltrates in tumor. The number, frequency, and composition of immune infiltrates within the tumor may be assessed before and after exposure to encorafenib with and without binimetinib in combination with nivolumab and ipilimumab using IHC of the FFPE tumor biopsy specimen. IHC assays may be performed using, but not limited to, the following markers: CD8, CD3, CD15, and PD-L1. The composition of tumor immune infiltrate may be assessed before and after treatment using IHC or multi-plex analysis of the FFPE tumor biopsy specimen. IHC assays may be performed using, but not limited to, the following markers: CD8, CD3, CD15, and PD-L1. Fresh and archival tumor samples may be subjected to correlative gene expression and/or IHC analysis.

Tumor DNA/RNA analysis: Fresh tumor biopsy samples may be evaluated by gene expression analysis using RNAseq, single cell RNA sequencing, qRT-PCR or other relevant techniques to interrogate pharmacodynamic effects, mechanism of action, and/or response or resistance to encorafenib with and without binimetinib in combination with nivolumab and ipilimumab. DNA/RNA derived from tumor tissue may be used for analysis of genomic correlates including but not limited to tumor mutational burden and T cell receptor repertoire.

Other exploratory tumor-based biomarker measures: Tumor tissue or derived RNA/DNA may also be evaluated by LCMS, genetic mutation and rearrangement detection methods, such as genome and/or exome sequencing, and/or quantitative PCR or RT-PCR as part of additional exploratory analyses of putative biomarkers possibly associated with response or resistance to encorafenib with and without binimetinib in combination with nivolumab and ipilimumab.

6. ADVERSE EVENTS

An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon

appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event.

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE. Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs.

NOTE:

The following hospitalizations are not considered SAEs in clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 SAE Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

REPORTING OF SAES

All events meeting the definition of a serious AE should be reported according to the departmental SAE checklist and SAE form. The initial SAE form should be sent to the following within 24 hours/1 business day of the Principal Investigator becoming aware:

1. Sponsor-Investigator
2. crssafetysubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met.

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections B and C of the departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

Follow-up reports:
Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form.

6.2 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy. It is expected that wherever possible, the clinical rather than

laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.3 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary, for subject safety). In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section6.1.1. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form

6.4 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section6.1.1for reporting details).

6.5 Other Safety Concerns

Any significant worsening noted during interim or final physical examinations, electrocardiogram, X-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

7. DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- SAEs
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

Minutes from the disease center DSMB meetings are available to those who are unable to attend in person.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria Version 5.0. All study treatment associated AEs that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to participants or others (including AEs). DSMC progress reports, to include a summary of all serious AEs and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with participants in long-term (survival) follow-up or protocols in data analysis only, will be reviewed bi-annually.

Both the UPMC Hillman Cancer Center DSMC as well as the individual disease center

DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

8. STATISTICAL CONSIDERATIONS

This is a combination Phase I/II open label study of encorafenib +/- binimetinib + nivolumab + ipilimumab in participants with unresectable or metastatic BRAFV600-mutant melanoma. Two cohorts that differ by treatment (triple or quadruple therapy) will be enrolled in phase I. The recommended Phase II dosing regimen will be identified when following criteria are met:

- at least 10 patients have been evaluated on a regimen with DLT <60%

- the PI, Data and Safety Committee, William Gooding statistician, and interested PI's from participating institutions review all clinical data to determine the RP2R

Phase II will enroll two high risk cohorts differing by symptoms ((1) symptomatic brain metastases and 2) elevated liver enzymes with hepatic metastases) at the selected schedule and dose. The two cohorts will be investigated for safety and efficacy

8.1 Objectives

Primary Objective

- To nominate a recommended phase II regimen (RP2R) of triple or quadruple therapy with encorafenib +/- binimetinib + nivolumab and + ipilimumab in *BRAF* mutated, metastatic melanoma.

Secondary Objectives

- To estimate the RECIST response rate of triple or quadruple therapy in high risk populations of *BRAF* mutated, metastatic melanoma.
- To estimate the CNS clinical benefit rate (CBR, defined as complete response [CR] + partial response [PR] + stable disease [SD] >6 months) per RANO-MB criteria of triple or quadruple therapy in BRAF mutated, metastatic melanoma to the CNS
- To describe the toxicity, by CTCAEv5, of triple or quadruple therapy in *BRAF* mutated, metastatic melanoma
- To summarize the progression-free survival of triple or quadruple therapy in high risk populations of *BRAF* mutated, metastatic melanoma

Exploratory Objectives

6. To evaluate association between treatment response and baseline tumor mutational burden, changes in the tumor microenvironment (IFN associated gene expression), T cell clonality, and other biospecimens before and after triple or quadruple therapy.

8.2 Endpoints

The primary endpoint is the frequency of DLTs that are classified as either possibly, probably, or definitely related to study treatment according to NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0). DLTs are specified in section 4.5.2. Adverse events and DLTs will be compiled separately for each phase I cohort (triple and quadruple therapy). Any patient receiving at least one dose any of study drug will be evaluable for toxicity.

Secondary endpoints include the clinical response rates in the phase II cohorts by RECIST criteria with a lower one sided 80% confidence interval. The clinical benefit rate (rate of complete response, partial response or stable disease) will also be computed with a lower one-sided confidence bound for the symptomatic brain metastasis group. Both clinical response and clinical benefit rates will apply to evaluable patients defined as having completed 4 weeks of therapy.

8.3 Sample Size Considerations

Twelve patients will be evaluated in each phase I cohort; 30 patients will be evaluated for clinical response and clinical benefit in each phase II cohort. The total enrollment, in the absence of early stopping, is 84 patients (24 phase I / 60 phase II). Inference regarding safety of each cohort will depend upon the proportion of patients with DLT. An upper 90% confidence bound on these estimates can be used as a “rule out” criteria by the investigator such that any an unacceptably high DLT rate that is greater than the upper confidence interval may be ruled out.

Table 8.1 Upper Confidence Bounds for DLT Rate

Number of DLTs Among 12 Treated	Upper Bound of 90% Confidence Interval (%)
0	17
1	29
2	39
3	48
4	56
5	64
6	71
7	78
8	85
9	90
10	95
11	99
12	100

For example (see table 8.1), if none of 12 patients have a DLT one could claim the DLT rate is no higher than 17%, If 6 of 12 patients have treatment-related DLT the upper confidence bound is 71%, that is, the observed data (6/12) is consistent with a rate up to but not higher 71% . thus, one can rule out a DLT rate of 72% or greater.

Phase II cohorts will be used to (1) further refine the safety profile by re-estimating the DLT rate and (2) providing a preliminary estimate of efficacy.

While the phase II cohorts are accruing, The DLT rate will be continuously monitored and the trial will be suspended if the DLT rate appears to be too high. We assume, a priori, the DLT rate is thought to be 50%. A continuous monitoring program will be implemented to detect if this assumption is an underestimate such that the rate were actually 60% or higher. Beginning with the 5th patient, continuous Bayesian monitoring calculates the probability that the DLT rate is too high and provides a stopping rule. We assume a prior

DLT probability of 50% and that the prior probability has a beta distribution with parameters 1.5 and 1.5, producing a mean of .5. As each evaluable patient is evaluated for DLT, accumulated data is used to derive the posterior probability. If the posterior probability of a DLT rate of 60% is 50% or greater, the stopping rule in the table is triggered.

The following tables provides rules for suspending the trial if the actual rate is as high as 60%:

Table 8.2 DLTs Triggering Trial Suspension at 60%

Number of Evaluable Patients (Inclusive)	Suspend if there are This many DLTs	Number of Evaluable Patients (Inclusive)	Suspend if there are This many DLTs
0-4	------	17	11
5-6	4	18-19	12
7	5	20-21	13
8-9	6	22	14
12	8	23-24	15
13-14	9	25-26	16
15-16	10		

For example, if 6 DLTs are observed among the first 9 patients the stopping rule for 60% DLT is enacted to signal trial suspension. The accumulated toxicities will then be evaluated by the Data and Safety Monitoring Committee for further action.

Inference from a complete 30 patient expansion cohort.

If either of the expansion cohorts runs to completion without stopping due to excess toxicity, confidence intervals can be used for inference. First, to rule out excess toxicity, an upper 90% one-sided confidence intervals (table 8.3) provides an upper bound to the DLT rate (analogous to the phase I approach). Secondly, a lower 80% one-sided confidence bound (table 8.4) can be used to rule out an ineffective regimen. (A narrower, 80% bound is used here since we want a decision that is only suggestive rather than definitive).

Table 8.3 Upper Confidence Bounds for DLT Rate

Number of DLTs Among 30 Treated	Upper Bound of 90% Confidence Interval (%)
0	7%
1	12%
2	17%
3	21%
4	25%
5	29%
6	32%
7	36%
8	40%
9	43%

Table 8.4 Lower Confidence Bounds for Response

10	46%
11	50%
12	53%
13	57%
14	60%
15	63%

Number of Responses Among 30 Treated	Lower Bound of 80% Confidence Interval (%)
0	0%
1	0%
2	3%
3	5%
4	8%
5	10%
6	13%
7	16%
8	19%
9	22%
10	25%
11	28%
12	31%

Operating characteristics of possible decision rules in phase II

If a 30-patient phase II cohort is completed the following decisions are possible:

If 23 or more DLTs are observed among 30 patients the combination can be considered as too toxic and a DLT rate of 75% or greater cannot be ruled out. The probability of 23 or more DLTs with a 75% DLT rate is 92%. If the actual rate is 40% or less, the probability of 14 or fewer DLTs is 82%

Considering a preliminary assessment of efficacy, three or fewer objective responses will suggest lack of efficacy with a response rate no better than 5%. The probability of observing 3 or fewer responses when the actual rate is 5% is 94%. However, if the actual response rate is 20% the probability of 4 or more responses is 87%.

8.4 Proposed Analysis of Primary and Secondary Endpoints

Based on NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0), the term toxicity is defined as AEs that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. The number of occurrences of each event will be tabulated by event and grade. In addition, the total number of patients experiencing AEs over their course of treatment will be characterized by type of AE and grade. For this summary grades will be grouped into Grade I/II vs III/IV. In addition, the number of patients experiencing a dose-limiting toxicity as defined in table 4.5.2 will be compiled. Inferences regarding recommended phase II regimen and safety in both phase I and phase II cohorts will be made by calculating the proportion of patients with a dose-limiting toxicity with a one sided upper 90% confidence bound.

For the phase II cohorts, both the objective response rate (complete or partial response) / total evaluable) and the clinical benefit rate (complete or partial response + stable disease / total evaluable) will be computed with lower 80% confidence bounds. Evaluable patients are those who got at least one dose of ipi/nivo. Progression-free survival will be estimated with 90% two-sided confidence intervals for each phase II cohort. For progression-free survival, an event is defined as disease-progression or death.

For exploratory biomarker analyses, Spearman's correlation will be used for continuous variables such as Ki67+, T cell-inflamed GEP, pathway enrichment scores, TMB and others. Wilcoxon rank-sum test will be used to compare TMB between groups. Fisher's exact test will be used to compare the fraction of mutated and non-mutated samples per gene and R vs NR between T cell-inflamed and non-inflamed groups. Recognizing RNAseq values are relative, we created a frozen reference set from TCGA using our previous work and bring newly collected samples to the same baseline by comparing to this reference. We transform new data into the reference set using linear regression and determining per sample T cell-inflamed score (>8.24; T cell-inflamed, <6.43; non-T cell-inflamed and others intermediate). Benjamini-Hochberg procedure will be used to control FDR from multiple comparisons. All tests will be two-sided.

9. STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment. If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), AE tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for

the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s): ipilimumab. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development.

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

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APPENDIX 1 RECIST 1.1 AND IMMUNE RESPONSE CRITERIA

RECIST version 1.1* and irRC/irRECIST** will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

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Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009 Dec 1; 15(23):7412-20.

In addition, volumetric analysis will be explored by central review for response assessment.

APPENDIX 2 DOSE REDUCTION FOR ENCORAFENIB RELATED ADVERSE EVENTS

Action	**Recommended Dose**
First Dose Reduction	300mg (four 75mg capsules) PO once daily
Second Dose Reduction	225mg (three 75mg capsules) PO once daily
Third Dose Reduction	150mg (two 75mg capsules) PO once daily
Subsequent Modification	Discontinue

Severity of Adverse Event	**Dose Modification**
New Primary Malignancies	
Non-cutaneous RAS positive malignancies	Permanently Discontinue
Uveitis	
Grade 1–3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold encorafenib and binimetinib for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue.
Grade 4	Permanently discontinue encorafenib and binimetinib.
Other Eye Disorders (i.e., non-Uveitis Events	

Severity of Adverse Event	**Dose Modification**
Grade 1–2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution.
Grade 3	Interrupt dosing of encorafenib and binimetinib and refer patient to ophthalmologist within 7 days. 1. 1. If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. 2. If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution.
Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
QTc Prolongation	
QTcF > 500 ms and ≤ 60 ms increase from baseline	1st occurrence: • Temporarily interrupt dosing of encorafenib until QTcF < 500 ms. Then resume treatment at 1 reduced dose level of encorafenib. 2nd occurrence: • Temporarily interrupt dosing of encorafenib treatment until QTcF < 500 ms. Then resume treatment at 1 reduced dose level of encorafenib. 3rd occurrence: • Permanently discontinue encorafenib.
QTcF > 500 ms and > 60 ms increase from baseline	Permanently discontinue.

Severity of Adverse Event	**Dose Modification**
Dermatologic (Except Hand-foot Skin Reactions)	
Grade 2 Grade 3 Grade 4	If no improvement within 2 weeks, withhold until Grade 0–1. Resume at same dose if first occurrence or reduce dose if recurrent. Withhold until Grade 0–1. Resume at same dose if first occurrence or reduce dose if recurrent Permanently discontinue.
Hand-foot Skin Reaction (HFSR)/Palmar-plantar Erythrodysesthesia Syndrome (Dose Adjustment for Encorafenib ONLY)	
Grade 1	Maintain dose of encorafenib. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications.

Severity of Adverse Event	**Dose Modification**
Grade 2	1st occurrence: • Maintain dose of encorafenib and HFSR should be closely monitored. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. • If no improvement ≤ 14 days, interrupt dosing of encorafenib until resolved to Grade ≤ 1. Resume treatment with encorafenib at current dose level. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Additional occurrence: • Treatment with encorafenib may be maintained or interrupted based upon the Investigator's discretion. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. If interrupted dosing of encorafenib per Investigator's judgment, interrupt until resolved to Grade ≤ 1. Resume treatment with encorafenib at the same dose level or 1 reduced dose level based upon the Investigator's discretion.

Severity of Adverse Event	**Dose Modification**
Grade 3	1st or additional occurrence: • Interrupt dosing of encorafenib until resolved to Grade ≤ 1. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Reassess the patient weekly. Then resume treatment at one reduced dose level of encorafenib. • Consider referral to dermatologist and manage HFSR per dermatologist's recommendation. 3nd occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤ 1, decision to resume treatment with encorafenib at one reduced dose level or permanently discontinue encorafenib should be based upon the Investigator's discretion.
Nausea/Vomiting	
Grade 1–2 Grade 3	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure. Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level. Note: Interrupt dosing of encorafenib and binimetinib for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).

APPENDIX 3 DOSE REDUCTION FOR BINIMETINIB RELATED ADVERSE EVENTS

Action	**Recommended Dose**
First Dose Reduction	30mg PO BID
Subsequent Modification	Discontinue

Severity of Adverse Event	Dose Modification
Cardiomyopathy	
Asymptomatic, absolute decrease in LVEF of > 10% from baseline that is also below the LLN	Withhold binimetinib for up to 4 weeks, evaluate LVEF every 2 weeks. Resume binimetinib at a reduced dose if the following are present: • LVEF is at or above the LLN and • Absolute decrease from baseline is 10% or less and • Patient is asymptomatic. If LVEF does not recover within 4 weeks permanently discontinue binimetinib
Grade 3–4 (Symptomatic congestive heart failure or absolute decrease in LVEF of > 20% from baseline that is also below LLN)	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks.
Venous Thromboembolism	
Uncomplicated DVT or PE	Withhold binimetinib. • If improves to Grade 0–1, resume at a reduced dose. • If no improvement, permanently discontinue binimetinib.
Life Threatening PE	Permanently discontinue encorafenib and binimetinib.
Serous Retinopathy	

Severity of Adverse Event	Dose Modification
Symptomatic serous retinopathy/ Retinal pigment epithelial detachments Retinal Vein Occlusion (RVO)	Withhold binimetinib for up to 10 days. • If improves and becomes asymptomatic, resume at the same dose. • If not improved, resume at a lower dose level or permanently discontinue binimetinib
Any Grade	Permanently discontinue binimetinib.
Uveitis	
Grade 1–3 Grade 4	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold binimetinib and encorafenib for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue binimetinib Permanently Discontinue
Other Eye Disorders (i.e., Non-retinal Events, non-Uveitis Events)	

Severity of Adverse Event	Dose Modification
Grade 1–2 Grade 3 Grade 4	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution. Interrupt dosing of encorafenib and binimetinib and refer patient to ophthalmologist within 7 days. • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
Interstitial Lung Disease	
Grade 2 Grade 3 or Grade 4	Withhold binimetinib for up to 4 weeks. • If improved to Grade 0–1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue Permanently discontinue
Rhabdomyolysis or Creatine Phosphokinase (CPK) elevations	
Grade 4 asymptomatic CPK elevation or Any Grade CPK elevation with symptoms or with renal impairment	Withhold binimetinib dose for up to 4 weeks. • If improved to Grade 0–1 resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue binimetinib

Severity of Adverse Event	Dose Modification
Dermatologic	
Grade 2	If no improvement within 2 weeks, withhold until Grade 0–1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 3	Withhold until Grade 0–1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 4	Permanently discontinue
Nausea/Vomiting	
Grade 1–2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level. Note: Interrupt dosing of encorafenib and binimetinib for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
Grade 4	Permanently discontinue encorafenib and binimetinib
Other Adverse Reactions (including hemorrhage)	

Severity of Adverse Event	Dose Modification
Recurrent Grade 2 or First occurrence of any Grade 3	Withhold for up to 4 weeks. • If improves to Grade 0–1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue.
First occurrence any Grade 4	Permanently discontinue or withhold for up to 4 weeks. • If improves to Grade 0–1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue.
Recurrent Grade 3	Consider permanently discontinuing.
Recurrent Grade 4	Permanently discontinue participants

APPENDIX 4 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. (http://ctep.cancer.gov/reporting/ctc.html)

APPENDIX 5 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

5.1a MEASURABILITY OF TUMOR

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan -(CT scan slice thickness no greater than 5 mm)
- Brain lesions: Intracranial lesions can be measured only by gadolinium-enhanced MRI. For brain metastases less than or equal to 10 mm LD, an MRI scan slice thickness of 1 mm is necessary. Lesions greater than 10 mm LD may use a slice thickness of 5 mm.
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Special considerations regarding lesion measurability

Bone Lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above.

However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

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

5.2a METHOD OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination. CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Baseline Documentation of ‘Target’ and ‘Non-Target’ Lesions

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of 10 lesions total (a maximum of 2 lesions per organ systemically and up to 5 brain lesions) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements. Brain lesions are considered target lesions if the lesion is □0.5 cm and □3 cm in longest diameter. Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short

axis ≥ 10 mm but < 15 mm) should not be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or "multiple liver metastases").

5.3a EVALUATION OF TARGET LESIONS

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target lesions that become "too small to measure": All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

1. if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

2. if an extracranial lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

5.4a EVALUATION OF NON-TARGET LESIONS

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol. Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

The concept of progression of non-target disease requires additional explanation as follows:

- When the patient also has measurable disease: To achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- When the patient has only non-measurable disease: To achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be

applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point.

5.5a NEW LESIONS

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

5.6a TIME POINT RESPONSE

A response assessment should occur at each time point specified in the protocol.

For patients who have measurable disease at baseline the table below provides a summary of the overall response status calculation at each time point.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	NO	CR

CR	Non-CR/non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or Not Evaluated	No	PR
SD	Non-PD or Not Evaluated	No	SD
Not all evaluated	Non-PD	No	Not Evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

5.7a MISSING ASSESSMENTS AND INEVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

5.8a BEST OVERALL RESPONSE: ALL TIMEPOINTS

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this circumstance, the best overall response can be interpreted as below:

Overall Response First Timepoint	**Overall Response Subsequent Timepoint**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD, or PR
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD

CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

5.9a SPECIAL NOTES ON RESPONSE ASSESSMENT

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the case report form (CRF). Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. Ifat the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

5.10a DURATION OF RESPONSE

Duration of overall response: The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met

for CR until the first date that recurrent disease is objectively documented. Duration of stable disease: Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

5.11a LESIONS THAT DISAPPEAR AND REAPPEAR

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumor had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently "disappeared" single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually "disappear" but are not visualized because they are beyond the resolving power of the imaging modality employed.

5.12a USE OF FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. Confirmatory CT is recommended.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

APPENDIX 6 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to nivolumab/urelumab or nivolumab/cabiralizumab.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- Pneumonitis:

Pulmonary Adverse Event Management Algorithm

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

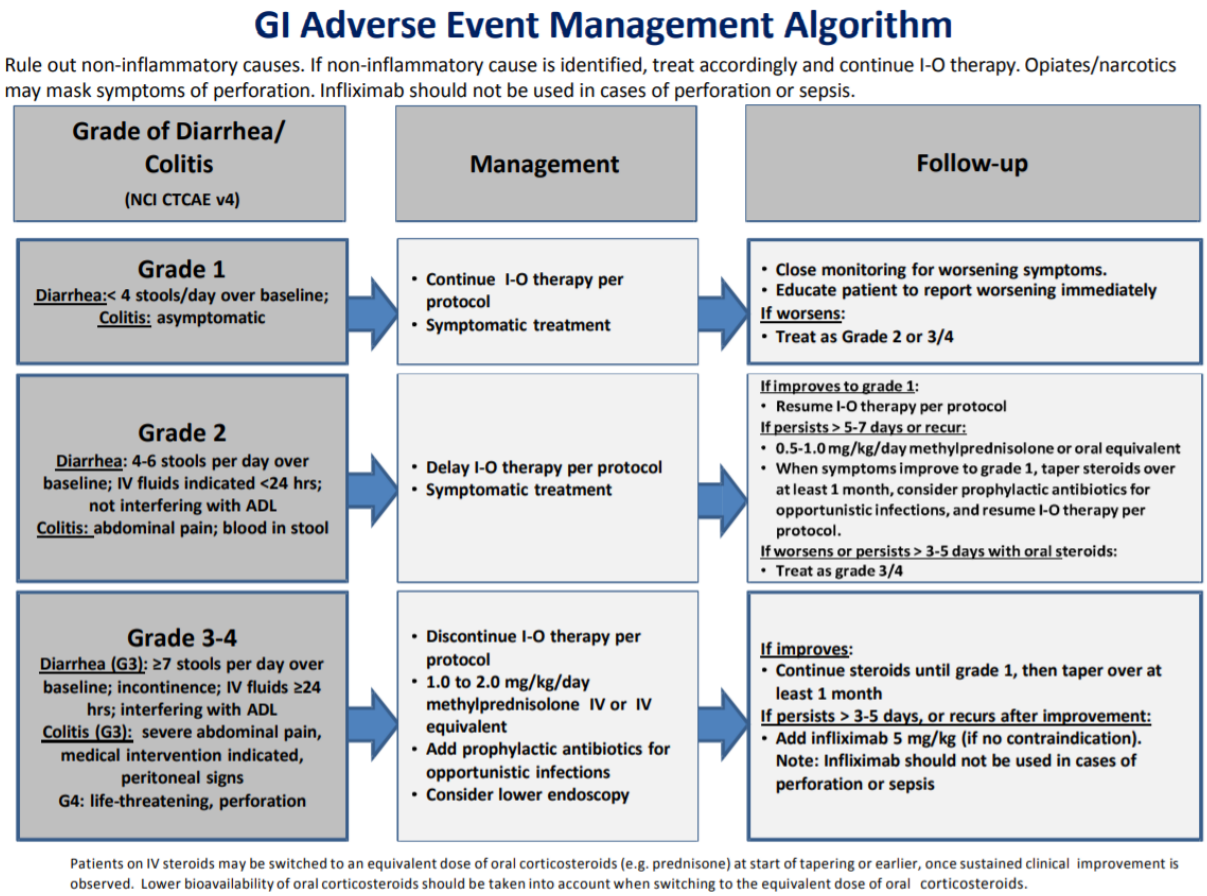
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms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

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

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3–4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- Diarrhea/Colitis:



Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

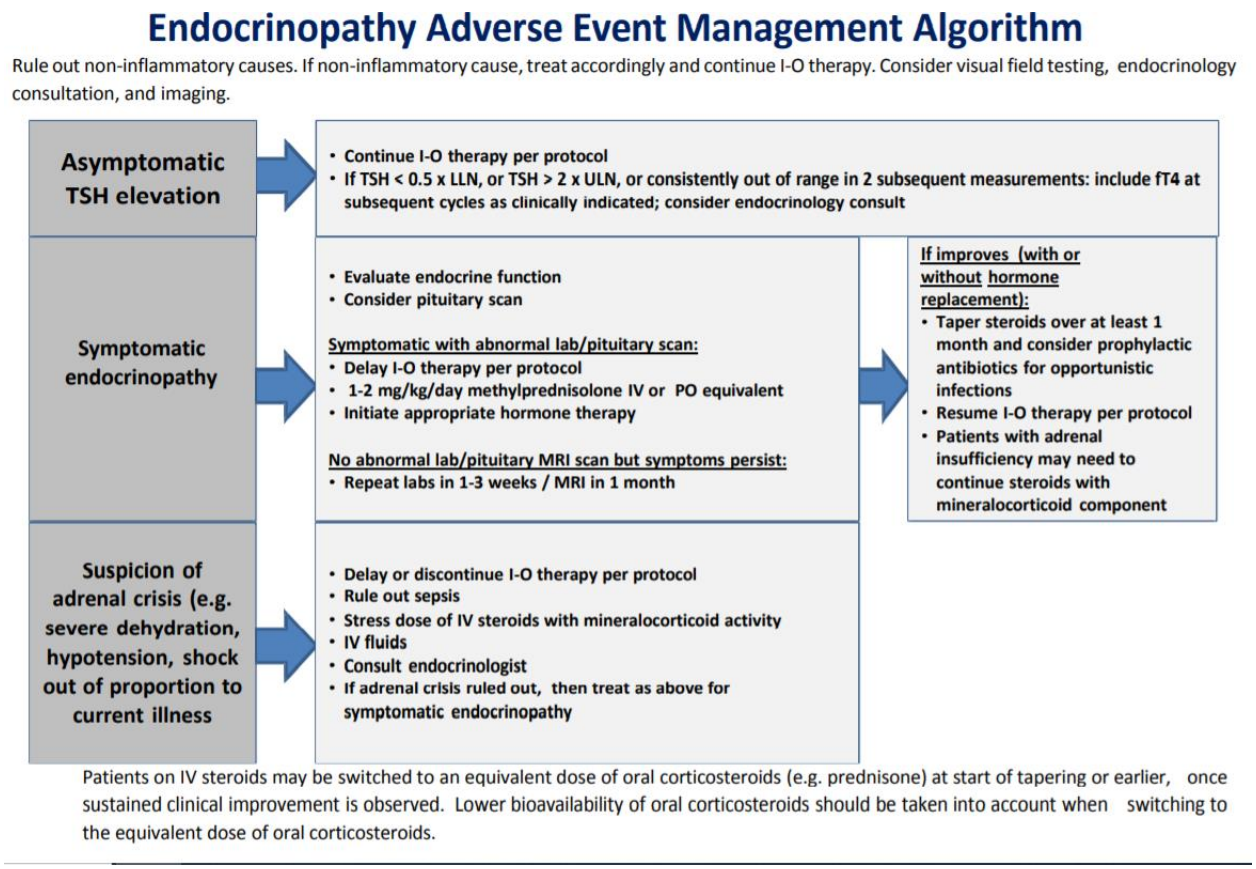
- All participants who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.

- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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



- For **T1DM** or **Grade 3–4** Hyperglycemia

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

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

Thyroid disorders can occur at any time during treatment. Monitor participants for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

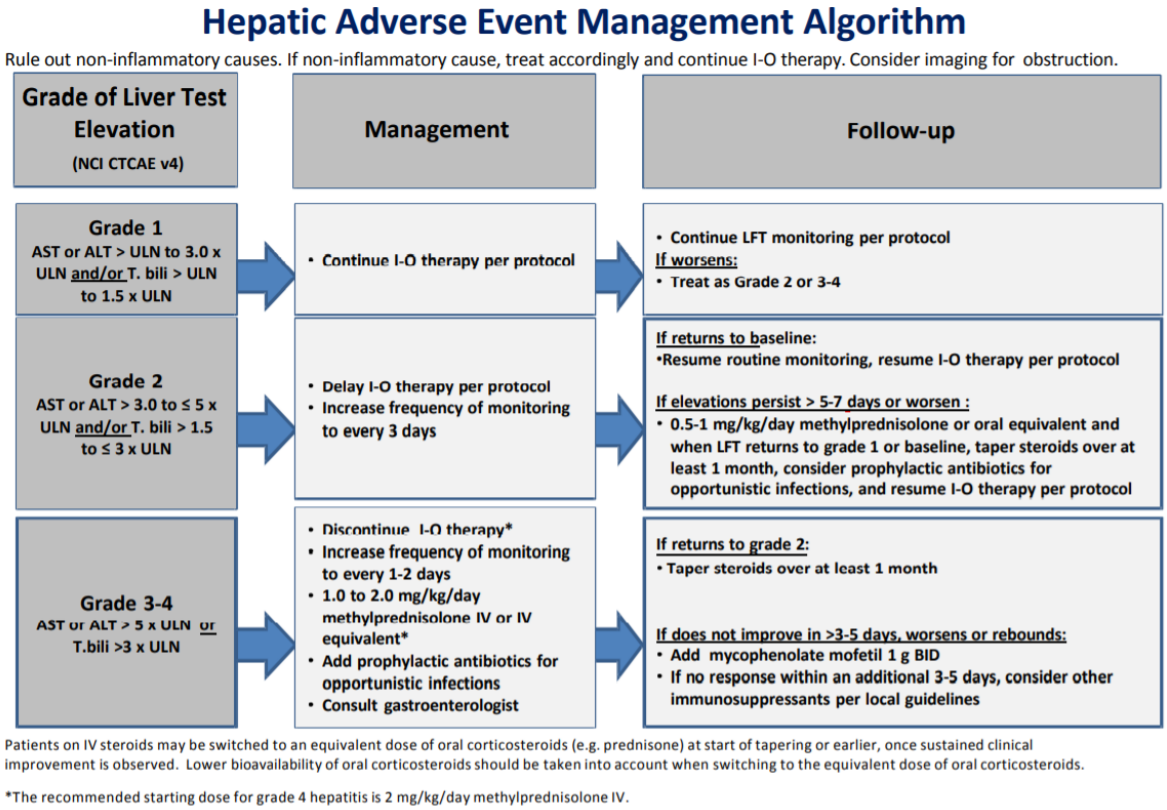
- **Grade 2** hyperthyroidism events (and **Grade 2–4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

- **Grade 3-4** hyperthyroidism

  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- Hepatic:



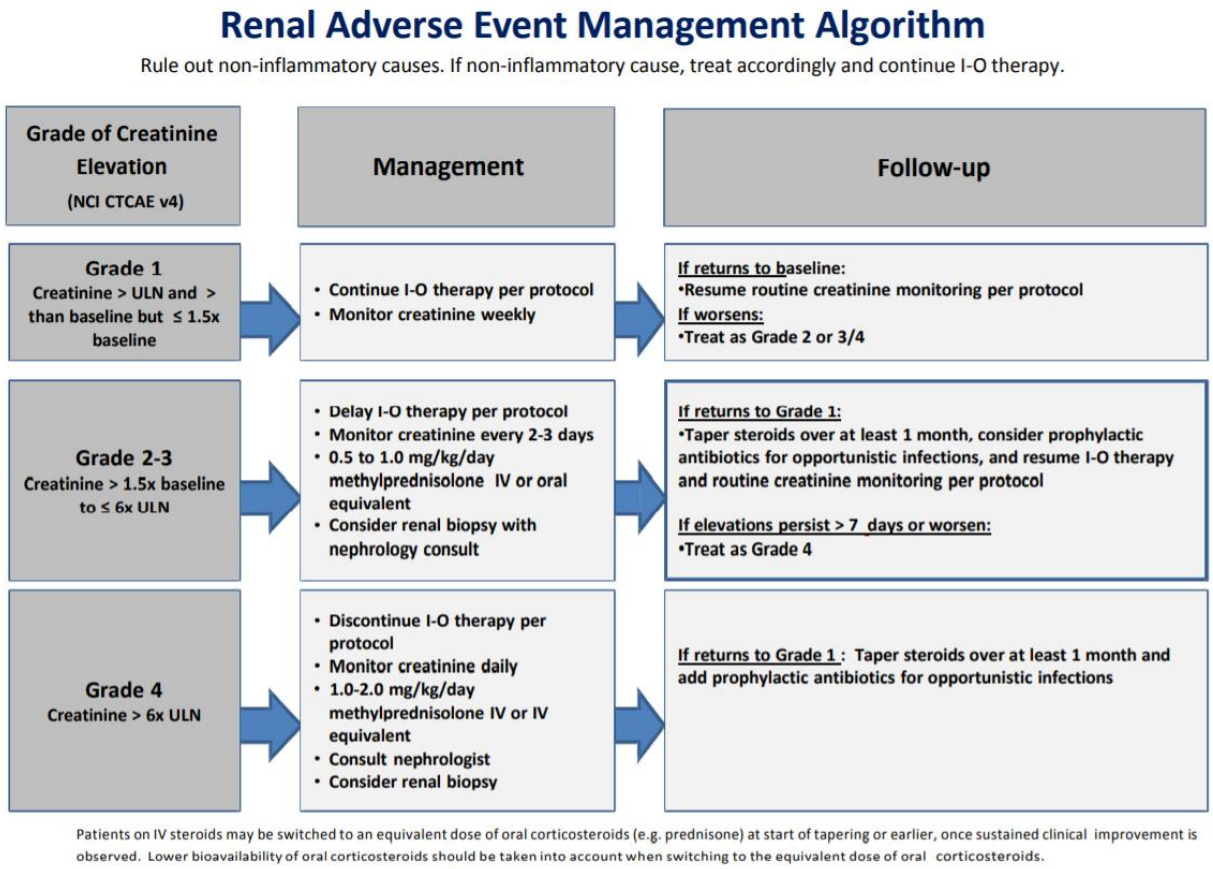
- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

  - Treat with IV or oral corticosteroids

- For **Grade 3–4** events, treat with intravenous corticosteroids for 24 to 48 hours.

- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

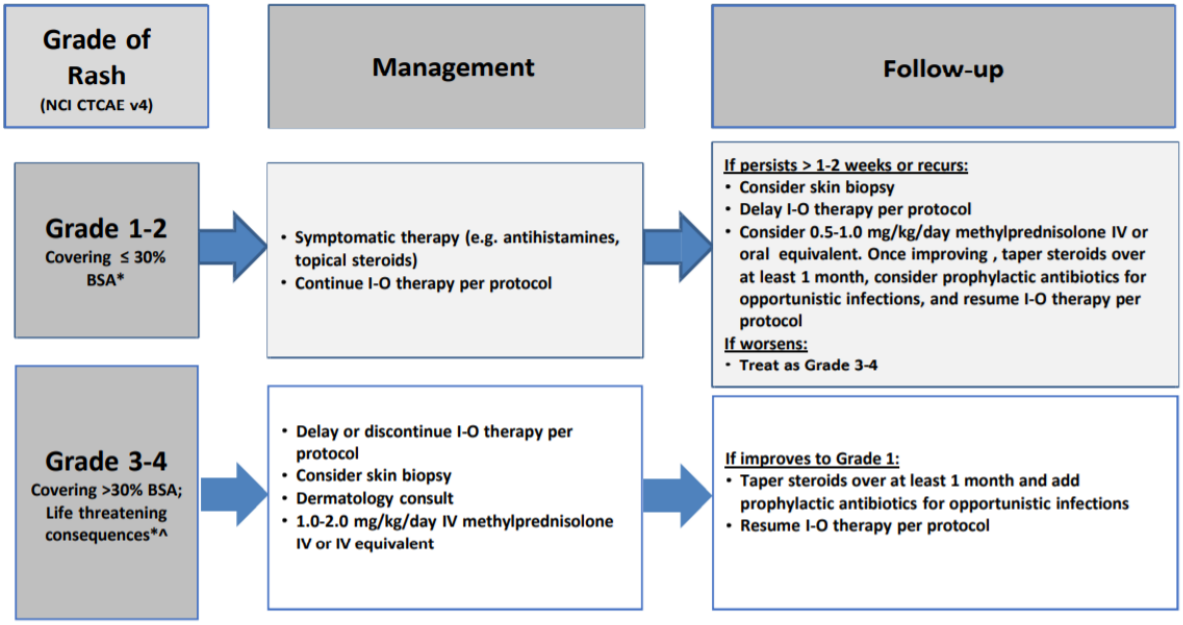
- Renal Failure or Nephritis:



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

Skin Adverse Event Management Algorithm

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



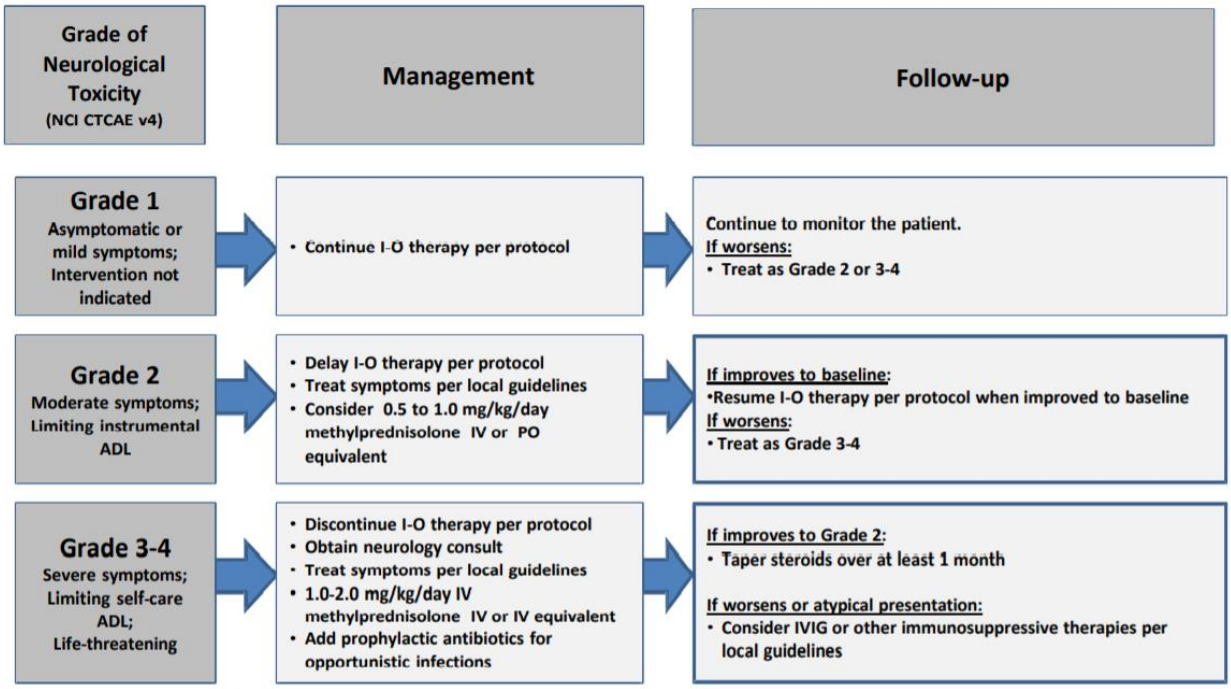
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

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



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

Myocarditis Adverse Event Management Algorithm

Grade of Myocarditis (NCI CTCAE v4)	Management	Follow-up

Grade 2
Symptoms with mild to moderate activity or exertion
	• Delay I-O therapy; hospitalization with cardiac monitoring
	• Urgent cardiology consultation for evaluation and management
	  ○ Troponin and BNP
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	• Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
		• If worsens, intensify treatment according to grade
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up
		• Retreatment may be considered after recovery and completion of steroid taper

Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy
	• Hospitalize to intensive cardiac monitoring
	• Cardiac evaluation to include:
	  – Troponin and BNP monitoring
	  – ECG ± continuous cardiac monitoring
	  – Echocardiogram
	  – Cardiac MRI
	  – Myocardial biopsy if feasible
	• Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Consider adding a second immunosuppressive agent
	Additionally, for Grade 4:
	• Hospitalize/transfer to institution with expertise in intensive cardiac monitoring
	• Consider ATG as second agent given its immediate effect
		• If no improvement, consider additional immunosuppression
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessments and cardiology follow-up

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging