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TITLE:

A Phase 1/2 Clinical Trial to Study the Safety and Tolerability of MK-3475 + Pegylated Interferon alfa-2b (PEG-IFN) and MK-3475 + Ipilimumab (IPI) in Subjects With Advanced Melanoma (MEL) and Renal Cell Carcinoma (RCC) (KEYNOTE 029)

IND NUMBER: 110080
EudraCT NUMBER: 2013-004072-36

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.3.3	Dose Modification and Supportive Care Guidelines for DRAEs for Pembrolizumab Monotherapy and Part 1C	Insertion of subheading "Dose modification and toxicity management for immune-related AEs associated with pembrolizumab" and associated program language. Revised dose modification table to include myocarditis-specific guidelines and actions in the event of myocarditis; revised action for all other immune-related Grade 3 AEs; and other clarifications.	Consistency and alignment with program-wide safety update to dose modification guidance
6.0	Trial Flow Chart	To all flow charts: amended survival status rows to allow assessment throughout the trial. Clarification of existing footnotes for survival status follow-up.	Clarification and alignment with program standards
7.1.5.3.2	Follow-up Visits	Addition of text: The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks).	
7.1.5.3.3	Survival Follow-up (SFU)	Clarification that subjects should be contacted *approximately* every 12 weeks. Deletion of redundant text.	
7.1.5.4	New Section: Survival Status	Addition of text to enable survival follow-up activities throughout the study.	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.1	Background	Insertion of latest program-aligned background information for pembrolizumab.	Alignment with program language
4.1.1	Pharmaceutical and Therapeutic Background	Deletion of redundant text now inserted in Section 4.1.	Deletion of repetition
4.2.3.2	Efficacy Endpoints	Clarification of clinical stability to include: • Absence of signs and symptoms *(including worsening of laboratory values)* indicating *clinically significant* disease progression.	Improved clarity and consistency with program language
5.2.3	Treatment after Initial Evidence of Radiologic Disease Progression	For the definition of clinical stability – insertion of text "clinically significant" to the bullet: • Absence of signs and symptoms (including worsening of laboratory values) indicating *clinically significant* disease progression	Improved clarity and consistency with program language
		Clarification of clinical stability to include …*clinically significant* disease progression Table 11 – insertion of abbreviations to footnote.	Clarification
5.8	Subject Withdrawal/Discontinuation Criteria	Cross-reference to Section 7.1.5 amended to Section 5.2.3	Correction

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.0	Trial Flow Chart	"also" replaced with "not" in Section 6.1.1.1 footnote #21, Section 6.1.1.2 footnote #22, and Section 6.2 footnote #19: "Copies of digital photographs should ~~also~~ *not* be submitted to the central imaging vendor unless otherwise noted by the Sponsor"	Correction
7.1.2.8	Assessment of Disease	Insertion of program language. Amended the definition of clinical stability: Absence of signs and symptoms indicating *clinically significant* disease progression, *including worsening of laboratory values*	Consistency with program language Alignment with Section 5.2.3 and programe language
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)	To Table 12: • Footnote c deleted and moved into a table note. • Additional information added to footnote e regarding hepatitis B/C testing. • Addition of footnote e to LDH. • Deletion of Anti-HDV.	Clarification/correction
7.2.3.1	Serious Adverse Events	Cross-reference to Table 14 amended to Table 16	Correction
Throughout		Minor typographical corrections.	Improved consistency/readability

1.0 TRIAL SUMMARY

Abbreviated Title	Phase 1/2 Study of Pembrolizumab (MK-3475) + PEG-IFN & Pembrolizumab + IPI in Subjects with Advanced MEL & RCC (KEYNOTE 029)
Trial Phase	Phase 1/2
Clinical Indication	Advanced or Metastatic Melanoma and Renal Cell Carcinoma
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous (pembrolizumab and IPI) and subcutaneous (PEG-IFN)
Trial Blinding	Unblinded Open-label
Treatment Groups	Part 1A: Treatment Group A: Pembrolizumab 2 mg/kg (or 200 mg)* IV every 3 weeks (q3w) + PEG-IFN 0.5µg/kg weekly Pembrolizumab 2 mg/kg (or 200 mg)* IV q3w + PEG-IFN 1µg/kg weekly Pembrolizumab 2 mg/kg (or 200 mg)* IV q3w + PEG-IFN 2µg/kg weekly; Pembrolizumab 2 mg/kg (or 200 mg)* IV q3w + PEG-IFN 3µg/kg weekly Treatment Group B: Pembrolizumab 2 mg/kg (or 200 mg)* IV q3w + IPI 1 mg/kg q3w Part 1B: Treatment Group B: Pembrolizumab 2 mg/kg (or 200 mg)* IV q3w + IPI 1mg/kg q3w *With the approval of Amendment 03, subjects continuing pembrolizumab treatment in Parts 1A and 1B will switch to a fixed dose of 200 mg q3w (not weight-based). *Prior to the approval of Amendment 03, the Sponsor notified sites and IRBs that Part 2 would not be initiated. Part 2 is deleted in Amendment 03.* Part 1C: Treatment Group B: Arm 1: Pembrolizumab 200 mg q3w + IPI 50 mg every 6 weeks (q6w) Arm 2: Pembrolizumab 200 mg q3w + IPI 100 mg every 12 weeks (q12w)
Number of trial subjects	Approximately 233 up to a maximum of approximately 293 (up to 43 in Part 1A, 90 to 150 in Part 1B and up to 100 in Part 1C) subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 32 months for Parts 1A and 1B, from the time the first subject signs the informed consent until the last subject's last visit. For Part 1C, the Sponsor also estimates that the trial will require approximately 32 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 contact. After a screening phase of up to 28 days, eligible subjects will receive assigned treatment on Day 1 of each dosing cycle and thereafter following a weekly (PEG-IFN) or q3w (IPI) schedule in Part 1A and 1B, and q6w or q12w schedule (IPI) in Part 1C. Pembrolizumab will be given q3w. A cycle is 6 weeks. In Part 1A, RCC and MEL subjects will be randomly assigned to receive pembrolizumab + PEG-IFN or pembrolizumab + IPI. Treatment with pembrolizumab + PEG-IFN doublet (Treatment Group A) will continue until up to two years of therapy have been administered, documented disease progression, unacceptable adverse events (AEs), 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. Treatment with pembrolizumab + IPI doublet (Treatment Group B) will continue for 2 cycles (12 weeks), followed by treatment with pembrolizumab single agent until up to 24 months of therapy have been administered, documented disease progression, unacceptable AEs, 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. In Part 1B, MEL subjects will receive pembrolizumab + IPI (Treatment Group B). Treatment duration will follow the same schema as described in Part 1A. Subjects in Part 1B who attain an investigator-determined complete response (CR) may consider stopping trial treatment with pembrolizumab, after all 4 doses of IPI and at least 24 weeks of pembrolizumab have been administered. In addition, if a confirmed CR per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 is attained, at least 2 additional doses of pembrolizumab must be received after CR is first documented. In Part 1C, MEL subjects will be randomly assigned to pembrolizumab + 2 dose regimens of IPI (Treatment Group B). Treatment with pembrolizumab + IPI will continue for a maximum of 4 cycles (24 weeks) in Arm 1 or 8 cycles (48 weeks) in Arm 2, followed by treatment with pembrolizumab single agent until up to 24 months of pembrolizumab have been administered, documented disease progression, unacceptable AEs, 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 in Part 1C who attain an investigator-determined CR may consider stopping trial treatment with pembrolizumab, after at least 24 weeks of pembrolizumab have been administered. In addition, if a confirmed CR per modified RECIST 1.1 is attained, at least 2 additional doses of pembrolizumab must be received after CR is first documented. In addition, and only in Part 1C, upon Sponsor consultation, subjects who attain an investigator-determined CR or a very good partial response [VGPR: partial response per RECIST 1.1 with Percent Change from Baseline (maximum reduction in tumor line length) >60%] may consider stopping treatment with IPI, after a minimum of one dose of IPI on either treatment arm.

	In Part 1A, 1B and 1C, upon Sponsor consultation, subjects who stop pembrolizumab with SD or better per modified RECIST 1.1 may be eligible for retreatment with pembrolizumab + IPI or pembrolizumab monotherapy if they progress after stopping pembrolizumab at the discretion of the Investigator if they meet the criteria for retreatment, as long as the Part to which the subject was initially enrolled remains open; this will be designated the Second Course Phase. Subjects in Part 1A who received PEG-IFN will not be allowed to restart Second Course Phase with pembrolizumab + PEG-IFN; these subjects can only receive pembrolizumab monotherapy in Second Course. The Second Course Phase will be administered for a maximum of 17 doses of pembrolizumab and 4 doses of IPI. After the end of treatment, each subject will be followed for a minimum of 30 days for AE monitoring [serious adverse events (SAEs) will be collected for up to 90 days after the end of treatment]. Subjects will go into survival follow-up (SFU) for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawal of consent, or lost to follow-up.
Randomization Ratio	Part 1A (MEL and RCC): 1:1. Part 1B (MEL): Single Arm Expansion. Part 1C (MEL): 1:1

A list of abbreviations used in this document can be found in Section 12.7.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multi-center, open-label, 3-part Phase 1/2 trial of intravenous (IV) pembrolizumab in combination with subcutaneous (SC) Pegylated Interferon Alfa-2b (PEG-IFN) or IV ipilimumab (IPI) in subjects with advanced or metastatic melanoma (MEL) or renal cell carcinoma (RCC).

The trial consists of three parts:

Part 1A is the phase I portion of the trial to define the preliminary maximum-tolerated dose (MTD) or maximum administered dose (MAD) for the combination doublets listed below and confirm the tolerability of the dose combination.

Treatment Group A: pembrolizumab + PEG-IFN

Treatment Group B: pembrolizumab + IPI

Subjects will be treated with doublets administered as detailed in Table 1 and Table 2.

If dose levels are open in Part 1A in both PEG-IFN and IPI dose finding Arms, subjects will be randomly assigned between the two combinations. Intermediate dose levels may be pursued, depending on emerging data from the current and other pembrolizumab studies.

Table 1 Dose Finding Scheme for Treatment Group A: pembrolizumab + PEG-IFN (Part 1A only)

Dose Level (DL)	Pembrolizumab Dose (mg/kg) IV	PEG-IFN Dose (µg/kg) SC Weekly
-1	2 mg/kg (or 200 mg)** q3w	0.5
1*	2 mg/kg (or 200 mg)** q3w	1
2	2 mg/kg (or 200 mg)** q3w	2
3	2 mg/kg (or 200 mg)** q3w	3
*Starting Dose **With the approval of Amendment 03, subjects continuing pembrolizumab treatment will switch to a fixed dose of 200 mg (not weight-based).		

Table 2 Dose for Treatment Group B: pembrolizumab + IPI (Part 1A and 1B)

Dose Level (DL)	Pembrolizumab Dose (mg/kg) IV	IPI Dose (mg/kg) q3w x 4 doses
1	2 mg/kg (or 200 mg)* q3w	1
*With the approval of Amendment 03, subjects continuing pembrolizumab treatment will switch to a fixed dose of 200 mg (not weight-based).		

Dose-limiting toxicities (DLTs) observed in Cycle 1 will be used to determine tolerability of the doublet and possible escalation to the next dose level (when applicable). A cycle is 6 weeks. The guidelines used for dose escalation and dose confirmation are shown in Table 5.

The rules applied for the dose finding algorithm are as follows:

In the pembrolizumab + PEG-IFN combination, an initial cohort of 3 subjects is enrolled. Subsequent dosing decisions within a dose combination will be based on the rules in Table 5. The dose confirmation part will continue until ≤4 of 14 subjects experience 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 5. In the pembrolizumab + IPI combination, an open-label run-in period (Part 1A), will be used to assess the safety and tolerability of the doublet therapy during the first cycle of treatment. A total of up to 18 subjects will be enrolled at dose level 1 (DL1) of pembrolizumab administered at a dose of 2 mg/kg q3w in combination with IPI administered at dose of 1 mg/kg q3w (for a total of 4 doses).

If ≤6 DLTs are observed in the 18 subjects enrolled, this dose level will be considered tolerable, and Part 1B will be initiated. Should this dose level (DL1) not be proven tolerable (>6 DLTs), the combination with IPI will not be further developed.

Part 1B is a single arm expansion cohort, designed to better characterize the safety and tolerability, as well as to evaluate preliminary efficacy of the combination pembrolizumab + IPI in MEL subjects. Pembrolizumab will be administered at a dose of 2 mg/kg q3w (or

200mg q3w) in combination with IPI administered at a dose of 1 mg/kg (for 4 doses). At least 90 and up to an additional 150 subjects with advanced or metastatic MEL will be enrolled in the expansion cohort at this dose level.

With the approval of Amendment 03, subjects continuing pembrolizumab treatment on Parts 1A and 1B will switch to a fixed dose of 200 mg q3w (not weight-based). The rationale for fixed dose regimen is outlined in Section 4.2.2.

Prior to the approval of Amendment 03, the Sponsor notified sites and IRBs that Part 2 would not be initiated. Part 2 is removed from the protocol in Amendment 03.

Part 1C is the phase I/II randomized portion of the trial and is to further evaluate safety and tolerability of pembrolizumab + IPI in advanced MEL subjects, as well as preliminary clinical efficacy of the combination. Part 1C will evaluate the below listed treatments.

Treatment Group B: pembrolizumab + IPI

Arm 1: pembrolizumab 200 mg q3w for a maximum of 24 months + IPI 50 mg q6w for a maximum of 4 doses.

Arm 2: pembrolizumab 200 mg q3w for a maximum of 24 months + IPI 100 mg q12w for a maximum of 4 doses. Part 1C subjects will be randomized to the treatment groups in a 1:1 ratio. There will be no stratification prior to the randomization of subjects.

Approximately 233 to a maximum of approximately 293 subjects (up to 43 in Part 1A, at least 90 and up to 150 in Part 1B, and up to approximately 100 in Part 1C) will be enrolled in this trial to examine the safety and efficacy of the combinations pembrolizumab + PEG-IFN and pembrolizumab + IPI. The Part 1B sample size is driven by the expected number of PD-L1 negative subjects. Assuming that the prevalence of PD-L1 negative subjects is ~25%, then 90 subjects would be expected to provide ~22 subjects with PD-L1 negative MEL. If less than 22 PD-L1 negative MEL were enrolled in the pembrolizumab + IPI Arm in Part 1A and 1B combined, enrollment will continue until at least 22 PD-L1 negative subjects are enrolled, up to a maximum of 150 subjects in Part 1B.

Parts 1A and 1B:

Subjects will undergo first imaging evaluation at week 12 (± 3 days). Subsequently, subjects will be evaluated every 6 weeks (42 days ± 3 days), independently of any treatment delays, with radiographic imaging to assess response to treatment, until week 30. Subjects will then undergo imaging evaluation every 12 weeks (84 ± 7 days). RECIST 1.1 will be used as the primary response rate efficacy endpoint. RECIST 1.1 will be adapted as described in Section 4.2.3.2 to adjust for the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare), and this adapted/modified RECIST 1.1 will be used by the sites for treatment decisions. The primary response rate efficacy endpoint will be based on independent central review using RECIST 1.1 [1]. Modified RECIST 1.1 will also be used by the local site to determine eligibility and make treatment decisions.

AEs will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) Version 4.0.

Treatment will continue as outlined in Table 1 and Table 2 until documented disease progression, unacceptable AEs, 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, completion of 24 months of treatment with pembrolizumab, or administrative reasons.

Subjects in the pembrolizumab + IPI Arm who initially attain clinical benefit (defined as modified RECIST 1.1 confirmed PR or SD $\geq$6 months), and experience disease progression while receiving single agent pembrolizumab will be eligible for reinduction with a maximum of 4 doses of IPI q3w as long as Part 1A or 1B remains open.

Subjects who attain an investigator-determined confirmed CR may consider stopping trial treatment after receiving at least 6 weeks of PEG-IFN treatment/all 4 doses of IPI and at least 24 weeks of pembrolizumab. In addition, if a confirmed CR per modified RECIST 1.1 is attained, at least 2 additional treatments of pembrolizumab must be received prior to treatment discontinuation. Upon consultation with the Sponsor, subjects who stop pembrolizumab with SD or better per modified RECIST 1.1 may be eligible for retreatment with a maximum of 17 doses of pembrolizumab and 4 doses of IPI if they progress after stopping pembrolizumab at the discretion of the investigator according to the criteria in Section 7.1.5.2.1, as long as the trial part to which the subject was initially enrolled remains open; this retreatment will be the Second Course Phase. Subjects enrolled in Part 1A who received PEG-IFN who are eligible for Second Course Phase will only be allowed to receive pembrolizumab monotherapy in Second Course. Response or progression in the Second Course Phase will not count towards the overall response rate (ORR) and progression-free survival (PFS) of the primary endpoint in this trial. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial remains open (refer to Section 7.1.5.2.1 for further details).

After the end of treatment, each subject will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment). Subjects who discontinue treatment for reasons other than disease progression will have SFU for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival (OS) until death, withdrawal of consent or the end of the trial, whichever comes first.

All subjects will be required to submit a tumor tissue sample for biomarker analyses and PD-L1 expression evaluation. In Part 1B, PD-L1 status must be assessed during screening, and if the tumor biopsy submitted is inadequate for determination of PD-L1 status by immunohistochemistry (IHC) at a central pathology laboratory, the subject will not be randomized. Subjects with an inadequate archival sample may obtain a new biopsy and

subjects with an inadequate newly obtained biopsy may undergo re-biopsy at the discretion of the investigator.

The primary safety objectives of the trial (Part 1A and Part 1B) are to determine the safety and tolerability of pembrolizumab in combination with PEG-IFN or IPI in subjects with advanced MEL and RCC. The primary efficacy objective of Part 1B of the trial is to evaluate the anti-tumor activity in PD-L1 negative MEL subjects treated with pembrolizumab in combination with IPI at DL1.

Part 1C: Part 1C of the trial will enroll approximately 100 subjects with advanced MEL.

The primary objectives for Part 1C are rate of drug-related adverse events (DRAEs) and ORR. Secondary objectives include PFS, OS and duration of response (DOR). The pharmacokinetic (PK) properties for pembrolizumab + IPI in each doublet setting will be investigated as an exploratory objective.

In Part 1C, subjects will undergo imaging evaluation every 6 weeks (± 3 days), independent of any treatment delays, with radiographic imaging to assess response to treatment, until week 24. Subjects will then undergo imaging evaluation every 12 weeks (84 ± 7 days). RECIST 1.1 will be used as the primary response rate efficacy endpoint and adapted/modified RECIST 1.1 will be used by the investigative sites for treatment decisions. The primary response rate efficacy endpoint will be based on independent central review using RECIST 1.1 [1]. Modified RECIST 1.1 will also be used by the treating investigator local site to determine eligibility.

AEs will be monitored throughout the trial and in severity according to the guidelines outlined in the NCI CTCAE Version 4.0.

Treatment with pembrolizumab + IPI doublets (Treatment Group B) will continue for a maximum of 4 cycles (24 weeks) in Arm 1 and 8 cycles (48 weeks) in Arm 2, followed by treatment with pembrolizumab single agent for up to 24 months of therapy, documented disease progression, unacceptable AEs, 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 in Part 1C who attain an investigator-determined confirmed CR may consider stopping trial treatment with pembrolizumab after receiving at least 24 weeks of pembrolizumab. In addition, if a confirmed CR per modified RECIST 1.1 is attained, at least two additional doses of pembrolizumab must be received prior to treatment discontinuation. Upon Sponsor consultation, subjects who attain an investigator-determined confirmed CR or a VGPR [partial response per RECIST 1.1 with Percent Change from Baseline (maximum reduction in tumor line length) >60%] may consider stopping treatment with IPI after a minimum of one dose of IPI on either Arm of treatment.

Upon Sponsor consultation, subjects who stop pembrolizumab with SD or better per modified RECIST 1.1 may be eligible for retreatment with pembrolizumab + IPI or pembrolizumab monotherapy if they progress after stopping pembrolizumab at the discretion

of the investigator according to the criteria in Section 7.1.5.2.1 as long as Part 1C remains open. Second Course Phase will be administered for a maximum of 17 doses of pembrolizumab and 4 doses of IPI.

After the end of treatment, each subject will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment). Subjects who discontinue treatment for reasons other than disease progression will have SFU for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for OS until death, withdrawal of consent or the end of the trial, whichever comes first.

All subjects will be required to submit a tumor tissue sample for biomarker analyses and PD-L1 expression evaluation. Confirmation of the tumor tissue sample adequacy for determination of PD-L1 status by IHC at a central pathology laboratory is not required prior to enrollment in Part 1C.

The trial will be conducted in conformance with Good Clinical Practices.

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.

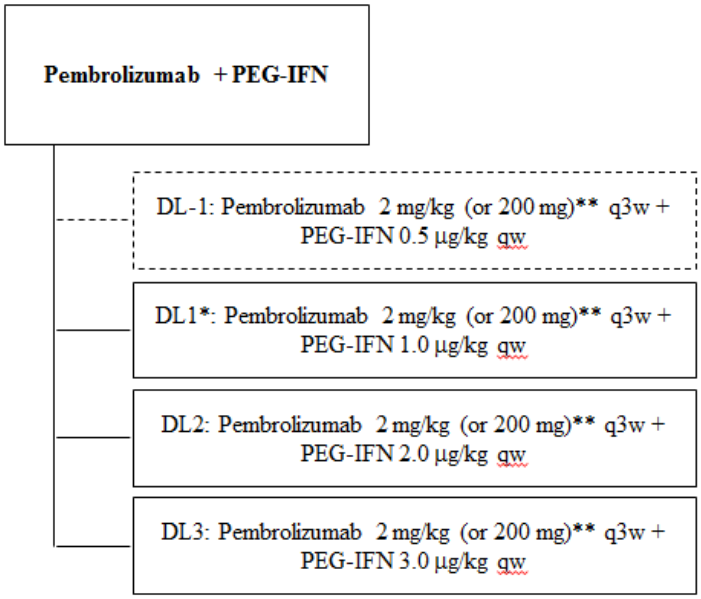
Based on the data from Part 1A, pembrolizumab + PEG-IFN combination will not be pursued any further due to lack of added efficacy with the combination compared with pembrolizumab monotherapy, as well as the added toxicities. Part 1B further supported the early efficacy of pembrolizumab + IPI seen in Part 1A and confirmed a DRAE rate of 42% (data cutoff date March 17, 2016). Based on the goal to further minimize the AE profile of pembrolizumab + IPI, Part 1C has been designed to investigate two different dosing regimens of pembrolizumab + IPI. The previously described Part 2 in this protocol has been deleted as it is no longer applicable based on now available data from Parts 1A and 1B.

Upon consultation with the Sponsor, subjects in Part 1A, 1B and 1C may be eligible for Second Course Phase if they progress after stopping pembrolizumab as long as the trial Part to which the subject was initially enrolled remains open as per Section 7.1.5.2.1. Subjects enrolled in Part 1A who received PEG-IFN who are eligible for Second Course Phase will only be allowed to receive pembrolizumab monotherapy.

Subjects may have the opportunity to transition to a pembrolizumab extension trial if available in the future after closure of this trial.

2.2 Trial Diagram

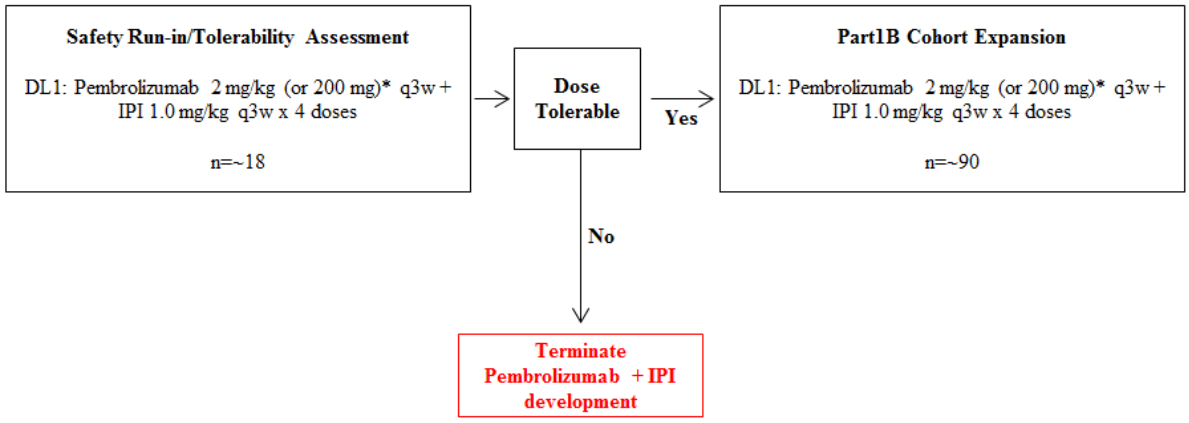
The trial design is depicted in Figure 1, Figure 2, and Figure 3 below.



*DL1 starting dose
**With the approval of Amendment 03, subjects continuing pembrolizumab treatment will switch to a fixed dose of 200 mg (not weight-based).

Figure 1 Pembrolizumab + PEG-IFN Dose finding: Part 1A

Note that if dose levels are opened in both PEG-IFN and IPI Arms, subjects will be randomly assigned to the two combinations.



*With the approval of Amendment 03, subjects continuing pembrolizumab treatment will switch to a fixed dose of 200 mg (not weight-based).

Figure 2 Pembrolizumab + IPI dose finding: Part 1A Safety run-in and Part 1B Expansion cohort in MEL subjects.

Expansion in MEL subjects will proceed once DL1 is declared safe on safety run-in (Part 1A).

With the approval of Amendment 03, subjects continuing pembrolizumab treatment on Parts 1A and 1B will switch to a fixed dose of 200mg q3w (not weight-based).

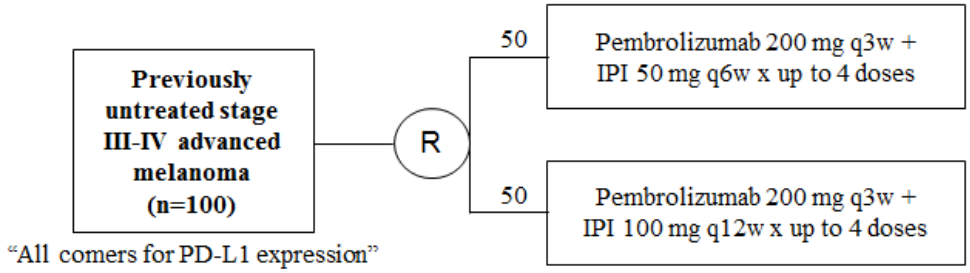


Figure 3 Part 1C – Phase I/II portion of the trial.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1. **Objective (Part 1A):** To establish a maximum tolerated dose (MTD) or a maximum administered dose (MAD) of pembrolizumab when given in combination with PEG-IFN to subjects with advanced MEL or RCC.

   Hypothesis: The DLTs observed in subjects with advanced MEL or RCC after IV administration of pembrolizumab in each combination will allow for definition of an MTD or a MAD.

2. **Objective (Part 1A, 1B):** To establish the tolerability of pembrolizumab when given in combination with IPI at the DL1 (pembrolizumab 2 mg/kg or 200 mg IV q3w + IPI 1 mg/kg q3w) in subjects with advanced MEL or RCC.

3. **Objective (Part 1A, 1B):** To determine the safety and tolerability of pembrolizumab in combination with PEG-IFN or IPI in subjects with advanced MEL or RCC.

   Hypothesis: IV administration of pembrolizumab in combination with PEG-IFN or IPI to subjects with advanced MEL or RCC is sufficiently well-tolerated to permit continued clinical investigation.

4. **Objective (Part 1C):** To establish the safety and tolerability of pembrolizumab in combination with either IPI 50 mg q6w or IPI 100 mg q12w in subjects with advanced MEL.

   Hypothesis: IV administration of pembrolizumab in combination with IPI to subjects with advanced MEL is sufficiently well-tolerated to permit continued clinical investigation.

5. **Objective (Part 1C):** To determine the rate of Grade 3-5 DRAEs.

   Hypothesis: IV administration of pembrolizumab in combination with either IPI 50 mg q6w or IPI 100 mg q12w will produce Grade 3-5 DRAEs that are <40-55% as

observed with the combination of pembrolizumab + IPI 1 mg/kg in Part 1A and 1B. The criteria are described in section 8 – SAP.

6. **Objective (Part 1C):** To evaluate efficacy of pembrolizumab + IPI in subjects with advanced unresectable/metastatic MEL in Part 1C.

   Hypothesis: IV administration of pembrolizumab in combination with either IPI 50 mg q6w or IPI 100 mg q12w will produce ORR rates similar to the 48% or higher observed with combinations of pembrolizumab + IPI 1 mg/kg in Part 1B.

3.2 Secondary Objective(s) & Hypothesis(es)

1. **Objective (Part 1B):** To evaluate efficacy of pembrolizumab in combination with IPI in subjects with advanced unresectable/metastatic MEL.

   Hypothesis: IV administration of pembrolizumab in combination with IPI to subjects with PD-L1 negative advanced MEL results in a clinically meaningful ORR through 24 weeks based on RECIST 1.1 by central independent review.

2. **Objective (Part 1B, 1C)**: To evaluate the efficacy of pembrolizumab administered intravenously in combination with IPI with respect to ordinal response score [derived from RECIST 1.1 definitions, with PR being divided into Moderate Partial Response (MPR) and VGPR based on the degree of tumor shrinkage] in subjects with advanced MEL (more details in Section 8.2.5.1.4).

3. **Objective (Part 1B, 1C)**: To evaluate the DOR in subjects with advanced MEL receiving pembrolizumab in combination with IPI.

4. **Objective (Part 1B, 1C):** To evaluate efficacy with respect to PFS of pembrolizumab in combination with IPI in subjects with advanced MEL.

5. **Objective (Part 1B, 1C):** To evaluate OS in subjects with advanced MEL receiving pembrolizumab in combination with IPI.

6. **Objective (Part 1A, 1B)**: To compare the rates of Grade ≥3 toxicities across all subjects treated with each doublet (pembrolizumab + PEG-IFN and pembrolizumab + IPI)**.**

   Hypothesis: Administration of pembrolizumab + PEG-IFN results in different rate of Grade 3-4 toxicity than pembrolizumab + IPI.

7. **Objective (Part 1B and 1C)**: To evaluate the relationship between PD-L1 expression on IHC to clinical outcomes (ORR, PFS and OS) in MEL subjects treated with pembrolizumab + IPI.

3.3 Exploratory Objectives

1. **Objective (Part 1A):** To evaluate efficacy with respect to PFS and ORR based on modified RECIST 1.1 by site investigator, ordinal response score, DOR and OS of pembrolizumab in combination with PEG-IFN or IPI in subjects with RCC.

2. **Objective (Part 1A):** To evaluate the relationship between PD-L1 expression on IHC to clinical outcomes (ORR, PFS and OS) in Part 1A RCC subjects treated with pembrolizumab + IPI or pembrolizumab + PEG-IFN.
3. **Objective (Part 1A, 1B, 1C):** To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of pembrolizumab utilizing pre- and post-treatment biopsies and blood sampling using in vitro assays.
4. **Objective (Part 1A, 1B, 1C):** To evaluate ORR as determined by RECIST 1.1 criteria using line length compared to RECIST 1.1 criteria using tumor volumetric changes of subjects with MEL and RCC treated with pembrolizumab + IPI and pembrolizumab + PEG-IFN.
5. **Objective (Part 1A, 1B, 1C)**: To evaluate the rate of pembrolizumab anti-drug antibodies (ADA) and impact on PK when pembrolizumab is given in monotherapy and in combination with PEG-IFN or IPI.
6. **Objective (Part 1B):** To evaluate the best objective response rate (ORR) by RECIST 1.1 in subjects on pembrolizumab + IPI after re-induction with IPI.
7. **Objective (Part 1A, 1B, 1C):** To evaluate the ORR by RECIST 1.1 in subjects treated with pembrolizumab + IPI or pembrolizumab monotherapy as part of Second Course Phase.
8. **Objective (Part 1A, 1B, 1C):** To evaluate the use of time to growth (TTG) modeling and simulation and correlate with clinical outcomes in MEL and RCC subjects treated with pembrolizumab + PEG-IFN and pembrolizumab + IPI.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab (previously known as SCH 900475 and MK-3475) 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 Investigator's Brochure (IB)/approved labeling for detailed background information on PEG-IFN, IPI, and MK-3475.

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 [2]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [3] [4] [5] [6] [7]. 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 MEL and RCC. TILs can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as MEL [8] [9].

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) [10] [11]. The structure of murine PD-1 has been resolved [12]. 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 [10] [13] [14] [15]. 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 [16] [17]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, regulatory T cells (T regs) and Natural Killer cells [18] [19]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [20]. 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 [1] [16] [21] [22] [23]. 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 [16]. 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 RCC [24], pancreatic carcinoma [25], hepatocellular carcinoma [26], and ovarian carcinoma [27]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with MEL [28]. This 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.

Based on the preliminary clinical data, PD-1 inhibitors such as pembrolizumab appear to be attractive candidates for pursuing the above goal. Nivolumab has an observed ORR of 28% in MEL subjects; pembrolizumab has shown a promising response rate of 25% in MEL subjects who have received prior IPI treatment in KEYNOTE 002 [29]. Specifically, a response rate of 36% was observed with pembrolizumab in MEL subjects who have not received prior IPI treatment in KEYNOTE 006 [30]. This response rate is much higher than the 11-15% response rate observed with IPI in IPI registration trials.

On September 4, 2014, the Food and Drug Administration (FDA) granted accelerated approval for pembrolizumab 2mg/kg q3w in advanced MEL following disease progression with IPI and, if BRAF V600 mutation positive, a BRAF inhibitor [31]. The approval was based on a strong efficacy and safety profile demonstrated in 4 MEL expansion parts of the Phase I trial (KEYNOTE 001) [32]; the B2 IPI-refractory population was the subject population for the approval. On December 18, 2015, the FDA granted full approval of pembrolizumab for the treatment of subjects with unresectable or metastatic MEL with pembrolizumab based on KEYNOTE 002 and 006 [30] [33].

4.1.1.2 Pegylated Interferon Alfa-2b (PEG-IFN)

PEG-IFN is a pleiotropic cytokine with anti-viral, anti-proliferative, anti-angiogenic and immunomodulatory properties. PEG-IFN is a modified form of IFN α-2b comprising a single molecule of polyethylene glycol (PEG) covalently linked to the IFN α-2b protein. PEG-IFN has shown good tolerability and similar efficacy to conventional interferon and dacarbazine single agent chemotherapy in stage IV MEL [34]. Based on the European Organization for Research and Treatment of Cancer (EORTC) 18991 trial, the United States (US) Food and Drug Administration (FDA) approved PEG-IFN for the adjuvant treatment of MEL subjects following definitive surgical resection, including complete lymphadenectomy [35] [36]. PEG-IFN α-2b was administered at 6 μg/kg/week subcutaneously for 8 weeks (induction phase) then at 3 μg/kg/week subcutaneously (maintenance phase) for an intended treatment duration of 5 years. There was an 18% reduction in the risk of relapse and death. PEG-IFN was safe and relatively well tolerated. The median length of therapy with PEG-IFN α-2b was >12 months. The most commonly observed side-effects were fatigue, alanine and aspartate aminotransferase elevations and fever, myalgia, anorexia and nausea. A total of 525 deaths were reported during the trial (262 in the PEG-IFN group and 263 in the observation group). The most frequent causes of death were infection, malignant disease and cardiovascular disease. 31% of the 608 subjects who were treated with PEG IFNα-2b discontinued therapy due to Grade 3-4 AEs: fatigue (25%), anorexia (15%), depression (16%), liver function tests (13%), headache (12%), nausea (12%), and pyrexia (11%).

IFN-α used to be the mainstay of therapy for advanced RCC. ORRs ranged from 15-25%, with 5-10% of these subjects having durable responses. Targeted therapies with VEGF and mTOR inhibitors have largely replaced IFN-based regimens due to the ease of use and the higher efficacy, notably in term of PFS. Nevertheless, IFN-α remains an option in metastatic RCC. Furthermore, some front-line trials with an IFN-α comparator vs. a targeted therapy (sorafenib) did not show a PFS advantage [37], and the majority of trials did not show an OS advantage. The pegylated form of IFN-α is easier to use, may have less side effects [38] and

it is not an unreasonable choice especially in subjects who failed prior standard targeted therapies.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on PEG-IFN.

4.1.1.3 Ipilimumab (IPI)

Ipilimumab (Yervoy®) is an immunoregulatory agent that blocks CTLA-4 to promote anti-tumor immunity. In a Phase III study of 676 subjects with unresectable or metastatic MEL whose disease had progressed while receiving prior therapy for metastatic disease, IPI administered at 3 mg/kg q3w for up to 4 doses with or without a gp100 peptide vaccine was compared with gp100 alone [39]. The median OS was 10.1 months and 10.0 months for the IPI alone and IPI plus gp100 Arms respectively, while the median OS was 6.4 months for the gp100 alone Arm ($p<0.001$). An ORR of 10.9% was observed in IPI alone Arm, while the IPI plus gp100 Arm and gp100 alone Arm had lower response rates, 5.7% and 1.5%, respectively. The median duration of response was 11.5 months in the IPI plus gp100 Arm, and not reached in the IPI alone Arm with a median follow-up period of 27.8 months. The median time to progression was 2.86 months for the IPI alone Arm and 2.76 months for the other two Arms. In the IPI alone Arm, 97% of the subjects experienced an AE and Grade 3-4 AEs occurred in 46% of the subjects. The most common AEs related to IPI were immune-related events, which occurred in approximately 60% of the subjects treated with IPI and 32% of the subjects treated with gp100. The frequency of Grade 3-4 immune-related AEs was 15%. The immune-related AEs most often affected the skin and gastrointestinal tract, including pruritus, rash, vitiligo, diarrhea, and colitis.

Based on the above Phase III trial, IPI was approved by the FDA for treatment of subjects with unresectable or metastatic MEL and by the European Commission for treatment of subjects with previously-treated advanced MEL. The recommended regimen is 3 mg/kg administered q3w for a total of four doses.

A reduction of the risk of death (28%; $p<0.001$) was also demonstrated for IPI in the first-line setting when combined with dacarbazine in comparison with dacarbazine alone, and the ORRs were 15% and 10% (Investigator assessment per RECIST 1.1) in the IPI/dacarbazine Arm and dacarbazine alone Arm, respectively [40]. The IPI/dacarbazine Arm did show a statistically significant PFS improvement [hazard ratio (HR) 0.76; $p=0.006$] over the dacarbazine alone Arm. Median OS in the IPI/dacarbazine and dacarbazine Arms was 11.2 months and 9.1 months, respectively. The one-year OS rate for the IPI/dacarbazine Arm was 47.3%; the rate for the dacarbazine Arm was 36.3%.

In RCC, a Phase I/II trial by Yang revealed an ORR 9.8% [41], across different dose levels, in subject's treatment naïve and previously treated with interleukin-2. Given the greater response rates seen with tyrosine kinase inhibitors, IPI was not further developed as monotherapy in RCC.

Refer to the approved labeling for detailed background information on IPI.

4.1.2 Pre-clinical Trial with Pembrolizumab

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 [28] [42] [43] [44] [25] [45]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials are being conducted in advanced MEL, non-small cell lung cancer (NSCLC), head and neck cancer, triple negative breast cancer, gastric cancer, bladder cancer and hematologic malignancies. For trial details please refer to the IB.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

MEL is the sixth most common malignancy in men and the seventh most common malignancy in women. The incidence of MEL is increasing worldwide, with a growing fraction of subjects with advanced disease for which prognosis remains poor. The median survival for subjects with metastatic MEL has been under 1 year. The 5-year survival rate of subjects with visceral involvement is under 10%. Treatment options for metastatic MEL have been limited to chemotherapeutic agents such as dacarbazine and high-dose interleukin-2 immunotherapy in a small percentage of subjects. In the past few years there has been steady progress in the development of targeted therapy and immunotherapy for metastatic MEL. Since 2011, three new agents were approved for the treatment of BRAF mutant MEL: vemurafenib, dabrafenib and trametinib, which produce response rates of 22-57% and have demonstrated a survival advantage relative to chemotherapy [46] [47] [48]. It is important to note these agents are not indicated for up to 60% of MEL subjects whose tumors do not contain a BRAF mutation [47] [46] [49] [50]. In addition, a major limitation with kinase inhibitors in the treatment of BRAF mutant MEL is a nearly universal development of resistance to these agents leading to the lack of response durability. Although high RRs offer benefits to the majority of subjects with BRAF mutant MEL, most subjects develop resistance rather quickly and experience progressive disease (PD).

IPI, an anti-CTLA4 monoclonal antibody, was also approved in 2011 for the treatment of subjects with unresectable or metastatic MEL based on the data described in Section 4.1.1.3. More recently, IPI has demonstrated increased efficacy in combination with nivolumab in 2 randomized phase III clinical trials. In CheckMate 069 [51], 142 patients with previously untreated metastatic MEL were randomly assigned to receive IPI 3 mg/kg combined with

either nivolumab, 1 mg/kg, or placebo once q3w for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxic effects. ORR was 61% in the group that received both IPI and nivolumab versus 11% in the group that received IPI monotherapy (p<0.001). After a minimum follow-up of 18 months, median PFS was not reported with the combination therapy and was 4.3 months with IPI monotherapy [HR 0.34; 95% confidence interval (CI): 0.2, 0.57; p<0.0001] [52]. The 12- and 18-month PFS rates were 55.1% and 53.4%, respectively, for the combination, and 16.2% and 8.1%, respectively, for IPI alone. At 18 months of follow-up, OS rates in BRAF wild-type patients were 73% for the combination versus 56% for IPI alone, and median OS had not been reached in either group (HR 0.56; 95% CI: 0.29, 1.10; p=0.089). Grade 3–4 DRAEs were reported more frequently with the combination than with IPI alone (55% vs. 22%) and led to discontinuation in 30% and 9% of patients, respectively [52]. In CheckMate 067, 945 subjects with unresectable stage III or IV MEL were randomly assigned in a 1:1:1 ratio to receive nivolumab 3 mg/kg every 2 weeks, nivolumab 1 mg/kg q3w plus IPI 3 mg/kg q3w for 4 doses followed by nivolumab 3 mg/kg every 2 weeks for Cycle 3 and beyond, or IPI 3 mg/kg q3w for 4 doses [53]. The median PFS was 11.5 months (95% CI: 8.9, 16.7) with nivolumab plus IPI, 2.9 months (95% CI: 2.8, 3.4) with IPI (HR 0.42; 99.5% CI: 0.31, 0.57; p < 0.001), and 6.9 months (95% CI: 4.3, 9.5) with nivolumab (HR for the comparison with IPI, 0.57; 99.5% CI: 0.43, 0.76; p<0.001). DRAEs of Grade ≥ 3 were reported in 16.3% of the subjects treated with nivolumab, 55.0% of the subjects treated with the combination, and 27.3% of those treated with IPI alone. On September 30, 2015, the FDA granted accelerated approval to nivolumab in combination with IPI for the treatment of subjects with BRAF V600 wild-type, unresectable or metastatic MEL. Approval was based on demonstration of an increase in the ORR, prolonged response durations, and improvement in PFS observed in CheckMate 069 trial.

RCC is the seventh most common cancer among US men and ninth among US women. Twenty percent of people present with advanced disease, and an additional 30% of those who present with localized disease will eventually develop distant metastases and become largely incurable. The targeted drugs, pazopanib, sunitinib, sorafenib, axitinib, bevacizumab, everolimus, and temsirolimus transformed the management of metastatic RCC after demonstration of superiority to cytokine therapy and placebo in pivotal phase III trials [54] [55] [56] [57]. Cytokine-based treatment with interleukin-2 (IL-2) or interferon-α (IFN-α) used to be the mainstay of therapy for RCC and can still benefit a small proportion of subjects.

More recently, nivolumab has been shown to improve OS in the second-line setting for subjects with previously treated advanced clear-cell RCC compared with everolimus; 25 months (95% CI: 21.8, not estimable) with nivolumab and 19.6 months (95% CI: 17.6, 23.1) with everolimus) [58]. The HR for death with nivolumab versus everolimus was 0.73 (98.5% CI: 0.57, 0.93; P=0.002). ORR was greater with nivolumab than with everolimus (25% vs. 5%; odds ratio, 5.98 (95% CI: 3.68, 9.72); P<0.001). The median PFS was 4.6 months (95% CI: 3.7, 5.4) with nivolumab and 4.4 months (95% CI: 3.7, 5.5) with everolimus (HR 0.88; 95% CI: 0.75, 1.03; P=0.11).

This is a multi-center, open-label, 3-part Phase I/II trial of pembrolizumab in combination with PEG-IFN or IPI in subjects with advanced or metastatic MEL and RCC. Subjects with

advanced or metastatic MEL with any prior lines of therapy (Part 1A and 1B) and subjects with advanced or metastatic RCC with ≥1 line of therapy (Part 1A only) as well as subjects with advanced or metastatic MEL with no prior lines of therapy (Part 1C) will be enrolled in this trial.

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

4.2.1.1 Rationale for Evaluating anti-PD-1 Therapy in Advanced Melanoma and Renal Cell Carcinoma

4.2.1.1.1 Rationale for Pembrolizumab

Pembrolizumab is a highly specific humanized anti-PD-1 antibody, which has shown to be very well-tolerated and lead to ORRs in MEL subjects of 36% [59]. KEYNOTE 006, a phase III trial, has demonstrated superior efficacy of pembrolizumab compared to IPI in PFS, OS and ORR, with an estimated 46.4% 6-month PFS rate versus 26.5% for IPI. The ORR was 32.9% for pembrolizumab versus 11.9% for IPI. Responses were ongoing in 96.7% of subjects after a median follow-up of 7.9 months. One-year estimates of survival for subjects receiving pembrolizumab q3w were 68.4% compared with IPI 58.2% (HR for death as compared with IPI 0.69; 95% CI: 0.52, 0.90; p=0.0036). Because the OS results were superior to IPI, the external Data Monitoring Committee (DMC) recommended stopping the study early to allow patients on IPI who progressed the option of receiving pembrolizumab [30].

Blockage of the PD-1/PD-L1 pathway also appears to be effective in a heavily pre-treated population with metastatic RCC [60] [61], leading to ORRs of up to approximately 29%.

4.2.1.1.2 Rationale for PEG-IFN

IFNα, the active component of PEG-IFN, is a pleiotropic cytokine, with anti-angiogenic and immunomodulatory properties. In MEL, IFNα is approved in the adjuvant setting. While IFN treatment as monotherapy has shown some clinical activity in metastatic MEL [62], IFN in metastatic MEL is only used as part of bio-chemotherapy combination regimens, albeit rarely [63] [64].

In RCC, IFNα has shown similar clinical activity as sorafenib, a tyrosine kinase inhibitor, in the first line setting [38]. Currently in metastatic RCC, IFNα is used in combination with bevacizumab [54], an anti-angiogenesis antibody targeting VEGF-A (vascular endothelial growth factor-A).

4.2.1.1.2.1 Hypothesis for Pembrolizumab + PEG-IFN Combination Therapies

Internal pre-clinical studies have shown that IFNα increases the expression of PD-L1 in RCC and MEL cell lines, as well as in breast cancer histoculture (data not published). In a pre-clinical study by Terawaki and others, IFNα increased PD-1 expression in tumor infiltrating lymphocytes (TILs) in MC38 (mouse colorectal) model [65].

This study also evaluated the potential additive anti-tumor effect of the combination IFNα and anti-PD-1. In their experiment, mice received SC tumor implants in the flank, then received IFNα daily from Days 1–13. Anti-PD-1 (4H2) antibody was given at doses of 6 or 20 mg/kg on Days 0 and 3, or of 10 mg/kg three times with a 6-day interval. Figure 4A illustrates the mean tumor volumes in mice treated with IFNα, anti-PD-1 or the combination, showing a greater tumor control when both agents were given in combination. Figure 4B illustrates the individual tumor volumes in these mice. The median size of tumors was smaller in the animals treated with the combination IFNα+Anti-PD-1 and a greater number of mice had profound responses (tumors smaller than 100mm^3, dashed line). None of the 15 animals treated with IFNα had profound responses, whereas a total of 9 out of 30 animals treated with 4H2 (at 3 and 10 mg/kg), and 12 out of 30 animals treated with IFNα+4H2 (at 3 and 10 mg/kg) were nearly disease free.

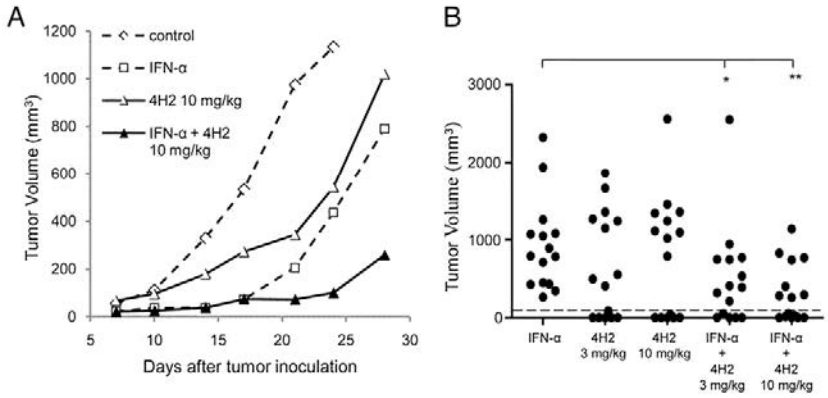


Figure 4 Effect of IFNα and Anti-PD-1 in MC38 models

4.2.1.1.3 Rationale for IPI

IPI (Yervoy®) is approved for treatment of metastatic MEL, as it has shown OS advantage compared with peptide vaccine [66]. IPI monotherapy has shown modest activity in RCC [41]; however, it is not being further developed as a single agent.

4.2.1.1.3.1 Hypothesis for Pembrolizumab + IPI Combination Therapies

Pre-clinical studies have shown that concomitant CTLA-4 and PD-1 blockage elicited greater response rates than either single agent in MC38 mouse models [67]. Notably, while no mice treated with anti-CTLA-4 or anti-PD-1 were free of disease at the end of the experiment, 7-60% of mice treated with the combination at various dose levels were tumor free. This served as the foundation to explore anti-CTLA-4 in combination with anti-PD-1 in the clinical setting.

In a Phase 1 trial in subjects with MEL, IPI (anti-CTLA-4) combined with nivolumab (anti-PD-1) led to response rates ranging from 21-53%. These may represent greater responses than nivolumab monotherapy [68] [69] and historical responses to IPI in monotherapy (approximately 20-31% and 10%, respectively) [66]. As mentioned above, both anti-PD-1 antibodies nivolumab and pembrolizumab demonstrated superiority over single-agent IPI in

previously untreated subjects (pembrolizumab), and over chemotherapy both in untreated subjects and after failure of IPI (nivolumab, pembrolizumab). The addition of IPI to nivolumab is associated with a higher response rate and a better PFS; however, it is associated with a high rate of Grade 3-4 DRAEs.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (KEYNOTE 001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (q2w) in subjects with advanced solid tumors. All three dose levels were well-tolerated and no dose-limiting toxicities were observed. This first in human trial of 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). No MTD has been identified to date.

PK data analysis of pembrolizumab administered q3w 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 starting the dose escalation with a q3w dosing schedule for pembrolizumab.

The dose of pembrolizumab with Amendment 03 is 200 mg q3w. The dose recently approved in the United States and several other countries for treatment of MEL and NSCLC subjects is 2 mg/kg q3w. Information on the rationale for selecting 200 mg q3w is summarized below.

An integrated body of evidence suggests that 200 mg q3w is expected to provide similar response to 2 mg/kg q3w, 10 mg/kg q3w and 10 mg/kg q2w. A flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with MEL as well as NSCLC 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 dose.

A population 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 (1) considerably overlap with those obtained from the 2 mg/kg dose and (2) maintain the individual patient exposures within the exposure range established in MEL to be 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 types, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with MEL 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 MEL, NSCLC, and other tumor types support a lack of

meaningful difference in PK 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 types 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. Based on the existing data, 200 mg q3w is the appropriate dose for pembrolizumab.

In the pembrolizumab + PEG-IFN treatment Arms, the dose finding portion of this trial will evaluate up to four doses of PEG-IFN, 0.5 μg/kg, 1 μg/kg, 2μg/kg, and 3 μg/kg, administered SC weekly. A lower dose of PEG-IFN, 0.5 μg/kg/week, will be evaluated as DL-1, if needed.

As single agent, PEG-IFN is tolerated at doses higher than 3 μg/kg weekly dose; the MTD was defined at 7.5-9 μg/kg and 6 μg/kg weekly, respectively, in subjects with CML and solid tumors [70] [71]. These studies showed a trend toward a dose-related increase of AEs. Lower rates of AEs were also seen when single agent non-pegylated IFNα was given at lower (5MU total/week) versus higher doses (25 MU total/week) in a randomized trial in RCC subjects [72]).

In combination with other immune-modulators, PEG-IFN 3 μg/kg/week was found to be tolerable when given with IL-2 three times per week in subjects with RCC [73]. More recently, PEG-IFN was tolerated at 2 μg/kg/week in combination with standard dose IPI, in subjects with MEL [74].

In addition to the greater tolerability, lower PEG-IFN doses (3μg/kg/week and below, or the equivalent of non-pegylated IFN) have shown biological activity as single agent and in combinations. In RCC, a Phase I trial using PEG-IFN doses of 0.5-2μg/kg revealed an ORR of 14% [75]. A previously mentioned RCC trial used low dose non-pegylated IFNα, 0.5 MU twice/day (5 MU total/week), versus higher doses of IFNα, 5 MU/day (25 MU total/week) showing the same ORR 6.7%, including a CR, and yielded a trend to better OS in the low dose IFN group, 25.5 months and 17.5 months, respectively [72]. These doses correspond to less than 0.25μg/kg to approximately 1μg/kg weekly doses of PEG-IFN [70] In addition, larger trials used non-pegylated IFNα at 9 MIU/kg three times/week (27 MU/week corresponding approximately to PEG-IFN 1μg/kg weekly), yielded an ORR of 13% [76] [77]. In MEL, low dose PEG-IFNα2a (with same active principle, but a different PEG moiety) yielded an ORR of 6% in 48 subjects [36], including a CR.

In the combination setting, low dose IFNα (9 MU/week) with bevacizumab [78] appeared to have similar efficacy and a favorable side effect profile compared with historical data on standard dose IFNα (27 MU/week) plus bevacizumab [79]. Despite small numbers (3 PR/10 evaluable subjects), results of low dose PEG-IFN in combination with IPI also appear promising [74].

Given the toxicities associated with higher doses of IFN, this trial will investigate doses of up to 3 μg/kg/week of PEG-IFN. These are biologically active doses, aiming at priming the immune system and increasing responses to anti-PD-1 therapy. The overall dosing strategy is

intended to emphasize dose intensity with pembrolizumab rather than PEG-IFN, due to the known safety and efficacy of both agents.

In the pembrolizumab + IPI treatment Arms of Part 1A and 1B, pembrolizumab will be evaluated in combination with IPI 1 mg/kg. The schedule of IPI will follow the approved drug label of q3w. In a Phase I study by Sznol at ESMO 2013, efficacy of nivolumab 3 mg/kg + IPI 1 mg/kg (ORR 40% (95% CI 16-68%) and Aggregate Clinical Activity Rate (ACAR; defined as CR + PR + unconfirmed CR+ unconfirmed PR+ immune-related PR+ SD >24 week + irSD >24 week) 73%] appeared to have similar efficacy as nivolumab 1mg/kg + IPI 3 mg/kg (ORR 53% (95% CI 28-77%) and ACAR 65%) [68]. In addition, the combination of nivolumab 3 mg/kg + IPI 1 mg/kg showed lower rate of Grade 3-4 DRAEs compared with nivolumab 1 mg/kg + IPI 3 mg/kg (44% versus 65%, respectively). A total of 6/28 (21%) of patients experienced Grade 3-4 toxicities that were found to be dose-limiting.

The overall dosing strategy is intended to emphasize dose intensity with pembrolizumab rather than IPI; in addition, the dosing paradigm of anti-PD-1+ anti-CTLA4 combination will explore the lowest therapeutic dose of anti-PD-1 (pembrolizumab at 2 mg/kg q3w) and a lower dose than recommended monotherapy dose of anti-CTLA4 (IPI at 1 mg/kg q3w x 4 doses) in Part 1A as a safety run-in, due to known safety and efficacy profile of both agents. Up to 18 subjects will receive pembrolizumab 2 mg/kg q3w + IPI 1 mg/kg q3w x 4 doses. Once DL1 (pembrolizumab 2mg q3w + IPI 1mg/kg q3w x4 injections) is declared safe, dose expansion at DL1 in MEL subjects (Part 1B) will proceed.

In the pembrolizumab + IPI treatment Arms of Part 1C, the dose of pembrolizumab will be 200 mg q3w based on the rationale provided above. The dose of IPI will be 50 mg fixed dose q6w (Arm 1) and 100 mg IPI fixed dose q12w (Arm 2). The dose of IPI approved in the US and several other countries for treatment of MEL is 3 mg/kg q3w. Information on the rationale for selecting IPI 50 mg q6w and 100 mg q12 w is summarized below.

Results of 153 MEL patients in Part 1B show that lower doses of IPI (1 mg/kg q3w) in combination with pembrolizumab 2mg/kg q3w have a confirmed ORR of 57% by independent central review and a comparable rate of Grade 3-4 DRAEs to nivolumab 3 mg/kg + IPI 1 mg/kg (42 vs 44%) [53] or nivolumab 3 mg/kg + IPI 3mg/kg (55% and 54% for CheckMate 067 and CheckMate 069, respectively) [53] [80]. In Part 1B, 72% of the subjects were able to complete all 4 planned doses of IPI, however, DRAEs were present in 42% of the subjects. To improve the safety and tolerability of the combination, pembrolizumab + IPI, lower doses as well as increased dosing interval of IPI will be explored in Part 1C.

An integrated body of evidence suggests that in combination with a PD-1 inhibitor, IPI 50 mg q6w and 100 mg q12w is expected to provide a similar response to IPI 1 mg/kg q6w and IPI 1 mg/kg q12w, respectively. Both IPI 1 mg/kg q6w and 1 mg/kg q12w have been shown to be effective when combined with nivolumab 3 mg/kg in subjects with NSCLC [81]. Simulations of PK profiles suggest that the systemic exposure and trough concentrations (Ctrough=pre-dose serum concentration of drug) for IPI 50 mg q6w are between those for IPI 1 mg/kg q12w and IPI 1 mg/kg q6w, and those for IPI 100 mg q12w overlap with IPI 1mg/kg q12w. The increased dosing interval (q6w or q12w) compared to the approved dosing

interval for IPI monotherapy (q3w) may potentially increase the duration of time with IPI coverage and maintain IPI exposure for a longer time interval, while the lower Cmax (Cmax=maximum serum concentration of drug) may improve tolerability. The existing data suggest IPI 50 mg q6w and IPI 100 mg q12w are appropriate doses for IPI in combination with pembrolizumab 200 mg q3w.

The proposal to use fixed dose for IPI compared to weight-based dosing is supported by the published population PK analysis for IPI [82]. An allometric relationship is reported between IPI clearance and body weight, with estimated allometric coefficient of 0.642, which is consistent with no advantage for weight-based dosing compared to a fixed dose with respect to controlling exposure variability [83].

A fixed dose regimen is expected to simplify the dosing regimen (potentially reducing dosing errors), as well as be more convenient for physicians. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities, as well as reducing waste.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in combination with PEG-IFN or IPI in subjects with advanced MEL and RCC. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including 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, potential immune-related adverse events (irAEs) will be collected and designated as immune-related ECIs as described in Section 7.2.3.2.

4.2.3.2 Efficacy Endpoints

The primary efficacy objective of this trial is to evaluate the anti-tumor activity of pembrolizumab in subjects with advanced MEL treated with pembrolizumab in combination with PEG-IFN or IPI. Response rates per RECIST 1.1 and volumetric analysis will be evaluated.

The primary response rate efficacy endpoint will be based on independent central review using RECIST 1.1 (see Appendix 12.6) [1]. RECIST 1.1 will also be used by the local site to determine eligibility and make treatment decisions. For this later purpose, RECIST 1.1 will be adapted to account for the unique tumor response profile seen with treatment of pembrolizumab and this adapted/modified RECIST 1.1 will be used by the sites for treatment decisions. Modified RECIST 1.1 will also be used by the local site to determine eligibility. The primary efficacy endpoint is ORR, based on RECIST 1.1. Secondary endpoints are listed

in section 3.2. As data permits, same efficacy endpoints will also be evaluated in Part 1A RCC subjects.

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses which may be functionally anergic. 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 criteria may not provide an accurate assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptation:

If radiologic imaging shows 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 as per treatment calendar. If repeat imaging confirms PD, subjects will be discontinued from trial therapy (exception noted in Section 7.1.2.8). 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 decision should be based on the clinical judgment of the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating clinically significant disease progression
- No decline in Eastern Cooperative Oncology Group (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 that are deemed clinically unstable or who have biopsy proven new metastatic lesions are not required to have repeat imaging for confirmation of PD.

Note: Treatment may be continued despite modified RECIST 1.1 defined progression if the subject is clinically stable and is considered to be deriving clinical benefit by the investigator. In these cases, subjects should continue to undergo imaging as outlined in the footnote in Table 11.

Retrospective central review of all imaging time points may be performed for this study using volumetric analysis. Additional information is included in the Site Imaging Manual.

4.2.3.3 Planned Exploratory Biomarker Research

Tumor tissue for biomarker analysis from formalin fixed paraffin embedded tumor tissue sample or newly obtained formalin fixed biopsy of a tumor lesion not previously irradiated must be provided in the form of a tissue block or at least ten unstained slides and received by the central vendor before randomization.

Subjects must submit the tumor sample during screening. Subjects will be eligible to participate regardless of the level of PD-L1 expression. Subjects who do not submit a sample adequate for PD-L1 determination will not be enrolled in Part 1A or 1B. Subjects with an archival sample considered not acceptable may obtain a new biopsy. Subjects with a newly obtained biopsy considered not acceptable may undergo re-biopsy at the discretion of the investigator. Note for Part 1C: adequacy of the tumor sample for determination of PD-L1 status by IHC at the central pathology laboratory prior to enrollment is not required. Additional biopsy sample submission is encouraged but not mandatory for Part 1C when the sample is inadequate for PD-L1 testing.

Note: A fine needle aspirate, frozen sample, plastic embedded sample, bone, bone marrow, cell block, clot, or cytologic specimen will not be acceptable.

If new scientific data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of subjects, then only new biopsies will be acceptable for determination of PD-L1 status.

Biomarker research to identify factors important for pembrolizumab monotherapy or treatment doublets may also be pursued. For example, pre- and post-dose tumor (post-treatment tumor biopsies are optional at 12 weeks and upon progression) and blood samples from this study may undergo proteomic, genomic and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab monotherapy or doublets therapy and other immunologic targets.

Assays may include but are not be limited to:

Multiparametric (Two-Color) IHC

Spatial association of PD-1+ tumor infiltrating lymphocytes (TILs) and PD-L1+ cells (tumor and myeloid cells) suggests “induction” of PD-L1. Interferon-gamma production by antigen-specific PD-1+ CD8+ T cells is hypothesized to drive local intratumoral upregulation of PD-L1 on adjacent tumor and myeloid cells, leading to a “stalled Cytotoxic T Lymphocyte (CTL)” response which may be predictive of response to pembrolizumab therapy. By assessing both of the required elements, i.e. PD-L1 positive cells and PD-1+ T cells, a two-color IHC assay may be a better predictor of response than PD-L1 positivity alone.

Transcriptional Analyses

Messenger RNA (mRNA) expression profiling will be completed to assess expression of approximately 600 genes and attempt to define a gene set critical for clinical response to pembrolizumab. The hypothesis to be tested is that pembrolizumab responders will exhibit a "stalled CTL" response within the tumor reflected in the physical proximity between PD-1 and PD-L1 expression and the presence of an aborted (e.g., weak but discernible) interferon-gamma transcriptional program will be detectable by profiling analyses. Global profiling will also be pursued.

Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-10).

Genetic Analysis

New data are emerging that suggest we can define certain tumor types as being 'hypermutated'. There is a potential that this hypermutated state may correlate with response to pembrolizumab therapy, and/or that the converse, 'hypomutated' state may correlate with non-response.

DNA isolated from blood or tumor tissue will be analyzed in order to identify genetic alterations and to evaluate specific genetic alterations that may correlate with clinical response to pembrolizumab. These and other additional biomarker or genomic research to identify factors important for pembrolizumab therapy (for example, HLA genotype) may also be pursued.

4.2.3.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on blood and tumor tissue specimens 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 with advanced MEL (Part 1A, Part 1B and Part 1C) or RCC (Part 1A only) of at least 18 years of age 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. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have histologically or cytologically confirmed diagnosis of cancer that is recurrent, metastatic, or persistent and meet the following corresponding requirements for the cohort of the study they will enroll into.
    a. MEL: histologically confirmed diagnosis of unresectable stage III or metastatic MEL not amenable to local therapy (Part 1A, Part 1B, and Part 1C).
        i. Subject may not have a diagnosis of uveal or ocular MEL.
    b. RCC: histologically confirmed diagnosis of advanced/unresectable or metastatic RCC with predominantly clear cell elements (Part 1A only).
4. MEL subjects may have received any number of prior lines of therapy for metastatic disease for Part 1A and 1B. RCC subjects must have received ≥1 prior line of therapy for metastatic disease.

    Note for Part 1C: Subjects must have previously untreated stage III-IV advanced or metastatic MEL.

    Note for Part 1C: Prior adjuvant or neoadjuvant therapy is allowed as long as that therapy did not include compounds targeting PD-1, PD-L1, BRAF or MEK. Also, subjects who received prior adjuvant or neoadjuvant therapy may only participate in Part 1C if they did not discontinue therapy due to a DRAE and all related AEs have either returned to baseline or stabilized (e.g., endocrinopathies). Prior adjuvant or neoadjuvant therapy with anti-CTLA-4 will only be permitted if relapse did not occur during treatment or within 6 months of treatment discontinuation.

5. Have measurable disease based on RECIST 1.1. Cutaneous lesions and other superficial lesions that are detectable only by physical examination are not considered measurable lesions for the purposes of this protocol, but may be considered as non-target lesions. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
6. Must provide a tumor sample (archival or newly obtained biopsy) that is adequate for determination of PD-L1 status by IHC at a central pathology laboratory prior to enrollment. Subjects must submit the tumor sample during screening. Subjects will be eligible to participate regardless of the level of PD-L1 expression. Subjects who do not submit a sample adequate for PD-L1 determination will not be enrolled.

   Note for Part 1C: Adequacy of the tumor sample for determination of PD-L1 status by IHC at a central pathology laboratory prior to enrollment is not required.

   Note: A fine needle aspirate, frozen sample, plastic embedded sample, bone, bone marrow, cell block, clot, or cytologic specimen will not be acceptable.

   Subjects with an inadequate archival sample may obtain a new biopsy and subjects with non-acceptable newly obtained biopsy may undergo re-biopsy at the discretion of the investigator. Additional biopsy sample submission is encouraged but not mandatory for Part 1C when the sample is inadequate for PD-L1 testing.
7. Have a performance status of 0 or 1 on the ECOG Performance Scale.
8. Demonstrate adequate organ function as defined in Table 3. All screening labs should be performed within 10 days of treatment initiation.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥30 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN (or < 3x ULN in subjects with Gilbert's syndrome)
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for subjects with liver metastases)
Albumin	≥3.0 g/dL
Coagulation	
International normalized ratio (INR) **OR** prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

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

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

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

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

9. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia) for Part 1 A and B (Note: This sentence does not apply to Part 1C subjects as they are not permitted to have had prior chemotherapy). If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
10. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of trial medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 - Contraception, for the course of the trial through 120 days after the last dose of trial drug.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

12. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 - Contraception, starting with the first dose of trial therapy through 120 days after the last dose of trial therapy.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.1.3 Subject Exclusion Criteria

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

1. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (ie, CTLA-4, OX-40, CD137) or has previously participated in a pembrolizumab clinical trial.
2. Has received prior anti-cancer therapy, monoclonal antibody, chemotherapy, or an investigational agent or device within 4 weeks or 5 half-lives (whichever is longer) before first dose of trial drug or not recovered (≤ Grade 1 or at baseline) from AEs due to previously administered agents. Exception to this rule would be use of denosumab, which is not excluded.

    Note: Subjects with ≤ Grade 2 neuropathy are an exception and may qualify for the trial.

    Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting trial treatment.

    Note for Part 1C: Prior chemotherapy or targeted small molecule therapy (including BRAF and MEK inhibitors) for the treatment of Stage III unresectable/Stage IV melanoma are not allowed prior to study treatment.
3. Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1.
4. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial drug.
5. 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.
6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging 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 not using steroids for at least 7 days prior to trial treatment.

    Note for Part 1C: Baseline MRI brain scan will be conducted for all subjects.

7. Has severe hypersensitivity (≥Grade 3) to any pembrolizumab excipients (excipients are listed in the pembrolizumab IB).
8. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
9. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
10. Has an active infection requiring systemic therapy.
11. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
12. Has a known history of or is positive for hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (hepatitis C virus [HCV] RNA [qualitative] is detected). Note: Without known history, testing needs to be performed to determine eligibility. Hepatitis C antibody (Ab) testing is allowed for screening purposes in countries where HCV RNA is not part of standard of care.
13. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
14. Has received any prior therapy with IFN-α (in neoadjuvant, adjuvant or metastatic settings). Note: This criterion only applies to Part 1A.
15. Has severe cardiovascular disease, i.e. arrhythmias, requiring chronic treatment, congestive heart failure (NYHA Class III or IV) or symptomatic ischemic heart disease.
16. Has hepatic decompensation (Child-Pugh score > 6 [class B and C]).
17. Has uncontrolled thyroid dysfunction.
18. Has uncontrolled diabetes mellitus.
19. Has received a live vaccine within 30 days prior to the first dose of trial drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
20. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
21. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the trial.

- 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 treatment(s) to be used in this trial are outlined below in Table 4. The dosing schedules for each doublet combinations are outlined in Section 6 - Trial Flow Chart.

Table 4 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Use
pembrolizumab	200 mg	q3w	IV infusion	Experimental
pembrolizumab	2 mg/kg	q3w	IV infusion	Experimental
PEG-IFN	0.5 µg/kg	Weekly	SC	Experimental
PEG-IFN	1 µg/kg	Weekly	SC	Experimental
PEG-IFN	2 µg/kg	Weekly	SC	Experimental
PEG-IFN	3 µg/kg	Weekly	SC	Experimental
IPI	1 mg/kg	q3w	IV infusion	Experimental
IPI	50 mg	q6w	IV infusion	Experimental
IPI	100 mg	q12w	IV infusion	Experimental

Trial treatment for Cycle 1 should begin within 7 days of randomization.

All supplies indicated in Table 4 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased 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 trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

The dose amount required to prepare study treatments (pembrolizumab, PEG-IFN, and IPI) will be based on the subject's weight in kilograms (kg). Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

With the approval of Amendment 03, subjects continuing pembrolizumab treatment on Parts 1A and 1B will switch to a fixed dose of 200mg q3w (not weight-based). The rationale for the fixed dose regimen is outlined in Section 4.2.2.

In Part 1C, subjects will receive a fixed dose of pembrolizumab 200 mg q3w. IPI will be administered as a fixed dose of 50 mg q6w (Arm 1) or 100 mg q12w (Arm 2). The rationale for fixed dose regimen is outlined in Section 4.2.2.

5.2.1.2 Rules for Dose Finding (Part 1A)

Dose limiting toxicities (DLTs) observed in Cycle 1 will be used to determine escalation to the next dose level. A cycle is 6 weeks. The study is using a design based on the modified TPI method [84].

The rules applied for the dose finding algorithm are as follows:

Subjects will be initially assigned between combinations (pembrolizumab + PEG-IFN or pembrolizumab + IPI). For the pembrolizumab + PEG-IFN combination, an initial cohort of 3 subjects will be enrolled. Subsequent dosing decisions will be based on the rules in Table 5. For the pembrolizumab + IPI combination, a run-in cohort of up to 18 subjects will be enrolled. If both combinations are open for enrollment, eligible subjects will be randomly assigned to a combination; otherwise, subjects will be enrolled to the combination that is open for enrollment.

Dose Finding Rules for pembrolizumab + PEG-IFN Combination (Part 1A)

Dose finding will continue until ≤4 of 14 subjects experience a DLT at a given dose combination level. 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 5. The decisions are generated from Ji et al. (2010) [84] using the parameters in the table with a conservative adjustment by treating 5 or more DLTs observed in any dose combinations as unacceptably toxic (denoted as DU in Table 5).

Table 5 Dose Finding Rules

			Number of subjects treated at current dose										
		3	4	5	6	7	8	9	10	11	12	13	14
Number of toxicities	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	DU	DU	DU	DU	DU
	6				DU	DU	DU	DU	DU	DU	DU	DU	DU
	7					DU	DU	DU	DU	DU	DU	DU	DU
	8						DU	DU	DU	DU	DU	DU	DU
	9							DU	DU	DU	DU	DU	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 DLT rate = 30% Epsilon1=Epsilon2=0.05 Source: Ji et al. (2010) [84]												

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 de-escalating to a lower dose. 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.

The maximum number of subjects who are enrolled at a certain 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 5). For example, if 0/3 subjects have experienced a DLT at a given dose level, no more than an additional 5 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 5 of the additional subjects experience a DLT (i.e., 5/8 subjects with DLT in Table 5). An exception to the rule above is that a minimum of 3 subjects must be enrolled upon each dose decision.

If enrollment expands to 14 subjects for a dose level and ≤4 of the 14 subjects develop a DLT, then the dose finding is expected to stop. However, additional dose expansion to 14 subjects at a lower dose combination may be considered at the discretion of the Sponsor in consultation with the study investigators even if enrollment has expanded at a higher dose combination with ≤4 of the 14 subjects experiencing a DLT. If enrollment expands to 14 subjects for a dose level and >4/14 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 5, the observed rate of

subjects with DLT at the MTD will always be below 30% (i.e., ≤ 4/14) due to the conservative adjustment by treating 5 or more DLTs observed in any dose combinations as unacceptably toxic.

Safety Run-in/Dose Finding Rules for pembrolizumab + IPI Combination (Part 1A)

If ≤6 DLTs are observed in the 18 subjects enrolled in DL1 (Part 1A), this dose will be considered tolerable. If > 6 DLTs are observed in the 18 subjects enrolled, this dose level (DL1) will be proven not tolerable, and the combination with IPI will not be further developed.

If DL1 is considered tolerable, at least 90 and up to additional 150 MEL subjects will be enrolled in the expansion cohort (Part 1B) at DL1 for further evaluation of safety and tolerability.

5.2.1.2.1 Definition of Dose-Limiting Toxicities

All toxicities will be graded using NCI CTCAE Version 4.0 (Appendix 12.5). Dose-limiting hematologic and non-hematologic toxicities will be defined differently. Dose-limiting toxicities (DLT) assessment will be based on events occurring during DLT assessment period, which is defined as the Cycle 1. The DLT portion of the study applies to Part 1A only. Dose-limiting toxicities include all adverse experiences that are clearly not related to disease progression or intercurrent illness if judged by the investigator to be possibly, probably or definitely related to study treatments.

Hematological DLTs

1. Any Grade 3 or higher hematologic toxicity with the exception of
    - Grade 3 neutropenia
    - Grade 3 anemia

Non-Hematological DLTs

1. Grade 4 non-hematologic toxicity (not laboratory).
2. Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care with the exception of:
    - Hypersensitivity/infusion reactions lasting ≤2 days.
3. Any Grade 3 or higher non-hematologic laboratory value if:
    - Medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week

4. Febrile neutropenia Grade 3 or Grade 4:
    - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour
    - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated
5. Thrombocytopenia <25,000/mm^3 if associated with:
    - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
    - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit
6. Grade 5 toxicity (i.e., death)
7. Delay in the scheduled administration of any component of therapy (IPI, PEG-IFN, pembrolizumab) of >14 days
8. A delay of >14 days due to drug-related toxicity in initiating Cycle 2
9. Unable to complete at least 80% of any of the three treatments during the first course of therapy due to treatment-related toxicity (even if not meeting above DLT criteria)

5.2.1.2.2 Replacement of Subjects in DLT Period (Part 1A)

Replacement of subjects in DLT Period applies to Part 1A only. In order to determine safety, all subjects selected must meet the criteria for evaluability for Cycle 1. Subjects are considered non-evaluable and will be replaced if:

- they are randomized but not treated,
- they discontinue from the trial prior to completing all safety evaluations due to reasons other than DRAEs,
- they received <90% of the total pembrolizumab infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a drug-related event,
- they received <80% of PEG-IFN or IPI intended for the trial during first Cycle 1 and did not experience a drug-related event.

Non-evaluable subjects will not be counted toward the cohort total for DLT evaluation. Subjects who experience a DLT in Cycle 1 should be discontinued from the trial. However, if it has been determined that the subject is deriving clinical benefit from the study therapy, the subject may be allowed to continue at a lower dose.

5.2.1.3 Dose Modification (Escalation/Titration/Other)

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

- Treatment Group A: pembrolizumab + PEG-IFN (Part 1A)
- Treatment Group B: pembrolizumab + IPI (Part 1A, 1B and 1C)

Toxicities common to PEG-IFN, IPI, and pembrolizumab include, but are not limited to rash, endocrinopathy, hepatotoxicity, diarrhea, and pneumonitis. Therefore, it is possible that these and/or other toxicities may be exacerbated when pembrolizumab is given in combination with either PEG-IFN or IPI.

The dose levels for the doublets for this trial are provided in Table 1 and Table 2.

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.

If possible, the investigator may attribute each toxicity event to pembrolizumab, PEG-IFN, or IPI alone such that a stepwise dose reduction or increase in dosing schedule, upon resolution of the event to baseline, can be made according to Table 6, Table 8, Table 9, and Table 10.

Subjects requiring an increase in dosing schedule due to toxicity may resume pembrolizumab upon resolution of toxicity to Grade 0-1 or baseline. This dose would be considered Day 1 of the next cycle and should be in alignment with the new schedule.

For example: A subject is CURRENTLY on Cycle 3 of a pembrolizumab q3w schedule. Subject has an AE on D22 resulting in increase of dosing schedule of pembrolizumab and resolution of AE is on C3D36, drug administration should resume on D37 (now called C4D1).

Permanent discontinuation of PEG-IFN but not pembrolizumab is appropriate if in the opinion of the investigator and the Sponsor, the toxicity is clearly related to PEG-IFN. Pembrolizumab treatment may resume upon resolution of toxicity to Grade 0-1 or baseline. If in the opinion of the Investigator and the Sponsor the toxicity is related to the combination of 2 agents, both drugs should be modified according to the recommended dose modifications.

Subjects who experience an unacceptable toxicity that is attributed to IPI in the opinion of the investigator and the Sponsor, may permanently discontinue IPI, but may continue with pembrolizumab, upon resolution of toxicity to Grade 0-1 or baseline, until unacceptable toxicity or progression. Subjects who discontinue pembrolizumab due to untoward toxicities may not continue on the trial receiving only PEG-IFN or IPI.

Study treatments will be withheld for drug-related ≥ Grade 3 hematologic toxicities (excluding Grade 3 neutropenia and anemia), ≥ Grade 3 non-hematologic toxicity, including laboratory abnormalities; and severe or life-threatening AEs as per Table 6 and Table 8. This will also apply to subjects included in Part 1C receiving IPI + pembrolizumab combination.

In Part 1C, isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 7 days ±3 days of onset will not require treatment discontinuation. If not resolved to < Grade 4 within this window, trial treatment may continue with Sponsor consultation. Exceptions for restarting treatment according to the Dose Modification and Supportive Care Guidelines per Table 9 and Table 10 should be followed.

For subjects who experience a recurrence of the same AE(s) at the same grade or greater with rechallenge of study treatment(s), a consultation between the Sponsor and the investigator should occur to determine whether the subject should continue on the trial. However, for a subject who experiences a recurrence of the same SAE at the same grade or greater with rechallenge, the subject must discontinue trial treatment.

Investigators should refer to the appropriate IB/label for PEG-IFN, pembrolizumab, and IPI for additional information regarding the background of each drug and the management of other AEs or potential safety-related issues. Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to trial therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on trial therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's trial record.

5.2.1.3.1 Dose Modification Guidelines for pembrolizumab + PEG-IFN or pembrolizumab + IPI Combination Therapy

5.2.1.3.1.1 Dose Modification Guidelines for Treatment Group A (Part 1A Only): pembrolizumab + PEG-IFN

Table 6 Dose Modification Guidelines for DRAEs for pembrolizumab + PEG-IFN

Toxicity	Grade	Cycle Number	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	Any	C1	Please refer to Section 5.2.1.2.1			
	1, 2	C2 and Beyond	No	N/A	N/A	N/A
	3 *Excludes Grade 3 neutropenia, and anemia*		Yes	Toxicity resolves to Grade 0-1 or baseline	*Subject is dosed at DL1-DL3:* May decrease PEG-IFN dose to next dose level below for each occurrence *Subject is dosed at DL(-1):* May discontinue PEG-IFN and increase dosing interval of pembrolizumab by 1 week° for each occurrence	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4		Yes	Toxicity resolves to Grade 0-1 or baseline and after Sponsor consultation	*Subject is dosed at DL1-DL3:* May decrease PEG-IFN dose to next dose level below *Subject is dosed at DL(-1):* May discontinue PEG-IFN and increase dosing interval of pembrolizumab by 1 week°	

Toxicity	Grade	Cycle Number	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Non-hematological Toxicity Note: Exception to be treated similar to Grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue <u>PEG-IFN should be permanently discontinued if subject experiences Grade 3 liver toxicity.</u> For additional information regarding irAEs, reference Section 5.6.1.	Any	C1	Please refer to Section 5.2.1.2.1.			
	1	C2 and Beyond	No	N/A	N/A	N/A
	2		Consider withholding for persistent symptoms. For Grade 2 Ocular, Liver and GI toxicity, hold both	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 5.6.1 for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4 weeks* <u>*Subject is dosed at DL1-DL3:*</u> May decrease PEG-IFN dose to next lower dose level for each occurrence <u>*Subject is dosed at DL(-1):*</u> May discontinue PEG-IFN and increase dosing interval of pembrolizumab by 1 week°	Toxicity does not resolve within 12 weeks of last infusion
	3		Yes	Toxicity resolves to Grade 0-1 or baseline	<u>*Subject is dosed at DL1-DL3:*</u>May decrease PEG-IFN dose to next dose level below <u>*Subject is dosed at DL(-1):*</u> May discontinue PEG-IFN and increase dosing interval of pembrolizumab by 1 week°	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4		NA	NA	NA	Permanently discontinued

° Subject may resume pembrolizumab upon resolution of toxicity to baseline. This dose would be considered Day 1 of the next cycle and should be in alignment with the new schedule. For example: A subject is CURRENLTY on Cycle 3 of a pembrolizumab q3w schedule. Subject has an AE on D22 resulting in increase of dosing schedule of pembrolizumab and resolution of AE is on C3D36, drug administration should resume on D37 (now called C4D1).

For Part 1A, in an individual subject, following a reduction in the dose of pembrolizumab and PEG-IFN a subsequent increase in the dose will not be permitted.

5.2.1.3.1.2 Dose Modification Guidelines for PEG-IFN

Follow criteria listed in Table 6 for withholding study drug and dose modification for pembrolizumab + PEG-IFN. In addition,

- withhold PEG-IFN dose for the following:
  - Grade 3 or higher thrombocytopenia
  - Grade 3 or higher flu-like symptoms (including fever, associated tachycardia, myalgia, fatigue or chills)
  - Depressed mood/Neuropsychiatric disorder
- reduce dose of PEG-IFN to lower dose level if CrCl decreases below 50 mL/min.

Please refer to criteria for PEG-IFN dose modification, as shown in Table 7.

Table 7 Recommended Dose Reduction for PEG-IFN

Dose Level	Dosage and Schedule
PEG-IFN Treatment at DL3	SC 3 µg/kg/weekly
Dose Modification #1	SC 2 µg/kg/weekly
Dose Modification #2	SC 1 µg/kg/weekly
Dose Modification #3	SC 0.5 µg/kg/weekly
	Permanently discontinue if unable to tolerate 0.5 µg/kg/weekly

5.2.1.3.1.2.1 Dose Modification for Management of Depression

Subjects who develop mild depression during the trial may continue their study medication and should be monitored weekly (by visit or by phone) for 4 to 8 weeks. If the subject's status is stable at that time, the subject may resume the normal visit schedule with instructions to call the study center immediately if the subject feels that the depression has worsened. If the subject's condition worsens, see instructions for moderate and/or severe depression below.

Subjects who develop moderate depression during the trial should have their dose of PEG-IFN reduced (Table 7) at the discretion of the investigator. Subjects should be monitored weekly (by visit or phone for 4 to 8 weeks, depending on the subjects' status) to assure that their status is stable. These subjects may remain on reduced PEG-IFN dosing if the condition is considered stable and does not interfere with the subject's normal activities. Other clinical management intervention may be instituted as necessary. Subjects will be instructed to call the study center immediately if they feel their depression has worsened.

If the subject's condition worsens, the subject should immediately discontinue PEG-IFN, and a physician should make a priority assessment of the severity of the subject's condition. Appropriate therapeutic measures should be instituted, and the subject should be followed

weekly or biweekly (depending on the physician's clinical judgment) by visit or by phone until the subject's status has returned to baseline conditions.

5.2.1.3.1.2.2 Interruption or Discontinuation of PEG-IFN

Follow criteria for subject discontinuation listed in Table 6.

In addition, treatment with PEG-IFN should be permanently discontinued for any of the following reasons:

- The subject experiences new onset of ventricular arrhythmia or cardiovascular decompensation.
- The subject develops severe depression (≥ Grade 3).
- The subject experiences a persistent or worsening severe (≥ Grade 3) neuropsychiatric disorder.
- The subject experiences new or worsening retinopathy.
- The subject experiences ≥Grade 3 liver toxicity (AST, ALT or bilirubin) or hepatic decompensation (Child-Pugh score > 6 [class B and C]).
- The subject develops hypothyroidism, hyperthyroidism or diabetes mellitus that cannot be effectively managed.
- The subject experiences drug-related ≥ Grade 3 fever, flu-like symptoms, fatigue, or chills.
- The subject experiences drug-related ≥ Grade 3 injection reactions at site of SC administration.
- The subject is unable to tolerate PEG-IFN at 0.5 µg/kg/weekly dose.

All subjects enrolled in the pembrolizumab + PEG-IFN treatment group should have a baseline ophthalmologic exam including visual acuity, visual field and color discrimination by an ophthalmologist.

Any subject complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete ophthalmologic examination. In addition, because these ocular events may occur in conjunction with other disease states, periodic visual examinations during the trial are recommended, per standard of care, in subjects with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension.

If a subject's study treatment has been interrupted for more than 4 weeks for PEG-IFN and/or 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 with pembrolizumab + PEG-IFN who require discontinuation of PEG-IFN for toxicity may continue treatment with pembrolizumab. The reason for discontinuation must be recorded. For subsequent management of toxicities on pembrolizumab, see Section 5.2.1.3.3.

5.2.1.3.2 Dose Modification Guidelines for Treatment Group B: pembrolizumab + IPI

Table 8 Dose Modification Guidelines for DRAEs for pembrolizumab + IPI (Part 1A and 1B)

Toxicity	Grade	Cycle Number	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Any	Any	C1	Please refer to Section 5.2.1.2.1.			
Hematological Toxicity	1, 2	C2 and Beyond	No	N/A	N/A	N/A
	3 *Excludes Grade 3 neutropenia, and anemia*	C2	Yes	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4[§] weeks*: May decrease dose of IPI to 0.3 mg/kg for first occurrence. Any subsequent occurrences, discontinue IPI *Clinical AE does not resolve within 4[§] weeks*: Discontinue IPI	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
		C3° and beyond	*Please refer to* **Table 9** and **Table 10** Dose Modification and Supportive Care Guidelines for DRAEs for pembrolizumab monotherapy and Part 1C			
	4	C2	Yes	Toxicity resolves to Grade 0-1 or baseline and after Sponsor consultation	*Clinical AE resolves within 4[§] weeks*: May decrease dose of IPI to 0.3 mg/kg for first occurrence. Any subsequent occurrences, discontinue IPI *Clinical AE does not resolve within 4[§] weeks*: Discontinue IPI	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	C3° and beyond	*Please refer to* **Table 9** and **Table 10** Dose Modification and Supportive Care Guidelines for DRAEs for pembrolizumab monotherapy and Part 1C			

Toxicity	Grade	Cycle Number	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Non-hematological Toxicity Note: Exception to be treated similar to Grade 1 toxicity: • Grade 2 alopecia • Grade 2 fatigue For additional information regarding irAEs, reference Section 5.6.1.	1	C 2 and beyond	No	N/A	N/A	N/A
	2	C2	Consider withholding for persistent symptoms. For Grade 2 Ocular, Liver and GI toxicity, hold both drugs	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4[§] weeks*: May resume treatment at same schedule (reference Section 5.6.1 for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4[§] weeks*: May decrease dose of IPI to 0.3 mg/kg for first occurrence. Any subsequent occurrences, discontinue IPI	Toxicity does not resolve within 12 weeks of last infusion
	2	C3° and beyond	*Please refer to* **Table 9** and **Table 10** Dose Modification and Supportive Care Guidelines for DRAEs for pembrolizumab monotherapy and Part 1C			
	3	C2	Yes	Toxicity resolves to Grade 0-1 or baseline	*Permanently discontinue IPI for Grade 3 Immune-related AE.* *Clinical AE resolves within 4[§] weeks:* May decrease dose of IPI to 0.3 mg/kg for first occurrence. Any subsequent occurrences, discontinue IPI *Clinical AE does not resolve within 4[§] weeks*: Discontinue IPI	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	3	C3° and beyond	*Please refer to* and **Table 10** Dose Modification and Supportive Care Guidelines for DRAEs for pembrolizumab monotherapy and Part 1C			
	4	C2 and beyond	NA	NA	NA	Permanently discontinued

°Scheduled treatment with pembrolizumab + IPI doublet is administrated for 2 cycles (12 weeks), followed by treatment with pembrolizumab single agent.
[§] IPI should be permanently discontinued for subject's failure to complete full treatment course of IPI within 16 weeks from administration of first dose.
Note: Subject may resume pembrolizumab upon resolution of toxicity to baseline. This dose would be considered Day 1 of the next cycle and should be in alignment with the new schedule. For example: A subject is CURRENTLY on Cycle 3 of a pembrolizumab q3w schedule. Subject has an AE on D22 resulting in increase of dosing schedule of pembrolizumab and resolution of AE is on C3D36, drug administration should resume on D37 (now called C4D1).

5.2.1.3.2.1 Dose Modification Guidelines for IPI

Please refer to criteria for IPI dose modification included in the approved label and described above in Table 8 for Part 1A and 1B and in Table 9 and Table 10 for pembrolizumab monotherapy and Part 1C.

5.2.1.3.2.1.1 Interruption or Discontinuation of IPI

In Part 1B, IPI should be permanently discontinued for subjects who fail to complete the full treatment course of IPI within 16 weeks from administration of first dose.

In Part 1C, IPI should be permanently discontinued for subjects who fail to complete the full treatment course of IPI within 30 weeks from administration of first dose for the IPI 50 mg q6w dose regimen and within 60 weeks for the IPI 100 mg q12w dose regimen.

If a subject's study treatment has been interrupted for more than 2 doses of IPI (with or without pembrolizumab being 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 with pembrolizumab + IPI who require discontinuation of IPI due to toxicity may continue treatment with pembrolizumab. The reason for discontinuation must be recorded.

5.2.1.3.3 Dose Modification and Supportive Care Guidelines for DRAEs for Pembrolizumab Monotherapy and Part 1C

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

Adverse events 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 trial 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, or 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 9.

Table 9 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs for Pembrolizumab Monotherapy and Part 1C

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 should 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	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects 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	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects 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) • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects 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 [a]	Grade 2	Withhold	• 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 [a]	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia[b]	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	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 [b]	Withhold or permanently discontinue [c]		
Hyperthyroidism[b]	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 [b]	Withhold or permanently discontinue [c]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	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		

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
Myocarditis	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 [d]	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		

AE=adverse event; ALT=alanine aminotransferase; AST= aspartate aminotransferase; CTCAE= Common Toxicity Criteria for Adverse Events; GI=gastrointestinal; irAE=immune related adverse event; IV=intravenous; T1DM=Type 1 diabetes mellitus.

NOTES:

[a] For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subject should be discontinued.

[b] For subjects 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).

[c] Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

[d] In Part 1C, isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 7 days ±3 days of onset will not require treatment discontinuation. If not resolved to < Grade 4 within this window, trial treatment may continue with Sponsor consultation.

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

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 10.

Table 10 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 therapy or infusion interruption but responds promptly to symptomatic treatment (eg, 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 (eg, 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 study drug treatment.	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).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids 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 study drug treatment.**	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		

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion of pembrolizumab, trial treatments should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. Refer to Table 9 for exception with regard to amylase and lipase abnormalities. For information on the management of AEs, see Section 5.6.1.

5.2.2 Timing of Dose Administration

Trial treatment should be administered following the schedule on Section 6 and after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6). Unless otherwise specified, trial treatment may be administered up to 3 days, before or after the scheduled day of each cycle due to administrative reasons.

The specific time of treatment 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.

All trial treatments will be administered on an outpatient basis.

The Pharmacy Manual contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration. The local product labels and institutional standards for PEG-IFN and IPI should be referenced.

Pembrolizumab

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). Pembrolizumab should always be administered first when in combination with either PEG-IFN or IPI.

PEG-IFN

PEG-IFN is a once-weekly SC injection that may be self-injected. Subjects should be premedicated with acetaminophen 500 to 1000 mg orally 30 minutes prior to the first dose of PEG-IFN and as needed for subsequent doses.

The first dose of trial treatment will be administered at the trial site on Day 1. Acetaminophen [500-1000 mg orally (po)] will be given in the clinic 30 minutes prior to the first dose of PEG-IFN. Subjects should be monitored for 1-2 hours after the first dose. Acetaminophen (500-650 mg po every 4-6 hours) should be continued as needed, and should not exceed 3000 mg/day.

Subsequent dosing will be performed once weekly by the subject (i.e., unsupervised at his/her home) at approximately the same time of day. Subjects may choose to take PEG-IFN with acetaminophen at bedtime to minimize common "flu-like" symptoms (including chills, fever, muscle aches, joint pain, headaches, and tiredness).

IPI

In Part 1B, IPI will be administered once q3w for a total of 4 doses.

In Part 1C, IPI will be administered once q6w for a maximum of 4 doses (Arm 1) and once q12w for a maximum of 4 doses (Arm 2).

IPI will be administered as a 90 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 90 minutes as possible. For additional instructions regarding dosing please refer to the IPI label.

The pharmacists will prepare IPI per the instructions in the label.

5.2.3 Treatment after Initial Evidence of Radiologic Disease Progression

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 as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

In Part 1A and 1B, tumor imaging will be assessed first at week 12 (± 3 days), then every 6 weeks (42 ± 3 days) until week 30. Subsequently, tumor imaging will be performed every 12 weeks (84 ± 7 days). In Part 1C, tumor imaging will be assessed every 6 weeks (± 3 days) until week 24. Subsequently, tumor imaging will be performed every 12 weeks (84 ± 7 days).

If radiologic imaging shows 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 as per treatment calendar. If repeat imaging confirms PD, subjects will be discontinued from study therapy (exception noted in Section 7.1.2.8). 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).

When feasible, subjects should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the first evidence of disease progression is at the investigator's discretion based on the clinical status of the subject as described in Table 11 below. Subjects that are deemed clinically unstable or who have biopsy proven new metastatic lesions are not required to have repeat imaging for confirmation of PD.

Note: Treatment may be continued despite modified RECIST 1.1 defined progression if the subject is clinically stable and is considered to be deriving clinical benefit by the investigator. In these cases, subjects should continue to undergo imaging as outlined in the footnote in Table 11.

Clinical Stability is defined as:

- Absence of signs and symptoms (including worsening of laboratory values) indicating clinically significant 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

Table 11 Imaging and Treatment after 1st Radiologic Evidence of PD

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment (exception noted in Section 7.1.2.8)	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments, **as per the schedule noted at the bottom of this table.**	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments, **as per the schedule noted at the bottom of this table.**	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

CR = complete response; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.
In Parts 1A and 1B, tumor imaging will be assessed first at week 12 (± 3 days), then every 6 weeks (42 ± 3 days) until week 30. Subsequently, tumor imaging will be performed every 12 weeks (84 ± 7 days).
In Part 1C, tumor imaging will be assessed first at week 6 (± 3 days), then every 6 weeks (42 ± 3 days) until Week 24. Subsequently, tumor imaging will be performed every 12 weeks (84 ± 7 days).

5.2.4 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are two Part 1A treatment arms. Subjects will be

assigned randomly in a 1:1 ratio to pembrolizumab + PEG-IFN and pembrolizumab + IPI, respectively, when both dose combination treatment groups are open for enrollment.

In Part 1B, subjects with advanced MEL will be enrolled in the pembrolizumab + IPI treatment group.

In Part 1C, subjects with advanced MEL will be randomized 1:1 to the following treatment groups:

- Arm 1: pembrolizumab 200 mg q3w + IPI 50 mg q6w
- Arm 2: pembrolizumab 200 mg q3w +IPI 100 mg q12w

5.4 Stratification

In Part 1A and 1C, there will be no stratification prior to randomization.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination 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 Director. 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 eCRF including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the screening visit and up to 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 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 Phase (including Second Course Phase) 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, PEG-IFN, or IPI
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, 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., FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from a drug-related AE of suspected immunologic etiology. Please note that inhaled or topical steroids are allowed, and systemic steroids at doses ≤ 10 mg/day prednisone or equivalent are allowed, as described in Section 5.6.
- Local surgery resulting from disease progression is prohibited. However, if indicated for palliative measure and after Sponsor approval, local surgery may be permitted beyond Week 12 tumor assessment.

Subjects who, in the assessment of 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.

5.6 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 are outlined along with the dose modification and supportive care guidelines in Section 5.2.1.3.3 Table 9 and Table 10 (pembrolizumab monotherapy and Part 1C). 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 trial treatment.

Note: If after the evaluation of the event, it is determined not to be related to trial treatment, the investigator does not need to follow the treatment guidance. Refer to Table 6 and Table 8 in Section 5.2.1.3.1 and Section 5.2.1.3.2, respectively for guidelines regarding dose modification for DRAEs (Part 1A and 1B).

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

5.6.2 Guidelines for Pembrolizumab/PEG-IFN Combination Therapy

5.6.2.1 PEG-IFN Dosing Considerations

Subjects can expect to get "flu-like" symptoms when taking PEG-IFN. Subjects may choose to take PEG-IFN with acetaminophen at bedtime to minimize common "flu-like" symptoms (including chills, fever, muscle aches, joint pain, headaches, and tiredness). Subjects should maintain hydration if experiencing "flu-like" symptoms.

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 may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they meet 1 of the following criteria:

- She is postmenopausal, defined as at least 12 months with no menses without an alternative medical cause. In women < 45 years of age who are not using hormonal contraception or hormonal replacement therapy, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening.
- She has a congenital or an acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving trial drug and for 120 days after the last dose of trial drug by complying with 1 of the following:

- Practice abstinence from heterosexual activity.

  Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and European Research Councils (ERCs)/Institutional Review Boards (IRBs). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

- Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

- Single method (1 of the following is acceptable):
  - Intrauterine device (IUD)
  - Vasectomy of a female subject's male partner
  - Contraceptive rod implanted into the skin
- Combination method (requires use of 2 of the following):
  - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - Cervical cap with spermicide (nulliparous women only)
  - Contraceptive sponge (nulliparous women only)
  - Male condom or female condom (cannot be used together)
  - Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the trial medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the trial. In order to participate in the trial, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of trial medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) throughout the trial period up to 120 days after the last dose of trial medication. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the trial.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will be immediately discontinued from trial treatment. 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 trial 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 trial personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 7.2.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab 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 breastfeeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

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

- Confirmed radiographic disease progression outlined in Section 5.2.3 (exception if the Sponsor approves treatment continuation).
- Unacceptable adverse experiences as described in Section 7.2
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires systemic treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis

- A confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to withdraw the subject
- Completed a maximum of 24 month of treatment with pembrolizumab

  Note: 24 months of pembrolizumab is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for a maximum of 17 doses of pembrolizumab and 4 doses of IPI if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1 and the study remains open.
- 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 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than PD 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 by telephone for OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Treatment after CR

Discontinuation of treatment with pembrolizumab may be considered for subjects who have attained an investigator-determined confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two additional doses of pembrolizumab beyond the date when the initial CR was declared. Upon Sponsor consultation, subjects who stop pembrolizumab with SD or better per modified RECIST 1.1 may be eligible for retreatment with pembrolizumab + IPI or pembrolizumab monotherapy for a maximum of 17 doses of pembrolizumab and 4 doses of IPI if they progress after stopping pembrolizumab at the discretion of the investigator according to the criteria in Section 7.1.5.2.1 as long as the trial Part to which the subject was initially enrolled remains open.

In Part 1C and upon Sponsor consultation, subjects who attain an investigator-determined CR or a VGPR per modified RECIST 1.1 may consider stopping treatment with IPI after a minimum of one dose of IPI on either Arm of treatment. Subjects who then experience radiographic disease progression may be eligible for Second Course Phase. Additional details are provided in Section 7.1.5.2.1.

5.9 Subject Replacement Strategy

Additional subjects may be enrolled in a given treatment group to ensure that the required number of evaluable subjects in each treatment group is achieved. A subject that discontinues the trial for PD or a DRAE will not be replaced and will be counted in the evaluable population of subjects for the respective treatment group. Further details are provided in Section 8.0.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. Part 1A and 1B will be considered complete when all enrolled subjects are a minimum of 24 weeks post initial trial treatment administration. At this point, a database lock may occur to allow analysis of the data. Part 1C will be considered complete for publication purposes when all enrolled subjects are a minimum of 72 weeks post initial treatment administration. At this point, database lock may occur to allow analysis of the data. Any remaining subjects may continue to receive trial treatment and be seen by the investigator per usual standard of care for this subject population. In addition, the investigator will be expected to monitor for and report any SAEs, events of clinical interest, and pregnancies as detailed in Section 7.2.3.1 (SAEs). The subject is considered on study until such time that he/she meets any of the discontinuation criteria and written notification is given to the Sponsor.

5.11 Clinical Criteria for Early Trial Termination

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

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (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 Treatment Phase: Part 1A (MEL and RCC) and Part 1B and 1C (MEL only)

6.1.1.1 Treatment Group A: pembrolizumab + PEG-IFN Combination Therapy (Part 1A only)

pembrolizumab q3w + PEG-IFN Combination Therapy															
Trial Period:	**Screening**	**Treatment**										**End of Treatment**	**Post-treatment**		
Cycle [1]:		**1**						**2**		**3 and Beyond**			**Safety Follow-Up**	**Follow-Up Visits [2]**	**Survival Follow-Up [3]**
Day:	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**22**	**1**	**22**	**At Time of Discon**	**30 Days post Discon**	**Every 12 Weeks**	**Every 12 Weeks**
Scheduling Window Days [4]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**
Administrative Procedures															
Informed Consent [5]	X														
Informed Consent for Future Biomedical Research [6]	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior [7] and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X		
Treatment Randomization		X													
Post-treatment Discontinuation Anti-Cancer Therapy Status														X	X
Survival Status		<----------												---------->	X
Clinical Procedures/Assessments															
Full Physical Examination	X	X			X			X		X		X			
Ophthalmologic Examination [8]		X	As clinically indicated												
Directed Physical Examination			X			X			X	As clinically indicated					
ECOG Performance Status	X	X	X		X	X		X	X	X		X			
12-Lead Electrocardiogram (ECG) [9]	X	As clinically indicated													
Vital Signs and Weight [10]	X	X	X	X	X	X	X	X	X	X	X	X	X		
AE Monitoring [11]		X	X	X	X	X	X	X	X	X	X	X	X	X	

pembrolizumab q3w + PEG-IFN Combination Therapy														
Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Post-treatment**		
Cycle [1]:		**1**						**2**		**3 and Beyond**		**Safety Follow-Up**	**Follow-Up Visits[2]**	**Survival Follow-Up[3]**
Day:	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**22**	**1**	**22**	**At Time of Discon**	**30 Days post Discon**	**Every 12 Weeks**	**Every 12 Weeks**
Scheduling Window Days [4]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**
Laboratory Procedures/Assessments performed by LOCAL laboratory															
Complete Blood Count (CBC) with Differential[12,13,14]	X	X	X	X	X	X	X	X	X	X		X			
Urinalysis[12,13,14]	X	X	X	X	X	X	X	X		X		X			
Comprehensive Chemistry Panel[12,13,14]	X	X	X	X	X	X	X	X		X		X			
Lactate Dehydrogenase (LDH)[12]	X														
T3, FT4 and TSH [12,13, 14]	X							X		X		X			
PT/INR and aPTT[12]	X														
Pregnancy Test- Urine or Serum (Beta Human Chorionic Gonadotropin) β-hCG[15]	X														
Drug Dispensation, Administration, and Associated Analyses															
Pembrolizumab Administration[16]		X			X			X	X	X	X				
PEG-IFN Dosing Diaries Dispensation		X						X		X					
PEG-IFN Administration/Dispensation[17]		X	X	X	X	X	X	X	X	X	X				
PKs of Pembrolizumab[18]	Please refer to Section 7.1.3.2 (Table 13 and Table 14).														
Total IgG[18]															
Anti-Pembrolizumab Antibodies (ADA)[18]															
Efficacy Measurements															
Tumor Imaging[19, 20]	X									X				X[2]	
Digital Photography: Cutaneous Lesions[21]	X	As clinically Indicated													
Tissue and Blood Collections and Pharmacodynamic Assessment															
Tumor Tissue Collection [22, 23]	X									X		X			
Correlative Blood Sample Collection [24]	X									X		X			
Blood Sample Collection for Genetics [25]		X													
Blood for Future Biomedical Research [26]		X													

1. Treatment cycles are 6 weeks. Imaging should always be performed as scheduled and follow calendar days, regardless of any treatment delays.
2. Subjects who discontinue trial treatment due to a reason other than disease progression should continue follow-up and assessment by radiologic imaging (and digital photography if applicable) every 12 weeks (± 1 week) for the first year after discontinuation, then every 6 months (± 2 weeks) for years two through five, and every 12 months (± 4 weeks) after year five. Imaging follow-up should continue until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the trial, whichever occurs first.
3. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone approximately every 12 weeks after the last contact date to assess for survival status. In certain situations, survival data may be requested more frequently than every 12 weeks as per Section 7.1.5.3.3. Updated survival status may be requested by the Sponsor at any time during the course of the study. 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 that have a death event previously recorded).
4. In general, the window for each visit is ± 3 days unless otherwise noted.
5. 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 the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
6. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained.
7. Prior medications – All concomitant medications received within 28 days prior to the screening visit and up to 30 days after the last dose of trial treatment should be recorded.
8. All subjects should have a baseline ophthalmologic exam including visual acuity, visual field and color discrimination by an ophthalmologist. Fundus photography should be performed in subjects with history of clinically significant retinal disease (defined as macular degeneration, retinal detachment and moderate/severe non-proliferative diabetic retinopathy and any proliferative diabetic retinopathy). Enrollment of subjects with clinically significant retinal disease will require consultation with the sponsor on risk-benefit associated to treatment with pembrolizumab + PEG-IFN. Any subject complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete ophthalmologic examination. In addition, because these ocular events may occur in conjunction with other disease states, periodic visual examinations during the trial are recommended in subjects with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PEG-IFN should be considered in subjects who develop new or worsening ophthalmological disorders.
9. ECG should be performed at screening and as clinically indicated thereafter. ECGs are performed locally.
10. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
11. Record all AEs occurring within 30 days after the last dose of trial treatment and all SAEs (related and unrelated to trial treatment) / ECIs occurring up until 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
12. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
13. After Cycle 1, lab samples can be collected up to 72 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. After Cycle 8, lab samples should be collected every two cycles on D1 (i.e.; C8 D1, C10 D1, C12 D1, etc.)
14. Unresolved abnormal labs that are DRAEs should be followed until resolution.
15. For women of reproductive potential, a urine pregnancy test should 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.
16. Pembrolizumab will be administered as a 30 minute IV infusion. 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). Pembrolizumab should always be administered first when given in combination.
17. The first dose of PEG-IFN will be administered at the trial site at C1D1. Subsequent dosing will be performed once weekly (±1 day) by the subject (i.e., unsupervised at his/her home) at approximately the same time of day. Directions for the self-administration of SC injections of PEG-IFN can be found in the Pharmacy Manual.

18. PK samples should be collected during: C1D1: pre- and post-dose, at C1D8 (post-dose), C1D22 (pre-dose), C2D22 (pre-dose), C4D1 (pre-dose), C7D1 (pre-dose) and every 3 cycles thereafter and at 30 days after discontinuation of pembrolizumab treatment. Total IgG should be collected simultaneous with pre-dose pembrolizumab PK sampling. ADA (simultaneous with pre-dose PK sampling, except for the C2D22): C1D1 (pre-dose), C1D22 (pre-dose), C4D1 (pre-dose), C7D1 (pre-dose) and every 3 cycles thereafter and at 30 days after discontinuation of pembrolizumab treatment Pre-dose: within 60 minutes before infusion of pembrolizumab. Post-dose: within 30 minutes after the end of infusion of pembrolizumab C1D1 and at C1D8. A detailed PK/ADA scheme is described in Section 7.1.3.2.
19. A scan must be performed within 28 days prior to starting treatment with pembrolizumab. 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. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. The first imaging assessment should be performed 12 weeks (± 3 days) after the first dose of trial treatment, and continue to be performed every 6 weeks (42 ± 3 days) until week 30, regardless of any treatment delays. Following week 30, tumor imaging will be performed approximately every 12 weeks (84 ± 7 days) (or as clinically indicated) while the patient remains on trial therapy. Subjects who discontinue trial treatment for a reason other than disease progression should continue to be assessed in Follow-up Phase with the first scan occurring 12 weeks (84 +/- 7 days) from the date of the last scan on study. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. The Sponsor will collect radiological assessments for retrospective analysis by a central vendor unless otherwise noted by the Sponsor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.
20. Per the modified RECIST 1.1 used in this protocol, if imaging shows PD, the imaging assessment should be performed no sooner than 4 weeks later in order to confirm PD as described in Section 4.2.3.2.
21. For subject with MEL only: Qualitative digital photography should be performed at baseline and at time of scheduled tumor assessments for cutaneous lesions. Cutaneous lesions are not considered measurable for the purposes of this protocol, but may be considered to be non-target lesions for tumor assessments by investigators. Copies of digital photographs should not be submitted to the central imaging vendor unless otherwise noted by the Sponsor.
22. Collection of archival tumor tissue for purpose of biomarker analysis. Written subject consent is required for collection of archival tumor tissue. Tumor sample should be adequate for biomarker analyses assessment. Subjects with an inadequate archival sample may obtain a new biopsy and subjects with an inadequate newly obtained biopsy may undergo re-biopsy at the discretion of the investigator. Specific instructions for tissue collection and shipment are provided in the Laboratory Manual.
23. A newly obtained biopsy of a tumor lesion is desirable but not mandatory. Written subject consent is required for newly obtained biopsies. Newly obtained biopsies should be limited to readily accessible tumor lesions (e.g., skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using computed tomography (CT) guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis. Specific instructions for tissue collection and shipment are provided in the Laboratory Manual.
24. Blood samples should be obtained prior to Cycle 1, Cycle 3, and at discontinuation.
25. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.
26. If the subject signs the Future Biomedical Research consent, any leftover samples may be stored for future biomedical research.

6.1.1.2 Treatment Group B: pembrolizumab + IPI Combination Therapy (Part 1A, Part 1B and Part 1C)

pembrolizumab q3w + IPI Combination Therapy																							
Trial Period:	**Screening**	**Treatment**																		**End of Treatment**	**Post-treatment**		
Cycle [1]:		**1**						**2**		**3 and 4**		**5**		**6**		**7**		**8 and Beyond**			**Safety Follow-Up**	**Follow-Up Visits[2]**	**Survival Follow-Up[3]**
Day:	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**At Time of Discon**	**30 Days Post-Discon**	**Every 12 Weeks**	**Every 12 Weeks**
Scheduling Window Days [4]:	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7
Administrative Procedures																							
Informed Consent[5]	X																						
Informed Consent for Future Biomedical Research[6]	X																						
Inclusion/Exclusion Criteria	X																						
Demographics and Medical History	X																						
Prior and Concomitant[7] Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Treatment Randomization		X																					
Post-Treatment Discontinuation Anti-Cancer Therapy Status																						X	X
Survival Status		<- ->																					X

pembrolizumab q3w + IPI Combination Therapy																								
Trial Period:	**Screening**	**Treatment**																		**End of Treatment**	**Post-treatment**		
Cycle [1]:		**1**						**2**		**3 and 4**		**5**		**6**		**7**		**8 and Beyond**			**Safety Follow-Up**	**Follow-Up Visits[2]**	**Survival Follow-Up[3]**
Day:	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**At Time of Discon**	**30 Days Post-Discon**	**Every 12 Weeks**	**Every 12 Weeks**
Scheduling Window Days [4]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**
Clinical Procedures/Assessments																							
Full Physical Examination	X	X			X			X		X		X		X		X		X		X			
Directed Physical Examination			X	X		X	As clinically indicated																
ECOG Performance Status	X	X	X		X	X		X		X		X		X		X		X		X			
12-Lead Electrocardiogram (ECG)[8]	X	As clinically indicated																					
Vital Signs and Weight[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AE Monitoring[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments performed by LOCAL laboratory																							
CBC with Differential[11, 12,13]	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X			
Urinalysis [11, 12,13]	X	X	X	X	X	X	X	X		X		X		X		X		X		X			
Comprehensive Chemistry Panel[11, 12,13]	X	X	X	X	X	X	X	X		X		X		X		X		X		X			
LDH[11]	X																						
T3, FT4 and TSH[11, 12,13]	X							X		X		X		X		X		X		X			
PT/INR and aPTT[11]	X																						
Pregnancy Test-Urine or Serum β-hCG[14]	X																						

pembrolizumab q3w + IPI Combination Therapy																							
Trial Period:	**Screening**	**Treatment**																		**End of Treatment**	**Post-treatment**		
Cycle [1]:		**1**						**2**		**3 and 4**		**5**		**6**		**7**		**8 and Beyond**			**Safety Follow-Up**	**Follow-Up Visits [2]**	**Survival Follow-Up [3]**
Day:	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**At Time of Discon**	**30 Days Post-Discon**	**Every 12 Weeks**	**Every 12 Weeks**
Scheduling Window Days [4]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**
Drug Dispensation, Administration, and Associated Analyses																							
Pembrolizumab Administration[15]		X			X			X	X	X	X	X	X	X	X	X	X	X	X				
IPI Administration Part 1B[16]		X			X			X	X														
IPI Administration Part 1C, Arm 1[16]		X						X		X													
IPI Administration Part 1C, Arm 2[16]		X								X[17]		X				X							
PKs of Pembrolizumab[18a,b]	Please refer to section 7.1.3.2 (Table 14 and Table 15)																						
Total IgG[18a,b]																							
PKs of IPI[18a,b]																							
Anti-Pembrolizumab Antibodies[18a,b]																							
Efficacy Measurements																							
Tumor Imaging Part 1A and 1B[19,20]	X									X		X		X				X[20]				X[2]	
Tumor Imaging Part 1C[19,21]	X							X		X		X				X[21]		X[21]				X[2]	
Digital Photography: Cutaneous Lesions[22]	X	As Clinically Indicated																					

pembrolizumab q3w + IPI Combination Therapy																					
Trial Period:	**Screening**	**Treatment**																		**End of Treatment**	**Post-treatment**		
Cycle [1]:		**1**						**2**		**3 and 4**		**5**		**6**		**7**		**8 and Beyond**			**Safety Follow-Up**	**Follow-Up Visits [2]**	**Survival Follow-Up [3]**
Day:	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**At Time of Discon**	**30 Days Post-Discon**	**Every 12 Weeks**	**Every 12 Weeks**
Scheduling Window Days [4]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**
Tissue and Blood Collections and Pharmacodynamic Assessment																							
Tumor Tissue Collection[23]	X									X										X			
Correlative Blood Sample Collection, Part 1A and 1B[24]	X									X										X			
Correlative Blood Sample Collection, Part 1C[24]	X									X				X				X		X			
Blood Sample Collection for Genetics[25]		X																					
Blood for Future Biomedical Research[26]		X																					
Blood for Peripheral Blood Mononuclear Cells (PBMC), Part 1C[27]		X			X			X[27]												X			
Blood for Serum and Plasma Biomarker Analyses, Part 1C[27]		X			X			X[27]												X			
Blood for T-Cell Receptor (TCR) DNA, Part 1C[27]		X			X			X[27]												X			
Blood for Circulating Tumor (ctDNA), Part 1C[27]		X			X			X[27]												X			

1. Treatment cycles are 6 weeks. Imaging should always be performed as scheduled and follow calendar days, regardless of any treatment delays.
2. Subjects who discontinue trial treatment due to a reason other than disease progression should continue follow-up and assessment by radiologic imaging (and digital photography if applicable) every 12 weeks (± 1 week) for the first year after discontinuation, then every 6 months (± 2 weeks) for years two through five, and every 12 months (± 4 weeks) after year five. Imaging follow-up should continue until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
3. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone approximately every 12 weeks after the last contact date to assess for survival status. In certain situations, survival data may be requested more frequently than every 12 weeks as per Section 7.1.5.3.3. Updated survival status may be requested by the Sponsor at any time during the course of the study. 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 that have a death event previously recorded).
4. In general, the window for each visit is ± 3 days unless otherwise noted.
5. 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 the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
6. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained.
7. Prior medications – All concomitant medications received within 28 days prior to the screening visit and up to 30 days after the last dose of trial treatment should be recorded.
8. ECG should be performed at screening and as clinically indicated thereafter. ECGs are performed locally.
9. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
10. Record all AEs occurring within 30 days after the last dose of trial treatment and all SAEs (related and unrelated to trial treatment)/ECIs occurring up until 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
11. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
12. After Cycle 1, lab samples can be collected up to 72 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. After Cycle 8, lab samples should be collected every two cycles on D1 (i.e.; C8 D1, C10 D1, C12 D1, etc.)
13. Unresolved abnormal labs that are DRAEs should be followed until resolution.
14. For women of reproductive potential, a urine pregnancy test should 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.
15. Pembrolizumab will be administered as a 30 minute IV infusion. 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). Pembrolizumab should always be administered first when given in combination.
16. In Part 1A and B, IPI will be administered for a total of 4 doses. In Part 1C, IPI will be administered for a maximum of 4 doses. Subjects will be administered IPI as a 90 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 90 minutes as possible. For additional instructions regarding dosing please refer to the IPI label. Subjects who initially attain clinical benefit (defined as modified RECIST 1.1 confirmed PR or SD>6 mo), and experience disease progression while receiving single agent pembrolizumab will be eligible for reinduction with 4 doses of IPI q3w as long as Part 1A or 1B remains open. Those subjects should follow the assessments detailed in Cycle 2 and beyond.

17. IPI will be administered only on Cycle 3 and not on Cycle 4.
18. For PK samples, predose: within 60 minutes before infusion of pembrolizumab. Post-dose: within 30 minutes after the end of infusion of pembrolizumab. A detailed PK/ADA scheme is described in Section 7.1.3.2.
    a. Parts 1A and 1B: PK samples should be collected during C1D1 (pre- and post-dose), C1D8 (post-dose), C1D22 (pre-dose), C2D22 (pre-dose), C4D1 (pre-dose), C7D1 (pre-dose) and every 3 cycles thereafter and at 30 days after discontinuation of pembrolizumab treatment Total IgG should be collected simultaneous with pre-dose pembrolizumab PK sampling. ADA (simultaneous with pre-dose PK sampling, except for C2D22): C1D1 (pre-dose), C1D22 (pre-dose), C4D1 (pre-dose), C7D1 (pre-dose) and every 3 cycles thereafter and at 30 days after discontinuation of pembrolizumab treatment.
    b. Part 1C: PK samples will be collected during C1D1, C2D1, C3D1, C5D1, C7D1, C9D1, and every 2 cycles thereafter until treatment discontinuation. A PK sample at 30 days after discontinuation of pembrolizumab treatment is not required for Part 1C.
19. A scan must be performed within 28 days prior to starting treatment with pembrolizumab. 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. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. The Sponsor will collect radiological assessments for retrospective analysis by a central vendor unless otherwise noted by the Sponsor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual. Per the modified RECIST 1.1 used in this protocol, if imaging shows PD, the imaging assessment should be performed no sooner than 4 weeks later in order to confirm PD as described in Section 4.2.3.2.
20. In Part 1A and B, the first imaging assessment should be performed 12 weeks (± 3 days) after the first dose of trial treatment, and continue to be performed every 6 weeks (42 ± 3 days) until week 30, regardless of any treatment delays. Following week 30, tumor imaging will be performed approximately every 12 weeks (84 ± 7 days or as clinically indicated) while the subject remains on trial therapy.
21. In Part 1C, the first imaging assessment should be performed 6 weeks (± 3 days) after the first dose of trial treatment, and continue to be performed every 6 weeks (42 ± 3 days) until week 24, regardless of any treatment delays. Following week 24, tumor imaging will be performed approximately every 12 weeks (84 ± 7 days or as clinically indicated) while the subject remains on trial therapy. Subjects who discontinue trial treatment for a reason other than disease progression should continue to be assessed in Follow-up Phase with the first scan occurring 12 weeks (84 ± 7 days) from the date of the last scan on study. In Part 1C, a baseline brain MRI will be performed to rule out brain metastasis.
22. For subject with MEL only: Qualitative digital photography should be performed at baseline and at time of scheduled tumor assessments for cutaneous lesions. Cutaneous lesions are not considered measurable for the purposes of this protocol, but may be considered to be non-target lesions for tumor assessments by investigators. Copies of digital photographs should not be submitted to the central imaging vendor unless otherwise noted by the Sponsor.
23. A newly obtained biopsy sample of at least one tumor lesion is preferred in all subjects and is mandatory for subjects who do not have an acceptable archival tumor tissue sample for PD-L1 evaluation. PD-L1 status must be assessed during screening, and if the tumor biopsy submitted is inadequate for determination of PD-L1 status by IHC at a central pathology laboratory, the subject will not be randomized. Subjects with an inadequate archival sample may obtain a new biopsy and subjects with an inadequate newly obtained biopsy may undergo re-biopsy at the discretion of the investigator. Confirmation of the tumor tissue sample adequacy for determination of PD-L1 status by IHC at a central pathology laboratory will not be required prior to enrollment in Part 1C. Additional biopsy sample submission is encouraged but not mandatory for Part 1C when the sample is inadequate for PD-L1 testing. Additional biopsy sample approximately at C3D1 and at disease progression are highly desirable when it is feasible. Newly obtained biopsies should be limited to readily accessible tumor lesions (e.g., skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Written subject consent is required for collection of tumor tissue. Specific instructions for tissue collection and shipment are provided in the Laboratory Manual.

24. In Part 1A and 1B blood samples should be obtained prior to Cycle 1, Cycle 3, and at discontinuation. In Part 1C blood samples should be obtained prior to Cycle 1 Day 1, at Cycle 3 Day 1, at Cycle 4 Day 1 and then every 12 weeks (cycles 6 and beyond), and at Time of Discontinuation.
25. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.
26. If the subject signs the Future Biomedical Research consent, any leftover samples may be stored for future biomedical research.
27. In Part 1C, blood for PBMC, serum and plasma biomarker analyses, TCR DNA and circulating tumor DNA should be collected at Cycle 1 Day 1, Cycle 1 Day 22, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 6 Day 1 and at Time of Discontinuation.

6.2 Second Course Phase: All Parts - All Treatment Groups (MEL and RCC)

For subjects enrolled in pembrolizumab q3w + PEG-IFN or pembrolizumab q3w + IPI: Second Course Phase																				
Trial Period:	**SECOND COURSE PHASE: Treatment**																**End of Treatment**	**Post-treatment**		
Cycle[1]:	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8 and beyond**			**Safety Follow-Up**	**Follow-Up Visits[2]**	**Survival Follow-Up[3]**
Day:	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**At Time of Discon**	**30 Days post Discon**	**Every 12 Weeks**	**Every 12 Weeks**
Scheduling Window Days[4]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**
Administrative Procedures																				
Eligibility Criteria[5]	X		X		X		X		X		X		X		X					
Concomitant Medication Review[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Post-Treatment Discontinuation Anti-Cancer Therapy Status																			X	X
Survival Status	<--->																			X
Clinical Procedures/Assessments																				
Full Physical Examination	X		X		X		X		X		X		X		X		X			
Directed Physical Examination		X	As clinically indicated																	
ECOG Performance Status	X	X	X		X		X		X		X		X		X		X			
Vital Signs and Weight[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AE Monitoring[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

For subjects enrolled in pembrolizumab q3w + PEG-IFN or pembrolizumab q3w + IPI: Second Course Phase																				
Trial Period:	**SECOND COURSE PHASE: Treatment**																**End of Treatment**	**Post-treatment**		
Cycle [1]:	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8 and beyond**			**Safety Follow-Up**	**Follow-Up Visits [2]**	**Survival Follow-Up [3]**
Day:	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**1**	**22**	**At Time of Discon**	**30 Days post Discon**	**Every 12 Weeks**	**Every 12 Weeks**
Scheduling Window Days [4]:	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**
Laboratory Procedures/Assessments																				
CBC with Differential [9,10,11]	X		X		X		X		X		X		X		X[10]		X			
Urinalysis [9,10,11]	X		X		X		X		X		X		X		X[10]		X			
Comprehensive Chemistry Panel [9,10,11]	X		X		X		X		X		X		X		X[10]		X			
LDH [9]	X																			
T3, FT4 and TSH [9,10,11]	X		X		X		X		X		X		X		X[10]		X			
Pregnancy Test- Urine or Serum β-hCG [12]	X																			
Drug Dispensation, Administration, and Associated Analyses																				
Pembrolizumab Administration [13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
IPI Administration Part 1B [14]	X	X	X	X																
IPI Administration Part 1C, Arm 1 [14]	X		X		X		X													
IPI Administration Part 1C, Arm 2 [14]	X				X				X				X							
Efficacy Measurement																				
Tumor Imaging Part 1A and 1B [15,16,17]	X				X		X		X		X				X[16]				X	
Tumor Imaging Part 1C [15,17,18]	X		X		X		X		X				X[18]		X[18]				X	
Digital Photography: Cutaneous Lesions [19]	X	As clinically indicated																		

1. Treatment cycles are 6 weeks. Imaging should always be performed as scheduled and follow calendar days, regardless of any treatment delays. Subjects may receive Second Course Phase for a maximum of 17 doses of pembrolizumab and 4 doses of IPI. Subjects enrolled in Part 1A who received PEG-IFN who are eligible for Second Course Phase will only be allowed to receive pembrolizumab monotherapy.
2. Subjects who discontinue Second Course Phase due to reasons other than disease progression should continue follow-up and assessment by radiologic imaging (and digital photography if applicable) every 12 weeks (± 1 week) for the first year after discontinuation, then every 6 months (± 2 weeks) for year two through five, and every 12 months (± 4 weeks) after year five. Imaging follow-up should continue until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
3. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone approximately every 12 weeks after last contact to assess for survival status. In certain situations, survival data may be requested more frequently than every 12 weeks as per Section 7.1.5.3.3. Updated survival status may be requested by the Sponsor at any time during the course of the study. 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 that have a death event previously recorded).
4. In general, the window for each visit is ± 3 days unless otherwise noted.
5. Subjects who either a) stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to modified RECIST 1.1 (subjects treated with at least 24 weeks of pembrolizumab before discontinuing therapy and received at least two treatments with pembrolizumab beyond the date when the initial CR was declared or b) had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability may restart treatment if they meet the criteria specified in Section 7.1.5.2.1.
6. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit.
7. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
8. Record all AEs occurring within 30 days after the last dose of trial treatment and all SAEs (related and unrelated to trial treatment) / ECIs occurring up until 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
9. Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose. See Section 7.1.3 for details regarding laboratory tests.
10. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. After Cycle 8, lab procedures should be collected every two cycles on D1 (i.e.; C8 D1, C10 D1, C12 D1, etc.). Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests.
11. Unresolved abnormal labs that are DRAEs should be followed until resolution.
12. For women of reproductive potential, a urine pregnancy test should 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.
13. Pembrolizumab will be administered as a 30 minute IV infusion. 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). Pembrolizumab should always be administered first when given in combination.
14. IPI will be administered for a total of 4 doses for subjects that were previously included in Part 1B and for up to 4 doses for subjects that were previously included in Part 1C. Subjects will be administered IPI as a 90 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 90 minutes as possible. For additional instructions regarding dosing please refer to the IPI label. Subjects who initially attain clinical benefit (defined as modified RECIST 1.1 confirmed PR or SD>6 mo), and experience disease progression while receiving single agent pembrolizumab will be eligible for reinduction with up to 4 doses of IPI q3w as long as Part 1A or 1B remain open. Those subjects should follow the assessments detailed in Cycle 2 and beyond.

15. A scan must be performed within 28 days prior to starting treatment with pembrolizumab. 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. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies.
16. For subjects that were previously included in Part 1A and Part 1B, the first imaging assessment should be performed 12 weeks (± 3 days) after the first dose of trial treatment, and continue to be performed every 6 weeks (42 ± 3 days) until week 30, regardless of any treatment delays. Following week 30, tumor imaging will be performed approximately every 12 weeks (84 ± 7 days) (or as clinically indicated) while the subject remains on trial therapy. For subjects that were previously included in Part 1A and 1B, a baseline brain MRI will be performed to rule out brain metastasis.
17. Subjects who discontinue trial treatment for a reason other than disease progression should continue to be assessed in Follow-up Phase with the first scan occurring 12 weeks (84 + 7 days) from the date of the last scan on study. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. The Sponsor will collect radiological assessments for retrospective analysis by a central vendor unless otherwise noted by the Sponsor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual. Per the modified RECIST 1.1 used in this protocol, if imaging shows PD, the imaging assessment should be performed no sooner than 4 weeks later in order to confirm PD as described in Section 4.2.3.2.
18. For subjects that were previously included in Part 1C, the first imaging assessment should be performed 6 weeks (± 3 days) after the first dose of trial treatment, and continue to be performed every 6 weeks (42 ± 3 days) until week 24, regardless of any treatment delays. Following week 24, tumor imaging will be performed approximately every 12 weeks (84 ± 7 days or as clinically indicated) while the subject remains on trial therapy. For subjects that were previously included in Part 1C, a baseline brain MRI will be performed to rule out brain metastasis.
19. For subject with MEL only: Qualitative digital photography should be performed at baseline and at time of scheduled tumor assessments for cutaneous lesions. Cutaneous lesions are not considered measurable for the purposes of this protocol, but may be considered to be non-target lesions for tumor assessments by investigators. Copies of digital photographs should not be submitted to the central imaging vendor unless otherwise noted by the Sponsor.

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 or qualified designee 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 immediately 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. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the disease for which the subject has enrolled in this trial will be recorded separately and not listed as medical history.

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 for the disease for which the subject has enrolled in this trial 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 Safety Follow-up visit. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up visit should be recorded.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5.3 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.4 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.5 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-cancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into SFU.

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.

Drug administration should start within 7 days from assignment of a randomization number.

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab doses for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of first dose of PEG-IFN will be witnessed by the investigator and/or trial staff on Day 1. Drug accountability will be collected during the study. Compliance with PEG-IFN administration will be measured by subjects: 1) receiving unscheduled study agent injections; 2) missing an injection. Numbers and percentages of subjects and injection visits with any deviation in these measures will be reported.

The instructions for preparing and administering trial treatments will be provided in the Study Manuals.

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 (Section 6) and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the trial 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.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1 and the separate guidance document in the administrative binder regarding the identification, evaluation, and management of AEs of a potential immunological etiology.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

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 exams are described in Section 6. 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 require a full physical exam as defined in Section 6, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the trial treatment. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. 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 (Section 6). Height will be measured at Screening.

7.1.2.4 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures at Screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points for standard 12-lead ECGs must be performed as per Section 6 – Trial Flow Charts. Clinically significant abnormal findings seen on the follow-up ECGs should be recorded as adverse events.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 12.4) at screening, additional time points for assessment of ECOG must be performed as per Section 6 – Trial Flow Charts.

7.1.2.6 Tumor Tissue Collection

Tumor tissue for biomarker analysis from formalin fixed paraffin embedded tumor tissue sample or newly obtained formalin fixed biopsy of a tumor lesion not previously irradiated must be provided in the form of a tissue block or at least ten unstained slides and received by the central vendor and tested for PD-L1 status by IHC before randomization. Subjects will be enrolled in the trial regardless of the expression. Subjects who do not submit a sample adequate for PD-L1 determination will not be enrolled. Subjects with an archival sample considered not adequate may obtain a new biopsy. Subjects with a newly obtained biopsy considered not adequate may undergo re-biopsy at the discretion of the investigator. Note for Part 1C: adequacy of the tumor sample for determination of PD-L1 status by IHC at a central pathology laboratory prior to enrollment is not required. Additional biopsy sample submission is encouraged but not mandatory for Part 1C when the sample is inadequate for PD-L1 testing.

Note: A fine needle aspirate or cytologic specimen will not be acceptable. Core needle or excisional biopsies, or resected tissue is required. Newly obtained formalin fixed specimens are encouraged.

If new scientific data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of subjects, then only new biopsies will be acceptable for determination of PD-L1 status.

If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue biopsies that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the subject has signed the FBR consent.

Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

7.1.2.7 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM). Tumor imaging is strongly preferred to be acquired by computed tomography (CT). Magnetic resonance imaging (MRI) should be used only when CT is contraindicated or for imaging of the brain. The same imaging technique regarding modality and the use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden.

At least 1 year after the last subject has enrolled in Parts 1A, 1B and 1C, the Sponsor may elect to halt central vendor imaging collection and continue with investigator assessment only. If this switch will occur, the decision will be announced through an administrative memo from the Sponsor.

7.1.2.8 Assessment of Disease

The primary measure for assessment of tumor response will be based on independent central review using RECIST 1.1 [1]. RECIST 1.1 will be used by independent central review as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of trial therapy). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Modified RECIST 1.1 will be applied by the site as the basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy).

RECIST 1.1 will be adapted as follows to account for the unique tumor response seen in this class of therapeutics.

If RECIST 1.1 defined progression has been assessed then the subject will be discontinued from trial treatment unless, in the opinion of the investigator, the subject is deriving clinical benefit from the therapy and the subject does not have any signs or symptoms of clinical instability as discussed in Table 11 Imaging and Treatment after 1st Radiologic Evidence of PD in Section 5.2.3.

Clinically stable is defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating clinically significant 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

Note: Treatment may be continued despite modified RECIST 1.1 defined progression if the subject is clinically stable and is considered to be deriving clinical benefit by the investigator. In these cases, subjects should continue to undergo imaging as outlined in the footnote in Table 11.

7.1.2.9 Ophthalmologic Examination

All subjects receiving pembrolizumab + PEG-IFN should have a baseline ophthalmologic exam including visual acuity, visual field and color discrimination by an ophthalmologist. Fundus photography should be performed in subjects with history of clinically significant retinal disease (defined as macular degeneration, retinal detachment and moderate/severe non-proliferative diabetic retinopathy and any proliferative diabetic retinopathy). Enrollment of subjects with clinically significant retinal disease will require consultation with the sponsor on risk-benefit associated to treatment. Any subject randomized in the pembrolizumab + PEG-IFN treatment group complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete ophthalmologic examination. In addition, because these ocular events may occur in conjunction with other disease states, periodic visual examinations during the trial are recommended in subjects with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PEG-IFN should be considered in subjects who develop new or worsening ophthalmological disorders.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Trial Laboratory Manual. Refer to the Trial Flow Chart (Section 6) for the timing of laboratory assessments.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 12.

Table 12 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT/INR
Platelet count	Alanine aminotransferase	Protein	aPTT
WBC (total and differential)[d]	Amylase	Specific gravity	Total T3 or free T3, FT4, and TSH[b]
RBC	Aspartate aminotransferase	Microscopic exam, if abnormal results are noted	Anti-HCV[e]
Absolute lymphocyte count[d]	Bicarbonate[c]		HCV viral load[e]
Absolute neutrophil count[d]	Calcium		HCV genotype[e]
	Chloride		anti-HBs[e]
	Creatinine		HBsAg[e]
	Glucose		Anti-HBc (total and IgM)[e]
	LDH[e]		HBeAg[e]
	Lipase		anti-HBe[e]
	Magnesium		HBV viral load[e]
	Phosphorus		
	Potassium		AFP[e]
	Sodium		CRP[e]
	Total bilirubin		GGT[e]
	Direct bilirubin		
	Total protein		
	Blood urea nitrogen		

[a] Perform on women of childbearing potential only 72 hours prior to Day 1 of Cycle 1. Pregnancy tests must be repeated prior to every cycle if required or as specified per local regulatory guidance.
[b] T3 is preferred; if not available, free T3 may be tested.
[c] If this test is not done as part of local standard of care, this test does not need to be performed.
[d] Report % or absolute results per standard of practice. Report the results in the same manner throughout the trial.
[e] These tests should be performed at screening, and then as clinically indicated, except for AFP and GGT, which should only be performed as clinically indicated. For the purpose of determining eligibility, perform HBsAg and HCV viral load. Anti-HCV is allowed for screening purposes in countries where HCV viral load is not part of standard of care. All other hepatitis tests should be performed per standard of care.
Note: If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Laboratory Manual.

AFP=alpha-fetoprotein; aPTT=activated partial thrombin time; CRP=C-reactive protein; FT4=free thyroxine; GGT=gamma-glutamyl transferase; HBc=hepatitis B core; HBeAg=hepatitis B e antigen; HBe=hemoglobin E; HBs=hepatitis B surface; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; IgM=gamma M immunoglobulin; INR=insulin receptor; LDH=lactate dehydrogenase; PT=prothrombin time; RBC=red blood cells; T3=triothyronine; TSH=thyroid stimulating hormone (thyrotropin); WBC=white blood cells.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of trial treatment. An exception is hepatitis and thyroid serologies, which may be performed within 28 days prior to first dose. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. After Cycle

8, lab procedures should be collected every two cycles on D1 (i.e., C8 D1, C10 D1, C12 D1, etc.).

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of trial treatment. Unresolved abnormal laboratory values that are DRAEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within the normal range.

7.1.3.1.1 Serum/Urine β-hCG

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal will be tested for pregnancy within 72 hours of receiving the first dose of study medication, and must be excluded in the event of a positive or borderline-positive test result. If a urine test is positive or not evaluable, a serum test will be required.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

Blood samples for PK, ADA and total IgG analyses will be collected at the time points described in Table 13 and below. The actual date and time of each blood sample collection will be recorded in the eCRF. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Table 13 Pharmacokinetic, Total IgG, and ADA Assessments

	Treatment												
pembrolizumab Dose Number	**1**	**2**	**3**	**4**	**5**	**7**	**9**	**13**	**17**	**19**	**21 and every 4th dose thereafter**	**25, 31, 37, 43, 49**	**30 day post-pembrolizumab treatment**
Cohort A													
Pembrolizumab	X	X		X		X		X		X		X	X
Cohort B q3w													
Pembrolizumab	X	X		X		X		X		X		X	X
IPI	X			X	X								
Cohort B q6w and q12w													
Pembrolizumab	X		X		X		X	X	X	X	X		
IPI q6w	X		X		X	X	X						
IPI q12w	X				X		X	X	X				
All pembrolizumab Antibody Test	X	X				X		X		X		X	X
Total IgG Assessment													
At all pre-dose pembrolizumab PK	X	X		X		X		X		X		X	

Table 14 Timing of PK and ADA Assessments, Parts 1A and 1B

Drug	Study Part	Pembrolizumab Dose Number	Time of PK and ADA Blood Sample Collection
IPI (PK and ADA)	Treatment Phase	Dose 1 and 4	Predose IPI: within 60 min before the infusion of IPI Postdose IPI: within 30 min after end of infusions of IPI (only PK)
		Dose 5 (q3w)	Predose pembrolizumab: within 60 min before the infusion of pembrolizumab
pembrolizumab (total IgG[a], PK and ADA)	Treatment Phase	Dose 1	Predose pembrolizumab: within 60 min before the start of the infusion and prior to a potential IPI or PEG-IFN dosing on the same day[d] Only for pembrolizumab (**not for total IgG and ADA**): Postdose pembrolizumab: within 30 min after the end of the infusion Only for pembrolizumab (**not for total IgG and ADA**): Postdose pembrolizumab: at Day 8 (and prior to a potential IPI or PEG-IFN dosing on that same day)
		Dose 2, 4, 7, 13, etc.[b]	Predose pembrolizumab: within 60 min before the start of the infusion[d] For ADA: Predose pembrolizumab within 60 min before start of the infusion EXCEPT for the 4th dose of pembrolizumab
		30 day post pembrolizumab treatment[c]	Obtain a PK blood sample at 30 days (±7 days) after the last dose of pembrolizumab and at the same time that the blood sample is obtained for anti-pembrolizumab antibody testing

a. Total IgG should be collected simultaneous with every pre-dose pembrolizumab PK sampling.
b. After Dose #7 of pembrolizumab, obtain PK and total IgG blood samples before dosing of every 6th dose for the duration of the study (i.e., pembrolizumab dose 13, 19, 25, 31, 37, 43, and 49).
c. Post-treatment samples may not be collected if the subject has started treatment with a new anti-cancer therapy.
d. Predose pembrolizumab samples should be obtained at the same time that blood samples are drawn for total IgG and anti-pembrolizumab antibody testing (ADA).

Table 15 Timing of PK and ADA Assessments, Part 1C

Drug	Study Part	Pembrolizumab Dose Number	Time of PK and ADA Blood Sample Collection
IPI[a] (PK and ADA)	Treatment Phase	Arm 1 (50 mg q6w): dose 1, 3, 5, 7, 9	Predose IPI: within 60 min before the infusion of IPI Postdose IPI: within 30 min after end of infusions of IPI (only PK)
		Arm 2 (100 mg q12w): dose 1, 5, 9, 13, 17	
Pembrolizumab[a] (total IgG[b], PK, and ADA)	Treatment Phase	Dose 1, 3, 5, 9, then every 4th dose thereafter	Predose pembrolizumab: within 60 min before the start of the infusion[c]

NOTE: Only three samples will be collected at visits which require IPI and pembrolizumab PK. The predose sample will be the baseline for both pembrolizumab and IPI PK assessments.
NOTE: All PK and ADA samples should be taken at the same time.
a At time points with both pembrolizumab and IPI samples, predose IPI and predose pembrolizumab samples can be obtained from the same extraction.
b Total IgG should be collected simultaneous with every pre-dose pembrolizumab PK sampling.
c Predose pembrolizumab samples should be obtained at the same time that blood samples are drawn for total IgG and anti-pembrolizumab antibody testing (ADA).

7.1.3.2.1 Blood Collection for Serum MK-3475

Sample collection, storage and shipment instructions for serum samples will be provided in the Laboratory Manual.

7.1.3.2.2 Blood Collection for Anti-MK-3475 Antibodies (ADA)

Sample collection, storage and shipment instructions for serum samples will be provided in the Laboratory Manual.

Every effort should be taken to collect samples at 30 days after end of pembrolizumab treatment for ADA.

Simultaneous PK sampling is required for interpretation of ADA analysis.

7.1.3.2.3 Blood Collection for total IgG

Endogenous IgG levels were found in internal unpublished studies to be a factor significantly affecting the exposure of pembrolizumab. Additional information about individual IgG levels is required to confirm this effect, in particular when patients do receive immune modulatory co-medications such as PEG-IFN and IPI.

Total IgG should be collected simultaneous with every pre-dose pembrolizumab PK sampling.

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 correlative blood samples
- Leftover blood for genetics sample
- Leftover archival tumor tissue or leftover newly obtained biopsy samples taken throughout the study

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 final 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. In Part 1A and 1B and upon Sponsor consultation, subjects who

either a) stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to modified RECIST 1.1 (subjects treated with at least 24 weeks of pembrolizumab before discontinuing therapy and received at least two treatments with pembrolizumab beyond the date when the initial CR was declared) or b) had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability may restart trial Second Course Phase if they meet the criteria specified in Section 7.1.5.2.1. Additionally in Part 1C and upon Sponsor consultation, subjects who a) attain an investigator-determined CR or b) a VGPR and complete treatment with at least one dose of IPI on either Arm of treatment may discontinue treatment with IPI with the option of restarting the Second Course Phase if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2) and SFU (described in Section 7.1.5.3.3).

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

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or

reproducible. Documentation of equipment calibration must be retained with the study documentation as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for study objectives See Protocol-specific Administrative Binder and Site Imaging Manual.

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

Within 28 days prior to treatment randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in the Trial Flow Chart (Section 6). Screening procedures may be repeated.

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 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, performed by the local study site laboratory, will be required.
- Tumor imaging must be performed within 28 days prior to the first dose of trial treatment.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a 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 the Trial Flow Chart (Section 6). Specific procedure-related details are provided in Section 7.1.

After a screening phase of up to 28 days, eligible subject will receive assigned treatment on Day 1 of each dosing cycle and thereafter following a weekly (PEG-IFN) or every 3, 6 or

12 weeks (IPI) schedule, depending on the part and the treatment group in which the subject is enrolled. Pembrolizumab will be given q3w. A cycle is 6 weeks. Additional information regarding the DLT assessment period can be found in Section 5.2.1.2.1.

Treatment with pembrolizumab + PEG-IFN doublet will continue until up to two years of therapy have been administered, documented disease progression, unacceptable AEs, 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.

In Parts 1A and 1B, treatment with pembrolizumab + IPI doublet will continue for 2 cycles (12 weeks), followed by treatment with pembrolizumab single agent until up to 24 months of therapy have been administered, documented disease progression, unacceptable AEs, 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.

In Part 1C, treatment with pembrolizumab + IPI doublet will continue for a maximum of 4 cycles (24 weeks) or 8 cycles (48 weeks), for Arm 1 and Arm 2, respectively, followed by treatment with pembrolizumab single agent until up to 24 months of therapy have been administered, documented disease progression, unacceptable AEs, 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.

7.1.5.2.1 Second Course Phase

Upon Sponsor consultation, subjects who stop pembrolizumab with SD or better per modified RECIST 1.1 may be eligible for retreatment with pembrolizumab + IPI at a dose of pembrolizumab of 200 mg q3w or pembrolizumab 200 mg q3w monotherapy if they progress after stopping pembrolizumab, at the discretion of the investigator, as long as the Part to which the subject was initially enrolled remains open. This retreatment is termed the Second Course Phase of this trial. Subjects enrolled in Part 1A who received PEG-IFN and who are eligible for the Second Course Phase will only be allowed to receive pembrolizumab monotherapy. The Second Course Phase will be administered for a maximum of 17 doses of pembrolizumab and 4 doses of IPI. The Second Course Phase of this trial is only available if the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to modified RECIST 1.1.
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy.
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

OR

- Subject had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability.

- **AND**
  - Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab.
  - Did not receive any anti-cancer treatment since the last dose of pembrolizumab.
  - Have a performance status of 0 or 1 on the ECOG Performance Scale.
  - Demonstrate adequate organ function as detailed in Section 5.1.2.
  - Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
  - Female subjects of childbearing potential should be willing to adhere to the contraception requirements outlined in Section 5.7.2 for the course of the study through 120 days after the last dose of study medication. Subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
  - Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
  - Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects in the Second Course Phase will restart retreatment with pembrolizumab + IPI at a dose of pembrolizumab of 200 mg q3w or pembrolizumab 200 mg q3w monotherapy. Subjects will not be allowed to restart the Second Course with pembrolizumab + PEG-IFN. The Second Course Phase will be administered for a maximum of 17 doses of pembrolizumab and 4 doses of IPI.

Visit requirements are outlined in Section 6.2 – Trial Flow Chart for Second Course of Treatment. Treatment beyond confirmed PD is not permitted for Second Course Phase.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-up Visit

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 anticancer treatment, whichever comes first.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy should also be followed and recorded.

Subjects who are eligible for retreatment with pembrolizumab may have up to 2 safety follow-up visits, 1 after the Initial Treatment Period and 1 after the Second Course Treatment.

7.1.5.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (± 1 week) for the first year after discontinuation, then every 6 months (± 2 weeks) for years two through five, and every 12 months (± 4 weeks) after year five to monitor disease status. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of trial [or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.2.1]. Information regarding post-trial anticancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.2 will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in the Trial Flow Chart (Section 6) for retreatment with pembrolizumab.

7.1.5.3.3 Survival Follow-up (SFU)

Subjects who experience confirmed disease progression or start a new anticancer therapy, will move into the SFU Phase and should be contacted by telephone approximately every 12 weeks from the last contact date to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.1.5.4 Survival Status

To ensure current and complete survival data are 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 external Data Monitoring Committee 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 that have a previously recorded death event in the collection tool).

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

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

For purposes of this trial, an overdose is any dose higher than 20% over the prescribed dose for pembrolizumab or IPI, or any dose exceeding the prespecified dose of pembrolizumab by

≥1000 mg (5 times the dose) for pembrolizumab 200 mg fixed dosing, or any dose exceeding the prescribed dose for PEG-IFN by 50%. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, PEG-IFN 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 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).

7.2.2 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 trial 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 16 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 trial treatment, or 30 days following cessation of trial 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 trial 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. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the SPONSOR within 24 hours of the event:
   a. Grade ≥ 3 diarrhea
   b. Grade ≥ 2 colitis
   c. Grade ≥ 2 pneumonitis
   d. Grade ≥ 3 hypo- or hyperthyroidism
   e. Grade ≥ 2 Depression

A separate guidance document has been provided entitled "Pembrolizumab Events of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document

can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the SPONSOR within 24 hours of the event.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiological causes. If lab results or symptoms indicated a possible immune-related ECI then additional testing should be performed to rule out other etiologic causes. If no other cause was found, then it is assumed to be immune-related.

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.

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

7.2.4 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 16 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 mid 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 or 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.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the trial. If, after the trial 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 trial. Post hoc exploratory analyses will be clearly identified in the CSR. No separate SAP will be issued for this trial.

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 Part 1

The primary purpose of Part 1A of this trial is to investigate the safety and tolerability of MK-3475 in combination with PEG-IFN or IPI in adult subjects with MEL or RCC. The primary purpose of Part 1B of this trial is to further characterize the safety, tolerability and preliminary efficacy of the MK-3475 in combination with IPI in MEL subjects. Descriptive tables that summarize the number and percentage of subjects that experience adverse events as categorized in the NCI CTCAE Version 4 will be generated by dose level for the all subjects as treated population.

At the end of the Part 1A of the trial, the dose-response relationship, as the percentage of subjects experiencing at least one DLT in Cycle 1, for each dose level in the MK-3475+PEG-IFN combination will be estimated using a Bayesian pooling of adjacent violators analysis as outlined by Ji et al [84] using all DLT data from the trial with a conservative adjustment as described in Section 5.2.1.2. For the MK-3475+IPI combination, the percentage of subjects experiencing at least one DLT in Cycle 1 will be summarized for both Part 1A and 1B. The dose-response profile, along with other tolerability data, will be used to determine the recommended Phase 2 dose (RP2D) for MK-3475+PEG-IFN.

The Part 1A sample size of the trial depends primarily on clinical considerations rather than on statistical considerations. Specifically, the final number of subjects enrolled in the trial will depend on empirical safety (DLT) observations. However, it is estimated that a maximum of 25 subjects evaluable for safety and tolerability will be enrolled in Part 1A for the MK-3475+PEG-IFN combination, and a maximum of 18 subjects will be enrolled in Part 1A for the MK-3475+IPI combination.

The Part 1B sample size is driven by the expected number of PD-L1 negative subjects. Assuming that the prevalence of PD-L1 negative subjects is ~25%, then 90 subjects would be

expected to provide ~22 subjects with PD-L1 negative MEL. If less than 22 PD-L1 negative MEL were enrolled in the MK-3475+IPI arm in Part 1A and 1B combined, enrollment will continue until at least 22 PD-L1 negative subjects are enrolled, up to a maximum of 150 subjects in Part 1B. Historical data has shown a response rate of 15% for PD-L1 negative MEL subjects treated with MK-3475 monotherapy. With 22 subjects with PD-L1 negative MEL, the study provides 80% power to rule out a lower bound on the ORR of 15% if the true ORR for MK-3475+IPI in PD-L1 negative subjects is 40%. If no less than 7 responses are observed, 22 PD-L1 negative subjects will allow excluding a 15% ORR lower bound of the 95% CI.

The Part 1C sample size provides adequate precision for the estimation of the ORR and the rate of grade 3-5 DRAEs for the regimens being assessed, with guidelines provided to assess whether the therapies maintain the ORR seen with pembrolizumab and standard dose ipilimumab, while substantially reducing the rate of grade 3-5 DRAEs.

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

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

This trial is open-label; the subject, the trial site personnel, and the Sponsor are not blinded to individual treatment group assignment for Part 1 of the study. The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Subjects in Part 1A and 1C will be randomly assigned to treatment combination (pembrolizumab + PEG-IFN or pembrolizumab + IPI) if both combinations are open for enrollment.

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the trial are stated in Section 3.

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.2.3.1 Safety Endpoints

Safety measurements of interest are described in Section 4.2.3.1.

Part 1A: The primary Part 1A safety endpoint is the DLT rate.

Part 1B and 1C: For Part 1B and Part 1C, all ECIs listed in the irAE guidance as well as Grade ≥ 2 Depression are prespecified as events of interest (Tier-1 events).

8.2.3.2 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint will be the **ORR** defined as the proportion of the subjects in the analysis population who have best response as CR or partial response (PR). Responses are based on central independent review using RECIST 1.1.

Ordinal response score, per RECIST 1.1, defined as the best overall response calculated as the following:

1=Complete Response

2=Very Good Partial Response [>60% tumor reduction]

3=Moderate Partial Response [>30% - ≤60% tumor reduction]

4=Stable Disease

5=Progressive Disease

Ordinal response scores are based on central independent review using RECIST 1.1.

Additional secondary efficacy endpoints include PFS, defined as the time from randomization to the first documented disease progression (based on central independent review using RECIST 1.1) or death due to any cause, whichever occurs first, duration of response among subjects who achieve a best response as CR or PR per RECIST 1.1 and OS. Pharmacokinetic endpoints include area under the curve (AUC), Cmax, and clearance.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

ORR, DOR, PFS, and OS analyses will be restricted to those patients with measurable disease at baseline based on central independent review.

8.2.4.2 Safety Analysis Populations

For Part 1A safety analyses related to DLT rate, the DLT evaluable population will be used. The DLT evaluable population consists of all DLT evaluable subjects. In order to be considered evaluable, the subject must complete the first cycle of combination therapy or discontinue from the trial due to a DRAE. Subjects who discontinue prematurely due to a non drug-related cause are not included in the DLT evaluable population (refer to Section 5.2.1.2.2 for detailed DLT replacement criteria).

For all other Part 1 safety analyses, the APaT population will be used for the analysis of safety data. The APaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most subjects, this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in

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

Details on the approach to handling missing data for safety analyses are provided in Section 8.2.5 Statistical Methods.

8.2.5 Statistical Methods

8.2.5.1 Statistical Methods for Efficacy Analyses

8.2.5.1.1 Progression-free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve for each treatment group in the Part 1B and 1C of the trial.

8.2.5.1.2 Overall Survival (OS)

The Kaplan-Meier method will be used to estimate the OS curve in each treatment group.

8.2.5.1.3 Objective Response Rate (ORR)

Exact 90% confidence intervals for ORR will be calculated for the true ORR for the treatments investigated in Part 1C.

8.2.5.1.4 Ordinal Response Score

The frequency distribution of the ordinal response score will be estimated by calculating number of patients in each category divided by the total number of patients in the FAS population. Subjects with missing data will be considered non-responders.

8.2.5.1.5 Duration of Response (DOR)

If sample size permits, duration of response will be summarized descriptively using Kaplan-Meier curves medians and quartiles. Only the subset of subjects who show a CR or PR will be included in this analysis.

8.2.5.1.6 Pharmacokinetic Parameters

Pharmacokinetic parameters will be summarized using descriptive statistics.

Table 17 summarizes the analysis strategy for primary and secondary efficacy endpoints.

Table 17 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis:				
ORR (Part 1C)	P	Exact 90% confidence intervals for true ORR	FAS	Subjects with missing data are considered as non-responders
Secondary Objectives:				
DOR	P	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
ORR (Part 1B)	P	Exact test of binomial parameter	FAS	Subjects with missing data are considered as non-responders
PFS	P	Estimation: Kaplan-Meier method for PFS curve estimation in each treatment group	ITT	Censored at last disease assessment
OS	P	Summary statistics using Kaplan-Meier method	ITT	Censored at last date known alive
PK	P	Descriptive Statistics	All treated subjects	Missing data excluded from analysis
Ordinal Response Score (Part 1B and 1C)	P	Descriptive Statistics	FAS	Subjects with missing data are considered as non-responders

8.2.5.2 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.

Part 1A

DLTs will be listed. Adverse experiences will be summarized as counts and frequencies for each dose level. Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

ECIs of a potential immunologic etiology 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 pembrolizumab and IPI, their 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.

Part 1B and Part 1C

All ECIs listed in irAE guidance and Tier 2 or 3 safety parameters listed in Table 18 will be described via inferential and descriptive statistics.

Table 18 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	All ECIs in irAE guidance	X	X	X
	Grade ≥ 2 depression	X	X	X
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 ≥4/1% of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4/1% of subjects in all of the treatment groups)			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 1 or not already pre-specified as Tier-2 endpoints.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

For all subjects enrolled at the RP2D for pembrolizumab + PEG-IFN and Phase 2 Dose for pembrolizumab + IPI in Part 1B, the incidence of Grade 3-5 adverse experiences will be compared between pembrolizumab + IPI and pembrolizumab + PEG-IFN using the Miettinen and Nurminen method [85].

8.2.5.3 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.

For Part 1A RCC subjects, individual efficacy listing and/or descriptive statistics (as data permits) will be summarized to evaluate the efficacy for pembrolizumab + IPI and pembrolizumab + PEG-IFN using the same efficacy endpoints as described in Section 8.2.5.1.

8.2.6 Multiplicity

No adjustment will be made for multiplicity in Part 1.

8.2.7 Sample Size and Power Calculations

8.2.7.1 Part 1

The Part 1A sample size of the trial depends primarily on clinical considerations rather than on statistical considerations. Specifically, the final number of subjects enrolled in the trial will depend on empirical safety (DLT) observations. However, it is estimated that a maximum of 25 subjects evaluable for safety and tolerability will be enrolled in Part 1A for the pembrolizumab + PEG-IFN combination, and a maximum of 18 subjects will be enrolled in Part 1A for the pembrolizumab + IPI combination.

The Part 1B sample size is driven by the expected number of PD-L1 negative subjects. Assuming that the prevalence of PD-L1 negative subjects is ~25%, then 90 subjects would be expected to provide ~22 subjects with PD-L1 negative MEL. If less than 22 PD-L1 negative MEL were enrolled in the pembrolizumab + IPI arm in Part 1A and 1B combined, enrollment will continue until at least 22 PD-L1 negative subjects are enrolled, up to a maximum of 150 subjects in Part 1B. Historical data has shown a response rate of 15% for PD-L1 negative MEL subjects treated with pembrolizumab monotherapy. With 22 subjects with PD-L1 negative MEL, the study provides 80% power to rule out a lower bound on the ORR of 15% if the true ORR for pembrolizumab + IPI in PD-L1 negative subjects is 40%. With 7 or more responses out of 22 PD-L1 negative patients, a 95% CI would exclude a 15% or lower ORR.

The Part 1C sample size is designed to provide adequate precision for the estimation of the true rate of Grade 3-5 DRAEs and the ORR for the treatments evaluated. The sample size for part 1C will be 100 patients (50 patients per treatment arm).

With 50 patients per treatment arm, a 95% upper bound for the true rate of Grade 3-5 DRAE would be:

Observed number of patients experiencing Grade 3-5 DRAEs	95% upper bound for true rate of Grade 3-5 DRAEs
10 (20%)	32%
12 (24%)	36%
13 (26%)	38%

With 50 patients per treatment group, an observed rate of Grade 3-5 DRAEs of 26% or less would suggest a meaningful reduction in the rate of DRAEs compared to other combinations of IPI and anti-PD-1 inhibitors (pembrolizumab or nivolumab), as the 90% upper bound for the true rate of Grade 3-5 DRAEs excludes 40%.

With 50 patients per treatment, a 95% upper bound for the true ORR would be:

Observed number of patients experiencing an objective response	95% lower bound for true ORR	95% upper bound for true ORR
20 (40%)	28%	53%
22 (44%)	32%	57%
24 (48%)	36%	60%

With 50 patients per treatment group, an observed ORR of 48% or more would suggest that the combination ORR was consistent with that of other combinations of IPI and anti-PD-1 inhibitors (pembrolizumab or nivolumab) (as the 90% CI excludes 35%).

8.2.8 Interim Analyses

Part 1A and 1B will be considered complete when all enrolled subjects are a minimum of 24 weeks post initial trial treatment administration. At this point a database lock may occur to allow analysis of the data. Part 1C will be considered complete for publication purposes when all enrolled subjects are a minimum of 72 weeks post initial treatment administration. At this point database lock may occur to allow analysis of the data. If the study remains open, additional analyses of the data can occur to monitor the study and report on later subject follow-up.

8.2.9 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the trial. Percent compliance with drug administration will be calculated for each subject for pembrolizumab, IPI, and IFN separately.

Percent compliance will be calculated as following:

$$\text{Percent Compliance} = \frac{\text{Number of Doses Taken}}{\text{Number of Doses Should be Taken}} \text{ X } 100$$

For IFN administered once a week, "Number of Doses that Should be Taken" will be calculated as 1 plus the number (integer) of 1-week intervals that fit between the date of the first dose and the date of the last dose. For pembrolizumab and IPI administered q3w "Number of Doses Should be Taken" will be calculated as 1 plus the number (integer) of 3-week intervals that fit between the date of the first dose and the date of the last dose. For IPI administered q6w and q12w "Number of Doses Should be Taken" will be calculated as 1 plus the number (integer) of 6-week or 12-week intervals, respectively, that fit between the date of the first dose and the date of the last dose.

8.2.10 Extent of Exposure

For a pembrolizumab regimen, a subject's extent of exposure to pembrolizumab is defined as the total number of doses of pembrolizumab the subject received. A subject's exposure to a dose of IPI or IFN is defined as the total number of days on therapy for that dose.

Summary statistics may be provided on Extent of Exposure for the APaT population in Parts 1B and 1C.

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 utilized in the trial are:

Table 19 Product Descriptions

Product Name & Potency	Dosage Form
pembrolizumab 100 mg/4 mL	Solution for Infusion
Pegylated Interferon alfa-2b 300 mcg	Lyophilized Powder for Injection
Ipilimumab 50 mg and 200 mg	Solution for Infusion
NOTE: The investigator will be responsible for providing the following items: syringes, alcohol swabs, and sterile water for injection, USP (vial or ampule). .	

Pegylated Interferon alfa-2b and IPI will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee, every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product. The trial site is responsible to record the lot number, manufacturer and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor. However, as any locally sourced combination therapies specified in Table 19 of the protocol are approved drugs in the US, investigational sites participating in this trial that are located in the US are not required to collect information regarding the source (manufacturer/lot/expiry date) on trial documentation. Drug accountability and manufacturer information will be retained with the hospital pharmacy at the clinical site.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open-label pembrolizumab 100 mg/ 4mL vials, Pegylated Interferon alfa-2b 300 mcg kits, and IPI 50 mg and 200 mg kits for dosing Parts 1A, 1B, and 1C subjects.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

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 separately.

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, leftover tumor tissue and leftover 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, leftover tumor tissue and leftover blood 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 contacting 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.

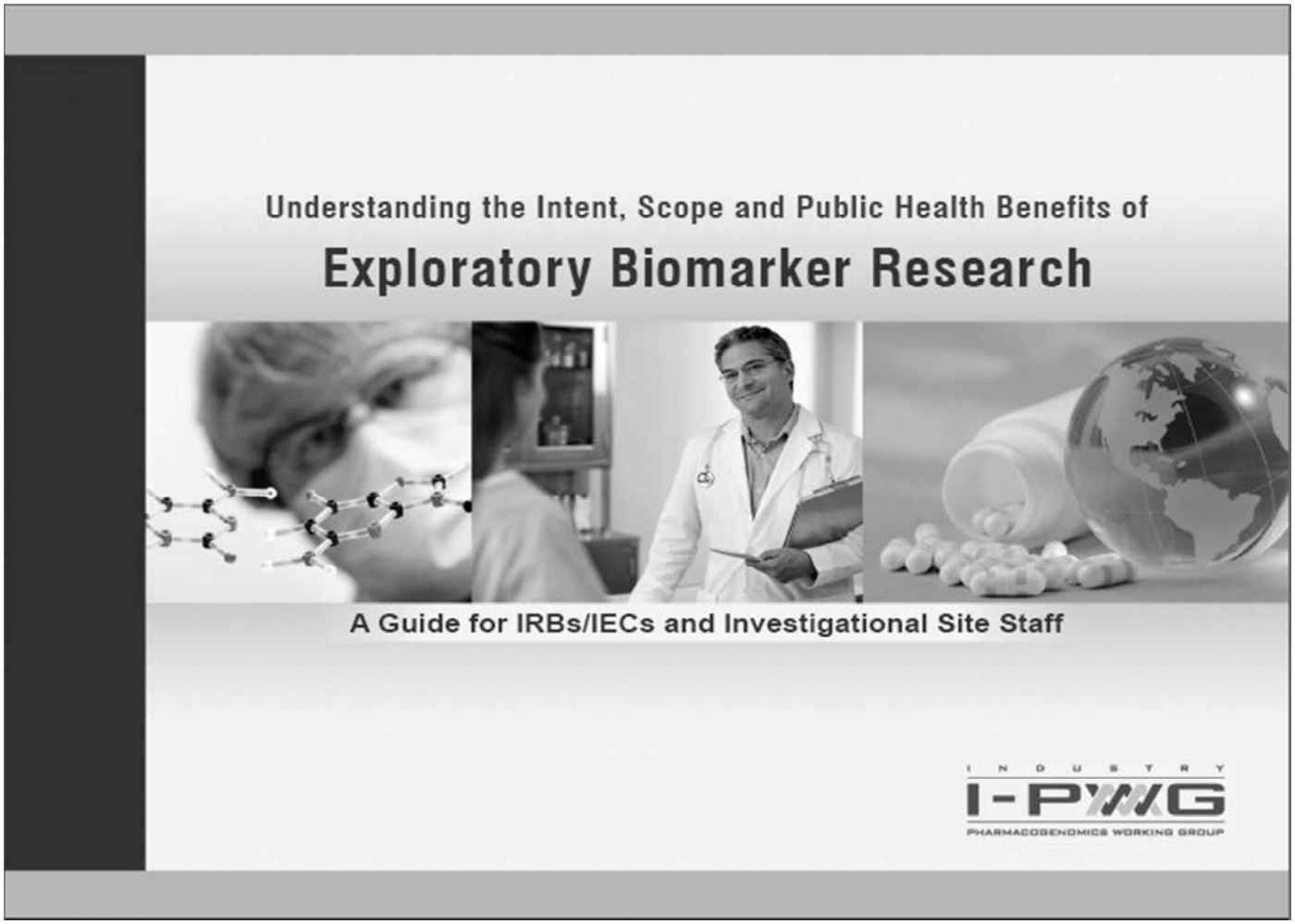
13. Questions

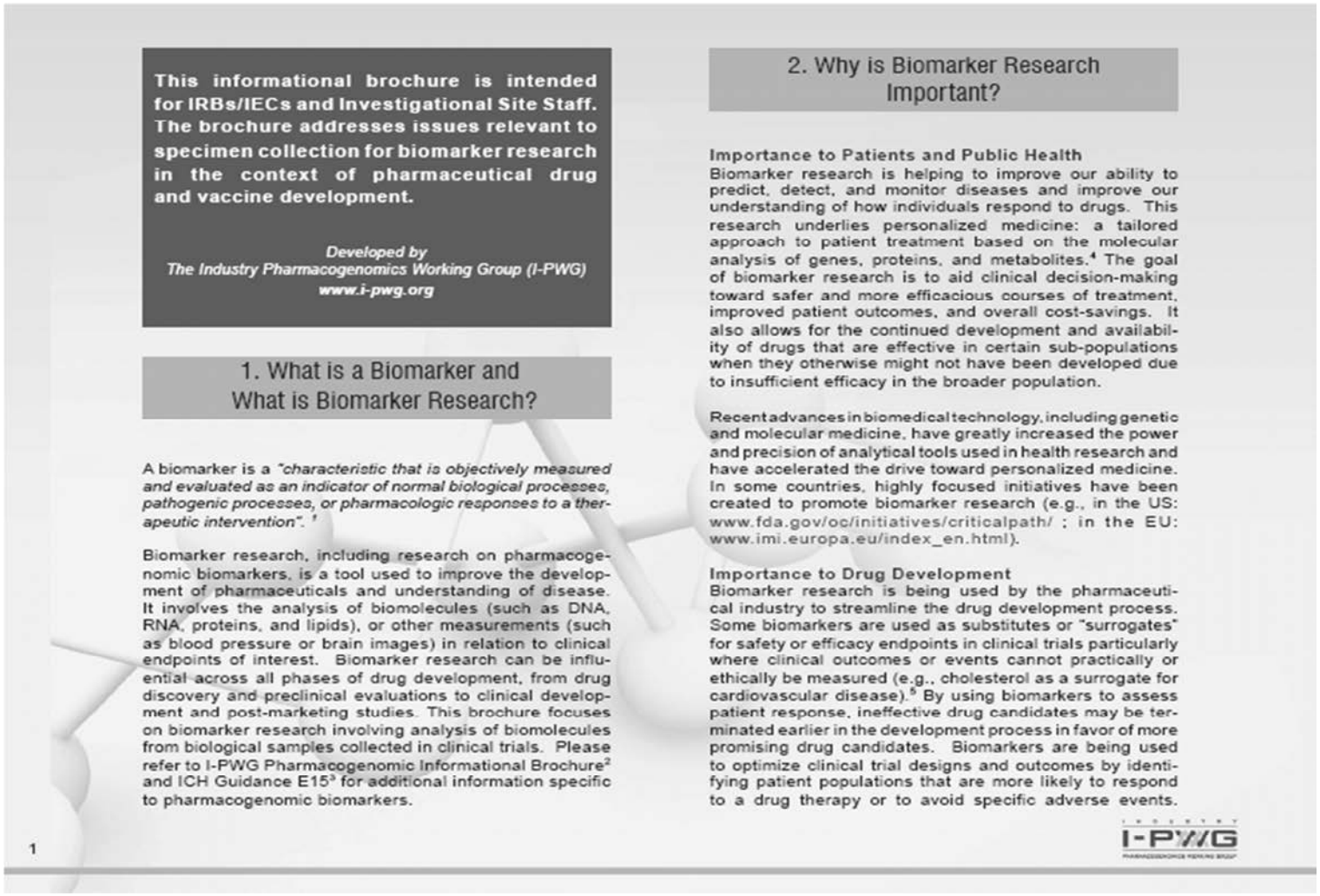
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Understanding 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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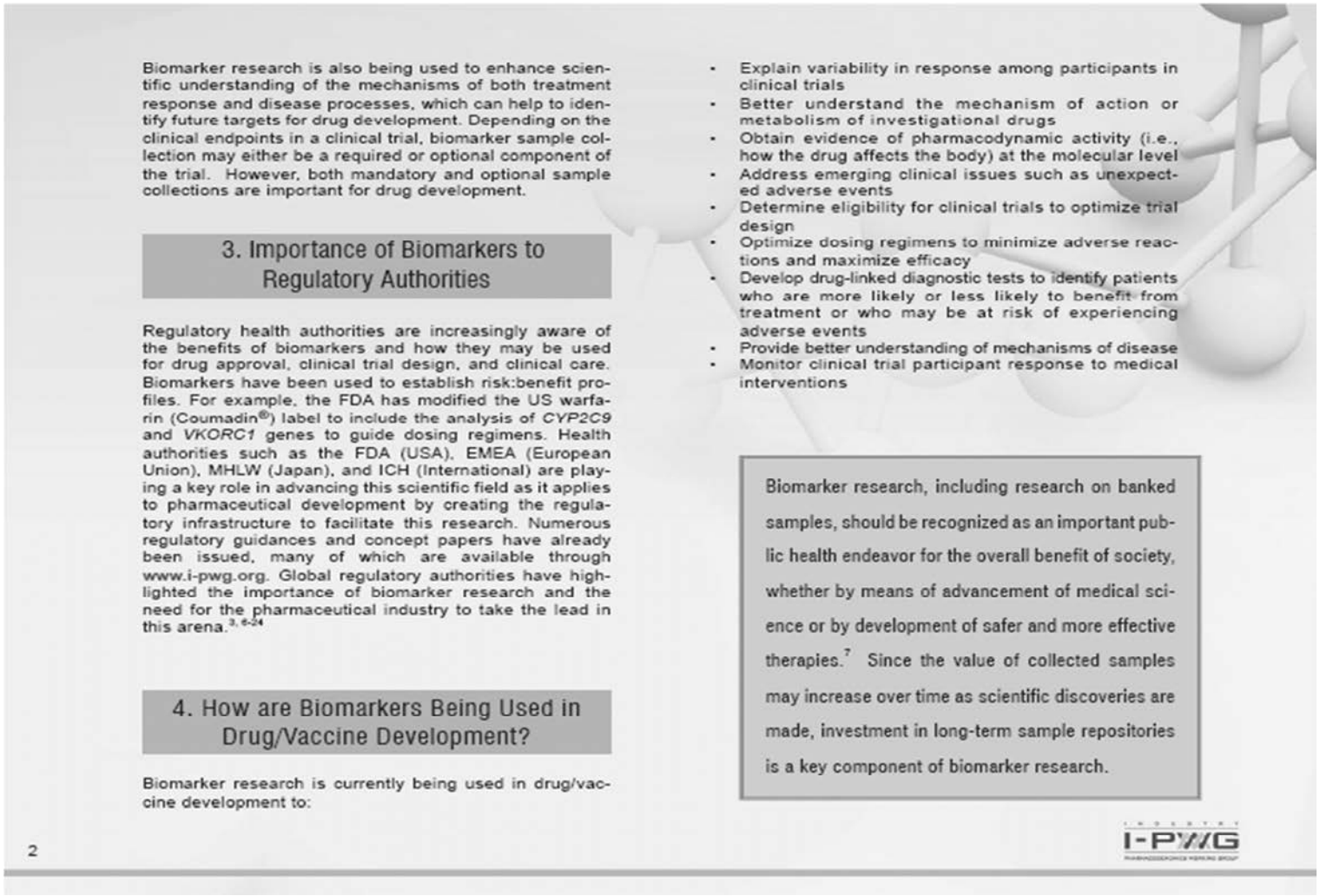
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either 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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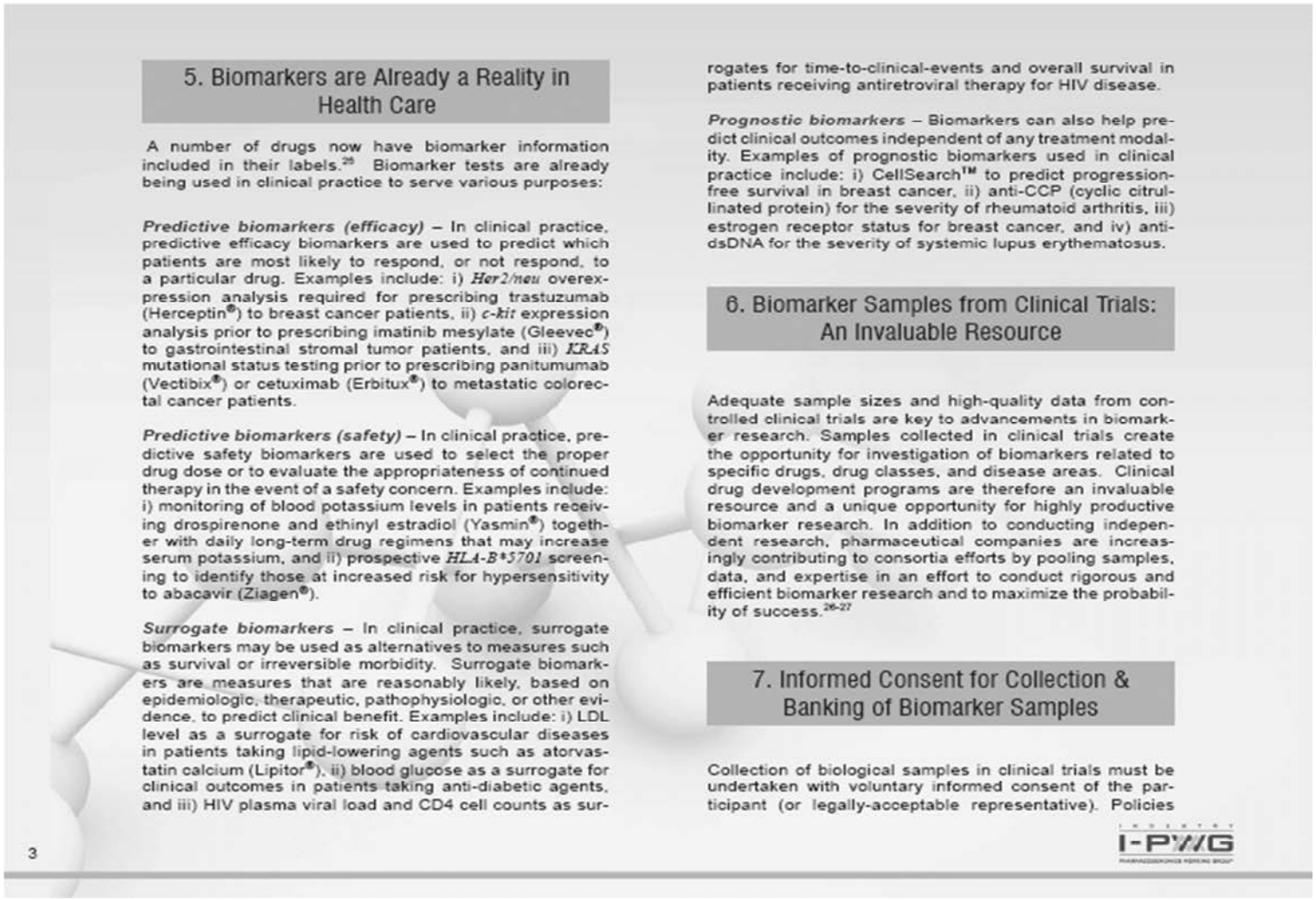

5. Biomarkers are Already a Reality in Health Care

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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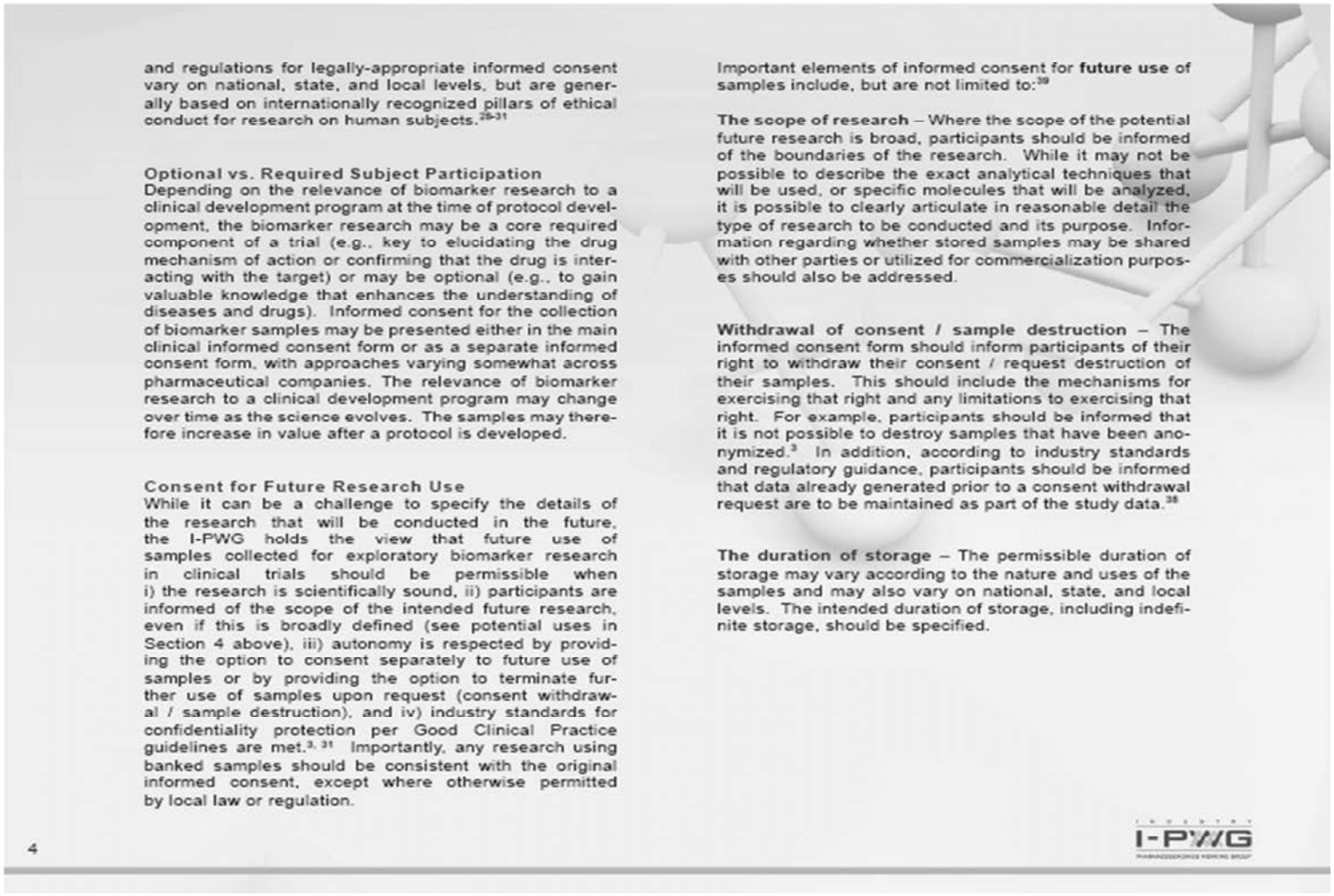

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

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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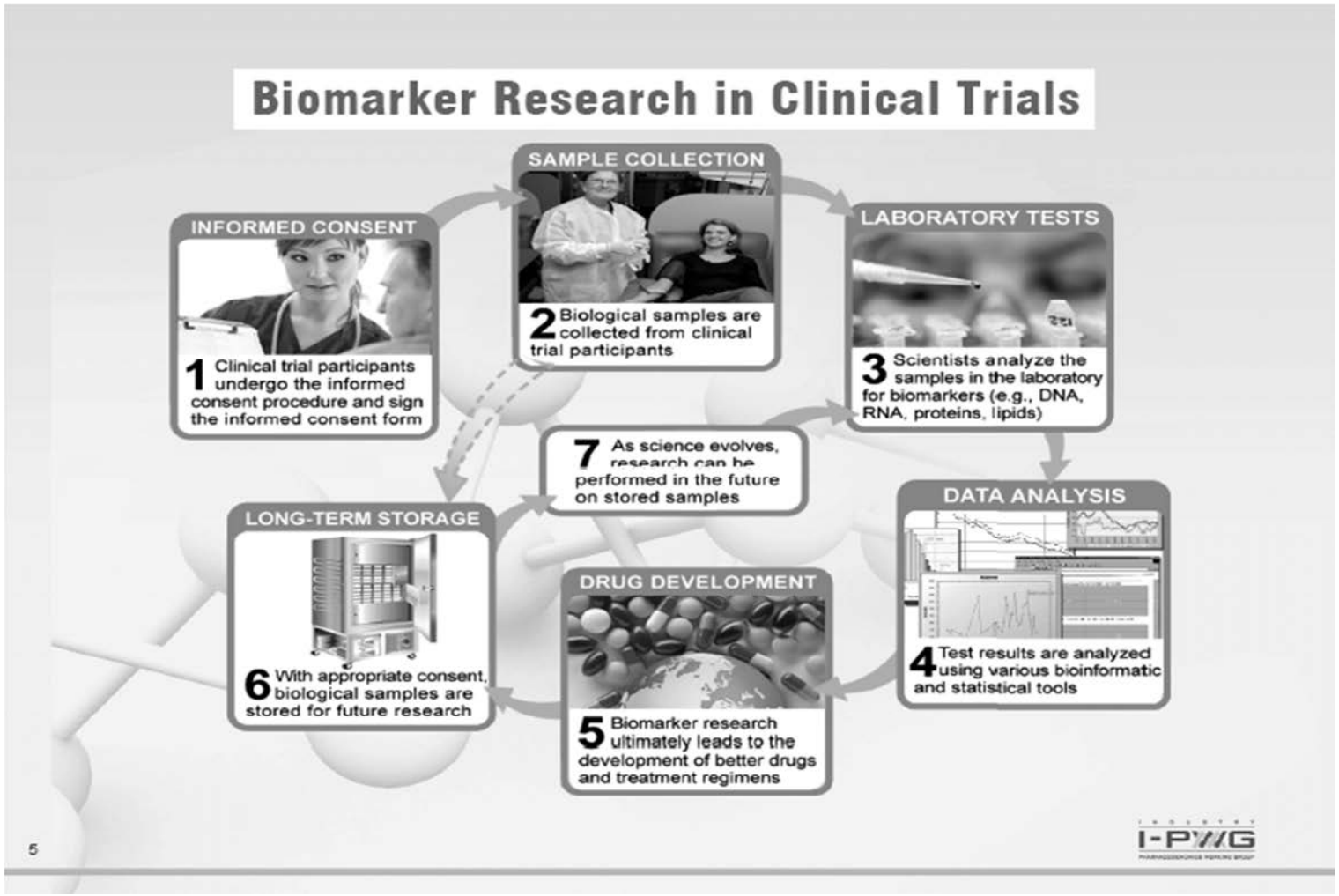
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
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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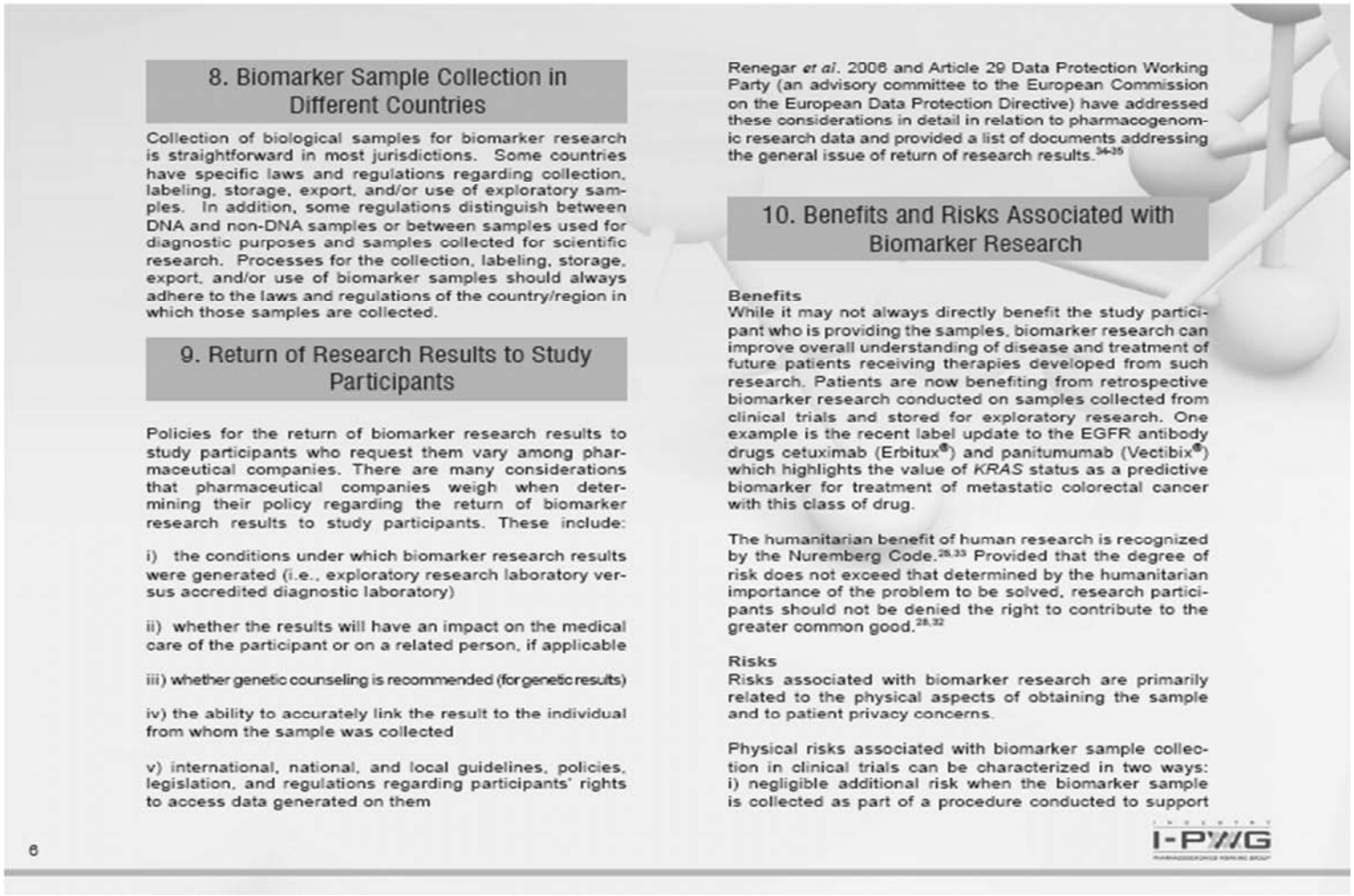

8. Biomarker Sample Collection in Different Countries

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*. 2006 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.[34-35]

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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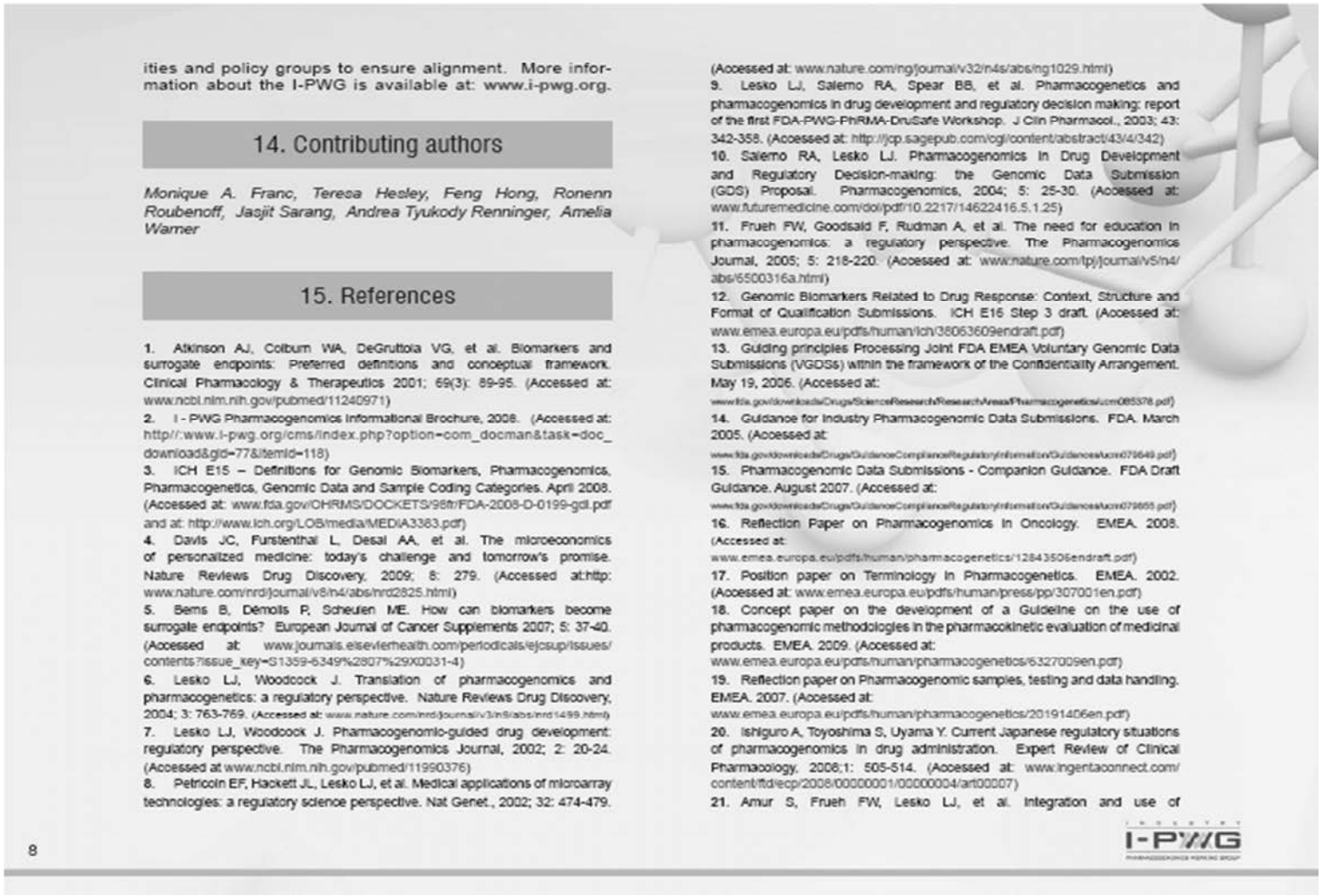

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
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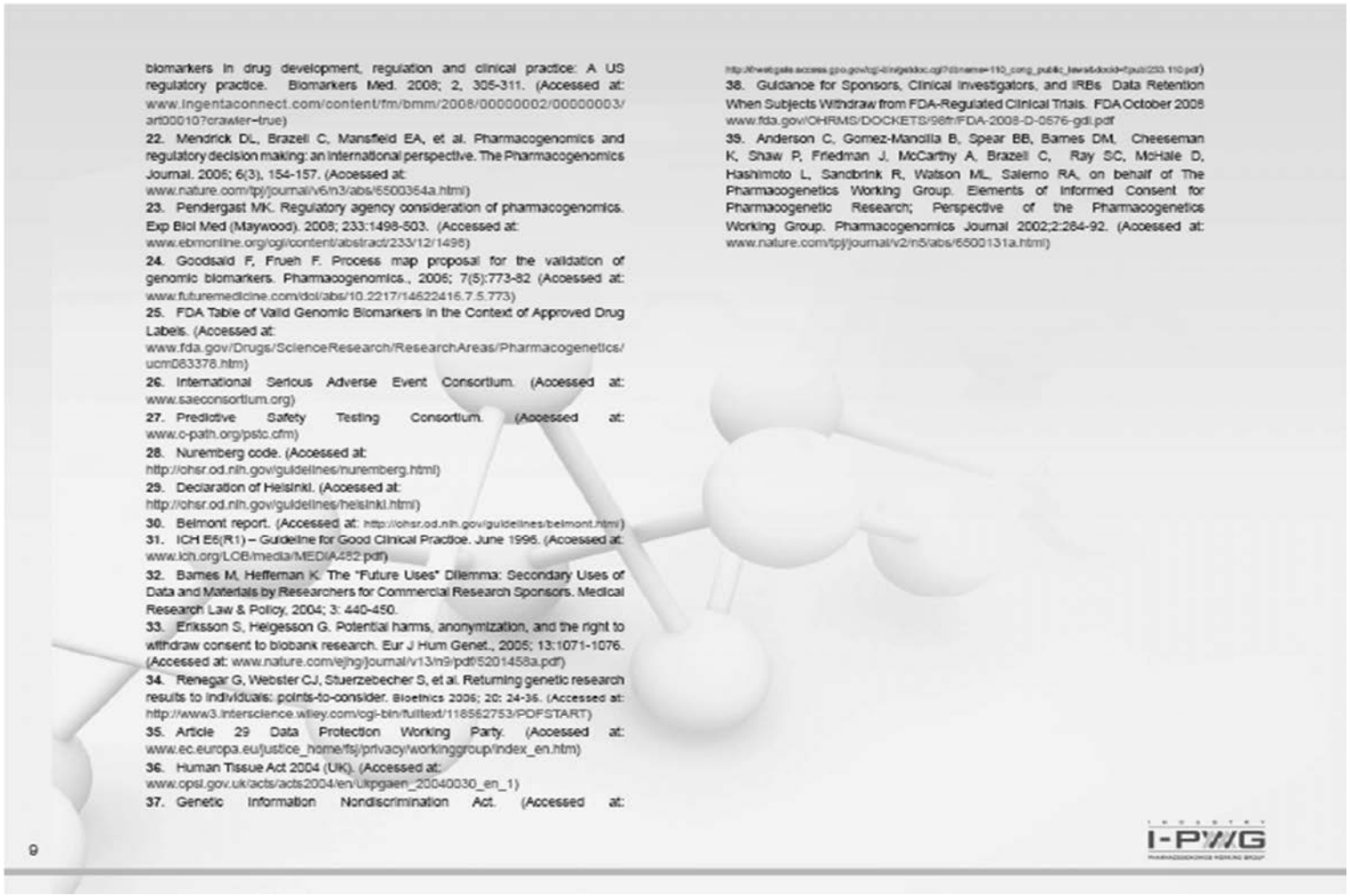

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12.4 ECOG Performance Status

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 self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
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

12.5 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI CTCAE Version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

12.6 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

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

* As published in the European Journal of Cancer [1]

12.7 List of Abbreviations

Abbreviation/Term	Definition
ACAR	Aggregate Clinical Activity Rate
AE	Adverse event
ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Antigen Presenting Cells
APaT	All-Patients-as-Treated
aPTT	Activated partial thromboplastin time
AUC	Area Under Curve
AST	Aspartate aminotransferase
β-hCG	Beta human chorionic gonadotropin
BORR	Best objective response rate
CBC	Complete blood count
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CrCl	Calculated creatinine clearance
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTL	Cytotoxic T Lymphocytes
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DL	Dose Level
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DRAE	Drug-related Adverse Event
ECI	Events of clinical interest
ECI-ie	Events of clinical interest with a potential immunologic etiology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERC	Ethics review committee

Abbreviation/Term	Definition
FAS	Full analysis set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FLC	Free Light Chain
FT4	Free T4
GCP	Good Clinical Practice
Hb	Hemoglobin
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMiD	Immunomodulatory
INR	International normalized ratio
IPI	Ipilimumab
irAEs	Immune-related adverse events
IRB	Institutional Review Board
ISS	International Staging System
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intent-To-Treat
IV	Intravenous
Kg	Kilogram
LDH	Lactate dehydrogenase
LMWH	Low molecular weight heparin
mAb	Monoclonal antibody
MAD	Maximum administered dose
MC38	Mouse Colorectal Model 38
mcL	Millimeters
MEL	Melanoma
MG	Milligram
mg/kg	Milligram per kilogram
mL	Milliliter
Mg	Microgram
µg/kg	Microgram per kilogram

Abbreviation/Term	Definition
MRI	Magnetic resonance imaging
MPR	Moderate Partial Response
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum tolerated dose
mRNA	Messenger Ribonucleic acid
mTOR	Mammalian target of rapamycin
NA or N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural Killer
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective l response rate
OS	Overall survival
OTC	Over-the-counter
PBMC	Peripheral blood mononuclear cells
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed-death receptor-1
PD-L1	Programmed-death receptor-ligand 1
PD-L2	Programmed-death receptor-ligand 2
PEG-IFN	Pegylated Interferon Alfa-2b
PET	Positron emission tomography
PFS	Progression-free survival
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK-PD	Pharmacokinetic-Pharmacodynamic
po	orally
PR	Partial response
PT	Prothrombin time
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
RR	Response rate
q2w	Every 2 weeks
q3w	Every 3 weeks
q6w	Every 6 weeks
q12w	Every 2 weeks

Abbreviation/Term	Definition
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SC	Subcutaneous
sCR	Stringent Complete Response
SFU	Survival follow-up
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoC	Standard of Care
SJS	Stevens-Johnson Syndrome
SOP	Standard Operating Procedures
SPEP	Serum protein electrophoresis
TCR	T cell receptor
T1DM	Type 1 Diabetes Mellitus
TIL	Tumor-infiltrating lymphocytes
TPI	Toxicity Probability Interval
TSH	Thyroid stimulating hormone
TTP	Time To Progression
VEGF	Vascular endothelial growth factor
VGPR	Very Good Partial Response
ULN	Upper limit of normal
US	United States

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

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 7.0 – 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	
TITLE	
SIGNATURE	
DATE SIGNED	