Official Protocol Title:	A Phase I/II Study to Assess the Safety and Efficacy of MK-3475 in Combination with Trametinib and Dabrafenib in Subjects with Advanced Melanoma
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TITLE:

A Phase I/II Study to Assess the Safety and Efficacy of MK-3475 in Combination with Trametinib and Dabrafenib in Subjects with Advanced Melanoma

IND NUMBER: 110,080

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 6	05-DEC-2019	Revised to add dose modification requirements for cases of severe cutaneous adverse reactions (SCARs) that have been reported during treatment with dabrafenib in combination with trametinib.
Amendment 5	21-MAR-2019	Enrollment for Part 5 Dose expansion phase removed from the protocol in Amendment 05. Updated language for contraception requirements and rash management.
Amendment 4	18-MAY-2018	Update protocol operation after the final analysis of Part 3 including unblinding
Amendment 3	13-DEC-2017	To implement a safety update regarding myocarditis, and update for compliance with latest dose modification guidance; To increase clarity and ensure alignment with study specific dose modification guidelines; To ensure the collection of survivor information throughout and following study participation regardless of discontinuation of treatment

Document	Date of Issue	Overall Rationale
Amendment 2	4-OCT-2016	Additional dose levels were added, as a tolerable dose level for (MK+T) was not identified in BRAF wild-type melanoma subjects in Part 1 of the study.
Amendment 1	10-NOV-2014	Implementation of the monotherapy dose/schedule for MK-3475 at 2 mg/kg Q3W
Original Protocol	31-JAN-2014	Not applicable

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.6.1.1.4	General Guidelines for Clinically Significant Toxicities	Table 17 - Added language and footnote related to Severe Cutaneous Adverse Reactions	Alignment with updated Investigator Brochure for dabrafenib and trametinib combination therapy
5.6.1.1.10.4	Severe Cutaneous Adverse Reactions	Added language related to Severe Cutaneous Adverse Reactions	Alignment with updated Investigator Brochure for dabrafenib and trametinib combination therapy
12.10	List of Abbreviations	Added SCARs definition	Update Abbreviations Table

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase I Study of MK-3475 in Combination with Trametinib and Dabrafenib
Trial Phase	I/II
Clinical Indication	The treatment of subjects with advanced or metastatic melanoma in all parts of the trial. Additionally, the treatment of subjects with advanced (unresectable and/or metastatic) solid tumors in Parts 4 and 5 dose escalation and confirmation only.
Trial Type	Interventional
Type of control	No treatment control in Parts 1, 2, 4, and 5. Placebo (standard, active therapy with a placebo add-on) in Part 3.
Route of administration	Intravenous Pembrolizumab (MK-3475) Oral (trametinib) Oral (dabrafenib)
Trial Blinding	Parts 1, 2, 4, 5: Unblinded Open Label Part 3: Double-blind
Treatment Groups	In Part 1 (3+3 design), a cohort of 3 or 6 subjects with BRAF mutant [V600 E or K] melanoma will receive pembrolizumab 2 mg/kg q3weeks in combination with trametinib 2 mg QD and dabrafenib 150 mg BID. Additionally in Part 1 (3+3 design), a cohort of 3 or 6 subjects with BRAF wild type [without V600 E or K] melanoma will receive pembrolizumab 2 mg/kg q3weeks in combination with trametinib 2 mg QD. Approximately 12 subjects will be enrolled in Part 1 (~6 for the pembrolizumab + dabrafenib + trametinib (MK+D+T) combination therapy and ~6 for the pembrolizumab + trametinib (MK+T) combination therapy). In Part 1, and only in the event the (MK+D+T) combination therapy is not tolerable, a cohort of 3 or 6 subjects with BRAF mutant [V600 E] melanoma will receive pembrolizumab 2 mg/kg q3weeks in combination with dabrafenib 150 mg BID (3+3 design). Approximately 6 subjects will be enrolled for the pembrolizumab + dabrafenib (MK+D) combination therapy, but only if the (MK+D+T) combination therapy is not tolerable. Part 2 will expand cohort(s) from Part 1 for dose confirmation. Approximately 45 subjects will be enrolled in Part 2, ~11 for (MK+D+T) and ~34 for (MK+T).

	In Part 3, approximately 120 subjects with BRAF mutant [V600 E or K] melanoma will be randomized 1:1 to either: (a) pembrolizumab 2 mg/kg q3weeks, trametinib 2 mg QD, dabrafenib 150 mg BID, or, (b) placebo (saline IV), trametinib 2 mg QD, dabrafenib 150 mg BID. Note: The triplet dose combination of all treatments used in Part 3 will be confirmed by Parts 1 and 2 of the study. In Part 4 (3+3 design), a cohort of 3 or 6 subjects with BRAF wild type [without V600E or K] melanoma or solid tumors [irrespective of BRAF status] will receive pembrolizumab 200 mg q3weeks in combination with either trametinib 2 mg QD or 1.5 mg QD after receiving a 2-week or 4-week monotherapy run-in with trametinib in either a concurrent or intermittent dosing regimen. Approximately 24 subjects total are estimated for enrollment in Part 4 for the (MK+T) combination therapy, ~6-24 subjects for the concurrent dosing regimen and ~6-18 subjects for the intermittent dosing regimen. Part 5 will confirm the dose(s) identified in Part 4 in BRAF wild type [without V600E or K] melanoma or solid tumors [irrespective of BRAF status] in subjects.
Number of trial subjects	Approximately 77 subjects will be enrolled in the investigation of the (MK+D+T) combination therapy (this total includes 17 subjects from specific arms in Parts 1 and 2, and 60 subjects in the blinded active (MK+D+T) arm from Part 3). Additionally, 60 subjects will receive PBO (saline IV) + (D+T) in Part 3 of the study. ~ Approximately 50 subjects will be enrolled in the investigation of the (MK+T) combination therapy (Parts 1, 2, 4, and 5). In the overall study, ~Approximately 190 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 48 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of up to 28 days, eligible subjects will receive assigned treatment on Day 1 of the dosing cycle. Treatment with pembrolizumab, trametinib, and/or dabrafenib will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons or completion of 24 months of trial treatment. In Parts 4 and 5 treatment with pembrolizumab and trametinib will discontinue at 24 months. pembrolizumab treated subjects who attain a complete response after at least 6 months of study treatment may consider stopping pembrolizumab treatment (at the discretion of the investigator after receiving at least two doses beyond the initial determination of complete response), while continuing on treatment with trametinib and/or dabrafenib. After the end of all treatments, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects will have post-treatment follow-up for disease status, including initiating a non-study

	cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up. Once the subject has achieved the study objective or the study has ended, the subject is discontinued from this study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.

Randomization Ratio	Part 3: 1:1

A list of abbreviations used in this document can be found in Section 12.10.

2.0 TRIAL DESIGN

2.1 Trial Design

This study (KEYNOTE 022) is a multi-center, worldwide, Phase I/II 5-part trial of intravenous (IV) pembrolizumab (MK-3475) in combination with oral dabrafenib and/or trametinib in subjects with advanced or metastatic melanoma (or solid tumors in Parts 4 and 5) to be conducted in conformance with Good Clinical Practices. Approximately 190 subjects evaluable for safety, tolerability, and efficacy will be enrolled in the overall study. The final number will depend on empirical safety data and observed Dose Limiting Toxicities (DLTs).

Due to the various combinations of treatment evaluated in the 5 parts of this study, the following abbreviations will be utilized to clarify the combinations (Table 1) when discussed within protocol text.

Table 1 Study Treatment Combinations

Drug Combination	Abbreviation	When Combination is Active in Study
MK-3475 + dabrafenib + trametinib	(MK+D+T)	Parts 1, 2, & 3
MK-3475 + dabrafenib	(MK+D)	Activated only if triplet combination does not move forward in Parts 1 & 2
MK-3475 + trametinib	(MK+T)	Parts 1, 2, 4 & 5
Placebo (saline IV) + dabrafenib + trametinib	(PBO+D+T)	Part 3 only

Part 1 is a nonrandomized, multi-site, open-label portion of the study using a traditional 3+3 design to evaluate safety, tolerability, and dosing of pembrolizumab in combination with dabrafenib and trametinib (MK+D+T) in BRAF mutation-positive (V600 E or K) melanoma subjects. A cohort of 3-6 subjects will be enrolled with the dose combination listed in Table 2 for the duration of the study. Dose modifications based upon observed toxicities and in accordance with the criteria outlined in the protocol are allowed but may meet DLT criteria if made during the DLT evaluation period.

Table 2 Parts 1 and 2: (MK+D+T) Study Treatment Arm

Dose Level	Pembrolizumab	Dabrafenib	Trametinib
1	2 mg/kg Q3W	150 mg BID	2 mg QD

Approximately 6 subjects (range 3-12) will be enrolled in the (MK+D+T) combination dose evaluation portion of the study. Subjects will be evaluated for DLTs for 6 weeks. Subjects who withdraw from the study for reasons other than DLT or subjects who are not evaluable for DLTs before the completion of 6 weeks of treatment may be replaced. See Section 5.9 for additional information.

Additionally, in Part 1, dosing of pembrolizumab in combination with trametinib only (MK+T) will be explored in BRAF mutation-negative (without V600 E or K) melanoma subjects, to evaluate safety, tolerability, and efficacy of (MK+T) in Part 2 (Table 3) in this population. In the event that DL1 for (MK+T) in Part 1 is not tolerable, the Dose Level Minus (-1) option (DL-1) will be selected and opened as listed in Table 3. A cohort of 3-6 subjects will be enrolled sequentially at the (MK+T) dose combination. Approximately 6 subjects (range 3-12) will be enrolled in the (MK+T) combination dose evaluation portion of the study, resulting in a total of ~12 subjects overall in Part 1 of the study. In the event that DL-1 for (MK+T) is not tolerable, additional dosing level combination(s) will be further explored in Parts 4 and 5.

Table 3 Parts 1 and 2: (MK+T) Study Treatment Arm(s)

Dose Level	Pembrolizumab	Trametinib
1	2 mg/kg Q3W	2 mg QD
DL -1	2 mg/kg Q3W	1.5 mg QD

In the event that Dose Level 1 (DL1) for (MK+D+T) in Part 1 is not tolerable, a Dose Level Minus (-1) option (DL-1) will be selected and opened (a single DL-1 will be chosen from the options listed in Table 5 based on clinically observed toxicity; e.g. pyrexia attributed to dabrafenib would open DL-1b, or rash due to trametinib would open DL-1a). In addition, if one of the DL-1 options for MK+D+T is opened, the back-up combination of pembrolizumab and dabrafenib 150 mg BID (MK+D) will be explored in Part 1 (and Part 2 if the (MK+D+T) combination DL-1 is not tolerated) in BRAF mutation-positive (V600 E) melanoma subjects. Approximately 6 subjects will be enrolled if this portion of the study must be activated. A cohort of 3-6 subjects will be enrolled sequentially at the dose combination listed in Table 4. Additional lower doses of this combination (MK+D) may be enrolled based on the tolerability of the DL1 in Part 1 (and/or Part 2 if necessary). Please refer to Section 5.2.4.1 for the rules utilized in determining when DLTs will trigger enrollment of patients at DL-1.

In the event that DL-1 for (MK+D+T) in Part 1 or Part 2 is not tolerable, this combination will not be further explored in Part 3.

Table 4 Parts 1 and 2: (MK+D) Study Treatment Arm

Dose Level	Pembrolizumab	Dabrafenib
1	2 mg/kg Q3W	150 mg BID

Table 5 Parts 1 and 2: (MK+D+T) Dose Level Minus (-1) Options

For kinase-inhibitor related AEs:

Dose Levels	Pembrolizumab	Dabrafenib	Trametinib
DL -1a	2 mg/kg Q3W	150 mg BID	1.5 mg QD
DL -1b	2 mg/kg Q3W	100 mg BID	2 mg QD
DL -1c	2 mg/kg Q3W	100 mg BID	1.5 mg QD

For immune-related AEs:

Dose Levels	Pembrolizumab	Dabrafenib	Trametinib
DL -1	1 mg/kg Q3W	150 mg BID	2 mg QD

Unclear cause of AEs:

Dose Levels	Pembrolizumab	Dabrafenib	Trametinib
DL -1	1 mg/kg Q3W	100 mg BID	1.5 mg QD

Part 2 is a nonrandomized, multi-site, open-label portion of the study using an expansion cohort to further evaluate safety and confirm dose of (MK+D+T). Approximately 11 subjects will be enrolled in the Part 2 (MK+D+T) dose confirmation.

Also in Part 2, an expansion cohort will be used to further evaluate safety and preliminary efficacy in the (MK+T) combination. After 14 subjects are enrolled on the (MK+T) dose confirmed in Part 2 (including subjects from both Parts 1 and 2), 26 additional subjects will be enrolled at the same dose, resulting in a total of 40 patients in Parts 1 and 2 on the (MK+T) combination. Approximately 34 subjects will be enrolled in (MK+T) Part 2 of the study. In Part 2, for the (MK+D+T) and (MK+T) cohorts, ~a total of ~45 subjects will be enrolled. In the event that DL1 and DL-1 for (MK+T) in Part 1 is not tolerable, Part 2 for this combination will not open, and instead the combination will be further explored in Parts 4 and 5.

Part 3 is a randomized (1:1), active-controlled, multi-site, two-arm study of the confirmed dose of the triplet combination (MK+D+T) versus placebo in combination with D+T (PBO+D+T). Approximately 120 subjects will be enrolled in Part 3. Subjects will be stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs. 1) and Lactate Dehydrogenase (LDH) level (>1.1 x ULN vs. ≤1.1 x ULN).

Part 4 is a nonrandomized, multi-site, open-label portion of the study using a traditional 3+3 design to evaluate pembrolizumab in combination with trametinib only (MK+T) in BRAF mutation-negative (without V600 E or K) melanoma or solid tumor [irrespective of BRAF status] subjects. A cohort of 3-6 subjects will be enrolled in the initial combination (DL1) proposed for both the concurrent and intermittent dosing regimens in Table 6 and Table 7 . It should be noted that the concurrent and intermittent dosing regimens in these tables have been named such based on the *initial* proposed dose within each regimen: cDL1 and iDL1, respectively. There is, in fact, a potential for intermittent dosing within the concurrent dosing regimen table (Table 6) if, and only if, dose(s) must de-escalate (e.g., cDL1 is not tolerated). The choice of the dosing regimen for a new subject will be determined using 1:1 randomization whenever both regimens are opened for enrollment. Dose escalation or de-escalation will occur for each dosing regimen as outlined in Table 6 and Table 7, following the algorithms provided in each respective table. The escalation and de-escalation for (MK+T) in the concurrent and intermittent dosing regimens will occur simultaneously in Part 4 until a dose has been identified for each regimen. Subjects will be evaluated for DLTs for a period of 6 weeks, commencing with the initial dose of pembrolizumab in Cycle 1. Subjects who withdraw from the study for reasons other than DLT or subjects who are not evaluable for DLTs before the completion of 6 weeks of combination treatment may be replaced. See Section 5.9 for additional information.

Dose modifications based upon observed toxicities and in accordance with the criteria outlined in the protocol are allowed but may meet DLT criteria if made during the DLT evaluation period. Approximately 24 subjects are estimated for enrollment in the (MK+T) combination dose evaluation in Part 4, with anywhere from 6-24 subjects for the concurrent dosing regimen and 6-18 subjects for the intermittent dosing regimen.

Upon identification of a preliminary maximum tolerated dose for both the concurrent and intermittent dosing regimens, each regimen will proceed to Part 5 for dose confirmation using a modified TPI (mTPI) design. In the event that tolerable concurrent and intermittent dosing regimens are identified, the Sponsor may choose to pursue one or both for dose confirmation in Part 5. For each regimen, a total of 14 subjects evaluable for DLT will be treated with the identified dose across Part 4 and 5 by the end of the dose confirmation. In the event that a tolerable dose for either dosing regimen of (MK+T) cannot be identified in Part 4, that particular dosing regimen will not be further explored in Part 5.

In Part 5, the expansion cohort(s) will be used to further evaluate safety and preliminary efficacy in the (MK+T) combination(s). Dose expansion requires only BRAF wild type [without V600E or K] melanoma to be enrolled. During the study it was found that the accrual of BRAF wild type melanoma subjects was limited, reflecting recent changes in the standard of care for these patients which include checkpoint inhibition in combination with

other drugs not compatible with this study design. The expansion cohort will not be pursued further following the completion of Part 5 dose confirmation.

Table 6 Parts 4 and 5: Concurrent (MK+T) Study Treatment Arm(s) and Escalation/De-Escalation Algorithm

Dose Level	Trametinib Monotherapy Run-In	Pembrolizumab	Trametinib	Dosing Regimen
cDL3	2 Weeks 2 mg QD	200 mg Q3W	2 mg QD	Concurrent dosing of pembrolizumab and trametinib starting at Week 3
cDL2b	4 Weeks 2 mg QD	200 mg Q3W	2 mg QD	Concurrent dosing of pembrolizumab and trametinib starting at Week 5
cDL2a	2 Weeks 1.5 mg QD	200 mg Q3W	1.5 mg QD	Concurrent dosing of pembrolizumab and trametinib starting at Week 3
cDL1	4 Weeks 1.5 mg QD	200 mg Q3W	1.5 mg QD	Concurrent dosing of pembrolizumab and trametinib starting at Week 5
cDL-1b	4 Weeks 2 mg QD	200 mg Q3W	2 mg QD	pembrolizumab dosing starting at Week 5 with intermittent 2 weeks OFF trametinib/2 weeks ON trametinib
cDL-1a	4 Weeks 1.5 mg QD	200 mg Q3W	1.5 mg QD	pembrolizumab dosing starting at Week 5 with intermittent 2 weeks OFF trametinib/2 weeks ON trametinib

Start at cDL1.
If cDL1 is tolerated, test cDL2a and cDL2b concurrently.
If cDL2a and cDL2b both tolerated, test cDL3.
If cDL3 is tolerated, preliminary MTD is cDL3.
If cDL3 is not tolerated, preliminary MTD is cDL2a.
If cDL2a is tolerated and cDL2b is not tolerated, preliminary MTD is cDL2a.
If cDL2b is tolerated and cDL2a is not tolerated, preliminary MTD is cDL2b.
If cDL2a and cDL2b both not tolerated, preliminary MTD is cDL1.
If cDL1 is not tolerated, test cDL-1a.
If cDL-1a is tolerated, test cDL-1b.
If cDL-1b is tolerated, preliminary MTD is cDL-1b.
If cDL-1b is not tolerated, preliminary MTD is cDL-1a.
If cDL-1a is not tolerated, no tolerable dose for the regimen is identified.

Table 7 Parts 4 and 5: Intermittent (MK+T) Study Treatment Arm(s) and Escalation/De-Escalation Algorithm

Dose Level	Trametinib Monotherapy Run-In	Pembrolizumab	Trametinib	Dosing Regimen
iDL2	2 Weeks 2 mg QD	200 mg Q3W	2 mg QD	pembrolizumab dosing starting at Week 3 with intermittent 1 week OFF trametinib/2 weeks ON trametinib
iDL1	2 Weeks 1.5 mg QD	200 mg Q3W	1.5 mg QD	pembrolizumab dosing starting at Week 3 with intermittent 1 week OFF trametinib/2 weeks ON trametinib
iDL-1b	2 Weeks 2 mg QD	200 mg Q3W	2 mg QD	pembrolizumab dosing starting at Week 3 with intermittent 2 weeks OFF trametinib/2 weeks ON trametinib
iDL-1a	2 Weeks 1.5 mg QD	200 mg Q3W	1.5 mg QD	pembrolizumab dosing starting at Week 3 with intermittent 2 weeks OFF trametinib/2 weeks ON trametinib
Start at iDL1. If iDL1 is tolerated, test iDL2. If iDL2 is tolerated, preliminary MTD is iDL2. If iDL2 is not tolerated, preliminary MTD is iDL1. If iDL1 is not tolerated, test iDL-1a. If iDL-1a is tolerated, test iDL-1b. If iDL-1b is tolerated, preliminary MTD is iDL-1b. If iDL-1b is not tolerated, preliminary MTD is iDL-1a. If iDL-1a is not tolerated, no tolerable dose for the regimen is identified.				

After radiological assessment at screening, the first radiological assessment will be performed following 2 cycles of study treatment (±7 days), unless there is clinical indication (based on Investigator's assessment) warranting earlier radiologic imaging. The same imaging technique as used at screening should be used throughout the study. After the first on-treatment imaging assessment, subjects will be evaluated every six (6) weeks up to Month 18 with radiographic imaging to assess response to treatment. Following Month 18, imaging assessment will occur every twelve (12) weeks. Investigators will make all treatment-based decisions using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Imaging from Parts 1, 2, 4, and 5 for (MK+D+T) and (MK+T) and Part 3 (non-inclusive of IA) will be investigator-assessed using RECIST 1.1 for determination of endpoints (including ordinal response), but also collected and held, and may be centrally-read later by independent radiologists, retrospectively. Imaging for the first 80 patients up to Week 36 in Part 3 (subjects included in the interim analysis) will be centrally-read using RECIST 1.1 for determination of efficacy endpoints. Refer to Section 8.2.3 for additional information on endpoints. RECIST 1.1 will be adapted as described in Section 4.2.3.1 due to the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare), and this

adapted RECIST will be used by the sites for treatment decisions. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. In general, study treatment will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. Subjects who attain an investigator-determined confirmed complete response (CR) per RECIST after at least 6 months of pembrolizumab treatment could potentially stop trial treatment of pembrolizumab and continue treatment with trametinib and/or dabrafenib, in accordance with standard care, until disease progression or the end of study, whichever comes first.

Subjects in Part 3 who remain on study treatment with pembrolizumab and who have not progressed after 24 months will discontinue pembrolizumab treatment and may continue treatment with trametinib and/or dabrafenib, off study and in accordance with standard care. Please refer to Section 5.2.5 and Section 7.1.5.4 for additional details.

Subjects in Parts 4 and 5 who have not progressed after 24 months will discontinue pembrolizumab and trametinib treatment. They may continue treatment with pembrolizumab or trametinib off study and in accordance with standard of care. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects who stop study treatment for reasons other than disease progression should continue to have disease assessments until progression is documented. Subjects will have post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up.

A primary objective of the trial is to assess safety and tolerability of (MK+D+T) and confirm the maximum tolerated dose (MTD) or maximum administered dose (MAD) in subjects with advanced melanoma with BRAF V600 E or K mutations, and the primary safety analysis will include descriptive tables that summarize the number and percentage of subjects who experience dose limiting toxicity (DLT) at each dose level for (MK+D+T). Safety and tolerability will also be assessed for (MK+T) therapy in subjects with advanced melanoma without BRAF V600 E or K mutations and solid tumors [irrespective of BRAF status]. As a back-up strategy in the event Dose Level 1 (DL1) of (MK+D+T) is not tolerable, safety and tolerability will also be evaluated for (MK+D) in subjects with advanced melanoma with BRAF V600 E mutations.

A primary efficacy evaluation of (MK+T) in Part 2, Part 4 and Part 5 will include the analysis of the overall response rate (ORR) per RECIST 1.1 by investigator-assessment in subjects with solid tumors or advanced melanoma without BRAF V600 mutations taking (MK+T), in order to establish whether this combination therapy is active and warrants further investigation. An efficacy evaluation of (MK+D+T) with respect to progression-free survival (PFS) will also be performed.

The database will be locked for (MK+D+T) analysis of Parts 1 and 2 approximately six months after the enrollment of the last (MK+D+T) subject in Part 2. The database will be locked for (MK+T) analysis of Parts 1 and 2, or, Part 4 and 5, approximately six months after the enrollment of the last (MK+T) subject in Part 2 or Part 5. Part 3 will not be unblinded when these analyses take place. Details are described in Section 8.2.1.

Key pharmacokinetic (PK) properties of (MK+D+T) and (MK+T) will be investigated as a secondary objective.

In Part 3, the primary objective of the randomized, double-blind Phase II portion of the study is to compare the progression free survival (PFS) of (MK+D+T) to (PBO+D+T) in subjects with BRAF V600 E or K mutations. In addition, assessment of ORR, response duration, and overall survival (OS) will also be evaluated as secondary endpoints.

An Interim Analysis (IA) of Part 3 will be conducted to inform a potential early Go/No Go decision for initiation of Phase III before the completion of Part 3. The IA will be performed when the first 80 subjects randomized into this part of the study have completed their Week 36 visit and have their central radiology assessment at Week 36 available, or, have discontinued prior to Week 36. The primary endpoint for the IA is the ordinal response at Week 36 including the following five categories (consistent with RECIST 1.1 definitions, with the exception of PR being divided into MPR and VGPR based on the degree of tumor shrinkage): Complete Response (CR), Very Good Partial Response (VGPR), Moderate Partial Response (MPR), Stable Disease (SD), and Progressive Disease (PD). These categories are further defined in Section 8.1. Subjects who discontinued prior to Week 36 will be assigned to one of these categories for Week 36 according to the reason for discontinuation (see the endpoint definition). Secondary and exploratory endpoints including the use of tumor kinetic parameters for the IA are further defined in Section 8.2.

As exploratory objectives in this study, key candidate biomarkers will be evaluated in tumor tissue and peripheral blood that may correlate with clinical response to treatment and/or with the development of disease progression, and to further explore the relationship between study treatment and pharmacodynamic response. Subgroup analyses are summarized in Section 8.1.4.

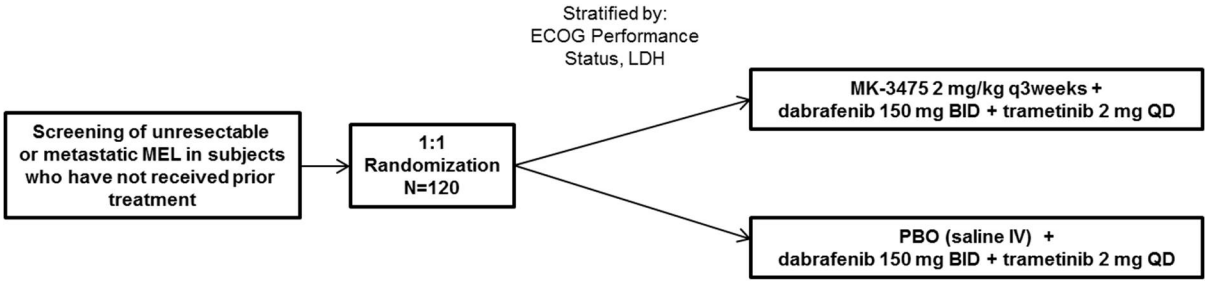
Part 3 of this trial will use a standing internal Data Monitoring Committee (siDMC) to monitor safety information and efficacy in the study. The siDMC will oversee the conduct of the study in accordance with Good Clinical Practice (GCP) and as described in the siDMC charter. The siDMC will also evaluate the data at the planned IA and make recommendations of stopping or continuing the study according to the siDMC charter. In addition, the trial may be stopped early at the recommendation of the siDMC if the risk/benefit ratio to the trial population as a whole is unacceptable. Details are described in Section 8.0 – Statistical Analysis Plan.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

Following the dose confirmation and dose expansion portions of the trial (Parts 1 and 2), Part 3 will evaluate the clinical efficacy of the confirmed triplet dose (MK+D+T) as compared to (PBO+D+T). The trial design for Part 3 is depicted in Figure 1.

Figure 1 Trial Diagram: Part 3



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Parts 1 and 2:

(1a) **Objective:** To evaluate the safety and tolerability and identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of pembrolizumab administered intravenously in combination with oral dabrafenib and trametinib in subjects with advanced (unresectable or metastatic) melanoma with BRAF V600 E or K mutations.

Hypothesis: Pembrolizumab dosed intravenously on a q3week schedule combined with twice daily oral dabrafenib and once daily oral trametinib is sufficiently well-tolerated based on assessment of clinical and laboratory adverse events (AEs) to permit clinical investigation.

(1b) **Objective:** To evaluate the safety and tolerability and identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of pembrolizumab administered intravenously in combination with oral trametinib in subjects with advanced (unresectable or metastatic) melanoma without BRAF V600 E or K mutations.

Hypothesis: Pembrolizumab dosed intravenously on a q3week schedule combined with once daily oral trametinib is sufficiently well-tolerated based on assessment of clinical and laboratory adverse events (AEs) to permit clinical investigation.

(1c) **Objective:** To evaluate the safety and tolerability and identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of pembrolizumab administered intravenously in combination with oral dabrafenib in subjects with advanced (unresectable or metastatic) melanoma with BRAF V600 E mutations. (**Note**: this objective will only be evaluated if DL1 of the MK+D+T triplet (objective 1a) is not tolerated).

Hypothesis: Pembrolizumab dosed intravenously on a q3week schedule combined with twice daily oral dabrafenib is sufficiently well-tolerated based on assessment of clinical and laboratory adverse events (AEs) to permit clinical investigation.

Part 2:

(2) **Objective:** To confirm the safety and tolerability of the preliminary maximum tolerated dose (MTD) or maximum administered dose (MAD) of pembrolizumab administered intravenously in combination with oral dabrafenib and trametinib in subjects with advanced (unresectable or metastatic) melanoma with BRAF V600 E or K mutations.

Hypothesis: Pembrolizumab dosed intravenously on a q3week schedule combined with twice daily oral dabrafenib and once daily oral trametinib is sufficiently well-tolerated at the MTD/MAD based on assessment of clinical and laboratory adverse events (AEs) to permit further clinical investigation.

(3) **Objective:** To confirm the safety and tolerability of the preliminary maximum tolerated dose (MTD) or maximum administered dose (MAD) of pembrolizumab administered intravenously in combination with oral trametinib in subjects with advanced (unresectable or metastatic) melanoma without BRAF V600 E or K mutations.

Hypothesis: Pembrolizumab dosed intravenously on a q3week schedule combined with once daily oral trametinib is sufficiently well-tolerated at the MTD/MAD based on assessment of clinical and laboratory adverse events (AEs) to permit further clinical investigation.

(4) **Objective:** To evaluate the efficacy of pembrolizumab administered intravenously in combination with oral trametinib in subjects with advanced (unresectable or metastatic) melanoma without BRAF V600 E or K mutations with respect to Objective Response Rate (ORR).

Hypothesis: Pembrolizumab dosed intravenously on a q3week schedule combined with once daily oral trametinib is effective in attaining objective responses based upon RECIST 1.1 by the investigator review in subjects with melanoma without BRAF V600 E or K mutations.

Part 3:

(5) **Objective:** To evaluate the efficacy with respect to progression-free survival (PFS) of pembrolizumab administered intravenously in combination with oral dabrafenib and trametinib in subjects with advanced (unresectable or metastatic) melanoma with BRAF V600 E or K mutations, compared with placebo administered intravenously in combination with oral dabrafenib and trametinib alone.

Hypothesis: Pembrolizumab dosed intravenously combined with twice daily oral dabrafenib and once daily oral trametinib (at doses determined in Parts 1 & 2 of the study) improves progression-free survival (PFS) based upon RECIST 1.1 by the investigator review compared with placebo dosed intravenously combined with oral dabrafenib and trametinib treatment.

Part 4:

(6) **Objective:** To evaluate the safety and tolerability and identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of pembrolizumab administered intravenously in combination with oral trametinib in subjects with advanced (unresectable or metastatic) melanoma without BRAF V600 E or K mutations or advanced (metastatic and/or unresectable) solid tumors, irrespective of BRAF status.

Hypothesis: Pembrolizumab dosed intravenously on a q3week schedule combined with oral trametinib is sufficiently well-tolerated based on assessment of clinical and laboratory adverse events (AEs) to permit clinical investigation.

Part 5:

(7) **Objective:** To confirm the safety and tolerability of the preliminary maximum tolerated dose (MTD) or maximum administered dose (MAD) of pembrolizumab administered intravenously in combination with oral trametinib in subjects with advanced (unresectable or metastatic) melanoma without BRAF V600 E or K mutations or advanced (metastatic and/or unresectable) solid tumors, irrespective of BRAF status.

Hypothesis: Pembrolizumab dosed intravenously on a q3week schedule combined with oral trametinib is sufficiently well-tolerated at the MTD/MAD based on assessment of clinical and laboratory adverse events (AEs) to permit further clinical investigation.

(8) **Objective:** To evaluate the efficacy of pembrolizumab administered intravenously in combination with oral trametinib in subjects with advanced (unresectable or metastatic) melanoma without BRAF V600 E or K mutations or advanced (metastatic and/or unresectable) solid tumors, irrespective of BRAF status with respect to Objective Response Rate (ORR).

Hypothesis: Pembrolizumab dosed intravenously on a q3week schedule combined with oral trametinib is effective in attaining objective responses based upon RECIST 1.1 by the investigator review in subjects with melanoma without BRAF V600 E or K mutations.

3.2 Secondary Objective(s) & Hypothesis(es)

Parts 1 and 2:

(1) **Objective:** To evaluate the efficacy of pembrolizumab administered intravenously in combination with oral dabrafenib and trametinib in subjects with advanced (unresectable or metastatic) melanoma with BRAF V600 E or K mutations with respect to Objective Response Rate (ORR).

Parts 1, 2, 3, 4, and 5:

(2) **Objective:** To evaluate the pharmacokinetics (PK) of pembrolizumab, dabrafenib, and/or trametinib when pembrolizumab is administered intravenously in combination with oral dabrafenib and/or trametinib.

Part 3:

(3) **Objective:** To evaluate the efficacy of pembrolizumab administered intravenously in combination with oral dabrafenib and trametinib in subjects with advanced (unresectable or metastatic) melanoma with BRAF V600 E or K mutations with respect to Objective Response Rate (ORR), Response Duration, and overall survival (OS), compared with oral dabrafenib and trametinib alone.

3.3 Exploratory Objective(s)

(1) **Objective:** To evaluate key biomarkers (via tumor biopsy and peripheral blood sample) at baseline and 10-14 days after administration of oral dabrafenib and/or trametinib in combination with intravenously administered pembrolizumab, and determine the relationship between key biomarkers and clinical response.

(2) **Objective:** To evaluate key biomarkers (via tumor biopsy and peripheral blood sample) at the time of progression after administration of oral dabrafenib and/or trametinib in combination with intravenously administered pembrolizumab, and determine the relationship between key biomarkers and clinical progression.

(3) **Objective:** To evaluate the use of tumor kinetic parameters including time to growth (TTG) modeling and simulation to evaluate the effect of pembrolizumab administered intravenously in combination with oral dabrafenib and trametinib in subjects with advanced (unresectable or metastatic) melanoma with BRAF V600 E or K mutations. These tumor kinetics parameters may be correlated with clinical outcomes.

(4) **Objective:** To evaluate the efficacy of pembrolizumab administered intravenously in combination with oral dabrafenib and trametinib in subjects with advanced (unresectable or metastatic) melanoma with BRAF V600 E or K mutations with respect to Best Overall Response, 5-Category Best Overall Response, 5-Category Ordinal Response by Week, Percentage of Subjects with Complete Response, Percentage of Subjects with Partial Response, Percentage of Subjects with Deep Response, Best

Target Lesion Response, Time to Confirmed Response, Percentage of Subjects with Sustained Response at Week 36 (see Section 8.2.3.1 for endpoint definitions), EuroQol (EQ-5D), and EORTC (QLQ-C30) compared with oral dabrafenib and trametinib alone in Part 3.

(5) **Objective:** To evaluate the potential for development of anti-drug antibodies (ADA) after administration of pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. Refer to the appropriate Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475, trametinib or dabrafenib.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2-37]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant melanoma (MEL) and renal cell carcinoma (RCC). TILs can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as MEL [38; 39].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down -modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [40; 41] The structure of murine PD-1 has been resolved [42]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of

signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [40; 43-45]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [46; 34]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T-regs and Natural Killer cells [47; 48]. Expression has also been shown during thymic development on $CD4^-CD8^-$ (double negative) T-cells as well as subsets of macrophages and dendritic cells [30]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [49; 50; 46; 51]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [49]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (RCC) [52], pancreatic carcinoma [53], hepatocellular carcinoma [54], and ovarian carcinoma [55]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with MEL [56].

The observed correlation of clinical prognosis with PD-L expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [57; 58; 59; 53; 60; 61]. In addition, the combination of gemcitabine and anti-PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors [53]. In-house experiments have confirmed the in vivo efficacy of PD -1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

Pembrolizumab (previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. The first clinical results for pembrolizumab based on a total of 135 subjects with advanced melanoma were reported in the NEJM. The confirmed response rate across all dose cohorts, evaluated by central radiologic review according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, was 38% (95% confidence interval [CI], 25 to 44), with the highest confirmed response rate observed in the cohort that received 10 mg per kilogram every 2 weeks (52%; 95% CI, 38 to 66). The response rate did not differ significantly between subjects who had received prior ipilimumab treatment and those who had not (confirmed response rate, 38% [95% CI, 23 to 55] and 37% [95% CI, 26 to 49], respectively). Responses were durable in the majority of subjects (median follow-up, 11 months among subjects who had a response); 81% of the subjects who had a response (42 of 52) were still receiving treatment at the time of analysis in March 2013. The overall median progression-free survival among the 135 subjects was longer than 7 months. Common adverse events attributed to treatment were fatigue, rash, pruritus, and diarrhea; most of the adverse events were low grade [62].

4.1.1.2 Trametinib and Dabrafenib

The mitogen-activated protein kinase pathway (also known as MAPK-pathway) is a critical signal transduction pathway in normal and cancer cells. The MAPK pathway is a three-tiered kinase cascade consisting of the rapidly-activated fibrosarcoma kinase (RAF kinase), mitogen-activated extracellular signal-related kinase (MEK kinase), and extracellular signaling-regulated kinase (ERK or MAPK).

BRAF, one of three structurally related RAF-kinase isoforms (A-, B-, and C-RAF or RAF-1), is part of the MAPK-signal transduction pathway which controls cell cycle progression, differentiation, and survival. Under physiological conditions, signal transduction through the MAPK-pathway is tightly regulated through multiple negative feedback mechanisms. However, constitutive pathway activation through multiple genetic alterations is a hallmark of malignant tumors. For the serine-threonine kinase RAF alone over 45 cancer-associated mutations [63-65] are currently known. Most of these mutations constitutively activate the RAF-kinase. In melanoma, more than 80% of the BRAF mutations cause a substitution of the amino acid glutamate (E) for valine (V) at position 600 (V600E) of the BRAF protein, whereas approximately 3-20% of melanoma mutations are a substitution of lysine (K) for valine at position 600 (V600K) [66-71]. The BRAF V600E mutation occurs at a high frequency in specific cancers, including approximately 60% of melanoma [63], 30 to 50% of papillary thyroid, 5 to 20% of colorectal, and approximately 30% of ovarian cancer [65]. Although BRAF-mutations were initially identified in premalignant, benign cutaneous nevi, there is overwhelming pre-clinical and clinical evidence that these mutations confer ‘oncogenic addiction’ to melanoma cells and are thus a key driver of advanced and metastatic disease and a prime target for therapeutic intervention with targeted small-molecule inhibitors [72]. While the introduction of BRAF inhibitors represent a significant advance in the treatment of BRAF V600 mutation-positive metastatic melanoma subjects [73], limitations of this novel therapy have already been identified. As has been the pattern with other highly selective small molecule kinase inhibitors (e.g. imatinib in bcr-abl chronic

myelogenous leukemia; erlotinib and gefitinib in epidermal growth factor receptor-mutant non-small cell lung cancer [NSCLC]) the rapid onset of drug resistance restricts the efficacy of vemurafenib and limits the median duration of response to only 6.7 months (data from the vemurafenib Phase III study BRIM3). Understanding the specific mechanisms of resistance to BRAF-inhibitors is critical for the development of more effective strategies to inhibit the MAPK-pathway in order to delay or prevent the onset of resistance in BRAF-mutant melanoma.

In a majority of cell models and melanoma samples, acquired resistance to BRAF inhibitors was associated with a reactivation of the MAPK-pathway indicating that the 'addiction' to this pathway remains unchanged [74]. In these resistant BRAF mutant melanomas, the MAPK-pathway can be reactivated through secondary activating mutations of the upstream NRAS- or the downstream MEK1-kinase or an overexpression of the RAF1- and COT-kinase. In addition, activation of further upstream RTKs most probably due to alterations in molecular feedback loops affecting in particular the IGF-IR (insulin-like-growth factor receptor) and the PDGFR (platelet-derived growth factor) have also been detected. Although all of these molecular events enable the melanoma cell to circumvent BRAF-inhibition in order to re-activate the MAPK-pathway, this activation renders most of the BRAF-inhibitor resistant tumors susceptible to an inhibition of the downstream MEK-kinase. Experimental data generated with a BRAF- and MEK-inhibitor combination therapy in BRAF-mutant melanoma cell lines in vitro and xenografts in vivo support this concept by demonstrating activity of the combination therapy in models of acquired BRAF resistance. More importantly, superior anti-tumor activity of the BRAF- and MEK inhibitor combination as compared to each agent as monotherapy was also observed in BRAF-sensitive models. These data clearly indicate that a concomitant and more potent inhibition of the MAPK-pathway at the critical level of the BRAF- and MEK-kinases leads to a more pronounced tumor inhibition, thus significantly delaying the onset of resistance. In addition, pre-clinical safety data obtained with this combination therapy in a rat-model indicate that the potential for proliferative skin lesions and secondary cutaneous malignancies is reduced in comparison to treatment with a BRAF-inhibitor alone [75].

Dabrafenib (GSK2118436), a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is a potent and selective inhibitor of B-RAF kinase activity with a mode of action consistent with adenosine triphosphate (ATP)-competitive inhibition, and is approved as monotherapy in BRAF V600E-mutant advanced/metastatic melanoma. Trametinib (GSK1120212), a pyrido-pyrimidine derivative, is a potent and highly selective allosteric non-competitive inhibitor of MEK1/MEK2 activation and kinase activity [76] has been approved as monotherapy in BRAF (V600E)-mutant and BRAF (V600K)-mutant melanoma. The safety, tolerability, PK and clinical activity of trametinib + dabrafenib combination therapy has been evaluated in subjects with BRAF-mutant melanoma in a Phase I/II study [77], and demonstrated good efficacy with 76% ORR and 9.4 month median PFS at the highest dose combination.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Pembrolizumab (previously known as SCH 900475) is a potent and highly-selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab contains the S228P stabilizing mutation and has no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer subjects, and primates. In T- cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T- cells. A one-month repeat dose GLP-toxicity study with four months observation post dosing revealed no major safety findings. The no observed adverse event level (NOAEL) was ≥200 mg/kg. (For details on the pre-clinical data of pembrolizumab, see the IB). Based on the preliminary clinical data, PD-1 inhibitors such as pembrolizumab appear to be attractive therapeutic candidates. Recently, the first clinical results from an ongoing study of pembrolizumab in subjects with advanced melanoma reported a confirmed response rate of 38% (95% confidence interval [CI], 25 to 44) across all tested dose cohorts.

Pharmacologic inhibition of the mitogen-activated protein kinase (MAPK) pathway has proved to be a significant advance in the treatment of metastatic melanoma. The use of vemurafenib and dabrafenib, agents that inhibit BRAF and block MAPK signaling in subjects with melanoma and the BRAF V600E mutation, has been associated with prolonged survival and progression-free survival, respectively, in randomized phase 3 trials involving subjects with previously untreated melanoma [78-83]. Trametinib mediates blockade of MAPK kinase at the level of MEK, which is downstream of BRAF in the MAPK pathway and has been associated with improved progression-free and overall survival in BRAF V600 melanoma (comprising both V600E and V600K mutations) [84; 85]. In spite of these advances, 50% of subjects who are treated with BRAF or MEK inhibitors have disease progression within 6 to 7 months after the initiation of treatment [80; 83].

In preclinical models, rapid recovery of MAPK pathway signaling has been associated with BRAF inhibitor resistance, and complete inhibition of the MAPK pathway is needed to induce cell death in BRAF V600 melanoma [86; 87]. This can be achieved by combining a BRAF inhibitor with a MEK inhibitor [86; 87]. The emergence of cutaneous squamous cell carcinoma early in the course of BRAF-inhibitor therapy has been associated with paradoxical MAPK pathway activation during BRAF inhibition [88]. In an experimental model of squamous cell carcinoma, the addition of a MEK inhibitor to a BRAF inhibitor reduced this effect [88].

In an attempt to delay resistance to BRAF inhibition and explore the safety of combination therapy with BRAF and MEK inhibition, a Phase I/II open-label study involving 247 subjects

investigating the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib in subjects with metastatic BRAF V600 melanoma was recently reported [85]. Subjects were randomly assigned to receive combination therapy with dabrafenib (150 mg twice daily) plus trametinib (1 or 2 mg once daily) or dabrafenib monotherapy. Dose-limiting toxic effects were infrequently observed in subjects receiving combination therapy with the highest tested dose of 150 mg of dabrafenib twice daily and 2 mg of trametinib once daily (combination 150/2), with only 1/24 subjects treated at this dose experiencing a DLT (recurrent neutrophilic panniculitis). Cutaneous squamous-cell carcinoma was seen in 7% of subjects receiving combination 150/2 and in 19% receiving monotherapy (P = 0.09), whereas pyrexia was more common in the combination 150/2 group than in the monotherapy group (71% vs. 26%). Median progression-free survival in the combination 150/2 group was 9.4 months, as compared with 5.8 months in the monotherapy group (hazard ratio for progression or death, 0.39; 95% confidence interval, 0.25 to 0.62; P<0.001). The rate of complete or partial response with combination 150/2 therapy was 76%, as compared with 54% with monotherapy (P = 0.03).

While the benefit of combination MAPK pathway inhibition has been demonstrated, progression-free survival was still limited at 9.4 months (although this does represent a significant improvement on previously reported PFS), and complete responses (CR) were rare (<10%). Therefore, treatment with dabrafenib and trametinib can be characterized as having high response rate with modest duration of response. Conversely, the response rates from early clinical data of anti PD-1 therapies are generally <40%, but responses appear to be durable [62]. It would therefore be desirable to combine the high response rate of MAPK inhibition, either singly or in combination (dabrafenib + trametinib) with the duration of response of pembrolizumab, which could present a new standard of care for subjects with advanced or metastatic melanoma with BRAF V600 mutations.

Early reports of attempts at combining MAPK inhibitors with immunotherapies have produced unexpected toxicity. Ribas et al. reported that ipilimumab combined with vemurafenib in a planned Phase I trial resulted in unexpected hepatotoxicity, leading to the discontinuation of the trial by the sponsors. Other immunotherapy combinations with tyrosine kinase inhibitors (TKIs) or other immunotherapies are ongoing, and clinical results remain preliminary. However, in light of the possibility of unacceptable toxicity for a 3-drug combination (pembrolizumab + dabrafenib + trametinib), a contingency cohort of pembrolizumab + dabrafenib (without the MEK inhibitor trametinib) is planned to be initiated in case the starting dose of the MK+D+T triplet combination cohort is not tolerable.

The data for MAPK pathway inhibition in melanoma without BRAF mutations (BRAF 'wild type') is limited. Neither dabrafenib nor trametinib are indicated for the treatment of BRAF unmutated melanoma. However, trametinib has demonstrated modest clinical activity in BRAF wild type melanoma [84], and preclinical data reporting synergy in BRAF unmutated melanoma cell lines when MEK inhibitors are administered with anti-PD1 therapy suggest that some synergy may be seen clinically when combining these two treatment modalities [103]. In addition, it has recently been reported that treatment of melanoma with either BRAF inhibitor alone or BRAF + MEK inhibitor was associated with an increased expression of melanoma antigens, an increase in CD8+ T-cell infiltrate, and an increase in

expression of PD-1 and PD-L1, as well as a decrease in immunosuppressive cytokines [interleukin (IL)-6 and IL-8] [89].

Based on this preclinical and translational data, this study will plan to evaluate the safety, tolerability, and preliminary efficacy of pembrolizumab in combination with trametinib in subjects with advanced or metastatic melanoma without BRAF mutations (BRAF wild type).

Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

4.2.2 Rationale for Dose Selection/Regimen/Modification

In the first-in-human study (PN001, refer to IB), pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). PK data analysis of pembrolizumab administered in Q2W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing Q2W and Q3W dosing schedules.

Two randomized cohort evaluations of melanoma subjects in PN001 receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating of 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The ORR was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (FAS). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab at 10 mg/kg Q2W versus 10 mg/kg Q3W. The ORR was 30.9% (38/123) in the 10 mg/kg Q2W group and 24.8% (30/121) in the 10 mg/kg Q3W group (APaT). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Moreover, population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Importantly, the analysis revealed no significant impact of tumor burden on exposure. Taken together, these data support the use of lower doses (2 mg/kg Q3W) in all solid tumor indications.

An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dosing.

A population pharmacokinetic (PK) model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. PK properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. In summary, the existing data support 200 mg Q3W as the appropriate dose for pembrolizumab in Parts 4 and 5 of this protocol.

Dabrafenib and trametinib have been evaluated in combination in a recent [85] Phase I/II study in which the highest tested dose combination consisted of oral dabrafenib 150mg twice daily with oral trametinib 2 mg once daily (full single-agent dose of both agents). In comparison with subjects receiving dabrafenib monotherapy, subjects receiving combination therapy had more frequent and more severe pyrexia and chills (71% vs 26% all grades, 5% vs 0% grade 3 or 4); they also had more frequent gastrointestinal toxic effects (e.g., nausea and vomiting), but most of these events were grade 1 or 2. Pyrexia was generally manageable with antipyretic agents. However, recurrent fevers required the use of low dose oral glucocorticoids.

Frequency of grade 3 or 4 AE's was reported as 58% in the 150/2 dabrafenib/trametinib combination cohort vs 43% in the dabrafenib monotherapy cohort. An intermediate cohort, 150mg twice daily dabrafenib with 1mg daily trametinib, was also evaluated, and reported

48% grade 3 or 4 AEs, with 9% grade 3 or 4 pyrexia. However, dose-limiting toxic effects were only observed at the highest tested dose (combination 150/2), with only 1/24 subjects treated at this dose experiencing a DLT (recurrent neutrophilic panniculitis).

Median PFS for dabrafenib monotherapy was reported as 5.8 months (4.6-7.4), for the 150/1 combination 9.2 months (6.4-11.0), and for the 150/2 combination 9.4 months (8.6-16.7). Overall response rate was highest for the 150/2 combination of dabrafenib and trametinib, which reported 76% (62-86) complete or partial responses, vs 50% (36-64) for the 150/1 combination and 54% (40-67) for dabrafenib monotherapy.

Therefore, while the rate of grade 3 or 4 AEs was higher in the 150/2 combination cohort vs dabrafenib monotherapy or the 150/1 combination cohort, the response rate and PFS of the 150/2 combination was superior to either of the other groups (and only reported a ~4% DLT rate), and will be used as the starting dose levels for this protocol (in both the triplet combination cohorts, and the doublet cohorts, with the option to down-dose one or both of dabrafenib and/or trametinib if toxicities in the combination arise).

4.2.2.1 Starting Dose for This Trial

The starting dose of pembrolizumab will be 2 mg per kg body weight administered intravenously every 3 weeks. This was the lowest tested dose from the ongoing PN 001 which recently reported results from an interim analysis showing efficacy at this dose level with 25% confirmed objective response rate and tolerable AE profile. This lowest tested dose for pembrolizumab was chosen as a starting dose due to the potential for unforeseen or additive toxicity when administered in combination with MAPK inhibitors dabrafenib and trametinib, whose AE profile when administered in combination with each other has been investigated in a Phase I/II trial. In addition, given the recently reported hepatotoxicity when another immunotherapy/MAPK inhibitor combination was tested - ipilimumab and vemurafenib in combination [62] – the lowest tested dose of pembrolizumab was selected for this combination protocol.

The starting dose of dabrafenib will be the FDA/EMA-approved dose of 150 mg orally twice daily (for triplet combination cohort, and if needed, (MK+D) cohort).

The starting dose of trametinib will be the FDA-approved dose of 2 mg orally once daily (for both the triplet combination cohort and the (MK+T) cohort).

The starting doses of dabrafenib and trametinib are based on the approved single agent doses, as well as Phase I/II data showing that combination therapy with the full single-agent doses of both drugs resulted in the maximum efficacy (76% PR+CR), with a tolerable side effect profile (58% grade 3-4 AEs) [85]. This dose combination is currently under study in a Phase 3 study (MEK115306; NCT01584648).

4.2.2.2 Maximum Dose/Exposure for This Trial

In Parts 1, 2, and 3 of this trial, the maximum dose of pembrolizumab will be 2 mg per kg body weight administered intravenously every 3 weeks. In Parts 4 and 5, the maximum dose of pembrolizumab will be 200 mg.

The maximum dose of dabrafenib will be 150 mg orally twice daily (for triplet combination cohort, and if needed, (MK+D) cohort).

The maximum dose of trametinib will be 2 mg orally once daily (for both the triplet combination cohort and the (MK+T) cohort).

The maximum doses of dabrafenib and trametinib are based on the approved single agent doses, as well as the highest doses tested in combination in the Phase I/II trial (full single-agent doses for each drug).

4.2.2.3 Rationale for Dose Interval and Trial Design

Pembrolizumab will initially be evaluated at the lowest tested dose (2 mg/kg IV Q3W) from the ongoing PN 001 which recently reported interim analysis data.

The MAPK inhibitors dabrafenib (150 mg orally BID) and trametinib (2 mg PO QD) will start at their full single-agent doses in Part 1 (for both the triplet combination cohort and the doublet cohorts). This dose combination was shown to be the maximally efficacious combination in the Phase I/II trial, with an acceptable AE profile, and represents the approved single-agent dose for both drugs. No data on higher dose combinations have been reported to date.

Given the potential for additive, overlapping, or unforeseen AEs when the agents are used in combination, down-dosing of one, two, or all three agents (in the case of the triple combination) is allowed, based on clinical observation of the AE profile. Down dosing of the compounds is outlined in Section 5.2.1.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

The primary efficacy endpoint of the trial is Progression Free Survival (PFS) in Part 3. PFS is an acceptable scientific endpoint to demonstrate superiority of a new antineoplastic therapy, especially if it is believed that the median time to Overall Survival (OS) with the new therapy may be significantly longer than that seen with standard of care. RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Images will be read by investigators and collected and held for potential central-read by independent radiologists later, as determined by the Sponsor.

For the (MK+T) cohort, the primary efficacy endpoint of the study is objective response rate (ORR) based on a best overall response (BOR) analysis in subjects with advanced or metastatic melanoma without BRAF mutation. Modified RECIST 1.1 (see discussion below) will be used to assess response rate by investigators/sites and collected and held for potential central-read by independent radiologists later, as determined by the Sponsor.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptations:

If radiologic imaging shows initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued / resumed. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the Site Imaging Manual).

In subjects who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive pembrolizumab treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

4.2.3.1.2 Interim Analysis

An interim analysis of Part 3 will be conducted to inform a potential early Go/No Go decision for initiation of Phase III before the completion of Part 3, as well as assess for futility. It will be conducted when the first 80 subjects randomized into the study will have completed 36 weeks (if not discontinued earlier) and have the respective data based on a central radiology assessment available. The primary endpoint for the interim analysis is the ordinal response at Week 36 with the following categories (consistent with RECIST 1.1 definitions, with the exception of PR being divided into MPR and VGPR based on the degree of tumor shrinkage): Complete Response (CR), Very Good Partial Response (VGPR) defined as partial response with Percent Change from Baseline (maximum reduction in tumor line length >60%), Moderate Partial Response (MPR) defined as partial response that is not VGPR, Stable Disease (SD), and Progressive Disease (PD). As this interim analysis is planned for a landmark in time, responses may or may not represent confirmed responses at the time of the analysis. The interim analysis will only include subjects randomized in Part 3 of the study.

The IA of ordinal response will be based on central-read of images. Additionally, a sensitivity analysis of 36-week ordinal response, BOR classified by ordinal response, and summaries of the ordinal response by time, will be based on investigator-read data. Investigators will be required to collect ordinal response data when RECIST 1.1 data is collected.

Ordinal response analysis was selected as the primary endpoint for the interim analysis as it relies on seeing more tumor shrinkage with addition of pembrolizumab to the dabrafenib+trametinib combination alone (versus improving RECIST 1.1-defined response rate based on a 30% decrease in the sum of longest tumor dimensions). When applied at a landmark in time at Week 36, there is significant “attrition” of responses to dabrafenib+trametinib doublet. The ordinal analysis at Week 36 integrates a degree of tumor shrinkage with the durability of tumor shrinkage; in addition, improvement in this endpoint will detect the ability of pembrolizumab to prevent tumor progression compared to the dabrafenib+trametinib doublet alone.

4.2.3.1.3 Secondary

Secondary endpoints include evaluation of pharmacokinetic properties of pembrolizumab, dabrafenib, and/or trametinib, when used in combination. Pharmacokinetic endpoints are further discussed in Section 4.2.3.3.

4.2.3.2 Safety Endpoints

The primary safety objective of this study is to characterize the safety and tolerability of different combinations of pembrolizumab and/or trametinib and/or dabrafenib in adult subjects with advanced melanoma. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE Version 4.0 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received

pembrolizumab and/or trametinib and/or dabrafenib, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, AEs of potentially immunologic etiology (AEs of special interest [AEOSI]) will be identified using a pre-specified list of terms and summarized.

Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs and physical examinations.

4.2.3.3 Pharmacokinetic Endpoints

The accumulation of robust PK and ADA data has allowed for the adequate characterization the clinical pharmacology of pembrolizumab across indications. Therefore, the collection of PK and ADA samples are being discontinued for subjects enrolled under Amendment 04. Blood samples for PK and ADA collected prior to Amendment 04 may be stored. Analysis will be performed only if required. Plasma samples will be obtained to characterize the pharmacokinetics of dabrafenib and its metabolites including hydroxy- and desmethyl-dabrafenib and trametinib when given in combination with pembrolizumab using a sparse sampling approach. The population pharmacokinetic parameters of dabrafenib and trametinib including oral clearance (CL/F), volume of distribution (Vc/F) and other parameters as appropriate, will be determined using previously validated pharmacokinetic models. Dabrafenib and trametinib exposure such as average concentration (C_{avg}) and/or minimum concentration (C_{min}) will be derived.

4.2.3.4 Patient Reported Outcomes

The EuroQol EQ5D and EORTC QLQ-C30 are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability. The subject reported outcomes will only be utilized in Part 3 of the study. Electronic EORTC QLQ-C30 and EuroQol EQ-5D will be completed by the subject prior to all other study procedures. It is most relevant and strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification.

4.2.3.4.1 EuroQol (EQ-5D)

The EuroQol-5D (EQ-5D) is a standardized instrument for use as a measure of health outcome. The EQ-5D will provide data for use in economic models and analyses including developing health utilities or QALYs. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (5). Each dimension is rated on a three point scale from 1 (extreme problem) to 3 (no problem). The EQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the

assessment. The EQ-5D will always be completed by subjects first before completing the EORTC QLQ-C30.

4.2.3.4.2 EORTC (QLQ-C30)

The EORTC-QLQC30 is the most widely used cancer specific HRQoL instrument, which contains 30 items and measures five functional dimensions (physical, role, emotional, cognitive, and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality of life scale. This instrument is translated and validated into more than 80 languages.

4.2.3.5 Biomarker Research

Additional biomarker research to identify factors important for pembrolizumab therapy will be pursued. Pre- and post-treatment tumor and blood samples from Parts 1,2, 4, and 5 (required, optional in Part 3) of this study may undergo proteomic, genomic and transcriptional analyses (both DNA and RNA analyses). Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and other immunologic targets. Expression of candidate biomarkers in tumor tissue will be evaluated both at baseline and 10-14 days after initiation of therapy with pembrolizumab in combination with dabrafenib and/or trametinib, including immune signaling markers on the surface of tumor cells, phenotypic and functional immune cell markers on TIL (which may include PD-1, PD-L1, CD8, and possibly other biomarkers), and DNA/RNA changes. These and other additional biomarker or genomic research to identify factors important for pembrolizumab therapy (for example, HLA genotype) may also be pursued.

4.2.3.6 Future Biomedical Research

The Sponsor may conduct Future Biomedical Research on specimens routinely and specifically collected during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects

receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects of at least 18 years of age with advanced or metastatic melanoma (or solid tumor in Parts 4 and 5) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have a histologically confirmed diagnosis of advanced (unresectable Stage III) or metastatic (Stage IV) melanoma or a histologically or cytologically-documented, locally-advanced or metastatic solid malignancy, and have at least one measurable lesion as defined by RECIST 1.1 on imaging studies (CT or MRI). Cutaneous lesions and other superficial lesions that are detectable only by physical examination and subcutaneous lesions detectable by CT are not considered measurable lesions for the purposes of this protocol, but may be considered as non-target lesions.

- Mucosal or ocular melanoma are excluded.

- For solid tumors other than melanoma, the subject must be a participant in Part 4 or 5 (dose confirmation only), have a malignancy that is incurable and has either: (a) failed prior standard therapy, (b) for which no standard therapy exists, or (c) standard therapy is not considered appropriate by the patient and treating physician. There is no limit to the number of prior treatment regimens, but prior treatment(s) should not include compounds targeting PD-1, PD-L1, BRAF, or MEK. Treatment must end at least 4 weeks prior to randomization.

2. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

3. Be ≥ 18 years of age on day of signing the informed consent.

4. Have BRAF mutation testing as determined at a local laboratory and either:

    a. Have a BRAF mutation-positive (V600 E or K) tumor to be eligible for treatment with pembrolizumab+trametinib+dabrafenib, trametinib+dabrafenib

or pembrolizumab+dabrafenib (if this part of the study is performed). If a subject's initial specimen does not test BRAF mutation-positive, a newly obtained specimen (different from the sample previously submitted) may be submitted for testing. If the newer specimen tests BRAF mutation-positive, the subject meets this eligibility criterion.

b. Have a BRAF mutation-negative (wild type) tumor to be eligible for treatment with pembrolizumab+trametinib.

- Criterion 4a is applicable only to enrollment of melanoma subjects in Parts 1, 2, and 3 of the trial design. Criterion 4b is applicable only to enrollment of melanoma subjects in Parts 1, 2, 4, and 5 of the trial design. The inclusion criterion does not apply to solid tumor subjects in Parts 4 and 5 (dose confirmation only).

  Note: Local laboratory testing for BRAF mutation is acceptable provided the methodology can detect both V600E and V600K mutations.

5. For BRAF mutation-negative (wild type) subjects who have received prior therapy for metastatic or advanced melanoma, must have documented progression of at least one measurable lesion by RECIST 1.1 on imaging studies (CT or MRI).

6. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.

7. Have an anticipated life expectancy of at least 3 months.

8. Be able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

9. Have adequate organ function as defined in Table 8 below:

Table 8 Inclusion Criteria Laboratory Parameters

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine	≤1.5 X upper limit of normal (ULN)
Calculated creatinine clearance[a]	≥50 mL/min
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Alkaline Phosphatase	If > 2.5 X ULN, then liver fraction should be ≤ 2.5 X ULN
Albumin	≥ 2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
a Calculate creatinine clearance using standard Cockcroft-Gault formula (Appendix 12.7). Creatinine clearance must be ≥50 mL/min to be eligible.	

10. Have provided tissue for biomarker analysis from a newly or recently-obtained biopsy (within 90 days of Study Day 1) of a tumor lesion not previously irradiated.

    Note: Study Day 1=First dose(s) of study treatment. Vendor acknowledgment of evaluability does not need to be obtained prior to allocation.

11. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible.

12. A female participant is eligible to participate if she is not pregnant (see Appendix 12.14), not breastfeeding, and at least one of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 12.14 OR
    b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 12.14

during the treatment period and for at least 120 days after the last dose of study treatment.

13. Male subjects should agree to use an adequate method of contraception as outlined in Appendix 12.14 starting with the first dose of study medication through 120 days after the last dose of study medication.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of treatment.

2. Is either:

   1) BRAF mutation-positive and has received prior systemic therapy for metastatic or advanced melanoma.

   Note: Prior adjuvant or neoadjuvant therapy is allowed (i.e., does not count as prior systemic therapy) as long as that therapy did not include compounds targeting PD-1, PD-L1, BRAF, or MEK. Treatment must end at least 4 weeks prior to randomization. Prior adjuvant therapy with anti-CTLA-4 will only be permitted if relapse did not occur during treatment or within 6 months of treatment discontinuation.

   or

   2) BRAF mutation-negative and has received >1 prior systemic therapy for metastatic melanoma**.**

   Note: Prior adjuvant or neoadjuvant therapy does not count as prior line of systemic therapy, but should not include compounds targeting PD-1, PD-L1, BRAF, or MEK. Treatment must end at least 4 weeks prior to randomization.

   - The BRAF exclusion criterion does not apply to solid tumor subjects in Parts 4 and 5 (dose confirmation only).

3. Has received prior therapy with compounds targeting the PD-1, PD-L1, BRAF, MEK or other molecules in the MAPK pathway.

   Note: Examples of BRAF inhibitors include, but are not limited to, dabrafenib and vemurafenib. An example of a MEK inhibitor includes, but is not limited to, trametinib.

4. Is BRAF mutation-positive and has received prior systemic therapy with ipilimumab or other CTLA-4 blocking antibodies.

5. Has had chemotherapy, radioactive, or biological cancer therapy within four weeks prior to the first dose of trial treatment, or who has not recovered to CTCAE Grade 1 or better from the clinically significant AEs due to cancer therapeutics administered more than four weeks prior to the first dose of trial treatment.

6. Is expected to require any other form of systemic or localized antineoplastic therapy while in study.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include early stage cancers (carcinoma in situ or stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, or in situ breast cancer that has undergone potentially curative therapy. For dabrafenib-containing treatment regimens in this study, subjects with any malignancy with confirmed activating RAS mutation are excluded.

   Note: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility.

8. Has known active central nervous (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by MRI for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are off systemic steroids for at least two weeks.

9. Has an active infection requiring systemic therapy.

10. Has an active autoimmune disease, or a documented history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections are not excluded from the study. Subjects with hypothyroidism stable on hormone replacement are not excluded from the study.

11. Has previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody (mAb).

12. Is on chronic systemic steroid therapy (>10 mg/day prednisone or equivalent) within two weeks before the planned date for first dose of study treatment or on any other form of immunosuppressive medication. (Subjects that are expected to require premedication with corticosteroid for pembrolizumab will not be eligible for this study.)

13. Currently uses a prohibited medication as described in Section 5.5.2.

14. Has history or evidence of cardiovascular risk including any of the following:

    1) Current LVEF < LLN as determined by echocardiogram;

    2) A QT interval corrected for heart rate using the Bazett's formula (QTcB; [90]) ≥480 msec;

    3) A history or evidence of current clinically significant uncontrolled arrhythmias;

       Exception: Subjects with atrial fibrillation controlled for > 30 days prior to randomization are eligible.

    4) A history (within 6 months prior to randomization) of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty or stenting;

    5) A history or evidence of current ≥Class II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines [91];

    6) Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy;

    7) Subjects with intra-cardiac defibrillators;

    8) Abnormal cardiac valve morphology (≥grade 2) documented by echocardiogram (subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered in study.

15. Has uncorrectable electrolyte abnormalities (e.g. hypokalaemia, hypomagnesaemia, hypocalcaemia), long QT syndrome or taking medicinal products known to prolong the QT interval.

16. Has known history of prior or current retinal vein occlusion (RVO).

    Note: In the event history of RVO is not known, an ophthalmic exam is required.

17. Has known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).

18. Has had an allogeneic tissue/solid organ transplant, prior stem cell or bone marrow transplant.

19. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

20. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

21. Has a known history of or is positive for Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected).

    Note: In those countries, where standard of care uses only Hepatitis C antibody testing as evidence of status of Hepatitis C, HCV RNA testing is not required.

22. Has received a live vaccine within 30 days prior to first dose.

23. Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the trial.

24. Has a clinical history suggestive of a condition which could impact the safety or efficacy of the subject in the study.

25. Is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).

26. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of trial treatment.

27. Is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in. A cycle of treatment in this protocol is defined as six weeks, except as noted in the table.

Table 9 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	1mg/kg*	Q3W	IV infusion	Days 1 and 22 of each cycle in Parts 1, 2, or 3	Experimental
Pembrolizumab	2mg/kg	Q3W	IV infusion	Days 1 and 22 of each cycle in Parts 1, 2, or 3	Experimental
Pembrolizumab	200 mg	Q3W	IV infusion	Days 1 and 22 of each cycle in Parts 4 or 5, with the exception of Cycle 1**	Experimental
Placebo (saline IV)	--	Q3W	IV infusion	Days 1 and 22 of each cycle	Experimental
Trametinib	1.5mg*	1.5mg QD	Oral	Day 1 up until study treatment discontinuation	Experimental
Trametinib	2mg	2mg QD	Oral	Day 1 up until study treatment discontinuation	Experimental
Dabrafenib	150mg*	75mg BID	Oral	Day 1 up until study treatment discontinuation	Experimental
Dabrafenib	200mg*	100mg BID	Oral	Day 1 up until study treatment discontinuation	Experimental
Dabrafenib	300mg	150mg BID	Oral	Day 1 up until study treatment discontinuation	Experimental

*Dose/Potency activated only in the event dose reduction required.
**Cycle 1 in Parts 4 and 5 are longer in length due to trametinib run-in of two or four weeks.

For dosing regimens initiating with four weeks of trametinib monotherapy, pembrolizumab dosing occurs on Days 29 and 50. For dosing regimens initiating with two weeks of trametinib monotherapy, pembrolizumab dosing occurs on Days 15 and 36.

Please note, the term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or a combination of those study treatments.

Trial treatment should begin on the day of randomization or as close as possible to the date on which the subject is allocated/assigned.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale.

In Parts 1, 2, and 3 of this trial, the dose amount required to prepare the pembrolizumab infusion solution will be based on the subject's weight in kilograms (kg). In Parts 4 and 5, a flat dose (independent of the subject's weight) for pembrolizumab infusion is required. Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

Trametinib and dabrafenib will be administered as per the approved product labels.

5.2.1.2 Dose Modification

It should be noted that for dose modifications in Part 3 of the study, changes could occur for either pembrolizumab or placebo (saline IV) in combination with trametinib and dabrafenib, depending on the study arm assignment. Detailed dose modification and toxicity management guidelines for each study treatment are provided in Section 5.6 (Table 16 to Table 35).

5.2.1.2.1 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 10 below and in Section 5.6. See Section 5.6 for detailed supportive care guidelines, including use of corticosteroids for specific AEs.

Table 10 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab must be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis (see also Table 22)	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis (see also Table 18)	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with 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.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin See also Section 5.6.1.1.15	Grade 2	Withhold See also Table 30	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue Note: For Grade 3 events see Table 30 for detailed management and dose modification guidelines based on specific hepatic laboratory abnormalities	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia See also Section 5.6.1.1.6	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis See also Table 19	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism See also Section 5.6.1.1.6	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Hypothyroidism See also Section 5.6.1.1.6	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction See also Table 23	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis See also Section 5.6.1.1.12	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs See also Section 5.6.1.3 and Table 35	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

For subjects who experience a recurrence of the same AE(s) at the same grade or greater with rechallenge of pembrolizumab, a consultation between the Sponsor and investigator should occur to determine whether the subject should continue in the trial. **However, for a subject who experiences a recurrence of the same <u>serious</u> adverse event at the same grade or greater with rechallenge of pembrolizumab, the subject must discontinue pembrolizumab.**

Dose increase of pembrolizumab will not be permitted in individual subjects unless a dose level of pembrolizumab is dropped during the trial. If this occurs then those subjects who were assigned the dropped dose may switch to the remaining dose level at the discretion of the investigator.

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

See Section 5.6.1.2

Other allowed dose interruption for pembrolizumab
Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.1.2.2 Trametinib Dose Modification

Please refer to Section 5.6.1.1.4.

5.2.1.2.3 Dabrafenib Dose Modification

Please refer to Section 5.6.1.1.4.

5.2.2 Timing of Dose Administration

A maximum of 28 days has been provided to screen subjects prior to first dose.

5.2.2.1 Pembrolizumab Dose Administration

Pembrolizumab should be administered every 21 days (for Q3W schedule) after all procedures and assessments have been completed except for the post-infusion PK sample time points listed in the Study Flow Chart. Pembrolizumab may be administered within 72 hours before or after the planned date of treatment for administrative reasons only (e.g., scheduling an infusion around a holiday).

The specific time of pembrolizumab administration (e.g., time of the week for first administration; time of the day for each administration) should take into consideration PK sampling time points and study visit procedures.

Pembrolizumab will be administered as a 30 minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Subjects do not need to be observed for any specific period of time after the infusion, but should be provided instructions to notify study personnel if symptoms of infusion reaction occur after any pembrolizumab infusion.

The Procedures/Pharmacy Manuals contain specific instructions for pembrolizumab dose calculation, preparation of the infusion fluid, and administration.

5.2.2.2 Trametinib and Dabrafenib Dose Administration

Both trametinib and dabrafenib should be administered in the morning at approximately the same time every day. The second dose of dabrafenib should be administered approximately 12 hours after the morning dose. Study medication should be taken orally with approximately 200 mL of water under fasting conditions, either 1 hour before or 2 hours after a meal.

The specific time of trametinib and dabrafenib administration should take into consideration PK sampling time points and study visit procedures.

If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next dose as originally scheduled.

If a subject misses a dose of dabrafenib, the subject may take the dose immediately if the next dose is scheduled for at least 6 hours later. If the next scheduled dose is due in less than 6 hours, the subject should skip the dose and resume dosing at the next scheduled dose.

If a subject misses a dose of trametinib, the subject may take the dose immediately if the next dose is scheduled for at least 12 hours later. If the next scheduled dose is due in less than 12 hours, the subject should skip the dose and resume dosing at the next scheduled dose.

Subjects should start treatment as soon as possible after randomization but no later than 72 hours post-randomization.

5.2.3 Trial Blinding/Masking

Parts 1, 2, 4, and 5 are open-label in the trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

In Part 3, a double-blind/masking technique will be used. Pembrolizumab and placebo will be dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel.

The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

5.2.4 Rules for Dose Escalation and Confirmation

5.2.4.1 Dose Escalation

5.2.4.1.1 Dose Escalation (Part 1)

Dose limiting toxicities (DLTs) observed in Cycle 1 (i.e., Cycle 1, initiated with the first pembrolizumab dose) will be used to determine escalation to the next dose level. The study is using a 3+3 design followed by dose confirmation based on the TPI method [92] and has 2 parts: a dose escalation part, and a dose confirmation part according to the TPI approach. The guidelines used for dose escalation and dose confirmation are shown in Table 11.

The rules applied for the dose escalation part are as follows:

An initial cohort of 3 subjects is enrolled at Dose Level 1.

- If 0/3 subjects develops a DLT, then dose escalation will terminate with this finding, Dose Level 1 will be considered the preliminary MTD/MAD, and the study will proceed to the dose confirmation stage.
- If 1/3 subjects develops a DLT, another 3 subjects will be enrolled at this dose level.
    - If ≤1 of the 3 new subjects develops a DLT (for a total of ≤2/6 subjects with a DLT at this dose level), then dose escalation will terminate with this finding, Dose Level 1 will be considered the preliminary MTD/MAD, and the study will proceed to the dose confirmation stage.
    - If >1 of the 3 new subjects develop a DLT (for a total of >2/6 subjects with a DLT at this dose level), 3 subjects will be enrolled at Dose Level -1.
        - If 0/3 subjects develops a DLT at Dose Level -1, then dose escalation will terminate with this finding, Dose Level -1 will be considered the preliminary MTD/MAD, and the study will proceed to the dose confirmation stage.
        - If 1/3 subjects develops a DLT at Dose Level -1, another 3 subjects will be enrolled at Dose Level -1. If ≤2/6 subjects develop a DLT at Dose Level -1, then dose escalation will terminate with this finding, Dose Level -1 will be considered the preliminary MTD/MAD, and the study will proceed to the dose confirmation stage.
        - If ≥2/3 subjects or >2/6 subjects develop a DLT at Dose Level -1, the dose escalation part of the study will terminate and the combination will not be studied further.

- If ≥2/3 subjects develop a DLT, 3 subjects will be enrolled in Dose Level -1.
    - If 0/3 subjects develops a DLT at Dose Level -1, then dose escalation will terminate with this finding, Dose Level -1 will be considered the preliminary MTD/MAD, and the study will proceed to the dose confirmation stage.
    - If 1/3 subjects develops a DLT at Dose Level -1, another 3 subjects will be enrolled at Dose Level -1. If ≤2/6 subjects develop a DLT at Dose Level -1, then dose escalation will terminate with this finding, Dose Level -1 will be considered the preliminary MTD/MAD, and the study will proceed to the dose confirmation stage.
    - If ≥2/3 subjects of >2/6 subjects develop a DLT at Dose Level -1, the dose escalation part will terminate and the combination will not be studied further.

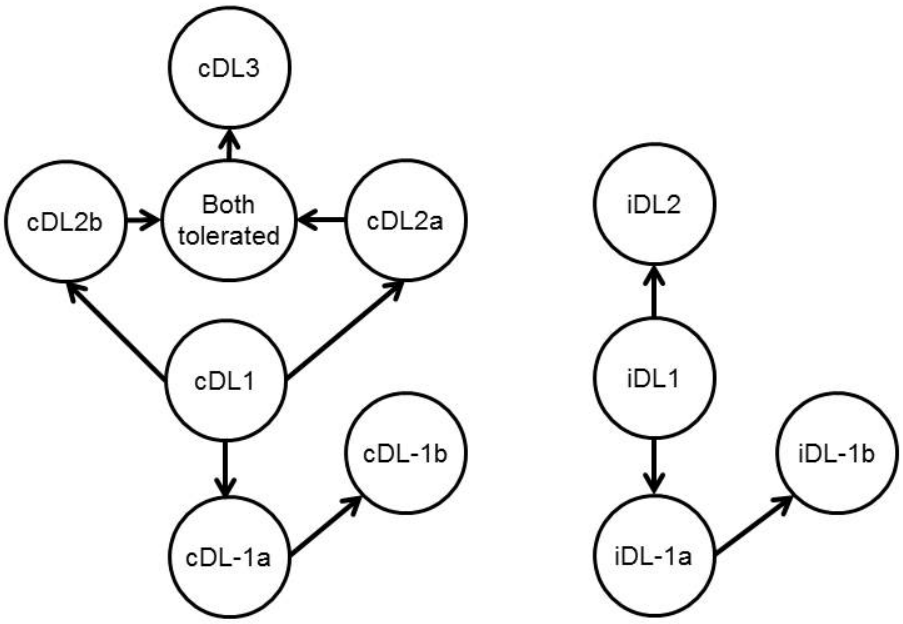
It is conceptually acceptable to de-escalate to an intermediate, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired in lieu of proceeding directly to the dose confirmation stage of the study. If this approach is taken, 3 new subjects should be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

There may be >3 or >6 subjects enrolled at any given dose cohort due to replacement of subjects who were not evaluable or further evaluation of safety or pharmacokinetics at a dose level.

5.2.4.1.2 Dose Escalation (Part 4)

Dose limiting toxicities (DLTs) observed in Cycle 1 (i.e., following the trametinib run-in period in Cycle 1, initiated with the first pembrolizumab dose) will be used to determine escalation to the next dose level. The study is using a 3+3 design followed by dose confirmation based on the modified Toxicity Probability Interval (mTPI) method [104] and has 2 parts: a dose escalation part, and a dose confirmation part according to the mTPI approach. The guidelines used for dose escalation (Table 6 and Table 7) and dose confirmation (Table 12 and Table 13) are provided. A flow diagram for the concurrent and intermittent regimens is included in Figure 2.

Figure 2 Flow Diagram: Part 4 Concurrent (cDL) and Intermittent (iDL) Dose Levels



Each treatment regimen (concurrent and intermittent) will be tested simultaneously, and subjects will be assigned to these treatment arms using 1:1 randomization whenever both regimens are open for enrollment. For each regimen, an initial cohort of 3 subjects is enrolled at Dose Level 1. The dose levels for the concurrent and intermittent treatment arms are shown in Table 6 and Table 7, respectively. Of note, for the concurrent dosing regimen, Dose Levels 2a and 2b will be tested simultaneously, and to proceed to Dose Level 3, both Dose Level 2a and 2b must be found to be tolerable.

The rules applied for the dose escalation part are as follows:

- If 0/3 subjects develop a DLT, then dose escalation will advance to the next Dose Level(s).
- If 1/3 subjects develop a DLT, another 3 subjects will be enrolled at this dose level.
    - If ≤1 of the 3 new subjects develops a DLT (for a total of ≤2/6 subjects with a DLT at this dose level), then dose escalation will advance to the next Dose Level(s). If this occurs at Dose Level 3 (concurrent regimen) or Dose Level 2 (intermittent regimen), then dose escalation will terminate with this finding,

the respective Dose Level will be considered the MTD/MAD, and the study will proceed to the dose confirmation stage.

- If >1 of the 3 new subjects develop a DLT at Dose Level 1 (for a total of >2/6 subjects with a DLT), 3 subjects will be enrolled at Dose Level -1a. If this occurs at any other dose level for either regimen, then dose escalation will terminate with this finding, the previous lower dose level will be considered the preliminary MTD, and the study will proceed to the dose confirmation stage.
  - If 0/3 subjects develop a DLT at Dose Level -1a, then dose escalation will advance to Dose Level -1b.
  - If 1/3 subjects develops a DLT at Dose Level -1a, another 3 subjects will be enrolled at Dose Level -1a. If ≤2/6 subjects develop a DLT at Dose Level -1a, then dose escalation will advance to Dose Level -1b. Of note, if Dose Level -1b is subsequently found to be tolerable, the dose escalation will terminate with this finding, Dose Level -1b will be considered the preliminary MTD, and the study will proceed to the dose confirmation stage.
  - If ≥2/3 subjects or >2/6 subjects develop a DLT at Dose Level -1a, the dose escalation part of the study will terminate and the dosing regimen will not be studied further.

- If ≥2/3 subjects develop a DLT at Dose Level 1, 3 subjects will be enrolled in Dose Level -1a.
  - If 0/3 subjects develop a DLT at Dose Level -1a, then dose escalation will advance to Dose Level -1b. Of note, if Dose Level -1b is subsequently found to be tolerable, the dose escalation will terminate with this finding, Dose Level -1b will be considered the preliminary MTD, and the study will proceed to the dose confirmation stage.
  - If 1/3 subjects develop a DLT at Dose Level -1a, another 3 subjects will be enrolled at Dose Level -1a. If ≤2/6 subjects develop a DLT at Dose Level -1a, then dose escalation will advance to Dose Level -1b. Of note, if Dose Level -1b is subsequently found to be tolerable, the dose escalation will terminate with this finding, Dose Level -1b will be considered the preliminary MTD, and the study will proceed to the dose confirmation stage.
  - If ≥2/3 subjects or >2/6 subjects develop a DLT at Dose Level -1a, the dose escalation part will terminate and the combination will not be studied further.

It is conceptually acceptable to de-escalate to an intermediate, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired in lieu of proceeding directly to the dose confirmation stage of the study. If this approach is taken, 3

new subjects should be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

There may be >3 or >6 subjects enrolled at any given dose cohort due to replacement of subjects who were not evaluable or further evaluation of safety or pharmacokinetics at a dose level.

Patients who experience a DLT will be allowed to remain on study if they meet the following criteria: (1) the investigator believes it is appropriate for patients to remain on study, and (2) the event has resolved and no longer meets the definition of DLT.

5.2.4.2 Dose Confirmation

5.2.4.2.1 Dose Confirmation (Part 2)

The objective of dose confirmation is to refine the estimate of the MTD. Dose confirmation involves the expansion of at least 1 dose combination studied in the dose escalation stage of the study.

Dose confirmation will begin with expansion of the preliminary MTD identified in the dose escalation stage described above. The dose confirmation part will continue based on the TPI method [92] until 14 subjects are studied at the selected dose (combined from dose escalation and dose confirmation) with ≤5 of 14 subjects experiencing a DLT. As subjects become evaluable for DLT assessment, the number of subjects who are evaluable for DLT versus the number of subjects who developed a DLT will be continuously assessed and de-escalation and re-escalation to eligible doses will occur as shown in Table 11.

Table 11 Part 2 Dose Confirmation Rules

Number of toxicities	Number of patients treated at current dose										
	4	5	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	D	S	S	S	S	S	S	S
4	DU	DU	DU	DU	DU	D	D	S	S	S	S
5		DU	DU	DU	DU	DU	DU	D	D	D	S
6			DU	DU	DU	DU	DU	DU	DU	DU	D
7				DU	DU	DU	DU	DU	DU	DU	DU
8					DU	DU	DU	DU	DU	DU	DU
9						DU	DU	DU	DU	DU	DU
10							DU	DU	DU	DU	DU
11								DU	DU	DU	DU
12									DU	DU	DU
13										DU	DU
14											DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic

Target MTD = 25%
a=1; b=1; k1=1.5; k2=0.5; pow=1.1 per [92]

If de-escalation to Dose Level -1 is required, but Dose Level -1 was not studied in the Part 1 of the study, 3+3 design rules described in Section 5.2.4.1 will be applied to Dose Level -1 before 0/3 or ≤2/6 DLTs are observed at this dose and Dose Level -1 enters the dose confirmation stage with the rules shown in Table 11.

Subjects may be enrolled continuously (i.e., without waiting for Cycle 1 completion of subjects who have received the first dose) unless a DLT is observed at the particular dose. Once a DLT is observed, the number of subjects who are enrolled at that dose but are not yet fully evaluable for DLT assessment may not exceed the number of remaining subjects who are at risk of developing a DLT before the dose would be considered unacceptably toxic (denoted as DU in Table 11). For example, if 3/8 subjects have experienced a DLT at a given dose level, no more than an additional 2 subjects should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 2 additional subjects experience a DLT (i.e., 5/10 subjects with DLT in Table 11). To find out how many more subjects can be enrolled, one can count steps in diagonal direction (down and to the right) from the cell (8 subjects, 3 toxicities) to the first cell marked DU.

If enrollment expands to 14 subjects for a dose level, and ≤5 of the 14 subjects develop a DLT, then the dose confirmation will stop. If enrollment expands to 14 subjects for a dose level and >5/14 subjects develop a DLT, then the next lower dose may be expanded to further explore the dose-response relationship. Note that while 25% has been the target toxicity rate used to generate the guidelines in Table 11, the observed rate of subjects with DLT at the MTD may be slightly above or below 25%.

5.2.4.2.2 Dose Confirmation (Part 5)

The objective of dose confirmation is to refine the estimate of the MTD. Dose confirmation involves the expansion of at least 1 dose combination studied in the dose escalation stage of the study.

Dose confirmation will begin with expansion of the preliminary MTD identified in the dose escalation stage described above. As in Part 4, each treatment arm (concurrent and intermittent) will be tested simultaneously, and subjects will be assigned to these treatment arms using 1:1 randomization whenever both regimens are open for enrollment. The dose confirmation part will continue based on the mTPI method [104] with a target DLT rate of 30% until 14 subjects are studied at the selected dose (combined from dose escalation and dose confirmation) with ≤6 of 14 subjects experiencing a DLT. As subjects become evaluable for DLT assessment, the number of subjects who are evaluable for DLT versus the number of subjects who developed a DLT will be continuously assessed and de-escalation and re-escalation to eligible doses will occur as shown in Table 12. Table 12 outlines the dose escalation and de-escalation sequences depending on the preliminary MTD defined in Part 4 for the concurrent and intermittent dosing regimens.

If, for example, de-escalation to Dose Level -1a is required, but Dose Level -1a was not studied in Part 4, the 3+3 design rules described in Section 5.2.4.1.2 will be applied to Dose Level -1a before (1) 0/3 or ≤2/6 DLTs are observed at this dose, and, (2) Dose Level -1a enters the dose confirmation stage with the rules shown in Table 13.

Table 12 mTPI Dosing Sequences

Concurrent Dosing Regimen		**Intermittent Dosing Regimen**	
Preliminary MTD from Part 4	**Sequence**	**Preliminary MTD from Part 4**	**Sequence**
cDL-1a	*cDL-1a* -> cDL-1b -> cDL1 -> cDL2a -> cDL3	iDL-1a	*iDL-1a* -> iDL-1b -> iDL1 -> iDL2
cDL-1b	cDL-1a <- *cDL-1b* -> cDL1 -> cDL2a -> cDL3	iDL-1b	iDL-1a <- *iDL-1b* -> iDL1 -> iDL2
cDL1	cDL-1a <- *cDL1* -> cDL2a -> cDL3	iDL1	iDL-1a <- *iDL1* -> iDL2
cDL2a	cDL-1a <- cDL1 <- *cDL2a* -> cDL3	iDL2	iDL-1a <- iDL1 <- *iDL2*
cDL2b	cDL-1a <- cDL1 <- *cDL2b* -> cDL3		
cDL3	cDL-1a <- cDL1 <- cDL2a <- *cDL3*		

Subjects may be enrolled continuously (i.e., without waiting for Cycle 1 completion of subjects who have received the first dose) unless a DLT is observed at the particular dose. Once a DLT is observed, the number of subjects who are enrolled at that dose but are not yet fully evaluable for DLT assessment may not exceed the number of remaining subjects who are at risk of developing a DLT before the dose would be considered unacceptably toxic (denoted as DU in Table 13). For example, if 3/8 subjects have experienced a DLT at a given dose level, no more than an additional 3 subjects should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 additional subjects experience a DLT (i.e., 6/11 subjects with DLT in Table 13). To find out how many more subjects can be enrolled, one can count steps in diagonal direction (down and to the right) from the cell (8 subjects, 3 toxicities) to the first cell marked DU.

If enrollment expands to 14 subjects for a dose level, and ≤6 of the 14 subjects develop a DLT, then the dose confirmation will stop. If enrollment expands to 14 subjects for a dose level and >6/14 subjects develop a DLT, then the next lower dose may be expanded to further explore the dose-response relationship. Note that while 30% has been the target toxicity rate used to generate the guidelines in Table 13, the observed rate of subjects with DLT at the MTD may be slightly above or below 30%.

Table 13 Part 5 Dose Confirmation Rules

	Number of subjects treated at current dose											
Number of toxicities	3	4	5	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
7					DU	DU	DU	DU	DU	DU	DU	D
8						DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU
10								DU	DU	DU	DU	DU
11									DU	DU	DU	DU
12										DU	DU	DU
13											DU	DU
14												DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target toxicity rate = 30%
Flat non-informative prior Beta (1,1) is used as a prior and ε1=ε2=0.05 [104].

5.2.4.3 Dose Limiting Toxicity

Toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0. A DLT evaluable subject is defined as a subject who receives treatment for the 6-week dose-limiting toxicity (DLT) observation period and who receives at least 66% of all planned treatments. A subject who does not receive at least 66% of planned treatment due to AEs that are unrelated to study treatment will not be considered evaluable for DLTs and may be replaced as needed during dose escalation or dose confirmation. More than 3 or 6 subjects may be enrolled to a given dose level if needed to replace subjects who are not evaluable for DLT or to ensure a thorough evaluation of a given dose level during the dose escalation part of the study. An event will be considered a dose-limiting toxicity (DLT) if it occurs during the first cycle of treatment in dose identification and confirmation subjects (first 6 weeks after initiating pembrolizumab treatment) and meets at least one of the following criteria:

• Clinically significant hematologic toxicity (e.g. grade 4 neutropenia lasting more than 7 days or accompanied by neutropenic fever, or Grade 4 thrombocytopenia of any duration)

• Clinically significant Grade ≥3 non-hematologic toxicity that has not been previously identified for either pembrolizumab or dabrafenib/trametinib and cannot be controlled with routine supportive measures (e.g. anti-emetics)

• Clinically significant Grade ≥3 non-hematologic toxicities that are known to occur with either pembrolizumab or dabrafenib/trametinib but that cannot be controlled using the recommended product-specific supportive measures (e.g. steroids for pembrolizumab-related immune toxicities)

• Drug-related toxicity, regardless of CTCAE grade, that results in an interruption of any component of study therapy during Cycle 1 for more than 21 consecutive days and cannot be controlled within 2 weeks from its onset

• Any other Grade 2 or greater non-hematological toxicity that in the judgment of the investigator and Sponsor is dose limiting, with the exception of mild or moderate immune-mediated adverse reactions or symptomatic endocrinopathy attributable to pembrolizumab

• Liver chemistries meeting stopping guidelines (as outlined in Section 5.6.1.1.15):

1. ALT or AST ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT/AST≥3xULN and INR>1.5, if INR measured)

   NOTE: If serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT or AST ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations suggest liver injury.

2. ALT or AST ≥ 8xULN

3. ALT or AST ≥ 5xULN but <8 xULN persists for ≥2 weeks

4. ALT or AST ≥ 3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash or eosinophilia.

5. ALT or AST ≥ 5xULN but <8 xULN and cannot be monitored weekly for >2 weeks.

The following will NOT be considered a DLT for the purposes of this protocol:

• Clinically insignificant laboratory values of any grade (i.e. asymptomatic amylase, lipase elevations).

• Cutaneous squamous cell carcinoma (cuSCC), basal cell carcinoma, and new primary melanomas which are manageable with surgical excision alone.

Note: Dose reduction of pembrolizumab is prohibited during Cycle 1 of Parts 1, 2, 4, and 5 (excluding the subjects enrolled into the MK+T cohort after MTD/MAD is confirmed in Parts 2 and 5 of the MK+T arms). Dose reduction of dabrafenib and trametinib during all parts of the trial should follow the label instructions or protocol guidance where appropriate.

5.2.5 Treatment Duration

Subjects who have a confirmed complete response after at least 6 months of study treatment and 2 doses of pembrolizumab treatment beyond CR may stop pembrolizumab at the investigator's discretion. Trametinib and/or dabrafenib treatment may be continued until PD or unacceptable toxicity or until completion of 24 months of treatment.

All subjects who continue pembrolizumab treatment to 24 months and who did not discontinue prior to 24 months due to PD or unacceptable toxicity will discontinue pembrolizumab at that time. Beyond 24 months, trametinib and/or dabrafenib treatment may be continued off study as per standard of care.

The Part 3 final analysis did not demonstrate a statistically significant increase in PFS in the experimental arm compared to the control arm. Subjects in the Part 3 experimental arm experienced a higher rate of Grade 3-5 AEs, SAEs, and discontinuations due to AEs compared to the control arm. Therefore, there is no further rationale to offer re-challenge with triplet therapy and Second Course treatment will not be offered to any subject in KEYNOTE-022. In exceptional cases and upon Sponsor consultation and approval, trametinib and/or dabrafenib may be continued on study after completion of 24 months of treatment with pembrolizumab combined with trametinib and dabrafenib or placebo combined with trametinib and dabrafenib. These subjects can continue in accordance with the flow chart in Section 6.2 until the study is closed by the Sponsor. At the time of study closure, the subjects would move to local supply and continue care under their local treating physician.

In the event a Part 3 subject discontinued study treatment due to documented disease progression, and the unblinding of treatment alters a subject's eligible therapy options outside of the trial, a PI may request to have the subject's treatment assignment unblinded after discussion with Sponsor. All precautions will be taken to ensure the Sponsor and blinded site personnel remain blinded to the subject's treatment.

After completion of pembrolizumab and/or trametinib at 24 months in Part 4 and 5, subjects will be discontinued from the trial. Subjects who are discontinued from the trial may move to followup until progression or survival follow-up if they opt to continue on any oncologic therapy. This would include pembrolizumab or trametinib and would be sourced locally as per standard of care. At the time of study closure, the subjects would move to local supply and continue care under their local treating physician.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 arms. Subjects will be assigned randomly in an 1:1 ratio to (1) the confirmed triplet dose of pembrolizumab, trametinib 2 mg QD, dabrafenib 150 mg BID, or, (2) placebo of pembrolizumab (saline IV), trametinib 2 mg QD, dabrafenib 150 mg BID, respectively. Randomization will occur **only** in Part 3 of the trial in the blinded portion of the study. Subjects in Parts 1 and 2 of the study (open label) will be assigned study treatment without randomization. Subjects in Parts 4 and 5 of the study (open label), will be assigned study treatment (concurrent vs. intermittent dosing regimen) in a 1:1 fashion whenever more than one regimen is open for enrollment.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. Eastern Cooperative Oncology Group Performance Status (0 vs. 1)

2. Lactate Dehydrogenase (LDH) level (>1.1 x ULN vs. ≤1.1 x ULN)

Stratification is applicable only to Part 3 of this study. No stratification is utilized in Parts 1, 2, 4, and 5.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. Listed below are some specific restrictions for concomitant therapy or vaccination during the course of the trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Use of anticoagulants such as warfarin is permitted; however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin. See Section 5.5.3 Medications to be Used with Caution.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 90 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phases of this trial:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab, trametinib, and dabrafenib.
- Radiation therapy.
- Live vaccines within 30 days prior to the first dose of study therapy and while participating in study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist) are live attenuated vaccines, and are not allowed.
- Antiretroviral drugs

  Note: Subjects with known HIV are ineligible for study participation.
- Herbal remedies (e.g., St. John's wort).

- Glucocorticoids for any purpose other than to manage adverse events.

- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibitor, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in Table 14) may only be used under special circumstances (e.g., as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the medical monitor is required in these situations. The list may be modified based on emerging data.

Table 14 Prohibited Concomitant Medications

PROHIBITED – strong inducers of CYP3A or CYP2C8, since concentrations of dabrafenib may be decreased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	rifamycin class agents (e.g., rifampin, rifabutin, rifapentine)
Anticonvulsant	carbamazepine, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan, St-John's wort
PROHIBITED – Strong inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	clarithromycin, telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	itraconazole, ketoconazole, posaconazole, voriconazole
Hyperlipidemia	gemfibrozil
Antiretroviral	ritonavir, saquinavir, atazanavir
Miscellaneous	conivaptan

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5.3 Medications to be Used with Caution

The following medications should be used with caution during the Screening and Treatment Phases of this trial, as their concentrations may be altered by dabrafenib or they may alter dabrafenib concentrations:

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.

- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases. Transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) and transporters may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in Table 15.

- Therapeutic level dosing of warfarin can be used with approval by the medical monitor and close monitoring of PT/INR by the site. Warfarin exposure has been shown to decrease (37% decrease) due to dabrafenib-mediated enzyme induction. Conversely, if dabrafenib dosing is reduced, interrupted, or discontinued, warfarin exposure may be increased. Thus, warfarin dosing may need to be adjusted based on PT/INR during and after treatment with dabrafenib. Prophylactic low dose warfarin may be given to maintain central catheter patency.

- Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib pharmacokinetics. In an ad-hoc analysis, no differences in C_{max} and AUC were noted between subjects who reported taking pH-elevating products relative to other subjects. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these medicinal products that increase gastric pH should be used with caution when administered with dabrafenib.

Table 15 Medications to be used with Caution

USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Moderate CYP3A and CYP2C8 Inhibitors**
Antiarrhythmics	diltiazem, verapamil
Antibiotic	Erythromycin
Antifungal	Fluconazole
Miscellaneous	Aprepitant
USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction**
Analgesics	alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	disopyramide, dronedarone, mexiletine, propafenone, quinidine
Antibiotics	chloramphenicol, doxycycline, erythromycin, moxifloxacin
Anticoagulants/ Antiplatelets	cilostazole, warfarin
Anticonvulsants	divalproex, lamotrigine, valproate, zonisamide
Antidepressants and Antipsychotics	aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone, amitriptyline, clomipramine, imipramine
Antidiabetics	glyburide, saxagliptin, tolbutamide, nateglinide, pioglitazone, repaglinide, rosiglitazone
Antifungals	caspofungin, fluconazole, terbinafine
Antihistamines	astemizole, chlorpheniramine, ebastine
Antihypertensives	amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil
Antimigraine Agents	diergotamine, eletriptan, ergotamine
Corticosteroids	dexamethasone, methylprednisolone, oral budesonide
Erectile Dysfunction Agents	sildenafil, tadalafil, vardenafil
HMG-CoA Reductase Inhibitors	atorvastatin, lovastatin, simvastatin, rosuvastatin, pravastatin
Hypnotics and Sedatives	alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	everolimus, sirolimus, tacrolimus
Miscellaneous	aprepitant, cisapride, darifenacin, digoxin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone
Selective Aldosterone Blockers	Eplerenone
USE WITH CAUTION: Co-administration of drugs that increase gastric pH should be used with caution when administered with dabrafenib as exposure to dabrafenib may be decreased	
pH altering agents	dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine
Abbreviations: CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A.	

Questions regarding concomitant medications should be directed to the medical monitor for clarification.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology associated with pembrolizumab are outlined along with the dose modification guidelines in Section 5.2.1.2, Table 10. Additional toxicity management guidelines are provided below in Table 16 to Table 35. Where appropriate, these guidelines include the use of oral or IV 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 study treatment.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 10 in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

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

Adverse Event Management Guidelines, including dose modification algorithms, are provided in this section for subjects treated with:

- Trametinib+dabrafenib
- Pembrolizumab (or saline IV)+trametinib and/or dabrafenib
- Pembrolizumab

Note: Dose modification guidelines for a given toxicity (e.g., hepatotoxicity) may not be identical for each treatment; therefore it is important to refer to the algorithm described for the combination treatment or specific single-agent. An overview of the available dose modification guidelines is presented in Table 16 along with the location of the toxicity- and treatment-specific guidance.

All AEs are to be graded according to NCI-CTCAE v4 (http://ctep.cancer.gov). All dose modifications and the reason for the dose modification must be documented in the eCRF.

Investigators should refer to the appropriate IB for trametinib, dabrafenib and pembrolizumab for additional information regarding the background of each drug and the management of other AEs or potential safety-related issues.

Events of Clinical Interest (ECIs) are selected non-serious and serious adverse experiences that must be reported to Merck **within 24 hours** regardless of attribution to trial treatment.

5.6.1.1 Pembrolizumab+Trametinib and/or Dabrafenib, or, Trametinib+Dabrafenib Combination Safety Management Guidelines

Dose modifications and stopping criteria for the management of toxicities are presented in this section for subjects treated with the combination of dabrafenib and/or trametinib +/- pembrolizumab. Toxicities common to dabrafenib, trametinib, and pembrolizumab include, but are not limited to, ocular toxicities, skin-related toxicities, diarrhea, pneumonitis, and pyrexia. Therefore, it is possible that these and/or other toxicities may be exacerbated when dabrafenib, trametinib, and pembrolizumab are combined. For this reason, it is important to note that the management guidelines for the combination of dabrafenib + trametinib + pembrolizumab may differ for a given AE from the management guidelines for single-agent dabrafenib, single-agent trametinib, combination of dabrafenib+trametinib, or single-agent pembrolizumab.

5.6.1.1.1 Dose Level Reduction of Trametinib and/or Dabrafenib for Subjects beyond the DLT Period

The dose level reductions for subjects beyond the DLT evaluation period for dabrafenib and trametinib for this study are provided in Table 5 and Table 16.

Table 16 Dose Level Reduction Guidelines

Dose Level	Dabrafenib Dose/Schedule	Trametinib Dose/Schedule
Starting Dose	150 mg BID	2 mg once daily
-1 (1st Dose reduction)	100 mg BID	1.5 mg once daily
-2 (2nd Dose reduction)	75 mg BID	1.0 mg once daily
Abbreviation: BID = twice daily		

If an AE resolves to grade 1 or baseline at the reduced dose level, and no additional toxicities are seen after 4 weeks of study treatment at the reduced dose, the dose may be increased to the previous dose level after discussion with the Sponsor. Please refer to Section 5.2.1.2.1 and Section 5.6.1.1 for additional information on dose modification and associated supportive care guidelines for pembrolizumab, trametinib, and/or dabrafenib.

5.6.1.1.2 Interruption or Discontinuation of Trametinib, Dabrafenib and/or Pembrolizumab

If a subject's study treatment has been interrupted for more than 21 days for dabrafenib, trametinib, and/or 2 doses of pembrolizumab have been withheld, the investigator must contact the Sponsor to review the subject's condition in order to resume the treatment.

Subjects being treated on combination therapy who require discontinuation of one or more medications for toxicity may continue the remaining treatment(s). The reason for

discontinuation must be recorded. For subsequent management of toxicities on the remaining treatment(s), please refer to the relevant IB for the medication.

5.6.1.1.3 Immune-related Adverse Events

Adverse events of special interest of a potential immunologic etiology may be defined as an adverse event associated with drug exposure and consistent with an immune phenomenon. irAEs may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

General principles of irAE identification and evaluation:

Before each dose investigators are to review a subject's AEs, concomitant medications and clinical evaluation results e.g., vital signs, laboratory results, physical exam findings, etc., as outlined in Section 7.1 to monitor for new or worsening irAEs and ensure continued dosing is appropriate.

Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants [93-95]. If an irAE is suspected, the subject should return to the study site as soon as possible instead of waiting for their next scheduled visit. Subjects who experience a new or worsening irAE should be contacted and/or evaluated at the study site more frequently.

If an irAE is suspected, a thorough evaluation should be conducted in an effort to possibly rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before diagnosing an irAE. Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis of an immune-related toxicity. Higher grade and persistent lower grade irAEs typically necessitate interrupting or permanently discontinuing treatment and administration of systemic steroids or other immunosuppressive agents (such as TNF blockers) when systemic steroids are not effective.

Identification and treatment of irAEs: Based on literature review and consideration of mechanism of action of pembrolizumab, guidelines have been developed regarding how to identify, evaluate and manage irAEs that may occur in subjects receiving pembrolizumab (see Section 5.2.1.2.1). It is possible that irAEs other than those listed in this document may be observed in subjects receiving pembrolizumab, therefore all AEs of unknown etiology associated with drug exposure should be evaluated to determine if it is possibly immune-related. This section is meant to be a general guidance; therefore, recommendations in the current document might not be all inclusive. As such investigators are encouraged to contact the Sponsor as needed to discuss cases that warrant separate discussion outside of the scope of current guidelines. Permanent discontinuation of pembrolizumab, trametinib, and/or

dabrafenib due to an irAE may be the subject of discussion between the Sponsor and treating investigator.

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

- Clinical course of the event
- Course of treatment
- Evidence supporting recovery
- Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

5.6.1.1.4 General Guidelines for Clinically Significant Toxicities

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and which do not have specific guidelines are provided in Table 17.

Table 17 Dose Modification Guidelines for Events Considered Related to Study Treatment

CTCAE Grade	Action and Dose Modification
Grade 1 or Grade 2 (tolerable)	• Continue study treatment at current dose level • Monitor closely • Provide supportive care according to institutional standards
Grade 2 (Intolerable)	• Interrupt study treatment if clinically indicated • Monitor closely • Provide supportive care according to institutional standards - If treatment was interrupted, when toxicity resolves to grade 1 or baseline, restart study treatment: dose-reduced for 1st or 2nd occurrence (dabrafenib and/or trametinib only) - if > 2 dose-reductions are required, permanently discontinue study treatment
Grade 3	• Interrupt study treatment • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to grade 1 or baseline, restart study treatment **reduced by one dose level or discontinue at investigator's discretion after discussion with sponsor** • If the grade 3 toxicity recurs, interrupt study treatment • When toxicity resolves to grade 1 or baseline, restart study treatment **reduced by another dose level or discontinue at investigator's discretion after discussion with sponsor** • **Discontinue study treatment at next occurrence**
Grade 4	• Interrupt study treatment • **Permanently discontinue pembrolizumab** • Monitor closely • Provide supportive care according to institutional standards • May restart dabrafenib and/or trametinib **reduced by one dose level** once toxicity resolves to grade 1 or baseline, or discontinue at investigator's discretion • If the grade 4 toxicity recurs, either **permanently discontinue all study treatment or**, if the subject is clinically benefiting, discuss continuation of study treatment with the Sponsor.
Any Grade[a]	• Any signs of symptoms of Severe Cutaneous Adverse Reactions (SCARs), permanently discontinue dabrafenib and trametinib immediately

a. Cases of SCARs, including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms, which can be life-threatening or fatal, have been reported during treatment with dabrafenib in combination with trametinib. Before initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, dabrafenib and trametinib should be permanently discontinued.

Note: With the exception of cases of SCARs, when an individual subject's adverse reactions are effectively managed, dose re-escalation following the same dosing steps as de-escalation may be considered.

5.6.1.1.5 Diarrhea

Subjects 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 subjects 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.

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer.

Episodes of diarrhea have occurred in subjects receiving dabrafenib, trametinib, or both therapies in combination, as well as in subjects receiving pembrolizumab. Other, frequent causes for diarrhea including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by C. difficile or other pathogens, partial bowel obstruction, etc., should be clinically excluded.

Guidelines regarding management and dose reduction for diarrhea considered to be related to study treatment by the investigator are provided in Table 10 and Table 18.

Table 18 Management and Dose Modification Guidelines for Diarrhea

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Uncomplicated Diarrhea[a] Grade 1 or 2	• Diet: stop all lactose containing products; eat small meals, ADA colitis diet recommended • Hydration: 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth) • Consider GI consultation and endoscopy to evaluate for colitis for Grade 2 diarrhea persisting > 1 week • If symptoms worsen or persist > 3 days, treat as Grade 3 • Loperamide[c]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours. • Diarrhea > 24h: loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea > 48h: loperamide 2 mg every two hours; maximum 16 mg/day. Add budesonide (9mg/day) or other second-line therapies (octreotide, oral diphenoxylate hydrochloride, atropine sulfate four times daily, or tincture of opium) and oral antibiotics • Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy or lasting >1 week may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	• Continue study treatment, unless: • If diarrhea is grade 2 for > 48h: interrupt study treatment until diarrhea resolves to grade ≤ 1. • Restart study treatment at the same dose level.

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Uncomplicated Diarrhea[a] **Grade 3 or 4** **OR** **Any Complicated Diarrhea[b]**	• Clinical evaluation mandatory; rule out bowel perforation • Consider consultation with Gastroenterologist and confirmation biopsy with endoscopy • Loperamide[c]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours • Hydration: intravenous fluids if clinically indicated • Antibiotics (oral or intravenous) if clinically indicated • Intervention should be continued until the subject is diarrhea free for ≥ 24 hours • In addition to symptomatic treatment and hydration, immediate treatment with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) is recommended. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in subjects with diffuse and severe ulceration and/or bleeding. • If IV steroids followed by high dose oral steroids do not reduce initial symptoms within 48 to 72 hours, consider alternative treatment. Discontinue alternative treatment upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. . • If symptoms persist despite the above treatment a surgical consult should be obtained. • Intervention may require hospitalization for subjects at risk of life-threatening complications	Grade 3 • Interrupt all study treatment until diarrhea resolves to grade ≤1 • pembrolizumab may be restarted after diarrhea resolves to grade ≤1 and steroid taper (if initiated) is completed • Restart dabrafenib and/or trametinib reduced by one dose level[d] • If dabrafenib and/or trametinib was already dose reduced twice, **permanently discontinue dabrafenib and/or trametinib.** Grade 4 • **Permanently discontinue pembrolizumab** • Follow Grade 3 rules for dabrafenib and/or trametinib.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

a. **Uncomplicated diarrhea** defined by the absence of symptoms such as, cramping, nausea/vomiting ≥grade 2, decreased performance status, pyrexia, sepsis, neutropenia grade ≥3, frank bleeding, and/or dehydration requiring intravenous fluid substitution

b. **Complicated diarrhea** defined by the presence of symptoms such as, cramping, nausea/vomiting ≥grade 2, decreased performance status, pyrexia, sepsis, neutropenia grade ≥3, frank bleeding, and/or dehydration requiring intravenous fluid substitution

c. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea

d. Escalation of study treatment to previous dose level is allowed after consultation with the Sponsor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

5.6.1.1.6 Endocrine Events

Subjects should be carefully monitored for signs and symptoms of endocrine events (such as adrenal insufficiency, hypophysitis, hyperthyroidism, hypothyroidism). If symptoms (such as hypotension or arrhythmia) indicate possible new or worsening cardiac abnormalities, additional testing and/or a cardiology consultation should be considered. All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. An endocrinology consultation is recommended.

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

Guidelines regarding management and dose reduction for endocrine events considered to be related to study treatment by the investigator are provided in Table 10 and Table 19.

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

- Insulin replacement therapy is recommended for Type 1 diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Table 19 Management and Dose Modification Guidelines for Endocrine AEs

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1 or 2	• Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values • If hypophysitis or other symptomatic endocrinopathy (other than hypo- or hyperthyroidism) is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • For Grade 2 hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism, treat with prednisone 40 mg p.o. or equivalent per day. When symptoms improve to grade 1 or less, initiate steroid taper over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered. • Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy. • In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care. • Consultation with an endocrinologist may be considered.	• Continue study treatment • Interrupt pembrolizumab for Grade 2 events other than hypo- or hyperthyroidism (treatment may be continued while treatment for ≤Grade 2 thyroid disorder is initiated)
Symptomatic pan-hypopituitarism **OR** **Grade 3-4**	• Consider Endocrinology consultation • Rule out infection and sepsis with appropriate cultures and imaging. • Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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. • Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization, endocrine consultation, and intravenous methylprednisolone should be initiated.	• Interrupt pembrolizumab until AE resolves to grade ≤1 • Restart pembrolizumab. • If 2 interruptions of pembrolizumab are clinically indicated, **permanently discontinue study pembrolizumab** • NOTE: Interrupt or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. • NOTE: pembrolizumab may be continued for Grade 3-4 hypothyroidism if thyroid replacement is initiated.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events
Note: Hyperglycemia (≥Grade 3) requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Monitor serum glucose levels as clinically appropriate during treatment with dabrafenib in subjects with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

5.6.1.1.7 Vision Changes

Subjects should be carefully monitored for signs and symptoms of vision changes (such as uveitis, iritis, retinal pigment epithelial detachment [RPED], and Retinal Vein Occlusion [RVO]). Symptoms may include (but not limited to): blurred vision, diffuse erythema and a prominent blush on the sclerae, dryness of the eyes, pain, or photophobia. All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts).

Episodes of visual changes have been observed in subjects receiving dabrafenib, trametinib or the combination of both therapies, as well as in subjects receiving pembrolizumab. In addition, ocular AEs are known to be related to trametinib. The causal relationship between a change in vision and the study treatment should be carefully explored and an ophthalmologist should be consulted. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then close monitoring is acceptable and it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal (e.g., RPED) or retinovascular abnormalities (e.g., branch or central RVO). For events of visual changes regardless of severity for which an ophthalmic examination is conducted, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Guidelines regarding management and dose reduction for visual changes and/or ophthalmic examination findings considered to be related to study treatment are provided in Table 20.

Management guidelines for Retinal Pigment Epithelial Detachment (RPED) are provided separately in Table 21.

Table 20 Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1	• Consult ophthalmologist within 7 days of onset (preferably prior to next dose of pembrolizumab) • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics as appropriate.	• If dilated fundoscopic examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retinal specialist/ophthalmologist. • If RPED and RVO excluded, continue (or restart) trametinib at same dose level • If RPED suspected or diagnosed: see RPED dose modification table below; **report as SAE.** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE.** Uveitis: Interrupt pembrolizumab and consider interrupting dabrafenib until symptoms resolve and exam shows resolution • Non-RPED/RVO: Discontinue pembrolizumab if symptoms persist despite treatment with topical and systemic immunosuppressive therapy.
Grade 2 and **Grade 3**	• Consult ophthalmologist immediately • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics as appropriate. • For Grade 3 visual changes, consider treatment with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day as appropriate. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks.	• Interrupt pembrolizumab and trametinib until signs and symptoms resolve to baseline • If RPED and RVO excluded, restart trametinib at same dose level • If RPED diagnosed, see RPED dose modification table below**; report as SAE.** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE** • Non-RPED/RVO: Discontinue pembrolizumab if symptoms persist despite treatment with topical and systemic immunosuppressive therapy. • Uveitis: Interrupt pembrolizumab and dabrafenib, treat with topical steroids until symptoms resolve and exam shows resolution
Grade 4	• Consult ophthalmologist immediately • Report as SAE • Management as per Grade 3 above	• **Interrupt trametinib** • **Permanently discontinue pembrolizumab** • If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study medical monitor • **If RVO or RPED diagnosed, permanently discontinue trametinib**

Abbreviations: RPED = Retinal Pigment Epithelial Detachment; CTCAE = Common Terminology Criteria for Adverse Events; RVO = retinal vein occlusion; SAE = serious adverse event

a. Refers to CTCAE Version 4.0 'Eye disorders – Other, specify

Table 21 Recommended Dose Modifications for Trametinib for Retinal Pigment Epithelial Detachments (RPED)

CTCAE Grade	Action and Dose Modification
Grade 1 RPED[a] (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED[a] (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib • Retinal evaluation monthly • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily
a) Refers to CTCAE Version 4.0 'Retinopathy'	

5.6.1.1.8 Pneumonitis

Subjects should be carefully monitored for signs and symptoms of pneumonitis, interstitial lung disease, or acute interstitial pneumonitis. If symptoms (such as chest pain and/or tightness or dyspnea) indicate possible new or worsening cardiac abnormalities, additional testing and/or a cardiology consultation should be considered. All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.

Pneumonitis has been observed in subjects receiving trametinib, as well as in subjects receiving pembrolizumab. To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms, evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described in Table 10 and Table 22.

It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics. If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

Table 22 Management and Dose Modification Guidelines for Pneumonitis

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation of pulmonologist recommended	• Continue study treatment at current dose
Grade 2	• CT scan (high-resolution with lung windows) • Consider frequent Chest X-ray for monitoring • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist, consider Infectious Disease consultation • Conduct in-person evaluation approximately twice per week • Bronchoscopy with biopsy and/or BAL recommended • Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. • When symptoms improve to Grade 1 or less, steroid taper (if systemic corticosteroids initiated) should be started and continued over no less than 4 weeks.	• Interrupt study all treatment until recovery to grade ≤1 • Treatment with pembrolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg PO daily or less. Repeat chest imaging monthly as clinically indicated. • Treatment with dabrafenib and trametinib at one dose level reduction may be resumed if the event improves to ≤ Grade 1 within 4 weeks; escalation to previous dose level after 4 weeks may be possible after discussion with sponsor • If no recovery to grade ≤1 within 4 weeks or second episode of Grade 2 or higher pneumonitis on re-challenge, **permanently discontinue all study treatment**
Grade 3	• Hospitalize patient • CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Bronchoscopy with biopsy and/or BAL if possible • Immediate treatment with intravenous steroids (methylprednisolone 125 mg). When symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. • If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider alternate therapy (treat with additional anti-inflammatory measures). Discontinue alternate therapy upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsening during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and consider alternate therapy as needed.	• **Permanently discontinue pembrolizumab** • Interrupt dabrafenib and trametinib until recovery to ≤ Grade 1 • After consultation with Sponsor, dabrafenib and trametinib may be restarted **reduced by one dose level** • If no recovery to grade ≤1 within 4 weeks, **permanently discontinue dabrafenib and trametinib**
Grade 4	• Same as grade 3	• **Permanently discontinue all study treatment**
Abbreviations: BAL= bronchoalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events		

5.6.1.1.9 Renal Events

Subjects should be carefully monitored for signs and symptoms of renal insufficiency (such as nephritis, renal failure, or creatinine elevations). All attempts should be made to rule out

other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.

Cases of renal insufficiency have occurred in subjects receiving dabrafenib and the combination of dabrafenib and trametinib, as well as in subjects receiving pembrolizumab. Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and concomitant medications should be modified if clinically possible.

Guidelines regarding management and dose reduction for renal insufficiency considered to be related to study treatment by the investigator are provided in Table 10 and Table 23.

Table 23 Management and Dose Modification Guidelines for Renal Insufficiency

Serum Creatinine Level	Adverse Event Management	Action and Dose Modification
Serum creatinine increase >0.2 mg/dL (18 umol/L) but ≤ 0.5 mg/dL (44 umol/L) above baseline	• Recheck serum creatinine within 1 week • Serum creatinine increase > 1 week: contact Sponsor • For Grade 2 creatinine elevations, treat with prednisone 1-2 mg/kg p.o. daily (when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks) • If pyrexia is present, treat pyrexia as per guidelines[a]	• Continue study treatment at the same dose level • For Grade 2 creatinine elevations, interrupt pembrolizumab
Serum creatinine increase >0.5 mg/dL (44 umol/L) above baseline or serum creatinine >2 mg/dL (> 177 umol/L)	• Monitor serum creatinine ≥ 2-times per week • Hospitalization may be necessary if serum creatinine cannot be monitored frequently • If pyrexia is present, treat pyrexia per guidelines[a] • Consult nephrologist if clinically indicated • Perform ultrasound and/or renal biopsy if clinically indicated, for example: 1. Renal insufficiency persists despite volume repletion 2. Subject has new rash or signs of hypersensitivity (such as elevated eosinophil count) • For ≥ Grade 3 creatinine elevations, treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	• Interrupt study treatment until serum creatinine recovers to baseline • Restart study treatment[b] • For Grade 3-4 creatinine elevations, **permanently discontinue pembrolizumab**

Abbreviations: NSAIDS = non-steroidal anti-inflammatory drugs

a. NSAIDs can induce renal insufficiency, especially in subjects with dehydration; encourage oral fluids or consider intravenous fluids as clinically indicated. See guidelines for pyrexia.

b. Investigator may restart at either the same (pembrolizumab, dabrafenib and/or trametinib) or a reduced dose level (dabrafenib and/or trametinib). Escalation of study treatment to previous dose level is allowed if another episode of renal insufficiency does not occur after 4 weeks of dose reduction. Consultation with Sponsor is required before restarting study treatment if there is evidence of thrombotic microangiopathy.

5.6.1.1.10 Skin Events

Subjects should be carefully monitored for signs and symptoms of skin AEs, such as pruritis or rash. All attempts should be made to rule out other causes such as metastatic disease, infection or allergic dermatitis.

5.6.1.1.10.1 Rash

Rash is a frequent AE observed in subjects receiving trametinib, dabrafenib, or the combination of both therapies, as well as in subjects receiving pembrolizumab. Guidelines for rash management are based on experience with other MEK inhibitors and EGFR inhibitors [96, 97] and are provided below (Table 24 and Table 25).

Table 24 Guidelines for Supportive Care of Rash

Type of Care	Action
Prevention/Prophylaxis: Start from Day 1	• Avoid unnecessary exposure to sunlight Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. Sunscreen should be used during the day when exposed to the sun; emollient cream should be used at night or when not being exposed to the sun. Sunscreens should not be applied concomitantly with moisturizers such as emollient cream. • Use thick, alcohol-free emollient cream (eg, glycerine and cetomacrogol cream) on dry areas of the body at least twice daily.
Symptomatic Care (rash): Start from Day 1 of rash and implement for a total of 6 weeks	• Topical steroids and antibiotics should be applied once daily and more often as needed from Day 1. • Use mild-strength topical steroid (hydrocortisone 1% cream) and • topical antibiotic (eg, clindamycin) or oral antibiotics (eg, doxycycline 100 mg BID, minocycline 100 mg BID)
Symptomatic Care (other) [a]	• Pruritic lesions: cool compresses and oral antihistamine therapies • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream • Desquamation: thick emollients and mild soap • Paronychia: antiseptic bath, local potent corticosteroids in addition to oral antibiotics; if no improvement, consult dermatologist or surgeon • Infected lesions: appropriate bacterial/fungal culture-driven systemic or topical antibiotics
Abbreviations: BID = twice daily; SPF = sun protection factor a. Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management	

Immediate Evaluation for Potential Skin ECIs

A. Photographs:

Every attempt should be made to get a photograph of the actual skin lesion or rash as soon as possible. Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC.

– Take digital photographs of:

  o the head (to assess mucosal or eye involvement),

  o the trunk and extremities, and

  o a close-up of the skin lesion/rash.

– If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.

– The time/date stamp should be set in the 'ON' position for documentation purposes.

– Photographs should be stored with the subject's study records.

– The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. Past Medical History:

Collect past medical history relevant to the event, using the questions in Appendix 12.11 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

C. Presentation of the Event:

Collect information on clinical presentation and potential contributing factors using the questions in Appendix 12.12 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:

Measure vital signs (pulse, sitting BP, oral temperature, and respiratory rate) and record on the Vital Signs eCRF. Perform standard laboratory tests (CBC with manual differential and serum chemistry panel, including LFTs).

E. Focused Skin Examination:

Perform a focused skin examination using the questions in Appendix 12.13 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the narrative.

F. Dermatology Consult

Refer the subject to a dermatologist as soon as possible.

– For a "severe rash", the subject must be seen within 1-2 days of reporting the event.

– For clinically significant rash, the subject should be seen within 3-5 days.

The dermatologist should submit a biopsy sample to a certified dermatopathology laboratory or to a pathologist experienced in reviewing skin specimens.

The site should provide the dermatologist with all relevant case history, including copies of clinical photographs and laboratory test results.

Guidelines for management and dose reduction for rash considered to be related to study treatment are provided in Table 25.

Table 25 Management and Dose Modification Guidelines for Rash

CTCAE Grade	Adverse Event Management	Action and Dose Modification (apply to both Dabrafenib and Trametinib for Part 3 and to Trametinib only for Part 4 and 5)
Grade 1	• Initiate prophylactic and symptomatic treatment measures. • Consider use of topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl) or moderate strength topical steroid[a] • Reassess after 2 weeks	• If tolerable, continue study treatment at the same dose. • If intolerable despite best supportive care, **reduce dabrafenib and/or trametinib by one dose level[c]**
Grade 2	• Initiate prophylactic and symptomatic treatment measures • Use moderate strength topical steroid[a] • Reassess after 2 weeks • Treatment with oral steroids at the physician's discretion	• If tolerable, continue study treatment at the same dose. • If intolerable despite best supportive care, reduce **dabrafenib and/or trametinib by one dose level. If rash recovers to ≤Grade 1 within 2 weeks, resume dabrafenib and/or trametinib at previous dose level[c]** • **If intolerable despite dose reduction interrupt dabrafenib and/or trametinib until recovery to ≤Grade 1, then restart at the reduced dose [b]** • **Consider holding pembrolizumab**
Grade 3	• Use moderate strength topical steroids[a] PLUS oral steroids (eg, methyl-prednisolone dose pack, 1 mg/kg prednisone or equivalent once per day, or dexamethasone 4 mg four times orally daily). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Consult dermatologist, consider biopsy	• Interrupt all study treatments until rash recovers to Grade ≤1 • **Restart[b]** pembrolizumab (after appropriate steroid tapering) and reduce **dabrafenib and/or trametinib by one dose level[c]** • If no recovery to Grade ≤2 within 4 weeks, permanently discontinue dabrafenib and/or trametinib • Consider discontinuing pembrolizumab
Grade 4	• Same as Grade 3	• **Permanently discontinue all study treatment**

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.
a. Moderate-strength topical steroids: hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream
b. Approval of Sponsor is required to restart study treatment after ≥21 days of interruption.
c. Escalation of study treatment to previous dose level may be considered if either improvement of Grade 1 rash per investigators' judgment or no rash is evident 4 weeks after dose reduction or after restarting study treatment.

5.6.1.1.10.2 Hand-Foot Skin Reactions (HFSR)

Episodes of Hand-foot Skin Reaction (HFSR) have been observed in subjects receiving dabrafenib. Guidelines for management of HFSR are based on experience with other kinase inhibitors [98, 99].

Lifestyle modification: avoidance of hot water, traumatic activity, constrictive footwear, or excessive friction on the skin and the use of thick cotton socks and gloves, and shoes with padded insoles

Symptomatic treatments: apply moisturizing creams frequently, topical keratolytics (e.g. urea 20-40 % cream, salicylic acid 6%, tazarotene 0.1% cream, fluorouracil 5% cream), clobetasol propionate 0.05% ointment for erythematous areas, topical lidocaine 2%, and / or systemic pain medication such as non-steroidal anti-inflammatory drugs, codeine, and pregabalin for pain.

Dose modification may also be required. Refer to Table 24 for rash guidelines.

5.6.1.1.10.3 New Malignancies

Cutaneous squamous cell carcinoma and keratoacanthoma have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib (see dabrafenib and trametinib combination IB). These treatment-related cuSCC should be surgically removed according to institutional practice. Dose modifications or interruptions of the study treatment are not required for cuSCC. Occurrence of cuSCC must be reported as an SAE.

New cutaneous and non-cutaneous malignancies that are reported to the Investigator should be reported as a SAE, excluding basal cell carcinoma. A biopsy of the new malignancy should be taken, where possible, and submitted for further analyses. Testing of these biopsies may include RAS mutation testing and analysis of proteins related to the action of dabrafenib. Genomic alterations, which include but not limited to DNA, RNA and protein analysis of these biopsy specimens may be performed, and would be restricted to the analysis of pathway mutations known to be associated with, and relevant to, BRAF-mutant tumors or pathway activation. Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue every 3 months for up to 6 months or until initiation of another anti-neoplastic therapy.

5.6.1.1.10.4 Severe Cutaneous Adverse Reactions

Cases of Severe Cutaneous Adverse Reactions (SCARs), including Stevens-Johnson syndrome, and Drug Reaction with Eosinophilia and Systemic Symptoms, which can be life-threatening or fatal, have been reported during treatment with dabrafenib in combination with trametinib. Before initiating treatment, subjects should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, dabrafenib and trametinib should be permanently discontinued.

5.6.1.1.11 Fever

Subjects should be carefully monitored for signs and symptoms of fever, chills, or pyrexia. All attempts should be made to rule out other causes such as metastatic disease, hypersensitivity, bacterial or viral infection.

Episodes of fever have been observed in subjects receiving dabrafenib monotherapy or in combination with trametinib (see dabrafenib and dabrafenib + trametinib combination IBs), as well as in subjects receiving pembrolizumab. In a minority of cases the fever which occurred with dabrafenib and trametinib was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness.

Fever accompanied by hypotension, dehydration requiring IV fluids, renal insufficiency, or severe (≥Grade 3) rigors/chills, in the absence of an obvious infectious cause should be reported as an SAE.

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take non-steroidal anti-pyretics as appropriate to control fever. In subjects experiencing fever associated with rigors, severe chills, dehydration, hypotension, etc., renal function should be monitored carefully.

Guidelines regarding management and dose reduction for fever considered to be related to study treatment are provided in Table 26.

Table 26 Management and Dose Modification Guidelines for Fever

Adverse Event	Adverse Event Management	Action and Dose Modification

Fever[a]	1st Event[b]:
	• Clinical evaluation for infection and hypersensitivity[c]
	• Laboratory work-up[c]
	• Hydration as required[d]
	• Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment [e,f]
	
	2nd Event[g]
	• Clinical evaluation for infection and hypersensitivity[c]
	• Laboratory work-up[c]
	• Hydration as required[d]
	• Within 3 days of onset of fever
	  • Optimize anti-pyretic therapy[e]
		1st Event:
		• Interrupt dabrafenib
		• Continue trametinib and pembrolizumab
		• If fever does not resolve within 48 hours, hold trametinib and pembrolizumab
		• Once fever resolves to baseline, restart study treatment at the same dose level
		  • If fever was associated with dehydration, hypotension, or renal insufficiency, **reduce dabrafenib by one dose level**
		2nd Event:
		• **Interrupt dabrafenib**
		• Continue trametinib and pembrolizumab
		• If fever does not resolve within 48 hours, hold trametinib and pembrolizumab
		• Once fever resolves to baseline, restart study treatment at the same dose level
		  • If fever was associated with dehydration, hypotension, or

Adverse Event	Adverse Event Management	Action and Dose Modification

	Subsequent Events:
	• Clinical evaluation for infection and hypersensitivity[c]
	• Laboratory work-up[c]
	• Hydration as required[d]
	• Within 3 days of onset of fever:
	  • Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated[f]
	  • Optimize oral corticosteroid dose as clinically indicated for recalcitrant fever[g]
	  • If corticosteroids have been tapered and fever recurs, restart steroids
	  • If corticosteroids cannot be tapered consult Sponsor
		renal insufficiency, **reduce dabrafenib by one dose level**
		Subsequent Events:
		• **Interrupt dabrafenib and pembrolizumab**
		• Continue trametinib
		• Once fever resolves to baseline, restart pembrolizumab at the same dose level, restart dabrafenib **reduced by one dose level**[g]
		• If dabrafenib must be reduced to <75 mg BID, permanently **discontinue dabrafenib**

a. Fever is defined as a body temperature equal to or above 38.5 Celsius or 101.3° Fahrenheit.
b. For subjects experiencing fever complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended. For subjects experiencing rigors/chills without fever, work-up and supportive care, including interruption of study treatment, are recommended.
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, BUN, CRP, liver-function tests, blood culture, and urine culture.
d. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing fever complicated by dehydration/hypotension.
e. Anti-pyretic treatment may include ibuprofen, or suitable anti-pyretic medication according to institutional standards. Acetaminophen should be used with caution, especially in subjects with elevated liver enzymes. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of fever.
f. In subject experiencing fever complicated by rigors, severe chills, etc., which cannot be controlled with anti-pyretic medication, oral corticosteroids may be started at the 2nd event and doses should be gradually increased for subsequent events.
g. Dabrafenib should be reduced by one dose level after three episodes of fever complicated by rigors, severe chills, etc., which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of fever is observed in the 4 weeks subsequent to dose reduction.

5.6.1.1.12 Cardiovascular Events

Cardiovascular adverse events have been seen in subjects receiving either dabrafenib, trametinib or both in combination. See the IBs for additional information. Pembrolizumab dose modification guidance and stopping criteria for myocarditis are provided in Table 10.

5.6.1.1.12.1 Left Ventricular Ejection Fraction (LVEF)

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and in combination with dabrafenib. Therefore, ECHOs must be performed to assess cardiac ejection fraction in regular intervals as outlined in the protocol. All ECHOs will be collected.

Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 27.

Table 27 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinic	LVEF-drop (%) or CTCAE grade	Action and Dose Modification

Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN	• Interrupt dabrafenib and trametinib and repeat ECHO within 2 weeks[a]
		• If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline)
		  • Consult with the Sponsor and request approval for restart
		  • Restart treatment with trametinib reduced by one dose level
		  • Restart dabrafenib at previous dose level[b]
		  • Repeat ECHO 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter
		• If LVEF **does not recover** within 4 weeks
		  • Consult with cardiologist
		  • **Permanently discontinue trametinib**
		  • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution
		  • Consult with Sponsor[d]

Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	• **Permanently discontinue trametinib** • **Discontinue dabrafenib** • **Report as SAE** • **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks **or until resolution[e]** • Consult with Sponsor[c]

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

a. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.
b. If recurrent episodes of LVEF reduction occur with dabrafenib treatment, consult medical monitor.
c. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
d. Once LVEF recovers, restarting dabrafenib can be considered in consultation with Sponsor.
e. Once LVEF recovers, including resolution of symptoms, restart of dabrafenib only, can be considered in consultation with Sponsor.

5.6.1.1.13 Hypertension

Increases in blood pressure have been observed in subjects receiving trametinib.

5.6.1.1.13.1 Monitoring of Hypertension

All blood pressure assessments should be performed under the following optimal conditions:

1. the subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor
2. the subject is relaxed comfortably for at least 5 minutes
3. restrictive clothing has been removed from the cuff area and the right cuff size has been selected
4. the subjects arm is supported so that the middle of the cuff is at heart level
5. the subject remains quiet during the measurement.

In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final blood pressure measurement. The averaged value should be recorded in the eCRF.

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg in three consecutive visits with blood pressure assessments from two readings collected as described above. Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in Study Procedures. Ideally, subsequent blood pressure assessments should be performed within one week.

Asymptomatic hypertension is defined as an increase of SBP >140 mm Hg and/or DBP >90 mm Hg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension.

5.6.1.1.13.2 Management of Hypertension

For subjects experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described in Table 28.

Table 28 Management and Dose Modification Guidelines for Hypertension

Hypertension	Action and Dose Modification
(Scenario A) • Asymptomatic and persistent[a] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or • Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Continue study treatment at the current dose • Adjust current or initiate new antihypertensive medication • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled[b] BP • If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, • or • Failure to achieve well-controlled BP within 2 weeks in Scenario A	• Interrupt dabrafenib and trametinib if clinically indicated • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP • Once BP is well controlled[b], restart study treatment **reduced by one dose level**
(Scenario C) • Symptomatic[c] hypertension or • Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment	• Interrupt dabrafenib and trametinib • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication during the next 2 weeks as indicated to achieve well-controlled BP • Referral to a specialist for further evaluation and follow-up is recommended • Once BP is well controlled, restart study treatment **reduced by one dose level**
(Scenario D) • Refractory hypertension unresponsive to above interventions or hypertensive crisis.	• **Permanently discontinue dabrafenib and trametinib** • Continue follow-up per protocol.

Abbreviations: BP = blood pressure; DBP = diastolic blood pressure; mmHg = millimetres mercury; SBP = systolic blood pressure;

a. Hypertension detected in two separate readings during up to three consecutive visits
b. Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits.
c. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.

5.6.1.1.14 Prolonged QTc

Guidelines for dose modification and stopping criteria due to QTC-prolongation are provided in Table 29.

Table 29 Withholding and Stopping Criteria for QTc-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec, OR • uncorrected QT>600 msec, OR • QTcB>530 msec for subjects with bundle branch block	• Interrupt dabrafenib and trametinib until QTcB prolongation resolves to grade 1 or baseline • Test serum potassium, calcium, phosphorus, and magnesium. If <LLN correct with supplements to within normal limits • Review concomitant medication usage for a prolonged QTc • If event resolves, restart dabrafenib and trametinib at current dose level[b] • **If event does not resolve, permanently discontinue study treatment** • **If event recurs, permanently discontinue study treatment**

Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula

a. Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.
If the QTc prolongation resolves to grade 1 or baseline, the subject may resume dabrafenib and/or trametinib if the investigator and Sponsor agree that the subject will benefit from further treatment.

b. If the QTc prolongation resolves to grade 1 or baseline, the subject may resume dabrafenib and/or trametinib if the investigator and Sponsor agree that the subject will benefit from further treatment.

5.6.1.1.15 Hepatic Laboratory Abnormalities

The following AE terms, if considered ≥ Grade 2 or if requiring dose modification or use of systemic corticosteroids for treatment of the AE, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Hepatitis
- Hepatitis, Autoimmune
- Transaminase elevations
- Bilirubin abnormalities
- Any increase in Liver Function Tests (LFTs) ≥ grade 3 or any increase from grade 0 to grade 2

Subjects should be carefully monitored for signs and symptoms of elevations in AST, ALT, total bilirubin, fever, malaise and/or upper quadrant abdominal pain. All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.

Drug Induced Liver Injury (DILI)

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:

- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event. Dose modification guidance and stopping criteria for hepatic laboratory abnormalities are provided in Table 10 (for pembrolizumab) and Table 30 (all study drugs).

Table 30 Management and Dose Modification Guidelines for Hepatic Laboratory Abnormalities

Event	Adverse Event Management	Action and Dose Modification
AST or ALT ≥ 5.0x ULN	• Monitor hepatic laboratory tests more frequently until returned to baseline values (consider weekly) • For Grade 2 AST, ALT, or bilirubin elevations, treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections	• Hold pembrolizumab when AST or ALT >3.0x to 5.0x ULN and/or total bilirubin >1.5x to 3.0x ULN • Resume pembrolizumab when LFT returns to ≤Grade 1 or baseline • **Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week**

Event	Adverse Event Management	Action and Dose Modification
AST or ALT >5.0xULN to ≤8.0xULN without bilirubin elevation (defined as total bilirubin[a] ≤2.0xULN, or direct bilirubin ≤35%)	• Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary • Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks. • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity. • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.	• **Discontinue pembrolizumab if AST/ALT >5.0x ULN and/or total bilirubin >3.0xULN** • Hold dabrafenib, and/or trametinib if (any criteria are met): - AST/ALT >5.0x ULN - AST/ALT >3x ULN AND total bilirubin >2x ULN - Total bilirubin > 3x ULN • Interrupt dabrafenib and/or trametinib until recovery to Grade ≤1 • After consultation with Sponsor, dabrafenib and/or trametinib may be restarted **reduced by one dose level** • If no recovery to grade ≤1 within 2 weeks, **permanently discontinue study treatment**
AST or ALT >3.0 x ULN with concomitant elevation in bilirubin (defined as total bilirubin[a] ≥2.0 x ULN with direct bilirubin >35%) OR meeting any liver chemistry stopping criteria (see 5.6.1.1.15.1)	• Same as grade 3	• **Permanently discontinue all study treatment**
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events a. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin flix ULN, then the event should be promptly reported as an SAE.		

Note: in the event of a drug-induced liver injury (DILI) adverse event (as outlined in the study protocol), please follow the DILI guidance outlined in the site Administrative Binder.

5.6.1.1.15.1 Liver Chemistry Stopping Criteria

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

Liver chemistry stopping criteria 1-5 are defined as:

1. AST/ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) (or AST/ALT≥3xULN and INR>1.5, if INR measured)

NOTE: If serum bilirubin fractionation is not immediately available, study treatment should be discontinued if AST/ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

2. AST/ALT ≥ 8xULN

3. AST/ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks

4. AST/ALT ≥ 3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash or eosinophilia.

5. AST/ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for >2 weeks.

When any of the liver chemistry stopping criteria 1 - 5 is met, do the following:

- **Immediately discontinue subject from** study treatment
- Report the event to Sponsor **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE
    - All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE**.
    - NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- Follow up for overall survival is required following discontinuation from study treatment.
- Do not rechallenge with study treatment.

In addition, for subjects meeting liver stopping criterion 1:

- Make every reasonable attempt to have subjects return to clinic **within 24 hours** for repeat liver chemistries, liver event follow up assessments, and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For subjects meeting any of the liver stopping criteria 2 – 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;
- Subjects meeting criterion 5 should be monitored as frequently as possible.

5.6.1.1.15.2 Liver Event Follow-up Assessments

For subjects meeting any of the liver chemistry stopping criteria 1 – 5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
  - Hepatitis C RNA
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
  - Hepatitis E IgM antibody.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 10 days of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin ≥2xULN.

- Obtain complete blood count with differential to assess eosinophilia.

- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash or eosinophilia as relevant on the AE form. Please note that treatment with trametinib often associates with rash which is usually acneiform and affects the scalp, face, neck, chest, and upper back. Discuss with Sponsor as needed.

- Record use of concomitant medications such as acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form.

The following assessments are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).

- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by HPLC assay more than 1 week following acetaminophen use).

- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE**: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/.

5.6.1.1.15.3 Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3xULN **but** <8xULN which exhibit a decrease to ALT ≥3xULN, but <5xULN **and** bilirubin <2xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:

- Notify the Sponsor within 24 hours of learning of the abnormality to discuss subject safety
- Continue study treatment
- Return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline values

- If at any time the subject meets any of the liver chemistry stopping criteria 1 – 5, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

5.6.1.1.15.4 Drug Restart/Rechallenge Following Liver Events that are Possibly Related to Study Treatment

Approval by Sponsor for study treatment restart can be considered where:

The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of study treatment restart/rechallenge must be obtained, as required.

If the restart/rechallenge is approved by Sponsor in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.

The subject must also provide signed informed consent specifically for the study treatment restart/rechallenge. Documentation of informed consent must be recorded in the study chart.

Study treatment must be administered at the dose specified by Sponsor.

Subjects approved by the Sponsor for restart/rechallenge of study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

5.6.1.1.15.5 Drug Restart Following Transient Resolving Liver Events Not Related to Study Treatment

Approval by Sponsor for drug restart can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Ethics Committee or Institutional Review Board approval of study treatment restart/rechallenge must be obtained, as required.
- If restart of study treatment is approved by Sponsor in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by Sponsor.

Subjects approved by the Sponsor for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and

then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study treatment must be stopped.

A dose reduction below 75 mg BID for dabrafenib and 1 mg once daily for trametinib is not allowed. If a dose reduction below 75 mg BID for dabrafenib is required, dabrafenib will be permanently discontinued, but the subjects will be allowed to continue trametinib. If a dose reduction below 1 mg once daily for trametinib is required, then trametinib will be permanently discontinued, but these subjects will be allowed to continue dabrafenib.

Note: Approval from the Sponsor is required to restart study treatment after ≥21 days of interruption.

5.6.1.1.16 Hematologic Events

Subjects should be carefully monitored for signs and symptoms of hematologic events (such as autoimmune hemolytic anemia, aplastic anemia, disseminated intravascular coagulation (DIC), or neutropenia). All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

Dose modification and supportive care guidelines for hematologic adverse events are described in Table 31. Guidelines for dose modification for neutropenia are provided in Table 32.

Table 31 Management and Dose Modification Guidelines for Hematologic Adverse Events

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 2	• Consider Hematology consultation • Consider systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. • When symptoms improve to Grade 1 or less, steroid taper (if systemic corticosteroids initiated) should be started and continued over no less than 4 weeks.	• Interrupt pembrolizumab until improvement to ≤Grade 1 • Consider interruption of dabrafenib and/or trametinib
Grade 3	• Hematology consultation • Treat with methylprednisolone 125mg IV or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate. • When symptoms improve to Grade 1 or less, steroid taper (if systemic corticosteroids initiated) should be started and continued over no less than 4 weeks.	• Interrupt all study treatment until improvement to ≤Grade 1 • Restart dabrafenib and/or trametinib at reduced dose
Grade 4	• Same as grade 3	• **Permanently discontinue all study treatment**
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events		

Table 32 Management and Dose Modification Guidelines for Neutropenia

CTCAE Grade	Action and Dose Modification
Grade 2	• Consider interrupting dabrafenib and/or trametinib if clinically indicated • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to ≤Grade 1, restart study treatment at current dose level
Grade 3	• Interrupt dabrafenib and/or trametinib • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to ≤Grade 1, restart dabrafenib and/or trametinib at reduced dose. May titrate dose up to previous level if tolerated
Grade 4	• Interrupt all study treatment • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to ≤Grade 1, restart pembrolizumab at current dose. Restart dabrafenib and/or trametinib at reduced dose. May titrate dose up to previous level if tolerated • If the Grade 4 toxicity recurs, either permanently discontinue all study treatment or, if the subject is clinically benefitting, discuss continuation of treatment with the Sponsor
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events	

5.6.1.1.17 Neurologic Events

Subjects should be carefully monitored for signs and symptoms of neurologic events. All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

Dose modification and supportive care guidelines for neurologic adverse events are described in Table 33.

Table 33 Management and Dose Modification Guidelines for Neurologic Adverse Events

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 2	• Consider Neurology consultation and possible biopsy for diagnosis • Consider systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. • When symptoms improve to Grade 1 or less, steroid taper (if systemic corticosteroids initiated) should be started and continued over no less than 4 weeks.	• Consider interrupting pembrolizumab
Grade 3	• Neurology consultation and consider biopsy for diagnosis • Treat with systemic corticosteroids prednisone 1-2 mg/kg p.o. (or equivalent). If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines. • When symptoms improve to Grade 1 or less, steroid taper (if systemic corticosteroids initiated) should be started and continued over no less than 4 weeks.	• **Permanently discontinue pembrolizumab** • Consider interrupting dabrafenib and/or trametinib
Grade 4	• Same as grade 3	• **Permanently discontinue pembrolizumab** • Consider interrupting dabrafenib and/or trametinib
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events		

5.6.1.1.18 Infusion Reactions

Subjects should be carefully monitored for signs and symptoms of infusion reaction (such as allergic reaction, anaphylaxis, cytokine release syndrome, or serum sickness). The AE should be reported regardless of etiology.

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

5.6.1.2 Pembrolizumab Infusion Reaction Treatment Guidelines

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 34.

Pembrolizumab subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Management of Infusion Reactions: acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; hypotension; myalgia (muscle pain); nausea; pruritis/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting.

Table 34 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine** Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov IV=intravenous; NSAIDs= non-steroidal anti-inflammatory drugs; PO=oral administration.		

5.6.1.3 Supportive Care Guidelines for Adverse Events with an Immune-Etiology (irAEs)

Adverse events of a potential immunologic etiology (irAEs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the Sponsor.

Recommendation to evaluate and manage irAEs are provided in Section 5.6.1.1.3 and Section 5.2.1.2.1, Table 10. Recommendations to managing irAEs that are not detailed elsewhere in the protocol are detailed in Table 35.

Table 35 General Approach to Handling irAEs

irAE	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold pembrolizumab	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold pembrolizumab Discontinue if grade 4 or grade 3 and unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.7.2 Contraception

Pembrolizumab and other study medications may have adverse effects on a fetus in utero. Refer to Appendix 12.14 for approved methods of contraception.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 12.14) from the day of study medication initiation throughout the study period up to 120 days after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.7.3 Use in Pregnancy

If a female subject inadvertently becomes pregnant while on treatment with pembrolizumab or trametinib or dabrafenib, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse

experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab or trametinib or dabrafenib is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.3 – Post-Treatment Follow-Up Phase.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or legal representative (such as parent or legal representative) withdraws consent.
- The subject's treatment assignment has been unblinded by the investigator, Merck subsidiary or through the emergency unblinding call center.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the subject at unnecessary risk from continued administration of study drug/vaccine

- The subject has a confirmed positive serum pregnancy test.
- Documented disease progression

  Note: If a subject has confirmed progression of disease, i.e., persistent tumor increase of 20% or greater compared to nadir and/or worsening or increased number of new lesions, (via a second scan at least 28 days from the date of the scan showing initial radiological progression by RECIST 1.1), the subject should not receive further trial treatment on study. If a subject has unconfirmed progression of disease and is clinically stable, it is at the discretion of the investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the scan suggesting progression of disease. Clinical Stability is defined as:

  1) Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values) indicating disease progression.

  2) No decline in ECOG performance status.

  3) Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

- Unacceptable adverse experiences as described in Section 5.2.1.2 and Section 5.6
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 - Trial Flow Chart and Section 7.1.5 - Visit Requirements. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment as described in Section 7.2.3.1). Subjects will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. After documented disease progression each subject will be followed for overall survival until death or withdrawal of consent, or the end of the study, whichever occurs first.

Discontinuation of pembrolizumab after CR

Discontinuation of pembrolizumab may be considered for subjects who have attained a confirmed response per RECIST 1.1 that have been treated for at least 6 months and had at least two doses of pembrolizumab treatment beyond the date when the initial CR was declared. See Section 5.2.5 for more information.

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

Subjects may be allowed to begin treatment again if deemed medically appropriate..

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or legal representative (such as parent or legal representative) withdraws consent from the trial.
- The subject is lost to follow-up

Specific details regarding procedures to be performed at the time of withdrawal from the trial including specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

In Parts 1, 2, 4, and 5, additional subjects may be enrolled in a given cohort to ensure that the required number of evaluable subjects in each cohort is achieved. A subject who discontinues the trial for progressive disease or a drug-related AE will not be replaced and will be counted in the evaluable population of subjects for the respective cohort. Further details are provided in Section 8.2.4.2.

5.9.1 Parts 1, 2, 4, and 5: Subject Replacement Strategy - Dose Limiting Toxicity

Any subject who does not complete the 6-week DLT evaluation period in Parts 1, 2, 4, or 5 (i.e., Cycle 1, initiated with the first pembrolizumab dose) and does not experience any DLT will be replaced, except those who discontinue due to non-DLT toxicity that is nevertheless drug-related (or suspected to be drug-related). In addition, any subject who misses ≥50% of PK or PD samples or misses 3 consecutive doses of study medication immediately prior to PK blood sampling may be replaced at the discretion of the Sponsor. In Parts 4 and 5, any subject who discontinues trametinib during the trametinib monotherapy run-in period is not considered evaluable for DLTs for the MK+T combination, even if the subject discontinued due to a DLT, and will be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last trial visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete.
2. Poor adherence to protocol and regulatory requirements.
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug(s).

Statistical criteria for stopping the trial are provided in Section 8.0 – Statistical Analysis Plan.

Enrollment will not be halted during the planned interim analysis.

In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

Further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

6.1 Treatment Phase

6.1.1 Parts 1 and 2: Pembrolizumab Q3W Dosing with Trametinib and/or Dabrafenib

Trial Period:	Screening[9]	Treatment (6-Week Cycle)									End of Treatment
Visit Number:	1	2	3	4	5	6	7	8	9	≥ 10	Discontinuation[23]
Days	(-28 to -1)	1	8	15	22	29	36	1	22	1,22	
Cycle		1						2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	
Administrative Procedures											
Informed Consent[1]	X										
Informed Consent for Future Biomedical Research (optional)	X										
Inclusion/Exclusion Criteria	X										
Subject Identification Card	X										
Demographics and Medical History[2]	X										
Prior and Concomitant Medication Review[3]	X	X	X	X	X	X	X	X	X	X	X
Treatment Assignment		X									
Survival status [28]		←---→									
Clinical Procedures / Assessments											
Full Physical Examination[27]	X	X						X		X[24]	
Directed Physical Examination			X	X	X	X	X		X	X[24]	X
Vital Signs and Weight[4]	X	X	X	X	X	X	X	X	X	X	X
12-Lead Electrocardiogram (ECG)[5]	X	X						X		X[25]	
ECHO	X					X				X[25]	
Review Adverse Events[6,7,8]		X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X						X		X[25]	X

Trial Period:	Screening[9]	Treatment (6-Week Cycle)									End of Treatment
Visit Number:	1	2	3	4	5	6	7	8	9	≥ 10	Discontinuation[23]
Days	(-28 to -1)	1	8	15	22	29	36	1	22	1,22	
Cycle		1						2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	
Laboratory Procedures / Assessments[9]											
Pregnancy Test - Urine or Serum β-HCG[10]	X										
CBC with Differential[11]	X	X	X	X	X	X	X	X	X	X[25]	X
Comprehensive Chemistry Panel[11]	X	X	X	X	X	X	X	X	X	X[25]	X
Urinalysis[11]	X	X	X	X	X	X	X	X	X	X[25]	X
PT/INR and aPTT[12]	X	As clinically indicated									
Calculated Creatinine Clearance	X										
T3, FT4 and TSH[11,13]	X	X						X		X[13]	X
Hepatitis B and C[14]	X										
Blood for Future Biomedical Research[15] (optional)		X									
Drug Dispensation, Administration, and Associated Analyses											
pembrolizumab Administration (30-minute infusion)		X			X			X	X	X	
Pharmacokinetics of pembrolizumab[16]		X			X			X		X[25]	
Anti-pembrolizumab Antibodies[17]		X						X		X[25]	
Dispensation of Drug Kit		X			X			X	X	X[25]	
Pharmacokinetics of Dabrafenib and/or Trametinib[18]					X			X		X[25]	X
Efficacy Measurements											
Tumor Imaging[19]	X									X[25]	X
Tissue Collection and Pharmacodynamic Assessment											
BRAF Testing[20]	X										
Tumor Tissue Collection[21]	X		X[21]								X[26]
Correlative Blood Sample[21]	X	X						X			X
Blood for Genetics[22]		X									

1 Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Day 1). Assign Baseline number when the study informed consent is signed.
2 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator.
3 Prior Medications - Report all medications taken within 30 days of Visit 1 and all treatments for a prior cancer even if taken greater than 30 days prior to Visit 1. Concomitant Medications - Enter new medications started during the trial through the Safety Follow-Up visit. After the Safety Follow-Up visit, record all medications taken for SAEs and ECIs as defined in Section 7.2.
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose. Height will be measured at Visit 1 only.
5 Electrocardiogram (12-lead ECG) should be performed at Screening and post-infusion at visits indicated in the flow chart.
6 Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
7 Any adverse experience of unknown etiology associated with trial treatment exposure should be evaluated to determine if it is possibly an Event of Clinical Interest (ECI).

8 Evaluate patients for symptoms or clinical signs of non-cutaneous, new primary/recurrent malignancies before initiation of treatment, periodically during treatment, or as clinically indicated. Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.
9 Routine laboratory tests (chemistry; hematology) for screening should be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
10 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
11 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests.
12 Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
13 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Following Cycle 4, testing will be performed every other cycle. In countries where T3 results are not available, FT3 results may be reported. See Section 7.1.3 for details regarding laboratory tests.
14 Testing will be performed by the local laboratory at Screening. Hepatitis B and Hepatitis C serologies should be obtained for subjects without a known history of Hepatitis B or C. Those with a known history are ineligible. Include HCV RNA (qualitative) and HBsAg.
15 Informed consent for Future Biomedical Research (FBR) samples must be obtained before the DNA sample is drawn. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.
16 Pre-dose and post-dose serum samples for PK of pembrolizumab will be collected on Day 1 and Day 22 of Cycle 1 and Day 1 of Cycle 2. Thereafter, only pre-dose (C_{trough}) PK serum samples will be collected at Day 1 of every alternate cycle (i.e., Day 1 of Cycle 3, Day 1 of Cycle 5, etc.). All pre-dose (C_{trough}) samples should be collected within 24 hours before the start of infusion of pembrolizumab and, if blood is collected for anti-pembrolizumab antibodies, at the same time blood sample for anti-pembrolizumab antibodies is collected. All post-dose PK samples should be collected within 30 minutes after the end of infusion of pembrolizumab. One additional post-dose sample should be collected between 24 and 96 hours following C1D1. Procedures for collection of samples are described in the Procedures Manual.
17 Blood for anti-pembrolizumab antibodies should be collected on Day1of Cycles 1, 2, 3 and every other cycle thereafter (Cycle 5, Cycle 7, etc.). During pembrolizumab treatment, all samples should be drawn within 24 hours before infusion of pembrolizumab at the same time as blood collection for pre-dose (C_{trough}) PK serum samples of pembrolizumab.
18 On C1D22, both pre-dose and post-dose plasma samples for PK of trametinib and dabrafenib will be collected. On C1D22, morning dose(s) should be withheld until after PK (pre-dose) sample has been drawn. On C1D22, post-dose PK samples for trametinib and/or dabrafenib should be drawn (1) at the same time as when the post-dose pembrolizumab PK sample is drawn (the end of infusion), and, (2) at approximately 4-6 hours post-dose. On C2D1, subjects should take their morning dose at home. A post-dose sample will be obtained during study visit. Thereafter, PK plasma samples will be collected at Day 1 of every alternate cycle (i.e., Day 1 of Cycle 3, Day 1 of Cycle 5, etc.) during study visit. If visit is in the morning, subjects will be asked to withhold their morning dose; if visit is in the afternoon, subjects will be asked to take their morning dose as usual. Procedures for collection of samples are described in the Procedures Manual.
19 The initial tumor imaging will be performed within 28 days prior to the date of allocation. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. CT scans are the required modality for measurable disease unless a subject has a clinical condition, e.g., severe contrast allergy. The same imaging technique has to be used for the subject throughout the study. The visit window for subsequent imaging is +/- 7 days. If there is progressive disease, radiologic assessment/tumor imaging should be obtained at least four weeks from scan date for confirmation. CT timing should follow calendar days and should not be adjusted for delays in cycle starts. The process for collection of CT images is described in the Procedures Manual. Tumor imaging will be performed every 6 weeks (or whenever clinically indicated) starting at Week 13 while the subject remains on study therapy; after 18 months, tumor imaging will be performed every 12 weeks (or whenever clinically indicated) while the subject remains on study therapy. Per the modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, the imaging assessment should be repeated at a minimum of 4 weeks later in order to confirm progressive disease as described in Section 4.2.3.1.
20 BRAF V600 E or K mutation analysis should be performed by sites during screening in subjects without documented BRAF status. This specimen may be collected any time from the initial diagnosis to the study entry and may be an archival tissue sample (within 6 months of study entry). BRAF analysis may be performed at a local laboratory, provided that the methodology is able to detect V600E and/or V600K mutations. A sample from the originally-tested tissue block must be collected and stored at the central laboratory for possible assay at a later date (i.e., in the event that BRAF status must be confirmed). Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

21 In order to be eligible for the study, all subjects must provide a tumor tissue specimen for biomarker analysis and blood samples for pharmacodynamic assessment. The tissue specimen may be collected any time from the initial diagnosis to the study entry and may be an archival tissue sample (within 9o days of Study Day 1=first dose(s) of study treatment) if it is not feasible to obtain a fresh biopsy not previously irradiated. Site documentation that the sample has been shipped to the biomarker analysis laboratory is sufficient evidence to meet eligibility criterion. If a tumor biopsy was obtained of a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous. The tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. Additionally, a fresh biopsy should be obtained 10-14 days following initiation of study treatment for Parts 1 and 2 of the study. The fresh biopsy at 10-14 days following initiation of study treatment is optional in Part 3 of the study. Detailed instructions for blood sample collection, tissue collection, processing and shipment are provided in the Laboratory and Procedures Manual, respectively. Any leftover blood or tumor tissue may be stored for future research if the subject signs the optional FBR consent.
22 Blood for genetics sample will be collected to explore host genetics and to identify genetic predictors which may have a role in therapeutic response to pembrolizumab.
23 The discontinuation visit should be scheduled at the time of permanent discontinuation of all treatments (pembrolizumab, trametinib, and/or dabrafenib). The window for this visit is +10 days. Required assessments for this visit are identified in the study flow chart; additional assessments that are not flagged as required may be performed if clinically indicated (e.g., coagulation tests, thyroid function tests, etc.).
24 Perform a full physical examination on the first day of each cycle and a directed physical examination on Day 22 of each cycle. Example: full physical exam on C3D1, directed physical exam on C3D22, full physical exam on C4D1, directed physical exam on C4D22, etc.
25 Day 1 and 22 of Cycle 3: CBC with Differential, Comprehensive Chemistry Panel, Urinalysis
Day 1 ONLY from C4D1 onwards: CBC with Differential, Comprehensive Chemistry Panel, Urinalysis
Day 1 ONLY of every cycle (e.g., C3D1, C4D1, C5D1, etc.): ECOG Performance Status
Day 1 and 22 of every cycle (e.g., C3D1, C3D22, C4D1, C4D22, etc.): Dispensation of Drug Kit
Day 1 ONLY of every cycle (e.g., C3D1, C4D1, C5D1, etc.) until 18 months, then Day 1 ONLY of every other cycle: Tumor Imaging
Day 1 ONLY of every alternate cycle, as indicated (e.g., C3D1, C5D1, C7D1, etc.): ECG, ECHO, Pharmacokinetics of pembrolizumab and/or trametinib and/or dabrafenib, Anti-pembrolizumab Antibodies testing
26 pembrolizumab treated subjects in the Treatment Phase – Additional optional biopsy at disease progression is highly desired when feasible. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
27 Dermatological examination will be part of full physical examination on the first day of each cycle.
28 Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants who have a death event previously recorded).

6.1.2 Part 3: Pembrolizumab Q3W Dosing With Trametinib and Dabrafenib

Trial Period:	**Screening[9]**	**Treatment (6-Week Cycle)[24,25]**					**End of Treatment**
Visit Number:	1	2	3	4	5	≥ 6	Discontinuation[25]
Days	(-28 to -1)	1	22	1	22	1,22	
Cycle		1		2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	
Administrative Procedures							
Informed Consent[1]	X						
Informed Consent for Future Biomedical Research (optional)	X						
Inclusion/Exclusion Criteria	X						
Subject Identification Card	X						
Demographics and Medical History[2]	X						
Prior and Concomitant Medication Review[3]	X	X	X	X	X	X	X
Treatment Assignment		X					
Survival Status [30]		←	-	-	-	-	→
Clinical Procedures / Assessments							
Full Physical Examination[29]	X	X		X		X[26]	
Directed Physical Examination			X		X	X[26]	X
Vital Signs and Weight[4]	X	X	X	X	X	X	X
12-Lead Electrocardiogram (ECG)[5]	X	X		X		X[27]	
ECHO	X		X			X[27]	
Review Adverse Events[6,7,8]		X	X	X	X	X	X
ECOG Performance Status	X	X		X		X[27]	X
Laboratory Procedures / Assessments[9]							
Pregnancy Test - Urine or Serum β-HCG[10]	X						
CBC with Differential[11]	X	X	X	X	X	X[27]	X

Trial Period:	**Screening[9]**	**Treatment (6-Week Cycle) [24,25]**					**End of Treatment**
Visit Number:	1	2	3	4	5	≥ 6	Discontinuation[25]
Days	(-28 to -1)	1	22	1	22	1,22	
Cycle		1		2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	
Laboratory Procedures / Assessments[9]							
Comprehensive Chemistry Panel[11]	X	X	X	X	X	X[27]	X
Urinalysis[11]	X	X		X		X[27]	X
PT/INR and aPTT[12]	X	As clinically indicated					
Calculated Creatinine Clearance	X						
T3, FT4 and TSH[11,13]	X	X		X		X[13]	X
Hepatitis B and C[14]	X						
Blood for Future Biomedical Research[15] (optional)		X					
Drug Dispensation, Administration, and Associated Analyses							
pembrolizumab Administration (30-minute infusion)		X	X	X	X	X	
Pharmacokinetics of pembrolizumab[16]		X	X	X		X[27]	
Anti-pembrolizumab Antibodies[17]		X		X		X[27]	
Dispensation of Drug Kit		X	X	X	X	X[27]	
Pharmacokinetics of Dabrafenib and/or Trametinib[18]			X	X		X[27]	X
Efficacy Measurements							
Tumor Imaging[19]	X					X[27]	X
Patient Reported Outcomes (PRO)							
EuroQol EQ-5D[20]		X		X		X	X
EORTC QLQ-C30[20]		X		X		X	X

Trial Period:	Screening[9]	Treatment (6-Week Cycle) [24,25]					End of Treatment
Visit Number:	1	2	3	4	5	≥ 6	Discontinuation[25]
Days	(-28 to -1)	1	22	1	22	1,22	
Cycle		1		2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	
Tissue Collection and Pharmacodynamic Assessment							
BRAF Testing[21]	X						
Tumor Tissue Collection[22]	X	X[22]					X[28]
Correlative Blood Sample[22]	X	X		X			X
Blood for Genetics[23]		X					

1 Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Day 1). Assign Baseline number when the study informed consent is signed.
2 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator.
3 Prior Medications - Report all medications taken within 30 days of Visit 1 and all treatments for a prior cancer even if taken greater than 30 days prior to Visit 1. Concomitant Medications - Enter new medications started during the trial through the Safety Follow-Up visit. After the Safety Follow-Up visit, record all medications taken for SAEs and ECIs as defined in Section 7.2.
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a subject's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose. Height will be measured at Visit 1 only.
5 Electrocardiogram (12-lead ECG) should be performed at Screening and post-infusion at visits indicated in the flow chart.
6 Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
7 Any adverse experience of unknown etiology associated with trial treatment exposure should be evaluated to determine if it is possibly an Event of Clinical Interest (ECI).
8 Evaluate subjects for symptoms or clinical signs of non-cutaneous, new primary/recurrent malignancies before initiation of treatment, periodically during treatment, or as clinically indicated. Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.
9 Routine laboratory tests (chemistry; hematology) for screening should be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests
10 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
11 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. LDH analysis required (stratification factor). See Section 7.1.3 for details regarding laboratory tests.
12 Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.

13 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Following Cycle 4, testing will be performed every other cycle. In countries where T3 results are not available, FT3 results may be reported.
14 Testing will be performed by the local laboratory at Screening. Hepatitis B and Hepatitis C serologies should be obtained for subjects without a known history of Hepatitis B or C. Those with a known history are ineligible. Include HCV RNA (qualitative) and HBsAg. See Section 7.1.3 for details regarding laboratory tests.
15 Informed consent for Future Biomedical Research (FBR) samples must be obtained before the DNA sample is drawn. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.
16 Pre-dose and post-dose serum samples for PK of pembrolizumab will be collected on Day 1 and Day 22 of Cycle 1 and Day 1 of Cycle 2. Thereafter, only pre-dose (C_{trough}) PK serum samples are collected at Day 1 of every alternate cycle (i.e., Day 1 of Cycle 3, Day 1 of Cycle 5, etc.). All pre-dose (C_{trough}) samples should be collected within 24 hours before the start of infusion of pembrolizumab and, if blood is collected for anti-pembrolizumab antibodies, at the same time blood sample for anti-pembrolizumab antibodies is collected. All post-dose PK samples should be collected within 30 minutes after the end of infusion of pembrolizumab. One additional post-dose pembrolizumab sample should be collected between 24 and 96 hours following C1D1. Procedures for collection of samples are described in the Procedures Manual.
17 Blood for anti-pembrolizumab antibodies should be collected on Day1 of Cycles 1, 2, 3 and every other cycle thereafter (Cycle 5, Cycle 7, etc.). During pembrolizumab treatment, all samples should be drawn within 24 hours before infusion of pembrolizumab at the same time as blood collection for pre-dose (Ct_{rough}) PK serum samples of pembrolizumab.
18 On C1D22, both pre-dose and post-dose plasma samples for PK of trametinib and dabrafenib will be collected. On C1D22, morning dose(s) should be withheld until after PK (pre-dose) sample has been drawn. On C1D22, post-dose PK samples for trametinib and/or dabrafenib should be drawn (1) at the same time as when the post-dose pembrolizumab PK sample is drawn (the end of infusion), and, (2) at approximately 4-6 hours post-dose. On C2D1, subjects should take their morning dose at home. A post-dose sample will be obtained during study visit. Thereafter, PK plasma samples will be collected at Day 1 of every alternate cycle (i.e., Day 1 of Cycle 3, Day 1 of Cycle 5, etc.) during study visit. If visit is in the morning, subjects will be asked to withhold their morning dose; if visit is in the afternoon, subjects will be asked to take their morning dose as usual. Procedures for collection of samples are described in the Procedures Manual.
19 The initial tumor imaging will be performed within 28 days prior to the date of allocation. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. CT scans are the required modality for measurable disease unless a subject has a clinical condition, e.g., severe contrast allergy. The same imaging technique has to be used for the subject throughout the study. The visit window for subsequent imaging is ± 7 days. If there is progressive disease, radiologic assessment/tumor imaging should be obtained at least four weeks from scan date for confirmation. CT timing should follow calendar days and should not be adjusted for delays in cycle starts. Response status will be assessed by the investigator. The process for collection of CT images is described in the Procedures Manual. Tumor imaging will be performed every 6 weeks (or whenever clinically indicated) starting at Week 13 while the subject remains on study therapy; after 18 months, tumor imaging will be performed every 12 weeks (or whenever clinically indicated) while the subject remains on study therapy. Per the modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, the imaging assessment should be repeated at a minimum of 4 weeks later in order to confirm progressive disease as described in Section 4.2.3.1.
20 Patient Reported Outcomes (PROs) are to be administered by trained site personnel and completed electronically by subjects prior to all other study procedures in the following order: EuroQol EQ-5D first, followed by EORTC QLQ-C30. EuroQol EQ-5D and EORTC QLQ-C30 are to be performed at C1D1, C2D1, C3D1 and Day 1 of every other cycle thereafter (C5D1, C7D1, etc.) as well as the End of Treatment, and 30-day Safety Follow-up visit. Subjects that complete 24 months on trial and opt to continue dabrafenib and trametinib will not be required to complete PROs at the 30-Day Safety follow up visit. It is most relevant and strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification.
21 BRAF V600 E or K mutation analysis should be performed by sites during screening in subjects without documented BRAF status. This specimen may be collected any time from the initial diagnosis to the study entry and may be an archival tissue sample (within 6 months of study entry). BRAF analysis may be performed at a local laboratory, provided that the methodology is able to detect V600E and/or V600K mutations. A sample from the originally-tested tissue block must be collected and stored at the central laboratory for possible assay at a later date (i.e., in the event that BRAF status must be confirmed). Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

22 In order to be eligible for the study, all subjects must provide a tumor tissue specimen for biomarker analysis and blood samples for pharmacodynamic assessment. The tissue specimen may be collected any time from the initial diagnosis to the study entry and may be an archival tissue sample (within 90 days of Study Day 1=first dose(s) of study treatment) if it is not feasible to obtain a fresh biopsy not previously irradiated. Site documentation that the sample has been shipped to the biomarker analysis laboratory is sufficient evidence to meet eligibility criterion. If a tumor biopsy was obtained of a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous. The tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. Additionally, a fresh biopsy should be obtained 10-14 days following initiation of study treatment for Parts 1 and 2 of the study. The fresh biopsy at 10-14 days following initiation of study treatment is optional in Part 3 of the study. Detailed instructions for blood sample collection, tissue collection, processing and shipment are provided in the Laboratory and Procedures Manual, respectively. Any leftover blood or tumor tissue will be stored for future research if the subject signs the optional FBR consent.
23 Blood for genetics sample will be collected to explore host genetics and to identify genetic predictors which may have a role in therapeutic response to pembrolizumab.
24 Telephone Contact at Days 8, 15, 29, and 36 of Cycle 1 only. Review Adverse Events and Concomitant Medications.
25 The discontinuation visit should be scheduled at the time of permanent discontinuation of all treatments (pembrolizumab, trametinib, and/or dabrafenib). The window for this visit is +10 days. Required assessments for this visit are identified in the study flow chart; additional assessments that are not flagged as required may be performed if clinically indicated (e.g., coagulation tests, thyroid function tests, etc.).
26 Perform a full physical examination on the first day of each cycle and a directed physical examination on Day 22 of each cycle. Example: full physical exam on C3D1, directed physical exam on C3D22, full physical exam on C4D1, directed physical exam on C4D22, etc.
27 Day 1 and 22 of Cycle 3: CBC with Differential, Comprehensive Chemistry Panel
Day 1 ONLY from C3D1 onwards: Urinalysis
Day 1 ONLY from C4D1 onwards: CBC with Differential, Comprehensive Chemistry Panel
Day 1 ONLY of every cycle (e.g., C3D1, C4D1, C5D1, etc.): ECOG Performance Status
Day 1 and 22 of every cycle (e.g., C3D1, C3D22, C4D1, C4D22, etc.): Dispensation of Drug Kit
Day 1 ONLY of every cycle (e.g., C3D1, C4D1, C5D1, etc.) until 18 months, then Day 1 ONLY of every other cycle: Tumor Imaging
Day 1 ONLY of every alternate cycle (e.g., C3D1, C5D1, C7D1, etc.): ECG, ECHO, Pharmacokinetics of pembrolizumab and/or trametinib and/or dabrafenib, Anti-pembrolizumab Antibodies testing
28 Additional optional biopsy at disease progression is highly desired when feasible. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
29 Dermatological examination will be part of full physical examination on the first day of each cycle.
30 Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants who have a death event previously recorded).

6.1.3 Parts 4 and 5: 4-Week Monotherapy Trametinib + 6-Week Treatment Cycle(s) of Pembrolizumab Q3W Dosing With Trametinib

Trial Period:	**Screening[9]**	**4-Week Monotherapy Trametinib + 6-Week Combination Treatment Cycle(s)**													**End of Treatment**
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	12	13	≥ 14	Discontinuation[23]
Days	(-28 to -1)	1	8	15	22	29	36	43	50	57	64	1	22	1,22	
Cycle		1										2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Administrative Procedures															
Informed Consent[1]	X														
Informed Consent for Future Biomedical Research (optional)	X														
Inclusion/Exclusion Criteria	X														
Subject Identification Card	X														
Demographics and Medical History[2]	X														
Prior and Concomitant Medication Review[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Assignment		X													
Survival Status[30]		←	-	-	-	-	-	-	-	-	-	-	-	-	→
Clinical Procedures / Assessments															
Full Physical Examination[27]	X	X				X						X		X[24]	
Directed Physical Examination			X	X	X		X	X	X	X	X		X	X[24]	X
Vital Signs and Weight[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead Electrocardiogram (ECG)[5]	X					X						X		X[25]	
ECHO	X									X				X[25]	
Review Adverse Events[6,7,8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X				X						X		X[25]	X

Trial Period:	Screening[9]	4-Week Monotherapy Trametinib + 6-Week Combination Treatment Cycle(s)													End of Treatment
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	12	13	≥ 14	Discontinuation[23]
Days	(-28 to -1)	1	8	15	22	29	36	43	50	57	64	1	22	1,22	
Cycle		1										2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Laboratory Procedures / Assessments[9]															
Pregnancy Test - Urine or Serum β-HCG[10]	X														
CBC with Differential[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[25]	X
Comprehensive Serum Chemistry Panel[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[25]	X
Urinalysis[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[25]	X
PT/INR and aPTT[12]	X	As clinically indicated													
Calculated Creatinine Clearance	X														
T3, FT4 and TSH[11,13]	X	X				X						X		X	X
Hepatitis B and C[14]	X														
Blood for Future Biomedical Research[15] (optional)		X													
Drug Dispensation, Administration, and Associated Analyses															
pembrolizumab Administration (30-minute infusion) [28,29]						X			X			X	X	X	
Pharmacokinetics of pembrolizumab[16]						X			X			X		X[25]	
Anti-pembrolizumab Antibodies[17]						X						X		X[25]	
Dispensation of pembrolizumab						X			X			X	X	X[25]	
Dispensation of Trametinib		X				X			X			X	X	X[25]	
Dosing Regimen Trametinib (cDL1, cDL2b regimens only)[28]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Dosing Regimen Trametinib (cDL-1b, cDL-1a regimens only)[29]		X	X	X	X			X	X			X	X	X	
Pharmacokinetics of Trametinib[18]									X			X		X[25]	X

Trial Period:	Screening[9]	4-Week Monotherapy Trametinib + 6-Week Combination Treatment Cycle(s)													End of Treatment
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	12	13	≥ 14	Discontinuation[23]
Days	(-28 to -1)	1	8	15	22	29	36	43	50	57	64	1	22	1,22	
Cycle		1										2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Efficacy Measurements															
Tumor Imaging[19]	X													X[25]	X
Tissue Collection and Pharmacodynamic Assessment															
BRAF Testing[20]	X														
Tumor Tissue Collection[21]	X						X								X[26]
Correlative Blood Sample[21]	X					X						X			X
Blood for Genetics[22]		X													

1 Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Day 1). Assign Baseline number when the study informed consent is signed.
2 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator.
3 Prior Medications - Report all medications taken within 30 days of Visit 1 and all treatments for a prior cancer even if taken greater than 30 days prior to Visit 1. Concomitant Medications - Enter new medications started during the trial through the Safety Follow-Up visit. After the Safety Follow-Up visit, record all medications taken for SAEs and ECIs as defined in Section 7.2.
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose. Height will be measured at Visit 1 only.
5 Electrocardiogram (12-lead ECG) should be performed at Screening and post-infusion at visits indicated in the flow chart.
6 Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
7 Any adverse experience of unknown etiology associated with trial treatment exposure should be evaluated to determine if it is possibly an Event of Clinical Interest (ECI).
8 Evaluate patients for symptoms or clinical signs of non-cutaneous, new primary/recurrent malignancies before initiation of treatment, periodically during treatment, or as clinically indicated. Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.
9 Routine laboratory tests (chemistry; hematology) for screening should be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
10 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
11 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests.
12 Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
13 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Following Cycle 4, testing will be performed every other cycle. In countries where T3 results are not available, FT3 results may be reported. See Section 7.1.3 for details regarding laboratory tests.

14 Testing will be performed by the local laboratory at Screening. Hepatitis B and Hepatitis C serologies should be obtained for subjects without a known history of Hepatitis B or C. Those with a known history are ineligible. Include HCV RNA (qualitative) and HBsAg.
15 Informed consent for Future Biomedical Research (FBR) samples must be obtained before the DNA sample is drawn. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.
16 Pre-dose and post-dose serum samples for PK of pembrolizumab will be collected on Day 29 and Day 50 of Cycle 1 and Day 1 of Cycle 2. Thereafter, only pre-dose (C_{trough}) PK serum samples will be collected at Day 1 of every alternate cycle (i.e., Day 1 of Cycle 3, Day 1 of Cycle 5, etc.). All pre-dose (C_{trough}) samples should be collected within 24 hours before the start of infusion of pembrolizumab and, if blood is collected for anti-pembrolizumab antibodies, at the same time blood sample for anti-pembrolizumab antibodies is collected. All post-dose PK samples should be collected within 30 minutes after the end of infusion of pembrolizumab. One additional post-dose sample should be collected between 24 and 96 hours following C1D29. Procedures for collection of samples are described in the Procedures Manual.
17 Blood for anti-pembrolizumab antibodies should be collected on Day 29 of Cycle 1 and Day 1 of Cycle 2, 3, and every other cycle thereafter (Cycle 5, Cycle 7, etc.). During pembrolizumab treatment, all samples should be drawn within 24 hours before infusion of pembrolizumab at the same time as blood collection for pre-dose (C_{trough}) PK serum samples of pembrolizumab.
18 On C1D50, both pre-dose and post-dose plasma samples for PK of trametinib will be collected. On C1D50, morning dose(s) should be withheld until after PK (pre-dose) sample has been drawn. On C1D50, post-dose PK samples for trametinib should be drawn (1) at the same time as when the post-dose pembrolizumab PK sample is drawn (the end of infusion), and, (2) at approximately 4-6 hours post-dose. On C2D1, subjects should take their morning dose at home. A post-dose sample will be obtained during study visit. Thereafter, PK plasma samples will be collected at Day 1 of every alternate cycle (i.e., Day 1 of Cycle 3, Day 1 of Cycle 5, etc.) during study visit. If visit is in the morning, subjects will be asked to withhold their morning dose; if visit is in the afternoon, subjects will be asked to take their morning dose as usual. Procedures for collection of samples are described in the Procedures Manual.
19 The initial tumor imaging will be performed within 28 days prior to the date of allocation. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. CT scans are the required modality for measurable disease unless a subject has a clinical condition, e.g., severe contrast allergy. The same imaging technique has to be used for the subject throughout the study. The visit window for subsequent imaging is +/- 7 days. If there is progressive disease, radiologic assessment/tumor imaging should be obtained at least four weeks from scan date for confirmation. CT timing should follow calendar days and should not be adjusted for delays in cycle starts. The process for collection of CT images is described in the Procedures Manual. Tumor imaging will be performed every 6 weeks (or whenever clinically indicated) starting at Week 17 while the subject remains on study therapy; after 18 months, tumor imaging will be performed every 12 weeks (or whenever clinically indicated) while the subject remains on study therapy. Per the modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, the imaging assessment should be repeated at a minimum of 4 weeks later in order to confirm progressive disease as described in Section 4.2.3.1.
20 BRAF mutation testing is only required for melanoma subjects; BRAF mutation testing is not required for solid tumor subjects. BRAF V600 E or K mutation analysis should be performed by sites during screening in subjects without documented BRAF status. This specimen may be collected any time from the initial diagnosis to the study entry and may be an archival tissue sample (within 6 months of study entry). BRAF analysis may be performed at a local laboratory, provided that the methodology is able to detect V600E and/or V600K mutations. A sample from the originally-tested tissue block must be collected and stored at the central laboratory for possible assay at a later date (i.e., in the event that BRAF status must be confirmed). Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
21 In order to be eligible for the study, all subjects must provide a tumor tissue specimen for biomarker analysis and blood samples for pharmacodynamic assessment. The tissue specimen may be collected any time from the initial diagnosis to the study entry and may be an archival tissue sample (within 90 days of Study Day 1=first dose(s) of study treatment) if it is not feasible to obtain a fresh biopsy not previously irradiated. Site documentation that the sample has been shipped to the biomarker analysis laboratory is sufficient evidence to meet eligibility criterion. If a tumor biopsy was obtained of a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous. The tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. Additionally, a fresh biopsy should be obtained 10-14 days following initiation of pembrolizumab study treatment for Parts 4 and 5 of the study. Detailed instructions for blood sample collection, tissue collection, processing and shipment are provided in the Laboratory and Procedures Manual, respectively. Any leftover blood or tumor tissue may be stored for future research if the subject signs the optional FBR consent.
22 Blood for genetics sample will be collected to explore host genetics and to identify genetic predictors which may have a role in therapeutic response to pembrolizumab
23 The discontinuation visit should be scheduled at the time of permanent discontinuation of all treatments (pembrolizumab and trametinib). The window for this visit is +10 days. All study treatments must be discontinued after 24 months. Required assessments for this visit are identified in the study flow chart; additional assessments that are not flagged as required may be performed if clinically indicated (e.g., coagulation tests, thyroid function tests, etc.).
24 Perform a full physical examination on the first day of each cycle and a directed physical examination on Day 22 of each cycle. Example: full physical exam on C3D1, directed physical exam on C3D22, full physical exam on C4D1, directed physical exam on C4D22, etc

25 Day 1 and 22 of Cycle 3: CBC with Differential, Comprehensive Chemistry Panel, Urinalysis
Day 1 ONLY from C4D1 onwards: CBC with Differential, Comprehensive Chemistry Panel, Urinalysis
Day 1 ONLY of every cycle (e.g., C3D1, C4D1, C5D1, etc.): ECOG Performance Status
Day 1 and 22 of every cycle (e.g., C3D1, C3D22, C4D1, C4D22, etc.): Dispensation of Drug Kit
Day 1 ONLY of every cycle (e.g., C3D1, C4D1, C5D1, etc.) until 18 months, then Day 1 ONLY of every other cycle: Tumor Imaging
Day 1 ONLY of every alternate cycle, as indicated (e.g., C3D1, C5D1, C7D1, etc.): ECG, ECHO, Pharmacokinetics of pembrolizumab and/or trametinib and/or dabrafenib, Anti-pembrolizumab Antibodies testing
26 pembrolizumab treated subjects in the Treatment Phase – Additional optional biopsy at disease progression is highly desired when feasible. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
27 Dermatological examination will be part of full physical examination on the first day of each cycle.
28 The following dosing regimens reflect the intended dosing of the subject at study initiation. The original dosing code should be utilized to determine when the subject should be dosed during the study. The dose timing associated with the original dosing code should continue to be used to bring the patient back into the schedule (1) if the patient ultimately dose reduced (e.g., due to AE) or (2) following study treatment interruption:
cDL1 = Subject allocated to study on 4 weeks of 1.5 mg QD trametinib, pembrolizumab 200 mg Q3W dosed at week 5 (Day 29) and week 8 (Day 50) with continuous dosing of trametinib in Cycle 1. Cycle 2 and beyond: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22) with continuous dosing of trametinib in the cycle.
cDL2b = Subject allocated to study on 4 weeks of 2 mg QD trametinib, pembrolizumab 200 mg Q3W dosed at week 5 (Day 29) and week 8 (Day 50) with continuous dosing of trametinib in Cycle 1. Cycle 2 and beyond: MK-347 dosed at week 1 (Day 1) and week 4 (Day 22) with continuous dosing of trametinib in the cycle.
29 The following dosing regimens reflect the intended dosing of the subject at initiation and the original dosing code should be utilized to determine when the patient should be dosed during the study The dose timing associated with the original dosing code should continue to be used to bring the patient back into the schedule (1) if the patient ultimately dose reduced (e.g., due to AE) or (2) following study treatment interruption:
cDL-1a = Subject allocated to study on 4 weeks of 1.5 mg QD trametinib, pembrolizumab 200 mg Q3W dosed week 5 (Day 29) and week 8 (Day 50) with no dosing of trametinib during weeks 5 and 6 (Days 29-42), dosing of trametinib during weeks 7 and 8 (Days 43-56), and no dosing of trametinib during weeks 9 and 10 (Days 57-70) of Cycle 1. Cycles 2, 4, and even-numbered cycles: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22), with dosing of trametinib during weeks 1 and 2 (Days 1-14), no dosing of trametinib during weeks 3 and 4 (Days 15-28), and dosing of trametinib during weeks 5 and 6 (Days 29-42). Cycles 3, 5, and subsequent odd-numbered cycles: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22), with no dosing of trametinib during weeks 1 and 2 (Days 1-14), dosing of trametinib during weeks 3 and 4 (Days 15-28), and no dosing of trametinib during weeks 5 and 6 (Days 29-42).
cDL-1b = Subject allocated to study on 4 weeks of 2 mg QD trametinib, pembrolizumab 200 mg Q3W dosed week 5 (Day 29) and week 8 (Day 50) with no dosing of trametinib during weeks 5 and 6 (Days 29-42), dosing of trametinib during weeks 7 and 8 (Days 43-56), and no dosing of trametinib during weeks 9 and 10 (Days 57-70) of Cycle 1. Cycles 2, 4, and even-numbered cycles: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22), with dosing of trametinib during weeks 1 and 2 (Days 1-14), no dosing of trametinib during weeks 3 and 4 (Days 15-28), and dosing of trametinib during weeks 5 and 6 (Days 29-42). Cycles 3, 5, and subsequent odd-numbered cycles: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22), with no dosing of trametinib during weeks 1 and 2 (Days 1-14), dosing of trametinib during weeks 3 and 4 (Days 15-28), and no dosing of trametinib during weeks 5 and 6 (Days 29-42).
30 Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants who have a death event previously recorded).

6.1.4 Parts 4 and 5: 2-Week Monotherapy Trametinib + 6-Week Treatment Cycle(s) of Pembrolizumab Q3W Dosing With Trametinib

Trial Period:	Screening[9]	2-Week Monotherapy Trametinib + 6-Week Combination Treatment Cycle(s)											End of Treatment
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	≥ 12	Discontinuation[23]
Days	(-28 to -1)	1	8	15	22	29	36	43	50	1	22	1,22	
Cycle		1								2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Administrative Procedures													
Informed Consent[1]	X												
Informed Consent for Future Biomedical Research (optional)	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History[2]	X												
Prior and Concomitant Medication Review[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Assignment		X											
Survival Status[31]		←	-	-	-	-	-	-	-	-	-	-	→
Clinical Procedures / Assessments													
Full Physical Examination[27]	X	X		X						X		X[24]	
Directed Physical Examination			X		X	X	X	X	X		X	X[24]	X
Vital Signs and Weight[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead Electrocardiogram (ECG)[5]	X			X						X		X[25]	
ECHO	X							X				X[25]	
Review Adverse Events[6,7,8]		X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X		X						X		X[25]	X

Trial Period:	Screening[9]	2-Week Monotherapy Trametinib + 6-Week Combination Treatment Cycle(s)											End of Treatment
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	≥ 12	Discontinuation[23]
Days	(-28 to -1)	1	8	15	22	29	36	43	50	1	22	1,22	
Cycle		1								2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Laboratory Procedures / Assessments[9]													
Pregnancy Test - Urine or Serum β-HCG[10]	X												
CBC with Differential[11]	X	X	X	X	X	X	X	X	X	X	X	X[25]	X
Comprehensive Serum Chemistry Panel[11]	X	X	X	X	X	X	X	X	X	X	X	X[25]	X
Urinalysis[11]	X	X	X	X	X	X	X	X	X	X	X	X[25]	X
PT/INR and aPTT[12]	X	As clinically indicated											
Calculated Creatinine Clearance	X												
T3, FT4 and TSH[11,13]	X	X		X						X		X	X
Hepatitis B and C[14]	X												
Blood for Future Biomedical Research[15] (optional)		X											
Drug Dispensation, Administration, and Associated Analyses													
pembrolizumab Administration (30-minute infusion) [28,29,30]				X			X			X	X	X	
Pharmacokinetics of pembrolizumab[16]				X			X			X		X[25]	
Anti-pembrolizumab Antibodies[17]				X						X		X[25]	
Dispensation of pembrolizumab				X			X			X	X	X[25]	
Dispensation of Trametinib		X		X			X			X	X	X[25]	
Dosing Regimen Trametinib (cDL2a, cDL3 regimens only)[28]		X	X	X	X	X	X	X	X	X[28]	X[28]	X	
Dosing Regimen Trametinib (iDL1, iDL2 regimens only)[29]		X	X		X	X		X	X	X[29]	X[29]	X	
Dosing Regimen Trametinib (iDL-1b, iDL-1a regimens only)[30]		X	X			X	X			X[30]	X[30]	X	
Pharmacokinetics of Trametinib[18]							X			X		X[25]	X

Trial Period:	Screening[9]	2-Week Monotherapy Trametinib + 6-Week Combination Treatment Cycle(s)											End of Treatment
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	≥ 12	Discontinuation[23]
Days	(-28 to -1)	1	8	15	22	29	36	43	50	1	22	1,22	
Cycle		1								2		≥ 3	
Scheduling Window (Days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Efficacy Measurements													
Tumor Imaging[19]	X											X[25]	X
Tissue Collection and Pharmacodynamic Assessment													
BRAF Testing[20]	X												
Tumor Tissue Collection[21]	X				X								X[26]
Correlative Blood Sample[21]	X			X						X			X
Blood for Genetics[22]		X											

1 Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Day 1). Assign Baseline number when the study informed consent is signed.
2 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator.
3 Prior Medications - Report all medications taken within 30 days of Visit 1 and all treatments for a prior cancer even if taken greater than 30 days prior to Visit 1. Concomitant Medications - Enter new medications started during the trial through the Safety Follow-Up visit. After the Safety Follow-Up visit, record all medications taken for SAEs and ECIs as defined in Section 7.2.
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose. Height will be measured at Visit 1 only.
5 Electrocardiogram (12-lead ECG) should be performed at Screening and post-infusion at visits indicated in the flow chart.
6 Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
7 Any adverse experience of unknown etiology associated with trial treatment exposure should be evaluated to determine if it is possibly an Event of Clinical Interest (ECI).
8 Evaluate patients for symptoms or clinical signs of non-cutaneous, new primary/recurrent malignancies before initiation of treatment, periodically during treatment, or as clinically indicated. Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.
9 Routine laboratory tests (chemistry; hematology) for screening should be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
10 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
11 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests.
12 Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.

13 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Following Cycle 4, testing will be performed every other cycle. In countries where T3 results are not available, FT3 results may be reported. See Section 7.1.3 for details regarding laboratory tests.
14 Testing will be performed by the local laboratory at Screening. Hepatitis B and Hepatitis C serologies should be obtained for subjects without a known history of Hepatitis B or C. Those with a known history are ineligible. Include HCV RNA (qualitative) and HBsAg.
15 Informed consent for Future Biomedical Research (FBR) samples must be obtained before the DNA sample is drawn. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.
16 Pre-dose and post-dose serum samples for PK of pembrolizumab will be collected on Day 15 and Day 36 of Cycle 1 and Day 1 of Cycle 2. Thereafter, only pre-dose (C_{trough}) PK serum samples will be collected at Day 1 of every alternate cycle (i.e., Day 1 of Cycle 3, Day 1 of Cycle 5, etc.). All pre-dose (C_{trough}) samples should be collected within 24 hours before the start of infusion of pembrolizumab and, if blood is collected for anti-pembrolizumab antibodies, at the same time blood sample for anti-pembrolizumab antibodies is collected. All post-dose PK samples should be collected within 30 minutes after the end of infusion of pembrolizumab. One additional post-dose sample should be collected between 24 and 96 hours following C1D15. Procedures for collection of samples are described in the Procedures Manual.
17 Blood for anti-pembrolizumab antibodies should be collected on Day 15 of Cycle 1 and Day 1 of Cycle 2, 3, and every other cycle thereafter (Cycle 5, Cycle 7, etc.). During pembrolizumab treatment, all samples should be drawn within 24 hours before infusion of pembrolizumab at the same time as blood collection for pre-dose (C_{trough}) PK serum samples of pembrolizumab.
18 PK for trametinib on C1D36:
cDL2a, cDL3, iDL-1a , iDL-1b: both pre-dose and post-dose plasma samples will be collected. On C1D36, morning dose(s) should be withheld until after PK (pre-dose) sample has been drawn. On C1D36, post-dose PK samples for trametinib should be drawn (1) at the same time as when the post-dose pembrolizumab PK sample is drawn (the end of infusion), and, (2) at approximately 4-6 hours post-dose.
iDL1, iDL2: Pre-dose plasma will be collected.
PK for trametinib on C2D1:cDL2a, cDL3, iDL-1a , iDL-1b: Subject should take morning dose at home. A post-dose sample will be obtained during study visit.
iDL1, iDL2: Pre-dose plasma will be collected.
Thereafter, for all regimens, PK plasma samples will be collected at Day 1 of every alternate cycle (i.e., Day 1 of Cycle 3, Day 1 of Cycle 5, etc.) during study visit. If visit is in the morning, subjects will be asked to withhold their morning dose; if visit is in the afternoon, subjects will be asked to take their morning dose as usual. Procedures for collection of samples are described in the Procedures Manual.
19 The initial tumor imaging will be performed within 28 days prior to the date of allocation. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. CT scans are the required modality for measurable disease unless a subject has a clinical condition, e.g., severe contrast allergy. The same imaging technique has to be used for the subject throughout the study. The visit window for subsequent imaging is ±7 days. If there is progressive disease, radiologic assessment/tumor imaging should be obtained at least four weeks from scan date for confirmation. CT timing should follow calendar days and should not be adjusted for delays in cycle starts. The process for collection of CT images is described in the Procedures Manual. Tumor imaging will be performed every 6 weeks (or whenever clinically indicated) starting at Week 15 while the subject remains on study therapy; after 18 months, tumor imaging will be performed every 12 weeks (or whenever clinically indicated) while the subject remains on study therapy. Per the modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, the imaging assessment should be repeated at a minimum of 4 weeks later in order to confirm progressive disease as described in Section 4.2.3.1.
20 BRAF mutation testing is only required for melanoma subjects; BRAF mutation testing is not required for solid tumor subjects. BRAF V600 E or K mutation analysis should be performed by sites during screening in subjects without documented BRAF status. This specimen may be collected any time from the initial diagnosis to the study entry and may be an archival tissue sample (within 6 months of study entry). BRAF analysis may be performed at a local laboratory, provided that the methodology is able to detect V600E and/or V600K mutations. A sample from the originally-tested tissue block must be collected and stored at the central laboratory for possible assay at a later date (i.e., in the event that BRAF status must be confirmed). Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
21 In order to be eligible for the study, all subjects must provide a tumor tissue specimen for biomarker analysis and blood samples for pharmacodynamic assessment. The tissue specimen may be collected any time from the initial diagnosis to the study entry and may be an archival tissue sample (within 90 days of Study Day 1=first dose(s) of study treatment) if it is not feasible to obtain a fresh biopsy not previously irradiated. Site documentation that the sample has been shipped to the biomarker analysis laboratory is sufficient evidence to meet eligibility criterion. If a tumor biopsy was obtained of a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous. The tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. Additionally, a fresh biopsy should be obtained 10-14 days following initiation of pembrolizumab study treatment for Parts 4 and 5 of the study. Detailed instructions for blood sample collection, tissue collection, processing and shipment are provided in the Laboratory and Procedures Manual, respectively. Any leftover blood or tumor tissue may be stored for future research if the subject signs the optional FBR consent.
22 Blood for genetics sample will be collected to explore host genetics and to identify genetic predictors which may have a role in therapeutic response to pembrolizumab.
23 The discontinuation visit should be scheduled at the time of permanent discontinuation of all treatments (pembrolizumab and trametinib). The window for this visit is +10 days. All

study treatments must be discontinued after 24 months. Required assessments for this visit are identified in the study flow chart; additional assessments that are not flagged as required may be performed if clinically indicated (e.g., coagulation tests, thyroid function tests, etc.).
24 Perform a full physical examination on the first day of each cycle and a directed physical examination on Day 22 of each cycle. Example: full physical exam on C3D1, directed physical exam on C3D22, full physical exam on C4D1, directed physical exam on C4D22, etc.
25 Day 1 and 22 of Cycle 3: CBC with Differential, Comprehensive Chemistry Panel, Urinalysis
Day 1 ONLY from C4D1 onwards: CBC with Differential, Comprehensive Chemistry Panel, Urinalysis
Day 1 ONLY of every cycle (e.g., C3D1, C4D1, C5D1, etc.): ECOG Performance Status
Day 1 and 22 of every cycle (e.g., C3D1, C3D22, C4D1, C4D22, etc.): Dispensation of Drug Kit
Day 1 ONLY of every cycle (e.g., C3D1, C4D1, C5D1, etc.) until 18 months, then Day 1 ONLY of every other cycle: Tumor Imaging
Day 1 ONLY of every alternate cycle, as indicated (e.g., C3D1, C5D1, C7D1, etc.): ECG, ECHO, Pharmacokinetics of pembrolizumab and/or trametinib and/or dabrafenib, Anti-pembrolizumab Antibodies testing
26 pembrolizumab treated subjects in the Treatment Phase – Additional optional biopsy at disease progression is highly desired when feasible. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
27 Dermatological examination will be part of full physical examination on the first day of each cycle.
28 The following dosing regimens reflect the intended dosing of the subject at study initiation. The original dosing code should be utilized to determine when the subject should be dosed during the study. The dose timing associated with the original dosing code should continue to be used to bring the patient back into the schedule (1) if the patient ultimately dose reduced (e.g., due to AE) or (2) following study treatment interruption:
cDL2a = Subject allocated to study on 2 weeks of 1.5 mg QD trametinib, pembrolizumab 200 mg Q3W dosed at week 3 (Day 15) and week 6 (Day 36) with continuous dosing of trametinib in Cycle 1. Cycle 2 and beyond: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22) with continuous dosing of trametinib in the cycle.
cDL3 = Subject allocated to study on 2 weeks of 2 mg QD trametinib, pembrolizumab 200 mg Q3W dosed at week 3 (Day 15) and week 6 (Day 36) with continuous dosing of trametinib in Cycle 1. Cycle 2 and beyond: MK-347 dosed at week 1 (Day 1) and week 4 (Day 22) with continuous dosing of trametinib in the cycle.
29 The following dosing regimens reflect the intended dosing of the subject at initiation and the original dosing code should be utilized to determine when the patient should be dosed during the study The dose timing associated with the original dosing code should continue to be used to bring the patient back into the schedule (1) if the patient ultimately dose reduced (e.g., due to AE) or (2) following study treatment interruption:
iDL1 = Subject allocated to study on 2 weeks of 1.5 mg QD trametinib, pembrolizumab 200 mg Q3W dosed week 3 (Day 15) and week 6 (Day 36) with no dosing of trametinib during week 3 (Days 15-21), dosing of trametinib during weeks 4 and 5 (Days 22-35), no dosing of trametinib during week 6 (Days 36-42), and dosing of trametinib during weeks 7 and 8 (Days 43-56) of Cycle 1. Cycles 2, 3, and beyond: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22), with no dosing of trametinib during week 1 (Days 1-7), dosing of trametinib during weeks 2 and 3 (Days 8-21), no dosing of trametinib during week 4 (Days 22-28), and dosing of trametinib during weeks 5 and 6 (Days 29-42).
iDL2 = Subject allocated to study on 2 weeks of 2 mg QD trametinib, pembrolizumab 200 mg Q3W dosed week 3 (Day 15) and week 6 (Day 36) with no dosing of trametinib during week 3 (Days 15-21), dosing of trametinib during weeks 4 and 5 (Days 22-35), no dosing of trametinib during week 6 (Days 36-42), and dosing of trametinib during weeks 7 and 8 (Days 43-56) of Cycle 1. Cycles 2, 3, and beyond: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22), with no dosing of trametinib during week 1 (Days 1-7), dosing of trametinib during weeks 2 and 3 (Days 8-21), no dosing of trametinib during week 4 (Days 22-28), and dosing of trametinib during weeks 5 and 6 (Days 29-42).
30 The following dosing regimens reflect the intended dosing of the subject at initiation and the original dosing code should be utilized to determine when the patient should be dosed during the study The dose timing associated with the original dosing code should continue to be used to bring the patient back into the schedule (1) if the patient ultimately dose reduced (e.g., due to AE) or (2) following study treatment interruption:
iDL-1a = Subject allocated to study on 2 weeks of 1.5 mg QD trametinib, pembrolizumab 200 mg Q3W dosed week 3 (Day 15) and week 6 (Day 36) with no dosing of trametinib during weeks 3 and 4 (Days 15-28), dosing of trametinib during weeks 5 and 6 (Days 29-42), and no dosing of trametinib during weeks 7 and 8 (Days 43-56) of Cycle 1. Cycles 2, 4, and even-numbered cycles: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22), with dosing of trametinib during weeks 1 and 2 (Days 1-14), no dosing of trametinib during weeks 3 and 4 (Days 15-28), and dosing of trametinib during weeks 5 and 6 (Days 29-42). Cycles 3, 5, and subsequent odd-numbered cycles: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22), with no dosing of trametinib during weeks 1 and 2 (Days 1-14), dosing of trametinib during weeks 3 and 4 (Days 15-28), and no dosing of trametinib during weeks 5 and 6 (Days 29-42).
iDL-1b = Subject allocated to study on 2 weeks of 2 mg QD trametinib, pembrolizumab 200 mg Q3W dosed week 3 (Day 15) and week 6 (Day 36) with no dosing of trametinib during weeks 3 and 4 (Days 15-28), dosing of trametinib during weeks 5 and 6 (Days 29-42), and no dosing of trametinib during weeks 7 and 8 (Days 43-56) of Cycle 1. Cycles 2, 4, and even-numbered cycles: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22), with dosing of trametinib during weeks 1 and 2 (Days 1-14), no dosing of trametinib during weeks 3 and 4 (Days 15-28), and dosing of trametinib during weeks 5 and 6 (Days 29-42). Cycles 3, 5, and subsequent odd-numbered cycles: pembrolizumab dosed at week 1 (Day 1) and week 4 (Day 22), with no dosing of trametinib during weeks 1 and 2 (Days 1-14), dosing of trametinib during weeks 3 and 4 (Days 15-28), and no dosing of trametinib during weeks 5 and 6 (Days 29-42).
31 Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants who have a death event previously recorded).

6.2 Post-Treatment Follow-Up ONLY for Subjects Who Discontinue Pembrolizumab Due to SD, PR or CR and Continue on Dabrafenib and/or Trametinib

Trial Period:	**Treatment (6-Week Cycle)**					**End of Treatment**
Visit	**Post SD, PR or CR Treatment Cycle and beyond**					Discontinuation[10]
Days	1	22	1	22	1,22	
Scheduling Window (Days)	±3	±3	±3	±3	±3	
Administrative Procedures						
Prior and Concomitant Medication Review[1]	X	X	X	X	X	X
Survival Status[17]	<--->					
Clinical Procedures / Assessments						
Review Adverse Events[2,3,4]	X	X	X	X	X	X
Full Physical Examination[14]	X		X		X[11]	
Directed Physical Examination		X		X	X[11]	X
Vital Signs and Weight[5]	X	X	X	X	X	X
12-Lead Electrocardiogram (ECG)	X		X		X[12]	
ECHO	X		X		X[12]	
ECOG Performance Status	X		X		X[12]	X
Laboratory Procedures / Assessments[6]						
CBC with Differential[7]	X	X	X	X	X[12]	X
Comprehensive Chemistry Panel[7]	X	X	X	X	X[12]	X
Urinalysis[7]	X		X		X[12]	X
PT/INR and aPTT[8]	As clinically indicated					
T3, FT4 and TSH[7]	X		X		X[13]	X
Drug Dispensation, Administration, and Associated Analyses						
Dispensation of Drug Kit	X	X	X	X	X	
Efficacy Measurements						
Tumor Imaging[9]	X		X		X[12]	X

1 Prior Medications - Report all medications taken within 30 days of Visit 1 and all treatments for a prior cancer even if taken greater than 30 days prior to Visit 1. Concomitant Medications - Enter new medications started during the trial through the Safety Follow-Up visit.
2 Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
3 Any adverse experience of unknown etiology associated with trial treatment exposure should be evaluated to determine if it is possibly an Event of Clinical Interest (ECI).
4 Evaluate subjects for symptoms or clinical signs of non-cutaneous, new primary/recurrent malignancies before initiation of treatment, periodically during treatment, or as clinically indicated. Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.
5 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a subject's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose. Height will be measured at Visit 1 only.
6 Routine laboratory tests (chemistry; hematology) for screening should be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
7 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. In countries where T3 results are not available, FT3 results may be reported. See Section 7.1.3 for details regarding laboratory tests.

8 Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
9 CT scans are the required modality for measurable disease unless a subject has a clinical condition, e.g., severe contrast allergy. The same imaging technique has to be used for the patient throughout the study. The visit window for imaging is ± 7 days. If there is progressive disease, radiologic assessment/tumor imaging should be obtained at least four weeks from scan date for confirmation. CT timing should follow calendar days and should not be adjusted for delays in cycle starts. Response status will be assessed by the investigator and/or the central vendor, depending on what part of the study and treatment arm the subject has discontinued. The process for collection of CT images is described in the Procedures Manual. Tumor imaging will be performed every 6 weeks (or whenever clinically indicated) starting at Week 13 while the subject remains on study therapy; after 18 months, tumor imaging will be performed every 12 weeks (or whenever clinically indicated) while the subject remains on study therapy. Per the modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, the imaging assessment should be repeated at a minimum of 4 weeks later in order to confirm progressive disease as described in Section 4.2.3.1.
10 The discontinuation visit should be scheduled at the time of permanent discontinuation of all treatments (pembrolizumab, trametinib, and/or dabrafenib). The window for this visit is +10 days. Required assessments for this visit are identified in the study flow chart; additional assessments that are not flagged as required may be performed if clinically indicated (e.g., coagulation tests, thyroid function tests, etc.).
11 Perform a full physical examination on the first day of each cycle and a directed physical examination on Day 22 of each cycle. Example: full physical exam on C3D1, directed physical exam on C3D22, full physical exam on C4D1, directed physical exam on C4D22, etc.
12 Day 1 and 22 of Cycle 3: CBC with Differential, Comprehensive Chemistry Panel
Day 1 ONLY from C3D1 onwards: Urinalysis
Day 1 ONLY from C4D1 onwards: CBC with Differential, Comprehensive Chemistry Panel
Day 1 ONLY of every cycle (e.g., C3D1, C4D1, C5D1, etc.): ECOG Performance Status
Day 1 ONLY of every cycle (e.g., C3D1, C4D1, C5D1, etc.) until 18 months, then Day 1 ONLY of every other cycle: Tumor Imaging
Day 1 ONLY of every alternate cycle (e.g., C3D1, C5D1, C7D1, etc.): ECG, ECHO
13 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Following Cycle 4, testing will be performed every other cycle.
14 Dermatological examination will be part of full physical examination on the first day of each cycle.
15 Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants who have a death event previously recorded).

6.3 Post-Treatment: Follow-Up

Trial Period:	**Post-Treatment**				
Visit	Safety Follow-Up[9]	Follow-Up[10] Visit 1	Follow-Up[10] Visit 2	Follow-Up[10] ≥ Visit 3	Survival Follow-Up[1] ≥ Visit 1
Time from Last Dose of Trial Treatment	30 Days	3 Months	6 Months	≥ 9 Months	Every 3 Months
Scheduling Window (Days)	± 3	± 7	± 7	± 7	± 30
Administrative Procedures					
Review Medications	X				
Subsequent Antineoplastic Therapy Status	X	X	X	X	X
Survival Status[1]	←	-	-	-	→ X
Clinical Procedures / Assessments					
Review Adverse Events[2,3]	X	X	X	X	
Vital Signs and Weight[4]	X				
Directed Physical Examination[11]	X	X	X		
12-Lead Electrocardiogram (ECG)	X				
ECOG Performance Status	X				
Efficacy Measurements					
Tumor Imaging[5]	X	X	X	X	
Laboratory Procedures / Assessments					
CBC with Differential[6]	X				
Comprehensive Chemistry Panel[6]	X				
Laboratory Procedures / Assessments					
Urinalysis	X				
PT/INR and aPTT[7]	As clinically indicated				
T3, FT4 and TSH	X				

Other Analyses					
Patient Reported Outcomes (PRO)					
EuroQol EQ-5D[8]	X				
EORTC QLQ-C30[8]	X				

1 Once a subject experiences disease progression, starts a new antineoplastic therapy, or continues off study on any combination of treatments received during the trial, the subject moves into the Survival Follow-up Phase and should be contacted by telephone every 3 months to assess for survival status and start of new antineoplastic therapy, if applicable. In addition, follow-up will be required at time of study completion if last follow-up was >30 days prior. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants who have a death event previously recorded), as per Section 7.1.5.
2 Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days of the last dose of trial treatment or until the start of new anti-cancer treatment, whichever comes first. After this time, report only SAEs and ECIs that are considered related to trial treatment.
3 Evaluate subjects for symptoms or clinical signs of non-cutaneous, new primary/recurrent malignancies before initiation of treatment, periodically during treatment, or as clinically indicated. Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure.
5 The same imaging technique should be used in a subject as was used earlier in the trial. Subjects who discontinue study treatment due to reasons other than disease progression, should continue to be assessed every 3 months by radiologic imaging. Monitoring should continue until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first.
6 See Section 7.1.3 for details regarding laboratory tests.
7 Coagulation factors (PT/INR and aPTT) should be determined throughout the study when clinically indicated.
8 PROs apply to Part 3 Post-Treatment subjects only: Patient reported outcomes (PROs) are to be administered by trained site personnel and completed electronically by subjects prior to all other study procedures in the following order: EuroQol EQ-5D first, followed by EORTC QLQ C-30. Subjects that complete 24 months on trial and opt to continue Dabrafenib and Trametinib will not be required to complete PROs at the 30-Day Safety follow up visit (Flow Chart 6.2). Subjects who complete 24 months on trial and move to Follow-Up or Survival Follow-Up will complete ePROs at the 30-Day Safety Follow-Up visit. pembrolizumab. PROs do not apply to Part 1, Part 2, Part 4, or Part 5It is most relevant and strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification.
9 The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.
10 Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-up Phase and should be assessed every 3 months by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. After Follow-up Visit 3 subjects only need to be assessed every 3 months by radiologic imaging to monitor disease status, development of drug related SAEs and ECIs, and initiation of new antineoplastic therapy. Unless otherwise noted in the flow chart, every effort should be made to collect subject information until the start of new antineoplastic therapy, disease progression, or death, whichever occurs first.
11 Dermatological examination will be part of directed physical examination as indicated.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any conditions diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. In addition, record any prior cancer other than melanoma even if diagnosed greater than 10 years prior to Visit 1. Melanoma history will be recorded separately and not listed as Medical History. A particular attention should be focused in identifying possibly immune related adverse events and managing these AEs effectively early on. Please refer to Section 5.6.1.1.3 for guidelines to manage irAEs.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial treatment. In addition, record all treatments for a prior cancer other than melanoma even if taken greater than 28 days prior to starting trial treatment. Prior treatments for melanoma will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial through the 30-day Safety Follow-up Visit. After the Safety Follow-up Visit record all medications related to reportable SAEs and ECIs as defined in Section 7.2.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 randomization number.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified treatment ≥ 12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

In exceptional cases and upon Sponsor consultation and approval, subjects receiving trametinib and/or dabrafenib in Part 3 may continue on study after completion of 24 months of treatment with pembrolizumab combined with trametinib and dabrafenib or placebo combined with trametinib and dabrafenib. These subjects can continue in accordance with the flow chart in Section 6.2 until disease progression, unacceptable toxicity, or the study is closed by the Sponsor. At the time of study closure, the subjects would move to local supply and continue care under their local treating physician.

After completion of pembrolizumab and/or trametinib at 24 months in Part 4 and 5, subjects will be discontinued from the trial. Subjects will be discontinued from the trial, move to follow -up until progression or survival follow-up if they opt to continue on any oncologic therapy. This would include pembrolizumab or trametinib and would be sourced locally as per standard of care.

Administration of trial medication pembrolizumab will be witnessed by the investigator and/or trial staff. The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.5). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

An immune related adverse event (irAE) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event immune related. Immunological, serological and histological (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Following the guidance described in Section 7.2.3.2., certain AEs should also be reported to the Sponsor as ECIs.

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exam are described in Section 6 - Trial Flow Chart. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

For cycles that do not required a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2.1 Dermatologic Exam

Dermatological exams should be performed as part of the physical exam. The time points for the dermatological exam are described in Section 6 - Trial Flow Chart. Exams may be performed by the investigator or may be referred to a dermatologist, at the discretion of the investigator. If possible, the same physician should perform each exam for the duration of the study (i.e., if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and during the Follow-up period as specified in the Trial Flow Chart. Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Visit 1 only.

7.1.2.4 12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points for standard 12-lead ECG are described in Section 6 – Trial Flow Chart.

7.1.2.5 Echocardiogram (ECHO)

An ECHO will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional timepoints for ECHO are described in Section 6 – Trial Flow Chart.

7.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.6) at screening, prior to the administration of each dose of trial treatment and during the Follow-up period as specified in the Trial Flow Chart.

7.1.2.7 Tumor Imaging and Assessment of Disease

See Section 4.2.3.1.1 and Section 6.0 – Trial Flow charts and associated footnotes for more information on tumor imaging and assessment of disease.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 36.

Table 36 Laboratory Tests

Hematology	Chemistry[a]	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test – Urine and/or Serum β-human chorionic gonadotropin (β-hCG)[b]
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Triiodothyronine (T3)[c]
Red blood cell count	Bicarbonate	Microscopic exam, if abnormal results are noted	Free thyroxine (FT4)
Absolute Neutrophil count	Calcium		Thyroid stimulating hormone (TSH)
Absolute lymphocyte count	Chloride		Anti-pembrolizumab Antibodies
	Creatinine		PK
	Glucose		Blood for FBR
	Lactic Acid Dehydrogenase (LDH)[d]		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine or calculated creatinine clearance (CrCl)		
	Uric acid		
	Magnesium		
	Total cholesterol		
	Triglycerides		

[a]In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis.
[b]Perform on women of child bearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
[c]In countries where T3 results are not available, free triiodothyronine (FT3) results may be reported.
[d]LDH required for Part 3 (stratification factor).

Laboratory safety tests for screening should be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 48 hours prior to dosing.

Results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 Blood Collection for PK Serum MK-3475

Sample collection, storage and shipment instructions for serum samples is provided in the Procedures Manual.

7.1.3.2.2 Blood Collection for PK Plasma Trametinib

Sample collection, storage and shipment instructions for plasma samples is provided in the Procedures Manual.

7.1.3.2.3 Blood Collection for PK Plasma Dabrafenib and Metabolites (Hydroxy- and Desmethyl-dabrafenib)

Sample collection, storage and shipment instructions for plasma samples is provided in the Procedures Manual.

7.1.3.2.4 Anti-MK-3475 Antibodies

Sample collection, storage and shipment instructions for serum samples is provided in the Procedures Manual.

7.1.3.3 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Blood for genomics use
- Leftover tumor tissue
- Leftover correlative blood samples

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the end of trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call-center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed. Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Monitor notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

At the end of the trial, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Approximately 28 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of the trial treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
- Tumor imaging must be performed within 28 days prior to the date of allocation.

Subjects may be rescreened after initially failing to meet inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of repeating a screening test if performed within the specified time frame and the results meet the inclusion/exclusion criteria.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures.

7.1.5.3 Post-Treatment Follow-up Phase

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures. Second Course Phase

The Part 3 final analysis did not demonstrate a statistically significant increase in PFS in the experimental arm compared to the control arm. Subjects in the Part 3 experimental arm experienced a higher rate of Grade 3-5 AEs, SAEs, and discontinuations due to AEs compared to the control arm. Therefore, there is no further rationale to offer re-challenge with triplet therapy and Second Course Phase will not be offered to subjects in KEYNOTE-022.

7.1.5.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an siDMC review, interim and/or final analysis. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects who have a previously recorded death event in the collection tool).

7.1.5.5 Treatment After the End of the Study

Upon study completion, subjects are discontinued and may be enrolled in an extension study.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

Dabrafenib

In the event of a dabrafenib overdose, defined as administration of more than 300 mg as a single dose or 600 mg per day (the highest dose tested in clinical studies to date), the investigator should contact the Clinical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. There is no specific antidote for an overdose of dabrafenib or trametinib. Patients who develop adverse reactions should receive appropriate symptomatic treatment. In case of suspected overdose, dabrafenib should be withheld and supportive care instituted. Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Haemodialysis is not expected to enhance the elimination of dabrafenib as it is highly bound to plasma proteins.

Trametinib

In the event of a trametinib overdose, defined as administration of more than 3.0 mg once daily (the maximum tolerated dose defined in the MEK111054 Study), the investigator should contact the Clinical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. No specific treatment is recommended. The investigator will use clinical judgment to treat any overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Clinical Monitor based on the clinical evaluation of the subject.

Note: In the event of an overdose of either dabrafenib or trametinib, a plasma sample for PK analysis may be requested by the Clinical Monitor on a case-by-case basis. This plasma sample should be collected as soon as possible, but within 10 days from the date of the last dose of on-study dosing. Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported..

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 37 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent)

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up

period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent)

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. Specific hepatic events, Grade ≥2, OR, any grade resulting in dose modification or use of systemic steroids to treat the AE:

   – Hepatitis
   – Autoimmune hepatitis
   – Transaminase elevations

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3. - Immediate Reporting of Adverse Events to the Sponsor.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 37. The investigator's assessment of causality is required for each adverse event. Refer to Table 37 for instructions in evaluating adverse events.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

Table 37 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate Standing Internal Data Monitoring Committee (siDMC) will monitor the interim data from this trial. The siDMC comprises members of Sponsor Senior Management, none of whom are directly associated with the conduct of this trial. The siDMC will monitor the trial at an appropriate frequency (see Section 8.2.9 - Interim Analyses) for evidence of adverse effects of trial treatment and efficacy targets/dose selection/futility, as described in the detailed monitoring guidelines. The siDMC will determine whether the trial should continue (or other modifications, pre-specified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to trial participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Parts 1 and 2: Pembrolizumab in Combination with Trametinib and Dabrafenib

The primary purpose of Part 1 and Part 2 is to investigate the safety and tolerability of pembrolizumab in combination with trametinib and dabrafenib in adult subjects with advanced melanoma. Descriptive tables that summarize the number and percentage of subjects who experience a DLT (dose limiting toxicity) as well as AE summaries will be generated for MK+D+T (as well as for MK+D, if MK+D combination is studied) by dose level for the all subjects as treated population. Percentage of subjects treated with the confirmed dose of (MK+D+T) (across Parts 1 and 2) that attained Objective Response will be estimated.

The final number of subjects enrolled in Part 1 and Part 2 of (MK+D+T) will depend on empirical safety (DLT) observations. The sample size of Part 1 will range from 3 (0/3 DLTs on Dose Level 1) to 12 subjects (6 subjects on Dose Level 1 followed by de-escalation and enrollment of 6 subjects into Dose Level -1); a likely size of 6 subjects is used as an

estimated size of Part 1 for operation purposes. If the safety of MK+D+T Dose Level 1 is acceptable, the sample size of Part 2 will range from 8 (if 6 subjects enrolled in Dose Level 1 in Part 1 are followed by enrollment of 8 more patients in Dose Level 1 in Part 2) to 24 subjects (if 3 subjects enrolled in Dose Level 1 in Part 1 are followed by enrollment of 10 more subjects in Dose Level 1 in Part 2 with 5/13 DLTs, followed by de-escalation and enrollment of 14 subjects on Dose Level -1); 11 subjects is used as an estimated size of Part 2 for operational purposes.

However, the most likely scenario is that after the MAD is identified in dose escalation (Part1), the enrollment will continue on that dose in Part 2 until 14 subjects across Parts 1 and 2 are enrolled on that dose. Thus, the most likely scenarios will include 14 subjects enrolled across Parts 1 and 2 combined (used for operational purposes), with the range across Parts 1 and 2 being 14 to 27.

8.1.2 Parts 1, 2, 4, and 5: Pembrolizumab in Combination With Trametinib

The safety and tolerability of (MK+T) (Table 3) in adult subjects with advanced melanoma will be investigated in dose escalation (Part 1) and dose confirmation (TPI design of Part 2) of the study.

The final number of subjects enrolled in Part 1 and Part 2 of (MK+T) will depend on empirical safety (DLT) observations. The sample size of Part 1 will range from 3 (0/3 DLTs at Dose Level 1) to 12 subjects (6 subjects at Dose Level 1 followed by de-escalation and enrollment of 6 subjects at Dose Level -1); a likely size of 6 subjects is used as an estimated size of Part 1 for operation purposes. If the safety of (MK+T) Dose Level 1 is acceptable, the sample size of Part 2 will range from 34 (if 6 subjects enrolled at Dose Level 1 in Part 1 are followed by enrollment of 34 more patients at Dose Level 1 in Part 2) to 50 subjects (if 3 subjects enrolled at Dose Level 1 in Part 1 are followed by enrollment of 10 more subjects at Dose Level 1 in Part 2 with 5/13 DLTs, followed by de-escalation and enrollment of 40 subjects at Dose Level -1); 34 subjects is used as an estimated size of Part 2 for operational purposes.

The safety and tolerability of the concurrent (Table 6) and intermittent (Table 7) dosing regimens of (MK+T) in adult subjects with melanoma or solid tumors will be investigated in dose escalation (Part 4) and dose confirmation (modified TPI design of Part 5) of the study. After 14 subjects are observed for DLTs on the (MK+T) dose of the concurrent regimen confirmed in Part 4 of the study and 14 subjects are observed for DLTs on the (MK+T) dose of the intermittent regimen confirmed in Part 4 of the study (across the dose escalation and confirmation parts combined), the choice of the regimen (concurrent or intermittent) for the efficacy expansion will be complete.

The final numbers of subjects enrolled in Parts 4 and 5 will depend on empirical safety (DLT) observations for both regimens. For operational purposes, the sample sizes of Parts 4 and 5 are estimated as follows.

The minimum size of Part 4 for the concurrent dosing cohort is 6 subjects which can occur if the first dose is rejected with 3 subjects and the dose below it is rejected with 3 subjects. Assuming 6 subjects per dose in the 3+3 design, the maximum size of Part 4 for the concurrent dosing cohort is 24 subjects. The minimum size of Part 5 TPI (dose confirmation) is then 8 subjects; the estimated sample size of the Part 5 TPI is increased to 16 subjects to allow for dose escalation and de-escalation steps, in the event this becomes necessary. Thus, for operational purposes, the maximum estimated subject numbers for enrollment in the concurrent dosing cohort in Parts 4 and 5 are 24 and 16 , respectively, for a total of 40 subjects across Parts 4 and 5.

Similarly, the minimum size of Part 4 for the intermittent dosing cohort is 6 subjects, which can occur if the first dose is rejected with 3 subjects and the dose below it is rejected with 3 subjects. Assuming 6 subjects per dose in the 3+3 design, the maximum size of Part 4 for intermittent dosing cohort is 18 subjects. The minimum size of Part 5 TPI (dose confirmation) is then 8 subjects; the estimated sample size of the Part 5 TPI part is increased to 16 subjects to allow for dose escalation and de-escalation steps, in the event this becomes necessary. Thus, for operational purposes, the maximum estimated subject numbers for enrollment in the intermittent dosing cohort in Parts 4 and 5 are 18 and 16, respectively, for a total of 34 subjects across Parts 4 and 5.

An efficacy evaluation of (MK+T) with respect to progression-free survival (PFS) will also be performed by Kaplan-Meier method.

8.1.3 Part 3: Pembrolizumab in Combination with Trametinib and Dabrafenib

8.1.3.1 Final Efficacy Analyses

The primary analysis population in Part 3, Intent-to-Treat Set (ITT), will include all randomized subjects. Primary endpoint in Part 3 is the Progression-Free Survival (PFS) per RECIST 1.1 defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first. The treatment groups will be compared in PFS by stratified log-rank test. While the randomization is stratified by ECOG PS (0 vs. 1) and LDH (>1.1xULN vs. ≤1.1xULN), due to a very low number of subjects enrolled in the stratum ECOG=1 and LDH ≤1.1xULN, the two strata with ECOG=1 (ECOG=1 and LDH ≤1.1xULN; ECOG=1 and LDH >1.1xULN) will be combined for all analyses. A Cox proportional hazard model stratified using the same strata with Efron's method of tie handling will be used to estimate the hazard ratio and its 95% confidence interval. The Kaplan-Meier method will be used to estimate the PFS survival curve.

Secondary endpoints include objective response rate (ORR) per RECIST 1.1, response duration per RECIST 1.1, and overall survival (time to death).

The analysis strategy for primary and efficacy endpoints are provided in Table 38.

Table 38 Analysis Strategy for Primary and Secondary Efficacy Endpoints in Part 3

Endpoint (Description, Time Point)	Approach†	Statistical Method‡	Analysis Population	Missing Data Approach
Progression-free-survival	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method Kaplan-Meier method for PFS curve estimation in each treatment group	ITT	Censored at last assessment
Objective response rate	S	Stratified Miettinen and Nurminen method [100]	ITT	Subjects with missing data are considered as non-responders
Response Duration	S	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Overall survival	S	Summary statistics using Kaplan-Meier method	ITT	Censored at last date
† P=Primary , S=Secondary				

8.1.3.1.1 Power of the Final Efficacy Analysis of Part 3

If the true hazard ratio is 0.5, the study will need approximately 74 PFS events to have 80% power to reject a null hypothesis of equal PFS distributions in the two groups at one-sided 0.025 Type I error. Approximately 120 subjects will be randomized in 1:1 ratio to accumulate this number of events with 0.5-year enrollment period and 2-year total study duration assuming the median PFS in the (PBO+D+T) group is 10 months (rounded up estimate of 9.4 months provided in Flaherty et al. paper [101]) and yearly dropout rate is 5%. The observed hazard ratio needs to be approximately 0.62 or lower for the treatment effect to be statistically significant. This ratio translates to approximately 6.2 months increase in median duration.

8.1.3.2 Safety Analyses of Part 3

The All-Subjects-as-Treated population will be employed for safety analyses. There will be no Tier 1 events in this study. Tier 2 and Tier 3 safety endpoints will be evaluated as described in Section 8.2.5.4.

8.1.3.3 Interim Analysis of Part 3

One interim analysis of Part 3 will be conducted to inform potential early Go/No Go decision for initiation of Phase III study before the completion of Part 3. The data from the first 80 subjects randomized into the study will be used in the interim analysis. The interim analysis

will be conducted when the first 80 subjects randomized into the study will have completed their Week 36 visit and have their central radiology assessment at Week 36 available or have discontinued prior to Week 36.

Results of the interim analysis will be reviewed by the siDMC. The endpoint(s), timing, and purpose of the interim analysis are summarized in the Table 39. The decision rules and other statistical details are further described in Section 8.2.9.

Table 39 Summary of Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
• 5-category ordinal response at Week 36	First 80 randomized subjects either complete Week 36 visit or discontinue prior to Week 36 visit	• Start Phase III prior to Part 3 completion • Futility

8.1.4 Subgroup Analyses

Subjects with high PD-L1 expression level are of special interest in this study. The PFS hazard estimates (95% CIs) and ORR estimates (95% CI) will be provided for the subgroups of PD-L1 positive subjects and PD-L1 negative subjects.

8.2 Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

8.2.1 Responsibility for Analysis/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

Parts 1, 2, 4, and 5 of this trial are conducted as open-label trials, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The database will be locked for analysis of Parts 1 and 2 for (MK+D+T) 6 months after the enrollment of the last (MK+D+T) Part 2 subject. The database will be locked for analysis of Parts 1 and 2, 4, and 5 for (MK+T) 6 months after the enrollment of the last (MK+T) Part 5 subject. Part 3 will not be unblinded when these analyses takes place.

Part 3 of this study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

Planned interim analysis of Part 3 is described in Section 8.2.9. Blinding to Part 3 treatment assignment will be maintained at all investigational sites. The results of the interim analysis will not be shared with the investigators prior to the completion of the study. Subject-level unblinding will be restricted to an internal unblinded statistician and scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.Treatment-level results and/or subject-level data of the interim analysis will be provided by the unblinded statistician to the standing internal Data Monitoring Committee (siDMC) which consists of SPONSOR personnel. Limited additional SPONSOR personnel may be unblinded to the treatment level results of the interim analysis, if required, in order to act on the recommendations of the siDMC. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The processes by which recommendations and decisions are reached and communicated are documented in the siDMC charter for the SPONSOR. The protocol-specific siDMC charter will be referenced in the CSR. Prior to final study unblinding, individuals who have been unblinded at any level will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the interim analyses. Key aspects of the interim analyses are described in Section 8.2.9.

The Sponsor, the investigator, and the subject will be unblinded after database lock for the final analysis of Part 3. At unblinding, the Sponsor will inform each investigator of the trial treatment allocated to subjects at their site. Subjects who are receiving treatment with pembrolizumab in combination with trametinib and dabrafenib will be allowed to continue treatment per protocol after being informed of the results of the final analysis. These subjects will continue to follow the dose modification and toxicity management guidelines as per protocol. Combinations other than the therapy they are already receiving will not be allowed for these subjects.

Subjects who are receiving treatment with placebo in combination with trametinib and dabrafenib will be allowed to continue trametinib and dabrafenib per protocol (without placebo) after being informed of the final analysis results. These subjects will continue to follow the dose modification and toxicity management guidelines as per protocol.These subjects will not be allowed to cross over to the treatment arm with pembrolizumab in combination with trametinib and dabrafenib.

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy Endpoints

Efficacy endpoints and their definitions are presented below.

8.2.3.1.1 Primary Endpoint

Progression-free Survival (PFS): is defined as the time from randomization in Part 3 (or the start of treatment in other Parts) to progressive disease (PD) or death, whichever occurs earlier, based upon RECIST 1.1 by the investigator review. Subjects without documented PD/death will be censored at the last disease assessment date.

8.2.3.1.2 Secondary Endpoints

Objective Response Rate (ORR): is defined as the percentage of subjects who have achieved confirmed complete response (CR) or partial response (PR) according to RECIST 1.1 by the investigator review. Subjects with missing outcome on objective response will be considered non-responders.

Response Duration: is defined as the time interval between the date of the first confirmed response (CR/PR) (the response prior to confirmation) and the date of first documented disease progression based upon RECIST 1.1 by the investigator review. Response duration will be only determined for confirmed responses.

Overall survival (OS): is defined as the time from randomization (or the start of treatment when there is no randomization) to death due to any cause. Subjects without documented death at the time of analysis will be censored at the date last known to be alive.

5-Category Ordinal Response at Week 36 – an ordinal endpoint that classifies the response at Week 36 into one of 5 categories: CR, VGPR defined as partial response with percent reduction from baseline in tumor line length >60%, MPR defined as partial response with percent reduction from baseline in tumor line length ≤60%, SD, and PD, where CR, PR, SD and PD categories are based upon RECIST 1.1 by central review. This will be the primary endpoint of the interim analysis of Part 3. See details of the definition in the description of the **5-Category Ordinal Response at a Timepoint.**

8.2.3.1.3 Exploratory Endpoints

Best Overall Response per RECIST 1.1 [Appendix 12.4]: the best response attained during the study with 4 categories based upon RECIST 1.1 by the investigator review: Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD). Categories of CR and PR need to be confirmed in this endpoint.

5-Category Best Overall Response (BOR-5) – an ordinal endpoint that represents the best response attained during the study with 5 categories: CR (confirmed), Very Good Partial Response (VGPR) defined as confirmed partial response with maximum percent reduction

from baseline in tumor line length >60%, Moderate Partial Response (MPR) defined as confirmed partial response with maximum percent reduction from baseline in tumor line length ≤60%, SD, and PD. In this endpoint, CR, PR, SD and PD categories are based upon RECIST 1.1 by the investigator review and the RECIST 1.1 category of PR is split into two categories: VGPR and MPR.

5-Category Ordinal Response at a Timepoint – an ordinal endpoint that classifies the response at given timepoint into one of 5 categories: CR, VGPR defined as partial response with percent reduction from baseline in tumor line length >60%, MPR defined as partial response with percent reduction from baseline in tumor line length ≤60%, SD, and PD. In this endpoint, CR, PR, SD and PD categories are based upon RECIST 1.1 by the investigator review. No confirmation will be required for complete or partial responses at a timepoint. Subjects who discontinued prior to timepoint will be assigned to one of these categories according to their reason for discontinuation. Subjects who discontinued for the following reasons will be included in the PD category: documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, noncompliance with trial treatment or procedure requirements, investigator's decision to withdraw the subject, subject withdraws consent. Subjects who discontinued due to pregnancy of the subject or for administrative reasons will be included in the SD category. Subjects who attained an investigator-determined confirmed complete response (CR) per RECIST 1.1 and stopped the trial treatment will be included in the CR category. The categories are assigned scores 1 to 5 for analysis: CR=1, VGPR=2, MPR=3, SD=4, PD=5.

Percentage of Subjects with CR based upon RECIST 1.1 by the investigator review

Percentage of Subjects with PR based upon RECIST 1.1 by the investigator review

Percentage of Subjects with Deep Response (DR) where DR is a response that is either CR or VGPR by the investigator review.

Best Target Lesion Response - maximum percent reduction in tumor line length over target lesions by the investigator review.

Time to Confirmed Response – defined only for subjects with confirmed response by the investigator review. The time interval between the date of randomization and the date of the first confirmed response (CR/PR) (the response prior to confirmation).

Percentage of Subjects with Sustained Response at Week 36 (used in the interim analysis) - subjects who achieved response (confirmed CR or PR) prior to Week 36 but have not yet progressed at Week 36 by central review.

Tumor growth kinetics endpoints: growth rate constant (GST) and time-to-growth (TTG) and other as appropriate. These endpoints will be used in Modeling and Simulations analysis.

EuroQol (EQ-5D) and **EORTC (QLQ-C30) endpoints**

Additional supportive analyses of PFS, objective response rate, best overall response, and duration of response will be conducted using modified RECIST 1.1 criteria, in which a confirmation assessment of disease progression must be obtained at least 4 weeks after the initial disease assessment indicating progressive disease.

8.2.3.2 Safety Endpoints

The primary safety endpoint in Parts 1, 2, 4, and 5 of the study is DLT. In Part 3, there will be no Tier 1 safety endpoints; Tier 2 and Tier 3 safety endpoints will be evaluated as described in 8.2.5.4. Safety will be monitored by cumulative data reviews throughout the trial. The toxicities and grades experienced by subjects who have received study treatment, including adverse events (AEs), serious adverse events (SAEs) and events of clinical interest (ECIs) will be summarized. Other safety measures evaluated in all parts of the study include laboratory safety assessments, ECGs, vital signs, and physical examinations.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The primary analysis population in Part 3, Intent-to-Treat Analysis Set (ITT), will include all randomized subjects. The ITT will serve as the primary population for the analyses of PFS, OS, and ORR in this study. Analysis of response duration is based on all confirmed responders.

In Parts 1, 2, 4, and 5 of the study the All-Subjects-as-Treated (ASaT) will be used for efficacy analyses. Analysis of response duration will be based on all confirmed responders in the ASaT.

8.2.4.2 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this study. In all parts of the study, the ASaT population consists of all subjects who received at least one dose of study treatment. In Parts 4 and 5, subjects treated during the trametinib run-in period will be included in the ASaT population even if they discontinued treatment before receiving pembrolizumab. In case of treatment administration errors, subjects will be analyzed according to the treatment they actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

The DLT analysis will be performed on a DLT-evaluable population.

In Parts 1 and 2, a DLT evaluable subject is defined as a subject who receives at least 66% of all planned treatments during the 6-week DLT observation period (i.e., Cycle 1, initiated with

the first pembrolizumab dose) or a subject who discontinues the DLT observation period due to a DLT. In Parts 4 and 5, a DLT evaluable subject is defined as a subject who receives at least 66% of all planned treatments during the 6-week DLT observation period (i.e., following the trametinib run-in period in Cycle 1, initiated with the first pembrolizumab dose) or a subject who discontinues the DLT observation period due to a DLT. In Parts 4 and 5, any subject who discontinues trametinib during the trametinib monotherapy run-in period is not considered evaluable for DLTs for the (MK+T) combination, even if the subject discontinued due to a DLT.

8.2.5 Statistical Methods

8.2.5.1 Statistical Methods for Efficacy Analyses

Parts 1, 2, 4 and 5 in Subjects Treated with (MK+D+T) or (MK+T)

The best overall response and PFS based on the investigator review per RECIST 1.1 in subjects along with baseline characteristics will be listed. Percentage of subjects that attained Objective Response will be estimated.

Part 3

The analysis strategy for primary and secondary endpoints in Part 3 is summarized in Table 40.

Table 40 Analysis Strategy for Primary and Secondary Efficacy Endpoints in Part 3

Endpoint (Description, Time Point)	Approach†	Statistical Method‡	Analysis Population	Missing Data Approach
Progression-free-survival	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method Kaplan-Meier method for PFS curve estimation in each treatment group	ITT	Censored at last assessment
Objective response rate	S	Stratified Miettinen and Nurminen method [100]	ITT	Subjects with missing data are considered as non-responders
Response Duration	S	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Overall survival	S	Summary statistics using Kaplan-Meier method	ITT	Censored at last date
† P=Primary , S=Secondary				

Primary endpoint in Part 3 is PFS. The treatment groups will be compared in PFS by stratified log-rank test. While the randomization is stratified by ECOG PS (0 vs. 1) and LDH (>1.1xULN vs. ≤1.1xULN), due to a very low number of subjects enrolled in the stratum ECOG=1 and LDH ≤1.1xULN, the two strata with ECOG=1 (ECOG=1 and LDH ≤1.1xULN; ECOG=1 and LDH >1.1xULN) will be combined for all analyses A Cox proportional hazard model with a factor for treatment group stratified using the strata above with Efron's method of tie handling will be used to estimate the hazard ratio and its 95% confidence interval. The Kaplan-Meier method will be used to estimate the PFS survival curve, the median PFS and its 95% CI, PFS at 44 weeks (10.1 months) and its 95% CI, and PFS at 74 weeks (17 months) and its 95% CI will be estimated. The time points chosen for estimation are close to the expected time of median PFS in the (PBO+D+T) treatment group (44 weeks) and the respective smallest detectable median in the (MK+D+T) treatment group. Both time points are placed 2 weeks after the scheduled visit as lower variability of the Kaplan-Meier estimate is expected outside of the clinic visit window.

For PFS, subjects without documented PD/death will be censored at the last disease assessment date or, if they started new anti-cancer treatment, at the last disease assessment before initiation of the new anticancer treatment (Table 40). Two sensitivity analyses of PFS will be performed. The rules for defining the time of progression or censoring in the primary and two sensitivity PFS analyses are provided in Table 41.

Table 41 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death

ORR will be estimated as the percentage of responders among subjects in each treatment group. 95% CIs for within-group ORRs will be provided using the Clopper-Pearson method [102]. The treatment comparison between arms will be based on Miettinen and Nurminen's method [100] based on difference in proportions stratified using strata from the PFS analysis.

The response duration analysis will include subjects who achieved objective response. The responders who have not yet progressed by the last disease assessment will be censored at the last disease assessment date. The treatment groups will be compared in response duration by log-rank test stratified using strata from the PFS analysis. A Cox proportional hazard model with a factor for treatment group stratified using the strata from the PFS analysis with Efron's method of tie handling will be used to estimate the hazard ratio and its 95% confidence interval. The Kaplan-Meier method will be used to estimate the response duration survival curve, the 25-th percentile and the median of response duration and their 95% CIs.

Time to response analysis will include all subjects who achieved objective response, and thus, will contain no censored endpoints. The Kaplan-Meier method will be used to estimate the time to response survival curve, the 25th percentile and the median of response duration and their 95% CIs.

The treatment groups will be compared in OS by log-rank test stratified using the strata from the PFS analysis. A Cox proportional hazard model with a factor for treatment group stratified by the covariates above with Efron's method of tie handling will be used to estimate the hazard ratio and its 95% confidence interval. The Kaplan-Meier method will be used to estimate the OS survival curve, the 25th percentile and the median of OS and their 95% CIs. Subjects without documented death at the time of analysis will be censored at the date last known to be alive.

Best Overall Response (BOR) will be summarized by treatment groups, with frequency of categories presented. BOR-5 will be analyzed by ANOVA on scores 1 to 5 assigned to the response categories: CR=1, VGPR=2, MPR=3, SD=4, PD=5. ANOVA will include factors for treatment group, ECOG PS (0 vs. 1) and LDH (>1.1xULN vs. ≤1.1xULN). The variances in the two treatment groups will be allowed to be unequal. The desired effect of the addition of pembrolizumab to the (PBO+D+T) combination is to shift BOR response towards lower scores, [lower the treatment group mean score of (MK+D+T) compared to (PBO+D+T)].

Individual Best Target Lesion Responses (maximum percent reduction in tumor line length over target lesions) will be plotted for each treatment group separately in a waterfall plot.

Descriptive statistics according to the individual scoring will be provided for EuroQol (EQ-5D) and EORTC (QLQ-C30) by cycle and at the end of treatment for each treatment arm separately; additional modeling might be performed.

An exploratory analysis that relates PFS to BOR-5 will be conducted for each treatment group separately. Subjects will be classified according to their BOR; five PFS Kaplan-Meier curves will be plotted for each category of BOR and examined for presence of trend across the categories. In addition, potential of the 5-category Ordinal Response at a landmark to predict the PFS beyond the landmark will be explored in the following way. Subjects who had not experienced PD by Week 12 will be classified into 4 categories according to their 5-category Ordinal Response at Week 12. Four overlaid Kaplan-Meier curves for PFS beyond Week 12 will be plotted and examined for presence of trend across the categories. Similar

exploratory analysis will be performed for 5-category Ordinal Response at later weeks, although diminishing size of the data set will lead to higher variability of Kaplan-Meier curves.

8.2.5.2 Pharmacokinetic Analysis

Serum concentrations of pembrolizumab will be summarized by planned visit and time and PK data will be compared to the existing population PK model. Graphical, non-compartmental and potentially exploratory compartmental analyses will be used for the analysis of the PK data.

Plasma concentrations of dabrafenib, hydroxy-dabrafenib, desmethyl-dabrafenib, and trametinib will be summarized by planned visit and time. PK parameters such as oral clearance (CL/F), volume of distribution (Vc/F) and other measures of exposure (average concentration [C_{avg}], and/or minimum concentration [C_{min}]) will be derived using previously validated models and summarized.

8.2.5.3 Biomarker Analysis

In Parts 1, 2, 4, and 5, the key biomarker will be the PD-L1 expression measured using 0-5 Allred Proportion Scores (APS) for PD-L1 staining in melanoma using the Dako assay. The mean change from baseline to Day 10-14 after administration of oral dabrafenib and/or trametinib in combination with intravenously administered pembrolizumab in PD-L1 expression will be estimated and the 95% CI for the change will be provided.

8.2.5.4 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, ECG measurements and physical examinations.

In Parts 1, 2, 4, and 5, DLTs will be listed. Adverse experiences will be summarized as counts and frequencies for each dose level in Parts 1, 2, 4, and 5 of the study. Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

AEs of potentially immunologic etiology (AEs of special interest, AEOSI) will be identified using a pre-specified list of terms.

Part 3. The analysis of safety results in Part 3 will follow a tiered approach (Table 42). The tiers differ with respect to the analyses that will be performed. There are no Tier 1 events in this study; safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters will be classified as belonging to "Tier 2" or "Tier 3," based on the number of events observed. Membership in

Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints.

AEs of potentially immunologic etiology (AEs of special interest [AEOSI]) will be identified using a pre-specified list of terms and summarized.

Table 42 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Grade 3-5 AE		X	X
	Onset and Duration of First Grade 3-5 AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Specific AEs, SOCs, or PDLCs‡ (incidence ≥4 subjects in at least one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4 subjects in all of the treatment groups), AEOSI			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

† Adverse Experience references refer to both Clinical and Laboratory AEs.
‡ Includes only those endpoints not pre-specified as Tier-2 endpoints.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.2.5.5 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by descriptive statistics or categorical tables. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed.

8.2.6 Multiplicity

There will be no multiplicity control across the primary and secondary endpoints tests in this study or across the interim and final analysis.

8.2.7 Sample Size and Power Calculations

If the true hazard ratio is 0.5, the study will need approximately 74 PFS events to have 80% power to reject a null hypothesis of equal PFS distributions in the two groups at one-sided 0.025 Type I error. Approximately 120 subjects will be randomized in 1:1 ratio to accumulate this number of events with 0.5-year enrollment period and 2-year total study duration assuming the median PFS in the (PBO+D+T) group is 10 months (rounded up estimate of 9.4 months provided in Flaherty et al. paper [101]) and yearly dropout rate is 5%.

The observed hazard ratio needs to be approximately 0.62 or lower for the treatment effect to be statistically significant. This ratio translates to approximately 6.2 months increase in median duration.

8.2.8 Subgroup Analyses and Effect of Baseline Factors

The hazard ratio estimate and its 95% confidence interval for PFS and the ORR estimate and its 95% CI will be provided in the subgroups of subjects who are PD-L1 positive and PD-L1 negative. In addition, we will explore the treatment effect on the PFS (hazard ratio estimates and 95% CI) within each of the following subgroups: Age (≤ 65 vs. > 65 years), Sex (female vs. male), Race (white, non-white), ECOG status (0 vs. 1), LDH (>1.1xULN vs. ≤1.1xULN). The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. The number of subjects in each subgroup and the number (percent) of subjects with the PD will be also provided by treatment group. If a subgroup has no subjects with the PD in at least one of the treatment groups, the hazard ratio estimate and its 95% CI will not be derived.

8.2.9 Interim Analyses

Interim analysis of Part 3 will be conducted to inform potential early Go/No Go decision for initiation of Phase III study before the completion of Part 3. The data from the first 80 subjects randomized into the study will be used in the interim analysis. The interim analysis will be conducted when the first 80 subjects randomized into the study will have completed their Week 36 visit and have their central radiology assessment at Week 36 available or have discontinued prior to Week 36.

8.2.9.1 Primary Endpoint for the Interim Analysis

The primary endpoint for the interim analysis is the ordinal response at Week 36 with the following five categories: CR, VGPR, MPR, SD, and PD determined by central review. Subjects who discontinued prior to Week 36 will be assigned to one of these categories for Week 36 according to their reason for discontinuation (see the endpoint definition).

8.2.9.2 Analysis of the Primary Endpoint for the Interim Analysis

The two treatment groups will be compared in the primary endpoint by Analysis of Variances (ANOVA) on scores 1 to 5 assigned to the response categories: CR=1, VGPR=2, MPR=3, SD=4, PD=5. ANOVA will include factors for treatment group and the strata from the PFS analysis. The variances in the two treatment groups will be allowed to be unequal. The desired effect of the addition of pembrolizumab to the (PBO+D+T) combination is to shift the ordinal response towards lower scores [lower the treatment group mean of (MK+D+T) compared to (PBO+D+T)].

8.2.9.2.1 Interim Decision Rules

If analysis of the ordinal response at Week 36 results in a statistically significant comparison in favor of the (MK+D+T) combination at one-sided Type I error of 0.025, the decision to

initiate Phase III study without waiting for PFS results will be considered. If the analysis shows that (MK+D+T) is worse than (PBO+D+T) at one-sided 0.05 Type I error, the futility will be established and the decision not to initiate a Phase III study may be considered.

8.2.9.2.2 Power of the Interim Analysis

The true mean of the ordinal endpoint at Week 36 in the high dose dabrafenib and trametinib combination treatment group in Flaherty et al. study [101] is projected to be 3.51 (an average of Week 32 and Week 40 means in Flaherty et al. study [101]). The following assumptions were used to derive the distribution of the ordinal endpoint at Week 36 in (MK+D+T) treatment group. We assumed that the subjects in (MK+D+T) treatment group reach their Best Overall Response by Week 36 and retain it at Week 36. We further assumed that the Best Overall Response in subjects in the (MK+D+T) treatment group is the same as the Best Overall Response in the high dose dabrafenib and trametinib combination treatment group in the Flaherty et al. study [101]. Therefore, the assumed distribution of the ordinal endpoint at Week 36 in (MK+D+T) treatment group matches the distribution of the Best Overall Response in the high dose dabrafenib and trametinib combination treatment group in the Flaherty et al. study [101], with the mean of 2.59. Thus, the true between-treatment difference in the mean ordinal response under the alternative hypotheses is 0.92; the standard deviation that corresponds to the specified distributions of the ordinal response at Week 36 is approximately 1.29. Under the null hypotheses (the ordinal response in the (MK+D+T) treatment group at Week 36 is the same as in the (PBO+D+T) treatment group), the true difference in means is 0 and the standard deviation is 1.53.

Power for Superiority Decision

With 40 subjects per treatment group, between-treatment difference of 0.92 and standard deviation of 1.29, the interim analysis has approximately 88% power to establish superiority of (MK+D+T) in ordinal response at Week 36. The smallest difference in treatment means detectable at one-side 0.025 Type I error is approximately 0.57 (with the mean in the (MK+D+T) treatment group lower than the mean in the (PBO+D+T) treatment group).

Observed Difference Required for Futility Decision

With 40 subjects per treatment group and standard deviation of 1.53, the observed difference in the treatment means of the ordinal response should be at least 0.56 (with mean in the (MK+D+T) treatment group higher than the mean in the (PBO+D+T) treatment group) to reject the null hypothesis of the equal means at one-sided 0.05 Type I error.

Interpretation of the Difference in the Means of the Ordinal Endpoint

The difference of 0.57 in the treatment group means can be achieved if, for example, the responses of 57% of subjects in one treatment group are moved one category down on the ordinal scale (VGPR to CR, or MPR to VGPR, or SD to MPR, or PD to SD); or the responses of 20% of subjects are moved 2 categories down (from MPR to CR, or SD to

VGPR, or PD to MPR) and the responses of another 17% of subjects are moved one category down.

8.2.9.2.3 Secondary and Exploratory Endpoints at the Interim Analysis

Secondary endpoints at the Interim Analysis

1) Percentage of subjects with Deep Response (DR) at Week 36 defined as either CR or VGPR at Week 36

2) Percentage of subjects with CR at Week 36

3) Ordinal response at Week 36 with the following five categories: CR, VGPR, MPR, SD, and PD determined by the investigator review

Exploratory endpoints at the Interim Analysis

1) Percentage of subjects with PR at Week 36

2) Best Overall Response (analyzed as an ordinal endpoint)

3) Best Percent Reduction in Tumor Line Length by Week 36

4) Percentage of subjects with sustained response at Week 36 -subjects who achieved response (confirmed CR or PR) prior to Week 36 but have not yet progressed at Week 36

5) Tumor growth kinetics endpoints: growth rate constant (GST) and time-to-growth (TTG)

Analysis of Secondary and Exploratory Endpoints

Binary secondary and exploratory endpoints will be compared between the two treatment groups by Fisher's exact test. All analyses will be performed at two-sided Type I error 0.05; there will be no control of Type I error across the primary and secondary hypotheses.

Summaries of the ordinal response (based on investigator review) distribution by week, including frequencies of categories and the mean response, will be provided.

A sensitivity analysis of the ordinal response at Week 36 based on the investigator review will be performed using the analysis described for the ordinal response at Week 36 based on central review.

Power of the Analyses of Secondary Endpoints at the Interim Analysis

If the true percentage of subjects with CR at Week 36 in (PBO+D+T) group is 10% (approximate expected percentage) and the true percentage of subjects with CR at Week 36 in (MK+D+T) group is 35%, the power for comparison of the percentages of subjects with CR at Week 36 is 71%. If the true percentage of subjects with DR at Week 36 in (PBO+D+T) group is 37.5% (approximate expected percentage) and the true percentage of

subjects with CR at Week 36 in (MK+D+T) group is 70%, the power for comparison of the percentages of subjects with CR at Week 36 is 79%.

If there are 4 subjects out of 40 (10%) with CR at Week 36 in the (PBO+D+T) treatment group, the (MK+D+T) treatment group should have at least 12 subjects with CR (36 %) at Week 36 for the comparison to be statistically significant. If there are 15 subjects with DR (37.5%) at Week 36 in the (PBO+D+T) treatment group, the (MK+D+T) treatment group should have at least 24 subjects with DR at Week 36 (60%) for the comparison to be statistically significant.

8.2.10 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

8.2.11 Extent of Exposure

For a pembrolizumab regimen, a subject's extent of exposure to pembrolizumab (or matching IV placebo) is defined as the total number of doses of pembrolizumab (or matching IV placebo) the subject received. A subject's extent of exposure to dabrafenib or trametinib will be described through the cumulative dose of each drug.

Summary statistics will be provided to characterize Extent of Exposure, Time on Study Treatment (in months; calculated as the total number of days from the first post-randomization dose date to the date of the last dose of study medication multiplied by 12/365.24), and, for dabrafenib and trametinib, the Average Daily Dose. The summary statistics will be provided for the APaT population in Part 3, for each treatment group separately.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 43.

Table 43 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg / 4 mL	solution for IV infusion
Trametinib 2 mg	tablets
Trametinib 0.5 mg	tablets
Dabrafenib 75 mg	capsules
Dabrafenib 50 mg	capsules

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Open label vials of pembrolizumab and open label bottles of trametinib and dabrafenib will be provided. No kitting is required.

9.3 Clinical Supplies Disclosure

Parts 1, 2, 4, and 5 of the trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

Part 3 of the trial is blinded but provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are provided.

At unblinding, trial personnel will dispense unblinded supplies. Additional details are included in the pharmacy and procedures manuals.

The emergency unblinding call center will use the randomization schedule for the trial to unblind subjects and to unmask treatment for Part 3 of this trial. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will provide random code/disclosure envelopes or lists to the emergency unblinding call center.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Monitor notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying

worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are

requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the

trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to

the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.2

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.2

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The DNA, tumor and blood specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The DNA, tumor specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced

to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

If specimens are collected for a specific genotype or expression analysis as an objective to the main trial, this analysis is detailed in the main body of this protocol (**Section 8.0 – Statistical Analysis Plan**). These specimens will be processed, analyzed, and the remainder of the specimen will be destroyed. The results of these analyses will be reported along with the other trial results. A separate specimen will be obtained from properly-consented subjects in this protocol for storage in the biorepository for Future Biomedical Research.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens.

Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial

administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

Merck has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

13. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

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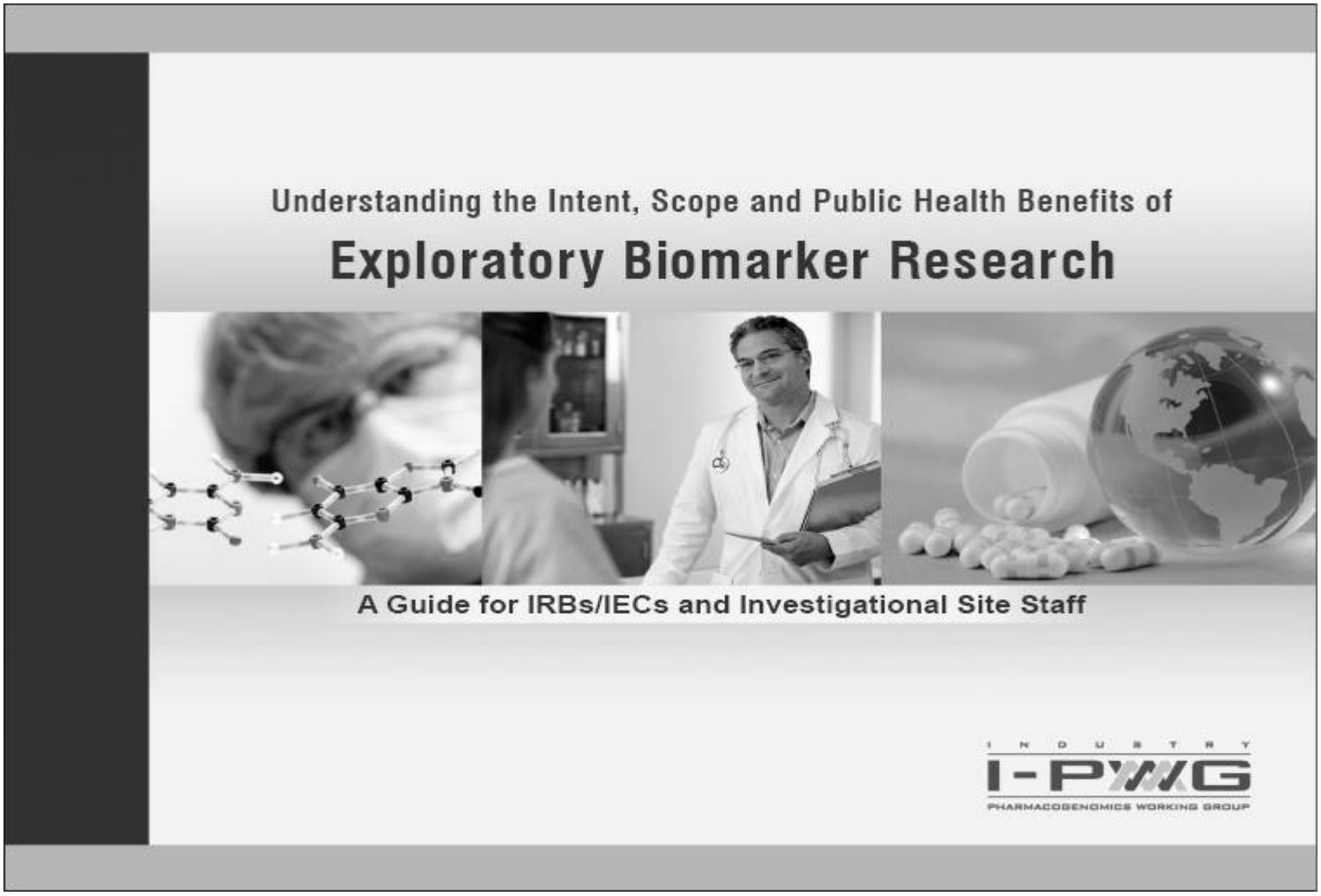
12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site StaffUnderstanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff



This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development

Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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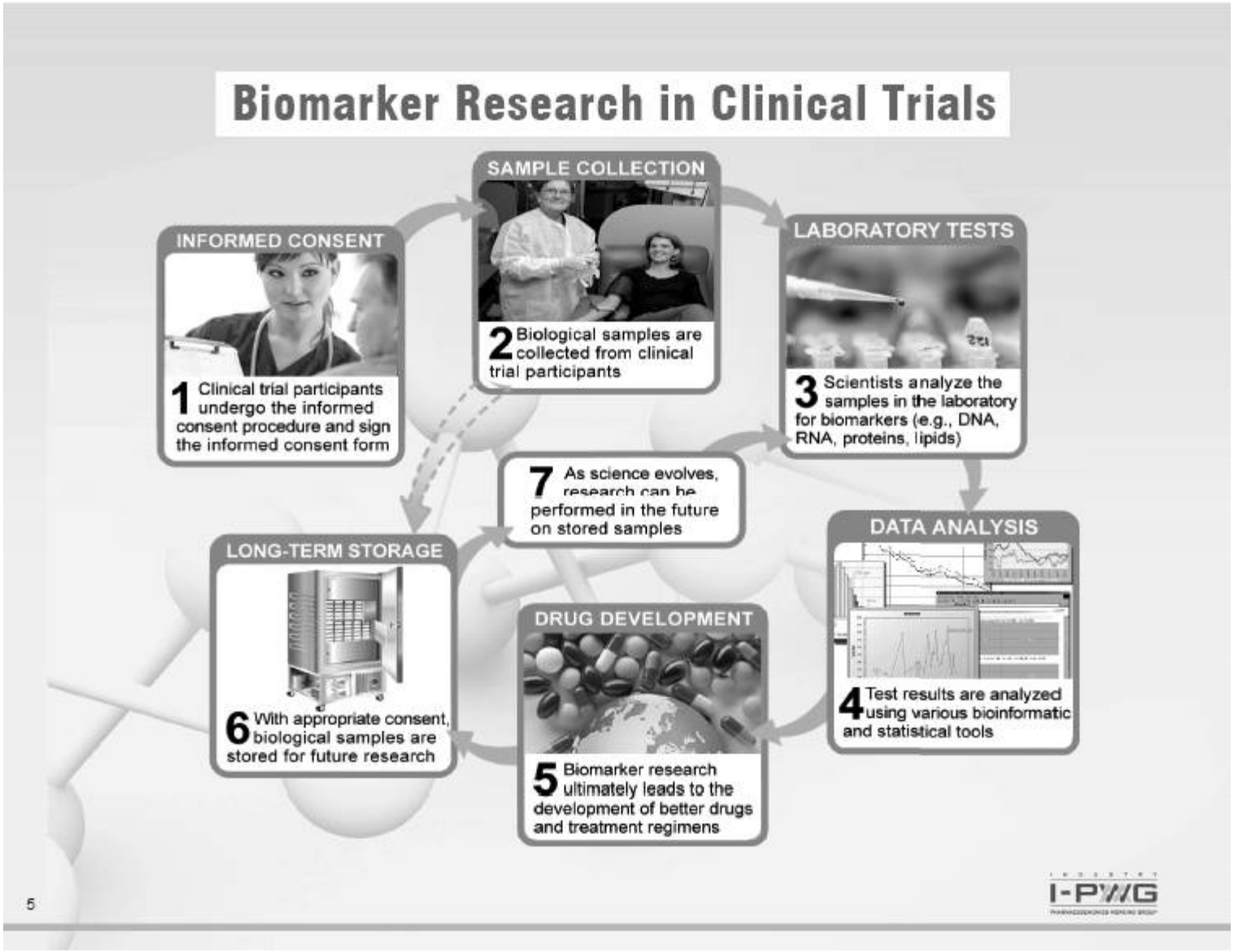
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-36]

10. Benefits and Risks Associated with Biomarker Research

Benefits
While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks
Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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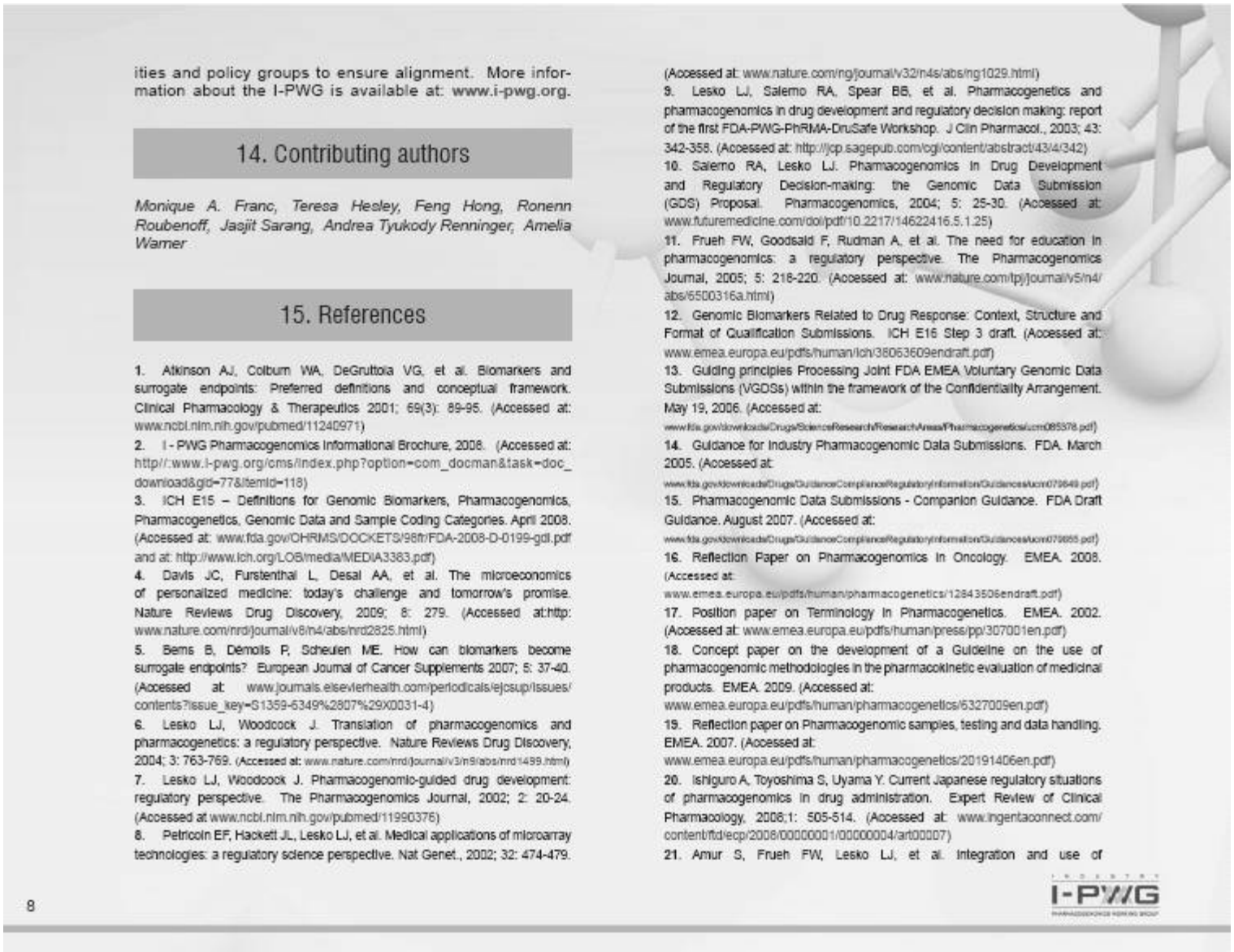

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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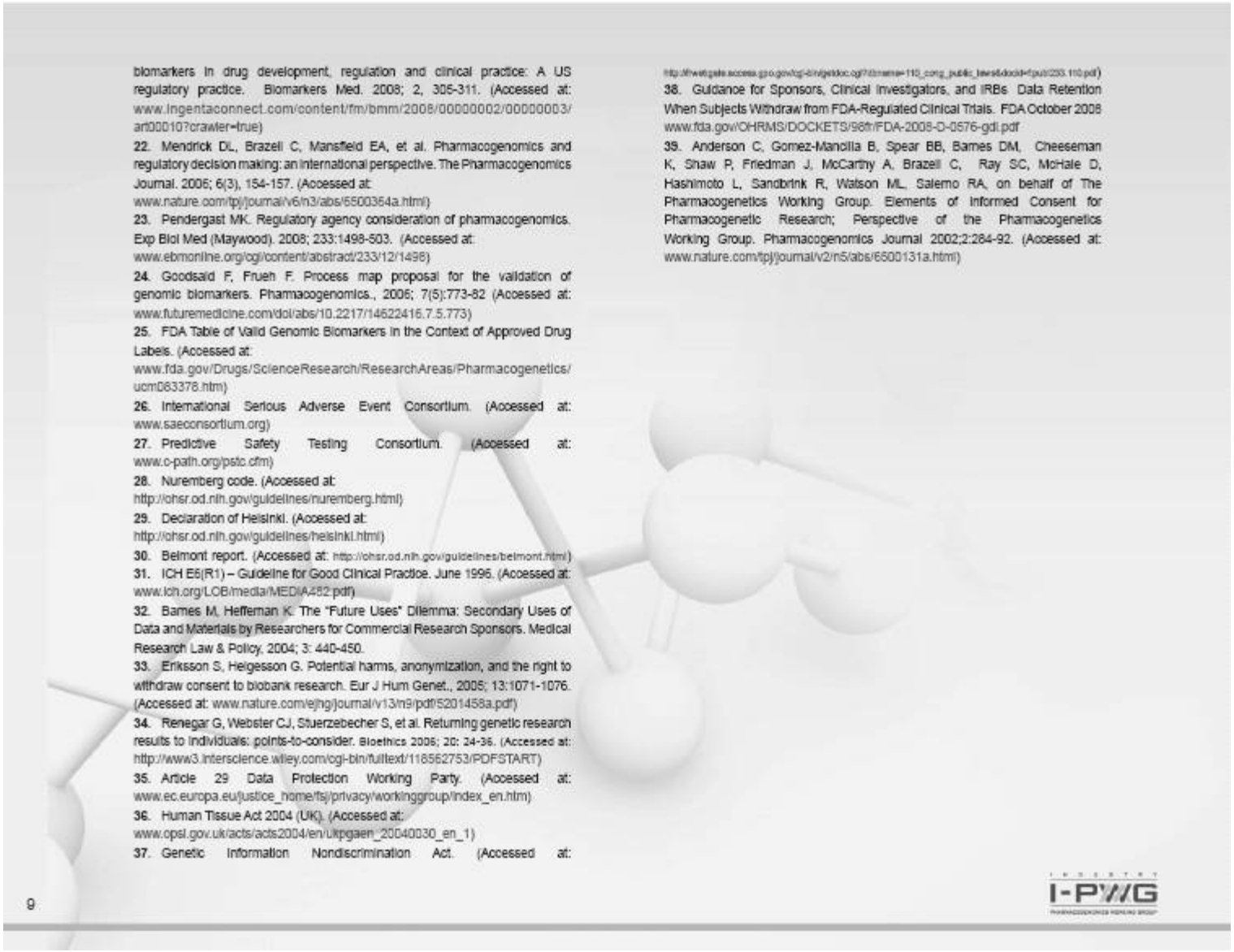

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www.i-pwg.org

12.4 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be used 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 tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

12.5 Common Terminology Criteria for Adverse Events (CTCAE) v4.0

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

12.6 ECOG Performance Status

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

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655

http://ecog-acrin.org/resources/ecog-performance-status

12.7 CCG Formula

$$\text{ClCr (mL/min)} = \frac{Q \times (140 - \text{age[yr]}) \times \text{idealbodyweight[kg]}^*}{72 \times \text{serum creatinine [mg/dL]}}$$

Q = 0.85 for females
Q = 1.0 for males

-- OR--

$$\text{ClCr (mL/min)} = \frac{K \times (140 - \text{age[yr]}) \times \text{idealbodyweight[kg]}^*}{\text{Serum creatinine [umol/L]}}$$

K = 1.0 for females
K = 1.23 for males

*Calculation of Ideal Body Weight Using the Devine Formula
Ideal body weight:
Males = 50.0 kg + (2.3 kg x each inch over 5 feet) or 50.0 kg + (0.906 kg x each cm over 152.4 cm)
Females = 45.5 kg + (2.3 kg x each inch over 5 feet) or 45.5 kg + (0.906 kg x each cm over 152.4 cm)

Example: Male, actual body weight = 90.0 kg, height = 68 inches
Ideal body weight = 50.0 + (2.3) (68-60) = 68.4 kg.
This subject's actual body weight is >30% over ideal body weight. Therefore, in this case, the subject's ideal body weight of 68.4 kg should be used in calculating estimated CrCl.

Reference

Devine, BJ. Case Number 25 Gentamicin Therapy: Clinical Pharmacology Case Studies. Drug Intelligence and Clinical Pharmacy. 1974; 8:650-655

12.8 NYHA Functional Classification System

The NYHA Functional Classification: Class I, II, II or IV Heart Failure provides a simple way of classifying the extent of heart failure. It places subjects in one of 4 categories based on the level of limitation experienced during physical activity:

Class	**Symptoms**
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.
The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.	

12.9 Sample Patient Daily Dosing Diary

PATIENT DAILY DOSING DIARY DAY 1 – 21

A Phase I/II Study to Assess the Safety and Efficacy of MK-3475 in Combination with Trametinib and Dabrafenib in Subjects with Advanced Melanoma

Patient #: _____ **Cycle #:** _____

Your Trametinib dose is: _____**mg Once Daily** **AND** **Your Dabrafenib dose is:** _____**mg Twice Daily**

- **Complete this form each time you take your study drug. If you miss a dose or do not take it as prescribed, make a note of this in the last column below.**
- **Extra columns are provided if you take more than one capsule or tablet strength. If you only take one strength, you can leave these extra columns blank.**
- **Please bring all of your medication bottles (including empty bottles), any leftover capsules/tablets and this completed form to your next clinic visit.**

Day	Date MM/DD/YY	Time Dose was Taken	Trametinib Dose				Dabrafenib Dose - AM				Dabrafenib Dose - PM				Comments
			Tablet Strength	# of Tabs	Tablet Strength	# of Tabs	Capsule Strength	# of Caps	Capsule Strength	# of Caps	Capsule Strength	# of Caps	Capsule Strength	# of Caps	
Example	*07-13-11*	*8:30 am*	*2 mg*	*1*	*N/A*	*0*	*75 mg*	*2*	*N/A*	*0*	*75 mg*	*2*	*N/A*	*0*	
1	___/___/___	:													
2	___/___/___	:													
3	___/___/___	:													
4	___/___/___	:													
5	___/___/___	:													
6	___/___/___	:													
7	___/___/___	:													
8	___/___/___	:													
9	___/___/___	:													
10	___/___/___	:													
11	___/___/___	:													
12	___/___/___	:													
13	___/___/___	:													
14	___/___/___	:													
15	___/___/___	:													
16	___/___/___	:													

Version 1.0 Dec-2013

12.10 List of Abbreviations

Abbreviation/Acronym	Definition
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
AE	Adverse Event
AEOSI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
b-HCG	Beta- Human Chorionic Gonadotropin
BID	Twice Daily
BOR	Best Overall Response
BP	Blood Pressure
CBC	Complete Blood Count
CDC	Complement-Dependent Cytotoxicity
C_{max}	Observed Maximum Concentration
CPK	Creatine Phosphokinase
CR	Complete Response
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Observed Trough Concentration
cuSCC	Cutaneous Squamous Cell Carcinoma
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DILI	Drug-Induced Liver Injury
DL1	Dose Level 1
DLT	Dose Limiting Toxicity
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
EC_{50}	Half-Maximal Effective Concentration
ECG	Electrocardiogram
ECHO	Echocardiogram
ECI	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
FT4	Free Thyroxine
GCP	Good Clinical Practice

Abbreviation/Acronym	Definition
GLP	Good Laboratory Practice
HFSR	Hand-Foot Skin Reaction
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IC_{50}	Half-Maximal Inhibitory Concentration
IFNγ	Interferon gamma
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-2	Interleukin-2
irAE	immune-related Adverse Event
IRBs/ERCs	Institutional Review Boards/Ethics Committees
irECIs	immune-related Events of Clinical Interest
IUS	Intrauterine Hormone-releasing System
IUD	Intrauterine Device
IV	Intravenous
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MAD	Maximum Administered Dose
MAPK	Mitogen-Activated Protein Kinase
MEL	Melanoma
MK+D	Pembrolizumab + Dabrafenib
MK+D+T	Pembrolizumab + Dabrafenib + Trametinib
MK+T	Pembrolizumab + Trametinib
mmHg	millimeters mercury
MPR	Moderate Partial Response
MRI	Magnetic Resonance Imaging
msec	milliseconds
MTD	Maximum Tolerated Dose
mTPI	modified Toxicity Probability Interval
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease

Abbreviation/Acronym	Definition
PFS	Progression Free Survival
PGt	Pharmacogenetic
PGx	Pharmacogenomics
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PBO+D+T	Placebo (saline IV) + Dabrafenib + Trametinib
PO	By mouth
PROs	Patient Reported Outcomes
PT/INR	Prothrombin Time/International Normalized Ratio
QD	Once daily
QTc	corrected QT Interval
QTcB	QT interval on electrocardiogram corrected using the Bazett's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RVO	Retinal Vein Occlusion
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCARs	Severe Cutaneous Adverse Reactions
SD	Stable Disease
siDMC	standing internal Data Monitoring Committee
$t_{1/2}$	Half life
T_3	Triiodothyronine
TBD	To Be Determined
TILs	Tumor-Infiltrating Lymphocytes
TKIs	Tyrosine Kinase Inhibitors
T_{max}	Time to reach C_{max}
TNFα	Tumor Necrosis Factor alpha
TPI	Toxicity Probability Interval
TSH	Thyroid Stimulating Hormone
TT	Tetanus Toxoid
TTG	Time to Growth
ULN	Upper Limit of Normal
VGPR	Very Good Partial Response

12.11 Past Medical History Related to Dermatologic Event

Past Medical History:

Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No

If yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No

List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc): _____

_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.? □ Yes □ No

Describe the agent and type of allergic response: _____

_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response: _____

_____

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response: _____

_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____

_____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No

12.12 Presentation of the Dermatologic Event

Presentation of the event:

Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug? _____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind? _____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? □ Yes □ No

If so what kind? _____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind? _____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind? _____

7. Has the subject come into contact with any family or house members who are ill? □ Yes □ No

If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. *Molluscum Contagiosum*)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind? _____

i. Anaphylaxis? □ Yes □ No
ii. Signs of hypotension? □ Yes □ No
iii. Signs of dyspnea? □ Yes □ No
iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s): _____

_____

13. Is the rash pruritic (itchy)? □ Yes □ No

12.13 Focused Skin Examination

Focused Skin Examination:

Key information should be summarized and entered on the Adverse Experience eCRF.

Primary Skin Lesions Description

Color: _____

General description:

_____

_____

Describe the distribution of skin reaction, skin eruption, or rash on the body:

_____

_____

Is skin reaction, skin eruption, or rash resolving or continuing to spread?

_____

Any associated signs on physical examination? _____

12.14 Contraceptive Guidance

12.14.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  This applies to women who have undergone sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, this applies only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

12.14.2 Contraception Requirements

Female Participants

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Intrauterine hormone-releasing system (IUS) • Intrauterine device (IUD) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

- Hormonal-based methods (eg, oral contraceptives) are not considered as highly effective methods of contraception due to potential drug-drug interactions with dabrafenib and/or trametinib

Male contraception and infertility risks:

Dabrafenib and Trametinib may cause infertility in males, which may be irreversible. Male subjects including those who have had a vasectomy 6 months prior to screening must agree to use a condom during intercourse while taking the drug and not to father a child during the study and for the period of 120 days following stopping of study treatment. In addition, it is advised that their female partner uses a highly effective form of birth control method (contraception) if she is sexually active and may become pregnant. If a male participant fathers a child while in this study, they are asked to report the pregnancy to the study doctor. Consent from their partner will be needed to allow your study doctor to medically follow this pregnancy until delivery to monitor the mother`s and child`s safety.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.2 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	SIGNATURE	DATE
_____	_____	_____